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Face processing in a case of high functioning autism with developmental prosopagnosia

Hanna B. Cygan[1,3]*, Hanna Okuniewska[2], Katarzyna Jednoróg[3], Artur Marchewka[4], Marek Wypych[4] and Anna Nowicka[3]

[1] Laboratory of Social Psychology, Department of Ergonomics, Central Institute for Labour Protection, National Research Institute, Warsaw, Poland, [2] Faculty of Psychology, University of Warsaw, Warsaw, Poland, [3] Laboratory of Psychophysiology, Department of Neurophysiology, Nencki Institute of Experimental Biology, Polish Academy of Science, Warsaw, Poland, [4] Laboratory of Brain Imaging, Neurobiology Center, Nencki Institute of Experimental Biology, Polish Academy of Science, Warsaw, Poland,
** Email: hacyg@ciop.pl*

The ability to "read" the information about facial identity, expressed emotions, and intentions is crucial for non-verbal social interaction. Neuroimaging and clinical studies consequently link face perception with fusiform gyrus (FG) and occipital face area (OFA) activity. Here we investigated face processing in an adult, patient PK, diagnosed with both high functioning autism spectrum disorder (ASD) and developmental prosopagnosia (DP). Both disorders have a significant impact on face perception and recognition, thus creating a unique neurodevelopmental condition. We used eye-tracking and functional magnetic resonance imaging (fMRI) method. Eye-tracking and fMRI results of PK were compared to results of control subjects. Patient PK showed atypical gaze-fixation strategy during face perception and typical patterns of brain activations in the FG and OFA. However, a significant difference between PK and control subjects was found in the left anterior superior temporal sulcus/middle temporal gyrus (aSTS/MTG). In PK the left aSTS/MTG was hypo-activated in comparison to the control subjects. Additionally, functional connectivity analysis revealed decreased inter-hemispheric connectivity between right and left aSTS/MTG in 'ASD and DP' patient during face recognition performance as compared to the control subjects. The lack of activity in the left aSTS/MTG observed in the case of the clinical subject, combined with the behavioral, eye-tracking, and neuropsychological results, suggests that impairment of the cognitive mechanism of face recognition involves higher level of processing. It seems to be related to insufficient access to semantic knowledge about the person when prompted by face stimuli.

Key words: developmental prosopagnosia, autism spectrum disorder, superior temporal sulcus, fMRI, eye tracking

INTRODUCTION

The unique ability to read complex information from subtle feature configurations ascribed to human faces has been the focus of numerous experimental studies. Many of these have investigated perception and/or recognition of this specific stimulus in developmental conditions that include impairment in face processing as a core symptom. One of these conditions is developmental prosopagnosia (DP), a disorder that selectively disturbs face perception. It is characterized by the inability to explicitly recognize the identity of a familiar person based on the visual appearance of his/her face, typically in the absence of other cognitive impairments such as memory deficits or impairments in non-face object recognition (Avidan et al. 2011, Le Grand et al. 2006). Even so, patients affected by this disorder are known to implicitly recognize familiar faces despite their inability to recognize them explicitly (Avidan and Bermann 2008, De Haan et al. 1992, Rivolta et al. 2010, Schweinberger and Burton 2003, Tranel and Damasio 1985). For instance, when they were requested to complete a matching task with both famous and unknown faces in which they decided whether two consecutive images have the same identity or not, the in-

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dividuals with prosopagnosia were significantly slower and less accurate than the control participants (Avidan and Berman 2008). More importantly, like the controls, they were faster and more accurate at matching famous compared with unknown faces. These results provide the solid evidence for the existence of implicit familiarity processing in prosopagnosia and suggest that, despite the marked impairment in explicit face recognition, these individuals still have some familiarity representation which manifests in the form of covert recognition (Avidan and Berman 2008). Interestingly, some studies concerning cases of DP showed typical patterns of brain activity in the core system of face perception, including fusiform gyrus (FG) and occipital face area (OFA) (Avidan et al. 2005, Avidan and Behrmann 2008, DeGutis et al. 2007, Hadjikhani and De Gelder 2002, Hasson et al. 2003). Other functional magnetic resonance imaging (fMRI) studies in individuals with DP reported much stronger activations to faces than to control stimuli in several cortical regions: FG, inferior occipital gyrus, and superior temporal sulcus (STS) (Susilo and Duchaine 2013). In addition, it was shown that DP individuals have reduced face-selectivity in the FG comparing to non-prosopagnosic individuals (Furl et al. 2011). Although the exact mechanism of DP impairment is still a matter of debate, the most common view relates recognition dysfunction displayed by prosopagnosic individuals to a loss of specific modes of face processing, such as the use of configural (Levine and Calvanio 1989) and holistic (Farah et al. 1995) information, leaving intact the encoding of individual feature-based information (Avidan et al. 2011, Huis in 't Veld et al. 2012).

Another developmental disorder that disturbs proper interpretation of face stimuli is autism spectrum disorder (ASD). Facial information is crucial for non-verbal social interaction, and impaired face processing, including disturbed orientation towards faces, eye contact or understanding face expressions, is a commonly observed aspect of social deficits present among people with autism (Dawson et al. 2005, Nomi and Uddin 2015). This impairment may be due to the atypical face-viewing strategies applied by people with ASD, characterized by reduced attention to central face features, especially the eyes (Hernandez et al. 2009, Klin et al. 2002a, 2002b, Klin and Jones 2008) and/or a bias towards detail-based processing, i.e. the tendency to interpret visual stimuli in parts rather than as a whole (Nakahachi et al. 2008).

Findings of fMRI studies in this field are rather inconsistent. Some indicate alterations in FG activation in ASD subjects while looking at faces (Critchley et al. 2000, Dalton et al. 2005, Grelotti et al. 2005, Humphreys et al. 2008, Pierce et al. 2001, Schultz et al. 2000). However, there is also strong evidence supporting the notion about normal activation of core brain areas (FG and OFA) related to static face processing (Hadjikhani et al. 2004, 2007, Kleinhans et al. 2009, Nomi and Uddin 2015, Weisberg et al. 2014), especially when the experimental task focuses on face identity match (Corbett et al. 2009) or recognition of personally familiar faces (Pierce et al. 2004). On the other hand, recent studies have also highlighted the complex relationship between face perception and functional activity of the autistic brain (Nomi and Uddin 2015, Weisberg et al. 2014). For example, some ASD studies revealed abnormal activation in broader face-specific areas including the superior temporal sulcus/middle temporal gyrus (STS/MTG) (Critchley et al. 2000, Hadjikhani et al. 2007, Pelphrey et al. 2007, Philip et al. 2012, Wicker et al. 2008). In typically developing population, STS/MTG is involved in reading specific facial features, such as eye-gaze or emotional expression (Fusar-Poli et al. 2009, Garrido et al. 2009, Haxby et al. 200, Iidaka 2014, Nasr and Tootell 2012). Such ability is strongly disturbed in ASD (Dalton et al. 2005, Pelphrey et al. 2007, Nomi and Uddin 2015).

The relation between prosopagnosia and ASD is still a matter of debate. Several case studies have been reported describing individuals exhibiting symptoms of both disorders. It was also suggested that the prevalence of DP is greater in ASD than in the part of population that do not fall on the autism spectrum. Nevertheless, the exact co-occurrence of the two conditions requires further investigation (Cook et al. 2015). Interestingly, even though it is rarely diagnosed, DP seems to occur more frequently than ASD: 2% (Kennerknecht et al. 2006) *vs.* 1-1.5% (www.who.int) of the general population.

Some of the previous reports suggested a causal link between DP and ASD describing patients with childhood-onset prosopagnosia demonstrating ASD-like features, e.g., low abilities in reading facial expressions, social withdrawal, difficulties in establishing relationships etc. (Barton et al. 2003, Kracke 1994, McConachie 1976, Pietz et al. 2003). On the other hand several authors proposed that the presence of social developmental dysfunction (including ASD and Asperger's syndrome – AS) impedes the development of normal face processing (Barton et al. 2004). If there is a failure to develop normal social interest in others, even to the point of avoiding looking at faces, a normal perceptual expertise with faces may not develop (Swettenham et al. 1998). Then the symptoms of prosopagnosia would evolve secondarily in the majority of the ASD cases. However, this seems not to be the case. The two disorders may appear in parallel but each of them may constitute independent sets of core symptoms. That notion is supported by findings of a very recent study that examined face recognition in control

subjects and two clinical groups – one with DP and one with ASD (Cook et al. 2015). Assessment of DP and ASD symptoms was also done in both clinical groups. A part of the ASD group met the diagnostic criteria for prosopagnosia and a part of the DP group met the criteria for clinically significant levels of autistic traits. Importantly, results showed that once prosopagnosic traits were accounted for, the severity of autistic symptoms was no longer predictive of face recognition ability among subjects with ASD (Cook et al. 2015). In general, one may conclude that it is likely that the co-occurrence of DP and ASD is underestimated as the symptoms of ASD eclipse poor face recognition which can be treated as a consequence of social dysfunctions. As a result, the actual co-occurrence is rarely recognized in patients and the mechanism of the interaction of the two is still poorly understood.

