TEMPOROBASAL SULCAL MORPHOLOGY: CONFIGURAL PATTERNS AND NEUROCOGNITIVE RELEVANCE IN HEALTHY ADULTS AND PATIENTS WITH TEMPORAL LOBE EPILEPSY

By

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In loving memory of my great-uncle Mietek, who was killed by the Nazis and never had the luxury of pursuing his doctoral dreams.

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LIST OF ABBREVIATIONS

CS	Collateral Sulcus
LH	Left Hemisphere
MRI	Magnetic Resonance Image
MTL	Medial Temporal Lobe
OTS	Occipitotemporal Sulcus
oRS	Ono's Rhinal Sulcus (definition of the rhinal sulcus used by Ono et al. (1990))
RH	Right Hemisphere
SCRaP:aTB	Sulcus Classification Rating Protocol: anterior Temporobasal Sulci
RS	Rhinal Sulcus
TLE	Temporal Lobe Epilepsy
UF/UCR	Control group whose data were collected through a collaboration between the University of Florida and the University of California-Riverside
UW-C	Control group whose data were collected at the University of Wisconsin-Madison
UW-TLE	Patient group (temporal lobe epilepsy) whose data were collected at the University of Wisconsin-Madison

Abstract of Dissertation Presented to the Graduate School
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Major: Psychology

We evaluated the presence of connections between the collateral (CS), rhinal (RS), and occipitotemporal (OTS) sulci in healthy adults and individuals with temporal lobe epilepsy (TLE). These anterior temporobasal (aTB) sulci contribute to the morphology of memory-related structures and are landmarks for neuroimaging analyses. To our knowledge the only direct comparison of aTB sulcal connections in healthy adults and TLE patients (Kim et al., 2008) found dramatic overrepresentation of CS-RS connections in TLE. However, these data are not consistent with the most referenced normative study of sulcal prevalence (Ono et al., 1990) or with another study that reported aTB sulcal connectivity in TLE patients (Novak et al., 2002). This discrepancy may be due to methodological differences.

The following series of studies has four main outcomes: (1) We developed a reliable rating protocol (including training materials and rating forms) for identification of the three aTB sulci and their interconnections. Notably, the final version of the protocol differentiated between "true" and "pseudo" (e.g., shallow, perforated or otherwise ambiguous) connections. (2) We characterized the frequencies of four sulcal pattern types in a sample of 200 healthy undergraduate students. Our results largely replicated Kim et al. (2008) when both true- and

pseudo- connections were counted as “connections”; when only true connections were counted, our results were consistent with Ono et al. (1990), suggesting a possible explanation for the discrepancy between these two studies. (3) We characterized the frequency of sulcal pattern types in 79 TLE patients and 70 age-matched controls. We did not find significant group differences consistent with those reported by Kim et al. regardless of whether pseudoconnections were included. However, our findings are consistent with Novak et al. (2002) when pseudoconnections were excluded. (4) We tested the prediction that presence of a CS-RS connection would be associated with worse performance on tests of free recall. Although we did not find an overall effect, we successfully demonstrated that patients with a CS-RS connection in the right hemisphere displayed worse visual memory than patients without this connection. To our knowledge this is the first demonstration of a relationship between aTB sulcal morphology and cognition.

CHAPTER 1
BACKGROUND

Introduction

The surface of the human cortex is convoluted with folds, called sulci (singular = sulcus). Although some global features of cortical folding are consistent across humans, there is tremendous inter-individual variability and some inter-hemispheric variability (Ono, Kubik, & Abernathey, 1990; Paus, et al., 1996). Morphometric features such as sulcal width and depth at least partially reflect developmental changes (e.g., cortical atrophy) over time such as occurs during aging and disease (Kochunov, et al., 2005). In contrast, gross morphologic factors such as shape and connections with neighboring sulci are more likely associated with initial cortical development and organization (Dubois, et al., 2008; Ono, et al., 1990; Sowell, et al., 2002).

The two studies described here focus on morphology by examining inter-sulcal connections and their significance for pathology and cognition. Our overall goal was to characterize the frequency of connections between three sulci on the ventral surface of the temporal lobe in healthy individuals and in adults with temporal lobe epilepsy (TLE). The following background reviews the literature that forms the basis of the current investigation. This includes: (a) research on sulcal variability as it relates to clinical disorders, demographic factors, and neurocognition, and (b) research specific to the three sulci of interest, collectively known as anterior temporobasal (aTB) sulci. Following this review, the rationale for use of TLE as a model for investigating temporobasal sulcal morphology is presented and defended.

Sulcal Morphology

The precise nature of morphologic variability, its underlying causes, and its functional consequences are not yet known. Sulcal development begins during gestation and continues through the first year of life (Ono, et al., 1990). Some have postulated that sulcal morphology is

a result of other developmental processes, including axonal sprouting and/or synapse formation (Armstrong, Schleicher, Omran, Curtis, & Zilles, 1995; Nakamura, et al., 2007; Rakic, 1988) or tension between myelinated fibers (Van Essen & Drury, 1997). Genetics contributes (Kippenhan, et al., 2005; Lohmann, von Cramon, & Steinmetz, 1999; Rakic, 2004) but does not appear to be the sole determinant (Bartley, Jones, & Weinberger, 1997), and intra-uterine environment may play a critical role (Dubois, et al., 2008). Evidence also suggests that sulcal development and maturation continue into adolescence and early adulthood, including increased asymmetry in the location of the sylvian fissure (Sowell, et al., 2002). Sulcal development therefore may be affected by environment and experience, as has been demonstrated for white matter connectivity throughout the nervous system since the classic research on ocular deprivation by Hubel and Wiesel (1977). Potential interactions between genetic, epigenetic, and environmental factors also may explain why some sulcal patterns are more prevalent in clinical populations (Dubois, et al., 2008; Eckert, et al., 2006; Fornito, Whittle, et al., 2006; Fornito, et al., 2004; Hiemenz & Hynd, 2000; Kikinis, et al., 1994; Kippenhan, et al., 2005). Characterization of sulcal patterns and variability therefore may provide insight into risk factors and etiology of neurological and/or psychiatric disorders.

Functional correlates of sulcal morphology have been less extensively studied than other neuroanatomic measures, such as regional or whole brain volume. However, there is a small collection of research studies demonstrating group differences in sulcal patterns, and these differences may have functional implications. One of the most extensively studied sulci is the paracingulate (PCS), which is located dorsal to the cingulate cortex. This sulcus is present in only about 30-60% of individuals (Paus, et al., 1996; Yucel, et al., 2001), and its presence is associated with structural features of surrounding cortex, including variations in cytoarchitecture

(Vogt, Nimchinsky, Vogt, & Hof, 1995), regional volume (Fornito, Whittle, et al., 2006; Paus, et al., 1996) and cortical thickness (Fornito, et al., 2008). For example, Fornito et al. demonstrated that presence of the PCS is associated with a significant increase in the volume of the paracingulate cortex and a corresponding decrease of cingulate cortex volume. PCS presence is often asymmetric between cortical hemispheres such that it is present in one hemisphere and absent or less prominent in the other (Huster, Westerhausen, Kreuder, Schweiger, & Wittling, 2007; Yucel, et al., 2001). Frequency of asymmetry differs between men and women, but the precise nature of these relationships remains controversial (Wallentin, 2009), which may be due in part to methodological differences(Leonard, Towler, Welcome, & Chiarello, 2009). For example, there is some evidence of greater leftward asymmetry in men (Huster, et al., 2007; Yucel, et al., 2001) and other evidence of greater asymmetry in women (Leonard, et al., 2009). Regarding clinical populations, adults with schizophrenia are significantly less likely than controls to have a prominent left PCS (Yucel, et al., 2001).

PCS prominence may have functional relevance as well. For example, individuals with asymmetric PCS prominence favoring the left hemisphere demonstrate better spatial working memory and verbal fluency than those with symmetric or rightward asymmetric PCS prominence (Fornito, et al., 2004), and this finding held true both in healthy adults and in individuals with schizophrenia (Fornito, Yucel, et al., 2006). The authors argue that these associations are specific to frontally mediated functions because leftward PCS asymmetry did not confer any benefit on a verbal test of associative learning. Several functional imaging studies also have identified differences in functional activation patterns associated with PCS presence versus absence. For example, Crosson et al. (1999) found that the neighboring cingulate sulcus was consistently active during a word generation task only in the absence of a prominent PCS. Similarly, Artiges

et al. (2006) found that anterior cingulate cortex activation during a priming task differed depending on PCS presence or absence such that presence was associated with left anterior cingulate activity whereas absence was associated with right-sided activity. In contrast, activation was bilateral in patients with schizophrenia with an absent PCS.

Unlike the PCS, the three orbitofrontal sulci on the ventral surface of the frontal lobe are visible in almost all brains, but the patterns of connections among them is variable. Chiavaras and Petrides (2000) defined three distinct patterns of connections. In 50 healthy adults, they found that Type I (characterized by a connection between the transverse and lateral orbital sulci and an unconnected medial orbital sulcus) was the most common pattern and was present in 56% of hemispheres, whereas Type III (absence of connections among any of the three sulci) was the least prevalent, found in only 14% of hemispheres. Additionally, patterns II and III were disproportionately represented in the left hemisphere. Using this same classification system, Nakamura et al. (2007) replicated the relative frequency of the three patterns in a second sample of 50 healthy adults and reported the same pattern of hemispheric asymmetry. Notably, Nakamura's group successfully replicated the findings of Chiavaras et al. (2000) despite significant differences in the mean age of their groups (41 vs 25 years old, respectively). This supports the assumption that sulcal patterns, once established, remain stable during adulthood.

Nakamura et al. (2007) also evaluated orbitofrontal sulcal patterns in adults with schizophrenia and found the opposite distribution pattern as in the healthy controls: Type III was the most frequent pattern in this population, and was twice as prevalent as in the control group; conversely, Type I was the least frequent. These patterns also had apparent functional correlates. In the patient group, presence of a Type I pattern in either hemisphere was associated with better cognitive performance (e.g., higher scores on the WAIS-III Perceptual Organization Index)

whereas Type III was associated with worse performance (e.g., lower scores on the WAIS-III Verbal Comprehension Index). Notably, this general pattern of structure-function relationships was not found in the control group. Rather, Type III was associated with higher IQ and working memory in healthy adults.

Temporobasal Sulci

The current study examined the three primary sulci on the anterior, basal surface of the temporal lobe, collectively called anterior temporobasal (aTB) sulci. These are the collateral sulcus (CS), rhinal sulcus (RS) and occipitotemporal sulcus (OTS; sometimes referred to as the inferior temporal sulcus; (Ono, et al., 1990). Figure 1-1 presents a sample surface rendering of the temporobasal region and a brief description of neuroanatomic landmarks.

The three primary temporobasal sulci contribute to the surface morphology of the medial temporal lobe (MTL), which is strongly implicated in learning and memory (Squire, Stark, & Clark, 2004; Squire & Zola-Morgan, 1991; Suzuki & Amaral, 2004; Van Hoesen, 1995). MTL dysfunction has been linked to an "uncanny number" of disorders (Van Hoesen, 1995), including neurodegenerative (e.g., Alzheimer's, Huntington's, and Parkinson's diseases), neurodevelopmental (e.g., autism and Down's syndrome), and neuropsychiatric (e.g., panic, PTSD, and schizophrenia) disorders. Although the hippocampus initially received the most scientific attention, more recent research suggests that structures within the neighboring parahippocampal gyrus are also critical components of the MTL memory system (Eichenbaum, Yonelinas, & Ranganath, 2007; Insausti, Insausti, Sobreviela, Salinas, & Martinez-Penuela, 1998; Suzuki & Amaral, 2004), and their dysfunction may in fact precede hippocampal pathology in some disorders (Braak & Braak, 1995). Careful characterization of MTL anatomy, physiology, and function is therefore of great clinical import, and understanding the functional role of sulcal variability should be a key part of that effort.

It is reasonable to expect that configurations of and connections between temporobasal sulci may affect the size, location and shape of surrounding structures, and there is some evidence of such a relationship (Taylor & Probst, 2008). With respect to the collateral sulcus in particular, Pruessner et al. (2002) acknowledged that variations in the CS including connections with nearby sulci would likely "have a significant impact on the volume of the structures surrounding [it]." They therefore developed an extension of the widely used protocol by Insausti et al. (1998) that corrects for CS variability in measuring the volume of nearby cortical structures, including the entorhinal, perirhinal, and parahippocampal cortices. This was a valuable and timely methodological contribution: Increased interest in the parahippocampal gyrus has inspired a surge of imaging research, which is confounded by the number of different measurement protocols and reliance upon sulci as boundary landmarks for cortical structures. However, Pruessner and colleagues only indirectly addressed the functional relevance of sulcal patterns. That is, they proposed a way of *correcting* for sulcal variability, but they did not evaluate whether that variability itself has functional significance.

Temporal Lobe Epilepsy: A Model Population for Sulcal Research

Given the limited information on the functional correlates of temporobasal sulcal patterns, it is difficult to draw inferences about the effect of these patterns on risk for or development of temporal lobe disorders. Temporal lobe epilepsy (TLE) is ideally suited as a model through which to address this research question for several reasons, including (a) the nature of TLE and its associated neuropathology and risk factors; (b) potential clinical implications; and (c) accessibility of the population.

Regarding the nature of TLE, there are several characteristic features that are potentially relevant for sulcal research. First, earlier onset is associated with poor cognitive development (Hermann, Hansen, Seidenberg, Magnotta, & O'Leary, 2003; Hermann & Seidenberg, 2002),

worse clinical outcome (Pittau, et al., 2009), and white matter abnormalities (Hermann & Seidenberg, 2002). Additionally, brain-related trauma (e.g., infection or injury) during the pre-, peri-, or post-natal periods is a risk factor for later development of TLE (French, et al., 1993). The time-frame of initial temporal lobe seizure onset is therefore more likely to coincide with a period of sulcal development than is the case in some other temporal lobe disorders, such as Alzheimer's disease or acquired forms of amnesia.

The nature of the physiological underpinnings of TLE also is suggestive of a potential link with sulcal development. TLE is characterized by episodes of abnormal neuroelectrical activity originating in and propagated by white matter fibers in the temporal lobe. Onset of TLE during childhood has been shown to have neurodevelopmental effects on white matter development (Hermann & Seidenberg, 2002), which may be reflected in sulcal development. For example, continuity between the CS and RS no doubt affects the possible trajectory of fiber tracts extending from and to the parahippocampal gyrus.

TLE is also an ideal population because of the continued clinical need for advances in scientific research, particularly with respect to prediction of disease onset, severity, and response to treatment. Epilepsy onset is sometimes preceded by any of a number of risk factors, including febrile seizures, infections that affect the nervous system (e.g., encephalitis), and traumatic brain injury. For example, early febrile seizures have been linked to developmental hippocampal abnormalities, which in turn increase future susceptibility to seizures (Fernandez, et al., 1998; Lewis, et al., 2002). However, these events do not always lead to development of epilepsy, and there is often a latency period of several years between the initial incident and onset of spontaneous, recurring seizures (Mathern, Babb, Vickrey, Melendez, & Pretorius, 1995). To date, there are no effective clinical approaches to predict – let alone prevent – which patients will

eventually develop epilepsy after a stress-inducing precipitating event. Because of the links between sulcal morphology and early development, it is conceivable that specific temporobasal sulcal patterns may directly confer additional risk of developing epilepsy or may have an indirect effect by increasing vulnerability to risk factors such as infection.

Outcome prediction is another area of active clinical research to which sulcal morphology may be relevant. Cognitive deficits in TLE are variable and influenced by a combination of factors, and it remains difficult to predict progression of cognitive decline and cognitive outcome following treatment (Elger, Helmstaedter, & Kurthen, 2004; Helmstaedter & Kockelmann, 2006). Clinical response to treatment is similarly difficult to predict. Although some forms of epilepsy are effectively managed with anti-epileptic medication, TLE is often – but not always – resistant to pharmacological intervention (Engel, 1994; Kwan & Brodie, 2000). However, it is expensive and potentially invasive to conduct the tests necessary to confirm that a patient's seizures are focal in origin and are specifically localized to the temporal lobe. Surgical intervention is therefore often seen as a last resort in light of potential morbidity, and patients typically undergo years of pharmacotherapy before being considered for surgery (Lachhwani & Luders, 2003). Unfortunately, uncontrolled seizures may lead to further structural damage or neurocognitive impairment and can have deleterious psychosocial effects (Vingerhoets, 2006). Conversely, surgery is not an ideal option for all patients, and may in fact lead to significant cognitive decline in some cases (Helmstaedter, 2004). It is therefore essential to continue research that may improve treatment planning and outcome prediction, including careful examination of clinical and functional correlates of neuroanatomic variability.

Finally, TLE is among the most extensively researched temporal lobe disorders, in part due to its prevalence and accessibility (Seidenberg, Pulsipher, & Hermann, 2007). According to the

Epilepsy Foundation, epilepsy is the third most prevalent neurological disorder in the United States. TLE is among the more common types of seizure disorders. Because of its focal nature, its association with cognitive morbidity, and its poor responsiveness to anti-epileptic medication, TLE is also the seizure disorder most commonly treated with surgery (Helmstaedter, 2004). TLE patients are therefore well represented in most research-oriented comprehensive epilepsy centers. This, combined with the mostly focal nature of TLE-related cortical atrophy (particularly in individuals with mesial TLE), has stimulated an abundance of research on the pathophysiology of the disease and on structure-function relationships in the temporal lobe. Therefore, there are already several well-validated measures of structure and function in this population that could serve as criteria against which sulcal morphology could be evaluated; conversely, sulcal characterization in TLE also has the potential to enhance future research in this active, productive field.

Summary

The literature review above suggests that (a) sulcal morphology is of potential clinical and neurocognitive relevance; (b) anterior temporobasal (aTB) sulci are of particular interest for research on memory and memory-related disorders; and (c) TLE is well suited for research on aTB sulcal morphology. Very few studies have evaluated temporobasal sulcal patterns in healthy adults and/or in patients with TLE, and comparisons between studies are complicated by the use of different approaches for sulcal identification and pattern classification. The overall goal of the current study was to replicate and extend the findings of one of these investigations (Kim et al., 2008). This was accomplished in two parts: Study 1 sought to clarify the methods used by Kim et al. and establish normative data for classification of the four temporobasal configural patterns. Study 2 was designed to replicate the clinically relevant findings in Kim et al. using a different

population of TLE patients and age-matched controls, and to extend these findings by providing new data on the relationship between sulcal pattern and neurocognition.

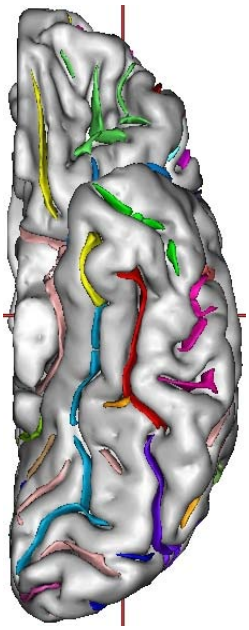

Figure 1-1. Sample rendering of the temporobasal surface, with CS (turquoise), RS (yellow) and OTS (red) labeled by BrainVISA. Generally speaking, the CS (turquoise) runs parallel to the medial edge of the temporal lobe, with its anterior end approximately level with the pons. The RS (yellow) extends anterior to the pons and sometimes appears to be continuous with the CS, as depicted in this sample. The OTS (red) is located lateral to the CS and RS and is often parallel to the CS. Its configuration is the most variable of the three sulci. (Ono, et al., 1990)

CHAPTER 2
STUDY 1

Statement of the Problem

Methodological Challenges in Sulcal Identification and Classification

Methodological consistency is critical for comparing and extending published findings; sulcal research is no exception. For example, differences in methodology are thought to be responsible for differences in reported PCS frequency (Paus, et al., 1996) and for the ongoing controversy about sex differences in PCS asymmetry (Leonard, Towler, Welcome, & Chiarello, under review; Wallentin, 2009). Methods used to identify and classify temporobasal sulci are even more inconsistent than for the PCS, as are published data. A consistent, reliable, easily replicated method of temporobasal sulcal identification and classification is therefore needed.

To our knowledge only four published studies include data regarding the frequency of connections between any of the aTB sulci in healthy adults (Kim, Bernasconi, Bernhardt, Colliot, & Bernasconi, 2008; Novak, et al., 2002; Ono, et al., 1990; Zhan, et al., 2009). All four report the proportion of hemispheres with a CS-RS connection, but only two (Kim et al.; Ono et al.) also evaluate connections with the OTS. Moreover, results differ across studies with respect to the frequency of CS-RS connections, ranging from 28% (Ono et al., 1990) to 53% (Zhan et al., 2009). Such discrepancies may reflect methodological differences in the identification and classification of connections.

The classification scheme proposed by Kim et al. (2008) was chosen as the basis for the current study for several reasons: (1) it is one of the only studies that presents data for connections between all three aTB sulci; (2) it is based on the methods described by Ono et al. (1990), and appears to be a refined, updated extension of that seminal publication; (3) like the current study, Kim and colleagues derived their ratings from cortical surface renderings

generated from serial magnetic resonance images, whereas Ono et al. conducted post-mortem analysis; (4) the authors focus on the anterior region of the temporobasal surface, which is the most relevant for medial temporal lobe morphology and pathology; and (5) the authors used the same rating scheme to compare sulcal connections in both healthy adults and individuals with TLE.

The rating system developed by Kim et al. includes classification of each hemisphere into one of the following four subtypes (Figure 2-1) (1) CS-RS connection, (2) 2: CS-OTS connection; No RS connections, (3) OTS-RS connection; No CS connections, (4) No connections

Though arguably the most comprehensive rating system currently available, Kim et al provide little in the way of specific methodological detail, which complicates direct replication. First, to identify the sulci of interest Kim et al. used automated sulcal extraction and labeling via a public-domain software platform called BrainVISA (http://brainvisa.info/). However, BrainVISA's sulcal recognition protocol has an overall recognition rate of about 76% (Riviere, et al., 2002), and Kim et al. do not provide guidelines for visual verification.

Second, BrainVISA does not generate explicit data on connections between sulci. Therefore, human raters must visually classify inter-sulcal relationships and configural patterns. Guidelines for pattern identification are extremely limited, and most studies (including Kim et al. (2008)) simply refer to *The Atlas of the Cerebral Sulci* (Ono et al., 1990). This atlas is a seminal publication and the most widely referenced source for sulcal morphology. While it remains a useful reference, it is cumbersome and flawed when relied upon for training raters on a classification scheme that requires in-depth familiarity with select sulcal features. For example, the Atlas is based on only 25 brains and may not capture the full spectrum of variability in

healthy adults. This is evident in the limited number of visual examples, of which there is, on average, only one per sulcal feature. Moreover, these visual examples are small, two-dimensional, black and white photographs, which makes it difficult to observe anatomic subtleties. The Atlas also is based on observations of fixed, post-mortem brains, which raises questions about generalizability to *in vivo* ratings.

With respect to connections between temporobasal sulci, the Atlas is inconsistent at times: For example, some sulcal relationships are represented in multiple sections, often with conflicting prevalence values, and some prevalence statistics add up to far less than 100%. Additionally, the classification schemes published in the literature do not clearly map onto those presented in the Atlas. For example, the pattern groupings described by Kim et al. (2008) are increasingly exclusive. In other words, Type 1 includes all cases with a CS-RS connection, regardless of other sulcal relationships, whereas Type 2 is characterized by a connection between the CS and OTS in the absence of a CS-RS connection, and Type 3 is defined by presence of an RS-OTS connection in the absence of a CS-RS or CS-OTS connection. In contrast, Ono et al. (1990) present the prevalence of each connection separately without mutual exclusivity, such that the prevalence of CS-OTS and RS-OTS connections presumably includes those with and without additional aTB connections.

Normative Data

Due to methodological limitations described in detail above, there are no adequate normative data available to facilitate comparisons with clinical populations. Prevalence of CS-RS connections has been characterized by several groups but with inconsistent results: Reported frequencies range from 28-53% for the left hemisphere and 28-41% for the right hemisphere. Moreover, prevalence of connections with the OTS cannot be compared across studies due to methodological inconsistencies (preceding section). We therefore used findings from Kim et al.

(2008) for comparison. In a sample of 51 healthy adults, Kim's group found an unequal distribution of pattern type (effect size = .59) in each hemisphere: Type 1 was most frequent (RH: 41%; LH: 47%), followed by Type 2 (RH: 35%; LH: 31%), Type 4 (RH: 20%; LH: 16%) and Type 3 (RH: 4%; LH: 6%). The distribution of types was similar in each hemisphere and the majority (82%) of participants had the same sulcal pattern in both hemispheres. There were no differences between men and women.

Aims and Predictions

The overarching goal of Study 1 was to characterize the frequency of temporobasal sulcal patterns in healthy adults using a reliable rating protocol.

Aim 1.1: Development of a Reliable Protocol for Temporobasal Sulcal Identification and Pattern Classification

The first aim of this study was to develop a reliable method for visual identification of the three primary temporobasal sulci (CS, RS, and OTS) and their inter-connections. Reliability was defined as $\kappa \geq .75$.

