January 2009

Medial Temporal Lobe Structure and Function

Meghana Karnik
Washington University in St. Louis

WASHINGTON UNIVERSITY IN ST. LOUIS

Division of Biology and Biomedical Sciences
Neuroscience

Dissertation Examination Committee:
John G. Csernansky, Chair
Deanna Barch, Co-Chair
Steven E. Petersen
David Gillespie
Joseph Price
Lawrence Snyder
Brian Suarez

MEDIAL TEMPORAL LOBE STRUCTURE AND FUNCTION

by
Meghana Sunil Karnik

A dissertation presented to the
Graduate School of Arts and Sciences
of Washington University in
partial fulfillment of the
requirements for the degree
of Doctor of Philosophy

August, 2009

Saint Louis, Missouri

ABSTRACT OF THE DISSERTATION

Medial Temporal Lobe Structure and Function

by

Meghana Sunil Karnik

Doctor of Philosophy in Biology and Biomedical Sciences

(Neuroscience)

Washington University in St. Louis, 2009

Professor John G. Csernansky, Chairperson

My main goal was to examine the relationship between brain structure and function, specifically medial temporal lobe structure and episodic memory, in various groups of subjects who had schizophrenia, were at risk for schizophrenia because of genetic and disease influences, or who were healthy, in order to explore the influence of genetic and disease influences on brain structure-function relationships. Most of what is known about the neural structures thought to subserve episodic memory has been gleaned from studies of experimental lesions in animals, traumatic brain injury in humans, functional activation in healthy individuals, and age-related changes in specific structure-function relationships. By comparison, there has been a paucity of research on the variability of normative structure-function relationships and how such relationships might be influenced by disease.

In conducting this work, I began with the assumption that medial temporal lobe structure-function relationships would be influenced by genetic factors.

Thus, I chose to study the relationship between medial temporal lobe structure and episodic memory performance in the context of a disease known to have a strong genetic basis, namely schizophrenia. Moreover, schizophrenia has been frequently associated with altered medial temporal lobe structure and deficits in episodic memory. In this project, I subdivided the medial temporal lobe into two structural groupings – the hippocampus and the parahippocampal gyrus (PHG) and its subregions: entorhinal cortex, perirhinal cortex, and parahippocampal cortex (ERC, PRC and PHC. respectively). The subdivision of the PHG into its subregions was novel, and required the development of new methods for cortical assessment and parcelation.

The specific aims of this project were:

1. To collect cognitive data and high resolution MR scans in groups of individuals with schizophrenia, healthy controls, and their siblings.
2. To extract a measure of episodic memory performance by selecting measures from the cognitive testing that assesses episodic memory.
3. To make measurements of hippocampal volume and the volume and thickness of the parahippocampal gyrus and its subregions.
4. Using a combined database of cognitive and structural data, to examine the relationship between medial temporal lobe

structure and episodic memory performance in health and disease.

Acknowledgements:

There are many individuals without whose grace, generosity and wisdom my success, and even my survival, would have been impossible. Here, I hope to thank all of them, but first, I thank God. It has been my habit to approach you in peril and in greed, but today I come to you with gratitude. Sri Bhagavan, thank you for granting me the strength to bear what I must, the intelligence and wisdom to do what is right, and above anything else, thank you for blessing me with the love and support of the wonderful people who have shaped my life.

The first of these are my parents and brother. I have learned invaluable lessons from each of you: Baba, from you I learned that all actions should be driven by thought and that I should always be open-minded and brave enough to face thoughtful challenges to my beliefs. Baba, for my integrity, I thank you. Ayee, my guru, the most valuable lesson I learned from you was the necessity of compassion and empathy. From you, I learned that all life is divine and that the thing that is truest about all people is that part of them that is also a part of God. Ayee, for my faith in the people of this world, I thank you. Tha-Tha, growing up as your little sister, I was annoying and spoilt. As my big brother and de facto babysitter, you had every opportunity to make me pay for being such a nuisance. You didn't; instead you were always loving, patient and forgiving with me. Today, I use the way you treated me when we were kids as the standard by which I treat other people. Tha-Tha, thank you for showing me how to be a good person.

Throughout my schooling, I have had a number of truly wonderful teachers; I am grateful to each of them. In particular, today I thank Dr. John Csernansky, my mentor. I also thank my thesis committee for their insight and patience. Deanna, you in particular were especially generous with your time and guidance. Thank you.

Additionally, I would like to thank Sally Vogt and Dr. Paul Taghert. Without your support and crusading on my behalf, I am not certain I would have made it this far. Thank you, my champions.

I also thank the members of the Conte Center, past and present, for making our lab a truly enjoyable place to work. In particular, I want to thank three people without whom I would have no hope of graduating: Lori Ingram, Lei Wang and Mike Harms. Lori, if this process could

be likened to a voyage, then you were the fair wind and the calm sea that made it possible. Thank you. Lei and Mike, you are brilliant scientists who are also very good people. I have been very lucky in the big-brother department, both in family and in science. Thank you both for all of your help and advice.

Oh, my friends! It is said that friends are the family one earns, and you are each my family. Thanking all of you separately would entail the writing of a complete other dissertation on my good fortune. Suffice it to say that if ever I stand, it is because you pick me up when I fall. If ever I do good, it is because you guide me away from doing ill. And if ever I am happy, it is because I have friends like you. By thanking one of you, I thank you all: Mrs. Slovick, thank you.

Finally, I thank my true love, Michael Bradley Henry. I was raised to see God in all people, and I try very hard to do so. But darling, there is no need to try where you are concerned. You are both the reward and the preserver of my faith. For that, and for everything else, thank you.

Dedication:

I dedicate this dissertation to all the people and the places that aided in my development, but most especially, I dedicate this dissertation to the fair people of Saint Louis-where I finally started to grow up.

Table of Contents

ABSTRACT OF THE DISSERTATION ii
Acknowledgements: v
Dedication: vii
Table of Contents viii
List of Figures x
List of Tables xii
1. Introduction and Overview 1
2. Background and Study Design: 4
MTL Connectivity: 6
Hippocampus: 6
PHG: 7
ERC: 7
PRC: 8
PHC: 8
Significance of variation in MTL connectivity: 9
Functional Maturity of the MTL and effect of MTL lesions on Memory Performance: 10
Recognition Memory Tasks: 10
Relational Memory Tasks: 13
MTL Specificity in Different Aspects of Memory: 15
Determinants of MTL Structure: 21
Schizophrenia and the MTL: 25
Hippocampus and Memory in Schizophrenia and Health: 27
PHG and Memory in Schizophrenia and Health: 35
Study Design: 38
3. Subject Recruitment and Demographics: 41
4. Memory Performance in Schizophrenia: 44
5. Hippocampus in Schizophrenia 49
6. PHG in Schizophrenia 55
PHG: 67
ERC: 70
PRC: 71
PHC: 73
PHG Findings: 76
7. MTL Structure and Episodic Memory Performance 78
Control Subjects: 82
Control Siblings: 85
Schizophrenia Subjects: 89
Schizophrenia Siblings: 92
Significance of Findings: 95
8. Post Hoc Analysis of Antipsychotic Treatment and MTL structure 99
9. Discussion 103
Purpose and Aims: 103

Episodic Memory Domain Findings: 105
Hippocampal Volume Findings: 106
PHG Findings: 112
Overall Significance of MTL structural Findings: 117
Significance of Findings: 124
Future Directions: 125
Summary and Conclusions: 129
References: 132

List of Figures

Figure 1: Lesions in the MTL over the course of AD. Trans-entorhinal region in figure corresponds to the PRC. (Braak et al., 2000) 24
Figure 2: Global landmarking of the whole brain with anterior, posterior, superior, inferior and lateral (left and right) brain boundaries defined after having set the anterior and posterior commisure. (Wang et al., 2005) 50
Figure 5: PHG gray-white surface cutting. A: Delineating the path of cut, Calcarine Sulcus, depth of Collateral Sulcus, Temporal Pole mark boundaries of PHG surface. B: The cut made by the path, Red is PHG surface, while blue is 59
Figure 7: Temporal Pole was set as the anterior-most boundary of the PHG 61
Figure 11: ERC extends medially to the Subiculum. The lateral boundary of the ERC is the point where the cortex goes from being exposed to being buried. This is where PRC begins. The lateral-most boundary of the PRC is the depth of Collateral Sulc 66
Figure 12: Scatter plot of Episodic Memory Domain z-scores by total PHG Volume in healthy control subjects 82
Figure 13: Scatter plot of Episodic Memory Domain z-scores by average PHG Thickness in healthy control subjects 82
Figure 14: Scatter plot of Episodic Memory Domain z-scores by total ERC Volume in healthy control subjects 83
Figure 15: Scatter plot of Episodic Memory Domain z-scores by average ERC Thickness in healthy control subjects 83
Figure 16: Scatter plot of Episodic Memory Domain z-scores by total PRC Volume in healthy control subjects 83
Figure 17: Scatter plot of Episodic Memory Domain z-scores by average PRC Thickness in healthy control subjects 84
Figure 18: Scatter plot of Episodic Memory Domain z-scores by total PHC Volume in healthy control subjects 84
Figure 19: Scatter plot of Episodic Memory Domain z-scores by average PHC Thickness in healthy control subjects 84
Figure 20: Scatter plots of Episodic Memory Domain z-scores by total Hippocampal Volume in healthy control subjects 85
Figure 21: Scatter plots of Episodic Memory Domain z-scores by total PHG Volume in control siblings 85
Figure 22: Scatter plots of Episodic Memory Domain z-scores by average PHG Thickness in control siblings 86
Figure 23: Scatter plots of Episodic Memory Domain z-scores by total ERC Volume in control siblings 86
Figure 24: Scatter plots of Episodic Memory Domain z-scores by average ERC Thickness in control siblings 86
Figure 25: Scatter plot of Episodic Memory Domain z-scores by total PRC Volume in control siblings 87
Figure 26: Scatter plot of Episodic Memory Domain z-scores by average PRC Thickness in control siblings 87
Figure 27: Scatter plot of Episodic Memory Domain z-scores by total PHC Volume in control siblings 87

Figure 28: Scatter plots of Episodic Memory Domain z-scores by average PHC Thickness in control siblings 88
Figure 29: Scatter plot of Episodic Memory Domain z-scores by total Hippocampal Volume in control siblings 88
Figure 30: Scatter plots of Episodic Memory Domain z-scores by total PHG Volume in schizophrenia subjects 89
Figure 31: Scatter plots of Episodic Memory Domain z-scores by average PHG Thickness in schizophrenia subjects 89
Figure 32: Scatter plot of Episodic Memory Domain z-scores by total ERC Volume in schizophrenia subjects 90
Figure 33: Scatter plot of Episodic Memory Domain z-scores by average ERC Thickness in schizophrenia subjects 90
Figure 34: Scatter plot of Episodic Memory Domain z-scores by total PRC Volume in schizophrenia subjects 90
Figure 35: Scatter plot of Episodic Memory Domain z-scores by average PRC Thickness in schizophrenia subjects 91
Figure 36: Scatter plot of Episodic Memory Domain z-scores by total PHC Volume in schizophrenia subjects 91
Figure 37: Scatter plot of Episodic Memory Domain z-scores by average PHC Thickness in schizophrenia subjects 91
Figure 38: Scatter plot of Episodic Memory Domain z-scores by total Hippocampal Volume in schizophrenia subjects 92
Figure 39: Scatter plot of Episodic Memory Domain z-scores by Total PHG Volume in schizophrenia siblings 92
Figure 40: Scatter plot of Episodic Memory Domain z-scores by average PHG Thickness ($r = 0.37$, $p = 0.04$) in schizophrenia siblings 93
Figure 41: Scatter plot of Episodic Memory Domain z-scores by Total ERC Volume in schizophrenia siblings 93
Figure 42: Scatter plot of Episodic Memory Domain z-scores by average ERC Thickness in schizophrenia siblings 93
Figure 43: Scatter plot of Episodic Memory Domain z-scores by total PRC Volume in schizophrenia siblings 94
Figure 44: Scatter plot of Episodic Memory Domain z-scores by average PRC Thickness in schizophrenia siblings 94
Figure 45: Scatter plot of Episodic Memory Domain z-scores by total PHC Volume in schizophrenia siblings 94
Figure 46: Scatter plot of Episodic Memory Domain z-scores by average PHC Thickness ($r = 0.40$, $p = 0.03$) in schizophrenia siblings 95
Figure 47: Scatter plot of Episodic Memory Domain z-scores by total Hippocampal Volume ($r = 0.47$, $p < 0.01$) in schizophrenia siblings 95
Figure 48: The left (red) and right (blue) ERC. As can be seen, the left ERC appears to extend slightly into hippocampal tissue. The ERC also bilaterally extends into tissue we define as PRC. 114

List of Tables

Table 1: Summary of Conte Center Subject Demographic Data 43
Table 2:: Episodic Memory Domain Data by Group. Least Squares Mean values are average z-scores for each group. 46
Table 3: Least Square Means (LSM) comparison of Groups for Episodic Memory Performance. P values to test Null Hypothesis: LSM (i) = LSM (j) 47
Table 4: Hippocampal Volume Data. Least Square Mean values are in cubic millimeters. 53
Table 5: Least Square Means (LSM) comparison of groups for hippocampal volume. P values to test Null Hypothesis: LSM (i) = LSM (j) 54
Table 6: Summary of PHG volume data: Least Square Mean values are in cubic millimeters. 67
Table 7: Summary of PHG thickness data: Least Square Mean values are in millimeters. 67
Table 8: Least Square Means (LSM) comparison of groups for PHG volume. P values to test Null Hypothesis: LSM (i) = LSM (j) 68
Table 9: Least Square Means (LSM) comparison of groups for PHG thickness. P values to test Null Hypothesis: LSM (i) = LSM (j) 69
Table 10: Least Square Means (LSM) comparison of groups for PHG thickness with whole cortical thickness included as a fixed effect. P values to test Null Hypothesis: LSM (i) = LSM (j) 70
Table 11: Summary of ERC volume data: Least Square Mean values are in cubic millimeters. 70
Table 12: Summary of ERC thickness data: Least Square Mean values are in millimeters. 70
Table 13: Summary of PRC volume data: Least Square Mean values are in cubic millimeters. 71
Table 14: Summary of PRC thickness data: Least Square Mean values are in millimeters. 71
Table 15: Least Square Means (LSM) comparison of groups for PRC thickness. P values to test Null Hypothesis: LSM (i) = LSM (j) 72
Table 16: Least Square Means (LSM) comparison of groups for PRC thickness with whole cortical thickness included as a fixed effect. P values to test Null Hypothesis: LSM (i) = LSM (j) 73
Table 17: Summary of PHC volume data: Least Square Mean values are in cubic millimeters. 73
Table 18: Summary of PHC volume data: Least Square Mean values are in millimeters. 74
Table 19: Least Square Means (LSM) comparison of groups for PHC volume. P values to test Null Hypothesis: LSM (i) = LSM (j) 74
Table 20: Least Square Means (LSM) comparison of groups for PHC thickness. P values to test Null Hypothesis: LSM (i) = LSM (j) 75
Table 21: Measures with a significant effect of schizophrenia or risk for schizophrenia. Mixed Model Accounting for Sibling and Hemisphere Covariance;

Fixed effect: Hemisphere, Group, Hemisphere by Group Interaction, and Gender, N = 169. *Appropriate 76
Table 22: Summary of Significant Correlations of MTL structural measures with Episodic Memory domain in Schizophrenia Siblings 96
Table 23: Summary of Fisher's z-score transformation analysis comparing standardized correlation coefficients from structural measures by memory performance across groups 97
Table 24: Correlation Coefficients ≥ |0.30| for the relationship between Duration of time (in months) on Typical Antipsychotics and MTL Structure 101
Table 25: Correlation Coefficients ≥ |0.30| for the relationship between Duration of time (in months) on Atypical Antipsychotics and MTL Structure 102

1. Introduction and Overview

The purpose of this study was to examine the relationship between structural measures of a specific region of the brain and the functions thought to be associated with it in the context of health and disease. While there have been many attempts to study relationships between brain structure and function in the context of experimental lesions in animals and brain injury in humans, there have been relatively few studies of such relationships under conditions that are more subtle, and arguably, more relevant to human neuropsychiatric disease. My focus in this study was on the structure of the human medial temporal lobe, and its function in both health and disease. Specifically, my first goal was to assess if there was variation in measures of medial temporal lobe structure that could be attributed to schizophrenia or familial risk for schizophrenia. My second goal was to determine if structural variation of the medial temporal lobe related to memory performance in each of my four subject groups: schizophrenia subjects, schizophrenia siblings, healthy controls, and healthy control siblings.

This study has particular relevance for current attempts to improve our understanding of schizophrenia because 1) memory deficits are thought to be fundamental to this disorder and responsible for substantial disability, 2) abnormalities of medial temporal lobe structure have been reported in subjects with schizophrenia, and 3) there is ongoing work to improve episodic memory deficits in patients with schizophrenia as a means of reducing the disability associated with the illness.

In addition to the observations in current literature concerning the disruption of memory performance, and the abnormalities of medial temporal lobe structure in schizophrenia subjects, my work was based on the following premises: 1) brain structure influences behavior, and 2) the medial temporal lobe is a necessary substrate for memory.

My study was also based on the premise that each aspect of the relationship between medial temporal lobe structure and memory performance could be influenced by a number of factors including genes, environmental insults and, disease states. Schizophrenia seemed an ideal choice as a model disease because it is thought to be influenced by genetic as well as environmental factors. I considered the siblings of the schizophrenia subjects in this study to have special importance because other work (see Delawalla, et al., 2006) has shown them to have many of the same cognitive and neurobiological features as subjects with schizophrenia, although they are not affected by as many of the same confounding factors, such as treatment with psychotropic drugs.

In the following chapter, I provide background information on the medial temporal lobe by describing the connectivity of its substructures. I also describe the functional relevance of these structures and their connectivity, particularly in the context of memory. Next, I discuss the factors that can affect the structures of the medial temporal lobe including genetic and environmental influences. After doing this, I provide a short description of schizophrenia, a disorder characterized by abnormalities of both brain structure and cognition. Finally, I

present findings, along with their limitations, from the current literature on the structure of the medial temporal lobe in both health and schizophrenia. I also express my hypotheses about what I had expected to find when examining these brain structures in my four groups of subjects, and how I expected my measures of medial temporal lobe structure to relate to memory performance in each of my samples.

2. Background and Study Design:

The ways in which function is embodied in the structure of the brain has been a mystery fascinating scholars for millennia. In 450 BC, the Greek physician, Alcmaeon, performed the first recorded dissections of animal brains. From his findings, he concluded that the brain was the seat of intelligence. Aristotle, however, supported the more widely accepted theory of the time that it was the heart that was responsible for thought; the brain's role was to cool blood. It was not until 170 BC that Galen, a Roman physician, cemented the idea that the brain was the substrate for mental function. However, according to Galen, the ventricles of the brain were the regions responsible for memory, emotion and cognition.

Humanity's understanding of the brain and its function has come a long way since those early days of discovery. Because of recent advances in neuroscience research, we have learned a great deal about functional localization in the brain. There remains, however, a great deal more to be understood. For example, does normative variation in brain structure relate to variation in cognitive function? How do neuropsychiatric disease states affect brain structure, brain function and the relationships between the two? In this dissertation, I hope to add to what is known about brain structure-function relationships.

Specifically, I will focus on the structure and function of the Medial Temporal Lobe (MTL), a region consisting of the hippocampus and the parahippocampal gyrus (PHG). The PHG can be further subdivided into the

entorhinal cortex (ERC), the perirhinal cortex (PRC), and the parahippocampal cortex (PHC). Together, these anatomically connected regions of the brain are thought to play an essential role in the conscious memory of facts and events. As I will later show, their connectivity suggests what kind of role each specific structure may play in memory, and also some other cognitive processes that each of these structures may be involved in. The function and connectivity of these structures are thought to be conserved over rodents, non-human primates, and humans.

Indeed, most of what we know about MTL structural development has been learned from observing its development in rodents and monkeys. In monkeys, neurogenesis in the hippocampus begins at embryonic day 38 and is mostly complete by birth (Alvarado and Bachavalier, 2000; Lavenex et al., 2007). It eventually tapers off from the fourth through sixth month of infancy, with a low level continuing through adult life. Different parts of the PHG appear to develop at different rates. For example, ERC cell generation precedes cell generation in the hippocampus by approximately two days in the monkey (Alvarado and Bachavalier, 2000). However, in the case of the PRC, the rhinal sulcus is barely an indentation by the fourth month of gestation, and after birth, it requires at least six months to develop functional maturity. Still by birth, the PRC can be distinguished cytoarchitecturally (Alvarado and Bachavalier, 2000). And finally, because the PHC receives its major inputs from brain regions that take between several months (parietal cortex) to two years (dorsolateral prefrontal cortex) to

mature, it most likely undergoes a prolonged functional maturation as compared to the other structures of the MTL (Alvarado and Bachavalier, 2000).

MTL Connectivity:

Understanding the connectivity of each of the MTL structures may provide insight into its function. Below is a description of the connectivity of each of the MTL structures I will be exploring in this dissertation. Disruptions of these circuits during abnormal development of the MTL could be at least partially responsible for deficits in both memory, and other cognitive processes.

Hippocampus:

The hippocampus shares rich interconnectivity with the PHG substructures; a great deal of direct input to this region comes from the ERC, and lesser inputs come from the PRC and PHC. The anterior hippocampus receives inputs from the septal nucleus and the lateral and caudo-medial ERC (Sahay and Hen, 2007). This hippocampal region projects to the mammilllary complex, the dorsal lateral septum and the lateral ERC. The posterior hippocampus receives input from the rostromedial ERC and the medial septal nucleus, and projects to the prefrontal cortex, the amygdala, the nucleus accumbens, the hypothalamus, the medial ERC, the bed nucleus of the stria terminalis and the rostral and ventral lateral septum (Sahay and Hen, 2007; Moser and Moser, 1998). Through

the PHG, the hippocampus also receives input from several cortical areas including the frontal, temporal, parietal, occipital and cingulate cortices.

PHG:

The PHG as a whole receives a great deal of sensory information from both unimodal and polymodal association areas, which is passed on to the hippocampus for further processing. Additionally, the PHG has reciprocal connections back to the neocortex, and reciprocal connections with the amygdala and the striatum. However, each of the subregions of the PHG connects differentially to the cortex, the hippocampus, and the nuclei of the amygdala (Suzuki, 1996). This suggests that each of these regions may serve unique functions. Below, I will describe the connectivity of each of the PHG substructures: ERC, PRC, and PHC.

ERC:

The ERC is directly and reciprocally connected to both the PRC (lateral ERC) and PHC (medial ERC) and several cortical areas including the orbitofrontal, piriform, and retrospenial cingulate cortices (Aggleton and Brown, 1999; Suzuki, 1996). However, the bulk of the cortical input the ERC receives comes from the PRC and PHC (Suzuki and Amaral, 1994). As mentioned above, the ERC then transmits this input to the hippocampus, from which it also receives input. The ERC also receives strong inputs from several nuclei in the amygdala

(Suzuki, 1996), although its return connections to this region are substantially weaker.

PRC:

The PRC gets the bulks of its cortical input from visual areas in the inferotemporal cortex (~64%), and a majority of its remaining cortical input from the PHC (Suzuki, 1996). In addition to the above major inputs, the PRC also receives cortical input from the somatosensory association areas of the insular cortex, the orbitofrontal cortex and the dorsal bank of the superior temporal sulcus (Suzuki, 1996). As mentioned earlier, the major output of the PRC is the ERC, with weaker output to the PHC and hippocampus as well. Of the PHG substructures, the amygdala shares the most robust interconnectivity with the PRC.

PHC:

In addition to the various connections between the PHC and the MTL structures described above, the PHC shares robust connectivity with several other cortical areas as well. Input from the visuospatial processing areas of the posterior parietal cortex, the retrosplenial cortex, the superior temporal gyrus and sulcus and the dorsolateral prefrontal cortex are the major sources of cortical input to the PHC (Burwell, 2000). The PHC also projects to the hippocampus and has substantial projections to the dorsolateral prefrontal cortex (Suzuki,

1996, Aggleton and Brown, 2005). Compared to the other PHG substructures, the PHC shares very little interconnectivity with the amygdala.

Significance of variation in MTL connectivity:

The different kinds and levels of connectivity between each of the MTL structures and other brain regions suggest that these structures may play different roles in cognition. For example, the rich interconnectivity the PHC has with the visuospatial processing areas and the dorsolateral prefrontal cortex suggest that this region may be involved in the processing and formation of visuospatial memory and working memory. As pointed out by Burwell, based on the above connectivity, this region of the PHG may also be involved in attention (2000). Similarly, the PRC may also be involved in the formation and processing of visual memory. However, its robust connectivity to the amygdala suggests a potential role for this region in the processing of emotional stimuli as well. The ERC, with the heavy input it receives from the PRC and PHC, and therefore, the cortical regions connected to these two structures, and with the input it receives from the retrospenial cortex, along with the significant output it sends to the hippocampus, certainly plays a role in pre-processing sensory signals. As has been suggested (Witter et al., 2000; Iijima et al., 1996), the large number of parallel loops of information through the ERC to and from the hippocampus and other cortical areas including the prefrontal cortex suggest that this structure may be involved in the monitoring and short-term maintenance of information

processing in the hippocampus. The input received from the amygdala also suggests that the ERC may be involved in the processing of emotional signals as well. The ERC also receives unimodal input from olfactory associated areas such as the olfactory bulb and the piriform cortex.

Functional Maturity of the MTL and effect of MTL lesions on Memory Performance:

Functional maturity of the MTL is observed through two basic paradigms: those involving recognition memory tasks, and those involving relational memory tasks. Recognition memory tasks involve the ability to discriminate between an item previously seen and an item that is novel. Relational memory tasks however, require the subject to be able to remember the relationships between items. Both kinds of tasks rely upon the MTL, with some structures being more heavily recruited for one kind of task over another. Also, adult-level performance emerges earlier for some tasks than for others.

Recognition Memory Tasks:

Recognition memory as tested through the preferential looking (PL) task has been found in monkeys as early as two weeks after birth (Bachevalier et al. 1993) and, found within the first few days of life in humans (Pascalis and de Schonen 1994). As described by Alvarado and Bachevalier (2000), PL is split

into three segments: the first where the subject is exposed to a visual stimulus during a familiarization period: the second which is a delay interval, during which no stimuli are present, and the third, the comparison period, when the familiar stimulus is presented side by side with a novel stimulus, during which the subject's eye movements are recorded. Recognition is inferred from the subject's tendency to prefer, and thus fixate longer on, the novel stimulus. Memory can be further taxed by varying the duration of the delay interval.

Both neonatal and adult damage to monkey MTL structures negatively affects performance on PL. Adult damage to either the hippocampus (Zola et al., 2000) or the PRC (Clark et al., 1997) impairs recognition at ten second delay intervals. Adult damage to the PHC, however, impairs damage at delay intervals greater than thirty seconds (Bachevalier and Nemanic et al., 2008). Extensive neonatal damage to the MTL (hippocampus and PHG) eliminates the preference for novelty in adult monkeys (Pascalis and Bachevalier, 1999).

Another task that measures recognition memory is the Delayed Non-Matching to Sample (DNMS) task. In this task, the subject is presented with a sample object that covers a baited food well. The subject moves the object to take the reward. After a short delay when the subject cannot see the testing tray comes the choice test. During the choice test, the sample and a novel object are presented over the lateral wells of the test tray, but only the well under the novel object is baited. Using new stimuli for each trial, the subject must learn to pick the item not previously seen. Increasing either the number of items to be remembered or the delay period increases the difficulty of this task. Despite

showing long-lasting memory on the PL task as infants, three-month old monkeys cannot master DNMS at ten second delays. In fact, performance at the adult level on the DNMS task does not emerge until the age of one or two (Bachevalier, 1990). Human infants take a similar amount of time to perform proficiently on the DNMS, not reaching adult-level performance until the age of 2 (Diamond 1990). Additionally, the ability to remember across increasingly longer delays also improves with age (Diamond 1990).

Performance on DNMS is vulnerable to medial temporal lobe MTL damage. Damage to ERC and PRC or PRC alone is enough to impair both acquisition and performance (Suzuki et al. 1993; Zola Morgan et al. 1993; Alvarez et al. 1995). Damage to PHC only slightly slows down acquisition of the task and affects memory performance at only the longest delays (10 min) (Nemanic et al. 2000). The effect of hippocampal damage on DNMS task performance in monkeys has been under debate recently. Some studies have shown that hippocampal damage is associated with only mild or no impairments (Murray and Mishkin, 1998; Bachevalier et al., 1999) . Others, however, have found poorer performance on the DNMS task after hippocampal lesions (Beason-Held et al., 1999). Possible explanations for this could lie in the effects of differing methods used to make lesions in each study.