Here, we investigated the case of a patient who suffers from both disorders: a young adult male (referred to as PK) with diagnoses of ASD and DP. Our study describes a detailed in-depth assessment of this single case using a variety of psychological and neurophysiological methods, with a focus on face processing, which was investigated with eye tracking and fMRI methods. We explored the individual set of symptoms to determine the relationship between the two disorders in the case of PK. We aimed to unveil the neurocognitive mechanism of PK's face recognition deficit and identify the nature of a complex interplay between these two clinical conditions in PK's specific case. Specifically, we were interested in whether some effects not reported previously in individuals with ASD or individuals with PD would be observed in the case of our 'ASD and DP' patient. We hypothesized that the PK's face recognition impairment would be reflected in deficient functional organization of a cortical face recognition network including FG, OFA, and STS.

METHODS

Subjects

Clinical subject

PK is a 37-year-old man diagnosed with ASD who reported for neuropsychological assessment. Formal assessment of PK handedness by means of the Edinburgh Inventory (Oldfield 1971) revealed that he was right-handed. His laterality quotient was 0.73. His subjective complaints referred to difficulties in remembering and recognizing faces of people he had seen or met before, especially when he meets them in new situations and/or places.

Information constituting the medical history was based on self-report and documentation shared by PK. The subject was born during the 26th week of pregnancy with a weight of 1280 g, 42 cm height, and 10 points on the Apgar scale. At school age, PK was diagnosed with obesity and impaired visuomotor coordination. In 2007, at 30 years of age, PK received an Asperger's syndrome diagnosis from a psychiatrist. Identification of ASD symptoms was based on a clinical interview and examination with a battery of tests as reported in the documentation. These tests included: Asperger Syndrome Diagnostic Scale – ASDS (Myles et al. 2001), Autism Quotient – AQ (Baron-Cohen et al. 2001), Faces Test (trials reported in clinical assessment), and the Rotter Incomplete Sentence Blank – RISB (Jaworowska et al. 2003). The diagnosis was subsequently confirmed using the Autism Diagnostic Observation Schedule – ADOS (Lord et al. 2000) during the present experiment.

PK was administered a set of standardized psychological instruments for the assessment of cognitive, social, and emotional functions (Table I and Table II). The following instruments were used for the assessment of social abilities and autistic symptoms: ADOS, Questionnaire of Emotional Intelligence – INTE (Ciechanowicz et al. 2000, Schutte et al. 1998) and Emotional Intelligence Scale – SIE-T (Matczak et al. 2005). The results confirmed symptoms typical for ASD. In the self-evaluative INTE Questionnaire PK reported difficulties in recognizing and understanding his own and others' emotions and also in using the emotions to interpret social behaviors. Furthermore, the SIE-T revealed decreased recognition of complex emotions from people's faces. ADOS scoring confirmed the clinical diagnosis of ASD.

PK underwent assessment using the Wechsler Intelligence Scale – WAIS-R, PL (Brzeziński et al. 2004) and Raven's Advanced Progressive Matrices (Jaworowska and Szustrowa 1991). WAIS-R results revealed a high level of intellectual abilities with an advantage in verbal over nonverbal skills. A more explicit discrepancy between subtests appeared in non-verbal tests. The worst performance was in the Picture Arrangement subtest – the subtest most sensitive to social skills. PK earned the highest score on the Comprehension and Vocabulary subtests. In addition, the subject showed good ability to deal with abstract social conventions, rules and expressions. However, this assessment shows theoretical knowledge of social rules that can be assigned to high general knowledge. Importantly, the results of the ASD symptoms assessment revealed that PK presents difficulties in making use of social rules in real life situations.

PK's result in Raven's Advanced Progressive Matrices (RPM) indicates very well developed abstract

reasoning and learning abilities. This result supports evidence that individuals with high functioning ASD demonstrate a significant advantage, relative to controls, in their RPM scores over their Wechsler scores (Soulières et al. 2011).

PK showed very good performance in visual perception and visual memory on the Benton Visual Retention Test (Jaworowska 2017). PK made no mistakes during the examination. His performance was equally good in the picture reproduction task irrespective of whether it took place directly after presentation or after a delay.

The Right Hemisphere Language Battery (RHLB-PL) (Łojek 2007) was used for assessment of pragmatic language skills. PK showed very good performance in the majority of subtests from the RHLB attaining maximal scores (10 points out of 10) during the examination. However, the results of two tests – Emotional Prosody and Discourse from the RHLB were significantly lower compared to other subtests (6 and 5 points out of respectively). He showed some difficulties in discrimination and identification of intonation that indicated changes in emotion. Discourse analysis revealed lowered accuracy in narrative, variety, turn taking, prosody, eye contact and gesticulation. Reduced performance on two scales stands in agreement with the results of ADOS assessment and confirms symptoms characteristic for ASD (see Table I).

Diagnosis performed by a neuropsychologist revealed substantial difficulties in face recognition (Table II). During a series of experimental trials PK performed three (not standardized) recognition tasks

Table I. PK's scores on psychological assessment.

Test/battery	Results							
Autism Diagnostic Observation Schedule – ADOS	Reciprocal Social Interaction			Communication			Stereotyped Behaviors	
	5 (cutoff=4)			4 (cutoff= 2)			2	
Questionnaire of Emotional Intelligence INTE								
Ten-scale score (1–10)	2							
Emotional Intelligence Scale SIE-T								
Ten-scale score (1–10)	4							
Wechsler Memory Scale – Family Pict	Direct Recognition			Delayed Recognition				
Ten-scale score	10			10				
Wechsler Memory Scale – Faces	Direct Recognition			Delayed Recognition				
Ten-scale score	5			9				
Retest	Direct Recognition			Delayed Recognition				
Ten-scale score	8			8				
Wechsler Intelligence Scale	Verbal			Performance			Full Scale	
IQ score	140			126			136	
Raven's Advanced Progressive Matrices								
Percentile score	98							
Benton Visual Retention Test	total correct			total error			% correct	
Reproduced designs	10			0			100	
The Right Hemisphere Language Battery (RHLB-PL)	Inferential Meaning	Lexical - Semantic	Humor	Metaphor Picture	Metaphor Written	Linguistic Prosody	Emotional Prosody	Discourse
Ten-scale score	10	10	10	10	10	10	6	5
Face Recognition Test	Familiar Faces		Familiar Inverted Faces		Unfamiliar Faces		Unfamiliar Inverted Faces	
	57%		57%		100%		95%	

with colored pictures: 1) Recognition of famous person task: During the task 50 digital photographs of famous people were presented with no time limitation. PK was asked three questions each time a photograph was presented to him: *Is this person famous? Is it an actor or politician? What's his/her name?* 2) Gender recognition task: 97 digital photographs were presented. PK was asked to judge the gender of each person in the photograph. 3) Age recognition task: 47 digital photographs were presented. PK was asked to judge the approximate age of each person in the photograph. PK did not have any problems with age and gender discrimination (Table II). This result stands in line with previous reports from a group study on developmental prosopagnosia (Chatterjee and Nakayama 2012).

To examine basic memory for faces, PK was administered two subtests from the Wechsler Memory Scale battery: Family Pictures and Faces (WMS III) (Wechsler 1997). The results indicated very good memory in the case of specific social stimuli composed of drawn pictures of a family.

The test of face memory was administered twice (Table I). PK reported being able to recognize only one person from the set of stimuli and guessing on the rest. This subjective report may suggest a kind of implicit memory for faces in the case of PK. Such an effect was previously reported in subjects with DP (e.g. Barton et al. 2001, Schweinberger and Burton 2003).

Control subjects – Eye tracking experiment

PK and ten control subjects (all males, ages 24-50) participated in the eye tracking study. All control participants had normal or corrected to normal vision. The age difference between PK and the control subjects was insignificant (P=0.6), as revealed by a nonparametric bootstrap analysis (Hasson et al. 2003, see the description in the *Statistical analysis*).