Aim 1.2: Temporobasal Sulcal Patterns in Healthy Adults

Aim 1.2 sought to characterize the frequency of connections between all three aTB sulci in a large sample of healthy adults using the protocol developed in Aim 1.1. Because this protocol is based on sulcal pattern types defined by Kim et al. (2008), we predicted that results would replicate the authors' key findings in their healthy control group such that:

- The four pattern types would not be equally represented; rather, Type 1 would be most prevalent, followed by Type 2, Type 4, and Type 3, respectively. In other words, the rank order of prevalence from highest to lowest would be 1-2-4-3.
- The distribution of pattern types would be similar for men and women.
- The majority ($\geq$ 75%) of participants would have the same configural pattern in both hemispheres.

Methods

Magnetic resonance images (MRIs) and demographic data for Study 1 were initially collected as part of a prior research study led by Christiana M. Leonard, Ph.D., Emeritus Professor of Neuroscience at the University of Florida, in collaboration with the University of California – Riverside. To facilitate discussion, this sample will be referred to as "UF/UCR." Information about study participants, image acquisition, and image pre-processing is based on Chiarello et al. (2008) and Leonard et al. (2008).

Participants

The initial sample included 100 male and 100 female undergraduate students from the University of California – Riverside, yielding 200 samples of each brain hemisphere. However, 10 hemispheres (4 right hemispheres, 6 left hemispheres) were omitted from analyses due to errors during image processing. The current study therefore included 196 right hemispheres (99 males, 97 females) and 194 left hemispheres (99 males, 95 females). This sample size easily exceeds the required sample size of 32 (power = .80) projected by G*Power based on Kim et al. (2008). All participants provided informed consent prior to enrolling in the study. Participants were native English speakers with normal or corrected-to-normal vision and did not have a reported history of brain injury, disease or contraindications for MRI. Participants' mean age was 21.6 years old (*SD* = 3.5).

Image Acquisition: Magnetic Resonance Imaging (MRI)

Structural magnetic resonance images were obtained on a 1.5 Tesla GE scanner. Images were reviewed for neuropathology by a neuroradiologist (Ronald Otto, M.D., Computerized Diagnostic Imaging Center, Riverside, CA), transferred to compact discs, and then sent to the University of Florida. Image preprocessing was performed using FSL scripts (http://www.fmrib.ox.ac.uk/; (Smith, et al., 2004). Extraction of the brain parenchyma from scalp

and skull was performed with BET (Smith, 2002) before registration (FLIRT; (Jenkinson & Smith, 2001) to a 1 mm isovoxel study-specific template image aligned into the Talairach planes. No warping was performed.

Automated Sulcal Identification and Labeling

Each brain hemisphere was individually processed with BrainVISA, a public-domain brain image analysis software platform that allows for three-dimensional reconstruction of the brain surface using serial MRI scans (Riviere, et al., 2002). Within BrainVISA, a specialized toolbox automatically recognizes and labels most cortical sulci (developed by the Laboratoire de Neuroimagerie Assistée par Ordinateur (LNAO): Neurospin, Life Science Division). After extraction of sulcal folds, the program uses a congregation of neural networks trained to identify and automatically color-label cortical sulci by maximizing similarity of sulcal features and relations. The result is a surface rendering of each hemisphere, with sulci filled in using a designated color.

Variables of Interest

The primary anatomic variable in all analyses was sulcal pattern type, which included the 4 Types proposed by Kim et al. (2008; Figure 2-1). Left and right hemispheres were analyzed separately to avoid artificially inflating power. Participants with the same sulcal pattern in the right and left hemisphere were classified as "symmetric"; those with different pattern types in each hemisphere were classified as "asymmetric."

Procedures

Aim 1.1: Development of a Reliable Protocol for Temporobasal Sulcal Identification and Configural Pattern Classification

Images from the UF/UCR sample were used in the development of a reliable rating protocol called the "Sulcal Classification Rating Protocol: anterior Temporobasal Sulci"

(SCRaP:aTB), which included a training manual (Appendix A) and an accompanying Excel-based tracking log (Appendix B).

Initial rating criteria and training materials were developed based on a careful review of measurement conventions available in the published literature (Ono, et al., 1990; Pruessner, et al., 2002; Wen, Rhoton, & Marino, 2006) and in consultation with Christiana Leonard, PhD, who has extensive knowledge and experience in measurement of gross cerebral morphology. Subsequent modifications were based on analysis of discrepant ratings and discussion amongst raters regarding: (a) sources of confusion about criteria described in training materials; (b) validity of criteria in training materials; and (c) recommended changes for the tracking log (i.e., addition or removal of variables to be recorded). As part of this process, post-mortem brains and structural MRIs were reviewed to supplement surface renderings from BrainVISA. During all stages of development, raters were blind to each participants' sex, age, and group, and ratings were accomplished independently without prior knowledge of other raters' responses.

Four raters participated at different levels of the development process:

1. Gila Z Reckess (GR), MS, Principal Investigator and primary protocol developer; "expert rater" for all rounds of protocol development and testing.
2. Christiana Leonard (CL), PhD, neuroanatomist and protocol development consultant; "expert rater" for Round 1.
3. Jordan Robson (JR), undergraduate research assistant; "naïve" rater for Round 1.
4. Callie Beck (CB), BS, graduate research assistant; secondary rater for Rounds 2-4.

The rating protocol was tested and modified until the predetermined criterion value of inter-rater reliability ($\kappa \geq .75$) was achieved for the composite pattern rating. Percent agreement also was evaluated for each individual rating category to assist in identifying areas of weakness during each step of development. After reliability was established in a subset of the sample, GR and CB completed ratings on the full dataset to verify stability of inter-rater reliability.

Aim 1.2: Temporobasal Sulcal Patterns in Healthy Adults

The final SCRaP:aTB protocol developed in Aim 1.1 (above) was used to generate ratings for the full UF/UCR samples. A consensus meeting was convened to finalize those ratings deemed discordant during reliability analysis in Aim 1.1. Additionally, presence or absence of hemispheric symmetry was determined for each individual.

Results

Aim 1.1: Development of a Reliable Protocol for Temporobasal Sulcal Identification and Configural Pattern Classification

Protocol development: Kappa coefficients for each round of development are presented in Table 2-1. The criterion value for inter-rater reliability ($\kappa \geq .75$) for pattern classification was achieved on the 4th round of protocol development. For the left hemisphere ($N = 25$), reliability was .75. For the right hemisphere ($N = 25$), one rating level (Type 3) was used only once by one rater and was not used by the second rater. Therefore, an exact Kappa coefficient could not be calculated. When estimated by dropping the problematic rating, reliability was .79; when estimated by adding a "fake" participant weighted at .00001, reliability was .74. For the full UF/UCR sample, Cohen's Kappa remained high (LH: $\kappa = .74$; RH: $\kappa = .77$).

Sulcal Identification: Percent agreement between raters is summarized in Tables 2-2 (CS; OTS) and 2-3 (RS); agreement with BrainVISA is presented in Table 2-4. For the CS, agreement between raters improved across each of the four rounds of protocol development and reached over 98% for the full sample. Of those sulci identified as the CS by each rater, 87% were labeled as the CS by BrainVISA. Agreement for OTS identification also consistently improved across protocol development. In the full UF/UCR sample, agreement reached over 89% and 92% for the left and right hemispheres, respectively. Agreement between visual ratings and automated labeling by BrainVISA varied by hemisphere and by rater: Of those identified as the OTS in the

right hemisphere by CB and GR, BrainVISA labeled 77% and 78%, respectively; for the left hemisphere, concordance was only 58% (CB) and 59% (GR).

Identification of the RS yielded the most variability. During Rounds 1-3, raters were asked to identify two subtypes of the RS – a medial and a lateral variant. Agreement for the medial variant ranged from 28% (GR-CL) to 80% (GR-JR) in the first round, and agreement between GR and CB was 72% and 52% on Rounds 2 and 3, respectively. Agreement for the lateral variant ranged from 32% (GR-CL) to 64% (GR-JR) for Round 1 and was 64% and 52% on Rounds 2 and 3, respectively. During consensus meetings, two main challenges were identified: (1) Difficulty differentiating between the two variants; and (2) Validity of Ono's RS samples, which often extend farther lateral and/or posterior than expected based on comparative neuroanatomy (Insausti et al., 1993; Novak et al., 2002; Van Hoesen et al., 2000). These concerns were addressed in Round 4 by removing the distinction between the two variants, simplifying identification and rating criteria, adding examples of complex cases, and renaming the sulcus as, "Ono's RS (oRS)" in all materials. Agreement during this round reached 88% and remained at that level for the full sample (RH: 91%; LH: 89%). Agreement with BrainVISA ranged from 74% (CB) to 76% (GR) in the right hemisphere and from 68% (CB) to 71% (GR) in the left hemisphere.

Inter-sulcal connections (Table 2-5): By Round 3 of protocol development, agreement for ratings of individual sulcal connections was as follows: CS-oRS: 72%; CS-OTS: 84%; oRS-OTS: 88%. Based on qualitative inspection of rating discrepancies, we observed that there were numerous examples of highly ambiguous connections, and that raters tended to vary in their perception and interpretation of such cases. Examples include: (a) a perforated appearance of one or both sulci at their juncture; (b) a connecting branch whose depth is shallower than both

adjoining sulci; and (c) dramatic differences in depth between the two connecting sulci (Figure 2-2). Therefore, a "pseudoconnection" option was added to each connection category in an attempt to further minimize discordance. When ratings were completed for the full sample, absolute agreement between connection ratings ranged from 76% to 86% in the right hemisphere and 66% to 82% in the left hemisphere. However, when "pseudoconnection" and "connection" ratings were combined, agreement was higher (RH: 87%-91%; LH: 88%-90%).

Aim 1.2 Temporobasal Sulcal Patterns in Healthy Adults

Pattern distributions (Figure 2-3): As predicted, the four sulcal pattern types were not equally represented in either the right [$\chi^2(3, N = 196) = 80.61, p < .001, V = .64$] or left [$\chi^2(3, N = 194) = 89.63, p < .001, V = .68$] hemisphere. In the ***left hemisphere***, the distribution of pattern types was consistent with Kim et al. (2008) [$\chi^2(3, N = 194) = 4.23, p = .24, V = .15$] such that Type 1 was most frequent ($N = 91$; 47%), followed by Type 2 ($N = 67$; 35%), Type 4 ($N = 31$; 16%), and then Type 3 ($N = 5$; 3%). A different distribution was found in the ***right hemisphere***, such that Type 1 ($N = 80$; 41%) and Type 4 ($N = 76$; 39%) were present in almost equal proportions. Type 2 was found in 37 (19%) of brains and Type 3 in 3 (2%). Compared with Kim et al., Type 2 was less frequent ($z = -3.87$; $p < .001$) and Type 4 was more frequent ($z = 6.07$; $p < .001$), resulting in a highly significant Goodness of Fit [$\chi^2(3, N = 196) = 54.56, p < .001, V = .53$].

Hemispheric symmetry (Table 2-6): With respect to hemispheric symmetry, only 51% of participants had the same pattern in the right and left hemisphere, which is substantially less than the 82% reported by Kim et al. Symmetry proportions differed by pattern type as well. Symmetrical patterns were seen in 71% of participants with Type 1 in the right hemisphere; 68% of those with Type 2; 33% of those with Type 3, and only 23% of those with Type 4. Low

symmetry for Type 4 is consistent with the greater proportion of this pattern in the right hemisphere compared with the left.

Sex differences (Figure 2-4): Analysis of sex differences was complicated by problematically small expected frequencies for Type 3. Therefore, the Exact Test was used to calculate significance using all four levels, and follow-up analysis was conducted with only Types 1, 2, and 4. In the ***right hemisphere***, men and women had very similar pattern distributions [4 Types: $\chi^2(3, N = 196) = 2.89$, $p = .44$, $V = .12$; 3 Types: $\chi^2(2, N = 193) = 2.53$, $p = .28$, $V = .11$]. The largest discrepancies were that men had more instances of Type 1 [Men: 45%; Women: 36%; *OR* = 1.48] and fewer instances of Type 2 [Men: 15%; Women: 23%; *OR* = .61]. In the ***left hemisphere***, there also was no significant association between pattern type and sex [4 Types: $\chi^2(3, N = 194) = 5.38$, p .16, $V = .17$; 3 Types: $\chi^2(2, N = 189) = 3.66$, $p = .16$, $V = .14$]. Men had a slightly larger proportion of Type 4 [Men: 19%; Women: 13%; *OR* = 1.64] and, as in the right hemisphere, they had a smaller proportion of Type 2 [Men: 28%; Women: 41%; *OR* = .57].

Discussion

Aim 1.1: Development of a Reliable Protocol for Sulcal Identification and Pattern Classification

Through the procedures described in Aim 1.1 we successfully developed a protocol entitled “Sulcal Classification Rating Protocol: anterior Temporobasal Sulci” (SCRaP:aTB), which includes accompanying training and tracking materials (Appendix A and B). This protocol demonstrates strong inter-rater reliability in a large sample of healthy young adults.

The SCRaP:aTB materials included several design features that were intended to improve clarity and ease of use. The training manual was created using Microsoft Office PowerPoint (versions 2003 and 2007) and combines verbal descriptions and visual examples of each rating,

with only one rating described per slide. Additional slides included tips and answers to questions that frequently arose during the initial development of the protocol. Additionally, the manual included a color key to ensure consistent naming of each color used by BrainVISA. Second, the tracking log was created using Microsoft Office Excel (versions 2003 and 2007). Each rating column consisted of a dropdown menu of available responses to ensure uniformity of response type across raters. Additionally, the log only required manually ratings of individual sulcal colors and connections, and composite ratings were then automatically generated. For example, programmed formulas automatically classified each hemisphere into one of the four sulcal patterns based on a combination of ratings for the three inter-sulcal relationships (CS-oRS; CS-OTS; oRS-OTS). Cells that included formulas and reference cells for dropdown menus were hidden from view. Finally, design elements were consistent across materials when possible. For example, the training manual presented information in the same order as presented in the tracking log, and screenshots of the tracking log were included at the beginning of respective subsections in the manual. Slides in the training file and cells in the tracking log were color-coded based on the labeling scheme in BrainVISA to provide visual consistency.

Of the changes made during development of this protocol, three seemed most influential. First, multiple examples were added for each rating option, including examples of situations that might pose particular difficulty. Use of high-resolution, full-color images and inclusion of numerous examples represents a significant improvement over training materials in the sulcal atlas by Ono et al. (1990), which has a much more limited selection of samples and uses black-and-white photographs of post-mortem specimens. Second, identification of sulcal connections often was complicated by the presence of some especially ambiguous junctures between sulci and it was difficult to determine whether these ambiguities were due to limitations in image

processing or actual anatomic ambiguities. Examples are presented in Figure 2-2 and include situations in which one or both sulci are perforated or shallow at the inter-sulcal juncture. These were identified as “pseudoconnections” and, when combined with the “connection” rating, yielded improved inter-rater agreement.

Finally, the RS posed several challenges for reliability when based on Ono’s descriptions. Ono and colleagues describe a medial and lateral variant of the RS; however, the lateral variant extends close to the temporal pole in some examples, and the posterior ends of both variants extend up to or past the anterior boundary of the pons. As Van Hoesen and colleagues (2000) point out, both of these characteristics are not consistent with the classical definition of the RS as the boundary separating the olfactory and non-olfactory portions of the brain, and the authors question the validity of surface-based morphology rating systems like Ono’s sulcal Atlas. Novak et al. (2002) describe similar challenges. They concluded that “Differentiation between the anterior segment of the CS and the human homolog of the RS was methodologically not possible in [their] study,” and ultimately decided to use Ono’s definition of the RS to facilitate comparisons. Similarly, we chose to refer to this sulcus as “Ono’s rhinal sulcus” (oRS) to acknowledge that ratings are based on the definitions used in most surface-based studies of sulcal morphology rather than on the “true” rhinal sulcus.

Aim 1.2: Temporobasal Sulcal Patterns in Healthy Adults

Replication of Kim et al. (2008) was partially successful. As predicted, there were no significant differences between the distribution of pattern types in men and women (Figure 2-4). In terms of relative pattern distribution, the UF/UCR sample replicates Kim et al. for the left but not the right hemisphere (Figure 2-3). However, Type 1 is most frequent and Type 3 is least frequent for both hemispheres, which is consistent with Kim’s findings. Individual pattern types

are discussed in more detail below, including the nature and magnitude of their respective frequencies.

Type 1 (CS-oRS connection) appears in 41% of right hemispheres and 47% of left hemispheres, which is almost identical to frequencies reported by Kim and colleagues. Due to the nature of the pattern classification system, Type 1 is the only one that also can be compared with the other three published evaluations of aTB sulcal patterns in healthy adults. For the left hemisphere (Figure 2-5), our results are consistent with Hanke et al. (1997) and with the older adult and young adult samples in Zhan et al. (2009). For the right hemisphere (Figure 2-6), our findings also are consistent with Hanke et al. and the young adult sample in Zhan et al. but not with the latter's older adult group ($p = .05$). Notably, the only study not consistent with our findings for either hemisphere (RH: $p = .05$; LH: $p = .01$) is Ono et al. (1990), who reported a CS-oRS connection in only 28% of each hemisphere. There are several possible explanations for this discrepancy. First, Ono et al. has by far the smallest sample (25) of all these studies, which may compromise the quality of their results by offering an unrepresentative sample. Second, Ono and colleagues evaluated post-mortem brains whereas the current study is based on MRI analysis. However, Hanke et al. also conducted post-mortem analysis with a much larger sample (184) and found results consistent with ours. A third possibility is that at least a subset of samples identified as "pseudoconnections" in the current study may not be true connections despite their inclusion in the Type 1 frequencies, and that these subtleties are easier to differentiate post mortem. Indeed, only 25% of right hemispheres and 31% of left hemispheres were rated as having a true CS-oRS connection, which is much closer to Ono's published findings ($p > .60$; unfilled bar in Figures 2-5 and 2-6).

The striking rarity of Type 3 also replicates Kim et al. (2008) for both the right and left hemisphere. This pattern is characterized by a connection between the oRS and OTS in the absence of any CS connections. Therefore, its low prevalence may relate to the number of restrictions included in its definition. In other words, a hemisphere is classified as Type 3 only if it has not already met criteria for Types 1 or 2. The prevalence of oRS-OTS connections without these restrictions is 23% for the right hemisphere and 29% for the left hemisphere, which is still less than the proportion of CS-oRS connections but is much higher than suggested by the prevalence of Type 3. Similar to the discrepancies noted for the CS-oRS, the prevalence of oRS-OTS connections in our sample is approximately two times higher than reported by Ono (p = .003), but is almost identical (9% and 11% in the right and left hemisphere, respectively; p = .80) when only "true" connections are considered (Table 2-7). The same phenomenon is found with respect to the prevalence of connections between the CS and OTS in the left hemisphere: Our findings are consistent with Ono et al. when only true connections are recognized (p = .20) but not when pseudoconnections are also included (p = .02); for the right hemisphere, the difference between our results and Ono's approaches significance (p = .05) even when pseudoconnections are excluded (Table 2-7).

Finally, the prevalence of Types 2 and 4 in our sample replicate Kim et al. (2008) for the left hemisphere, such that Type 2 accounts for approximately one-third of the sample whereas Type 4 is found in just under 20%. In contrast, the proportion of right hemisphere samples classified as Type 2 (19%) is about half that reported by Kim and colleagues (35%), whereas Type 4 occurs almost twice as often (39% vs 20%). This highlights another difference between our and Kim's sample: Kim's group reported the same distribution of patterns in the right and left hemisphere, whereas the hemispheres appear qualitatively different in the current study.

Moreover, the majority (82%) of Kim's participants had the same pattern in each hemisphere, whereas only half of our sample demonstrated intra-individual symmetry. It seems logical that Kim and colleagues found greater within-individual symmetry given their reported similarities between hemispheres. However, this does not fully account for the higher proportion of asymmetry in our sample. For example, Type 1 appeared in almost half of each hemisphere in our sample, yet only 60% of those with Type 1 in the left hemisphere had this same pattern in the right hemisphere. Viewed another way, only 29% of individuals have Type 1 in both hemispheres. Overall concordance between our and Kim's findings suggests that methodological differences do not fully account for discrepancies between asymmetry findings, though they certainly may contribute.

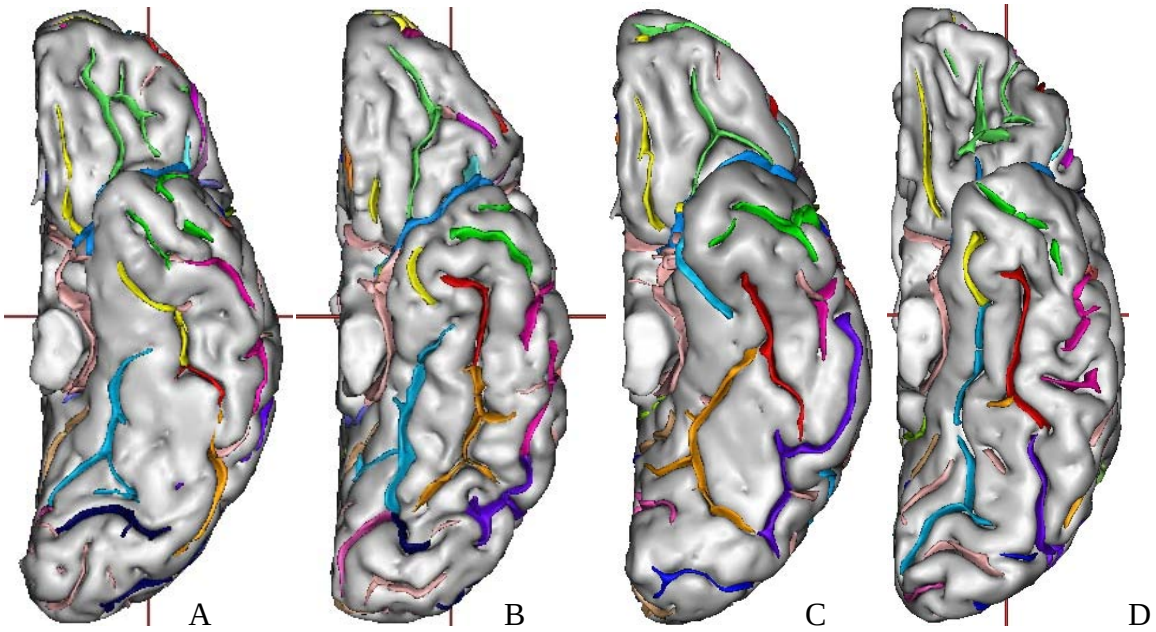

Figure 2-1. Samples of each pattern type described by Kim et al. A) Type 1, characterized by a connection between the CS and RS; B) Type 2, characterized by a connection between the CS and OTS in the absence of a CS-RS connection; C) Type 3, characterized by a connection between the RS and OTS in the absence of a CS-RS or CS-OTS connection; D) Type 4, characterized by the absence of connections.

Table 2-1. Inter-rater reliability (κ) across rounds of protocol development

Round	Raters	*N*	Kappa
1	GZR; TL; JR	25	.34-.78
2	GZR; CB	25	.73
3	GZR; CB	25	.50
4	GZR; CB	50	.75
Full sample (RH)	GZR; CB	196	.77
Full sample (LH)	GZR; CB	194	.74

Table 2-2. Inter-rater agreement (%) for identification of the collateral (CS) and occipitotemporal (OTS) sulci

Round	CS	OTS
1	84	64
2	92	84
3	92	88
4	100	92
Full sample (RH)	98	92
Full sample (LH)	98	89

Table 2-3. Inter-rater agreement (%) for identification of the rhinal sulcus (RS)

Round	RS (medial)	RS (lateral)	oRS
1	28	32	--
2	72	64	--
3	52	52	--
4	--	--	88
Full sample (RH)	--	--	91
Full sample (LH)	--	--	89

Table 2-4. Agreement (%) between visual ratings and BrainVISA labels

	CS		oRS		OTS	
Hemisphere	GR	CB	GR	CB	GR	CB
Right	87	87	76	74	78	77
Left	87	87	71	68	59	58

Table 2-5. Inter-rater agreement (%) for inter-sulcal connections

	Hemisphere	
Connection	Left	Right
CS-oRS	66 (89)	76 (91)
CS-OTS	75 (90)	78 (87)
oRS-OTS	82 (88)	86 (90)

Note: Values in parentheses are the % agreement when "pseudo" and "true" connections are considered equivalent.

