INFLUENCES OF TEMPORAL LOBE EPILEPSY AND TEMPORAL LOBE RESECTION ON OLFACTION

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Running Head: Temporal Lobe Epilepsy and Human Olfaction

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Abstract

Although temporal lobe epilepsy (TLE) and resection (TLR) impact olfactory eloquent brain structures, their influences on olfaction remain enigmatic. We sought to more definitively assess the influences of TLE and TLR using three well-validated olfactory tests and the tests' associations with the volume of numerous temporal lobe brain structures. The University of Pennsylvania Smell Identification Test and an odor detection threshold test were administered to 71 TLE patients and 71 age- and sex-matched controls; 69 TLE patients and controls received an odor discrimination/ memory test. Fifty-seven patients and 57 controls were tested on odor identification and threshold before and after TLR; 27 patients and 27 controls were similarly tested for odor detection/discrimination. Scores were compared using analysis of variance and correlated with pre- and post-operative volumes of the target brain structures. TLE was associated with *bilateral* deficits in all test measures. TLR further decreased function on the side *ipsilateral* to resection. The hippocampus and other structures were smaller on the focus side of the TLE subjects. Although post-operative volumetric decreases were evident in most measured brain structures, modest contralateral volumetric *increases* were observed in some cases. No meaningful correlations were evident pre- or post-operatively between the olfactory test scores and the structural volumes. In conclusion, we demonstrate that smell dysfunction is clearly a key element of both TLE and TLR, impacting odor identification, detection, and discrimination/memory. Whether our novel finding of significant post-operative increases in the volume of brain structures contralateral to the resection side reflects plasticity and compensatory processes requires further study.

Introduction

Olfaction plays a significant role in everyday life, influencing the flavor of foods, nutrition, safety, and aesthetics. Temporal lobe epilepsy (TLE) and resection (TLR) damage limbic-related structures involved in olfactory perception, including the hippocampus and amygdala. Olfactory testing is potentially a unique probe of such damage.

Despite a large literature on this topic, the influences of TLE and TLR on olfaction are far from clear. Many studies are limited by testing procedures of questionable reliability, small sample sizes, and the failure to assess each side of the nose separately. Results from *threshold* studies have been variable. Thus, in the case of TLE, some have reported lowered olfactory thresholds (i.e., enhanced sensitivity; [4, 8, 24, 41, 46]), whereas others have seen no such effects [7, 18, 19, 21, 29, 32, 43, 49] or have seen elevated thresholds [26]. In the case of TLR, one study found bilaterally elevated detection and recognition thresholds (i.e., lessened sensitivity) following either left or right TLR [39], whereas another found elevated recognition, but not detection, thresholds [22]. Although most studies have reported no influences of TLR on odor detection thresholds, brief tests of questionable sensitivity have been commonly employed [18, 19, 21, 22, 29]. The sole study to compare olfactory thresholds pre- and post-operatively in the same subjects found *n*-butanol thresholds to be unaffected by left-side resection in their 10 left-side epilepsy patients; their 11 right-side TLR patients exhibited elevated thresholds on the right side of the nose [32].

Studies of the influences of TLE and TLR on *suprathreshold* measures are similarly confusing. For example, Hudry et al. [25] found poorer performance on a delayed multi-odor matching task in patients with left- than with right-side foci. In contrast, Abraham and Mathai [1] reported decreased bilateral performance on an odor-matching task in patients with right-side but not left-side foci, as well as in patients who had undergone right, but not left, TLR. Carroll et al. [5] noted larger odor memory decrements for non-nameable, but not nameable, common odorants (e.g., coconut, coffee, nail varnish, and garlic) in right-side, but not left-side, TLE patients. In seeming accord with the findings of Abraham and Mathai [1], Rausch et al. [40] found larger right-side than left-side TLR influences on an odor discrimination/memory task. More recently, Jones-Gotman et al. [30] and Haehner et al. [21] found poorer bilateral odor identification in TLR patients, with poorest performance on the resected side. Other investigators have found no differences between left- and right-side foci and/or resections on bilaterally-administered olfactory tests, including tests of identification, odor memory, and discrimination [9, 18, 19, 27, 29, 42, 49].

In the pre- and post-operative study by Martinez et al. [32], odor discrimination was lower only following right-side resection, with improvement occurring on the left side.

We sought to more definitively establish the influences of both TLE and TLR on the ability to smell by employing relatively large sample sizes, well-validated psychophysical tests, and sex-, age-, and race-matched controls. The influence of the epileptogenic focus was determined and, in the case of TLR, tests were administered pre- and post-operatively. In a subset of patients, olfactory test scores were correlated with volumes of temporal lobe structures both before and after TLR.