Control subjects – Functional magnetic resonance imaging experiments

PK and twelve control subjects (all males, ages 22-39) participated in fMRI study (one control subject also took part in the eye tracking study). All control participants had normal or corrected to normal vision and had never presented neurological or psychiatric disorders. The age difference between PK and the control subjects was insignificant (P=0.4), as revealed by a nonparametric bootstrap analysis (Hasson et al. 2003).

All procedures performed in our study were in accordance with the ethical standards of the responsible committee on human experimentation and with the 1964 Helsinki declaration and its later amendments.

The experimental protocol was approved by the local Ethics Committee (University of Social Sciences and Humanities, Warsaw, Poland). Informed consent was obtained from all individuals included in the study.

Apparatus and Procedures

Eye-tracking

Eye tracking was used to study PK's face perception gaze-patterns in comparison to the control group. We employed a method previously used to test eye movement-based memory effects in DP (Bate et al. 2008). The set of face stimuli consisted of twenty photographs of famous people and twenty of unknown people, downloaded from the Internet. All were emotionally neutral. The set of unknown faces was matched to the set of famous faces as closely as possible in respect to gender and age. All photographs were edited in Adobe Photoshop. Each face was displayed in color from the neck upwards on a white background. Each stimulus was adjusted to 650 pixels in height and 500 pixels in width, equalized in luminance and displayed at the center of a color

Table II. PK's scores on face recognition and perception trials.

Task	Number of trials	Correct answer	Incorrect answer	„don't know"	% correct
Famous/not famous	50 (30fam; 20n-fam)	23 (8fam; 15 n-fam)	25 (22fam; 3n-fam)	2	46
Actor/politician distinction	50	8	41	1	16
Name recognition	50	6	0	44	12
Matching pictures of one person	13	8	5	—	61
Gender recognition	97	97	0	—	100
Age recognition	47	47	0	—	100
Basic emotion recognition	70	58	12	—	83

monitor. Eye movements were recorded using a *Remote Eyetracking Device* system. The experiment was designed and performed using the SMI Eyetracking system with sampling rate of 250 Hz.

Each subject was seated in a quiet room, approximately 60 cm from the screen. A calibration of eye fixation position was conducted prior to the experiment. After the calibration phase, participants immediately started the recognition test. During the test, subjects viewed the sequence of 40 stimuli (20 known and 20 unknown) in a random order, with the duration of 5 sec. per face. Subjects made a recognition judgment for each face, pressing the right key on a response pad if the face was familiar to them and the left key if the face was unknown.

To analyze eye movements, the scan path for each face was plotted. Five areas of interest (AOIs) were defined: right eye, left eye, mouth, nose, and 'other'. These were analogous to the AOIs in the Bate et al. study (2008). Any fixations falling outside of the defined feature areas were defined as 'other'. Before the analysis, the AOI's were drawn on each of face stimulus using the tool included in the SMI software. Fixations longer than 80 ms were included in subsequent analyses.

Three eye tracking measures (the number of fixations, average fixation duration and the mean percentage dwell time for each of the five AOI's) and one behavioral measure (reaction times of familiarity decision) were analyzed. The mean percentage dwell time reflects a general indication of viewing strategy. During normal face recognition process visual attention typically focuses on the inner facial features with fewer eye fixations directed to the external features (Bate et al. 2008). Fixation measures, in turn, are an index of the amount of visual sampling directed to particular feature of a picture. These measures are considered to reflect the amount of information needed to identify an object (i.e., face in the case of our study).

Functional magnetic resonance imaging (fMRI)

MRI data acquisition took place at the Laboratory of Brain Imaging, Neurobiology Center, Nencki Institute of Experimental Biology on a 3-Tesla MR scanner (Siemens Magnetom Trio TIM, Erlangen, Germany) equipped with a 32-channel phased array head coil.

Functional data were acquired using a T2*-weighted gradient echo echo-planar imaging (EPI) sequence with

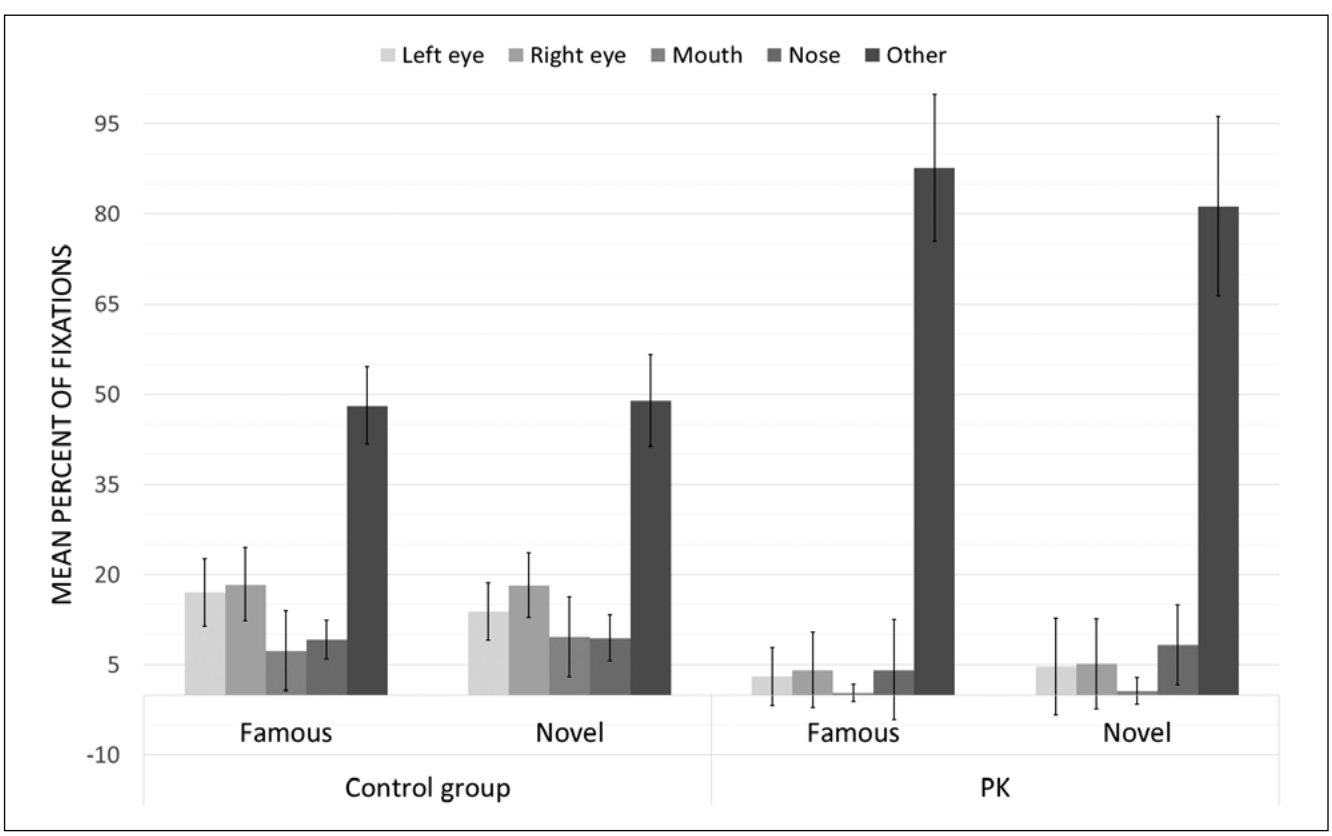

Fig. 1. Results of eye tracking examination. Proportions of fixations directed towards 5 specified AOIs (Left eye, Right eye, Mouth, Nose, Other) during the famous face recognition task in the eye tracking experiment. Mean percent of fixations (and standard deviations – SD) are presented for each AOI separately for PK and 10 control subjects in the two experimental conditions: Famous Face and Novel Face.

the following parameters: time repetition=2190 ms, time echo=30 ms, flip angle=90°, in plane resolution=64×64 mm, field of view=192 mm, and 33 axial slices with 3.6 mm slice thickness with no gap between slices. Detailed anatomical data of the brain were acquired with a T1-weighted (T1w) MP-RAGE (time repetition=2530 ms, time echo=3.32 ms) sequence. Head movements were minimized with cushions placed around the participants' heads.

