Brain Imaging and Behavior DOI: 10.1007/s11682-021-00626-1

The structural neural correlates of atypical facial expression recognition in autism spectrum disorder

Running title: Emotion recognition in autism

Author names and author affiliation:

Shota Uono[1 *], Wataru Sato[2], Takanori Kochiyama[3], Sayaka Yoshimura[1], Reiko Sawada[1,4], Yasutaka Kubota[5], Morimitsu Sakihama[6], Motomi Toichi[1,4]

1 Graduate School of Medicine, Kyoto University, Shogoin-Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan.

2 Kokoro Research Center, Kyoto University, 46 Shimoadachi, Sakyo-ku, Kyoto 606-8501, Japan.

3 ATR Brain Activity Imaging Center, 2-2-2, Hikaridai, Seika-cho, Souraku-gun, Kyoto 619-0288, Japan

4 The Organization for Promoting Neurodevelopmental Disorder Research, 40 Shogoin-Sannocho, Sakyo-ku, Kyoto 606-8392, Japan

5 Health and Medical Services Center, Shiga University, 1-1-1, Baba, Hikone, Shiga 522-8522, Japan

6 Rakuwa-kai Otowa Hospital, 2 Otowa Chinji-cho, Yamashina-ku, Kyoto 607-8062, Japan

[*]Corresponding author:

Shota Uono, Department of Developmental Disorders, National Institute of Mental Health, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-higashi, Kodaira, 187-8551 Japan.

E-mail: uono@ncnp.go.jp

Abstract

Previous studies have demonstrated that individuals with autism spectrum disorder (ASD) are worse at recognizing facial expressions than are typically developing (TD) individuals. The present study investigated the differences in structural neural correlates of emotion recognition between individuals with and without ASD using voxel-based morphometry (VBM). We acquired structural MRI data from 27 high-functioning adults with ASD and 27 age- and sex-matched TD individuals. The ability to recognize facial expressions was measured using a label-matching paradigm featuring six basic emotions (anger, disgust, fear, happiness, sadness, and surprise). The behavioural task did not find deficits of emotion recognition in ASD after controlling for intellectual ability. However, the VBM analysis for the region of interest showed a positive correlation between the averaged percent accuracy across six basic emotions and the grey matter volume of the right inferior frontal gyrus in TD individuals, but not in individuals with ASD. The VBM for the whole brain region under each emotion condition revealed a positive correlation between the percent accuracy for disgusted faces and grey matter volume of the left dorsomedial prefrontal cortex in individuals with ASD, but not in TD individuals. The different pattern of correlations suggests that individuals with and without ASD use different processing mechanisms for recognizing others' facial expressions.

Keywords: autism spectrum disorder; dorsomedial prefrontal cortex; facial expression recognition; inferior frontal gyrus; voxel-based morphometry

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by qualitative impairments in social communication as well as repetitive and stereotyped behaviour and restricted interests (American Psychiatric Association [APA], 2013). One of the distinctive features is a difficulty communicating through facial expressions to regulate social interactions. A meta-analysis also showed that individuals with ASD are less accurate at recognizing facial expressions than are typically developing (TD) individuals (Uljarevic & Hamilton, 2013). Previous studies have demonstrated that facial expressions enhance social cognitive functions, such as joint attention (Uono et al., 2009; de Jong et al., 2008) and imitation (Grecucci et al., 2013), in TD individuals but not in individuals with ASD. Other studies have suggested that the degree of emotion recognition impairment is associated with the severity of autistic symptoms (Humphrey et al., 2007; Uono, Sato, & Toichi, 2011, 2013; Wallace et al., 2011) and functional outcomes (García-Villamisar et al., 2010; Otsuka, Uono, Yoshimura, Zhao, & Toichi, 2017; Wallace et al., 2011). These findings indicate a need to elucidate a group difference in the underlying neurocognitive mechanisms for emotion recognition between individuals with and without ASD and to explain individual differences among individuals with ASD.

A growing number of functional magnetic resonance imaging (MRI) studies have demonstrated specific brain regions associated with emotion recognition in TD individuals. Meta-analysis studies have indicated that the superior temporal sulcus (STS) region (Allison, Puce, & McCarthy, 2000) and prefrontal regions, including the inferior frontal gyrus (IFG) and amygdala, become engaged in the processing of emotional facial expressions (Dricu & Fruhholz, 2016; Fusar-Poli et al., 2009; Sabatinelli et al., 2011). It has been suggested that these regions are associated with specific stages of processing in emotion recognition. The STS region is involved in perceptual processing of dynamic aspects of faces (Haxby, Hoffman, & Gobbini, 2000).

The IFG matches the visual representation of another's action with one's own motor representations and allows an understanding of another's intentions (Gallese, Keysers, & Rizzolatti, 2004; Rizzolatti, Fogassi, & Gallese, 2001). The amygdala extracts the emotional meaning from biologically salient stimuli (Calder, Lawrence, & Young, 2003). The importance of these regions in emotion recognition has also been supported by lesion and stimulation studies (Adolphs, Tranel, Damasio, & Damasio, 1994; Dal Monte et al., 2013; Pitcher, 2014; Shamay-Tsoory, Aharon-Peretz, & Perry, 2009).

Functional MRI studies in individuals with ASD have revealed atypical activation in brain regions where TD individuals recruit for emotion recognition. When they process facial expressions implicitly and explicitly, multiple studies have demonstrated that individuals with ASD show reduced activation in brain regions, including the STS region (Kim et al., 2015; Pelphrey, Morris, McCarthy, & Labar, 2007; Sato, Toichi, Uono, & Kochiyama, 2012; Spencer et al., 2011; Wicker et al., 2008), the IFG (Dapretto et al., 2006; Kleinhans et al., 2010; Ogai et al., 2003; Schulte-Rüther et al., 2011; Wicker et al., 2008), and the amygdala (Kim et al., 2015; Pelphrey, Morris, McCarthy, & Labar, 2007; Sato, Toichi, Uono, & Kochiyama, 2012; Spencer et al., 2011; Wicker et al., 2008), although other studies have reported heightened activation in these regions (Critchley et al., 2000; Dalton et al., 2005; Kim et al., 2015; Monk et al., 2010; Weng et al., 2011). A recent meta-analysis showed that individuals with ASD show hypo-activation in the amygdala when they process emotional face versus non-face information (Aoki, Cortese, & Tansella, 2015). Interestingly, some studies have reported enhanced brain activation in parietal and occipital regions, and considered them to reflect compensatory processing (Dapretto et al., 2006; Hubl et al., 2003; Kleinhans et al., 2010; Wang, Dapretto, Hariri, Sigman, & Bookheimer, 2004), depending on the effective processing of local visual information in individuals with ASD (Samson, Mottron, Soulieres, & Zeffiro, 2012). Thus, previous functional MRI studies suggest that atypical function in social brain regions and compensatory function

involved in other brain regions can explain the individual difference in emotion recognition in individuals with ASD.

An investigation of brain structures can provide complementary findings of the neural correlates underlying altered emotion recognition. Voxel-based morphometry (VBM) studies have demonstrated that the volumes of specific brain regions reflect individual differences in visual and cognitive abilities (Kanai & Rees, 2011). This approach enables an investigation of the association between task performance and structures in the entire brain, and it elucidates neural correlates of emotion recognition in individuals with ASD, given the possibility that a different processing strategy induces a different effect on the experimental and baseline tasks in functional MRI studies. Research on potential associations between emotion recognition and brain structure will provide insight into the roles of regions identified and associated cognitive processes in the ability to recognize facial expressions in typical and atypical individuals.

Structural imaging studies in TD individuals have identified associations between the percent accuracy for emotion recognition and grey matter (GM) volume in the IFG, STS region (Uono et al., 2017), and amygdala (Dziobek, Fleck, Rogers, Wolf, & Convit, 2006; Zhao, Yan, Chen, Zuo, & Fu, 2013). One study of structural individual differences in ASD used a region of interest (ROI) approach for the amygdala. That study revealed a significant association with restricted and repetitive behaviour but not with emotion recognition (Dziobek et al., 2006), suggesting that the association between emotion recognition and GM volume differs between individuals with and without ASD. Some meta-analyses of VBM studies reported a volume increase or decrease in the IFG (DeRamus & Kana, 2015; Via, Radua, Cardoner, Happé, & Mataix-Cols, 2011), the STS region (Cauda et al., 2011; Yang et al., 2016), and the amygdala (Cauda et al., 2011; Via et al., 2011), as well as in other brain regions. Recent studies using multivariate morphometry analysis have revealed GM volumetric changes at the

network level in individuals with ASD. Grecucci et al. (2016) demonstrated morphometric changes in the brain network consisting of the broad temporal cortex and the inferior frontal cortex; these changes were associated with the degree of social impairment and stereotypical behaviour. Kochiyama et al. (2017) demonstrated an overall volume reduction in the abovementioned social brain regions (i.e., IFG, STS, and amygdala) in high-functioning individuals with milder ASD. Based on these findings, we focused on the pattern of correlation between the ability to recognize facial expressions and GM volume of the bilateral IFG, STS region, and amygdala in high-functioning individuals with and without ASD.

