Post-print version of Greimel, Nehrkorn, Fink, Kukolja, Kohls, Müller, Piefke, Kamp-Becker, Remschmidt, Herpertz-Dahlmann, Konrad & Schulte-Rüther (2012). Neural mechanisms of encoding social and non-social context information in autism spectrum disorder, Neuropsychologia, 50, 3440-3449.
doi: 10.1016/j.neuropsychologia.2012.09.029 (Publisher version available at: https://www.sciencedirect.com/science/article/pii/S0028393212004010).

Neural mechanisms of encoding social and non-social context information in autism spectrum disorder

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Highlights

The influence of context on neural mechanisms of object encoding was studied in ASD

ASD and controls encoded objects presented with a social or non-social context

Abnormal activation in ASD was predominantly observed in the social context condition

ASD subjects showed atypical fronto-parietal activation in the social context condition

Socioemotional impairment in ASD extends into domains beyond social cognition

Abstract

Individuals with autism spectrum disorder (ASD) often fail to attach context to their memories and are specifically impaired in processing social aspects of contextual information. The aim of the present study was to investigate the modulatory influence of social vs. non-social context on neural mechanisms during encoding in ASD. Using event-related fMRI, 13 boys with ASD and 13 typically developing boys comparable for age and IQ were investigated during encoding of neutral objects presented either with a social (faces) or a non-social (houses) context. A memory paradigm was then applied to identify brain activation patterns associated with encoding of subsequently recollected versus non-recollected objects.

On the behavioural level, no significant between-group differences emerged. In particular, no differential effects of context on memory performance were observed. Neurally, however, context-specific group differences were observed in several brain regions. During encoding of subsequently recollected objects presented with a face, ASD subjects (compared to controls) showed reduced neural activation in the bilateral inferior frontal gyrus, bilateral middle frontal gyrus and right inferior parietal lobule. Neural activation in the right inferior frontal gyrus was positively correlated with memory performance in controls, but negatively in ASD individuals. During encoding of subsequently non-recollected objects presented in the non-social context, ASD subjects showed increased activation in the dorsal MPFC.

Our findings suggest that in ASD subjects, fronto-parietal brain regions subserving memory formation and the association of contextual information are activated atypically when a social context is presented at encoding. The data add to findings from related research fields indicating that in ASD, socioemotional impairment extends into domains beyond social cognition. Increased activation in the dorsal MPFC in ASD individuals might reflect supervisory cognitive processes related to the suppression of a distracting non-social context.

Keywords: autism, fMRI, encoding, context, face

1. Introduction

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder characterised by impairments in social interaction, communication, as well as restrictive interests and behaviour (American Psychiatric Association, 1994). In addition, the disorder is associated with a specific profile of impaired and spared memory processes. Generally speaking, ASD subjects predominantly show deficits when retrieval of mnemonic information is not supported by any cues (i.e., free recall) (Tager-Flusberg, 1991), whereas performance is relatively unimpaired when cued retrieval tests, such as item recognition or cued recall, are administered (Bowler, Gaigg, & Gardiner, 2008; Bowler, Gardiner, & Grice, 2000).

Furthermore, based on the observation that ASD individuals often fail to attach context or personal meaning to their memories, a few behavioural studies have investigated memory for contextual information (e.g., temporal or spatial information; also referred to as "source memory") in ASD (Bennetto, Pennington, & Rogers, 1996; Farrant, Blades, & Boucher, 1998; Russell & Jarrold, 1999). Results from these studies are contradictory, presumably due to differences between the studies in the experimental procedures (e.g., incidental or intentional encoding of context; supported vs. unsupported test procedures) and materials (e.g., type of contextual information) employed. The latter claim is supported by O´Shea et al. (2005), who found that children with ASD do not show a generalized memory impairment for context, but rather a specific deficit when *social aspects* of contextual information (in particular faces) had to be recalled. This finding fits well with robust evidence for face processing deficits in ASD and with the notion that individuals with ASD generally show less social interest and motivation than typically developing (TD) individuals, probably resulting from a lack of experience with faces during critical developmental periods (Dawson, Webb, & McPartland, 2005; Schultz, 2005).

To our knowledge, the putative differential modulatory influence of social vs. non-social context on memory performance in ASD individuals has not been examined to date. Moreover, the neural mechanisms associated with these influences are largely unknown. In TD individuals, only few studies have investigated modulatory effects of social or emotional context information on brain responses during encoding or retrieval processes. In two functional magnetic resonance imaging (fMRI) studies, adult subjects encoded words embedded in a social/emotional (Skinner, Grady, & Fernandes, 2010; Maratos, Dolan, Morris, Henson, & Rugg, 2001) vs. neutral context and were scanned during retrieval of these words, when no context was presented. While in both studies no behavioural effect of context was observed, a modulatory influence of context was detected on the neural level in two ways: First, the retrieval of words encoded in socioemotional (vs. neutral) context was associated with enhanced activation in brain regions implicated in memory formation in general (Spaniol et al., 2009), including the hippocampus, the ventrolateral and dorsolateral prefrontal cortexand prefrontal areas. Second, during retrieval of words initially embedded in a socioemotional context, brain structures subserving socioemotional processing (fusiform gyrus and amygdala) were activated.

Other neuroimaging studies in TD adults have focused on the influence of emotional context (e.g., positive vs. negative) on neural processes during *successful episodic encoding* (i.e., subsequently recollected material) of neutral information (Erk et al., 2003; Erk, Martin, & Walter, 2005). Consistent with Maratos et al. (2001) and Skinner et al. (2010), these studies demonstrated that during successful encoding, emotional context differentially modulated brain activation patterns in regions implicated in memory formation including the dorsolateral prefrontal cortex, the hippocampus and the parahippocampal gyrus (see Spaniol et al., 2009 for a meta-analysis of the involvement of these areas in successful encoding). Moreover, the studies by Erk and colleagues could show a differential effect of emotional context in brain

areas implicated in socioemotional processing, including the amygdala and the fusiform gyrus (Erk et al., 2003; Erk, Martin, & Walter, 2005).

Exploring the neural underpinnings of social versus non-social context effects on episodic memory formation in ASD might help to understand why persons affected by the disorder often show deficits in attaching personal meaning or context to their memories. Given the specific impairment of individuals with ASD in the social domain (Dawson et al., 2005), it is of particular interest to elucidate whether and how modulatory influences of social context on episodic memory in ASD might differ from TD individuals. Thus, the main aim of this event-related fMRI study was to investigate the influence of social and non-social context on neural mechanisms during successful encoding of neutral items in children and adolescents with ASD. For this purpose, ASD subjects and a TD control group comparable for age, gender and IQ were scanned during encoding of neutral objects embedded either in a social (i.e., faces) or a non-social (i.e., houses) background (context). Subsequently, retrieval was tested using a recognition task and the data then used to identify brain activation patterns associated with successful encoding (i.e., recollected vs. non-recollected objects).