Given the similarity between the PL and DNMS tasks, it is interesting to note the difference in maturity required for attaining a high level of performance on each. Several studies have ruled out the following potential explanations for this difference: differing abilities to detect the novel stimulus (Overman et al.

1993), simple immaturity in reaching ability (Diamond 1990; Overman et al. 1993), and the inability to retain the sensory information for long periods (Gunderson and Swartz 1985). Instead, the differences of development between the two tasks appear to be related to an inability in younger subjects during the DNMS trials to associate the reward with the abstract quality of novelty (Bachevalier 1990; Overman et al. 1993; Diamond 1995; Diamond et al. 1999). Therefore, it is likely that, unlike the PL task, the DNMS task requires cognitive abilities beyond simple recognition. It is also likely that these abilities depend in part upon neural substrates outside of the medial temporal lobe that mature during the first years of life in primates. This theory is further supported by the effect of hippocampal and PHG lesions on each of the two tasks. The fact that hippocampal lesions can hinder the performance on the PL, but not the DNMS task, while lesions to the rhinal structures can hinder performance on both tasks suggests that the DNMS may be more dependent on the varied cortical interplay between the PHG structures and other cortical areas for successful completion.

Relational Memory Tasks:

Two examples of relational memory tasks are Biconditional Discrimination and Transverse Patterning. In the first, four stimuli are presented, A, B, C and D. Objects A and D are both stimuli in whose presence, the correct signal stimulus object to choose is either B (when A is present), or C (when D is present). Choosing the “correct” signal stimulus is rewarded. Normal monkeys between

the ages of six months and one year performed worse on this task than adult monkeys. However, one year-old monkeys with damage to the hippocampus and the PHC performed worse on this task than the younger animals.

The second task requires subjects to learn a set of arbitrary discriminations. As described by Debra Titone, in this paradigm, “when A and B are paired, A is correct; when B and C are paired, B is correct; and when A and C are paired, C is correct. The third of these discriminations is relatively difficult to learn because the AC discrimination goes against a logical inference about what stimulus should be reinforced given that A is reinforced over B, and B is reinforced over C.” Children are unable to perform this task until approximately five years of age. There is also evidence that damage to the hippocampus in monkeys, both neonatal (Alvarado et al. 1995) and adult (Alvarado et al. 1998) severely hinders performance on this task. Human adults, who have lesions to the MTL, and specifically to the hippocampal formation, also show severe impairment on this task.

Additionally, lesions to the medial diencephalon and, specifically to the mediodorsal thalamic nuclei have also been associated with deficits in performance of this task (Aggleton and Brown, 1999). Deficits caused by lesions to this region are very similar to lesions in the MTL (McKee and Squire, 1992). This thalamic nucleus shares rich connections with the prefrontal cortex, and it could be a disruption in these circuits that are responsible for poor performance on this task in lesioned animals and human subjects.

MTL Specificity in Different Aspects of Memory:

That the MTL is a necessary substrate for memory is widely accepted. With the help of animal and human lesion studies and functional neuroimaging studies from the last decade, we are seeking to gain a better understanding of what aspects of memory the hippocampus, and the substructures of the PHG are each involved in. As discussed in the previous section, monkey lesion studies suggest distinct roles for the hippocampus, PRC and PHC in memory processing. From these studies, we know that in monkeys, the hippocampus is important for both recognition and relational memory tasks (Zola et al., 2000; Alvarado et al. 1995; Alvarado et al. 1998) while the PRC is necessary for accomplishing recognition memory tasks (Suzuki et al., 1993), and the PHC is necessary for remembering the relationship between objects (Suzuki et al., 1993). More recently, Malkova and Mishkin (2003) have shown that spatial memory, a kind of relational memory, in monkeys relies on an intact PHC, and not an intact hippocampus, as had been previously thought (Parkinson et al., 1988; Angeli et al., 1993). The reason for this difference in findings is likely due to the nonselective nature of the lesions made in the earlier studies where both hippocampus and PHC were ablated.

Although experiments with animals, and specifically non-human primates, have provided significant insight into the roles of MTL structure in memory, studies of human subjects with MTL lesions were among the first to suggest that such a role may exist. Arguably, the most famous such case is that of patient, HM. Although, HM was not the first observed case of anterograde amnesia, this

individual soon became one of the most intensely studied cases of the condition. HM's amygdala, hippocampus, ERC and PRC were bilaterally removed as a treatment for seizures. Post-operatively, he showed no change in personality, nor did he show any loss of intelligence. However, he suffered severe memory impairments. He could remember verbal stimuli for only fifteen minutes, but only if he was able to devote his entire attention to their rehearsal. If a distraction interrupted this process, all of his rehearsing up to that point would be to no avail; the complete episode would be forgotten (Milner, 2005). By sitting through years of experiments, HM provided scientists with a great deal of data on anterograde amnesia. However, his lesions were not restricted to the MTL structures, nor were they restricted to specific structures within the MTL, and therefore, studies of more specific human lesions were needed to fully appreciate the importance of these structures for episodic memory. Two such studies were those of human subjects, RB (Zola-Morgan et al., 1986) and NC (Gold and Squire, 2006). RB had suffered ischemia-induced memory loss. Approximately six months after his ischemic episode, and until his death five years later, RB participated in neuropsychological testing to evaluate his cognitive function. Upon his death, his brain was histologically examined. From the histological analysis performed on his brain, the bulk of the brain damage he suffered from his ischemic episode was localized bilaterally, to the hippocampus, specifically to the CA1 subfield of the hippocampus. NC had a history of schizo-affective disorder, seizures, alcoholism and was diagnosed with sleep-apnea shortly before death. Histological examination of her brain exposed bilateral lesions in her

hippocampus (dentate gyrus, subfields CA1 and CA3) and ERC (layer three). From their neuropsychological testing, it was apparent that both RB and NC suffered from significant anterograde amnesia, having deficits in recall of stories, word lists, and diagrams. They both also performed poorly on tasks of paired-associate learning. Subjects who have bilateral damage to PRC and PHC also appear to have deficits in diagram recall, paired associate performance, word recognition, word recall and face recognition (Buffalo et al., 1998). It should be noted though that the two subjects with the above PHG damage had hippocampal damage as well. Compared to subjects who had damage restricted to the hippocampus or diencephalon, these subjects had greater deficits in memory performance at longer delay intervals (> 6 seconds) suggesting the additional impairment was due to lesions in the PHG.

The evidence from both animal and human lesion studies suggests that in humans the structures of the MTL may play differential roles in memory. The evidence gleaned from human neuroimaging studies, suggesting that there is some functional dissociation in the MTL is compelling. However, there remains some debate as to whether or not such dissociation actually exists. Generally speaking, there are two competing views in the current literature. I will discuss them both below.

The first has progressively built in the last decade on initial findings that suggested that the hippocampus and the PHC were most involved in recollection (Davachi et al., 2003; Raganath et al., 2004; Kahn et al., 2004; Lehn et al., 2009) or the ability to recover event-specific contextual details as a memory is retrieved

(Yonelinas, 2001) while the rhinal cortex (ERC and PRC) was most involved in semantic memory, or knowledge of objects, concepts, faces and words (Davies et al., 2004; Lee et al., 2006) and item memory or familiarity (Davachi et al., 2003; Raganath et al., 2004), a process through which the subject senses that an item or event has been experienced before (Yonelinas, 2001), but does not access the contextual elements surrounding the episode when the memory was encoded.

The above findings, which suggest dissociable, but complementary roles for each MTL structure in memory, do not seem surprising, particularly considering both the differentiated connectivity and, the high level of interconnectivity of these structures. However, the tasks that have been used to uncover what these roles might be are limited by a number of factors. For example, all of the tasks used in the studies discussed above use some form of visual or spatial cues for source memory. The use of visual/spatial tasks for recollection may have prevented the visualization of temporal-source related activity as a predictor of subsequent memory. For example, the temporal order in which the words were presented might provide contextual information to aid in recall. In fact, a recent study has lent further support to the role of the hippocampus in source memory by showing its involvement in the specific recall of temporal sequences (Lehn et al., 2009). Also, as pointed out by Kafkas and Migo (2009) recollections beyond those specific to the task may be confounding activity thought to be specific to item or source memory performance. As an example, certain words being studied might be particularly meaningful to the

subject, and therefore have the potential to skew measures of recollection. An elegant study of spatial and non-spatial associative memory, where the items used to test both forms of associative memory were originally meaningless shapes, has addressed this latter concern, and also shown the importance of the PHC during the retrieval of both types of memories (Aminoff et al., 2007).

The second view is that item memory and source memory are actually on a single spectrum with item memory reflecting weaker memory and source memory, of which relational memory is a subset, being indicative of stronger memory (Squire et al., 2004). According to this perspective, the structures of the MTL contribute equally to memory in a way that is difficult to dissociate (Squire et al., 2004). Support for this latter view comes from studies where activation of specific MTL structures was not preferentially predictive of performance on item memory or source memory tasks (Gold et al., 2006). It should be noted however, that despite Gold and group's (2006) conclusion that hippocampus and PRC encoding activation predicted item memory and source recollection to a similar degree, their results actually demonstrate a trend-level significance for right PRC activation predicting item memory to a greater degree than source recollection.

Based on MTL connectivity, and on findings from animal lesion, human lesion and neuroimaging studies, all of the MTL structures are important for memory. If the dissociation theory is correct, then the hippocampus and PHC subserve associative memory, and the processing of contextual information, with the PHC being especially important for processing spatial memory as well. In

contrast, the rhinal cortex structures appear to be involved in item memory with the PRC being especially involved in visual memory processing.

The memory tasks that I used in this dissertation were tests that would be cumulatively sensitive to damage anywhere in the MTL. The tasks included were tests of verbal memory that required indirect temporal processing and either higher level processing (Logical Memory, a subtest of the Wechsler Memory Scale, third edition, or the WMS-III) or intact categorization skills (CVLT) to complete, and a test of visual and spatial memory (Family Pictures, a subtest of the WMS-III). Each of these tasks could be sensitive to disruption of multiple MTL structures: Logical Memory requires subjects to remember the temporal order of story elements, and would therefore be sensitive to disruptions of both the PRC and the hippocampus; the CVLT requires subjects to recall consecutively presented items of the same category, and would therefore be sensitive to disruptions of the ERC, PRC and the hippocampus; Family Pictures requires the recollection of spatial locations of objects and family member activity, and would therefore be sensitive to disruptions of the ERC, PRC and the PHC. All of these tests are thought to measure episodic memory, or the memory of an event with a clear relation to time and space (Tulving, 2001). By combining all three of these measures, I produced a robust measure of global episodic memory performance that would be sensitive to disruption anywhere in the MTL, regardless of the specific role in memory which a given structure subserved. These tests were specifically chosen not only because of their expected recruitment of the MTL, but also because of their sensitivity to cognitive deficits in schizophrenia subjects

(Hawkins, 1998; Weickert et al., 2000), the constituents of one of my two key experimental groups in this study.

Determinants of MTL Structure:

Throughout the course of an individual's life, several factors influence the structure of the MTL through a combination of genes, environment and experience. The first two factors are particularly influential perinatally.

For example, several signaling molecules exercise regional control over the developing cortex and hippocampus, with specific genes being differentially expressed in the brain, some in the MTL, and some in other areas of the cortex (Ragsdale and Grove, 2001). For example, limbic system-associated membrane protein (LAMP) is expressed in the developing and adult hippocampus, PHG, and other limbic structures, but shows little to no expression in non-limbic brain regions (Pimenta et al., 1996; Reinoso et al., 1996). Similarly, cadhedrin molecule, cad-8, and the ephrin receptor, A5, are expressed in the PHG and other limbic cortices during development, but not elsewhere. Additionally, certain proteins act as collaborative signals to induce the expression of region-specific proteins like LAMP. Examples include transforming growth factor and neuregulin (Eagleson and Levitt, 1999). The above proteins are thought to be involved in axon guidance (Eagleson and Levitt, 1999), and could therefore play crucial roles in determining MTL structure. Polymorphisms on any of the genes encoding these proteins could result in abnormal development of the MTL.

Environmental factors such as difficult births, prenatal stress, and convulsive episodes can affect the structure of the brain. For example, hypoxia-ischemia at term is associated with damage to hippocampal CA1 neurons, deep layers of cerebral cortex and cerebellar Purkinje cells (Rees and Inder, 2005). Additionally, infection/inflammation and premature births are associated with white matter damage which might affect surrounding gray matter structure (Rees and Inder, 2005). In rats, it has been observed that prenatal stress of the mother causes an increase in glucocorticoids in fetal blood that could affect hippocampal structure post-natally (Takahashi, 1998). Environmental factors such as poor nutrition can also affect MTL structure in the developing infant. For instance, poor nutrition in birds during early postnatal development had smaller hippocampi and fewer neurons in the hippocampus compared to normal birds (Pravosudov et al., 2005). Another factor capable of influencing MTL structural development is the seizure: Seizures in rats corresponding to the age of infancy in humans are associated with smaller volumes of hippocampus and perirhinal cortex when these rats reach adulthood (Nairismagi et al., 2006). The richness of the external environment can also influence the development of the MTL. For example, deprived rearing conditions in neonatal mice have been associated with smaller hippocampi with lower neuron density in adulthood (Kempermann, 1997).

There are also several factors occurring past the age of infancy that can affect MTL structure. One such example effects MTL structure when it takes place postnatally as well: the seizure. Seizures in P21 rats (corresponds to prepubescent childhood in humans) caused by exposure to kainic acid are

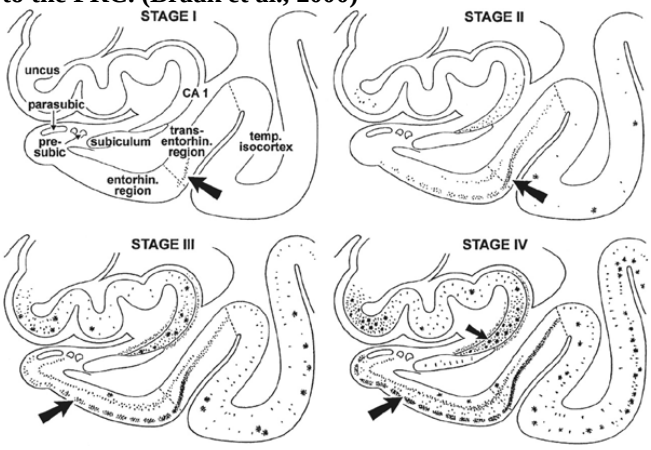
associated with neural damage in CA1 and CA3 of the hippocampus and the ERC and PRC (Rizzi et al., 2003 and Ravizza et al., 2005). In humans, Bernasconi et al. (2000) reported that subjects with a history of temporal lobe epilepsy had volume reductions in the ERC.

Episodes of ischemia as adults can also affect brain structure, and brain function. As an example, in 1986, Zola-Morgan and colleagues presented their findings on patient RB. RB had suffered ischemia-induced memory loss. From the histological analysis performed on his brain, the bulk of the brain damage he suffered from his ischemic episode was localized bilaterally, to the hippocampus, specifically to the CA1 subfield of the hippocampus. Based on the tasks where he showed deficits in performance (paired associate learning, story recall, and diagram recall) his deficits were most-likely the result of deficits in relational and visuo-spatial learning.

Other factors that affect the structure of the brain, but can manifest later in life are neuropsychiatric diseases states such as Alzheimer's disease and schizophrenia. These diseases are thought to be caused by a combination of genetic and environmental factors, though the exact etiology of these two disorders remains unknown, and is a matter of continued study.

Alzheimer's disease (AD), for example, is a neuro-degenerative disorder characterized by dementia and atrophy of MTL structures (Kohler et al., 1998), with the ERC and PRC being among the first (Braak et al., 2000) to show signs of atrophy (Figure 1).

Figure 1: Lesions in the MTL over the course of AD. Trans-entorhinal region in figure corresponds to the PRC. (Braak et al., 2000)



In fact, smaller ERC volumes in elderly subjects presenting with cognitive complaints may be predictors for later development of AD (De Toledo-Morrell et al., 2000). A number of studies of subjects with AD, and those at risk for AD, have also shown positive correlations between memory and measurements of MTL structure. For example, Kohler et al. (1998) found a significant positive correlation between the volume of PHG and a measure of delayed recall on a visual memory task, WMS-R Visual Reproduction, $r = 0.67$, $n = 17$. A similar positive correlation was found between the volume of the hippocampus in these subjects and delayed recall on a measure of verbal memory or list learning, CVLT, $r = 0.78$, $n = 26$. De Toledo-Morrell et al. (2000) also found positive correlations between measures of MTL structure and measures of memory in AD at-risk subjects. The memory task used was the Buschke task, a task where subjects are asked to learn a list of four items presented four at a time pictorially. Subjects were scored based on the percentage of correctly recalled items both

immediately, and after a 45 – 60 minute delay. De Toledo-Morrell's group found that both immediate and delayed memory were positively correlated with volume of the ERC and volume of the hippocampus, with significant correlations between ERC volume and immediate free recall and hippocampal volume and delayed free recall. The authors suggest that this implies temporally-based differential roles for the ERC and hippocampus in memory. One could also argue that the different modalities of processing involved in this task (both visual and verbal) may also influence these results.

Schizophrenia and the MTL:

Another disease state where the structures of the MTL have been found to be affected by a disease process is schizophrenia. This disorder emerges in men in their late teens and early twenties, while women are generally diagnosed in their mid-twenties to early-thirties (NIMH, 2007). Schizophrenia is a psychiatric disorder characterized by a number of potential symptoms including: delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, affective flattening, alogia and/or avoliton (DSM-IV). It is thought that those who go on to develop schizophrenia are born with a predisposition for the disorder based on the interplay of several possible genes (Braff et al., 2007). In fact, unlike the general population, which has approximately a one percent chance of developing schizophrenia, first-degree relatives of schizophrenia subjects have approximately a ten percent chance of developing the disorder

(Tsuang, 2000). First-degree relatives of schizophrenia subjects also show similar abnormalities in brain structure (Lawrie et al., 2001; van Erp et al., 2002; van Erp et al., 2004; Seidman et al., 2002) and cognition (meta-analysis: Sitskoorn et al., 2004; Delawalla et al., 2006) as their affected siblings. In schizophrenia subjects, a genetic predisposition, coupled with a number of potential environmental insults (pre- and perinatal insults such those discussed earlier), produces a heterogeneous disorder characterized by cognitive impairments such as problems with executive function, memory, and the inability to sustain attention (NIMH, 2007), and structural abnormalities of the brain. Despite having lower mean values on measures of brain structure and cognitive performance, schizophrenia subjects show great variance on these measures (Heinrichs, 2004; van Erp et al., 2004; Keri and Janka, 2004). The cognitive deficits associated with schizophrenia can be quite severe, and are stable; they remain even after treatment improves psychotic symptoms (Saykin et al., 1991; Gruzelier et al., 1988). The MTL, as a likely neural substrate for memory, and as a possible substrate for other cognitive and behavioral processes disrupted in schizophrenia, has been a brain region of considerable interest to schizophrenia researchers.

Below, I will discuss what is known about how the structures of both the hippocampus and the PHG relate to memory in schizophrenia subjects, and also what I expect this relationship to be in my subjects. I will begin with a discussion of the hippocampus, and in the following section, I will describe what is known about the PHG in this context.

Hippocampus and Memory in Schizophrenia and Health:

To date, findings on MTL structure in schizophrenia have been varied. Despite certain negative findings showing no abnormalities of hippocampal structure in schizophrenia subjects (Krabbendam et al., 2000; DeLisi et al., 1997; Sanfilipo et al., 2002), several groups have found smaller hippocampi in schizophrenia subjects compared to healthy controls (Nelson et al., 1998 (meta-analysis); Whitworth et al., 1998; Velakoulis et al., 1999; Gur et al., 2000; Seidman et al., 2002; Tepest et al., 2003; Sim et al., 2006). There may be several reasons for the discrepancies in findings for the hippocampus. One possibility, as suggested by Antonova et al., in 2004, could be that since hippocampal volume reduction might be restricted to gray matter reductions, a lack of segmentation of gray matter from white matter could skew the results of those not finding a disease-effect. Additionally, the size of the slices being segmented, and the kinds of segmentation techniques used might also affect whether or not an effect is seen. For example, DeLisi's group (1997) used relatively thick (5 mm) slices with 2 mm gaps between slices in their analysis of hippocampus. This could result in the group missing small but meaningful changes in volume. Although Sanfilipo's group did not have any gaps between the slices they collected, the slices they used were relatively thick (2.8 mm), and could face the same problems of poor precision faced by DeLisi et al. Krabbendam's group also used relatively thick slices (3 mm), and additionally,

had difficulty in segmenting the hippocampus separately from the amygdala. Although interconnected, the amygdala and hippocampus are distinct structures, and the inclusion of the amygdala in their measure of anterior hippocampal volume may have confounded their results of the hippocampus proper.

The findings for the relationship between structural measures of MTL and cognitive performance in schizophrenia subjects have not been consistent. For the most part though, the literature has shown positive relationships such that larger hippocampal volume is associated with better performance. One such study showed that larger hippocampal volume was positively related to both verbal (performance on tasks of story recall, list learning and paired associates) and visuo-spatial memory (design reproduction) (Gur et al., 2000). More recently, Nestor et al. found in 2007 that hippocampal volume was positively correlated with several aspects of memory in schizophrenia subjects: right hippocampal volume correlated with overall visual memory, and with the recognition elements of both visual and verbal memory. Left hippocampal volume correlated with both recognition and recall aspects of verbal memory. These findings differ, however, from those of Thoma et al. (2008) who found positive correlations between posterior hippocampal volume and visual memory in schizophrenia subjects, but negative correlations between anterior hippocampal volume and both verbal and spatial memory in these same subjects. What this relationship would have been had the whole hippocampus been examined instead of the two regions separately is unknown.

There is also considerable disagreement over what the normative relationship between MTL structure and cognitive performance is. Also, age might be capable of affecting whether this relationship is positive or negative. There are currently three major hypotheses concerning how hippocampal volume correlates with memory in healthy control subjects, with the third being dependent on age-related changes to hippocampal structure. The first is the "bigger is better" hypothesis (Van Petten, 2004) that suggests that irrespective of any structurally determining factors, a bigger hippocampus is associated with better memory performance, and a smaller hippocampus is associated with poorer memory performance. Because of the accepted role of the MTL in memory, because of the numerous studies showing a relationship between hippocampal volume and memory performance in subjects with neurodegenerative diseases such as Alzheimer's disease and other forms of dementia, and because of the naturally occurring variability in both hippocampal volume and memory performance in healthy controls, this was one of the the earliest hypotheses concerning the relationship between MTL structure and memory performance. The two other hypotheses discussed below were posited after numerous studies presented results conflicting with this hypothesis. I will discuss the results from some of those studies shortly.

Support of the "bigger is always better" hypothesis however, comes from studies showing a positive relationship between hippocampal volume and memory performance. For example, Reiman et al. (1998) found a moderate ($r \geq 0.30$) positive relationship between list learning and memory in healthy control

subjects. Similarly, O'Driscoll et al. (2001) found a moderate positive relationship between delayed story recollection and hippocampal volume in healthy control subjects. Gur et al. (2000) found that the hippocampus correlated positively with spatial memory in control subjects. Similarly, in 2003, Driscoll et al. found a moderate positive correlation between hippocampal volume and memory performance in their control subjects. Rosen et al. (2003) found a positive correlation between left hippocampal volume and verbal memory recall in a sample of healthy, non-demented older adults.

It should be noted however, that findings from the Rosen et al. (2003) study more aptly support the second hypothesis discussed below than this first hypothesis. Indeed, several studies that were thought to initially provide support to the "bigger is better" view regardless of factors affecting structure, can be thought to better support the second hypothesis listed here since they relate hippocampal volume to memory performance in older subjects who are likely to have experienced age-related shrinkage of the brain. They do not disprove the first hypothesis, but when their results are taken in the context of the numerous studies like the following, where the "bigger is better" hypothesis in healthy, but not aging adults fails to hold, and given that the above studies examine the structure-function relationship in older adults, their findings can be thought to more specifically support the second hypothesis than the first. Examples of studies that examine the structure-function relationship in healthy, but not aging adults include: Torres et al. (1997), Raz et al., (1998), MacKay et al. (1998), Tisserand et al. (2000), and Maguire et al. (2003). All of these studies failed to

find significant relationships between hippocampal volume and memory performance (either verbal, visual/spatial, or both) in their subjects.

Also, of the four studies described earlier where a relationship was observed between hippocampal volume and memory performance in healthy adults, one study (Reiman et al., 1998) used subjects who were between 50 and 62 years of age, an age range during which age-related brain shrinkage has already begun, thus possibly rendering this study more likely to support the second hypothesis discussed below than the “bigger is better” hypothesis discussed here. Furthermore, one of the remaining three studies (Driscoll, et al., 2003) to provide support for this hypothesis has not been replicated because of the uniqueness of the visual task (Virtual Morris water maze) used in exploring the relationship between hippocampal volume and visual memory.

Given the number of studies that have failed to find a relationship between hippocampal volume and memory performance in healthy adults, and the lack of reasoning for expecting to see such a positive relationship in young adults, I do not expect this hypothesis to be true in my young adult control subjects or my young adult control siblings.

The second hypothesis concerning how hippocampal volume relates to memory states that a normally developed hippocampus of any size will support normal function, but that tissue loss within the structure will be associated with poorer function (Van Petten, 2004). In other words according to this hypothesis, in healthy adults, who are not experiencing significant age-related brain shrinkage, hippocampal size does not relate to memory performance. However,

changes in hippocampal volume that are the result of pathological tissue loss could disrupt normal hippocampal function such that larger structures which have had presumably less tissue-loss are associated with better memory performance, and smaller structures which have presumably lost more tissue are associated with poorer memory performance. Thus, this hypothesis suggests that in an adult, but not aged, population, a relationship between memory and hippocampal volume will be unobservable, but that in populations that have experienced pathogenic, or age-related tissue loss, the bigger the hippocampus, the better the memory performance, and the smaller the structure, the poorer the performance. Support for this hypothesis comes from studies of both healthy older subjects who have most likely experienced age-related brain shrinkage (Golomb et al., 1994; Lupien et al., 1998; Convit et al., 2003; Driscoll et al., 2003; Rosen et al., 2003; Lye et al., 2006), from studies of subjects who have experienced tissue loss as a result of a pathological condition such as Alzheimer's Disease (Kohler et al., 1998; De Toledo-Morrell et al., 2000) and Temporal Lobe Epilepsy (Reminger et al., 2004), and from studies of healthy non-aging adult controls where a relationship between hippocampal volume and memory could not be observed (see above).

And the final hypothesis concerning how hippocampal volume relates to memory claims that age can modify the nature of this relationship in a way opposite to that just discussed; hippocampal tissue loss is not associated with poorer memory performance, but instead, is associated with better memory performance. According to this hypothesis, one would expect to find a negative

relationship between hippocampal volume and memory performance in normally developing children and adolescents. The reason for this being that the young developing brain undergoes a loss of gray matter in the whole brain beginning around 11 years of age, and in the temporal lobes beginning around year 17 (Giedd et al., 1999) as a result of loss of neurons, axonal branches and synapses that do not support efficient brain function (Van Petten, 2004). Thus, according to this hypothesis, the efficiently functioning brain of a young person will experience significant neural pruning and as a result of this, a smaller hippocampus will relate to better memory performance. Support for this hypothesis can be found from studies of young subjects such as Pruessner et al., 2007 and Sowell et al. 2001).

Some caveats of the supporting studies of the above hypotheses should be noted before proceeding. For example, the sample size of the Pruessner (2007) study (n = 13) were fairly small. Also, the Sowell (2001) study did not isolate hippocampus; this group looked at a large portion of the MTL, including amygdala, hippocampus and PHG.

For my study of the hippocampus and other MTL structures in schizophrenia subjects, healthy control subjects and their respective siblings, I believe the second hypothesis is most likely to correctly reflect the relationship between brain structure and cognition. In my control groups, I do not expect to see a relationship between MTL structure and memory performance because my subjects are too old to be undergoing developmental pruning, but too young to be experiencing significant age-related shrinkage of the brain. I also do not believe

the first “bigger is better” hypothesis adequately reflects the relationship between healthy brain structure and memory performance, as numerous studies have failed to replicate results supporting this hypothesis, and because the original reasoning to suspect the veracity of this hypothesis is based partially on data from, and neuropathogenic theory surrounding subjects with compromised MTL structure and memory. It is not however, based on any anatomical or molecular theory concerning the relationship between normative MTL structure and memory performance.

