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Preserved proper naming following left anterior temporal lobectomy is associated with early age of seizure onset

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Summary

Purpose—Anterior temporal lobectomy (ATL) is an effective surgical option for managing pharmacoresistant temporal lobe epilepsy. Many patients with left ATL develop postsurgical difficulties with proper name retrieval, although curiously, some patients have entirely intact proper naming following left ATL. Here, we tested the hypothesis that early age of seizure onset would be a reliable factor "protecting" patients from developing proper naming defects following left ATL.

Methods—Proper naming of unique persons (Famous Faces Test, 155 items) and places (Landmark Test, 65 items) was measured in 23 patients who had undergone left ATL for pharmacoresistant epilepsy. Data were collected for a number of variables, including age of seizure onset, age at surgery, handedness, IQ, and seizure outcome. The patients were sorted into two groups based on proper naming performance: (1) Unimpaired: 7 patients performed normally on both the Faces and Landmark tests; (2) Impaired: 16 patients performed abnormally on one or both of the tests.

Results—In support of our hypothesis, the Unimpaired group had a significantly earlier age of seizure onset (M = 2.1 years) than the Impaired group (M = 15.1 years). Moreover, a correlation analysis indicated a strong association between age of seizure onset and naming outcome (R = −0.569). The groups were comparable (and statistically indistinguishable) on nearly all other variables.

Conclusions—These findings document the importance of age of seizure onset in predicting proper naming outcome following left ATL (with earlier being better), and extend understanding of brain reorganization and plasticity.

Keywords

Epilepsy; Temporal lobectomy; Proper naming

The prevalence of epilepsy worldwide has been estimated to be approximately 0.5–1.0%, and among this population, approximately 30–40% has medically intractable epilepsy, i.e., seizures that are not well controlled with antiepileptic medications, or what is called "pharmacoresistant epilepsy" (Kwan and Brodie, 2000; Jeha et al., 2006). Lack of efficacy of at least two medications, defined as persistent seizures despite maximum drug doses, is required for both the "strict" and "loose" definitions of medical intractability (Berg et al., 2006), but in most cases, patients are tried on many different drugs in an effort to control their seizures. Once intractability is declared for those patients with complex partial epilepsy that is not resulting from a cortical malformation, tumor, or arteriovenous malformation, additional investigations, such as video-EEG monitoring, magnetic resonance imaging, positron emission tomography,

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neuropsychological testing, and sodium amobarbital testing, are typically pursued in an attempt to identify a focus amenable for surgical removal.

Most frequently, a standard anterior temporal lobectomy (ATL) is performed; this typically entails resection of the temporal tip, anterior parts of the parahippocampal and inferior temporal gyri, and portions of mesial structures (amygdala/hippocampus). ATL has been proven to be more efficacious in controlling seizures when compared to medication alone or an alternative surgical procedure, such as a focal cortical resection (Wiebe et al., 2001). In patients who have an ATL, 81% may achieve an Engel Class I outcome 6 months after surgery, i.e., freedom from recurrent seizures, occurrence of only nondisabling seizures such as auras or simple partial seizures, or occurrence of generalized/disabling seizures only after attempted withdrawal of antiepileptic medications (Cohen-Gadol et al., 2006). The probability for maintaining an Engel Class I outcome has been reported to be 78% at one year, 76% at two years, 74% at five years, and 72% one decade after surgery (Cohen-Gadol et al., 2006). Other studies have reported similar results with a probability of 80% or slightly higher for achieving an Engel Class I outcome within 6 months after surgery (Clusmann et al., 2004; Lowe et al., 2004; also see Foldvary et al., 2000; Yoon et al., 2003). Furthermore, quality-of-life assessments have shown significantly improved social functioning in patients for up to one year after epilepsy surgery (Engel et al., 2003).

There is, however, another side to this picture. Together with improved control of disabling seizures and improved level of social functioning, ATL can produce cognitive “side effects.” For example, many patients develop postsurgical difficulties with language and memory following left ATL (Stafiniak et al., 1990; Saykin et al., 1995), and such deficits have been shown to persist (Langfitt and Rausch, 1996; Bartha et al., 2004; Alpherts et al., 2006; Hermann et al., 2007). There is considerable variability in outcome, though, and patient profiles literally run the gamut from severe defects to no discernable change following surgery. A number of variables have been studied in an attempt to identify which factors are associated with relatively better and relatively worse outcomes following surgery. Variables that have been shown to predict relatively negative (poorer) cognitive outcomes include older age at seizure onset, male gender, older age at the time of surgery, normal appearing hippocampal material at resection, and a strong preoperative neuropsychological performance (Gleissner et al., 2002; Hermann et al., 2007; Griffin and Tranel, 2007). Just as a focal resection has not correlated with improved efficacy of controlling seizures, the amount of tissue resected has not been consistently proven to be an effective predictor of cognitive performance after left ATL (Griffin and Tranel, 2007). Likewise, a specific approach or technique for surgical resection has not been shown to be correlated with an improved ability in visual confrontational naming. Specifically, naming can be impaired after tailored resections in the left temporal lobe, after standard resections sparing the superior temporal gyrus, and after standard resections including excision of the superior temporal gyrus (Hermann et al., 1999).

