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Altered Dynamics of the fMRI Response to Faces in Individuals with Autism

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Abstract

Abnormal fMRI habituation in autism spectrum disorders (ASD) has been proposed as a critical component in social impairment. This study investigated habituation to fearful faces and houses in ASD and whether fMRI measures of brain activity discriminate between ASD and typically developing (TD) controls. Two identical fMRI runs presenting masked fearful faces, houses, and scrambled images were collected. We found significantly reduced habituation to fearful faces but not houses in ASD. In addition, amygdala habituation to faces had robust discriminability (ASD versus TD; area under the curve (AUC) = .852, $p < .000$). In contrast, habituation to houses had no predictive value (AUC = .573, $p = .365$). Amygdala habituation to emotional faces may be useful for quantifying risk in ASD.

Keywords

Habituation; faces; houses; amygdala; fusiform; adaptation

Face processing abnormalities in autism spectrum disorders (ASD) and their concomitant social dysfunction have been hypothesized to be associated with reduced habituation (Kleinhans et al. 2009; Pellicano et al. 2007; Swartz et al. 2013; Webb et al. 2010).

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Habituation is the progressive reduction in behavioral responsiveness to repeated similar stimuli (Thompson and Spencer 1966). It is a simple form of learning, observed across species, that underlies animals' capacity to perceptually deemphasize static conditions or inconsequential stimuli in favor of novel, potentially more relevant environmental features or events. It is thought to reflect plasticity (Prescott 1998) and can be disrupted by neural lesions (Thompson and Spencer 1966). This mechanism can also be identified in fMRI studies, as the neural signature of stimulus repetition is decreased activation, or repetition suppression (Ishai et al. 2004; Murray et al. 2006). Reductions in the fMRI signal following repetition is thought to indicate greater processing efficiency (Grill-Spector et al. 2006) and habituation paradigms in fMRI experiments have been used to make inferences about neural sensitivities in specific cortical regions (Fang et al. 2005).

fMRI studies of face processing in typically developing individuals have shown that activation in the amygdala (Breiter et al. 1996; Fischer et al. 2003; Ishai et al. 2004) and fusiform gyrus (Ishai et al. 2004) habituate rapidly over repeated stimulus exposure. Reduced habituation of neurons in the amygdala is thought to impact social orienting responses (Fischer et al. 2003; Dawson et al. 2004) and novelty detection (Wilson and Rolls 1993). Previous work by our group and others has shown that abnormal habituation of amygdala activation to faces is a robust indicator of ASD dysfunction (Kleinhans et al. 2009; Swartz et al. 2013; Wiggins et al. 2013). Specifically, amygdala responses appear to occur more slowly in ASD; that is, amygdala activation does not decrease over time in response to repeated stimuli as quickly as is observed in typically developing individuals. We proposed that atypical amygdala habituation to faces in ASD may reflect difficulty extracting and interpreting important social information from faces and the social environment and difficulty discriminating between salient and non-salient social information. Stimulus overload, secondary to the failure of amygdala neurons to adapt to less important stimuli, may contribute to avoidance of faces and social interactions, and subsequently, the atypical development of the brain networks involved in social cognition. Consistent with this theory, individuals with the most severe social impairments exhibit the least amount of amygdala habituation to faces (Swartz et al. 2013; Kleinhans et al. 2009).

A limitation of prior fMRI studies on habituation in ASD is that only neutral and emotional face stimuli were used in the experiments. Thus, it is not known whether abnormal neural habituation is specific to faces, or a more domain-general mechanism that affects a wide range of complex visual stimuli. This study was designed to address these shortcomings by directly comparing habituation to emotional faces and houses within the same paradigm. In contrast to our original study on habituation to neutral faces (Kleinhans et al. 2009), this paradigm included fearful faces, which are known to show faster repetition suppression than neutral faces (Ishai et al. 2004), and houses, a complex visual stimuli. In addition, the stimuli in this experiment were presented at a rapid rate (23 ms), which controls for factors related to attention and expectations (Grill-Spector et al. 2006). Because the parameters of this study were similar to a study that reported sensitization to faces in ASD, we hypothesized that we would observe altered temporal dynamics of the amygdala BOLD response over time in response to rapid face detection, potentially characterized by increased activation over time that exceeds the peak levels reached by the control group. We did not

predict group differences in habituation to houses, based on previous studies of habituation to non-social visual stimuli in ASD (Verbaten et al. 1991; Webb et al. 2010).

