Behavioral/Cognitive

Diminished Repetition Suppression Reveals Selective and Systems-Level Face Processing Differences in ASD

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Repeated exposure to a stimulus results in reduced neural response, or repetition suppression, in brain regions responsible for processing that stimulus. This rapid accommodation to repetition is thought to underlie learning, stimulus selectivity, and strengthening of perceptual expectations. Importantly, reduced sensitivity to repetition has been identified in several neurodevelopmental, learning, and psychiatric disorders, including autism spectrum disorder (ASD), a neurodevelopmental disorder characterized by challenges in social communication and repetitive behaviors and restricted interests. Reduced ability to exploit or learn from repetition in ASD is hypothesized to contribute to sensory hypersensitivities, and parallels several theoretical frameworks claiming that ASD individuals show difficulty using regularities in the environment to facilitate behavior. Using fMRI in autistic and neurotypical human adults (females and males), we assessed the status of repetition suppression across two modalities (vision, audition) and with four stimulus categories (faces, objects, printed words, and spoken words). ASD individuals showed domain-specific reductions in repetition suppression for face stimuli only, but not for objects, printed words, or spoken words. Reduced repetition suppression for faces was associated with greater challenges in social communication in ASD. We also found altered functional connectivity between atypically adapting cortical regions and higher-order face recognition regions, and microstructural differences in related white matter tracts in ASD. These results suggest that fundamental neural mechanisms and system-wide circuits are selectively altered for face processing in ASD and enhance our understanding of how disruptions in the formation of stable face representations may relate to higher-order social communication processes.

Key words: autism; diffusion weighted imaging; faces; fMRI; functional connectivity; repetition suppression

Significance Statement

A common finding in neuroscience is that repetition results in plasticity in stimulus-specific processing regions, reflecting selectivity and adaptation (repetition suppression [RS]). RS is reduced in several neurodevelopmental and psychiatric conditions including autism spectrum disorder (ASD). Theoretical frameworks of ASD posit that reduced adaptation may contribute to associated challenges in social communication and sensory processing. However, the scope of RS differences in ASD is unknown. We examined RS for multiple categories across visual and auditory domains (faces, objects, printed words, spoken words) in autistic and neurotypical individuals. We found reduced RS in ASD for face stimuli only and altered functional connectivity and white matter microstructure between cortical face-recognition areas. RS magnitude correlated with social communication challenges among autistic individuals.

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Introduction

A common finding in neuroscience is that repeated exposure to a stimulus results in reduced neural response, as indexed by electrophysiological recordings in nonhuman primates (Miller et al., 1991) and humans (Korzeniewska et al., 2020), and by fMRI in humans (Grill-Spector and Malach, 2001). This form of brain plasticity is referred to as repetition suppression, and is associated with enhanced behavioral speed or accuracy (Gabrieli et al., 1996; Dobbins et al., 2004; Horner and Henson, 2008). Repetition suppression is thought to reflect stimulus selectivity, learning, and the strengthening of perceptual expectations (Summerfield et al., 2008), and has been interpreted as the rapid, experience-driven sharpening of cellular responses (Desimone, 1996) or the product of predictive coding through adaptive changes in the brain (Auksztulewicz and Friston, 2016).

Reduced plasticity or repetition suppression has been found in multiple disorders, including prominently dyslexia (Perrachione et al., 2016; Beach et al., 2022; Gertsovski and Ahissar, 2022), schizophrenia (Möhring et al., 2015), and bipolar disorder (J. Lee et al., 2019). Multiple studies report that autism spectrum disorder (ASD), a neurodevelopmental condition characterized by challenges in social communication and repetitive behaviors and restricted interests, is associated with reduced ability to exploit repetition and regularities in the environment to facilitate behavior (Palmer et al., 2017). These difficulties may be related to the insistence for sameness and adherence to routine characteristic of autistic individuals (Nordt et al., 2016).

Findings of reduced plasticity in response to repetition parallel theoretical frameworks positing that reduced adaptation to the environment may be a core problem in ASD (Pellicano and Burr, 2012; Lawson et al., 2014; Sinha et al., 2014; Van de Cruys et al., 2014) and could contribute to both sensory hypersensitivities and difficulties with social communication observed in ASD. Diminished repetition suppression could reflect mechanistic differences in rapid neural plasticity in ASD, which may underlie the broad reduction in adaptation to the environment seen in these individuals. Indeed, two studies reported reduced repetition suppression for repeated face presentation in ASD adults (Jiang et al., 2013; Ewbank et al., 2017). However, some studies investigating repetition suppression in other visual domains (e.g., objects) found no evidence for differences in repetition suppression in ASD (Ewbank et al., 2017; Utzerath et al., 2018). No studies have investigated whether repetition suppression for auditory or linguistic domains, such as human speech or written words, is also reduced in autistic[1] individuals, possibly paralleling the communication challenges in ASD (e.g., Kjelgaard and Tager-Flusberg, 2001). Therefore, the scope of reduced repetition suppression in ASD, and its relationship to variation among autistic individuals, are so far unknown.

Here, we assessed the status of repetition suppression in ASD in two modalities (vision, audition) and with four stimulus categories (faces, objects, printed words, and spoken words). We used an *a priori* ROI approach focused on cortical regions most associated with the perception of faces (right fusiform gyrus [FusG]), spoken words (bilateral superior temporal gyrus), printed words (left FusG), and objects (bilateral lateral occipital cortex [LOC]). Across these stimuli, we could address one primary, preregistered hypothesis and two alternative hypotheses: (1) that autistic individuals may show reduced repetition suppression to a broad range of stimuli, as seen in other disorders, and individual differences in repetition suppression would be related to ASD symptom severity (preregistered, https://osf.io/5vsjn); (2) that reduced repetition suppression in ASD may be found only for stimuli related to their differences in social communication or repetitive behaviors, namely, faces and spoken words; and (3) that reduced repetition suppression in ASD may be limited to explicitly social stimuli, namely faces. To better understand the systems neuroscience of atypical repetition suppression in ASD, we also measured functional connectivity and the microstructure of white matter tracts between atypically adapting cortical regions and the rest of the brain.

[1]Throughout the manuscript, we use identity-first language (e.g. "autistic individuals") rather than person-first language (e.g. "individuals with autism") to respect the preferences of many in the autistic community (Vivanti, 2020; Bottema-Beutel et al., 2021).

