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Blunted neural response to emotional faces in the fusiform and superior temporal gyrus may be marker of emotion recognition deficits in pediatric epilepsy

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Abstract

Individuals with epilepsy are at risk for social cognition deficits, including impairments in the ability to recognize nonverbal cues of emotion (i.e., emotion recognition [ER] skills). Such deficits are particularly pronounced in adult patients with childhood-onset seizures and are already evident in children and adolescents with epilepsy. Though these impairments have been linked to blunted neural response to emotional information in faces in adult patients, little is known about the neural correlates of ER deficits in youth with epilepsy. The current study compared ER accuracy and neural response to emotional faces during functional magnetic resonance imaging (fMRI) in youth with intractable focal epilepsy and typically developing youth. Relative to typically developing participants, individuals with epilepsy showed a) reduced accuracy in the ER task and b) blunted response to emotional faces (vs. neutral faces) in the bilateral fusiform gyri and right superior temporal gyrus (STG). Activation in these regions was correlated with performance, suggesting that aberrant response within these face-responsive regions may play a functional role in ER

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Declaration of competing interest
None.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the 1964 Declaration of Helsinki and its later amendments.

impairments. Reduced engagement of neural circuits relevant to processing socioemotional cues may be markers of risk for social cognitive deficits in youth with focal epilepsy.

Keywords

Epilepsy; Emotion recognition; Neural response; Faces; Social cognition; Youth

1. Introduction

Individuals with epilepsy often experience impaired psychosocial functioning, which can markedly reduce quality of life (e.g., [1,2–4]). It has been suggested that these deficits in social and occupational achievement may be related to disease-related impairments in social-cognitive abilities (e.g., [5,6,7]) that are critical for successful social interactions. In particular, patients with epilepsy have been found to show deficits in emotion recognition (ER) skills [8]—or the capacity to understand emotional information embedded in nonverbal cues, like facial expressions or tone of voice. These impairments are particularly pronounced in adults with childhood-onset seizures (e.g., [9], review by [10]), suggesting that early disruption to the integrity of relevant neural networks may have a detrimental effect on subsequent social-cognitive capacity. Indeed, adults with epilepsy show blunted neural response to emotional faces in regions relevant to face processing, including occipital cortices, the mesial temporal lobe, and the inferior frontal cortex [9,11–14]. Though children and adolescents with epilepsy also show deficits in ER [15–17], no work has examined the neural underpinnings of such impairments in a pediatric sample. The current study examines neural response to facial emotional stimuli in youth with epilepsy, to better understand how brain responses to socioemotional cues may be linked to ER capacity in a group of individuals at risk for adverse social outcomes ([18], review by [19], review by [20]).

1.1. Predictors of ER impairments in individuals with epilepsy

Studies have demonstrated that epilepsy is associated with difficulties identifying emotions across several nonverbal modalities (e.g., [21,22]), though most of the extant research has focused on the recognition of emotion in facial expressions. A large body of literature has investigated whether the presence of mesial temporal structural damage, the laterality of seizure focus, or other illness-related variables differentially predict the severity of ER impairments in adult patients. The evidence is mixed for many of the above factors (review by [10]), but ER deficits are most consistently predicted by both a) seizure onset focus within the temporal lobe and b) childhood-onset seizures.

Large cohort studies have suggested that patients with (mesial) temporal lobe epilepsy (TLE) are particularly at risk for ER deficits (e.g., [8]). Given the involvement of temporal lobe structures in the processing of socioemotional information, it is unsurprising that seizure foci in this region would impair social cognitive functions. Lesion studies have suggested that individuals with damage to the amygdala or broader temporal lobe struggle to identify emotions in facial stimuli [23,24]. Mesial temporal sclerosis (MTS) and temporal lobectomy have been associated with poorer recognition of fear, particularly if damage occurred in the right hemisphere [9,14]. In addition, there is evidence that patients with

mesial TLE show differential activation of the amygdala in response to expressions of fear in movie scenes: compared with control participants who show bilateral amygdala response, activation in individuals with epilepsy was blunted and restricted to the hemisphere contralateral to their seizure onset zone [11,12]. Beyond the mesial temporal lobe, broader neural networks underlying face processing may also be impaired in adults with epilepsy. When viewing fearful faces, adults with left [13] and right mesial TLE [9] showed blunted activation in right occipital regions. Patients with right mesial TLE also had reduced response to emotional faces in the inferior frontal cortex [9,14] and left fusiform gyrus (FG) [12] relative to control participants. Decreased engagement of these regions was linked to deficits in ER performance [9], suggesting that differential activation in these circuits may affect the capacity to identify emotional stimuli.