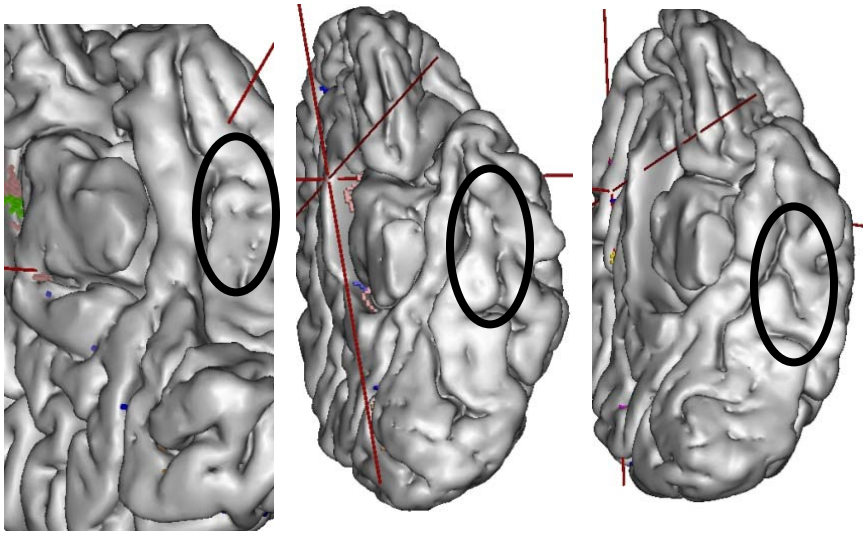

Figure 2-2. Sample "pseudoconnections."

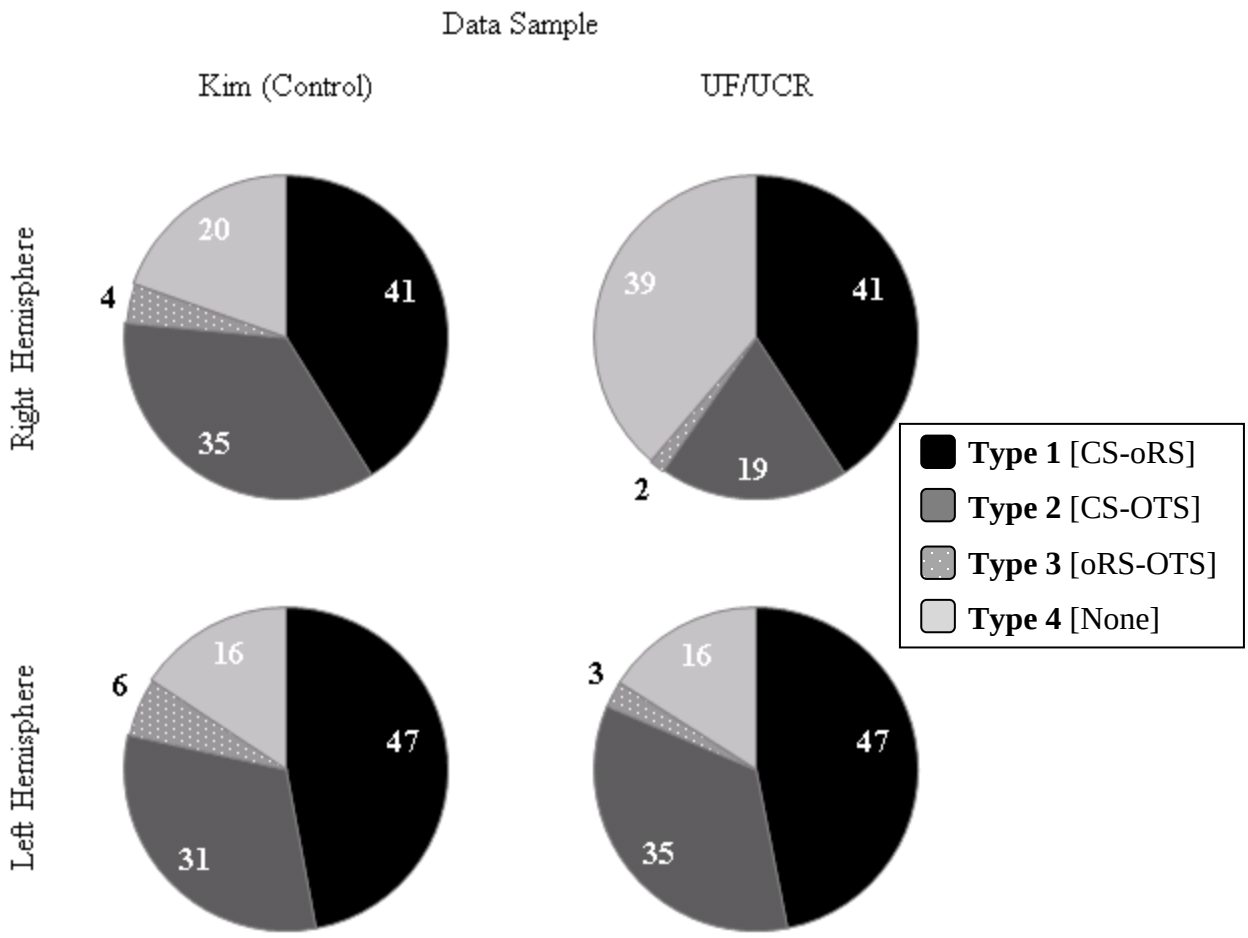

Figure 2-3. Prevalence (%) of each pattern type in the UF/UCR sample (N = 196) compared with the control group described by Kim et al. (N = 51). The distribution of types in the UF/UCR sample differed significantly from Kim et al. for the right hemisphere ($p < .001$) but not for the left ($p > .05$).

Table 2-6. Cross-tabulation of pattern type agreement in the right and left hemisphere.

	Left Hemisphere								
	Type 1		Type 2		Type 3		Type 4		
Right Hemisphere	*N*	%	*N*	%	*N*	%	*N*	%	Total
Type 1	55	71%	8	10%	4	5%	10	13%	77
Type 2	11	30%	25	68%	0	0%	1	3%	37
Type 3	0	0%	0	0%	1	33%	2	67%	3
Type 4	25	33%	33	44%	0	0%	17	23%	75
TOTAL	91		66		5		30		192

Note: Percentages are reported relative to the right hemisphere (e.g., of those with T1 in the RH, % who also have T1 in the LH).

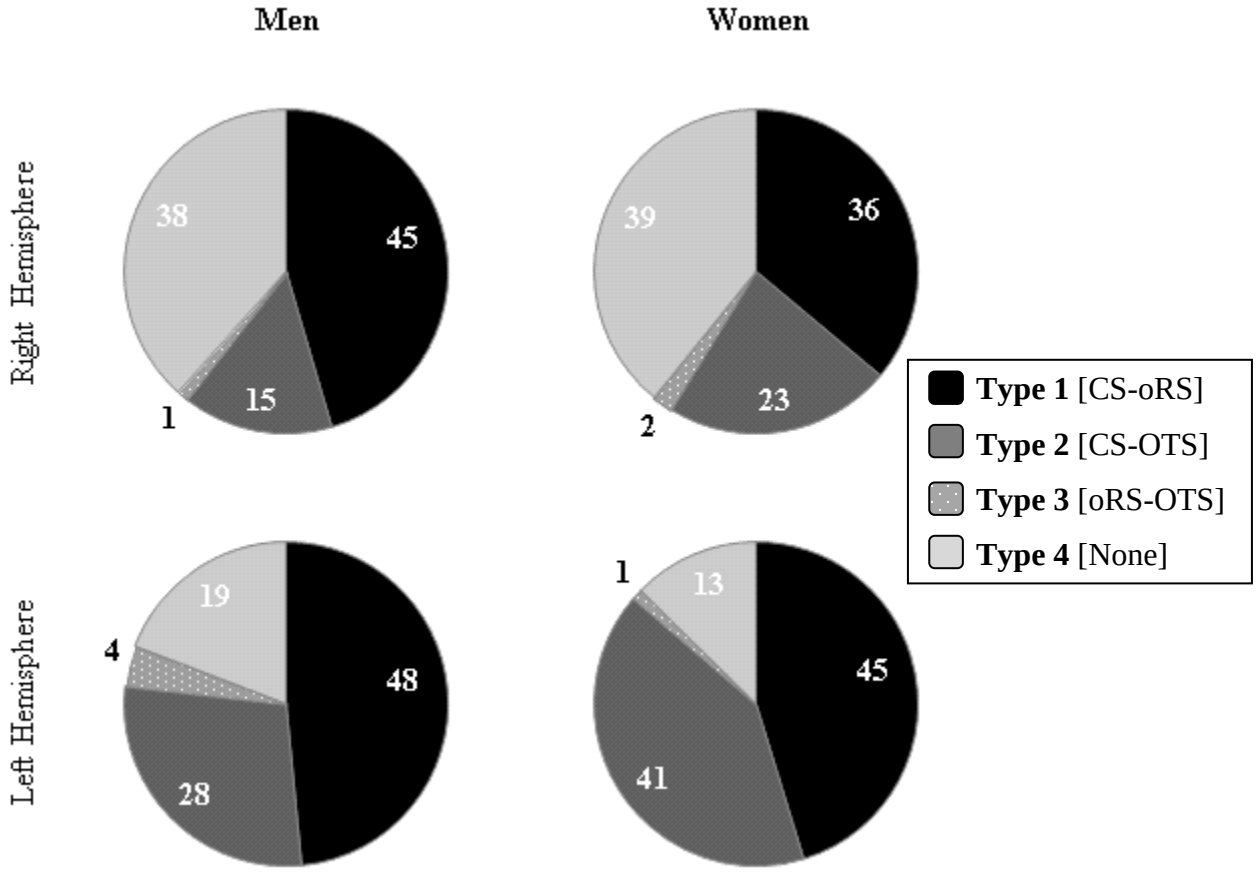

Figure 2-4. Prevalence (%) of each pattern type in men (N = 99) and women (N = 95) in the UF/UCR sample. There were no significant associations between sex and type in either hemisphere (p > .05).

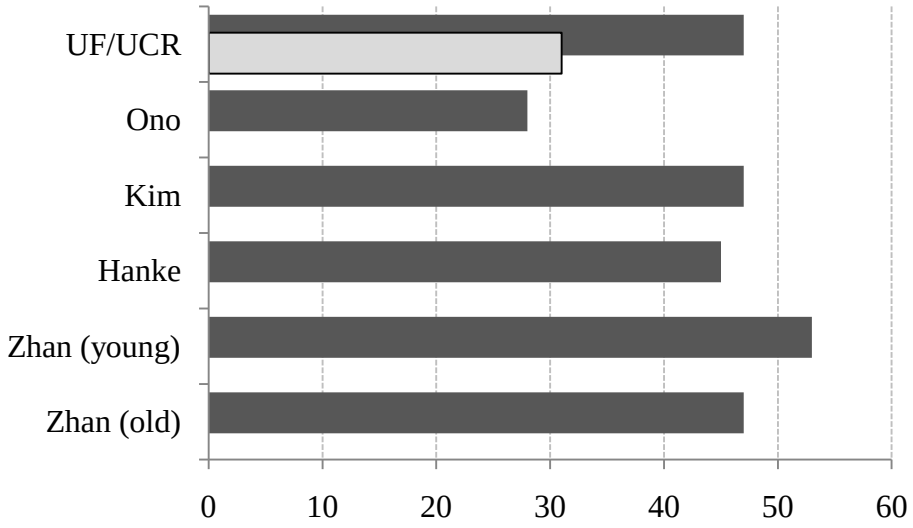

Figure 2-5. Prevalence (%) of CS-RS connections in the left hemisphere in healthy adults, including results from the current study (UF/UCR) and previously published data. The unfilled bar represents the proportion of "true" connections in the UF/UCR sample (i.e., omitting those rated as a "pseudoconnection").

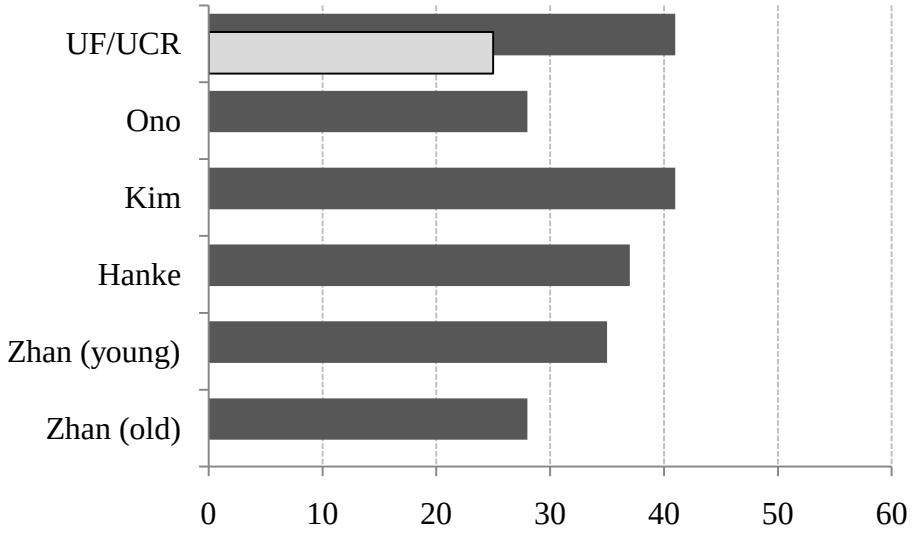

Figure 2-6. Prevalence (%) of CS-RS connections in the right hemisphere in healthy adults, including results from the current study (UF/UCR) and previously published data. The unfilled bar represents the proportion of "true" connections in the UF/UCR sample (i.e., omitting those rated as a "pseudoconnection").

Table 2-7. Comparison of inter-sulcal connection frequencies in UF/UCR and Ono et al.

	Ono (*N* = 25)		UF/UCR (*N* = 196)	
Connection	Left	Right	Left	Right
CS-OTS	44	20	61 (35)	34 (10)
oRS-OTS	12	8	29 (11)	23 (9)

Note: Values in parentheses represent prevalence for only “true” connections.

CHAPTER 3
STUDY 2

Statement of the Problem

To our knowledge, only two studies have evaluated the frequencies of aTB sulcal connections in individuals with TLE (Kim et al., 2008; Novak et al., 2002), and these studies reported very different findings: Whereas Novak's group found CS-RS connections in 28% and 38% of right and left hemispheres, respectively, Kim and colleagues reported frequencies of 72% and 77%. Both found very few CS-OTS and oRS-OTS connections: Novak et al. identified a CS-OTS connection in only 2 patients (4%); Kim et al. reported a connection in 3 right hemispheres (4%) and 3 left hemispheres (4%). Though these proportions are similar, there are two important methodological differences that prohibit direct comparison: (1) Novak's group reported values in terms of patients, whereas Kim et al. reported the number of hemispheres; and (2) Kim et al. reported only the number of hemispheres in which there was a CS-OTS connection in the absence of a CS-RS connection. With respect to RS-OTS connections, Novak et al. found only one such case (2%) whereas Kim et al. reported 12% in the right hemisphere and 9% in the left hemisphere. The same methodological limitations apply here as for the OTS-CS.

In addition to differences in classification methods and findings, Novak et al. (2002) evaluated sulcal connections only in TLE patients and did not compare these findings with healthy controls. Therefore, Kim et al. (2008) is the only study that directly compared the two groups. Novak also included patients ranging from 3-48 years old, which may contribute to differences between their and Kim's results. However, Novak and colleagues reported no relationship between sulcal pattern and age.

Comparison Study: Key Findings

Kim et al. (2008) served as the basis of replication for Study 2. Using the rating system described in Study 1 (above), the authors compared temporobasal sulcal patterns in 69 patients with unilateral TLE (33 men) and 51 healthy adults (25 men). The distribution of pattern frequencies for both groups are summarized in Figure 3-1.

Based on these reported frequencies, we calculated effect sizes using G*Power 3.0. In brief, Kim et al. (2008) found significant group differences such that Type 1 was more frequent in the TLE group whereas Type 2 was less frequent (overall effect size = .74). There were no group differences for Types 3 and 4. Seizure lateralization was not significantly associated with sulcal pattern, which is consistent with Novak et al. (2002). Additionally, there were no significant hemispheric differences, and the majority of patients had the same sulcal pattern in both hemispheres (77% of TLE). Regarding the effect of sex, Type 1 was more frequent in men and Type 4 was more frequent in women (effect size = .77).

Kim and colleagues (2008) suggest that Type 1 represents a “simplified arrangement” associated with neurodevelopmental abnormalities, which may directly or indirectly increase risk for development of TLE. They did not evaluate the relationship between neurocognitive functioning and aTB pattern type, and to our knowledge no one has evaluated whether such relationships exist. However, there is a precedent for exploring neurocognitive relevance based on studies that focused on morphologic relationships between other sulci (e.g., Nakamura et al., 2007; literature review above).

Aims and Predictions

The overall goal of Study 2 was to characterize the distribution and neurocognitive relevance of temporobasal sulcal patterns in adults with temporal lobe epilepsy (TLE) in comparison with healthy adults.

Aim 2.1: Temporobasal Sulcal Patterns in TLE

The goal of Aim 2.1 was to characterize the distribution of pattern types in a group of individuals with TLE and compare this distribution with that of healthy controls. We predicted that this comparison would replicate group differences in Kim et al. (2008) by demonstrating:

- Different distribution of sulcal pattern types in TLE versus healthy controls, with the patient group demonstrating a greater proportion of Type 1 and a smaller proportion of Type 2;
- No relationship between seizure lateralization and sulcal pattern distribution;
- Significant differences between the distribution of patterns in men and women, with men displaying a greater proportion of Type 1 and a smaller proportion of Type 4;
- Pattern symmetry (i.e., same pattern in both hemispheres) in at least 75% of patients.

Aim 2.2: Neurocognitive Relevance of Sulcal Patterns

Specific Aim 2.2 sought to evaluate the relationships between temporobasal sulcal pattern and neurocognition in healthy adults and in individuals with TLE. Predictions were based on two factors: (1) The MTL is most closely associated with learning and memory, and (2) Kim et al's finding of disproportionately high frequencies of pattern Type 1 in epilepsy patients. Therefore, we predicted:

- Type 1 would be associated with worse memory performance than the other pattern types.
- Sulcal pattern would be more strongly associated with delayed free recall than with memory tests that are less dependent on MTL integrity (i.e., immediate retrieval, or recognition) or with tests of language ability, which are thought to be more dependent on lateral neocortex.
- The relationship between pattern type and memory performance would be stronger in patients than in healthy controls.

Methods

Data for Study 2 were collected as part of a prior research study led by Bruce Hermann, Ph.D., Professor of Neurology at the University of Wisconsin – Madison. This study was

reviewed and approved by the University of Wisconsin School of Medicine and Public Health Human Subjects Research Committee, who later approved data sharing with UF investigators for the analyses included in the current study. The following information about study participants, neuropsychological assessment, and image acquisition is based on Hermann et al. (2007) and Oyegbile et al. (2004). The control and patient groups will be referred to as UW-C and UW-TLE, respectively.

Participants

Analyses were conducted on a total of 70 healthy control participants (28 male) and 79 individuals with temporal lobe epilepsy (22 male). This is more than adequate according to calculations with G*Power based on Kim et al. (2008), which indicated that replication will require approximately 45 participants in each group to achieve a power of .80. Participants were all between 14–59 years old. The groups did not differ in mean age [TLE: M = 35.56, SD = 11.12; Control: M = 33.40, SD = 12.59, p > .05], but both were significantly older than the UF/UCR sample used in Study 1 [TLE: $t(275) = -15.91$, $p < .001$; Control: $t(266) = -7.77$, $p < .001$].

Participants in the patient group each met criteria for definite or probable TLE. Definite TLE was defined as presence of spontaneous seizures with temporal lobe onset confirmed by continuous video-EEG monitoring; probable TLE was diagnosed based on a consensus conference review of interictal EEG, neuroimaging, developmental and clinical history, with particular attention paid to presence of clinical semiology with features indicative of complex partial seizures of temporal lobe origin. Patients were included in this study only if they met the following additional criteria: (a) no MRI abnormalities other than atrophy; and (b) no other neurological disorder. Of the 79 TLE participants, 47 had EEG-confirmed seizures of temporal lobe origin (17 left-lateralized; 21 right-lateralized; 6 bilateral; 2 bilateral with slight leftward

bias; 1 bilateral with slight rightward bias). A subset of patients underwent anterior temporal lobectomy after completing the study (12 left ATL; 15 right ATL).

The healthy control group was comprised of friends and relatives of the epilepsy participants. Inclusion criteria were: (a) no current substance abuse or medical or psychiatric condition that could affect cognitive functioning; (b) no episode of loss of consciousness greater than five minutes; and (c) no history of developmental learning disorder or repetition of a grade in school.

Image Acquisition

Structural MRI scans were acquired with a 1.5 Tesla GE Signa scanner. According to Hermann et al. (2007), acquisition sequences included T1-weighted, three-dimensional SPGR, Proton Density, and T2-weighted images. Images from 14 individuals (13 TLE, 1 Control) yielded errors during initial acquisition/pre-processing due to severe motion during scanning. Samples deemed useable were de-identified, transferred to external disk, and mailed to the University of Florida.

Automated Sulcal Identification and Labeling

MRIs were processed with BrainVISA version 3.2 using the default parameters available through the Pipeline 2007. For those images that resulted in processing errors (TLE: 18/81; Control: 9/72), parameter adjustments were conducted until sulci could be adequately visualized. Images from four participants (2 TLE, 2 Control) yielded fatal errors during image processing and therefore were not included in analyses. Finally, one TLE patient was included in only the right hemisphere group due to imaging errors in the left hemisphere.

Procedures

Aim 2.1: Temporobasal Sulcal Patterns in TLE

Sulcal patterns in the UW-TLE group were compared with the age-matched UW-C sample. Sulcal identification and pattern classification for the UW-C and UW-TLE groups was achieved via the same methods as for Aim 1.2. In Study 1, inclusion of pseudoconnections yielded results that were largely consistent with those reported by Kim et al. (2008) for healthy adults. Therefore, pseudoconnections were included as connections for Study 2 as well.

Inter-rater reliability was acceptable for left hemisphere ratings in both groups (UW-C: κ = .81; UW-TLE: κ = .76) but was slightly worse for the right hemisphere (UW-C: κ = .66; UW-TLE: κ = .68). Final ratings were determined during consensus conference, and raters remained blind to participant group and demographics throughout this process. Similar to Aim 1.2, Pearson chi-square and Goodness of Fit analyses were conducted. Alpha of .05 was used as the criterion for significance, and Cramer's V was calculated as a measure of effect size.

Aim 2.2: Neurocognitive Relevance of Temporobasal Sulcal Pattern

As part of a prior study, each of the 149 participants from UW completed a comprehensive neuropsychological assessment covering each major cognitive domain. Because the current study is the first to evaluate the relationship between temporobasal sulcal pattern and neurocognition, hypotheses focused on broad indices of memory function rather than evaluating more discrete relationships between sulcal pattern and individual test scores. Follow-up analyses were conducted using individual subtests if warranted. Dependent variables included the following neuropsychological measures:

Wechsler Memory Scale—Third Edition (WMS-III;(Wechsler, 1997b): The WMS-III is a battery of memory tests designed to assess major aspects of memory, including verbal and nonverbal memory, and immediate and delayed recall. All subtests include an immediate recall

trial followed by a delayed recall test 25-35 minutes later. At the end of the immediate recall test, examinees are informed that they will be asked to recall the items after a delay. The five modality-specific index scores served as dependent variables in the current study. These include:

- AUDITORY IMMEDIATE RECALL. This index score reflects an individual's ability to remember information immediately after it has been orally presented. It is derived from performance on two subtests: (1) Logical Memory (LM) I, which is a story recall test in which participants are asked to recall two short (i.e., one paragraph) stories read aloud by the examiner; (2) Verbal Paired Associates (VPA) I, which is a verbal association memory test consisting of eight word pairs read aloud in the form of a list. On each of four trials, the examinee is presented with the first word from each pair and asked to recall the second member of the pair. Word pairs are presented in a different order on each of four learning trials, and examinees are provided with feedback and corrections to facilitate learning. The score for VPAI is the sum of correct responses on all four learning trials.

- AUDITORY DELAYED RECALL. This index measures an individual's ability to freely recall (i.e., without cues) orally presented information after a 25- to 35-minute delay. The two contributing subtests include delayed recall of stories (LM-II) and word pairs (VPA-II).

- AUDITORY RECOGNITION, DELAYED. Participants' ability to recognize information from the LM and VPA subtests is assessed immediately after the free recall trials. For LM, recognition is evaluated by a series of yes/no questions about the stories presented during LM-I; for VPA, participants must identify the previously presented word pairs from among a series of new pairs.

- VISUAL IMMEDIATE RECALL. This index score measures an individual's ability to recognize visually presented information. It is based on two subtest: (1) Faces I, during which an individual is presented with a series of face pictures followed by an immediate recognition test; and (2) Family Pictures (FP) I, during which participants are shown a series of four visual scenes and are asked to recall the people in each scene and each character's action within the scene.

- VISUAL DELAYED RECALL. This index score is comprised of delayed tests of each of the visual measures described above (Faces and Family Pictures). Participants' recall is assessed 25-35 minutes after completion of the immediate recall tasks.

In addition to test of recall and recognition, Study 2 included three measures of language functioning and an overall estimate of intellectual ability. These are briefly described below:

Wechsler Adult Intelligence Scale – Third Edition, seven-subtest short form (WAIS-III; (Pilgrim, Meyers, Bayless, & Whetstone, 2000; Wechsler, 1997a): This is an assessment of general intellectual functioning. Only the Full Scale IQ (FSIQ) was included in analysis. FSIQ

is a composite index score based on performance on each of seven subtests, including (a) tests of verbal knowledge and reasoning (Vocabulary; Similarities; Information); (b) measures of nonverbal reasoning (Picture Completion; Block Design); (c) tests of mental flexibility and working memory (Arithmetic; Digit Span; Letter-Number Sequencing); and (d) measures of psychomotor speed (Digit Symbol; Symbol Search).