Materials and Methods

Participants

We report data from $N = 53$ English-speaking adult participants between the ages of 18 and 45 [$n = 28$ ASD (9 female, 19 male); $n = 25$ neurotypical (NT, 9 female, 16 male); Table 1]. All participants completed the Kaufmann Brief Intelligence Test (KBIT) matrix-reasoning and verbal intelligence subscales (Kaufman and Kaufman, 2004), and the KBIT matrix reasoning subscale was used as a measure of nonverbal intelligence. To confirm participants' self-reported autism diagnosis, the Autism Diagnostic Observation Schedule (ADOS, ADOS-2) (Lord et al., 2000) was administered by a research-reliable staff member to all autistic participants. The ADOS is a diagnostic semi-structured interview between an administrator and participant. A calibrated severity score was calculated using the revised algorithm for each participant (Hus and Lord, 2014). The final sample was a subset of the $N = 68$ ($n = 39$ ASD, $n = 29$ NT) originally recruited for participation. Across all participants, exclusion criteria included history of hearing or visual impairments (not including corrected-to-normal vision), incidental findings on MRI ($n = 12$), and KBIT matrices standard score <80 ($n = 3$). For NT participants, additional exclusion criteria were a family history of ASD or other neurologic disorder. Handedness was not an exclusion criterion ($n = 6$ left-handed, $n = 47$ right-handed). Certain participants did not complete all four tasks or showed excessive motion on only a subset of tasks. Therefore, final sample sizes differed by task: $n = 53$ for the faces and spoken words tasks (28 ASD, 25 NT), $n = 51$ for objects (26 ASD, 25 NT), and $n = 48$ for printed words (23 ASD, 25 NT) (Table 1). All participants provided written informed consent and were compensated for their time in accordance with the Massachusetts Institute of Technology Committee on Use of Humans as Experimental Subjects (Massachusetts Institute of Technology Institutional Review Board).

Experimental design

Hypothesis preregistration. Initial hypotheses and analyses plans were preregistered at the Open Science Framework website, OSF (https://osf.io/5vsjn, Experiment 1). Based on prior findings of category-general repetition suppression differences in dyslexia (Perrachione et al., 2016) and other disorders, we hypothesized that ASD individuals would also show category-general repetition suppression reductions compared with NT individuals, and that individual differences in the magnitude of repetition suppression would negatively correlate with ASD symptom severity.

Repetition suppression tasks. To measure repetition suppression, participants completed four rare-target detection tasks performed under two blocked conditions (repeating and nonrepeating) while in the scanner (for additional details, see Perrachione et al., 2016). The manipulation of repetition was orthogonal to the detection task. The structure of each task was the same, but the stimulus category (type of stimulus) varied across tasks (Fig. 1). Participants passively attended to one kind of stimulus category (faces, objects, printed words, or spoken words) in each task (total of two runs of each task, see below for task presentation details). The order of tasks was counterbalanced across participants. Within each task, participants viewed (or heard) blocks of repeating and nonrepeating stimuli, as well as rest blocks (9.6 s per block; total of 10 blocks of repeating and 10 blocks of nonrepeating stimuli per run of

Table 1. Participant characteristics[a]

	ASD	NT
N	28 (9 F/19 M)	25 (9 F/16 M)
Age (yr)	27.65 ± 7.28	27.5 ± 5.47
KBIT Matrices Standard Score	107.14 ± 15.06	113.16 ± 13.42
ADOS Communication	3.57 ± 1.52	—
ADOS Social	7.68 ± 2.51	—
ADOS Restricted and Repetitive Behaviors	2.82 ± 1.76	—
ADOS Total	11.25 ± 3.61	—
ADOS Calibrated Severity Score	14.71 ± 4.74	—

[a]Data are group means ± SD.

each task). The order of the blocks was pseudorandomized such that the same condition was not presented for two sequential blocks. During "repeat" blocks, a single stimulus was repeated 8 times. During "nonrepeat" blocks, eight unique stimuli were presented. Stimuli remained on the screen for 700 ms (with the exception of spoken word stimuli, which varied in length within the allowable 700 ms), with a 500 ms interstimulus interval. Rest blocks were the same length as other task blocks, and participants fixated on a light gray "+" and waited for the next stimulus to appear. Within each task, a total of 160 unique stimuli were assigned to the nonrepeat condition, and 20 unique stimuli were assigned to the repeat condition. In each block, one stimulus was designated as the "target," which was indicated to participants either by vertically inverting the image (faces, objects, printed words conditions) or time-reversing the recording (spoken words). A total of 20 stimuli were designated as targets in each condition. Participants were asked to press a button when they detected the target stimulus to ensure that they maintained attention to the stimuli in each block.

Task stimuli. Visual stimuli were presented in the center of a 1024 × 768 pixel display with a dark gray background. Face stimuli consisted of 180 grayscale photographs of male and female individuals. Each photograph was cropped close to the face to minimize hair and background (size: 256 × 256 pixels). Object stimuli consisted of 180 color photographs of objects in isolation on a white background of 256 × 256 pixels. Printed word stimuli consisted of 180 monosyllabic nouns (bold, Arial font) on a white background box of 256 × 256 pixels. Words were between 3 and 5 letters in length. Spoken word stimuli consisted of 180 monosyllabic nouns spoken in isolation by one adult female native English speaker, and recorded at 44.1 kHz and 16 bits. Audio stimuli were filtered to match the frequency response of the Sensimetrics insert ear MRI compatible earphones. Recordings of each word were between 234 and 591 ms in duration. Participants fixated on a white "+" while listening to spoken words.

Imaging acquisition. Data were acquired on Siemen's PRISMA 3T scanner with a 32-channel head coil. At the beginning of each scanning session, a high-resolution T1-weighted (T1w) volume was acquired (parameters: TR = 2530 ms, TE 1/2/3/4 = 1.69/3.55/5.41/7.27 ms, voxel size = 1.0 mm^3, slices = 176, FOV = 256 mm^3). T2*-weighted EPI functional scans were collected using simultaneous multislice acquisition (interleaved, acceleration factor = 5) and contained 348 volumes per run (total of 696 volumes per task; parameters: TR = 850 ms, TE = 32 ms, voxel size = 2.5 mm^3, slices = 55, FOV = 210 mm^3). Diffusion-weighted scans were also acquired using EPI sequences (parameters: TR = 3000 ms, TE = 86 ms, voxel size = 2.0 × 2.0 × 2.2 mm, 64 noncollinear directions collected at b = 1000 and b = 3000 s/mm^2, four non–diffusion-weighted volumes (b = 0), FOV = 220 mm^3).

Preprocessing. Preprocessing was performed using fMRIPrep (Esteban et al., 2019). Each T1w volume was corrected for intensity nonuniformity and skull-stripped. Spatial normalization to the ICBM 152 Nonlinear Asymmetrical template version 2009c was performed through nonlinear registration with ANTs version 2.1.0, using brain-extracted versions of both the T1w volume and template. Brain tissue segmentation of CSF, white matter, and gray matter was performed on the brain-extracted T1w using FSL *fast*. Functional data were motion-corrected using FSL *mcflirt* and coregistered to the T1w image using boundary-based registration with FSL *flirt*. The motion correcting transformations, BOLD-to-T1w transformation and T1w-to-template (MNI) warp were concatenated and applied in a single step using ANTs. Normalized functional images were smoothed with a 6 mm FWHM Gaussian kernel to reduce uncorrelated spatial noise. Framewise displacement was calculated for each functional run. Outliers were defined as any volume for which framewise displacement was >0.5 mm. Participants with > 20% of volumes marked as outliers were excluded from further analysis for that task.