The present study acquired structural MRI data from 27 high-functioning adults with ASD who showed relatively mild symptoms and 27 age- and sex-matched TD controls. The ability to recognize facial expressions was measured using a label-matching paradigm featuring six basic emotions. Using VBM, we examined whether the pattern of correlation between the GM volume in **the social brain regions** (bilateral IFG, STS region, and amygdala) and emotion recognition performance was different between the groups.

2. Materials and Methods

2.1 Participants

Twenty-seven participants with ASD, above 18 years of age and with normal intellectual abilities, were included (6 women and 21 men; mean (M) age = 27.4 years, *SD* = 8.6). The participants in the ASD group were outpatients who had been referred to the Division of Human Health Science of Kyoto University Graduate School of Medicine and Rakuwakai Otowa Hospital due to **social challenges**. The diagnosis was **initially based on** the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) (**APA**, 2000), via a stringent procedure in which every ASD diagnostic criterion was investigated in interviews with participants and

their parents by at least two psychiatrists with expertise in neurodevelopmental disorders. Diagnoses of ASD were accepted in the confirmed absence of disagreement. The group consisted of 14 (3 women and 11 men) individuals with Asperger's disorder and 13 (3 women and 10 men) with pervasive developmental disorder not otherwise specified (PDD-NOS). **We confirmed that all of the participants in the ASD group also met the diagnostic criteria for ASD under the DSM-5 (APA, 2013).** IQ was measured using the Japanese version of the Wechsler Adult Intelligence Scale, third edition [full-scale IQ (FIQ): M = 109.7, SD = 13.1; verbal IQ (VIQ): M = 112.2, SD = 14.4; performance IQ (PIQ): M = 104.6, SD = 14.9]. The mean FIQ scores of all participants in the ASD group were within the normal range (> 85). The exclusion criteria were a history of or current psychotic disorder, substance or alcohol abuse, traumatic head injuries, or any other neurological conditions affecting brain function. None of the participants had neurological or psychiatric problems, other than those associated with ASD, nor were any participants taking medications.

Symptom severities were assessed using the Childhood Autism Rating Scale (CARS) (Schopler, Reichler, & Renner, 1986) in participants who accepted an additional detailed interview ($N = 21$). It includes 15 items used to assess behaviour relevant to autism and general impression. Each item is scored from 1.0 to 4.0 in 0.5 increments, with higher scores indicative of more severe symptoms. The total CARS score in the ASD group ($M = 24.8$, $SD = 3.5$) was higher than those of previous studies investigating participants with Asperger's disorder and PDD-NOS (Koyama, Tachimori, Osada, Takeda, & Kurita, 2007; Uono et al., 2011). This confirmed that symptoms in the ASD group were sufficiently severe.

Twenty-seven TD individuals were recruited from Kyoto University and its related organizations. Data relating to these participants were reported in our recent paper (Uono et al., 2017). The participants were carefully selected to match those in the ASD group in terms of sex (6 women and 21 men) and age [$M = 24.9$, $SD = 5.1$, $t(52) = 1.27$,

$p = 0.21$]. The IQ scores of the TD group (FIQ: $M = 121.1$, $SD = 9.5$, $t(52) = 3.66$, $p < 0.001$; VIQ: $M = 121.1$, $SD = 10.5$, $t(52) = 2.58$, $p = 0.012$; PIQ: $M = 116.6$, $SD = 11.0$, $t(52) = 3.39$, $p = 0.001$) were significantly higher than those of the ASD group. They completed a Japanese version of the Autism-Spectrum Quotient (AQ) (Baron-Cohen et al., 2001). The AQ score of the participants ($M = 20.6$, $SD = 5.9$) was in good agreement with that of a previous standardization study with young Japanese ($M = 20.7$, $SD = 6.4$) (Wakabayashi, Baron-Cohen, Wheelwright, & Tojo, 2006). A psychiatrist or psychologist confirmed that none of the participants had any neurological or psychiatric symptoms at a clinical level, based on the Japanese version of the Mini International Neuropsychiatric Interview (Otsubo et al., 2005). All participants in both groups were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971), and had normal or corrected-to-normal visual acuity.

Following an explanation of the procedures, all participants provided written informed consent. The experiment was approved by the local ethics committee of the Primate Research Institute, Kyoto University. The experiment was conducted in accordance with the guidelines of the Declaration of Helsinki 1964 and its later amendments.

2.2 Emotion recognition task

The emotion recognition task was controlled using Presentation (version 14.9, Neurobehavioral System; https://www.neurobs.com/) software implemented on a Windows computer (HPZ200SFF; Hewlett-Packard Co., Palo Alto, CA, USA). A total of 48 photographs of faces expressing the six basic emotions (anger, disgust, fear, happiness, sadness, and surprise) from four Caucasian and four Japanese models (Ekman & Friesen, 1976; Matsumoto & Ekman, 1988) were presented individually on a 19-inch CRT monitor (HM903D-A; Iiyama Corp., Hoofddorp, the Netherlands) in random order in each block. Written labels of the six basic emotions were presented around each photograph. The participants were asked to indicate which of the labels

best described the emotion expressed in each photograph. An experimenter carefully recorded a verbal response. They were instructed to take into consideration all six alternatives. Each photograph remained on the screen until the participants made a verbal response. **No time limit was established for the task investigating the deliberate processing of facial expressions.** The emotion recognition task consisted of four blocks (two Caucasian and two Japanese face blocks) of 12 trials. The position of the labels on the monitor was counterbalanced across blocks, and the order of the blocks was counterbalanced across participants. All participants appropriately understood the meanings of the written labels. Two practice trials were set to familiarize participants with the procedure.

2.3 MRI acquisition

MRI acquisition was conducted on a different day as that of emotion recognition task. **A forehead pad was used to stabilize the head position during image acquisition.** Image scanning was performed on a 3-T scanning system (MAGNETOM Trio, A Tim System, Siemens, Erlangen, Germany) at the ATR Brain Activity Imaging Centre using a 12-channel array coil. T1-weighted high-resolution anatomical images were obtained using a magnetization-prepared rapid gradient-echo sequence (repetition time = 2,250 ms, echo time = 3.06 ms, flip angle = 9°, inversion time = 1,000 ms, field of view = 256 × 256 mm, matrix size = 256 × 256, and voxel size = 1 × 1 × 1 mm). **Expert radiologists at the ATR Brain Activity Imaging Centre checked and confirmed the quality of the images of all participants.**

2.4 Data analysis

2.4.1 Emotion recognition task

The percent accuracy in each emotion category and the total average score were calculated. **We conducted analysis of variance using emotion (anger, disgust, fear, happiness, sadness, and surprise) as a within-participant factor and the group (ASD and TD) as a between-participant factor. Subsequently, we added the FIQ**

score as a covariate, because we found a significant group difference in the IQ score [$t(52) = 3.66$, $p < 0.001$].

Moreover, we assessed whether the percent accuracy for each emotion condition was greater than the value attributable to chance (16.7%). **To investigate how the general cognitive function affects the emotion recognition ability, we calculated Pearson's correlation coefficients between the average percent accuracy in the ASD and TD groups, along with the IQ scores (VIQ and PIQ).**

The significance level of all tests was set to 0.05, **unless otherwise indicated.**

2.4.2 Image analysis: pre-processing

Image and statistical analyses were performed using the SPM8 statistical parametric mapping package (http://www.fil.ion.ucl.ac.uk/spm) and the VBM8 toolbox (http://dbm.neuro.uni-jena.de) implemented in MATLAB R2012b (MathWorks, Natick, MA, USA). Prior to the analysis, two of the study authors (WS and TK) independently confirmed the absence of macroscopic lesions or artefacts in the T1 images. Image pre-processing was performed using the default settings of the VBM8 toolbox. Structural T1 images were segmented into GM, white matter, and cerebrospinal fluid, using an adaptive maximum a posteriori approach (Rajapakse, Giedd, & Rapoport, 199). Intensity inhomogeneity in the MRI was modelled as slowly varying spatial functions and thus was corrected in the estimation. The segmented images were used for a partial volume estimate using a simple model with mixed tissue types to improve segmentation (Tohka, Zijdenbos, & Evans, 2004). A spatially adaptive non-local means denoising filter was applied to address spatially varying noise levels (Manjon et al., 2010). A Markov random field clean-up was used to improve image quality. The grey and white matter images in native space were subsequently normalized to standard stereotactic space defined by the Montreal Neurological Institute using diffeomorphic anatomical registration and the exponentiated Lie algebra algorithm approach (Ashburner, 2007).

We used the predefined templates provided with the VBM8 toolbox, derived from 550 healthy brains in the IXI-database (http://www.brain-development.org). The normalized GM images were modulated using Jacobian determinants with nonlinear warping only (i.e., m0 image in VBM8 outputs) to exclude the effect of total intracranial volume. Finally, the normalized modulated GM images were resampled to a resolution of 1.5 × 1.5 × 1.5 mm and smoothed using an isotropic Gaussian kernel 12 mm full-width at half-maximum to compensate for anatomical variability among participants.