Boston Naming Test (BNT; (Goodglass & Kaplan, 1983): The BNT assesses picture-naming ability and has been shown to be impaired in patients with intractable language-dominant TLE (e.g., Busch et al., 2008; Loring et al., 2008). The total number of correct responses was converted to standardized scores using demographically corrected normative data (Heaton, 2004).

Semantic fluency – Animals (Benton, Hamsher, & Sivan, 1994): Fluency tasks assess a combination of functions, including language, processing speed, and executive function (e.g., planning). However, semantic fluency additionally requires intact storage and retrieval of items within a category, and has been shown to depend at least in part on the integrity of the temporal lobe (e.g., Henry et al., 2004). The variant used in the current study requires the examinee generate the names of as many animals as possible in one minute. The number of acceptable responses was converted to a Standard Score based on demographically corrected norms (Heaton, 2004).

Controlled Oral Word Association Test (Benton, et al., 1994): This is a test of phonemic fluency and requires the examinee to rapidly produce as many words as possible beginning with the letter C, F, and L, respectively. The examinee is provided with 60 seconds for each letter. The overall score is the total number of words produced across three trials (one for

each letter). Standardized scores were computed using age- and education-adjusted normative data.

Results

Aim 2.1: Temporobasal Sulcal Patterns in TLE

Comparison between UW-C and UF/UCR:

The distribution of sulcal patterns in the UW-C is depicted in Figure 3-2, alongside those from the UF/UCR sample. There were no significant differences between the control samples [RH: $\chi^2(3, N = 266) = 3.17, p = .30, V = .12$; LH: $\chi^2(3, N = 264) = 3.33, p = .34, V = .11$] and 51% of each sample had the same pattern in each hemisphere (pattern symmetry; Table 3-1). However, the proportion of pattern types in the left hemisphere appears qualitatively different between samples such that Types 1, 2, and 4 are more evenly represented in the UW-C group. Indeed, Goodness of Fit analysis of the UW-C group was no longer significant when Type 3 was omitted [$\chi^2(2, N = 68) = 2.24, p = .33, V = .18$] but remained highly significant in the UF/UCR group [$\chi^2(2, N = 189) = 28.95, p < .001, V = .39$]. The largest discrepancy was for Type 4: The odds of a UW-C participant having a Type 4 pattern was 1.82 times higher than for the UF/UCR sample. With respect to sex-related differences (Figure 3-3), there was no association between sex and pattern type in the left hemisphere [$\chi^2(2, N = 68) = .78, p = .68, V = .12$]. Analysis for the right hemisphere approached statistical significance [$\chi^2(2, N = 66) = 5.61, p = .06, V = .29$] and the distributions appeared qualitatively different: Men had a greater proportion of Type 1 [Men: 57.14%; Women: 30.95%] and less Type 2 [Men: 7.14%; Women: 23.81%]. The nature of these discrepancies is consistent with those in the UF/UCR sample, though the differences are larger in magnitude.

Comparison between UW-C and UW-TLE:

Pattern distribution (Figure 3-4): Pattern Type 3 was identified in only 1 hemisphere in the patient group. Because Type 3 is characterized by an oRS-OTS connection in the absence of any CS connections, it was combined with Type 4 (no connections) to accommodate chi-square assumptions. The resulting pattern category (Type 3-4) is therefore defined by the absence of any CS connections.

For the ***right hemisphere***, there was no significant association between group and pattern type [$\chi^2(2, N = 149) = .56$, $p = .65$, $V = .08$]. Consistent with findings in the control group, Type 1 was most frequent ($N = 36$; 46%), followed by Type 3-4 ($N = 27$; 34%) and Type 2 ($N = 16$; 20%). Goodness of Fit analysis using expected frequencies based on Kim et al. yielded a large, highly significant effect [$\chi^2(2, N = 79) = 57.97$, $p < .001$, $V = .86$] such that Types 2 ($z = 6.83$; $p < .001$) and 3-4 ($z = 2.03$; $p = .02$) were more prevalent in our sample and Type 1 was significantly less prevalent ($z = -2.80$; $p < .01$).

The ***left hemisphere*** distribution also differed from Kim et al. [$\chi^2(2, N = 78) = 106.93$, $p < .001$, $V \geq 1.00$]: Type 3-4 was the most prevalent ($N = 31$; 40%), followed closely by Type 1 ($N = 28$; 36%); Type 2 represented about one-quarter of the sample ($N = 19$; 24%). Relative to Kim's patient group, Types 2 ($z = 8.46$; $p < .001$) and 3-4 ($z = 4.25$; $p < .001$) were significantly more prevalent in our sample whereas Type 1 ($z = -4.12$; $p < .001$) was significantly less frequent. Also contrary to predictions, there was no significant association between group and pattern type in our study [$\chi^2(2, N = 148) = 2.17$, $p = .34$, $V = .12$]. However, there appear to be some subtle group differences. For example, the odds of having Type 3-4 is 1.65 times higher for patients than controls, whereas the odds of Type 2 are 1.42 times higher for controls.

Hemispheric symmetry (Table 3-2): Only 58% of patients had the same sulcal pattern type in each hemisphere, which is a similar symmetry percentage to that in the control group (51%). This proportion is significantly less than the percent symmetry described by Kim et al. [77%; $\chi^2(1, N = 147) = 6.02$, $p = .01$, $V = .20$]. Of the total sample, the percentage of patients with the same pattern in both hemispheres was 24% for Type 1, 13% for Type 2, and 21% for Type 4. Type 3 was found in only 1 hemisphere and therefore no patients had a symmetric Type 3 pattern.

Seizure lateralization: Follow-up analyses were conducted with the subset of patients for whom seizure lateralization was confirmed (Right Temporal Lobe (RTL) onset: $N = 21$; Left Temporal Lobe (LTL) onset: $N = 17$). There was no association between side of onset and pattern type [RH: $\chi^2(2, N = 38) = .48$, $p = .79$, $V = .11$; LH: $\chi^2(2, N = 38) = .59$, $p = .75$, $V = .12$] and symmetry proportions were very similar [RTL: 62%; LTL: 53%; $\chi^2(1, N = 38) = .31$, $p = .58$, $V = .09$].

Sex differences: There was no association between sex and pattern type for either hemisphere. [RH: $\chi^2(2, N = 79) = 2.46$, $p = .29$, $V = .18$; LH: $\chi^2(2, N = 77) = .71$, $p = .70$, $V = .10$]. The absolute value of all standardized residuals was less than 1.0.

Aim 2.2: Neurocognitive Relevance of Sulcal Patterns

Separate MANOVAs (2 total) were conducted for the right and left hemisphere to examine the relationship between sulcal pattern type and cognitive performance in controls and patients with TLE. Pattern Type 3 was very infrequent, and frequencies of Type 2 were relatively low in both hemispheres in the patient group and for the right hemisphere of the control group. Given the large number of variables included in the model and the unequal and small sample size for Types 2-4, we decided to combine these three types for comparison with Type 1. This enhanced our ability to evaluate our predictions, all of which specifically relate to Type 1.

There were 9 dependent variables, including 5 modality-specific indices of memory from the WMS-III, 3 tests of language functioning, and an estimate of overall intellectual ability. Four outliers ($z < -3.00$) were dropped from the control group, including 1 of each of the following: Auditory Delay; Auditory Immediate; Visual Immediate; Letter fluency. Follow-up univariate analyses were performed for each dependent variable. Bonferroni corrections were performed at each level of analysis to mitigate possible family-wise error. Figures 3-5 (RH) and 3-6 (LH) summarize the mean memory scores for each sulcal pattern in patients and controls; Figures 3-7 (RH) and 3-8 (LH) summarize scores for nonmemory measures. Error bars represent 95% confidence intervals.

For each hemisphere, there was a highly significant, moderately sized main effect of participant group such that controls performed better than patients [RH: $F(9, 130) = 12.86$, $p < .001$, $r = .30$; LH: $F(9, 129) = 12.10$, $p < .001$, $r = .29$], and this effect was consistent across all dependent variables. The specific details of this relationship are not central to the current study and therefore were not evaluated via follow-up analysis.

Analysis of each hemisphere passed Box's M test for multivariate normality ($p > .05$). The main effect of pattern type was not significant [RH: $F(9, 130) = 1.32$, $p = .23$, $r = .10$; LH: $F(9, 129) = .62$, $p = .78$, $r = .07$]. There also was no significant interaction effect between group and pattern [RH: $F(9, 130) = .75$, $p = .66$, $r = .08$; LH: $F(9, 129) = .33$, $p = .96$, $r = .05$]. These findings did not change when run without Bonferroni correction.

Follow-up univariate analysis of the three auditory memory variables failed to reveal significant associations with pattern type or significant interactions between pattern type and group, regardless of whether Bonferroni corrections were used. Note that the three auditory memory variables failed Levene's Test ($p < .05$) and the distribution of each of these variables

within each pattern group (Type 1 and Type 2-4, participant groups combined) was negatively skewed. Additionally, these three variables were highly correlated (r = .68-.83). Square root transformation resolved these issues of non-normality but did not alter the results of univariate or multivariate analysis.

Immediate and delayed visual recall did not demonstrate problems with normality, but were highly correlated with each other (r = .87). Bonferroni-corrected decomposition of the interaction term revealed two significant results, each with a relatively small effect size. In the patient group, Type 1 was associated with (1) lower Visual Delayed Index scores, with significance in the right hemisphere [$F(1, 138) = 8.04$, $p < .01$, $r = .23$] and approaching significance in the left [$F(1, 137) = 3.98$, $p = .05$, $r = .20$]; and (2) lower Visual Immediate Memory scores in the right hemisphere only [$F(1, 138) = 5.86$, $p = .02$, $r = .20$]. The relative contributions of individual visual memory subtests were evaluated via follow-up MANOVA. With respect to delayed visual memory, patients with a Type 1 pattern in either hemisphere performed worse on the Faces task [RH: $F(1, 77) = 6.23$, $p = .02$, $r = .27$; LH: $F(1, 76) = 4.21$, $p = .04$, $r = .23$] and there were no differences on the Family Pictures task ($p > .05$). For immediate visual memory, the relationship between pattern type and Faces I approached significance for the right hemisphere [$F(1, 77) = 3.66$, $p = .06$, $r = .21$]; again, there were no significant differences for memory of Family Pictures.

With respect to nonmemory measures, Bonferroni-corrected follow-up analysis revealed a significant association between letter fluency and pattern type in patients only, such that individuals with Type 1 in the right hemisphere performed worse than those with one of the other three pattern types [$F(1, 138) = 7.29$, $p < .01$, $r = .22$].

Discussion

Aim 2.1: Temporobasal Sulcal Patterns in TLE

Comparison with Kim et al. (2008)

The current study failed to replicate any of the four key findings from Kim et al. (2008). For each hemisphere, Kim and colleagues found that Type 1 was present in 3 out of 4 TLE patients. In contrast, we found this pattern in only 36% of left hemispheres and 46% of right hemispheres, which is a similar proportion to that in the control group. Second, Kim's group found that Type 2 was disproportionately underrepresented in patients compared to controls. In our sample, the prevalence of Type 2 was almost identical for the right hemisphere; for the left hemisphere, there was a smaller proportion of Type 2 in the patient group but the difference did not reach statistical significance. Third, only 58% of our patient sample had the same sulcal pattern type in each hemisphere, whereas Kim et al. reported hemispheric symmetry in more than 75% of their sample. Finally, we failed to replicate the significant association between sex and pattern type found by Kim's group.

There are several possible explanations for discrepancies between our findings and the comparison study. First, methodological differences could be to blame, including those related to image acquisition or processing, rating procedures for sulci and their connections, or group demographics. However, results from Study 1 replicate most of the key findings from Kim's group with respect to healthy controls despite known differences in age, use of a newer version of BrainVISA, and implementation of the rating protocol developed through Aim 1.1. Moreover, results from a second control group (UW-C) were not significantly different than those presented in Study 1 despite the second sample being older (on average), comprised of a smaller proportion of males, and collected at a different site. This relative consistency between our two control groups provides evidence of external validity for the SCRaP:aTB and suggests that variation in

MRI acquisition and processing parameters does not compromise sulcal pattern ratings. Additionally, the absence of significant sample differences supports the hypothesis that sulcal configural patterns do not change from adolescence to adulthood. A follow-up one-way ANOVA further demonstrates that there is no association between age and pattern type in the UW-C sample [$F(3,66) = .78$, $p = .51$] or in the combined sample [$F(3,262) = .23$, $p = .88$]. This is consistent with the lack of association between age and sulcal pattern in young versus older adults (Zhan et al., 2009) and in epilepsy patients ranging in age from 3 to 48 (Novak et al., 2002). Nonetheless, there were some differences between results from each of our control groups and between our findings and those reported by Kim and colleagues. For example, the relationship between sex and pattern distribution approaches significance for the right hemisphere in our UW-C sample but not for the UF/UCR sample or for Kim's control group. Sample size is a confounding variable, particularly since there is an unequal number of men and women in the UW-C sample. Nonetheless, this discrepancy may warrant further attention and is important to consider if using the UW data as a normative sample for research relevant to sex-related differences.

A second possible explanation for our failure to replicate group differences is that the patient sample evaluated by Kim et al. (2008) was more severely affected, as it was comprised of individuals with intractable TLE, most of whom later underwent surgical resection. In contrast, the UW-TLE sample includes individuals with "probable" and "definite" TLE, and only 27 (34%) have since undergone surgical resection to treat medically intractable seizures. Therefore, our sample may include patients with a less severe disease. Moreover, 15 additional TLE patients were excluded from analysis due to severe motion during image acquisition ($N = 13$) or fatal errors during processing with BrainVISA ($N = 2$), compared to only 3 controls (1 imaging error,

2 BrainVISA errors). It is plausible that this group of patients may be a more severe or otherwise qualitatively different group than those included in analysis.

The number of UW-TLE patients who have since undergone surgery is only about half the sample size needed to replicate Kim et al. based on *a priori* power analysis and therefore was not evaluated separately in the current study. However, it does seem that pattern Type 1 is slightly more prevalent in this sub-sample (Figure 3-9). For the right hemisphere, the odds of having Type 1 are 1.74 times higher in the surgical group than in the overall patient sample, and 2.06 times higher than the control group. For the left hemisphere, the odds are 1.92 times higher than the whole TLE sample and 1.62 times higher than controls. Distributions were similar regardless of the side of resection.

Comparison with Novak et al. (2002)

Novak et al. (2002) is, to our knowledge, the only other study that has evaluated the prevalence of aTB connections in patients with TLE. The patient sample in this second study is more comparable to Kim's sample in that it included only surgical candidates with medically intractable epilepsy. Nonetheless, Novak and colleagues found much lower frequencies of CS-RS connections than Kim et al. (Table 3-3), suggesting that disease severity may not fully account for discrepancies between our findings and those of Kim and colleagues.

Kim et al. partially attribute differences between their and Novak's results to the latter group's analysis of coronal slices rather than surface morphology. Direct analysis of serial slices allows for more careful analysis of sulcal connections below the cortical surface and therefore may be more analogous to the observations and manipulations of cortical tissue that are feasible during post-mortem analysis. Indeed, Novak et al. (2002) noted that their results were consisted with post-mortem data presented by Ono et al. (1990). In Study 1, we demonstrated that our findings in healthy adults were consistent with Ono et al. when only true connections were

counted, whereas successful replication of Kim et al. depended on inclusion of pseudoconnections. Similarly, the frequency of CS-oRS connections in our patient sample did not differ significantly from Novak's results when only true connections were considered, whereas the difference approached significance when pseudoconnections were included in analysis. This discrepancy was even more compelling for our surgical group (Table 3-4). Moreover, a true oRS-OTS connection was found in only 1 hemisphere in the surgical group, as occurred in Novak's sample. True CS-OTS connections also were comparably infrequent (1/27) in the right hemispheres of our surgical group, though more were identified in the left hemisphere (6/27).

Aim 2.2: Neurocognitive Relevance of Temporobasal Sulcal Patterns

Aim 2.2 tested the predictions that (a) Type 1 would be associated with worse memory performance than Types 2, 3, or 4; (b) Sulcal pattern type would be most strongly associated with measures of delayed free recall; and (c) There would be a stronger relationship between pattern type and memory performance in patients than controls.

Contrary to our predictions, there were no overall differences in cognition between pattern Type 1 and Types 2-4. Despite the absence of Omnibus effects, there was a significant finding for visual memory such that presence of Type 1 in the right hemisphere was associated with worse performance on both immediate and delayed recall in patients but not controls. This finding is in the direction of our predictions (T1 < T2-4) and is consistent with the theory of material specificity, which posits that the language nondominant (typically right) MTL preferentially contributes to nonverbal (e.g., visual) memory (Milner, 1970).

In discussing the lack of significant differences between pattern distributions in patients and controls, we suggested that our findings may be confounded by the composition of our patient sample. Specifically, findings reported by Kim et al. (2008) are based on a sample of

medically intractable TLE patients, the majority of whom later underwent surgical resection; in contrast, only 27 of our 79 TLE participants later underwent surgery. As depicted in Figures 3-5 to 3-8, mean performance for the UW-TLE sample was not in the clinically impaired range (SS < 70) on any measure. Of the 79 patients, only 13 performed in the clinically impaired range on any of the WMS-III indexes, and only 5 had IQ scores below 70. This could be interpreted as further evidence that the sample is less "severe" than expected, though it should be noted that the patient group did perform significantly worse than controls across all tests.

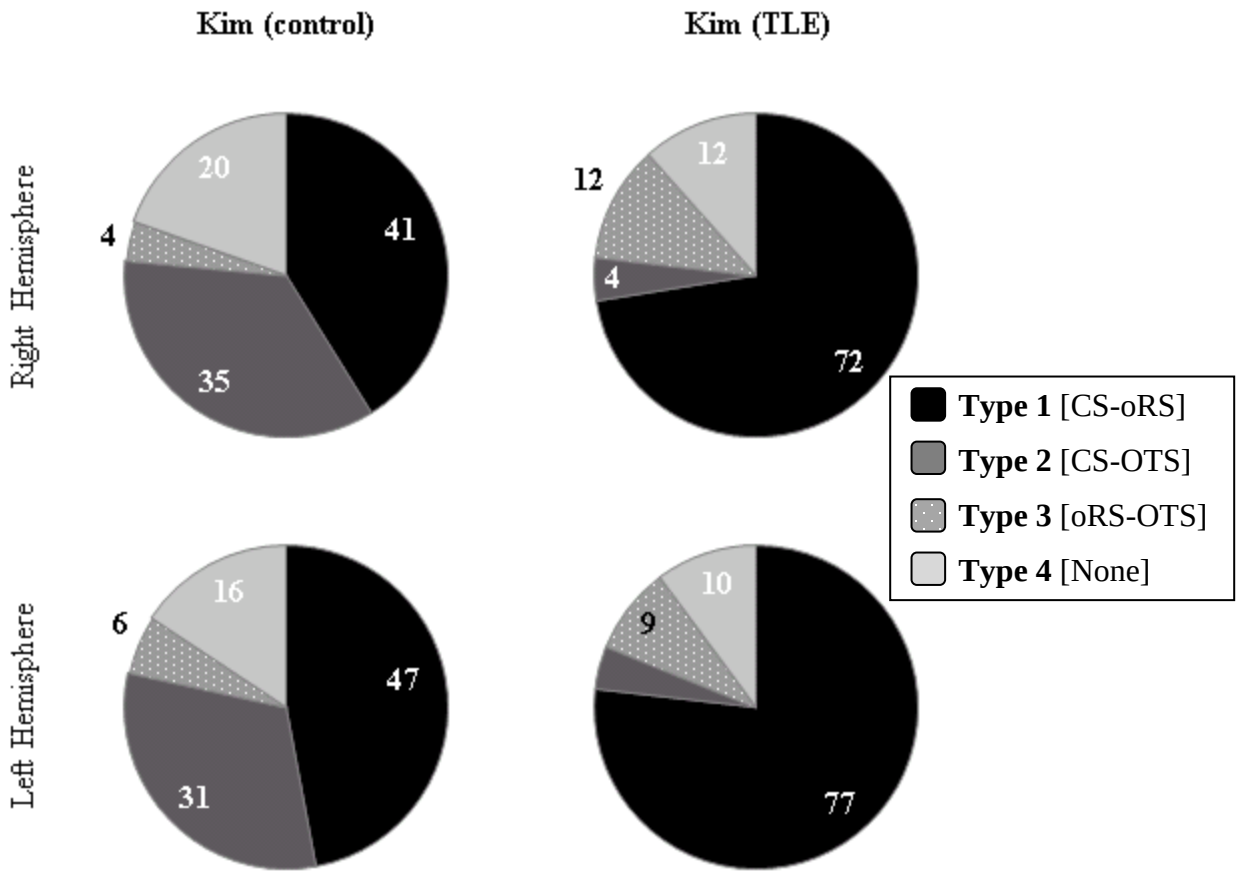

Figure 3-1. Prevalence (%) of each pattern type in the two samples reported by Kim et al. (2008; Control: $N = 51$; TLE: $N = 69$).

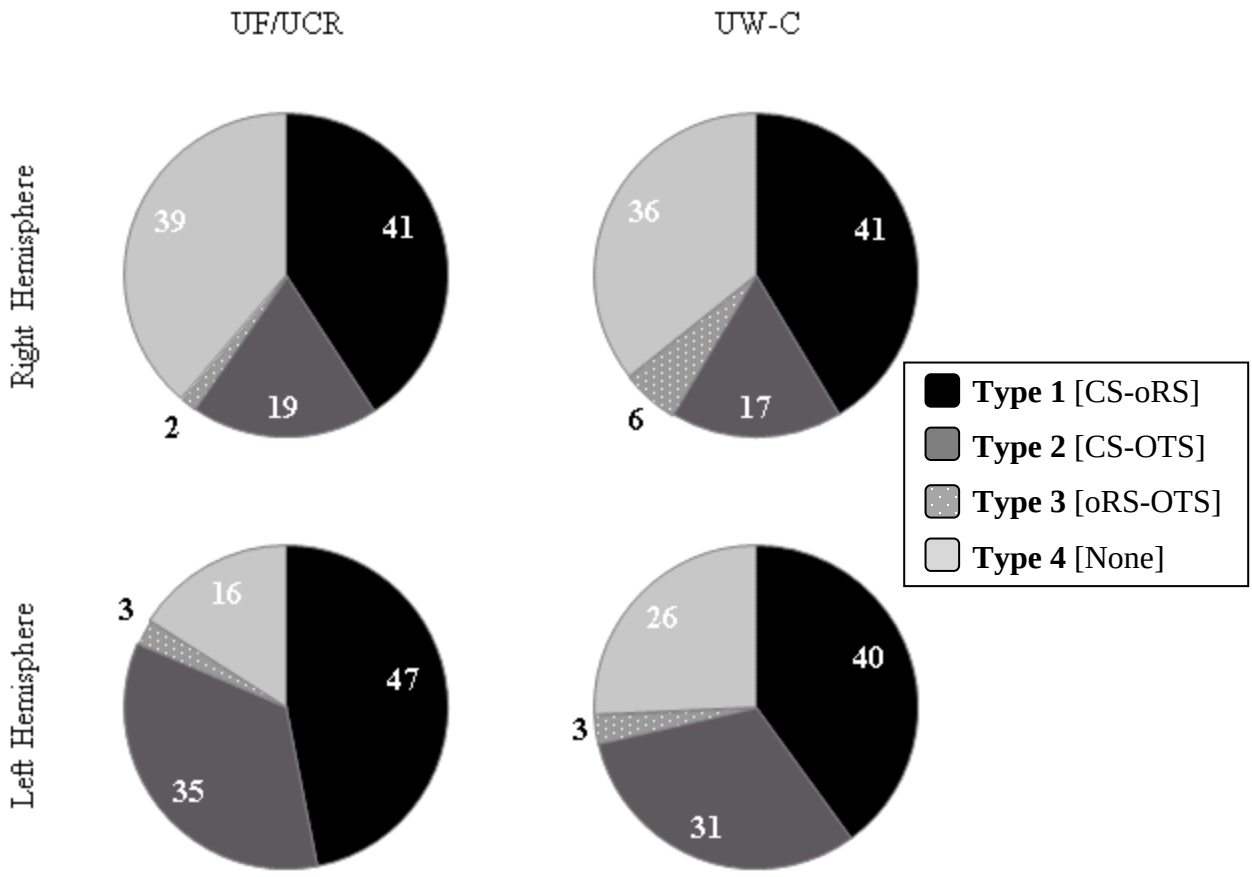

Figure 3-2. Prevalence (%) of each pattern type in the UW-C sample (N = 70) compared with the UF/UCR sample (N = 196). Chi-square comparison between the two samples was not significant ($p > .05$) for either hemisphere.