Statistical analysis

In-scanner performance. To determine whether individuals successfully maintained attention throughout the task, participants were asked to press a button every time they saw an inverted stimulus (in the domains of faces, objects, and printed words) or heard temporally reversed speech. Hit rate (number of hits/number of targets) was compared between groups (Table 2). In-scanner behavioral data were incomplete for $n = 3$ participants on the spoken word task and $n = 1$ participant on the printed word task; therefore, these participants were excluded from calculations of hit rate in those tasks.

fMRI modeling and analysis. All first- and second-level modeling was done in SPM12. Normalized and smoothed images were entered into a first-level GLM. For each run, repeating and nonrepeating blocks were entered as regressors. Outliers were entered as nuisance regressors. We operationalized repetition suppression as the difference (contrast) between activation during nonrepeating blocks versus activation during repeating blocks (nonrepeat > repeat) for each stimulus category. *A priori*, atlas-based ROI analyses were used to determine whether there were group differences in repetition suppression in areas canonically associated with processing these stimulus categories. Single-subject contrast images were masked with ROIs from the Brainnetome Atlas (Fan et al., 2016) to investigate repetition suppression within core regions of the face (right FusG, ventrolateral area 37), speech (bilateral STG, rostral area 22), reading (left FusG, ventrolateral area 37), and object processing (bilateral LOC) networks. The Brainnetome altas parcels are based on functional connections as well as anatomic features (Fan et al., 2016). The selected regions are the primary selective processing regions for each kind of stimulus used and encompassed areas exhibiting repetition suppression to these stimuli in prior research (Perrachione et al., 2016). We confirmed the appropriateness of these ROIs in our sample by overlaying their locations on the statistical parametric maps of whole-brain, group-level repetition suppression for each stimulus category across all participants (Fig. 2). We further confirmed that repetition suppression effects in our unilateral ROIs also exhibited the known functional asymmetries for printed words (left FusG) and faces (right FusG) by comparing the differences in repetition suppression magnitude for each ROI versus its analog in the contralateral hemisphere. Indeed, repetition suppression was greater in the right FusG for faces and in the left FusG for words (paired *t* tests for faces $t_{(52)} = 7.09$, $p < 0.001$, Cohen's $d = 0.64$ (right > left) and printed words $t_{(47)} = 4.48$, $p < 0.001$, $d = 0.42$ (left > right)). Parameter estimates were extracted from ROIs using REX as implemented in the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012), and a series of linear regression models were used to determine whether group (ASD, NT) was a significant predictor of repetition suppression when accounting for other confounding factors. Group was the model term of interest, and we included several covariates of no interest including age, nonverbal intelligence score (KBIT matrix reasoning), sex, a covariate for sex × group interaction, and mean framewise displacement. For each stimulus category, the model was specified as follows:

$$Y_{\text{BOLDfromROI}} \sim X_{\text{Group}} + X_{\text{Age}} + X_{\text{Sex}} + X_{\text{Sex:Group}} + X_{\text{KBITmatrices}} + X_{\text{meanFD}} \quad (1)$$

Task-based functional connectivity. Task-based functional connectivity analyses were performed using the CONN toolbox as implemented in MATLAB (Whitfield-Gabrieli and Nieto-Castanon, 2012). fMRI data were first preprocessed in CONN (realigned, normalized to segmented structural image, and spatially smoothed at 6 mm FWHM). Data were high-pass filtered at 0.01 Hz and denoised using CompCor (Behzadi et

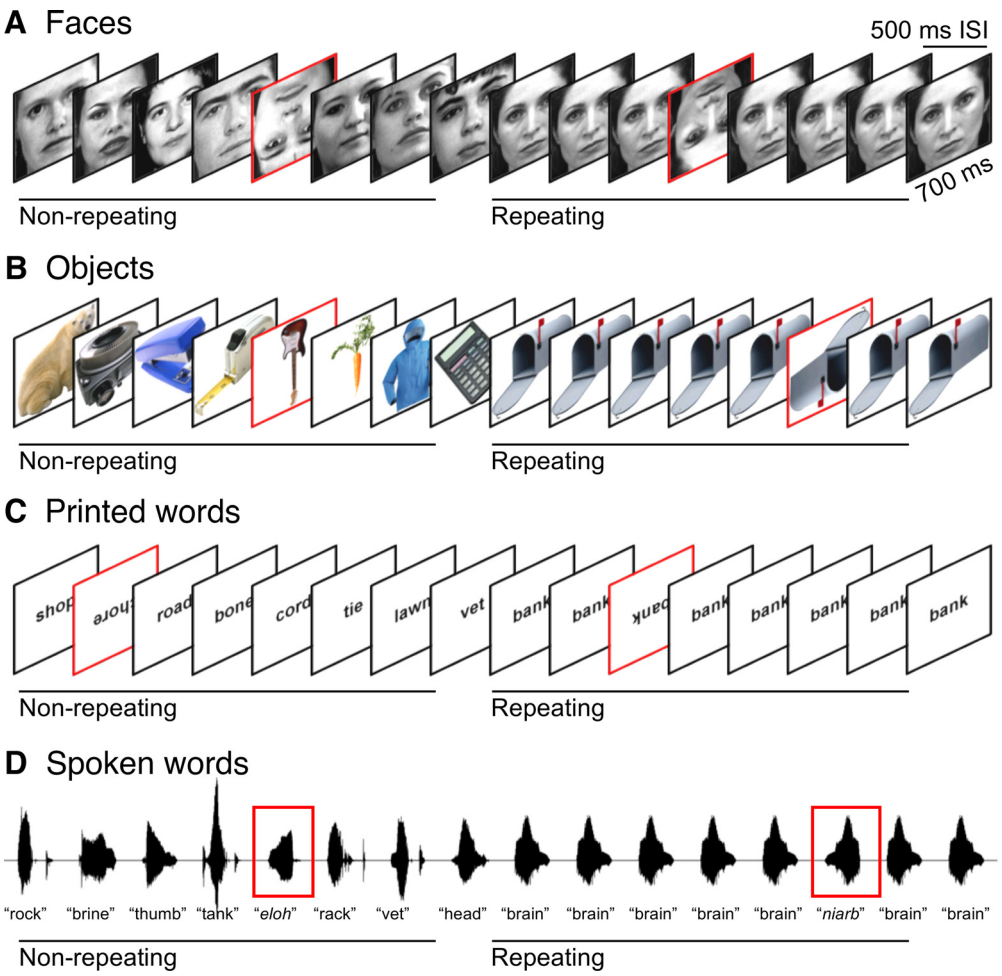

Figure 1. Repetition suppression task schematic. Example blocks of nonrepeating and repeating stimuli are shown for each stimulus category: (***A***) faces, (***B***) objects, (***C***) printed words, and (***D***) spoken words. Participants monitored for the rare target stimulus, which was vertically (visual stimuli) or temporally (auditory stimuli) inverted (shown here with a red border).

