

Neural correlates of moral reasoning in autism spectrum disorder

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In our study, we tried to clarify whether patients with autism spectrum disorder (ASD) reveal different moral decision patterns as compared to healthy subjects and whether common social interaction difficulties in ASD are reflected in altered brain activation during different aspects of moral reasoning. 28 patients with high-functioning ASD and 28 healthy subjects matched for gender, age and education took part in an event-related functional magnetic resonance imaging study. Participants were confronted with textual dilemma situations followed by proposed solutions to which they could agree or disagree. On a neural level, moral decision making was associated with activation in anterior medial prefrontal regions, the temporo-parietal junction and the precuneus for both groups. However, while patients and healthy controls did not exhibit significant behavioral differences, ASD patients showed decreased activation in limbic regions, particularly the amygdala, as well as increased activation in the anterior and the posterior cingulate gyrus during moral reasoning. Alterations of brain activation in patients might thus indicate specific impairments in empathy. However, activation increases in brain regions associated with the ‘default mode network’ and self-referential cognition also provide evidence for an altered way of patients’ cerebral processing with regard to decision making based on social information.

Keywords: autism spectrum disorder; decision making; morality; neuroimaging; fMRI

INTRODUCTION

Although it is a relatively new field of research, already a wealth of studies approaching behavioral characteristics and neural underpinnings of moral cognition has accumulated (e.g. Moll *et al.*, 2002; Schleim *et al.*, 2010; Bzdok *et al.*, in press). In solving moral tasks, the ventromedial prefrontal cortex (VMPFC), lateral orbitofrontal cortex, temporal and limbic regions seem to play a key role (Moll *et al.*, 2002; Hiraishi *et al.*, 2007; Young *et al.*, 2007; Zahn *et al.*, 2009; Schleim *et al.*, 2010).

Additionally, a recent study (Young *et al.*, 2010) could show a reduced capacity of moral decision making based on the comprehension of the mental states of other individuals, especially in case of attempted harms, if the right temporo-parietal junction (TPJ) was temporarily inhibited by transcranial magnetic stimulation in healthy participants.

Moral reasoning as a sophisticated element of social cognition requires a broad understanding of social contexts. Correspondingly, mental disorders, which are related to deficits in empathy and Theory of Mind (ToM), might interfere with adequate moral decision making (de Oliveira-Souza *et al.*, 2008). For autism spectrum disorders (ASDs), this linkage was already suggested in a few behavioral studies (Blair, 1996; Moran *et al.*, 2011; Zalla *et al.*, 2011; Shulman *et al.*, 2012) and—to the authors’ knowledge—in only one (case) study using functional magnetic resonance imaging (fMRI; Hiraishi *et al.*, 2007). Particularly, Moran *et al.* (2011) revealed subtle weaknesses in moral decisions in patients with ASD with regard to the ability to differentiate between intentional and attempted harms. Likewise, Zalla *et al.* (2011) reported impairments of ASD patients with regard to provide welfare-based moral justifications.

According to the main diagnostic classification systems of ICD-10 and DSM-IV, ASDs as pervasive developmental disorders are characterized by the three core features of deficits in communication, repetitive stereotyped behavior and impaired social interaction.

While the literature is indecisive regarding the question of global ToM- and empathy-deficits in ASD (Frith and Happé, 1994; Castelli, 2005; Silani *et al.*, 2008; Senju *et al.*, 2009; Bird *et al.*, 2010; Chevallier, 2012), there seems to be substantial convergence that also high-functioning adults with ASD exhibit at least subtle deficits in empathy (Schulte-Rüther *et al.*, 2010; Zalla *et al.*, 2011) and/or ToM (Kana *et al.*, 2009; Senju *et al.*, 2009; Moran *et al.*, 2011), which also seem to affect patients’ ability to make adequate moral decisions (Hiraishi *et al.*, 2007; Moran *et al.*, 2011; Zalla *et al.*, 2011; Shulman *et al.*, 2012).

Furthermore, most of the recent studies examining morality-associated aspects of social cognition, such as ToM (Kana *et al.*, 2009) and empathy (Schulte-Rüther *et al.*, 2010), revealed dysfunctions in respective brain networks in ASD patients, which have been related to patients’ social impairments (Lombardo *et al.*, 2011).

Anatomical and functional alterations were mainly found in the prefrontal cortex (PFC), particularly the medial PFC and in the TPJ (Kana *et al.*, 2009; Martineau *et al.*, 2010; Schulte-Rüther *et al.*, 2010; Lombardo *et al.*, 2011). Common dysfunctions in these areas in ASD might well come along with deficits in moral reasoning (Blair, 1996; Moran *et al.*, 2011; Zalla *et al.*, 2011; Shulman *et al.*, 2012), and hence result in altered brain activation during moral tasks.

Nonetheless, so far studies on moral understanding in clinical samples mainly focused on patients with psychopathy (e.g. de Oliveira-Souza *et al.*, 2008), who were said to exhibit a contrariwise profile of empathy deficits as compared to patients with ASD, namely intact cognitive elements, but impairments in affective aspects of empathy (Blair, 2008; Krippel and Karim, 2011). However, at the same time potential overlaps between Asperger’s syndrome and sociopathy/psychopathy were suggested (Anckarsäter *et al.*, 2008). More, though there is no evidence for a general overrepresentation of patients with

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ASD in forensic settings, a first long-term study on deviant behavior in pervasive developmental disorders (Mouridsen *et al.*, 2008) revealed a tendency in patients with ASD to particular criminal delinquency, such as arson (Haskins and Silva, 2006; Mouridsen *et al.*, 2008, in line with Allen *et al.*, 2008; Anckarsäter *et al.*, 2008). Yet, the underlying factors and potential relationships are still unclear, but might be partly related to changes in moral reasoning and its underlying neural networks.

Hence, a better understanding of moral reasoning in patients with ASD could provide helpful new approaches for specific therapeutic interventions and was the underlying reason for our exploration.

