It’s All in the Eyes: Subcortical and Cortical Activation During Grotesqueness Perception in Autism

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters.

Citation
Zürcher, Nicole R., Nick Donnelly, Ophélie Rogier, Britt Russo, Loyse Hippolyte, Julie Hadwin, Eric Lemonnier, and Nouchine Hadjikhani. 2013. It’s all in the eyes: subcortical and cortical activation during grotesqueness perception in autism. PLoS ONE 8(1): e54313.

Published Version
doi:10.1371/journal.pone.0054313

Citable link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:11181041

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA
It’s All in the Eyes: Subcortical and Cortical Activation during Grotesqueness Perception in Autism

Nicole R. Zürcher¹, Nick Donnelly², Ophélie Rogier¹, Britt Russo¹, Loyse Hippolyte¹, Julie Hadwin², Eric Lemonnier³,⁴, Nouchine Hadjikhani¹,⁵*

1 Brain Mind Institute, EPFL, Lausanne, Switzerland, 2 School of Psychology, University of Southampton, Southampton, United Kingdom, 3 Centre de Ressources Autisme de Bretagne, CHRU Brest Hôpital Bohars, Bohars, France, 4 Université de Brest, CHRU Brest Hôpital Bohars, Bohars, France, 5 MGH-HMS-MIT A. Martinos Center for Biomedical Imaging, Harvard Medical School, Charlestown, Massachusetts, United States of America

Abstract

Atypical face processing plays a key role in social interaction difficulties encountered by individuals with autism. In the current fMRI study, the Thatcher illusion was used to investigate several aspects of face processing in 20 young adults with high-functioning autism spectrum disorder (ASD) and 20 matched neurotypical controls. “Thatcherized” stimuli were modified at either the eyes or the mouth and participants discriminated between pairs of faces while cued to attend to either of these features in upright and inverted orientation. Behavioral data confirmed sensitivity to the illusion and intact configurational processing in ASD. Directing attention towards the eyes vs. the mouth in upright faces in ASD led to (1) improved discrimination accuracy; (2) increased activation in areas involved in social and emotional processing; (3) increased activation of cortical areas involved in face processing, including its social and emotional aspects, can be enhanced in autism. This suggests that impairments in face processing in autism may be caused by a deficit in social attention, and that giving specific cues to attend to the eye-region when performing behavioral therapies aimed at improving social skills may result in a better outcome.

Citation: Zürcher NR, Donnelly N, Rogier O, Russo B, Hippolyte L, et al. (2013) It’s All in the Eyes: Subcortical and Cortical Activation during Grotesqueness Perception in Autism. PLoS ONE 8(1): e54313. doi:10.1371/journal.pone.0054313

Editor: Christina Schmitz, Lyon Neuroscience Research Center, France

Received August 22, 2012; Accepted December 12, 2012; Published January 14, 2013

Copyright: © 2013 Zürcher et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: This work was supported by the Swiss National Science Foundation (PP00P3-130191 to NH) and by the Velux Stiftung; by the Centre d’Imagerie Biomédicale (CIBM) of the University of Lausanne (UNIL), the Swiss Federal Institute of Technology Lausanne (EPFL), the University of Geneva (UniGe), the Centre Hospitalier Universitaire Vaudois (CHUV), the Hôpitaux Universitaires de Genève (HUG) and the Leenaards and the Jeantet Foundations. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: nouchine@nmr.mgh.harvard.edu

Introduction

Autism spectrum disorders (ASD) are neurodevelopmental disorders affecting close to 1% of the population, that are characterized by three behaviorally defined symptoms: impaired social interaction, deficits in communication and restrictive and repetitive behavior [1]. Decreased attention to faces, difficulties in reading facial expressions and emotions, failure to orient towards the eye region of the face and difficulties in understanding eye gaze have been reported in numerous studies (e.g. [2,3,4]). These aspects are determinant elements in diagnosis of ASD (e.g. [2,3,4]).

Typical face perception is based on configurational processing, which refers to the sensitivity of the spacing between features of a face, such as eyes and mouth. Those relations, commonly referred to as second-order relations [7], are automatically computed for typical upright faces. Inversion interferes with configurational processing and inverted faces are processed using a feature-based strategy (e.g. [8,9]).

In ASD, there has been a debate whether typical upright faces are processed configururally (e.g. [10,11]) or using a feature-based strategy [12,13]. A recent review of behavioral studies in face processing in ASD has concluded that face identity processing is qualitatively similar between people with ASD and individuals with neurotypical development, but that people with ASD have specific deficits discriminating the eyes during face processing [14].

One of the behavioral paradigms thought of as providing support for configurational processing of faces is the Thatcher Illusion (TI). In the TI the eyes and mouth are inverted relative to the rest of the face [15]. When thatcherized faces are presented upright, they appear weird and grotesque, whereas this effect vanishes when they are presented inverted. The relationship between the TI and configurational processing has been the subject of investigation [8,16,17,18]. Recent studies have confirmed that configurational processing is present in typical upright faces, as well as in upright faces which have been thatcherized at only one feature [19]. In contrast, the role of configurational processing in fully thatcherized faces is unclear [19,20]. Furthermore, we have recently shown that the efficacy of the illusion relies on a network of areas involved in social and emotional processing and which are engaged in mentalizing, including the medial prefrontal (mPFC)/orbitofrontal cortex and the posterior cingulate/precuneus. Discrimination between a typical face and a thatcherized face led to increased activation in the face-processing network when the faces were presented inverted [21]. Studies investigating face processing in normal inverted faces have yielded discrepant results. The face inversion effect has been specifically associated with decreased activation for inverted faces in the fusiform face area (FFA) [22]...
but also with increased activation in the object responsive lateral occipital cortex [23,24].

Our previous work in a neurotypical population demonstrated the pre-eminent role of the eyes in generating the TI [21]. When looking at faces, adults with neurotypical development have a natural tendency to attend more to the eye region [25], and this is not the case in individuals with ASD [2,3,4]. There is evidence that people with ASD, rather than having non-specific difficulties in face processing, are specifically impaired with the processing of the eyes [26,27]. To our knowledge, no fMRI study has so far addressed the contribution of the different features (eyes and mouth) to the TI in ASD. The current study employed Thatcherized stimuli modified to tease apart the relative contribution of different facial features to the TI to further examine the neural substrate of face processing in individuals with ASD.

Previous studies have shown that cueing to the eyes can improve performance in a configural face processing paradigm [11] and elicit typical brain activation in areas associated with face processing in individuals with ASD (e.g. [4,11,28]). Given that the eyes have been demonstrated to play a primary role in driving the TI [21], we hypothesized that cueing to the eyes would increase the sensitivity to the TI and therefore lead to heightened discrimination accuracy as well as to increased activation in cortical areas involved in social and emotional processing in participants with ASD.

Individuals with ASD have a natural tendency to avoid looking at the eyes and experimental designs requiring them to look at the eye region have led to increased amygdala activation [4,29]. Together with the superior colliculus and the thalamus, the amygdala belongs to the subcortical extrageniculostriate route involved in rapid face detection. Given the use of cues to attend to the eye region in the current TI paradigm, we hypothesized that participants with ASD would show increased activation in this subcortical route.