Age of onset of recurrent seizures has been demonstrated to be a significant predictor of cognitive outcome following ATL, with an earlier age of seizure onset being associated with better cognitive outcome (e.g., Powell et al., 1985; Saykin et al., 1989; Stafiniak et al., 1990; Hermann et al., 1995, 2007; Griffin and Tranel, 2007). Also, when risk factors for epilepsy (e.g., head injury, complicated febrile seizures) have been present at age 5 or earlier, postsurgical declines in naming are more limited, and this may be due to cerebral reorganization of language functions prompted by or associated with brain injury before age 5 (Stafiniak et al., 1990; Pataraia et al., 2004, 2005). Other studies have shown that it is early age of onset of recurrent seizures, rather than the age at which identifiable risk factors or overt brain injury occurred, that is the key factor predicting better outcome (Hermann et al., 2002).

Against this background, we have been intrigued by some of the dramatically different patterns of outcomes in our patients with left ATL. We have focused especially on a specific aspect of word retrieval, viz., proper naming. The reason for this is that proper name retrieval—i.e., naming specific persons and places—has been strongly linked to the left anterior temporal region in both lesion (Barr et al., 1990; Graff-Radford et al., 1990; Ellis et al., 1991; Damasio et al., 2004, 1996; Fukatsu et al., 1999; Tsukiura et al., 2002; Seidenberg et al., 2002; Glosser et al., 2003; Snowden et al., 2004; Lah et al., 2004; Tranel, 2006) and functional imaging (Grabowski et al., 2001; Tsukiura et al., 2002, 2003) studies. In patients with left ATL, a notable impairment of proper name retrieval is a frequent postsurgical finding: the majority of left ATL patients complain of this problem, and the defect is obvious on careful examination with appropriate neuropsychological testing. There are, however, striking exceptions: some patients are entirely unscathed by the surgical resection and have normal proper naming following left ATL. The goal of the current study was to identify what factors might account for such exceptions. Based on the literature reviewed earlier, we hypothesized that "protected" proper naming would be associated with a significantly earlier age of onset of epilepsy. We also studied a range of other factors (e.g., age at surgery, education, IQ, seizure outcome) to determine whether age of onset of epilepsy was predictive of proper naming outcome over and above what could be explained by such other factors.

Methods

Participants

The participants were 23 patients who had undergone left ATL for medically intractable epilepsy, selected from our Patient Registry of the Division of Cognitive Neuroscience at the University of Iowa. (We started initially with 24 left ATL patients. Sodium amobarbital testing revealed 23 patients with left hemisphere language dominance, and 1 with right hemisphere language dominance; we excluded this latter patient from the study and focused on the 23 patients with standard left hemisphere language dominance.) In accordance with their enrollment in the Patient Registry, the patients were free of a history of mental retardation, learning disability, and substance abuse, and they did not have dementia. Patients were also free of a history of psychiatric disease, as determined by staff clinical neuropsychologists (who were not part of the current study) based on extensive clinical interviews and formal personality assessment (including the Beck Depression Inventory-II, the State-Trait Anxiety Inventory, and the Minnesota Multiphasic Personality Inventory-2). The patients have been extensively characterized neuropsychologically and neuroanatomically, following the standard protocols of the neuropsychology (Tranel, 2007) and neuroanatomy (Damasio and Frank, 1992) arms of our research program. The neuropsychological, neuroanatomical, and experimental data were collected when the patients were in the chronic phase of recovery. All patients provided informed consent to participate in these studies, in accord with the Human Subjects Committee of the University of Iowa and Federal regulations.

Background demographic and neuropsychological data for the participants are provided in Table 1. (The table gives data for the overall group, and also as a function of subgroups broken down according to proper naming performances; see below.) Handedness, measured with the Geschwind-Oldfield Questionnaire which has a scale ranging from full right-handedness (+100) to full left-handedness (−100), was distributed as follows: 20 subjects were fully right-handed (+90 or greater); 1 was primarily right-handed (+80); 1 was fully left-handed (−100); and 1 was primarily left-handed (−80). The demographic and neuropsychological data were drawn from the database associated with the Patient Registry of which the participants are a part, and representative data for IQ, memory, language (including pre- and postsurgical naming), visual perception, and depressive symptomatology, are provided in the Table, along with data for demographic parameters and various seizure-related variables. We also collected

data for the postoperative occurrence of seizures, use of antiepileptic medications, and the pathology of resected material.

Stimuli for proper naming experiments

The stimuli were persons (presented as faces) and landmarks. Person naming was assessed with the Iowa Famous Faces Test (Tranel, 2006). Briefly, this test includes 155 faces of famous actors, sports figures, and politicians. There are 43 females and 112 males, and most of the pictures are in color (n = 136). Landmark naming was assessed with the Landmark Recognition and Naming Test (Tranel et al., 2005). This test contains 65 famous landmarks, depicted in color photographs free of identifying text, of which 52 are artifactual kinds (e.g., Leaning Tower of Pisa) and 13 are natural kinds (e.g., Devil's Tower).

Procedure

The stimuli were prepared as slides, and they were presented on a computer monitor as a powerpoint presentation, one at a time, in free field. The Famous Faces and Landmark Tests were each given in a block, with a fixed order of stimulus presentation. We have developed a detailed method for administering and scoring these tests, so that both recognition and naming of the items can be carefully ascertained. The tests are administered to each participant individually, in our laboratory, by a trained experimenter. The subject is presented each of the pictures, one-at-a-time, and asked to identify them. The experimenter records the subject's responses verbatim. No time limit is imposed, and no instructions (or encouragement) for fast responding are provided. The procedure is designed so that data regarding both recognition and naming of the items can be collected. *Naming* is defined as production of a specific proper noun corresponding to the stimulus. If the subject does not name a stimulus correctly, they are prompted to give specific information about characteristics of the stimulus, and if this information is provided, they are given credit for accurate recognition.