In order to investigate different specific aspects of moral reasoning with potentially different empathic requirements (Greene *et al.*, 2004), we developed a set of dilemmas comprising two moral categories: social-ethical dilemmas (SE) and individual gain vs collective losses (IND) dilemmas.

Behaviorally, we expected longer reaction times in ASD patients due to difficulties in executive functions such as decision making (Channon *et al.*, 2001) and in information processing (O'Connor and Kirk, 2008).

There is no prior fMRI research on ASD and moral decision making. However, given the widely suggested impairments of patients with ASD in ToM and empathy and the proposed relation of morality and both of these aspects of social cognition, we expected that patients would reveal decreased brain activation, mainly in the medial PFC and the TPJ, during moral decision making and additionally reduced activation in emotion-related areas (e.g. amygdala). As we hence hypothesized that conceivable empathy and ToM deficits in patients with ASD would affect their ability of moral decision making, we expected this effect to be strongest in case of the more personal dilemmas of the IND condition (see also Greene and Haidt, 2002; Greene *et al.*, 2004) which particularly require to (theoretically) put oneself into direct confrontation with another subject (Zalla *et al.*, 2011).

MATERIALS AND METHODS

Participants

Thirty patients (17 males) with high-functioning ASD were recruited at the in- and outpatient facilities of the RWTH Aachen University Hospital and at local self-help groups and therapy centers. In line with recent studies (Via *et al.*, 2011) and with the upcoming DSM-V and ICD-11, we refer to 'autism spectrum disorders' without distinguishing between different autistic subgroups. Patients were either diagnosed at a special autism facility at the Department of Psychiatry, Psychotherapy and Psychosomatic Medicine of the RWTH Aachen University Hospital ($n = 9$) or had already been diagnosed with ASD by an experienced psychiatrist elsewhere ($n = 21$).

Participants had to meet the following criteria for inclusion: age between 18 and 55 years, no neurological disorders, no MRI contraindications (metal implants, tattoos, pregnancy, etc.). Patients with current psychiatric comorbidities were excluded. All participants were native German speakers and screened for mental disorders by means of the Structured Clinical Interview for DSM-IV (SCID; Wittchen *et al.*, 1997). fMRI data of two male patients were excluded afterward due to movement artifacts ($n = 1$) or the fact that the diagnosis of Asperger's syndrome ($n = 1$) could not be confirmed. One male and one female healthy participant had to be excluded due to an incidental finding of brain abnormality and due to movement artifacts, respectively. Thus, 28 autistic patients were included in the final analysis as well as 28 gender-, age- and education-matched healthy controls (HCs) (see Table 1). Four of the ASD patients and two healthy subjects were left-handed. All of the other participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). Five patients were medicated with selective serotonin

Table 1 Demographical, neuropsychological and psychopathological data

	HC Mean (\pm s.d.)	ASD Mean (\pm s.d.)	<i>t</i>	<i>df</i>	<i>P</i>
Age (years) ($n = 28/28$)	31.29 (± 9.03)	31.39 (± 8.97)	-0.05	54	0.965
Education (years) ($n = 28/28$)	12.89 (± 0.32)	12.68 (± 0.82)	1.29	54	0.202
IQ ($n = 28/27$)	114.04 (± 9.55)	109.07 (± 9.12)	1.97	53	0.054
Digit span forward ($n = 27/19$)	9.30 (± 1.44)	9.05 (± 2.09)	0.47	44	0.642
Digit span backward ($n = 27/19$)	9.93 (± 7.32)	8.32 (± 2.40)	0.92	44	0.361
Lexical fluency ($n = 26/19$)	16.65 (± 5.34)	16.42 (± 6.56)	0.13	43	0.896
Lexical flexibility ($n = 26/19$)	16.62 (± 4.88)	16.84 (± 4.18)	-0.16	43	0.871
Semantic fluency ($n = 25/19$)	17.68 (± 4.61)	18.05 (± 5.76)	-0.24	42	0.813
Semantic flexibility ($n = 25/19$)	17.28 (± 2.85)	17.67 (± 4.46)	-0.35	41	0.730
Difference score TMT-B-TMT-A (s) ($n = 26/19$)	14.69 (± 8.67)	18.05 (± 13.50)	-1.02	43	0.320
AQ ($n = 28/26$)	10.07 (± 5.93)	37.69 (± 7.85)	-14.66	52	<0.001*
TAS20 ($n = 28/25$)	38.93 (± 10.10)	59.92 (± 11.57)	-7.00	51	<0.001*
NSAd ($n = 27/26$)	4.75 (± 2.50)	4.36 (± 2.02)	1.20	54	0.241

Independent two-sample *t*-test: $P < 0.05$, Bonferroni-corrected: * $P < 0.004$.

HC = healthy control subjects; ASD = patients with autism spectrum disorders; s.d. = standard deviation; AQ = autism quotient; NSAd = scale for socially desirable behavior; TAS20 = Toronto Alexithymia Scale; TMT-A/-B = trail making test.

reuptake inhibitors (SSRIs), one with a tricyclic antidepressant (see Supplementary Table S1).

ASD traits of patients were assessed using the Autism Diagnostic Observation Schedule—Generic (ADOS-G, Module 4; Lord *et al.*, 1999). ASD patients had an averaged ADOS-G score of 7.26 (± 4.35 ; see Supplementary Table S2). Since the sensitivity of the ADOS-G in its current version has recently been questioned for ASD in adults (Bastiaansen *et al.*, 2011; Lai *et al.*, 2011), we also included patients who did not meet the ADOS criteria for ASD (cut-off <7). However, all patients fulfilled the cut-off for ASD according to the Autism Spectrum Quotient (AQ; Baron-Cohen *et al.*, 2001; for further details see Section 2 in the Supplementary Data and Supplementary Table S2a and S2b). The Hamilton Depression Scale (Hamilton, 1960) revealed no current depressivity in ASD patients with a mean score of 2.94 (± 3.85).

