



**Rapid neural categorization of angry and fearful faces is specifically impaired in boys with ASD**

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Complete List of Authors:	<p>Van der Donck, Stephanie; KU Leuven, Center for Developmental Psychiatry; KU Leuven, Leuven Autism Research (LAuRes)  Dzhelyova, Milena; Université catholique de Louvain, Institute of Research in Psychological Sciences, Institute of Neuroscience  Vettori, Sofie; KU Leuven, Center for Developmental Psychiatry; KU Leuven, Leuven Autism Research (LAuRes)  Mahdi, Soha Sadat; KU Leuven, Center for Developmental Psychiatry; UZ Leuven, Medical Imaging Research Center, MIRC  Claes, Peter; KU Leuven, Department of Electrical Engineering (ESAT/PSI) &amp; Department of Human Genetics; UZ Leuven, Medical Imaging Research Center, MIRC  Steyaert, Jean; KU Leuven, Center for Developmental Psychiatry; KU Leuven, Leuven Autism Research (LAuRes)  Boets, Bart; KU Leuven, Center for Developmental Psychiatry; KU Leuven, Leuven Autism Research (LAuRes)</p>
Key Words:	Autism spectrum disorders, Electroencephalography (EEG), Emotion recognition, Facial expression

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11 **Authors:**  
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14 Stephanie Van der Donck<sup>a,b</sup>, Milena Dzhelyova<sup>c</sup>, Sofie Vettori<sup>a,b</sup>, Soha Sadat  
15

16  
17 Mahdi<sup>a,d</sup>, Peter Claes<sup>d,e</sup>, Jean Steyaert<sup>a,b</sup>, Bart Boets<sup>a,b</sup>  
18  
19

20  
21  
22 <sup>a</sup> Center for Developmental Psychiatry, Department of Neurosciences, KU Leuven, Leuven,  
23  
24 Belgium.  
25

26  
27 <sup>b</sup> Leuven Autism Research (LAuRes), KU Leuven, Leuven, Belgium.  
28

29  
30 <sup>c</sup> Institute of Research in Psychological Sciences, Institute of Neuroscience, Université de  
31  
32 Louvain, Louvain-La-Neuve, Belgium.  
33

34  
35 <sup>d</sup> Medical Imaging Research Center, MIRC, UZ Leuven, Leuven, Belgium.  
36

37  
38 <sup>e</sup> Department of Electrical Engineering (ESAT/PSI) & Department of Human Genetics, KU  
39  
40 Leuven, Leuven, Belgium  
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44 **Running head**  
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47 Lower neural sensitivity to facial anger and fear in ASD  
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56 We declare no financial or other conflicts of interest.  
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## Abstract

**Background.** Difficulties with facial expression processing may be associated with the characteristic social impairments in individuals with autism spectrum disorder (ASD). Emotional face processing in ASD has been investigated in an abundance of behavioral and EEG studies, yielding, however, mixed and inconsistent results.

**Methods.** We combined fast periodic visual stimulation with EEG to assess the neural sensitivity to implicitly detect briefly presented facial expressions among a stream of neutral faces, in 23 boys with ASD and 23 matched typically developing (TD) boys. Neutral faces with different identities were presented at 6 Hz, periodically interleaved with an expressive face (angry, fearful, happy, sad in separate sequences) every fifth image (i.e. 1.2 Hz oddball frequency). These distinguishable frequency-tags for neutral and expressive stimuli allowed direct and objective quantification of the expression-categorization responses, needing only four sequences of 60 seconds of recording per condition.

**Results.** Both groups show equal neural synchronization to the general face stimulation and similar neural responses to happy and sad faces. However, the ASD group displays a threat-disadvantage, with significantly reduced responses to angry and fearful faces, compared to TD boys. At the individual subject level, these neural differences allow to predict membership of the ASD-group with an accuracy of 87%. Whereas TD participants show a significantly lower sensitivity to sad faces than to the other expressions, ASD participants show an equally low sensitivity to all the expressions.

**Conclusions.** Our results indicate an emotion-specific processing deficit, instead of a general emotion-processing problem: boys with ASD are less sensitive than TD boys to rapidly and implicitly detect angry and fearful faces. The implicit, fast and straightforward nature of FPVS-EEG opens new perspectives for clinical diagnosis.

**Keywords:** Autism, EEG, Facial emotion processing, FPVS, implicit expression detection

## Introduction

Quick and adequate facial emotion processing is important for successful everyday social interactions, which is a daily struggle for many individuals with autism spectrum disorder (ASD), who are characterized by impaired social communication and interaction, including deficits in non-verbal communicative behavior (American Psychiatric Association, 2014).

### **Facial emotion processing in ASD**

As difficulties in recognizing others' emotions are thought to contribute (partially) to the social deficits typically encountered in ASD (Gaigg, 2012), facial emotion processing has been investigated in an abundance of studies using different research techniques, yet failing to draw consistent conclusions.

The mixed results in terms of group differences in behavioral studies (Lozier, Vanmeter, & Marsh, 2014; Uljarevic & Hamilton, 2013) range from intact emotion processing in ASD groups (Lacroix, Guidetti, Rogé, & Reilly, 2014; Tracy, Robins, Schriber, & Solomon, 2011), over emotion-specific impairments for negative (Whitaker, Simpson, & Roberson, 2017; Wingenbach, Ashwin, & Brosnan, 2017) or positive (Griffiths et al., 2017; Law Smith, Montagne, Perrett, Gill, & Gallagher, 2010) expressions, to a general emotion recognition deficit (Evers, Steyaert, Noens, & Wagemans, 2015; Xavier et al., 2015). These highly variable results may reflect the phenotypic heterogeneity in ASD but may also result from the variability and limited sensitivity of (certain) behavioral measures (Harms, Martin, & Wallace, 2010).

Electroencephalography (EEG) studies investigating the neural underpinnings of facial emotion processing in ASD also describe inconsistent results. Some studies report similar neural patterns in children and adolescents with ASD compared to typically developing controls (TDs) (O'Connor, Hamm, & Kirk, 2005; Wong, Fung, Chua, & McAlonan, 2008), whereas others have reported distinct neural responses in ASD groups (Batty, Meaux, Wittemeyer, Rogé, & Taylor, 2011; Kang et al., 2018; Tye et al., 2014). These neural group differences have been found for all

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3 six basic expressions, as well as for neutral faces (Black et al., 2017; Monteiro, Simões, Andrade, &  
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5 Castelo Branco, 2017).

### 7 **Fast periodic visual stimulation EEG**

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10 Recently, EEG has been combined with Fast Periodic Visual Stimulation (FPVS) to  
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12 selectively capture implicit neural sensitivity to brief changes in facial expressions. FPVS-EEG  
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14 relies on the principle that brain activity synchronizes to a periodically flickering stimulus (Adrian  
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16 & Matthews, 1934), and elicits a brain response at exactly the same frequency (Norcia,  
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18 Appelbaum, Ales, Cottareau, & Rossion, 2015).