We expected that ASD subjects would show atypical activation patterns during successful encoding of objects embedded in a social (but not in a non-social) context. More precisely, we predicted deviant activation in ASD individuals in brain structures involved in successful memory formation (i.e., hippocampus, the ventrolateral and dorsolateral prefrontal), and social/face processing (i.e., amygdala, fusiform gyrus). This hypothesis was based on (1) findings on the modulatory effect of socioemotional context on brain activation in TD subjects (Skinner et al., 2010; Maratos et al., 2001; Erk et al., 2003; Erk et al., 2005) as well as on (2) neuroimaging studies on face processing in ASD that have repeatedly reported abnormal neural activation in the amygdala and the fusiform gyrus (Schultz, 2005).

2. Material and methods

2.1 Participants

Thirteen male children and adolescents with ASD between 9 and 19 years of age, diagnosed with Asperger syndrome (*n=7*), high-functioning autism (*n=5*) or atypical autism (*n*=1), and 13 male controls participated in the study. Only right-handed subjects (Oldfield, 1971) with an IQ≥80 (based on the WISC-III (Wechsler, 1991) or WAIS-III (Wechsler, 1997)) were included. Pubertal maturation was evaluated by using Tanner´s Staging (Tanner & Davies, 1985), a 5-point scale for the assessment of primary and secondary sexual development. Groups did not differ significantly in age, IQ, or Tanner stages (Table 1).

ASD subjects were recruited from the Department of Child and Adolescent Psychiatry in Aachen and Marburg. ASD subjects had been diagnosed prior to the study by experienced clinicians according to ICD-10 (World Health Organization, 1993) and DSM-IV (American Psychiatric Association, 1994). Diagnosis was confirmed by the Autism Diagnostic Observation Schedule-Generic (ADOS-G) (Lord et al., 2000; Rühl, Bölte, Feineis-Matthews, & Poustka, 2004), a standardized observational instrument for assessing behaviour relevant to autism, and a semi-structured interview for caregivers of children with ASD (Autism Diagnostic Interview-Revised) (LeCouteur et al., 1989; Bölte, Rühl, Schmötzer, & Poustka, 2006), which were conducted by certified examiners (E.G., I.K.-B.). Additionally, parents completed the Social Communication Questionnaire (Rutter, Bailey, & Lord, 2003; Bölte & Poustka, 2006) and the Social Responsiveness Scale (Constantino, 2002).

With regard to psychiatric comorbidity, one subject showed symptoms of ADHD and one subject had been diagnosed with comorbid chronic tic disorder. TD controls were screened to exclude any psychiatric disorder using the Child Behaviour Checklist (Achenbach, 1993; Döpfner, Schmeck, & Berner, 1994).

One ASD participant was medicated with an atypical neuroleptic at the time of testing. None of the other ASD subjects and control subjects received any medication. None of the controls or ASD subjects suffered from any relevant somatic or neurological disorders.

The study was approved by the institutional review board of the University Hospital of the RWTH Aachen and was performed in accordance with the latest version of the Declaration of Helsinki, in compliance with national legislation. All participants were informed in detail about the experimental procedures and the aims of the study, and provided written informed consent (subjects aged ≥ 18 years) or assent (subjects aged < 18 years). For children or adolescents, additional written informed consent was obtained from at least one parent/legal custodian, after the parent(s)/legal custodian(s) had been informed about all aspects of the study.

2.2 Procedure

The experiment comprised an (1) encoding and a (2) retrieval session. Scanning was only performed during the first session since this study focused on the influence of social and non-social context on neural mechanisms during encoding. Response collection and stimulus presentation during the encoding and the retrieval session were controlled by the software Presentation 11 (Neurobehavioral Systems, Albany, CA, USA).

2.2.1 Encoding

Stimulus material during encoding: During the encoding session, N=200 stimuli were presented. Stimuli consisted of an object superimposed on a background context (Fig. 1). Objects were framed by a red box to clearly separate them from the background. Half of the objects (n=100) showed artificial (i.e., man-made; e.g., a tool or an instrument) objects, while the other half (n=100) represented natural (i.e., not man-made; e.g., a vegetable or an animal)

objects. All artificial and natural objects were non-social, i.e., the stimuli did not contain (parts of) human characters or social symbols.

Half of the objects shown during the encoding session contained animacy features (e.g., a bicycle, a penguin), and half of the objects did not involve animacy (e.g., an apple; a socket). To rule out that animacy would potentially confound the results, the proportion of objects with vs. without animacy features was counterbalanced across object types (natural/artificial). Each object was only shown once. The background context was either a photograph of a neutral face (social context; taken from the Facial Emotions for Brain Activation (FEBA) database (Gur et al., 2002) or a photograph of a house (non-social context). Twenty different individual context pictures (10 faces and 10 houses) were employed. Each of these context stimuli was presented ten times during the entire encoding session, each time superimposed by a different artificial or natural object. The number of artificial and natural objects shown with a face or a house, respectively, was counterbalanced.

Task procedure during encoding: classification task: On each trial, the background (i.e., context) was shown first without the object to be encoded for 1 sec (see Fig. 1). Then, the background and the object were presented together for 2 sec. Subjects were instructed to memorise all objects and to also pay attention to the background. To ensure that subjects attended to the stimuli, they had to indicate whether the object was “natural” or “artificial” (classification task) using their right index or middle finger, respectively. The different trial types (artificial object + house, artificial object + face, natural object + house, natural object + face) were presented pseudo-randomly. Trials were separated by a fixation cross (duration: 1 sec) and randomly intermixed with a total of 100 null-events showing a fixation cross for 2 sec.

To familiarise participants with task requirements, subjects practised the task outside the scanner. Stimuli shown during the practice session were not included into the fMRI stimulus set.

The experimental paradigm employed was designed to parallel encoding of real-world contextual information while at the same time ensuring maximal experimental control. Unlike in other fMRI studies on the modulatory influences of social information on memory formation (e.g., Erk et al., 2003; 2005), we presented target objects and contextual information in the same modality, so that both items could easily be integrated. Faces and houses occur very frequently in real-life situations and may thus represent ecologically valid background contexts facilitating incidental encoding. Moreover, incidental encoding of contextual information was further facilitated by choosing background images in unobtrusive colours.