Methods and Materials

Participants

This study is a secondary analysis of previously published (Kleinhans et al. 2011) and unpublished data designed to follow-up and extend our previous study on habituation in ASD (Kleinhans et al. 2009). Twenty-seven adults with an ASD (2 women, 25 men, age range 18–44) and 25 typically developing (TD) controls (2 women, 23 men, age range 18–40) were included. Most participants were also included in earlier fMRI studies by our group (Kleinhans et al. 2009; Kleinhans et al. 2008; Kleinhans et al. 2010). Diagnoses for all participants were confirmed with the Autism Diagnostic Interview-Revised (ADI-R, Lord et al. 1994), the Autism Diagnostic Observation Schedule (ADOS, Lord et al. 2000) and clinical judgment based on all available information. The breakdown of DSM-IV diagnoses for the ASD group is as follows: 11 individuals with autistic disorder, 14 individuals with Asperger's disorder, and 2 individuals with pervasive developmental disorder-not otherwise specified. The ASD and control groups did not significantly differ on age, gender, verbal IQ, performance IQ, or full-scale IQ. Control participants were screened for current and past psychiatric disorders, history of a developmental learning disability, and contraindications to MR imaging. Clinical and demographic information is reported in Table 1.

This study was approved by the University of Washington Human Subjects Institutional Review Board. Informed written consent was obtained from all study participants.

fMRI Data Acquisition

Structural and functional MRIs were performed on a 1.5T Signa MR imaging system (General Electric, Waukesha). FMRI series were collected using an echo-planar pulse sequence (TR/TE 3000/30msec, 21 slices; 6mm thick with 1mm gap, 64×64 matrix, 90 volumes total per run). Each fMRI scan lasted 4 minutes 30 seconds. An SPGR was collected for fMRI registration and anatomical localization (TR= 33 milliseconds, TE= minimum, flip angle =30°, field of view =24 cm, 256 × 256 matrix, scan thickness =1.5 mm, acquisition plane= coronal plane).

Two identical runs were collected within the same scanning session. The fMRI task included 78 pictures of individuals facing forward with a fearful facial expression and 98 houses. The task was described to the participants as a series of images that looked like a flashing checkerboard. Participants were instructed to attend to the pictures at all times and to press the button each time a fixation cross appeared. A fixation cross appeared for 500 ms in the center of the screen pseudo randomly throughout the experiment at an average rate of 1 per 7.157 sec (ISI range = 2 sec – 20 sec). The presence of faces and houses was not mentioned to the participants.

A block-design was used to present four different stimulus types: fearful faces masked by a scrambled image (30 sec per block), houses masked by a scrambled image (30 sec per block), pairs of scrambled images (18 sec per block) and a blank screen (9 sec per block),

which was presented to provide participants a respite from the flashing stimuli (see Kleinhans et al. 2011). The order of the blocks was as follows: Blank-Scramble-Face-House-Face-Scramble-Blank-House-Scramble-House-Face-Blank. The 3 volumes acquired during the first Blank block were not included in the statistical analyses. During the Face and House blocks, pictures were presented for 23 ms then backwards masked with their own scrambled image. The 23 ms rate represented the fastest rate at which controls and ASD subjects did not differ on accuracy of identifying faces vs. houses in a behavioral pre-test administered prior to scanning (see Kleinhans et al. 2011 for details). A scrambled image mask was used instead of a neutral face mask in order to guard against confounding rapid emotional face processing impairments with known impairments in neutral face processing in ASD. The duration of the mask varied (range 63 ms– 150 ms) in order to jitter the inter-stimulus interval between the mask and next picture. Two picture-mask pairs were presented per second; 60 pictures were presented per 30 second block. Each picture was repeated an average of 4 times across the two runs (range 2–8 repetitions). During the scramble blocks, two scrambled images were presented in succession with the same timing parameters as the stimuli in the Face and House blocks.

