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The Functional Anatomy of Non-Verbal (Pitch Memory) Function in Left and Right Anterior Temporal Lobectomy Patients

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Abstract

An fMRI pitch memory task was administered to left and right anterior temporal lobectomy (ATL) patients. The goal was to verify the neuroanatomical correlates of non-verbal memory, and to determine if pitch memory tasks can identify cognitive risk prior to ATL. The data showed that the bilateral posterior superior temporal lobes implement pitch memory in both ATL patients and NCs (normal controls), indicating that the task can be accomplished with either anterior temporal lobe resected. NCs activate the posterior temporal lobes more strongly than ATL patients during highly accurate performance. In contrast, both ATL groups activate the anterior cingulate in association with accuracy. While our data clarifies the functional neuroanatomy of pitch memory, it also indicates that such tasks do not serve well to lateralize and functionally map potentially “at risk” non-verbal memory skills prior to ATL.

Keywords

pitch memory; tone discrimination; non-verbal memory; epilepsy; temporal lobectomy

Introduction

Anterior temporal lobectomy (ATL) is an effective treatment for intractable temporal lobe epilepsy. ATL consists of the total or partial extirpation of anterior regions of the temporal lobe, amygdala, uncus, hippocampus, and parahippocampal gyrus [1, 2]. In the context of the dominant temporal lobe, these areas are strongly associated with various aspects of verbal episodic memory, lexical retrieval, and category knowledge. Therefore, patient outcome with regards to disruption of these crucial cognitive systems becomes a primary concern when undertaking resective procedures such as ATL [2]. While a vast amount of

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research has been reported on verbal episodic memory in temporal lobe epilepsy (TLE) patients [3-12], much less research has been dedicated to examining the behavioral integrity and functional anatomical correlates of non-verbal skills [8, 13]. As a result of this lack of research it is much more difficult to predict the risk to skills such as non-verbal memory following resective temporal lobe surgery. Recent work on memory for pitch, using formats that call upon short-term and working memory, has suggested this function is highly dependent on the temporal lobes. In this project, we examine pitch memory in patients who have undergone either a left or right ATL to clarify the functionality of the non-dominant temporal lobe, and to assess whether such a task can be used to identify cognitive risk to non-verbal memory functions following temporal lobe surgery for intractable epilepsy.

Schlaug and colleagues have reported on studies of pitch memory in normal populations, generally finding that such tasks are associated with bilateral activation of the temporal lobes, often with stronger activity in the left than the right hemisphere [14-16]. For instance, Gaab et al. [15] utilized a sparse fMRI sampling paradigm in the context of a task requiring comparison of the first and last tone in a sequence (5-6 second interval between tones). They found greater left than right temporal lobe activation, with judgment accuracy associated with left supramarginal activity. Gaab and colleagues [14] also utilized tone sequences and a similarity judgment paradigm, and trained participants on the task. Initially, all participants showed bilateral superior temporal gyrus activation, in addition to bilateral inferior frontal and inferior parietal activation. After training, both strong and weak learners displayed bilateral superior temporal gyrus activation, along with additional left hemisphere activation sites. Schulz et al. [16] examined a tone sequence judgment task in musicians and found that both musicians and non-musicians produced bilateral superior temporal gyrus activation. Vines et al. [17] had participants perform a tone sequence judgment task during transcranial direct current stimulation over the left supramarginal gyrus, achieving successful knock out of performance; however, no such effect was observed when stimulating the right supramarginal gyrus. Lastly, Bidet-Caulet and colleagues [13] examined TLE patients using a short-term memory tone comparison task, and found both TLE groups were impaired relative to controls with no change in patient performance before or after surgery, suggesting that both temporal lobes contribute significantly to task performance. They also found that a more extensive resection was associated with more significant deficits on the task.

In contrast, Zatorre and colleagues [18-25] have demonstrated the importance of the right temporal lobe in pitch memory and processing in both normal controls and epilepsy patients. For instance, Zatorre and Samson [25] used a target/comparison tone task to show that patients with right ATL and patients with right frontal lesions had the most significant deficit in pitch memory relative to controls. Zatorre et al. [24] in a PET study with normal controls used an 8-tone melody task and had participants judge whether the first and last tones were similar in pitch. Several activations in frontal (right inferior frontal, bilateral mid-frontal), parietal (bilateral inferior parietal, right superior parietal), and cingulate cortex were observed, in addition to right middle temporal activation. Lastly, Grimault et al. [18] presented tone sequences of varying length and participants judged whether two sequences were similar and observed left superior temporal activation with a trend toward right superior temporal lobe activation (both Brodmann Area (BA) 22).