In addition to involvement of the temporal lobe, age at epilepsy onset appears to be an important predictor of ER deficits. Emotion recognition impairments in adult patients are particularly pronounced if seizure onset occurred during early childhood (e.g., [9], review by [10]). Youth with TLE [16,17,25], as well as children with generalized epilepsy [25] and frontocentral focal epilepsy [16], already show deficits in facial ER compared with typically developing youth. In contrast to work with adults, pediatric studies do not find that the level of ER impairments are differentially predicted by the subtype of epilepsy, by seizure frequency, or by the lateralization of seizure focus [15,26]; however, some studies find that an earlier age of onset and longer duration of illness are associated with poorer ER skills even in pediatric populations ([15–16], c.f., [17,26]). As such, seizures occurring during childhood or adolescence may disrupt the organization and fine-tuning of neural networks relevant to social cognitive functions in a nonspecific manner, independent of specific pathology or seizure focus. To date, no work has examined neural correlates of ER deficits in children and adolescents with epilepsy. Thus, it is unknown whether differential engagement of relevant neural networks is present in youth with epilepsy, or whether seizures and related pathology create a cumulative risk factor for pronounced ER impairments with age.

The current study investigates potential neural underpinnings of ER deficits in children, adolescents, and emerging adults (hereby, “youth”) with intractable focal epilepsy. We compared a) ER ability and b) neural activation to emotional faces in an ER task during functional magnetic resonance imaging (fMRI) in youth with focal epilepsy relative to typically developing youth. We hypothesized that participants with epilepsy would be less accurate in identifying emotions in facial expressions than typically developing youth. Based on fMRI studies with adult patients, we also expected that youth with epilepsy would show blunted activation to emotional faces in relevant face-processing regions, such as the FG [9,12,13], amygdala [11,12], and inferior frontal cortex [9,14]. We further hypothesized that differential patterns of brain activation would be associated with poorer ER accuracy in youth with epilepsy.

2. Materials and methods

2.1. Participants

The sample included 25 youth diagnosed with intractable focal epilepsy (16 males; aged 9 to 21 years, mean age = 14.28, standard deviation (SD) = 3.36) and 41 typically developing youth (15 males; aged 8 to 19 years, mean age = 14.00, SD = 3.38). Participants with epilepsy were recruited through the epilepsy monitoring unit of a large children's hospital (United States). One additional adolescent with epilepsy was recruited but did not complete the task in the scanner. Typically developing youth were recruited via a digital flyer distributed to hospital employees. Written parental consent and written participant assent/consent was obtained prior to study participation. All procedures were approved by the local Institutional Review Board.

All participants were 1) between the ages of 8 to 21 years at recruitment, 2) fluent in English, 3) had an intelligence quotient (IQ) > 70 (see below for details), and 4) were deemed able to complete the planned fMRI protocol. Additional inclusion criteria for the group with epilepsy included a primary diagnosis of intractable focal epilepsy. Participants were excluded if they had uncorrected hearing, vision, or motor deficits that would impair task participation or had metal implants or other conditions contraindicated for MRI. Because pediatric epilepsy is often comorbid with conditions that would impede the completion of functional studies (e.g., cerebral palsy or other movement disorders, intellectual disability, the installation of metal implants for treatment of seizures), the broad inclusion/exclusion criteria described above were implemented to recruit a sample of patients with comparable independent function despite variation in the characteristics of their illness (see details below).

Self-report of race indicated that 65.2% of the sample was Caucasian, 13.6% was Black or African American, 4.5% was Asian or Pacific Islander, and 16.7% was multiracial or of other ethnicities. Handedness was assessed using the Edinburgh Handedness Inventory [27]: 82% of participants were right-handed, 10% left-handed, and 8% reported no preference. Intelligence quotient was measured using the Wechsler Intelligence Scale for Children (WISC)/Wechsler Adult Intelligence Scale (WAIS). Typically developing youth completed the matrix reasoning and vocabulary subtests during the study visit. Scaled scores for the same subtests (recorded by trained neuropsychologists as part of patients' full IQ evaluation) were pulled from their electronic medical records by two independent coders. Typically developing youth's scores ranged from low average to very superior for both subscales; youth with epilepsy ranged from moderate disability to high average or very superior, for vocabulary and matrix reasoning, respectively (Table 1). Independent samples t -test analyses revealed that the two groups differed in mean scores on the vocabulary subscale, $t(64) = 5.19$, $p < .001$, and on the matrix reasoning subscale, $t(64) = 2.06$, $p = .04$. Groups did not differ in age ($p = .74$), but a chi-square analysis revealed that they differed in gender composition, $\chi^2(1, N = 66) = 4.69$, $p = .03$ (Table 1). As such, IQ and gender were included in relevant analytical models (see Sections 2.4, 3.1, and 3.2 below).