The experiment consisted of two parts: Localizer (Experiment I) and Face Recognition (Experiment II). The stimuli were generated using Adobe Photoshop CS5H® software (Adobe Systems Incorporated) and the experimental paradigms were written in Presentation® (Neurobehavioral Systems, Inc., Albany, CA) software. Stimuli were presented on a 21" LCD MR compatible screen located in the back of the MR room. Participants viewed the stimuli through an angled mirror attached to the head coil.

fMRI Experiment I – Localizer

To localize brain regions selectively involved in face perception, we used a similar procedure to that of Monzalvo et al. (2012). With permission from Monzalvo and colleagues, we used the same set of stimuli except for the word condition in which the selection of French nouns was replaced with an analogous set of Polish nouns. Four categories of visual stimuli (houses, faces, words, and a revolving checkerboard) were presented in separate blocks and repeated four times. There were 15 different black drawings of the same size on a white background of unknown neutral faces, houses, and three to four-letter regular neutral Polish nouns. Each block of faces, houses, or words was repeated 4 times and lasted 17.3 s. For the checkerboard category, which was also repeated 4 times, a round black and white checkerboard was continuously rotated for 15.5 s. A fixation cross appeared for 10 s between the blocks. In addition, a star was randomly presented twice within each block in order to engage the subject's attention. Participants were instructed to press a single target button using the right index finger each time the star appeared (Monzalvo et al. 2012). Experiment I lasted seven minutes in total.

fMRI Experiment II – Face Recognition

The second experiment followed Experiment I after a short break. The visual stimuli consisted of black and white digital photographs of two categories of faces: familiar *vs.* unfamiliar. The category of familiar faces consisted of photographs of personally familiar people (e.g. a friend, a family member, a partner) and famous people (from various fields, e.g., politics, entertainment, sports). The photos of personally familiar person were delivered by subjects whereas photos of famous and unknown persons were downloaded from the Internet. Possible differences in the luminance of pictures were addressed by matching the color (gray-scale) statistics of all images to the same image (arbitrarily chosen from the stimuli set). Prior to the experiment each participant confirmed familiarity of the famous people. Presented faces were emotionally neutral and the photographs were adjusted in their height, width and luminance. Inverted pictures of the same faces, familiar

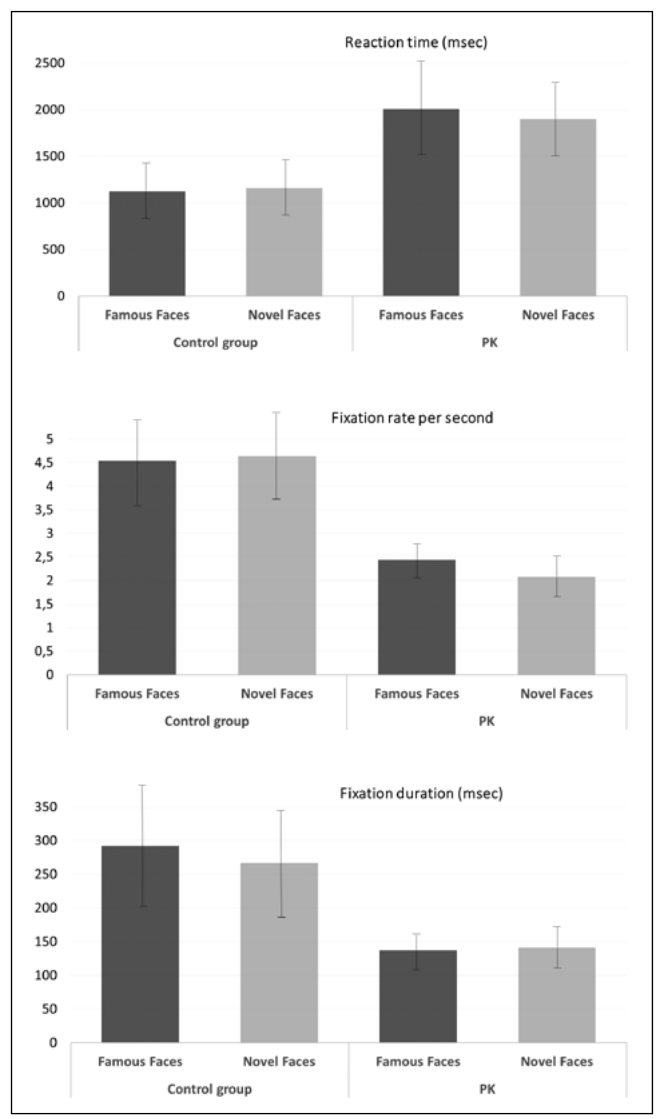

Fig. 2. Results of eye tracking examination. Reaction times (upper panel), fixation rates per second (middle panel), and fixation durations (lower panel) during the famous face recognition task in the eye tracking experiment. Mean values and standard deviations are presented separately for PK and 10 control subjects in the two experimental conditions: Famous Face and Novel Face.

figures (regular geometric shapes), and unfamiliar figures created by scrambling the pictures of faces were also used. The inverted face condition was included in order to control for low-level visual features of perception (Huis in 't Veld et al. 2012). Experiment II used an event-related design. Pictures were presented in pseudo-randomized order to avoid the occurrence of stimuli from one category in more than three consecutive trials. Each image was presented for 5 s and followed by a fixation cross presented randomly for 4, 5, or 6 s. The experimental procedure and examples of visual stimuli are presented in Fig. 3.

Within each experimental condition seven single pictures were presented, three times each (21 presentations per condition). The experiment lasted approximately 22 minutes. Subjects' task was to recognize familiar *vs.* unfamiliar stimuli, i.e. participants were instructed to press one of two buttons using index fingers of right and left hands each time an image appeared on the screen, deciding whether it was familiar or unfamiliar. Responses were given using response pads placed in both of the subject's hands.

fMRI data analysis

Statistical Parametric Mapping (SPM12b, Wellcome Trust Center for Neuroimaging, London, UK) running on MATLAB R2013b (The Math-Works Inc. Natick, MA, USA) was used for data preprocessing and statistical analyses. First, functional images were motion corrected. Structural images from single subjects were then co-registered to the mean functional image. High-dimensional Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra (DARTEL) was used to create a group-specific template and flow fields based on segmented tissue from T1w images (Ashburner 2007). The functional images were normalized to Montreal Neurological Institute (MNI) space using compositions of flow fields and group-specific template to a 2 mm isotropic voxel size. Finally, the normalized functional images were smoothed with an 8 mm isotropic Gaussian kernel.

In the first-level of statistical analysis, all experimental conditions and head movement parameters were entered into the design matrix. The data were modeled for each fMRI run and for each experiment using the canonical hemodynamic response function convolved with the experimental conditions (four in the Localizer experiment: Faces, Houses, Checkerboard, and Words; six in the Face Recognition experiment: Familiar Faces, Unfamiliar Faces, Inverted Familiar Faces, Inverted Unfamiliar Faces, Familiar Figures, Unfamiliar Figures).

The following single *t*-tests ($T_{(184)}$; $P<0.001$), with family wise error (FWE) correction at the cluster level, were computed for each subject in the Localizer experiment: Faces > All (other conditions), Houses > All, Checkerboards > All, and Words > All. Based on numerous previous findings (e.g. Hasson et al. 2003, Kanwisher and Yovel 2006, Haist et al. 2013), the Faces > All contrast was used as a localizer of face sensitive regions (FG and OFA) of interest (ROIs) for further analysis of the data from our Face Recognition experiment (Fig. 2). ROIs were individually localized for each subject and created as a 10 mm sphere around bilaterally specified peaks for two structures: the FG and OFA. Additionally, we used estimated values from the independent Face Recognition experiment contrast 'Unfamiliar Face *vs.* Unfamiliar Figure' to localize ROIs that were possibly sensitive for cognitive processes involved in recognition of familiar faces (Avidan et al. 2013, Garrido et al. 2009, Gobbini and Haxby 2007) and/or face inversion effects (Yovel and Kanwisher 2005), namely the bilaterally anterior and posterior STS/MTG. Here ROIs were again defined separately for each subject as a 10 mm sphere around peak coordinates (Table IV). For the control group, averaged coordinates of all participants were presented. Those ROI's were used in further anal-

Table III. Results of the eye tracking examination for PK and the Control group. Mean values and standard deviations (in parenthesis) are presented.

	PK		Control group	
Task	Famous Faces	Novel Faces	Famous Faces	Novel Faces
Reaction time (msec)	2008.19 (779.15)	1899.47 (656.7)	1122.23 (431.95)	1158.75 (438.35)
Percent of correct responses	20%	100%	89% (7.3%)	98% (2.2%)
Fixation rate per second	2.44 (0.61)	2.08 (0.79)	4.54 (1.35)	4.64 (1.31)
Fixation duration (msec)	137.36 (36.36)	141.42 (52.21)	291.94 (176.07)	266.97 (123.57
Proportion inner (%)	13.10 (11.79)	22.06 (14.90)	51.90 (6.52)	51.11 (7.63)

yses which showed that only in case of the left anterior MTG, was the difference between PK and controls significant.