Post scan debriefing—Immediately upon exiting the scanner, each participant was about the rapidly presented stimuli. First, the participant was verbally asked, “Were you able to see the faces and the houses?” If the participant answered no, the questioning was terminated. If the participant responded “yes,” the examiner asked, “Were you able to see the facial expressions?” If the participant responded no, the questioning was terminated. However, if the participant responded “yes,” s/he was asked, “what type of facial expressions did you see?” All answers were written down.

fMRI Processing and Statistical Analysis

fMRI data analyses were performed using the FMRIB Software Library version 3.3 (FSL; <http://www.fmrib.ox.ac.uk/fsl/>). The following preprocessing steps were applied: the first two volumes were discarded; motion correction was conducted using MCFLIRT; nonbrain structures were removed using Brain Extraction Tool; data were spatially smoothed using a Gaussian kernel of FWHM 5 mm and temporally smoothed using a high-pass filter of sigma = 72 s. Motion related components, identified using Multivariate Exploratory Linear Optimized Decomposition into Independent Components, and the six standard motion parameters generated by MCFLIRT were filtered from the data prior to statistical analyses. Time series statistical analyses were carried out using FMRIB's Improved Linear Model (FILM) with local autocorrelation correction (Woolrich et al. 2001). Individual FMRI data were registered to the high resolution Spoiled Gradient Recalled image and then warped to the MNI152 standard image with an affine transformation using FLIRT (FMRIB's Linear Image Registration Tool) and resampled to 2 mm³ voxels. Eight, first-level analyses were conducted Face₁>Scramble₁; Face₂>Scramble₂; House₁>Scramble₁; House₂>Scramble₂; Face₁>House₁, House₁>Face₁, Face₂>House₂, House₂>Face₂. All habituation analyses used the Scramble condition as the baseline. The Face>House and House>Face contrasts were only used to create the functional localizers in the fusiform gyrus.

Differences in habituation to faces and houses were tested using FSL and Predictive Analytics SoftWare Statistics 18.0.0. (PASW) software. First, we used the standard FSL general linear model approach. We ran a whole-brain repeated-measures higher-level group analysis using FLAME (FMRIB's Local Analysis of Mixed Effects). To investigate between-group differences in habituation, four analyses were conducted 1) paired-samples two-group t-test Face 1 > Face 2; 2) paired-samples two-group t-test Face 2 > Face 1; 3) paired-samples two-group t-test House 1 > House 2; 2) paired-samples two-group t-test House 2 > House 1. Statistical corrections for multiple comparisons were conducted using whole-brain cluster-thresholding based on Markov Chain Monte Carlo sampling set at $z > 2.3$ (voxel height), $p < .05$ (cluster extent). In addition, four a-priori regions of interest (ROI) were anatomically defined on MNI152 and tested separately for each statistical analysis. The brain regions of each ROI mask were: right amygdala, left amygdala, right fusiform gyrus, and left fusiform gyrus. Statistical corrections for multiple comparisons were conducted using cluster-thresholding based on Markov Chain Monte Carlo sampling for each ROI.