Secondary analyses were conducted to examine how variations in illness characteristics were associated with ER and neural activation during the task (see Sections 2.4.3 and 3.3). For

youth with epilepsy, two independent coders tabulated information about the type of epilepsy as indicated by a pediatric neurologist in the medical record (frontal, temporal, frontotemporal, or other), lateralization of seizure foci (left, right, or bilateral), age at seizure onset (in years), presence of MTS (determined based on MR scan reports by neuroradiologists), and the number and type of antiepileptic drugs (AEDs) prescribed at the time of study. A third rater (M.M.) resolved any disagreements between the two coders when needed. The majority of youth with epilepsy were diagnosed with TLE (56%), with others having frontal (20%), frontotemporal (16%), or other (8%) forms of focal epilepsy (Table 2). Approximately half had left-sided seizure foci (52%), with 40% having right-sided and 8% having bilateral onset sites (Table 2). Age at seizure onset was recorded as ranging from 1 to 16 years ($M = 7.28$, $SD = 4.45$). Eight patients (32%) had MTS, whereas 17 (68%) did not. On average, patients were prescribed 2 AEDs at the time of study (range: 1 to 4); other than midazolam/Versed (rescue), which was prescribed to 58% of patients in the sample, the most commonly prescribed AEDs were lacosamide/Vimpat (38%), oxcarbazepine/Trileptal (35%), and clobazam/Onfi (27%). No participant was diagnosed with autism. Three participants had a history of prior focal resective surgeries (resections in either the left anterior frontal and temporal lobe, the left orbital frontal lobe, or the right occipital–parietal region), without any resection of mesial temporal structures. Analyses were performed with and without these patients to verify that these prior surgeries did not impact results (see Footnote 3).

2.2. Task

Participants completed a forced-choice facial ER task in the MRI scanner. Youth were presented with 90 pictures of adolescents' facial expressions (conveying anger, fear, happiness, sadness, or neutral) selected from the National Institute of Mental Health's Child Emotional Faces Picture Set (NIMH-CHEPS; [28]). Participants were asked to identify the intended emotion in each picture by pressing the appropriate button on Lumina hand-held response devices inside the scanner.

Each trial of the task was composed of stimulus presentation (1 s in duration) followed by a 5-second response period. Stimuli were presented in an event-related design with a jittered intertrial interval between 1 and 8 s (mean: 4.5 s). A fixation cross was presented during the intertrial intervals, and a pictogram of response labels was shown during the response period. All stimuli were viewed on a computer monitor at the head of the magnet bore, via a mirror attached to the head coil. The task was split into three 6-minute runs of 30 faces, each containing a balanced number of stimuli per emotion type (presented in a pseudorandomized order).

³The effect of Group persisted when participants with prior resective surgeries were excluded from analyses, though the cluster identified in the L-FG was below cluster-forming threshold at 23 voxels (R-STG: 29 voxels, R-FG: 27 voxels). We conclude that including these patients—none of whom had resections in the fusiform gyrus, superior temporal gyrus, or mesial temporal structures—did not impact reported results. As such, we opted to retain them in analyses to maximize our sample size. Details are available from the first author upon request.

2.3. Image acquisition and processing

Magnetic resonance imaging data were collected on two Siemens 3-Tesla scanners running identical software, using standard 32- and 64-channel head coil arrays.¹ The imaging protocol included three-plane localizer scout images and an isotropic 3D T1-weighted anatomical scan covering the whole brain (magnetization-prepared rapid acquisition with gradient echo (MPRAGE)), with a 1-millimeter isotropic voxel size. Imaging parameters for the MPRAGE were the following: 176 contiguous sagittal slices, repetition time (TR) = 2200–2300 ms, echo time (TE) = 2.45–2.98 ms, and field of view (FOV) = 248–256 mm. Functional MRI data (T2*-weighted scans) were obtained with echo planar imaging (EPI) acquisitions, with a voxel size of $2.5 \times 2.5 \times 3.5$ –4 mm, and the phase-encoding axis oriented in the anterior–posterior direction. Parameters were 36 contiguous axial slices, TR = 1500 ms, TE = 30–43 ms, and FOV = 240 mm.

Echo planar images were preprocessed and analyzed in AFNI, version 18.0.11 [29]. Functional images were aligned to the first volume, oriented to the anterior commissure / posterior commissure (AC/PC) line, and coregistered to the T1 anatomical image. Images then underwent nonlinear warping to the Talairach template and were spatially smoothed with a Gaussian filter (FWHM, 6 mm kernel). Voxel-wise signal was scaled within-subject to a mean value of 100. Volumes in which at least 10% of the voxels were signal outliers (above 200) or contained movement greater than 1 mm between their subsequent volume were censored after first-level analyses. Following this procedure, 5.9% of volumes were censored.

