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Multimodal imaging of the amygdala in non-clinical subjects with high vs. low autistic-like social skills traits

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ABSTRACT

Recent clinical and theoretical frameworks suggest that social skills and theory of mind impairments characteristic of autism spectrum disorder (ASD) are distributed in the general population on a continuum between healthy individuals and patients. The present multimodal study aimed at investigating the amygdala's function, perfusion, and volume in 56 non-clinical subjects from the general population with high (n = 28 High-SOC) or low (n = 28 Low-SOC) autistic-like social skills traits. Participants underwent magnetic resonance imaging to evaluate the amygdala's functional connectivity at rest, blood perfusion by means of arterial spin labelling, its activation during a face evaluation task and lastly grey matter volumes. The High-SOC group was characterised by higher blood perfusion in both amygdalae, lower volume of the left amygdala and higher activations of the right amygdala during processing of human faces with fearful value. Resting state analyses did not reveal any significant difference between the two groups. Overall, our results highlight the presence of overlapping morpho-functional alterations of the amygdala between healthy individuals and ASD patients confirming the importance of the amygdala in this disorder and in social and emotional processing. Our findings may help disentangle the neurobiological facets of ASD elucidating aetiology and the relationship between clinical symptomatology and neurobiology.

1. Introduction

Growing evidence indicates that social skills and theory of mind impairments characteristic of autism spectrum disorder (ASD) are distributed across the general population, constituting a continuum between healthy individuals and patients (Abu-Akel et al., 2019; Constantino and Todd, 2003; Ruzich et al., 2015). They greatly impact on patients' functioning and quality of life (Frye, 2018; Tobin et al., 2014; van Heijst and Geurts, 2015) and are thus central to understanding spectrum psychopathology. These autistic-like social skills traits often manifest as difficulties in social-emotional reciprocity, abnormal social interactions, deficits in verbal and non-verbal communicative behaviours and difficulties in understanding social relationships and emotions (American Psychiatric Association, 2013). Previous studies have indicated that these impairments manifest in the earliest phases of childhood possibly driven by alterations of several neurobiological systems (DiCicco-Bloom et al., 2006; Frye, 2018). Notably, these traits often found in ASD patients are thought to arise from deviations of neurobiological factors also possibly distributed on a continuum between patients, high functional ASD individuals and healthy people (Xu et al., 2022). For example, previous studies illustrated the existence of ASD-specific structural and functional brain markers showing that social

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skills and theory of mind alterations are associated with alterations of specific neurobiological structures in ASD patients including the amygdala and the prefrontal cortex (Boedhoe et al., 2020; Cai et al., 2018; Kleinhans et al., 2008; van Rooij et al., 2018; Yang et al., 2016; Zhu et al., 2018). Among all the potential neural correlates, the amygdala is a nucleus that has been studied in several psychiatric conditions from both structural and functional perspectives and suggested to be involved in many key cognitive functions including salience, valence, reward, social learning and processing of emotions (Adolphs and Spezio, 2006; Baron-Cohen et al., 2000; Hennessey et al., 2018) constituting a key region of the social brain network, a complex neural circuit that elaborates social cues, interactions and contexts (Dunbar, 2009; Zovetti et al., 2021). In relation to ASD, the amygdala theory of autism originally proposed by Baron-Cohen suggests that ASD might arise from both structural and functional abnormalities of this region (Baron-Cohen et al., 2000). Since its conception, several studies have supported this theory indicating the presence of structural and functional amygdalar alterations in ASD patients and its involvement in theory of mind, social skills, and emotion regulation processes (Allely et al., 2014; Hennessey et al., 2018; Sato and Uono, 2019).

In autistic-like traits in the general population, there have been no studies so far to test the hypothesis of an association with amygdala function or structure. The study of the neural amygdala correlates in healthy individuals with high ASD traits could help disentangle the neurobiological underpinnings of ASD, ultimately elucidating its aetiology and supporting the hypothesis of the existence of a neurobiological continuum between healthy individuals and ASD patients. Moreover, amygdala alterations associated with social skills impairments in healthy individuals could possibly constitute a transdiagnostic neural correlate of the trait itself.

Therefore, the present multimodal study aimed at evaluating amygdala function, perfusion, and structure in healthy individuals phenotyped with high ASD social skills deficits against matched healthy controls with low ASD social skills traits. We chose a sample of healthy non-clinical ASD individuals to eliminate confounding effects including those of comorbidity associated with clinical ASD. Specifically, we (I) evaluated the amygdala's functional activity at rest and its functional connectivity (FC) with the medial and dorsomedial prefrontal cortex and with the whole brain by means of ROI-to-ROI and seed-to-voxels respectively, (II) the cerebral blood perfusion by means of arterial spin labelling (ASL), (III) it's activity during a face evaluation task and lastly (IV) the amygdala's grey matter volumes (GM) comparing the high vs. low groups. Overall, we expected altered functional connectivity at rest in the high vs. low-ASD group, higher blood perfusion levels and aberrant amygdala's activations during the execution of the face evaluation task.