Schizophrenia is a heterogeneous disorder likely caused by a combination of various genetic factors working in concert with specific environmental insults that together disrupt MTL structure to varying degrees. Since schizophrenia subjects show abnormalities in brain structure and cognition, it is possible that the variance found in these two potentially related measures is functionally meaningful such that smaller volumes are associated with poorer cognitive performance and larger volumes are associated with better performance. This is in keeping with the line of reasoning offered by the second hypothesis which is supported by results from several studies of individuals with neuropathology of the MTL and deficits in memory performance. Since control subjects show no cognitive deficits, and since our control subjects are practically all adults, I would not expect to see a relationship between hippocampal volume and cognition in these subjects. As the two sibling groups share half of the same genetic makeup of their respective siblings, I would expect that schizophrenia and schizophrenia siblings share similar structure-function relationships, and that such a relationship

would be nearly as difficult to observe in control siblings as it is in control subjects themselves.

PHG and Memory in Schizophrenia and Health:

The PHG and its substructures have not been evaluated as thoroughly as the hippocampus, but there is some evidence to suggest that they are also smaller in schizophrenia subjects compared to healthy controls (Job et al., 2002; Joyal et al., 2002; Turetsky et al., 2003; Prasad et al., 2004). However, there have been others who have found no abnormalities of PHG structure in schizophrenia subjects (Krabbendam et al., 2000; Sanfilipo et al., 2002; Sim et al., 2006).

There are a number of possible reasons for this disparity in findings. As mentioned earlier, the comparative thickness of the image slices used by Krabbendam (2000) and Sanfilipo (2002) could have confounded their results, particularly in the case of a structure as thin and long as the PHG. Differences in findings may also be attributed to a lack of consistency in defining structural boundaries. For example, Sim et al., 2006, defined the PHG such that the posterior portion of it was not included. This means that a large portion of the parahippocampal cortex was neglected from their measurements. In the case of Turetsky et al., 2003, the PRC was defined to include Brodmann's Area (BA) 35 and 36. Although, both areas are part of the PRC, BA 36, might be better considered part of the fusiform gyrus and not part of the PHG, proper. Prasad's

group (2004) included hippocampal tissue in their ERC segmenting, while Joyal's group (2002) included some of the tissue on the medial bank of the collateral sulcus in their measurement of ERC, a method not used frequently by others while defining the ERC due to the difficulty in finding a reliable anatomical marker to mark the medial-most boundary of the ERC and PRC.

Developing an accurate and reliable means of segmenting the PHG, one of my goals in this project, will prove useful in determining the true effect of schizophrenia on this brain structure.

There have been a few reported instances of a relationship between PHG structure and cognition in schizophrenia subjects. For example, increasing volume of the PHG has been found to be associated with better executive function as evidenced through better performance on the Stroop Test in chronic schizophrenia subjects (Krabbendam et al., 2000). Other associations include those between PHG and verbal intelligence (DeLisi et al., 1991; Hoff et al., 1992) and PHG and verbal memory (DeLisi et al., 1991). Unlike all of the afore-mentioned findings where the associations between PHG volume and cognition were positive, Sanfilipo et al. (2002) found an inverse relationship between PHG volume and verbal intelligence in male patients. Regardless of direction, the relationships between PHG structure and cognition seem to be specific to schizophrenia as no similar associations were observed in comparison control subjects (Krabbendam et al., 2000; DeLisi et al., 1991). To the best of my knowledge no one has examined the relationship between PHG structural

measures and memory performance in healthy controls and schizophrenia subjects, something I will explore in this dissertation.

In summary, although there have been some findings suggesting both abnormalities in PHG structure and correlations between PHG volume and cognition in schizophrenia subjects, both the methods used to determine PHG structure, and the findings of how structure relates to cognition have been varied. The notable associations between PHG structure and cognition in older subjects suffering from cognitive impairments suggest a possible link between this brain region and the cognitive disturbances associated with schizophrenia. Also, the rich interconnectivity of the PHG with several cortical and non-cortical brain regions coupled with the level of cognitive disruption observed in schizophrenia suggest that a detailed and reliable study of PHG structure and how it relates to various cognitive processes is warranted. One of the key goals of this dissertation was to conduct just such a study. Because similar factors influence both the structure of the hippocampus and the structure of the PHG, and because of their high level of interconnectivity, my hypotheses about the structure of the PHG and the relationship between PHG structure and cognitive performance in schizophrenia subjects, control subjects and their respective siblings were similar to my analogous hypotheses about the hippocampus. Namely, I expected to find abnormalities in measures of PHG in my schizophrenia and schizophrenia sibling group, but not in my control or control sibling groups. I also expected that these abnormalities would be functionally meaningful such that smaller PHG measures would associate with poorer

cognitive performance in my two experimental groups, but not in my two control groups.

Study Design:

As discussed in earlier sections of this chapter, there is significant evidence to support the view that the MTL is involved in several aspects of memory processing. Additionally, both genetic and environmental influences are capable of effecting MTL structure. Certain disease states such as Alzheimer's disease, a disease thought to have both environmental and genetic causes is capable of altering the structure of the MTL, thereby effecting memory performance. It is believed that schizophrenia is caused by both genetic and environmental factors. We also know that schizophrenia is a disorder characterized by memory deficits, and that there have been numerous reports of abnormalities in MTL structure in populations of schizophrenia subjects. Given the above premises, this study was designed to test the following three hypotheses:

1. Both schizophrenia subjects and their first-degree relatives who share approximately half of their genes (unaffected siblings) will have deficits in memory performance compared to control subjects and their siblings.

2. Both schizophrenia subjects and their unaffected siblings will have smaller measures of MTL structure compared to control subjects and their siblings.
3. There will be a positive correlation between measures of MTL structure and memory performance in schizophrenia subjects and their siblings, but not necessarily in control subjects or their siblings.

As mentioned earlier, schizophrenia subjects show great variance on measures of cognitive performance and brain structure. Since the MTL structures are neural substrates of memory, and schizophrenia subjects show deficits in memory performance, it is possible that schizophrenia-linked variation in these structures is functionally meaningful, i.e., smaller/thinner structures may be related to poorer memory performance, and larger/thicker structures may be related to better memory performance in our schizophrenia subjects and in their siblings. However, since healthy control subjects do not show memory deficits, normative variation in MTL structure may not be functionally meaningful, and so a relationship between memory performance and MTL measures may not be observable in the two control groups.

In order to test the above hypotheses, the following experimental design was adopted: First, cognitive data and high resolution MR scans in the four groups of subjects were collected. Next, tasks measuring episodic memory were isolated from the cognitive testing. Following this step, measurements of hippocampal volume, and volume and thickness of the PHG and its

substructures were made. The cognitive and structural measures were then analyzed to determine if group differences existed for any measures. Finally, using a combined database of the cognitive and structural data from all of our subjects, I examined the relationship between MTL structure and episodic memory performance in each group of subjects.

In the following chapters, I will present the methods by which all of the above steps were accomplished along with my results and interpretations.

3. Subject Recruitment and Demographics:

The subjects in this study were recruited through the Conte Center for the Neuroscience of Mental Disorders (CCNMD) at Washington University in St. Louis. The sample included 39 individuals with DSM-IV schizophrenia (33 male, 6 female); 33 siblings of individuals with schizophrenia (15 males, 18 female); 47 healthy control participants (26 male, 21 female); and 50 siblings of healthy controls (14 male, 36 female). Schizophrenia participants were recruited from local inpatient and outpatient treatment facilities. Control subjects were recruited using local advertisements from the same community. Clinical and general neuropsychological testing data from a group of subjects largely overlapping with this sample have been reported previously by Delawalla et al. (2006). Additional details related to subject recruitment procedures can be found in that publication.

Participants from any of the four groups were excluded if they (1) met DSM-IV criteria for substance abuse or dependence within the past 6 months; (2) had a clinically unstable or severe medical disorder, or a medical disorder that would confound the assessment of psychiatric diagnosis or render research participation dangerous; (3) had head injury (past or present) with documented neurological sequelae or loss of consciousness; and (4) met DSM-IV criteria for mental retardation (mild or greater in severity). In addition, control participants were excluded if they had a lifetime history of any Axis I psychiatric disorder and or a first-degree relative with a psychotic disorder. Further, participants in the schizophrenia sibling and control sibling groups were excluded if they had a

lifetime history of Axis I psychotic disorders (including bipolar disorder) or current major depression, but not other Axis I disorders.

The schizophrenia group had significantly more male participants than female participants [$\chi^2(1) = 17.33$, $p < .0001$], while the control sibling group had significantly more female participants [$\chi^2(1) = 8.82$, $p < .01$]; the Yates Correction was applied to both calculations of χ^2. The control and control sibling groups had significantly more Caucasian subjects [$\chi^2(6) = 12.3$, $p < .05$] than did the schizophrenia and schizophrenia sibling groups. Control and control sibling participants had more years of education than schizophrenia participants, but not more education than the schizophrenia sibling participants ($F_{3,137} = 4.6$, $p < .01$). The groups did not differ significantly on age ($F_{3,137} = 0.9$, $p = .45$) or parental socioeconomic status ($F_{3,137} = 0.8$, $p = .48$). We did not control for education in any analysis, since cognitive disturbances associated with the risk for developing schizophrenia may impair educational achievement. A brief summary of our subject data can be found below (Table 1).

Table 1: Summary of Conte Center Subject Demographic Data

	Controls	Control Sibs	Schizophrenia Subjects	Schizophrenia Sibs	Total
African American	9	11	17	12	49
Caucasian	38	39	22	21	120
Total	**47**	**50**	**39**	**33**	**169**
Gender (M/F)	26/21	14/36	33/6	15/18	
Age Range	14- 27	15 - 27	17 - 31	14 - 28	
Age Mean	21.1	20.4	22.5	22.1	

4. Memory Performance in Schizophrenia:

Several studies have shown that schizophrenia subjects and their first degree relatives show deficits in episodic memory performance (meta-analysis Sitskoorn et al., 2004; Delawalla et al., 2006). This kind of memory is defined quite expectedly as the memory of specific episodes of experience, experiences that are characterized by their relationship to time and space (Wheeler et al., 1997; Tulving et al., 2001). This memory is not simply the recall of an individual item, but also the recall of the circumstances under which that item was experienced.

The tasks used in this study are thought to measure episodic memory, and consist of Logical Memory I (WMS-III), Family Pictures I (WMS-III), and the CVLT. The CVLT and Logical Memory tasks are thought to measure verbal memory and the Family Pictures task is thought to assess visual-spatial memory.

In the CVLT, subjects heard a list of sixteen words over five immediate-recall trials. The list consisted of words from four different categories; four words per category. Adjacent words were not from the same category, so high levels of recall would suggest usage of semantic clustering strategies (Delis et al., 1988). The measure of the CVLT used in this study was the total number of words recalled over all five trials. The other test of verbal memory we used was the Logical Memory task. Logical Memory however, is a test of story memory. In this task, our subjects were asked to retell two stories they had just heard. In contrast, Family Pictures is thought to be a test of visual memory. In this task, our subjects were asked to recall the details of scenes depicted in family

photographs they were shown. Such details included who was in the scene, what they were doing and where they were located.

Because subjects need to recall related words that were consecutively presented, therefore remembering the temporal and semantic relationships of the words to one another, the CVLT serves as a measure of episodic memory. Similarly, Logical Memory requires subjects to retell a story, and thus, recall its elements in sequential order, thereby also measuring episodic memory. The visual-spatial aspect of episodic memory can be addressed by Family pictures because in this task participants are asked to recall the locations of individuals and things seen in presented photographs, thus showing an awareness of the spatial relationships between items and people in the photographs. As indicated above, these tasks each measure different aspects of episodic memory. In order to determine how our schizophrenia subjects and their siblings compared to healthy controls and their siblings in overall episodic memory performance, we grouped performance on these tasks together to create a single Episodic Memory Domain score for each of our subjects. Below, I will describe how this was accomplished.

Since the domain score was a measure of overall episodic memory performance that would be sensitive to disruption anywhere in the MTL, in order to determine how MTL structure related to episodic memory performance, I examined all of our structural measures against the domain score in each of our four groups. The findings from these analyses will be discussed in a future chapter.

In order to evaluate group differences in overall episodic memory performance, I used a mixed model analysis, keeping group and gender as fixed effects. We chose this form of analysis over a simple ANCOVA or GLM analyses because, unlike those methods, the mixed model approach accounts for sibling-related covariance across observations.

My a priori fixed contrasts were between schizophrenia subjects and controls, schizophrenia subjects and control siblings, schizophrenia siblings and controls, schizophrenia siblings and control siblings, and both sibling groups against their respective comparison groups (i.e., schizophrenia subjects versus schizophrenia siblings, controls versus control siblings).

My analysis of our data (Table 2) revealed a significant effect of group on memory performance ($F_{3, 64} = 19.41$, $p < 0.0001$).

Table 2:: Episodic Memory Domain Data by Group. Least Squares Mean values are average z-scores for each group.

Group	Schizophrenia Subjects n = 37	Schizophrenia Siblings n = 33	Controls n = 47	Control Siblings n = 48
Mean (SE)	- 0.80 (0.14)	0.04 (0.09)	0.41 (0.09)	0.36 (0.09)

Schizophrenia subjects performed significantly worse than controls and control siblings ($p < 0.0001$) and performed worse than their own siblings ($p < 0.0001$). Also, schizophrenia siblings performed worse than controls and control

siblings ($p < 0.05$ in both cases) (Table 3). In summary, schizophrenia siblings performed at an intermediate level between their affected siblings and the two control groups. A subset of these findings has been previously published (Delawalla et al., 2006).

Table 3: Least Square Means (LSM) comparison of Groups for Episodic Memory Performance. P values to test Null Hypothesis: LSM (i) = LSM (j)

i/j	Schizophrenia Sibling	Control	Control Sibling
Schizophrenia Subject	**< 0.0001**	**< 0.0001**	**< 0.0001**
Schizophrenia Sibling		**0.02**	**0.04**
Control			0.63

Our findings support those of other studies showing memory deficits in schizophrenia subjects and their siblings (Sitskoorn et al., 2004; Delawalla et al., 2006). These results also suggest the involvement of genetic factors associated with schizophrenia in mediating memory performance. Thus, the results of my analysis of memory performance in schizophrenia and schizophrenia siblings as compared to control and control siblings supported my first hypothesis of this dissertation: Both schizophrenia subjects and their first-degree relatives who share approximately half of their genes (unaffected siblings) will have deficits in memory performance compared to control subjects and their siblings.

In the following chapters, we will explore if the neural substrates of episodic memory are affected by schizophrenia and the risk for schizophrenia,

and how our measures of these brain regions relate to memory performance in each of our four groups of subjects.

5. Hippocampus in Schizophrenia

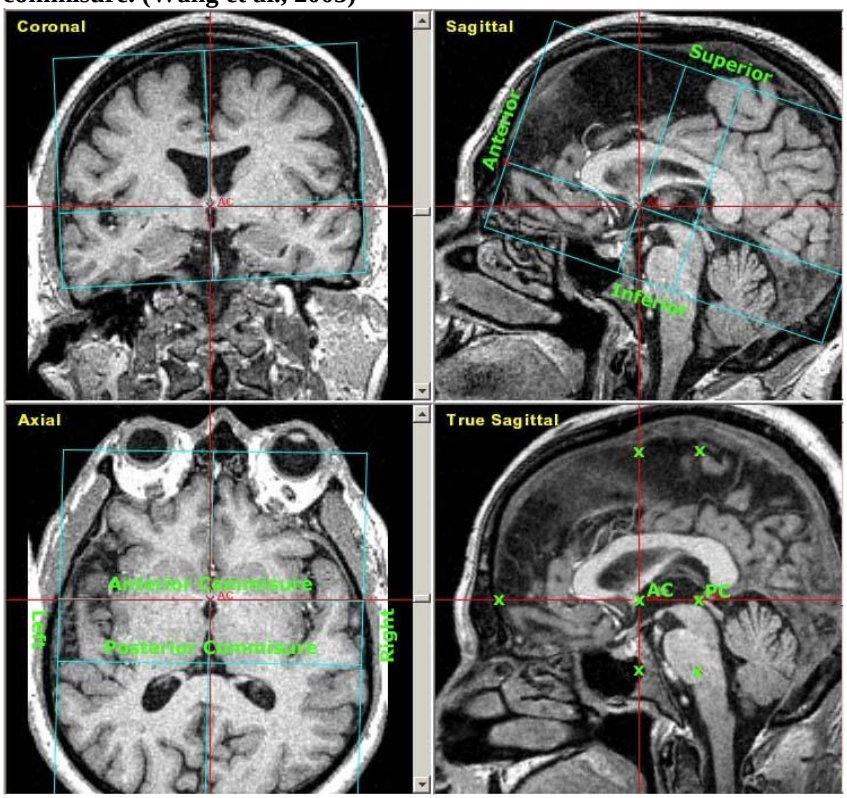
The first structure of the MTL that we will explore is the hippocampus. There are a number of studies showing structural abnormalities of this region in schizophrenia subjects (Nelson et al., 1998 (meta-analysis); Whitworth et al., 1998; Velakoulis et al., 1999; Gur et al., 2000; Seidman et al., 2002; Tepest et al., 2003; Sim et al., 2006). There is also considerable evidence from both human and animal studies to infer that the hippocampus is a neural substrate for memory.

All MR scans were collected on the same Magnetom SP-4000 1.5-Tesla Siemens imaging system with a standard head coil using a turbo-FLASH sequence that acquired three-dimensional datasets with $1mm^3$ isotropic voxels across the entire cranium (Venkatesan and Haacke, 1997). MR datasets were reformatted using Analyze^{TM} software (Analyze-AVW, 2004), and signed 16-bit MR datasets were compressed to unsigned 8-bit MR datasets by linearly rescaling voxel intensities such that voxels with intensity levels at two standard deviations above the mean of white matter (corpus callosum) were mapped to 255, and voxels with intensity levels at two standard deviations below the mean of CSF (lateral ventricle) were mapped to 0. The white matter and CSF means and standard deviations were obtained by sampling voxels from these respective regions. Further details related to the methods for image preprocessing can be found in prior publications from our research group (Csernansky, et al. 2004).

Prior to hippocampal mapping, landmarks were placed in all MR scans at the anterior, posterior, superior, inferior, and lateral brain boundaries and at

points where the anterior and posterior commissures intersected the midsagittal plane (Haller, et al., 1997) (Figure 2).

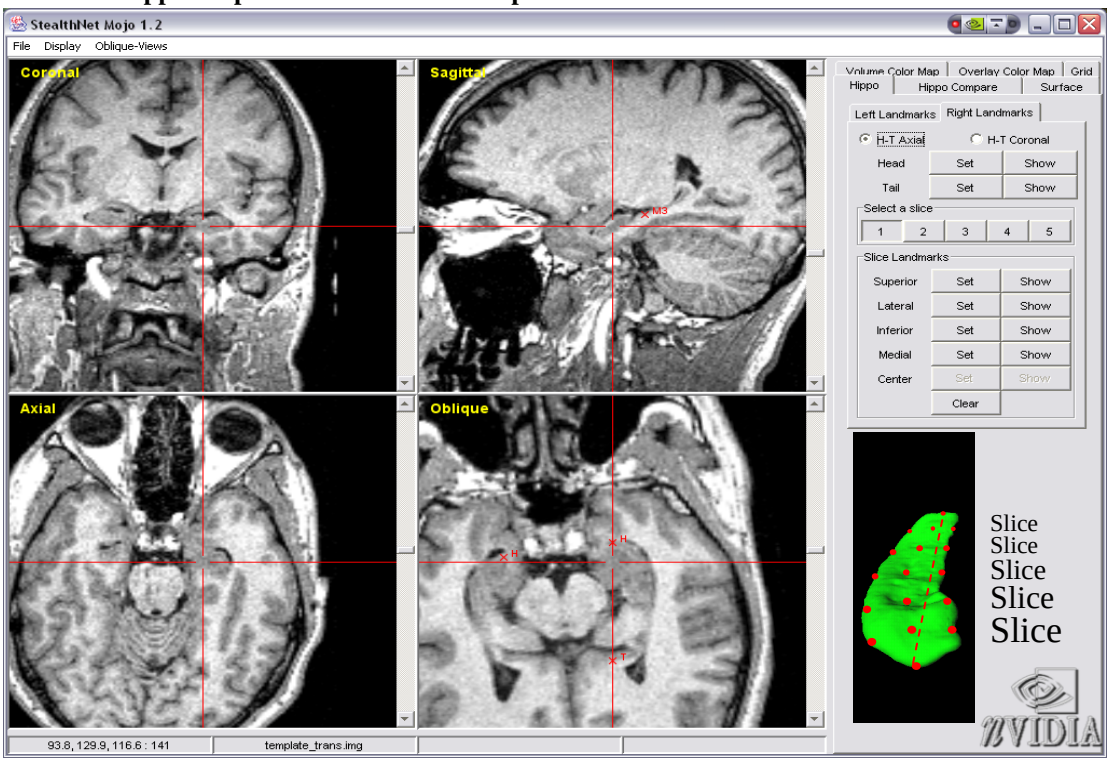
Figure 2: Global landmarking of the whole brain with anterior, posterior, superior, inferior and lateral (left and right) brain boundaries defined after having set the anterior and posterior commisure. (Wang et al., 2005)



Points at the anterior and posterior boundaries of the hippocampus were demarcated, defining an anterior/posterior axis. The hippocampus was manually outlined in the template MR scan using atlas guidelines (Duvernoy, 1998; Mai et al., 1997). Briefly, the hippocampus as we defined it included the cornu ammonis (CA), the dentate gyrus and the subiculum. It extended anteriorly from the point where the gray matter of the structure was first adjacent to the trigone of the lateral ventricle up through the temporal horn. The hippocampus was evident in

five equally distanced slices along an anterior-to-posterior axis; four landmarks, (superior, lateral, inferior, medial) surrounding the hippocampus, were placed in each slice (Figure 3).

Figure 3: Head and Tail of hippocampus set new axis (Oblique view) through which five equidistant, perpendicular slices are generated to landmark. Bottom right green image shows surface of hippocampus oriented anterior to posterior with head and tail



The template for the human hippocampus was generated by using an MR scan collected from another healthy comparison subject that was not otherwise included in the analysis.

Transformation of the template onto the target MR scans occurred in two steps (see Miller et al., 1997 for details). First, the MR scan designated as the

template was coarsely aligned to each target scan using the previously placed landmarks. Second, a high-dimensional transformation was applied to achieve an optimal voxel-by-voxel match. During the transformation, the movement and deformation of voxels in the template MR scan were constrained by assigning them the physical properties of a fluid. The reliability of this process, including landmark placement and both steps of the template transformation, was found to be equivalent (interclass correlation coefficient = 0.86) to manual outlining by experts for defining the neuroanatomical boundaries of the hippocampus (Haller et al., 1997).

To quantify hippocampal volume, a triangulated graph was superimposed onto the surface of the hippocampus within the template MR scan; this graphical surface was then carried along as the template was transformed onto the target scans. When the transformations were completed, surfaces were generated for the hippocampus in all of the target scans (Csernansky et al., 2004, Joshi, Miller, and Grenander, 1997). Left and right hippocampal volumes in the target scans were determined by calculating the volumes enclosed by these transformed surfaces. These methods for hippocampal assessment have been previously developed and are reported in a prior publication (see Csernansky, et al. 2002).

Total cerebral volumes and thicknesses (excluding the brainstem and cerebellum) had been previously derived through the use of FreeSurfer software. Briefly, FreeSurfer was used to map and generate left and right pial surfaces and gray-white surfaces. Gray matter volumes were computed as the volume enclosed by these surfaces. A summary of this data is presented in Table 4.

Table 4: Hippocampal Volume Data. Least Square Mean values are in cubic millimeters.

Group	**Schizophrenia Subjects n = 36**	**Schizophrenia Siblings n = 31**	**Controls n = 46**	**Control Siblings n = 49**
Mean (SE)	5017 (95)	5327 (97)	5347 (80)	5349 (580)

To analyze this data, I again used a mixed model approach. In the first round of this analysis, the fixed effects were condition, gender, hemisphere and condition by hemisphere interactions. In the second round, I included a measure of whole brain volume as a fixed effect. Again, like in my episodic memory model, this model accounted for sibling covariance. Additionally, in the models for my structural measures, hemisphere covariance was also accounted for.

We found a significant group effect on hippocampal volume ($F_{3, 157} = 2.98$, $p < 0.03$). This effect seemed to be driven by the difference of the schizophrenia group from the three other groups (Table 5).

Table 5: Least Square Means (LSM) comparison of groups for hippocampal volume. P values to test Null Hypothesis: LSM (i) = LSM (j)

i/j	Schizophrenia Sibling	Control	Control Sibling
Schizophrenia Subject	**0.03**	**< 0.01**	**0.01**
Schizophrenia Sibling		0.87	0.86
Control			0.99

The observed group effect lost significance when including whole brain volume as a fixed effect in the model ($F_{3, 157} = 1.13$, $p = 0.39$). This finding suggests that although hippocampal size might be abnormal in schizophrenia subjects, there are likely to be additional brain regions in schizophrenia subjects also showing similar structural abnormalities. These results do however support, in part, my hypothesis concerning my expected MTL structural findings: schizophrenia subjects will have smaller measures of MTL structure compared to control subjects. I had however expected to find similar results in the siblings of schizophrenia subjects as well.

In Chapter 7, we will explore whether the abnormality of the hippocampus we have observed here in schizophrenia subjects is functionally meaningful in terms of episodic memory performance, and whether a subtle structural difference exists in the siblings of schizophrenia subjects compared to the two control groups that though unobservable by these methods, may still prove to be functionally meaningful as well.

6. PHG in Schizophrenia

We next examine the effect of schizophrenia and the familial risk for schizophrenia on the PHG and its substructures: the ERC, PRC and PHC. Each of these structures shares rich connectivity with various unimodal and polymodal cortical areas (Aggleton and Brown, 1999; Suzuki, 1996; Suzuki and Amaral, 1994; Aggleton and Brown, 2005). Additionally, each of these structures is also thought to be a neural substrate for memory (Suzuki et al. 1993; Zola Morgan et al. 1993; Alvarez et al. 1995; Buffalo et al., 1998; Malkova and Mishkin 2003).

The preprocessing of MR scans for segmenting the PHG was already done in order to prepare the images for hippocampal mapping, and was described in Chapter 5 of this dissertation. However, unlike the hippocampus, which was treated as a solid gray matter structure of measurable volume, the PHG was treated as a "carpet" of gray matter of measurable volume and thickness. The following methods for assessment of the PHG and its sub-regions were developed specifically for this project. Specifically, these methods were designed to quantify the gray matter volume and thickness of this region.

To quantify the gray matter volume and thickness of the PHG and its component subregions, the following method was developed.

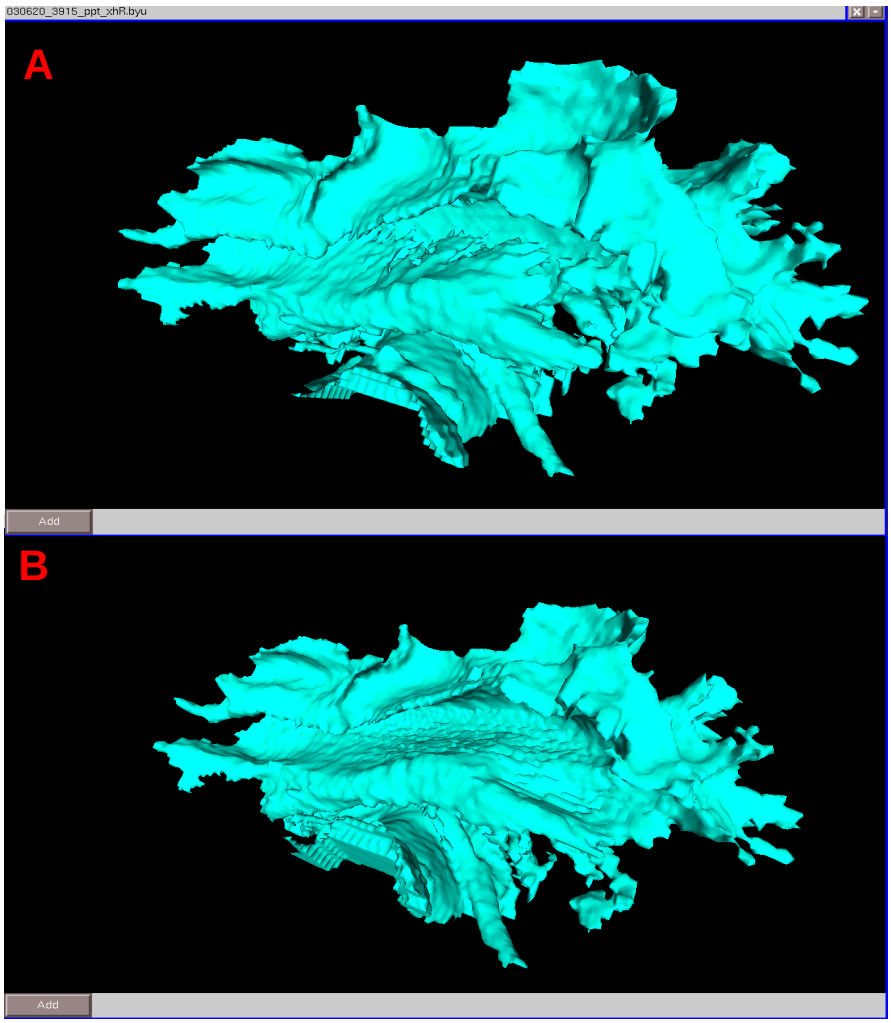
First, in a template scan, a 3D region of interest (ROI) subvolume encompassing the entire PHG in the left and right hemispheres was outlined using Analyze™. This ROI was more readily viewed in coronal sections. In each section, an enclosure consisting of the gray matter of the PHG and its neighboring gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) was drawn by hand. Using the global landmarks already present from processing of the hippocampus, the template ROI was registered to each

of our subjects. In order to do this for all of the scans, we calculated an atlas scaling factor that represented the amount of expansion or contraction necessary to align the target scans with Talairach atlas space.