2.4. Analysis

2.4.1. Emotion recognition accuracy—Performance on the task was indexed using the unbiased hit rate (H_u ; [30]), which is a measure of accuracy that accounts for response biases. Values of H_u range from 0 (no hit rates, all false alarms) to 1 (all hit rates, no false alarms). Responses made less than 150 ms following the stimulus period were censored from analyses because of physiologic implausibility. A value of H_u was calculated for each emotional category. As recommended by Wagner [30], values were then arcsine-transformed before analyses.

Post-data collection, spurious signals from the scanner were found to have interfered with software (E-Prime) used for stimulus display and participant response recording for 30 of 66 participants (21 typically developing youth, 9 youth with epilepsy). To ensure valid responses only were included in analyses of ER accuracy, these participants were removed from all behavioral analyses (but retained in analyses of neural activation). This conservative approach yielded a final sample size of 36 (20 typically developing youth, 16 youth with epilepsy) for ER performance data. A general linear model was performed to examine the effect of Group (between-subject variable, 2 levels: youth with epilepsy, typically developing youth), Emotion type (within-subject variable, 5 levels: anger, fear, happiness, sadness, neutral), and mean-centered Age (between-subject variable, continuous) on H_u .

¹Because of scanner updates during data collection, 8 participants (5 typically developing youth, 3 youth with epilepsy) were tested on a different scanner than the other 58 participants. The effect of Group reported in the manuscript persisted when ‘scanner’ was added to the model as a nuisance variable. Details are available from the first author upon request.

Because groups differed on gender distribution, Gender (between-subject variable, 2 levels: female, male) was also included in the model. Greenhouse–Geisser corrections were applied based on results of Mauchly's test of sphericity. A secondary analysis was computed with matrix reasoning and vocabulary scores as mean-centered continuous covariates, to determine whether results were independent of group differences in IQ.

2.4.2. Neural response to emotional faces—At the subject level, the hemodynamic response function was convolved with a base function that included a regressor for the presentation of each type of emotional facial stimuli (i.e., faces expressing anger, fear, sadness, or happiness) contrasted to the neutral facial stimuli (i.e., faces expressing no emotion). This model enabled us to examine group differences in emotion-general responses (average response to all emotions vs. neutral), as well as in emotion-specific responses (e.g., fear vs. neutral). In addition to these four regressors, nuisance regressors for motion (six affine directions) and scanner drift (within each run) were included. The contrast images produced for each participant were then fit to a multivariate model (3dMVM in AFNI; [31]) for group-level analyses. The model tested the effect of Group (epilepsy vs. typically developing), Emotion category (anger, fear, sadness, happiness), and mean-centered Age on whole-brain activation in the full sample ($n = 66$). Gender (female vs. male) was also included in the full factorial model. Within this model, F -statistics were computed for the main effects of Group, Emotion, Age, and Gender, and for the interactions of Group $\times$ Age and Group $\times$ Emotion. We employed the standard false discovery rate correction factor for all fMRI analyses by combining a conservative threshold ($p < .001$) with a cluster-size correction (minimum size of 27 voxels). This cluster-size threshold correction was generated using the spatial autocorrelation function of 3dclustsim (Montecarlo simulations with study-specific smoothing estimates, two-sided thresholding and first-nearest neighbor clustering, $\alpha = 0.05$ and $p < .001$; [32]). Following this procedure, we report clusters larger than 27 contiguous voxels. Regions were identified at their center of mass in the Talairach–Tournoux atlas. Mean activation in the voxels within defined clusters was extracted for follow-up analyses relating neural activation to ER performance or illness-related variables. Inspection of the data revealed that one participant with epilepsy was an outlier (i.e., below 3 SDs from the mean) for the contrast of interest in the defined clusters; values for this participant were Winsorized (to the 5th percentile) prior to analyses.

2.4.3. Associations between neural response/ER and illness-related variables—Within the group of youth with epilepsy ($n = 24$), we conducted secondary analyses to determine whether ER accuracy or neural response to emotional faces was predicted by illness-related variables, including a) the type of epilepsy (between-subject variable, 4 levels: frontal, temporal, frontotemporal, other), b) the lateralization of seizure focus (between-subject variable, 3 levels: left, right, bilateral), the c) age at seizure onset (between-subject variable, continuous), or d) the presence of MTS (between-subject variable, 2 levels: yes, no). Separate univariate analyses of variance (ANOVAs) were performed to examine the effect of each of the above variables on ER accuracy (average H_u across emotion categories). For neural response, separate multivariate ANOVAs were performed to investigate the effect of each independent variable on activation to emotional

faces in all regions demonstrating group differences (see Section 3). Pillai's trace tests were considered at the omnibus level for the multivariate analyses.