Table 3-1. Cross-tabulation of pattern type agreement in the right and left hemisphere for UW-C.

	Left Hemisphere								
	Type 1		Type 2		Type 3		Type 4		
Right Hemisphere	*N*	%	*N*	%	*N*	%	*N*	%	Total
Type 1	18	62%	5	17%	1	3%	5	17%	29
Type 2	3	25%	7	58%	0	0%	2	17%	12
Type 3	1	25%	3	75%	0	0%	0	0%	4
Type 4	6	24%	7	28%	1	4%	11	44%	25
Total	28		22		2		18		70

Note: Percentages are reported relative to the right hemisphere (e.g., of those with T1 in the RH, % who also have T1 in the LH).

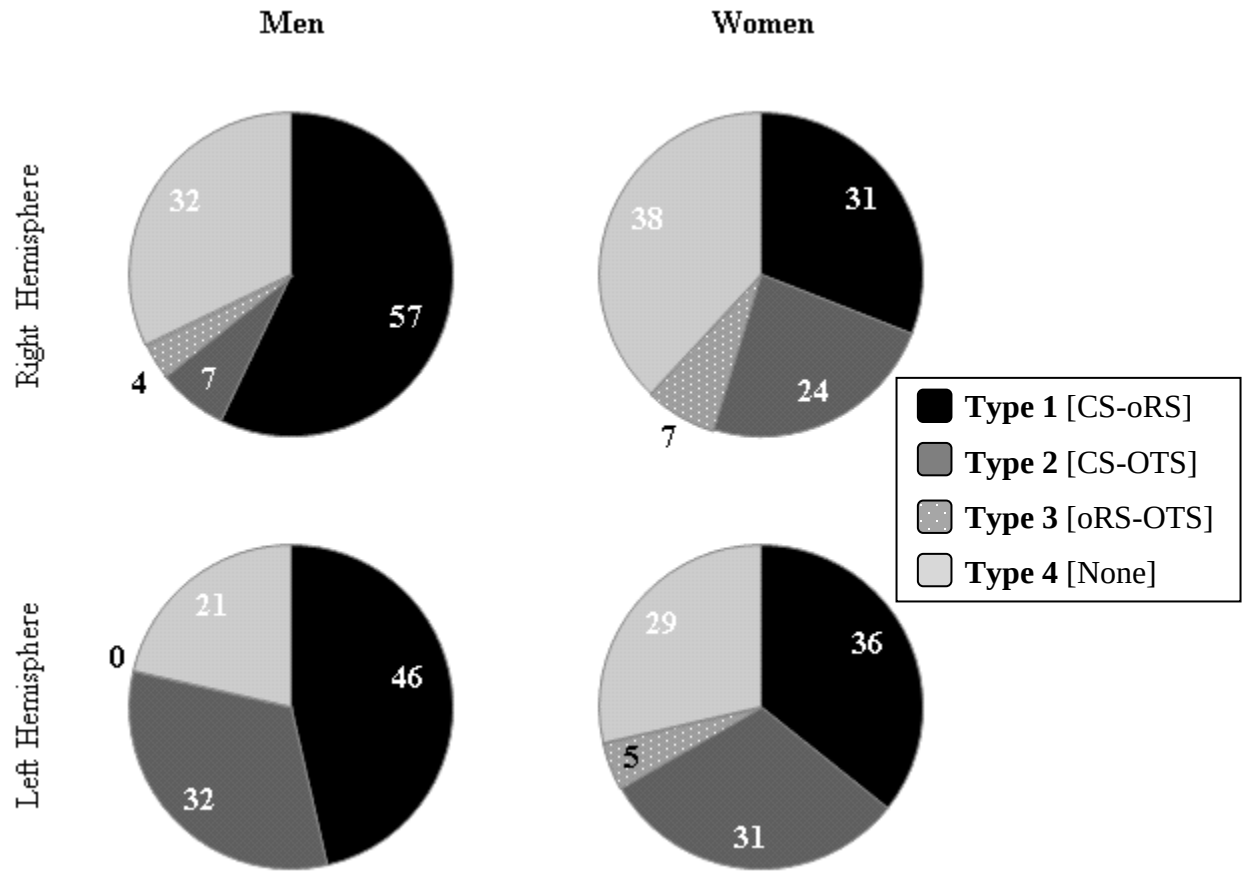

Figure 3-3. Prevalence (%) of each pattern type in men (N = 28) and women (N = 42) in the UW-C sample. The association between sex and pattern approached significance for the right hemisphere (p = .05).

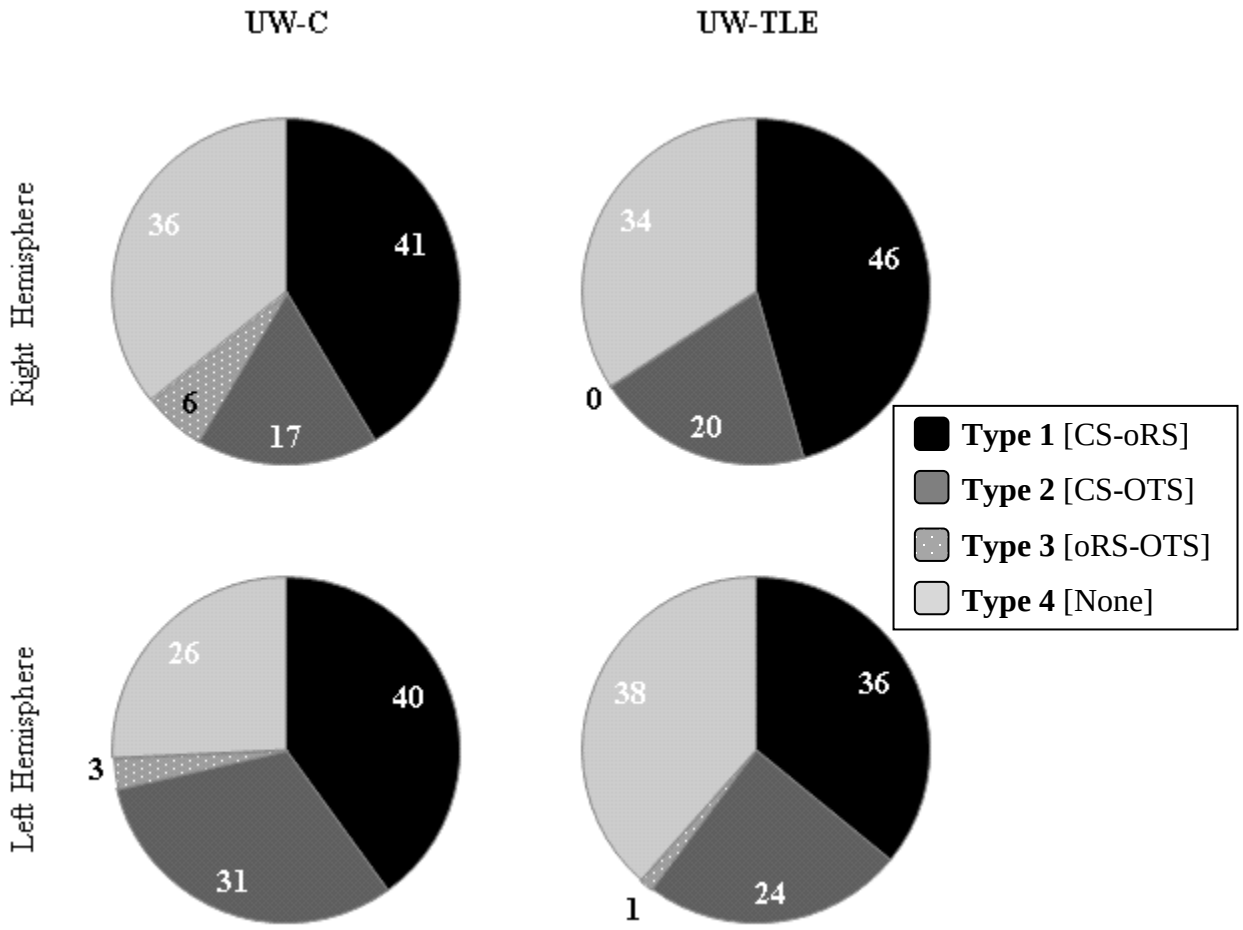

Figure 3-4. Prevalence (%) of each pattern type in the UW-TLE sample (N = 79) compared with the age-matched control group, UW-C (N = 70). Chi-square comparison between the two samples was not significant ($p > .05$) for either hemisphere.

Table 3-2. Cross-tabulation of pattern agreement in the right and left hemisphere for UW-TLE

	Left Hemisphere								
	Type 1		Type 2		Type 3		Type 4		
Right Hemisphere	*N*	%	*N*	%	*N*	%	*N*	%	Total
Type 1	19	53%	4	11%	1	3%	12	33%	36
Type 2	4	25%	10	63%	0	0%	2	13%	16
Type 3	0	0%	0	0%	0	0%	0	0%	0
Type 4	5	19%	5	19%	0	0%	16	62%	26
Total	28		19		1		30		78

Note: Percentages are reported relative to the right hemisphere (e.g., of those with T1 in the RH, % who also have T1 in the LH).

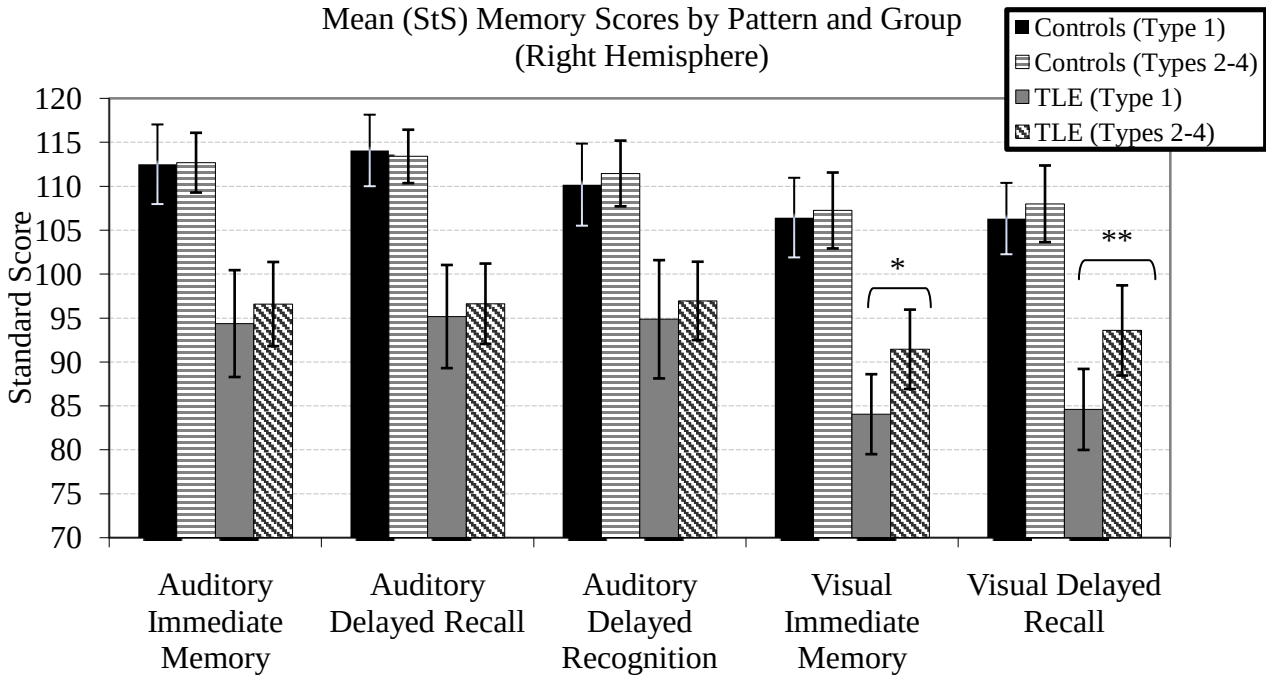

Figure 3-5. Mean scores on five Index variables in the WMS-III relative to pattern type in the right hemisphere. Standard Scores are presented, with 95% confidence intervals (error bars). The control group obtained higher scores on all measures, regardless of pattern type. Bonferroni-adjusted univariate comparisons revealed a significant relationship between pattern type and verbal memory in the patient group (Delay: $p = .005$; Immediate: $p = .02$).

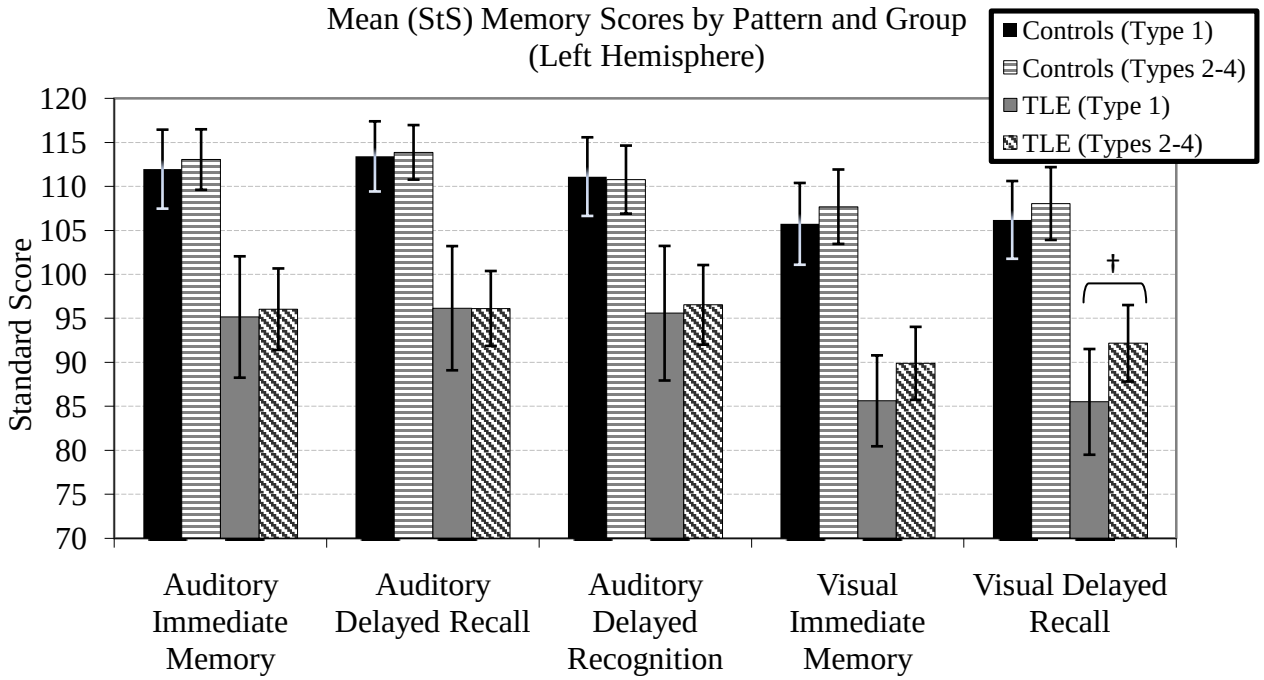

Figure 3-6. Mean scores on five Index variables in the WMS-III relative to pattern type in the left hemisphere. Standard Scores are presented, with 95% confidence intervals (error bars). The control group obtained higher scores on all measures, regardless of pattern type. Base on Bonferroni-adjusted univariate comparisons, the relationship between pattern type and verbal delayed recall approached significance in the patient group (p = .05).

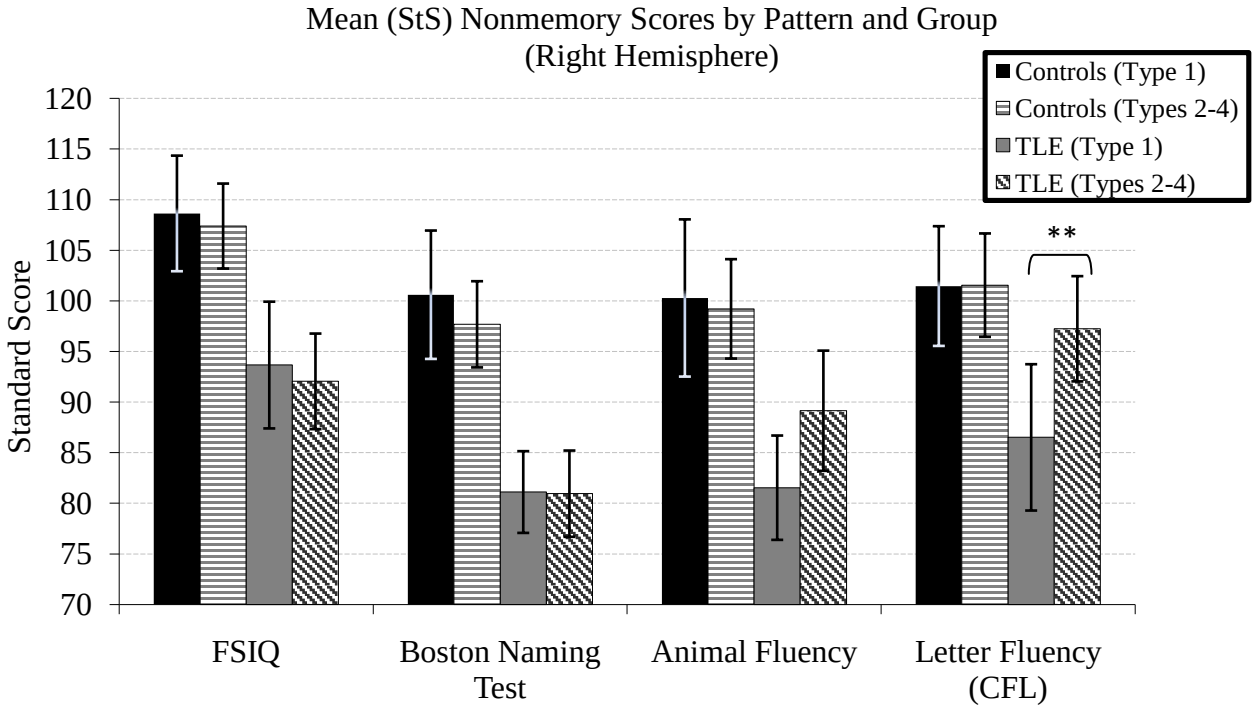

Figure 3-7. Mean IQ and language performance relative to sulcal pattern in the left hemisphere. Standard Scores are presented, with 95% confidence intervals (error bars). The control group obtained higher scores on all measures, regardless of pattern type. Based on Bonferroni-adjusted univariate comparisons, the only significant association with sulcal pattern was for Letter Fluency in the patient group (p = .008).

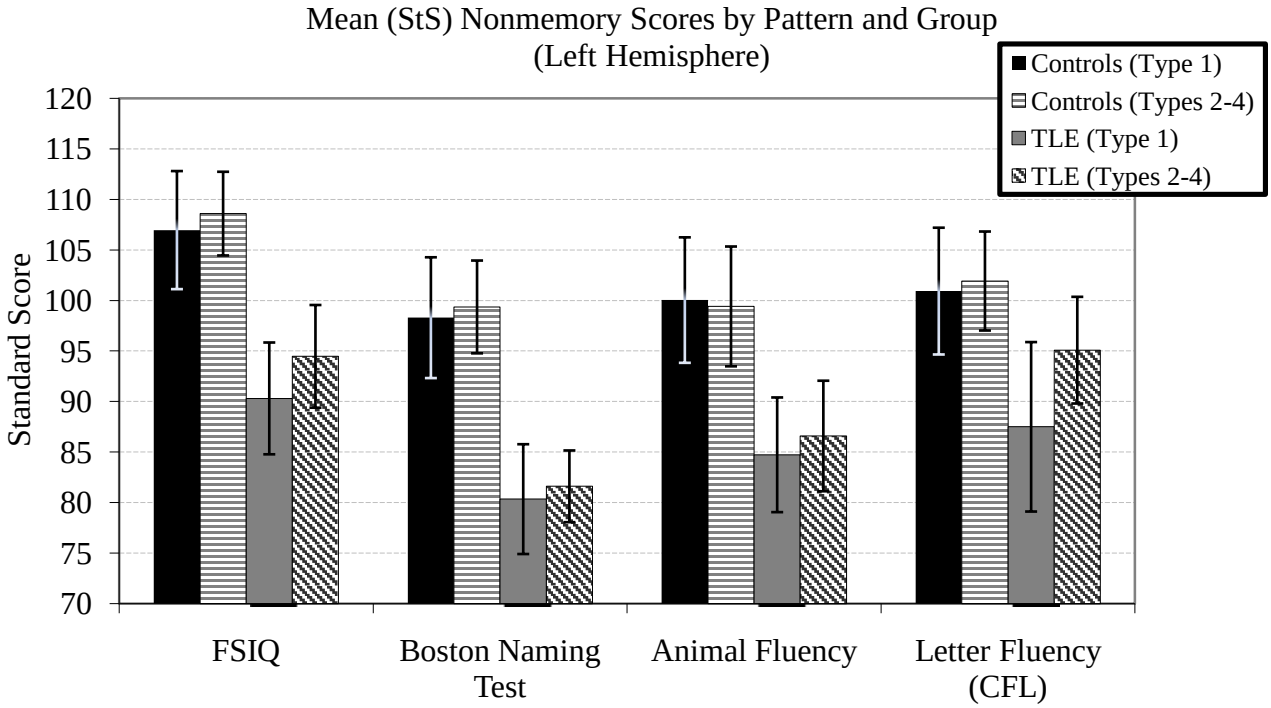

Figure 3-8. Mean IQ and language performance relative to sulcal pattern in the left hemisphere. Standard Scores are presented, with 95% confidence intervals (error bars). The control group obtained higher scores on all measures, regardless of pattern type. Bonferroni-adjusted univariate comparisons revealed no significant effect of pattern type in either group ($p > .05$).

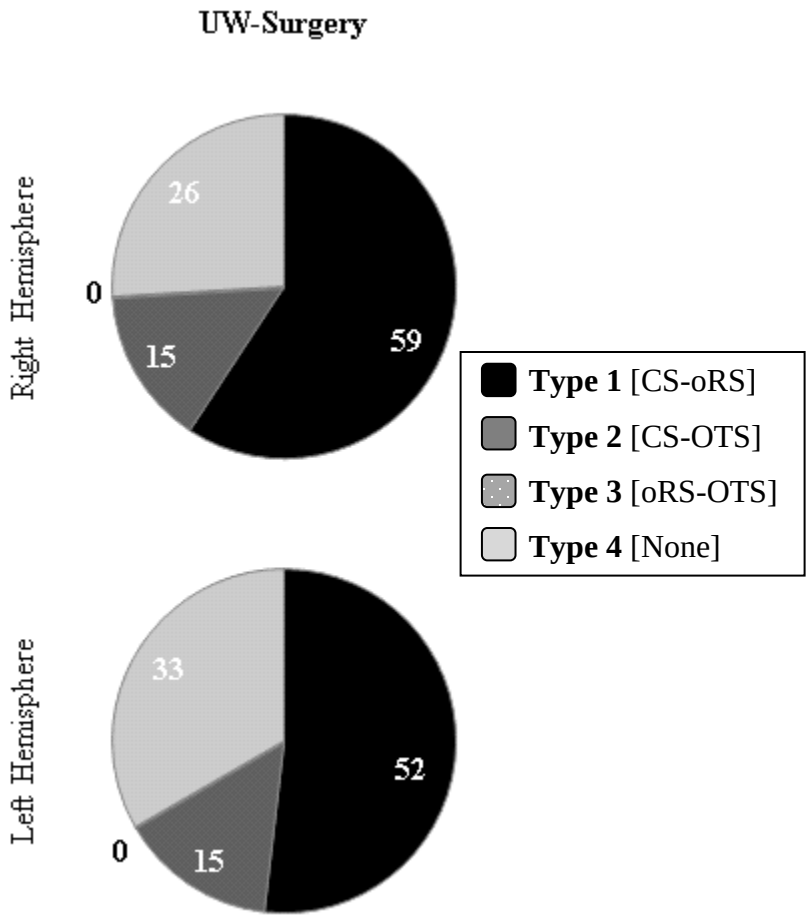

Figure 3-9. Prevalence (%) of each pattern type in the subset of UW-TLE patients who later underwent surgical resection for intractable seizures (*N* = 27).

Table 3-3. Prevalence (%) of CS-oRS connections in epilepsy patients

	Hemisphere	
Sample	Left	Right
UW-TLE (*N* = 79)	36 (24)	46 (27)
UW-Surgery (*N* = 27)	41 (33)	59 (37)
Kim (*N* = 69)	77	72
Novak (N = *50)*	38	28

Note: Values in parentheses represent prevalence (%) of "true" connections.

CHAPTER 4
GENERAL DISCUSSION

The experiments described here provide help resolve discrepancies in the literature regarding the prevalence of aTB sulcal connections in healthy adults and individuals with TLE, and extend the literature by demonstrating neurocognitive correlates of sulcal connections. These findings, their implications, and the limitations of the current study are discussed below.

aTB Sulcal Patterns: Identification and Normative Data

To our knowledge the current study developed the most detailed protocol for identification of the three main anterior temporobasal sulci and their inter-connections. In addition to facilitating future research on the structural, clinical, and functional correlates of sulcal patterns in this region, use of the SCRaP:aTB may improve methodological consistency for structural and functional neuroimaging analysis of the parahippocampal region.