2. Methods

2.1. Participants

Neuroimaging, phenotype, and demographic data were obtained from a total of 56 healthy non-psychiatric participants. As part of a larger study recruiting psychiatrically healthy ("neurotypical") individuals from the general population in the area of Marburg, Germany (Nenadic et al., 2021), we selected individuals with high (N= 28; 16 females and 12 males; mean age 26.28, ± 4.71; High-SOC) or low (N= 28; 16 females and 12 males; mean age 26.10, ± 4.56; Low-SOC) social skills deficits recruited from the general population. High-SOC and Low-SOC groups were balanced by sex, age and handedness as shown in Table 1. Across the entire sample, three participants were left-handed (5.35%) and two were ambidextrous (3.35%). The sample was part of a larger cohort of healthy individuals (Nenadic et al., 2021). Specifically, we plotted the distribution of the AQ social skills subscale of the entire sample (n = 376) and selected all participants with a social skills total score of at least five on this subscale (top 8%) leading us to a subsample of 28 individuals (High-SOC group). The High-SOC group was then matched for age and sex with other 28 individuals with low social skills deficits (Low-SOC group) chosen for from the lowest 8% part of the distribution. High-SOC and Low-SOC groups were balanced by sex, age and handedness as shown in Table 1. Across the entire sample, three participants were left-handed (5.35%) and two were ambidextrous (3.35%). The entire subsample of 56 subjects was used in all subsequent analyses. Overall, the distribution of ASD traits in our sample was in line with previous studies conducted on the general healthy population (Ruzich et al., 2015). Demographic and clinical details of the two groups can be seen in Table 1.

Table 1
Demographic and clinical characteristics of all participants (both groups).

Variable	Low-SOC	High-SOC	Statistic	p-value
Sex (F/M)	16/12	16/12	$\chi2 = 0$	1
Age, mean (sd)	26.10 (4.56)	26.28 (4.71)	T= 0.14	0.88
Handedness, mean (sd)	85.30 (48.15)	84.21 (43.13)	$T = -0.08$	0.93
AQ social skills, mean (sd)	1 (0.37)	5.9 (1.22)	$T = -20.35$	**<0.01**

AQ: autism quotient questionnaire; High-SOC: participants scoring high (top 8%) on the social-skills AQ subscale; Low-SOC: participants scoring low on the social-skills AQ subscale. Sd: standard deviation.

Participants were assessed with the multiple-choice vocabulary test (Mehrfachwahl-Wortschatz-Intelligenztest, (Lehrl, 2005)) to exclude the presence of intellectual disability and were screened with the German version of the structured clinical interview (DSM-IV, SKID-I) to exclude the presence and history of any psychiatric disorder, substance abuse and first-degree psychotic disorders (Wittchen et al., 1997). Additional exclusion criteria were neurological disorders, major medical conditions or pregnancy. Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). All subjects gave written consent before participating in the study. The study protocol was approved by the Ethics Committee of the Philipps University Medical School (protocol number 61/18) according to the latest version of the Declaration of Helsinki (World Medical Association, 2013).

2.2. Phenotyping autism spectrum traits

All participants were phenotyped with the German version of the Autism Quotient questionnaire to evaluate and quantify ASD traits (Baron-Cohen et al., 2001). Briefly, the AQ is a self-report measure composed of 50 items on a Likert-like scale quantifying autistic-like traits through a total score and through five different subscales measuring different facets of ASD; social skills, communication, attention to detail, attention switching, and imagination.

Although the AQ was first developed to measure autistic-like traits in clinical ASD individuals, it can also be used to reliably assess the general nonclinical population as shown in previous studies (Ruzich et al., 2015; Schröder et al., 2021).

In the present study, we focused on the social skills subscale of the AQ questionnaire, a diagnostic questionnaire designed to measure the expression of Autism-Spectrum traits in an individual, by his or her own subjective self-assessment. Briefly, this subscale quantifies the participants' social skills deficits, a key domain of ASD that has been suggested to be distributed on a continuum between ASD patients and healthy individuals (Constantino and Todd, 2003). Previous studies have shown in detail the psychometric properties of the AQ, characterized by a test–retest-stability of r= 0.78 and r= 0.60–0.81 for the AQ total score and its subscales respectively (Hoekstra et al., 2008). We previously assessed the internal consistency of the AQ social skills subscale in a cohort from which this sample was drawn, computing a Cronbach's alpha of $\alpha = 0.501$ (Schröder et al., 2021).