2.4.3 Image analysis: statistical analysis

To examine which brain regions were associated with the group difference in the association between GM volume and emotion recognition, we performed a general linear model analysis with group (TD and ASD) and the group-interacted emotion recognition scores (average percent accuracy across conditions for the TD and ASD groups; percent accuracy was overall mean centred) as the effect-of-interest factors, and age, sex, and FIQ as the effect-of-no-interest covariates. We expected a significant interaction between average percent accuracy across conditions and group, which was tested using *T*-statistics. Simple effect analyses were conducted to interpret the significant interaction. **For the ROI analysis, we identified voxels in the bilateral IFG (right, 7454 voxels; left, 6591 voxels), STS region (right, 25065 voxels; left, 21001 voxels), and amygdala (right, 388 voxels; left, 396 voxels). The anatomical masks were determined by tracing strict anatomical borders using PickAtlas (Maldjian et al., 2003). We performed a small volume correction (Worsley et al., 1996) with a height threshold of $p < 0.001$ (uncorrected); family-wise error correction ($p < 0.05$) for multiple comparisons was applied to the extent threshold. Other areas were corrected for the entire brain volume using the same threshold as that for the ROI analysis. Finally, we confirmed that the association remained significant when the PIQ or VIQ score was used as a covariate to replace the FIQ score.** The identified brain structures were anatomically labelled using Talairach Client

(Lancaster et al., 2007) and the SPM Anatomy Toolbox (Eickhoff et al., 2005). Whole-brain analyses were also conducted using the percent accuracy for each emotion condition (except happiness and surprise) as an independent variable.

3. Results

3.1 The emotion recognition task

Total percent accuracy and the percent accuracy under each emotion condition are shown in Table 1. **ANOVA showed a significant main effect of group ($F(1, 52) = 4.639$, $p = 0.036$), suggesting that the individuals with ASD were worse at recognizing emotions than were the TD individuals. There was also a significant main effect of emotion [$F(5, 260) = 59.487$, $p < 0.001$] and an interaction between group and emotion [$F(5, 260) = 3.162$, $p = 0.009$]. The follow-up simple effect analysis showed that the ASD group was less accurate at recognizing fearful facial expressions [$F(1, 52) = 8.652$, $p = 0.005$], but not other facial expressions [$F(1, 52) < 3.250$, $p > 0.077$], compared to the TD group. However, when the FIQ score was added to the model as a covariate, the main effect of group [$F(1, 51) = 1.062$, $p = 0.308$] and interaction between group and emotion [$F(5, 255) = 0.926$, $p = 0.464$] did not remain significant.** The performances under all emotion conditions were significantly higher than chance in both groups [$t(26) > 4.60$, $p < 0.001$] after α-level adjustment using the Bonferroni correction for multiple comparisons ($\alpha = 0.0042$).

The correlation analysis revealed a group difference in the association between the **PIQ** score and the average percent accuracy for emotion recognition. A positive correlation was found in the ASD group (**$r = 0.44$, $p = 0.023$**) but not in the TD group (**$r = 0.08$, $p = 0.703$**), suggesting that cognitive processing reflected in the **PIQ** measure contributes to facial expression recognition in the ASD group. Although the correlation in the ASD group did not remain significant when the α-level was adjusted using Bonferroni correction for multiple comparisons ($\alpha = 0.0125$), it showed a medium effect size. **There was no significant correlation between the VIQ score and the average**

percent accuracy in either group (ASD: $r = 0.27$, $p = 0.172$; TD: $r < 0.01$, $p = 0.980$).

3.2 Group difference in the association between GM volume and total percent accuracy across conditions

The ROI analysis showed a significant interaction between total percent accuracy for emotion recognition and group in the right IFG (x = 51, y = 24, z = 7), indicating that the association between the score and GM volume in the right IFG differed between the ASD and control groups (Figure 1 and Table 2). The simple effect analysis revealed a significant positive correlation between GM volume of the right IFG and total percent accuracy in the control (x = 53, y = 26, z = 6) but not in the ASD group. At the liberal height threshold ($p < 0.01$), GM volume in the ASD group was negatively correlated with total emotion recognition. **When the PIQ or VIQ score was added as a covariate to replace the FIQ score, the cluster in the right IFG remained significant in the interaction and simple effect analyses (Supplementary Table 1).** No significant clusters were observed in the analyses of other ROIs or the whole brain.

3.2 Group difference in the association between GM volume and accuracy in each emotion condition

The whole-brain analysis showed a significant interaction between the score for disgusted face recognition and group in the left dorsomedial prefrontal cortex (dmPFC: x = −8, y = 32, z = 55), indicating that the association between the score and GM volume in the left dmPFC differed between the groups (see Figure 2 and Table 3). The simple effect analysis revealed a significant positive correlation between GM volume of the left dmPFC and disgusted face recognition only in the ASD group (x = −5, y = 11, z = 60). **When the PIQ or VIQ score was added as a covariate to replace the FIQ score, the cluster in the left dmPFC remained significant in the interaction and simple effect analyses (Supplementary Table 2).** No significant cluster for interactions was observed between the score for other emotion conditions and group.

4. Discussion

The present study investigated the structural neural correlates for emotion recognition from facial expressions in high-functioning adults with ASD. Consistent with a previous meta-analysis study (Uljarevic and Hamilton 2013), the results showed that the ASD group was less accurate at recognizing facial expressions, particularly fearful expressions, than was the TD group. **However, when considering the IQ score, we found similar group accuracies for emotion recognition. The PIQ score rather than the VIQ score** was positively correlated with emotion recognition performance in the ASD but not the TD group. A recent study found that detail-focused visuospatial processing included in the IQ measures explain individual differences in emotion recognition performance in the ASD group (Otsuka et al., 2017). Another study suggested that individuals with ASD recruit a rule-based matching strategy for perceiving facial expressions to a greater degree than do TD individuals (Walsh, Vida, & Rutherford, 2014). These findings suggest that individuals with ASD rely heavily on visuospatial and **other** cognitive processes **rather than on verbal function itself** when recognizing facial expressions. The effectiveness of such a processing strategy might explain individual differences in emotion recognition in individuals with ASD.

The ROI analysis showed that GM volume in the right IFG was positively correlated with total emotion recognition in the TD group but not in the ASD group. The association between GM volume in the right IFG and total emotion recognition remained significant after controlling for intellectual abilities. The results were consistent with the finding that the IFG, along with the temporal cortex, constituted the characteristic brain network in ASD (Grerucci et al., 2016; Sato et al., 2017). The results were also consistent with the controversial hypothesis that mirror neuron system dysfunction, including the IFG, explains the social cognitive dysfunction in ASD (Dapretto et al., 2006; Oberman & Ramachandran, 2007; Hamilton, 2013). We suggest that the group difference in the right IFG reflects the crucial role of matching the visual

representation of the other's action with one's own motor representations, because previous studies demonstrated that a facial response congruent with an observed facial expression enhances emotion recognition (Hyniewska & Sato, 2015; Niedenthal, 2007; Oberman, Winkielman, & Ramachandran, 2007; Sato, Fujimura, Kochiyama, & Suzuki, 2013), and the IFG is activated as in TD individuals who observe and imitate another's facial expressions (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Hennenlotter et al., 2005; Pfeifer, Iacoboni, Mazziotta, & Dapretto, 2008). The increase in GM volume in the right IFG in TD individuals might be related to the effectiveness of facial mimicry and/or activation of shared representation of observed and own facial motion contributing to accurate emotion recognition. However, the tendency for a negative correlation in the ASD group could be counterintuitive. Although behavioural studies have demonstrated that individuals with ASD show diminished facial mimicry (McIntosh, Reichmann-Decker, Winkielman, & Wilbarger, 2006; Yoshimura, Sato, Uono, & Toichi, 2015) and reduced activation of the right IFG in response to facial expressions (e.g., Sato et al., 2012), other studies have reported that individuals with ASD have delayed (Oberman, Winkielman, & Ramachandran, 2009) and atypical (Beall, Moody, McIntosh, Hepburn, & Reed, 2008) facial responses in response to another's emotional facial expressions. The proneness of such facial responses, which is possibly associated with increased volume of the right IFG in the ASD group, might impair rather than enhance the performance of facial expression recognition. Considering that individuals with ASD have deficits in emotion recognition across stimulus domains (Phillip et al., 2010), it was important to investigate how vocal and facial emotion recognition was associated with the IFG to elucidate its functional role (i.e., facial mimicry).