The results of our Face Recognition experiment were then analyzed within specified ROIs (Table IV). The following single *t*-tests were computed: Familiar Face *vs.* Familiar Figure, Familiar Face *vs.* Familiar Inverted Face, Familiar Inverted Face *vs.* Familiar Figure, and Familiar Figure vs. Unfamiliar Figure. The lst contrast was computed to control the effect of familiarity per se.

The Montreal Neurological Institute coordinates were translated to Talairach space using GingerALE software (www.brainmap.org). TalairachClient 2.4.2 was then used to identify the activated structures (Lancaster et al. 2000, www.talairach.org). fMRI group analyses were overlaid on the smoothed grey matter tissue taken from tissue probability maps (TMP.nii) implemented in the SPM12 package.

fMRI – Functional connectivity analysis

The connectivity analysis was additionally applied to clarify the results of the fMRI experiment. We performed functional connectivity analysis using the CONN fMRI connectivity toolbox (v15h, www.nitrc.org/projects/conn, Whitfield-Gabrieli and Nieto-Castanon 2012). The preprocessing of fMRI data for connectivity analysis was similar to that described above, but with an additional step of slice timing taken between motion correction and DARTEL normalization. To eliminate the impact of highly moved volumes on the correlations coefficients 'motion scrubbing' was performed. For each highly moved volume one additional column was added into the design matrix, allowing the variability of the blood-oxygen-level dependent (BOLD) signal related to the salient movements to be removed. The scrubbing was performed using the ART toolbox incorporated in CONN. The threshold of extensive motion was set to default to "conservative" values of a z-value equal to 3, and a differential motion of 0.5 mm. Then temporal filtering (0.008-0.09 Hz) and de-noising (additional regressors generated from white matter and cerebrospinal fluid signals were added to the design matrix) were performed as standard steps of the CONN pipeline.

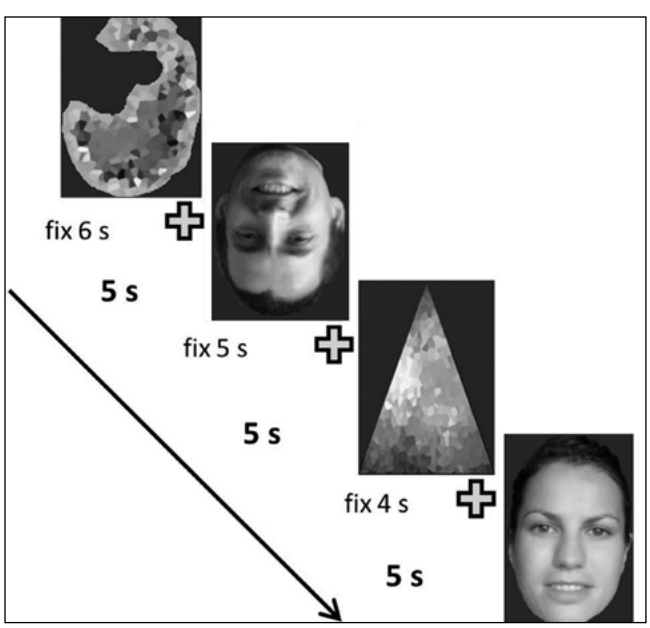

Fig. 3. Experimental procedure – Face Recognition (Experiment II). Examples of 4 trials with four different stimuli that were used in the study: face, inverted face (exemplar photos of one of the authors and a person that gave a permission to use this image), a familiar figure, and an unfamiliar figure. The order of stimuli was pseudo-randomized, with the constraint of no more than three stimuli of the same type presented on consecutive trials.

In the next step, ROI-to-ROI connectivity was computed for each subject and in four experimental conditions: Familiar Face, Unfamiliar Face, Familiar Figure and Unfamiliar Figure. The last two conditions were introduced to the analysis as a control for face recognition conditions. The ROIs used were selected from the same individually assessed ROIs as described above. We focused on the analysis of ROIs referring to four structures: right FG, left FG, right anterior STS, and left anterior STS. Fisher's Z-transform of Pearsons' correlation coefficients between the BOLD signals from the ROIs during particular experimental conditions was used as a measure of connectivity.

Statistical analysis

For the statistical comparison of PK's results with control participants we employed a nonparametric bootstrap analysis (Hasson et al. 2003) that examined the null hypothesis of no difference between PK's results and the group results of the 10 control subjects for each of the analyzed parameters.

In the nonparametric bootstrap analysis, we took the following steps: A subgroup of 10 participants was randomly selected with replacement from the group of 11 participants (including the controls and PK). The mean and the standard deviation of effect sizes in this subgroups were then calculated; The difference between the remaining subject (selected randomly in stage 1) and the mean of the random group, normalized by standard deviation, was estimated. This procedure was repeated 10^4 times and the distribution of the differences was calculated. The observed difference between PK's result in the selected parameter and the results of 10 control participants, normalized by the standard deviation of the

control group placed in this distribution, represents the probability of finding an actual difference.

RESULTS

Eye-tracking

Results of eye tracking examination were statistically analyzed using a nonparametric bootstrap analysis (Hasson et al. 2003). In general, eye tracking measures revealed atypical patterns of eye fixations made by PK while observing face stimuli (see Figs 1 and 2 and Table III). PK's reaction times in the face recognition task were significantly longer than the control group for both novel (P=0.02) and famous (P=0.02) faces. He also recognized significantly fewer famous faces than control subjects (P=0.02). PK's numbers of fixation were significantly lower (P=0.02) and fixation durations were significantly shorter (P=0.04) in comparison to control subjects. Importantly, approximately 87% of fixations for famous faces and 81% for novel ones were directed by PK to the external features of face pictures other than the eyes, nose, and mouth. In contrast, control participants directed more than a half of their fixations towards inner facial features These differences between PK and control subjects were statistically significant for both novel (P=0.03) and famous (P=0.03) faces.

fMRI Experiment I – Localizer

We identified two structures – the FG and OFA – in all participants (including PK). Peak coordinates were identified among reported clusters from the 'Faces *vs.* All' contrast. In most cases the FG and OFA were activated bilaterally. However, in one control subject they were found only in the right hemisphere. The significance threshold was reduced to P=0.01 in this case to identify peak coordinates in the left hemisphere. Fig. 4 illustrates the results of the 'Faces *vs.* All' contrast for PK and for control subjects with family-wise error correction (FWE) for multiple comparisons at the cluster level and a significance threshold of P<0.001 (cluster size > 50 voxels).

fMRI Experiment II – Behavioral results

Subjects' responses were correct if familiar stimuli were judged as familiar and unfamiliar stimuli were judged as unfamiliar. Correct responses were ana-

Table IV. Talairach coordinates of all Face-Related Regions of Interest (ROIs). Values of peak coordinates for PK and mean and extreme (in parentheses) values of peak coordinates for control subjects are presented.

		Peak coordinates (min, max)		
		x	y	z
Right Fusiform Gyrus	Control	39 (36,42)	-52 (-64,-37)	-15 (-18,-11)
	PK	38	-58	-14
Left Fusiform Gyrus	Control	-38 (-42,-35)	-47 (-69,-39)	-13 (-20,1)
	PK	-36	-51	-14
Right Occipital Face Area	Control	43 (33,50)	-79 (-93,-75)	-3 (-18,16)
	PK	44	-88	-3
Left Occipital Face Area	Control	-42 (-51,-30)	-81 (-94,-70)	-3 (-14,22)
	PK	-47	-81	4
Right Anterior Superior Temporal Sulcus	Control	57 (45,71)	-9 (-16,2)	-16 (-23,-6)
	PK	51	-10	-15
Left Anterior Superior Temporal Sulcus	Control	-57 (-66,-48)	-13 (-31,-3)	-11 (-20,4)
	PK	-57	8	-15
Right Posterior Superior Temporal Sulcus	Control	48 (37,55)	-60 (-76,-52)	20 (4,33)
	PK	55	-57	16
Left Posterior Superior Temporal Sulcus	Control	-49 (-57,-40)	-60 (-70,-46)	21 (12,33)
	PK	-57	-43	15

lyzed using a nonparametric bootstrap analysis (Hasson et al. 2003). PK had a correct response rate of 57% for both upright and inverted faces when recognizing familiar stimuli in the Recognition of Familiar Faces and Familiar Inverted Faces tasks. Importantly, he recognized faces of the same people in both positions. In the case of Unfamiliar Faces, he was 100% correct when the faces were presented upright and gave one incorrect answer when faces where inverted (95% correct). In contrast, the control group's mean accuracy rates were as follows: Familiar Faces – 98% (SD=4.05%), Inverted Familiar Faces – 95% (SD=7.1%), Unfamiliar Faces – 99% (SD=1.3%), and Unfamiliar Inverted Faces – 96% (SD=7.8%). Importantly, on a group level control subjects recognized significantly fewer faces in the inverted than upright position (T=2.55; *P*=0.027). PK's recognition rates for Familiar Faces and Familiar Inverted Faces were significantly lower than recognition rates in the control group (in both cases *P*=0.02). Differences between PK and the control group were insignificant in the case of Unfamiliar Faces, Unfamiliar Inverted Faces, Familiar Figures, and Unfamiliar Figures (Fig. 5).