2.3. MRI data acquisition

MRI images were acquired on Siemens Tim Trio 3 Tesla MRI system (12-channel head matrix Rx-coil; Siemens, Erlangen, Germany). For the morphometric analyses (T1 sequence), the following parameters were used: Repetition time (TR) = 1900 ms; echo time (TE) = 2.26 ms; time of inversion (TI) = 90 ms; bandwidth = 200 Hz/Px. One hundred and seventy-six slices (sagittal orientation) with a slice thickness of 1 mm and a voxel resolution of 1 × 1 × 1 mm were acquired. The field of view was 256 mm, flip angle was 9°, and the phase encoding direction was anterior–posterior. Acquisition time was 4 min and 26 s. For the BOLD resting state analyses, images were acquired with a sequence with the following parameters: TR = 2000 ms, TE = 30 ms, FOV = 210 × 210 mm2, slices number = 33, for a total acquisition time of 8 min. Lastly, perfusion images (ASL sequence) were acquired with a pulsed arterial spin labeling (pASL) sequence at rest, using Siemens' Proximal Inversion with Control of Off-Resonance Effects (PICORE Q2T) protocol including 16 slices with 7 mm thickness and a distance factor of 25%, with TR=3000 ms, TE=11 ms, inversion time 2 TI2=2200 ms, TI1=700 ms, and saturation stop time=1600 ms, a field of view of 230 mm and flip angle of 90°, 153 measurements and a resulting voxel size of 3.6 × 3 × 6 × 6.0 mm. fMRI data images were acquired on a Siemens Magnetom TrioTim syngo MR B17 with the following parameters: TA: 14:20, PAT: Off, voxel size: 2.0 × 2.02 × 2.4 mm, TR=1610 ms, TE=36 ms, FoV=256mm. Field map parameters were FoV=230 mm, TR=400 ms, TE1=4.92 ms, TE2=7.38 ms, flip angle=60deg.

2.4. Emotional face evaluation fMRI task

All participants underwent an emotional face evaluation task during fMRI scan after T1 and ASL sequences. Participants were presented a face localisation paradigm (see (Hildesheim et al., 2020)), consisting of grayscale photographs of 30 faces with a neutral expression, 30 faces with a fearful expression (both directly facing the camera and acquired from the Karolinska Directed Emotional Faces (KDEF) database (Lundqvist et al., 1998), as well as of 30 houses (images provided by (Goh et al., 2010)). Stimuli were presented in a blocked design, with each block (300 ms per stimulus, 14.5 s in total) consisting of 20 images drawn from the respective data set and followed by a 5.6 s pause (showing a fixation cross) and 14 blocks per each of the three conditions. After half of the blocks, there was a 30 second break during which the German word for break ("pause") was presented. Participants were instructed to indicate the occurrence of two identical images in a row by pressing a button with their right index finger. The paradigm was conducted and presented using the software package Presentation (Neurobehavioural Systems, San Francisco, CA, United States). The entire sequence lasted 14 min and 42s.

In brief, participants viewed pictures of either neutral or fearful faces, and houses in a block design and are asked to indicate the occurrence of two identical images in a row by pressing a button with their right index finger. The task was set up as block design, with six face and house trials, respectively, per block. Blocks had a duration of 44 (faces) and 32 s (houses), respectively. Five house blocks, and four faces blocks were presented in alternating order, starting with a houses block (Fig. 2). Blocks were separated by short inter-block-intervals (1.5–5.5 s). The paradigm lasted 14 min 42 s.

2.5. Structural data preprocessing

Structural preprocessing was done through CAT12 (C. Gaser, Structural Brain Mapping Group, Jena University Hospital, Jena, Germany; http://dbm.neuro.uni-jena.de/cat/) implemented in SPM12 (Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) with default options (SPM standard tissue probability map, affine regularisation) (D'Agostino et al., 2004) with the ICBM space template. Strength of SPM inhomogeneity correction and accuracy were set to medium and average respectively. Affine pre-processing was set to rough; strength of local adaptive segmentation was set to medium. Skull stripping was done through the adaptive probability region-growing approach. For spatial registration, shooting registration (Ashburner and Friston, 2011) with optimised shooting approach was applied, using adaptive threshold and lower initial resolution to improve both accuracy and calculation time (IXI555 MNI 152). Images were visually inspected for anatomic deviations and signal or segmentation artefacts and using the quality parameters implemented in the CAT12 toolbox.