2.2.2 Retrieval

30 minutes after the end of the encoding session, N=300 objects were presented without a background context on a computer screen outside of the scanner in a separate room. 200 of these objects had been presented during the encoding session (old objects) and 100 objects (n=50 artificial, n=50 natural) were new objects. Again, half of the new objects contained animacy features, while the other half did not involve animacy characteristics. New and old objects were intermixed pseudo-randomly. Stimuli were presented for 3 sec followed by a fixation cross (1 sec). Subjects were instructed to indicate via button press whether they recollected the respective item (i.e., whether it had been presented definitely during the encoding session), or not. If they did not recollect the item, they could indicate whether they were sure that it was a new item (i.e., not presented during the encoding session) or whether they were uncertain. Since previous studies suggest that modulatory effects of context types

on memory processes are most evident for items that are explicitly recollected (Skinner et al., 2010), subsequent data analysis focused on the distinction between recollected and non-recollected items. Furthermore, a preliminary analysis indicated that "uncertain" responses were not very frequent among participants and that there were no significant differences in the number of "uncertain" responses between groups (p=.205) and contexts (p=.847), respectively.

2.3 MRI acquisition

Scanning was performed on a 3 Tesla Trio system (Siemens, Erlangen, Germany) using a standard head coil. During the encoding session, whole brain echoplanar T2*-weighted images (EPIs) were acquired (TE=30 ms, TR=2200 ms, flip angle=90°, FOV=200 mm, matrix size=64×64, voxel size=3.1×3.1×3 mm^3, 36 slices, slice thickness=3 mm). After acquisition of functional scans, high-resolution T1-weighed anatomical images were collected using a rapid acquisition gradient-echo (MP-RAGE) pulse sequence (TE=3.93 ms, TR=2200 ms, FOV=256 mm, matrix size=256×256, voxel size=1×1×1 mm^3, slice thickness=1 mm).

2.4 Behavioural data analysis

2.4.1 Classification task during encoding

A 2×2 MANOVA with the factors object type (natural vs. artificial) and group (ASD vs. TD) was calculated to analyse the proportion of correct object classifications (correctly judged as artificial or natural) and reaction times (RTs) of correct classifications during the classification task at encoding. The MANCOVA was followed by 2×2 ANOVAs with the factor object type and group in case of significant or marginal significant effects (marginal significant effects were followed up only for explorative reasons). A multivariate approach was chosen to reduce the number of tests and thus the risk of alpha-error inflation.

2.4.2 Memory task during retrieval

A 2×2 MANOVA with the factor background context (house vs. face) and group (ASD vs. TD) was calculated to analyse the proportion of recollected objects and the RTs to recollected and non-recollected objects. If significant effects were revealed in the multivariate analysis, the MANCOVA was followed by 2×2 ANOVAs with the factor background and group.

For new objects, the factor background type was not applicable. Consequently, independent t-tests were conducted to compare groups with regard to the proportion of new objects that were correctly rejected (i.e. correctly non-recollected). Moreover, RTs to correct rejections, and RTs to new objects that were incorrectly classified as "old" (i.e., false alarms) were compared between groups using independent t-tests. To minimize Type I error, the alpha-level of .05 was adjusted for these three comparisons applying Holms´ procedure.

2.4.3. Correlational analyses on the relationship between behavioural data and IQ/autistic pathology

To assess the relationship between primary behavioural variables and IQ, explorative correlational analyses were performed which are described in the Appendix (A.1). Similarly, explorative analyses on the relationship between primary behavioural variables and autistic pathology (based on the ADOS-G) are summarized in the Appendix (A.1).

2.5 MRI data analysis

Imaging data were analysed with SPM5 (Wellcome Department of Imaging Neuroscience, London, UK: http://www.fil.ion.ucl.ac.uk) implemented in MATLAB 7.2 (The Mathworks, Inc., Natrick, MA, USA). The first five functional images of each subject were discarded. The remaining 550 volumes were realigned, spatially normalised to standard stereotactic Montreal

Neurological Institute (MNI) coordinates and spatially smoothed with an 8-mm full-width half-maximum Gaussian kernel. Anatomical images were coregistered to the mean EPI image and normalised into MNI space, applying the parameters derived from normalization of functional images.

For the statistical analysis, four event types were defined for the encoding session dependent on the background context during encoding and subjects´ responses during the retrieval session: (1) objects presented with a house which were recollected during the retrieval session (RecolHouse); (2) objects presented with a face which were recollected during the retrieval session (RecolFace); (3) objects presented with a house which were not recollected during the retrieval session (NonRecolHouse); and (4) objects presented with a face which were not recollected during the retrieval session (NonRecolFace).

Events were modeled as stick functions which were convolved with a model of the hemodynamic response and its first-order temporal derivative. Model parameters were estimated for each voxel according to the General Linear Model. To account for residual movement-related variance, realignment parameters were included into the model as regressors.

For group analyses, a second-level random-effects analysis was implemented. Individual contrast images coding for each event type were analysed by a flexible factorial ANOVA (mixed model; factors: condition X group X subject). Violations of sphericity assumptions were accounted for by applying the non-sphericity correction in SPM5 (modelling of covariate components). The following contrasts were assessed for group differences:

(1) Recol vs. NonRecol: Objects which were recollected during the retrieval session vs. objects which were not recollected during the retrieval session, i.e. (RecolHouse+RecolFace) vs. (NonRecolHouse+NonRecolFace); (2) RecolHouse vs. NonRecolHouse; (3) RecolFace

vs. NonRecolFace. Additionally, the interaction contrast (4) (RecolHouse – NonRecolHouse) vs. (RecolFace – NonRecolFace) was assessed for group differences.

In addition to the contrasts described above, we computed exploratory whole-brain simple effect contrasts relative to baseline to decompose interaction effects and to confirm the validity of the experimental approach (RecolHouse>Baseline; NonRecolHouse>Baseline; RecolFace>Baseline; NonRecolFace>Baseline). Simple effects were calculated separately for the ASD and the control group and are summarized in the Appendix (Supplementary Tables A. 3 – A. 6).

Results are reported that met the statistical threshold of $p<.001$ at the voxel level and $p<.05$, corrected for multiple comparisons at the cluster-level using Gaussian random fields theory. Cluster-level correction provides a stringent protection against false positives. In particular, a family-wise error (FWE) cluster-level correction at $p<.05$ implies that only one out of 20 inferences on random fields (without any true signal) will resolve in a single false positive cluster. In order to reduce the impact of the whole-brain correction procedure for anatomically and cytoarchitectonically circumscribed brain regions, for which we had specified hypotheses regarding differential group effects, we performed additional region of interests (ROI) analyses in the hippocampus, the amygdala and the fusiform gyrus. ROI definitions were based on neuroanatomical toolboxes available for SPM5 (Anatomy Toolbox (Eickhoff et al., 2005), WFU PickAtlas (Maldjian, Laurienti, Kraft, & Burdette, 2003)). For ROI analyses we report results with a height threshold of $p<.05$ (FWE corrected within each particular ROI at the voxel-level).