In summary, three hypotheses were tested in this study: Directing visual attention towards the eyes in a TI discrimination task, leads to (1) better behavioral performance (2) increased activation in cortical areas involved in social and emotional processing and (3) increased activation in subcortical areas in individuals with ASD.

Materials and Methods

Participants

Twenty neurotypical controls (NT) and 20 normally intelligent individuals with ASD were enrolled in the study. All participants had normal or corrected to normal vision. Two NT and 4 ASD had to be excluded due to excessive movement during data acquisition. Sixteen participants with ASD (3 females, 23.5 years ±6.8 (mean ± SD)) and 18 NT participants (2 females, 25.8 years ±5.3) were included in the data analysis. Performance intelligence quotient (PIQ) was assessed using the Wechsler Non-verbal Scale or the Wechsler Abbreviated Scale of Intelligence [30,31] and all participants had a PIQ in the normal range. Scores on the first series of the Raven’s Progressive Matrices Advanced were also obtained [32]. Groups were matched for age, PIQ and Raven’s score.

Participants with ASD were assessed by experienced clinicians on the Autism Diagnostic Observation Schedule (ADOS) and on the Autism Diagnostic Interview-Revised (ADI-R) [5,6]. Seven had a diagnosis of Autism, 7 of Asperger’s syndrome and 2 were in the broad spectrum – Pervasive Developmental Disorder not otherwise specified (PDD-NOS). See Table 1 for participants’ characteristics.

The Lausanne University Hospital Ethical Committee approved the protocol and all procedures followed the Declaration of Helsinki. None of the participants were compromised in their capacity to assent/consent, and each of them, or their legal guardian for two minor participants, provided written informed consent after complete description of the study. The subjects in the photograph in Figure 1 gave written informed consent, as outlined in the PLOS consent form, to publication of their photograph.

Behavioral Assessment

In addition to the ADOS and the ADI-R diagnostic tests, and in order to quantify the presence of autism traits, all participants completed the Autism Quotient (AQ) and Empathy Quotient (EQ) self-report questionnaires [27,33]. Student t-tests were conducted to assess differences between groups.

Stimuli

The stimuli used have been described in detail in previous studies [21,34]. Sixteen identities were used. Thatcherized faces were paired with the non-thatcherized versions of the same faces, to create three types of stimulus pairs (face with Thatcherized eyes vs. typical face, face with Thatcherized mouth vs. typical face, and both features Thatcherized vs. typical face) for each identity. It is important to note that the discriminability of the features used in this study (eyes and mouth) has been shown to be equal when the features were presented in isolation with no face contexts [35].

Task Paradigm Used during fMRI (see Figure 1)

Visual stimuli, presented using the E-Prime software package (Psychological Software Tools, Pittsburgh, PA), were back-projected onto a screen positioned at the head of the scanner bore and viewed by the participants through an oblique mirror mounted on the head coil. The experiment was composed of two runs, each consisting of 16 blocks. Runs consisted of a single feature condition (eyes or mouth) alternating with the double feature condition. The sequence of the presentation of the two runs was counterbalanced across participants. A 3 second visual cue preceded each block and stated, “changes have been made to

Table 1. Participant characteristics.

|               | ASD   | NT    |
|---------------|-------|-------|
| N number      | 16    | 18    |
| Age, years    | 23.5 (6.8) | 25.8 (5.3) |
| Non-verbal reasoning |
| PIQ           | 108.7 (13.3) | 112.1 (9.0) |
| Raven’s matrices | 10.3 (1.9)   | 10.5 (1.0) |
| ADI-R Social  | 20.67 (3.94) | N/A   |
| Communication | 12.93 (4.20) | N/A   |
| Stereotypies  | 4.27 (1.83)  | N/A   |
| Development   | 2.93 (1.44)  | N/A   |
| ADOS Social   | 4.00 (1.37)  | N/A   |
| Communication | 7.88 (2.47)  | N/A   |

Note: Data are presented as the mean and standard deviation in parentheses. Abbreviations: PIQ = Performance IQ; ADI-R = Autism Diagnostic Interview- Revised, ADOS = Autism Diagnostic Observation Schedule, N/A = not applicable. doi:10.1371/journal.pone.0054313.t001
the eyes”, “changes have been made to the mouth” or “changes have been made to the eyes and mouth”. Each stimulus pair (modified face and its typical version) was presented for 1,350 ms during which participants responded. A fixation cross was then presented for 1,650 ms. Pairs of faces were presented in upright and inverted orientation, counterbalanced across blocks. Presentation of the target was counterbalanced between the left and the right side of the screen. Participants were told to press the button corresponding to the side of the location of the thatcherized stimulus. A button box was used to record participants’ responses to the stimuli. Behavioral data for two NT participants were lost due to a technical problem.

The main aim of the current study was to investigate the relative contribution of the eyes and the mouth to the TI in ASD; the double feature (modification to eyes and mouth) was also included in the experimental paradigm but does not represent the contrast of interest for the current study. In addition, double feature condition contrasts have to be interpreted with caution, because the cues given to look at the eyes or the mouth were found to have long lasting effects.

fMRI Data Acquisition

Anatomical and functional MR images of brain activity were collected in a 3T high-speed echoplanar-imaging device (Tim Trio, Siemens, Erlangen) using a 12-channel matrix coil. Participants lay on a padded scanner couch and wore foam earplugs. Foam padding stabilized the head. High-resolution (1.0×1.0×1.0 mm³) structural images were obtained at the beginning of the session with a multi-echo magnetization-prepared rapid acquisition gradient echo (ME-MPRAGE) sequence (176 slices, FOV = 256, 256×256 matrix, echo time (TE1) = 1.64 ms, (TE2) = 3.5 ms, (TE3) = 5.36, (TE4) = 7.22 ms; repetition time (TR) = 2530 ms; flip angle = 7°. The co-registered functional acquisition (45 AC-PC slices, FOV = 216, matrix = 64×64, TE = 30 ms, TR = 3,000 ms, 3 mm thick, 3.12 mm by 3.12 mm in-plane resolution, flip angle 90°) lasted 304 seconds. A separate face and object functional localizer run was also obtained in all participants. The localizer scan consisted of alternating blocks of upright faces and objects [36] during which participants had to perform a one-back task.

fMRI Data Analysis

FSL (FMRIB Software Library) package and techniques were used in data preprocessing and analysis. Specifically, FSL Brain Extraction Tool (BET) was used to remove non-brain tissue [37] and fMRI data processing was performed using FEAT (FMRI Expert Analysis Tool) version 5.98. [38,39,40]. Each functional run was first motion-corrected with MCFLIRT [41] and spatially smoothed with full width at half maximum of 8 mm. First-level analysis was performed using FILM (FMRIB's Improved Linear Model), which uses a nonparametric estimation of time series autocorrelation to pre-whiten each voxel's time series [42]. High pass temporal filtering with sigma = 50.0 s was applied to remove low frequency artifacts. Registration to high-resolution structural images was carried out using FMRI’s linear registration tool (FLIRT) [41] and registration to standard space was further refined using FMRI’s nonlinear registration tool (FNIRT, http://www.fmrib.ox.ac.uk/kl/fnirt/index.html). To examine the TI effect, contrasts were conducted between upright faces (involving configural processing and grotesqueness perception) and inverted faces (involving featural processing) for each single feature condition. Mixed effects GLM analyses were carried out across participants using the two stages of FLAME (FMRI’s Local Analysis of Mixed Effects) [43,44,45], an analysis allowing inference about the population from which the subjects were drawn. Threshold significance in the whole brain analysis for the
within group data was $p_{FDR} < 0.05$, corrected for multiple comparisons using false discovery rate (FDR). Activation between groups was compared using a two sample unpaired t-test available in FSL. Statistical maps were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $p < 0.05$ [40].