The main goal of development was to establish a reliable method of classifying aTB sulci into each of four pattern types first described by Kim et al. (2008). Data from two groups of healthy adults are summarized in Table 4-1, which we hope will serve as the basis for establishing normative data. There are striking similarities in pattern prevalence between these two groups and the healthy adults studied by Kim et al. (2008), despite demographic differences (e.g., age, sex) among the three samples. First, the prevalence of Type 1 (CS-RS connections) is similar in all hemispheres and comprises the largest portion of each distribution. Second, Type 3 (RS-OTS connection; no CS connections) is very infrequent in all hemispheres. Finally, frequencies of Types 2 and 4 are similar for the left hemisphere of all three samples. Therefore, the main discrepancy between Kim et al. and the current study was the finding of a smaller proportion of Type 2 and a larger proportion of Type 4 in the right hemisphere of both the

UF/UCR and UW-C sample. Additionally, only half of each sample in this study had the same aTB pattern type in each hemisphere, whereas Kim et al. (2008) report 82% symmetry.

In the SCRaP:aTB, pattern Types 1-4 are composites derived from ratings of individual connections between the CS, RS, and OTS. One limitation of the study by Kim et al. (2008) is that they do not report the prevalence of these individual connections, which prevents direct comparison with the most widely used reference of cerebral sulci (Ono et al., 1990). To address this limitation, we present the prevalence of each connection in Table 4-2. Note that the frequencies of CS-OTS and oRS-OTS connections are higher than those of Type 2 and 3 because they include all relevant instances, regardless of the presence of other sulcal connections.

Through the process of characterizing individual sulcal connections, we discovered a possible explanation for discrepancies in the literature. During protocol development we found that a proportion of sulcal connections were ambiguous and difficult to distinguish from processing artifacts. A “pseudoconnection” option was added to the rating protocol to distinguish such cases from those with less ambiguous, “true” connections. When only true connections are included in prevalence values, our findings are very similar to Ono’s (Figures 2-5, 2-6, 2-7, and 2-8); when pseudoconnections also are counted, our frequencies differ from Ono’s but are similar to others reported in the literature (Figures 2-5 and 2-6; note that these studies only report frequencies for CS-RS connections). Ono’s findings are based on post-mortem analysis, whereas most other studies employ serial magnetic resonance images. Post-mortem examination allows for manual manipulation of cortical tissue and therefore may enable more valid differentiation of true and pseudo-connections. On the other hand, Ono may have used more conservative rating procedures to account for the possibility of tissue damage incurred during post-mortem tissue preparation. Because the current study sought to replicate and extend Kim et al. (2008), we

included both pseudoconnections and connections in all analyses; however, we include the prevalence of "true" connections in Table 4-2 (data in parentheses) since these values may be of interest for future studies.

Clinical Relevance of aTB Sulcal Patterns

Only a small handful of studies have evaluated the prevalence of aTB sulcal connections in neurological populations, with some discrepancies between findings and methods. In the only direct comparison between healthy adults and individuals with TLE, Kim et al. (2008) report striking overrepresentation of pattern Type 1 (CS-RS connection) in patients with medically intractable TLE relative to healthy controls. They propose that Type 1 may represent a simplified sulcal pattern such that the CS and RS fail to separate during neurodevelopment. This is an intriguing hypothesis. The authors found no association between pattern type and side of seizure onset, and the majority of patients had the same pattern in both hemispheres. Combined, these observations suggest that seizures do not directly affect sulcal development; rather, lack of differentiation between the CS and RS may reflect genetic or neurodevelopmental factors associated with onset of spontaneous seizures, or may facilitate seizure propagation in the presence of other etiologies. Zhan et al. (2009) also found a significantly larger frequency of CS-RS connections in individuals with Alzheimer's disease compared with age-matched and younger adults, suggesting that this "simplified" morphologic pattern may represent a more general anatomic vulnerability to medial temporal lobe pathology.

Novak et al. (2002) also evaluated the prevalence of aTB sulcal connections in TLE, though they used different methods than Kim et al. (2008) and did not include a healthy comparison group. Novak et al. found a much lower prevalence of aTB sulcal connections in patients with TLE than reported by Kim and colleagues, and their findings are consistent with post-mortem results reported by Ono et al. (1990). Results presented by Novak et al. therefore

challenge the hypothesis proposed by Kim et al. Additionally, this raises concerns about significant methodological differences in the literature, which may complicate replication and extension by other research groups.

Neuroimaging methods in the current study were more analogous to those used by Kim et al. (2008) than by Novak et al. (2002). Therefore, our main analyses and classification system were based on the former. Nonetheless, we failed to replicate the finding of significant group differences in any of the four aTB pattern types proposed by Kim et al. despite having adequate sample size based on *a priori* power analysis. However, when only "true" (not "pseudo") connections were considered, our results replicate those of Novak et al. (Table 3-4). True connections may be more analogous to connections identified by Novak's group because direct analysis of serial slices allows for closer visualization of sulcal connections below the cortical surface.

Kim et al. (2008) discussed several potential reasons for the discrepancy between their findings and those of Novak et al. (2002). The fact that we were able to replicate Novak et al. using methods more similar to those used by Kim et al. provides counter-evidence for these explanations. For example, Kim et al. cite the higher resolution of their images relative to those used by Novak et al. as a possible reason for their discrepant results. Specifically, Kim used 1 mm slice thickness whereas Novak had only 2-4 mm slices. In the current study, slice thickness was 1.5 mm for the UW-C and UW-TLE samples and 1 mm for the UF/UCR sample (<1mm in the axial plane). Therefore, the resolution of our images was better than that in Novak's study and almost as good as Kim et al. It is unlikely that resolution fully accounts for differences between our and Kim's findings, particularly since we replicated many of their group's results in healthy adults. Kim and colleagues also note Novak's use of coronal slices rather than composite

renderings of the cortical surface. However, that criticism does not apply to the current study, which employed three-dimensional renderings of the cortical surface generated by the same computer program (BrainVISA) as used by Kim et al.

One potentially relevant difference between our study and Kim et al. (2008) is that our patient sample is more clinically heterogeneous and, on average, less severe. Only 47 of the 79 (59%) UW-TLE patients have "definite" TLE confirmed by video EEG, and only 27 (34%) have since undergone surgical resection to treat intractable seizures. In contrast, Kim's sample included only medically intractable cases of confirmed TLE, 64% of which underwent surgical resection. Pattern prevalence in our surgical subgroup (Figure 3-9) appears more similar to Kim's findings than for our overall sample but still does not replicate the dramatic overrepresentation of Type 1 relative to controls (note, however, that statistical analysis was not possible due to sample size). A counter-point to this argument is that Novak et al. (2002) report even lower frequencies of CS-oRS connections in a TLE group comprised entirely of surgical candidates.

Neurocognitive Relevance of aTB Sulcal Pattern

To our knowledge the current study is the first to directly evaluate the neurocognitive relevance of aTB sulcal pattern types; however, there is a precedent for doing so. For example, Nakamura et al. (2007) report significant associations between orbitofrontal sulcal patterns and cognition in healthy adults and patients with schizophrenia, and several groups have described associations between paracingulate sulcal morphology and cognitive functioning (e.g., Artiges et al., 2006; Crosson et al., 1999; Fornito et al., 2004).

Contrary to our predictions, we failed to demonstrate an overall association between CS-oRS connection and cognition or a specific association between sulcal pattern and verbal recall, which is typically associated with medial temporal lobe integrity. However, we did demonstrate

a significant relationship between sulcal pattern and visual memory, and this relationship was in the predicted direction. Specifically, presence of CS-oRS connection in the right hemisphere was associated with lower visual memory scores when compared with Types 2-4, and this relationship was only significant in the patient group. These findings must be interpreted with caution in light of nonsignificant omnibus results and the chance for family-wise error. Nonetheless, the nature of the effects is consistent with all three of our predictions: (1) that Type 1 would be associated with worse memory; (2) that associations would be strongest for delayed recall; and (3) that this relationship would be more robust in patients than controls. Moreover, the association between visual memory and sulcal pattern was larger in the right hemisphere, which is consistent with the classic theory of material specificity (Milner, 1970).

Demographic Considerations

Though not a primary focus of the current study, sex and age were explored in the context of aTB sulcal pattern type. Results from all three samples are summarized in Tables 4-3 (age) and 4-4 (sex).

Our two age-matched samples from the University of Wisconsin (UW-C and UW-TLE) were similar in age relative to the samples used by Kim et al. (2008) but were significantly older than the UF/UCR sample. Nonetheless, there were no significant differences in sulcal pattern distribution between the UW and UF/UCR samples and there were significant differences between our and Kim's findings. Moreover, our results in the patient group more closely replicate those reported by Novak et al. (2002), whose participants ranged in age from 3 to 48 years old. Therefore, it is not likely that age-related factors account for our key findings. Follow-up analyses confirm that there is no significant relationship between aTB sulcal pattern type and age in our samples ($p > .05$), which is consistent with the theory that sulcification occurs early during development. To our knowledge, Zhan et al. (2009) is the only study that has

formally compared aTB sulcal connections in older and younger adults, and they only describe the frequency of CS-oRS connections. The team found no significant group differences in either hemisphere.

Regarding differences between men and women, prior research suggests there is no association between sex and aTB sulcal pattern in healthy adults (Hanke et al., 1997; Kim et al., 2008; Zhan et al., 2008). In TLE, both Novak and Kim found that CS-oRS connections are more prevalent in men, whereas women more often have no CS connections. In the current study, there were no significant relationships between sex and pattern type in either control group or in the patient group. The only association with sex that approaches significance is for the right hemisphere in the UW-C control group, such that men have a higher prevalence of Type 1 (z = 1.3) and a lower prevalence of Type 2 (z = -1.3). This discrepancy warrants further attention in future studies and is important to consider if using the current data as a normative sample for research relevant to sex-related differences.

Conclusions

Characterization and replication of human cortical anatomy is difficult, as evidenced by the wide variability of methods and data published in even the most esteemed peer-reviewed journals. The current study is no exception – despite careful attention to methodological detail, we failed to replicate robust group differences in aTB sulcal morphology between TLE patients and controls reported by a recent study (Kim et al., 2008). However, we did succeed in replicating normative prevalence of CS-RS connections as reported by several previous studies, and we replicated the prevalence of CS-RS connections in TLE as reported by Novak et al. (2002). In developing this rating protocol and comparing results across studies, we identified a possible explanation for discrepancies in the literature.

A major premise of our cognitive predictions was that Kim et al. found a disproportionate overrepresentation of Type 1 in epilepsy patients and proposed that continuity between the CS and oRS represents a neurodevelopmentally primitive morphological configuration. The absence of group differences in the current study raises questions about the validity of this conceptualization. Given that there were no significant group differences in pattern prevalence, it is not surprising that there also were no overall associations between memory and pattern type. Differences in clinical severity between our patient sample and that of Kim et al. may explain our inability to replicate their key finding and, by extension, the relative insensitivity of our anatomic data to comparisons with neurocognitive measures. Nonetheless, we did identify one cognitive finding in the direction of our predictions, which is that patients with a CS-oRS connection in the right hemisphere perform worse on visual recall tasks than those without a connection. In the context of our positive findings in healthy adults and known limitations of our patient sample, this isolated finding may be meaningful and suggests that follow-up studies with more clinically severe samples may be warranted. Moreover, future studies may wish to formally evaluate the relationship between sulcal morphology and demographic variables (e.g., education, handedness) in healthy adults and clinical variables such as seizure frequency and severity, pre- and peri-natal injury, and genetic risk.

Table 4-1. Prevalence (%) of each pattern type in three healthy control samples

		Kim et al. (*N* = 51)		UF/UCR (*N* = 196)		UW-C (*N* = 70)	
Type	Description	Left	Right	Left	Right	Left	Right
1	CS-RS connection	47	41	47	41	40	41
2	CS-OTS; no CS-RS	31	35	35	19	31	17
3	RS-OTS; no CS-RS; no CS-OTS	6	4	3	2	3	6
4	No connections	16	20	16	39	26	36

Table 4-2. Prevalence (%) of inter-sulcal connections

	UF/UCR (*N* = 196)		UW-C (*N* = 70)	
Connecting Sulci	Left	Right	Left	Right
CS-oRS	47 (31)	41 (25)	40 (29)	41 (26)
CS-OTS	61 (35)	34 (10)	51 (23)	26 (9)
oRS-OTS	29 (11)	23 (9)	24 (7)	13 (4)

Note: Data in parentheses represent only "true" connection ratings (i.e., no pseudoconnections).

Table 4-3. Age ranges in each sample and in the comparison study

	Age		
Sample	*M*	*SD*	Range
Kim (control)	32.00	11.00	20-56
Kim (TLE)	32.00	9.00	16-49
UW-C	33.40	12.59	14-59
UW-TLE	35.56	11.12	14-59
UF/UCR	21.56	3.47	18-34

Table 4-4. Association between sex and pattern type in each sample

		Effect Size (*V*)	
Sample	M / F	Left	Right
UW-C	28 / 42	0.12	0.29
UW-TLE	22 / 57	0.10	0.18
UF/UCR	99 / 97	0.14	0.11

APPENDIX A
SCRAP:ATB TRAINING SLIDES

Sulcus Classification Rating Protocol: Anterior Temporobasal Sulci (SCRaP:aTB)

1

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FEBRUARY 2010

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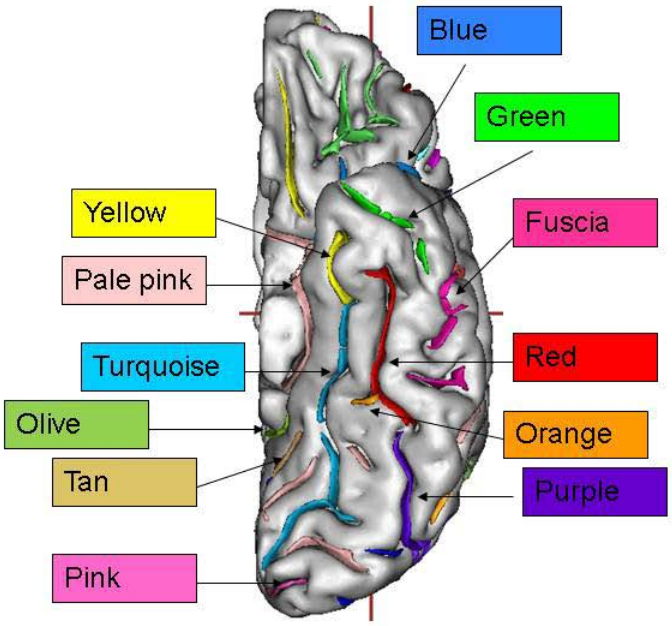
General Overview & Orientation

2

3

Color Key

This protocol uses surface renderings produced via BrainVisa (BV). Images include color-filled sulci based on an automatic labeling rubric. The most relevant colors are presented for reference in the image on the right.

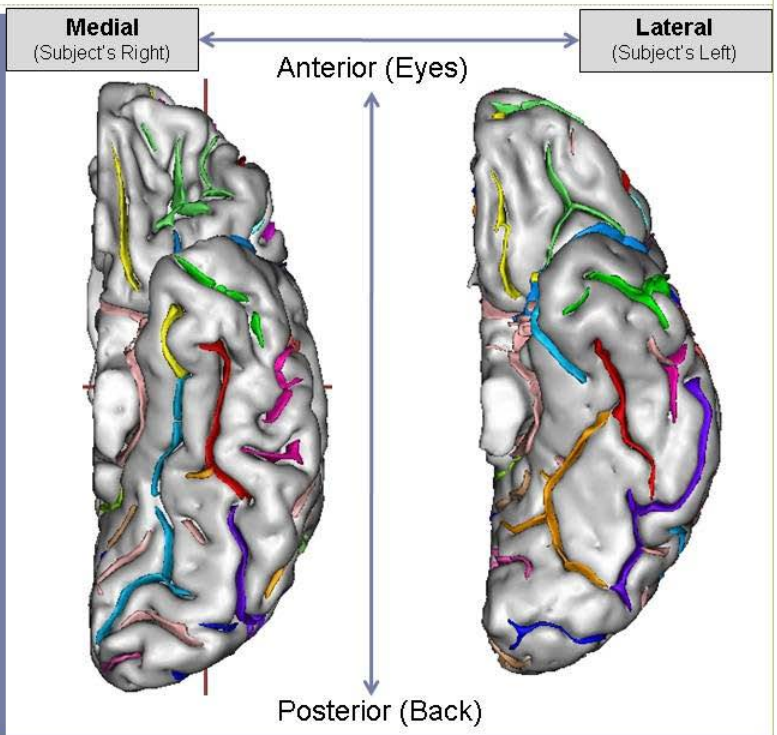


4

Ventral Surface (Left hemisphere)

These sample images show the VENTRAL surface of the LEFT hemisphere.

When viewing the ventral surface, note that the left and right sides of the 2D image are reversed relative to the subject's right and left. For example, for the left hemisphere (see samples on this slide), the lateral edge of the hemisphere is on the left from the subject's viewpoint but appears on the right side of the image on the screen.

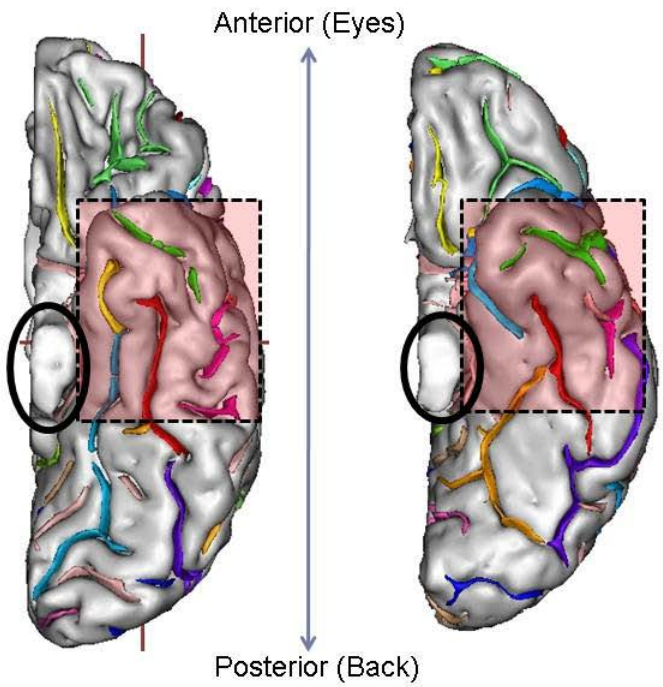


5

Anterior Temporobasal (aTB) region

This protocol focuses on the anterior half of the temporal lobe (highlighted with red overlay here).

Note the Pons (solid black circles), which is an important landmark.



aTB Sulci

6

- This protocol focuses on three main sulci:
  - Collateral Sulcus (CS)
  - Ono's Rhinal Sulcus (oRS)
  - Occipitotemporal Sulcus (OTS)
- The colors used above are those used by BV for these three sulci. Therefore, these colors are used throughout this training presentation and in the rating spreadsheet.

⚠ ***WARNING:*** *Despite the above, sulcal labels in BV are often incorrect and can be misleading. Therefore, when identifying the aTB sulci:*

DO NOT RELY ON THE BV COLOR LABELS.

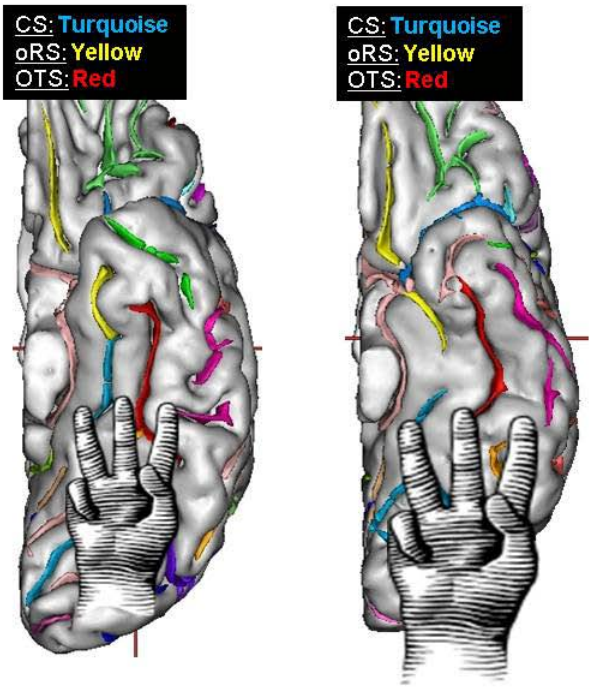
7

aTB Sulci: Overview

The temporobasal surface has 3 roughly anterior-posterior gyri, like 3 long fingers:

1. The CS and oRS form the lateral boundary of the first (most medial) gyrus
2. The OTS forms the boundary between the 2nd and 3rd gyri.

Note that these relationships may not always be as clear as in the images to the right, which are presented as prototypes for the purpose of general orientation.



Rating Spreadsheet

8

FILE		1. Collateral Sulcus (CS)		2. oRS	3. OTS	4. Sulcal relationships			
ID	Side	1(a) Color	1(b) Lat veer	2(a) Color	3(a) Color	4(a) CS-oRS	4(b) CS-OTS	4(c) oRS-OTS	NOTES

Slides 9-14

Slides 15-20

Slides 21-28

Slides 29-38

1. Collateral Sulcus (CS)

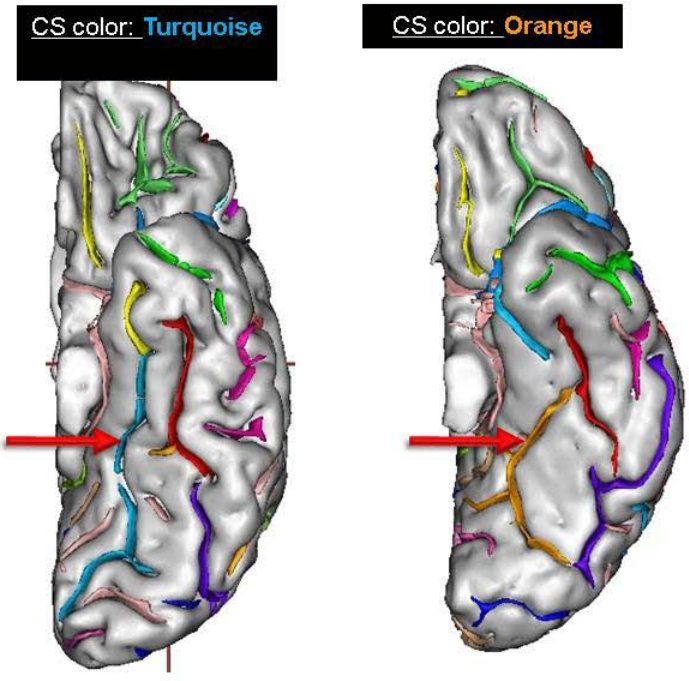
9

1. Collateral Sulcus (CS)	
1(a) Color	1(b) Lat veer
Absent	Yes
Unlabeled	No
Yellow	
Red	
Turquoise	
Orange	
Tan	
Pale Pink	
Green	
Fuscia	
Other	

10

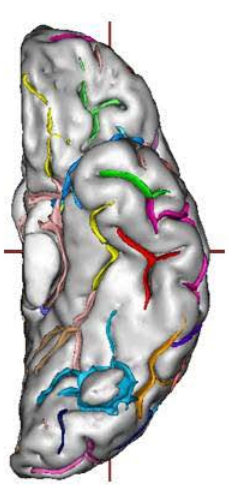
☑ Rating 1(a): CS Color

1. Identify the posterior edge of pons
2. Moving laterally, find *the most medial sulcus* that is oriented parallel to the medial edge of the hemisphere (anterior/posterior course)
3. Select the color of the CS *at this level*

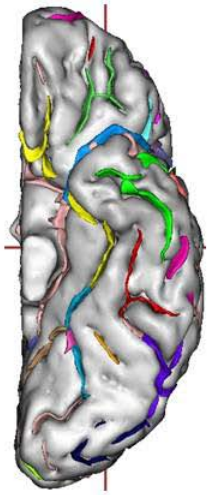


1(a): CS Color: Samples

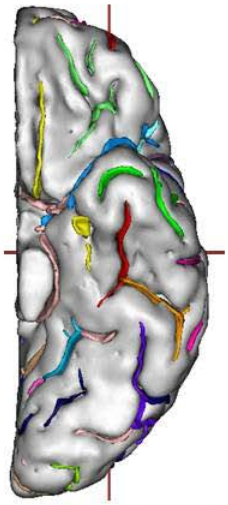
11



CS: Pale Pink



CS: Turquoise



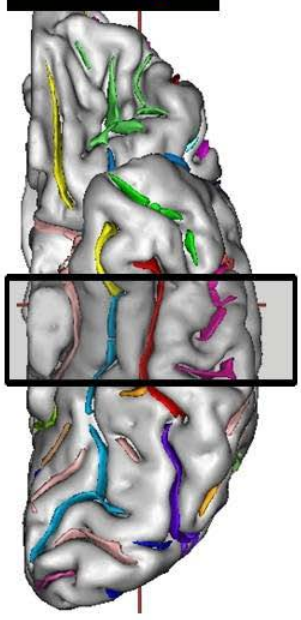
CS: Turquoise

12

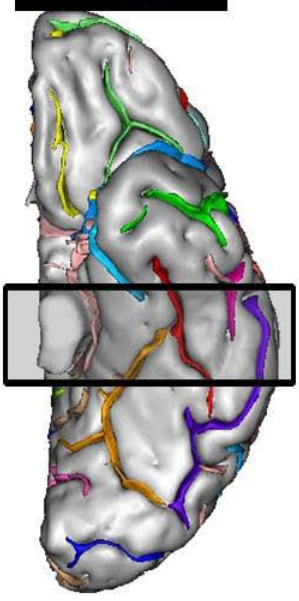
☑ Rating 1(b): CS Veer

1. Focus on the area lateral to the pons posterior to the widest portion of the pons (area outlined in black here).
2. Determine whether the anterior portion of the CS veers laterally such that the gyrus medial to the CS is wider towards the anterior end than the posterior portion.

