ANTERIOR TEMPOROBASAL SULCAL MORPHOLOGY
IN TEMPORAL LOBE EPILEPSY:
ASSOCIATION WITH CLINICAL AND COGNITIVE VARIABLES

By

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A THESIS PRESENTED TO THE GRADUATE SCHOOL
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To my husband:
The best ally, friend, companion, and teammate I’ve ever had

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I thank my parents for meaningfully teaching me the principles of a Gospel-centered life and for providing an example of righteous happiness. Finally, I thank my sweet husband for his sacrifices on my behalf and his unwearying support in all of my endeavors.

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LIST OF ABBREVIATIONS

ANCOVA	analysis of covariance
ANOVA	analysis of variance
CS	collateral sulcus
EEG	electroencephalogram
FSIQ	Full Scale Intelligence Quotient
OTS	occipitotemporal sulcus
RS	rhinal sulcus
SCRaP:aTB	Sulcal Classification Rating Protocol: Anterior Temporobasal Sulci
TLE	temporal lobe epilepsy
WAIS-III	Wechsler Adult Intelligence Scale—Third Edition
WMS-III	Wechsler Memory Scale—Third Edition

Abstract of Thesis Presented to the Graduate School
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The anterior temporobasal surface of the brain features the collateral and rhinal sulci. In some brain hemispheres these two sulci are continuous with each other and in other hemispheres they are separated from each other. Previous studies found an increased prevalence of collateral-rhinal connections in individuals with temporal lobe epilepsy (TLE) and Alzheimer's Disease, leading to the theory that this connection may reflect abnormal brain development and be a risk factor for disease related pathology. Because sulcal morphology is determined very early in development, we predicted that collateral-rhinal connection would be associated with a younger age of epilepsy onset. We also predicted that a collateral-rhinal connection would be associated with the presence of early adverse environmental events (e.g., illness, pre- or peri-natal complications) as well as a family history of neurological illness and epilepsy. Because of the anatomical structures affected by the morphology of the collateral and rhinal sulci, we also predicted that individuals with a collateral-rhinal connection would perform more poorly on a test of item memory but equally as well on a test of spatial memory.

Participants were 79 (23 male) individuals with definite or probable TLE. Mean age was 35.84±10.95 years. Scaled scores from Faces Immediate and Delayed and Spatial Span subtests of the Wechsler Memory Scale-III were used. A previously developed and validated rating protocol of sulcal connections was used and interrater reliability was determined to be $\kappa > .75$.

Presence of collateral-rhinal connection in the right hemisphere was associated with younger age of onset (99 months vs. 180 months, $p<.05$). This relationship was not seen in the left hemisphere.

There were no significant associations between the presence of a collateral-rhinal connection and presence of early adverse environmental events or presence of a family history of neurological disease or epilepsy.

Individuals with a right collateral-rhinal connection performed more poorly on Faces Immediate and Delayed ($p<.05$). No significant differences were found on Spatial Span performance, and no significant memory-morphology relationships were found for the left hemisphere.

A collateral-rhinal connection in the right hemisphere of TLE patients is related to a younger age of onset and is also associated with poorer performance on item memory but not spatial memory. These results lend support to the idea that a collateral-rhinal connection in the right hemisphere may be a sign of abnormal neurodevelopment but further research is needed to clarify this relationship. This also lends support to the distinction between item and spatial memory currently debated in the literature.

CHAPTER 1
INTRODUCTION

Literature Review

Sulci are folds in the surface of the human brain, which are thought to have evolved as a way to increase the surface area of the brain while staying within the fixed confines of the cranial space (Toro et al., 2008). Sulcal development may begin as early as 14 weeks of gestation (Dubois et al., 2008) and continues through the rest of gestation and into the first year of life (Dubois et al., 2008; Ono et al., 1990). During this critical period of sulcal development, gross morphologic characteristics such as presence or absence of particular sulci, location of sulci, and connections between sulci emerge.

There is significant variability in gross sulcal morphology both between individuals and between hemispheres of the brain in a single individual (Ono et al., 1990). Changes in sulcal characteristics may continue throughout the lifespan (Sowell et al., 2002) and especially as individuals age (Kochunov et al., 2005). However, these changes are more likely to affect characteristics such as depth and width of sulci rather than gross morphologic features such as the pattern of connectivity between sulci (Magnotta et al., 1999). The absence of an association between age and patterns of sulcal connections in several studies (Novak et al., 2002; Reckess, 2010; Zhan et al., 2009) indicates that there is no reason to believe that patterns of sulcal connections change with age.