Participants further completed the Toronto Alexithymia Scale (TAS20; Bagby *et al.*, 1994). In order to control for variance due to potential cognitive performance differences, a neuropsychological test battery was applied encompassing a German vocabulary test for crystalline intelligence estimation ('Wortschatztest'—WST; Schmidt and Metzler, 1992), a test on lexical and semantic verbal fluency ('Regensburger Wortflüssigkeitstest'—RWT; Aschenbrenner *et al.*, 2001), the German version of the digit span of the Wechsler Intelligence Scale for Adults (WIE; Von Aster *et al.*, 2006) and the Trail Making Test (TMT-A/-B; Reitan, 1958). Patients' emotion recognition performance was tested using the Penn Emotion Recognition Test (PERT40; Kohler *et al.*, 2004). Finally, the tendency for social desirable behavior was assessed ('Deutsche Kurzskaala zur Erfassung des Bedürfnisses nach sozialer Anerkennung'; NSAd; Stocké, 2009).

For an overview of the demographical and clinical data, see Table 1 (for additional data on the applied personality tests see Supplementary Tables S3 and S4).

After complete description of the study, written informed consent of each participant was obtained. All participants were paid for their participation after completing the study. The local Institutional Review Board of the Medical Faculty of RWTH Aachen University approved the protocol and the design fulfilled the guidelines of the Declaration of Helsinki (2008).

Task

Participants were asked to answer 60 short textual dilemma situations depicting close-to-reality situations, among them 20 social-ethical

Table 2 Dilemma examples for each moral condition

Social-ethical (SE)	Individual gain vs collective losses (IND)	High-level baseline (BL)
You want to have a child. Preferably, you would like to have a girl, who is slim, blond and healthy. Genetic testing would allow you to control for these criteria. 'I do not decide on genetic testing.'	You are currently in a professional probation period. You make a potentially job-endangering mistake, though it was not seen by anyone. It could have happened to anyone in the office. 'I do not intervene when a co-worker is blamed.'	You come home tired. Since your physician recommended more sportive activity to compensate for your office job, you applied for an aerobic course. However, today you are not in the mood. 'I go despite being tired.'

situations (SE condition), 20 decisions concerning individual gains vs collective losses (IND condition) and 20 non-moral daily dilemma situations as high-level baseline (BL condition).

Stimuli were standardized according to the following criteria:

- (1) Sentence structure of each dilemma: main clause beginning with 'You' and a verb (e.g. 'You want to have a child.')->main clause plus subordinate clause (e.g. 'Preferably, you would like to have a girl who is slim, blond, and healthy.')->main clause (e.g. 'Genetic testing would allow you to control for these criteria.')->proposed solution: main clause (e.g. 'I do not decide on genetic testing.');
- (2) Number of words: 35–40, among them 5–7 for the potential solution;
- (3) Solution sentence beginning with 'I' and a verb (for examples of each category—translated from German into English—see Table 2).

Stimuli were validated in a preceding pilot study including 31 healthy participants (for further information see Supplementary Figure S1). The two moral and the high-level BL (control) conditions did not differ significantly (Kruskal–Wallis tests) concerning realism [$\chi^2(2) = 1.96$, $P = 0.38$], the intensity of the perceived dilemma [$\chi^2(2) = 4.17$, $P = 0.12$] and how easy it was to put oneself into each situation [$\chi^2(2) = 1.91$, $P = 0.39$], respectively. There was only a significant difference for emotional intensity due to a weaker emotional involvement during the high-level BL dilemmas [$\chi^2(2) = 26.89$, $P < 0.01$].

For the target answer, we used Kohlberg's (Kohlberg *et al.*, 1983) 'moral pyramid' for orientation, and according to age and education of our participants set the target level to level 4 of the pyramid. This level specifies a sophisticated ability to pondering one's own interests and the interests of other people and society.

Stimuli were presented in an event-related design in a pseudo-randomized way using Presentation[®] 9.0 software (Neurobehavioral Systems Inc., San Francisco, CA, USA). Each dilemma text was presented for 13.5 s. After 9 s, a potential solution of the dilemma was presented underneath the text for 4.5 s and participants were asked to agree or disagree with the solution via left vs right button press using their right index or middle finger. Each dilemma was followed by a fixation cross with a jittered length of 5–7 s. Subjects also performed an empathy task described elsewhere.

Image acquisition

Images were acquired on a 3 T Siemens Trio MR scanner at the Department of Psychiatry, Psychotherapy and Psychosomatic Medicine, RWTH Aachen University. A 4 min magnetization-prepared rapid acquisition gradient echo image (MP-RAGE) T1-weighted sequence was used to acquire structural images (TR = 1900 ms, TE = 2.52 ms, TI = 900 ms, matrix = 256 × 256, 176 slices, FoV: 250 × 250 mm², alpha = 9°, voxel size = 1 × 1 × 1 mm³).

Functional data covered the whole brain and were obtained with an echo-planar imaging (EPI) sequence sensitive to the blood oxygenation level dependent (BOLD) effect (T2*, TR/TE = 2000/30 ms, FoV = 200 × 200 mm², matrix = 64 × 64, 36 slices, alpha = 76°, voxel size: 3.1 × 3.1 × 3.1 mm³, slice thickness = 3.1 mm, gap = 15%). For each participant, 609 volumes were acquired. This resulted in a scanning time of 25 min for the moral task and structural measurement. The first three images were discarded to account for T1 stabilization effects.

Data analysis

Functional data were processed and analyzed using statistical parametric mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 11 (The Mathworks, Inc., Natick, MA, USA). The 606 volumes of each participant were aligned to the mean image. Realigned images were normalized to the standard anatomical Montreal Neurological Institute (MNI) coordinate space resulting in a voxel size of 3 × 3 × 3 mm³ and smoothed with a Gaussian kernel of 8 mm full-width-at-half-maximum. Subsequently, a 1/128 Hz high-pass filter removed low frequency noise.