Based on this review, clearly the empirical data are mixed in terms of the potential lateralization of pitch memory functions. To assess the functionality of an important non-verbal skill in TLE, contribute to the cognitive neuroscience literature on the functionality of the anterior temporal lobes, and to determine the potential laterality or bilaterality of a pitch memory task as part of its evaluation for use in calculating cognitive risk and morbidity following temporal lobe surgery, we examined a non-verbal pitch working memory task in both normal controls (NCs) and ATL patients. If the bilateral temporal lobes are needed for

the task, as the work by Schlaug and others suggest, one would expect both left ATL and right ATL groups (LATL and RATL, respectively) to be impaired. If, on the other hand, one were to follow reports by Zatorre et al., one would expect the RATL group to be more significantly impaired on the task. Behaviorally, we hypothesize that both left and right ATL groups will perform with less accurately than normal controls.

Methods

Subjects

A total of five LATL subjects, five RATL subjects, and five NCs were recruited from the Thomas Jefferson Comprehensive Epilepsy Center for this study. The LATL group consisted of subjects who had received a left anterior temporal lobectomy as treatment for intractable left temporal lobe epilepsy. The RATL group consisted of subjects who had received a right anterior temporal lobectomy as treatment for intractable right temporal lobe epilepsy. Details of the Thomas Jefferson Comprehensive Epilepsy Center algorithm are described in Sperling et al. [26]. The anterior temporal lobectomy (ATL) involves an standardized “en bloc” resection including amygdalohippocampalectomy. Briefly, this resection includes the entire temporal pole, extending approximately 4 cm posteriorly to include the anterior regions of the parahippocampal, and superior/ middle/ inferior temporal gyri, and medially to include the uncus and mesial structures. The standard extirpated regions are well depicted in the Figures rendered in our results section (e.g., Figure 2). All ATL subjects underwent surgery at least six months prior to being scanned at the Thomas Jefferson Comprehensive Epilepsy Center. All patient participants met the following inclusion criteria: unilateral hippocampal sclerosis or gliosis as identified through MRI, unilateral temporal lobe seizure onset through surface video/EEG recordings, Full-Scale IQ (FSIQ) of at least 80. ATL and NC participants were excluded from the study on any of the following grounds: medical illness with central nervous system impact other than epilepsy; head trauma; prior or current alcohol or illicit drug abuse; psychiatric diagnosis or hospitalization for a Diagnostic and Statistical Manual of Mental Disorders (IV) psychiatric disorder; or any reported hearing loss. The healthy, normal controls were recruited from the Thomas Jefferson University community. Participants provided written informed consent and were paid for participation. The study was approved by the University Institutional Review Board for Research with Human Subjects. Prior to scanning all participants completed a self-report demographic questionnaire, which included questions about hearing loss. No participants reporting hearing loss were asked to participate. Additionally, all participants were screened with an informal auditory function test which utilized the same tones, volume, and equipment as those used during the experiment. We intended to exclude subjects based on hearing loss, however, all subjects reported normal hearing and could perceive the experimental stimuli during screening.

Table 1 displays the sample demographic and clinical data for the 10 ATL subjects. The ATL patients did not statistically differ from the NCs in education or age, though a trend for an age difference was present. Table 2 displays the mean demographic characteristics and mean task performance scores for all three groups. The ATL groups did not significantly differ by age, education, FSIQ, handedness, or surgery-to-scan interval.

Task Procedure and Data Acquisition

Subjects were situated in the scanner and a two button response pad was placed in their dominant hand. The subjects performed two different types of tasks, control (Single Tone Judgment Task) and experimental (Tone Recognition Task). The control task consisted of presenting the subjects with either a high or low pitch tone. The subject was then asked to indicate if the given tone was of a high or low pitch by pressing Button 1 or Button 2,