Because there is a critical period of neurodevelopment *in utero*, insults to the developing fetus can affect the normal development of the brain, as can genetic factors (Montenegro et al., 2002). One possible sign of abnormal brain development is abnormal patterns of connections between sulci (Kim et al., 2008). Abnormal patterns of sulcal connections have been found in a variety of developmental and neuropsychiatric disorders, including schizophrenia (Nakamura et al., 2007), Williams Syndrome (Galaburda & Bellugi, 2000), and Alzheimer's Disease (Zhan et al., 2009). For example, Nakamura and colleagues (2007) studied the configuration of the "H-shaped" sulcus, which helps define the boundary of four major orbitofrontal gyri. The configuration was characterized into three types based on the presence or absence of connections among the small sulci that make up the "H-shaped" sulcus. Their results showed that in a group of individuals with schizophrenia compared to controls, the distribution of the three types of configurations was opposite the distribution for the controls, such that the configuration type that was least common in controls was most common in patients and was associated with poorer functioning and smaller volume of intra-cranial contents.

Connections between anterior temporobasal sulci have been studied in Alzheimer's patients (Zhan et al., 2009) as well as in individuals with temporal lobe epilepsy (TLE; Kim et al., 2008; Reckess, 2010). Three sulci are generally referred to by the term "anterior temporobasal sulci" and include the collateral, rhinal, and occipitotemporal sulci. Figure 1 shows these sulci on the surface of the left hemisphere of the brain as generated by the public domain software program BrainVISA version 3.2 (Rivière et al., 2002). The position of these sulci on the surface of the medial temporal lobes allows them to contribute to the size and shape of the hippocampus, parahippocampal gyrus, and perirhinal and entorhinal cortices, all of which play a major role in the temporal lobe memory system (Eichenbaum & Lipton, 2008; Eichenbaum et al., 2007). In both Alzheimer's Disease (Zhan et al., 2009) and TLE patients (Kim et al.,

2008) compared to healthy individuals an increased prevalence of connections between the collateral and rhinal sulci have been found.

Kim and colleagues (2008) created a rating system to classify four different patterns of connections between the three anterior temporobasal sulci. Type 1 consisted of a single-branch, unbroken collateral sulcus connected with the rhinal sulcus anteriorly. Type 2 consisted of the collateral sulcus connected with the occipitotemporal sulcus but separated from the rhinal sulcus. Type 3 consisted of the collateral sulcus separated from the occipitotemporal and rhinal sulci but with the occipitotemporal and rhinal sulci connected. Type 4 consisted of no connections between the collateral, occipitotemporal, and rhinal sulci. After applying this rating system to the magnetic resonance images of the brains of individuals in their sample, they found an increased prevalence of the Type 1 pattern (collateral-rhinal connection) among individuals with TLE (77% had the connection in the left hemisphere, 72% in the right) compared to healthy individuals (47% left, 41% right).

In discussing these results, Kim, et al. characterized the collateral-rhinal connection as the most “simplified” of the patterns of sulcal connections, citing a study of cortical complexity measured by the degree of gyrification (Luders et al., 2004). Kim, et al. theorized that the collateral-rhinal connection may be an indication of incomplete maturation or disrupted connectivity of the entorhinal and perirhinal cortices that are adjacent to the collateral and rhinal sulci. They postulated that these mechanisms may directly or indirectly increase an individual’s vulnerability to the development of disease. However, Kim and colleagues did not report investigating any relationships between sulcal connectivity and clinical features of epilepsy, except finding no relationship between sulcal pattern type and history of febrile seizures and no association between sulcal pattern type and side of seizure focus in the brain. Their report did not investigate the relationship between pattern type and cognition.

Previous Research

Intrigued by this study, Reckess designed her dissertation research as an attempt to replicate and extend these findings (Reckess, 2010). After designing a reliable rating protocol based off of the methodology described by Kim, et al. (2008), she and the current author (CBD) rated the anterior temporobasal sulcal connection types using brain MR images of 79 individuals with TLE and 70 age-matched controls that she obtained through collaboration with the University of Wisconsin—Madison Epilepsy Research Group (Hermann et al., 2002a; Hermann et al., 2002b; Hermann et al., 2003; Hermann et al., 2007; Seidenberg et al., 2008; Seidenberg et al., 2007). The results failed to replicate the increased prevalence of the collateral-rhinal connection in her sample of TLE patients compared to controls; the prevalence of collateral-rhinal connections in TLE patients (36% left, 46 % right) was not significantly different from the prevalence among healthy controls (40% left, 41% right). She did, however, replicate the absence of a relationship between side of seizure focus in the brain and pattern type. Analysis of the relationship between anterior temporobasal sulcal connections and cognition revealed that a collateral-rhinal connection in the right hemisphere was associated with poorer visual delayed and immediate memory performance but not verbal memory performance as measured by index scores from the Wechsler Memory Scale—Third Edition (Wechsler, 1997a). This finding was among the first to suggest a relationship between temporobasal sulcal morphology and memory function.