Scoring of responses

All items that were named correctly were scored as being correctly recognized. For the naming response to be considered correct, it had to match the response produced by normal participants, as determined from previous work (cf., Tranel et al., 2005, 2006). For items not named correctly, the information the subject had produced regarding characteristics of the item was used to judge whether the subject had produced an acceptable identification of the stimulus. If no information was generated, or if the information generated was inaccurate, vague, or nonspecific (e.g., "some actor"), the item was scored as a recognition failure. If detailed and accurate information about the stimulus was provided, the item was scored as a recognition success. For each category, the naming score was then calculated as the number of correctly named items, divided by the number of correctly recognized items. This procedure does not penalize subjects for failing to name items they do not recognize.

Neuropsychological data quantification and analysis

For each subject and each category (Faces, Landmarks), the number of correct naming responses was divided by the number of correct recognition responses and multiplied by 100 to yield a percent correct naming score. These scores were compared with those of normal participants, using data from previous studies. Specifically, we have shown previously that normal participants score at an average of 85% (SD = 11.1) correct for Face Naming (Tranel, 2006), and at an average of 88% correct (SD = 8.0) for Landmark Naming (Tranel et al., 2005).

In the current study, we operationalized "unimpaired" and "impaired" as follows. Taking a conservative approach, we classified as "Unimpaired" all participants who scored within 1 SD

of the normal mean or higher on *both* the Faces and Landmarks tests. For the Famous Faces test, this corresponds to a score of ≥74% correct; for the Landmarks Test, this corresponds to a score of ≥80% correct. These levels are high enough to assure that the scores in the Unimpaired participants reflect well preserved proper naming performances for both Faces and Landmarks. Participants were classified as "Impaired" if they scored below 74% correct on the Faces Test or below 80% correct on the Landmarks Test, or both. This approach to classifying the proper naming performances of the participants was designed so that the participants classified as "unimpaired" could be clearly said to be normal insofar as the accuracy of their proper naming was concerned, i.e., their proper naming accuracy for both persons and landmarks was well within the range of normal participants. The approach is conservative, on purpose, in classifying participants as unimpaired. Because our study was aimed at identifying factors that would serve to "protect" patients with ATL from developing proper naming defects postsurgically, we wanted to make sure that the unimpaired participants did indeed have normal accuracy of proper naming.

We also performed a correlation analysis to determine the extent to which the factor of Age at Seizure Onset was associated with proper naming outcome. In this analysis, the outcome variable was a single proper naming score, which we formulated by combining (adding) each participant's percent correct scores for the Faces and Landmarks Tests, and then subtracting this from the combined (added) percent correct normal means to yield a "Difference from Normal" summary score for each participant. Note that this calculation yields positive scores for patients who performed above the normal level, and negative scores for patients who performed below the normal level, with larger numbers (in either direction) indicating a greater discrepancy from normal. We also conducted a logistic regression analysis using Age at Seizure Onset as the predictor variable and naming classification (Unimpaired v. Impaired; see below) as the outcome variable.

Results

Unimpaired and impaired subgroups

According to the criteria outlined above, we ended up with the following subgroups, based on proper naming performance: (1) *Unimpaired*: 7 patients scored normally on both the Faces (≥74% correct) and Landmark (≥80% correct) tests; (2) *Impaired*: 16 patients scored abnormally on one or both of the Faces and Landmark tests. Data regarding proper naming performances in the two groups are presented in Table 2. For the Unimpaired group, the mean correct performance on the Famous Faces Test was 92.4%, which is actually somewhat above the mean performance of normal participants (M = 85.0%). For the Impaired group, the mean correct performance on the Famous Faces Test was 59.2%, which is more than 2 SD's below the mean of the normal participants. On the Landmark Test, the mean correct performance for the Unimpaired group was 86.1%, which is very similar to the mean performance of normal participants (M = 88.0%). The mean Landmark Test naming performance of the Impaired group, by contrast, was 65.3%; again, this is more than 2 SDs below the mean of the normal participants. The between-group differences for both Face naming ($t(21) = 4.02$, $p = 0.001$) and Landmark naming ($t(21) = 3.64$, $p = 0.002$) were significant, as expected based on the fact that the groups were formed a priori based on the Face and Landmark naming performances. (By contrast, the groups were not different in terms of their *recognition* of Faces ($p = 0.78$) and Landmarks ($p = 0.52$).)

Another issue that arises in this context regards naming response latency. In particular, it could be that even if subjects are able to generate normal accuracy scores, they could have significantly prolonged response latencies that might be indicative of non-normal proper name retrieval and production. This consideration is important for the participants who are being classified as "unimpaired" according to the rules enumerated above. In the current study, the

Faces and Landmarks tests were not administered with time pressure, and we did not record response latencies. However, we do have data that speak to the issue of response latency. Specifically, in a previous study that was focused on a different issue (the influence of emotional facial expression on face naming), we did measure face naming response latency (Gallegos and Tranel, 2005). That study happened to include 4 left ATL subjects who ended up in the Unimpaired group in the current study. For these 4 Unimpaired subjects, the average response latency for naming familiar faces was 2813 ms (SD =1152), which is actually somewhat *faster* than the average response latency for the Iowa-based normal participants in the study (M = 3060 ms, SD = 1752). Thus, for the Faces category in 4 of the Unimpaired participants, we have data that support the conclusion that the naming latencies in the Unimpaired participants are normal. (Incidentally, the Gallegos and Tranel study also reported on 4 of the left ATL subjects who fell into the Impaired group in the current study, and those subjects had an average face naming response latency of 3792 ms (SD = 1100), which is more than seven tenths of a second slower than the normal latency. This helps corroborate the current designation of these subjects as "impaired.")