respectively. The control task used tones identical to those used for the experimental stimuli. An equal number of tones above and below the pitch of the target tone were presented. The goal of the control task was to account for brain activation associated with auditory processing without a tone memory demand. In the experimental task, a Tone Recognition paradigm was used. The subject was presented with a target tone, followed by 5 interference tones, and then a final comparison tone. The subject was asked to indicate if the target and comparison tones were the same or different by pressing Button 1 or Button 2, respectively. All trials consisted of 3.5 seconds of stimulus sound, followed by 3 seconds of response time, and then a 3 second inter-trial interval. Tone duration was .30 seconds. The cognitive demands of the task differed in that the experimental task required holding more tones in mind, as part of an inherent increase in working memory demand, and then making a comparison between the two tones. The control task required recognition of a tone and effecting a comparison to a tone representation in long term memory. The stimulus pool utilized a random sampling of twelve simple (pure) tones ranging from 320 to 635 hz with an average of 435 hz, for the target, interference, and comparison tones (n.b., the range for normal hearing is approximately 20hz to 20Khz, with a normal-age related decline in the higher frequencies; our stimuli are at the lower/middle end of the spectrum, well below the frequencies associated with age-related decline). For the experimental trials the average difference between the initial target tone and the final comparison tone was 58hz, with the difference ranging from 40- 65hz. For the control task the frequency range from the low to the high tones was not more than 115hz and 80hz on average. Tone volume was set at approximately 60-70 db (SPL). The tones and tone differences were chosen to achieve close equivalence and standardization between the experimental and control trials and across subjects. High quality noise reduction headphones were used (Avotec model SS 3100, 40dbA Noise Reduction) to reduce background scanner noise, which registered at approximately 90 db (SPL) without such reduction. It is important to note that the scanner noise was systematic across the control and experimental trials, and, therefore, would cancel out during comparison of these conditions. Control and experimental trials were presented in a random order for a total of 96 trials, divided into 36 control trials and 60 experimental trials. The entire procedure was bookended by rest periods of 30 seconds (visual fixation to asterisk) prior to the initiation of the first trial, followed by 30 seconds of rest following completion of the final trial. The sequence of events for the control and experimental tasks are illustrated in Figure 1. In order to ensure comprehension of the instructions and valid task performance, each subject was given a 4 trial practice session prior to scanning, with stimulus exposure, response times, and task parameters identical to those noted above.

Note, our analysis of the Tone Recognition Task focused on the stimulus presentation period (Control or Experimental, see Figure 1) and captured the following cognitive processing components, though could not distinguish between them: auditory processing of the target tone, holding the target tone in working memory, processing and suppression of the interference tones, auditory processing of the final tone, and the comparison judgment between target and final tone.

FMRI Parameters

Whole-brain functional magnetic resonance imaging (fMRI) scans were conducted involving 30 parallel axial slices. Participants were scanned with a General Electric LX 1.5 Tesla clinical system using a quadrature RF coil. A single-shot echoplanar gradient imaging sequence acquiring T2* signal was used with the following parameters: TE= 54 ms, TR= 3.0 seconds (interleaved collection, contiguous slices), FOV= 21 mm, $128 \times 128 \times 4$ data matrix, flip angle=90, bandwidth= 1470Hz/pixel. The in-plane resolution was 1.64×1.64 mm providing slices 4 mm in thickness. T1-weighted images (30 slices) were collected using a standard spin-echo pulse sequence in positions identical to the functional scans to

provide an anatomical reference to determine slice location of the echoplanar images (TE= 9 ms, TR= 450 ms, 256×256 mm).

Subjects were placed in the headcoil using a stereotaxic crosshair light beam and positional markers on the headcoil to align and center their head in the coil. Shimming was conducted at each location prior to acquisition to reduce system inhomogeneities and artifactual fluctuations in signal across images. Each EPI imaging series started with four discarded scans to allow for T1 signal stabilization.

Image Post-processing and Statistical Analysis

SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5>) was utilized for the post-processing of all images. Slice timing correction was used to adjust for variable acquisition time over slices in a volume, with the middle slice in every volume used as reference. A six parameter variance cost function rigid body affine registration was used to realign all images within a session to the first volume, after the initial three volumes were discarded to account for stabilization of T1 signal. Motion regressors were computed and later used as a regressor of no interest in the first level, subject specific analysis. To maximize mutual information, coregistration between functional scans and the NMI305 template was carried out using six iterations and resampled with a 7th-Degree B-Spline interpolation. Functional images were then normalized and wrapped into standard space (NMI305) to allow for signal averaging across participants. We utilized the standard normalization method in SPM5, which minimizes the sum-of-squared differences between the participant's image and the template (MNI305), while maximizing the prior probability of the transformation. This spatial normalization begins by determining the optimum twelve-parameter affine transformation to account for differences in position, orientation and overall brain size. After affine transformation, a nonlinear transformation is applied to correct for gross differences in head shape that were not accounted for by the affine transformation. The nonlinear deformations are described by the lowest frequency components of a three-dimensional discrete cosine transform basis function [27]. The three major parameter estimation settings involving nonlinear frequency cutoff, nonlinear regularization, and the number of nonlinear iterations, were all set to the SPM defaults, namely: 25mm, medium regularization, and 16 nonlinear iterations, respectively. Next, a 128 Hz high-pass temporal filter was applied to remove low frequency fluctuations (whitening procedures to remove artifacts such as aliased biorhythms and correct for temporal autocorrelation). All images were smoothed by convolution with a Gaussian kernel, with a full width at half maximum of 8mm in all directions to increase the signal to noise ratio, account for residual inter-participant differences in anatomy, and to meet the assumptions of the statistical tests (e.g., normality).