Left and right amygdalae volumes of both High and Low-SOC groups for volumetric analyses were extracted using CAT12's own function and defined according to the CoBrA atlas (Computational Brain Anatomy Laboratory at the Douglas Institute, Verdun, Canada; Entis et al., 2012; Treadway et al., 2015; Winterburn et al., 2013). This atlas was chosen as it was specifically created to examine sub-cortical regions in neurodegenerative and neurodevelopmental disorders such as ASD.

2.6. Functional data preprocessing – resting state data

Preprocessing of functional resting-state images was done through the CONN toolbox with default options (Whitfield-Gabrieli and Nieto-Castanon, 2012). fMRI images were converted into BIDS format and imported into the toolbox. Functional data was realigned using the SPM12 realign & unwarp procedure (Andersson et al., 2001). Briefly, fMRI scans are co-registered and resampled to a reference image using b-spline interpolation also addressing potential motion distortions. Temporal misalignment was corrected through the standard SPM12 slice-timing correction procedure (Henson et al., 1999), where the functional data is time-shifted and resampled using sinc-interpolation to match the time in the middle of each acquisition time. Functional and anatomical data were then normalized into standard MNI space and segmented into grey matter, white matter, and CSF tissue classes using SPM12 unified segmentation and normalization procedure (Ashburner and Friston, 2005). Lastly, functional data was smoothed using spatial convolution with a Gaussian kernel of 8 mm full width half maximum, in order to increase BOLD signal-to-noise ratio across all 56 subjects. ROI definition and calculation was performed on unsmoothed data.

For the resting state analyses, we used a combined approach employing both ROI-to-ROI and seed-to-voxel methods. The first technique characterizes the individual FC between pairs of regions among a pre-defined set of chosen ROIs (i.e., both amygdalae and medial (mPFC) and dorsomedial prefrontal cortex (dmPFC) regions) generating a ROI-to-ROI connectivity matrix. Each element of this matrix is defined as the Fisher-transformed bivariate correlation coefficient between pair of ROIs BOLD timeseries. ROI-to-ROI FC was examined with Functional Network Connectivity (FNC) multivariate parametric statistics. Briefly, FNC analyses the entire set of connections between all pairs of ROIs in terms of the within- and between- network connectivity sets (Jafri et al., 2008), performing a multivariate parametric GLM analysis for all connections. CONN employs a standard criterion for thresholding ROI-to-ROI parametric maps while appropriately controlling the family-wise error rate uses FNC (FDR-corrected $p < 0.05$ cluster-level threshold) to select among all ROI-to-ROI FC sets those significant together with a post-hoc uncorrected $p < 0.05$ threshold (connection-level) to further characterize the pattern of individual connections that show some of the largest effects within each significant set (Whitfield-Gabrieli and Nieto-Castanon, 2012). Conversely, seed-to-voxel analysis characterizes FC of a set of chosen ROIs (i.e., left and right amygdala) creating a seed-based connectivity map. This map represents the degree of FC between the seed and every brain voxel. Briefly, seed-based maps are computed as the Fisher-transformed bivariate correlation coefficients between the ROI BOLD timeseries and each individual voxel BOLD timeseries. Seed-to-voxel FC was examined through the standard Random Field Theory (RFT) parametric statistics. Briefly, clusters of interest are initially defined through RFT

(uncorrected $p < 0.001$) and then an FDR-corrected $p < 0.05$ cluster-level threshold is used to select among the resulting clusters those significant (Whitfield-Gabrieli and Nieto-Castanon, 2012).

2.7. Functional data preprocessing – task-based data

Amygdala task-based activations were acquired following a slab-based procedure. Due to slab-based acquisition, normalisation was not satisfactory for a significant portion of the data. Therefore, based on the contrast faces vs. houses, manual identification of amygdala peak voxel localisation per subject was conducted by experienced medical observers and validated with a standard atlas mask (Neuromorphometrics). Here, script-based placement and extraction of mean activation values of 4 mm spheres was run at the respective individual activation peaks previously identified.

2.8. Functional data preprocessing – rCBF data

During pre-processing, all 153 images underwent motion correction and realignment, as well as CBF quantification in native space. All 76 single CBF images were co-registered with the individual anatomical T1 scans, normalised in MNI space and smoothed with a Gaussian kernel of $6 \times 6 \times 6$mm. Mean perfusion values of whole amygdala were extracted using MarsBar and right and left whole amygdala masks provided in the Neuromorphometrics atlas. Other details of the procedure can be found elsewhere (Cantisani et al., 2018).