For each subject, we determined the three trial types of the SE, the IND and the BL condition for the whole duration of each trial. These contrast effects were taken to the second level. Applying the general linear model (GLM), a flexible factorial analysis was performed contrasting SE vs BL, IND vs BL and both moral conditions pooled vs (weighted) BL contrasts for each group separately as well as comparing the ASD and the HC group.

In order to prevent confounds with alexithymia (Bird *et al.*, 2010), we correlated brain activation in patients and HCs during the Moral vs BL contrast with the TAS20 score. Moreover, due to the inter-individual variability regarding the ADOS-G Module 4 criteria for ASD, we additionally correlated brain activation with the overall ADOS score in order to control for misinterpretations due to diagnostic differences.

One-sample analyses were family wise error (FWE) corrected ($P < 0.05$) for multiple comparisons with a threshold extent of 20 voxels. For group comparisons (representing a less robust difference of a difference) and multiple regression analyses calculated separately for patients and non-autistic subjects, a more liberal Monte-Carlo corrected threshold was chosen. Monte-Carlo simulations were computed using AlphaSim by Ward (2000) implemented in AFNI 2011 (Cox, 2012).

Assuming a per voxel probability threshold of $P = 0.001$, after 1,000 simulations a cluster size of 18 contiguous resampled voxels was indicated to correct for multiple comparisons at $P < 0.05$.

As this is the very first study on moral reasoning in ASD, there is no prior data to perform adequate regions of interest analyses (Poldrack and Mumford, 2009).

Anatomical localization was performed using the WFU Pick Atlas implemented as a tool in SPM 8.

Analysis of the behavioral data

Behavioral data were analyzed using the IBM[®] Statistical Package for Social Sciences (SPSS) 20. As Kolmogorov–Smirnov tests demonstrated normal distribution of the reaction times during the fMRI task (SE condition: $Z = 0.76$, $P = 0.62$; IND condition: $Z = 1.10$, $P = 0.18$; BL condition: $Z = 0.51$, $P = 0.96$), a 2 × 3 repeated measures ANOVA was performed with the between-subject factor group (ASD and healthy subjects) and the within-subject repeated measures factor condition (SE, IND, BL). Non-parametric χ^2 tests were applied to analyze the decisions made. For further group comparisons, we used *t*-tests for independent samples ($P < 0.05$), if not otherwise specified.

RESULTS

Behavioral data

The 2 × 3 repeated measures ANOVA analyzing reaction times (Figure 1) yielded a significant main effect of condition [$F(2,108) = 6.02, P < 0.01$]. The main effect of group marginally failed to reach significance [$F(2,108) = 3.25, P = 0.08$]. No significant group × condition interaction was found [$F(2,108) = 0.98, P = 0.38$].

Post hoc paired *t*-tests ($P < 0.02$, Bonferroni-corrected) on mean reaction times revealed a significant difference between the SE and BL condition [$t(55) = 3.21, P < 0.01$] as well as between the IND and the BL condition [$t(55) = 2.97, P < 0.01$], with longer reaction times for the moral conditions, respectively, but no differences between the SE and IND condition [$t(55) = 0.67, P = 0.51$].

There was no significant difference between the two groups with regard to the answering pattern in terms of the Kohlberg-targets [SE condition: Pearson $\chi^2(1) = 2.29, P = 0.13$; IND condition: Pearson $\chi^2(1) = 1.90, P = 0.17$] or the amount of misses (no answer given until the beginning of the next dilemma) with 0.4% of all answers in the HC group and 1.8% of all answers in the ASD group [Pearson $\chi^2(1) = 0.34, P = 0.56$].

Imaging data

One-sample analyses

Pooling both moral conditions revealed activation patterns in the HC group bilaterally in the TPJ region, the medial frontal gyrus and the precuneus (Table 3 and Figure 2).

In ASD patients, the same contrast yielded activation in the medial frontal gyri, the middle frontal gyrus and the precuneus bilaterally, in the left TPJ, the left inferior temporal gyrus and in the right supramarginal gyrus (Table 3 and Figure 2).

Comparing the SE dilemmas with the IND condition revealed a significant signal change in the posterior cingulate gyrus for the HC and the ASD group (Table 3).

The opposite contrast of IND vs SE yielded no significant signal change in the ASD group, while the HC group showed stronger activation in the left TPJ region, the left cerebellar declive, the right inferior frontal gyrus (IFG), the right middle temporal gyrus and the right lingual gyrus (Table 3).

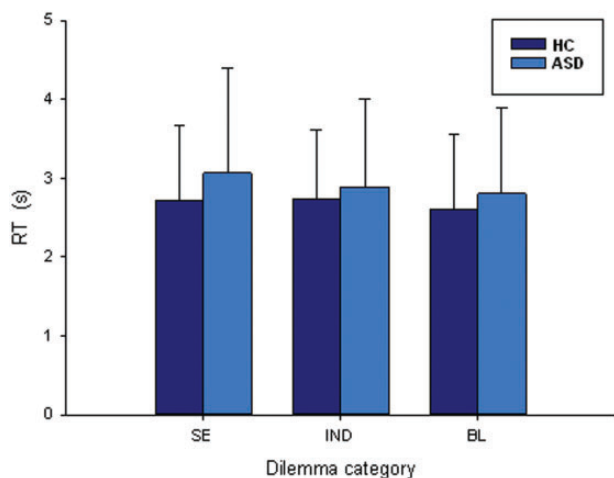


Fig. 1 Group comparisons for mean reaction times (RT ± SD) during moral decision making between healthy controls (HC) and autistic patients (ASD) with significantly longer reaction times for the SE and the IND conditions as compared to the BL. Group differences marginally failed to reach significance. SE = social-ethical dilemmas; IND = individual gain vs altruistic losses; BL = non-moral daily dilemma high-level baseline; RT = Reaction times; s = seconds.