al., 2007) to remove noise components arising from white matter and cerebrospinal areas, and participant-specific motion parameters. Task-based functional connectivity analyses were performed as a weighted GLM. The right FusG ROI used in the univariate fMRI analysis was used as the seed for seed-to-voxel functional connectivity. At the first-level, whole-brain correlation maps were computed for each condition (non-repeating, repeating contrast). At the second level, we examined whether seed-to-voxel functional connectivity patterns for nonrepeating versus repeating faces differed by group (group × condition interaction). Results were thresholded at $p < 0.001$ (voxelwise, uncorrected), with a cluster correction for multiple comparisons at FDR < 0.05. As above, linear mixed effects models were used to determine whether group differences remained significant when controlling for confounding factors (age, KBIT nonverbal intelligence, sex, a covariate for sex × group interactions, and mean framewise displacement).

Diffusion weighted imaging analysis. $N = 24$ ASD and 23 NT adults had usable diffusion-weighted images (DWIs). *QSIPrep* (Cieslak et al., 2021) was used to preprocess the DWIs. Using *MRtrix3* (Tournier et al., 2019), DWI images were denoised (Veraart et al., 2016), corrected for Gibbs ringing (Kellner et al., 2016), and corrected for B1 field inhomogeneity (Tustison et al., 2010). After B1 bias correction, the mean intensity of the DWI series was adjusted so all the mean intensity of the b = 0 images matched across each separate DWI scanning sequence. Head-motion and Eddy current correction with outlier replacement was performed in FSL (Andersson and Sotiropoulos, 2016). We used a *fieldmap-less* approach for susceptibility distortion correction (Huntenburg, 2014; Wang et al., 2017). Finally, the image was resampled to 1.2 mm isotropic voxels and aligned to ACPC space. *TractSeg* (Wasserthal et al., 2018a) was used to reconstruct white matter tracts and perform tractometry with fractional anisotropy (FA) values. The diffusion tensor was fit to the preprocessed DWI images, and FA maps were calculated. These maps were registered to an MNI FA template provided by TractSeg, and this transformation was applied to each participant's FA maps, diffusion images, and brain masks. B-vectors were rotated accordingly. Multitissue fiber response functions were estimated using *MRtrix3* (Dhollander et al., 2016, 2019). Fiber orientation densities (FODs) were estimated via multishell multitissue constrained spherical deconvolution (Tournier et al., 2004, 2008; Jeurissen et al., 2014). FODs were intensity-normalized (Raffelt et al., 2017). The first three principal FOD peaks were extracted and flipped along their *x* axis to correct their orientation. These peaks were fed into *TractSeg* to segment the right inferior longitudinal fasciculus (ILF) and inferior fronto-occipital fasciculus (IFOF) (Wasserthal et al., 2018b, 2019, 2020). We generated a fixed large number (5000) of fibers per instance to reduce inter-run variability accounting for the stochastic nature of reconstruction. FA values were calculated for 100 nodes along the length of the tract (Chandio et al., 2020). At each node, we used a nonparametric permutation-based statistical comparison (Nichols and Holmes, 2002) with 5000 iterations to look for group differences (two-sampled *t* tests) in FA, accounting for multiple comparisons given the correlative structure between adjacent nodes (Yeatman et al.,

Table 2. In-scanner behavioral performance by stimulus category[a]

Task	ASD	NT
Faces	0.95 ± 0.12	0.97 ± 0.07
Objects	0.89 ± 0.08	0.94 ± 0.05
Spoken words	0.89 ± 0.15	0.94 ± 0.08
Printed words	0.97 ± 0.06	0.96 ± 0.07

[a]Data are mean ± SD hit rate.

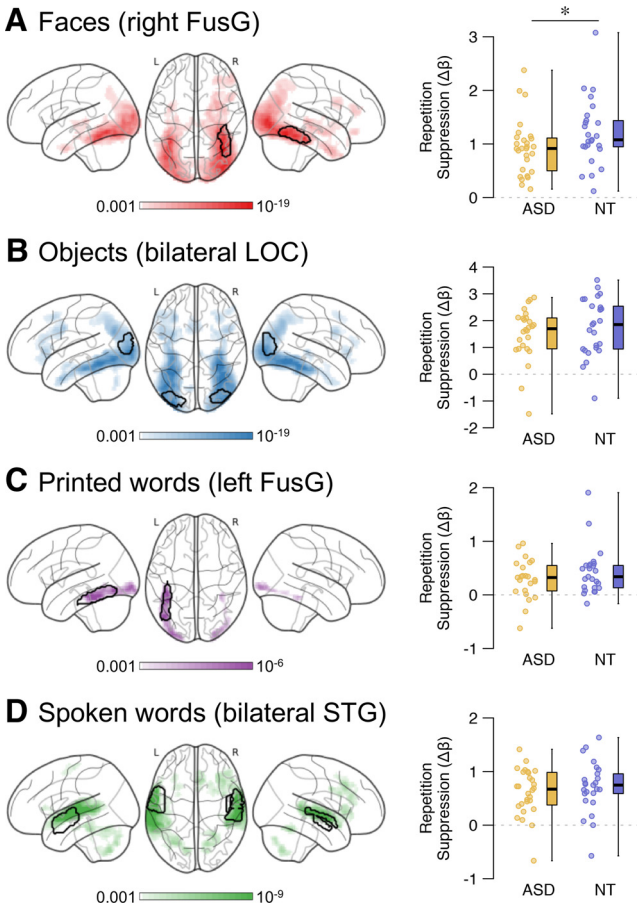

Figure 2. Repetition suppression for each stimulus category ROIs by group. Left, Glass brains show voxelwise *p*-values for statistical parametric maps for the group-level univariate no-repeat > repeat contrast across all participants (voxel $p < 0.001$, cluster $p_{FWE} < 0.05$). Thick black outlines indicate *a priori* ROIs. Right, Values extracted from these ROIs. ***A***, The ASD group had significantly less repetition suppression to faces in the right FusG ROI than the NT group. ***B–D***, For all other stimulus category ROIs, the ASD and NT groups did not differ in the magnitude of repetition suppression. Points indicate mean repetition suppression (difference between nonrepeating and repeating conditions) for each participant. *$p < 0.005$.

2012). As before, we linearly regressed out age, KBIT nonverbal intelligence, sex, and a covariate for sex × group interactions. We additionally regressed out motion, as indexed by mean framewise displacement, as motion artifacts have been shown to confound group comparisons involving ASD (Yendiki et al., 2014).