The whole-brain analysis in each emotion category showed that GM volume in the left dmPFC was positively correlated with disgusted face recognition in the ASD but not the TD group. Previous VBM studies revealed that increased GM volume in the

dmPFC correlates with the theory of mind ability measured by the Reading the Mind in the Eyes test (Hirao et al., 2008; Sato et al., 2016). Although some functional MRI studies have reported reduced activation in the dmPFC during the processing of emotional facial expressions in individuals with ASD (e.g., Sato et al., 2012), other studies suggest an important role of the dmPFC for social cognition in these individuals. For example, the dmPFC but not the IFG was activated in individuals with ASD when registering another's emotional state from facial expressions, while the reverse pattern of activation was found in TD individuals (Schulte-Rüther et al., 2011). The administration of transcranial magnetic stimulation to the dmPFC improves self-reported social function in individuals with ASD (Enticott et al., 2014). Previous fMRI studies in a normal population have linked the dmPFC to resolving conflict and volitional control of action (Nachev, 2006). Consistent with this, the dmPFC has been associated with the higher-order social judgements required to integrate several sources of information (Amodio & Frith, 2006; Martin, Dzafic, Ramdave, & Meinzer, 2017) and related to their explicit rather than implicit processing (Martin et al., 2017; Van Overwalle & Vandekerckhove, 2013). Based on the notion that individuals with ASD possess a detail-focused processing style which prevents social cognition (Happé & Frith, 2006), these findings suggest that people who have a large dmPFC can effectively recruit cognitive control to resolve conflicts between multiple inputs, and it might compensate for the atypical IFG function during emotion recognition. Furthermore, the specific association between disgusted face recognition and GM volume in the dmPFC might be explained by individuals with ASD who have social **challenges** and who are motivated to discriminate accurately disgusted faces, which signals the possibility of social exclusion (Rozin, Lowery, & Ebert, 1994).

The present study provides several implications for clinical intervention to emotion recognition in ASD. First, the atypical association between GM volume in the IFG and emotion recognition suggests that facial imitation training is an effective method to

improve emotion recognition in high-functioning individuals with ASD. Previous studies showed that facial imitation during the emotion recognition task improves the accuracy of recognizing facial expressions, especially in individuals with high autistic traits (Lewis & Dunn, 2017; Kowalik et al., 2021). Russo-Ponsaran, Evans-Smith, Johnson, Russo, and McKown (2016) demonstrated enhanced emotion recognition in individuals with ASD using repeated practice and training of facial imitation. Although the training-related changes remain unknown, the results suggest that training of facial imitation may develop an effective shared representation of observed and own facial motion; participants could understand the correspondence between facial expression and emotion when combined with repeated recognition task training. Given that individuals with ASD show atypical facial responses to another's facial expressions, facial imitation training through feedback might be helpful for individuals with ASD. Second, the positive associations **of the dmPFC and PIQ score with** emotion recognition **suggest** the usefulness of training cognitive and visual processing, at least in high-functioning individuals. A recent meta-analysis revealed the robust effect of training on emotion recognition through cognitive behavioural intervention (Zhang et al., 2020). Explicit instructions of specific emotions associated with facial expressions can improve emotion recognition ability (Russo-Ponsaran et al., 2016) and result in activation of **the medial prefrontal regions as well as other social brain regions in response to facial expressions in individuals with ASD (Bölte et al., 2018).** Attention to diagnostic features and/or the integration of information about facial parts induced by explicit knowledge of a link between emotions and facial expressions may improve the accuracy of emotion recognition.

Several limitations in the present study should be noted. First, most of participants recognized happy faces at the ceiling level. The ceiling effect caused a loss of ability to detect the group difference. A behavioural task in which the difficulty level is consistent across all emotion categories might allow us to detect group differences in the

association between GM volume and recognition of happy faces. Second, there was a significant group difference concerning IQ scores in the present study. Although the brain regions associated with **the accuracy of emotion recognition remain significant after controlling for IQ scores**, careful considerations of individual differences in cognitive functions (i.e., working memory) are needed to elucidate neurocognitive mechanisms underlying emotion recognition in the ASD group. **Third, no time limit was established for the task to investigate deliberate facial expression processing in the present study. Although the present study cannot use the reaction time to assess performance, the requirement of an accelerated response may reveal significant group differences in the association between performance and the volume of brain regions underlying rapid processing of emotional facial expressions (e.g., amygdala; Zhao et al., 2013). Further studies using various behavioural experiments are needed to assess structural neural correlates for the ability of emotion recognition. Fourth, the movements of the participants in the scanner may have affected our results; however, participants in the ASD group did not have comorbid diagnoses other than ASD, the scanning time for structural MRI was not too long, and experienced radiologists validated the quality of all images. A quantitative motion assessment in the scanner may be helpful to rule out this issue in future studies.** Fifth, the present study included a relatively small number of participants. To draw firm conclusions regarding the neural substrates that underlie emotion recognition in ASD, future studies should include larger, more diverse samples. Finally, the use of multivariate morphometry analysis is another promising approach, given behavioural and neural heterogeneity in autism. In contrast to univariate VBM analysis that reveals clusters of significant voxels, multivariate morphometry analysis considers voxel pattern covariations across brain regions (Grecucci et al., 2016; Sato, Kochiyama et al., 2017). A recent study demonstrated that multivariate morphometry analysis was more sensitive to morphometric changes, compared with univariate VBM

analysis (Pappaianni et al., 2018).

In summary, the present study revealed that GM volume in some regions was differentially correlated with emotion recognition performance from facial expressions between individuals with and without ASD. The ROI analysis showed that the total emotion recognition ability in TD individuals but not individuals with ASD was positively correlated with GM volume in the right IFG. The whole-brain analysis for each emotion condition revealed that disgusted face recognition in individuals with ASD but not TD individuals was positively correlated with GM volume in the left dmPFC. The IFG and the dmPFC have been linked with matching the visual representation of another's action with one's own motor representations and resolving conflicts from multiple inputs, respectively. Thus, the present results suggest that individuals with and without ASD use different processing styles to recognize another's facial expressions.

Acknowledgements: We thank ATR Brain Activity Imaging Center for their support in acquiring the data. We also thank Kazusa Minemoto, Emi Yokoyama and Akemi Inoue for their technical support.

Ethical approval: The experiment was approved by the local ethics committee of the Primate Research Institute, Kyoto University. The experiment was conducted in accordance with the guidelines of the Declaration of Helsinki 1964 and its later amendments.

Consent to participate: All participants provided written informed consent prior to participation.

Consent for publication: Not applicable.

Author contributions: SU, WS, TK, SY, RS, YK, MS, and MT conceived and designed the experiments. SU, WS, TK, SY, RS and YK performed the experiments. SU, WS, and TK analysed the data. SU and WS wrote the first draft of the manuscript, and all authors contributed to the writing of the manuscript.

Funding: This study was supported by the JSPS Funding Program for Next Generation World-Leading Researchers (LZ008), Grant-in-Aid for Young Scientists (B) (16K17360), and Grant-in-Aid for Scientific Research (C) (20K03478). The funding sources had no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Competing interests: The authors declare that they have no conflict of interest.

Availability of data and materials: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to information that could compromise research participant privacy/consent.

References

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. (1994). Impaired recognition of emtion in facial expressions following bilateral damage to the human amygdala. *Nature, 372*(6507), 669-672.

Allison, T., Puce, A., & McCarthy, A. (2000). Social perception from visual cues: role of the STS region. *Trends in Cognitive Sciences, 4*(7), 267-278.

Amodio, D. M., & Frith, C. D. (2006). Meeting of minds: the medial frontal cortex and social cognition. *Nature Reviews Neuroscience, 7*(4), 268-277. doi:10.1038/nrn1884

Aoki, Y., Cortese, S., & Tansella, M. (2015). Neural bases of atypical emotional face processing in autism: A meta-analysis of fMRI studies. *World Journal of Biological Psychiatry, 16*(5), 291-300. doi:10.3109/15622975.2014.957719

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *Neuroimage, 38*(1), 95-113. doi:10.1016/j.neuroimage.2007.07.007

Ashwin, C., Baron-Cohen, S., Wheelwright, S., O'Riordan, M., & Bullmore, E. T. (2007). Differential activation of the amygdala and the 'social brain' during fearful face-processing in Asperger Syndrome. *Neuropsychologia, 45*(1), 2-14. doi:10.1016/j.neuropsychologia.2006.04.014

American Psychological Association (2000). *Diagnostic and statistical manual for mental disorders (DSM-IV-TR)*. Washington, DC: Author.

American Psychological Association (2013). *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Arlington, VA: American Psychiatric Association.

Bölte, S., Ciaramidaro, A., Schlitt, S., Hainz, D., Kliemann, D., Beyer, A., Poustka, F., Freitag, C., & Walter, H. (2018). Training-induced plasticity of the social brain in autism spectrum disorder. *The British Journal of Psychiatry, 207*(2), 149-157. doi: 10.1192/bjp.bp.113.143784

Beall, P. M., Moody, E. J., McIntosh, D. N., Hepburn, S. L., & Reed, C. L. (2008). Rapid facial reactions to emotional facial expressions in typically developing children and children with autism spectrum disorder. *Journal of Experimental Child Psychology, 101*(3), 206-223. doi:10.1016/j.jecp.2008.04.004

Calder, A. J., Lawrence, A. D., & Young, A. W. (2003). Neuropsychology of fear and loathing. *Nature Reviews Neuroscience, 2*(5), 352-363.

