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Facial Emotion Recognition after Curative Nondominant Temporal Lobectomy in Patients with Mesial Temporal Sclerosis

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Summary: *Purpose:* The right (nondominant) amygdala is crucial for processing facial emotion recognition (FER). Patients with temporal lobe epilepsy (TLE) associated with mesial temporal sclerosis (MTS) often incur right amygdalar damage, resulting in impaired FER if TLE onset occurred before age 6 years. Consequently, early right mesiotemporal insult has been hypothesized to impair plasticity, resulting in FER deficits, whereas damage after age 5 years results in no deficit. The authors performed this study to test this hypothesis in a uniformly seizure-free postsurgical population.

Methods: Controls (n = 10), early-onset patients (n = 7), and late-onset patients (n = 5) were recruited. All patients had nondominant anteromedial temporal lobectomy (AMTL), Wada-confirmed left-hemisphere language dominance and memory support, MTS on both preoperative MRI and biopsy, and were Engel class I 5 years postoperatively. By using a standardized (Ekman and Friesen) human face series, subjects were asked to match the affect of one of two faces to that of a simultaneously presented target face. Target faces expressed fear, anger, or happiness.

Results: Statistical analysis revealed that the early-onset group had significantly impaired FER (measured by percentage of faces correct) for fear ($p = 0.036$), whereas the FER of the late-onset group for fear was comparable to that of controls. FER for anger and happiness was comparable across all three groups.

Conclusions: Despite seizure control/freedom after AMTL, early TLE onset continues to impair FER for frightened expressions (but not for angry or happy expression), whereas late TLE onset does not impair FER, with no indication that AMTL resulted in FER impairment. These results indicate that proper development of the right amygdala is necessary for optimal fear recognition, with other neural processes unable to compensate for early amygdalar damage. **Key Words:** Epilepsy—Facial emotion recognition—Curative anteromedial temporal lobectomy—Nondominant amygdala—Mesial temporal sclerosis.

Human facial expressions convey important emotional information, such that the mere observation of an angry or fearful face can elicit strong visceral responses, such as sweating and increased heart rate (1,2). Both lesion and neuroimaging studies have demonstrated that the amygdala plays a large role in processing and mediating autonomic and behavioral responses to emotionally relevant stimuli and participates in facial-expression processing and emotion recognition of visual stimuli (3–11). Additional evidence suggests that bilateral (but not unilateral) amygdala damage results in generalized facial emotion recognition (FER) failure, with fear being most severely affected (3,5,12,13).

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Patients with temporal lobe epilepsy (TLE) often incur damage to the amygdala and hippocampus, with mesial temporal sclerosis (MTS), neuronal loss and gliosis of the hippocampus, entorhinal cortex, and amygdala complex (14,15). MTS is often associated with early childhood febrile seizures and subsequent drug-resistant TLE (14–16). The standard of care for treating drug-resistant TLE is curative temporal lobectomy, which has demonstrated long-established efficacy and has recently been shown to be far superior to continued medical treatment of these patients in a randomized controlled trial, yielding seizure freedom in 60 to 80% of appropriately chosen patients (17–22). Three surgical methods of temporal lobectomy are most commonly used: anteromedial temporal lobectomy (AMTL), selective amygdalohippocampectomy, and temporal resection guided by intraoperative hippocampal electrocorticography, each with excellent rates of seizure control in appropriately chosen patients (23–25).

One consequence of temporal lobectomy is the resulting partial unilateral damage to the amygdala and surrounding structures after resection (23). Recent emotion-recognition studies involving this patient population revealed that patients with right-sided MTS (as compared with left-sided MTS or other temporal/extratemporal seizure loci) were impaired in the recognition of emotion displayed through facial expressions (26,27). Additionally, subjects with right-sided MTS demonstrated maximal impairment in the recognition of fear, some impairment in anger recognition, lesser impairment of sadness and disgust recognition, and virtually no impairment in happiness recognition (26,27). The presence of febrile convulsions and early-onset seizures (onset before age 6 years) strongly correlated with the severity of emotion-recognition impairment (26,27). Surprisingly, the results demonstrated that patients with right-sided MTS and drug-resistant epilepsy may be impaired in the recognition of emotions from facial expressions before lobectomy for epilepsy treatment (26). Conversely, one of these studies also reported certain subjects with unilateral right amygdalar lesions that exhibited no emotion-recognition impairment in any emotional category (26).