Current Study

Using the same sample and ratings generated as part of the Reckess dissertation, the purpose of the current study is to investigate the associations between sulcal patterning and clinical variables relevant to the presentation of epilepsy early in the developmental period. We were particularly interested in evaluating sulcal relationships with age of epilepsy onset, the presence of familial and environmental risk factors for neurologic disease, and cognition in a sample of adults with temporal lobe epilepsy.

Rationale and Prediction 1

Since abnormalities in brain development are associated with the development of disease, individuals with abnormal brain development that is present early in life should be more likely to develop disease earlier in the developmental period than individuals with more normal brain development. Therefore, if the collateral-rhinal connection is a sign of subtle, abnormal brain development, as has been proposed (Kim et al., 2008; Zhan et al., 2009), one would expect that disease would present itself earlier in individuals with this type of sulcal connection than in individuals without this type of connection and therefore, presumably, more normal brain development.

Therefore, we predicted that TLE patients who have a collateral-rhinal connection will have a younger age of onset of epilepsy when compared with TLE patients who do not have a collateral-rhinal connection.

Rationale and Prediction 2

Since sulcal development is influenced by genetic factors, if an individual has a collateral-rhinal connection it is more likely that other members of his or her family also have this connection. Therefore, if the collateral-rhinal connection is a sign of subtle, abnormal brain processes that increase the likelihood of developing disease, then a collateral-rhinal connection should be associated with an increased likelihood of a family history of neurologic disease.

Rationale and Prediction 3

Since sulcal development is influenced by early environmental factors, adverse events such as complications with pregnancy or illness or injury in early life could lead to abnormal brain processes that may increase the likelihood of development of disease. If the collateral-rhinal connection is a sign of the presence of subtle, abnormal brain processes, these processes may have begun with an adverse early event. Therefore, we predicted that the collateral-rhinal connection would be associated with a history of early adverse environmental events.

Rationale and Prediction 4

The study of memory is a large field of research and the understanding of how the brain processes and retrieves information advances. One way of conceptualizing the brain's organization that has been supported by a body of behavioral and anatomic studies (for a review see Eichenbaum & Lipton, 2008; Eichenbaum et al., 2007) is to distinguish between item memory and memory for contextual and spatial detail. These two types of memory involve distinct pathways in the brain with different anatomical substrates. Item memory (unimodal representations of remembered items) follows a pathway beginning in association areas of the neocortex that process unimodal sensory information. From there, projections enter the perirhinal cortex followed by the lateral entorhinal area before entering the CA3 and CA1 of the hippocampus. In contrast, spatial or contextual memory (involving complex relationships between items and their context) begins in polymodal association areas of the neocortex before projecting to the parahippocampal cortex followed by the medial entorhinal area before entering the CA3 and CA1 of the hippocampus. While there are interconnections between these areas, the pathways remain largely separated until they reach the hippocampus, at which point there are even still patterns of separation between the distinct areas of the hippocampus that differentially receive spatial versus item information (Eichenbaum & Lipton, 2008).

With this understanding of the organization of information input into the hippocampus, and because the morphology of the collateral and rhinal sulci directly affects the gross morphology of and interconnections between the perirhinal and lateral entorhinal cortices which are implicated in the pathway for the encoding of item information, we hypothesized that individuals with a collateral-rhinal connection would perform more poorly on a test of item memory than TLE patients without a collateral-rhinal connection but would perform equally well on a test of spatial memory.

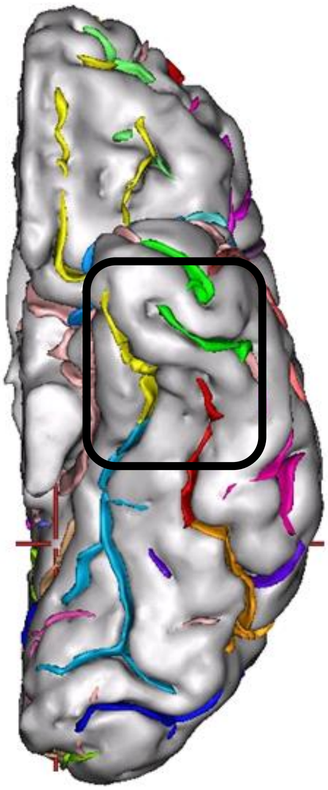

Figure 1-1. Image of the basal surface of the left hemisphere as imaged by BrainVISA software. The anterior temporobasal surface is outlined in black. Within this area, the red sulcus represents the occipitotemporal sulcus, the yellow represents the rhinal sulcus, and the turquoise represents the collateral sulcus.

CHAPTER 2
METHODS

Epilepsy patient data for this study were collected by colleagues at the University of Wisconsin—Madison Epilepsy Research Group in a previous research study that was reviewed and approved by the University of Wisconsin School of Medicine and Public Health Human Subjects Research Committee. After the collection of this data, a revision was approved by this same committee to allow sharing of the data with investigators at the University of Florida, which was also approved by the University of Florida Health Science Center Institutional Review Board (IRB-01). Informed consent was obtained from all subjects. Some descriptions contained in this section are adapted from Hermann, et al. (2007) and Oyebgile, et al. (2004).