Group comparisons

For the pooled Moral vs BL contrast, increased brain activation in ASD patients compared to non-autistic individuals was found in the posterior cingulate cortex bilaterally and in the right ventral-part of the ACC (Table 4).

For the separate analysis of dilemma processing and solution finding see Supplementary Table S5 and Supplementary Figure S2.

The group comparison on the SE vs BL contrast yielded hyperactivation in ASD patients compared to the HC group in the bilateral ACC, the left posterior cingulate gyrus, the right precuneus and in the right supramarginal gyrus (Table 4 and Figure 3A, B).

Table 3 Brain activation for all moral contrasts—one-sample analyses

Group(s)	Region	BA	Side	k	t	MNI-coordinates			
						x	y	z	
Moral vs BL									
HC	Precuneus	BA7	L + R	236	12.24	-3	-55	34	
	Angular gyrus	BA39	L + R	301	10.80	-48	-64	22	
ASD	Angular gyrus	BA39	R	31	5.59	48	-58	22	
	Medial frontal gyrus		L + R	536	10.87	0	50	22	
	Medial frontal gyrus	BA10	L + R	667	10.16	3	53	25	
	Middle frontal gyrus		L	50	6.01	-24	29	40	
	Middle frontal gyrus		R	34	5.91	30	29	46	
	Precuneus	BA7	L + R	319	9.46	-3	-55	37	
	Angular gyrus	BA39	L	196	8.03	-45	-61	25	
	Inferior temporal gyrus	BA20	L	34	5.58	-54	-4	-35	
	Supramarginal gyrus		R	83	6.55	60	-55	28	
	SE vs BL								
HC	Precuneus	BA7	L	313	14.65	-3	-55	34	
	Middle temporal gyrus		L	258	11.51	-48	-64	25	
	Medial frontal gyrus		L	377	9.18	-6	50	25	
	Medial frontal gyrus	BA10	L + R	42	8.00	-3	56	5	
	Middle frontal gyrus		L	31	6.29	-27	29	25	
ASD	Precuneus	BA7	L + R	394	10.22	-3	-55	34	
	Medial frontal gyrus		L + R	463	9.25	-9	50	19	
	Middle frontal gyrus		L	27	5.75	-24	29	40	
	Angular gyrus	BA39	L	174	8.11	-42	-61	25	
	Precentral gyrus		L	22	5.66	-57	-7	-29	
	IND vs BL								
	HC	Medial frontal gyrus	BA10	L + R	27	10.33	27	-79	-35
		Medial frontal gyrus	BA9	L + R	499	7.50	3	50	22
Angular gyrus		BA39	L + R	261	7.03	-48	-64	22	
Angular gyrus		BA39	R	70	5.62	60	-49	28	
Precuneus		BA7	L + R	75	6.06	-3	-55	34	
ASD		Medial frontal gyrus	BA2	L + R	561	10.17	3	53	25
		Middle frontal gyrus	BA8	L	31	5.95	-27	29	43
		Middle frontal gyrus		R	28	6.65	30	29	43
		Middle temporal gyrus		R	27	6.63	60	-19	-14
		Angular gyrus	BA39	L	93	6.18	-45	-61	25
	Supramarginal gyrus		R	109	6.62	60	-55	28	
	Precuneus	BA7	L + R	94	6.51	-3	-55	37	
	Uvula		R	32	5.84	30	-82	-35	
	Uvula		L	59	5.55	-24	-82	-32	
	SE vs IND								
HC	Posterior cingulate cortex		L + R	207	7.72	0	-58	28	
ASD	Posterior cingulate cortex	BA 31	L	67	5.89	-3	-52	28	
IND vs SE									
HC	Temporo-parietal junction		L	20	5.36	-57	-43	31	
	Inferior frontal gyrus	BA 47	R	25	5.35	51	35	-5	
	Lingual gyrus		R	81	5.42	12	-73	-2	
	Middle temporal gyrus		R	98	6.60	57	-25	-14	
	Declive		L	45	7.37	-21	-79	-22	
ASD	N.S.								

Whole-brain analyses; flexible-factorial ANOVA; threshold = $P < 0.05$ FWE corrected, extent threshold = 20 voxels; Moral = combined SE and IND dilemmas, SE = social-ethical dilemmas, IND = individual gain vs collective losses dilemmas, BL = (weighted) high-level baseline; ASD = patients with autism spectrum disorder; HC = Healthy controls; L = left; R = right, BA = Brodmann's Area; N.S. = not significant.