The Difference from Normal summary scores yielded a similar picture. In the Unimpaired group, 5 of the 7 patients had positive (above normal) scores, and for both of the patients with negative scores, the difference was slight (−1 in both cases). The average difference score for the Unimpaired patients was M = +5.6 (SD = 7.3). In the Impaired group, by contrast, 15 of the 16 patients had negative (below normal) scores, and the 1 exception was only slightly above normal (+1). The average difference score for the Impaired patients was M = −48.5 (SD = 25.7). A *t*-test contrasting these group means was significant (t(19.4) = 7.73, p = 0.000; mean difference = 54.1; 95% Confidence Interval of the mean difference = 39.4–68.7) (equal variances not assumed).

Predictors of proper naming performance following left ATL

We turn now to an analysis of the factors that might differentiate the Unimpaired and Impaired subgroups, vis-à-vis their proper naming performances. Table 1 provides an overview of how the two subgroups came out on a wide range of demographic and neuropsychological variables, and Table 3 presents data regarding the statistical contrasts of the continuous variables from Table 1.

In support of our hypothesis, there was a marked difference in Age at Seizure Onset between the groups. On average, patients in the Unimpaired group were just more than 2 years old (M = 2.1) when their seizures began; by contrast, patients in the Impaired group were more than 15 years old (M = 15.1) when their seizures began (Table 1). This difference was statistically significant (p = 0.000); moreover, the mean difference was more than 13 years, and the 95% Confidence Interval of the mean difference did not come close to including zero (Table 3). We followed this group comparison with a correlation analysis, which indicated that Age at Seizure Onset was strongly correlated with naming outcome (the Difference from Normal summary score) (R = −0.569, p = 0.005, $\eta^2 = 0.55$). Finally, in a logistic regression with Age at Seizure Onset as the predictor variable and group naming outcome (Unimpaired v. Impaired) as the outcome variable, the Chi-square was significant ($\chi^2(1) = 21.2$, p = 0.000), and 22 out of 23 patients were classified correctly (95.7% overall; all of the Impaired patients and all but 1 of the Unimpaired patients).

By contrast, the subgroups were comparable on nearly all of the other demographic and neuropsychological variables. Specifically, the two subgroups did not differ in Age at Testing: Faces, Age at Testing: Landmarks, Education, Chronicity: Faces, Chronicity: Landmarks, or Age at Surgery. There were no significant differences between the two subgroups in Verbal, Performance, and Full Scale IQ scores. On the various memory measures, the Unimpaired group was significantly higher than the Impaired group on the AVLT 30-minute recall measure,

but the two groups did not differ on any of the other four memory measures. The Unimpaired group was significantly superior to the Impaired group on the Controlled Oral Word Association Test, but the two subgroups were not significantly different on the Token Test or Facial Discrimination Test. The subgroups were very comparable on the Boston Naming Test presurgically, and although the Unimpaired group was somewhat higher than the Impaired group on postsurgical Boston Naming Test performance, this difference was not statistically significant. The two groups were not statistically different on the Beck Depression Inventory-II. Table 3 conveys the statistical outcomes in detail, and shows that the 95% Confidence Intervals for the mean differences between the two subgroups included zero for all of the variables except Age at Seizure Onset, AVLT-recall, and COWA. Moreover, if one applies a Bonferroni alpha correction to the 13 neuropsychological variables in Table 3, this yields a two-tailed significance level of 0.0038. Hence, with a corrected alpha level, neither the AVLT-recall nor COWA results remain statistically significant.

There is some indication from the Boston Naming Test that naming improved slightly (by 1.6 points) post-ATL in the Unimpaired patients and declined slightly (by 3.9 points) post-ATL in the Impaired patients. In addition, in looking through the error types from the BNT, there was a tendency for the Impaired patients to make more paraphasic errors, compared with the Unimpaired patients, and this finding is reminiscent of previous work that has shown that paraphasic errors on the BNT may be more sensitive to temporal lobe epilepsy than overall naming score (Schefft et al., 2003; Fargo et al., 2005). The magnitude of change (from before to after ATL surgery) on the BNT—and the postsurgical between-group difference—is small, especially compared with the large between-group differences observed on the proper naming tests (as shown in Table 2 and reported for the Difference from Normal summary scores). Nonetheless, the fact that the BNT performance worsened in the Impaired patients is consistent with the notion that the ATL surgery contributed to the postsurgical proper naming impairments in these patients.

Other variables

Data for the variables of lesion size, seizure outcome, medications, and pathology are provided in Table 4, broken down as a function of the two subgroups (Unimpaired, Impaired). Additional details are summarized below.

Lesion size—All of the patients in this study underwent a standard surgical procedure (all resections were performed at our institution). In this procedure, the neurosurgeon initiates a corticectomy in the left middle temporal gyrus, and carries the resection inferiorly to include the inferior temporal gyrus and anteriorly to include the temporal pole. The resection is then carried mesially until the collateral sulcus and temporal horn of the lateral ventricle are encountered. The resection is then carried more mesially to include to varying extents the hippocampus and amygdala.

We investigated the lesion sizes of the participants with an eye to whether there might be any systematic differences between the Impaired and Unimpaired groups. In the Impaired group, and anterior-posterior resection measurement ranged from 1.5 to 4.5 cm, with 8 of the 16 patients having a resection measuring between 3 cm and 4 cm. One patient in this group had part of the superior temporal gyrus resected, and in the other 15, the superior temporal gyrus was spared. In the Unimpaired group, the anterior-posterior measurement ranged from 3 cm to 5.5 cm, with 6 of the 7 patients having resections measuring between 3 cm and 4.5 cm. Three patients in this group had part of the superior temporal gyrus resected, and in the other four, the superior temporal gyrus was spared. These data indicate that the Impaired and Unimpaired groups did not differ in terms of lesion size, and if anything, the Unimpaired group may have had somewhat more extensive resections, which would operate against the direction of our

findings. We did not measure specifically the relative extent of damage to the hippocampus in the two groups, but this is (a) unlikely to be different, based on the surgical reports, and (b) not of direct relevance to the main question, given that the hippocampus is not believed to play a major role in retrieval of previously learned proper names and faces (obviously its role in new learning of names and faces would be more substantial).