ROI Analyses

Regions of interest (ROIs) comprised cortical and subcortical areas involved in face and face inversion processing. The cortical ROIs comprised the fusiform face area (FFA), the lateral occipital cortex (LOC) and the pars opercularis of the inferior frontal gyrus (IFG) previously shown to be activated for discrimination of inverted thatcherized faces [21]. Subcortical ROIs consisted of the pulvinar nucleus of the thalamus (PUL) and the amygdala (AMY), both involved in rapid face detection. To avoid circularity, ROIs were defined by anatomical constraints or by independent functional constraints. The AMY and IFG were specified by labels corresponding to the 25% probability cortical and subcortical Harvard-Oxford atlases. The PUL was defined within the thalamic mask of the 25% probability Harvard-Oxford subcortical atlas, following anatomical landmarks [46]. Anatomical ROIs were then mapped back to each participant. An independent functional experiment with faces and objects was performed to define the functional ROIs for the FFA and LOC at the subject level. As there is strong evidence for right hemispheric dominance in face processing (e.g. [47,48]), cortical ROIs were restricted to the right hemisphere. Subsequently, for each ROI, the percentage BOLD signal change was extracted from the mean (for all subcortical ROIs) or from the peak (for all cortical ROIs) of the parameter estimate at the subject-level for the contrasts of interest using FSL’s Featquery. A one-sample t-test against zero was conducted in order to determine whether the percent signal change for the contrast across orientation (upright vs. inverted) was significantly different from zero, indicating that there was increased activation for one or the other Orientation. Effects of Feature (eyes vs. mouth), Group (ASD vs. NT) and Feature x Group interactions were assessed with ANOVAs.

Results

Behavioral Assessment Questionnaires

ASD participants had an AQ score of 30.4 ± 4.6 (mean ± SD) and an EQ score of 25.8 ± 6.7. NT scored significantly lower on the AQ ($t(32) = 9.58, p < 0.001$) and significantly higher on the EQ ($t(32) = 4.78, p < 0.001$) with mean scores of 14.6 ± 5.0 and 39.6 ± 9.6 respectively.

Behavioral Performance during the Thatcher Illusion Discrimination Task (Figure 2)

To assess how efficient participants were at discriminating thatcherized stimuli, we analyzed error rates, indicating wrong choice or omission, as well as reaction times. Error rates were analyzed in an ANOVA repeated over Feature (eyes vs. mouth) and Orientation (upright vs. inverted) with Group as the between-subject factor. As predicted, there was a significant Orientation effect ($F(1,30) = 259.43, p < 0.001$, partial eta-squared $\eta^2_p = 0.90$) and no Orientation x Group interaction ($F(1,30) = 0.26, ns$, $\eta^2_p = 0.009$). Follow-up t-tests confirmed that both groups showed the orientation effect for both features (all $p < 0.05$), demonstrating the presence of the Thatcher Illusion (gotesque-ness detected in upright orientation but not inverted) in both ASD and NT. The interaction between Feature, Orientation and Group was significant ($F(1,30) = 7.40, p = 0.01$, $\eta^2_p = 0.20$). Follow-up t-tests demonstrated that for NT error rates did not differ between eyes and mouth in upright orientation (eyes: (mean ± SEM) 5.0 ± 1.3, mouth: 6.8 ± 1.6, ns), while in inverted orientation they made more errors when cued to the mouth (eyes: 37.8 ± 5.0, mouth: 58.3 ± 3.4, $p < 0.05$). ASD on the other hand, made fewer errors when cued to the eyes compared to when cued to the mouth in upright orientation (eyes: 13.6 ± 3.1, mouth: 23.2 ± 3.2, $p < 0.05$) but only a trend for better discrimination of eyes compared to mouth in inverted presentation (eyes: 50.2 ± 4.2, mouth: 68.4 ± 4.6, $p = 0.06$). Moreover, NT showed higher accuracy than ASD for all conditions (all $p < 0.05$) apart for the condition in which discrimination was made based on the mouth in inverted thatcherized faces (see Figure 2). Reaction times were analyzed in an ANOVA repeated over Feature (eyes vs. mouth) and Orientation of context (upright vs. inverted) with Group as the between-subject factor. A significant Orientation x Group effect ($F(1,30) = 8.17, p < 0.01$, $\eta^2_p = 0.21$) was found. Follow up t-tests showed that this was due to faster reaction times in ASD for the inverted condition (NT upright (mean ± SEM): 840 ms ± 15, ASD upright: 844 ms ± 16, NT inverted: 896 ms ± 25; ASD inverted: 690 ms ± 56, $p < 0.01$).

Within-group Whole Brain Activation, for ASD and NT

Attending to the eyes (see figures 3 and 4, left panels, Table 2). In ASD only, attending to the eyes in upright faces resulted in activation in the subcortical route, amygdala, thalamus pulvinar, and superior colliculus as well as in the hippocampus and the anterior cingulate. For both groups, attending to the eyes in upright faces lead to significant activation in emotion processing and mentalizing areas (mPFC, orbitofrontal cortex, posterior cingulate cortex/precuneus cortex, posterior insula; see activation in...
yellow), whereas attending to inverted faces lead to significant activation in extrastriate visual areas associated with face and object processing (lateral occipital cortex; see activation in blue). NT in addition showed activation in the cerebellum, pallidum and in motor regions of the thalamus.

Attending to the mouth (see figures 3 and 4, right panels, table 2). Attending to the mouth in upright faces resulted in comparable patterns of activation for NT as observed when attending to the eyes (see activation in yellow) whereas ASD exhibited no activation in this condition. For inverted faces, patterns of activation for both groups were comparable to the activation observed when they were cued to the eyes (see activation in blue).

Between-group Whole Brain Activation Analyses

Attending to the eyes (see table 3, figure 5). For upright faces, ASD showed increased activation compared to controls in the thalamus, the caudate, and at a more liberal threshold ($p<0.01$) in the superior colliculus. No area showed more activation in NT vs. ASD for upright faces. For inverted faces, NT exhibited more activation in several areas including the IFG, the anterior insula, anterior cingulate, pallidum, prefrontal cortex and cerebellum. ASD did not show increased activation in any area compared to NT when attending to the eyes in inverted faces.