Materials and Methods

Subjects

One hundred forty-two subjects participated in the odor identification and threshold testing components of the experiment (Table 1). Seventy-one were TLE patients who exhibited either left (n = 35) or right (n = 36) foci, and 71 were age- and sex-matched normal controls. All patients had unilateral TLE (confirmed by the UPenn Neuroradiology Service via appropriate clinical, EEG, and imaging findings) and a history of intractable seizure activity, with most being candidates for anterior TLR. None had any other history of neurological illness, traumatic brain injury, or current psychiatric illness. No evidence of nasosinus disease was evident upon an upper airway otolaryngology examination. Odor discrimination/memory (OMT) performance was assessed in 69 of the TLE patients and 69 matched controls. Odor identification and detection thresholds were tested before and after TLR in 57 of the patients (27 left & 30 right foci; 25 men and 32 women; respective mean (SD) ages = 35.59 (10.80) & 36.45 (8.60)]. The OMT was administered to 27 patients before and after TLR. Suitable MRI images were available pre- and post-operatively for 25 of the TLR patients for most of the studied brain regions [8 men; 4 left foci and 4 right foci; respective mean (SD) ages 57.00 (14.14) and 43.25 (12.55): 17 women: 7 left foci and 10 right foci, 34.57 (12.72) and 39.27 (6.59)]. Pre- and post-resection volumetric data were available for a subset of 20 of these patients. The median (IQR) time between the operation and the post-operative testing was 174 (133) days.

The controls were healthy volunteers who learned of the study through word of mouth, poster advertisements, or other sources. They were selected on the basis of age and sex to match as closely as possible the demographics of the patients that were being contemporaneously evaluated. All received the same upper airway examination as the

patients to rule out nasosinus disease. None had a history or evidence of neurological illness, traumatic brain injury, drug abuse, nasal disease, or current psychiatric illness. Informed written consent was obtained from all participants, the study was approved by the University of Pennsylvania's Office of Regulatory Affairs. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants were paid $20/hour for their time.

INSERT TABLE 1 ABOUT HERE

Olfactory Tests

Three well-validated and standardized olfactory tests were administered by a trained technician separately to each side of the nose, with the order of the side of testing being systematically counterbalanced. The side opposite to that being tested was occluded using Microfoam™ tape (3M Corporation, Minneapolis, MN) [11]. The *University of Pennsylvania Smell Identification Test (UPSIT)* is a widely used forced-choice microencapsulated odor identification test [14] that focuses on the ability to identify 40 different odorants at the suprathreshold level. In this study, two of the four booklets of 20 odorants were administered to the left side of the nose and two to the right, with the booklets counterbalanced across sides. This approach has been found previously to be reliable (test-retest *r* for 20 items = 0.86; [12]. For the purposes of exposition, the test scores were multiplied by two to place the test scores on the standard 40-item UPSIT scale. *The Smell Threshold Test* (STT) measures a subject's ability to detect low concentrations of the rose-like odorant phenyl ethyl alcohol (PEA), an agent with minimal intranasal trigeminal nerve reactivity. The test-retest reliability of this measure is r = 0.88 [13]. In this study, the stimuli were presented using wide-mouth sniff bottles held over the tip of the nose. The subject did not need to recognize the quality of the stimulus, only to discern whether its intensity differed from that of a blank. The threshold was defined as the mean of the last four of seven staircase reversals. The *Odor Memory/Discrimination Test* (OMT) assesses short-term odor memory and odor discrimination using a Brown-Petersen paradigm [6]. This 12-item four-alternative forced-choice test employs 10-, 30-, and 60-sec delay intervals between the presentation of the target odorants and the first of four successively presented odors from which the targets are selected. The OMT has a test-retest reliability of ~ 0.70 [13].

Brain Region Volumetric Analyses

The MRI volumetric structural analyses employed 1.5T or 3T T1-weighted MPRAGE images. The scans were preprocessed using the Brain Extraction Tool (BET: Version 1.2; FMRIB Image Analysis Group (www.fmrib.ox.ac.uk/ analysis/research/bet), which removed non-brain tissue from all structural images. Quantitative region of interest (ROI) based analyses of pre- and post-surgical brain volumes were performed using the ITK-SNAP image analysis program (www.itksnap.org). ITK-SNAP is an interactive medical image segmentation tool that provides user-guided semi-automated and manual segmentation. Whole brain, bilateral hemisphere, and cerebellar ROIs were segmented using the semi-automatic algorithm based on regional intensity differences in tissue structure [48]. Substructures of the hippocampus and amygdala, as well as the parahippocampal gyrus (most of which is occupied by the entorhinal cortex), fusiform gyrus, inferior temporal gyrus, middle, temporal gyrus, and the superior temporal gyrus, were manually segmented on each side of the brain by trained operators. The pre- and post-surgical hippocampal anatomical boundaries were defined using anatomical atlases [15, 31], as well as previously described methods for segmental temporal lobe regions [47]. Although coronal slices were used to perform all segmentations, axial and sagittal planes were used continuously as references to distinguish and confirm the anatomical boundaries and landmarks in three-dimensional space in consecutive slices. The inter-rater reliability of measuring the structures was > 0.90.