Carr, L., Iacoboni, M., Dubeau, M. C., Mazziotta, J. C., & Lenzi, G. L. (2003). Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. *Proceedings of the National Academy of Sciences of the United*

States of America, 100(9), 5497-5502. doi:10.1073/pnas.0935845100

Cauda, F., Geda, E., Sacco, K., D'Agata, F., Duca, S., Geminiani, G., & Keller, R. (2011). Grey matter abnormality in autism spectrum disorder: an activation likelihood estimation meta-analysis study. *Journal of Neurology, Neurosurgery and Psychiatry, 82*(12), 1304-1313. doi:10.1136/jnnp.2010.239111

Chechlacz, M., Novick, A., Rotshtein, P., Bickerton, W. L., Humphreys, G. W., & Demeyere, N. (2014). The neural substrates of drawing: a voxel-based morphometry analysis of constructional, hierarchical, and spatial representation deficits. *Journal of Cognitive Neuroscience, 26*(12), 2701-2715. doi:10.1162/jocn_a_00664

Critchley, H., Daly, E., Bullmore, E. T., Williams, S. C. R., Van Amelsvoort, T., Robertson, D. M., . . . Murphy, D. G. M. (2000). The functional neuroanatomy of social behaviour: Changes in cerebral blood flow when people with autistic disorder process facial expressions. *Brain, 123*(11), 2203-2212.

Dal Monte, O., Krueger, F., Solomon, J. M., Schintu, S., Knutson, K. M., Strenziok, M., . . . Grafman, J. (2013). A voxel-based lesion study on facial emotion recognition after penetrating brain injury. *Social Cognitive and Affective Neuroscience, 8*(6), 632-639. doi:10.1093/scan/nss041

Dalton, K. M., Nacewicz, B. M., Johnstone, T., Schaefer, H. S., Gernsbacher, M. A., Goldsmith, H. H., . . . Davidson, R. J. (2005). Gaze fixation and the neural circuitry of face processing in autism. *Nature Neuroscience, 8*(4), 519-526. doi:10.1038/nn1421

Dapretto, M., Davies, M. S., Pfeifer, J. H., Scott, A. A., Sigman, M., Bookheimer, S. Y., & Iacoboni, M. (2006). Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorders. *Nature Neuroscience, 9*(1), 28-30. doi: 10.1038/nn1611

de Jong, M.C., van Engeland, H., Kemner, C. (2008). Attentional effects of gaze shifts are influenced by emotion and spatial frequency, but not in autism. *Jounal of the American Acadeny of Child and Adolescent Psychiatry, 47*(4), 443-454. doi:10.1097/CHI.0b013e31816429a6.

DeRamus, T. P., & Kana, R. K. (2015). Anatomical likelihood estimation meta-analysis of grey and white matter anomalies in autism spectrum disorders. *Neuroimage: Clinical, 7*, 525-536. doi:10.1016/j.nicl.2014.11.004

Dricu, M., & Fruhholz, S. (2016). Perceiving emotional expressions in others: activation likelihood estimation meta-analyses of explicit evaluation, passive perception and incidental perception of emotions. *Neuroscience and Biobehavioral*

Reviews, 71, 810-828. doi:10.1016/j.neubiorev.2016.10.020

Dziobek, I., Bahnemann, M., Convit, A., & Heekeren, H. R. (2010). Thr role of the fusiform-amygdala system in the pathophysiology of autism. *Archives of General Psychiatry, 67*(4), 397-405.

Dziobek, I., Fleck, S., Rogers, K., Wolf, O. T., & Convit, A. (2006). The 'amygdala theory of autism' revisited: linking structure to behavior. *Neuropsychologia, 44*(10), 1891-1899. doi:10.1016/j.neuropsychologia.2006.02.005

Eickhoff, S. B., Stephan, K. E., Mohlberg, H., Grefkes, C., Fink, G. R., Amunts, K., & Zilles, K. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *Neuroimage, 25*(4), 1325-1335. doi:10.1016/j.neuroimage.2004.12.034

Ekman, P., & Friesen, W. V. (1976). *Pictures of facial affect*. Palo Alto, CA: Consulting Psychologists Press.

Enticott, P. G., Fitzgibbon, B. M., Kennedy, H. A., Arnold, S. L., Elliot, D., Peachey, A., . . . Fitzgerald, P. B. (2014). A double-blind, randomized trial of deep repetitive transcranial magnetic stimulation (rTMS) for autism spectrum disorder. *Brain Stimulation, 7*(2), 206-211. doi:10.1016/j.brs.2013.10.004

Fink, G. R., Halligan, P. W., Marchetti, J. C., Frith, C. D., Frackowiak, R. S., & Dolan, R. J. (1997). Neural mechanisms involved in the processing of global and local aspects of hierarchically organized visual stimuli. *Brain, 120*(10), 1779-1791. doi:10.1093/brain/120.10.1779

Happé, F., & Frith, U. (2006). The weak coherence account: detail-focused cognitive style in autism spectrum disorders. Journal of Autism and Developmental Disorders, 36(1), 5-25. doi:10.1007/s10803-005-0039-0.

Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., . . . Politi, P. (2009). Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *Journal of Psychiatry and Neuroscience, 34*(6), 418-432.

Gallese, V., Keysers, C., & Rizzolatti, G. (2004). A unifying view of the basis of social cognition. *Trends in Cognitive Sciences, 8*(9), 396-403. doi:10.1016/j.tics.2004.07.002

García-Villamisar, D., Rojahn, J., Zaja, R. H., & Jodra, M. (2010). Facial emotion processing and social adaptation in adults with and without autism spectrum disorder. *Research in Autism Spectrum Disorders, 4*(4), 755-762. doi:10.1016/j.rasd.2010.01.016

Grecucci, A., Brambilla, P., Siugzdaite, R., Londero, D., Fabbro F., & Rumiati, R. I.

(2013). Emotional resonance deficits in autistic children. *Journal of Autism and Developmental Disorders*, 43(3), 616–628. doi:10.1007/s10803-012-1603-z

Grecucci, A., Rubicondo, D., Siugzdaite, R., Surian, L., & Job, R. (2016). Uncovering the social deficits in the autistic brain. a Source-based morphometric study. Frontiers in Neuroscience, 10, 388. doi:10.3389/fnins.2016.00388

Hamilton, A. F. d. C. (2013). Reflecting on the mirror neuron system in autism: a systematic review of current theories. *Developmental Cognitive Neuroscience, 3*(1), 91–105. doi:10.1016/j.dcn.2012.09.008

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2000). The distributed human neural system for face perception. *Trends in Cognitive Sciences, 4*(6), 223-233.

Hennenlotter, A., Schroeder, U., Erhard, P., Castrop, F., Haslinger, B., Stoecker, D., . . . Ceballos-Baumann, A. O. (2005). A common neural basis for receptive and expressive communication of pleasant facial affect. *Neuroimage, 26*(2), 581-591. doi:10.1016/j.neuroimage.2005.01.057

Hirao, K., Miyata, J., Fujiwara, H., Yamada, M., Namiki, C., Shimizu, M., . . . Murai, T. (2008). Theory of mind and frontal lobe pathology in schizophrenia: a voxel-based morphometry study. *Schizophrenia Research, 105*(1-3), 165-174. doi:10.1016/j.schres.2008.07.021

Hubl, D., Bölte, S., Feineis-Matthews, S., Langermann, H., Federspiel, A., Strick, W., . . . Dierks, T. (2003). Functional imbalance of visual pathways indicates alternative face processing strategies in autism. *Neurology, 61*(9), 1232-1237.

Humphreys, K., Minshew, N., Leonard, G. L., & Behrmann, M. (2007). A fine-grained analysis of facial expression processing in high-functioning adults with autism. *Neuropsychologia, 45*(4), 685-695.