Attending to the mouth. There were no significant differences between groups when participants were attending to the mouth, both for the upright and the inverted conditions.

At a more liberal threshold ($p<0.001$), NT showed higher activation in a large set of brain areas for upright faces, including areas associated with emotion processing (amygdala, orbitofrontal cortex) and mentalizing (mPFC, posterior cingulate/precuneus, temporal pole). There were no areas for which ASD showed increased activation compared to NT when attending to the mouth in upright faces. For inverted faces, NT exhibited more activation than ASD in the anterior insula, visual cortex, IFG (pars opercularis) and cerebellum (Crus I, VI, VIIIa), while the ASD group showed increased activation in the inferior lateral occipital cortex. IFG (pars triangularis) and superior temporal gyrus were significantly different between groups, with NT showing increased activation for upright faces and ASD for inverted faces.

A priori ROI analysis (see figures 6 and 7). For the cortical ROIs, the FFA, LOC and IFG, activation was significantly different from zero when comparing upright vs. inverted presentation in both groups and in both feature conditions, with increased activation observed for the inverted orientation (all $t>3.33$, $p<0.001$). For the FFA and LOC, ANOVAs revealed no main effect of Group, Feature, or Feature x Group interaction (all $F<3.1$) indicating that ASD showed similar activation than NT in face and object areas. In contrast, a significant Feature x Group interaction.
interaction was found for the IFG ($F_{(1,32)}=5.09, p<0.05$) due to increased activation in NT, specifically when cued to the eyes ($p<0.01$) (See Figure 6).

Results for the subcortical ROIs are shown in Figure 7. One sample $t$-tests against zero conducted to assess differences between orientation revealed a significant activation in ASD for AMY and PUL in both hemispheres, indicating that those areas showed increased activation for upright faces in the eye-cued condition (all $t(15)>2.22, p<0.05$). There was however no significant activation in the mouth-cued condition. For NT, no significant effect was found in either structure for either condition.

Discussion

Using a Thatcher Illusion paradigm, we demonstrated that when individuals with ASD were cued to attend to the eye-region (as opposed to the mouth) in upright faces, they showed increased face discrimination accuracy, enhanced activation in cortical areas involved in social and emotional processing and concurrent hyper-activation in subcortical areas.

Configural Processing and Importance of the Eyes, Evidence from Behavioral Data

The TI is one of the experimental paradigms allowing assessment of configural face processing. Consistent with previous findings [34,49], the behavioral data revealed that individuals with ASD as well as NT are sensitive to the TI, as illustrated by significantly decreased performance for discriminating between a Thatcherized and a typical face when presented inverted as opposed to upright, and the absence of a Group x Orientation interaction.

One of the behavioral marker for a loss of configural processing in faces is a reduced face inversion effect (FIE): the FIE is defined by the reduction in performance for inverted face recognition and identity matching relative to upright faces [8,50,51,52,53]. Initial studies have reported a reduced FIE in individuals with ASD (e.g. [54]). However, further studies have reported normal FIE in this population (e.g. [26,43,55]). Our data add to the body of literature suggesting that impairments in face processing in ASD are not due to a generalized configural processing deficit (reviewed in [11,27]). Individuals with ASD were however generally less accurate than NT in recognizing Thatcherized stimuli, independent of feature and orientation, supporting the hypothesis of difficulties in face processing. The significant interaction of Feature x Orientation x Group found in the current study for error rates resulted from the fact that NT were particularly impaired at discriminating the two faces during the single feature mouth condition in inverted faces. The accuracy of the NT did not differ across single features in the upright condition, due to a performance close to ceiling, but differed for the inverted condition, with cueing to the mouth rendering the task more difficult (See Figure 2). It has been shown that less salient facial regions such as the mouth are more affected by face inversion [56]. On the other hand, individuals with ASD...
Table 2. Within-group contrasts when participants are attending to the eyes and mouth, for upright and inverted conditions. $p_{FDR} < 0.05$.

| Brain region                           | EYES UP ASD | EYES UP CON | MOUTH UP ASD | MOUTH UP CON |
|----------------------------------------|-------------|-------------|--------------|--------------|
|                                        | Hemi x y z  | Z value     | x y z        | Z value      |
|                                        | RH          |             |              |              |
| amygdala                               | LH −24 −4 −24 3.51 | −30 −2 −20 4.9 | RH | |
| thalamus pulvinar                      | RH 12 30 6 3.03 | 28 −6 −16 3.18 |
| superior colliculus                    | LH −6 −32 −2 2.9 |
| anterior cingulate                     | RH 4 44 −2 5.54 |
| hippocampus                            | LH −2 44 −2 5.45 |
| medial prefrontal cortex               | RH 2 36 −16 4.57 4 36 −16 4.58 | 2 46 −16 8.98 |
| Subcallosal cortex                     | LH −6 36 −16 4.76 −4 36 −16 4.6 | −4 38 −24 7.93 |
| Orbitofrontal cortex                   | LH −3 28 28 18 4.04 −28 32 18 3.9 | −28 30 −18 4.02 |
| Posterior cingulate                    | LH −2 46 3 4.6 4 36 6.11 4 | 26 40 4.08 |
| Precuneus                              | LH 6 | 52 18 4.21 −2 38 36 6.7 | 0 58 22 9.02 |
| middle temporal gyrus posterior        | LH −6 36 16 4.07 10 56 26 8.23 | 2 58 22 9.02 |
| middle temporal, anterior              | LH −58 4 34 4.21 −64 14 −24 4.5 | 64 −10 −28 6.39 |
| Superior temporal gyrus posterior      | LH −60 36 0 3.85 −66 4 2.45 |
| Superior temporal gyrus anterior       | LH 52 2 16 3.85 |
| inferior parietal cortex               | LH −56 2 12 4.5 |
| posterior insula                       | RH 54 52 16 4.04 60 62 24 4.62 | 48 −62 28 5.23 |
| parahippocampal gyrus                  | LH 52 52 20 3.21 36 60 26 5.42 | −40 −74 36 6.88 |
| postcentral gyrus                      | RH 52 52 16 4.04 60 62 24 4.62 | 48 4 −62 28 5.23 |
| Precentral gyrus                       | RH 52 52 20 3.21 36 60 26 5.42 | −40 42 4 3.47 |
| caudate                                | LH 18 4 22 3 |
| Cerebellum Crus II                     | LH 18 4 22 3 |
| Occipital pole                         | RH 34 52 16 4.04 36 92 24 4.62 | 58 52 62 4.47 |
| inferior occipital gyrus               | LH 34 52 16 4.04 36 92 24 4.62 | 52 42 62 5 |
| fusiform gyrus (FFA)                   | RH 34 54 4 18 4.02 30 52 16 5.62 | 30 44 20 5.25 |

Thatcher Illusion in Autism
showed better performance when cued to the eyes compared to the mouth in upright faces, and a trend for better discrimination when cued to the eyes compared to mouth in inverted faces. High error rates for the inverted condition were due to higher number of omissions for this orientation. Reaction times did no differ between groups for the upright orientation, however for inverted faces, ASD showed faster reaction times, but did not make fewer errors than NT, suggesting they guessed the answer when the discrimination became particularly difficult.