Temporal Lobe Resection Procedures

The temporal lobe resections were performed in accord with a widely used standard protocol; namely, the en bloc anterior temporal lobe resection procedure described by Falconer and Taylor [20]. The amount of tissue resected from the language dominant temporal lobe, while variable, typically extended laterally 3.0 to 5.0 cm from the temporal tip, whereas in the non-dominant lobe such extension was from 4 to 5.5 cm from the tip. The amygdala and the hippocampus were included in the resections. In general, 2.5 to 3 cm of the hippocampus and parahippocampal gyrus were removed [35, 36].

Statistical Analyses

The data from each of the three olfactory test measures were subjected to individual analyses of variance (ANOVA) with the between subject factor of focus side and the within subject factor of nose side. Given the matching, subject group (epilepsy, control) was modeled as a within subject factor. A similar ANOVA was performed on the TLR data, except that the focus side

remained as a between subject factor and the pre-/post-operation condition replaced the within subject group factor. Given that preliminary analyses found that the delay interval of the odor memory/discrimination test was not significantly influenced by TLE or TLR (all *p*s > 0.05), the delay interval data were collapsed into a single value in all analyses to simplify the presentation of the findings.

Pearson correlations were computed between (a) the left and right side olfactory test scores and (b) the left and right side volumes of the hemispheres, cerebelli, hippocampi, amygdalae, parahippocampal gyri, fusiform gyri, inferior temporal gyri, middle temporal gyri, and superior temporal gyri. Separate correlations were computed between the test and volume measures for the ipsilateral nose side of the left- and right-focus patients, as well as for the combined left:right side focus group data. In the TLR patients, correlations were determined between (a) the differences in the pre- and post-operative olfactory test scores and (b) the differences in the pre- and post-operative volumes of each of these structures. These correlations were computed both on the raw volume data and on the data corrected for total brain volume. The frequency distributions of the regional brain volumes did not differ from normality, as indicated by visual inspection of the histograms and non-significant Shapiro-Wilk tests of normality.

Results

Influences of TLE on Odor Identification, Detection, and Discrimination/Memory

The mean (SEM) odor identification, threshold, and discrimination/memory test scores for the TLE group and the matched controls are presented in Figure 1. As can be observed in this figure, the test scores of the TLE patients were clearly lower than those of the controls for all three tests (respective subject group factor *p*s for each test analysis = 0.00001, 0.001 & 0.007; respective η^2s = 0.378, 0.159 & 0.103). An interaction, independent of focus side, was also present between nose side and subject group (TLE/control) for both the UPSIT (P = 0.007; η^2 = 0.099) and the OMT (P = 0.013; η^2 = 0.086), but not for the STT (P = 0.503, η^2 = 0.006). For the UPSIT, this reflected a significantly lower score on the right than on the left side of the nose in the TLE subjects (L&R means = 31.25 & 29.63, P = 0.028), but not in the control subjects (L&R means = 35.52 & 36.17, P = 0.090). For the OMT, this reflected a significant difference between the TLE and control scores on the right side of the nose [right TLE & right control means = 6.70 & 8.54, P = 0.001] but not on the left side of the nose [left TLE & left control means = 7.20 & 7.84, P = 0.178].

INSERT FIGURE 1 ABOUT HERE

Influences of TLR on Odor Identification, Detection and Discrimination/Memory

The mean (SEM) test scores obtained before and after temporal lobe resection are presented in Figure 2. For each test, the pre-/post-operation factor was statistically significant, reflecting poorer overall post-operative test performance [UPSIT $P = 0.003$, $\eta^2 = 0.151$; STT $P = 0.016$, $\eta^2 = 0.103$; OMT $P = 0.007$, $\eta^2 = 0.127$]. Three-way interactions were evident among the pre-post-operation factor, side of nose tested, and the side of resection [UPSIT $P = 0.005$, $\eta^2 = 0.137$; STT $P = 0.005$, $\eta^2 = 0.134$; OMT $P = 0.13$, $\eta^2 = 0.041$]. In all three cases, these interactions reflected greater decreased performance on the resected than on the non-resected side, with a tendency for the effects to be somewhat larger for the left than the right side of the nose [Figure 2; respective L- & R-side lesion *P* values for the L-side lesion patients: UPSIT – 0.002 & 0.590; STT – 0.001 & 0.731; OMT – 0.002 & 0.640; corresponding values for the R-side lesion patients: UPSIT – 0.165 & 0.014; STT – 0.662 & 0.055; OMT – 0.165 & 0.263]. Nevertheless, the magnitude of the left-side lesion deficit (left TLR score of the left lesion group minus the left matched control score) did not differ significantly from that of the right lesion deficit (right TLR score of the right lesion group minus the right matched control score) (*P*s> 0.20), implying that, within the variability of the test scores, the left and right operations induced a similar relative degree of homolateral dysfunction.