Bayesian segmentation via Brainworks™ was then used to classify the subvolume tissue within the PHG ROI as CSF, GM and WM by fitting the ROI histogram with Gaussian curves representing each tissue type. The threshold between gray matter and white matter was used to generate an isosurface, which represented the interface between the gray matter and white matter in the PHG ROI.

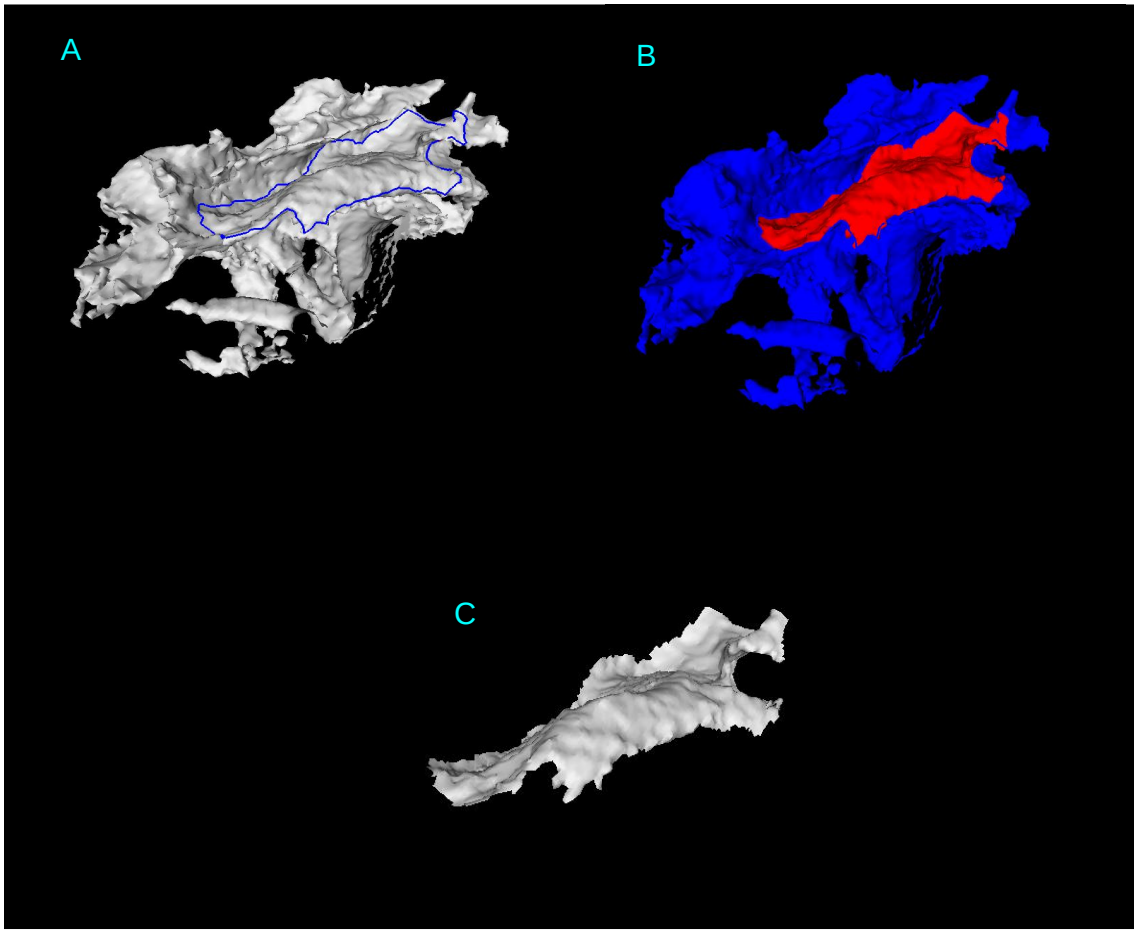
In almost all cases, the isosurface that was generated was not continuous; i.e., gaps were evident in it (Figure 4). To fill in these gaps, we used Analyze™ to raise the intensity of the portion of surface that had been left out. I set it at a value that we were certain would be considered white matter. This process involved slice-by-slice editing of approximately 100 slices per subject. I then used this edited image to regenerate the isosurface within the PHG ROI.

Figure 4: PHG ROI gray-white surface before (A) and after (B) Analyze™ editing.



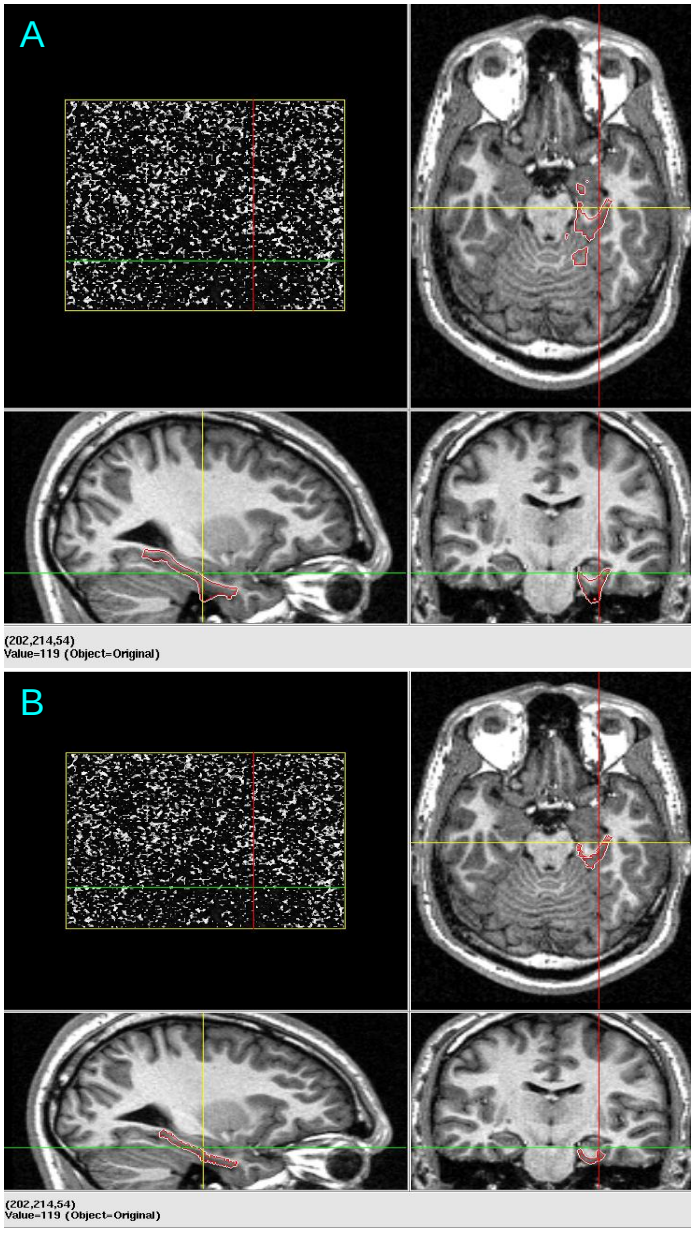
Having regenerated the isosurface within the ROI subvolume, I then extracted the subsurface that corresponded more exactly to the PHG. The first step of this process involved using Brainworks™ to draw a path across the larger ROI to cut out the PHG. I defined the boundaries of this subsurface as follows: The anterior-most boundary was the temporal pole, the posterior-most boundary was the calcarine sulcus, the medial-most boundary was the very edge of the ROI, and the lateral-most boundary was the Collateral Sulcus. Once I had delineated the path enclosing the PHG (Figure 5a), I made the cut (Figure 5b) and hid the remaining non-PHG surface (Figure 5c). I then proceeded to extract the PHG surface from the hidden ROI in the image. I performed a reliability analysis where the PHG surfaces of ten subjects were re-cut, and compared the surface areas of the re-cut surfaces to the original surfaces. The interclass correlation coefficient for this procedure was 0.93.

Figure 5: PHG gray-white surface cutting. A: Delineating the path of cut, Calcarine Sulcus, depth of Collateral Sulcus, Temporal Pole mark boundaries of PHG surface. B: The cut made by the path, Red is PHG surface, while blue is



Once the PHG surface had been defined, I used an automated procedure that used the isosurface within the PHG proper to generate binary images of PHG structure. However, in all of the study subjects, the PHG boundaries bled into other structures (Figure 6). I once more used Analyze™ for manual editing, in this case, to correct these errors.

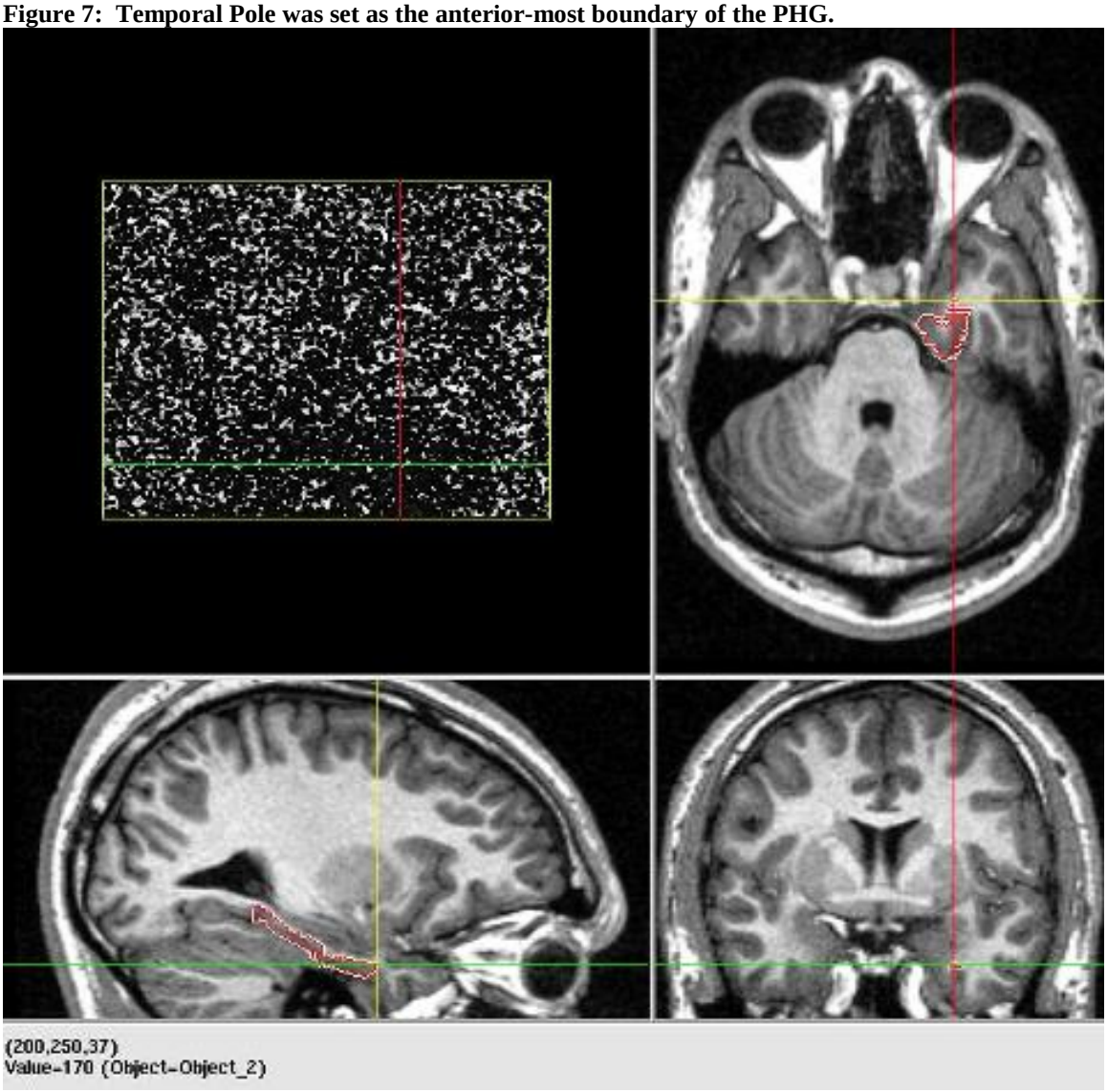
Figure 6: PHG binary images before (A) and after (B) editing. In pre-edited figure, PHG is seen to bleed into cerebellum and CSF.



The boundaries of the PHG were delineated with the help of MH Gado, MD, and J Price, PhD, and using the anatomical descriptions by Duvernoy(1991) and Mai (1997).

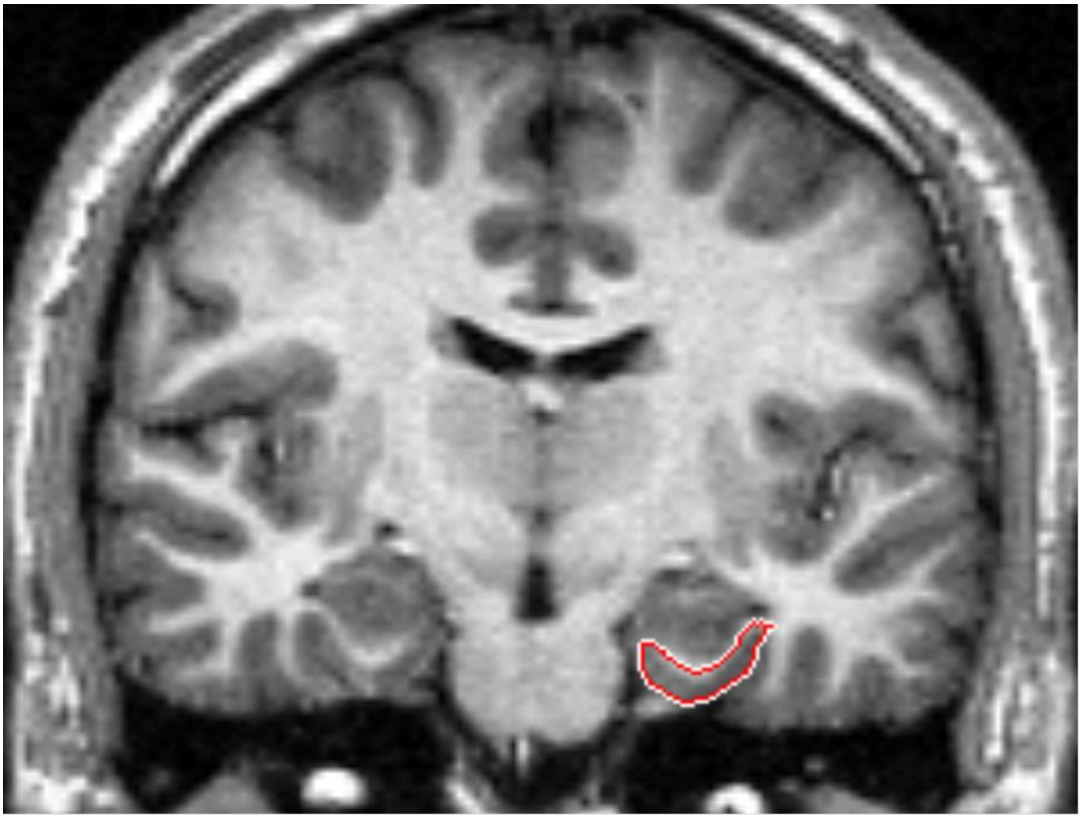
The anterior boundary of the PHG was set at the temporal pole (Figure 7).

Figure 7: Temporal Pole was set as the anterior-most boundary of the PHG.



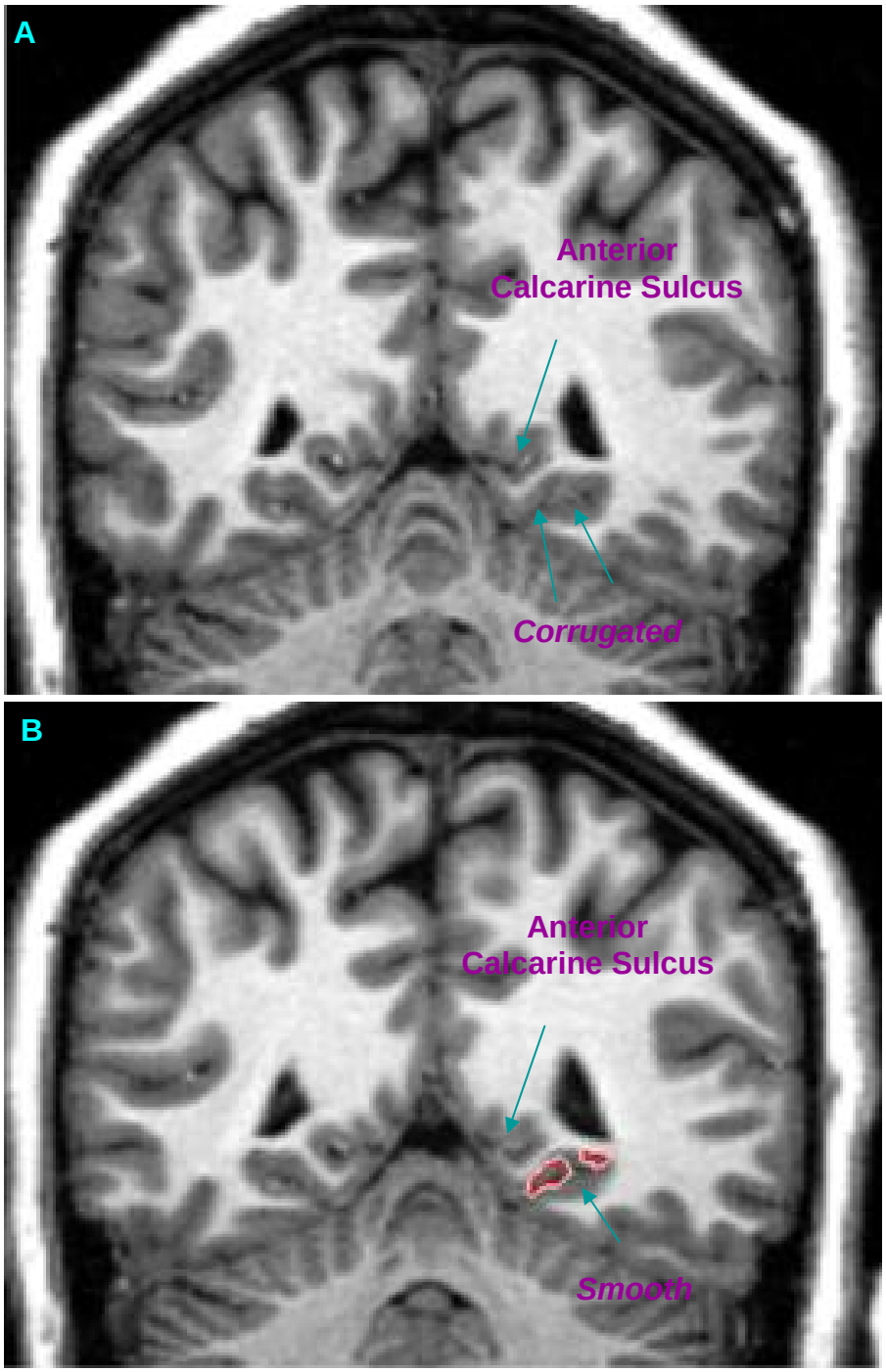
In the section through the body of hippocampus, the medial limit of the PHG was the parasubiculum (Figure 8). The collateral sulcus formed the lateral limit of the PHG (Figure 8).

Figure 8: The medial and lateral boundaries of the PHG.



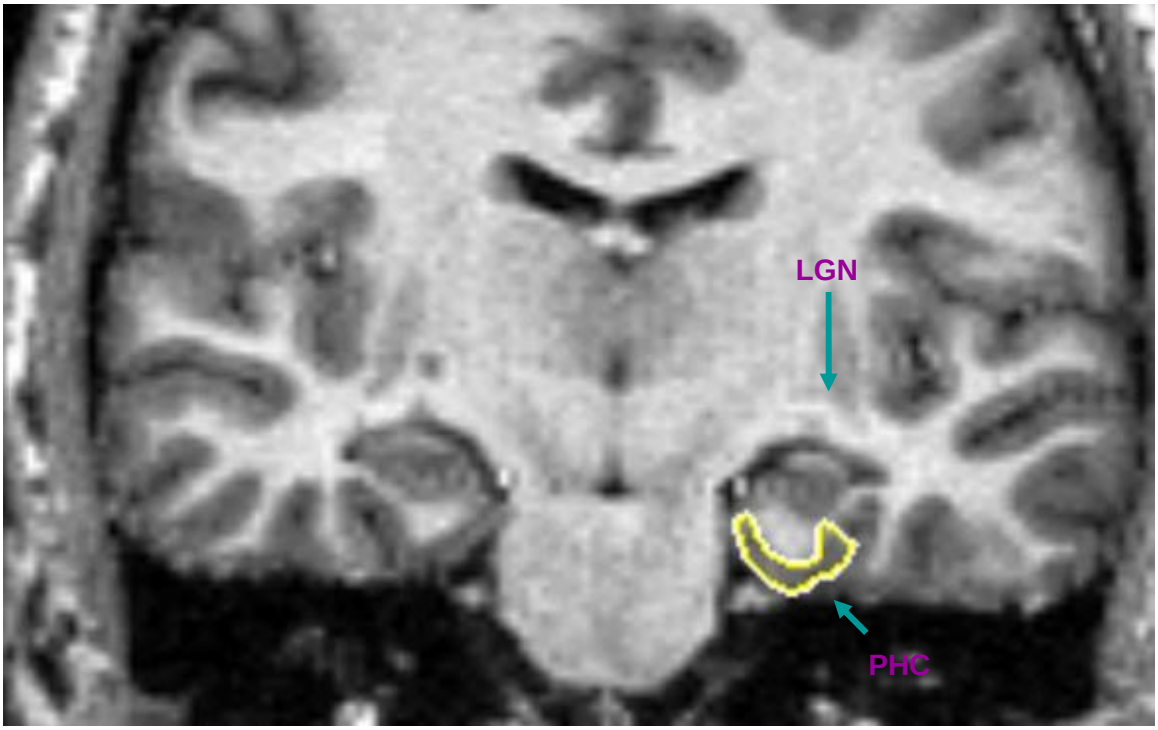
The most posterior boundary of the PHG was where the interior of the occipital gyrus went from being corrugated (Figure 9a) to becoming a single smooth curve (Figure 9b), below the cingulate gyrus, extending until the anterior calcarine sulcus (Slide 55, pg. 239, Mai, 1997). This definition included some portion of the occipital gyrus within the posterior PHG. However, the posterior boundary as defined was the most reliably visible anatomical endpoint across our subjects at the resolution of the available scans.

Figure 9: The posterior boundary of the PHG begins when the interior of the occipital gyrus goes from being branched (A), to being a smooth (B).



I then parcelated the PHG surface into two subregions, the anterior portion made up of the ERC and the PRC, and the posterior portion consisting of the PHC. The anterior boundary of the PHC with the other two structures was where the lateral geniculate nucleus of the thalamus appeared. In fact, this landmark was used to define the coronal cutting plane that cut the PHG into the afore-mentioned sub-regions (Figure 10). For this step, the interclass class correlation coefficient = 0.99.

Figure 10: Moving from anterior to posterior in the coronal view, PHC begins where the anterior-most portion of LGN appears.

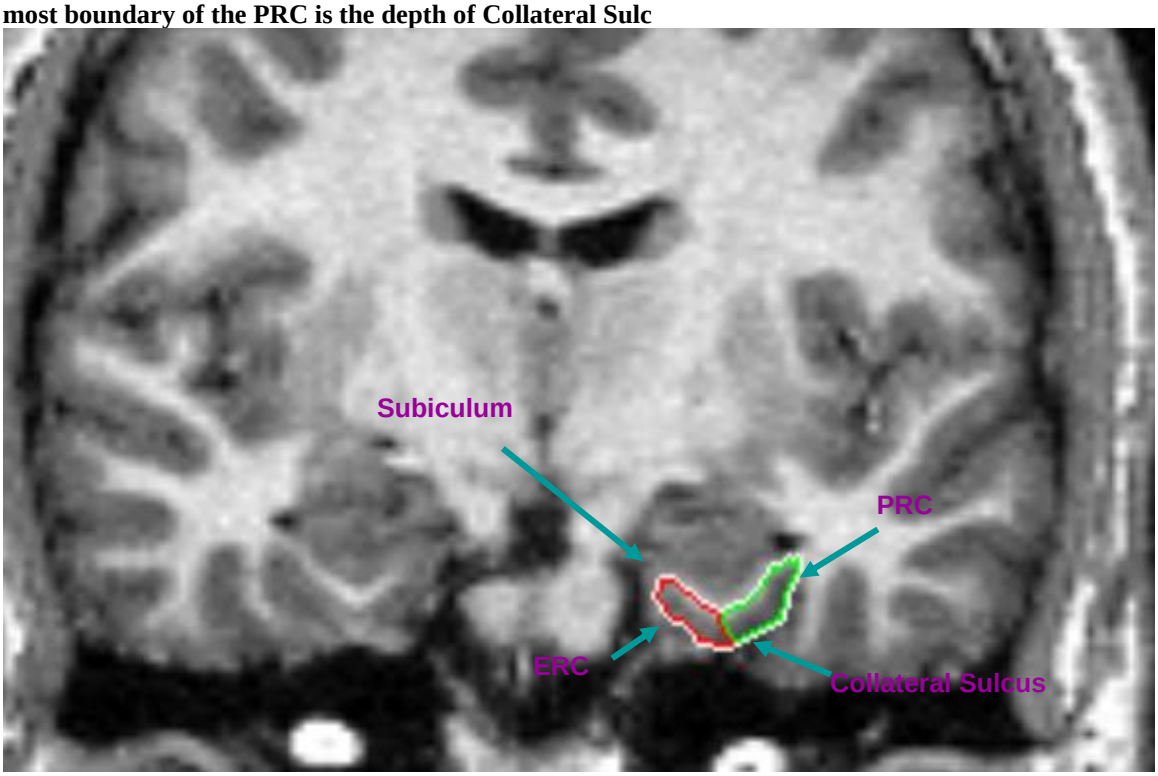


In the coronal view, the ERC boundary extended from the most medial, exposed tip of the PHG (below the Subiculum) to the trough of the exposed region of the gyrus (Figure 11). Since scan quality is often variable across subjects, the

cytoarchitectural boundary between ERC and PRC cannot always be visualized. Therefore, I defined the limit of ERC at the point where the cortex turned from exposed to buried (i.e., instead of going half way into the buried part). By being conservative in this way, I was able to include most of the ERC as defined by histology (Mai, 1997), while still using a consistent and clearly identifiable boundary. Regarding cutting of the ERC surface, the interclass correlation coefficient obtained for the cut and re-cut (n=10) was 0.96.

The PRC was adjacent to the most lateral part of the ERC and extended to the most interior part of the collateral sulcus (Figure 11). My definition of the PRC included BA 35 and completely excluded BA 36 within the PRC. My reasons for defining the PRC as such were three-fold: First, the collateral sulcus provided a relatively consistent boundary across subjects. Second, by being conservative in this way, my measurements were restricted to the PHG, thereby excluding the medial portion of the fusiform gyrus. And third, since both regions receive input from the same visual processing areas and then both project to both the ERC and the hippocampus, there was good reason to think that if there was to be a disease effect on this structure, both regions would be uniformly affected. Regarding the cutting of the PRC surface, the interclass correlation coefficient obtained for the cut and re-cut (n=10) was 0.99.