Behavioral correlations. Spearman correlations between repetition suppression measured in the atlas-based ROIs (described above) and ADOS scores were conducted in R.

Data availability

Code and neuroimaging data are available at OSF (https://osf.io/5vsjn).

Results

Behavioral results and in-scanner performance

There were no significant group differences in KBIT nonverbal IQ between groups ($t_{(51)} = 1.54$, $p = 0.13$). In the scanner, accuracy was high for all stimulus categories tested in both groups (Table 2). For detection of target stimuli (hit rate), there were no significant group (ASD vs NT) differences for faces ($t_{(46.5)} = 0.58$, $p = 0.57$, $d = 0.16$), spoken words ($t_{(40)} = 1.48$, $p = 0.15$, $d = 0.42$), or printed words ($t_{(44.4)} = -0.39$, $p = 0.70$, $d = 0.12$). For objects, however, the NT Group had a significantly higher hit rate than the ASD Group ($t_{(39.4)} = 2.47$, $p = 0.02$, $d = 0.70$; ASD < NT). However, after FDR adjustment for multiple comparisons, there were no significant group differences in hit rate.

Repetition suppression in ROIs

We first determined whether repetition suppression occurred within the *a priori*, independently defined, atlas-based ROIs that reflected stimulus-specific processing regions for each stimulus category (faces, objects, printed words, and spoken words). Repetition suppression values were extracted from each ROI for each stimulus category across both ASD and NT groups. One-sample *t* tests versus zero in each group determined that both ASD and NT groups showed significant repetition suppression for faces within the right FusG ROI (NT $t_{(24)} = 9.64$, $p < 0.001$, $d = 1.93$; ASD $t_{(27)} = 9.41$, $p < 0.001$, $d = 1.78$), objects in the bilateral LOC ROI (NT $t_{(24)} = 8.06$, $p < 0.001$, $d = 1.61$; ASD $t_{(25)} = 7.80$, $p < 0.001$, $d = 1.53$), printed words within the left FusG ROI (NT $t_{(24)} = 4.92$, $p < 0.001$, $d = 0.98$; ASD $t_{(22)} = 3.79$, $p < 0.001$, $d = 0.79$), and spoken words in the bilateral STG ROI (NT $t_{(24)} = 7.47$, $p < 0.001$, $d = 1.49$; ASD $t_{(27)} = 7.56$, $p < 0.001$, $d = 1.43$) (Fig. 2).

Group differences in repetition suppression

For each stimulus category (faces, objects, printed words, spoken words), a separate linear regression model was used to determine whether there was an effect of group (ASD, NT) on repetition suppression when controlling for age, sex, sex × group interaction, nonverbal IQ, and mean framewise displacement. We first assessed the significance of each linear regression model. Across all four models, only the model for faces was significant (faces adjusted $R^2 = 0.24$, model $p = 0.005$; objects model adjusted $R^2 = 0.11$, $p = 0.09$; printed words model adjusted $R^2 = -0.003$, $p = 0.45$; spoken words model adjusted $R^2 = -0.05$, $p = 0.73$). Within the model for repetition suppression to faces, the contrast on the group model term was significant ($\beta = 0.56$, SE = 0.18, $t_{(47)} = 3.04$, $p = 0.004$), with the ASD group showing reduced repetition suppression compared with the NT group (Fig. 2*A*). The group model term was not significant across other categories (group terms: objects $p = 0.11$ printed words $p = 0.21$; spoken words $p = 0.67$).

Temporal development of repetition suppression

Repetition suppression has a temporal component, with increasing suppression occurring as a function of increasing stimulus repetitions. It is possible that repetition suppression in ASD might have occurred with a delayed time course while nonetheless reaching NT levels, but that differences in the dynamics of RS between groups were obscured when averaging across entire blocks. We therefore examined early versus late suppression by modeling the first and second half of each block separately. We conducted linear mixed effects modeling for effects of group (ASD vs NT), timing (early vs late), and their interaction, while controlling the same confounding factors as before, and now also including participant as a random intercept to account for repeated measures. Repetition suppression was greater in NT than ASD across the entire time course (main effect of Group: $\beta = 0.28$, SE = 0.09, $t_{(46)} = 3.17$, $p = 0.003$). Repetition suppression was also stronger in the second half of the block than the first (main effect of timing: $\beta = 0.19$, SE = 0.06, $t_{(51)} = 3.07$, $p = 0.003$), but there was no group × timing interaction ($\beta = 0.08$, SE = 0.06, $t_{(51)} = 1.28$, $p = 0.21$) (Fig. 3).

Relation of repetition suppression in ASD with increased symptom severity

We examined the association between ASD symptom severity (as measured by the ADOS) and repetition suppression to faces in individuals with ASD to assess how individual differences in

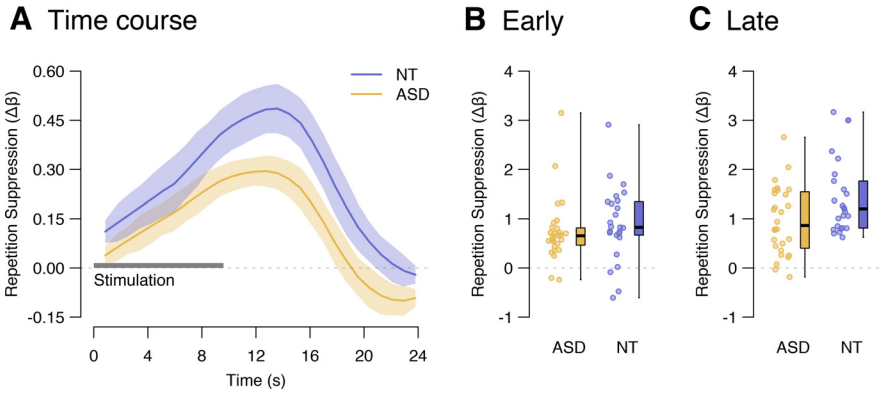

Figure 3. Temporal development of repetition suppression to faces. ***A***, The time course of repetition suppression magnitude in the right FusG ROI for each group, estimated with a finite impulse response model (mean ± SEM across participants). ***B***, Repetition suppression magnitude to faces in the right FusG ROI estimated over stimuli in the first half versus (***C***) second half of each task block. Across both groups, repetition suppression was stronger in the second half of the block than the first. Across the time course, repetition suppression was greater in the NT than the ASD group.

repetition suppression may relate to social and communication challenges. Lesser repetition suppression was associated with higher calibrated severity scores in ASD (Spearman's $\rho = -0.38$, $p < 0.05$). The calibrated severity score collapses across severity in multiple domains (Social Communication, Social Interaction, and Restricted and Repetitive Behaviors). We therefore also examined correlations between each ADOS subscore and repetition suppression to faces. After Bonferroni–Holm correction for multiple comparisons, only the association between lesser repetition suppression and greater social communication symptom severity was significant ($r = -0.46$, $p = 0.013$) (Fig. 4).