In conclusion, our behavioral data confirm that individuals with ASD are sensitive to the TI, supporting the presence of configural processing. In addition, they show that directing visual attention towards the eyes, the most salient feature in typical face processing, is key in driving the TI, leading to better face discrimination in ASD.

Experiments using the Thatcher Illusion have shown deficits in configural face processing along with preserved featural processing in individuals with prosopagnosia, a disorder characterized by severe impairments in recognizing familiar faces [18,19]. However,

Table 2. Cont.

| Brain region                        | Hemi | x    | y    | z    | Z value | x    | y    | z    | Z value |
|-------------------------------------|------|------|------|------|---------|------|------|------|---------|
| Lateral occipital cortex            | RH   | 38   | 92   | 12   | 4.26    | 40   | 82   | 4    | 6.07    |
| Inferior temporal, posterior        | RH   | 54   | 60   | 14   | 3.53    | 54   | 60   | 12   | 7.83    |
| superior parietal lobule            | RH   | 26   | 70   | 46   | 6.9    | 30   | 44   | 46   | 7.07    |
| frontal eye-fields                  | RH   | 26   | 4    | 64   | 3.08    | 34   | 2    | 54   | 4.96    |
| precentral gyrus                    | RH   | 50   | 2    | 28   | 4.43    | 54   | 8    | 8    | 5.24    |
| inferior frontal gyrus, pars        | RH   | 48   | 8    | 20   | 5.14    | 56   | 14   | 4    | 5.23    |
| inferior frontal gyrus, pars        | RH   | 54   | 36   | 8    | 3.08    | 52   | 28   | 4    | 3.11    |
| dorsolateral prefrontal cortex      | RH   | 48   | 30   | 32   | 4.03    | 48   | 28   | 30   | 4.89    |
| anterior/lateral thalamus           | RH   | 10   | 14   | 6    | 4.68    | 18   | 24   | 2    | 3.42    |
| pallidum                            | RH   | 18   | 0    | -4   | 3.8     | 18   | 12   | -2   | 3.14    |
| cerebellum Crus I                   | RH   | 40   | -64  | -26  | 3.78    | 40   | -56  | -36  | 3.38    |
| cerebellum Crus II                  | RH   | -28  | -64  | -36  | 3    | -42  | -66  | -34  | 6.11    |
| cerebellum Crus II                  | RH   | 36   | -60  | -44  | 2.57    | 36   | -60  | -44  | 2.57    |
| cerebellum VI                       | RH   | 8    | 70   | 28   | 2.82    | 34   | 64   | 24   | 5.61    |
| cerebellum VIIb                     | RH   | 36   | -62  | -52  | 3.42    | 36   | -62  | -52  | 3.42    |
| cerebellum Vilia                    | RH   | 18   | 50   | -52  | 2.82    | 18   | 50   | -52  | 2.82    |
| cerebellum vermis Viliia            | LH   | -4   | -60  | -40  | 5.59    |  -4  | -60  | -40  | 5.59    |

doi:10.1371/journal.pone.0054313.t002
er, while both individuals with ASD and individuals with prosopagnosia exhibit impairments in processing information from faces, the underlying causes are of very different nature. While prosopagnosia is essentially a disorder of face identification, linked with abnormal function of the FFA and/or occipital face area [36,58,59], face-processing difficulties in ASD are on the other hand mainly associated with deficits in emotional processing, possibly linked to reduced motivation to attend to social stimuli [60].

Enhancement of Social and Emotional Processing by Cueing to Eyes

Activation maps showed that an extensive network of areas involved in social and emotional processing was activated by the discrimination of upright thatcherized faces in both groups. Discrimination of upright faces while attending to the eye-region is the condition for which ASD and NT groups showed the least functional difference. Notably, whole brain analysis showed a similar increase in mPFC and posterior cingulate/precuneus activation for upright grotesque face discrimination while attending to the eyes in both groups. These regions have been implicated in emotional processing, including attribution of emotion/mentalizing [21,61,62,63,64,65]. The mPFC has a role in top down biasing towards treating information as socially relevant [66]. This underlines the fact that if the paradigm requires participants to attend to the eye-region in upright faces, brain activation in areas associated with social processing can be alike in ASD and NT groups. However, when participants were cued to mouths in upright faces, the NT group alone showed activation in the mPFC and the posterior cingulate cortex/precuneus cortex at a more liberal threshold ($p<0.001$). Most of our cognition occurs automatically and without awareness [66]. We speculate that activation in mPFC and posterior cingulate cortex/precuneus cortex could be due to a spontaneous orienting of NT to the eyes, when cued to the mouth, reflecting typical attention to the most salient region of the face, the eye region. Several studies have indeed demonstrated that NT point of regard naturally gravitates to the eyes [67,68]. We suggest that the lack of activation in the aforementioned areas in ASD is due to the fact that ASD, in contrast to NT, strictly follow the cueing instructions and perform the discrimination without implicit emotional processing induced by gazing to the eye-region. Our current findings are however limited by the fact that we did not collect eye-tracking data during fMRI image acquisition, and future eye-tracking studies should help clarifying this point. Amygdala activation correlates with time spent looking in the eye region of the face [69]. Supporting the notion that NT spontaneously re-orient towards the eye region,

Figure 5. Between-group statistical map for the upright vs. inverted eye-cued condition ($Z > 2.3$, corrected cluster significance of $p = 0.05$). This map shows brain regions that are significantly different between groups. To see whether the difference is due to ASD > NT or NT > ASD, refer to Table 3.

doi:10.1371/journal.pone.0054313.g005
increased amygdala activation was observed in the mouth-cued condition in NT. In line with this, a recent combined fMRI eye-tracking study reported increased amygdala activation when typicals as opposed to ASD first looked at the mouth reflecting increased re-orientation to the eye region in typicals [29]. Furthermore, previous research has shown that typically developing children cannot resist an uninformative gaze cue in attention paradigms, which is not the case in children with ASD [70].