Seizure outcome, medications, pathology

We collected data on postoperative seizure status, use of antiepileptic drugs (AEDs), and pathology of resected tissue (data were available for 22 patients, including all 7 Unimpaired patients and 15 of the 16 Impaired patients). In regard to seizure status, Engel Class I was achieved in 85.7% of the Unimpaired group (6 patients) and in 86.7% of the Impaired group (13 patients), whereas 1 patient in the Unimpaired group and 2 patients in the Impaired group continued to have recurrent complex partial seizures. Thus, confounding effects from persistent seizures would not appear to contribute to the findings regarding proper naming.

In regard to AEDs being taken at the time of the current study, the status of the patients in each subgroup is summarized in Table 4, and it can be seen that the distribution of numbers of patients taking various numbers of AEDs is fairly comparable for the 2 subgroups. We also looked into the specific types of AEDs that were being taken by the patients at the time of our study, as certain drugs (e.g., topiramate) have been reported to cause word-finding difficulties in a small percentage of patients (e.g., Mula et al., 2003). One patient in the Unimpaired group was taking topiramate (600 mg daily), and two patients in the Impaired group were taking topiramate (one was on 300mg daily, the other was on 100 mg daily). Three patients in the Unimpaired group and four patients in the Impaired group were taking phenytoin. One patient in the Unimpaired group and six patients in the Impaired group were taking lamotrigine, but this medication is generally regarding as having fewer cognitive side effects that other AEDs (Blum et al., 2006). Overall, there is no indication that unbalanced AED usage—in numbers of drugs or in types of drugs—in the Unimpaired versus Impaired groups can account for our findings regarding proper naming.

In regard to the pathology in our patients, none of the patients had a specific diagnosis of cortical heterotopia during pathological review of the surgical specimens. One patient in the Impaired group was determined to have cortical neuronal dysplasia, which was likely a cortical developmental pathology or malformation; however, a more specific pathological diagnosis was not obtainable for this case. One patient in the Impaired group had white matter gliosis diagnosed on pathology, but a more specific diagnosis was not provided. Four patients in the Unimpaired group and 12 patients in the Impaired group had mesial temporal/hippocampal sclerosis identified on either brain MRI or frozen section examination at the time of surgery. One patient in the Unimpaired group had a possible temporal lobe cyst, and one had left hemispheric atrophy as a result of encephalitis. One patient in each group had no identifiable pathology in the left anterior or mesial temporal lobe. Overall, these findings do not allow a definitive conclusion regarding possible developmental neuropathology in the Unimpaired group, although it is suspected that such pathology might be common, and could prompt cortical reorganization that would be one of the mechanisms contributing to the better naming outcome in these patients.

Additional variables

Several other variables warrant comment. One is sex: the Unimpaired group was predominantly female (5/7 or 71%), whereas the Impaired group was equally split between women and men (50:50). It is possible that female gender confers some slight protective advantage against developing proper naming defects following ATL, although our numbers are only slightly suggestive of such an effect (and with a small N, the numbers cannot be considered reliable,

and our study was not designed a priori to test sex as a predictor variable). This pattern is not inconsistent with the classic notion—not well supported empirically, but also not ever completely disproved—that women have somewhat less lateralized hemispheric specialization for language (e.g., Levy, 1972; McGlone, 1977; Inglis and Lawson, 1981; Hampson and Kimura, 1992). There are some interesting parallel findings from research on temporal lobectomy patients, showing that verbal memory abilities are less lateralized (compared with men) in women with left temporal lobe epilepsy, which appears to confer greater plasticity and recovery of function of these abilities following early left mesial temporal lobe injury in women (Trenerry et al., 1995). Data from functional imaging have also supported the notion of less lateralization of function in women, albeit with small effect sizes and uncertain mechanisms (e.g., Kansaku and Kitazawa, 2001; Phillips et al., 2001; Grabowski et al., 2003).

Another variable is handedness: there were two non-right-handers in the study, and both happened to be in the Unimpaired group. We would be reluctant to dismiss entirely the possibility that non-right-handedness (and the possible differences in hemispheric lateralization of function that non-right-handedness might imply) could be a protective factor against developing proper naming defects following left ATL. On the other hand, the Wada testing in our patients indicated that all of them, including the two left-handers, had standard left hemisphere language dominance. So it seems unlikely that handedness—and whatever difference in functional asymmetry that it is a proxy for—could be playing much of a role in our findings.

Discussion

The current findings support the hypothesis that early age of seizure onset has a “protective” effect in regard to the development of proper name retrieval defects following left ATL. This effect was robust: the average age of seizure onset in left ATL patients with normal proper naming following surgery (2.1 years) was 13 years younger than the average age of seizure onset in left ATL patients with impaired proper naming following surgery (15.1 years), and age of seizure onset was strongly correlated with proper naming outcome ($R = -0.569$). No other variable we looked at had such a potent influence, although several, including gender (female better than male) and handedness (non-right-handedness better than right-handedness), had small effects that cannot be ruled out as contributors. Overall, the findings provide consistent support for the notion that age of seizure onset, in and of itself, is a reliable variable predicting proper naming outcome following left ATL, and earlier is better than later. Most of the participants in the Unimpaired group (6/7), in fact, had seizure onset before 5 years of age (and the other was 5); by contrast, most of the participants in the Impaired group (13/16) had seizure onset after 7 years of age. These ranges generally conform to the definitions of “early onset” and “late onset,” respectively, typically encountered in the literature (e.g., Saykin et al., 1989; Stafiniak et al., 1990).