The general linear model (GLM) procedure of the Statistical Parametric Mapping software (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5>) was used to create a single-subject statistical model containing double gamma HRF sinusoid boxcar waveforms representing the key experimental condition (Tone Recognition Task, encoding of the stimulus) and control task (Single Tone Judgment Task, encoding of the stimulus), with additional columns for the initial and final rest periods, the inter-trial interval, and the response period. Correct responses to both tasks were binned separately, creating two columns (Correct and Incorrect) for each task. This yielded 8 covariates/regressors, with the six motion regressors also included in the design matrix. In all cases, regressors were formed using a sinusoid stimulus function representing the occurrence of each relevant epoch convolved with a canonical hemodynamic response function.

All statistical comparisons were specified by utilizing volumes associated with the relevant epochs to form the appropriate contrast or linear compound of parameter estimates with T statistics computed at every voxel to produce an SPM. This project's aim was to understand

the brain's response to successful performance on the experimental task and to optimize capturing the brain regions with strong functionality and integrity for developing an episodic memory engram of the initial target used for comparison to the second tone. Hence, our analyses focused on the encoding phase of the task and we conducted additional analyses that only utilized correct responses to the control and experimental stimuli. The statistical contrast of interest was the Tone Recognition Task minus Single Tone Judgment Task (correct trials only).

The subject-specific contrasts were thresholded at $p < .05$ (corrected) and then each was entered into a random effects statistical model using a one-sample t-test to determine significant activation against the null hypothesis. Alpha values were corrected for multiple non-independent comparisons and analyzed using the theory of Gaussian fields. Results used for statistical inference and interpretation were corrected at a cluster-level specificity of at least $p < 0.05$ (family-wise error rate) with the spatial extent threshold reflecting the expected voxels per cluster given the smoothness of the image [28].

Results

Behavioral Results

Behavioral performance of the RATL, LATL, and NC groups are displayed in Table 2. Behaviorally, on the control (Single Tone Judgment) task, the group difference in performance did not reach the level of statistical significance ($p = 0.0617$, one-way, three-level factor ANOVA). NCs performed better than LATL subjects, who in turn performed better than RATL subjects, but the group effect was not statistically significant. The difference between the RATL and NCs clearly approached significance (Scheffe post-hoc test, $p = .064$). On the experimental (Tone Recognition) task, the group effect was again not significant ($p = .0577$), though there clearly was a trend such that the LATL group performed over 20 percentage points lower than the NC group (Scheffe post-hoc test, $p = .066$), with RATL performance in between these two.

Activation Associated with the Tone Recognition Task: All Trials

We first examined the activation associated with the Tone Recognition trials (Tone Recognition minus Single Tone Judgment trials) within each of the three groups. The NCs produced bilateral activation on the superior temporal gyri (left BA 22 extending into BA 42; right BA 41), along with activation in the right precentral gyrus. Computation of an asymmetry index focused on the temporal lobe, including both anterior and posterior sections, showed no difference in the number of statistically significant voxels across the NC subjects. This bilateral activation suggests the experimental task did not lateralize to a single hemisphere.

The LATL group demonstrated activation of the left superior temporal gyrus (BA 41 and 22), the left inferior parietal lobule (BA 40), and the right dorsomedial thalamus. The RATL group showed bilateral activation of the superior temporal gyri (BA 22) and the left cuneus (BA 18). The activation in the RATL group displayed less spatial extent than the LATL group.

Next, we examined activation differences between the groups. The NC relative to LATL group (NC-LATL contrast) showed greater activation of the left superior temporal gyrus (BA 22) and the right fusiform gyrus (BA 37). The NC relative to the RATL group (NC-RATL contrast) showed left superior temporal gyrus (BA 22 extending into BA 42) and the left parahippocampal gyrus (BA 30) activation. The reverse comparisons, highlighting activation in the LATL or RATL groups relative to controls (LATL-NC contrast and RATL-NC contrast, respectively), showed that the LATL patients produced activation in several

left hemisphere areas involving parietal (BA 40), anterior cingulate (BA 32), and middle occipital gyrus (BA 19) regions. An additional right precentral gyrus region was also apparent. The RATL group compared to controls also showed left hemisphere activation involving left middle frontal gyrus (BA 9) and superior parietal cortex (BA 7).

Activation Associated with the Tone Recognition Task: Correct Response Trials

The above mentioned contrasts were further explored focusing only on the correctly completed trials for the experimental (Tone Recognition) and control (Single Tone Judgment) trials. The trials involved, on average, 39 of 60 the trials for the LATL group and 50 of 60 trials for RATL group, and 53 of 60 trials for the NC group. This allowed us to identify the activation more purely associated with accurate and successful performance. Table 4 displays the relevant activation data within each group. The NCs demonstrated diffuse bilateral activation of the superior temporal gyri (right BA 41, left BA 42), extending into the inferior frontal gyrus (see Figure 2A).