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20 Similar to previous studies (Dzhelyova, Jacques, & Rossion, 2017; Poncet, Baudouin,  
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22 Dzhelyova, Rossion, & Leleu, 2019), we applied this principle in a facial expression oddball  
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24 paradigm, by periodically interleaving a rapidly presented stream of neutral faces with expressive  
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26 faces. The periodic presentation at predefined frequency rates generates distinguishable  
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28 frequency-tags for the base and oddball stimuli, allowing direct quantification of the brain  
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30 responses (Liu-Shuang, Norcia, & Rossion, 2014). This makes FPVS-EEG a highly objective  
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32 measure. In addition, the rapid presentation enables a fast acquisition of many neural responses  
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34 indexing expression discrimination in only a few minutes of recording. Furthermore, FPVS-EEG  
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36 allows the collection of reliable discriminative responses not only at a group level, but also at an  
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38 individual level, allowing more insight in the heterogeneity within the autism spectrum.  
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### 42 **Present study**

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45 With the present study, we consolidate and extend the findings of a lower neural  
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47 sensitivity in school-aged boys with ASD to rapidly detect fearful faces, as compared to matched  
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49 TDs (Van der Donck et al., 2019). Here, by applying FPVS-EEG with several facial emotions, we can  
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51 broaden our understanding of the underlying neural nature of facial expression processing in  
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53 ASD: is this lower neural sensitivity emotion-specific (e.g. only for fear) or general (i.e.  
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55 generalizable to multiple expressions)?

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57 We included angry, fearful, sad and happy faces as oddball stimuli in rapidly presented  
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59 streams of neutral faces. These neutral faces act as forward and backward masks for the  
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3 expressive faces, allowing us to selectively isolate the sensitivity to the expressions by putting the  
4 emotional face processing system under tight temporal constraints (Dzhelyova et al., 2017),  
5 without the influences of mechanisms other than fast and automatic emotion extraction.  
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7 Notwithstanding the inconsistencies in the ASD-literature, group differences have most  
8 frequently been reported for negative expressions (Lozier et al., 2014; Uljarevic & Hamilton,  
9 2013). Accordingly, and in line with the lower fear discrimination responses (Van der Donck et al.,  
10 2019), we mainly expect to observe lower neural sensitivity in the ASD group for fearful, angry  
11 and sad faces.  
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20 Importantly, unlike our previous study (Van der Donck et al., 2019), we continuously  
21 changed the identity of the faces (i.e. every image). This impedes expression discrimination based  
22 on low-level visual features, demanding higher-level face processing. Therefore, we expect neural  
23 responses to be mostly visible over higher-level occipito-temporal regions.  
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## 30 Methods

### 31 Participants

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33 Participants were identical to the sample included in Van der Donck et al. (2019): 23 boys  
34 with ASD and 23 TD boys without intellectual disability ( $FSIQ \geq 70$ ), group-wise matched on  
35 chronological age and IQ. Additional behavioural measures (Emotion Recognition Task  
36 (Montagne, Kessels, De Haan, & Perrett, 2007) and Emotion-matching task (Palermo, O'Connor,  
37 Davis, Irons, & McKone, 2013)) showed intact emotion labelling in the ASD group, yet, a mild, but  
38 significant, impairment when matching facial expressions (Van der Donck et al., 2019). See Table  
39 1 for participant demographics and descriptive statistics.  
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50 **[Insert Table 1 about here]**

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52 Children with ASD were recruited via the Autism Expertise Centre at the university  
53 hospital and special need schools. TD participants were recruited via mainstream elementary  
54 schools and sport clubs. Exclusion criteria were the suspicion or presence of a psychiatric,  
55 neurological, learning or developmental disorder (other than ASD or comorbid ADHD in ASD  
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3 participants) in the participant or a first-degree relative. Children in the ASD group had a formal  
4 ASD-diagnosis, established by a multidisciplinary team, according to DSM-IV-TR or DSM-5 criteria  
5 (American Psychiatric Association, 2000, 2014), and scored above 60 (total *T*-score) on the Social  
6 Responsiveness Scale (SRS, parent version (Roeyers, Thys, Druart, De Schryver, & Schittekatte,  
7 2012)). TD boys scored below 60 on the SRS to exclude the presence of substantial ASD symptoms.  
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14 Four children were left-handed (2 TD), and three children reported colour-blindness (1  
15 TD). As this did not affect their neural responses nor their ability to detect the colour changes of  
16 the fixation cross, these participants were not excluded. All participants had normal or corrected-  
17 to-normal visual acuity. Among the participants with ASD, five had a comorbid diagnosis of ADHD  
18 and seven took medication (methylphenidate, aripiprazole).  
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25 The Medical Ethical Committee of the university hospital approved this study. Written  
26 informed consent according to the Declaration of Helsinki was obtained from the participants and  
27 their parents. Participants received a monetary compensation and a small present of their choice.  
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### 31 **Stimuli**

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33 The stimuli comprised full front images of 14 individuals (seven males, seven females)  
34 from the Karolinska Directed Emotional Faces database (Lundqvist, Flykt, & Öhman, 1998), all  
35 displaying neutral, fearful, happy, sad and angry expressions.  
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40 The colored images were set to a size of 300x450 pixels, equalizing 2.54°x3.29° of visual  
41 angle at 80 cm viewing distance, and were placed against a gray background. Mean pixel  
42 luminance and contrast of the faces were equalized during stimulus presentation.  
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### 46 **Design**

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48 The design was similar to previous studies (Dzhelyova et al., 2017; Poncet et al., 2019).  
49 Neutral faces from continuously changing identities (i.e. every image) were displayed through  
50 sinusoidal contrast modulation (0-100%) at a 6 Hz base rate, periodically interleaved with an  
51 expressive oddball stimulus every fifth image (6 Hz/5 = 1.2 Hz oddball rate). At the beginning of  
52 each sequence, a blank screen appeared for a variable duration of 2-5 seconds. After two seconds  
53 of gradually fading in (0-100%), the images were presented for 60 seconds, followed by two  
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seconds of gradually fading out (100-0%). Each of the four conditions (i.e. emotional expressions) was presented in a separate sequence and repeated four times, resulting in 16 sequences – all presented in a randomised order (Figure 1). The facial stimuli varied randomly in size between 80% and 120% of the original size.

**[Insert Figure 1 about here]**

## **Procedure**

Participants were seated in a dimly lit room at 80 cm viewing distance of a LCD 24-in. computer screen, placed at eye level. An orthogonal task was implemented to guarantee attentiveness of the participants. A fixation cross, presented on the nasion of the face, briefly (300 ms) changed color from black to red 10 times within every sequence. The participants had to respond as soon and accurately as possible when noticing the color changes.

### **EEG acquisition**

We recorded EEG activity using a BIOSEMI Active-Two amplifier system with 64 Ag/AgCl electrodes and two additional electrodes as reference and ground electrodes (Common Mode Sense active electrode and Driven Right Leg passive electrode). Vertical eye movements were recorded via one electrode above and one below the right eye. One electrode was placed at the corner of both eyes to record horizontal eye movements. We recorded EEG and electrooculogram at 512 Hz.