**Table 3. Between-group contrasts when participants are attending to the eyes.**

| AREA | X; Y; Z | Zscore |
|------|---------|--------|
| EYES UP>INV | NT>ASD | none |
| | ASD>NT | Caudate | 8; 10; 12 | 3.40 |
| | | Caudate | −18; 20; 4 | 3.16 |
| | | Left thalamus | −14; −28; 14 | 4.25 |
| EYES INV>UP | NT>ASD | Inferior frontal gyrus, pars opercularis | 54;16; −6 | 3.32 |
| | | Anterior insula | 36; 18; 0 | 3.53 |
| | | Anterior insula | −32;22; −4 | 3.39 |
| | | Pallidum | 16; 2; −4 | 3.11 |
| | | Middle cingulate | 10; 18; 38 | 3.19 |
| | | Middle cingulate | −4; 22; 42 | 3.38 |
| | | Precentral gyrus | 46; −4;60 | 3.41 |
| | | Precentral gyrus | −44; −10; 64 | 3.92 |
| | | Dorso-lateral prefrontal cortex | 40; 32; 30 | 3.23 |
| | | Middle frontal gyrus | 38;2; 60 | 3.77 |
| | | Superior frontal gyrus | 8; 0; 70 | 3.43 |
| | | Superior frontal gyrus | −20; 14; 68 | 3.45 |
| | | Supplementary motor area | 8; 6; 68 | 3.23 |
| | | Right thalamus | 18; −24; 14 | 3.95 |
| | | Cerebellum I-IV | 12; −46; −6 | 3.93 |
| | | Cerebellum I-IV | 0; −48; −22 | 3.16 |
| | | Cerebellum VIIIa | 20; −66; −52 | 3.67 |
| | | Cerebellum VIIIa | −20; −64; −25 | 3.18 |
| | | Cerebellum vermis VIIIa | −2; −68; −42 | 3.67 |
| | | Cerebellum VIIb | 26; −68; −52 | 3.22 |
| | | Cerebellum VIIb | −28; −68; −56 | 3.67 |
| | | Cerebellum vermis IX | −2; −56; −32 | 3.14 |
| | | Cerebellum VIIb | −24; −40; −46 | 3.08 |
| | | Cerebellum VI | −32; −52; −30 | 3.06 |
| ASD>NT | none |

| Z|>2.3, cluster corrected p=0.05.  
| doi:10.1371/journal.pone.0054313.t003

增加的 amygdala 活化在 NT 中被观察到，发生于嘴刺激条件。与之相应，最近的结合 fMRI 眼动追踪研究报告了典型相比 ASD 更早将目光放在嘴上，这反映了典型对眼睛区域的重新注意 [29]。此外，前期研究显示，典型儿童不能抵抗无信息的视线线索在注意任务中，而 ASD 中的儿童则不然 [70]。

**Face Processing Network**

面部处理网络涉及一套从顶叶到额叶的皮质和亚皮质区域，包括内侧枕叶皮质、前额叶皮质、眶额区、以及基底节（e.g. [71,72,73,74]）。关于在 ASD 中的 FFA 的作用有多种不同的观点。早期的研究没有控制视线模式，报告了在这一区域减少的激活（e.g. [75,76]），但随后的其他研究则提出了这一降低的激活可能源于在典型中的异常视线模式。这些更近期的研究表明，FFA 激活在脸正向呈现时在典型 [69] 和 ASD [4,28] 中均存在依赖性。

在当前研究中，歧视 Thatcher 化刺激导致扩展的面部处理网络在 ASD 和 NT 中对倒置脸的激活。第一，重要的是要指出，当在倒置脸的背景下，脸或视线是在视线上的刺激，那么在原始方向上，该指向刺激消失，这在倒置面孔时出现。此外，增加的激活在倒置面孔中也可以由于要完成任务的工作量分配而增加，以及由于在倒置面孔中不如原始方向那样在生态上像面孔。

表 3 中的数据显示，没有在 ASD 和 NT 中区分的区域存在。

Table 3. Between-group contrasts when participants are attending to the eyes.

| AREA | X; Y; Z | Zscore |
|------|---------|--------|
| EYES UP>INV | NT>ASD | none |
| | ASD>NT | Caudate | 8; 10; 12 | 3.40 |
| | | Caudate | −18; 20; 4 | 3.16 |
| | | Left thalamus | −14; −28; 14 | 4.25 |
| EYES INV>UP | NT>ASD | Inferior frontal gyrus, pars opercularis | 54;16; −6 | 3.32 |
| | | Anterior insula | 36; 18; 0 | 3.53 |
| | | Anterior insula | −32;22; −4 | 3.39 |
| | | Pallidum | 16; 2; −4 | 3.11 |
| | | Middle cingulate | 10; 18; 38 | 3.19 |
| | | Middle cingulate | −4; 22; 42 | 3.38 |
| | | Precentral gyrus | 46; −4;60 | 3.41 |
| | | Precentral gyrus | −44; −10; 64 | 3.92 |
| | | Dorso-lateral prefrontal cortex | 40; 32; 30 | 3.23 |
| | | Middle frontal gyrus | 38;2; 60 | 3.77 |
| | | Superior frontal gyrus | 8; 0; 70 | 3.43 |
| | | Superior frontal gyrus | −20; 14; 68 | 3.45 |
| | | Supplementary motor area | 8; 6; 68 | 3.23 |
| | | Right thalamus | 18; −24; 14 | 3.95 |
| | | Cerebellum I-IV | 12; −46; −6 | 3.93 |
| | | Cerebellum I-IV | 0; −48; −22 | 3.16 |
| | | Cerebellum VIIIa | 20; −66; −52 | 3.67 |
| | | Cerebellum VIIIa | −20; −64; −25 | 3.18 |
| | | Cerebellum vermis VIIIa | −2; −68; −42 | 3.67 |
| | | Cerebellum VIIb | 26; −68; −52 | 3.22 |
| | | Cerebellum VIIb | −28; −68; −56 | 3.67 |
| | | Cerebellum vermis IX | −2; −56; −32 | 3.14 |
| | | Cerebellum VIIb | −24; −40; −46 | 3.08 |
| | | Cerebellum VI | −32; −52; −30 | 3.06 |
| ASD>NT | none |

| doi:10.1371/journal.pone.0054313.t003

增加的 amygdala 活化在发生于嘴刺激条件下。在 NT 中。与之相应，最近的结合 fMRI 眼动追踪研究报告了典型相比 ASD 的早期视线指向眼睛区域在典型 [29]。此外，前期研究显示，典型儿童不能抵抗无信息的视线线索在注意任务中，而 ASD 中的儿童则不然 [70]。

**Face Processing Network**

面部处理网络涉及一套从顶叶到额叶的皮质和亚皮质区域，包括内侧枕叶皮质、前额叶皮质、眶额区、以及基底节（e.g. [71,72,73,74]）。关于在 ASD 中的 FFA 的作用有多种不同的观点。早期的研究没有控制视线模式，报告了在这一区域较少的激活（e.g. [75,76]），但随后的其他研究则提出了这一较少的激活可能是由于在典型中的异常视线模式。这些更近期的研究表明，FFA 激活在脸正向呈现时在典型 [69] 和 ASD [4,28] 中均存在依赖性。

在当前研究中，歧视 Thatcher 化刺激导致扩展的面部处理网络在 ASD 和 NT 中对倒置脸的激活。第一，重要的是要指出，当在倒置脸的背景下，脸或视线是在视线上的刺激，那么在原始方向上，该指向刺激消失，这在倒置面孔时出现。此外，增加的激活在倒置面孔中也可以由于要完成任务的工作量分配而增加，以及由于在倒置面孔中不如原始方向那样在生态上像面孔。

表 3 中的数据显示，没有在 ASD 和 NT 中区分的区域存在。
decreased activation of the IFG during face processing in ASD. This finding is relevant for a mirror neuron system hypo-activation theory in ASD [80,81]. Additional areas in which participants with ASD showed decreased activation compared to NT included the anterior insula and the cerebellum. The anterior insula is involved in the evaluation of task performance as well as in social and emotional processing; hypoactivation of this region in individuals with ASD is consistent with the findings from neuroimaging studies using social stimuli [82]. The role of the cerebellum in cognitive processing is still poorly understood. Here, differences in the cerebellum were systematically found between the ASD and NT groups for inverted face processing, in areas known to be functionally connected with motor and cognitive association areas [83]. The findings indicate that the role of cerebellum in face processing in individuals with ASD requires further investigation.