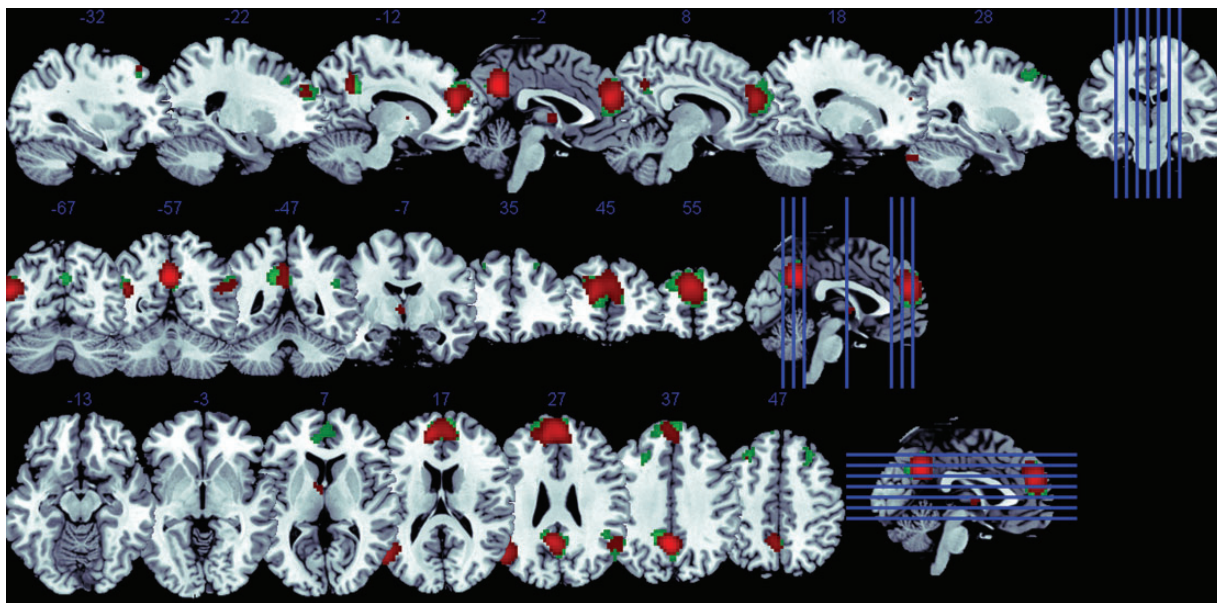


Fig. 2 One-sample analysis; pooled moral vs BL contrast; view: sagittal, coronal, axial; Red color = Healthy subjects; Green color = Patients with autism spectrum disorder; whole-brain analysis, flexible factorial analysis, $P < 0.05$ Family Wise Error corrected, spatial extent = 20 voxels.

Table 4 Brain activation for all moral contrasts—group comparisons

Group(s)	Region	BA	Side	k	t	MNI-coordinates		
						x	y	z
Moral vs BL								
HC > ASD	N.S.							
ASD > HC	Anterior cingulate cortex		R	23	4.33	6	41	-8
	Posterior cingulate gyrus	BA31	R	23	3.75	9	-61	22
	Posterior cingulate gyrus		L	21	3.65	-12	-61	13
SE vs BL								
HC > ASD	N.S.							
ASD > HC	Anterior cingulate cortex	BA32	L	18	3.94	-3	29	-8
	Anterior cingulate cortex	BA32	L + R	22	3.67	0	41	4
	Posterior cingulate gyrus		L	39	4.06	-18	-58	22
	Precuneus	BA7	R	34	3.75	12	-67	31
	Supramarginal gyrus		R	23	3.87	45	-46	31
IND vs BL								
HC > ASD	Amygdala		L	22	4.51	-15	-13	-20
	Inferior frontal gyrus		L	26	4.47	-39	35	10
ASD > HC	N.S.							
SE vs IND								
HC > ASD	N.S.							
IND vs SE								
HC > ASD	Amygdala		L	30	4.20	-24	-4	-23
	Insula		L	27	4.57	-39	5	4
	Posterior cingulate cortex		L	22	5.02	-9	-25	25

Whole-brain analysis; flexible-factorial ANOVA; threshold = $P < 0.05$ Monte-Carlo corrected; Moral = combined SE and IND dilemmas; SE = social-ethical dilemmas; IND = individual gain vs collective losses dilemmas; BL = (weighted) high-level baseline; ASD = patients with autism spectrum disorder; HC = Healthy controls; L = left; R = right, BA = Brodmann's Area; N.S. = not significant.

Comparing the HC and the ASD group regarding the IND vs BL contrast revealed reduced activation in the ASD group in the left amygdala and in the left IFG (Table 4 and Figure 3C, D).

The IND vs SE contrast revealed decreased activation for ASD patients compared to healthy subjects in the left amygdala, in the left insula and in the left posterior cingulate cortex (Table 4 and Figure 3E, F).

The SE vs IND contrast yielded no significant BOLD signal change (Table 4).

Group comparisons without medicated patients are found in Supplementary Table S1.

Correlation and covariate analyses

The correlation with the TAS20 and overall ADOS-G (Module 4) score yielded no significant results.

DISCUSSION

The aim of this study was to investigate the capacity of moral reasoning and its neural correlates in patients with ASD compared to non-autistic subjects by applying two different moral categories in order to determine potential specific deficits in moral decision making.

Despite a lack of behavioral differences between ASD patients and HC subjects, and despite comparable brain activation patterns for the single-group analyses, patients in comparison to HC subjects, as hypothesized, exhibited significant hypoactivations in the left amygdala, the left insula and the left IFG, for the individual gain vs collective losses dilemmas in particular (Figure 3C, D). On the other hand, we found increased activation in ASD patients in posterior regions, including the precuneus and particularly the posterior cingulate gyrus (Figure 3A, B), but also in the ACC, when comparing the ASD and the control group for the SE and pooled moral dilemmas.

These results of specific hypo- and hyperactivations in patients compared to healthy subjects might be interpreted in the light of different underlying phenomena.

Morality and empathy deficits in patients with ASD—differential activation during IND and SE dilemmas

For the IND vs BL and IND vs SE contrast (Figure 3C, F), we found decreased activation in ASD patients compared to healthy subjects in emotion- and empathy-related areas (Lamm et al., 2007; Schulte-Rüther et al., 2010) including areas of the human mirror neuron system (Schulte-Rüther et al., 2010), namely in the IFG, and of the limbic system, especially the amygdala, which is distinctively depicted by the parameter estimates (Figure 3D, F).