Subjects

This study analyzed data from 79 (23 male) subjects who were diagnosed as having complex partial seizures with definite or probable origin in the temporal lobe. The average age of the patient group was 35.8 ± 10.9 years. All patients were between the ages of 14 and 59 years and had a Wechsler Adult Intelligence Scale—Third Edition (WAIS—III) Full Scale IQ greater than 69. Table 1 presents other demographic and clinical information. Epilepsy subjects were excluded for either of the following criteria: (a) presence of MRI abnormalities other than atrophy evident on clinical reading or (b) presence of neurological disorder other than epilepsy.

Confirmation of the hemisphere of origin of the temporal lobe seizures by electroencephalography was obtained in 51 of the subjects with the results showing 23 with right temporal lobe origin, 19 with left temporal lobe origin, and 9 with seizures of bilateral temporal lobe origin. The sample included 27 individuals intending to proceed to neurosurgery to remove the focus of their seizures with 52 individuals who did not intend to have this procedure.

Subjects underwent evaluation of clinical history and characteristics of their epilepsy, and were asked to identify any initial precipitating injuries that occurred prior to the onset of epilepsy. They were asked about febrile seizures; closed head injury with more than 20 minutes of loss of consciousness; meningitis or encephalitis; a prenatal insult such as infection with a fever, significant bleeding, or medical treatment; a perinatal insult such as special procedures needed in the hospital or if the child was not able to go home from the hospital with the mother; or a non-cerebral disease with prolonged hospitalization such as pneumonia or kidney disease. Collectively, these will be referred to as “early adverse environmental events.”

Neuropsychological Testing

As part of their epilepsy clinical care at the University of Wisconsin, each subject completed a comprehensive neuropsychological assessment. Two subtests of the Wechsler Memory Scale – Third Edition (WMS-III) were chosen as adequately representative of item (Faces Immediate and Delayed) and spatial (Spatial Span) memory. The Faces subtest consists of the presentation of 24 pictures of faces followed by an immediate test of yes-no recognition in which the 24 targets are intermixed with 24 distracters. The delayed recognition trial is administered 25 to 35 minutes later, and involves the original 24 faces intermixed with 24 new distracters. The Spatial Span subtest is a variation on the Corsi Blocks test (Milner, 1971) and consists of a fixed array of blocks. The subject is asked to touch the blocks in the same order as demonstrated by the examiner. As with Digit Span, each successive pair of trials increases in length. The test continues until the examinee fails two trials at a given length. Scaled scores of the performance on these subtests were used in analyses (Wechsler, 1997b).

Image Acquisition

Brain scans were obtained on a 1.5 Tesla GE Signa Magnetic Resonance scanner. Scan parameters are described in Hermann, et al. (2007). Sequences that were acquired for each subject included (1) T1-weighted, three-dimensional spoiled gradient recalled (2) Proton Density, and (3) T2-weighted images. Images that were deemed usable by Hermann and colleagues were de-identified, copied to a data storage device, and mailed to the University of Florida.

Automated Sulcal Identification and Labeling

Processing of the images acquired from the University of Wisconsin was conducted at the University of Florida as part of a concurrent doctoral dissertation and is described elsewhere (Reckess, 2010). The MRIs were processed using BrainVISA version 3.2, a public-domain software platform for the analysis of brain images developed by Rivière and colleagues (Rivière et al., 2002) at the Laboratoire de Neuroimagerie Assistée par Ordinateur. BrainVISA contains a toolbox that automatically recognizes and labels cortical sulci by employing a congregation of neural networks that are trained in sulcal identification and labeling based on maximizing similarity of the processed image to catalogued sulcal features and relations. The resulting image is a three-dimensional representation of the surface of the brain with the sulci filled in using a color designated to identify a particular sulcus in a particular region. However, this color scheme is not always accurate, as has been described elsewhere (Reckess, 2010), and requires human raters to validate and check the labeling.

Rating System

The rating system used in this study was developed as part of the doctoral dissertation of Gila Reckess at the University of Florida (Reckess, 2010). Reckess created a manualized protocol to classify patterns of connectivity among the collateral, occipitotemporal, and rhinal sulci. This protocol is referred to as the Sulcal Classification Rating Protocol: Anterior Temporobasal Sulci (SCRaP:aTB) and is based on the rating system described by Kim, et al. (2008). While Reckess only partially replicated the findings presented by Kim, et al., she used sound methodology in creating the protocol, including reaching an inter-rater reliability of $\kappa > .75$. Also, the protocol delivered consistent ratings across two separate control groups with different collection sites, different average age of the sample, different sex proportions, and different image acquisition parameters. This between-group consistency offers evidence for the external validity of SCRaP:aTB. Therefore, while it is possible that the protocol may not be capturing the exact same nuances contained within the Kim, et al. system, it is an equally valid and accurate method of classification, a fact that justifies its use in this study. Based on the methodology and statistical reliability of SCRaP:aTB, we can conclude that the ratings Reckess developed are detecting reliable distinctions in the patterns of connectivity among the three major anterior temporobasal sulci.