Figure 11: ERC extends medially to the Subiculum. The lateral boundary of the ERC is the point where the cortex goes from being exposed to being buried. This is where PRC begins. The lateral-most boundary of the PRC is the depth of Collateral Sulc



For the analysis of the PHG structural measures, I again employed mixed models, accounting for sibling-related covariance. Like those in my analysis of hippocampal volume, the fixed effects in my first round of PHG models were hemisphere, condition, hemisphere by condition interactions, and gender. The analysis was repeated after inclusion of an appropriate whole brain covariate as a fixed effect. For measures of volume, cerebral cortical volume was used. For measures of thickness, overall cortical thickness was used.

PHG:

Summaries of the PHG volume data (Table 6) and PHG thickness data (Table 7) are presented below.

Table 6: Summary of PHG volume data: Least Square Mean values are in cubic millimeters.

Group	**Schizophrenia Subjects n = 39**	**Schizophrenia Siblings n = 33**	**Controls n = 47**	**Control Siblings n = 50**
Mean (SE)	2938 (82)	2890 (83)	3183 (92)	3289 (91)

Table 7: Summary of PHG thickness data: Least Square Mean values are in millimeters.

Group	**Schizophrenia Subjects n = 39**	**Schizophrenia Siblings n = 33**	**Controls n = 47**	**Control Siblings n = 50**
Mean (SE)	3.27 (0.04)	3.20 (0.04)	3.36 (0.05)	3.40 (0.04)

There was a significant group effect on the volume of the PHG ($F_{3, 87} = 4.07$, $p < 0.01$). The schizophrenia subjects and their siblings did not differ significantly from each other, nor did the healthy controls and control siblings differ. However the schizophrenia subjects and their siblings differed significantly from the controls and their siblings (Table 8).

Table 8: Least Square Means (LSM) comparison of groups for PHG volume. P values to test Null Hypothesis: LSM (i) = LSM (j)

i/j	Schizophrenia Sibling	Control	Control Sibling
Schizophrenia Subject	0.67	**0.05**	**< 0.01**
Schizophrenia Sibling		**0.02**	**0.002**
Control			0.34

When I included whole cortical volume as a fixed effect, the group effect ceased to be significant ($F_{3, 92} = 1.90$, $p = 0.14$).

For whole PHG thickness, there was also a significant effect of group ($F_{3, 86} = 4.23$, $p < 0.01$). The schizophrenia group differed significantly from the control sibling group ($t = -2.20$, $p < 0.05$) but not from the control group ($t = 1.32$, $p = 0.10$), while the schizophrenia siblings differed from the control group ($t = -2.71$, $p < 0.01$) and the control sibling group ($t = -3.42$, $p < 0.001$) (Table 9).

Table 9: Least Square Means (LSM) comparison of groups for PHG thickness. P values to test Null Hypothesis: LSM (i) = LSM (j)

i/j	Schizophrenia Sibling	Control	Control Sibling
Schizophrenia Subject	0.19	0.10	**0.03**
Schizophrenia Sibling		**< 0.01**	**< 0.001**
Control			0.50

When overall cortical thickness was included as a fixed effect, the group effect remained significant, $F_{3, 86} = 3.25$, $p < 0.05$. Schizophrenia subjects differed at the trend level from control siblings ($t = -1.68$, $p = 0.09$), but schizophrenia siblings differed significantly from both healthy controls ($t = -2.53$, $p = 0.01$) and control siblings ($t = -2.93$, $p < 0.01$) (Table 10).

Table 10: Least Square Means (LSM) comparison of groups for PHG thickness with whole cortical thickness included as a fixed effect. P values to test Null Hypothesis: LSM (i) = LSM (j)

i/j	Schizophrenia Sibling	Control	Control Sibling
Schizophrenia Subject	0.16	0.17	0.09
Schizophrenia Sibling		**0.01**	**< 0.01**
Control			0.64

ERC:

Summaries of the ERC volume (Table 11) and thickness (Table 12) data are presented below.

Table 11: Summary of ERC volume data: Least Square Mean values are in cubic millimeters.

Group	**Schizophrenia Subjects n = 39**	**Schizophrenia Siblings n = 33**	**Controls n = 47**	**Control Siblings n = 50**
Mean (SE)	406 (23)	401 (19)	439 (21)	467 (24)

Table 12: Summary of ERC thickness data: Least Square Mean values are in millimeters.

Group	**Schizophrenia Subjects n = 39**	**Schizophrenia Siblings n = 33**	**Controls n = 47**	**Control Siblings n = 50**
Mean (SE)	3.66 (0.07)	3.59 (0.07)	3.74 (0.07)	3.78 (0.06)

There was no significant group effect on either ERC volume ($F_{3, 90} = 1.74$, $p = 0.16$), or ERC thickness ($F_{3, 78} = 1.44$, $p = 0.24$). After including cortical volume or thickness, respectively, as a fixed effect, the group effect remained non-significant.

PRC:

Summaries of the PRC volume (Table 13) and thickness (Table 14) data are presented below.

Table 13: Summary of PRC volume data: Least Square Mean values are in cubic millimeters.

Group	**Schizophrenia Subjects n = 39**	**Schizophrenia Siblings n = 33**	**Controls n = 47**	**Control Siblings n = 50**
Mean (SE)	635 (40)	604 (39)	626 (33)	667 (38)

Table 14: Summary of PRC thickness data: Least Square Mean values are in millimeters.

Group	**Schizophrenia Subjects n = 39**	**Schizophrenia Siblings n = 33**	**Controls n = 47**	**Control Siblings n = 50**
Mean (SE)	3.66 (0.06)	3.53 (0.05)	3.75 (0.06)	3.76 (0.07)

The effect of group on the volume of the PRC was not significant ($F_{3, 93} = 0.51$, $p = 0.67$) with or without whole cortical volume as a fixed effect. However, there was a significant effect ($F_{3, 89} = 3.34$, $p < 0.05$) of group on the thickness of the PRC (Table 15). The effect appeared to be due to the difference between

the schizophrenia sibling group and the controls and their siblings. There was a significant difference ($p < 0.01$) between the schizophrenia siblings and both, the healthy controls ($t = -2.64$) and, the control siblings ($t = -2.70$).

Table 15: Least Square Means (LSM) comparison of groups for PRC thickness. P values to test Null Hypothesis: LSM (i) = LSM (j)

i/j	Schizophrenia Sibling	Control	Control Sibling
Schizophrenia Subject	0.12	0.34	0.30
Schizophrenia Sibling		**< 0.01**	**< 0.01**
Control			0.86

The results remained significant ($F_{3, 91} = 3.15$, $p < 0.05$) after covarying for whole cortical thickness (Table 16). There was a significant difference between the schizophrenia siblings and the healthy controls and their siblings ($t = -2.61$, $p = 0.01$ and $t = -2.60$, $p = 0.01$, respectively).

Table 16: Least Square Means (LSM) comparison of groups for PRC thickness with whole cortical thickness included as a fixed effect. P values to test Null Hypothesis: LSM (i) = LSM (j)

i/j	Schizophrenia Sibling	Control	Control Sibling
Schizophrenia Subject	0.13	0.34	0.32
Schizophrenia Sibling		**0.01**	**0.01**
Control			0.86

PHC:

Summaries of the PHC volume (Table 17) and thickness (Table 18) data are presented below.

Table 17: Summary of PHC volume data: Least Square Mean values are in cubic millimeters.

Group	**Schizophrenia Subjects n = 39**	**Schizophrenia Siblings n = 33**	**Controls n = 47**	**Control Siblings n = 50**
Mean (SE)	1953 (53)	1888 (55)	2107 (61)	2123 (56)

Table 18: Summary of PHC volume data: Least Square Mean values are in millimeters.

Group	**Schizophrenia Subjects n = 39**	**Schizophrenia Siblings n = 33**	**Controls n = 47**	**Control Siblings n = 50**
Mean (SE)	3.02 (0.04)	2.97 (0.04)	3.10 (0.04)	3.14 (0.04)

The effect of group on the gray matter volume of the PHC was significant ($F_{3, 88} = 3.62$, $p < 0.05$) (Table 19). Schizophrenia subjects and healthy controls differed only at the trend level ($t = -1.90$, $p = 0.06$), while schizophrenia subjects differed from control siblings ($t = -2.10$, $p < 0.05$). The schizophrenia siblings also differed significantly from both the healthy controls ($t = -2.65$, $p < 0.01$) and their siblings ($t = -3.02$, $p < 0.01$). However, when whole cortical volume was added as a covariate, the group effect was no longer significant.

Table 19: Least Square Means (LSM) comparison of groups for PHC volume. P values to test Null Hypothesis: LSM (i) = LSM (j)

i/j	Schizophrenia Sibling	Control	Control Sibling
Schizophrenia Subject	0.36	**0.06**	**0.04**
Schizophrenia Sibling		**< 0.01**	**0.003**
Control			0.83

The effect of group on the thickness of the PHC was also significant ($F_{3, 87} = 2.92$, $p < 0.05$) (Table 20). In the full sample, the schizophrenia siblings

differed significantly from both the healthy controls ($t = -2.30$, $p < 0.05$) and their siblings ($t = -2.89$, $p < 0.01$). However, these results were not significant after covarying for overall cortical thickness.

Table 20: Least Square Means (LSM) comparison of groups for PHC thickness. P values to test Null Hypothesis: LSM (i) = LSM (j)

i/j	Schizophrenia Sibling	Control	Control Sibling
Schizophrenia Subject	0.24	0.16	**0.06**
Schizophrenia Sibling		**0.02**	**< 0.01**
Control			0.51

PHG Findings:

To summarize, a group effect was observed on several measures of PHG structure (Table 21).

Table 21: Measures with a significant effect of schizophrenia or risk for schizophrenia. Mixed Model Accounting for Sibling and Hemisphere Covariance; Fixed effect: Hemisphere, Group, Hemisphere by Group Interaction, and Gender, N = 169. *Appropriate

Structure		NF/DF	F Value	p Value	Schizophrenia Subjects[a]	Schizophrenia Siblings[a]
PHG	Volume	3, 87	4.07	< 0.01	✓	✓
	Thickness	3, 86	4.23	< 0.01	✓	✓
	Thickness*	3, 86	3.25	0.03	✓	✓
PRC	Thickness	3, 89	3.34	0.03		✓
	Thickness*	3, 91	3.15	0.03		✓
PHC	Volume	3, 88	3.62	0.02	✓	✓
	Thickness	3, 87	2.92	0.04	✓	✓

We observed that schizophrenia subjects had smaller values on several measures of PHG structure. Furthermore, our schizophrenia siblings also showed abnormalities of the same structures as their affected siblings, in addition to abnormalities in other PHG structures as compared to our two control groups. This data therefore supports my second hypothesis for this dissertation: Both schizophrenia subjects and their unaffected siblings will have smaller measures of MTL structure compared to control subjects and their siblings. There is however, an unexpected aspect to these results in that our unaffected siblings of schizophrenia subjects appear to show more severe structural abnormalities than our schizophrenia subjects themselves.

There are a number of potential explanations for this finding which I will outline in future chapters.

In the next chapter, however, I will explore the relationships between my PHG structural measures and memory.

7. MTL Structure and Episodic Memory Performance

The involvement of the MTL structures in memory has been fairly well established as a result of both human and animal lesion studies. There is also substantial evidence to suggest that certain disease processes, such as Alzheimer's disease, are associated with memory deficits that are thought to be caused by disease specific effects on MTL structure. Schizophrenia, a disorder likely caused by both genetic and environmental factors, is also associated with memory deficits and possible abnormalities of MTL structure.

In this study, we sought to determine if our schizophrenia subjects and their unaffected siblings had deficits in memory performance and abnormalities in MTL structure compared to healthy controls and their siblings. As described in the previous three chapters, we found that our schizophrenia subjects and our subjects at familial risk for schizophrenia both had deficits in overall episodic memory performance compared to our two control groups. We also observed that these subjects had smaller measures of MTL structure compared to our two control groups.

Because schizophrenia is characterized by deficits in memory performance and because we have found both deficits in memory performance, and abnormalities in MTL structure in these subjects, we hoped to determine in this study if these differences in MTL structure between our two experimental groups (schizophrenia subjects and those at familial risk for schizophrenia) and our two control groups (healthy controls and their siblings) were related to

variation in episodic memory performance. If so, this would suggest that the group differences in MTL structure were functionally meaningful.

Our global episodic memory domain score is a composite measure of performance on each of our tasks combined. The memory tasks we utilized measure multiple aspects of episodic memory: Logical Memory and the CVLT both measure verbal memory with Logical Memory requiring higher level processing of story elements and their order, and the CVLT requiring the use of intact semantic memory and categorization skills; Family Pictures is a measure of visual-spatial memory and possibly semantic memory as well. Because our global episodic memory domain score is a robust measure of different aspects of episodic memory, it is also sensitive to damage anywhere in the MTL.

There are three hypotheses in the literature concerning the normative relationship between MTL structure and memory performance (See Background chapter for greater detail). The first states that a bigger structure is associated with better memory and a smaller structure is associated with poorer memory in healthy people regardless of other structural qualities. Numerous studies have failed to find such a relationship in healthy control subjects, and the reasoning for this hypothesis is based on evidence from studies of compromised MTL structure due to factors such as seizures or Alzheimer's disease. For these reasons, it is unlikely that this hypothesis is likely to predict the relationship between brain structure and memory performance in my control subjects and control siblings.

The second hypothesis concerning the relationship between MTL structure and memory performance claims that a normally developed and

structurally sound MTL formation will support memory performance regardless of size. However, according to this hypothesis, the loss of tissue in the MTL due to aging or disease will negatively impact memory performance.

The final hypothesis is based primarily on findings from children and adolescents where larger hippocampal volume was associated with poorer memory performance and smaller hippocampal volume was associated with better memory performance. It is thought that tissue loss in the young developing brains of these subjects is the result of loosing neurons, axonal branches and synapses that do not support efficient brain function. However, since most of the subjects in this study are too old to be experiencing developmental pruning, this hypothesis was likely not to apply to my subjects.

In order to determine how MTL structure related to memory performance in both health and disease, I performed a correlation analysis between each of our measures of MTL structure and our measure of global episodic memory performance in each of our four groups of subjects. I expected to find relationships between our structural measures and memory performance in both our schizophrenia subjects and our subjects at familial risk for schizophrenia (the schizophrenia siblings), but not in our two control groups. Thus, my expectations were most in keeping with the second of the above hypotheses concerning the relationship between MTL structure and memory performance.

I expected such results because schizophrenia is caused by a combination of genetic and environmental influences that lead the disorder to manifest as a disorder with differing levels of cognitive dysfunction and

abnormality in brain structures. Since our schizophrenia subjects show abnormalities in MTL structure and memory performance, it is possible that the variance found in these two potentially related measures is functionally meaningful such that smaller volumes and/or thicknesses are associated with poorer memory performance and larger volumes and/or thicknesses are associated with better memory performance. Because control subjects show no cognitive deficits, I would not expect to see the variation in their measures of MTL structure to be functionally meaningful. As the two sibling groups share half of the same genetic makeup of their respective siblings, I would expect that schizophrenia subjects and schizophrenia siblings share similar structure-function relationships, and that such a relationship would be nearly as difficult to observe in control siblings as it is in control subjects themselves.

In my correlation analysis, I looked at left and right combined measures of MTL structure. For volume, I looked at total volume for both the left and right sides, and for thickness, I averaged the values for both hemispheres. Due to the potential impact of gender on memory performance (Andreano and Cahill, 2009), and because my schizophrenia group has significantly more males than females, and my control sibling group has considerably more females than males, I have included gender as a covariate in my analyses. I am reporting correlations of at least moderate (Pearson's $r \geq 0.35$) size (Cohen, 1988) and p value < 0.05.

Below are my results:

Control Subjects:

There were no significant correlations between MTL structure and episodic memory performance in these subjects (Figures 12 - 20).

Figure 12: Scatter plot of Episodic Memory Domain z-scores by total PHG Volume in healthy control subjects

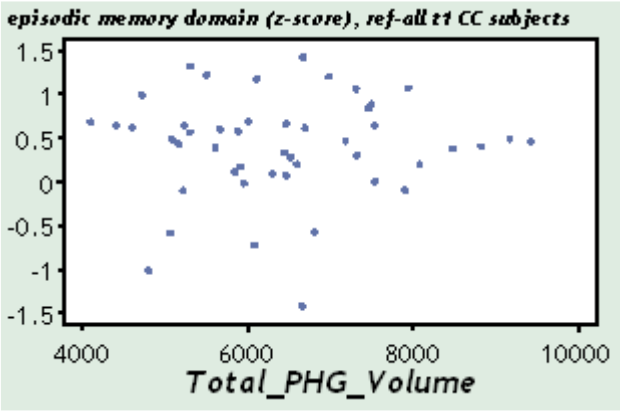


Figure 13: Scatter plot of Episodic Memory Domain z-scores by average PHG Thickness in healthy control subjects

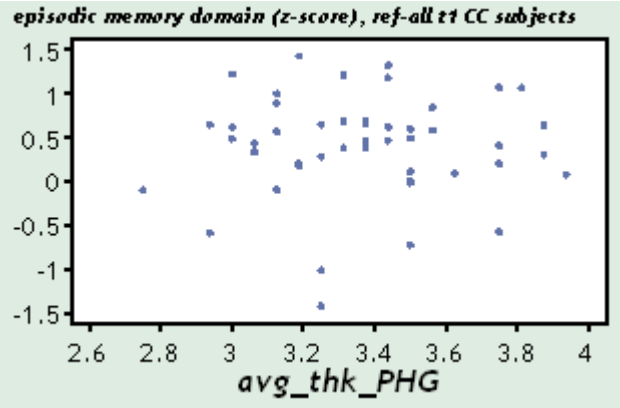


Figure 14: Scatter plot of Episodic Memory Domain z-scores by total ERC Volume in healthy control subjects

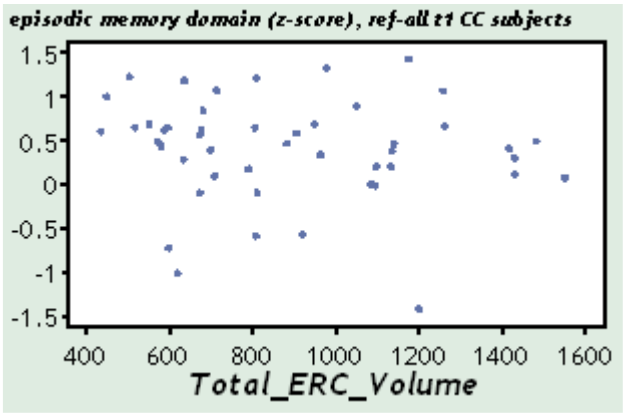


Figure 15: Scatter plot of Episodic Memory Domain z-scores by average ERC Thickness in healthy control subjects

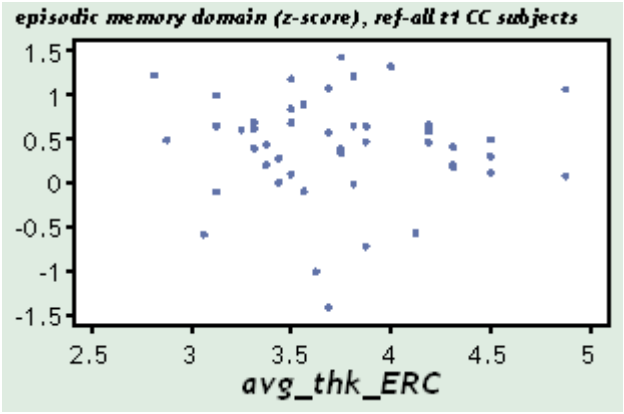


Figure 16: Scatter plot of Episodic Memory Domain z-scores by total PRC Volume in healthy control subjects

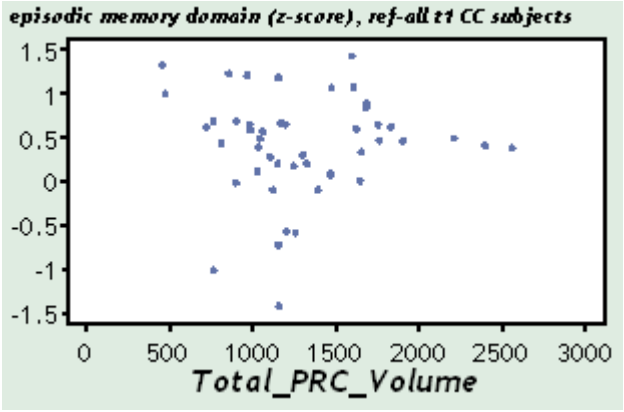


Figure 17: Scatter plot of Episodic Memory Domain z-scores by average PRC Thickness in healthy control subjects

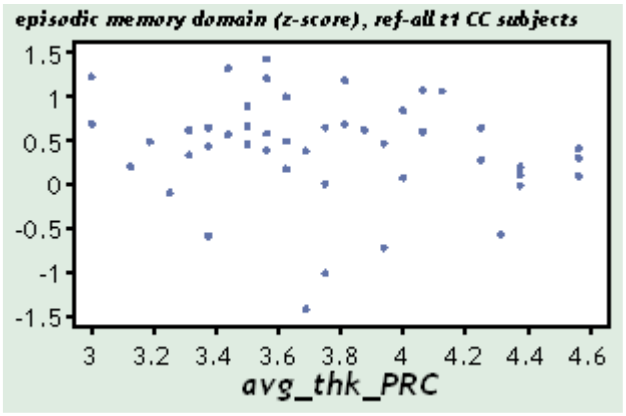


Figure 18: Scatter plot of Episodic Memory Domain z-scores by total PHC Volume in healthy control subjects

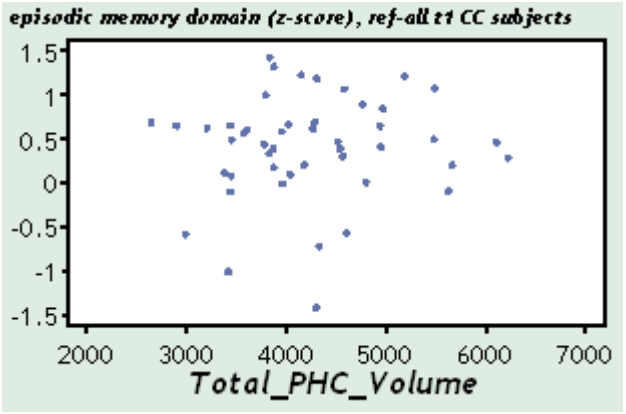


Figure 19: Scatter plot of Episodic Memory Domain z-scores by average PHC Thickness in healthy control subjects

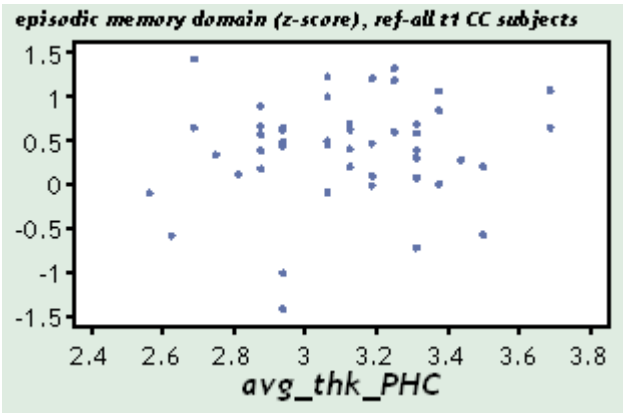
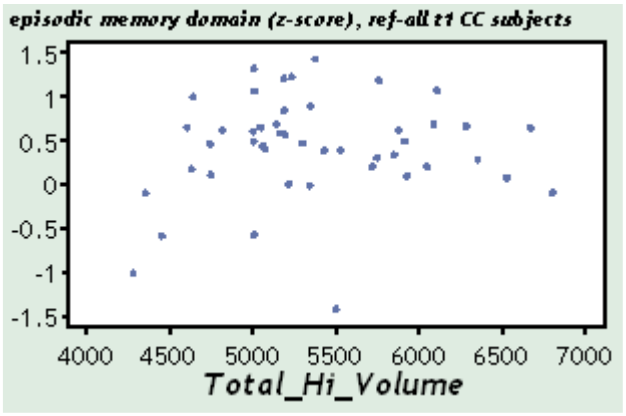


Figure 20: Scatter plots of Episodic Memory Domain z-scores by total Hippocampal Volume in healthy control subjects



Control Siblings:

There were no significant correlations between MTL structure and episodic memory performance in these subjects (Figure 21 - 29).