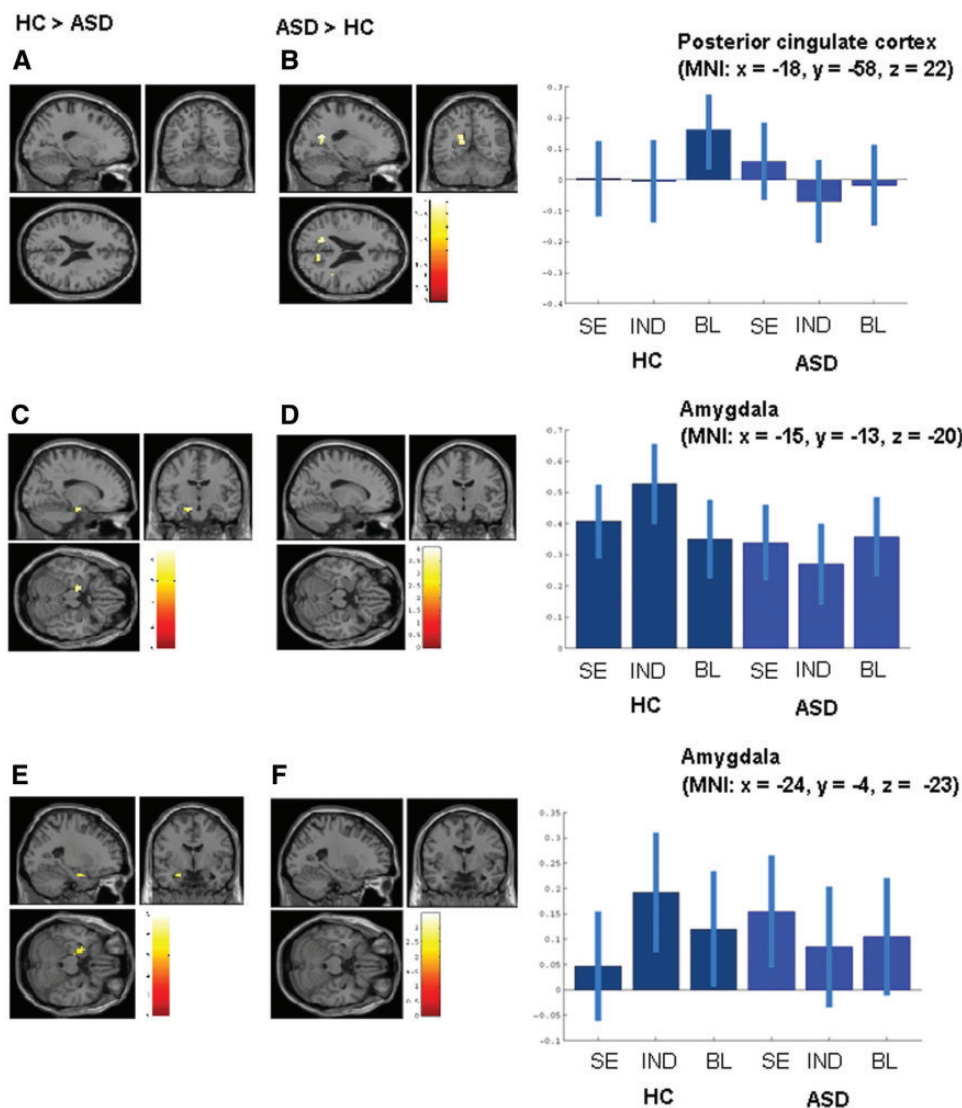


Fig. 3 Group comparisons for all moral contrasts; Left: **A** and **B**) SE vs BL contrast; **C** and **D**) IND vs BL contrast; **E** and **F**) IND vs SE contrast; whole-brain analysis, flexible factorial ANOVA, $P < 0.05$ Monte-Carlo corrected; Right: contrast estimates and 90% CI (extracted from activation clusters); HC = healthy control group; ASD = patients with autism spectrum disorders; SE = social-ethical dilemmas; IND = individual gain vs collective loss dilemmas; BL = non-moral daily dilemma high-level baseline.

Our two-person-situations pictured by the IND dilemmas (Figure 3C, D) in contrary to the SE condition (Figure 3A, B) not only ask for a certain ability to put oneself into context with another individual, but also to feel with the acting persons. Though general empathy deficits in ASD are questioned (Silani *et al.*, 2008; Bird *et al.*, 2010), the hypoactivations in ASD patients compared to healthy subjects particularly during the IND condition of our study might hence point to specific alterations in underlying networks of empathy.

This interpretation is in line with the findings of Zalla *et al.* (2011) in patients with ASD suggesting difficulties during solving those moral dilemmas which require knowledge about intentions of the agent and about the affective outcome of an action.

Also, in contrary to Bird *et al.* (2010), who suggested empathy deficits in ASD patients as an effect of alexithymia rather than ASD itself, our results were not affected by the score of the alexithymia scale TAS20.

Hypoactivations of empathy-related regions in patients compared to healthy subjects during our study were restricted to the left hemisphere. Unlike the right hemisphere, which predominantly seems to cover basal aspects of empathic emotions such as pain empathy, the

left hemisphere is proposed to be involved in the emotional evaluation of more sophisticated social-cognitive input (Bzdok *et al.*, 2012).

Hence, while there might not be a general empathic deficit based on ASD during basal emotion processing, our findings might indicate ASD-specific impairments in emotional involvement during processing of higher-level social situations, as depicted by our moral (IND) dilemmas.

Morality and executive dysfunctions

Interestingly, the network of brain regions, which we found comparably activated for both groups in the one-sample analyses of all moral contrasts (Figure 2), is also part of the ‘default mode network’, e.g. of regions activated during the so-called ‘brain resting state’.

For the SE condition and pooled moral contrast, group comparisons revealed abnormal hyperactivations for ASD patients in the posterior cingulate as a crucial part of this default network.

A recent study (Kennedy *et al.*, 2006) found that, unlike healthy subjects, ASD patients did not show reduced activation in default network regions comprising the VMPFC, the posterior cingulate gyrus and the precuneus during cognitively demanding tasks (see

also Wirth *et al.*, 2011). Likewise, an abnormal functional connectivity within default network regions was reported (Assaf *et al.*, 2010), especially between the medial PFC/ACC and the precuneus in ASD patients.

The 'default mode network' is considerably overlapping with regions associated with self-referential (Buckner and Carroll, 2006; see also below) and emotional (Vogt *et al.*, 1992) processing. Particularly, the posterior cingulate cortex also seems to subserve evaluative functions including self-reflection (Vogt *et al.*, 1992). Thus, alterations during 'resting state' might also indicate a putatively modified way of processing and evaluating (social) input, and consequently were suggested to be the underlying reason for social impairments of ASD patients (Kennedy *et al.*, 2006).