The LATL group showed bilateral activation of the superior temporal lobes (BA 21). Similar to the NC group, the activation was notably diffuse, with activations observed bilaterally across several brain regions (Figure 2B). The RATL group showed activation of the superior temporal gyri bilaterally (BA 22 in both hemispheres), the right middle frontal gyrus (BA 6), and the right cuneus (BA 18) which extended across the midline to the left cuneus. Again, the activation of the RATL group was less diffuse than the LATL and NC groups (Figure 2C).

NCs, when compared to the LATL group (NC-LATL contrast), had greater activation of the superior temporal gyri bilaterally (left BA 42, right BA 22) and the right middle frontal gyrus (BA 10; Figure 3A). The NC-RATL contrast also indicated bilateral activation of the superior temporal gyri (left BA 42, right BA 22; Figure 3B).

The LATL-NC contrast indicated LATL patients had greater activation of the left anterior cingulate (BA 33; Figure 4A). Similarly, the RATL-NC contrast also yielded greater activation of the left anterior cingulate (BA 32), though the activation here was more frontal (anterior) than observed in the LATL subjects and crossed the midline into the anterior portion of the right middle frontal gyrus (Figure 4B). These activation regions for the LATL-NC and RATL-NC contrasts overlapped with one another.

Finally, the LATL-RATL contrast yielded greater activation of the left hypothalamus, which was quite diffuse and encompassed a broad region of the left hemisphere and the right cingulate gyrus (BA 31), extending superiorly to the precentral gyrus, and the right superior temporal gyrus (BA 38; Figure 5A). This activation also extended to frontal regions. The reciprocal contrast, RATL-LATL, demonstrated greater activation of the right superior temporal gyrus (BA 41), more posterior than the activation seen the LATL-RATL contrast, and the right cuneus (BA 18), extending inferiorly to the right lingual gyrus and crossing the midline to the left cuneus (Figure 5B).

Discussion

Behaviorally, LATL patients performed poorest in terms of accuracy on the experimental (Tone Recognition) task, over 23 percentage points lower than the NC group. This difference, while very close to the threshold for statistical significance, still must be characterized as a trend in the data; a trend likely due to the low sample size and, therefore, low statistical power of our sample. The RATL subjects, on the other hand, performed similarly to the NCs, indicating that in this group there was the ability to overcome any processing constraints imposed by the extirpated right anterior temporal lobe. These

behavioral data suggest that the anterior left temporal lobe may be more important to highly accurate performance on the pitch memory task.

In terms of activation, the data involving all the trials regardless of performance accuracy showed considerable similarity across the three groups. The NC main effect data makes clear that the primary brain regions implementing this task are the bilateral temporal lobes, primarily posterior involvement, a fact that helps us understand why individuals who underwent an anterior resection of the temporal lobes can still carry out the task. The main effect data for both ATL groups confirm that, indeed, these bilateral posterior temporal regions are active, involving areas spared during the typical “en bloc” resection. The data from just the correct trials demonstrated a similar posterior temporal picture, but provided additional information indicating that the strength of the bilateral activation may be tied to accuracy. Combined, these data provide fairly compelling evidence that anterior temporal lobe may enhance accuracy on the task, but the task may be accomplished without it. Based on this, we conclude that our pitch memory task is primarily bilateral and posterior temporal in its implementation, providing neither a test for mapping out a well-lateralized function in the temporal lobes, nor a test of a cognitive function highly “at risk” with either a standard right or left ATL procedure.

In terms of the extant literature, our data showing bilateral temporal lobe activation agrees with Schlaug and colleagues [14-16], but differs from Zatorre et al. [24, 25] whose studies suggested that pitch memory was a more right temporal lobe, lateralized function. Moreover, our finding that the anterior left temporal lobe may contribute to highly accurate performance of this task is consistent with the findings of Gaab et al. [15] who also found the left temporal lobe to be associated with greater accuracy on a pitch memory task.

Comparisons between the NC and ATL groups provided additional insight into the functional neuroanatomy of this task. For instance, the posterior superior temporal gyrus (BA 42 and 22) appeared to show stronger activation in the NC group bilaterally, with the data suggesting that this difference is particularly strong in the context of accurate performance (i.e., correct trials). This may suggest there is some bilateral dampening of brain activation in the temporal lobe resected patients relative to the norm, contributing to their lower levels of accuracy. Despite this, there is clear evidence that both the left and right ATL patients can nevertheless carry out the task using preserved posterior temporal regions.