The separation of the Unimpaired and Impaired groups on the variable of age at seizure onset was not complete, and three patients in the Impaired group were between 4 and 5 years old when their seizure disorders began. So on a case by case basis, age at seizure onset is not a perfect predictor of naming outcome following left ATL, and we are not making any claims to that effect. Nonetheless, the three younger-onset Impaired patients are exceptions, and the weight of the findings is strongly in the direction of younger age at seizure onset being associated with better naming outcome.

It is also important to acknowledge that the Unimpaired group generally had slightly higher neuropsychological test performances than the Impaired group. Few of these differences were statistically significant (none of them, in fact, after alpha correction), but we would be reluctant to conclude that these differences are entirely meaningless. In fact, it would be fair to say that

the Unimpaired group was generally better off than the Impaired group, postsurgically, across a wide range of neuropsychological measures. This also leaves open the possibility that the Unimpaired patients were better off presurgically, too (although the Boston Naming Test data do not support that impression). In any case, the Unimpaired group's advantage was clearly much higher for the proper naming measures than for anything else we assessed, including other naming capacities (as indexed by the Boston Naming Test).

It can also be noted that age at surgery was somewhat lower in the Unimpaired group (31.4 years) compared with the Impaired group (36.0 years), although not significantly (and the 95% Confidence Interval of the mean difference included zero). Also, the Unimpaired participants had a longer time between age at ATL and age at proper name assessment than did the Impaired participants, by a little more than 2 years for both the Faces and Landmarks (although neither between-group difference was statistically significant). In principle, this could have contributed to better proper naming performances in the Unimpaired participants. From a practical standpoint, though, the vast majority of recovery in naming after ATL surgery takes place in the first few weeks and months, and by three years after surgery, change associated with recovery would be expected to be minimal. Thus, the chronicity difference between the Impaired and Unimpaired groups takes on even less practical meaning when looked at against the background of the patients being several years out from their surgery.

A number of studies have shown that longer duration of epilepsy is associated with poorer cognitive functioning (e.g., Saykin et al., 1989; Strauss et al., 1995; Hermann et al., 1997; Oyegbile et al., 2004). In the current study, participants in the Unimpaired group (with earlier age of seizure onset) had on average a longer duration of epilepsy than participants in the Impaired group (with later age of seizure onset). Specifically, the Unimpaired participants had epilepsy on average for some 29 years from onset to ATL surgery, whereas the Impaired participants had epilepsy on average for just more than 20 years from onset to ATL surgery. That the Unimpaired group fared better on proper naming outcome is thus different from what might be predicted based solely on the duration of epilepsy literature. However, we interpret our findings to suggest that early reorganization of function—prompted by early seizure onset—was a "protective" factor for proper naming in the Unimpaired participants, and we are not suggesting that there is anything advantageous in our sample to having a longer seizure duration. And as noted above, there remains the possibility that the Unimpaired participants were somewhat better off in general, given the findings in our study that the Unimpaired group tended to be slightly higher on most of the postsurgical neuropsychological variables. We are not eschewing this possibility, but we do not feel that it cancels the predictive value that we are ascribing to early age of seizure onset in regard to proper naming outcome.

Returning to the main focus of our study, it is useful to consider the subjective phenomenology of the patients, vis-à-vis their proper name retrieval abilities—that is, what do the patients feel about their ability, irrespective of their neuropsychological test performance? We conducted a retrospective review of the neuropsychology files of the 23 participants to determine whether they complained of proper name retrieval problems following surgery (e.g., in interviews with examiners, to their neurologist). This review indicated that in the 7 patients in the Unimpaired group, such complaints were rare, and the patients generally denied problems with proper naming following their ATL. Some of them did acknowledge problems in acquiring new proper names, noting that they seemed to require many more trials than normal for names to "stick," which is not surprising given the likelihood of hippocampal dysfunction in these patients (all patients had at least some hippocampal damage as a result of the ATL). In the 16 patients in the Impaired group, 14 complained specifically about having difficulty retrieving names for familiar persons and/or places following surgery. The other 2 patients denied such problems when asked about them, but following the administration of the Faces and Landmarks tests, both agreed that they were having more difficulty coming up with names for the items on these

tests than should have been the case. These behavioral observational data help corroborate the grouping of the participants as Unimpaired or Impaired, and support the experimental operationalization of Unimpaired and Impaired proper name retrieval.

Our findings are not the first to document an association between early age of seizure onset and better word retrieval after surgery for epilepsy, but they add to and extend evidence for the importance of age of seizure onset in predicting outcome following left ATL. They also extend our understanding of brain reorganization and plasticity. Much work has already been accomplished in an effort to explain the effects of seizures at an early age on the reorganization of language. One such study that explored brain plasticity and reorganization examined preoperative and postoperative confrontational naming using words categorized by age at acquisition (Bell et al., 2002). The late-onset epilepsy and the early-onset epilepsy groups were similar in their preoperative naming abilities for all age of acquisition categories, but the patients with late-onset epilepsy had a greater decline in naming after a left ATL, especially for words acquired later in development. Because the 2 groups had similar lexicons before surgery, the sparing of word retrieval in the early-onset group postoperatively implicates a process of functional reorganization providing a protective mechanism for naming. Does such a protective mechanism exist for proper naming? Given our robust findings of an earlier age of onset of epilepsy in those patients with spared proper naming, it appears that such a mechanism could indeed exist. This also leads to the interesting possibility that stratifying our faces and landmarks stimuli into specific age of acquisition categories could reveal age of acquisition effects for proper naming that would be akin to those observed for common naming (Bell et al., 2002). This is a topic for future research, and we would predict that such age of acquisition effects for proper naming might very well occur.