In an additional analysis we tested whether individual brain activations were related to memory performance during the retrieval session. Individual parameter estimates of regressors for the conditions RecolHouse and RecolFace were extracted if group comparisons for the contrasts RecolHouse vs. NonRecolHouse, and RecolFace vs. NonRecolFace yielded

significant results. Individual parameter estimates were extracted at voxels showing peak activation in the group comparisons and were correlated with the number of recollected objects (either from the social or non-social context condition) as a measure of individual memory performance.

Moreover, to examine whether IQ was related to brain activation patterns during encoding, we conducted additional whole-brain regression analyses across both groups with IQ as the independent variable. These regression analyses were conducted for the contrasts RecolFace versus NonRecolFace and RecolHouse versus NonRecolHouse. Similarly, for the ASD group, we conducted additional whole-brain regression analyses with the ADOS-G as the independent variable for the contrasts RecolFace versus NonRecolFace and RecolHouse versus NonRecolHouse. Results from the regression analyses are also reported at the statistical threshold of $p<.001$ at the voxel level and $p<.05$, corrected for multiple comparisons at the cluster-level using Gaussian random fields theory.

3. Results

3.1 Behavioural results

3.1.1 Classification task during encoding

The MANCOVA with the proportion of correct object classifications and RTs of correct classifications as dependent variables revealed a main effect of object type ($F(2,23)=3.74$, $p=.039$, $\eta_p=0.225$). Neither the main effect of group ($F(2,23)=0.48$, $p=.623$, $\eta_p=0.040$) nor the interaction between group and object type ($F(2,23)=0.69$, $p=.514$, $\eta_p=0.056$) proved to be significant. A follow up ANOVA revealed that, across both groups, the percent correct classifications of artificial objects ($M=98.0\pm2.3\%$) was higher compared to natural objects ($M=96.3\pm4.8$; $F(1,24)=6.29$, $p=.019$, $\eta_p=0.208$). Moreover, a follow up ANOVA for RTs to correctly classified objects revealed that responses to artificial objects ($M=1.00\pm0.15$ sec)

were marginally faster compared to natural objects (M=1.03±0.11 sec; F(1,24)=3.15, p=.089, η_p=0.116).

The percent of missing responses was very low and did not differ significantly between groups (M_{TD}=1.0+0.9%, M_{ASD}=0.6+1.2%; t(24)=1.03, p=.314).

3.1.2 Memory task during retrieval

The MANCOVA with the proportion of recollected objects and the RTs to recollected and non-recollected objects as dependent variables revealed a marginal significant main effect of group (F(3,23)=2.44, p=.091, η_p=0.250). No significant effect of background context was revealed (F(3,23)=0.301, p=.825, η_p=0.039). Moreover, the interaction between background context and group was non-significant (F(3,23)=0.611, p=.615, η_p=0.077).

Post-hoc explorative ANOVAs revealed that groups did not differ with regard to the percentage of recollected items (F(1,24)=2.39, p=.135; η_p=0.090) or RTs to recollected items (F(1,24)=0.13, p=.723; η_p= .005). By contrast, a significant main effect of group was revealed for RT to non-recollected items (F(1,24)=7.46, p=.012; η_p= .237), with faster responses to non-recollected items in the ASD compared to the control group.

No group differences were revealed for the percentage of correct rejections of new objects (t(24)=-0.47, p=.644). Similarly, RTs of correct rejections of new objects did not differ between groups (t(24)=-0.71, p=.487). Moreover, no significant or marginal significant group differences emerged with regard to RTs to new objects that were incorrectly judged as old (i.e., false alarms) (t(24)=1.94, p=.064) after applying Holms´ correction for multiple comparisons.

The percentage of missing responses was also very low during the retrieval session and did not differ significantly between ASD and control subjects (M_{TD}=0.6±0.5%, M_{ASD}=0.4±0.6%; t(24)=0.76, p=.453).

Response proportions and RTs for the control and ASD group are summarized in Table 2. Moreover, we report separate group results for the sensitivity index d´ ($d' = Z$(hits, i.e., proportion of recollected objects) - Z(false alarms, i.e, new objects that were incorrectly classified as “old”).

3.2 Fmri results

Separate group results of the mixed ANOVA for the contrasts Recol > NonRecol and NonRecol>Recol are provided in the Appendix (Table A.1, A.2). Briefly, controls showed increased activation to recollected relative to non-recollected items in bilateral fronto-occipital regions, the left superior parietal lobule, bilateral inferior temporal gyrus, right hippocampus and bilateral amygdala. ASD subjects exhibited increased neural activation to recollected compared to non-recollected objects in the left gyrus rectus, bilateral inferior temporal gyrus, bilateral fusiform gyrus, right hippocampus and bilateral amygdala. For the reverse contrast (NonRecol>Recol), controls showed significant increases in neural activation in widespread bilateral fronto-parietal regions and the left superior temporal gyrus. In ASD individuals, stronger activation to non-recollected relative to recollected items was observed in bilateral fronto-parietal regions, the middle cingulate cortex, right insula and right middle temporal gyrus.

3.2.1 Between-group differences

The following paragraphs summarise the results of the group comparisons for the contrasts (1) Recol vs. NonRecol, (2) RecolHouse vs. NonRecolHouse; (3) RecolFace vs. NonRecolFace; and the interaction (4) (RecolHouse – NonRecolHouse) vs. (RecolFace – NonRecolFace). Generally, ROI analyses did not reveal group differences in amygdala, fusiform gyrus or hippocampus activation

Recol versus NonRecol: Differential brain activations between groups were identified in the right inferior frontal gyrus (IFG; 52, 22, 26; t=5.22), left middle frontal gyrus (-48, 12, 40; t=4.48), and right inferior parietal lobule (IPL; 34, -50, 50; t=4.78) extending into the right superior parietal lobule (Fig. 2a). Extraction of parameter estimates revealed that these group differences were due to higher activity to recollected as compared to non-recollected objects in controls, while the reverse pattern was found in ASD subjects (Fig. 2b). Moreover, a differential group effect was found in the bilateral superior medial gyrus/dorsal medial prefrontal cortex (MPFC; 4, 30, 44; t=4.79), which was accounted for by stronger activity to non-recollected compared to recollected objects in the ASD group, but no difference in controls (Fig. 2a/b).

RecolFace versus NonRecolFace: Group differences in brain activation were detected in the right IFG (54, 26, 26; t=4.98) extending into the right middle frontal gyrus and in the left middle frontal gyrus extending into the left IFG (-46, 14, 38; t=4.67) (Fig. 3a). The differences were accounted for by greater activity to recollected compared to non-recollected objects in controls, while the ASD group exhibited stronger activation in these two brain regions to non-recollected as compared to recollected items (Fig. 3b).