### **EEG analysis**

*Preprocessing.* We processed all EEG data using Letswave 6 (<http://www.nocions.org/letswave/>) in Matlab R2017b (The Mathworks, Inc.). We cropped the data into segments of 70 seconds (4 s before and 6 s after each sequence), applied a fourth-order Butterworth bandpass filter (0.1-100 Hz) and resampled the data to 256 Hz. For two participants (1 ASD, 1 TD) who blinked on average more than 2SD above the mean (average number of blinks per second across participants = .20, SD = .24), we applied independent component analysis via the runica algorithm (Makeig, Bell, Jung, & Sejnowski, 1995) and removed the component that accounted for most of the variance. We re-estimated noisy or artifact-ridden channels through

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3 linear interpolation of the three spatially nearest, neighboring electrodes; on average across all  
4 participants, one electrode was interpolated. All data segments were re-referenced to a common  
5 average reference.  
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9 *Frequency domain analysis.* The preprocessed data segments were cropped to contain an  
10 integer number of 1.2 Hz cycles starting immediately after the fade-in until approximately 59.2  
11 seconds (71 cycles). After averaging the data in the time domain – per condition and for each  
12 participant individually – a fast fourier transformation (FFT) was applied, yielding a spectrum  
13 between 0 and 127.98 Hz with a spectral resolution of 0.017 (=1/60s).  
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20 The recorded EEG contains signals at frequencies that are integer multiples (harmonics)  
21 of the base and oddball frequencies. Only the amplitudes at the oddball frequency and its  
22 harmonics (i.e.  $n * F / 5 = 2.4 \text{ Hz}, 3.6 \text{ Hz}, \text{ etc.}$ ) are considered as an index of facial expression  
23 discrimination (Dzhelyova et al., 2017). We used two measures for these responses: (a) signal-to-  
24 noise ratio (SNR), being the amplitude value of a specific frequency bin divided by the average  
25 amplitude of the 20 surrounding frequency bins (Rossion, Prieto, Boremanse, Kuefner, & Van  
26 Belle, 2012), and (b) baseline-corrected amplitudes, calculated by subtracting the average  
27 amplitude level of the 20 surrounding bins from the amplitude of the frequency bin of interest  
28 (Retter & Rossion, 2016). For both measures, these 20 surrounding bins are the 10 bins on each  
29 side of the target frequency bin, excluding the immediately neighboring bins and the two bins with  
30 the most extreme values. We used SNR spectra for visualization because responses at high  
31 frequency ranges may be of small amplitude, but with a high SNR. Baseline correction expresses  
32 responses in amplitudes ( $\mu\text{V}$ ) that can be summed across significant harmonics to quantify the  
33 overall base and oddball response (Retter & Rossion, 2016).  
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50 To define the number of base and oddball harmonics to include in the analyses, we  
51 assessed the significance of the responses at different harmonics by calculating Z-scores – using  
52 the mean and standard deviation of the 20 frequency bins surrounding the bin of interest (Liu-  
53 Shuang et al., 2014) – on the FFT grand-averaged data across all electrodes and across electrodes  
54 in the relevant regions of interest (ROIs; cf. infra). Harmonics were considered significant and  
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3 relevant to include as long as the Z-score for two consecutive harmonics was above 1.64 ( $p < .05$ ,  
4 one-tailed) across both groups and across all conditions (Retter & Rossion, 2016). Following this  
5 principle, we quantified the oddball response as the sum of the responses of four harmonics (i.e.  
6 until  $4F/5 = 4.8$  Hz) and the base response as the summed responses of the base rate and its  
7 following two harmonics ( $2F$  and  $3F = 12$  Hz and  $18$  Hz, respectively).  
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14 In addition, analyses were performed at the individual subject level. We averaged the raw  
15 FFT spectrum per ROI and cropped it into segments centered at the oddball frequency and its  
16 harmonics, surrounded by 20 neighboring bins on each side that represent the noise level. These  
17 spectra were summed across the significant harmonics and transformed into an individual Z-  
18 score for each of the relevant ROIs.  
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24 *Determination of ROIs.* Visual inspection of the topographical maps and identification of  
25 the most responsive regions for emotional oddball and base rate stimulation (Dzhelyova et al.,  
26 2017) led to three ROIs. The left and right occipito-temporal (LOT and ROT) ROI were defined by  
27 averaging for each hemisphere the three channels with the highest summed baseline-corrected  
28 oddball response for each of the expressions (i.e. channels P7, P9 and PO7 for LOT, and P8, P10  
29 and PO8 for ROT). The medial-occipital ROI (MO) was defined by averaging the two channels with  
30 the largest common response at 6 Hz (i.e. channels Iz and Oz).  
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## 40 **Analyses**

### 41 **Quantification of physical stimulus characteristics**

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45 To assess to what extent neural discrimination responses are driven by low-level stimulus  
46 characteristics, we calculated the image-based difference between each of the emotional faces and  
47 each of the neutral faces in three manners. First, after aligning and cropping the faces to remove  
48 artefacts of hair and edges, a basic low-level image comparison was accomplished by computing  
49 the pixel-wise Euclidean distance (Op De Beeck, Wagemans, & Vogels, 2001) across the RGB-levels  
50 for each pair of neutral and expressive images per gender. Second, we created an average face per  
51 expression and gender, and again, calculated the Euclidean distance between the neutral and  
52 expressive faces. Third, to obtain a more higher-level image comparison, all face images were fed  
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3 to a well-established facial expression recognition deep learning neural network, which was pre-  
4 trained on the FER2013 (Goodfellow et al., 2013) dataset consisting of around 36,000 labeled  
5 images (<https://github.com/Wujie1010/Facial-Expression-Recognition.Pytorch>). The output of  
6 the last fully connected layer of this network is a 512-dimensional vector representing the most  
7 discriminating features in the input image. Hence, the mean pairwise Euclidean distance between  
8 these low dimensional representations of neutral faces and each of the four expression categories  
9 was calculated.

### 18 Statistical analyses

20 For statistical group-level analyses of the baseline-corrected amplitudes in each ROI, we  
21 applied a linear mixed-model ANOVA (function 'lmer' in R (Bates, Maechler, Bolker, & Walker,  
22 2015)), fitted with restricted maximum likelihood. Separate models were fitted with either the  
23 base or the oddball rate response as the dependent variable. *Expression* (anger, fear, happiness,  
24 sadness) and *ROI* (LOT, ROT, MO, and LOT, ROT for base and oddball responses, respectively) were  
25 added as fixed within-subject factors, and *Group* (ASD vs. TD) as a fixed between-subject factor.  
26 To account for the repeated testing, we included a random intercept per participant. Degrees of  
27 freedom were calculated using the Kenward-Roger method. Posthoc contrasts were tested for  
28 significance using a Bonferroni correction for multiple comparisons, by multiplying the p-values  
29 by the number of comparisons. All assumptions in terms of linearity, normality and constant  
30 variance of residuals were verified and met for all linear mixed-model ANOVAs.