Group differences in task-based functional connectivity during repetition suppression

To assess whether repetition suppression for faces was associated with differences in functional connectivity between cortical regions, we examined whether there were group differences in connectivity from the right FusG ROI while individuals attended to nonrepeating versus repeating faces (group × condition interaction). Whole-brain seed-to-voxel analyses revealed two significant clusters: the right anterior temporal lobe (ATL, $t_{(51)} = 5.81$, cluster $p_{FDR} = 0.03$) and the left orbitofrontal cortex (OFC, $t_{(51)} = 5.74$, cluster $p_{FDR} = 0.03$). The group × condition interaction term remained significant after controlling for age, sex, IQ, and other factors as above (ATL: $\beta = 0.009$, SE = 0.001, $t_{(51)} = 6.46$, $p < 0.001$; OFC: $\beta = 0.01$, SE = 0.002, $t_{(51)} = 5.92$, $p < 0.001$). The NT Group showed greater connectivity between right FusG and right ATL and left OFC for nonrepeating faces compared with repeating faces. However, the ASD group showed greater functional connectivity between right FusG and these regions for repeating faces than for nonrepeating faces. We conducted *post hoc* tests to determine whether this interaction was driven by group differences in the Repeating condition, the Nonrepeating condition, or both; these tests took form of Equation 1, but for each condition separately. These ANOVAs revealed a significant effect of Group in both conditions in both the right ATL (repeating: $F_{(1,46)} = 6.08$, $p < 0.02$, $\eta_p^2 = 0.12$; nonrepeating: $F_{(1,46)} = 21.21$, $p < 0.00{,}004$, $\eta_p^2 = 0.32$) and left OFC (repeating: $F_{(1,46)} = 10.29$, $p < 0.003$, $\eta_p^2 = 0.18$; nonrepeating: $F_{(1,46)} = 8.14$, $p < 0.007$, $\eta_p^2 = 0.15$) regions (Fig. 5).

Microstructural differences in white matter tracts supporting face processing

Differences in functional connectivity patterns associated with repetition suppression may be related to structural differences in white-matter tracts important for face recognition. We examined group differences in FA in two white matter pathways that connect visual face processing regions with higher-order temporal and frontal regions: right ILF and right IFOF. Compared with the NT Group, the ASD Group had reduced FA in an anterior segment of the right ILF ($d = 1.11$) (Fig. 6). There were no group differences in the right IFOF.

Discussion

By examining four stimulus categories across two modalities, this study provides new evidence to characterize the extent and specificity of neural repetition suppression differences in ASD. Face-specific repetition suppression was reduced in autistic individuals, and greater social communication challenges were associated with smaller repetition suppression among ASD individuals. There were no group differences in repetition suppression for objects, spoken words, or printed words. ASD individuals detected targets as well as NTs in all stimulus categories, suggesting similar attention in both groups. Last, functional connectivity between right FusG and higher-order face recognition regions in ATL and OFC, as well as microstructural differences in underlying white matter tracts, suggest a systems-level difference in face processing in ASD.

Category-specific repetition suppression reductions in ASD

Here, repetition suppression was operationalized as the difference in neural activation for novel versus repeating stimuli. Repetition suppression effects capture stimulus selectivity within brain regions (Grill-Spector and Malach, 2001), as well as plasticity associated with adapting to or learning about a repeating stimulus (Berlot et al., 2021). In the present study, we found less repetition suppression for faces in FusG in ASD, which might reflect reduced plasticity in tissue important for face perception. The FusG in particular is a key region for face processing and contains the fusiform face area (FFA), a region selective for face perception (Kanwisher and Yovel, 2006). Repetition suppression in FusG may reflect plasticity related to strengthening the representations of initially novel faces. Indeed, greater repetition suppression in this region is associated with better face and identity discrimination (Hermann et al., 2017). FusG and FFA are often structurally atypical in ASD (van Kooten et al., 2008; Libero et al., 2014; Ammons et al., 2021) and have altered functional organization and selectivity for faces (but not other visual stimuli, such as objects or houses) (Pierce et al., 2001; Deeley et al., 2007; Humphreys et al., 2008).

A key finding of the present study is that repetition suppression differences in ASD were limited to faces and not found for other visual or communicative stimuli, such as objects, speech, or printed words. Prior studies also reported reduced repetition suppression for faces in ASD individuals and in NT individuals with high autistic traits (Ewbank et al., 2015, 2017; although see Hendriks et al., 2021 for contradictory findings), despite others reporting typical repetition suppression for objects in ASD

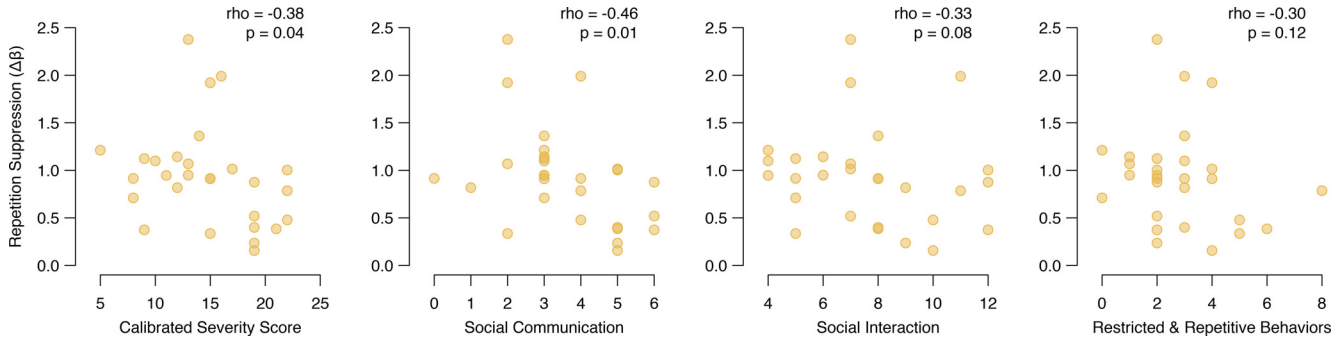

Figure 4. Greater challenges in autism are associated with reduced repetition suppression to faces in right FusG.