Moreover, differential group activation was found in the right IPL (34, -52, 48;t=4.54), which was mainly due to increased activity to recollected relative to non-recollected items in controls (Fig 3a/b).

RecolHouse versus NonRecolHouse: Differential brain activation between ASD subjects and controls was found in the bilateral superior medial gyrus extending into the ACC (dorsal MPFC; -2, 36, 44; t=3.98). This was due to greater activity for recollected compared to non-

recollected objects in controls, while the reverse relationship was true in ASD subjects (Fig. 4a/b).

[RecolHouse – NonRecolHouse] versus [RecolFace – NonRecolFace]: For the triple interaction contrast (memory effect x background x group), no significant group differences were observed.

3.2.2 Correlations of local brain activation with memory performance

In controls, activation in the right IFG (54, 26, 26) for the condition RecolFace was positively related to the number of recollected objects presented with a face during encoding ($r=.560$; $p<.05$), while a negative correlation was found in ASD individuals ($r=-.752$; $p<.01$).

Non-significant results were obtained for correlational analyses between behavioural performance data and activity in the remaining brain regions, in which the contrasts RecolHouse vs. NonRecolHouse and RecolFace vs. NonRecolFace yielded differential group results (all $ps>.05$).

3.2.3 Correlations of brain activation with IQ and the ADOS-G

Regression analyses did not reveal significant relationships between brain activation and IQ across both groups. Similarly, non-significant results were obtained in the regression analyses on the effect of autism severity (based on the ADOS-G) on brain activation patterns.

4. Discussion

The present fMRI study was set up to investigate the influence of social vs. non-social context on episodic memory formation in individuals with ASD and TD subjects. On the behavioural level, no differences between ASD and TD groups emerged. Further, no

differential effect of context on subsequent memory performance was observed. At the neural level, however, activation patterns during object encoding differed between the groups depending on the context in which objects were presented. It may seem striking that although at the behavioural level, no differential effects could be observed, distinct neural mechanisms were detected between groups. In this context it is worth stressing that functional measures can be more sensitive than behaviour (Wilkinson & Halligan, 2004).

4.1 Behavioural data

Our data are in accordance with previous studies in healthy individuals that also did not observe modulatory effects of social vs. non-social context on memory performance using recognition tasks (Erk et al., 2005; Maratos & Rugg, 2001; Maratos et al., 2001; Skinner et al., 2010). Recognitions tasks, as opposed to free recall tasks (Erk et al., 2003), may be less sensitive in detecting an influence of context on memory at the behavioural level (Maratos et al. 2001). In future studies, it remains to be clarified whether memory performance in ASD might be modulated by social context when free recall as opposed to item recognition is used during retrieval (Bowler, Gardiner, & Berthollier, 2004; Bowler et al., 2008). Furthermore, if possible, such studies should investigate larger samples of ASD and TD subjects to increase statistical power to detect potential (group) effects of context on memory performance.

4.2 fMRI data

We observed strong similarities in ASD and TD individuals related to the subsequent memory effect (SME, i.e., increased activation associated with subsequently recollected vs. non-recollected objects). However, direct group comparison revealed that activation patterns of the SME differed between groups in the IPL, IFG, middle frontal gyrus, and superior medial gyrus. Further assessment of group differences with respect to context type showed that these

differences were context-specific. More precisely, group differences in the IPL, IFG and middle frontal gyrus were found for the social context condition, whereas group differences in the superior medial gyrus were identified in the non-social context condition.

4.2.1 Encoding of objects presented with a social background

In line with our hypothesis, atypical activation patterns in ASD subjects were predominantly observed in the social context condition. This finding is in accordance with the notion that individuals with ASD generally show markedly reduced social interest in social stimuli (Dawson et al., 2005). Interestingly, group differences for the SME in the IFG and middle frontal gyrus were driven by increased activation during the encoding of recollected vs. non-recollected objects in controls, while the reverse was true in ASD subjects.

Several fMRI studies have shown that activation of dorsolateral and ventrolateral prefrontal regions is associated with successful encoding processes (see Spaniol et al., 2009 for a meta-analysis). It has been argued that these regions subserve memory formation by supporting manipulation, regulation and monitoring of memory processes (Fletcher & Henson, 2001). Moreover, previous research on context-dependent memory processes has shown increased activation in these prefrontal regions when items are successfully encoded in a social compared to a neutral context (Harvey, Fossati, & Lepage, 2007).

The positive correlation between right IFG activation and the proportion of recollected objects presented with a face in controls supports the role of the ventrolateral prefrontal cortex in successful encoding. An inverse SME (i.e., increased activation associated with subsequently non-recollected vs. recollected objects) in ASD subjects in regions implicated in successful encoding suggests a profound dysregulation in memory formation when a social context is presented during encoding. The activation pattern in ASD subjects in the ventrolateral and dorsolateral prefrontal cortex may reflect task-irrelevant mental activity resulting in a failure

of successful object encoding (Shrager, Kirwan, & Squire, 2008). This conclusion is supported by our finding of a negative relationship between IFG activity and retrieval success in ASD subjects. However, given the absence of an overall behavioral performance deficit in ASD subjects relative to controls, affected individuals seem to possess compensatory strategies to successfully encode objects presented with a social context. In future studies of ASD, it would be of great interest to examine the potential role of compensatory cognitive mechanisms during encoding of items embedded in a social context.

The encoding task employed in the present study placed high demands on subjects, as they were requested to maintain attention to both task-relevant (objects) and task-irrelevant information (background context). Thus, group differences in the activation of the dorsolateral and ventrolateral prefrontal cortex might also be explained by differential recruitment of attentional control processes (Konrad et al., 2005) in control versus ASD subjects (see, e.g., Solomon et al., 2009), particularly as there is robust evidence for deficits in executive function in ASD (Solomon, Ozonoff, Cummings, & Carter, 2008; Rossion & Gauthier, 2002). However, the fact that differential activations in the IFG were correlated with memory performance supports the notion that our findings in lateral prefrontal regions are indeed linked to memory formation processes.

To our knowledge, this study is the first to show that brain regions subserving memory formation in TD indiviudals are activated atypically in ASD subjects when a social context is presented during encoding. Deficits in processing of social information consitute a core diagnostic characteristic of ASD and have been in the spotlight of ASD research during the last decades. In particular, there is robust empirical evidence that persons affected by the disorder show deviant face processing styles that are marked by a diminished interest in faces (especially in socially relevant aspects of faces) from early on (Schultz, 2005). Our results add to findings from related research fields indicating that in ASD, impaired social cue processing

affects domains beyond social cognition since our data provide direct evidence that social processes atypically modulate memory processes (Dichter et al., 2008; Gaigg et al., 2008).