These studies raise the possibility that a critical period of life may exist for establishing the neural network underlying the ability to recognize facial expression. The results imply that early insult to the right mesiotemporal structures may be crucial to cause emotion-recognition deficits, whereas damage (structural or functional) that occurs later in life (seizure onset after 5 years of life) results in no deficit. These data contrast with the general notion that early damage is most likely to be compensated for by plastic processes. The provocative implication is that if the right anteromedial temporal lobe network is disrupted by epileptic activity in early childhood, physiologic phenomena of plastic reorganization are prevented (26,27). Because epilepsy affects the brain's ability to undergo functional reorganization, a critical period may exist in early childhood during which interictal/ictal seizure activity involving the right temporal lobe may affect the development of emotion-recognition ability (28).

Although this hypothesis would appear to apply generally to all patients with MTS and nondominant amygdalar damage, it has yet to be tested in an exclusively MTS population that underwent a uniform surgical method of temporal lobectomy on the nondominant hemisphere, resulting in long-term seizure freedom. This study was performed to examine this issue.

MATERIALS AND METHODS

Control subjects

Ten fluent English-speaking volunteers (five male, five female) participated in the study (mean age, 30.4 years) as controls. No subject had any history of a learning disability or neurologic injury. All controls provided informed consent, as dictated by the Columbia Human Subjects Protection Committee, and were right-handed as determined by an Edinburgh handedness questionnaire.

Patient selection/operative techniques/demographics

Patients were selected from the Columbia University Epilepsy Surgery Database. All surgeries were performed by a single surgeon (R.R.G.), and all patients underwent the same type of AMTL for medically intractable TLE regardless of findings by either pre- or postresection electrocorticography. Right-sided (nondominant) resections were carried out as previously described by Spencer et al. (23), consisting of 2.5- to 3.5-cm lateral neocortical resections of the superior, middle, and inferior temporal gyri with radical en bloc 3.5- to 4.5-cm amygdalohippocampectomies carried back to the level of the superior colliculus.

In addition to right-sided AMTL, eligible patients fulfilled the following inclusion criteria: (a) hippocampal atrophy with increased hippocampal signal ipsilateral to seizure onset documented by a neuroradiologist on preoperative magnetic resonance imaging (MRI); (b) documented age at TLE onset; (c) no other history of neurosurgery; (d) Wada-confirmed language dominance and memory support in the left hemisphere; (e) MTS documented by a neuropathologist on biopsy; and (f) Engel outcome scale class I at 5 years postoperatively (29,30). After determination of eligibility, selected patients were contacted by telephone and decided whether they wanted to participate in the study. Twelve patients agreed to participate, five with TLE onset after age 5 years, and seven with TLE onset before age 6 years. Age at time of surgery ranged from 13 to 52 years (mean, 30.3 years old). All patients had at least one TLE risk factor (average, 1.3; range, one to two), the most common of which was childhood febrile seizures (eight patients). Less-common risk factors included family history of seizures (two patients), meningoencephalitis (one patient), depression (one patient), excessive alcohol intake (one patient), head trauma (one patient), and mild static encephalopathy (one patient). Six patients were Engel class IA, two were class IB, two were class IC, and two were class ID. All patients who agreed to participate provided informed consent.

Experimental paradigm

The paradigm consisted of one experimental block, consisting of faces selected from the standardized Ekman and Friesen series (31). Patients and controls were asked to match the affect of one of two faces with that of a simultaneously presented target face, as described previously (32). Target faces expressed fear, anger, or happiness (Fig. 1) as described previously (32). Distracter faces were photographs of different people of the same sex expressing sadness, disgust, neutrality, surprise, happiness, anger, or fear. For each affect condition, 14 different target faces