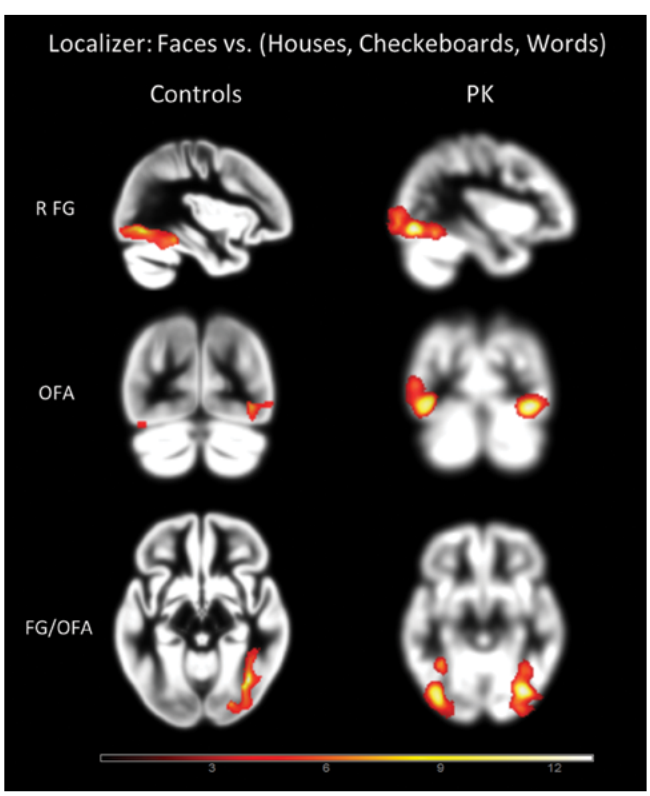

Fig. 4. Results of Localizer Experiment. Brain regions selectively involved in face perception (faces *vs.* all other stimuli: houses, words, and a revolving checkerboard). This contrast was used as a localizer of face sensitive regions (fusiform gyrus, FG and occipital face area, OFA) of interest for further analysis of the data from our Face Recognition experiment. Control subjects' and PK's results are presented separately on smoothed average normalized grey matter (GM) and normalized GM from PK, respectively.

fMRI Experiment II - fMRI results

We found significant differences (*P*=0.03) between PK and the control group in the left anterior STS/MTG in one contrast: 'Familiar Face *vs.* Familiar Figure'. Importantly, contrast estimates for all participants in the control group indicated positive values while PK's contrast values were negative (Fig. 6). We also found a negative contrast estimate value for PK in the left posterior superior temporal sulcus, while the mean value of contrast estimates in the control group was positive (Fig. 6). However, this difference did not reach statistical significance by means of the bootstrap analysis (*P*=0.11) due to the high variance of the results in the control group.

We found no significant differences between PK and control subjects in the rest of the analyzed ROIs (left and right FG, left and right OFA, right posterior STS/MTG, and right anterior STS/MTG). We also did not detect statistically significant differences in the analyzed ROIs in the three control contrasts: 'Familiar Face *vs.* Familiar Inverted Face'; 'Familiar Inverted Face *vs.* Familiar Figure', and 'Familiar Figure vs. Unfamiliar Figure'.

fMRI Experiment II - Functional connectivity results

The connectivity analysis was performed on two experimental conditions: Familiar Face, Unfamiliar Face, and two control conditions: Familiar Figure, Unfamiliar Figure. Statistical exploration with bootstrap analysis of the results of correlations between four ROI's (right FG, left FG, right anterior STS, and left anterior STS) revealed one significant difference between PK and control subjects (Fig. 7). In PK comparisons of Z scores from the first level analysis showed negative correlations between the left and right anterior STS during both Familiar and Unfamiliar Face recognition. In contrast, significantly stronger positive correlations between those two regions were observed in control subjects. These differences between PK and the control group were statistically significant for the Familiar Face (*P*=0.04) and the Unfamiliar Face (*P*=0.03) conditions. In the Familiar and Unfamiliar Figure conditions, connectivity patterns in PK and control subjects did not differ.

DISCUSSION

While previous studies have shown plausible links between ASD and DP (Duchaine et al. 2003, Ellis and Leafhead 1996, Kracke 1994, Njiokiktjien et al. 2001, Pietz et al. 2003), the relationship between these two dysfunctions remains unclear. Kracke (1994) de-

scribed a case of DP with AS, concluding that "face blindness" may be an essential symptom in this type of autism spectrum disorder. Barton et al. (2004) also investigated the relationship between these two conditions. In that study, over 60% of the subjects with social developmental disorders were shown to have impaired face recognition.

Nevertheless, the variety of findings reflects the heterogeneity of all symptoms observed in ASD, and the conclusion is that there is no simple dependence between AS and poor face processing seems to be fully justified. Examples of impaired face memory but not perception have also been demonstrated (Weigelt et al. 2013). It has also been proposed that adults with ASD typically spend less time looking at inner face features than healthy controls (Pelphrey et al. 2002).

Using eye tracking, we showed highly atypical gaze fixation patterns in PK. While observing facestimuli he concentrated his gaze away from the inner features of the face. Using fMRI, in turn, we observed differences in activation of the left anterior part of the STS/MTG between PK and controls during face recognition. Analysis revealed hypo-activation in this region in PK when compared to all control participants. Moreover, right and left anterior STS were under-connected in PK compared to control subjects in this task.

The results of our study suggest that, in the case of PK, the difficulties in face recognition may be related to overlapping mechanisms. The first mechanism is very common among ASD patients, i.e., a specific perceptual strategy that shifts attention away from the eyes of the observed face. Importantly, this atypical pattern of gaze fixations is absent in people diagnosed with DP only (Bate et al. 2008, Lê et al. 2003). In our experiment, the specific pattern of face perception revealed by eye tracking data indicated an ineffective method of face analysis during the face recognition task. Previous reports showed that ASD subjects tend to focus their gaze on the mouth and other lower features (Hernandez et al. 2009, Klin et al. 2002a, 2002b, Klin and Jones 2008, Wagner et al. 2013). In contrast, PK omitted all central parts of the face, including the mouth. This may reflect a strategy (e.g. identification of a characteristic haircut, face shape, eyebrows, etc.) that he developed to compensate for face recognition problems.

The second mechanism revealed by the fMRI results may be common for some prosopagnosic individuals and seems to involve semantic encoding of information associated with face stimuli. First of all, we found normal brain activations in PK's core face areas (FG, OFA). In the context of ASD research, this result is consistent