Hyniewska, S., & Sato, W. (2015). Facial feedback affects valence judgments of dynamic and static emotional expressions. *Frontiers in Psychology, 6*, 291. doi:10.3389/fpsyg.2015.00291

Kanai, R., & Rees, G. (2011). The structural basis of inter-individual differences in human behaviour and cognition. *Nature Reviews: Neuroscience, 12*(4), 231-242. doi:10.1038/nrn3000

Kim, S. Y., Choi, U. S., Park, S. Y., Oh, S. H., Yoon, H. W., Koh, Y. J., . . . Lee, C. U. (2015). Abnormal activation of the social brain network in children with autism spectrum disorder: an FMRI study. *Psychiatry Investigation, 12*(1), 37-45. doi:10.4306/pi.2015.12.1.37

Kleinhans, N. M., Richards, T., Johnson, L. C., Weaver, K. E., Greenson, J., Dawson, G., & Aylward, E. (2011). fMRI evidence of neural abnormalities in the

subcortical face processing system in ASD. *Neuroimage, 54*(1), 697-704. doi:10.1016/j.neuroimage.2010.07.037

Kleinhans, N. M., Richards, T., Weaver, K., Johnson, L. C., Greenson, J., Dawson, G., & Aylward, E. (2010). Association between amygdala response to emotional faces and social anxiety in autism spectrum disorders. *Neuropsychologia, 48*(12), 3665-3670. doi:10.1016/j.neuropsychologia.2010.07.022

Koyama, T., Tachimori, H., Osada, H., Takeda, T., & Kurita, H. (2007). Cognitive and symptom profiles in Asperger's syndrome and high-functioning autism. *Psychiatry and Clinical Neurosciences, 61*(1), 99-104. doi:10.1111/j.1440-1819.2007.01617.x

Kowallik, A. E., Pohl, M., Schweinberger, S. R. (2021). Facial imitation improves emotion recognition in adults with different levels of sub-clinical autistic traits. *Journal of Intelligence, 9*(1), 4. doi:10.3390/jintelligence9010004

Lancaster, J. L., Tordesillas-Gutierrez, D., Martinez, M., Salinas, F., Evans, A., Zilles, K., . . . Fox, P. T. (2007). Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. *Human Brain Mapping, 28*(11), 1194-1205. doi:10.1002/hbm.20345

Lewis, M. B., & Dunn, E. (2017). Instructions to mimic improve facial emotion recognition in people with sub-clinical autism traits. *Quartely of Journal of Experimental Psychology (Hove), 70*(11), 2357-2370. doi:10.1080/17470218.2016.1238950

Lux, S., Marshall, J. C., Ritzl, A., Weiss, P. H., Pietrzyk, U., Shah, N. J., . . . Fink, G. R. (2004). A functional magnetic resonance imaging study of local/global processing with stimulus presentation in the peripheral visual hemifields. *Neuroscience, 124*(1), 113-120. doi:10.1016/j.neuroscience.2003.10.044

Maldjian, J. A., Laurienti, P. J., Burdette, J. B., & Kraft, R. A. (2003). An automated method for neuroanatomical and cytoarchitectonic atlasbased interrogation of fMRI datasets. *Neuroimage 19*(3), 1233–1239. doi: 10.1016/s1053-8119(03)00169-1

Manjon, J. V., Coupe, P., Marti-Bonmati, L., Collins, D. L., & Robles, M. (2010). Adaptive non-local means denoising of MR images with spatially varying noise levels. *Journal of Magnetic Resonance Imaging, 31*(1), 192-203. doi:10.1002/jmri.22003

Martin, A. K., Dzafic, I., Ramdave, S., & Meinzer, M. (2017). Causal evidence for task-specific involvement of the dorsomedial prefrontal cortex in human social cognition. *Social Cognitive and Affective Neuroscience, 12*(8), 1209-1218.

doi:10.1093/scan/nsx063

Matsumoto, D., & Ekman, P. (1988). *Japanese and Caucasian facial expressions of emotion.* San Francisco, CA: Intercultural and Emotion Research Laboratory, Department of Psychology, San Francisco State University.

McIntosh, D. N., Reichmann-Decker, A., Winkielman, P., & Wilbarger, J. L. (2006). When the social mirror breaks: deficits in automatic, but not voluntary, mimicry of emotional facial expressions in autism. *Developmental Science, 9*(3), 295-302.

Monk, C. S., Weng, S.-J., Wiggins, J. L., Kurapati, N., Louro, H. M. C., Carrasco, M., . . . Lord, C. (2010). Neural circuitry of emotional face processing in autism spectrum disorders. *Journal of Psychiatry and Neuroscience, 35*(2), 105-114. doi:10.1503/jpn.090085

Nachev, P. (2006). Cognition and medial frontal cortex in health and disease. *Current Opinion in Neurology, 19*(6), 586-592.

Niedenthal, P. M. (2007). Embodying emotion. *Science, 316*(5827), 1002-1005. doi:10.1126/science.1136930

Oberman, L. M., & Ramachandran, V. S. (2007). The simulating social mind: the role of the mirror neuron system and simulation in the social and communicative deficits of autism spectrum disorders. *Psychological Bulletin, 133*(2), 310-327. https://doi.org/10.1037/0033-2909.133.2.310

Oberman, L. M., Winkielman, P., & Ramachandran, V. S. (2007). Face to face: blocking facial mimicry can selectively impair recognition of emotional expressions. *Social Neuroscience, 2*(3-4), 167-178. doi:10.1080/17470910701391943

Oberman, L. M., Winkielman, P., & Ramachandran, V. S. (2009). Slow echo: facial EMG evidence for the delay of spontaneous, but not voluntary, emotional mimicry in children with autism spectrum disorders. *Developmental Science, 12*(4), 510-520. doi:10.1111/j.1467-7687.2008.00796.x

Ogai, M., Matsumoto, H., Suzuki, K., Ozawa, F., Fukuda, R., Uchiyama, I., . . . Takei, N. (2003). fMRI study of recognition of facial expressions in high-functioning autistic patients. *Neuroreport, 14*(4), 559-563. doi:10.1097/01.wnr.0000061019.47393.71

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113.

Otsubo, T., Tanaka, K., Koda, R., Shinoda, J., Sano, N., Tanaka, S., . . . Kamijima, K. (2005). Reliability and validity of Japanese version of the Mini-International

Neuropsychiatric Interview. *Psychiatry and Clinical Neurosciences, 59*(5), 517-526.

Otsuka, S., Uono, S., Yoshimura, S., Zhao, S., & Toichi, M. (2017). Emotion Perception mediates the predictive relationship between verbal ability and functional outcome in high-functioning adults with autism spectrum fisorder. *Journal of Autism and Developmental Disorders, 47*(4), 1166-1182. doi:10.1007/s10803-017-3036-1

Pappaianni, E., Siugzdaite, R., Vettori, S., Venuti, P., Job, R., & Grecucci, A. (2017). Three shades of grey: detecting brain abnormalities in children with autism by using Source-, voxel- and surface-based morphometry. *The European Journal of Neuroscience, 47*(6), 690-700. doi:10.1111/Ejn.13704

Pelphrey, K. A., Morris, J. P., McCarthy, G., & Labar, K. S. (2007). Perception of dynamic changes in facial affect and identity in autism. *Social Cognitive and Affective Neuroscience, 2*(2), 140-149. doi:10.1093/scan/nsm010

Pfeifer, J. H., Iacoboni, M., Mazziotta, J. C., & Dapretto, M. (2008). Mirroring others' emotions relates to empathy and interpersonal competence in children. *Neuroimage, 39*(4), 2076-2085. doi:10.1016/j.neuroimage.2007.10.032

Philip, R., Whalley, H., Stanfield, A., Sprengelmeyer, R., Santos, I., Young, A., . . . Hall, J. (2010). Deficits in facial, body movement and vocal emotional processing in autism spectrum disorders. Psychological Medicine, 40(11), 1919-1929. doi:10.1017/S0033291709992364

Pitcher, D. (2014). Facial expression recognition takes longer in the posterior superior temporal sulcus than in the occipital face area. *Journal of Neuroscience, 34*(27), 9173-9177. doi:10.1523/JNEUROSCI.5038-13.2014

Rajapakse, J. C., Giedd, J. N., & Rapoport, J. L. (1997). Statistical approach to segmentation of single-channel cerebral MR images. *IEEE Transactions on Medical Imaging, 16*(2), 176-186.

Rizzolatti, G., Fogassi, L., & Gallese, V. (2001). Neurophysiological mechanisms underlying the understanding and imitation of action. *Nature Reviews Neuroscience, 2*(9), 661-670.

Rozin, P., Lowery, L., & Ebert, R. (1994). Varieties of disgust faces and the structure of disgust. *Journal of Personality and Social Psychology, 66*(5), 870-881.

Russo-Ponsaran, N. M., Evans-Smith, B., Johnson, J., Russo, J., & McKown, C. (2016). Efficacy of a facial emotion training program for children and adolescents with autism spectrum disorders. *Journal of Nonverbal Behavior, 40*(1), 13-38.

Sabatinelli, D., Fortune, E. E., Li, Q., Siddiqui, A., Krafft, C., Oliver, W. T., . . .

Jeffries, J. (2011). Emotional perception: meta-analyses of face and natural scene processing. *Neuroimage, 54*(3), 2524-2533. doi:10.1016/j.neuroimage.2010.10.011

Samson, F., Mottron, L., Soulieres, I., & Zeffiro, T. A. (2012). Enhanced visual functioning in autism: an ALE meta-analysis. *Human Brain Mapping, 33*(7), 1553-1581. doi:10.1002/hbm.21307

Sato, W., Fujimura, T., Kochiyama, T., & Suzuki, N. (2013). Relationships among facial mimicry, emotional experience, and emotion recognition. *PLoS One, 8*(3), e57889. doi:10.1371/journal.pone.0057889.g001

Sato, W., Kochiyama, T., Uono, S., Sawada, R., Kubota, Y., Yoshimura, S., & Toichi, M. (2016). Structural Neural Substrates of Reading the Mind in the Eyes. *Frontiers in Human Neuroscience, 10*. doi:10.3389/fnhum.2016.00151

Sato, W., Kochiyama, T., Uono, S., Yoshimura, S., Kubota, Y., Sawada, R., . . . Toichi, M. (2017). Reduced Gray Matter Volume in the Social Brain Network in Adults with Autism Spectrum Disorder. *Frontiers in Human Neuroscience, 11*, 395. doi:10.3389/fnhum.2017.00395

Sato, W., Toichi, M., Uono, S., & Kochiyama, T. (2012). Impaired social brain network for processing dynamic facial expression in autism spectrum disorders. *BMC Neuroscience, 13*, 99.