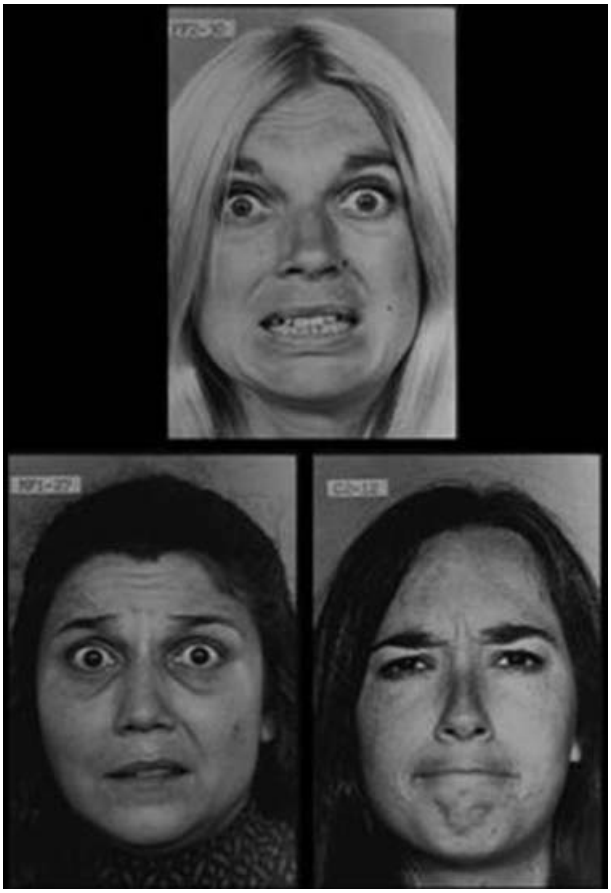

FIG. 1. Representative stimulus utilized in experimental paradigm. Subjects were instructed to select the face (bottom) whose affect matched that of the target face (top). All faces were selected from the Ekman and Friesen standardized face series.

were used (seven of each gender), yielding a total of 42 trials. Images were presented for a period of 5 s each, and subjects responded by pressing one of two buttons on a keyboard, allowing the determination of accuracy and reaction time for each subject. The entire paradigm was carried out by using the Presentation software system (Neurobehavioral Systems, Inc., Albany, CA, U.S.A.).

Data analysis

After data collection, subjects were segregated into three groups for statistical analysis: a control group, an early-onset (before age 6 years) TLE group, and a late-onset (after age 5 years) TLE group. Accuracy and reaction time were analyzed by using an analysis of variance (ANOVA) and unpaired *t* tests. Statistical analysis was carried out by using GraphPad Software, Inc. (San Diego, CA, U.S.A.).

RESULTS

Accuracy and reaction time data acquired across the three groups (Table 1) during the paradigm indicated that the happy expressions were less difficult for subjects to match than either fearful or angry expressions (Table 2). Mean accuracy (percentage correct ± SD) across the three groups was highest for the happy expressions (92.9 ± 6.6) followed by fearful (89.6 ± 11.8) and angry (81.2 ± 9.5). Mean reaction time (seconds ± SD) across the three groups was fastest for the happy expressions (2.4 ± 0.5), followed by angry (2.6 ± 0.7) and fearful (2.8 ± 0.6). ANOVA revealed a significant difference in mean performance accuracy between the three groups for fear ($p = 0.042$), but not anger ($p = 0.479$) or happiness ($p = 0.292$). No significant difference in mean performance reaction time ($p > 0.05$) was found for any expression between the three groups.

Statistical comparisons were made between the control group and early-onset group, and between the control group and the late-onset group. Analysis revealed that the early-onset group was significantly inferior with regard to mean accuracy for fearful expressions ($p = 0.036$) in comparison with the control group (Fig. 2). However, this inferiority was not significant for angry or happy faces when compared with the control group (all p values >0.05). No significant differences were noted between the control and late-onset groups for fearful ($p = 0.871$), angry ($p = 0.256$), or happy ($p = 0.608$) faces (Fig. 2). Likewise, no significant differences in reaction time were seen for happy, angry, and fearful faces between groups (all p values >0.05). A direct comparison of early- and late-onset groups with regard to fear recognition revealed an inferiority in the early-onset group not reaching statistical significance. No significant differences appeared with regard to age at surgery or years of postoperative seizure freedom between the early- and late-onset groups. Within the early- and late-onset groups, no findings were suggestive of a correlation between epilepsy-onset age and extent of FER deficits.

DISCUSSION

The "early-onset" hypothesis that right amygdalar damage before age 6 years results in permanent deficits in FER, whereas damage later than age 5 years does not alter plasticity, thereby not impairing FER, is based on two groundbreaking studies, each of which demonstrated that the disruptive influence of TLE in early childhood results in emotion-recognition impairment (26,27). Despite the widespread implications of these results, it is noteworthy that neither study examined a uniform TLE population, nor did either specify whether surgical patients (when tested) had the same surgical method of temporal lobectomy performed, nor did either attempt to assess the impact of long-term seizure freedom on the hypothesis. Finally, neither study attempted to assess whether their subjects' damage was in the nondominant hemisphere. Each of these aspects provides important information necessary to validate further the early-onset hypothesis.