Figure 6. Region of interest analysis. Percent BOLD signal change with standard errors for the contrast upright > inverted in cortical areas, including the right FFA, LOC and IFG. Negative values show that inverted faces led to significantly more activation than upright faces in those brain areas.
doi:10.1371/journal.pone.0054313.g006

Figure 7. Region of interest analysis. Percent BOLD signal change with standard errors for the contrast upright > inverted in subcortical areas including the amygdala and the pulvinar for the right hemisphere (rh) and the left hemisphere (lh). Areas that were significantly different across Orientation (upright vs. inverted) are represented in solid color, and only the contours of those that failed to reach significance are shown.
doi:10.1371/journal.pone.0054313.g007
Subcortical System

The superior colliculus, the pulvinar nucleus of the thalamus and the amygdala are key elements of the subcortical face-processing pathway [74,84]. Specifically for the condition in which they were cued to eyes in upright faces, individuals with ASD showed increased activation compared to NT individuals in these subcortical areas.

The development of eye contact seems to be disrupted in ASD, although apparently contradictory results have been reported, with some showing stronger neurophysiological response to direct gaze [85,86,87,88], while others showed no such effect [89,90]. Previous research has suggested that a global face-configuration in newborns activates the subcortical system as a means to orient towards faces, a phenomenon known as CONSPEC [91]. CONSPEC may also be the mechanism underlying eye-contact detection [92,93] that leads to the preference for the eye region seen in NT individuals during face processing, and seemingly absent in individuals with ASD. Expert face processing builds on the maturation of other circuits devoted to face processing, which require sufficient opportunity to process faces and depends on motivation and/or social orienting mechanisms. The subcortical system remains active in neurotypical adults during emotional face processing, allowing rapid orienting towards biologically-relevant stimuli [84,94,95,96,97,98]. In the current study, we saw a greater engagement of the subcortical route for discrimination of grotesque faces in individuals with ASD when cued to look at the eye-region in upright faces. We suggest that this effect may be due to an emotional response induced by looking at the eye-region, possibly resulting from an immature or hypersensitive subcortical system. Increased activation of the subcortical route, a region, possibly resulting from an immature or hypersensitive subcortical system. Increased activation of the subcortical route, a system normally engaged in emotional processing and location of threat in our environment [99], may lead to a mistaken interpretation of threat during face perception that underpins active disengagement from faces, especially from the eye-region in individuals with ASD.

Our data suggest abnormal involvement of the subcortical route during complex face discrimination in the ASD group. Further studies should address neural substrates of eye-contact aversion in individuals with ASD, and test whether an alteration in face-detection systems can provide a theoretical account of a behavior that jeopardizes smooth social interactions.

Conclusions

In conclusion, our data indicate that individuals with ASD are sensitive to the TI, supporting the presence of configural face processing. We observed large group similarities in the face-processing network in response to inverted thatcherized faces. Our results show that directing visual attention towards the eyes in upright faces leads to better behavioral performance and to increased activation in cortical areas involved in emotional and social processing.

Our data also indicate a heightened activation of subcortical areas in ASD when their attention is directed towards the eyes. This observation suggests a mechanism by which over-activity in the subcortical system could lead to unpleasant arousal and active eye-avoidance in people with ASD.

Given the ample evidence of difficulties in eye-discrimination in ASD, one key question has been whether a deficit in face-processing leads to a deficit in social attention, or whether it is the consequence of the latter [27]. Our findings indicate that face-processing, including its social and emotional aspects, may be enhanced in ASD when social attention is warranted by explicit cueing [28]. Our results may also have implications for behavioral therapies aimed at improving face processing. If social attentional processes underlie face-processing difficulties, then, to ensure improvement that generalizes to all aspects of face-processing, explicit cueing to the eyes should be a crucial component of the training.

Acknowledgments

We warmly thank all participants and their families for their time and effort. We thank K. Mététrailler for her support in participants’ recruitment, A. Lissot and T. Ruest for their technical support and C. Burget-Schwab for her administrative support.

Author Contributions

Conceived and designed the experiments: NZ ND JH NH. Performed the experiments: NZ BR NH. Analyzed the data: NZ OR NH. Contributed reagents/materials/analysis tools: EL. Wrote the paper: NZ ND NH.

References

1. APA (2000) Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR. Washington, DC: American Psychiatric Association.
2. Pelphrey KA, Saxon NJ, Reznick JS, Paul G, Goldman BD, et al. (2002) Visual scanning of faces in autism. J Autism Dev Disord 32: 249–261.
3. Klin A, Jones W, Schultz R, Volkmar F, Cohen D (2002) Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. Arch Gen Psychiatry 59: 809–816.
4. Dalton KM, Nacewicz BM, Johnstone T, Schaerfer HS, Gernsheimer MA, et al. (2005) Gaze fixation and the neural circuitry of face processing in autism. Nat Neurosci 8: 519–526.
5. Lord C, Rutter M, Le Couteur A (1994) Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 24: 639–683.
6. Lord C, Risi S, Lambrecht L, Cook EH Jr, Leventhal BL, et al. (2000) The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. J Autism Dev Disord 30: 205–223.
7. Maurer D, Grand RL, Mondloch CJ (2002) The many faces of configural processing. Trends in Cognitive Sciences 6: 255–260.
8. Bartlett JC, Scarry J (1995) Inversion and configuration of faces. Cognit Psychol 25: 281–316.
9. Carbon CC, Leder H (2005) When feature information comes first! Early processing of inverted faces. Perception 34: 1117–1134.
10. Nishimura M, Rutherford MD, Maurer D (2008) Converging evidence of configural processing of faces in high-functioning adults with autism spectrum disorders. Visual Cognition 16: 659–681.
11. Lopez B, Donnelly N, Hafsvik JA, Leekam SR (2004) Face processing in high-functioning adolescents with autism: evidence for weak central coherence. Visual Cognition 11: 673–684.
12. Davison G, Webb SJ, McPartland J (2005) Understanding the nature of face processing impairment in autism: insights from behavioral and electrophysiological studies. Developmental neuropsychology 27: 403–424.
13. Speer LL, Cook AE, McMahon WM, Clark E (2007) Face processing in children with autism: effects of stimulus contents and type. Autism: the international journal of research and practice 11: 265–277.
14. Weigelt S, Koldewyn K, Kanswieder N (2012) Face identity recognition in autism spectrum disorders: a review of behavioral studies. Neuroscience and biobehavioral reviews 36: 1060–1084.
15. Thompson P (1980) Margaret Thatcher: a new illusion. Perception 9: 483–494.
16. Stuerzel F, Spillmann L (2000) Thatcher illusion: dependence on angle of rotation. Perception 29: 957–942.
17. Carbon CC, Schweinberger SR, Kaufmann JM, Leder H (2005) The Thatcher illusion seen by the brain: an event-related brain potentials study. Brain Research Cognitive brain research 24: 554–555.
18. Carbon CC, Gruter T, Weber JE, Laeschow A (2007) Faces as objects of non-expertise: processing of Thatcherised faces in congenital prosopagnosia. Perception 36: 1635–1645.
19. Mesy N, Donnelly N, Menner T, McCarthy RA (2012) Discriminating Thatcherised from typical faces in a case of prosopagnosia. Neuropsychologia. 36: 1635–1645.
20. Donnelly N, Cornes K, Menner T (2012) An examination of the processing capacity of features in the Thatcher illusion. Attention, perception & psychophysics 74: 1473–1487.
53. Scapinello KF, Yarmey AD (1970) The role of familiarity and orientation in human neural systems for face and object perception. Neurosci 22: 189–199.