Sato, W., Uono, S., Kochiyama, T., Yoshimura, S., Sawada, R., Kubota, Y., . . . Toichi, M. (2017). Structural Correlates of Reading the Mind in the Eyes in Autism Spectrum Disorder. *Frontiers in Human Neuroscience, 11*, 361. doi:10.3389/fnhum.2017.00361

Schopler, E., Reichler, R. J., & Renner, B. R. (1986). *The Childhood Autism Rating Scale (CARS): For Diagnostic Screening and Classification of Autism*. New York: Irvington.

Schulte-Rüther, M., Greimel, E., Markowitsch, H. J., Kamp-Becker, I., Remschmidt, H., Fink, G. R., & Piefke, M. (2011). Dysfunctions in brain networks supporting empathy: an fMRI study in adults with autism spectrum disorders. *Social Neuroscience, 6*(1), 1-21. doi:10.1080/17470911003708032

Shamay-Tsoory, S. G., Aharon-Peretz, J., & Perry, D. (2009). Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. *Brain, 132*(Pt 3), 617-627. doi:10.1093/brain/awn279

Simard, I., Luck, D., Mottron, L., Zeffiro, T. A., & Soulieres, I. (2015). Autistic fluid intelligence: Increased reliance on visual functional connectivity with

diminished modulation of coupling by task difficulty. *Neuroimage: Clinical, 9*, 467-478. doi:10.1016/j.nicl.2015.09.007

Soulieres, I., Dawson, M., Samson, F., Barbeau, E. B., Sahyoun, C. P., Strangman, G. E., . . . Mottron, L. (2009). Enhanced visual processing contributes to matrix reasoning in autism. *Human Brain Mapping, 30*(12), 4082-4107. doi:10.1002/hbm.20831

Spencer, M. D., Holt, R. J., Chura, L. R., Suckling, J., Calder, A. J., Bullmore, E. T., & Baron-Cohen, S. (2011). A novel functional brain imaging endophenotype of autism: the neural response to facial expression of emotion. *Translational Psychiatry, 1*, e19. doi:10.1038/tp.2011.18

Tohka, J., Zijdenbos, A., & Evans, A. (2004). Fast and robust parameter estimation for statistical partial volume models in brain MRI. *Neuroimage, 23*(1), 84-97. doi:10.1016/j.neuroimage.2004.05.007

Uljarevic, M., & Hamilton, A. (2013). Recognition of emotions in autism: a formal meta-analysis. *Journal of Autism and Developmental Disorders, 43*(7), 1517-1526. doi:10.1007/s10803-012-1695-5

Uono, S., Sato, W., Kochiyama, T., Sawada, R., Kubota, Y., Yoshimura, S., & Toichi, M. (2017). Neural substrates of the ability to recognize facial expressions: a voxel-based morphometry study. *Social Cognitive and Affective Neuroscience, 12*(3), 487-495. doi:10.1093/scan/nsw142

Uono, S., Sato, W., & Toichi, M. (2011). The specific impairment of fearful expression recognition and its atypical development in pervasive developmental disorder. *Social Neuroscience, 6*(5-6), 452-463. doi:10.1080/17470919.2011.605593

Uono, S., Sato, W., & Toichi, M. (2013). Common and unique impairments in facial-expression recognition in pervasive developmental disorder-not otherwise specified and Asperger's disorder. *Research in Autism Spectrum Disorders, 7*(2), 361-368. doi:10.1016/j.rasd.2012.10.007

Uono, S., Sato, W., & Toichi, M. (2014). Reduced representational momentum for subtle dynamic facial expressions in individuals with autism spectrum disorders. *Research in Autism Spectrum Disorders, 8*(9), 1090-1099. doi:10.1016/j.rasd.2014.05.018

Van der Hallen, R., Evers, K., Brewaeys, K., Van den Noortgate, W., & Wagemans, J. (2015). Global processing takes time: A meta-analysis on local-global visual processing in ASD. *Psychological Bulletin, 141*(3), 549-573. doi:10.1037/bul0000004

Van Overwalle, F., & Vandekerckhove, M. (2013). Implicit and explicit social

mentalizing: dual processes driven by a shared neural network. *Frontiers in Human Neuroscience, 7*, 560. doi:10.3389/fnhum.2013.00560

Via, E., Radua, J., Cardoner, N., Happé, F., & Mataix-Cols, D. (2011). Meta-analysis of gray matter abnormalities in autism spectrum disorder: Should Asperger disorder be subsumed under a broader umbrella of autistic spectrum disorder? *Archives of General Psychiatry, 68*(4), 409-418.

Wakabayashi, A., Baron-Cohen, S., Wheelwright, S., & Tojo, Y. (2006). The Autism-Spectrum Quotient (AQ) in Japan: A cross-cultural comparison. *Journal of Autism and Developmental Disorders, 36*(2), 263-270. doi:10.1007/s10803-005-0061-2

Walsh, J. A., Vida, M. D., & Rutherford, M. D. (2014). Strategies for perceiving facial expressions in adults with autism spectrum disorder. *Journal of Autism and Developmental Disorders, 44*(5), 1018-1026. doi:10.1007/s10803-013-1953-1

Wang, A. T., Dapretto, M., Hariri, A. R., Sigman, M., & Bookheimer, S. Y. (2004). Neural correlates of facial affect processing in children and adolescents with autism spectrum disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 43*(4), 481-490. doi:10.1097/01.chi.0000111481.76722.66

Weng, S. J., Carrasco, M., Swartz, J. R., Wiggins, J. L., Kurapati, N., Liberzon, I., . . . Monk, C. S. (2011). Neural activation to emotional faces in adolescents with autism spectrum disorders. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 52*(3), 296-305. doi:10.1111/j.1469-7610.2010.02317.x

Wicker, B., Fonlupt, P., Hubert, B., Tardif, C., Gepner, B., & Deruelle, C. (2008). Abnormal cerebral effective connectivity during explicit emotional processing in adults with autism spectrum disorder. *Social Cognitive and Affective Neuroscience, 3*(2), 135-143. doi:10.1093/scan/nsn007

Worsley, K. J., Marrett, S., Neelin, P., Vandal, A. C., Friston, K. J., & Evans, A. C. (1996). A unified statistical approach for determining significant signals in images of cerebral activation. *Human Brain Mapping, 4*(1), 58-73.

Yang, X., Si, T., Gong, Q., Qiu, L., Jia, Z., Zhou, M., . . . Zhu, H. (2016). Brain gray matter alterations and associated demographic profiles in adults with autism spectrum disorder: A meta-analysis of voxel-based morphometry studies. *Australian and New Zealand Journal of Psychiatry, 50*(8), 741-753. doi:10.1177/0004867415623858

Yoshimura, S., Sato, W., Uono, S., & Toichi, M. (2015). Impaired overt facial mimicry in response to dynamic facial expressions in high-functioning autism spectrum

disorders. *Journal of Autism and Developmental Disorders, 45*(5), 1318-1328. doi:10.1007/s10803-014-2291-7

Wallace, G. L., Case, L. K., Harms, M. B., Silvers, J. A., Kenworthy, L., & Martin, A. (2011). Diminished sensitivity to sad facial expressions in high functioning autism spectrum disorders is associated with symptomatology and adaptive functioning. *Journal Autism and Develomental Disorders, 41*(11), 1475-86. doi:10.1007/s10803-010-1170-0.

Zhang, Q., Wu, R., Zhu, S., Le, J., Chen, Y., Lan, C., … Kendrick, K. M. (2021). Facial emotion training as an intervention in autism spectrum disorder: A meta-analysis of randomized controlled trials. *Autism Research, 14*(10), 2169-2182. doi: 10.1002/aur.2565.

Zhao, K., Yan, W. J., Chen, Y. H., Zuo, X. N., & Fu, X. (2013). Amygdala volume predicts inter-individual differences in fearful face recognition. *PLoS One, 8*(8), e74096. doi:10.1371/journal.pone.0074096

Table 1. Mean (with *SE*) percent accuracy for facial expression recognition.

	Anger	Disgust	Fear	Happiness	Sadness	Surprise	Total
ASD	55.1 (4.4)	60.6 (4.2)	41.7 (5.4)	98.6 (0.8)	83.3 (3.9)	94.9 (1.7)	72.4 (1.7)
TD	57.9 (4.0)	65.3 (3.9)	63.4 (5.0)	100 (0)	87.5 (2.3)	88.9 (4.0)	77.2 (1.5)

ASD, autism spectrum disorder; TD, typically developing.