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MO base rate data points of one participant were discarded due to extreme outliers  
(amplitude > 15  $\mu$ V). All analyses were performed with and without inclusion of colorblind  
children, ASD children with comorbidities, and ASD children on medication. As  
inclusion/exclusion did not influence the results, we report the analyses with all children  
included.

We also evaluated the significance of the expression-discrimination responses for all  
participants individually. Responses were considered significant if the z-score of the oddball  
frequency bin in the LOT or ROT region exceeded 1.64 (i.e.  $p < .05$ ; one-tailed).

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3 We performed a linear discriminant analysis (LDA) on the EEG data to classify participants  
4 as either belonging to the ASD or TD group. The input vectors comprised the most discriminative  
5 outcome measures, i.e. the response amplitudes to angry and fearful faces in the LOT and ROT  
6 regions. Assumptions of multivariate normal distribution and equal covariance matrices for both  
7 groups were checked and met. The competence of the classification model was assessed by means  
8 of permutation tests, which are robust for small sample sizes and possible over-fitting.  
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16 For performance on the fixation cross change detection task, assumptions of normality  
17 and homoscedasticity were checked using a Shapiro-Wilk and Levene's test, respectively. The  
18 assumption of homogeneous variances was met. Due to non-normal distribution of the data, we  
19 applied a Mann-Whitney U test. Due to equipment failure, data on this task is missing for two TD  
20 participants.  
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## 26 27 28 Results

### 29 30 31 **Characterization of the stimulus properties**

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33 For each of the four emotional expressions, the (average) difference with the neutral facial  
34 expressions is depicted in Figure 2. Results of the raw pixel data show that the Euclidian distance  
35 towards the neutral faces is largely similar for all expressions (Figure 2a). However, the two  
36 higher-level measures (average faces (Figure 2b) and the deep learning neural network face  
37 differentiation (Figure 2c)) reveal that especially the happy faces are the most distinctive from the  
38 neutral faces.  
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46 **[Insert Figure 2 about here]**

### 47 48 49 **Fixation cross change detection task**

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51 Results suggest a similar level of attention to the screen throughout the experiment for  
52 both groups, with equal accuracies ( $M_{ASD} = 90\%$ ,  $SD = 12$ ;  $M_{TD} = 95\%$ ,  $SD = 5$ ;  $W = 209$ ,  $p = .46$ ) and  
53 response times ( $M_{ASD} = .057$  s,  $M_{TD} = 0.54$  s;  $W = 271$ ,  $p = .50$ ) on this orthogonal task.  
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## General visual base rate responses

Robust brain responses were visible at 6 Hz base rate and harmonics, mostly distributed over medial-occipital sites. Figure 3 shows the highly significant main effect of *ROI* ( $F(2,481) = 547.49, p < .001$ ), with highest responses in the MO region and lowest responses in the LOT region ( $t(481)_{\text{LOT-MO}} = -30.98, t(480)_{\text{LOT-ROT}} = -5.26, t(481)_{\text{ROT-MO}} = -25.76$ , all  $p_{\text{Bonferroni}} < .001$ ). The absence of any other significant main and/or interaction effect indicates a similar synchronization to the flickering stimuli in both groups (all  $p > .17$ ).

**[Insert Figure 3 about here]**

## Expression discrimination responses

All four expressions elicited clear expression-discrimination responses at the oddball frequency and its harmonics (Figure 4), clearly distributed over lateral occipito-temporal sites.

**[Insert Figure 4 about here]**

Statistical analysis of the expression-discrimination responses revealed main effects of *Group* ( $F(1,44) = 9.66, p = .003$ ) and *Expression* ( $F(3,308) = 10.29, p < .001$ ), which were further qualified by a significant interaction between *Group* and *Expression* ( $F(3,308) = 4.58, p = .004$ ). Only angry ( $t(190)_{\text{ASD-TD}} = -3.86, p_{\text{Bonferroni}} = .003$ ) and fearful ( $t(190)_{\text{ASD-TD}} = -3.29, p_{\text{Bonferroni}} < .05$ ) faces elicited significantly higher responses in the TD compared to the ASD group. No group differences were found for happy and sad faces (all  $p_{\text{Bonferroni}} > .98$ ). Furthermore, the effect of expression only applied to the TD group, with significantly lower responses to sad faces, compared to the three other expressions ( $t(308)_{\text{anger-sad}} = 6.15, p_{\text{Bonferroni}} < .001$ ;  $t(308)_{\text{fear-sad}} = 4.01, p_{\text{Bonferroni}} = .001$ ;  $t(308)_{\text{happy-sad}} = 3.34, p_{\text{Bonferroni}} < .05$ ). In addition, the main effect of *ROI* ( $F(1,308) = 17.54, p < .001$ ) revealed significantly higher responses in ROT compared to LOT region. See Figure 5 for all significant effects.

Although not the scope of this study, an additional analysis to specifically check for a threat-bias showed significantly higher responses to threatening (anger and fear) versus non-threatening (happiness and sadness) stimuli ( $F(1,316) = 10.25, p = .002$ ), but only in the TD group

( $F(1,316) = 11.68, p < .001$ ;  $t(316)_{\text{threat-nonthreat}} = -4.68, p_{\text{Bonferroni}} < .0001$ ), not in the ASD group ( $t(316)_{\text{threat-nonthreat}} = 0.153, p_{\text{Bonferroni}} > .05$ ).

**[Insert Figure 5 about here]**

Expression-discrimination responses at the individual subject level are displayed in Table 2, revealing that the majority of participants did show robust individual responses.

**[Insert Table 2 about here]**

Despite the abundance of studies investigating biomarkers for ASD, a clinically applicable biomarker, reliable at the individual level, has not yet been developed (Mcpartland, 2016, 2017). We analyzed how well neural expression-discrimination responses for fearful and angry faces can predict group membership of our participants. By applying a leave-one-out cross validation, we assessed how well the LDA classification generalizes, revealing that 87% of the participants with ASD could be identified correctly. The overall accuracy of the LDA model to predict group membership was estimated at 76%. Figure 6 shows the linear differentiation between both groups, based on the full dataset. The robustness of the classification model was statistically assessed by carrying out 10,000 permutations, demonstrating a likelihood of obtaining the observed accuracy by chance of  $p = .002$ .

**[Insert Figure 6 about here]**

## Discussion

Using FPVS-EEG, we assessed whether there is a difference in the neural sensitivity of school-aged boys with and without ASD to implicitly detect briefly presented facial expressions in a stream of neutral faces, and whether this differential sensitivity would be general (all expressions) or emotion-specific.