Veer: NO



Veer: YES

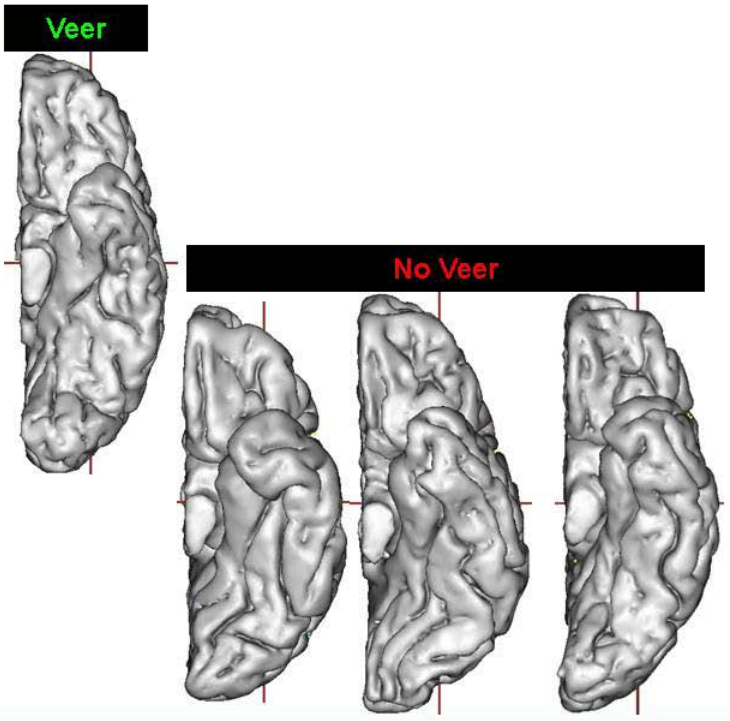


13

★ Rating Tips: CS Veer

✓ This rating is best done without color labels

✓Subtle variations in gyrus width are normal and therefore do not qualify as a "veer"

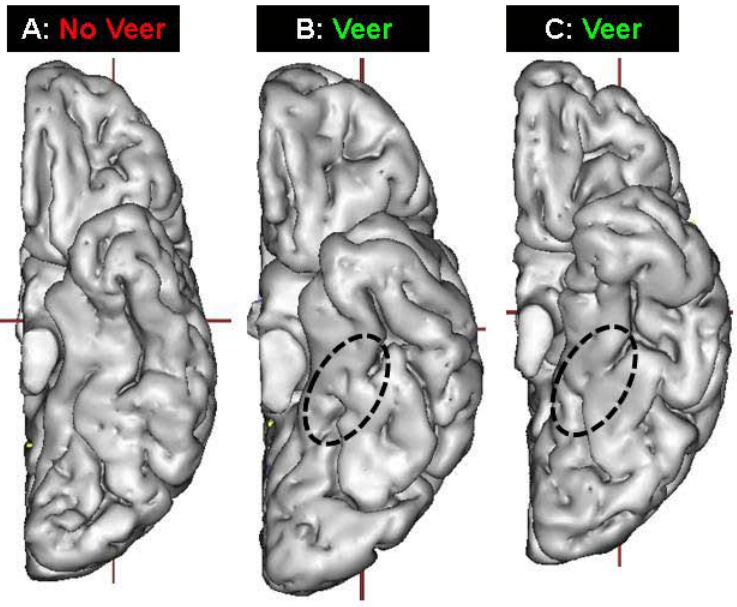


14

★ Rating Tips: Veer (cont)

✓ Rate whether the visible CS actually veers rather than whether it's "on its way" (sample A)

✓ If there are multiple segments of the CS at the level of the pons, base the "Veer" rating on the overall course, as if there were no gap between segments (samples B and C)



2. Ono's Rhinal Sulcus (oRS)

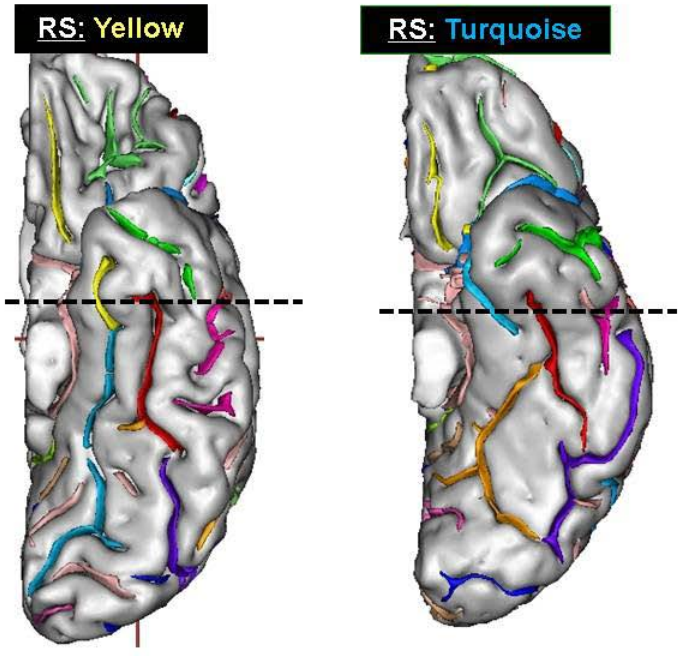
15

2. oRS	
2(a) Color	2(b) Edge
Absent	No
Unlabeled	Close
Yellow	Wrap
Red	
Turquoise	
Orange	
Tan	
Pale Pink	
Green	
Fuscia	
Other	

16

☑ Rating 2(a): oRS Color

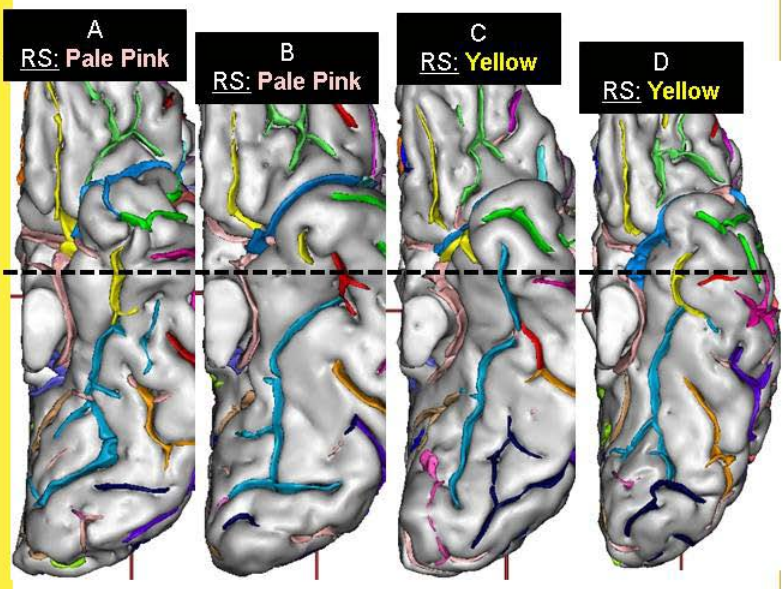
1. Imagine a cross-sectional line beginning just anterior to the pons (see dotted lines).
2. The *most medial sulcus* in this region is the oRS.
3. Identify the color of this sulcus.



17

★ Rating Tips: oRS

✓ Sometimes one sulcus may be the most medial one at this level, and yet there is another, more medial sulcus that ends anterior to this point. Choose this second sulcus if it extends close to this line (samples A, B, C) but not if it is only a short segment (sample D).



18

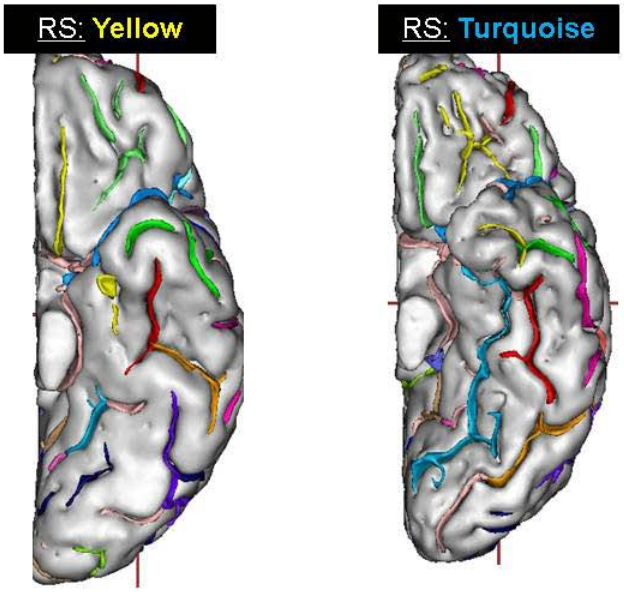
★ Rating Tips: oRS Colors

Multiple colors:

✓ If the oRS is labeled with more than one color, base ratings on the main color (the color that fills the largest portion of the sulcus).

✓ If there is no clear "main" color, choose the most posterior color.

✓ If a portion of the sulcus is unlabeled, choose the color that *is* there, even if it is only a small part of the sulcus.

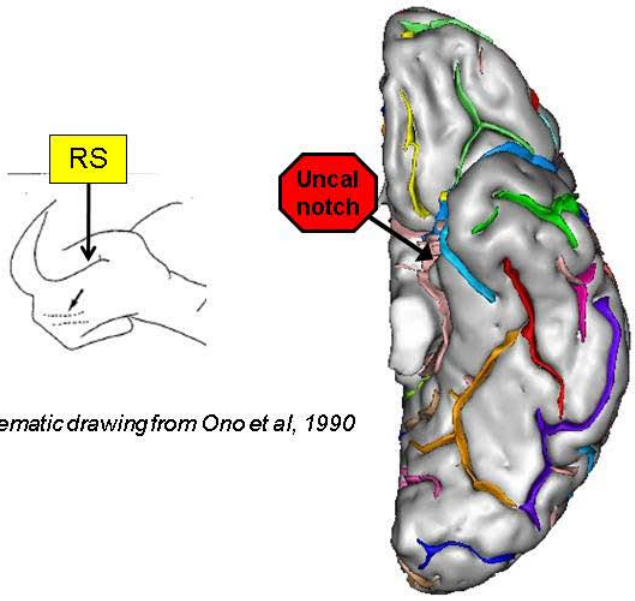


19

★ **Rating Tip:**
Area Medial to oRS

Sometimes (but not always) there is a short notch or indentation present at the very medial edge of the hemisphere, just anterior to the pons. This is known as the uncal or tentorial notch.

Notch vs oRS:
✓ More medial and close to the pons
✓ Very short
✓Not a "true" sulcus (sometimes just looks like a dent)

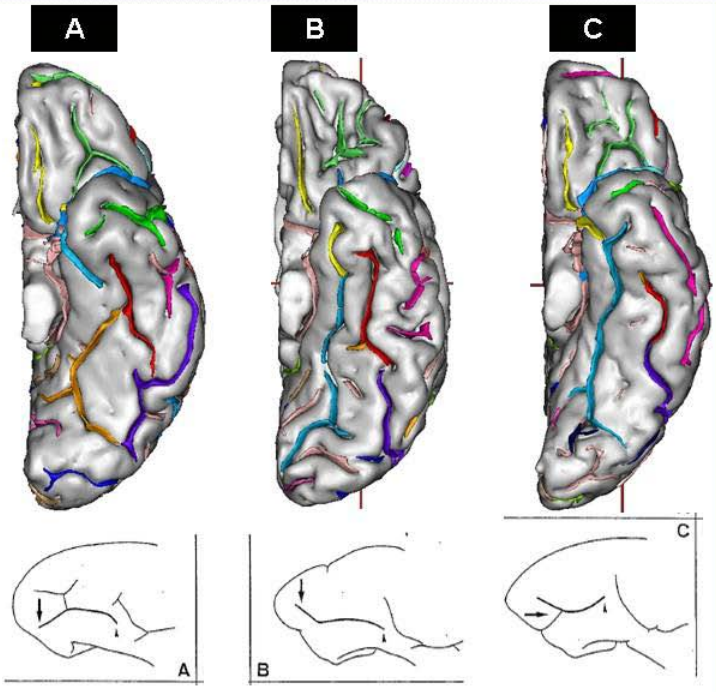


Schematic drawing from Ono et al, 1990

20

★ **Rating Tip:**
oRS Course

Course/Trajectory
✓ oRS may appear to angle towards the medial edge (Column A), extend towards the temporal pole (Column B), or both (Column C).



Schematic drawings from Ono et al, 1990

Occipitotemporal Sulcus (OTS)

21

3. OTS
3(a) Color

Absent
Unlabeled
Yellow
Red
Turquoise
Orange
Tan
Pale Pink
Green
Fuscia
Other

22

★ Rating Tip: OTS overview

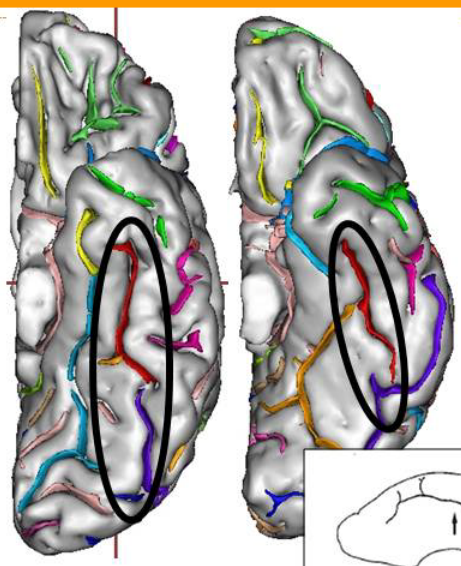
Location:

- Immediately lateral to CS (no sulci between CS/OTS)
- Forms the boundary between the 2nd and 3rd long gyri (see slide 7)
- May extend anterior to CS

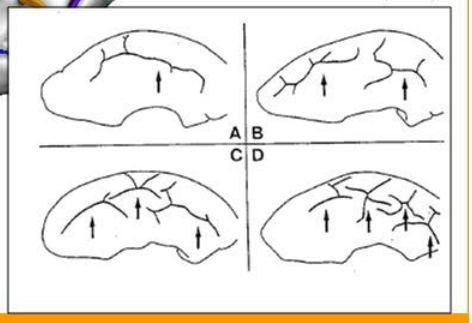
Course:

- Mostly anterior-posterior but may not follow a strictly longitudinal course

***NOTE:** The OTS is highly variable in shape and is often broken into multiple segments.*



Schematic drawings from Ono et al. (1990)

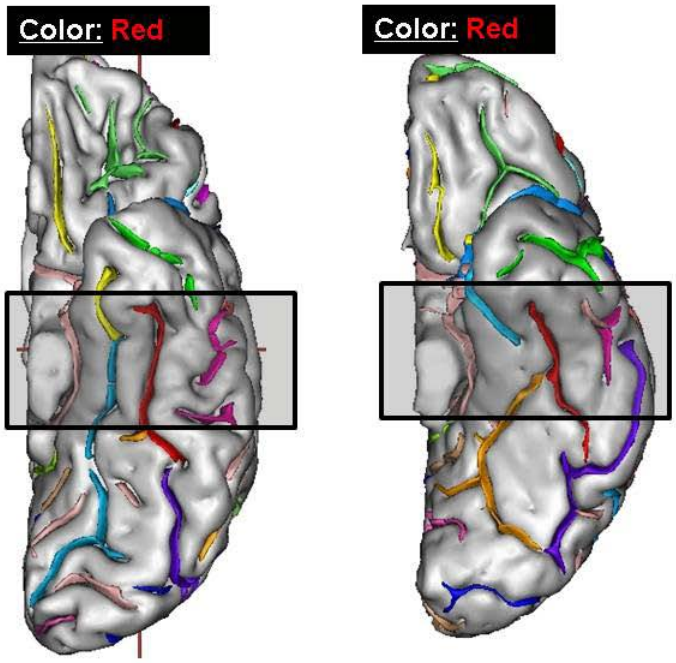


23

☑ Rating 3(a): OTS Color

1) Focus on the portion of the OTS anterior to the posterior edge of the pons

2) Identify the primary color of the OTS in this region



24

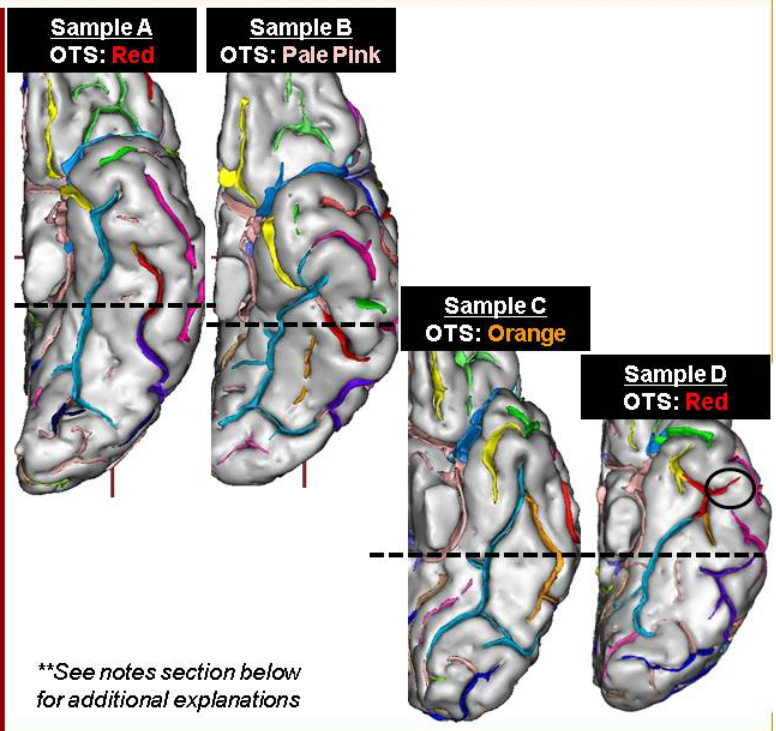
★ Rating Tip: Multiple Colors

If the sulcus has multiple colors in this region, follow these guidelines:

A. Base ratings on the *main* color in this region (sample A)

B. If there is no clear main color, base ratings on the *most anterior color* (sample B)

C. If the OTS connects with another sulcus in this region and it is difficult to differentiate the two sulci, use the color of the OTS at its most anterior *nonmerged* point (sample C).



***See notes section below for additional explanations*

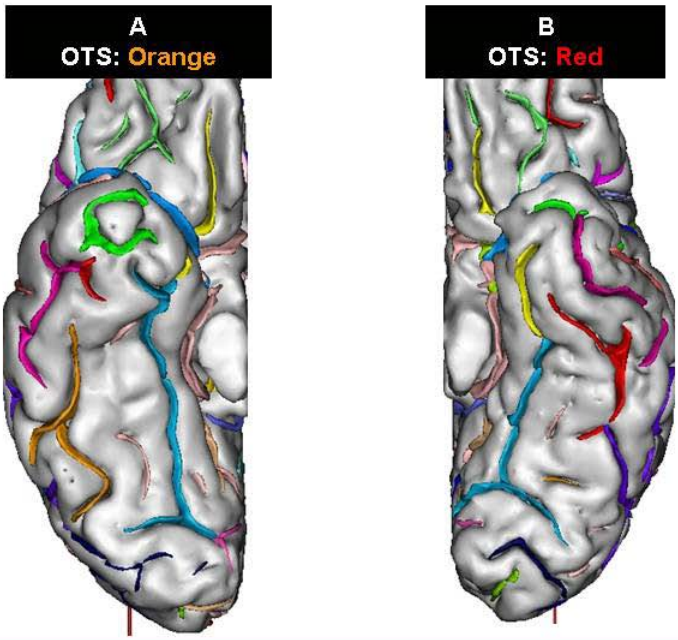
25

★Rating Tip: Double Parallel

The OTS can have two, parallel segments. In these cases, the more medial segment is often not labeled and may be subtle or appear perforated.

Rating:

- For the color rating, abide by the same rules as for a single OTS (see previous slide).
- When rating connections, make sure to pay attention to *both* segments.

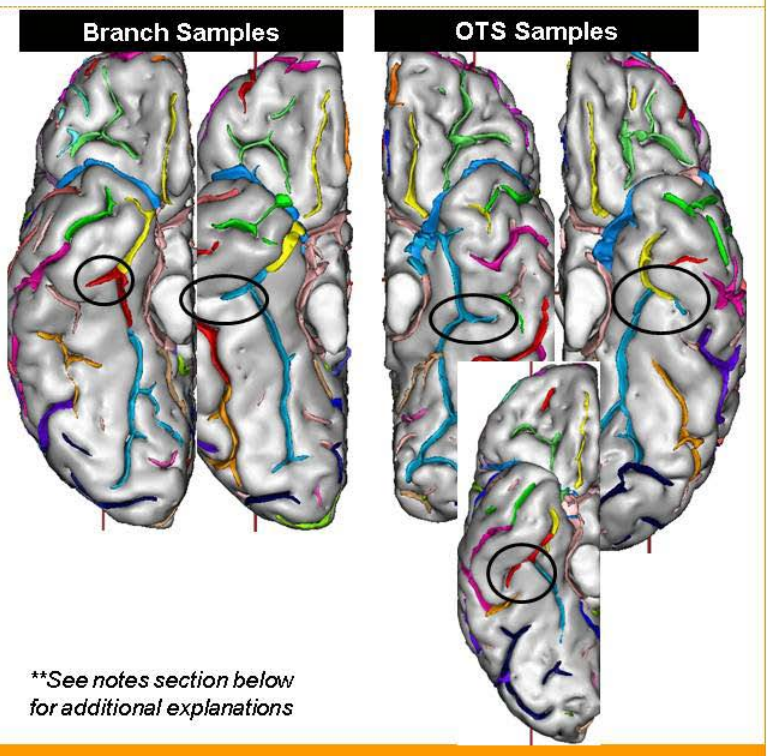


26

★Rating Tip: OTS vs Branches

To differentiate a branch of the CS or oRS from the OTS, use these rules:

- Branches have a medial-lateral course rather than anterior-posterior. Therefore, they do not form the medial or lateral boundary of a gyrus.
- A branch can occur at the junction of the CS/oRS, or anterior to the pons.