3. Results

3.1. Group differences in task accuracy (n = 36)

The average unbiased hit rate across both groups was 2.28 ($SD = 0.38$; raw hit rate of 86% [90% for typically developing youth, 82% for youth with epilepsy]). There was a main effect of Group on accuracy (H_U), $F(1, 31) = 11.58$, $p < .01$, $\eta^2 = 0.27$, such that typically developing youth ($M = 2.44$, $SE = 0.07$) were more accurate in the ER task than were youth with epilepsy ($M = 2.06$, $SE = 0.08$; see Table 3 and Fig. 1). There was also a main effect of Emotion type, $F(2.74, 84.84) = 10.48$, $p < .001$, $\eta^2 = 0.25$: post hoc comparisons indicated that happiness was the best recognized emotion, followed by anger, fear, and neutral (latter three not significantly different from one another, $ps > .09$), and sadness (which did not differ from neutral, $p = .18$; unless otherwise specified, all $ps < .05$). Group differences in accuracy were not more pronounced for one emotion type over the others (i.e., Group $\times$ Emotion $p = .25$). No other effects were significant ($ps > .09$).

To determine whether group differences in ER performance could be attributed to differences in cognitive abilities, we conducted a secondary analysis where mean-centered estimates of IQ (subscale scores for matrix reasoning and vocabulary) were added into the above model. The effects of Group ($p = .02$) and Emotion ($p < .01$) persisted, and no other effect was significant ($ps > .09$), indicating that group differences in ER accuracy were notable above and beyond differences in general cognitive function.²

3.2. Group differences in neural activation during task (n = 66)

There was a main effect of Group on activation to emotional faces (vs. neutral faces) in three regions: the right superior/middle temporal gyrus (R-STG), the right FG (R-FG), and the left FG (L-FG; see Table 4 and Fig. 2). Participants with epilepsy showed less activation in these regions when seeing emotional faces than did typically developing youth. There were also widespread yet weak effects of Emotion throughout the brain (see Appendix A), notably in the inferior temporal and frontal cortices where happy faces generally elicited greater deactivation than other emotions. Participants with and without epilepsy did not differ in emotion-specific activations (i.e., no Group $\times$ Emotion interaction), nor were there effects of Age, Gender, or of Group $\times$ Age on neural response to emotional faces.³

Of note, activation in the R-STG ($r = 0.35$, $p = .04$) and R-FG ($r = 0.39$, $p = .02$) was positively correlated with accuracy on the ER task ($n = 36$; Fig. 3), suggesting that engagement of these regions was relevant to task performance. Mean-centered IQ subscale scores were not correlated with activation in these regions (all $ps > .23$).

²An independent-samples t -test indicated that typically developing youth ($M = 1232$ ms; $SD = 395$ ms) responded significantly faster in the task than did youth with epilepsy ($M = 1802$ ms; $SD = 871$ ms). However, the effect of Group on H_U persisted when response times (averaged across all trials) was added as a covariate to the model, $F(1,30) = 6.82$, $p = .01$, $\eta^2 = 0.19$. This suggests that variations in processing speed were independent from emotion recognition accuracy.

3.3. Secondary analysis of associations between ER/neural activation and illness-related variables

Given restrictions on available valid behavioral data for youth with epilepsy, there were no patients with the ‘other’ type of epilepsy and only 1 patient with ‘bilateral’ lateralization. As such, only 3 levels of epilepsy type (frontal, temporal, frontotemporal) and 2 levels of localization of seizure focus (left, right) were considered in the models assessing the association between each of these variables and ER performance ($n = 16$ unless otherwise specified below). Neither epilepsy type ($p = .23$), lateralization of seizure focus ($n = 15$, $p = .55$), nor MTS ($p = .30$) predicted ER accuracy in their respective models. Age at seizure onset marginally predicted accuracy, $F(1, 14) = 4.02$, $p = .065$, $\eta^2 = 0.22$, whereby early onset was associated with poorer performance. However, given the small sample size for these secondary analyses of behavioral data, caution is warranted in interpreting the above results.

All participants with epilepsy were included in analyses examining the association between illness-related variances and neural activation in the R-STG, R-FG, and L-FG ($n = 25$). There were no omnibus effects of type of epilepsy ($p = .09$), seizure lateralization ($p = .54$), presence of MTS ($p = .40$), or age at onset ($p = .11$) on neural response to emotional faces in these areas.

4. Discussion

The current study examined ER accuracy and neural response to facial emotion displays in youth with intractable focal epilepsy compared with typically developing youth. Consistent with previous reports, participants with epilepsy were less accurate in identifying facial emotional expressions. In addition, they showed blunted neural response to emotional faces in the bilateral FG and right superior temporal gyrus (STG), compared with typically developing youth. In healthy adults, these regions are considered face-responsive and typically show potentiated activation to emotional (vs. neutral) expressions ([33–36], e.g., [37,38]). Reduced activation in these putative “face” areas was correlated with poorer ER performance, suggesting that aberrant neural response to facial emotions within these brain systems may be relevant to the social cognitive deficits often observed in youth with epilepsy.