TABLE 1. *Raw data of scores and reaction times (seconds) for all subjects*

Subject	Age of epilepsy onset	Overall correct	Overall reaction time	Happy correct	Happy reaction time	Fearful correct	Fearful reaction time	Angry correct	Angry reaction time
Control group									
1		40	3.20	13	2.76	14	3.46	13	3.37
2		39	1.40	13	1.39	13	1.13	13	1.67
3		39	2.37	14	1.95	14	2.41	11	2.74
4		32	2.65	12	2.51	11	2.73	9	2.70
5		37	3.08	11	3.15	14	2.95	12	3.15
6		38	2.67	13	2.82	13	2.40	12	2.77
7		32	2.73	12	2.96	11	2.67	9	2.55
8		40	2.12	14	2.11	14	1.96	12	2.29
9		41	2.46	14	2.27	14	2.41	13	2.71
10		39	2.65	13	2.41	13	2.72	13	2.81
Early-onset group									
1	4	35	2.88	14	2.26	10	3.20	11	3.18
2	1	38	2.23	13	2.25	13	2.08	12	2.35
3	3	35	2.64	14	2.10	12	2.99	9	2.82
4	0	39	3.23	14	2.39	14	3.76	11	3.53
5	5	36	2.29	13	2.25	12	2.14	11	2.48
6	2	36	2.70	13	2.21	10	3.04	13	2.85
7	5	33	3.34	13	3.11	8	3.53	12	3.40
Late-onset group									
1	10	38	1.66	13	1.58	14	1.45	11	1.94
2	7	36	3.60	14	2.83	12	3.67	10	4.30
3	6	35	1.85	12	1.80	13	1.96	10	1.79
4	21	37	3.21	13	3.33	13	3.21	11	3.10
5	28	37	2.28	11	2.61	14	1.94	12	2.27

To address these issues, we decided to examine the early-onset hypothesis by using a population of patients with unmistakable MTS (both on preoperative imaging and on biopsy), Wada test–confirmed left hemisphere language dominance and memory support, and long-term seizure freedom postoperatively. To account for the variability of surgical technique, all patients were resected by the same surgeon (R.R.G.) with the same surgical method of AMTL, the method of temporal lobectomy involving the least interpatient variability (23). It was our belief that a patient population meeting these stringent criteria would provide the best method of evaluating the early-onset hypothesis and would indirectly inform us whether AMTL had any impact on the early-onset hypothesis. For a suitable behavioral paradigm to test FER in this patient population, we decided to use the face-matching protocol previously described by Hariri et al. (32), because it was the paradigm that most clearly evoked an amygdalar response in their functional neuroimaging study.

The differences we found in FER for fearful facial expressions between early-onset AMTL patients, late-onset AMTL patients, and controls lend further support to the

TABLE 2. *Depiction of mean and standard deviation for facial emotion recognition (FER) data with regard to: (A) accuracy and (B) reaction time for all three groups.*

	Control group	Early-onset group (0–5 years old)	Late-onset group (≥ 6 years old)
A. Accuracy of FER across groups (% ± S.D.)			
Happy expressions	92.1 ± 7.1	95.9 ± 3.8	90 ± 8.1
Angry expressions	83.6 ± 11.2	80.6 ± 8.9	77.1 ± 6.0
Fearful expressions	93.6 ± 8.6	80.6 ± 14.7	94.3 ± 6.0
Total	89.8 ± 7.6	85.7 ± 4.8	87.1 ± 8.1
B. FER reaction time across groups (seconds ± S.D.)			
Happy expressions	2.4 ± 0.5	2.4 ± 0.3	2.4 ± 0.7
Angry expressions	2.7 ± 0.5	2.9 ± 0.5	2.7 ± 1.0
Fearful expressions	2.5 ± 0.6	3.0 ± 0.6	2.4 ± 0.9
Total	2.5 ± 0.5	2.8 ± 0.4	2.5 ± 0.9