INSERT FIGURE 2 ABOUT HERE

TLE and TLR Volumetric Brain Measures

In the case of all of the TLE patients for whom data were available prior to temporal lobe resection, the volumes of some brain regions were significantly smaller on the focus than on the non-focus side (Table 2), with stronger reductions for the whole hemisphere, hippocampus, and inferior temporal gyrus for individuals with a left epileptogenic focus and for the parahippocampal and inferior temporal gyrus for those with a right epileptogenic focus. The ipsilateral hippocampus in those with a right epileptogenic focus was also smaller, although this effect was statistically marginal ($P = 0.058$).

INSERT TABLE 2 ABOUT HERE

The volumes on the resected and non-resected sides of the brain are shown in Table 3 for those subjects whose pre-/post-resection data were available. Aside from a volume decrement in most brain regions on the side of the operation, the volume of a number of

structures on the side contralateral to the resection were significantly, albeit modestly, larger post-operatively than pre-operatively. This phenomenon was present mainly for the left-side resection group, although a significant volume increase in the parahippocampal gyrus was evidence in both resection groups. Note that meaningful post-operative data were lacking for the ipsilateral amygdala and hippocampi since the resections either eliminated or markedly attenuated these structures.

INSERT TABLE 3 ABOUT HERE

Correlations between Volume of Brain Structures and Olfactory Test Scores in the Non-Operated TLE Subjects

No significant correlations were observed between any of the olfactory test measures and the volumes of the TLE brain structures even after applying minimal alpha level constraints for minimizing type I errors for multiple tests comparisons (e.g., by increasing the significance criterion from 0.05 to 0.025). In general, the number of positive correlations were equivalent to the number of negative correlations, supporting the lack of a trend in the direction of the computed correlations The lack of meaningful correlations was apparent regardless of whether the analyses were performed separately on the volumes and olfactory test measures on the left focus side, the right focus side, or the groups combined into focus and non-focus sides independent of left and right side involvement. Similarly, no significant correlations were present when the percent volume differences between the focus and non-focus brain sides were correlated with the corresponding focus side minus non-focus side olfactory test score differences.

Relation of TLR Tissue Resection Volumes to Olfactory Test Scores

MRI-determined volumes of left- and right-side resected brain tissue were available for 25 of the patients for the left and right sides of the parahippocampal gyrus, fusiform gyrus, inferior temporal gyrus, middle temporal gyrus, and superior temporal gyrus. No usable post-operative data from the hippocampus and amygdala were available for operated side, since the temporal lobe resections largely ablated these structures. The correlations between (a) the differences in the pre- and post-operative olfactory test scores and (b) the differences in the pre- and post-operative volumes of each structure were not significant in any case and, as in the situation with the non-operated subjects, the number of positive correlations was essentially equivalent to the number of negative correlations.

Discussion

This study unequivocally demonstrates that TLE patients with either a left or a right epileptogenic focus experience *bilateral* deficits in detecting, identifying, and discriminating odorants. TLR, on the other hand, produces a greater deficit on the resected than on the non-resected side. In general, the magnitude of the dysfunction due to TLR is less than that due to epilepsy, per se. Interestingly, the TLE patients of this study exhibited, independent of focus side, somewhat larger odor identification deficits on the right than on the left side of the nose. Although a similar trend was noted for odor discrimination/memory, this effect was not statistically significant. The odor identification deficits were larger and less variable than the odor detection and odor discrimination/memory deficits, likely reflecting, in part, the somewhat lower reliabilities of the latter two tests [13].

Our finding that TLE produces bilateral deficits in odor identification and discrimination is in accord with a number of earlier, less definitive, studies [1, 5, 19, 21, 29, 30, 32]. However, our findings differ from studies reporting no effects of TLE on odor identification [27] or memory [19], as well as a study noting discrimination deficits only in patients with right-side foci [1]. Importantly, our findings that both TLE and TLR negatively impact odor detection thresholds differ from reports of no threshold deficits in TLE patients [1, 19, 32] or TLR patients.[17-19, 21, 24, 29, 49]. While our data are in accord with those of three studies noting threshold deficits in TLR patients [32, 38, 39], two of these studies evaluated olfactory function bilaterally and had no TLE control group, confounding TLR with TLE [38, 39]. In the sole study that examined the same epilepsy patients before and after TLR, the threshold deficit was confined to the right side of the nose [32].

What might account for the difference between our threshold findings and those of others? First, our single staircase threshold procedure is more reliable than single ascending series staircases procedures that have been employed in most previous studies, as it repeatedly samples the perithreshold region [13]. Second, we used half-$\log_{10}$ step odorant dilutions steps ranging from 10^{-9} to 10^{-2} vol/vol, unlike most other threshold procedures that employed binary dilutions. Third, our procedure for presenting stimuli differed from others which employed either squeeze bottles [32], jars or test tubes with small openings [29, 49], nose pieces that fit into the nares [18, 19], or felt-tip pen-like devices [21, 27]. Our wide-mouth sniff bottles were held over the tip of the nose, with one side of the nose occluded with tape, so that the effective stimulus concentration was likely greater than that produced by many other

procedures [11]. Fourth, we employed a comparatively large sample and, in the case of TLR, assessed performance before and after resection.