The rating process for the classification of the pattern type in this study involved independent raters (CBD and GZR, inter-rater reliability $\kappa > .75$) who were blind to patient demographics and diagnosis. The raters evaluated the entire sample of brains using the SCRaP:aTB. After this was completed, a series of consensus conferences were held to discuss and resolve any discrepancies that would affect the pattern classification for each hemisphere of each brain. Figure 2 shows examples of each of the four pattern types distinguished by SCRaP:aTB. It should be noted that Type 3 did not occur in the right hemisphere of any subject in the sample and occurred in the left hemisphere in only one individual. Because of this, the one instance of Type 3 was coded in analyses to be in the Type 4 group. Therefore subsequent analyses refer to only three connection types (collateral-rhinal, collateral-occipitotemporal, no connections).

Table 2-1. Demographic information

Age	35.8 ± 10.9 years
Education	12.9 ± 2.1 years
IQ	92.6 ± 16.3
Duration of epilepsy	22.3 ± 11.6 years

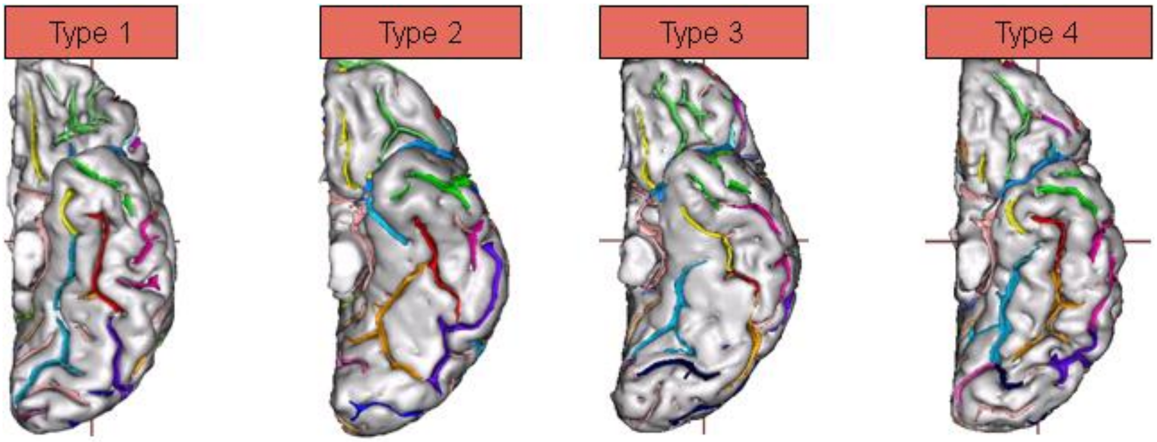

Figure 2-1. Examples of connection types from Sulcal Classification Rating Protocol: Anterior Temporobasal Sulci. Type 1 shows a connection between the yellow rhinal sulcus and the turquoise collateral sulcus in the absence of a connection with the red occipitotemporal sulcus. Type 2 shows a connection with the orange collateral sulcus and the red occipitotemporal sulcus in the absence of a connection with the turquoise rhinal sulcus. Type 3 shows a connection between the yellow rhinal sulcus and the red occipitotemporal sulcus in the absence of a connection with the turquoise collateral sulcus. Type 4 shows an absence of connection between any of the three anterior temporobasal sulci.

CHAPTER 3
RESULTS

Prediction 1

Groups were divided by presence versus absence of a collateral-rhinal connection. Due to (1) a positively skewed and leptokurtic distribution of age of onset for both right hemisphere groups and for the individuals without a collateral-rhinal connection in the left hemisphere and (2) a platykurtic distribution in individuals with a collateral-rhinal connection in the left hemisphere, nonparametric rank sum analysis was used. Interrater reliability for left hemisphere ratings was $\kappa = .76$ while kappa was .68 for right hemisphere ratings. There were 28 (36%) individuals with a collateral-rhinal connection in the left hemisphere versus 50 without and 36 (46%) with this connection in the right hemisphere versus 43 without. There were no significant differences in education, Full Scale IQ (Wechsler Adult Intelligence Scale-III), or duration of epilepsy between those with and without a left or right hemisphere collateral-rhinal connection (all $p > .05$). However, individuals with a collateral-rhinal connection in their right hemisphere had a significantly older age (38.5 $\pm$ 9.5 years) than those without a connection (32.6 $\pm$ 11.8 years) in the right hemisphere [$t(77) = 2.45$, $p = .02$]. Results indicated a significantly younger median age of epilepsy onset for individuals with a collateral-rhinal connection in the right hemisphere (99 months; 8 years 3 months) compared to those without (180 months; 15 years), ($Z = -1.800$, $p = .036$, $\eta^2 = .042$). This relationship was not significant in the left hemisphere ($p = .190$).