2.9. Statistical analyses - Resting state data

The default atlas (Harvard Oxford) was used in both ROI-to-ROI and seed-to-voxel analyses to select the source and target regions of interest including the left and right amygdala, the medial prefrontal cortex and the anterior nodes of the default mode network as parcellated in the CONN toolbox, which include the mPFC and the dmPFC. For the seed-to-voxel analyses, only the amygdalae were chosen as seed regions. Both ROI-to-ROI and seed-to-voxel analyses were conducted setting up a contrast comparing High-SOC (1) vs. Low-SOC (−1) groups including age (0) and sex (0) as covariates of no interest.

2.10. Statistical analyses – phenotype, structural, task-based, and rCBF data

Statistical analyses of demographic and phenotype data as well as extracted mean values of structural, task-based, and rCBF parameters were done with IBM SPSS version 20 (IBM, 2011). The presence of outliers was assessed through visual inspection (box plots, Tukey's Fences). Demographic and clinical differences between the two groups were quantified through t and chi-squared tests.

Mean ASL perfusion for both amygdalae were used as dependent variables in an independent samples *t*-test comparing the High vs Low-SOC groups quantifying the differences in perfusion levels.

Amygdala task-based fMRI activations were entered as dependent variables into an independent samples *t*-test comparing the High vs Low-SOC groups across different conditions: faces vs. houses, fearful vs. neutral faces and fearful faces vs houses.

Finally, amygdala volumes of both High and Low-SOC groups were entered as dependent variables into a GLM analysis. Age and total intracranial volume, sex and group (High-SOC vs. Low-SOC) were entered as covariates of no interest and fixed factors respectively. Between-subjects effects were examined to evaluate the association between groups on both amygdalae volumes. Cerebral blood flow and task-based fMRI data were missing for five and three participants respectively. Missing data were not replaced.

2.11. Laterality analyses

Since most of our results suggested the presence of laterality effects, we conducted post-hoc analyses computing a laterality index (LI) for every significant result (i.e., volumes, blood perfusion, specific task contrasts). Briefly, LI was computed for every participant by using the following formula in line with several other neuroimaging studies (Seghier, 2008).

$$LI = \frac{Left - Right}{Left + Right}$$

Roughly, a LI value greater than zero implies leftward laterality. Conversely, a LI value lower than zero suggests rightward laterality. Mean group LI values were calculated and differences quantified through *t*-tests.

3. Results

3.1. Demographics

Demographic and clinical statistics are given in Table 1.

3.2. Resting state functional connectivity

Both ROI-to-ROI and seed-to-voxel analyses showed no significant results. That is, FC between amygdalae and medial and dorsomedial prefrontal cortex ROIs and between amygdalae and whole brain did not differ between the High vs. Low-SOC groups.

3.3. Cerebral blood flow (rCBF)

On average, the High-SOC group showed significantly higher perfusion levels in both right (31.7 vs. 24.16; $p = 0.023$) and left amygdalae (33.24 vs. 24.73; $p = 0.009$) when compared with Low-SOC participants. Results are shown in Table 2 and Figs. 1(a) and 2.

3.4. Emotional face evaluation fMRI task (task-based fMRI)

On average, High-SOC participants showed greater activations only in the fearful vs. neutral condition only in the right amygdala when compared with Low-SOC subjects (0.24 vs. 0.07; p-value = 0.023) as shown in Table 3 and Fig. 1(b).

3.5. Amygdala volume analyses

Morphometric analyses revealed the presence of an effect of the group variable on the left amygdala volume with High-SOC participants, on average, being characterized by lower volumes ($p = 0.03$; Table 4). Specifically, estimated marginal means of left and right amygdalae volumes for the Low and High-SOC groups were 1.82, 1.82 and 1.75, 1.77 respectively (Fig. 1(c)).

3.6. Laterality index

Results of LI analyses are shown in Table 5. No significant differences

Table 2
Perfusion levels of the amygdalae (rCBF) in High vs. Low-SOC (social skills) groups.

	Group	Mean*	t	Effect Size	p-value
Left Amygdala	High-SOC	**33.24**	2.7	**0.62**	**.009**
	Low-SOC	24.73			
Right Amygdala	High-SOC	**31.70**	2.3	**0.55**	**.023**
	Low-SOC	24.16			

* mean cerebral blood flow expressed as ml of blood/(100 g tissue min).