In accord with our structural findings, smaller hippocampus and extra-hippocampal temporal lobe structures such as the entorhinal cortex and superior temporal gyrus have been observed on the focus or sclerotic side of TLE patients [2, 3, 16, 33, 44]. Relative to normal controls, some studies report no contralateral volume deficits in the hippocampus and related structures in TLE patients [23]. However, one such study found decrements in the volume of the contralateral superior temporal gyrus, but nowhere else [33]. Several other TLE studies have noted volume decrements contralateral to the focus side, *relative to controls*, in such structures as the amygdala, temporal pole, hippocampus, and parahippocampal gyrus, suggesting ipsilateral medial temporal lobe damage can extend to contralateral structures [2, 44]. Since we did not evaluate the volume of such structures in controls, we cannot determine whether such contralateral effects occurred in our TLE patients.

While ipsilateral decrements in the volume of brain structures related to resected structures were generally expected after TLR, our novel finding of slightly larger volumes of their contralateral counterparts was not. Such increases in volume suggest that contralateral compensation for iatrogenic damage may have occurred via enhanced synaptic connectivity or other processes that impact structural volumes, as documented in murine somatosensory cortex lesion studies [28]. While this post-surgical phenomenon for the hippocampus was reported in one study of epileptic patients [37], it was not observed in another [34]. The latter study also found no post-operative contralateral differences from controls in measured volumes of the temporopolar cortex and regions of the parahippocampal gyrus (perirhinal, entorhinal, and parahippocampal cortices). Without normal control data, it is unknown, although seemingly unlikely, whether the increased contralateral volumes we observed surpassed those expected in healthy controls, particularly if some preoperative contralateral damage was present in these structures. Other studies of post-operative volumes outside the hippocampus are essentially non-existent in TLR patients.

The basis for our finding that TLE had a significantly greater negative effect on odor identification on the right than on the left side of the nose regardless of focus side is unknown. It is generally assumed that ipsilateral olfactory projections from the bulb to the cortex overwhelm contralateral projections that occur via the anterior commissure. Under this assumption, right-hemisphere olfactory structures may be more vulnerable to damage in light

of evidence that this hemisphere may play a disproportionate role in central olfactory processing [50].

The anatomical or physiological basis for the alterations in smell function that we observed is not entirely clear, although damage to the temporal lobe structures we quantified may not be the direct cause of the olfactory dysfunction seen in either TLE or TLR. Thus, others have presented data that question whether damage to the amygdala and the hippocampus are involved in such disruption. Jones-Gotman and Zatorre [29] found, relative to controls, that bilateral UPSIT scores were as depressed in TLR patients with small hippocampal excisions as in those with large hippocampal excisions. This suggested that the amount of iatrogenic incursion into the hippocampus had little effect on the odor identification test scores. More recently, this same group compared UPSIT scores of TLRs performed at three institutions that differ in their impact on the amygdala and hippocampus [30]. In the first, the anterior lobe resections excised the amygdala and some of the hippocampus (n = 22). In the second, selective resection from the medial basal temporal region did not impact the temporal neocortex (n = 25), whereas in the third both the amygdala and hippocampus were believed to be spared, although later imaging found this not to be entirely true (n =23). Regardless of the type of surgery, however, UPSIT scores were similarly impaired, with greater impairment occurring in the nostril ipsilateral to the resection. These findings suggest that the TLR-related olfactory dysfunction is not necessarily due to damage to either the hippocampus or the amygdala, but may reflect damage to brain regions outside these areas (e.g., piriform cortex, periamygdaloid area) or to disrupted neural networks critical for olfactory function. Our UPSIT findings directly parallel those of Jones-Gotman and colleagues.

Our finding of no meaningful correlations between olfactory test measures and the volumes of temporal lobe structures associated with TLE similarly suggests that factors other than terminal cell loss within these structures may be responsible for the olfactory dysfunction of TLE, although this may not be the case for TLR. Some neurotransmitter processes directly or indirectly related to olfactory function and TLE appear to be altered early in the epileptogenic process when volumetric damage to temporal lobe structures would be minimal. For example, cholinergic neurons within basal forebrain structures, such as the septum, the nucleus basalis of Meynart, and the diagonal band of Broca, send processes both to the olfactory bulb and to the hippocampus. The degree of damage to such structures, notably the nucleus basalis, correlates with the degree of smell dysfunction observed among a range of neurodegenerative

diseases [10]. Moreover, damage to such forebrain cholinergic centers has been linked to hippocampal epileptogenesis [45]. As reviewed in the latter paper, several studies have found that immunotoxic lesions of septal cholinergic cells in rats increase seizure susceptibility and exacerbate seizure-induced neuronal loss in the hilus of the dentate gyrus. Spontaneous seizures are evident prior to mossy fiber sprouting which, classically, has been suggested to render hippocampal circuits hyperexcitable and epileptogenic. Nonetheless, sprouting of fibers immunoreactive to acetylcholinesterase have been associated with epileptic seizures in laboratory animals and with both atrophic and hypertrophic morphological alterations in the medial septum.