Next, we extracted summary scores of the fMRI data and tested two and three-way interaction effects using PASW. Additional procedures were conducted to obtain the data required to test the group by brain region by stimulus-type interaction effects. We focused on four regions of interest (ROIs) : right amygdala, left amygdala, right lateral fusiform (face processing region), and the right medial fusiform (house processing region). We limited our analyses to the right fusiform gyrus in order to reduce the data because of our relatively small sample size. The right hemisphere was selected because the right hemisphere is dominant for face perception in right-handed individuals (Caspers et al. 2013; Bukowski et al. 2013) and the majority of our study participants were right handed (26/27 ASD participants and 21/25 TD participants were right handed). Other cortical regions involved in face processing (e.g., temporal lobes, frontal lobes) were not included in the analyses because they have not been associated with rapid face detection (Johnson 2005) and were not significantly activated by our paradigm (see Online Resource 1, Online Resource 2). Functional localizers (as opposed to the anatomically based localizers used in the FSL-based analyses) were utilized for these analyses. Face-specific and house-specific ROIs in the fusiform gyrus were created by combining all participants ($N=54$, ASD and TD) into a higher-level group analysis using FLAME (FMRIB's Local Analysis of Mixed Effects) for the contrasts $\text{Face}_{1+2} > \text{House}_{1+2}$ (face-specific, lateral fusiform) and $\text{House}_{1+2} > \text{Face}_{1+2}$ (house-specific, medial fusiform) (see Figure 1). Anatomically-based right and left amygdala ROIs were hand drawn within our laboratory on the standard template brain using a previously validated method (Honeycutt et al. 1998). The average z-score within each ROI was computed for each contrast. Thus, each participant had eight scores: Average fearful face activation in the right and left amygdala and right lateral fusiform gyrus for run 1 and run 2, and average house activation in the right medial fusiform gyrus for run 1 and run 2. In addition, an fMRI habituation score was computed for each ROI by subtracting the mean z-score for run 2 from run 1. Average z-scores and habituation scores were imported into PASW.

Results

fMRI Behavioral Performance

Between-group differences on the fMRI behavioral task (button press to fixation cross) were tested using independent samples t-tests. There were 38 events per run, and no significant between group differences in performance were observed for hits, misses, number of incorrect responses, or false alarms ($p > .05$). See Table 2.

Post-scan debriefing results

Data were obtained from all study participants except one control. In the ASD group, 26/28 (93%) participants reported being able to see the faces; of those, 14/26 (54%) reported seeing facial expressions at least occasionally. Of the control participants, 21/24 (88%) reported being able to see the faces and 14/21 (67%) reported seeing facial expressions at least occasionally. Responses that were typical for both groups included: surprised, shocked, angry, excited. Very few participants used the terms “scared” or “fearful”.

fMRI Results

Motion parameters—An independent samples t-test was used to test between group differences in the average root mean square of the absolute motion (RMS_abs; movement relative to the fiducial time point) across the entire run and the average root mean square of the relative motion (RMS_rel movement relative to the previous time point). The average RMS_abs for run 1 was: ASD group mean = 0.272, standard deviation=0.235; TD group mean = 0.141, standard deviation =0.068, $p = .009$ and the average RMS_rel for run 1 was ASD group mean = 0.061, standard deviation = 0.040; TD group mean = 0.041, standard deviation = 0.016, $p = .019$. The average RMS_abs for run 2 was: ASD group mean = 0.255, standard deviation= 0.267; TD group mean = 0.145, standard deviation = 0.067, $p = 0.049$ and the average RMS_rel for run 2 was ASD group mean = 0.060, standard deviation = 0.042; TD group mean = 0.044, standard deviation = 0.020, $p = .085$.

FSL Fearful Faces 1 > Fearful Faces 2

The controls showed significant habituation in the right fusiform gyrus ($p < .05$, ROI volume corrected) while the ASD group showed significant habituation in the bilateral precuneous cortex ($p < .05$, whole brain corrected). In the between group comparison, the control group showed significantly greater habituation than the ASD group in the left amygdala ($p < .05$, ROI volume corrected). No between group differences were found in the fusiform gyrus or any other brain region at the whole brain level. Results are presented in Online Resource 3 and Online Resource 4.

FSL Houses 1 > Houses 2

In the whole brain analyses, the control group exhibited significant habituation in the right frontal pole and right Crus I of the cerebellum ($p < .05$, whole brain corrected). The ASD group did not exhibit significant habituation in any brain region.