Another interesting topic for future research is whether the “protective” effect of early age of seizure onset might also hold for visual recognition defects that frequently occur as a consequence of right ATL. It has been shown that right anterior temporal damage (including ATL) can produce impairments in the recognition of unique stimuli such as famous faces (Tranel et al., 1997; Seidenberg et al., 2002; Glosser et al., 2003; Damasio et al., 2004). It follows that in ATL patients, there could be a protective effect of early age of seizure onset for recognition impairments, akin to that observed in the current study for naming impairments. We would predict that such an effect would be likely, and it will be interesting to see if this prediction is upheld in future work.

Studies using receptive language-related activity sources from magnetoencephalography (MEG) data, co-registered with structural MRI data, have shown a greater amount of interhemispheric reorganization of language areas in patients with mesial temporal sclerosis. Moreover, those patients with mesial temporal sclerosis and recurrent seizure onset before age 5 have a greater atypical (bilateral or right) hemispheric lateralization of language before ATL (Pataraia et al., 2004, 2005). Even though localization data with MEG should be interpreted with caution, these findings add to the notion of brain plasticity and reorganization.

We do not have extensive presurgical data in our patients for proper naming of persons and landmarks, and thus our findings are limited to a postsurgical assessment conducted in the chronic phase after left ATL. A direct pre- to postoperative comparison would be facilitated by parallel datasets. Nonetheless, our patients did not typically complain of proper name retrieval deficits before surgery, and none of them had proper naming defects that were picked up in standard neuropsychological assessment. Moreover, as mentioned already, the Unimpaired and Impaired groups had very similar presurgical Boston Naming Test performances. Given that we identified a significantly earlier age of seizure onset in those patients with spared proper naming, the notion of reorganization of language may apply for proper nouns much as it has been posited to apply for common nouns. Further studies could

explore functional reorganization with MRI data as well as MEG data, and our results for proper nouns may provide a contribution to developing these studies and to elaborating theories for brain plasticity.

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Table 1

Demographic and neuropsychological data for the participants

Index/test	All participants	Unimpaired participants	Impaired participants
N	23	7	16
Age at testing: Faces	38.8 (9.5)	37.3 (11.6)	39.5 (8.8)
Age at testing: Landmarks	38.3 (9.9)	36.6 (11.6)	39.0 (9.4)
Sex	10M; 13W	2M; 5F	8M; 8F
Education	13.2 (2.2)	13.7 (1.7)	13.0 (2.4)
Chronicity: Faces	4.2 (3.7)	5.9 (4.0)	3.5 (3.2)
Chronicity: Landmarks	3.7 (3.2)	5.2 (4.5)	3.0 (3.1)
Handedness	21R; 2L	5R; 2L	16R; 0L
Age at seizure onset	11.2 (11.5)	2.1 (1.4)	15.1 (11.8)
Age at surgery	34.6 (11.0)	31.4 (13.3)	36.0 (10.0)
WAIS-III VIQ	93.6 (11.9)	98.3 (13.6)	91.6 (11.0)
WAIS-III PIQ	103.7 (11.6)	106.0 (18.5)	102.6 (7.6)
WAIS-III FSIQ	97.7 (10.9)	101.6 (13.8)	96.0 (9.4)
AVLT: Trial 5	10.4 (2.4)	11.6 (1.4)	9.8 (2.5)
AVLT: 30-min recall	7.1 (3.1)	9.4 (2.0)	6.1 (3.0)
AVLT: 30-min recognition	26.9 (2.9)	28.1 (1.8)	26.4 (3.1)
Visual retention test: Correct	7.8 (1.6)	7.9 (1.5)	7.8 (1.7)
Visual retention test: Errors	3.0 (2.8)	2.6 (1.8)	3.3 (3.2)
Token test	43.5 (0.8)	43.3 (1.1)	43.6 (0.6)
COWA	40.3 (13.3)	49.3 (13.5)	36.3 (11.5)
Boston Naming Test—pre	47.7 (10.2)	48.7 (11.4)	47.3 (10.0)
Boston Naming Test—post	45.5 (10.3)	50.3 (11.3)	43.4 (9.4)
Facial discrimination	44.6 (3.6)	43.6 (5.0)	45.0 (2.9)
Beck Depression Inventory-II	10.3 (6.8)	8.6 (8.1)	11.0 (6.3)

Age at testing is the participant's age at the time the proper naming studies were administered, in years, for Faces and Landmarks, respectively. Education is years of formal schooling. Chronicity refers to the time between the ATL operation and the assessment of proper naming, in years, for Faces and Landmarks, respectively. Age at seizure onset and age at surgery are in years. WAIS-III VIQ, Verbal IQ; WAIS-III PIQ, Performance IQ; WAIS-III FSIQ, Full Scale IQ (all from the Wechsler Adult Intelligence Scale-III); AVLT, Auditory-Verbal Learning Test (a 15-item word list learning test).