Differential brain activation in the right IPL was due to greater activation in controls during the encoding of recollected vs. non-recollected objects presented with a face, but no difference in ASD subjects. Like dorsolateral and ventrolateral prefrontal cortex, the IPL is implicated in successful encoding processes (Spaniol et al., 2009). Moreover, this region has been linked specifically to the association of contextual information (Erk et al., 2005). Interestingly, ASD subjects show specific memory impairments for social aspects of contextual information (in particular faces) (O´Shea et al., 2005), indicating a specific deficit of linking social context stimuli with items to be remembered. Accordingly, we suggest that in the present study, ASD individuals might have failed to link background faces to objects that were subsequently recollected. However, since the subjects in our study were not asked to recollect contextual information during retrieval, this claim remains speculative. In future studies it would be of particular interest to explicitly test source memory for context to investigate whether the absence of a SME in the IPL might be associated with specific impairments in ASD individuals to encode social context together with to be remembered items.

In ASD subjects, no atypical modulation of activation in the amygdala and the fusiform gyrus was observed for the social context condition, although these regions have been repeatedly implicated in the pathophysiology of the disorder (Schultz, 2005), and have been linked to social context effects in healthy subjects (Skinner et al., 2010; Maratos et al., 2001). Given that emotional faces provide more salient social cues than neutral ones, it would be interesting to use emotional facial expressions in future studies to further explore modulatory influences of social context on memory processes in ASD.

4.2.2 Encoding of objects presented with a non-social background

The only significant group difference for the SME when items were presented in the context of houses was located in the superior medial gyrus which forms part of the dorsal MPFC. This effect was mainly due to greater activation during the encoding of non-recollected vs. recollected objects presented with a house in ASD subjects. Among other functions, the dorsal MPFC has been implicated in goal directed-behaviour. Activation in this region has been reported during tasks that require cognitive control and online error monitoring (see Ridderinkhof et al., 2004 for a meta-analysis). In line with the result pattern in ASD individuals, increased activation in the dorsal MPFC in healthy subjects during cognitive control tasks has been reported for incorrect relative to correct trials (e.g., Fitzgerald et al., 2010). Moreover, evidence suggests that dorsal MPFC activation directly mediates performance adjustments, e.g., by post-error slowing of reaction times (di Pellegrino et al., 2007). Given these findings, we performed an explorative post-hoc analysis and found that activation during encoding of non-recollected objects tended to be related to higher reaction times for non-recollected items in ASD ($r=.53$; $p=.062$) but not in control subjects ($r=.30$; $p=.315$).

Thus, based on previous research and the present findings, we suggest that ASD subjects relative to controls engaged more in cognitive control processes during unsuccsessful encoding of objects presented in the non-social context. It might be speculated that houses (in comparison to faces) are more interesting context stimuli for subjects with ASD and may therefore interfere to a greater extent with focusing attention on the objects to be encoded. Thus, increased cognitive control may be engaged to re-focus on the task at hand, i.e., memorizing the objects (irrespective of context) and deciding whether they are artificial or non-artificial. In support of this idea, it has been shown that subjects with autism show preferential attention to object stimuli (incomparison to social stimuli) (Sasson, Turner-

Brown, Holtzclaw, Lam, & Bodfish, 2008) and are less prone to distraction from facial stimuli that are not relevant for task execution (Riby, Brown, Jones, & Hanley, 2011).

Episodic memory, at least as traditionally conceptualized, encompasses not only the "what" of an event and contextual knowledge about it, but also temporal and spatio-temporal information about an event (for a review of the transition of the concept see Tulving, 2002). The present study primarily focused on the question how contextual information linked to an "event" modulates subsequent recollection of this event. Due to restrictions inherent to our highly controlled experimental approach, other aspects of episodic memory (e.g., temporal and spatio-temporal associations) were not explicitly targeted. However, during retrieval, subjects were at least implicitly required to recollect whether they had seen the respective object *in the scanner during the encoding phase*; i.e., spatio-temporal and temporal associations were at least implicitly assessed. For a more comprehensive understanding of episodic memory processes in ASD, future fMRI studies should more explicitly target these important aspects of episodic memory in individuals affected by the disorder.

4.2.3 Correlations of brain activation with IQ and the ADOS-G

In the present study, we did not find a significant effect of autism pathology (based on the ADOS-G) on brain activation during the encoding task. This finding can be explained by the fact that the ADOS-G, while being the gold standard for diagnostic assessment, is not particularly appropriate for deriving a quantitative measure of impairment (and thus not particularly suited for investigating brain-behaviour relationships).

Due to the aim of creating homogenous groups, only high-functioning ASD individuals and control subjects with an IQ of 80 or higher were included in the present study. The restricted IQ range in our sample might explain the lack of an association between IQ and brain activation during the encoding task.

4.3 Limitations

A limitation of the present fMRI study is the rather small number of ASD and control subjects that were included. However, our ASD sample is clinically well characterized based on gold standard instruments, rendering potential influences by outliers unlikely. Moreover, even in our rather small sample, we were able to show significant between-group differences in activation patterns after applying established corrections for multiple comparisons. Despite these considerations, the findings of our study undoubtedly need to be replicated in future studies including a larger number of ASD and control subjects.

4.4 Conclusions

A deeper understanding of the neural processes subserving memory formation in ASD and the identification of modulatory influences of context is important to elucidate why persons suffering from ASD often have difficulties to attach contextual meaning to their memories. The present study provides important first insights into the neural mechanisms of memory formation in ASD, and the modulatory effects of different context types. In future studies, neural mechanisms of memory retrieval could be investigated along with explicit tests for recall of context. The results of the present study corroborate and extend previous findings on atypical modulatory effects of social processing on cognitive functions in persons suffering from ASD. We provide support for the idea that social impairments in ASD extend to domains beyond social cognition.

Acknowledgments

We are grateful to all participants with their families who took part in this study. We wish to thank our colleagues in the MR and Cognitive Neurology Section groups at the Institute of Neuroscience and Medicine (Research Center Juelich) for their support and helpful advice. Funding for this study was provided by the Deutsche Forschungsgemeinschaft (IRTG 1328; B.N., K.K., B.H.-D.).

Conflict of Interest

B.H.-D. is a consultant to Eli Lilly and has received industry research funding from AstraZeneca, Eli Lilly, Novartis, and Janssen Cilag. All other authors declare that they have no conflicts of interest.

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Tables

Table 1 Demographic data of the study sample

	controls (*n*=13)	ASD group (*n*=13)	***p***
age (Mean, SD)	14.2 (2.8)	15.9 (3.0)	.150
age range (Min-Max)	10.3-18.3	9-19.4	
IQ (Mean, SD)	111.5 (14.7)	108.0 (14.1)	.546
IQ range (Min-Max)	94-139	80-134	
Tanner stage	3.4 (1.6)	3.9 (1.3)	.646
Tanner stage range	1-5	1-5	

ASD=autism spectrum disorder; Min=Minimum; Max=Maximum.