FSL Fearful Faces 2 > Fearful Faces 1

The ASD group showed significantly increased activation to fearful faces at run 2 compared to run 1 in the left amygdala ($p < .05$, ROI volume corrected). The TD group did not exhibit increased activation to fearful faces at the second time point compared to the first in any brain region.

FSL Houses 1 > House 2

Neither the TD nor the ASD group showed significantly increased activation to houses at run 2 compared to run 1 in any brain region. Results of fMRI group-level analyses conducted with FLAME are reported in Online Resource 3.

FSL Correlation between fearful face habituation and social dysfunction

The ADOS social score was significantly correlated to the degree of habituation between run 1 and run 2 in the ASD group in the right amygdala ($p < .05$, corrected) (see Online Resource 5). These results signify that individuals with the greatest level of current clinical impairment demonstrated the least amount of neural habituation in response to repeated supraliminal exposure to fearful faces.

PASW Analyses

We investigated the role of stimulus-type, brain region, and diagnosis on habituation rates using the mean activation within our four a-priori regions of interest as our measure of brain activity. A $2 \times 2 \times 4$ repeated measures ANOVA was conducted with diagnosis as the between-group variable and time (run 1 vs. run 2) and brain region (right/left amygdala, right lateral fusiform, right medial fusiform) as the within-subject variables. The dependent variable was average z-score, which was nested under the 16 variables. The three-way interaction was significant [$F(3,48) = 3.808, p = .016$]. In addition, we found a diagnosis by time interaction [$F(1,50) = 18.53, p < .001$] and a brain region by time interaction [$F(3,48) = 3.027, p = .038$] but no significant interaction between brain region and diagnosis [$F(3,48) = .399, p = .755$]. Follow-up tests reveal that the ASD group showed significantly less habituation to faces in the right amygdala [$F(1,50) = 8.317, p = .006$], left amygdala [$F(1,50) = 30.521, p < .001$] right lateral fusiform [$F(1,50) = 4.612, p = .037$]. There was no group-by-time interaction effect for houses in the right medial fusiform [$F(1,50) = .733, p = .396$]. See Figure 2.

We evaluated the diagnostic discriminability of our habituation score for each brain region using Receiver Operating Characteristic curves (see Table 3 for results). Fearful face habituation in the amygdala and lateral fusiform ROIs were able to discriminate between the ASD and TD individuals ($p < .05$). Left amygdala habituation to fearful faces had the strongest predictive value ($AUC = .852, p < .001$); a threshold of habituation score 0 (indicating no reduction in activation across time) detected 21/27 (78%) participants with ASD and correctly excluded 16/25 (64%) of controls (see Figure 3). Habituation to houses had no predictive value ($AUC = .573, p = .365$). We computed a test of the significance of the difference between the areas under the left amygdala Face curve and the right medial fusiform house curve (Hanley and McNeil 1982) and found that face habituation in the left

amygdala was significantly more predictive than house habituation in the fusiform gyrus ($p < .004$, two-tailed).

Discussion

The goal of this study was to determine whether atypical neural habituation to emotional face stimuli reflect a general abnormality in neural habituation to complex visual stimuli, or is specific to these face stimuli. We presented masked fearful faces and masked houses over two scans and tested whether neural adaptation, characterized by reduced activation over time, was present to the same degree in individuals with ASD as in TD controls. Consistent with our prior work (Kleinhans et al. 2009), we found altered temporal dynamics of amygdala activation to faces exhibiting fear in ASD compared to the control group, which was characterized by slowly increasing activation over two runs. In addition reduced pattern of delayed activation to faces was observed in the right lateral fusiform gyrus, also known as the fusiform face area. In contrast, we did not find group differences in habituation to house stimuli within the medial fusiform gyrus, indicating that rapid house processing may not be sensitive to ASD pathophysiology. These results, along with previous work, indicate that measures of atypical neural dynamics in ASD may be especially robust in response to face stimuli (both neutral and emotional), and that the effect is larger in the amygdala than the fusiform face area. However, the extent that this finding extends to other emotionally salient or social stimuli such as touch and voices is currently unknown.