Regardless of the mechanisms involved, the present study definitively establishes, using state-of-the-art olfactory tests, that olfactory dysfunction is a primary element of TLE that is further exacerbated by TLR. Moreover, it shows, for the first time, that the volume of temporal lobe structures contralateral to resections actually increase in size, albeit modestly, postoperatively. Our research is in accord with the hypothesis that the olfactory dysfunction associated with TLE or TLR is not meaningfully associated with volumetric measures of a number of temporal lobe structures, including the parahippocampal gyrus that subsumes the entorhinal cortex, and raises the possibility that damage to other neural processes, such as neurotransmitter systems involved in olfactory neural networks, may well be involved. Several key questions remain unanswered. When does the olfactory dysfunction first appear? Is it progressive or stable, as occurs in Parkinson's disease, once it appears? Does it correlate with PET imaging of ligands, such as cholinesterase, implicating cholinergic processes? What neurocircuits are involved in these processes?

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Conflicts of Interest

RLD is President and major shareholder of Sensonics International, the company that manufactures and distributes olfactory and gustatory tests, including the commercial version of the University of Pennsylvania Smell Identification Test (UPSIT) used in this study. The remaining authors report no potential conflicts with commercial relationships of direct relevance to the current research.

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Table 1. Demographics of the study group that received the odor identification and threshold testing. See text for details.

	SUBJECT GROUP			
	Left Temporal Lobe Epilepsy (LTLE)	LTLE Control	Right Temporal Lobe Epilepsy (RTLE)	RTLE Control
Number of Subjects				
Men	18	18	13	13
Women	17	17	23	23
Total	35	35	36	36
Age (Years)				
Mean (SD)	36.91 (11.02)	36.20 (10.26)	36.83 (8.81)	36.81 (8.61)
Range	18-67	19-60	19-55	22-52
Education				
Mean (SD)	13.64 (2.76)	15.61 (2.74)	14.28 (2.25)	16.1 (2.55)
Range	6-20	10-21	12-20	12-21
Handedness				
Left/Right/Mixed/Unknown	6/27/2/0	2/29/0/4	3/33/0/0	1/29/1/5
Language Hemisphere				
Left/Right/Unknown	23/3/9	na	27/0/9	na
Age of Seizure Onset	8.35 (n = 16)	na	12.35 (n = 13)	na

na = not available

Table 2. Mean volume (SD) in mm^3 of left and right brain regions of unoperated temporal lobe epilepsy (TLE) patients as a function of focus side. Gray boxes show means and p values of structures that differed significantly between the non-focus and focus sides of the brain ($ps < 0.05$). N's based on cases in which data from both left and right sides of the brain were available. See text for details.

LEFT FOCUS								
Brain Structure	**N**	**Mean Volume Right (Non-Focus) Side**	**SD**	**Mean Volume Left (Focus) Side**	**SD**	**% Reduction on Focus Side**	**t value**	***p* value**
Amygdala	7	817.10	227.65	894.16	171.74	-8.62	0.66	0.532
Cerebellum	11	63,462.45	15,180.91	64,827.01	18,196.47	-2.15	0.59	0.571
Hemisphere	11	**485,443.17**	68,607.40	**456,694.32**	72,725.10	5.92	4.79	**0.001**
Hippocampus	11	**1,759.93**	152.18	**1.350.19**	441.68	23.28	3.14	**0.011**
Parahippocampal Gyrus	11	9,050.25	883.60	9,000.17	1,385.04	0.55	0.10	0.460
Fusiform Gyrus	11	12,730.92	1,897.83	12,129.03	2,070.00	4.73	0.71	0.243
Inferior Temporal Gyrus	11	**18,479.71**	2,807.78	**13,948.47**	2,543.64	24.52	3.97	**<0.001**
Middle Temporal Gyrus	11	19,932.20	2,644.38	18,982.45	3,354.99	4.76	0.73	0.237
Superior Temporal Gyrus	11	26,085.65	4,304.42	24,140.28	2,988.88	7.46	1.23	0.116
RIGHT FOCUS								
Brain Structure		**Mean Volume Left (Non-Focus Side)**	**SD**	**Mean Volume Right (Focus) Side**	**SD**	**% Reduction on Focus Side**	**t value**	**1-tailed p value**
Amygdala	12	924.70	271.88	1007.46	388.42	-8.95	0.84	0.419
Cerebellum	14	62,882.06	14,349.32	62,824.22	14,202.47	0.09	0.07	0.943
Hemisphere	14	477,715.65	80,466.52	483,381.57	79,884.22	-1.19	1.89	0.081
Hippocampus	14	1,741.88	311.13	1,533.05	544.68	11.99	2.08	0.058
Parahippocampal Gyrus	14	**9,925.52**	1,680.24	**8,791.20**	1,288.93	11.43	2.00	**0.028**
Fusiform Gyrus	14	13,131.89	1,831.84	12,359.77	1,699.10	5.88	1.16	0.129
Inferior Temporal Gyrus	14	**18,445.22**	3,367.02	**15,406.20**	2,738.82	16.48	2.62	**0.007**
Middle Temporal Gyrus	14	19,873.77	2,818.24	19,727.73	2,845.65	0.73	0.14	0.446
Superior Temporal Gyrus	14	25,675.22	4,012.47	25,222.81	3,426.01	1.76	0.32	0.375