The SE condition representing complex societal issues particularly required integrating prior personal knowledge order to adequately solve our moral task, and hence, our findings might point to altered processing of social information in ASD patients.

Behavioral studies revealed impairments of ASD patients in different aspects of information processing (Happé and Frith, 2006; O'Connor and Kirk, 2008), as well as executive dysfunctions (Hill, 2004), including impaired decision making (Channon *et al.*, 2001; Schmitz *et al.*, 2007). With it, difficulties in the processing of social information were proposed as the underlying factor of the social impairments in ASD (O'Connor and Kirk, 2008).

Though our sample of ASD patients did not significantly differ regarding the response patterns during moral reasoning, as compared to healthy participants, they tended to exhibit longer reaction times, especially during the SE condition, which might point to patients' altered social information processing and/or to executive dysfunctions including decision making.

Remarkably, we also found abnormal hyperactivation in our patients compared to non-autistic subjects in the ACC (area BA32 in particular), during the Moral vs BL and SE vs BL (Figure 3A, B) contrast. Hyperactivations of the ACC as a crucial area for conflict and error monitoring and decision making (Bush *et al.*, 2000), and of its adjacent regions (Dichter *et al.*, 2009), have been interpreted as compensatory mechanisms of ASD patients.

The idea of a 'failure to deactivate' during cognitively demanding tasks in ASD patients compared to control subjects in context with ACC hyperactivation might thus be a hint for an altered and putatively less efficient way of solving social situations. These deficits in information processing might aggravate social impairments and also be related to the increased ACC activation indicating the need for increased effort to solve complex social situations.

However, the distinct hypoactivations of empathy-related regions, during the IND vs BL and IND vs SE contrasts in particular (Figure 3C-F), described earlier, suggest that it is unlikely that the differential brain activation is only linked to cognitive deficits as executive dysfunctions or impaired reading comprehension.

Additionally, in contrary to the widely suggested deficits on the level of executive functions including verbal fluency in autistic patients (Turner, 1999), and despite patients' tendency to longer reaction times during our moral task, our autistic participants did not differ significantly from HCs (Table 1) on the respective neuropsychological tests, namely the Trail Making Test (TMT-A/-B) and the test for verbal fluency (RWT). Adequate performance of ASD patients during these tests is also in line with Spek *et al.* (2009), who found verbal fluency impairments in patients with Asperger's syndrome only in one specific category of the task, namely the putatively most 'social' subscale 'professions', while all of the others were preserved. Likewise, Lehnhardt *et al.* (2011) found no significant performance differences in high-functioning autistic adults during the TMT, and interpreted this finding with the heterogeneity of the autistic spectrum. Not least,

our high-functioning ASD group revealed a comparatively high educational and intellectual level, which might explain the rather preserved performance.

Moral decision making and altered self-reflection

A striking aspect of the one-sample contrasts (Figure 2) is the involvement of the particular network of prefrontal and posterior cortical midline structures also active during tasks investigating self-reflection (Johnson *et al.*, 2006; for a review: Buckner and Carroll, 2006) or self-other distinction (Uddin *et al.*, 2006). During group comparisons, we found abnormal hyperactivations in ASD patients especially in the posterior cingulate gyrus for the Moral vs BL and the SE vs BL contrast, also highlighted by the parameter estimates (Figure 3B for the SE vs BL contrast).

Several authors propose a close linkage between social or moral judgments and the understanding of others' and one's own mind (di Martino and Castellanos, 2003; Farley *et al.*, 2010; Zahavi, 2010). Consequently, tasks testing for social cognition and self-reflection result in similar brain activation patterns comprising the VMPFC, and posterior regions, such as the precuneus (Young *et al.*, 2007). Hence, social judgments, as reflected in our moral dilemmas, need a mature understanding of one's own inner life.

At the same time, behavioral data suggest impairments of ASD patients in different aspects of self-awareness, particularly with regard to agency (Farley *et al.*, 2010), and thus relate ASD to a disorder of the 'self' (Dritschel *et al.*, 2010; Zahavi, 2010).

The posterior cingulate cortex is suggested to be crucial for experiential self-reflection and here for the processing of outward-directed, i.e. social and contextual, elements of an event (Johnson *et al.*, 2006). Given a 'weak central coherence' in ASD patients (Happé and Frith, 2006) and our above suggestions of altered executive functions, they might need to put more effort in solving tasks which require combination of complex information. As the SEs in particular ask for integrating several aspects, i.e. on political decisions, and hence are related to the processing of the 'outward-directed' elements of an event, this might find its neural correlate in the most pronounced hyperactivation in ASD patients compared to non-autistic subjects (Figure 3A, B).

LIMITATIONS AND CONCLUSIONS

Our study has some limitations: Our stimuli were not designed to detect potential differences between ASD patients and HCs with regard to underlying motivations and beliefs behind a chosen solution during moral decision making, e.g. attempted vs intentional harms (Moran *et al.*, 2011; Zalla *et al.*, 2011; Shulman *et al.*, 2012).

Neither did we include a test for reading abilities and reading comprehension. However, we matched both groups according their educational level, and assessing verbal fluency suggested rather similar verbal abilities.

Despite comparable behavioral results and similar brain activation patterns for the single-group analyses, distinct group differences between ASD patients and controls were seen for the SE, IND and pooled moral dilemma conditions, in which ASD patients showed significantly reduced activation of empathy-related regions as compared to the HC group, particularly during the IND condition, and likewise putatively compensatory abnormal hyperactivations of regions associated with the 'default mode network' and also self-projective cognition.

Though according to our study ASD patients do not exhibit fundamental deficits in moral reasoning, these specific brain activation patterns propose an altered way of (meta-)cognitive processing of social information and indicate a neural endophenotype for ASD reflecting dysfunctions in the underlying network.

SUPPLEMENTARY DATA

Supplementary data are available at SCAN online.

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