The pattern of activation in the fusiform gyrus was different for faces and houses, and between ASD and controls. In the control group, fusiform face activation significantly habituated over time, in a pattern that was similar to what was observed in the amygdala (see Figure 2). The concordance between rates of habituation in the amygdala and fusiform is consistent with known structural and functional connectivity between these brain regions in healthy controls (Ishai et al. 2004). The ASD group, in contrast, showed discordant patterns of activation. No change in activation to faces over time was observed within the fusiform while increased activation over time as was observed in the amygdala. These findings support previous reports indicating that fusiform activation in ASD is not modulated by the emotional valence of a face to the same degree as in neurotypical adults, potentially due to abnormal connectivity between these regions (Kleinhans et al. 2008; Conturo et al. 2008) in ASD.

A striking feature of our results was the group by time interaction effect, which showed opposite directions of change in activation across time between individuals with ASD and controls, particularly within the amygdala. The ASD participants showed increased activation from the first to the second scan while the controls showed the expected decreased activation across time. In our original study, both groups showed the same general pattern with decreased activation over time, albeit with the ASD group showing less habituation than the controls, and only the most severely affected individuals showed increased activation over time. The stimuli type and timing parameters of each study likely contributed to the different patterns of results observed. Our original study presented neutral faces on the screen for 3 s, which provided time for participants to identify and process the faces. In contrast, this study used a rapid fearful face detection paradigm, with a 23 ms

presentation speed, necessitating a responsive, efficient, subcortical face processing system (Vuilleumier et al. 2003; Adolphs and Tranel 2003). Face information is transmitted in under 100 ms through this subcortical system (Eimer and Holmes 2002; Streit et al. 2003; Braeutigam et al. 2001; Pourtois et al. 2005). Unlike the cortical pathway, which is sensitive to high spatial frequency images of faces (Livingstone and Hubel 1988; Merigan and Maunsell 1993), the subcortical pathway processes low spatial frequency information (Vuilleumier et al. 2003; Adolphs and Tranel 2003). It appears that on average, the individuals in the ASD group did not engage the amygdala during the first scan (see Figure 2, average z-scores are negative at time 1), although fusiform face activation was present at a reduced level. However, normal appearing activation patterns emerged by the second scan, at which point the ASD group attained the same level of activation that was observed by the controls in the first scan. This suggests that the individuals with ASD may engage in slower, inefficient information processing (Bertone et al. 2005; Dawson et al. 2005), which may have been compounded by the simple motor response included in our paradigm (Kenworthy et al. 2013).

The results of this study are also partially consistent with a recent study by Swartz and colleagues (2013), which reported reduced habituation to neutral and sad faces, but not fearful and happy faces. For neutral and sad faces, the ASD group showed reduced habituation characterized by increased activation when comparing faces presented at the beginning of the run to faces presented at the end of the run. This pattern of activation is what we observed in our adult ASD group, albeit with fearful faces. It is unexpected that the fearful faces did not elicit a habituation response in either the control or ASD group in the Swartz study; however, the authors note that developmental differences may be a contributing factor. Our results are consistent with previous studies reporting fMRI habituation to fearful faces are based on adult participants (see, e.g., Breiter et al. 1996) but it is important to note that despite using uniformly fearful faces, participants reported seeing a range of expressions including surprised, shocked, angry, and excited. Very few participants reported that the faces looked “scared” or “fearful”. This study was not designed to address emotion-specific habituation effects, and given the range of findings that have been reported, we expect that abnormal patterns of activation are likely to be present across a range of neutral and emotional facial expressions in ASD.