Table 2 Performance during the retrieval session

	controls (M, SD)	**ASD group** (M, SD)
Response proportions (%)		
Old objects: Recollected items	62.3 (11.2)	54.0 (15.7)
Old objects: Non-recollected items	37.2 (11.0)	45.6 (15.7)
New objects: Correct rejections	92.1 (7.6)	93.4 (6.7)
Sensitivity index d´	1.9 (0.6)	1.8 (0.5)
Reaction times (ms)		
Old objects: Recollected items	1284.5 (139.3)	1263.9 (163.0)
Old objects: Non-recollected items	1712.7 (137.9)	1500.8 (253.2)
New objects: Correct rejections	1505.1 (367.4)	1593.5 (262.6)
New objects: False alarms	1534.6 (176.4)	1356.8 (278.6)

Response proportions and reaction times for previously seen objects correctly judged as old (recollected items) or incorrectly judged as new (non-recollected items), and for correct rejections of new objects or false alarms to new objects.
ASD=autism spectrum disorder.

Figures and Figure legends

Fig. 1

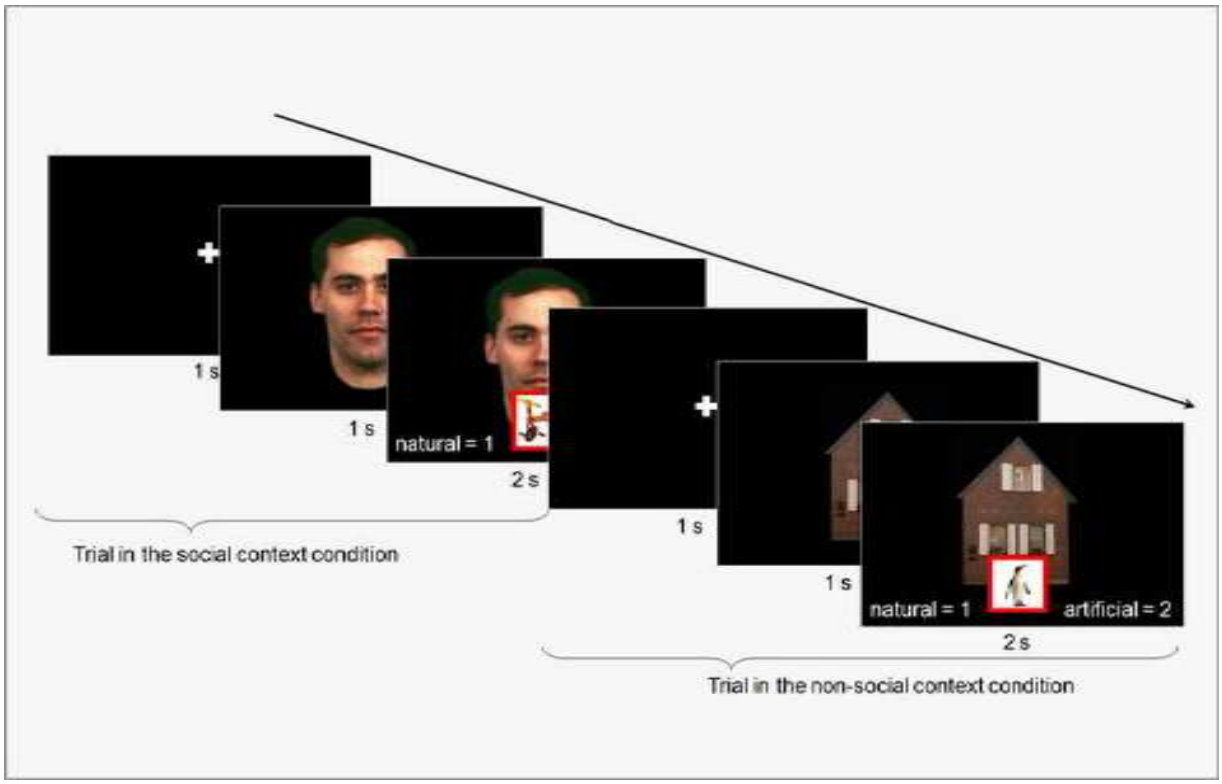

Fig. 1 Classification task during encoding: experimental time course.

On each trial, the context (social or non-social, respectively) was shown first without the object to be encoded. Then, the background and the object were presented together and subjects indicated whether the object was “natural” or “artificial”.