Figure 21: Scatter plots of Episodic Memory Domain z-scores by total PHG Volume in control siblings

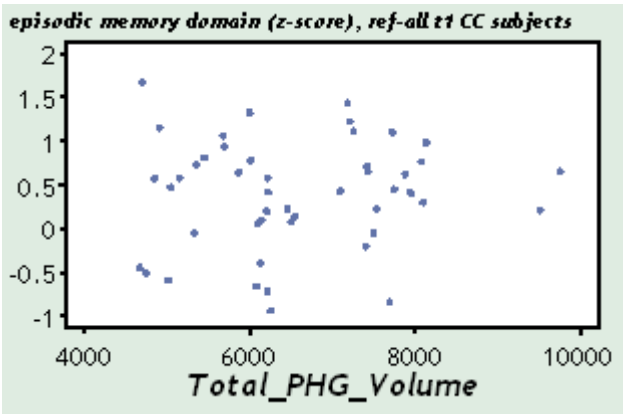


Figure 22: Scatter plots of Episodic Memory Domain z-scores by average PHG Thickness in control siblings

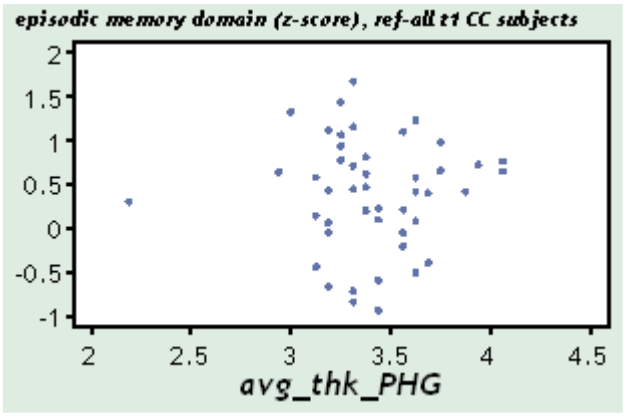


Figure 23: Scatter plots of Episodic Memory Domain z-scores by total ERC Volume in control siblings

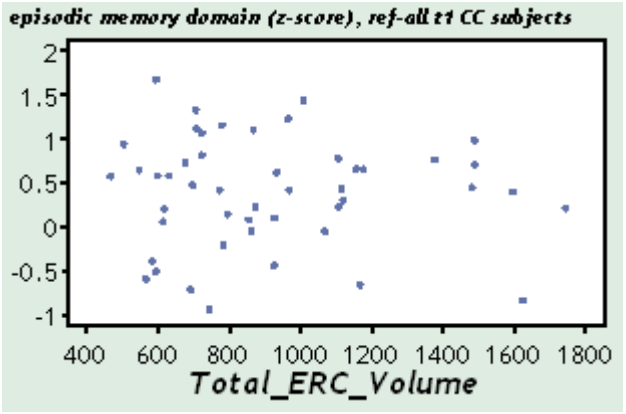


Figure 24: Scatter plots of Episodic Memory Domain z-scores by average ERC Thickness in control siblings

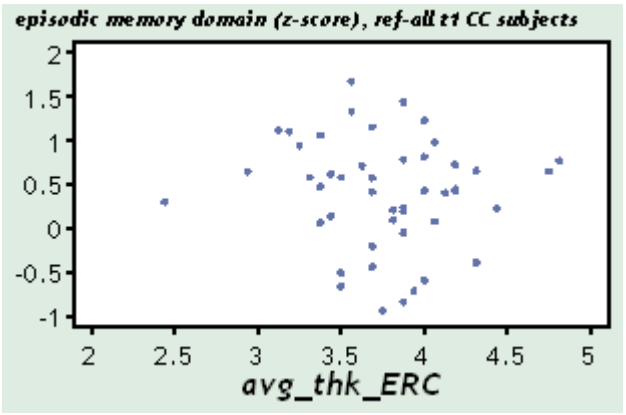


Figure 25: Scatter plot of Episodic Memory Domain z-scores by total PRC Volume in control siblings

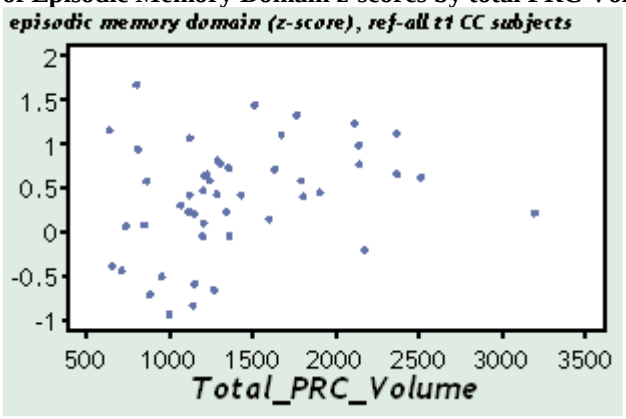


Figure 26: Scatter plot of Episodic Memory Domain z-scores by average PRC Thickness in control siblings

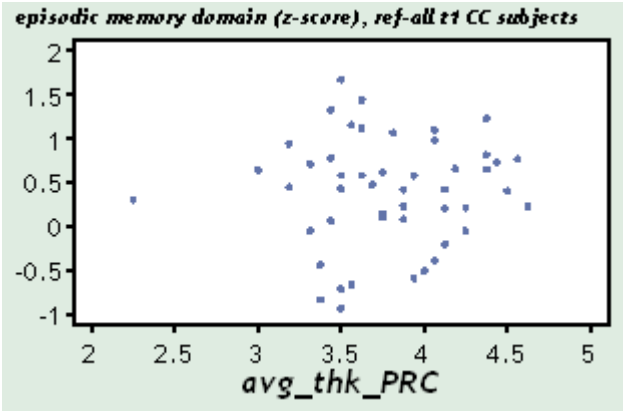


Figure 27: Scatter plot of Episodic Memory Domain z-scores by total PHC Volume in control siblings

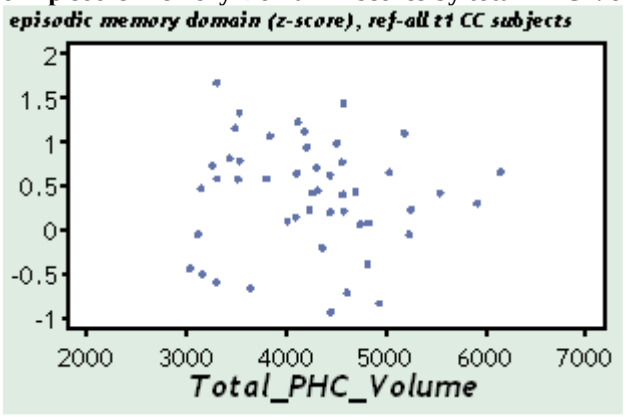


Figure 28: Scatter plots of Episodic Memory Domain z-scores by average PHC Thickness in control siblings

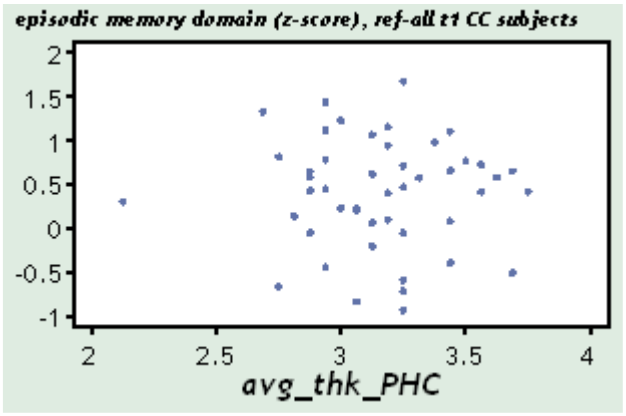
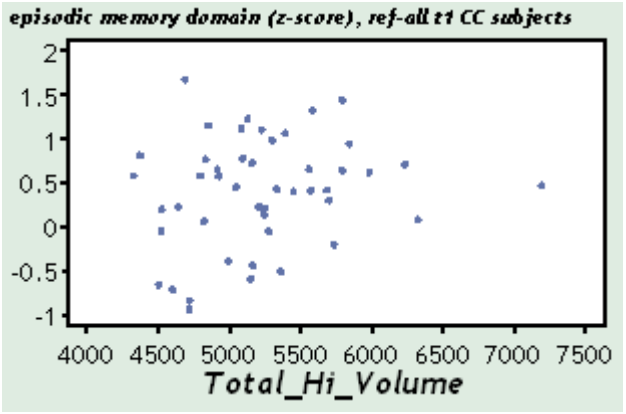


Figure 29: Scatter plot of Episodic Memory Domain z-scores by total Hippocampal Volume in control siblings



Schizophrenia Subjects:

There were no significant correlations between MTL structure and episodic memory performance in these subjects (Figure 21 - 29).

Figure 30: Scatter plots of Episodic Memory Domain z-scores by total PHG Volume in schizophrenia subjects

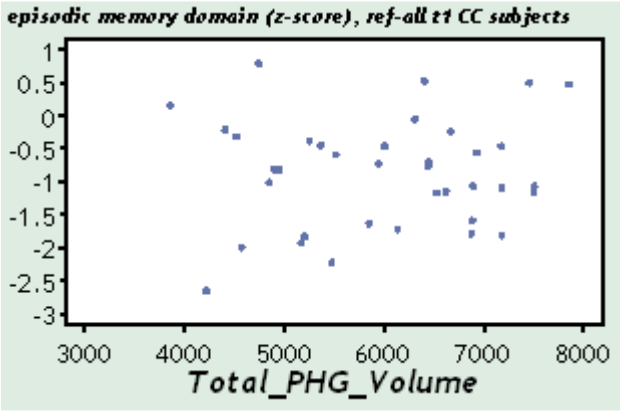


Figure 31: Scatter plots of Episodic Memory Domain z-scores by average PHG Thickness in schizophrenia subjects

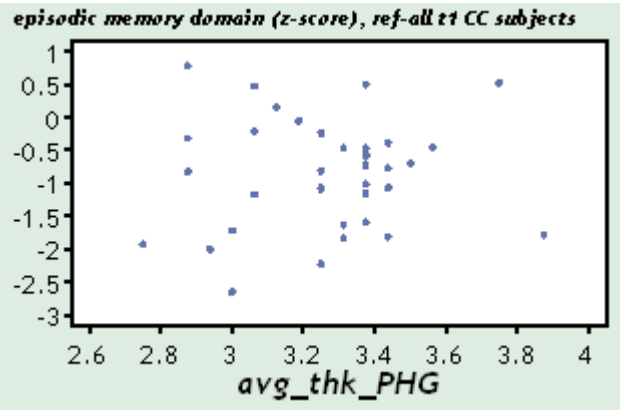


Figure 32: Scatter plot of Episodic Memory Domain z-scores by total ERC Volume in schizophrenia subjects

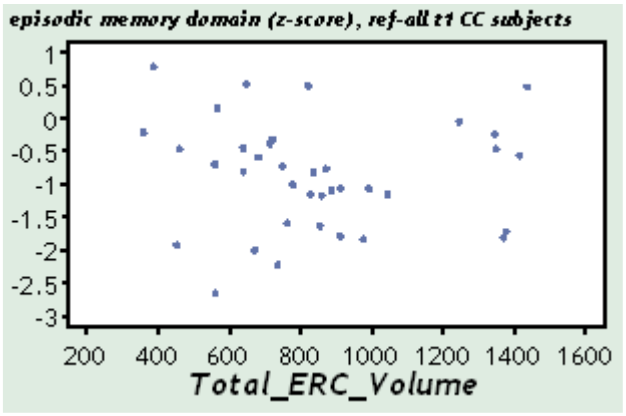


Figure 33: Scatter plot of Episodic Memory Domain z-scores by average ERC Thickness in schizophrenia subjects

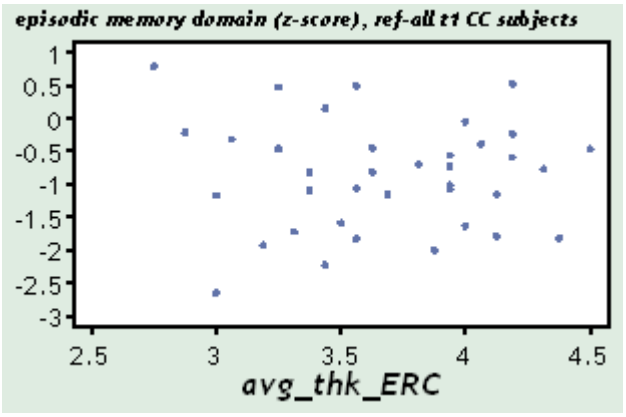


Figure 34: Scatter plot of Episodic Memory Domain z-scores by total PRC Volume in schizophrenia subjects

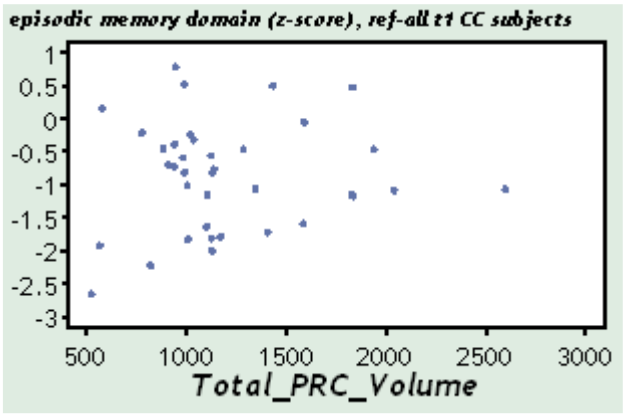


Figure 35: Scatter plot of Episodic Memory Domain z-scores by average PRC Thickness in schizophrenia subjects

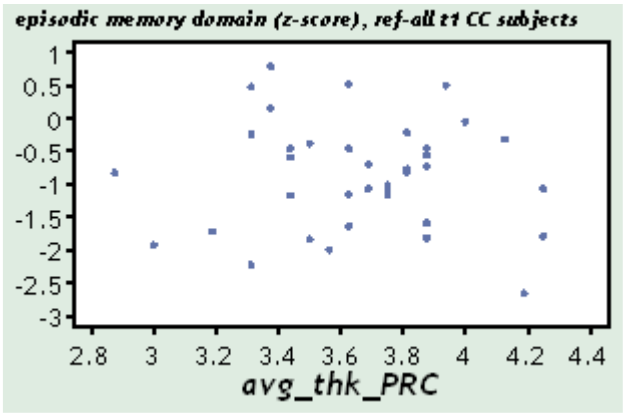


Figure 36: Scatter plot of Episodic Memory Domain z-scores by total PHC Volume in schizophrenia subjects

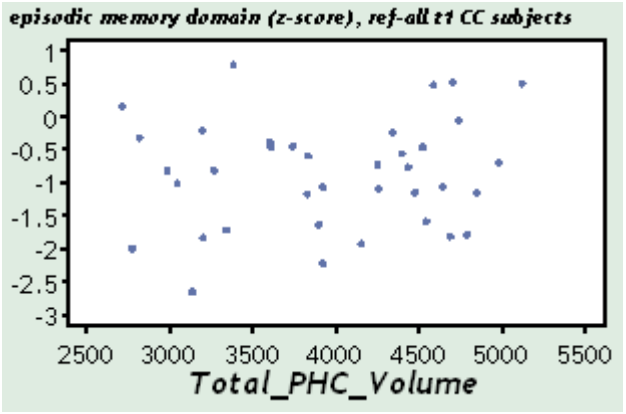


Figure 37: Scatter plot of Episodic Memory Domain z-scores by average PHC Thickness in schizophrenia subjects

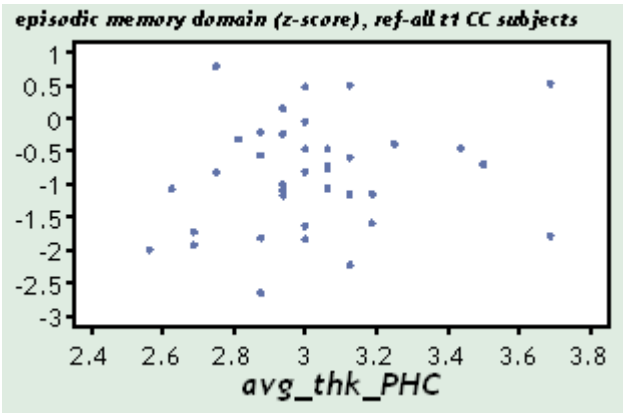
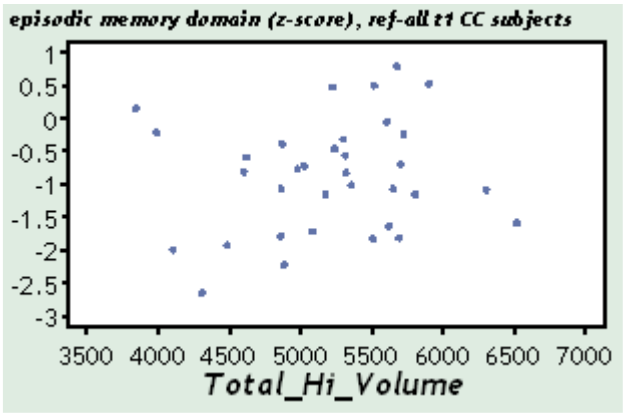


Figure 38: Scatter plot of Episodic Memory Domain z-scores by total Hippocampal Volume in schizophrenia subjects



Schizophrenia Siblings:

Several of my correlations (Figures 39 – 47) between measures of MTL structure and episodic memory performance in our schizophrenia siblings appeared to be moderately strong. These included average PHG thickness ($r = 0.37$, $p = 0.04$) (Figure 40), the average PHC thickness ($r = 0.40$, $p = 0.03$) (Figure 46), and total hippocampal volume ($r = 0.47$, $p < 0.02$) (Figure 47).

Figure 39: Scatter plot of Episodic Memory Domain z-scores by Total PHG Volume in schizophrenia siblings

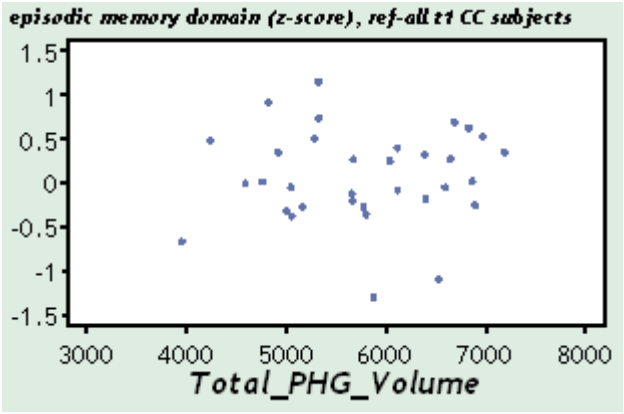


Figure 40: Scatter plot of Episodic Memory Domain z-scores by average PHG Thickness (r = 0.37, p = 0.04) in schizophrenia siblings

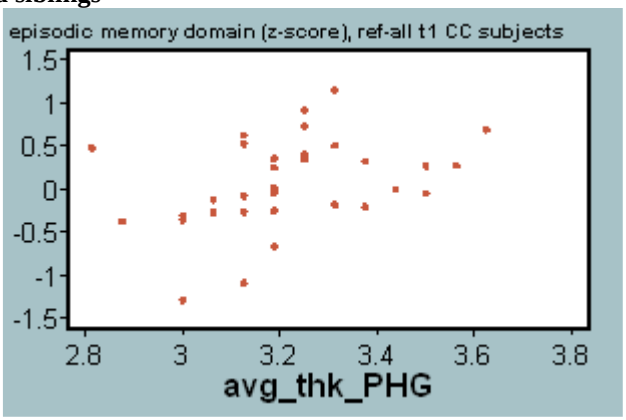


Figure 41: Scatter plot of Episodic Memory Domain z-scores by Total ERC Volume in schizophrenia siblings

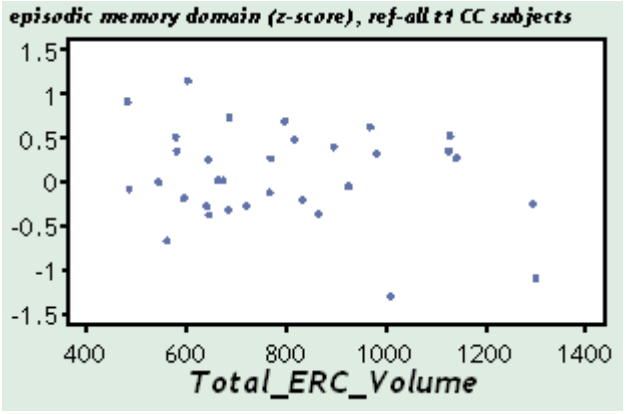


Figure 42: Scatter plot of Episodic Memory Domain z-scores by average ERC Thickness in schizophrenia siblings

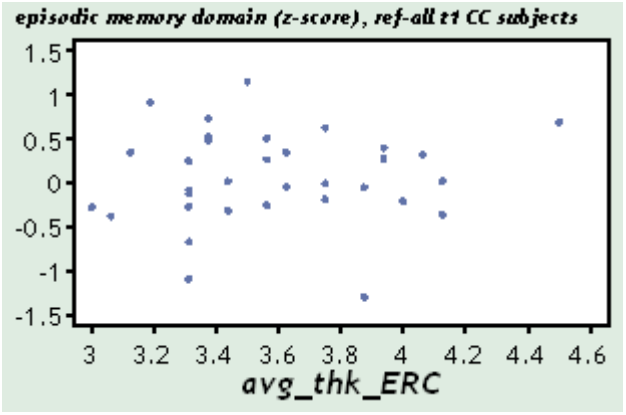


Figure 43: Scatter plot of Episodic Memory Domain z-scores by total PRC Volume in schizophrenia siblings

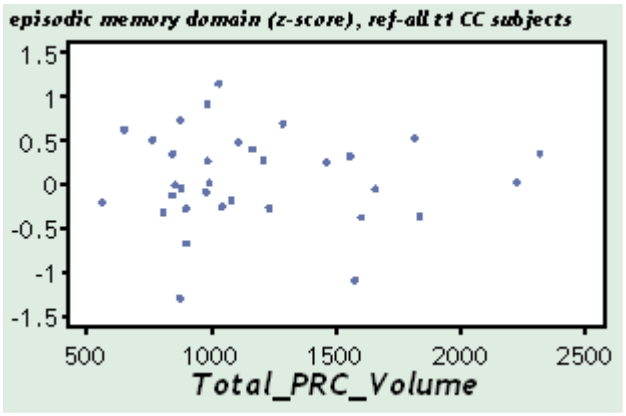


Figure 44: Scatter plot of Episodic Memory Domain z-scores by average PRC Thickness in schizophrenia siblings

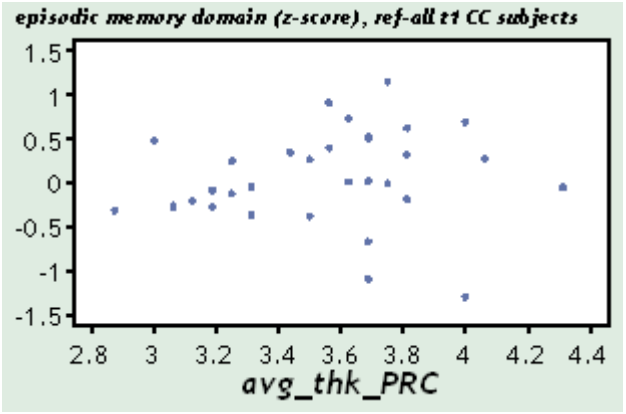


Figure 45: Scatter plot of Episodic Memory Domain z-scores by total PHC Volume in schizophrenia siblings

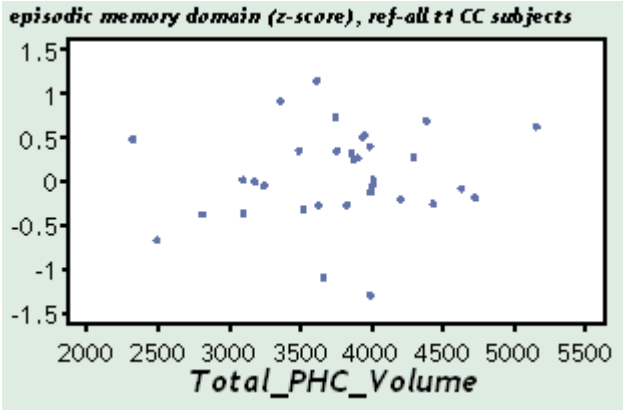


Figure 46: Scatter plot of Episodic Memory Domain z-scores by average PHC Thickness (r = 0.40, p = 0.03) in schizophrenia siblings

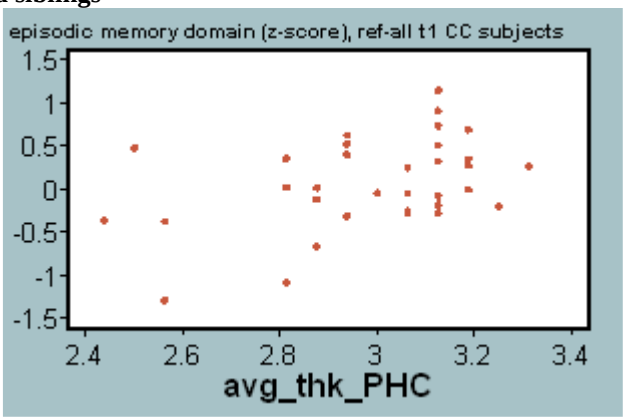
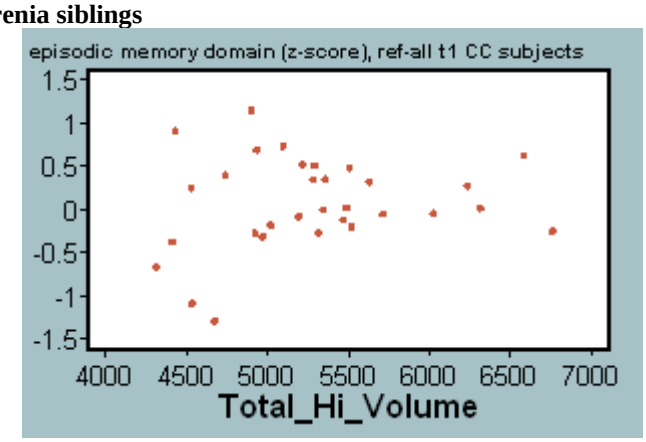


Figure 47: Scatter plot of Episodic Memory Domain z-scores by total Hippocampal Volume (r = 0.47, p < 0.01) in schizophrenia siblings



Significance of Findings:

The findings from these analyses support my hypothesis that a relationship between MTL structure and memory performance would be unobservable in control subjects and their siblings. Although, the results obtained from the schizophrenia sibling sample would not survive corrections for multiple comparisons, I did find three moderate correlations between MTL structure and memory performance in my schizophrenia siblings subjects (Table 22).

Table 22: Summary of Significant Correlations of MTL structural measures with Episodic Memory domain in Schizophrenia Siblings

Structural Measure	r value, p value
PHG Thickness	$r = 0.37$, $p = 0.04$
PHC Thickness	$r = 0.40$, $p = 0.03$
Hippocampal Volume	$r = 0.47$, $p < 0.01$

I performed a post-hoc Fisher's z-score transformation in order to compare the correlation coefficients from the schizophrenia sibling group to those for the same structural measures in each of the other three groups. Although not significant, a trend-level difference between the standardized schizophrenia sibling correlation coefficient for PHC thickness and the standardized control sibling correlation coefficient was found (Table 23).

Table 23: Summary of Fisher's z-score transformation analysis comparing standardized correlation coefficients from structural measures by memory performance across groups

Structural Measure	Group compared to Schizophrenia Siblings	Standard Error	z score, p value
Average PHG Thickness	Controls	0.24	z = 1.46, p = 0.14
	Control Siblings	0.24	z = 1.54, p = 0.12
	Schizophrenia Subjects	0.26	z = 1.35, p = 0.18
Average PHC Thickness	Controls	0.24	z = 1.08, p = 0.28
	Control Siblings	0.24	z = 1.88, p = 0.06
	Schizophrenia Subjects	0.26	z = 1.05, p = 0.30
Total Hippocampal Volume	Control	0.24	z = 1.54, p = 0.12
	Control Siblings	0.24	z = 1.18, p = 0.24
	Schizophrenia Subjects	0.26	z = 1.10, p = 0.28

These results, combined with the original correlations, suggest the possibility that familial risk for schizophrenia may affect the relationship between MTL structure and memory performance such that memory deficits observed in schizophrenia siblings may be the result of disruption of MTL structure, and therefore, the abnormalities in MTL structure observed in these subjects could be functionally meaningful.

However, it is important to note that because so many correlations (36) were tested, none of the moderate correlations reported in the schizophrenia siblings would survive correction for multiple comparisons. There was also no significant difference between correlation coefficients across groups. Thus, the

data provide some hints that the relationship between MTL structure and memory performance may be stronger in the schizophrenia siblings compared to the other groups, but not significantly so. At best, the results of my analyses provide weak support for my hypothesis that I would find an observable, positive relationship between MTL structure and memory performance in my schizophrenia sibling subjects.

I was unable to provide evidence to support my hypothesis concerning the relationship between MTL structure and memory performance in my schizophrenia subjects. It is possible that pharmacological factors may have affected the MTL structures of our schizophrenia subjects to the point of obscuring the natural relationship between measures of this brain region and memory performance in this group. Specifically, the higher incidence of prior drug abuse observed in our schizophrenia subjects, and the use of antipsychotic medications in this group may have influenced our ability to observe the predicted correlations.

8. Post Hoc Analysis of Antipsychotic Treatment and MTL structure

As mentioned in the last chapter, one explanation for our findings concerns the effects of antipsychotic medication, specifically, the effect of type of antipsychotic medication, on MTL structure in our schizophrenia subjects. The following three different groups have found an effect of antipsychotic drug treatment on volume of gray matter schizophrenia subjects. Two of the three studies (Dazzan et al., 2005 and Lieberman et al., 2005) indicate that treatment with a typical antipsychotic is associated with significant reductions in gray matter volumes. These reductions in gray matter volume were localized to particular regions of the cerebral cortex, specifically to the temporal and parietal lobes. Dazzan et al. (2005) studied subjects who had received a typical antipsychotic treatment for approximately 2 weeks, and found significant reductions in gray matter compared to subjects who had been drug-free for three weeks, or who had received an atypical antipsychotic treatment for two weeks. Lieberman et al (2005) found decreases in frontal gray matter volume associated with typical antipsychotics as early as twelve weeks, with an even stronger effect after fifty-two weeks. They found a similar effect of typical antipsychotic medication on the volume of temporal lobe gray matter at twenty-four and fifty-two weeks. Finally, Garver, et al. (2005), found that schizophrenia patients who received an atypical antipsychotic drug showed a significant increase in cortical gray matter volume after four weeks in comparison to patients who received a typical antipsychotic

treatment and to healthy control subjects. Although none of the above studies implicated the PHG as a specific target of the antipsychotic effect, all three were studies of global brain structure, and may have lacked the resolution to observe such an effect if there was one.

Because of the above studies, because my structural results suggested a greater influence of familial risk for schizophrenia than schizophrenia itself on PHG structure, and because treatment information had been collected from my schizophrenia subjects, I chose to conduct an exploratory post hoc analysis to determine if I could observe any effects of type of antipsychotic on MTL structure that would provide insight onto my results. Twenty-two of these subjects had been treated with only atypical antipsychotic drugs. Of the eleven schizophrenia subjects who had been treated with typical antipsychotic medications, only one patient had been treated exclusively with typical antipsychotic medication. The remainder of these subjects had been treated with a combination of typical and atypical drugs. To test the effect of type of treatment on each of our structural measures, I conducted partial correlation analyses where I assessed the relationship between total duration of time on typical or atypical antipsychotic drugs with each structural measure. I did this while controlling for duration of illness at the time of the scan because MTL shrinkage is associated with duration of illness in chronic schizophrenia subjects (Razi et al., 1999; Velakoulis et al., 1999; Wang et al., 2008). Since my interest was only on whether antipsychotic treatment type affected my measures of MTL structures over time, regardless of the potential impact of treatment on whole brain measures, or my measures

relative to whole brain measures, I did not include any whole brain covariates in my analyses. Because I had no reason to believe that the antipsychotic treatment effect acted differently depending upon gender, I also chose not to include that as a covariate.

Seven measures of MTL structure were correlated at $r \geq |0.30|$ with duration of time (in months) on typical antipsychotic medication, after controlling for duration of illness (Table 24).