***See notes section below for additional explanations*

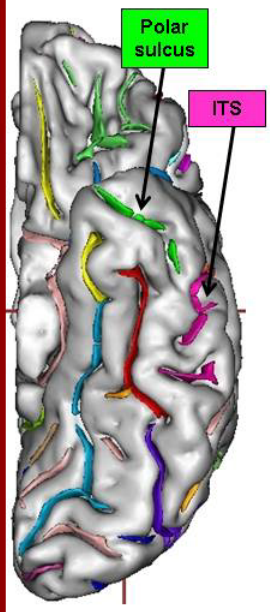
27

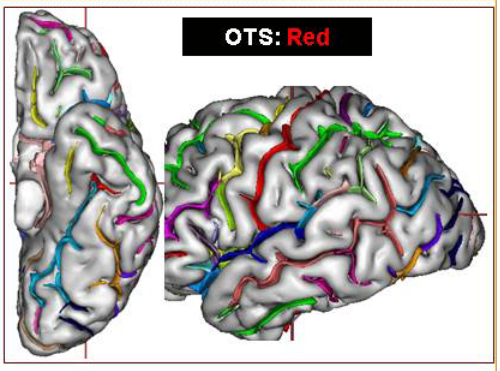
★Rating Tip:
Area lateral to OTS

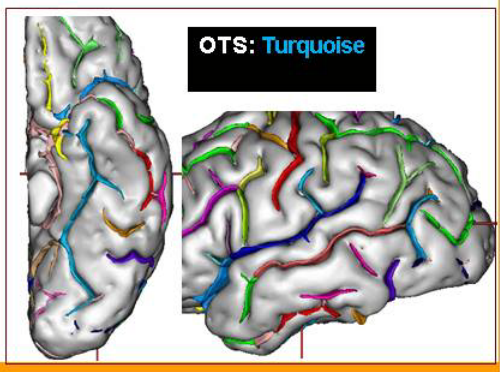
Inferior Temporal Sulcus (ITS):
- Lateral boundary of the 3rd gyrus
- Primarily on the *lateral* surface (OTS is primarily on the *basal* surface)

Polar Sulcus
- Extends into the temporal pole (more anterior than OTS)
- Often visible on lateral surface

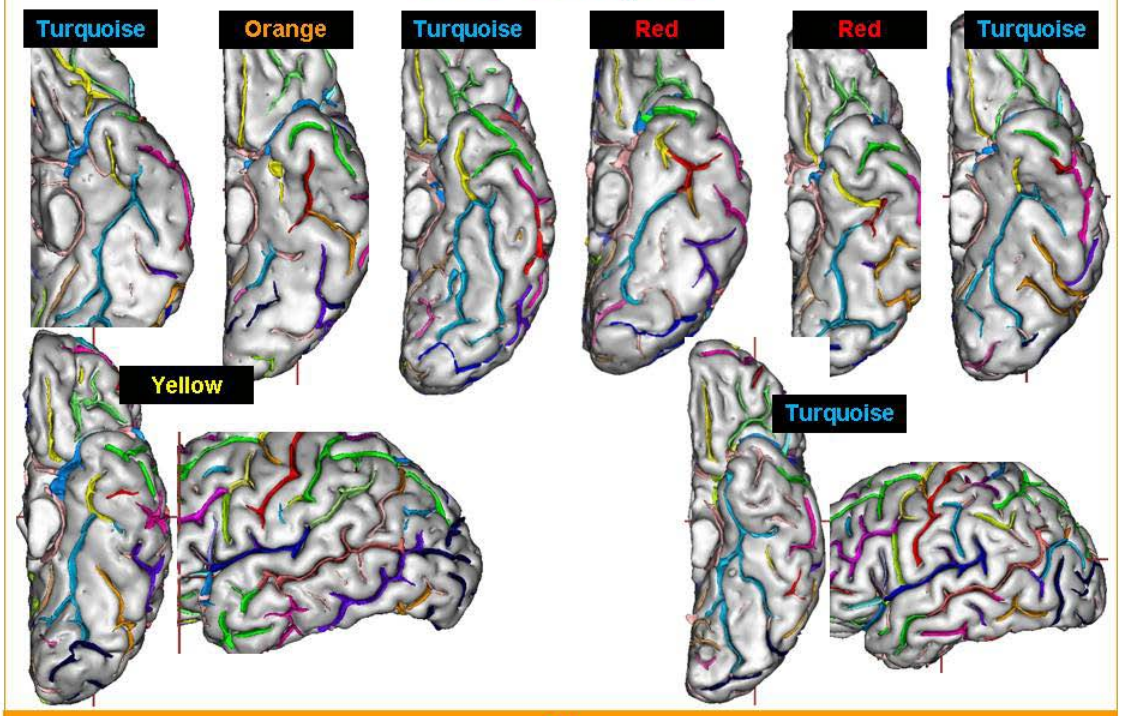
TIP: *To differentiate the OTS from more lateral sulci, it may be helpful to examine the lateral surface of the temporal lobe.*







OTS Samples



28

Sulcal Relationships

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4. Sulcal relationships		
4(a) CS-oRS	4(b) CS-OTS	4(c) oRS-OTS
Connection	Connection	Connection
Pseudoconnection	Pseudoconnection	Pseudoconnection
Overlap	None	None
None		

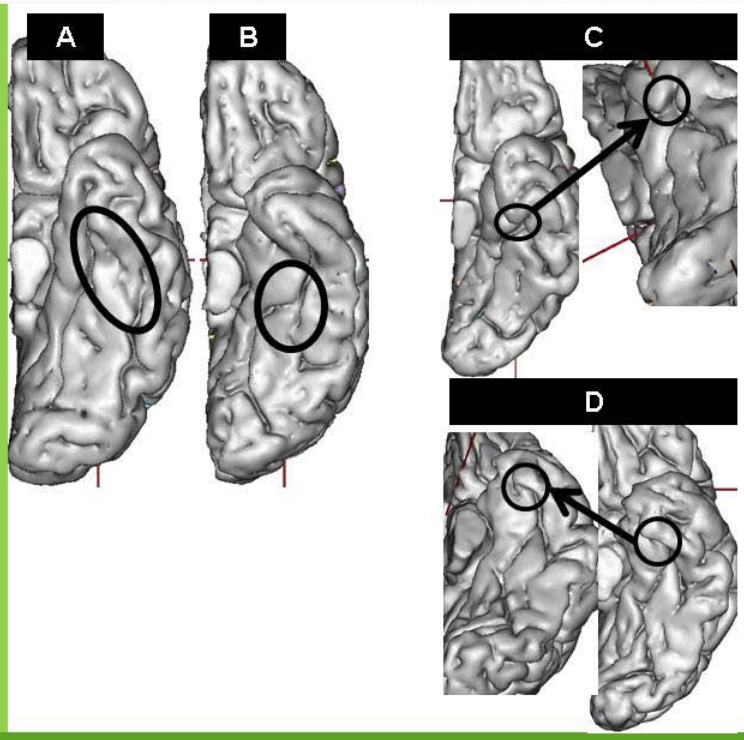
30

★ Rating Tip:
Pseudoconnection

Sometimes it is not clear whether two sulci are truly connected. Such cases are "Pseudoconnections."

Sample scenarios:

- One of the sulci may not be a clear/deep sulcus (Sample A)
- One sulcus may be shallower than the other sulcus at the point where they seem to connect (Sample B)
- There may be a very small gap between the sulci (Samples C & D)



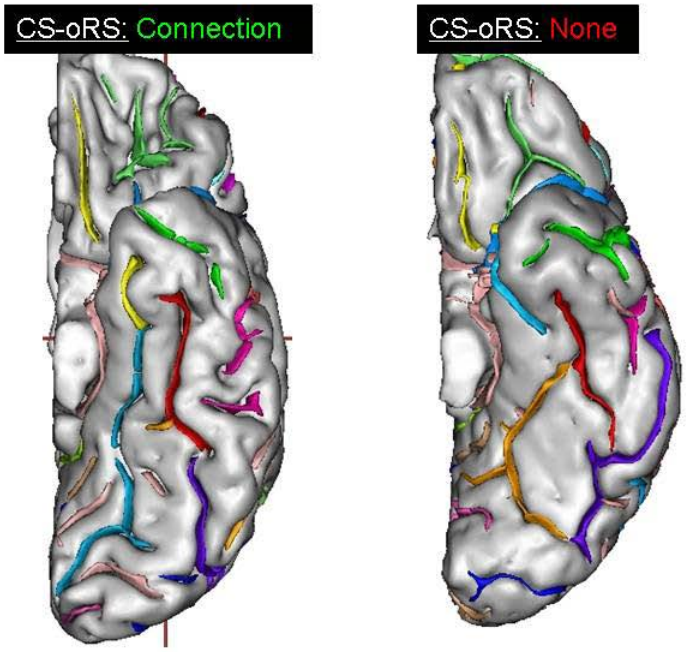
31

☑ Rating 4(a): CS-oRS

1. Determine the nature of the relationship between the CS and oRS

OPTIONS:

- Connection
- Pseudoconnection
- Overlap
- None

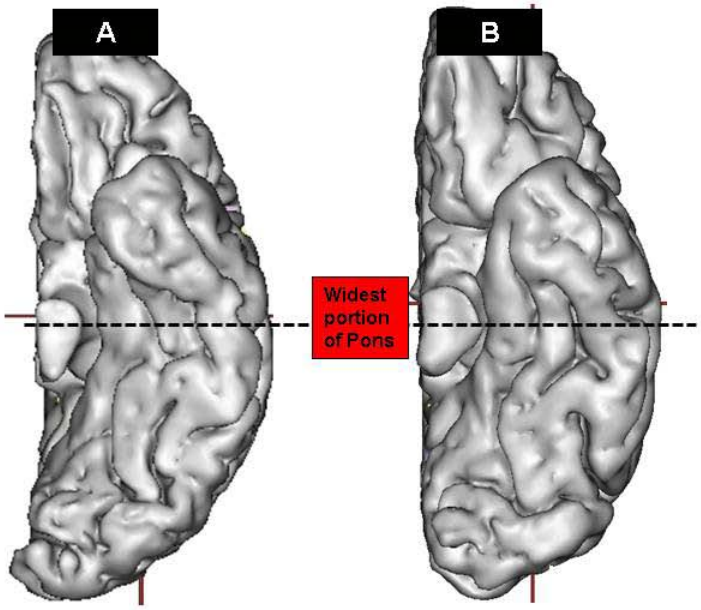


32

★ Rating Tip: CS-oRS Connection

- Sometimes the oRS appears to extend posterior to the widest portion of the pons, with a small gap between it and the CS. ***Rate these cases as a CS-oRS connection.***

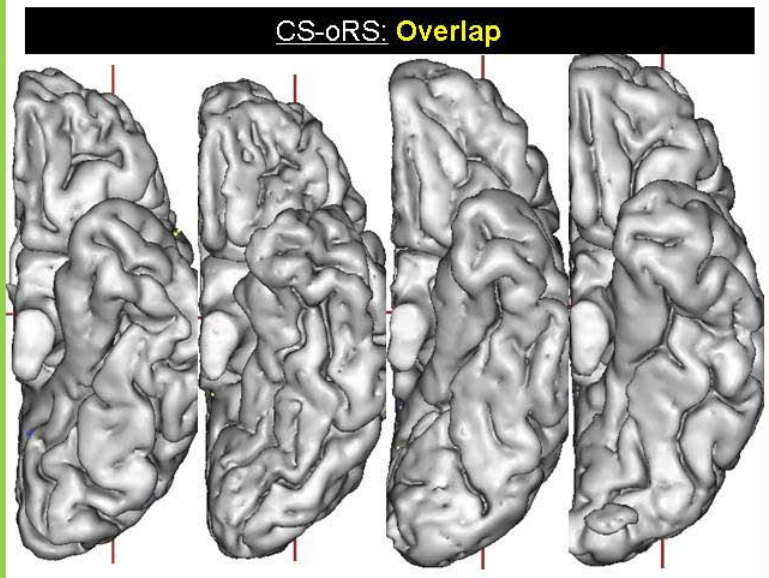
NOTE: Though this rating conflicts with the visual image, it is based on the assumption that the posterior portion of the oRS in these cases is actually the anterior portion of the CS.



33

★ Rating Tip:
CS-oRS Overlap

The "Overlap" option describes the scenario depicted in the images here, in which the CS extends sufficiently far anterior such that it becomes lateral to the oRS.

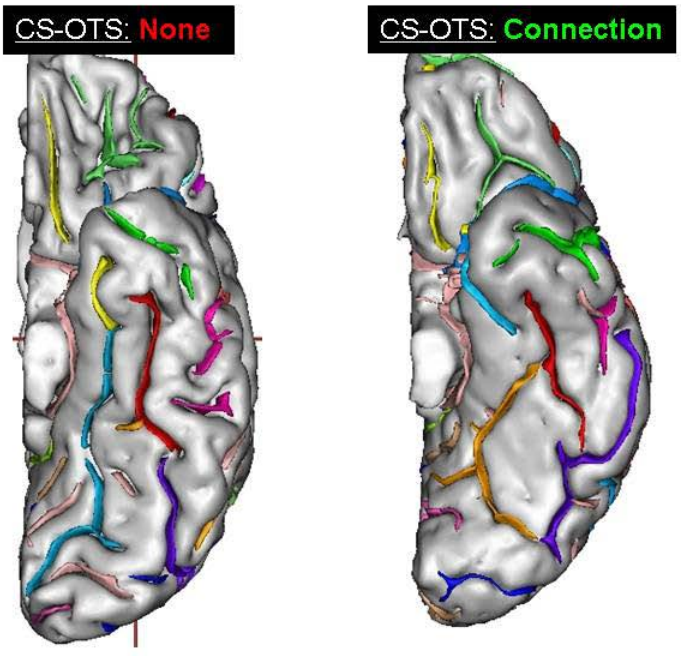


34

☑ Rating 4(b):
CS-OTS

1. Determine the nature of the relationship between the CS and OTS

OPTIONS:
- Connection
- Pseudoconnection
- None



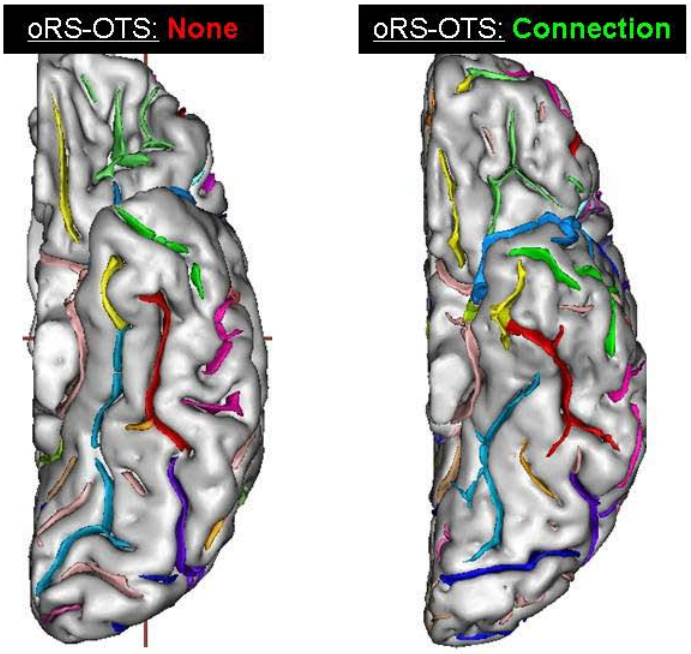
35

☑ Rating 4(c): oRS-OTS

1. Determine the nature of the relationship between the oRS and OTS

OPTIONS:

- Connection
- Pseudoconnection
- None



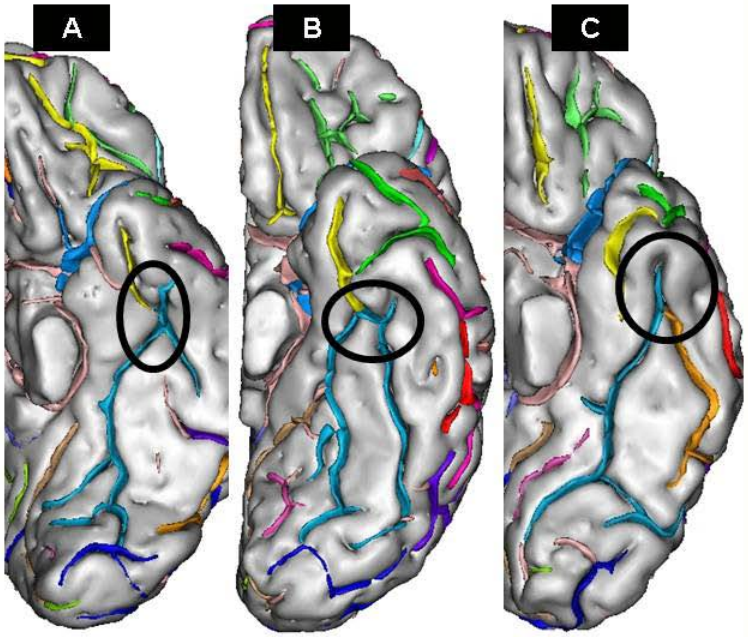
36

★ Rating Tip: OTS Connections

Connections with the OTS may take one of several forms:

- End-to-side connection (sample A)
- Connection via side branch (sample B)
- Convergence (sample C)

***NOTE:** You do not need to identify the type of connection, just whether there is a connection*



37

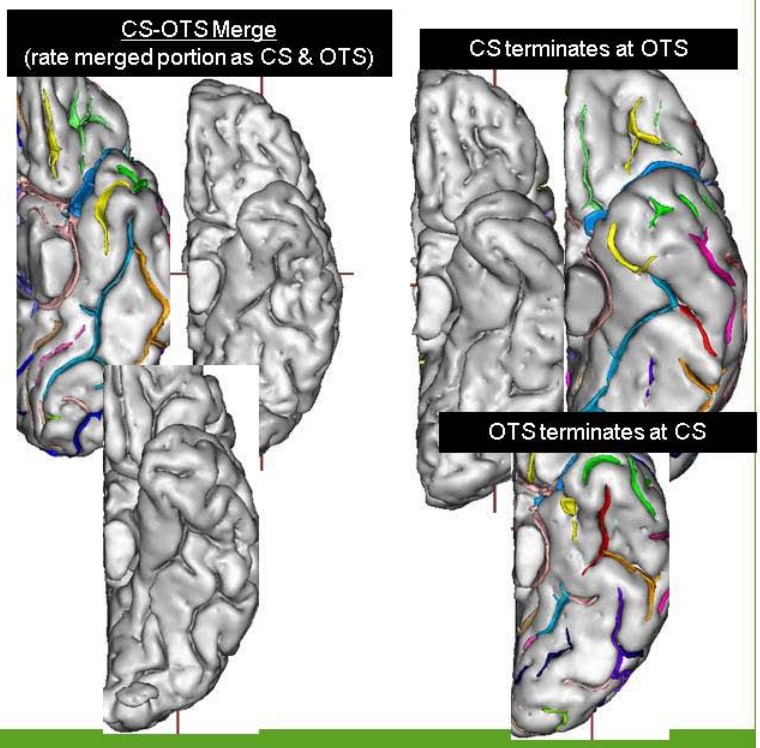
★ Rating Tips:
Inter-relationships

When the CS and OTS merge, sometimes it is difficult to determine where one ends and the other begins. Therefore, treat the merged portion of the sulcus as ***both*** the CS and OTS.

Sometimes it ***is*** possible to differentiate the two. For example:

A) If the CS hits the OTS at a sharp angle, it is terminating at rather than merging with the OTS.

B) If the OTS terminates at the CS, creating a sharp-angled junction.



38

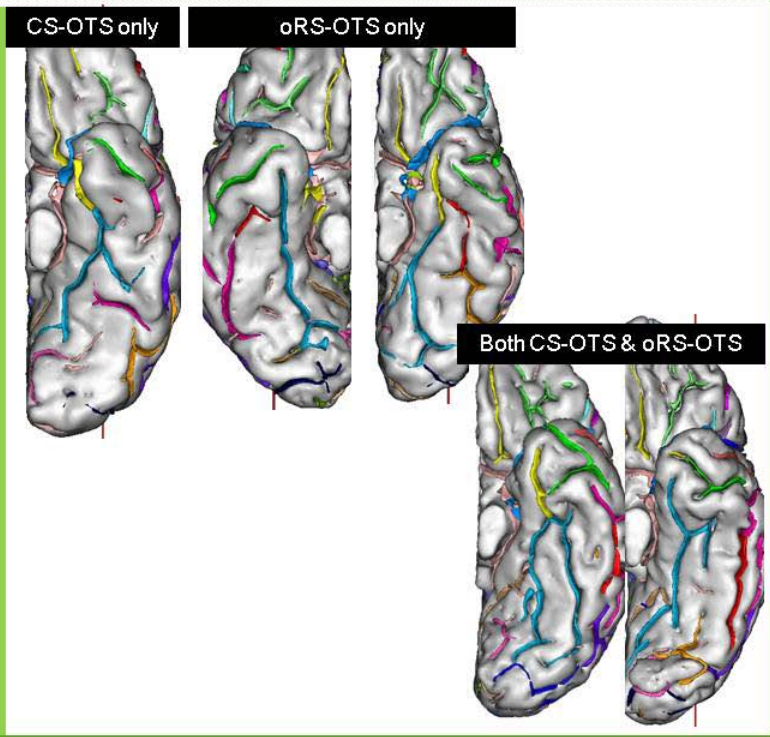
★ Rating Tips:
Inter-relationships

When the OTS connects with a continuous CS/oRS use these guidelines to determine whether the OTS is connected with the CS, oRS or both:

A. If the OTS connection occurs at the junction of the CS-oRS, rate it as connected with both. *(Note: The junction can often be identified by a change in course)*

B. If the OTS connection occurs anterior to the pons, rate it as only connected with the oRS.

C. If the OTS connects posterior to the widest portion of the pons, rate it as only connected with the CS.



General Tips

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- Remember: Because BV color labels are often incorrect, it may be best to first examine the hemisphere without labels to minimize being influenced by BV's labels.
- Rotating the hemisphere can be helpful, particularly when evaluating/rating connections.
- Try not to over-think the ratings – just take your best guess and fill in the "Notes" section in the final column of the spreadsheet if you would like to comment on particularly difficult ratings.

THANK YOU!!

Notes for Slides (1/3)

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- Slide 11:
  - Note that the Color ID is based on the color of the CS at the level of the posterior end of the pons.
- Slide 24:
  - General note: Remember to base ratings on the portion of the OTS anterior to the posterior edge of the pons (dotted black lines)

Notes for Slides (2/3)

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- Slide 24:
  - Rationale for sample ratings:
    - Red is the most predominant ("main") color in this region, even though orange is the most anterior color
    - In this case, red is NOT the main color anterior to the dotted line, even though it is the main color of the OTS as a whole. Therefore, the color is rated as pale pink, which is the most anterior color in this area.
    - The OTS in this case is labeled with orange and turquoise. It should be rated as "Orange" for two reasons: (1) the orange segment is larger than the turquoise segment; and (2) although turquoise is the most anterior color, that portion of the OTS seems to be merged with the CS; therefore, even if the turquoise portion were longer than the orange portion, the OTS would still be rated as "orange" based on criterion C on this slide.
    - This case is rated "Red" for two reasons: (1) red is the largest represented color, and (2) red is the most anterior color. Note, though, that if the portion of the OTS circled in black were absent, the sulcus would be rated as "orange" because of criterion C.

Notes for Slides (3/3)

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- Slide 26:
  - **Branch samples:** In both cases, the segment is at the junction of the CS/oRS and has a relatively lateral course.
  - **OTS Samples:** In the first sample, the segment is too far posterior to be a branch; In the second and third samples, the segments have a somewhat anterior-posterior course and helps form the lateral boundary of the second gyrus. They are therefore the OTS rather than a branch of the CS or oRS.
  - **OTS + Branch:** In this sample, the pale pink segment is a branch because it is medial-lateral and occurs at the junction between the CS and oRS. However, it is connected to a segment that has an anterior-posterior course, and that segment is therefore part of the OTS.

APPENDIX B
SCRAP:ATB RATING LOG WITH DROP-DOWN OPTIONS

FILE		1. Collateral Sulcus (CS)	2. oRS	3. OTS	4. Sulcal relationships			
ID	Side	1(a) Color	2(a) Color	3(a) Color	4(a) CS-oRS	4(b) CS-OTS	4(c) oRS-OTS	NOTES
	Left	Absent	Absent	Absent	Connection	Connection	Connection	
	Right	Unlabeled	Unlabeled	Unlabeled	Pseudoconnection	Pseudoconnection	Pseudoconnection	
		Yellow	Yellow	Yellow	Overlap	None	None	
		Red	Red	Red	None			
		Turquoise	Turquoise	Turquoise				
		Orange	Orange	Orange				
		Tan	Tan	Tan				
		Pale Pink	Pale Pink	Pale Pink				
		Green	Green	Green				
		Fuscia	Fuscia	Fuscia				
		Blue	Blue	Blue				
		Other	Other	Other				

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BIOGRAPHICAL SKETCH

Gila Zippora Reckess graduated from Roy C. Ketcham Senior High School in 1994. She earned a B.S. with college honors from Washington University in St. Louis in 1998, with a major in Psychology and a minor in Mathematics. She then earned an M.Sc. in Neuroscience from the University of Oxford in Oxford, England in 1999, based in part on her successful completion of two thesis projects: “The role of the cerebellum in hand-eye coordination” (Supervisor: Chris Miall, Ph.D., Department of Physiology), and “Examination of the role of V5 in Fourier and Non-Fourier motion using transcranial magnetic stimulation (TMS) in humans” (Supervisor: Vincent Walsh, Ph.D., Experimental Psychology).

Gila worked as a Features Editor for the Environmental News Network (ENN.com) from 1999-2000 and was a Senior Medical Sciences Writer and Editor in the Department of Medical Public Affairs at Washington University School of Medicine in St. Louis from 2000-2005. These experiences inspired Gila to pursue a career in neuropsychology, which combines her passion for cognitive neuroscience, research and clinical care. Gila received her Ph.D. from the University of Florida in the summer of 2011, having completed the neuropsychology track of the University of Florida’s APA-accredited Doctoral Program in Clinical Psychology, and a clinical internship at the APA-accredited Boston Consortium Internship in Clinical Psychology (8-month Major Rotation: Neuropsychology; 4-month Minor Rotation: General Mental Health and Center for Returning Veterans). She successfully defended her dissertation on July 23, 2010 under the mentorship of Russell Bauer, PhD, ABPP/CN, and Christiana Leonard, PhD, with generous support from an APA Dissertation Research Award. Gila accepted a position in the Postdoctoral Residency in Clinical Neuropsychology at the Johns Hopkins University School of Medicine, where she began her postdoctoral clinical and research training on September 1, 2011.