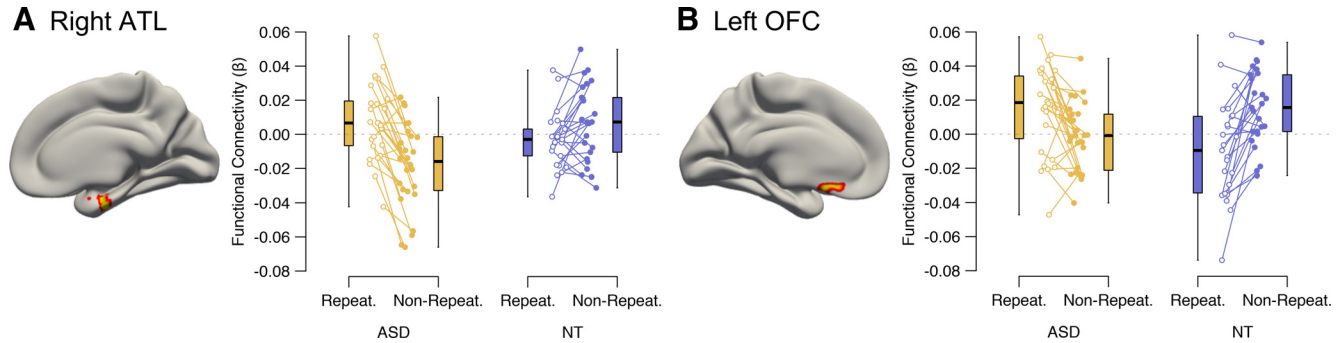

Figure 5. Group differences in functional connectivity during face perception. On average, participants in the ASD group showed an increase in functional connectivity between the right FusG ROI and both (***A***) right ATL and (***B***) left OFC during the repeating faces condition versus a decrease in functional connectivity between right FusG and these regions during the nonrepeating faces condition. The NT group showed the opposite pattern, with reduced connectivity for repeating and greater connectivity for nonrepeating faces. Conventions are the same as in Figure 2. Lines link points from the same participant.

(Ewbank et al., 2017; Utzerath et al., 2018). Autistic individuals also have reported difficulty with face and identity recognition and memory (Golarai et al., 2006), exhibit differences in gaze patterns to core face regions (Klin et al., 2002; Dalton et al., 2005; Papagiannopoulou et al., 2014; Frazier et al., 2017; but see Guillon et al., 2014 for contradictory conclusions about gaze patterns), have difficultly extracting relevant social information from faces (Adolphs et al., 2001), and show increased anxiety-related brain responses when processing facial features (Hadjikhani et al., 2017). Autistic individuals also self-report adverse physiological and emotional feelings during face and eye-gaze processing (Trevisan et al., 2017). Correspondingly, we found that reduced repetition suppression was associated with greater social communication challenges among autistic adults. These results link repetition suppression to social behavior. Indeed, NT individuals with high degrees of autistic traits show reduced neural adaptation for faces (Ewbank, 2015) and studies recruiting autistic individuals with fewer social challenges find reduced or no evidence of group differences in adaptation in the FFA (Hendriks et al., 2021).

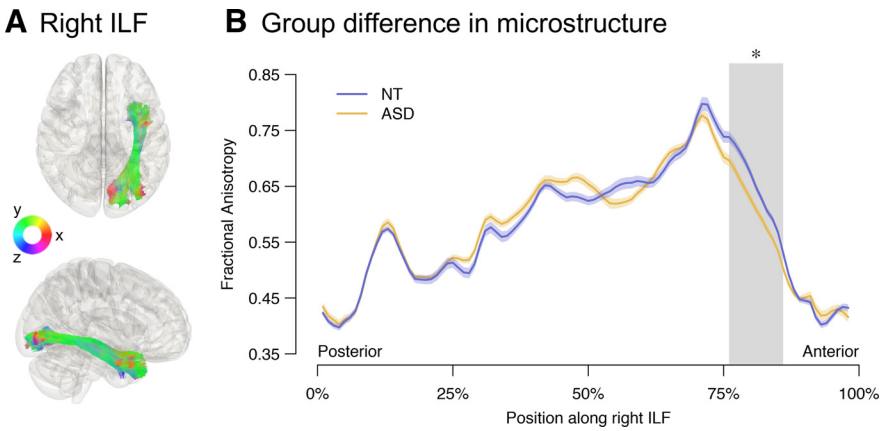

Figure 6. Local microstructural differences in right ILF in ASD. ***A***, Structural projections of the right ILF in a representative participant. Colors represent the primary diffusion direction of local segments. Note the primarily anterior-posterior gradient of the tract from visual areas along the inferior temporal lobe. ***B***, FA along the right ILF was significantly less in ASD versus NT in an extended portion of the tract located within ATL (marked by asterisk and gray shading; $\alpha_{FWE} = 0.00156$). Lines indicate group mean ± SEM across participants.

In addition to faces, voices also carry simultaneous communicative and social information (Perrachione et al., 2011); however, our speech task used only a single voice, and so the lack of a repetition suppression difference between groups should be interpreted as similar phonological-lexical encoding of speech in autism, not a lack of differences in processing voices themselves (e.g., Gervais et al., 2004; Schelinski et al., 2016) or differences in processing speech versus nonspeech (e.g., Alho et al., 2021). The category-specificity of diminished repetition suppression in ASD stands in contrast with other neurodevelopmental and psychological disorders, such as dyslexia or psychosis, wherein reduced repetition suppression has been found across stimulus categories (Williams et al., 2013; Perrachione et al., 2016;

Avery et al., 2019). This suggests that repetition suppression in signals, such as BOLD or EEG, likely reflect the aggregate outcome of several (yet-to-be distinguished) processes (Krekelberg et al., 2006), including those that affect perceptual processing globally (as observed previously in dyslexia) and others that affect processing within select perceptual or behavioral domains (as observed here in autism).

Repetition suppression as a systems-level response

What might cause the category-specific disruption of repetition suppression in ASD? Repetition suppression likely entails both bottom-up sensory mechanisms (e.g., habituation in stimulus-selective neuronal populations) and top-down cognitive mechanisms (e.g., response-altering perceptual expectations) (Summerfield et al., 2008). Changing repetition probability affects suppression magnitudes, suggesting that repetition suppression captures reductions in prediction error as individuals form expectations regarding the likelihood of repetition (Summerfield et al., 2008; Larsson and Smith, 2012; Beach et al., 2022). Despite intact repetition suppression for objects in LOC, early visual areas are less sensitive to expectations of repetition in ASD (Utzerath et al., 2018). Similarly, modulating familiarity of, or attention to, face stimuli in ASD can eliminate group differences in gaze duration (Dawson et al., 1990; Golarai et al., 2006) or FFA activation (Pierce et al., 2004; Bird et al., 2006; Pierce and Redcay, 2008). This suggests that perceptual selectivity may be intact (Bird et al., 2006), but that top-down modulation of perceptual regions is altered in ASD (Hadjikhani et al., 2004).