Table 3. Mean (SD) volume in mm^3 of targeted brain regions before and after temporal lobe resection (TLR). Dark gray boxes show mean values that *decreased* significantly ($p < 0.05$) on the *lesioned* side from the pre-op to the post-op periods, whereas light gray boxes indicate mean values that *increased* significantly across these two periods on the *non-lesioned* side. Sample sizes based upon data where equal numbers of pre- and post-non-resected volumes were available. See text for details.

LEFT RESECTION GROUP												
Brain Structure	**PRE-RESECTION**			**POST-RESECTION**		**COMPARATIVE STATISTICS**					
	N	**Mean (SD) Volume Resected Side (L)**	**Mean (SD) Volume Non-Resected Side (R)**	**Mean (SD) Volume Resected Side (L)**	**Mean (SD) Volume Non-Resected Side (R)**	**% Change Resected Side (L)**	**t**	***p****	**% Change Non-Resected Side (R)**	**t**	***p****
Amygdala	7	**878.59** (203.46)	**824.80** (163.10)	----**	**1,190.66** (185.29)	----**	----	----	+44.36	4.20	**0.014**
Cerebellum	8	**60,607.02** (17,905.88)	**60,949.41** (16,461.75)	**64,308.19** (15,523.96)	**63,182.63** (16,202.40)	+6.11	1.88	0.103	+3.66	1.48	0.181
Hemisphere	8	**485,208.71** (55,449.27)	**508,923.304** (59,190.20)	**455,839.12** (58,762.31)	**515,559.05** (61,107.11)	-6.05	10.64	**<0.0001**	+1.30	2.22	0.062
Hippocampus	7	**1,415.14** (453.60)	**1,728.88** (112.70)	----**	**1,854.00** (224.30)	----**	----	----	+7.24	2.61	**0.040**
Parahippocampal Gyrus	8	**9,582.51** (1,245.68)	**9,238.90** (800.86)	**6,304.37** (1,440.62)	**9,538.68** (939.76)	-34.21	10.77	**<0.0001**	+3.24	2.66	**0.032**
Fusiform Gyrus	8	**12,973.19** (1,164.14)	**13,425.11** (1,183.91)	**8,045.33** (1,729.12)	**14,016.86** (1,865.92)	-37.98	14.49	**<0.0001**	+4.41	4.11	**0.005**
Inferior Temporal Gyrus	8	**14,770.73** (2,141.89)	**19,066.23** (2,384.56)	**10,506.71** (2,407.59)	**19,858.13** (2,675.96)	-28.87	9.93	**<0.0001**	+4.15	2.77	**0.028**
Middle Temporal Gyrus	8	**20,233.18** (1,999.73)	**20,872.89** (2,505.39)	**16,811.28** (2,621.88)	**21,355.94** (2,774.80)	-16.91	7.90	**<0.0001**	+2.31	2.09	0.075
Superior Temporal Gyrus	8	**25,409.71** (1,954.22)	**28,101.40** (2,564.62)	**24,385.51** (2,871.79)	**28,994.99** (2,946.74)	-4.03	1.59	0.078	+3.18	2.37	**0.049**
RIGHT RESECTION GROUP												
Brain Structure	**PRE-RESECTION**			**POST-RESECTION**		**COMPARATIVE STATISTICS**					
	N	**Mean (SD) Volume Resected Side (R)**	**Mean (SD) Pre- Non-Resected Side (L)**	**Mean (SD) Volume Resected Side (R)**	**Mean (SD) Volume Non-Resected Side (L)**	**% Change Resected Side (R)**	**t**	**p**	**% Change Non-Resected Side (L)**	**t**	**P**
Amygdala	12	**1196.53** (561.74)	**914.97** (309.69)	----**	**1,162.06** (190.24)	----**	----	----	+27.00	2.05	0.074
Cerebellum	12	**62,216.72** (15,261.10)	**62,275.69** (14,968.83)	**60,135.31** (15,266.71)	**61,333.79** (15,079.60)	-3.35	0.75	0.468	-1.51	0.29	0.777
Hemisphere	12	**473,438.45** (70,960.82)	**467,450.53** (71,367.87)	**420,935.44** (82,256.35)	**459,685.87** (89,363.90)	-11.09	4.87	**<0.0001**	-1.67	0.64	0.538
Hippocampus	12	**1,321.65** (426.35)	**1,670.75** (284.82)	----**	**1,630.49** (285.19)	----**	----	----	-2.41	0.75	0.460
Parahippocampal Gyrus	12	**8,602.79** (800.87)	**9,625.17** (1,245.69)	**6,429.55** (1,044.80)	**9,963.04** (1,479.52)	-25.26	6.57	**<0.0001**	+3.50	3.77	**0.003**
Fusiform Gyrus	12	**12,087.22** (1,331.93)	**12,806.07** (1,183.91)	**7,223.85** (2,024.28)	**12,790.03** (1,400.77)	-40.24	9.93	**<0.0001**	-0.13	0.07	0.946
Inferior Temporal Gyrus	12	**17,859.85** (2,257.14)	**15,290.39** (6,906.79)	**11,711.55** (2,579.37)	**14,483.23** (1,961.29)	-34.43	7.62	**<0.0001**	-5.28	1.20	0.255
Middle Temporal Gyrus	12	**19,417.31** (2,505.41)	**19,498.08** (2,183.82)	**13,031.89** (2774.84)	**19,868.59** (2,608.24)	-32.53	8.46	**<0.0001**	+1.90	0.63	0.540
Superior Temporal Gyrus	12	**24,618.04** (2,564.65)	**25,213.12** (2,837.10)	**20,229.71** (4,012.47)	**25,365.23** (3,476.84)	-17.83	5.51	**<0.0001**	+0.60	0.25	0.809