Fig. 2a

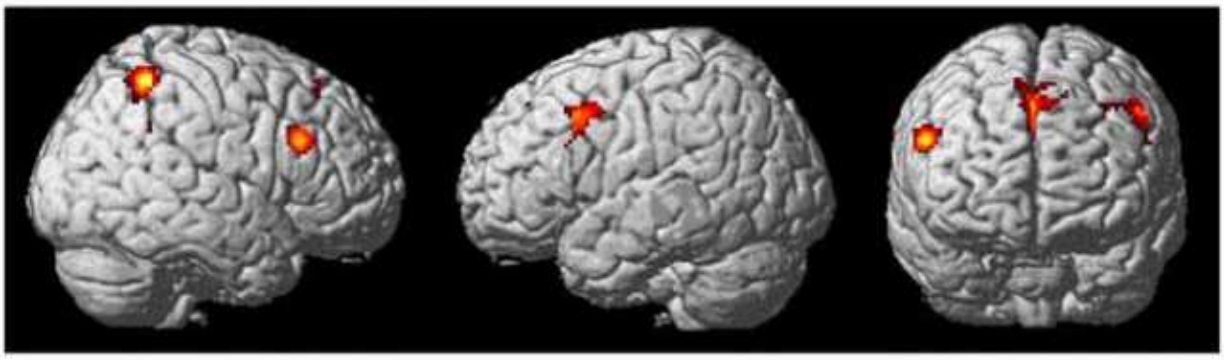

Fig. 2b

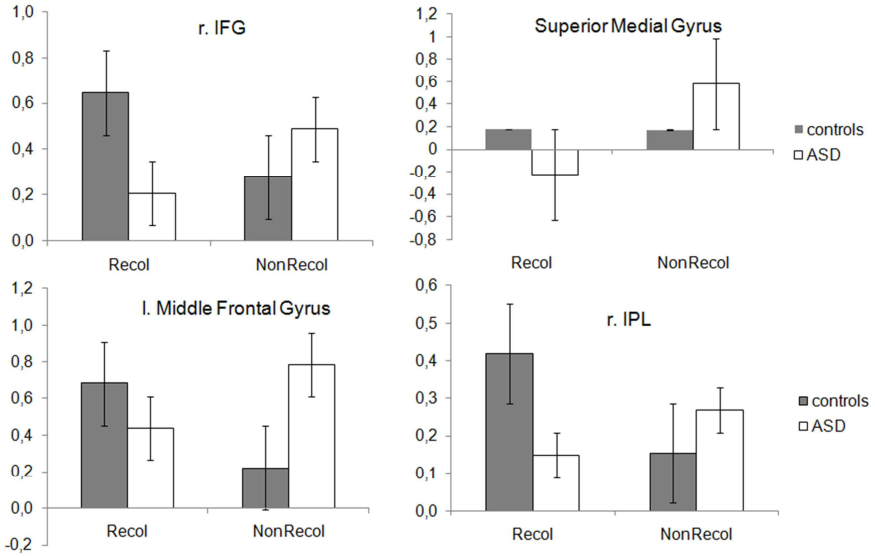

Fig. 2 Recol versus NonRecol

(a) Differential activation of controls and adolescents with autism spectrum disorder (ASD) for the whole-brain contrast Recol versus NonRecol in the right inferior frontal gyrus (IFG), superior medial gyrus, left middle frontal gyrus and right inferior parietal lobule (IPL), SPM(T) overlaid on a MNI single-subject template (cluster-level corrected at $p<.05$ for multiple comparisons across the whole brain). (b) The graphs depict parameter estimates of each activation, error bars indicate S.E.

Fig. 3a

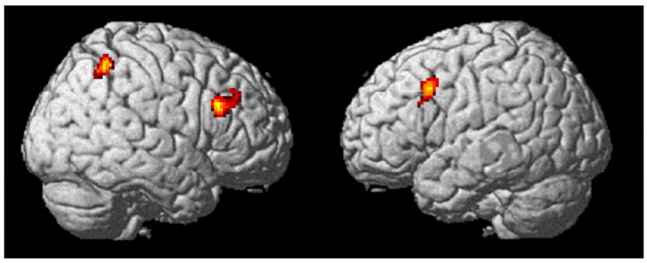

Fig. 3b

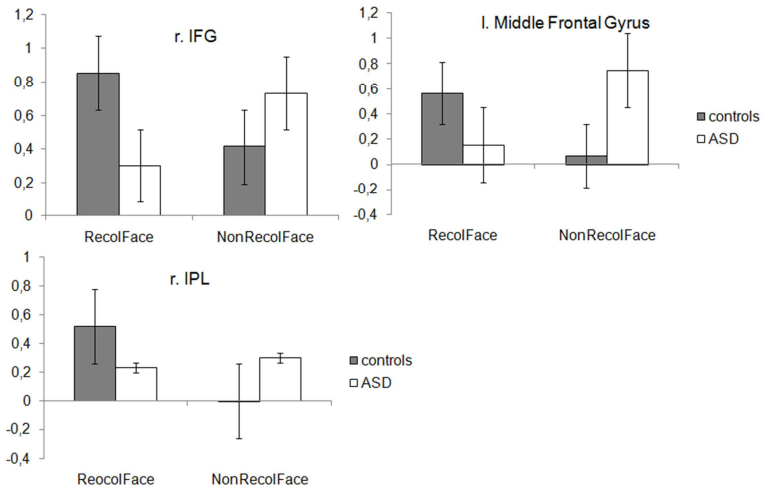

Fig. 3 RecolFace versus NonRecolFace

(a) Differential activation of controls and adolescents with autism spectrum disorder (ASD) for the whole-brain contrast RecolFace versus NonRecolFace in the right inferior frontal gyrus (IFG), left middle frontal gyrus and right inferior parietal lobule (IPL), SPM(T) overlaid on a MNI single-subject template (cluster-level corrected at $p<.05$ for multiple comparisons across the whole brain). (b) The graphs depict parameter estimates of each activation, error bars indicate S.E.

Fig. 4a

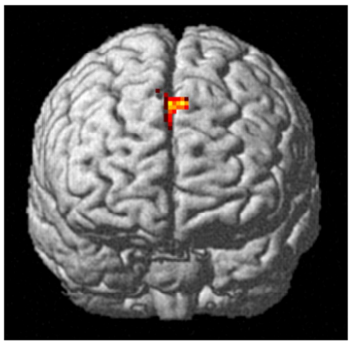

Fig. 4b

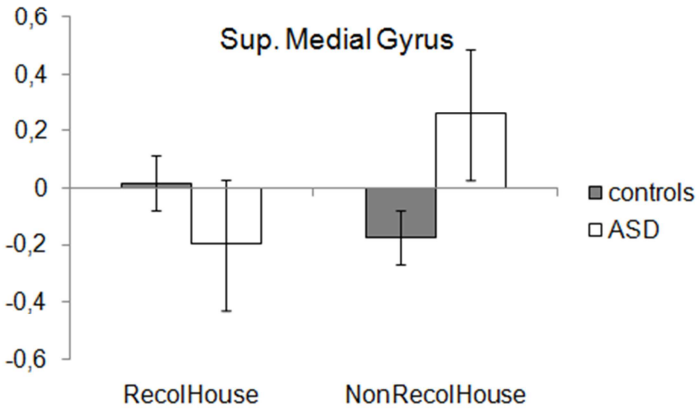

Fig. 4 RecolHouse versus NonRecolHouse

(a) Differential activation of controls and adolescents with autism spectrum disorder (ASD) for the whole-brain contrast RecolHouse versus NonRecolHouse in the superior medial gyrus, SPM(T) overlaid on a MNI single-subject template (cluster-level corrected at $p<.05$ for multiple comparisons across the whole brain). (b) The graphs depict parameter estimates, error bars indicate S.E.

Appendix A.1

Correlational analyses on the relationship between behavioural data and IQ/autistic pathology

To examine whether IQ was related to the proportion of correct object classifications and reaction times (RTs) of correct classifications during the classification task at encoding, we conducted an explorative analysis and included IQ as a covariate in the 2x2 MANOVA with the factors object type and group. This analysis did not reveal a significant effect of IQ on encoding parameters ($p=.299$). Similarly, in supplementary analyses we examined whether IQ had a significant influence on key retrieval parameters (proportion of recollected objects; RTs to recollected and non-recollected objects) and included IQ as a covariate in the 2x2 MANOVA with the factor background context and group. Again, no significant effect of IQ was revealed ($p=.986$).

Moreover, in explorative analyses we examined whether the ADOS-G significantly correlated with behavioural parameters during encoding (proportion of correct object classifications and RTs of correct classifications) and retrieval (proportion of recollected objects; RTs to recollected and non-recollected objects). However, all correlations were found to be non-significant (all $ps>.073$).