In contrast, relative to the NC group, both ATL groups showed greater left anterior cingulate activation, with this activation closely linked to accurate pitch memory performance. This may suggest that for accurate performance regardless of the side of the ATL, the left anterior cingulate plays a functional role, perhaps compensating for the absent anterior temporal lobe and its contributions, or offsetting the generally lower bilateral posterior superior temporal lobe activation seen in the ATL patients relative to controls. Other research literature has shown the anterior cingulate to be associated with error monitoring and the allocation of executive control and attentional resources [29]. This may suggest our ATL patients struggled with judgment and decision about a right or wrong response, found the task more difficult, or simply had to put forth more effort to complete the task than the NCs.

Another notable difference between the groups was that the LATL group, in the setting of accurate performance, demonstrated prominent left frontal activation relative to both the RATL group and the NCs. Diffuse and distributed activation has been associated with less correct, less efficient task performance [30]. Thus, it is possible that this left frontal lobe activation represents a form of extra-temporal recruitment necessary to maintain adequate performance. This interpretation is supported by our behavioral data, which demonstrated that among the three groups the LATL group had the worst performance on the pitch

memory task. A speculative possibility regarding the poor performance of the LATL group is that pitch memory processing was “crowded out” of the left hemisphere as pressure came to bear on the representational space for language in the left temporal lobe in the face of pathology.

It should not be overlooked that the RATL group showed stronger posterior activation compared to the LATL group. The areas involved included the occipital cortex and the right posterior temporal gyrus. Interestingly, these were not areas evident in the map comparing RATL activity to NC activity. Unlike the LATL group, which showed a consistent pattern of left frontal activity in comparison to both the NC and RATL groups, a fact that argues more strongly that it represents task compensatory activity, the unique aspects of RATL activation are not so consistent. The presence of this posterior temporal activity in conjunction with the fact that the RATL group performed better than the LATL group, may suggest that this right posterior temporal region is also important to accurate task performance, but the fact that this area is not active relative to the NCs argues against this conclusion. Hence, the nature of this occipital activation is unclear.

A criticism of the current study is that though all patients underwent standard “en bloc” ATL resections, such resections are never completely identical, a fact that limits our understanding of findings (e.g., which specific regions of the left anterior temporal lobe are important for accuracy?). It should be noted that the surgery-to-scan interval was similar in the two ATL groups. Nevertheless, a wide variety of neuroplasticity factors that differ among the patients could potentially result in variable levels of post-surgical cognitive reorganization and functional recovery of skills such as pitch memory. This may have affected our imaging results in unknown and unspecified ways. Also, because we did not use a sparse sampling there were some auditory selective attention demands present to the scanner noise from the tones. However, the noise was systematic across all aspects of the study and thus cancelled out in our analyses. In addition, high quality sound reducing headphones were used, and performance accuracy was strong verifying that the participants could clearly hear and register the stimuli. It is beyond the scope of this study to disentangle the finer-grained roles of pitch, tone, and melody in auditory processing, and to partition the brain regions relevant to each. Note, doing so would involve experimental manipulation of many task components and auditory processing parameters. Additionally, though all participants reported normal hearing and were able to perceive our experimental and control stimuli with equal ease, future work should include more precise audiological pre-testing. Lastly, as mentioned previously, the study is of low statistical power, a fact that makes the presence of strong shared results across all groups (bilateral posterior temporal activation), and trends toward group differences in performance (LATL accuracy lower) all the more impressive, though clearly still in need of replication.

We conclude that the bilateral superior posterior temporal lobes were utilized for our Tone Recognition Task, and, therefore, pitch memory, as operationalized here, would not serve well as a technique to potentially lateralize and anatomically map out an “at risk” non-verbal memory function in our unilateral temporal lobe epilepsy patients prior to surgery. Our behavioral data are consistent with the possibility that the left anterior temporal region is tied to accuracy and, therefore, makes some contribution to the task, a contribution which, if missing, may compel compensatory brain activity. Another finding reflective of the neurodynamics of accuracy is that the control subjects relative to ATL patients appeared to show enhanced posterior superior temporal lobe activation. Yet, our data also makes clear that the bilateral posterior temporal lobes are sufficient for reasonably successful pitch memory, and that the anterior temporal lobes are not absolutely necessary, a finding that helps us understand why these individuals whom underwent an anterior resection of a single temporal lobe can still carry out the task. Both ATL groups recruited the left anterior

cingulate, indicating that the task is either more difficult for them or requires more intensive error monitoring compared to healthy controls. Each ATL group, however, is also recruiting their own distinct regions in order to successfully complete the task. For instance, the LATL group may specifically recruit the left frontal cortex as a meaningful compensation for the missing anterior temporal lobe. Unfortunately, within the confines of this particular study it is not possible to determine which performance features or task components these recruited regions might reflect (e.g., identifying the pitch, comparing or judging tones, labeling the correct versus incorrect pitch, etc.), or to specify more precisely the functional neuroanatomy of pitch memory accuracy only broadly captured by our task.