Raw scores are presented, with Trial 5 = #/15, 30-min recall = #/15, and 30-min recognition = #/30. The Visual Retention Test requires reproduction of geometric designs from memory; raw scores for # correct (10 maximum) and # errors (no maximum) are presented. The Token Test, from the Multilingual Aphasia Examination, is a measure of aural comprehension; raw scores (44 maximum) are presented. COWA is the Controlled Oral Word Association test, a measure of word generation to letters (raw scores are presented). The Boston Naming Test is a 60-item test of visual confrontation naming. Raw scores for presurgical and postsurgical Boston Naming Test performance are presented. Facial Discrimination is the Facial Recognition Test of Benton et al. (1983), and is a measure of visuoperceptual discrimination and matching of unfamiliar faces (raw scores are presented; the maximum is 54). The Beck Depression Inventory-II is a self-report measure of depressive symptomatology; raw scores are presented. See the text and Table 3 for details regarding the statistical contrasts of the variables in this Table.

Table 2

Proper naming performances (in % correct; SDs in parentheses) as a function of group and category

Group	Famous faces	Famous landmarks
Unimpaired (n = 7)	92.4 (4.6)	86.1 (5.8)
Impaired (n = 16)	59.2 (21.4)	65.3 (14.5)
Normal participants[a]	85.0 (11.1)	88.0 (8.0)

[a] For Faces, the normal comparison participants are from Tranel (2006); for Landmarks, the normal comparison participants are from Tranel et al. (2005).

Table 3

Statistical data for continuous variables from Table 1

Variable	Levene's Test for Equality of Variances (F, p)	t (df)	p-value (2-tailed)	Mean Difference (SE)	95% confidence interval of the difference
Age at testing: Faces	0.38, 0.547	−0.50 (21)	0.619	−2.21 (4.39)	−11.34–6.91
Age at testing: Landmarks	0.24, 0.629	−0.53 (21)	0.600	−2.43 (4.56)	−11.92–7.06
Education	0.77, 0.391	0.72 (21)	0.481	0.71 (0.99)	−1.36–2.79
Chronicity: Faces	1.01, 0.327	1.33 (21)	0.198	2.18 (1.64)	−1.23–5.58
Chronicity: Landmarks	1.03, 0.322	1.17 (21)	0.254	2.02 (1.72)	−1.56–5.59
Age at seizure onset	7.52, 0.012	−4.36 (15.9)	0.000	−13.03 (2.99)	−19.37 to –6.68
Age at surgery	0.56, 0.464	−0.92 (21)	0.366	−4.61 (5.00)	−15.00–5.78
WAIS-III VIQ	0.15, 0.706	1.26 (21)	0.221	6.72 (5.33)	−4.36–17.80
WAIS-III PIQ	5.91, 0.024	0.47 (6.9)	0.656	3.38 (7.25)	−13.81–20.56
WAIS-III FSIQ	0.25, 0.626	1.14 (21)	0.269	5.57 (4.91)	−4.64–15.78
AVLT-Trial 5	2.25, 0.148	1.73 (21)	0.099	1.76 (1.02)	−0.36–3.88
AVLT-recall	1.01, 0.327	2.65 (21)	0.015	3.30 (1.25)	0.71–5.90
AVLT-recog	2.67, 0.117	1.39 (21)	0.181	1.77 (1.28)	−0.89–4.42
VRT-correct	0.00, 0.953	0.15 (21)	0.884	0.11 (0.73)	−1.40–1.62
VRT-errors	1.19, 0.288	−0.53 (21)	0.603	−0.68 (1.28)	−3.35–1.99
Token test	2.17, 0.156	−0.95 (21)	0.355	−0.34 (0.36)	−1.09–0.41
COWA	0.06, 0.810	2.37 (21)	0.028	12.97 (5.48)	1.58–24.37
BNT-pre	0.57, 0.457	0.30 (21)	0.770	1.40 (4.73)	−8.43–11.23
BNT-post	0.50, 0.486	1.51 (21)	0.145	6.85 (4.52)	−2.56–16.25
Facial discrim	3.29, 0.084	−0.86 (21)	0.397	−1.43 (1.65)	−4.87–2.01
BDI-II	0.04, 0.843	−0.78 (21)	0.443	−2.43 (3.11)	−8.89–4.04

For variables for which the Levene test indicated unequal variance, the *t*-test did not assume equal variance, and the df's were adjusted accordingly (this obtained for Age at Seizure Onset and WAIS-III PIQ). Otherwise, the *t*-test assumed equal variance, and the df's were 21. The Bonferroni corrected alpha level for the 13 neuropsychological variables in the Table is 0.0038. See Table 1 for definition of variables.

Table 4

Other variables: lesion size, seizure outcome, medications, pathology

Variable	Unimpaired participants (n = 7)	Impaired participants (n = 16)
Lesion size: range of anterior-posterior resection	3–5.5 cm (6/7 patients had resections ranging between 3 and 4.5 cm)	1.5–4.5 cm (8/16 patients had resections ranging between 3 and 4 cm
Postoperative seizure status	Engel Class I achieved in 6 patients (85.7%)	Engel Class I achieved in 13 patients (86.7%)
Medications: number of antiepileptic drugs	0 (1 patient), 1 (3 patients), 2 (1 patient), 3 (2 patients)	0 (1 patient), 1 (7 patients), 2 (7 patients)
Pathology of resected material	Mesial temporal/hippocampal sclerosis (4 patients); possible cyst (1 patient); atrophy (1 patient); no identifiable pathology (1 patient)	Mesial temporal/hippocampal sclerosis (12 patients); cortical neuronal dysplasia (1 patient); white matter gliosis (1 patient); no identifiable pathology (1 patient)

For postoperative seizure status, medications, and pathology, data were available for 15 of the 16 patients in the Impaired group, and for all 7 of the Unimpaired patients.