Our results indicate an equal neural synchronization to the general face stimulation and similar neural expression-discrimination responses for happy and sad faces, yet, a lower implicit sensitivity to angry and fearful faces in boys with ASD, as compared to TD boys. For the TD boys, fearful, angry and happy faces elicited stronger responses than sad faces. Given the equal

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3 performances of both groups on the orthogonal fixation cross task throughout all conditions, there  
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5 is no evidence to attribute differences in neural responses across conditions or across groups to  
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7 less motivation or attention of the participants.  
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### 10 **Similar topographical maps in boys with and without ASD**

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12 The base and oddball stimuli elicited neural responses with similar topographical  
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14 distributions in both groups. The base rate responses were mostly recorded over the middle  
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16 occipital sites, suggesting the dominance of low-level visual processing (Norcia et al., 2015). In  
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18 addition, both groups displayed more lateralized topographical activity patterns for the  
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20 expression-discrimination responses, suggesting the use of a similar emotional face processing  
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22 network in ASD and TD boys. However, considering the progressive development of typical facial  
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24 expression processing capacities during childhood, potential group differences in topography may  
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26 still appear in adolescence or adulthood.  
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30 In our previous study investigating fear discrimination responses within a stream of faces  
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32 with a single identity, the neural oddball responses were equally distributed across medial-  
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34 occipital and occipito-temporal sites (Van der Donck et al., 2019). Here, however, the expression-  
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36 discrimination responses are clearly distributed over occipito-temporal sites, with a right  
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38 hemisphere advantage, and thereby resemble the topographical patterns of adults (Dzhelyova et  
39  
40 al., 2017). These responses reflect the larger involvement of higher-level visual areas, probably  
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42 induced by the continuously changing identities, which impedes low-level discriminatory  
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44 processing to detect rapid changes in expression. Yet, even though also the ASD boys were  
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46 forced to mobilize a high-level processing approach with the current paradigm, this did not  
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48 necessarily entail an equivalent high-level processing performance, as evidenced by the  
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50 reduced neural sensitivity to changes in fearful and angry faces.  
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54 In adult populations, similar EEG paradigms elicited distinct topographical maps for  
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56 different facial expressions (Dzhelyova et al., 2017; Poncet et al., 2019), suggesting the activation  
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58 of (partially) distinct neural populations. Unlike these adult findings, the children's EEG responses  
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60 did not show these separate spatial signatures for different expression changes. Again, this may

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3 point towards the ongoing developmental specialization and refinement of the neural systems  
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5 involved in emotion processing (Leppänen & Nelson, 2009).  
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### 7 **Reduced neural sensitivity to expressive faces in ASD is emotion-** 8 **specific** 9

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12 We included four basic expressions (anger, fear, happiness, sadness) in our paradigm to  
13 assess the generalizability of the emotion processing impairment in ASD. Against a background of  
14 highly variable research findings (Black et al., 2017; Harms et al., 2010), we particularly expected  
15 a more pronounced impairment for discrimination of negative expressions.  
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21 The significant individual-subject discrimination responses in a large majority of  
22 participants across both groups indicate that boys with and without ASD can process facial affect  
23 fast and unintentionally, while attending faces without specifically focusing on the emotional  
24 expressions (Vuilleumier & Righart, 2011), allowing implicit detection of rapid emotion-changes.  
25 However, the response-amplitudes indicate a substantially reduced emotion-specific neural  
26 sensitivity in the ASD group: in contrast to studies describing a general emotion-processing deficit  
27 in ASD, we only observed selectively lower responses to angry and fearful faces, as compared to  
28 TDs. These findings confirm and extend our previously reported results (Van der Donck et al.,  
29 2019).  
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40 A threat-bias has often been reported in TD individuals, and has been related to  
41 evolutionary survival strategies (Hedger, Gray, Garner, & Adams, 2016; Lyyra, Hietanen, &  
42 Astikainen, 2014). The highest responses to anger and fear discrimination in the TD group do  
43 suggest a threat-detection advantage. The brain responses of the boys with ASD, however, do not  
44 point in that direction, despite reports of an anger-detection effect in ASD populations as well  
45 (May, Cornish, & Rinehart, 2016; Rosset et al., 2011). The threat-related content of the facial  
46 stimuli might selectively have boosted the oddball detection in the TD group only (Leung, 2019;  
47 Lyyra, 2014), resulting in the significant amplitude differences that allow a correct classification  
48 of 87% of the participants with ASD.  
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3 We found no group effect for the discrimination of sad faces. However, given the  
4 significantly lower detection responses in the TD group, possible floor effects may have masked  
5 potential group differences. Sadness has been found to be a difficult emotion to distinguish from  
6 neutrality (Gao & Maurer, 2010), possibly because it does not display very prominent, emotion-  
7 characteristic facial features (Calvo & Nummenmaa, 2008). This, combined with the complexity of  
8 continuously changing identities of the faces, might make it harder for children with and without  
9 ASD to detect the rapid changes to sadness in the blink of an eye.  
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18 Also happy faces elicited similar responses in both groups. Although recent reviews report  
19 differences in neural responses to happy faces (Black et al., 2017; Monteiro et al., 2017), happiness  
20 is recognized the earliest and easiest, needing only minimal signals (Whitaker et al., 2017). Intact  
21 detection of rapidly presented happy emotional faces in boys with ASD should therefore not be  
22 surprising.  
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### 29 **The emotional content of the faces drives the neural responses**

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31 One might argue that the neural expression-discrimination responses simply reflect the  
32 low-level perceptual stimulus-based differences between base and oddball stimuli. Here, we  
33 present convincing evidence that these responses are determined by higher-level socio-affective  
34 processing abilities, at least in the TD participants. Indeed, if responses had been fully determined  
35 by stimulus properties, we would expect that the pattern of neural expression-discrimination  
36 responses would mirror the pattern of stimulus-based differences for each of these emotions  
37 relative to the neutral baseline. However, overall, the fine-grained evaluation of the stimulus  
38 properties demonstrated that this is not the case, because here the happy faces are singled out as  
39 the most distinctive. Accordingly, pertaining to the oddball responses in the TD group, the pattern  
40 of the neural amplitudes for the facial expressions does not match the stimulus differences, as  
41 here the angry and fearful faces yielded the highest responses. This suggests that these amplitude  
42 differences are caused by higher-level socio-emotional relevance and saliency, possibly within the  
43 context of an evolutionary threat-superiority effect. In the ASD participants, however, the brain  
44 responses seem to be more in line with the intrinsic stimulus characteristics (yet, without  
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3 significant amplitude differences between the different emotions). Accordingly, contrary to the  
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5 TD group, this might suggest a stronger reliance on the physical stimulus features instead of the  
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7 emotional meaning of the stimulus.  
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### 10 **Limitations and future research**