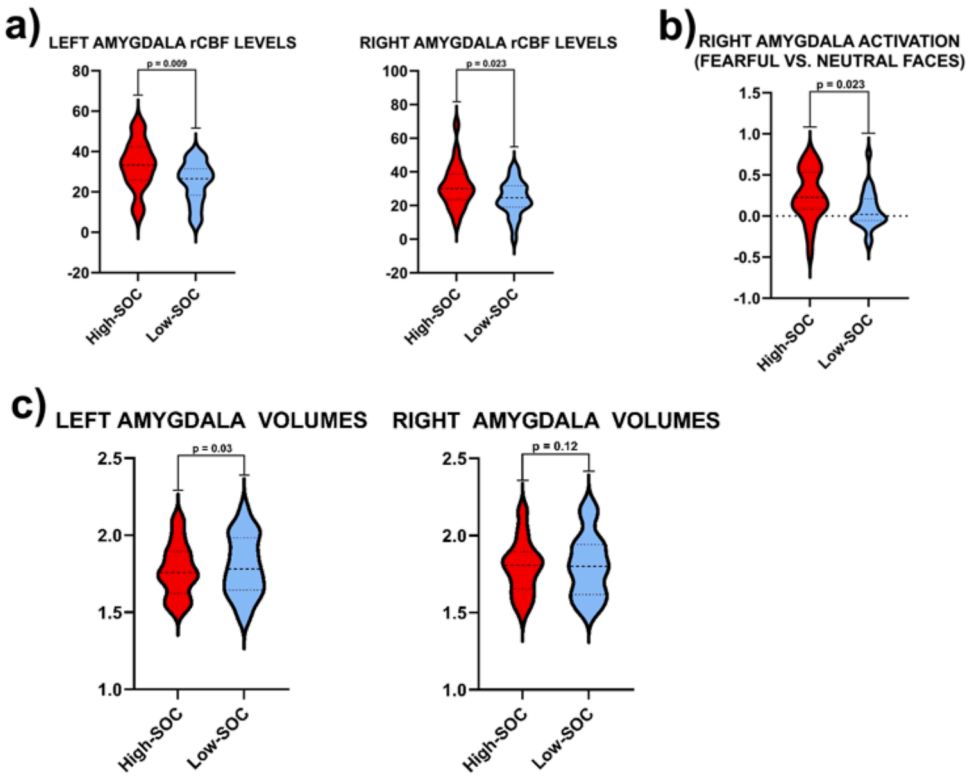

Fig. 1. a) Violin plots depicting right and left amygdala cerebral blood flow (arterial spin labelling; ASL) of both High and Low-SOC groups. Mean cerebral blood flow expressed as ml of blood/(100 g tissue min). b) Violin plots depicting activation levels of the right amygdala of both High and Low-SOC groups during the emotional face evaluation fMRI task. Change in BOLD signal (beta estimates) c) Violin plots depicting right and left amygdala volumes of both High and Low-SOC groups. Significance refers to the GLM analysis account for age, sex and intracranial volumes (see also Table 4). Mean amygdala volumes.

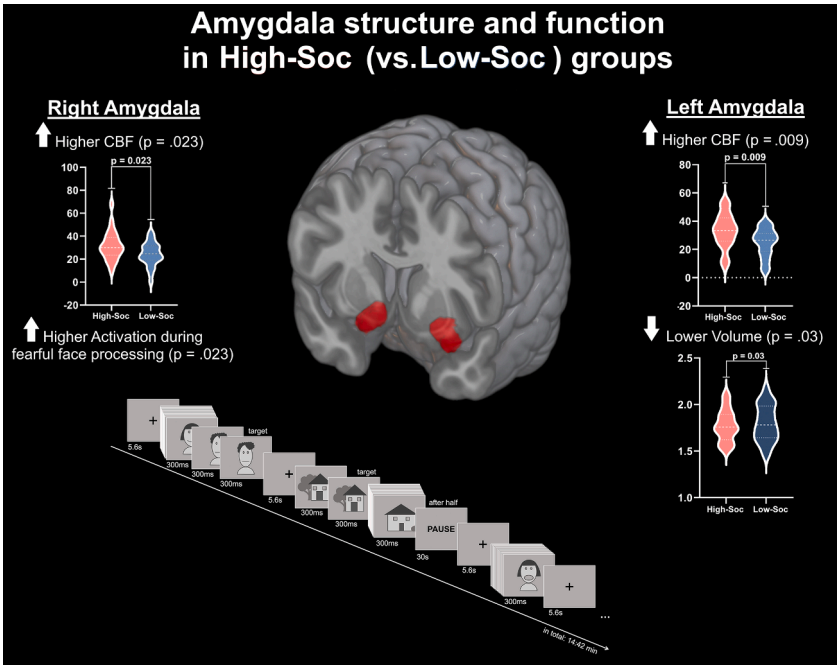

Fig. 2. Summary figure of structural and functional MRI findings for group comparisons of high-SOC vs. low-SOC subjects.

were found between the High and Low-SOC groups and no laterality effects were found when analysing volumes, cerebral blood flow and task activations.