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Figure 1.
Sequence of experimental events for the Control and Experimental Tasks.

Figure 2.

Activation during the Tone Recognition Task yielded by the main effect of NC (Figure 2A), the main effect of LATL (Figure 2B), and the main effect of RATL (Figure 2C) for the Correct Response trials. Abbreviations: BA, Brodmann area; STG, superior temporal gyrus; MFG, middle frontal gyrus; Cun, cuneus; K, cluster extent.

Figure 3.

Activation associated with the NC group relative to the LATL (Figure 3A) and RATL (Figure 3B) groups for the Correct Response trials. The rendered activations are 3-dimensional, as if looking through a glass brain. Abbreviations: BA, Brodmann area; STG, superior temporal gyrus; MFG, middle frontal gyrus; K, cluster extent.

Figure 4.

Activation associated with the two ATL groups (LATL, Figure 4A; RATLBA, Figure 4B) relative to the NCs for the Correct Response trials. The bottom two brain images show 3-dimensional rendered activations, as if looking through a glass brain. Abbreviations: BA, Brodmann area; AC, anterior cingulate; K, cluster extent.

Figure 5.

Activation differences between the two ATL groups (LATL - RATL, Figure 5A; RATL - LATL, Figure 5B) for the Correct Response trials. The rendered activations are 3-dimensional, as if looking through a glass brain. Abbreviations: BA, Brodmann area; Hyp, hypothalamus; STG, superior temporal gyrus; TTG, transverse temporal gyrus; CG, cingulate gyrus; Cun, Cuneus; K, cluster extent.

Table 1

Patient Demographic and Clinical Data

Patient #	Age (years)	Sex	Edinburgh Score *	Neuropathology **	Type of Seizures	Seizure Freq. in Past Year (SZs/month)	Duration of Epilepsy (years)	Education (years)	MRI Findings ***	Surgery Type ****	Surgery to Scan Interval (months)	FSIQ
1	55	F	80	Idiopathic	CPS,SPS	35	45	18	LMTS	SLTL	54	116
2	50	M	80	Head Injury(LOC)	CPS,2°GTC	1	18	13	IRTH	SRTL	6	99
3	43	F	36	MTS	CPS	8	43	12	LMTS	MLTL	6	101
4	31	F	89	Idiopathic	CPS,2°GTC	10	1.5	14	Normal	SLTL	6	104
5	39	M	80	MTS	SPS,CPS	30	9	14	LMTS,ILMTSI,ILTH	SLTL	18	97
6	40	F	100	MTS	CPS,TC	4	25	13	LMTS	SLTL	6	102
7	29	F	80	MTS	CPS,SPS	2	2	12	Normal	MRTL	12	105
8	32	F	100	MTS	SPS,CPS,2°GTC	15	27	16	RMTS	SRTL	6	96
9	29	M	80	Idiopathic	CPS,SPS	2.5	23	16	Normal	SRTL	28	94
10	45	M	56	MTS	CPS,TC,SPS	2	41	13	RMTS,IRTH,HA	SRTL	65	102

* Edinburgh score of 100 indicates complete right handedness.

** LOC, loss of consciousness; MTS, mesial temporal sclerosis.

LMTS, left mesial temporal sclerosis; IRTH, increased right temporal horn relative to left; ILMTSI, increased left mesial temporal signal intensity; ILTH, increased left temporal horn relative to right; RMTS, right mesial temporal sclerosis; HA, hippocampus asymmetry (left larger than right).

SLTL, standard left temporal lobectomy; SRTL, standard right temporal lobectomy; MLTL, modified left temporal lobectomy; MRTL, modified right temporal lobectomy.

Table 2

Mean Demographic Values and Behavioral Results

	LATL Subjects (n=5)	RATL Subjects (n=5)	NCs (n=5)
# of Males/Females	1/4	3/2	2/3
	<u>Mean ± SD</u>	<u>Mean ± SD</u>	<u>Mean ± SD</u>
Age (years)	41.6 ± 8.7 *	37.0 ± 9.8	27.4 ± 6.6 *
Years of Education	14.2 ± 2.3	14.0 ± 1.9	17.2 ± 2.2
Edinburgh Handedness Score	77.0 ± 24.4	79.2 ± 15.6	93.8 ± 2.5
FSIQ	104.0 ± 7.2	99.2 ± 4.4	---
Surgery-to-Scan Interval (months)	18.0 ± 20.8	20.8 ± 24.9	---
Single Tone Judgment Task Correct (%)	85.6 ± 14.6	70.0 ± 21.4 *	95.0 ± 2.3 *
Tone Recognition Task Correct (%)	65.4 ± 18.8 *	82.9 ± 13.7	88.7 ± 6.8 *