Table 24: Correlation Coefficients ≥ |0.30| for the relationship between Duration of time (in months) on Typical Antipsychotics and MTL Structure

Structure (n = 11)	r =	p value
Left PRC Volume	0.69	0.03
Left PHC Thickness	- 0.47	
Right PHG Volume	0.46	
Right PHG Thickness	- 0.30	
Right ERC Volume	0.51	
Right PRC Volume	0.69	0.03
Right PHC Thickness	- 0.63	0.05

Of these seven measures, three were inversely correlated with duration of typical antipsychotic treatments; that is, for these measures, longer durations of treatment were associated with smaller volumes or thicknesses. In contrast, in the group of subjects who had been treated with atypical antipsychotic drugs only, there were seven positive associations between duration of treatment and

MTL structure (Table 25); that is, longer duration of treatment with atypical drugs was associated with larger volumes or thicknesses.

Table 25: Correlation Coefficients ≥ |0.30| for the relationship between Duration of time (in months) on Atypical Antipsychotics and MTL Structure

Structure (n = 22)	r =	p value
Left PHG Volume	0.38	0.09
Left ERC Volume	0.72	0.0002
Left ERC Thickness	0.45	0.04
Left PHC Volume	0.30	
Right ERC Volume	0.42	0.05
Right ERC Thickness	0.30	
Right Hippocampal Volume	0.32	

These results will be interpreted in the following chapter.

9. Discussion

Purpose and Aims:

The purpose of this dissertation was to explore the structure and function of the brain in health and disease. Specifically, my goal was to determine if the structure of the MTL in schizophrenia subjects and their siblings differed significantly from the structure of the MTL in healthy control subjects and their siblings. Since the MTL is a known neural substrate of memory and, since schizophrenia subjects and those at familial risk for schizophrenia show deficits in episodic memory, I was also interested in determining if structural variation of the MTL in each of my four subject groups related to episodic memory performance in that group.

This study has particular relevance for current attempts to improve our understanding of schizophrenia because 1) episodic memory deficits are thought to be fundamental to the disorder and responsible for substantial disability, 2) abnormalities of MTL structure have been reported in subjects with schizophrenia, and 3) there is ongoing work to improve episodic memory deficits in patients with schizophrenia as a means of reducing the disability associated with the illness.

My study was also based on the premise that each aspect of this relationship could be influenced by a number of factors including genetics, environmental insults and disease states. For these reasons, I chose schizophrenia as a model disease because it is known to be influenced by

genetic as well as environmental factors. I considered the siblings of the schizophrenia subjects in this study to have special importance because they have been shown to have many of the same cognitive and neurobiological features as subjects with schizophrenia (Sitskoorn et al., 2004; Delawalla et al., 2006), although they are not affected by as many of the same confounding factors, such as treatment with psychotropic drugs.

My aims for this project were the following:

1. To collect cognitive data and high resolution MR scans in groups of individuals with schizophrenia, healthy controls, and their respective siblings.
2. To extract a measure of episodic memory performance by selecting measures from the cognitive testing that assessed episodic memory.
3. To make measurements of hippocampal volume and the volume and thickness of the parahippocampal gyrus and its subregions.
4. Using a combined database of cognitive and structural data, to examine the relationship between medial temporal lobe structure and episodic memory performance in health and disease.

Episodic Memory Domain Findings:

Our episodic memory domain consisted of tasks that were chosen, not only because of their sensitivity to cognitive deficits in schizophrenia subjects (Hawkins, 1998; Weickert et al., 2000), but also because they measured several different aspects of episodic memory, and would therefore be sensitive to disruption anywhere in the MTL.

Both subjects with schizophrenia and, their unaffected siblings performed significantly worse than healthy control subjects and their siblings. Also, of the former two groups, the schizophrenia subjects performed significantly worse than their unaffected siblings. These findings are in keeping with the literature on cognitive deficits in patients with schizophrenia and their siblings. More specifically, measures of cognitive deficits are increasingly being used as endophenotypes of schizophrenia (Cannon et al., 2000; Gur et al., 2007; Braff et al., 2007). Such measures have been helpful in improving our understanding of this disease with varying phenotypes determined by a combination of disease-specific genetic dosing and environmental insults (Marenco and Weinberger, 2000; Tsuang et al., 2001; Harrison and Weinberger, 2005).

By showing that our schizophrenia subjects performed significantly worse on tasks of episodic memory performance than our two control groups, and that our schizophrenia siblings show similar but attenuated deficits in memory performance, my results have replicated the findings of others who have shown similar results (Cannon et al., 2000). My findings are also consistent with the hypothesis that the cognitive deficits associated with schizophrenia may be

caused, at least in part, by genetic influences, though shared environmental factors could also account for these results.

Hippocampal Volume Findings:

My results related to the hippocampus were generally consistent with the prior work in our Center, and with the work of others, who have also found schizophrenia subjects to have smaller volumes of this structure as compared to healthy control subjects (Nelson et al., 1998; Sim et al., 2006). However, our findings of the volume reductions appeared to be proportional to overall decreases in brain volume, in that our schizophrenia subjects also have significantly smaller whole brain volumes compared to control subjects, and that their hippocampal reductions are proportionally similar to the reductions elsewhere in the brain. Based on our prior findings (Wang et al., 2001; Csernansky et al., 1998; Csernansky et al., 2002), it is likely that this result reflects a change in specific sub-regions of the hippocampus, rather than a uniform abnormality across the entire structure. Specifically, these studies, which have failed to find significant differences in hippocampal volume between schizophrenia subjects and control subjects after covarying for whole brain volume, have found significant inward deformation in the head of the hippocampus of schizophrenia subjects compared to healthy controls. Others who have performed automated voxel-based morphometry analyses rather than region of interest analyses, such as ours, have also found that schizophrenia

subjects have smaller hippocampal volumes than healthy control subjects (meta-analysis, Honea et al., 2005).

It should be noted that although our schizophrenia subjects had significantly smaller hippocampal volumes compared to both control groups and the schizophrenia siblings, the schizophrenia siblings did not differ significantly from the control subjects on this measure. This finding suggests that if there was a hippocampal subregion-specific deformation in the hippocampus of our siblings, its effect was too small for us to observe with our methods for evaluating whole hippocampal volume. In another study of schizophrenia sibling pairs and control subjects, with a different, and smaller sample of subjects, our lab has indeed found that schizophrenia siblings show significant differences in hippocampal volume compared to controls, and inward deformations in the head of the hippocampus analogous to those observed in schizophrenia subjects themselves (Tepest et al., 2003). Unlike our schizophrenia subjects and siblings, the schizophrenia sibling pairs from this study had a known family history of schizophrenia that may have strengthened the genetic predisposition in both the schizophrenia and schizophrenia sibling groups to abnormalities of brain structure. It is possible that had I looked at shape in our schizophrenia siblings, we may have observed a similar phenomenon. However, our subjects are entirely independent of the subjects from that earlier study, so it is possible that a lack of a significant difference between the schizophrenia sibling subjects and control subjects may simply imply that our findings reflect the effects of a

disease-specific process on hippocampal structure that is independent of genetic influences.

Several other studies examining the effect of schizophrenia on hippocampal volume in siblings or other first-degree relatives of schizophrenia subjects have been carried out. The results of these studies have often been contradictory, and therefore difficult to cumulatively interpret. Some have shown that first-degree relatives have smaller hippocampal volumes compared to control subjects (Seidman et al., 1999; Baare et al., 2001; O'Driscoll et al., 2001; Tepest et al., 2003; Van Erp et al., 2004), whereas others have found no significant difference between the hippocampal volumes of first-degree relatives of schizophrenia subjects and those of healthy controls (Staal et al., 2000; Narr et al., 2002; Schultze et al., 2003; Van Haren et al., 2004; Wood et al., 2004). Two of the studies listed above (Baare et al., 2001; Van Erp et al., 2004) where schizophrenia siblings had smaller volumes compared to controls were studies of monozygotic (MZ) and dizygotic (DZ) twins. The DZ twin pairs are most analogous to our subjects since this kind of pair consists of the schizophrenia subject, and the subject's first-degree relative with whom 50% of the same genes are shared, just as in our sibling pairs. In the case of the Baare et al. (2001) study, although both sets of twin pairs (schizophrenia subjects and their unaffected twin) were seen to have smaller hippocampal volumes compared to control subjects, the group consisting of only the unaffected halves of the DZ pairs, excluding the halves with schizophrenia, did not have smaller hippocampal volumes. In contrast, in the Van Erp et al. (2004) study, regardless of zygosity,

the unaffected twins of schizophrenia subjects had smaller hippocampal volumes compared to control subjects. However, even though dizygotic twins share only half of the same genes, they may also share similar environmental conditions during birth. Negative perinatal conditions have been found to be associated with an elevated risk for schizophrenia (Harrison and Weinberger, 2005), but such conditions have also been found to be associated with smaller gray matter volumes in dizygotic twins discordant for schizophrenia, but not in controls. Similarly, in a study of discordant monozygotic twins, Mc Neil et al. (2000) found that the twins affected by schizophrenia not only had smaller hippocampi than the unaffected twins, but that the smaller volumes were significantly related to labor-delivery complications. These studies suggest that although dizygotic twins are genetically similar to full-sibling pairs such as ours, findings from studies including them may not be entirely analogous to those from other studies of first-degree relatives of schizophrenia subjects. Of the two remaining studies I have cited, but not yet discussed where significantly smaller hippocampal volumes compared to control subjects were observed in first-degree relatives of schizophrenia subjects, the Seidman et al. (1999) study is the most dissimilar from ours. Unlike us, they included several subjects with diagnoses for bipolar disorder in their group of first-degree relatives of schizophrenia subjects. Given that bipolar disorder (Blumberg et al., 2003) has been associated with reductions in hippocampal volumes, it is difficult to conclude from their findings that the smaller volumes they observed in this group were due to familial risk for schizophrenia. Finally, O'Driscoll et al. (2001) found significantly smaller anterior

hippocampal volumes in the first-degree relatives of schizophrenia subjects than in controls. There was no difference between the two groups in measures of posterior hippocampal volume. This is in keeping with the findings of Tepest et al (2003) where inward deformations in the head of the hippocampus were observed in both schizophrenia subjects and their unaffected siblings. Given the localization of their finding in the hippocampus, it is possible that had the O'Driscoll group examined the entire hippocampus, as I had, and as all of the other groups listed above who found no significant difference between the hippocampal volumes of first-degree relatives and control subjects, then they too may not have found a significant difference.

The findings above suggest the following possibilities as to why although we observed a significant effect of schizophrenia on hippocampal volume, unlike others, we did not observe a significant difference between the volumes of the hippocampus in our schizophrenia siblings compared to our controls: First, there may be a minimal effect of genotype on hippocampal volume. Given that much of the evidence for a genetic effect on hippocampal volume comes from twin studies, and given that there is literature that suggests perinatal insults are associated with both the development of schizophrenia, and structural abnormalities of the hippocampus, it is possible that the findings from said twin studies reflect less an effect of shared genes, and more an effect of shared negative environment. It is also possible that some of the studies finding abnormalities in hippocampal structure in siblings or other first-degree relatives of schizophrenia subjects may have been observing the effect of other

neuropsychiatric conditions on the hippocampus, and not the effects of a genetic risk for schizophrenia. By excluding schizophrenia siblings who may have had such disorders, we had a purer sample from which to observe how familial risk for schizophrenia specifically affects hippocampal structure.

Alternatively, based on the findings of twin studies where unaffected siblings of MZ twin pairs discordant for schizophrenia had smaller hippocampal volumes than the analogous siblings of DZ twin pairs, and based on findings which suggest greater hippocampal abnormality in unaffected siblings with a higher genetic predisposition for schizophrenia than in siblings with no family history of schizophrenia, it is possible that degree of genetic liability for schizophrenia may affect hippocampal volume, such that the higher the liability, the greater the abnormality. It is possible that several of our schizophrenia siblings may not have had a strong family history for the disorder, and therefore, may not have had enough of a schizophrenia-related genetic influence to affect hippocampal structure. Another possibility based on the literature is that schizophrenia schizophrenia's effect on hippocampal structure is most pronounced in the anterior region (Tepest et al., 2003; Wang et al., 2001; Csernansky et al., 1998; Csernansky et al., 2002; Pegues et al., 2002; Narr et al., 2003). Since siblings of schizophrenia subjects have larger hippocampi compared to their affected siblings (meta-analysis, Boos et al., 2007), this effect in the anterior of the hippocampus would likely be more pronounced in schizophrenia subjects than it is in the siblings of schizophrenia subjects. By

measuring the volume of the hippocampus as a whole, we may have masked the more subtle abnormality of the anterior hippocampus in our sibling subjects.

PHG Findings:

My findings related to the measures of the whole PHG and of its sub-regions suggest that the genetic risk for developing schizophrenia is related to abnormal structural development of this part of the MTL. Specifically, the whole PHG and the PHC sub-region were most clearly altered in the subjects with schizophrenia and their siblings – the former group having more attenuated abnormalities. Given that the measures of the PHG remained significantly different in my two experimental groups compared to my two control groups even after including whole cortical thickness as a fixed effect suggests that the effects of schizophrenia and familial risk for schizophrenia on this part of the MTL were at least somewhat disproportionately greater than their effects on global brain structure. Because the PHG is such a relatively thin structure, the majority of which consists of the PHC, with only the small anterior portion split between the ERC and PRC, it is not surprising that the most significant effect observed was in the whole structure and its largest component, the PHC. The particularly small size of the ERC may have rendered any effect due to schizophrenia or the risk for schizophrenia especially difficult to visualize. One should note though that in the somewhat larger PRC, we were able to observe a significant effect of familial risk for schizophrenia on the thickness of the structure. It should also be noted

that the PRC as we have defined it actually contains some tissue that is considered part of the ERC. However, for the sake of consistency in our anatomical measures, we used the lip of the collateral sulcus as the boundary between the ERC and PRC. For this reason, we may have been unable to see an effect of schizophrenia or risk for schizophrenia in the ERC. It is therefore also possible that the significant result we did find in the PRC is due in part to the small portion of the structure that includes ERC.

Comparing my findings on the substructures of the PHG to others who have also used a region of interest approach is difficult because to the lack of consistency in defining the whole PHG and its substructures. For example, Sim et al., 2006, did not find an effect of schizophrenia on the subregions of the PHG, but their methods for defining the structure differed from the methods I used; the PHC was defined such that the posterior portion of it was not included. Since this is the largest region of the PHG, and the subregion where we found the most profound effect of schizophrenia, this exclusion might serve to explain the difference between my findings and theirs. The only two other groups known to have also examined the substructures of the PHG in subjects with schizophrenia and healthy control subjects found a significant effect of the disease on volume measures of these regions. Again, in the case of Turetsky et al., 2003, both the ERC and PRC were defined very differently from me: the PRC, as they defined it, included Brodmann's Area (BA) 35 and 36. In contrast, I included only BA 35 as a true part of the PHG. BA 36, in my view, might be better considered part of the fusiform gyrus. Turetsky et al., also included the piriform cortex in their

definition of PRC, something I did not do as this region might better be considered part of the olfactory cortex, and out of the anatomical bounds of the PHG. As for the ERC, they extended this structure laterally to the interior of the collateral sulcus. The remaining group, Prasad et al., 2004, also used a different definition for the PHG subregions. The ERC, in their view, included the uncus and, based on the figure included to illustrate their outline of this structure, possibly included some hippocampal tissue as well (Figure 48**)**.

Figure 48: The left (red) and right (blue) ERC. As can be seen, the left ERC appears to extend slightly into hippocampal tissue. The ERC also bilaterally extends into tissue we define as PRC.

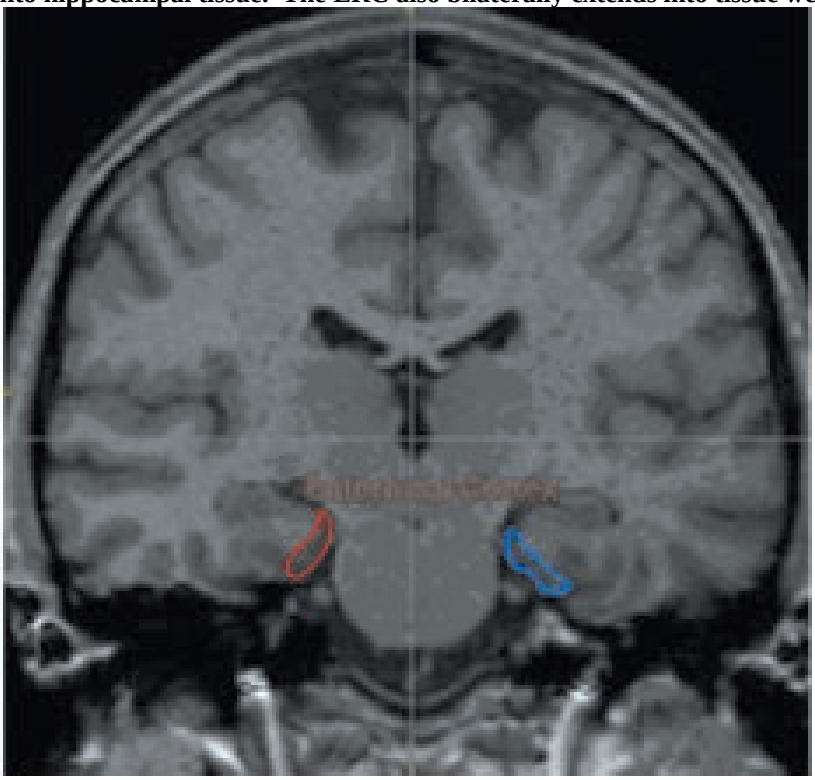


Figure 48 also suggests that they were not as conservative in marking the lateral boundary of the ERC as we were in that they extended the ERC slightly

into a region we would consider PRC. This latter difference stems from their extending the line along the gray-white junction until its intersection with the medial bank of the collateral sulcus. We were slightly more conservative in our definition and used the exterior lip of the PHC as the boundary of the structure. An advantage of my method lay in avoiding confusion when the gray-white junction became branched, as it did in a small percentage of our subjects.

Even though the effects of schizophrenia and the risk for schizophrenia on thickness of the whole PHG remained significant after including whole brain cortical thickness as a fixed effect, the volume measure for this region did not, nor did either of the measures for the PHC. In the case of PHG volume, the reason for this could be due to the measurement technique used to determine volume of this cortical region: Volume was calculated as the product of PHG thickness and the surface area of the gray-white surface upon which this part of the cortex rests. It is possible that this gray-white surface skewed our estimate of volume, and that this surface, and not the actual volume of gray matter was proportionately smaller in schizophrenia subjects and their siblings than the gray-white surface used to determine whole brain cortical volume in these subjects..

In the case of the PHC, it appears that the lack of significance after the inclusion of whole cortex covariates suggests that the effects of schizophrenia and risk for schizophrenia on structural measures of the PHC are proportional to their effects on the cortex globally. However, the PHC is the largest of the PHG substructures, and recent evidence suggests that the anterior and posterior portions of this structure may subserve different functions (Saleem et al.,2006;

Aminoff et al., 2007). The results of these studies in both non-human primates, and humans suggest that the more posterior region of the PHC may be more closely related to visual-spatial processing, and the more anterior region more deeply involved in memory and non-spatial contex processing. It is possible that schizophrenia and the risk for schizophrenia may have differential effects on the structures of each half of this structure, and that by measuring them together, and then including our whole cortex measures as covariates, we overpowered a potential modest effect.

As for comparing my findings in the siblings of the subjects with schizophrenia to the work of others, I found only two groups who examined whole PHG measures in schizophrenia siblings, and no one, to the best of my knowledge, has studied the PHG sub-structures in such subjects. Of the groups who studied whole PHG in siblings, DeLisi et al. (2006) showed evidence for deficits in the vicinity of the PHG. In contrast, Staal et al., (2000) found no significant differences between schizophrenia siblings and healthy controls for PHG. However, they used a different definition of PHG; i.e., the anterior boundary of the structure (the anterior-most appearance of the hippocampus) was a good deal more posterior than the guideline I used, and therefore did not include a large segment of both PRC and ERC. Additionally, the most posterior boundary set for the PHG was the posterior commissure, thus, leaving out much of the PHC.

Certainly one of the most interesting aspects of our findings is that our schizophrenia siblings differed significantly from the control and control sibling

groups on several measures of PHG structure where our schizophrenia subjects did not. Although, their siblings did not differ significantly from the schizophrenia subjects on any measure of PHG structure, these results suggest the familial risk for schizophrenia had a greater effect on PHG structure than schizophrenia itself. There are several potential explanations for this finding. For example, as described above, the differences in my definition of the PHG and its substructures may partially explain why my findings differ from those in the literature. Additionally, due to the limitations of delineating these structures in MR scans, certain calculated inaccuracies were introduced in the structural definitions for the sake of consistent segmenting across subjects. Specifically, because it provided the most consistent landmark, the posterior-most part of the PHG included part of the occipital gyrus. Additionally, as stated earlier, because of my definition of the PRC, a small portion of the ERC was included in that structural measure as well. These definitions could have caused small, but significant differences in PHG structure between schizophrenia subjects and the two control groups to remain hidden.

Overall Significance of MTL structural Findings:

We have found that several structures of the MTL are affected by schizophrenia including the hippocampus, the whole PHG and the PHC. We have also found that compared to our control groups, siblings of schizophrenia subjects have smaller measures of PHG structure and substructure, but not as

we measured it, hippocampal volume. Additionally, only two of our results survived the inclusion of a whole brain fixed effect: the whole PHG and the PRC; these were results where the siblings of schizophrenia subjects differed significantly from controls, but schizophrenia subjects did not.

There are a number of possible reasons for the different aspects of our above findings. For example, as already discussed, one possibility that may have prevented us from adequately capturing the effects of schizophrenia or schizophrenia risk on the ERC/PRC, and the hippocampus are our methods for measuring each structure. Another possible reason why we may not have seen an effect of schizophrenia, or as strong an effect of schizophrenia on measures of the PHG is discussed further below, and relates to the effect atypical versus typical antipsychotic treatment may have on MTL structure in our schizophrenia subjects. The effect treatment could have had on MTL structures in our schizophrenia subjects may also provide insight into why we saw an effect of risk for schizophrenia on several structures, but only weak effects of schizophrenia itself on those structures.

As indicated above, the effects of schizophrenia or risk for schizophrenia ceased to be significant on several measures of MTL structure after inclusion of a whole brain covariate. A potential explanation for this finding relates less to what we have observed in the MTL, and more to how the MTL relates to other cortical regions, and what the effects of schizophrenia may be in those regions. As discussed in the Background chapter of this dissertation, the MTL structures share rich interconnectivity with the regions within the cerebral cortex: the

hippocampus receives direct input from the prefrontal cortex (Moser and Moser, 1998), the PRC shares input with the insular cortex, the dorsal bank of the superior temporal sulcus, and the orbitofrontal cortex (Suzuki, 1996), and the PHC receives input from visuospatial processing areas of the posterior parietal cortex, the retrosplenial cortex, the superior temporal gyrus and sulcus (Burwell, 2000) and, shares reciprocal connectivity with the dorsolateral prefrontal cortex (Suzuki, 1996, Aggleton and Brown, 2005). Recent studies comparing schizophrenia subjects to controls have found in schizophrenia subjects wide-spread cortical thinning including in many regions the above MTL structures share connectivity with (Kuperberg et al., 2003; Narr et al., 2005; Goldman et al., 2009). Additionally, a recent study of white matter clusters (Spoletini et al., 2008) has shown that a significant fractional anisotropy reduction was found in the uncinate fasciculus. This cluster of white matter fiber tracts is known to link the MTL structures with the rostral superior temporal gyrus, the rostral inferior temporal gyrus, and the orbital, medial and prefrontal cortices. Moreover, this anisotropic reduction was significantly associated with a decrease of gray matter density in the anterior cingulate. Results such as this suggest that abnormalities in cortical gray matter that are observed in schizophrenia may be the result of disease-related disruptions in connectivity. Selemon and Goldman-Rakic (1999) also suggested that the volumetric differences observed between schizophrenia subjects and controls reflected a disruption in connectivity. Because they observed reductions in volume of the prefrontal cortex of schizophrenia subjects but also observed that neuronal density was no less in schizophrenia subjects

compared to controls, they hypothesized that interneuronal space decreases due to the loss of neural processes and synapses were causing the volume reductions in this region.

The above studies imply that there may be a link between MTL-cortical connectivity and volumetric changes in cortical areas. If this were the case, then it is not surprising that in our schizophrenia subjects, reductions in measures of MTL structure were proportional to reductions in measures of overall cortical structure. There is also some evidence to suggest that the longer the duration of schizophrenia, the thinner the cortex becomes (Waddington et al., 1991; Weigand et al., 2004), suggesting that the thinning of the cortex may be a disease-specific process. If widespread cortical thinning is contingent on, or exacerbated by, the manifestation of schizophrenia, but MTL structural abnormalities are at least partially dependent on genetic predisposition, then the findings in our unaffected schizophrenia siblings, both the finding that they differed significantly from our control groups on measures of PHG structure, and that some of these differences survived covarying for measures of whole cortex may not be surprising.

As has been discussed in the previous chapter, another potential explanation for the weaker difference between schizophrenia subjects and controls on measures of PHG structure compared to the difference between schizophrenia siblings and control subjects on measures of this region concerns the effect of typical versus atypical antipsychotic medication on MTL structure. In

the previous chapter, I presented the results of my post hoc correlational analysis to determine the nature of this effect.

There are several caveats as to how these results can be interpreted. First of all, it should be kept in mind that the available subject pool was relatively small, so the sample sizes for each analysis were therefore small as well. Also, there was only one subject who had been treated exclusively with typical antipsychotics. Hence, ten of the eleven subjects used in the analysis to evaluate the effect of typical antipsychotic medication on MTL structure had also been, or are currently being treated with atypical antipsychotic medication as well. The analysis of atypical antipsychotic medication involves subjects who have only ever been treated with atypical antipsychotics. For this reason, the results from the analysis of the atypical antipsychotic medication are likely to be more meaningful, and therefore more worthy of interpretation than those from the typical antipsychotic analysis.

Given the above caveats, these findings suggest that there may indeed have been an effect of drug treatment on the measurement of MTL structures in the schizophrenia subjects, and that the effects of drug treatment may have confounded my ability to detect disease-specific structural differences between by schizophrenia subjects and control groups. There were moderate positive correlations between duration of treatment with atypical antipsychotic medication and measures of both PHG and PHC, two structures where the difference between schizophrenia siblings and control subjects was greater than it was between schizophrenia subjects and controls. Specifically, the effect of atypical

antipsychotic treatment on ERC measures is quite pronounced, and may explain in part why we were not able to observe an effect of schizophrenia on this structure.

In summary, the results from my structural analysis support the hypothesis that schizophrenia and the risk for schizophrenia effect the structure of the MTL such that measures of this region are smaller in these subjects than they are in healthy control subjects and those genetically similar to them. My results also imply that the disease process of schizophrenia affects the structure of the whole brain in a way that is proportional to its effect on the MTL. My post hoc analyses suggest that the effect of schizophrenia on these structures may be even larger than we were able to observe due to the potentially confounding influence of antipsychotic medication.

Correlations between MTL and Episodic Memory Performance:

Schizophrenia subjects and their unaffected siblings have been found to show abnormalities in memory performance (Cirillo and Seidman, 2003; Delawalla et al., 2006), and in MTL structure (van Erp et al., 2004). The findings from this study support and extend those in the literature by showing that in addition to deficits in memory performance, schizophrenia subjects and their unaffected siblings also show abnormalities in PHG structure. It is thought that schizophrenia is likely caused by a combination of several potential genetic and environmental factors (Braff et al., 2007; Pantelis et al., 2005). Depending on the

specific combination in a given subject, these factors could affect MTL structure at varying levels. Given the above, it is possible that the variance in the measures of this brain region, and of the cognitive function it is thought to subserve will be functionally meaningful in schizophrenia subjects and their siblings. Hence, I hypothesized that a direct relationship between measures of MTL structure and episodic memory performance would be observed in our two experimental groups, more strongly in my schizophrenia subjects, and more weakly in their siblings, who share half of the same genes.

My findings supported my hypothesis that a relationship between MTL structure and episodic memory performance would not be observed in my control subjects and their siblings. However, my findings from this study did not support my hypothesis concerning this relationship in my schizophrenia subjects, although they weakly supported my hypothesis about this relationship in my schizophrenia siblings. Given that my siblings of schizophrenia subjects share only half of the same genes as their affected siblings, and therefore most likely a lower percentage of the genetic risk factors for schizophrenia, the weakness of the observed relationship in the schizophrenia siblings was not altogether surprising. The complete lack of an observable relationship in our schizophrenia subjects, however, was quite surprising. Below, I will offer potential explanations for this unexpected finding.

One potential explanation for why I was unable to observe a relationship between memory performance and MTL structure in the schizophrenia subjects may be due to the impact of disease-related factors on memory performance in

the schizophrenia subjects. Among such disease-related factors could be the history of drug or alcohol abuse (despite the absence of such abuse in the six months preceding study participation) present in our schizophrenia subjects (Smith et al., 2008). Such abuse could have affected the structure and function of other brain regions associated with memory performance to the point where the integrity of the relationship between memory performance and MTL structure in these subjects was obscured.