The impaired adaptation of amygdala neurons to ongoing stimuli may contribute to avoidance of faces and social interactions, and subsequently, the atypical development of the brain networks involved in social cognition. These findings suggest that the limbic system in ASD is slow to process socially salient stimuli. Because the development of face specialization appears to be driven by innate perceptual biases and fine-tuning of the visual system by experience (Simion et al. 2007), face information, which is conveyed with less than 100 ms latencies (Braeutigam et al. 2001; Eimer and Holmes 2002; Pourtois et al. 2005; Streit et al. 2003) may not be processed with the same depth in individuals with ASD. Reduced repetition suppression of neurons in the amygdala is thought impact social orienting responses (Fischer et al. 2003; Dawson et al. 2004) and novelty detection (Wilson and Rolls 1993). Previous work by our group and others has shown that abnormal habituation of amygdala activation to faces is a robust indicator of ASD dysfunction (Kleinhans et al. 2009; Wiggins et al. 2013; Swartz et al. 2013). Atypical amygdala

habituation to faces in ASD may reflect difficulty extracting and interpreting important social information from faces and the social environment and difficulty discriminating between salient and non-salient social information. Because development of face specificity is an experience driven process, information processing difficulties combined with limbic system dysfunction, may preclude individuals with ASD from developing the same level of expertise as typically developing children (Grelotti et al. 2002).

Our data further suggest that amygdala habituation to rapid face, but not house, detection might be a sensitive biomarker for quantifying risk at the individual level. We found reduced habituation in ASD was specific to emotional stimuli and especially pronounced in the amygdala. Given the strength of this finding, we proceeded to evaluate the diagnostic discriminability of our habituation score (average z-score run 1 minus average z-score run 2) using Receiver Operating Characteristic (ROC) curves. The results of the ROC curves indicated that left amygdala habituation to fearful faces had the strongest predictive value (area under the curve = .852, $p < .0001$), which, in addition, was the only area that met criteria for a moderate predictive value. In contrast, habituation to houses had virtually no predictive value. This lends greater support to our theory that measures of amygdala dysfunction are especially sensitive to autism.

Our method has potential clinical utility because of the robust interaction effect between ASD and controls (controls decrease activation over time, ASD increase activation) that can be captured at the individual level. A strength of our approach is that it facilitates identifying individuals who show clinically “reduced” habituation because each person is his/her own control. Our study showed that a threshold set at z-difference = 0, detected 21/27 (78%) participants with ASD and excluded 16/25 (64%) of TD participants (see Fig 7). Although this preliminary finding is promising, further work including high risk children with ASD and children with other developmental disorders is needed to further assess diagnostic utility of this measure.

It is important to note that our study did not find evidence of habituation to houses in either the ASD or control group in the medial fusiform gyrus. This was unexpected, because our non-face stimuli were limited to one exemplar category (i.e., houses) and the house pictures were repeated an average of four times, which would be expected to induce repetition suppression of neural activity (see e.g., Harvey and Burgund 2012). It is possible that group differences in neural habituation to houses might have been observed under different experimental conditions that would lead to neural habituation in the controls, such as increasing the number of stimuli repetitions or presenting the house stimuli for a longer period of time. Note that our whole-brain fMRI analyses did indicate that habituation to houses was present in the left frontal lobe and the cerebellum in the controls, but not the ASD group (see Online Resource 3). These results in addition to a sub-optimal house processing paradigm necessitate that question of habituation to non-social stimuli requires further study. It appears unlikely, however, that individuals with ASD have significant impairments in habituation to non-face stimuli, a result supported by EEG work in young children (Webb et al. 2010). Another factor to consider when interpreting the results of this study is that we did not collect eye-tracking data in the scanner. Although we did not find group differences in our behavioral task included to assess attention, it is possible that

between-group differences in scan paths, such as the ASD group taking longer to learn to fixate on the eyes of the face, contributed to these findings.