Prediction 2

To test the prediction that presence of a collateral-rhinal connection would be associated with a family history of neurologic disease, Pearson chi-squares were used.

A chi-square of the presence/absence of right hemisphere collateral-rhinal connection versus presence/absence of a family history of neurologic disorders revealed a chi-square of .521 with a 1-sided Fisher's exact p = .319. A chi-square of the presence/absence of left hemisphere collateral-rhinal connection versus presence/absence of a family history of neurologic disorders revealed a chi-square of .671 with a 1-sided Fisher's exact p = .287.

The analysis was then restricted to a family history of epilepsy. A chi-square divided by presence/absence of right hemisphere collateral-rhinal connection versus presence/absence of a family history of epilepsy revealed no significance (χ2 = .919, 1-sided Fisher's exact p = .253). A chi-square of left hemisphere collateral-rhinal connection and family history of epilepsy yielded similar results (χ2 = .000, 1-sided Fisher's exact p = .621).

Prediction 3

Chi-square was also used to test the prediction that collateral-rhinal connection would be associated with the presence of early adverse environmental events. A chi-square analysis of presence/absence of right hemisphere collateral-rhinal connection versus presence/absence of an adverse environmental event revealed no significance (χ^2 = .691, 1-sided Fisher's exact p = .278). A chi-square of left hemisphere collateral-rhinal connection and adverse environmental events yielded similar results (χ^2 = 1.479, 1-sided Fisher's exact p = .167).

Prediction 4

To test the prediction that individuals with a collateral-rhinal connection would perform more poorly on a test of item memory than individuals without a collateral-rhinal connection but would perform equally as well on a test of spatial memory, separate

ANCOVAs were conducted for each of three scores (Faces Immediate scaled score, Faces Delayed scaled score, and Spatial Span scaled score) in each of the two hemispheres (6 total analyses). The groups were divided by connection type such that there were three groups (collateral-rhinal connection, collateral-occipitotemporal connection, no connections between all three anterior temporobasal sulci). Full scale IQ from the WAIS-III (FSIQ) was used as a covariate based on significant, moderately-sized Pearson correlations between FSIQ and all three scores used ($r_{\text{FSIQ, Faces Imm.}} = .402$, $r_{\text{FSIQ, Faces Delay}} = .349$, $r_{\text{FSIQ, Spatial Span}} = .690$, all $p < .001$).

Lateralization of seizures was also considered as a possible covariate. 28 individuals did not have EEG lateralization data and were excluded from these preliminary analyses. One-way ANOVAs of lateralization of seizure effects on performance on the Faces Immediate and Delayed subtests failed to reach significance. Lateralization was therefore not included in subsequent Faces analyses and data from all 79 individuals were used. However, for performance on the Spatial Span subtest, the effect of lateralization of seizures was significant [$F(2,48)=3.285$, $p = .046$]. Significant group differences were found such that individuals with right hemisphere seizures performed significantly better than individuals with seizures originating from both hemispheres (Bonferroni corrected $p = .041$). Due to the significant association between Spatial Span performance and lateralization of seizures, two analyses in addition to the ones described above were planned involving the Spatial Span performance variable: 1. An ANCOVA using connection type in the right hemisphere as the independent variable and FSIQ and lateralization of seizures as the covariates with Spatial Span performance as the dependent variable. 2. An ANCOVA using connection type in the left hemisphere as the independent variable and FSIQ and lateralization of seizures as the covariates with Spatial Span performance as the dependent variable. These two analyses would exclude data from 28 individuals who did not have EEG lateralization data.

Helmert contrasts were planned for all analyses. In these contrasts individuals with a collateral-rhinal connection would be compared to all other subjects, followed by individuals with a collateral-occipitotemporal connection compared to individuals with no connections between the three anterior temporobasal sulci.

Results revealed no significant differences on any of the three measures for groups based on left hemisphere sulcal connectivity. However, for groups based on right hemisphere connectivity, significant differences were found [$F(2,79)=4.110$, $p = .02$) such that, on Faces Immediate and Faces Delay, individuals with a collateral-rhinal connection performed significantly lower than other individuals. No significant differences were found between the collateral-occipitotemporal connection group and the no-connection group. No significant differences were found on Spatial Span scores for groups based on sulcal morphology. This was also true based on the results of the analyses with the addition of the lateralization of seizures variable. Table 2 contains a summary of these analyses, while Figure 3 depicts the estimated marginal means for the groups based on right hemisphere sulcal connectivity using the analyses that included the entire sample.