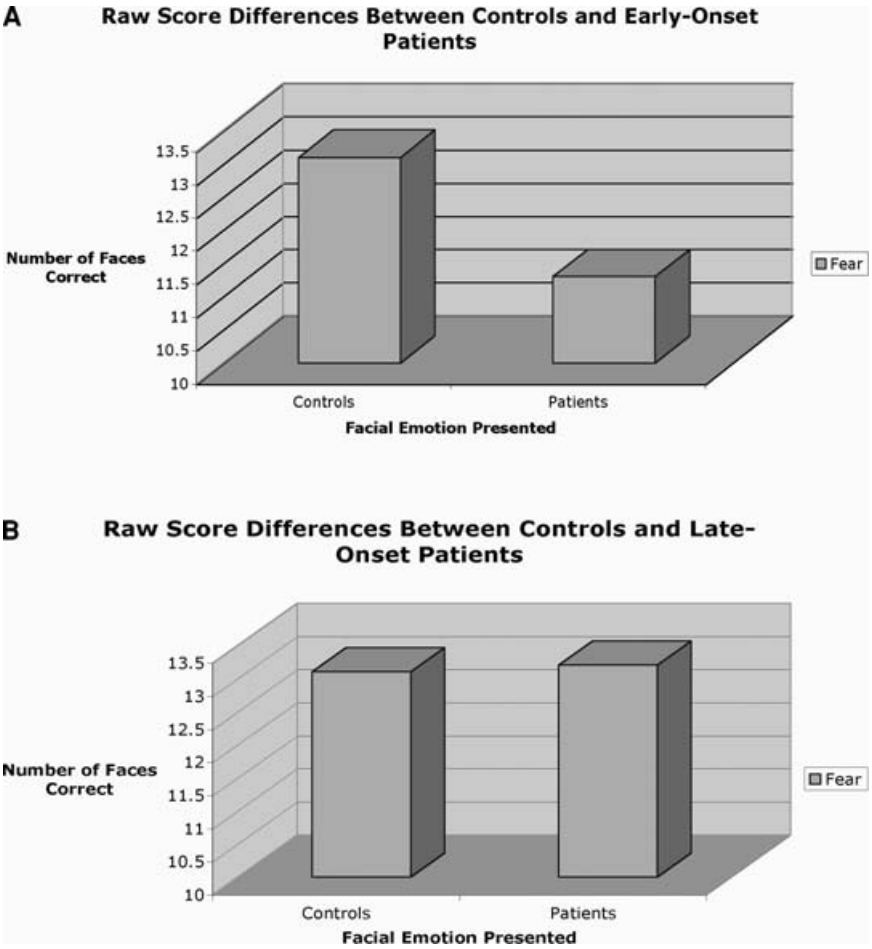

FIG. 2. Histograms depicting raw score differences in facial fear recognition between controls and (**A**) early-onset patients, (**B**) late-onset patients.

validity of the early-onset hypothesis. The additional finding within each AMTL group of no correlation between age at epilepsy onset and extent of FER deficits lends greater support to the functional distinction between early-onset and late-onset patients. Although the difference in FER for angry expressions was not statistically significant, this finding also supports the early-onset hypothesis, which would have predicted fear to be more impaired than anger. It remains unclear as to why FER for happy expressions is not impaired in early-onset patients, although the additional facial cues visible in happiness (i.e., clearly visible smile) may provide eye-tracking clues to early-onset patients not present in fearful or angry faces, as recently described (33).

In addition to the fact that this study lends support to the early-onset hypothesis in a uniform, left-hemisphere language dominant, MTS surgical patient population, it also sheds light on an interesting conclusion from our results. Assuming that the hypothesis is correct, and that all patients with TLE onset before age 6 years had impaired FER before surgery, these patients continued to have impaired FER postoperatively, although surgery produced dramatic and long-lasting seizure freedom/reduction. Therefore it appears reasonable to assume that the FER impairment in these patients was due more to the timing of their epileptic injury rather than the duration of their epilepsy. Conversely, patients without impaired FER before surgery continued to remain unimpaired after surgery. The implication of these findings is that AMTL, despite the amygdalar damage associated with the procedure, does not affect FER (presumably if performed after age 5 years). This may be important for informing AMTL candidates in the future who fear that surgery will result in FER deficits, as well as those who might otherwise associate resection with FER deficits. However, this aspect can be made definitive only by future studies comparing FER in the same patients before and after surgery. Of note, we did not examine the impact of left amygdalar damage on FER, because an examination of this population did not previously reveal any correlation with FER deficits (26).

The limitations of this study are (a) our inability to perform FER testing in these patients preoperatively, and (b) the relatively small sample size, which is due to (a) the relative rarity of temporal lobectomy patients, and (b) the stringent inclusion criteria (particularly 5-year Engel outcome class I data as a prerequisite for inclusion). Despite these shortcomings, the logical progression from the results demonstrated in this study is to determine which

neural processes are being affected during FER in this patient population. Only future imaging studies will be able to address this issue adequately.

CONCLUSIONS

In patients with MTS and confirmed left-hemisphere language dominance who have undergone nondominant AMTL, despite long-term postoperative seizure control/freedom, TLE onset before age 6 years continues to impair facial emotion recognition for frightened expressions (but not for angry or happy expressions), whereas TLE onset after age 5 years does not impair facial emotion recognition. These results indicate that proper development of the right amygdala is necessary for optimal fear recognition, with other neural processes unable to compensate for early amygdalar damage.

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