4.1. Deficits in facial emotion recognition in youth with epilepsy

Compared with typically developing youth, children and adolescents with intractable epilepsy were less accurate in a facial ER task. This pattern is consistent with prior reports of social cognitive deficits in this population, including difficulties identifying the intended emotion in facial stimuli [15–17]. Unlike in previous studies with adult patients [8,9,14,23] but consistent with existing work with youth [15,26], the presence of TLE, MTS, or right-hemisphere seizures did not predict greater deficits in ER. Early age of seizure onset predicted poorer performance at a trend level; though this effect was weak in our sample, it is consistent with previous work in both adults and children suggesting that the duration of illness is correlated with the level of impairments in social cognition [15,16]. Such findings suggest that repeated insults to the brain from seizures may disrupt the development of

normative emotional processing. However, the small sample size for this secondary analysis in the current sample restricts the conclusions that can be drawn from this result.

4.2. Blunted neural response to emotional faces in youth with epilepsy

Our findings suggest that impairments in ER noted at a behavioral level in youth with epilepsy may be subserved—or at least is accompanied by—differential responses to emotional stimuli at a neural level. Typically developing youth showed enhanced response to emotional (over neutral) faces in the FG and right STG. These areas are part of the core face processing network [39,40]: the FG clusters partially overlap with the fusiform face area (FFA), and the STG cluster, though more anterior than typical for the posterior superior temporal sulcus (STS), corresponds to the anterior superior temporal face area [40]. Although early theoretical models posited that the FFA and STS represented invariant and variant aspects of faces, respectively [41], evidence now suggests that both regions contribute to the perception of changeable facial information, including emotional expression (review in [40]). Indeed, FFA and right STS response has consistently been found to be potentiated by emotional information in faces (e.g., [33,34–38]), which likely reflects salience-enhanced perceptual processing. Thus, typically developing youth showed expected enhancement of activation in face-relevant regions of the brain when seeing emotional faces.

In contrast, emotional faces elicited a blunted response in the FG, and a *deactivation* in the R-STG, in youth with epilepsy. Emotional information may thus fail to enhance responses in these face-processing areas, as would be expected in typically developing children and adolescents. Models of emotion-modulated face perception implicate bidirectional circuits encompassing sensory regions and limbic areas. For instance, both animal and human models highlight re-entrant signals from the amygdala to the temporal cortex and FFA that enhance activation to emotional over neutral faces ([42,43], review by [44]). The amygdala has direct projections to both the FFA and occipital face area (OFA) within the inferior temporal cortex [45] and is connected to the (right) STS [39,46] in healthy adults. However, the integrity of these circuits is compromised in adults with epilepsy. Functional connectivity between the above regions when viewing fearful faces was reduced in adults with mesial TLE compared with healthy controls [47]. In addition, patients with amygdala atrophy from MTS [48] or from conditions like frontotemporal dementia [49] demonstrated blunted response to fearful faces in face-processing regions compared with control groups. Thus, it is possible that the blunted responses to emotional faces in the FG and STG noted in youth with epilepsy stem from aberrant feedback loops and disrupted function of face-processing networks in the temporal lobe. Such basic aspects of dynamic social perception are likely foundational for more complex social cognitive functions like social learning, mentalizing, and social attribution formation [50], which play a critical role in competent social functioning [51].

Given the central role of the amygdala in the modulation of emotion-enhanced responses in face-processing regions, it is notable that we did not find group differences in activation to emotional faces within the amygdala itself. Previous work with adult patients has noted blunted activation to emotional (fearful) faces in the amygdala, compared with healthy participants [11,12]. It is possible that the faces in the current ER task were too weak or brief

to elicit amygdala activation consistent enough to be detected [44], or that the cognitive demands associated with categorizing the stimuli resulted in top-down dampening of limbic engagement with the stimuli [52,53], c.f., [54]. Moreover, the majority of previous studies noted reduced amygdala activation in response to *fearful* stimuli specifically. The inclusion of angry, sad, and happy faces in our ER task may account for the differences in findings: indeed, activation patterns in healthy adults' amygdala was found to be sensitive to the difference between fear and other emotional stimuli but not to nuances between other emotions like anger and happiness [55]. In contrast, the same study found that activation patterns in the right STS distinguished neutral from all other emotional faces, as well as positive from negative emotions [55], which is consistent with the current results and with prior findings that the STS contributes to social perception tasks like ER ([45], review by [56]).