*Paired t-tests are one-tailed for resection sides and two-tailed for non-resection sides. **too few cases in which post- resection structures were present and could be reliably measured and compared.

Figure 1 caption. Odor identification, detection, and discrimination/memory test scores for as a function of side of nose tested and side of epileptic focus. Controls were age- and sex-matched to the epilepsy patients. See text for details.

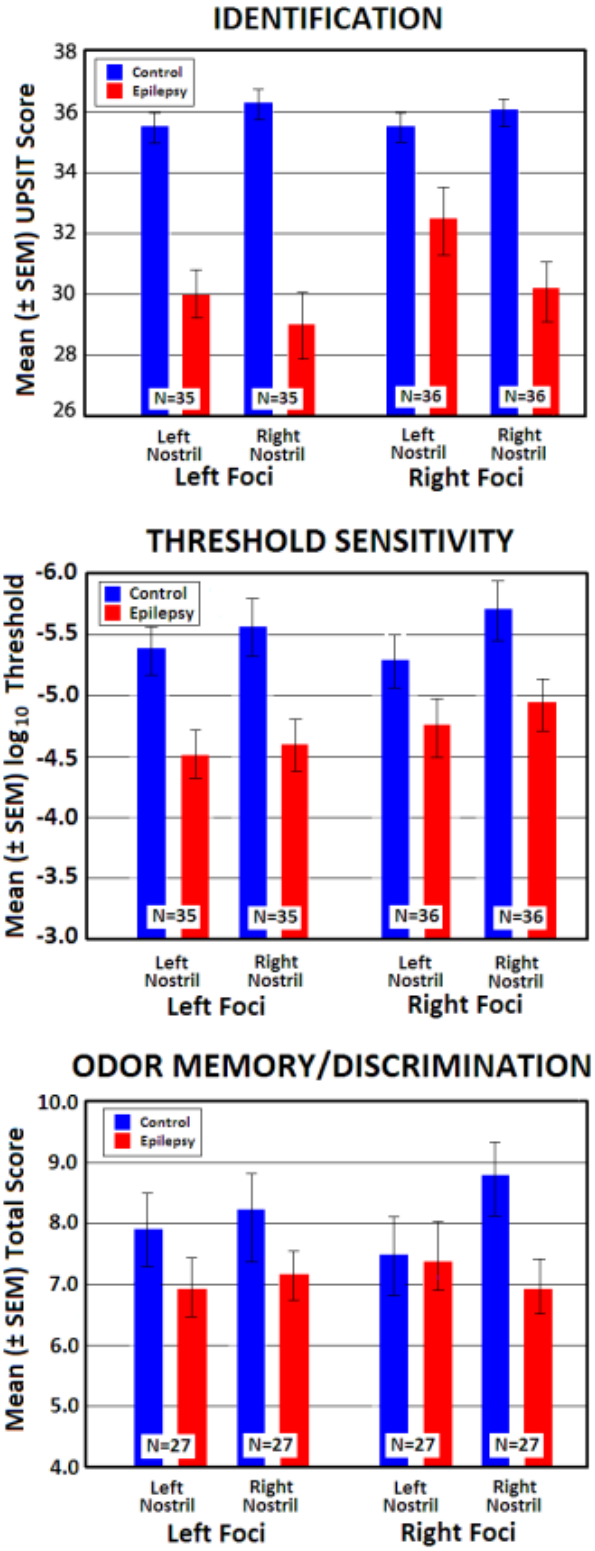

Figure 2. Pre- and post-operative olfactory test scores for tests of odor identication, detection threshold sensitivity and odor discrimination/memory as a function of side of nose tested and side of epileptic focus. See text for details.