Table 3-1. Summary of analysis of Wechsler Memory Scale subtest performance.

	WMS-III Subtest	Overall ANCOVA	CS-RS connected vs. others	CS-OTS connected vs. no connection	Partial Eta Squared
Right Hemisphere	*Faces Imm.*	*F(2,75)=3.138, p =.049	*p = .037	p = .359	.077
	Faces Delay	*F(2,75)=4.110, p = .02	**p =.006	p = .99	.099
	Spatial Span	F(2,75)=0.178, p = .838	p = .774	p = .574	
	Spatial Span+	F(2,41)=0.476, p = .625	p = .443	p = .486	
Left Hemisphere	*Faces Imm.*	F(2,74)=0.199, p = .82	p = .604	p = .78	
	Faces Delay	F(2,74)=1.738, p = .183	p = .075	p = .476	
	Spatial Span	F(2,74)=0.687, p =.501	p = .242	p = .913	
	Spatial Span+	F(2,40)=1.950, p = .156	p = .064	p =.323	

Summary of analysis of Wechsler Memory Scale subtest performance divided by hemisphere and subtest. The third column contains the F statistic of the main effect of sulcal morphology from the analysis of covariance and its significance. The fourth column contains the significance of the Helmert contrast comparing the individuals with a collateral-rhinal connection to individuals with any other connection type. The fifth column contains the significance of the Helmert contrast comparing individuals with a collateral-occipitotemporal connection to individuals with no connections between the three anterior temporobasal sulci.
WMS-III: Wechsler Memory Scale—Third Edition
ANCOVA: Analysis of covariance
CS: Collateral sulcus
RS: Rhinal sulcus
OTS: Occipitotemporal sulcus
+: These analyses included lateralization of seizure information and used a smaller sample.
*: $p < .05$
**: $p < .01$

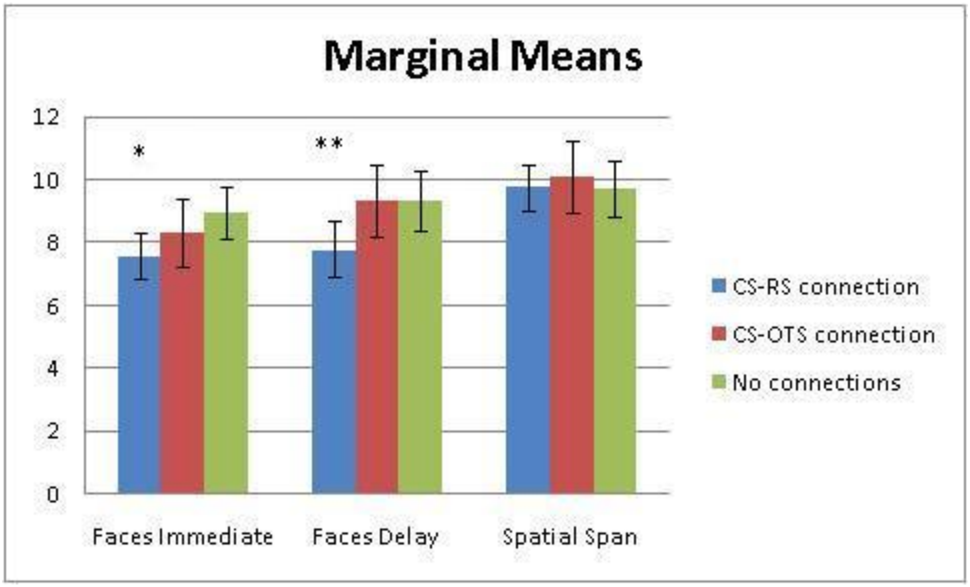

Figure 3-1. Estimated Marginal Means with Full Scale IQ as a covariate for right hemisphere sulcal morphology.

CS: Collateral sulcus
RS: Rhinal sulcus
OTS: Occipitotemporal sulcus
*: $p < .05$ for significant difference between collateral-rhinal connection performance compared to other two groups combined.
**: $p < .01$ for significant difference between collateral-rhinal connection performance compared to other two groups combined.

CHAPTER 4
DISCUSSION

The results of the above analyses lead to several findings: a collateral-rhinal connection in the right hemisphere of temporal lobe epilepsy patients was related to a younger age of disease onset; a collateral-rhinal connection in temporal lobe epilepsy patients was not significantly associated with a family history of neurologic disease or with a family history of epilepsy; a collateral-rhinal connection was not significantly associated with a history of an early adverse environmental event; and a collateral-rhinal connection in the right hemisphere was related to poorer performance on a test of item memory but not to performance on a test of spatial memory.