It is also possible that blunted responses to emotion in the FG and STG are independent of modulatory influences of limbic structures. Inhibited activation in these regions could be driven by differential top-down emotion regulation or salience-related signals emerging from other regions relevant to socioemotional processing, such as the inferior frontal cortex—an area that has also been noted to respond differently to emotional faces in adults with epilepsy compared with controls [9,14]. Regardless of the mechanism, this aberrant response in the face-processing system may represent a potential neural marker for social cognitive deficits in youth with epilepsy. Indeed, the extent to which R-FG and R-STG response was blunted was related to ER performance, suggesting that engagement of these regions may be mechanistically linked to behavioral outcomes such as the capacity to label nonverbal cues of emotion. Intractable epilepsy in childhood may thus interfere with both the development of neural networks relevant to face processing and to the growth of associated social cognitive functions [51,57]. Longitudinal work would benefit from examining how change in neural and behavioral responses to facial stimuli map onto social outcomes in this group of youth at risk for social and emotional problems in adulthood.

4.3. Strengths and limitations

This study is the first to examine differences in neural activation to emotional facial stimuli in youth with and without epilepsy. We thus extend prior work noting deficits in ER performance in youth with epilepsy [15–17] and studies noting aberrant neural response to fearful faces in adult patients (e.g., [9,12,13,14]). In doing so, we provide preliminary evidence that blunted response to emotional faces in face-processing regions of the brain (including the FG and right STG) in youth with epilepsy may contribute to—or at least accompany—deficits in ER.

Limitations must be noted. First, group differences in task performance complicate the interpretation of group differences in neural activation; we cannot rule out the possibility that both groups are simply performing the ER task differently (i.e., using different strategies) and thus, engaging different neural systems during the task (see [58]). Relatedly, including a non-emotion categorization task would have helped verify that group differences are not related to nonspecific effects of task difficulty. Second, we did not employ a localizer task to identify the precise location of face-specific responses within the FG and STG at an

individual level. Including such a paradigm would have enabled us to specify whether group differences were primarily evident in face-specific regions of the FG. Nonetheless, our findings highlight differential engagement of areas within both the ventral and dorsal face processing stream in youth with and without epilepsy. Third, the heterogeneity of epilepsy diagnoses, age of our sample, medication regimen, and location of seizure foci likely introduced noise to our data. For instance, there is some evidence that adult patients with right-lateralized seizures differ from those with left-sided seizures in both ER and neural responses to faces (though the evidence is mixed; see review by [10]). Our sample size did not permit the separate analysis of right- vs. left-sided epilepsy, though our secondary data analysis suggests that activation in the STG and FG was not associated with either the localization or type of epilepsy. Though larger studies would be required to examine whether subgroups of youth with epilepsy (e.g., taking specific medications, diagnosed with comorbid conditions like autism or attention-deficit/hyperactivity disorder) differed in their response to emotional stimuli, our findings are likely generalizable to a heterogeneous sample of youth with intractable focal epilepsy.

5. Conclusions

Compared with typically developing youth, children and adolescents with intractable focal epilepsy showed a) reduced capacity to accurately identify emotions in facial expressions and b) diminished response to emotional information in faces in the bilateral FG and right STG. Blunted engagement of these regions was related to poorer ER performance, suggesting that aberrant activation in these areas may be markers of social cognitive difficulties in youth with epilepsy. Our findings highlight the detrimental impact of intractable seizures on the function of face-processing neural networks and the capacity to understand emotional cues in one's social environment. Future work examining how these patterns are impacted by successful seizure control is important to understand how to palliate potential negative social outcomes in this group of at-risk youth.

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Appendix

Appendix A.

Effect of Emotion type on activation to emotional faces

Structure	<i>F</i>	<i>k</i>	<i>x</i>	<i>y</i>	<i>z</i>	Generalized η^2	Brodman areas
L inferior frontal gyrus	2.39	1212	−40	16	21	0.11	46*, 9, 6
R lingual gyrus	5.64	635	1	−76	11	0.05	17*, 18, 19

Structure	<i>F</i>	<i>k</i>	<i>x</i>	<i>y</i>	<i>z</i>	Generalized η^2	Brodmann areas
R inferior/middle frontal gyrus	5.10	450	42	6	38	0.07	9*, 6
B medial/superior frontal gyrus	15.58	395	-2	13	48	0.09	6*, 8, 32
R temporal-parietal junction	15.33	253	48	-52	36	0.08	40*, 39
R superior frontal gyrus	8.85	201	23	23	46	0.05	8*, 6
R inferior frontal gyrus/insula	5.22	190	42	23	3	0.05	47*, 45, 13
L middle occipital gyrus	5.77	156	-43	-68	3	0.05	37*, 39, 19
L postcentral gyrus	6.46	111	-35	-35	57	0.04	40*, 2, 3, 5
L precentral gyrus/insula	8.26	108	-48	-7	9	0.04	6*, 13, 22
L fusiform gyrus	10.64	76	-38	-46	-13	0.05	37*
L lingual gyrus	5.04	75	-11	-77	-6	0.05	18*
L superior parietal lobule	8.69	65	-30	-55	45	0.05	7*
L temporal-parietal junction	9.56	61	-48	-53	33	0.05	40*
L postcentral gyrus	9.75	58	-46	-19	50	0.04	3*, 4
R anterior cingulate	6.61	56	7	44	8	0.04	32*, 10
R inferior temporal gyrus	5.30	52	60	-19	-15	0.09	20*, 21
L superior frontal gyrus	8.09	44	-18	48	18	0.05	10*, 9
L middle frontal gyrus	10.25	27	-31	37	23	0.06	10*