Abnormal habituation might be related to amygdalar abnormalities such as reduced numbers of neurons (Schumann and Amaral 2006), volumetric deviations from age-matched controls (Schumann et al. 2004; Sparks et al. 2002; Munson et al. 2006; Pierce et al. 2001; Nacewicz et al. 2006; Aylward et al. 1999), biochemical alterations (Otsuka et al. 1999; Page et al. 2006; Endo et al. 2007; Gabis et al. 2008), and reduced connectivity between the amygdala and the prefrontal cortex (Swartz et al. 2013), which normally dampens the amygdalar response. Another potential mechanism of abnormal habituation is alterations in the ratio of excitatory and inhibitory neurotransmitters. Basic science research has provided convincing evidence that the potentiation of inhibitory connections (γ -amino butyric acid, GABAergic), rather than the depression of excitatory (glutamatergic) connections, drives the cellular mechanisms underlying habituation. Theoretically, the inhibition/excitation imbalance in ASD could be due to either increased glutamatergic (excitatory) signaling, reduced GABAergic signaling or an altered relationship between these two neurotransmitters. A future direction of our work is to investigate the roles of altered GABA and/or Glutamate levels in driving atypical fMRI habituation in the limbic system.

These results suggest that reduced habituation in ASD does not extend to all complex stimuli and reduced habituation to fearful faces is especially pronounced in the amygdala. Fearful face activation in the amygdala shows a unique group-by-time interaction effect, characterized by a pattern of decreased activation in the TD group, and increased activation in the ASD group. We propose that amygdala habituation to emotional faces may be an effective biomarker for quantifying risk at the individual level in ASD. Future studies that investigate the role of GABA and Glutamate may shed light on the biochemical mechanisms driving abnormal neural habituation in ASD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Medial and lateral fusiform masks based on the results of the $F > H$ contrast (lateral fusiform, yellow-orange cluster) and the $H > F$ contrast (medial fusiform, blue cluster). Slices are located at the following MNI coordinates (4, -46, -12). Images are presented in radiological convention (R=L).

Figure 2.
Results of the group by time two-way interaction effects shown by task and brain region. The ASD group is labeled with the red diamonds and the TD group is labeled with blue squares.

Figure 3. Individual habituation data for the left amygdala. The TD individuals are labeled with the blue diamonds and the ASD individuals are labeled with red circles. Higher habituation scores indicate a larger drop in fMRI activation from run 1 to run 2.

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Table 1

Participant demographics

	ASD		TD		p
	M	SD	M	SD	
Age	23.57	6.60	23.32	5.15	.900
FSIQ	110.81	15.68	112.92	12.29	.594
VIQ	110.81	16.50	111.64	11.62	.837
PIQ	108.26	15.87	111.16	14.09	.490
ADOS comm.	3.67	1.33			
ADOS social	8.52	2.72			
ADI-R comm.	13.70	5.02			
ADI-R social	16.96	5.30			
ADI-R rep.	5.59	2.83			

Note. FSIQ = full-scale IQ, VIQ = verbal IQ, PIQ = performance IQ, comm. = communication and language, rep. = restricted and repetitive behaviors.

Table 2

fMRI behavioral results

	ASD		TD		p
	M	SD	M	SD	
Run 1 Hits	37.86	0.35	37.88	0.34	.893
Run 1 Misses	0.14	0.351	0.13	0.34	.893
Run 1 Incorrect	0.07	0.26	0.08	0.28	.847
Run 1 False Alarms	0.38	0.62	0.21	0.51	.285
Run 2 Hits	37.72	0.65	37.54	1.18	.479
Run 2 Misses	0.28	0.65	0.83	2.10	.181
Run 2 Incorrect	0.00	0.00	0.38	1.84	.276
Run 2 False Alarms	0.07	0.26	0.71	1.83	.068

Note. Each scan had 38 targets.

Table 3
Results for the Receiver Operating Curve analysis for all brain regions (N=54)

Area Under the Curve						
Stimuli	Brain Region	Area	Std. Error	Asymptotic significance	Asymptotic 95% Confidence Interval	
Fear	Lateral fusiform	.702 ^b	.073	.0124	Lower Bound	Upper Bound
					.560	.845
House	Medial fusiform	.573	.080	.3646	.416	.731
Fear	Right amygdala	.739 ^b	.071	.0031	.599	.879
Fear	Left amygdala	.852 ^a	.052	.0000	.750	.954

^a moderate predictive value,

^b fair predictive value