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12 In the present study, we only included four basic expressions. As children will be  
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14 confronted with a wider range of facial emotions in daily life, adding also surprise and disgust,  
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16 and maybe even more complex or more subtle expressions, to the paradigm may increase the  
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18 ecological validity and give us a broader understanding of the abilities of individuals with ASD to  
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20 automatically and rapidly process socio-affective details.  
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23 Since studies have revealed a female advantage for facial expression processing, also in  
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25 children (McClure, 2000), it might be interesting to apply this paradigm in girls. Girls with ASD  
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27 tend to be better at masking their social difficulties than boys with ASD (Hull, Mandy, & Petrides,  
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29 2017), possibly concealing facial expression processing differences between girls with ASD and  
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31 TD girls on an explicit behavioral level. However, neural differences to rapidly detect facial  
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33 emotions might be uncovered with this implicit paradigm.  
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36 Our results confirm that FPVS-EEG is a highly sensitive and objective measure to detect  
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38 and quantify even small responses at an individual level, in a short amount of time, thanks to the  
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40 rapid, frequency-tagged stimulus presentation. Only four sequences of 60 seconds are required to  
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42 obtain reliable implicit neural expression-discrimination responses. With all its advantages, FPVS-  
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44 EEG is a well-suited technique to study populations that are otherwise difficult to include in  
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46 research because of cognitive or verbal constraints. Furthermore, the promising classification  
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48 results of the LDA demonstrate the potential of this approach to serve as a biomarker for socio-  
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50 communicative deficits. However, more research in (clinical) samples with a different IQ and/or  
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52 age is needed to understand the full potential of FPVS-EEG.  
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## Conclusion

Our results indicate an emotion-specific processing deficit instead of a general emotion-processing problem in ASD. Boys with ASD are less sensitive to rapidly and implicitly detect angry and fearful faces among a stream of neutral faces. There is no evidence of a negative emotion processing deficit in ASD, as their discrimination responses to sad faces were similar to those of TD boys. However, the overall lower responses to sadness in the TD group, as compared to the other expressions, may have concealed possible group differences. Additionally, the responses elicited by happy faces were equal in both groups.

The implicit and straightforward nature of FPVS-EEG, as well as the strength of the effects, pave the way to include populations that are often excluded from research due to cognitive or verbal constraints.

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## Correspondence to

Stephanie Van der Donck

Center for Developmental Psychiatry, Department of Neurosciences, KU Leuven

Kapucijnenvoer 7, 3000 Leuven, Belgium

Tel.: +32 494 80 91 96

Email: [stephanie.vanderdonck@kuleuven.be](mailto:stephanie.vanderdonck@kuleuven.be)

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For Peer Review

**Key points**

- Behavioral and ERP findings on facial emotion processing in autism reveal mixed results, ranging from intact processing, over emotion-specific impairments to a general deficit.
- Fast periodic visual stimulation EEG allows to rapidly and robustly quantify an individual's sensitivity for subtle socio-communicative facial cues.
- School-aged boys with autism show a substantially reduced neural sensitivity, selectively for the rapid and implicit categorization of angry and fearful faces.
- Neural responses to angry and fearful faces allow a correct prediction of group membership of 76%.
- This fast, objective, and implicit neural measure allows assessing populations that are often excluded from research due to cognitive or verbal constraints and shows great potential to serve as a biomarker for socio-communicative deficits.

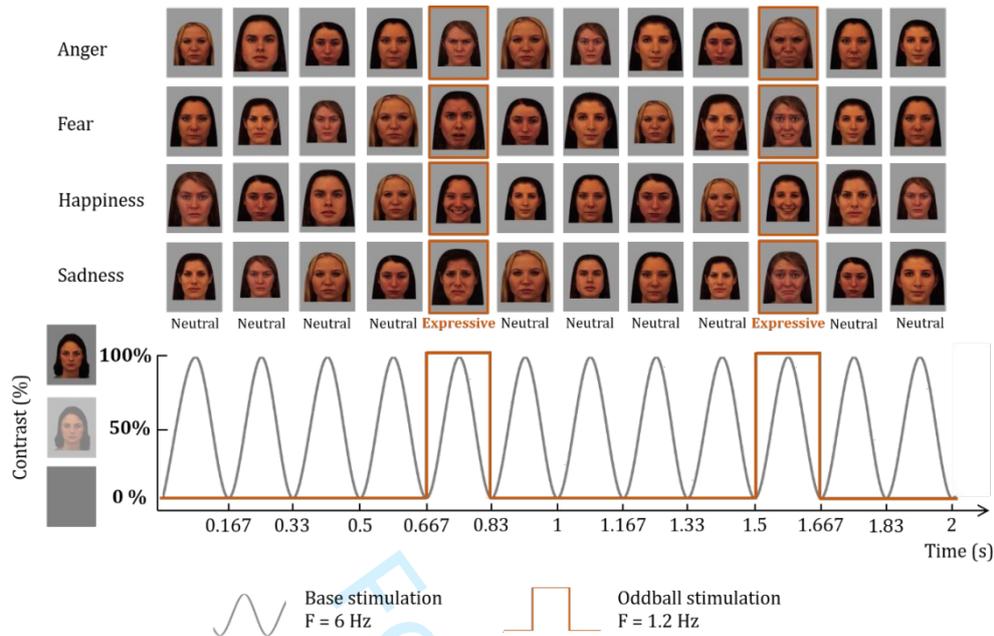
## Tables and figures

Measures	ASD group ( <i>N</i> = 23)	TD group ( <i>N</i> = 23)	Statistical comparison <sup>a</sup>	<i>p</i>
	Mean (SD)	Mean (SD)		
Age (years)	10.5 (1.4)	10.5 (1.4)	<i>t</i> (44) = .11	.91
Verbal IQ <sup>b</sup>	107 (11)	112 (11)	<i>t</i> (44) = -1.44	.16
Performance IQ <sup>b</sup>	104 (15)	108 (10)	<i>t</i> (44) = -1.16	.25
Full-scale IQ <sup>b</sup>	106 (9)	110 (9)	<i>t</i> (44) = -1.68	.10
Social Responsiveness Scale	85.13 (11.7)	41.65 (6)	<i>z</i> = 3.39	.000***
T score Total				
Emotion Recognition Task (% correct)	55.9 (32)	56.8 (34)	<i>F</i> (1,43) = 0.11	.74
Emotion-matching task (% correct)	63.1 (11)	69.4 (6.8)	<i>t</i> (37) = -2.29	.028*