54. Langlois T (1978) Recognition of faces: an approach to the study of autism. J Child Psychol Psychiatry 19: 255–268.

55. Lahaia A, Mottron L, Arguin M, Berthiaume C, Jemel B, et al. (2006) Face perception in high-functioning autistic adults: evidence for superior processing of face parts, not for a confounding face-processing deficit. Neuropsychologia 20: 30–41.

56. Barton JJ, Keenan JP, Bass T (2001) Discrimination of spatial relations and features in faces: Effects of inversion and viewing duration. British journal of psychology 99 Part 3: 527–549.

57. Malcolm GL, Leung C, Barton JJ (2004) Regional variation in the inversion effect for faces: differential effects for feature shape, feature configuration, and external contour. Perception 33: 1221–1231.

58. Becvar SE, Engel SA (2006) Behavioral deficits and cortical damage loci in cerebral achromatopsia. Cereb Cortex 16: 183–191.

59. Sorger B, Goebel R, Schütz G, Rossion B (2007) Understanding the functional neuroanatomy of acquired prosopagnosia. Neuroimage 35: 836–852.

60. Chavellier C, Kohls G, Trosch S, Scholz R (2012) The social motivation theory of autism. Trends in Cognitive Sciences 16: 231–239.

61. Meng M, Chertian T, Singal G, Sinha P (2012) Localization of face processing in the human brain. Proc Biol Sci 279: 2052–2061.

62. Maddock RJ (1999) The retinotopic cortex and emotion: new insights from functional neuroimaging of the human brain. Trends in neurosciences 22: 310–316.

63. Phan KL, Wager T, Taylor SF, Liberzon I (2002) Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage 16: 331–348.

64. Frith U, Frith CD (2003) Development and neurophysiology of mentalizing. Philosophical transactions of the Royal Society of London Series B, Biological sciences 358: 459–473.

65. Ishai A, Schmidt CF, Boosiger P (2003) Face perception is mediated by a distributed cortical network. Brain Res Bull 67: 87–93.

66. Frith CD, Frith U (2012) Mechanisms of social cognition. Annual review of psychology 63: 207–233.

67. Birmingham E, Bischof WF, Kingston A (2008) Gaze selection in complex social scenes. Visual Cognition 16: 341–355.

68. Kingstone A, Tipper C, Riste J, Nian E (2004) The eyes have it! an fMRI study. Investig. Binoc. Vis. Cogn. 55: 269–271.

69. Morris JP, Pelphey KA, McCarthy G (2007) Controlled scanpath variation alters fusiform face activation. Soc Cogn Affect Neurosci 2: 31–38.

70. Riste J, Mottron L, Friesen CK, Jarroco G, Burack JA, et al. (2005) Eyes are special but not for everyone: the case of autism. Brain Res Cogn Brain Res 24: 715–718. Epub 2005 Mar 23.

71. Hadzhiyev, Hoffman EA, Gobbini MI (2000) The distributed human neural system for face perception. Trends Cogn Sci 4: 225–233.

72. Ishai A (2008) Let’s face it: It’s a cortical network. Neuroimage 40: 415–419.

73. de Gelder B, Friesen I, Barton J, Hadjikhani N (2003) A modulatory role for the amygdala in facial expressions. Neuroimage 16: 395–403.

74. Morris JP, Pelphey KA, McCarthy G (2007) Controlled scanpath variation alters fusiform face activation. Soc Cogn Affect Neurosci 2: 31–38.

75. Schultz RT, Gauthier I, Klin A, Fulbright RK, Anderson AW, et al. (2000) Does the inferior temporal cortex distinguish between face-specific and object-specific processes? The Thatcher Illusion in Autism.
87. Grice SJ, Halit H, Farroni T, Baron-Cohen S, Bolton P, et al. (2005) Neural correlates of eye-gaze detection in young children with autism. Cortex; a journal devoted to the study of the nervous system and behavior 41: 342–353.
88. Joseph RM, Ehrman K, McNally R, Keehn B (2008) Affective response to eye contact and face recognition ability in children with ASD. J Int Neuropsychol Soc 14: 947–955.
89. Senju A, Tojo Y, Yaguchi K, Hasegawa T (2005) Deviant gaze processing in children with autism: an ERP study. Neuropsychologia 43: 1297–1306.
90. Elabbagh M, Volmin A, Cuhica G, Holmboe K, Garwood H, et al. (2009) Neural correlates of eye gaze processing in the infant broader autism phenotype. Biological psychiatry 65: 31–38.
91. Morton J, Johnson MH (1991) CONSPEC and CONLERN: a two-process theory of infant face recognition. Psychol Rev 98: 164–181.
92. Senju A, Johnson MH (2009) The eye contact effect: mechanisms and development. Trends in Cognitive Sciences 13: 127–134.
93. Batki A, Baron-Cohen S, Wheelwright S, Connellan J, Ahluwalia J (2000) Is there an innate gaze module? Evidence from human neonates. Inf Behav Dev 23: 223–229.
94. Vuilleumier P, Armony JL, Driver J, Dolan RJ (2003) Distinct spatial frequency sensitivities for processing faces and emotional expressions. Nat Neurosci 6: 624–631.
95. Pourtois G, Grandjean D, Sander D, Vuilleumier P (2004) Electrophysiological correlates of rapid spatial orienting towards fearful faces. Cereb Cortex 14: 619–633.
96. Brosch T, Sander D, Pourtois G, Scherer KR (2008) Beyond fear: rapid spatial orienting toward positive emotional stimuli. Psychological science 19: 362–370.
97. Winston JS, Vuilleumier P, Dolan RJ (2005) Effects of low-spatial frequency components of fearful faces on fusiform cortex activity. Current biology : CB 15: 1824–1829.
98. Vlamings PH, Goffaux V, Kemner C (2009) Is the early modulation of brain activity by fearful facial expressions primarily mediated by coarse low spatial frequency information? Journal of vision 9: 12 11–13.
99. Mohanty A, Egner T, Monti JM, Mesulam MM (2009) Search for a threatening target triggers limbic guidance of spatial attention. The Journal of neuroscience : the official journal of the Society for Neuroscience 29: 10563–10572.