Note. Clusters listed here represent areas in which there was a main effect of Emotion type on activation to emotional faces (happiness, anger, fear, sadness) vs. neutral faces. Group (youth with vs. without epilepsy), Age, and Gender are included in the model. Clusters were formed using 3dclustsim at $p < .001$ (corrected, with a cluster-size threshold of 27 voxels). R = right, L = left, B = bilateral. *k* = cluster size in voxels. *xyz* coordinates represent cluster's center of mass, in Talairach-Tournoux space. Generalized eta squared estimates (η^2) were obtained from the cluster's peak. Listed Brodmann areas include the area at the cluster's center of mass (denoted by *) and any areas that account for 5% or more of the cluster.

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Fig. 1.
Group differences in emotion recognition accuracy.

Fig. 2. Effect of Group on activation to emotional faces. Note. R = right, L = left. STG = superior temporal gyrus; FG = fusiform gyrus. The y axis represents mean activation to emotional faces (vs. neutral faces) within the specified cluster.

Fig. 3. Association between emotion recognition accuracy and neural activation to emotional faces. Note. Scatterplots include only participants with valid behavioral data. R = right. STG = superior temporal gyrus; FG = fusiform gyrus.

Table 1

Demographic variables for typically developing youth and youth with epilepsy.

	Typically developing youth	Youth with epilepsy
Age (in years)	14.00 (3.38)	14.15 (3.35)
Matrix reasoning	10.90 (2.97)	9.12 (3.63)
Vocabulary	12.20 (2.60)	8.58 (2.74)
Gender	15 males (36.6%)	17 males (65.4%)

Note. For age, matrix reasoning (scaled score) and vocabulary (scaled score), values represent the mean (standard deviation).

Table 2

Type and side of seizure onset in youth with epilepsy.

Epilepsy type	Epilepsy side			Total
	Left	Right	Bilateral	
Temporal	7	5	2	14
Frontotemporal	3	1	0	4
Frontal	2	3	0	5
Other	1	1	0	2
Total	13	10	2	25

Note. Values represent the number of youth with epilepsy in each category.

Table 3

Accuracy in emotion recognition task.

Emotion	Typically developing youth		Youth with epilepsy	
	H_u	H	H_u	H
Happiness	2.62 (0.09)	0.92 (0.03)	2.44 (0.11)	0.92 (0.03)
Fear	2.44 (0.11)	0.91 (0.03)	2.03 (0.13)	0.82 (0.04)
Anger	2.55 (0.11)	0.92 (0.04)	2.03 (0.13)	0.82 (0.04)
Sadness	2.21 (0.09)	0.88 (0.04)	1.89 (0.11)	0.79 (0.05)
Neutral	2.40 (0.09)	0.89 (0.03)	1.89 (0.10)	0.73 (0.04)

Note. H_u = unbiased hit rate, representing accuracy corrected for response bias (arcsine-transformed prior to analysis). H = hit rate, representing the percentage of correct responses for each emotion (uncorrected for response bias). Estimates of H are provided as a means of estimating performance relative to chance (i.e., 20%, or 1/5 labels) but are not used in analyses. Values represent the mean (standard error of the mean).

Table 4

Effect of Group on activation to emotional faces.

Structure	F	k	x	y	z	Generalized η^2	Brodmann area
Right superior/middle temporal gyrus (R-STG)	18.75	53	54	-20	-6	0.13	21*
R fusiform gyrus (R-FG)	18.71	35	30	-61	-11	0.16	37*, 19
L fusiform gyrus/lingual gyrus (L-FG)	19.43	29	-19	-69	-5	0.13	19*, 18

Note. Clusters listed here represent areas in which there was a main effect of Group on activation to emotional faces (happiness, anger, fear, sadness) vs. neutral faces. Emotion type, Age, and Gender are included in the model. Clusters were formed using 3dclusim at $p < .001$ (corrected, with a cluster-size threshold of 27 voxels). R = right, L = left. k = cluster size in voxels. xyz coordinates represent cluster's center of mass, in Talairach-Tournoux space. Listed Brodmann areas include the area at the cluster's center of mass (denoted by *) and any areas that account for 5% or more of the cluster.