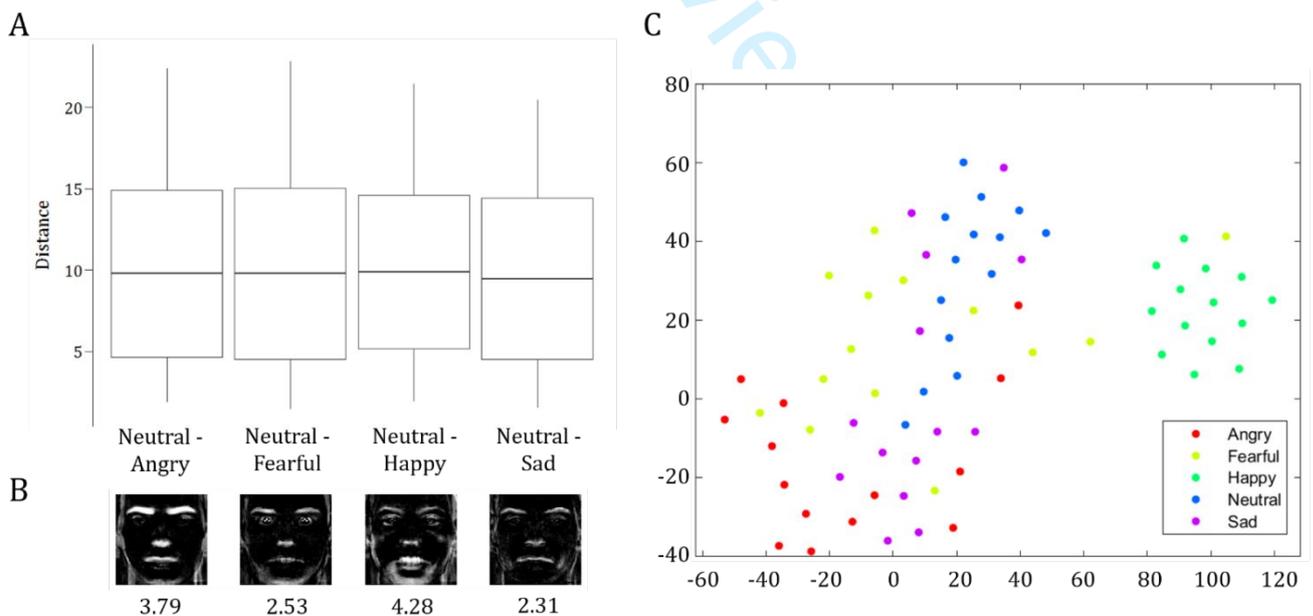
**Table 1.** Characteristics of the participant groups. <sup>a</sup>Statistical analyses using two-sample *t* test or Kolmogorov-Smirnov Z test (based on assumptions of normality and equal variances) or linear mixed-model ANOVA. <sup>b</sup>Assessed via an abbreviated version (Sattler, 2001) of the Wechsler Intelligence Scale for Children, third edition (WISC-III-NL; (Wechsler, 1992)), with subscales Picture Completion, Block Design, Similarities, and Vocabulary. \* *p* < .05 \*\*\* *p* < .001

	ASD ( <i>N</i> = 23)	TD ( <i>N</i> = 23)
Anger	18	22
Fear	18	21
Happiness	21	19
Sadness	17	15

**TABLE 2.** Number of individuals displaying significant emotion-discrimination responses for each of the conditions, based on statistical analysis of the individual subject data (i.e. *z*-scores > 1.64 (*p* < .05)).

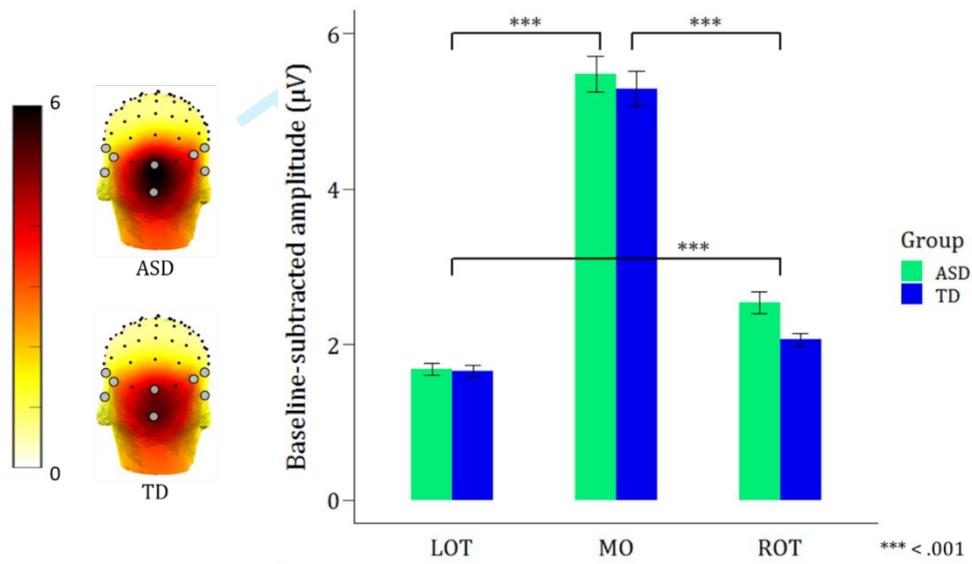


**Figure 1.** Fast periodic visual stimulation oddball paradigm: neutral faces are presented sequentially at a fast 6 Hz base rate, periodically interleaved with an expressive face – anger, fear, happiness, sadness – every fifth image (1.2 Hz oddball rate). The identity of the faces changes every image. Stimuli shown here: AF02, AF07, AF13, AF15, AF22, AF27, AF29 (Lundqvist et al., 1998).

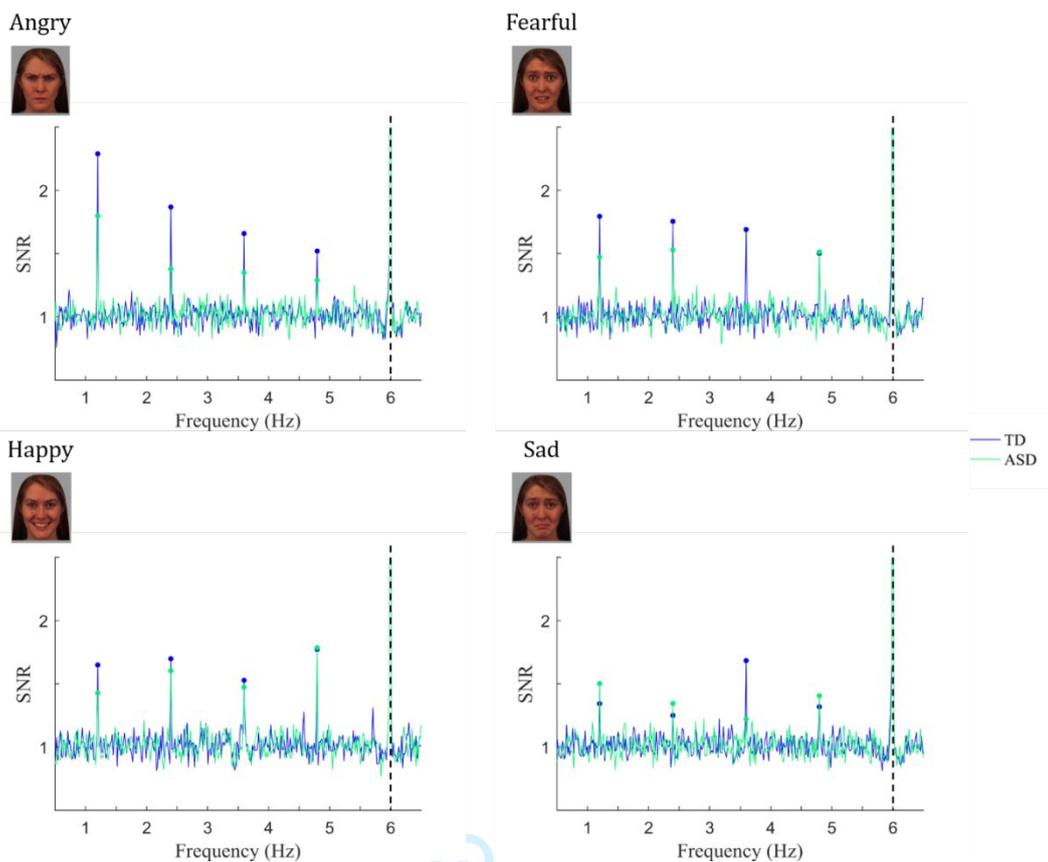


**Figure 2.** Physical characterization of the expressive versus neutral faces. **A.** Pixel-wise Euclidean distances (boxplots, based on mean  $\pm$  1SD, whiskers reflect the minimum and maximum