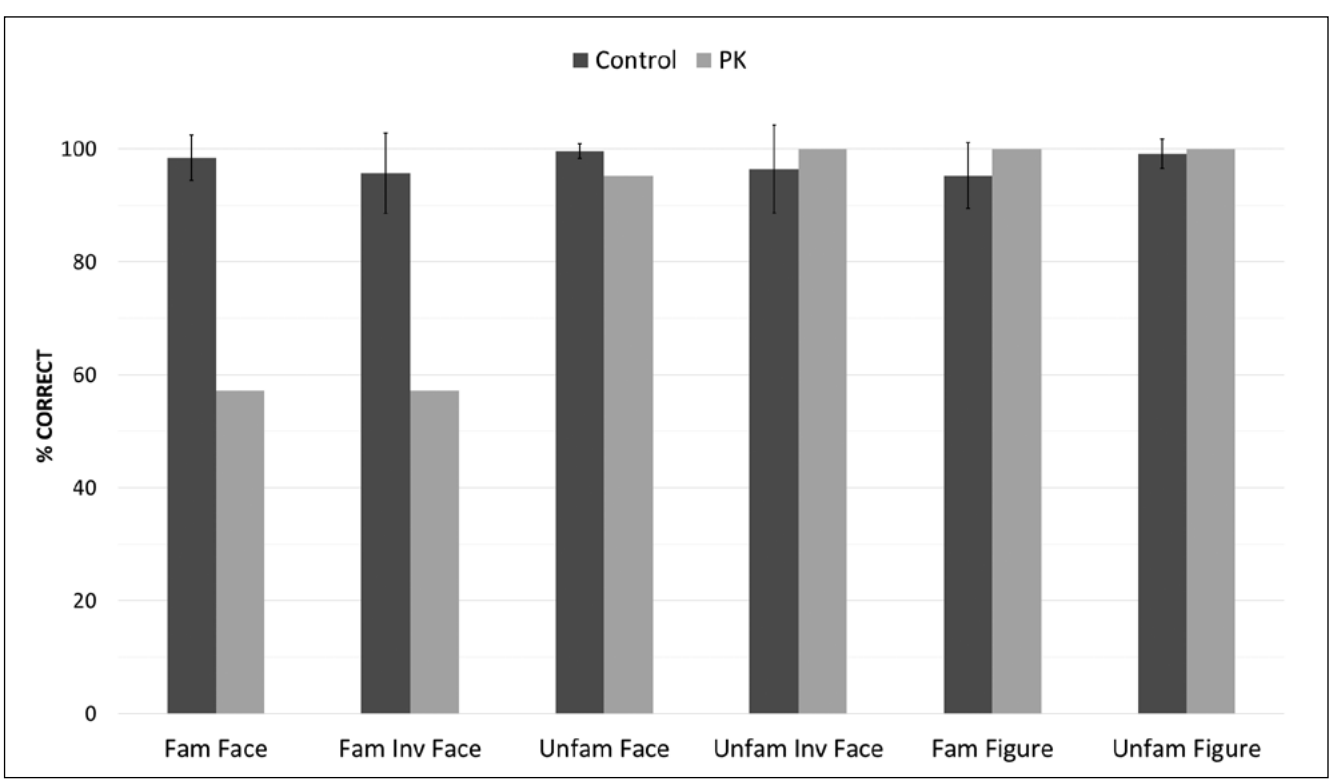

Fig. 5. Behavioral results. Mean percentage of correct responses in a task that required recognition of familiar *vs.* unfamiliar faces/figures. In the case of familiar faces, PK's results were significantly lower (and at chance level) in comparison to control participants. Vertical lines placed over the bars represent standard deviations of mean percentage in the control group.

with data showing normal activation in these structures during recognition of familiar faces (Pierce et al. 2004). Our result is also in line with many previously reported findings referring to DP (Avidan et al. 2005, 2013, Avidan and Behrmann 2008, Bentin et al. 2007, DeGutis et al. 2007, Furl et al. 2011, Hadjikhani and de Gelder 2002, Hasson et al. 2003).

Importantly, hypo-activation in the left anterior part of the STS/MTG differentiated PK from control subjects. We propose that this lack of activation in

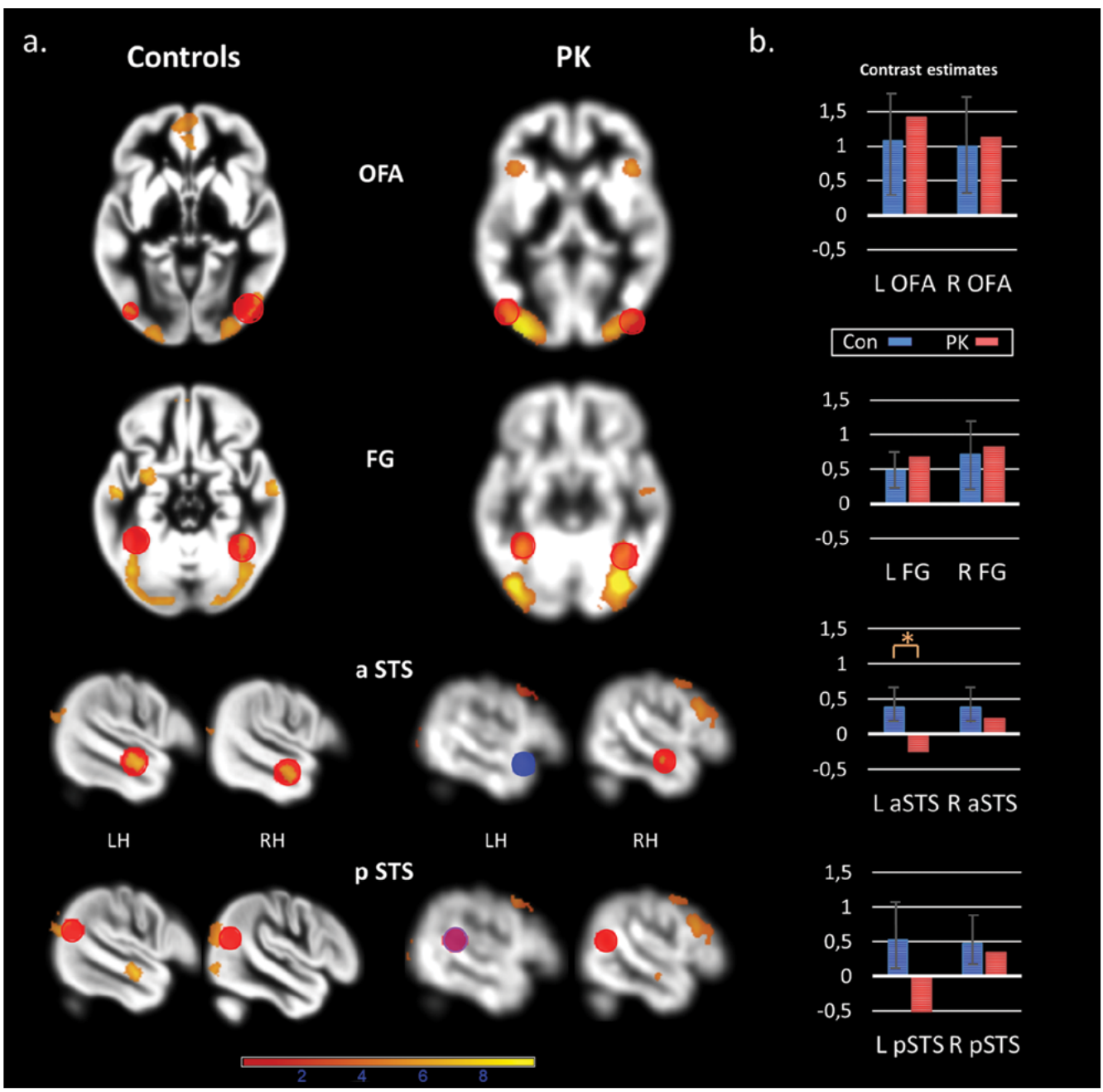

Fig. 6. Results of fMRI Region of Interest (ROI) analyses. Panel a. Note that yellow color represents activations in the 'Familiar Faces *vs.* Familiar Figures' contrast (PK's and control group). Significant differences between PK and control participants were found only in the left superior temporal sulcus/middle temporal gyrus (STS/MTG) while recognizing Familiar Faces in comparison to recognizing Familiar Figures (blue circle). In other ROIs, differences were insignificant (red circles). In the left posterior superior temporal sulcus (pSTS), PK's contrast value was negative and below the mean value of controls; however, the difference was not significant (violet circle). Control subjects' and PK's results are presented separately on GM tissues. Panel b. Contrast estimate values (presented in the y axes of each of the four graphs) in the ROIs that were analyzed in the current study (occipital face area, OFA; fusiform gyrus, FG; anterior STS, aSTS; posterior STS, pSTS): Mean (blue bars) and standard deviation (gray error bars) values in the control group; PK's values (red bars).

the left anterior STS is related to the impaired semantic information retrieval regarding face identity. Our supposition is based on the model of face processing proposed by Gobbini and Haxby (2007). It states that recognition of familiar faces involves the process of retrieval of biographic knowledge about the person,