4. Discussion

The aim of this study was a comprehensive multi-method evaluation of amygdala function and structure in relation to autism-related social skills traits in a cohort of non-clinical individuals. Specifically, we

Table 3
Differences in activation levels between High and Low-SOC groups in both amygdalae across the three conditions.

	Group	Mean*	t	Effect Size	p-value
			Faces vs. Houses		
Left Amygdala	High-SOC	0.88	0.49	0.13	.62
	Low-SOC	0.83			
Right Amygdala	High-SOC	0.85	0.76	0.21	.50
	Low-SOC	0.78			
			Fearful vs. Houses		
Left Amygdala	High-SOC	0.98	0.88	0.23	.38
	Low-SOC	0.88			
Right Amygdala	High-SOC	0.97	1.38	0.38	.17
	Low-SOC	0.82			
			Fearful vs. Neutral		
Left Amygdala	High-SOC	0.20	1.51	0.40	.13
	Low-SOC	0.10			
Right Amygdala	High-SOC	**0.24**	2.34	**0.60**	**.023**
	Low-SOC	**0.07**			

* BOLD signal mean value expressed in arbitrary units (change from baseline).

Table 4
Between subjects results of left and right amygdalae volumes of both High and Low-SOC groups. Age, sex and TIV were used as covariates of no interest.

	F statistic	Partial Eta Squared	p-value
Left Amygdala volume as dependent variable			
Age	0.12	0	.76
Sex	0	0	.99
TIV	43.66	0.46	<0.001
Group	5.09	0.09	**.03**
Right Amygdala volume as dependent variable			
Age	0.95	0.01	.33
Sex	0	0	.95
TIV	45.80	0.47	<0.001
Group	2.50	0.48	.12

High-SOC: participants scoring high (top 8%) on the social-skills AQ subscale;. Low-SOC: participants scoring low on the social-skills AQ subscale. TIV: total intracranial volume. Sd: standard deviation.

Table 5
Mean Laterality Index values of both High and Low-SOC groups of all the significant analyses. LI values greater than zero suggest the presence of leftward laterality. Conversely, values lower than zero suggest rightward laterality.

High-SOC (mean LI)	Low-SOC (mean LI)	t	p-value
Volume			
−0.006	−0.001	−1.14	.25
CBF			
0.019	0.017	0.02	.98
fMRI (Fearful vs. Neutral contrast)			
−0.086	0.297	−1.41	.16

CBF: cerebral blood flow (perfusion). fMRI: functional magnetic resonance task (modified Hariri task).

evaluated amygdala activity at rest and its connectivity with medial and dorsomedial prefrontal cortex regions, blood perfusion levels, activation during the processing of a face evaluation task, and compared amygdala volumes between the two groups.

Overall, the High-SOC group was characterized by higher blood perfusion in both amygdalae, lower volume of the left amygdala and higher BOLD activations of the right amygdala during the emotional regulation task. Resting state analyses did not reveal any significant difference of amygdala seed-to-voxel functional connectivity between groups. Some of these results are novel such as the differences in blood perfusion levels and amygdala's activations during the processing of emotional content in healthy individuals with high autistic traits. Finally, the absence of resting-state activation patterns does not support the recent theory of Sato & Uono suggesting that resting state alterations of the amygdala and its connectivity with the frontal regions may be at the base of social impairments (Sato and Uono, 2019).

Previous studies have shown that brain perfusion can be used to investigate the neurobiological traits of ASD, and autistic individuals have been previously reported to be characterized by alterations of the perfusion levels in several brain regions including the amygdala (Mori et al., 2020; Yerys et al., 2018). However, to our knowledge, our study is the first to investigate the perfusion of the amygdalae in healthy individuals phenotyped with high social impairments. Investigating brain deviations from the norm and their association with ASD traits in the non-clinical healthy population enables us to explore the continuum of autism, recognizing that traits associated with ASD exist on a spectrum, enabling us to gain insights into the broader range of autistic diversity and the interplay between neurodevelopmental factors and cognition. Likewise, our task fMRI analyses suggest that high social skills deficits as quantified by the AQ scale might be associated with higher BOLD activations of the right amygdala during the processing of fearful stimuli. Our findings are in line with previous reports of alterations of the amygdala activity in ASD individuals during emotion processing tasks (Yang et al., 2007). However, to our knowledge our study is the first that replicates these findings in a sample of healthy individuals with high autistic traits indicating that different neurobiological patterns of emotion recognitions might be revealed in healthy non-clinical individuals with high social skills impairments. Our structural findings of reduced left amygdala volumes in the High-SOC group are in line with previous studies indicating the key role of this limbic nuclei in processing social contexts and cues (Barnea-Goraly et al., 2014; Nacewicz et al., 2006). Lastly, whole-brain and seed-to-voxels resting state analyses showed no significant results with High-SOC participants showing no connectivity differences with the control group. A recent review (Sato and Uono, 2019) suggests that resting state alterations of the amygdala and its connectivity with prefrontal regions may be at the base of the condition's social impairments. However, no similar studies have been conducted on healthy individuals with high ASD traits and our lack of findings may be attributed to differences in the sample. Specifically, we might speculate that although that some facets of ASD symptomatology are distributed on a continuum between healthy individuals and patients, some of their neurobiological forms such as FC alterations may not be present in healthy individuals becoming manifest only in its most severe clinical manifestations.