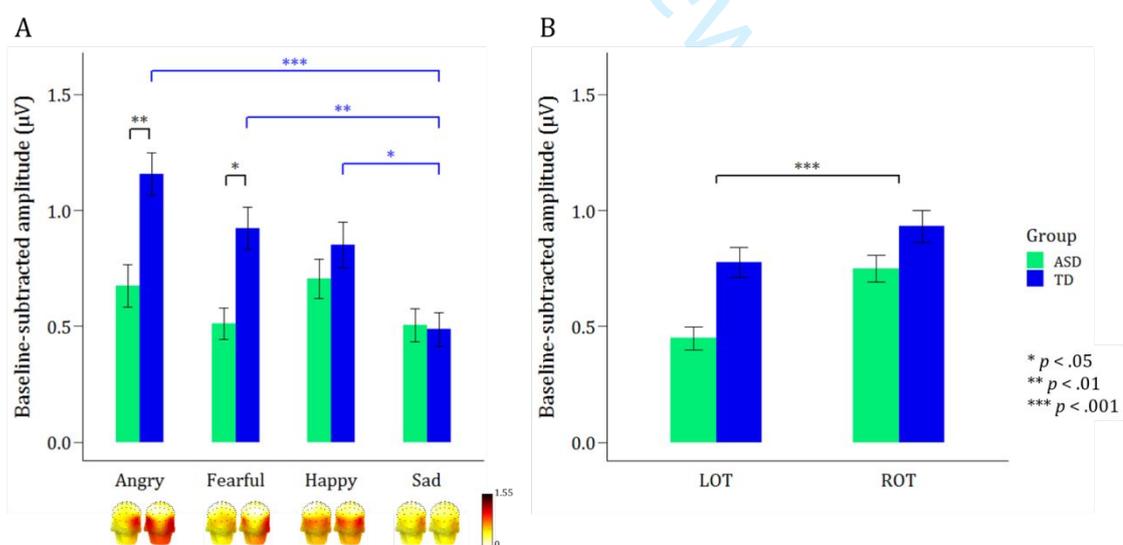
distance). **B.** Visualization and values of the mean Euclidean distance between the averaged neutral face and the average of each of the expressive faces. Lighter shadings indicate the face parts that are the most different from the neutral face. **C.** 2D visualization of the embedding space for all the face images, obtained from their 512-dimensional representations according to t-SNE algorithm (van der Maaten & Hinton, 2008). Mean Euclidean distances between neutral and sad, fearful, angry, or happy faces in this latent space equal 3.25, 4.31, 5.63, and 7.50, respectively.



**Figure 3.** Similar general visual responses to faces in ASD and TD. **Left:** Scalp distribution of the base rate responses. The three most leftward and three most rightward open circles constitute left and right occipito-temporal (LOT and ROT) regions, respectively. The two central open circles constitute the medial-occipital region (MO). **Right:** Summed baseline-subtracted amplitudes across the three harmonics of the base rate for each of the three ROIs, displaying a main effect of ROI. Error bars indicate standard errors of the mean.

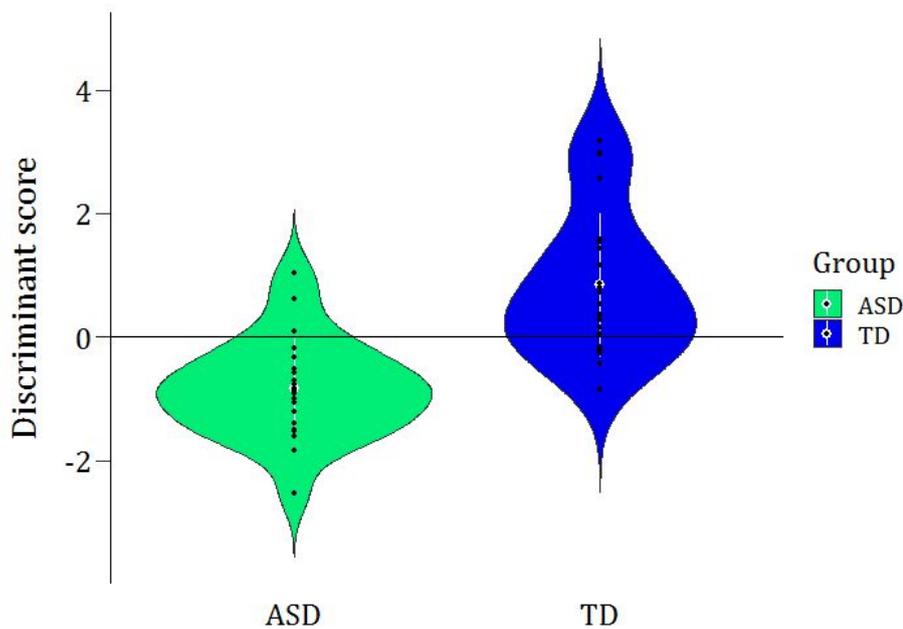


**Figure 4.** SNR-spectra visualizing the expression-discrimination responses, averaged over LOT and ROT regions, for each of the expressions and both groups. The significant first four harmonics are displayed; the dashed line indicates the 6 Hz base rate response.



**Figure 5.** Bar graphs of the summed baseline-subtracted amplitudes of both groups for the first four oddball harmonics (until 4.8 Hz) displaying mean expression-discrimination responses.

Error bars reflect standard errors of the mean. **A.** Scalp topographies and bar graphs (averaged across LOT and ROT regions) displaying the mean responses per expression. The *Group x Expression* interaction shows significantly lower responses in the ASD versus TD group for angry and fearful faces (black asterisks), and an overall lower response to sad faces as compared to the other expressions in TDs (blue asterisks). **B.** The main effect of *ROI* revealed a right hemisphere advantage, with significantly higher responses in ROT versus LOT region.



**Figure 6.** Violin plot with the decision boundary of the LDA classifier (horizontal line) reflecting the differentiation between both participant groups. Based on the responses to facial anger and fear, the LDA classifies 20/23 participants with ASD and 17/23 TD participants correctly, when fitted to the full dataset. Mean  $\pm$  1 SD is shown in white.