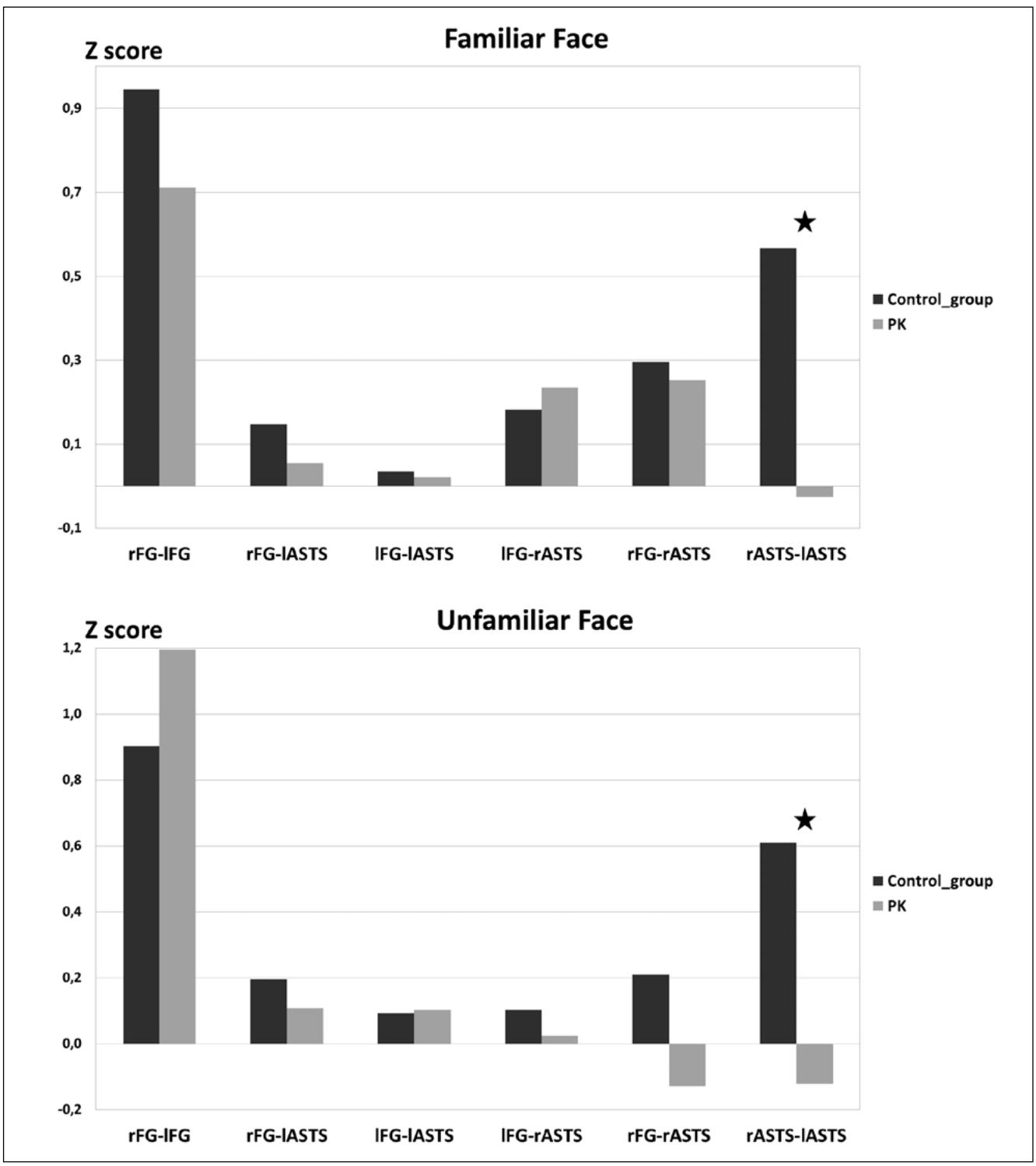

Fig. 7. Results of fMRI connectivity analysis. Comparison of Z scores representing connectivity values between four analyzed ROIs: right FG (rFG), left FG (lFG), right anterior STS (rASTS), left anterior STS (lASTS) for PK (red bars) and control subjects (blue bars). * indicates a statistically significant difference between PK and control subjects. Note that vertical lines placed over the bars represent standard deviations of mean values of Z scores in the control group.

which should be associated with activation of the anterior middle temporal gyrus (Gobbini and Haxby 2007, Haxby et al. 2002). This notion is strongly supported by the results of numerous studies (e.g. Brambati et al. 2010, Gorno-Temipini et al. 1998, Leveroni et al. 2000, Sergent et al. 1992). These early studies used famous faces as stimuli and established the anterior and middle temporal cortex as the brain regions typically modulated by face familiarity (see Natu and O'Toole 2011 for review). For example, Sergent et al. (1992) reported enhanced activation in the bilateral medial anterior temporal gyrus, temporal poles, and the medial temporal poles in the left hemisphere in a famous face identity versus an unfamiliar gender classification test. Gorno-Tempini et al. (1998), in turn, reported activity in the anterior left temporal gyrus when contrasting famous *vs.* non-famous conditions in a task that included faces as well as names as stimuli. This result points to the involvement of similar temporal areas in encoding of semantic knowledge about the person regardless of the stimulus type/modality. Interestingly, Gorno-Tempini and Price (2001) examined the neural response to famous and non-famous faces, and buildings. A direct comparison between famous and non-famous face responses did not show differences in activity in the FG or in the parahippocampal/lingual areas. However, a region in the right anterior MTG was more active for famous versus unfamiliar faces. Gorno-Tempini and Price (2001) also found a region in the left anterior MTG that showed a common effect of fame for faces and buildings. In the case of PK, his deficit was restricted only to the encoding of one type of person-identity-related stimuli (faces). Therefore, it is possible that the hypo-activity of the left anterior MTG/STS revealed in our study could have resulted from under-connectivity mechanism. Indeed, results of the connectivity analysis performed in our study revealed that such under-connectivity in PK refers to the interhemispheric neural communication between right and left anterior STS during face recognition. This result complement results of fMRI analysis showing hypo-activation of the left anterior STS in PK. Both results shed more light on the dysfunctional neural mechanism of face processing in our 'ASD and DP' patient.

Importantly, atypical development of the left STS/MTG was reported in a recent neuroimaging experiment that focused on structural abnormalities in patients with DP (Garrido et al. 2009). Using voxel based morphometry, the authors found reduced gray matter volume in the left STS/MTG among subjects with this disorder as compared to controls. Interestingly, abnormalities of the left anterior STS/MTG were not reported in previous functional and structural studies of ASD.

Additionally, it should be mentioned that in our study we observed hypo-activation in the left posterior STS/TPJ in PK (see Fig. 6B). However, this effect did not reach statistical significance when PK was compared to controls. Abnormal activity in this structure was previously related to the social cognition deficits observed in autism. It was shown that this brain area is underactive in ASD subjects during face perception, especially when the face stimulus is dynamic (gaze and facial expression shifts) (Redcay 2008, Saitovitch et al. 2012, Zilbovicius et al. 2013). In our study, faces were static but they differed in respect to their expressions, possibly causing the increase of activity in the posterior STS in a majority of the control participants and the lack of such activity in PK.

CONCLUSIONS

In summary, our behavioral, eye tracking, and fMRI investigations (including functional connectivity analysis) of PK's case revealed a specific configuration of dysfunctions associated with face processing. Specifically, we found alterations in gaze patterns (omitting the central facial features: eyes, mouth, nose) typical for individuals with ASD. On the other hand, we revealed a neurocognitive mechanism which could be related to the prosopagnosic deficit: normal activations of basic face processing areas (FG and OFA) and hypoactivation in the left anterior MTG/STS as well as the functional underconnectivity between right and left anterior MTG/STS. Therefore, PK's eye tracking and fMRI results indicate a kind of dissociation: his eye tracking results are common in individuals with ASD whereas his fMRI results are in line with findings reported in individuals with DP.

Brain imaging results are consistent with PK's behavioural performance. Covert memory for faces revealed by the WMS test suggests that basic face processing is generally intact in PK. Observed deficits in recognizing familiar faces are based on neural mechanism that impair access to semantic knowledge about the person, possibly due to a disconnection deficit (Brambati et al. 2010).

At the end, it is worthwhile to mention that any conclusion about the neural mechanisms of deficits drawn from a single case has to be treated with caution because of low statistical power. Therefore, effects reported in the current study should be verified in further investigations of larger groups of subjects with impaired face recognition abilities and ASD symptoms. Besides control groups with typically developed subjects, testing additional control groups: one with ASD only and one with DP only would shed more light

on neural basis of deficits observed in 'ASD and DP' patients. A better appreciation of co-occurrence of ASD and DP may help to understand the heterogeneity seen in these conditions. Nevertheless, in-depth assessment of PK made in our study constitutes an important contribution to the field of DP and ASD research,and highlights the need for further investigation of the interplay between those two clinical conditions. While numerous fMRI and eye tracking studies with individuals with ASD or DP constitute the main source of our knowledge about the neural and/or behavioural basis of deficits observed on the group-level in those clinical populations, our case report complements those studies focusing on neural correlates of disturbed functioning of a single 'ASD and DP' patient. Our investigation revealed effects specific for one subject that could be overlooked in group-level comparisons in which only effects common to many individuals are reported. Additionally, our study may be a starting point for group investigations of similar effects (i.e., dysfunction of the STS and under-connectivity of face-areas) in clinical populations with deficits in face perception/recognition.

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