* indicates statistical trends between p>0.05 and p<0.10

Table 3

Activation Clusters for All Trials

Comparison	P _{corr}	k _E	Talairach Coordinates				Brain Region, BA
			Z-score	x	y	z	
Main Effect NC	0.000	6772	5.22	-61	-19	5	L STG, BA 22
	0.000	2492	4.90	40	-34	15	R STG, BA 41
	0.000	3576	3.39	52	-7	46	R PCG, BA 4
Main Effect LATL	0.000	9051	5.03	-42	-27	7	L STG, BA 41
	0.007	895	4.42	-40	-36	50	L IPL, BA 40
	0.000	1920	4.38	44	-27	1	R Ins, BA 22
Main Effect RATL	0.000	1752	3.59	10	-17	12	R DMN
	0.000	2980	5.22	59	-33	9	R STG, BA 22
	0.000	3299	5.12	-59	-19	5	L STG, BA 22
NC - LATL	0.000	1618	3.92	-12	-75	24	L Cun, BA 18
	0.000	1470	3.75	-61	-19	5	L STG, BA 22
	0.000	2221	3.45	26	-51	-8	R FG, BA 37
NC - RATL	0.002	1046	4.16	-50	-8	-3	L STG, BA 22
	0.003	999	2.64	-14	-39	6	L PHG, BA 30
LATL - NC	0.009	867	4.56	-52	-38	52	L IPL, BA 40
	0.000	1308	3.87	-6	34	24	L AC, BA 32
	0.000	1748	3.58	44	17	38	R PCG, BA 9
RATL - NC	0.011	841	3.49	-34	-91	10	L MOG, BA 19
	0.001	1106	4.06	-4	40	22	L MFG, BA 9
	0.022	727	2.89	-38	-74	46	L SPL, BA 7
LATL - RATL	Null						
RATL - LATL	Null						

BA, Brodmann area; L STG, left superior temporal gyrus; L IPL, left inferior parietal lobule; R Ins, right insula; R DMN, right dorsomedial nucleus of the thalamus; R STG, right superior temporal gyrus; L Cun, left cuneus; R PCG, right precentral gyrus; R FG, right fusiform gyrus; L PHG, left parahippocampal gyrus; L AC, left anterior cingulate; L MOG, left middle occipital gyrus; L MFG, left middle frontal gyrus; L SPL, left superior parietal lobule.

Table 4

Activation Clusters for Correct Trials Only

Comparison	P _{corr}	k _E	Talairach Coordinates				Brain Region, BA
			Z-score	x	y	z	
Main Effect NC	0.000	7653	5.81	-65	-21	7	L STG, BA 42
	0.000	13226	5.17	57	-21	5	R STG, BA 41
Main Effect LATL	0.000	15957	4.73	48	-25	0	R STG, BA 21
Main Effect RATL	0.000	3244	5.46	-57	-23	3	L STG, BA 22
	0.000	2956	5.31	61	-33	9	R STG, BA 22
	0.001	1372	3.88	42	0	41	R MFG, BA 6
	0.000	2008	3.62	4	-82	24	R Cun, BA 18
NC - LATL	0.000	1715	4.60	-65	-19	7	L STG, BA 42
	0.001	1347	3.92	30	38	22	R MFG, BA 10
	0.000	1989	3.77	57	-21	5	R STG, BA 22
NC - RATL	0.001	1314	3.96	-65	-19	7	L STG, BA 42
	0.002	1220	3.77	46	-21	1	R STG, BA 22
LALT - NC	0.046	781	3.26	-4	20	17	L AC, BA 33
RATL - NC	0.014	949	3.97	-6	36	20	L AC, BA 32
LATL - RATL	0.000	1894	3.83	-6	-4	-3	L Hyp
	0.042	793	3.27	18	-23	38	R CG, BA 31
	0.037	810	3.01	34	3	-10	R STG, BA 38
RATL - LATL	0.004	1141	4.19	54	-17	14	R STG, BA 41
	0.000	1641	3.53	4	-82	24	R Cun, BA 18

BA, Brodmann area; R STG, right superior temporal gyrus; L STG, left superior temporal gyrus; R MFG, right middle frontal gyrus; R Cun, right cuneus; L AC, left anterior cingulate; L Hyp, left hypothalamus; R CG, right cingulate gyrus; R TTG, right transverse temporal gyrus.