Lower left volumes and higher right amygdala BOLD activations in the High-SOC group suggest the presence of possible lateralization effects associated with high social skills and theory of mind deficits. The left amygdala has been previously suggested to be a key region of the non-cortical social brain network involved in identification of emotional cues and social information (Baron-Cohen et al., 2000). Notably, previous studies have found lower left amygdala volumes in ASD patients (Rojas et al., 2004). Therefore, we hypothesize that lower volumes of the High-SOC participants may be reflective of their reduced social skills and high AQ scores indicating an alteration of the social brain network. Likewise, a systematic review on functional studies indicated the importance of the left amygdala activations in emotional processing in healthy individuals (Baas et al., 2004). However, the High-SOC group was characterised by higher activations of the right amygdala in response to emotional-salient stimuli and no effects were found in the left amygdala. One might speculate that our finding may be indicative of a compensatory effect as the right amygdala might support its left counterpart during the processing of the emotional task, however, additional studies are needed to better investigate this as a possible mechanism. Again, this might be indicative of the reduced or altered emotional and social skills characteristic of the High-SOC participants.

Lastly, higher blood perfusion in both amygdalae is a finding partially in contrast with studies on ASD patients which often indicate hypo-perfusion in patients (Mori et al., 2020; Yerys et al., 2018). Alterations of blood perfusion levels are thought to reflect regional changes in neuronal activity and brain function providing a reliable

neurobiological marker of a specific trait/condition (Yerys et al., 2018). Greater perfusion levels might, again, indicate compensatory effects, which would somewhat be in line with higher activations seen during the processing of the fMRI task. It is therefore conceivable that, in healthy individuals, greater perfusion levels might act as a protective mechanism in individuals characterised by higher social skills deficits, indicating non-linear relationship between symptom severity and activation and/or perfusion levels across the spectrum. However, this interpretation would have to be tested explicitly in a cohort with a greater (and more continuous) level of variability, including ASD patients (covering the full spectrum from health to disorder). Besides, current literature offers no insight about possible compensatory effects of blood perfusion of the amygdala and cerebral blood flow seems to be scarcely investigated in ASD patients and even less in healthy individuals with ASD traits, so this remains speculative.

Albeit some of our results may suggest the presence of laterality effects (e.g., fMRI activations, volume) our LI analyses did not reveal any significant laterality effect. This may be due to small sample size or the methodological limitations inherent to the LI index (Seghier, 2008), which might not fully capture the complexity of lateralisation. For example, previous studies showed how LI might be influenced by task selection, intrasubject and scan sessions variability (Seghier, 2008).

To conclude, our results establish associations between autism-like social communication deficits – as measured through the AQ scale – with amygdala structure and function alterations and suggest the presence of overlapping neurobiological key signatures of ASD between healthy individuals with social skills deficits and ASD patients confirming the importance of the amygdala in this disorder and in social and emotional processing in general. Our findings may help disentangle the neurobiological facets of ASD ultimately elucidating its aetiology and the relationship between clinical symptomatology and neurobiology.

CRediT authorship contribution statement

Niccolò Zovetti: Writing – original draft, Visualization, Formal analysis. **Tina Meller:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Data curation. **Ulrika Evermann:** Writing – review & editing, Project administration, Methodology, Data curation. **Julia-Katharina Pfarr:** Writing – review & editing, Project administration, Data curation. **Jonas Hoffmann:** Writing – review & editing, Resources, Methodology, Investigation. **Andrea Federspiel:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Sebastian Walther:** Writing – review & editing, Resources, Methodology. **Sarah Grezellschak:** Writing – review & editing, Project administration, Funding acquisition. **Andreas Jansen:** Writing – review & editing, Supervision, Resources, Methodology. **Ahmad Abu-Akel:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Igor Nenadić:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors have no competing interests to declare.

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