Consistent with these findings, we report group differences in structural and functional circuits connecting FusG to higher-order face processing areas. Compared with NT, ASD individuals showed reduced FA in anterior portions of right ILF, a white-matter tract connecting FusG to higher-level face recognition regions, such as ATL. These microstructural alterations parallel differences in task-based functional connectivity between FusG and right ATL/left OFC during face processing. In contrast to NT, ASD individuals showed reduced connectivity in these circuits for novel faces (usually more engaging for NT individuals), and increased connectivity for repetition of the same face (typically less engaging for NT individuals). Connectivity between these regions and FusG might reflect feedback propagation of identity-specific information that constrains face perception at lower levels, or increased attentional demands necessary for recognition of novel faces (Kriegeskorte et al., 2007; Nasr and Tootell, 2012). Indeed, both the FFA and ATL show increased activation during face recognition, with activation increase in ATL predicting face recognition performance (Nasr and Tootell, 2012). Reduced connectivity in this circuit for nonrepeating faces might be associated with poorer face recognition ability, particularly for highly variable face stimuli. Repeating faces, on the other hand, become predictable and therefore require less integration with higher-order face recognition regions over successive repetitions. In ASD, reduced sensitivity to repetition might result in increased attention to repeating faces, which are typically quickly recognized after a few repetitions in NT individuals, as reflected by increased connectivity in face recognition circuits.

Similarly, increased structural connectivity in anterior ILF, a white-matter tract connecting these regions, has been associated with face recognition performance (Tavor et al., 2014; Herbet et al., 2018) and predicts the degree of face selectivity within right FusG (Saygin et al., 2011). Alterations in right ILF have been consistently identified in ASD and linked to more fragmented visual processing (Boets et al., 2018). It is striking, therefore, that in the current study, the ASD group exhibited both reduced microstructural integrity in this tract, along with reduced connectivity for novel faces and increased connectivity for repeated faces. These alterations may relate to noted face processing difficulties in ASD, particularly in the domains of face perception, recognition, and memory (Klin et al., 1999; Carver and Dawson, 2002; Weigelt et al., 2012), as ATL and OFC are key regions for recognition and memory of individual faces. Faces of particular people elicit discrete activation patterns in ATL (Nakamura and Kubota, 1996; Kriegeskorte et al., 2007), which exerts hierarchical control over lower-level face processing regions to link face perception with memory and person-specific knowledge (Collins and Olson, 2014; Yang et al., 2016). ATL damage is associated with deficits in person memory, face recognition, and feelings of familiarity (Collins and Olson, 2014). Similarly, OFC damage can impair face recognition and detection of facial expression (Rolls, 2004, 2007). Together with reduced repetition suppression for faces, structural and connectivity findings point to systems-level differences that might affect the stability of face representations in support of face recognition (Hunter and Ames, 1988; Nordt et al., 2016). These results also provide context for interpreting prior findings of reduced structural (Koldewyn et al., 2014) and functional connectivity between FusG and face recognition regions during encoding of novel visual stimuli in ASD (Kleinhans et al., 2008; Lynn et al., 2018), namely, that such differences may relate to difficulty forming stable perceptual representations. These findings are consistent with a systems-level difference in face processing in ASD, whereby differences in rostral-caudal connectivity parallel (or potentially underlie) differences in perceptual adaptation.

Linking repetition suppression to theoretical frameworks in autism

These findings also complement an influential theoretical framework of autism implicating predictive coding, wherein reduced top-down influences over perception lead to upweighting incoming sensory information, reduced ability to differentiate novel from familiar events, and ultimately lower-order perceptual and higher-order social communication difficulties in ASD (Lawson et al., 2014; Sinha et al., 2014; Van de Cruys et al., 2014). Increased weighting of sensory input is consistent with behavioral hypersensitivities found in autism, as well as findings of reduced habituation (Kleinhans et al., 2009; Webb et al., 2010; Jamal et al., 2020), and increased neural activation for sensory stimulation (Green et al., 2015). This is also consistent with explanations positing that reduced repetition suppression is related to reduced attenuation of prediction error in autism (for review, see Palmer et al., 2017).

The current results provide additional support for these frameworks by linking individual differences in repetition suppression magnitude (a potential index of prediction errors) with challenges in social communication in autism. Likewise, increased connectivity between fusiform and frontotemporal face recognition regions in autism for repeating faces (e.g., augmented responses for expected stimuli and decreased responses for unexpected stimuli) could also signal increased feedforward signaling of sensory prediction errors or reduced top-down influence of predictions and expectations that would normally suppress these signals (Ewbank et al., 2011; Khan et al., 2015; S. M. Lee et al., 2022). Indeed, heightened processing of irrelevant stimuli and reduced differentiation between relevant and irrelevant stimuli have been noted in psychosis (another disorder characterized by challenges in predictive processing) (e.g., Sterzer et al., 2018) during tasks of associative learning which likely rely on prediction

(Corlett et al., 2007). Therefore, it is possible that differences in repetition suppression reflect more general differences in predictive processing mechanisms (Summerfield et al., 2008; Beach et al., 2022).

Reduced repetition suppression and strengths in ASD

While diminished repetition suppression was related to social communication challenges, it could also contribute unique strengths to ASD, including better performance on visual search and auditory detection (Foss-Feig et al., 2013). Reduced top-down influence over perception could increase attention to detail, potentially rendering autistic individuals less susceptible to biases created by expectation (Gomot et al., 2008; Bonnel et al., 2010; Rozenkrantz et al., 2021). Practically, reduced repetition suppression for faces could contribute to reduced stereotype or racial bias reported in ASD (Hughes et al., 2019): For instance, ASD children with face-recognition difficulties show reduced race-based face processing differences (Wilson et al., 2011).

Limitations

The present findings should be interpreted within the context of constraints on this study's scope. We assessed multiple hypothesis-driven stimulus categories that reflected auditory, visual, social, and communicative channels, but we did not test lower-level auditory or visual features, or other higher-level stimuli (bodies, houses). We also did not assess perceptual processing or other types of adaptation (e.g., retinal adaptation) beyond repetition suppression. Additional stimulus categories and task designs may reveal other systems-level or processing disruptions (e.g., Alho et al., 2021) that can be used to evaluate additional hypotheses about social or communication disruptions in autism. Separately, operationalization of repetition suppression as the difference between repeating versus nonrepeating stimuli leaves unresolved the extent to which these effects can be attributed uniquely to differences in neural adaptation to repeating stimuli versus novelty responses to changing stimuli in the absence of either a quantitative measure of neural activity or some additional baseline task (Fristen, 1997). Finally, the present results were also obtained from individuals with average-to-high IQs, and may therefore not be reflective of the entire autism spectrum.

In conclusion, in ASD, attenuation of repetition suppression was specific to face stimuli, was related to the degree of social communication challenges, and accompanied system-wide differences in functional connectivity and white matter microstructure in ventral temporal and frontal face-processing circuits. These findings enhance the systems neuroscience-level understanding of how disruptions in the formation of stable representations during face perception may contribute to difficulty with higher-order social communication processes in ASD.

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