The younger age of epilepsy onset associated with the collateral-rhinal connection in the right hemisphere supports the theory that presence of a collateral-rhinal connection may be a neurodevelopmental risk factor for the development of neurological disease. The balance between genetic and environmental factors in the development of disease was not elucidated in this study as there was no association between the possible indicator of abnormal neurodevelopment and a family history of disease or the presence of adverse environmental factors. The lack of significant associations may have been due to the reliance on retrospective reports of pre- and perinatal factors by the epilepsy patients, without outside validation of these reports directly from the medical record. It is also likely that an interaction between genetic, epigenetic, and environmental factors is the cause of the development of disease, so it is not surprising that simple associations were not found.

Due to the retrospective nature of this study, it is impossible to determine a cause-and-effect relationship between gross sulcal morphology and the onset of epilepsy. It may be that a collateral-rhinal connection conveys vulnerability to the development of the disease, as Kim, et al. suggested. However, it is also possible that the connection developed as a result of disease processes or some other factor early in development. A prospective study or a sample with pre- and post-onset-of-epilepsy brain images would be necessary to explore the causality of this relationship.

The finding that a collateral-rhinal connection in the right hemisphere was related to poorer performance on a test of item memory but not spatial memory is consistent with recent findings from anatomical and neuroimaging studies, and lends support to the idea that distinctions between item memory and spatial memory are useful (Eichenbaum & Lipton, 2008).The position of the collateral and rhinal sulci adjacent to the perirhinal and lateral entorhinal cortices allows their morphology to affect the morphology of these cortical areas and their interconnections. The perirhinal and lateral entorhinal cortices have been implicated in the processing of unimodal representations of remembered items (Suzuki & Eichenbaum, 2000) as well as familiarity or recognition of stimuli without recollection of stimulus associations (Eichenbaum et al., 2007). The type of stimuli presented in the Faces subtest of the WMS-III (Wechsler, 1997b) is unimodal (visual) and stimuli have no identifying information or associations other than any memory strategies that the patient may use to remember the faces. The contextual pathway processes information involving complex relationships between items and their context and utilizes projections to the parahippocampal cortex followed by the medial entorhinal area before entering the hippocampus (Eichenbaum & Lipton, 2008). These areas are further from the location where the connection between the collateral and rhinal sulci would be taking place than the entorhinal and perirhinal cortices are. The poorer performance of TLE patients with a collateral-rhinal connection in the right hemisphere indicates that this connection in the right hemisphere may adversely affect the functioning of the item memory pathway in the medial temporal lobe system while not significantly affecting the contextual memory pathway compared to TLE patients without a collateral-rhinal connection.

However, the Faces and Spatial Span subtests of the WMS-III are certainly not process pure measures of item and spatial memory. It is possible that other cognitive processes that are measured by these tasks could be confounded in this study. Also, considering the small effect sizes for the significant ANOVAs involving Faces Immediate (partial $\eta 2 = .077$) and Faces Delayed (partial $\eta 2 = .099$) as well as the standard error of measurement associated with these subtests (Faces Immediate = 1.44 scaled score; Faces Delay = 1.43 scaled score; Wechsler, 1997b), it is unclear if the statistically significant differences found in this study have clinical significance.

Future directions of study may include using experimental measures or more process-pure tasks to test performance of item memory versus spatial memory in groups based on sulcal connection patterns in TLE patients or other patient populations and controls. Extending the SCRaP:aTB rating system into other patient populations would provide further validation of this protocol and allow for comparisons of anterior temporobasal sulcal patterns to be made across patient populations using a standardized protocol.

This study explored gross sulcal morphology, clinical variables and neuropsychological performance in a large sample of temporal lobe epilepsy patients. Morphological ratings were based on a reliable protocol. Younger age of onset of epilepsy and poorer performance on a test of item memory were associated with a collateral-rhinal connection in the right hemisphere of temporal lobe epilepsy patients. These findings support the idea that a collateral-rhinal connection may be an indication of abnormal neurodevelopment that adversely affects the item memory pathway of the medial temporal lobe memory system.

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BIOGRAPHICAL SKETCH

Callie Jo Beck Dunn was born in 1985 in Burley, Idaho. The fifth of six children, Callie grew up in this quiet town until she graduated from Burley High School in May 2003 as one of its valedictorians. She then continued her education, enrolling in Brigham Young University (BYU) in June of 2003. As a freshman she began research with Dr. Ramona Hopkins at BYU and gained valuable experience in the utility of neuropsychology in a hospital setting. After putting her academic development on hold for 18 months to serve a religious mission to New Caledonia with the Church of Jesus Christ of Latter-day Saints, Callie graduated summa cum laude from BYU with a B.S. in psychology in August 2009 as the department valedictorian. She then began her graduate studies in the Department of Clinical and Health Psychology at the University of Florida in August 2009 working under the mentorship of Dr. Russell Bauer. In November of 2009, she met her future husband, Christopher Dunn. Callie and Chris were married two weeks after the defense of this thesis.