Table 2. Brain regions showing the group difference in the association between grey matter volume and total accuracy of facial expression recognition in the region-of-interest analysis.

.

	Side	BA	Coordinates			$T_{(47)}$-value	Corrected p-value **(peak-level)**	Cluster Size (voxels)
			x	y	z			
Interaction								
TD versus ASD								
Inferior frontal gyrus	R	45	51	24	7	4.16	**0.011**	**427**
Simple main effect in each group								
TD, positive correlation								
Inferior frontal gyrus	R	45	**54**	**26**	**6**	**3.52**	**0.058**	**122**

The coordinates of the peak in the MNI system are shown. Significant voxels in the region of interest analysis were identified at the height threshold of $p < 0.001$ (uncorrected), and then a family-wise error correction for multiple comparisons ($p < 0.05$) was applied to the extent threshold. ASD, autism spectrum disorder; BA, Brodmann's area; L, left; R, right; TD, typically developing individuals

Table 3. Brain regions showing the group difference in the association between grey matter volume and disgust recognition in the whole brain analysis.

	Side	BA	Coordinates			$T_{(47)}$-value	Corrected p-value **(peak-level)**	Cluster Size (voxels)
			x	y	z			
Interaction								
ASD versus TD								
Dorsomedial prefrontal cortex	L	6	−8	32	55	5.37	0.015	3905
Simple main effect in each group								
ASD, positive correlation								
Dorsomedial prefrontal cortex	L	6	−5	11	60	4.84	0.064	2443

The coordinates of the peak in the MNI system are shown. Significant voxels were identified at the height threshold of $p < 0.001$ (uncorrected), and then a family-wise error (FWE) correction for multiple comparisons ($p < 0.05$) was applied to the extent threshold in the whole brain. ASD, autism spectrum disorder; BA, Brodmann's area; L, left; R, right; TD, typically developing individuals

Figure Legends

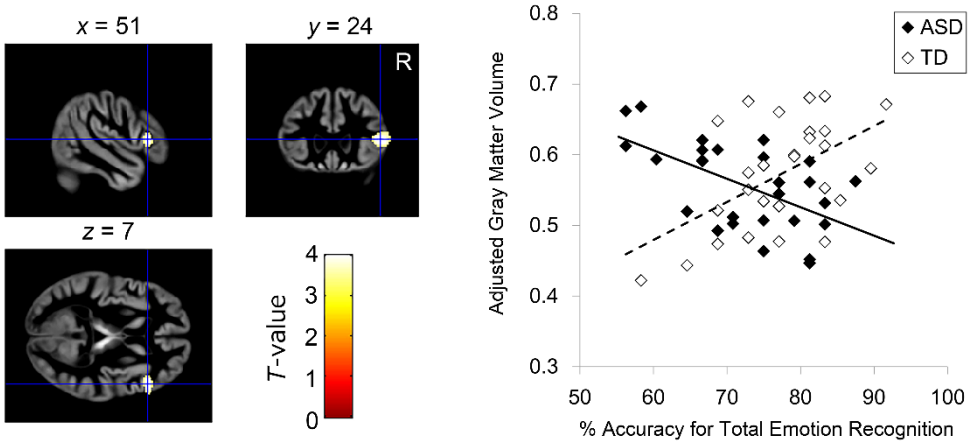

Figure 1. Brain regions showing a significant interaction between group and global emotion recognition in the region-of-interest analysis. Left panel: statistical parametric maps showing the interaction in the right inferior frontal gyrus. Significant voxels were identified at the height threshold of $p < 0.001$ (uncorrected), and then a family wise error correction ($p < 0.05$) for multiple comparisons was applied to the extent threshold. The areas are overlaid on the average grey matter image of participants in the current study. Blue crosses indicate the locations of the peak voxels. The red–yellow colour scale represents the T-value. L, left hemisphere; R, right hemisphere. Right panel: scatterplots of the adjusted grey matter volume as a function of the average percent accuracy across emotion conditions at the peak voxels for the typically developing (TD) and autism spectrum disorder (ASD) groups. Effects of no interest (age, sex, and full-scale intelligence quotient) were co-varied out.

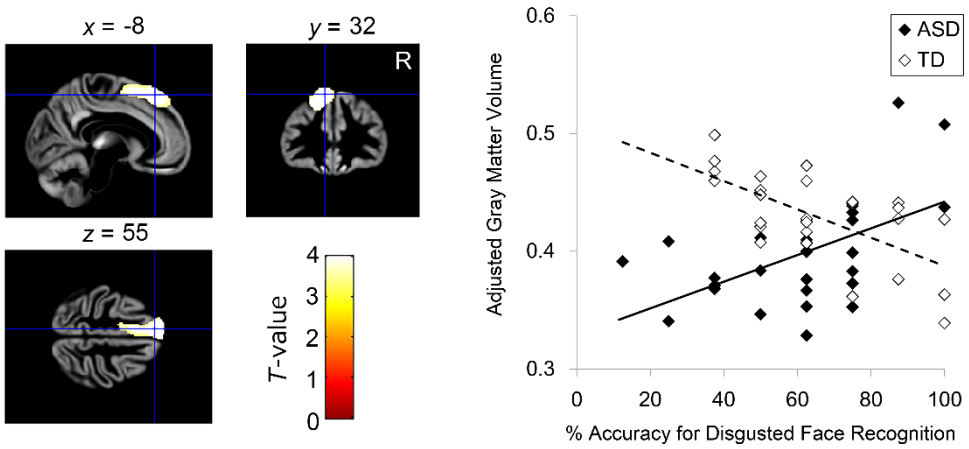

Figure 2. Brain regions showing a significant interaction between group and disgust recognition in the whole brain analysis. Left panel: statistical parametric maps showing the interaction in the left dorsomedial prefrontal cortex. Significant voxels were identified at the height threshold of $p < 0.001$ (uncorrected), and then a family wise error correction ($p < 0.05$) for multiple comparisons was applied to the extent threshold. The areas are overlaid on the average grey matter image of participants in the current study. Blue crosses indicate the locations of the peak voxels. The red–yellow colour scale represents the T-value. L, left hemisphere; R, right hemisphere. Right panel: scatterplots of the adjusted grey matter volume as a function of the averaged percent accuracy for disgusted faces at the peak voxels for the typically developing (TD) and autism spectrum disorder (ASD) groups. Effects of no interest (age, sex and full-scale intelligence quotient) were co-varied out.

Supplementary Table 1. Brain regions showing the significant group difference in the association between grey matter volume and total accuracy of facial expression recognition when VIQ or PIQ score was used as a covariate in the region-of-interest analysis.

	Side	BA	Coordinates			$T_{(47)}$-value	Corrected p-value (peak-level)	Cluster Size (voxels)
			x	y	z			
VIQ score as a covariate								
Interaction, TD versus ASD								
Inferior frontal gyrus	R	45	53	26	7	4.20	0.01	458
TD, positive correlation								
Inferior frontal gyrus	R	45	54	26	6	3.60	0.047	187
PIQ score as a covariate								
Interaction, TD versus ASD								
Inferior frontal gyrus	R	45	53	24	6	3.79	0.03	227
TD, positive correlation								
Inferior frontal gyrus	R	45	56	26	6	3.47	0.065	119

The coordinates of the peak in the MNI system are shown. Significant voxels in the region of interest analysis were identified at the height threshold of $p < 0.001$ (uncorrected), and then a family-wise error correction for multiple comparisons ($p < 0.05$) was applied to the extent threshold. ASD, autism spectrum disorder; BA, Brodmann's area; L, left; R, right; PIQ, performance intelligence quotient; TD, typically developing individuals; VIQ, verbal intelligence quotient

Supplementary Table 2. Brain regions showing the significant group difference in the association between grey matter volume and disgust recognition when VIQ or PIQ score was used as a covariate in the whole brain analysis.

	Side	BA	Coordinates			$T_{(47)}$-value	Corrected p-value (peak-level)	Cluster Size (voxels)
			x	y	z			
VIQ score as a covariate								
Interaction, ASD versus TD								
Dorsomedial prefrontal cortex	L	6	-8	32	55	5.39	0.014	3822
ASD, positive correlation								
Dorsomedial prefrontal cortex	L	6	-5	11	60	4.84	0.064	2414
PIQ score as a covariate								
Interaction, ASD versus TD								
Dorsomedial prefrontal cortex	L	8	-15	28	45	5.38	0.014	4167
ASD, positive correlation								
Dorsomedial prefrontal cortex	L	6	-5	11	60	4.89	0.056	2666

The coordinates of the peak in the MNI system are shown. Significant voxels were identified at the height threshold of $p < 0.001$ (uncorrected), and then a family-wise error correction for multiple comparisons ($p < 0.05$) was applied to the extent threshold in the whole brain. ASD, autism spectrum disorder; BA, Brodmann's area; L, left; R, right; PIQ, performance intelligence quotient; TD, typically developing individuals; VIQ, verbal intelligence quotient