Another potential explanation for the lack of a relationship between MTL structure and memory performance in schizophrenia subjects could stem from the effect of type of antipsychotic medication on MTL structure. As discussed earlier, all but one of our schizophrenia subjects have been treated with atypical antipsychotic medication, and this kind of treatment is associated with increases in cortical gray matter volume over time (Garver et al., 2005). It is possible that the effect of this treatment confounded my ability to assess correlations between MTL structure and memory that occurred as a result of the schizophrenia disease state.

Significance of Findings:

As a neural substrate for memory, several researchers have examined hippocampal structure in schizophrenia, but very few have examined the other structures of the MTL in the context of this disorder. By producing a reliable means of mapping the PHG and its substructures, we have not only been able to

extend the findings on the PHG in schizophrenia subjects, but, we have also provided novel evidence through our structural data from the first-degree relatives of schizophrenia subjects that genetic factors associated with the disorder may influence the structure of the MTL.

Through our correlations analyses, we have provided further support to the hypothesis concerning brain structure-function relationships in control subjects that posits that normative variation of hippocampal structure in healthy, adult subjects is not functionally meaningful in relation to memory performance. By showing similar findings in the PHG, we can extend this finding to all of the MTL structures.

Moreover, our correlation findings relating MTL structure to episodic memory performance in siblings of schizophrenia subjects, though far from conclusive, also suggest that the observed abnormalities in MTL structure in schizophrenia siblings may be functionally meaningful. And finally, while we failed to find relationships between measures of MTL structure and memory performance in our schizophrenia subjects, we did find evidence that antipsychotic drug may have influenced the MTL structural variables, and perhaps obscured such a relationship.

Future Directions:

Schizophrenia is most likely caused by a multitude of genetic and environmental factors. The major finding of my study is that the genetic factors

that predispose individuals to develop schizophrenia may also cause disruption in MTL structure and cognitive functions related to that structure. My findings provide a hint that such a disruption is functionally meaningful. An obvious next step in this exploration would be to investigate the influence of specific genetic polymorphisms recently associated with schizophrenia on the relationship between MTL structure and cognition. Among these polymorphisms, there are several with plausible influences on brain development, particularly, the development of the structures of the MTL.

One such example would be the set of polymorphisms that make up the schizophrenia risk haplotype for the neuregulin gene (Stefansson et al., 2002). Neuregulin-1 (NRG-1) serves a number of different functions in both the developing and adult brain (e.g., moderating the migration of neuronal precursors, aiding in glial development and survival, acting as a neurotrophic factor, and regulation of *N*-methyl-D-aspartate, GABAA and acetylcholine receptor subunit expression) (Rio et al., 1997; Anton et al., 1997; Law et al., 2004). Based on post-mortem studies, expression of NRG-1 is found in hippocampus, cingulate, thalamus, amygdala, brainstem, dorsolateral prefrontal cortex and cerebellum (Law et al., 2004). Stefansson et al. (2004) have found that a haplotype of the gene encoding NRG-1 containing 5 single nucleotide polymorphisms and two microsatellites was present at a higher frequency in Scottish and Icelandic schizophrenia subjects than in the respective controls from each region.

Another polymorphism of interest would be the Val66Met polymorphism of the gene encoding brain derived neurotrophic factor (BDNF). BDNF is highly expressed in human hippocampus (Murer et al., 2001), and is required for strengthening neurons and neural connections (Dijkhuizen and Ghosh, 2004). The Val66Met polymorphism is reported to be associated with smaller hippocampal volumes and poorer episodic memory performance in both healthy subjects (Bueller et al., 2006; Egan et al., 2003), and in schizophrenia subjects (Szeszko et al., 2005; Tan et al., 2005).

My findings also suggest that further work needs to be done to understand the effects of typical versus atypical antipsychotic drugs on brain structure, brain function and cognition. Drug treatment in my sample of subjects was not controlled. Much more could be learned about drug effects on brain structure and function in the context of a controlled prospective design. Additionally, it would be interesting to observe the activation of particular MTL sub-regions in subjects who are receiving different types of antipsychotic medication during different cognitive tasks, especially episodic memory tasks. While similar studies in unaffected siblings would be interesting, the ethics of exposing such individuals to antipsychotic drugs for experimental purposes, even on an acute basis, are controversial.

My experience with this study also suggests that some technical improvements in structural assessment would be helpful in the future. More specifically, in future work, it may be advisable to split the PHC into two regions, an anterior region and a posterior one, prior to assessing correlations between

structure, function and cognition. The results of a recent cytoarchitectonic study in non-human primates (Saleem et al., 2006) showed that these two sub-regions of the PHC may subserve separate functions, with the more posterior region being more closely related to visual processing, and the more anterior region more deeply involved in memory. Further studies of this type would be particularly important since the PHC was the PHG sub-region where I observed the strongest effect of schizophrenia on structure. Additionally, exploring if there is a differential effect of schizophrenia or risk for schizophrenia on anterior and posterior hippocampus would also be of interest.

Finally, I used schizophrenia as a model system to evaluate the effects of a neuropsychiatric disease known to have a genetic basis on both brain structure and cognition. I had the good fortune of having a dataset with patients and their unaffected siblings available to me. In the future, it is likely that approximately ten percent of these siblings will go on to develop schizophrenia (Guidry and Kent, 1999). Given this unfortunate likelihood, collecting additional data on a longitudinal basis would provide additional insights on brain structure, and the relationship between brain structure and cognition, that can further develop over time along with the appearance of active symptoms. Acquiring longitudinal data in healthy controls and their siblings would be quite useful as well, as it would offer the opportunity to examine how normative brain development affects brain structure and the relationship between structure and cognition.

Summary and Conclusions:

The purpose of this dissertation was to explore the relationship between a specific region of the brain and its functional substrate in health and disease. Human and animal lesion studies, along with functional neuroimaging and aging studies, all support the premise that one of the key neural substrates for episodic memory is the MTL. Schizophrenia is characterized by deficits in episodic memory. For these reasons, I chose to examine the relationship between variation in MTL structure and episodic memory performance in the context of health and schizophrenia. It is believed that brain structure, brain function, and the relationship between the two are influenced by a number of factors including genes, environment and disease states. Another reason I chose schizophrenia as my model disease is because the development of schizophrenia is influenced by both genetic and environmental factors. By examining MTL structure, episodic memory performance and the relationship between the two in the siblings of schizophrenia subjects, I hoped to observe the influence of familial risk for schizophrenia on each.

I found that schizophrenia and the risk for schizophrenia affect the structure of the MTL. I also found hints that being at familial risk for schizophrenia strengthens the relationship between the MTL structure and episodic memory performance. Surprisingly, in our subjects, I found that the effect of familial risk for schizophrenia had a stronger effect on MTL structure and the relationship between MTL structure and episodic memory performance than the disease itself. Possible explanations for these findings include: 1) By

including a small portion of lateral occipital gyrus tissue in the posterior limit of the PHG, and by setting an artificial boundary between the PRC and ERC at the lip of the collateral sulcus, my definitions of the PHG and its substructures obscured the relationship between certain measures of MTL structure and episodic memory performance. 2) Disease-related factors in the schizophrenia subjects such as a history of drug or alcohol abuse affected the structure and function of other brain regions associated with memory performance to the point that the integrity of the relationship between memory performance and MTL structure was obscured. 3) The effect of kind of antipsychotic treatment affected the structure of the MTL in such a way as to confound my ability to observe a relationship between my structural measures and episodic memory performance in our schizophrenia subjects.

Finally, there are several future directions in which this work can be taken. To begin, given my findings in subjects who are at genetic risk for developing schizophrenia, a study of the effect of specific genetic polymorphisms associated with schizophrenia on MTL structure and function would be a logical next step. Also, considering the results of my post hoc analysis on the effect of typical versus atypical antipsychotic treatment on measures of MTL structure, future exploration of this antipsychotic treatment effect on brain structure, brain activation and cognitive performance would be quite interesting. Additionally, a potential improvement to my study can be made by dividing the PHC into two portions, an anterior and a posterior segment as current literature suggests that the two halves of the PHC may be involved in different processes. Lastly, it would

be beneficial to continue to collect both cognitive and structural imaging data from our schizophrenia siblings, healthy control subjects and control siblings. There is an unfortunate likelihood that approximately ten percent of our schizophrenia siblings will go on to develop the disease. Longitudinal data in these subjects may provide insight on how the disease process modifies brain structure and the relationship between brain structure and cognition. The longitudinal data in our control subjects would provide insight into how normative development of the brain relates to cognitive performance.

References:

Aggleton JP, Brown MW. Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. Behav Brain Sci. 1999 Jun;22(3):425-44; discussion 444-89. Review.

Aggleton JP, Brown MW. Contrasting hippocampal and perirhinal cortex function using immediate early gene imaging. Q J Exp Psychol B. 2005 Jul-Oct;58(3-4):218-33.

Alvarado, M.C., Wright, A.A., and Bachevalier, J. 1995. Monkeys with early hippocampal formation lesions are impaired on the transverse patterning problem. Soc. Neurosci. Abst. 21: 1494

Alvarado, M.C., Mishkin, M., and Bachevalier, J. 1998. Neurotoxic lesions of the hippocampal formation impair monkeys' acquisition of the transverse patterning problem. Soc. Neurosci. Abst. 24: 928.

Alvarado MC, Bachevalier J. Revisiting the maturation of medial temporal lobe memory functions in primates. Learn Mem. 2000 Sep-Oct;7(5):244-56.

Alvarez P, Zola-Morgan S, Squire LR. Damage limited to the hippocampal region produces long-lasting memory impairment in monkeys. J Neurosci. 1995 May;15(5 Pt 2):3796-807.

Aminoff E, Gronau N, Bar M. The parahippocampal cortex mediates spatial and nonspatial associations. Cereb Cortex. 2007 Jul;17(7):1493-503. Epub 2006 Sep 21.

Angeli SJ, Murray EA, Mishkin M (1993) Hippocampectomized monkeys

can remember one place but not two. Neuropsychologia 31:1021–1030.

Anton ES, Marchionni MA, Lee KF, Rakic P. Role of GGF/neuregulin signaling in interactions between migrating neuron and radial glia in the developing cerebral cortex. Development 1997; 124:3501-3510.

Antonova E, Sharma T, Morris R, Kumari V. The relationship between brain structure and neurocognition in schizophrenia: a selective review. Schizophr Res. 2004 Oct 1;70(2-3):117-45.

Baaré WF, van Oel CJ, Hulshoff Pol HE, Schnack HG, Durston S, Sitskoorn MM, Kahn RS. Volumes of brain structures in twins discordant for schizophrenia. Arch Gen Psychiatry. 2001 Jan;58(1):33-40.

Bachevalier J. Ontogenetic development of habit and memory formation in primates. Ann N Y Acad Sci. 1990;608:457-77; discussion 477-84.

Bachevalier J, Brickson M, Hagger C. Limbic-dependent recognition memory in monkeys develops early in infancy. Neuroreport. 1993 Jan;4(1):77-80.

Bachevalier J, Beauregard M, Alvarado MC. Long-term effects of neonatal damage to the hippocampal formation and amygdaloid complex on object discrimination and object recognition in rhesus monkeys (Macaca mulatta). Behav Neurosci. 1999 Dec;113(6):1127-51.

Bachevalier J, Nemanic S. Memory for spatial location and object-place associations are differently processed by the hippocampal formation, parahippocampal areas TH/TF and perirhinal cortex. Hippocampus. 2008;18(1):64-80.

Beason-Held LL, Rosene DL, Killiany RJ, Moss MB. Hippocampal formation lesions produce memory impairment in the rhesus monkey. Hippocampus. 1999;9(5):562-74.

Bilder RM, Bogerts B, Ashtari M, Wu H, Alvir JM, Jody D, Reiter G, Bell L, Lieberman JA. Anterior hippocampal volume reductions predict frontal lobe dysfunction in first episode schizophrenia. Schizophr Res. 1995 Sep;17(1):47-58.

Blumberg HP, Kaufman J, Martin A, Whiteman R, Zhang JH, Gore JC, Charney DS, Krystal JH, Peterson BS. Amygdala and hippocampal volumes in adolescents and adults with bipolar disorder. Arch Gen Psychiatry. 2003 Dec;60(12):1201-8.

Braak H, Del Tredici K, Bohl J, Bratzke H, Braak E. Pathological changes in the parahippocampal region in select non-Alzheimer's dementias. Ann N Y Acad Sci. 2000 Jun;911:221-39.

Boos HB, Aleman A, Cahn W, Hulshoff Pol H, Kahn RS. Brain volumes in relatives of patients with schizophrenia: a meta-analysis. Arch Gen Psychiatry. 2007 Mar;64(3):297-304.

Braff D, Schork NJ, Gottesman II. Endophenotyping schizophrenia. Am J Psychiatry. 2007 May;164(5):705-7.

Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS. Hippocampal volume reduction in major depression. Am J Psychiatry. 2000 Jan;157(1):115-8.

Bueller JA, Aftab M, Sen S, Gomez-Hassan D, Burmeister M, Zubieta JK. BDNF Val66Met allele is associated with reduced hippocampal volume in healthy subjects.Biol Psychiatry. 2006 May 1;59(9):812-5. Epub 2006 Jan 25.

Buffalo EA, Ramus SJ, Clark RE, Teng E, Squire LR, Zola SM. Dissociation between the effects of damage to perirhinal cortex and area TE. Learn Mem. 1999 Nov-Dec;6(6):572-99.

Burwell RD. The parahippocampal region: corticocortical connectivity. Ann N Y Acad Sci. 2000 Jun;911:25-42.

Cannon TD, Huttunen MO, Lonnqvist J, Tuulio-Henriksson A, Pirkola T, Glahn D, Finkelstein J, Hietanen M, Kaprio J, Koskenvuo M. The inheritance of neuropsychological dysfunction in twins discordant for schizophrenia. Am J Hum Genet. 2000 Aug;67(2):369-82. Epub 2000 Jul 3.

Cirillo MA, Seidman LJ. Verbal declarative memory dysfunction in schizophrenia: from clinical assessment to genetics and brain mechanisms. Neuropsychol Rev. 2003 Jun;13(2):43-77.

Clark, R.E., Teng, E., Squire, L.R., and Zola, S. 1996. The visual paired-comparison task and the medial temporal lobe memory system. Soc. Neurosci. Abstr. 22: 281.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.)

Convit A, Wolf OT, Tarshish C, de Leon MJ. Reduced glucose tolerance is associated with poor memory performance and hippocampal atrophy among normal elderly. Proc Natl Acad Sci U S A. 2003 Feb 18;100(4):2019-22. Epub 2003 Feb 5.

Csernansky JG, Joshi S, Wang L, Haller JW, Gado M, Miller JP, Grenander U, Miller MI. Hippocampal morphometry in schizophrenia by high dimensional brain mapping. Proc Natl Acad Sci U S A. 1998 Sep 15;95(19):11406-11.

Csernansky JG, Wang L, Jones D, Rastogi-Cruz D, Posener JA, Heydebrand G, Miller JP, Miller MI. Hippocampal deformities in schizophrenia characterized by high dimensional brain mapping. Am J Psychiatry. 2002 Dec;159(12):2000-6.

Csernansky, J. G., Wang, L., Joshi, S. C., Ratnanather, J. T., and Miller, M. I., 2004, Computational anatomy and neuropsychiatric disease: probabilistic assessment of variation and statistical inference of group difference, hemispheric asymmetry, and time-dependent change: Neuroimage, v. 23 Suppl 1, p. S56-68.

Daselaar SM, Veltman DJ, Rombouts SA, Raaijmakers JG, Jonker C. Neuroanatomical correlates of episodic encoding and retrieval in young and elderly subjects. Brain. 2003 Jan;126(Pt 1):43-56.

Davachi L, Mitchell JP, Wagner AD. Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. Proc Natl Acad Sci U S A. 2003 Feb 18;100(4):2157-62. Epub 2003 Feb 10.

Davies RR, Graham KS, Xuereb JH, Williams GB, Hodges JR. The human perirhinal cortex and semantic memory. Eur J Neurosci. 2004 Nov;20(9):2441-6.

Dazzan P, Morgan KD, Orr K, Hutchinson G, Chitnis X, Suckling J, Fearon P, McGuire PK, Mallett RM, Jones PB, Leff J, Murray RM. Different effects of typical and atypical antipsychotics on grey matter in first episode psychosis: the AESOP study. Neuropsychopharmacology. 2005 Apr;30(4):765-74.

Delawalla Z, Barch DM, Fisher Eastep JL, Thomason ES, Hanewinkel MJ, Thompson PA, Csernansky JG. Factors mediating cognitive deficits and psychopathology among siblings of individuals with schizophrenia. Schizophr Bull. 2006 Jul;32(3):525-37. Epub 2006 May 19.

Delis DC, Freeland J, Kramer JH, Kaplan E. Integrating clinical assessment with cognitive neuroscience: construct validation of the California Verbal Learning Test. J Consult Clin Psychol. 1988 Feb;56(1):123-30.

DeLisi LE, Hoff AL, Schwartz JE, Shields GW, Halthore SN, Gupta SM, Henn FA, Anand AK. Brain morphology in first-episode schizophrenic-like psychotic patients: a quantitative magnetic resonance imaging study. Biol Psychiatry. 1991 Jan 15;29(2):159-75.

DeLisi LE, Sakuma M, Tew W, Kushner M, Hoff AL, Grimson R. Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. Psychiatry Res. 1997 Jul 4;74(3):129-40.

DeLisi LE, Szulc KU, Bertisch H, Majcher M, Brown K, Bappal A, Branch CA, Ardekani BA. Early detection of schizophrenia by diffusion weighted imaging. Psychiatry Res. 2006 Nov 22;148(1):61-6. Epub 2006 Oct 27.

de Toledo-Morrell L, Goncharova I, Dickerson B, Wilson RS, Bennett DA. From healthy aging to early Alzheimer's disease: in vivo detection of entorhinal cortex atrophy. Ann N Y Acad Sci. 2000 Jun;911:240-53.

Diamond A. Rate of maturation of the hippocampus and the developmental progression of children's performance on the delayed non-matching to sample and visual paired comparison tasks. Ann N Y Acad Sci. 1990;608:394-426; discussion 426-33.

Diamond A. 1995. Evidence of robust recognition memory early in life even when assessed by reaching behavior. J. Exp. Child Psychol. 59: 419–456.

Diamond, A., Churchland, A., Cruess, L., and Kirkham, N.Z. 1999. Early developments in the ability to understand the relation between stimulus and reward. *Dev. Psychol.* **35:** 1507–1517.

Dijkhuizen PA, Ghosh A. Regulation of dendritic growth by calcium and neurotrophin signaling. Prog Brain Res. 2005;147:17-27.

Driscoll I, Hamilton DA, Petropoulos H, Yeo RA, Brooks WM, Baumgartner RN, Sutherland RJ. The aging hippocampus: cognitive, biochemical and structural findings. Cereb Cortex. 2003 Dec;13(12):1344-51.

Duvernoy, HM. *The Human Brain Surface, Three-dimensional Sectional Anatomy and MRI*. New York: Springer, 1991.

Duvernoy, HM. *The Human Hippocampus.* New York: Springer, 1998.

Eagleson KL, Levitt P. Complex signaling responsible for molecular regionalization of the cerebral cortex. Cereb Cortex. 1999 Sep;9(6):562-8.

Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*. 2003 Jan 24;112(2):257-69.

Garver DL, Holcomb JA, Christensen JD. Cerebral cortical gray expansion associated with two second-generation antipsychotics. Biol Psychiatry. 2005 Jul 1;58(1):62-6.

Giedd JN, Jeffries NO, Blumenthal J, Castellanos FX, Vaituzis AC, Fernandez T, Hamburger SD, Liu H, Nelson J, Bedwell J, Tran L, Lenane M, Nicolson R, Rapoport JL. Childhood-onset schizophrenia: progressive brain changes during adolescence. Biol Psychiatry. 1999 Oct 1;46(7):892-8.

Gold JJ, Squire LR. The anatomy of amnesia: neurohistological analysis of three new cases. Learn Mem. 2006 Nov-Dec;13(6):699-710. Epub 2006 Nov 13.

Goldman AL, Pezawas L, Mattay VS, Fischl B, Verchinski BA, Chen Q, Weinberger DR, Meyer-Lindenberg A. Widespread reductions of cortical thickness in schizophrenia and spectrum disorders and evidence of heritability. Arch Gen Psychiatry. 2009 May;66(5):467-77.

Golomb J, Kluger A, de Leon MJ, Ferris SH, Convit A, Mittelman MS, Cohen J, Rusinek H, De Santi S, George AE. Hippocampal formation size in normal human aging: a correlate of delayed secondary memory performance. Learn Mem. 1994 May-Jun;1(1):45-54.

Gruzelier J, Seymour K, Wilson L, Jolley A, Hirsch S. Impairments on neuropsychologic tests of temporohippocampal and frontohippocampal functions and word fluency in remitting schizophrenia and affective disorders. Arch Gen Psychiatry. 1988 Jul;45(7):623-9.

Guidry J, Kent TA. New genetic hypothesis of schizophrenia. Med Hypotheses. 1999 Jan;52(1):69-75.

Gunderson, V.M. and Swartz, K.B. 1985. Visual recognition in infant pigtailed macaques after 24-h delay. Am. J. Primat. 8: 259–264.

Gur RE, Turetsky BI, Cowell PE, Finkelman C, Maany V, Grossman RI, Arnold SE, Bilker WB, Gur RC. Temporolimbic volume reductions in schizophrenia. Arch Gen Psychiatry. 2000 Aug;57(8):769-75.

Gur RE, Nimgaonkar VL, Almasy L, Calkins ME, Ragland JD, Pogue-Geile MF, Kanes S, Blangero J, Gur RC. Neurocognitive endophenotypes in a multiplex multigenerational family study of schizophrenia. Am J Psychiatry. 2007 May;164(5):813-9.

Haller, J. W., Banerjee, A., Christensen, G. E., Gado, M., Joshi, S., Miller, M. I., Sheline, Y., Vannier, M. W., and Csernansky, J. G., 1997, Three-dimensional hippocampal MR morphometry with high-dimensional transformation of a neuroanatomic atlas: Radiology, v. 202, p. 504-10.

Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol Psychiatry. 2005 Jan;10(1):40-68; image 5.

Hawkins, K.A., Indicators of Brain Dysfunction Derived from Graphic Representations of the WAIS-III/WMS-III Technical Manual Clinical Samples Data: A Preliminary Approach to Clinical Utility. The Clinical Neuropsychologist, 1998

Heinrichs RW. Meta-analysis and the science of schizophrenia: variant evidence or evidence of variants? Neurosci Biobehav Rev. 2004 Jul;28(4):379-94. Review.

Hoff AL, Riordan H, O'Donnell D, Stritzke P, Neale C, Boccio A, Anand AK, DeLisi LE. Anomalous lateral sulcus asymmetry and cognitive function in first-episode schizophrenia. Schizophr Bull. 1992;18(2):257-72.

Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. Am J Psychiatry. 2005 Dec;162(12):2233-45

Iijima T, Witter MP, Ichikawa M, Tominaga T, Kajiwara R, Matsumoto G. Entorhinal-hippocampal interactions revealed by real-time imaging. Science. 1996 May 24;272(5265):1176-9.

Job DE, Whalley HC, McConnell S, Glabus M, Johnstone EC, Lawrie SM. Structural gray matter differences between first-episode schizophrenics and normal controls using voxel-based morphometry. Neuroimage. 2002 Oct;17(2):880-9.

Joshi, S., Miller, M. I., and Grenander, U., 1997, On the geometry and shape of brain sub-manifolds.: Int J Pattern Recog Artificial Intell (Special Issue), v. 11, p. 1317-1343.

Joyal CC, Laakso MP, Tiihonen J, Syvälahti E, Vilkman H, Laakso A, Alakare B, Räkköläinen V, Salokangas RK, Hietala J. A volumetric MRI study of the entorhinal cortex in first episode neuroleptic-naive schizophrenia. Biol Psychiatry. 2002 Jun 15;51(12):1005-7.

Kafkas A, Migo EM. Familiarity and recollection in the medial temporal lobe. J Neurosci. 2009 Feb 25;29(8):2309-11.

Kahn I, Davachi L, Wagner AD. Functional-neuroanatomic correlates of recollection: implications for models of recognition memory. J Neurosci. 2004 Apr 28;24(17):4172-80.

Kempermann G, Kuhn HG, Gage FH. More hippocampal neurons in adult mice living in an enriched environment. Nature. 1997 Apr 3;386(6624):493-5.

Keri S, Janka Z. Critical evaluation of cognitive dysfunctions as endophenotypes of schizophrenia. Acta Psychiatr Scand. 2004 Aug;110(2):83-91. Review.

Köhler S, Black SE, Sinden M, Szekely C, Kidron D, Parker JL, Foster JK, Moscovitch M, Winocour G, Szalai JP, Bronskill MJ. Memory impairments associated with hippocampal versus parahippocampal-gyrus atrophy: an MR volumetry study in Alzheimer's disease. Neuropsychologia. 1998 Sep;36(9):901-14. Erratum in: Neuropsychologia 1999 Jan;37(1):123. Wincour G [corrected to Winocour G].

Krabbendam L, Derix MM, Honig A, Vuurman E, Havermans R, Wilmink JT, Jolles J. Cognitive performance in relation to MRI temporal lobe volume in schizophrenic patients and healthy control subjects. J Neuropsychiatry Clin Neurosci. 2000 Spring;12(2):251-6.

Kuperberg GR, Broome MR, McGuire PK, David AS, Eddy M, Ozawa F, Goff D, West WC, Williams SC, van der Kouwe AJ, Salat DH, Dale AM, Fischl B. Regionally localized thinning of the cerebral cortex in schizophrenia. Arch Gen Psychiatry. 2003 Sep;60(9):878-88.

Lavenex P, Banta Lavenex P, Amaral DG. Postnatal development of the primate hippocampal formation. Dev Neurosci. 2007;29(1-2):179-92.

Law AJ, Shannon Weickert C, Hyde TM, Kleinman JE, Harrison PJ. Neuregulin-1 (NRG-1) mRNA and protein in the adult human brain. Neuroscience. 2004;127(1):125-36.

Lawrie SM, Whalley HC, Abukmeil SS, Kestelman JN, Donnelly L, Miller P, Best JJ, Owens DG, Johnstone EC. Brain structure, genetic liability, and psychotic symptoms in subjects at high risk of developing schizophrenia. Biol Psychiatry. 2001 May 15;49(10):811-23.

Lee AC, Buckley MJ, Gaffan D, Emery T, Hodges JR, Graham KS. Differentiating the roles of the hippocampus and perirhinal cortex in processes beyond long-term declarative memory: a double dissociation in dementia. J Neurosci. 2006 May 10;26(19):5198-203.

Lehn H, Steffenach HA, van Strien NM, Veltman DJ, Witter MP, Haberg AK. A specific role of the human hippocampus in recall of temporal sequences. J Neurosci. 2009 Mar 18;29(11):3475-84.

Lieberman JA, Tollefson GD, Charles C, Zipursky R, Sharma T, Kahn RS, Keefe RS, Green AI, Gur RE, McEvoy J, Perkins D, Hamer RM, Gu H, Tohen M; HGDH Study Group. Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch Gen Psychiatry. 2005 Apr;62(4):361-70.

Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Nair NP, Thakur M, McEwen BS, Hauger RL, Meaney MJ. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. Nat Neurosci. 1998 May;1(1):69-73. Erratum in: Nat Neurosci 1998 Aug;1(4):329.

Lye TC, Grayson DA, Creasey H, Piguet O, Bennett HP, Ridley LJ, Kril JJ, Broe GA. Predicting memory performance in normal ageing using different measures of hippocampal size. Neuroradiology. 2006 Feb;48(2):90-9.

Mackay CE, Roberts N, Mayes AR, Downes JJ, Foster JK, Mann D. An exploratory study of the relationship between face recognition memory and the volume of medial temporal lobe structures in healthy young males. Behav Neurol. 1998;11(1):3-20.

Maguire EA, Valentine ER, Wilding JM, Kapur N. Routes to remembering: the brains behind superior memory. Nat Neurosci. 2003 Jan;6(1):90-5.

Mai, Jurgen, Assheuer, Joseph, and George Paxinos. *Atlas of the Human Brain.* Academic Press, 1997.

Malkova L, Mishkin M. One-trial memory for object-place associations after separate lesions of hippocampus and posterior parahippocampal region in the monkey. J Neurosci. 2003 Mar 1;23(5):1956-65.

Marenco S, Weinberger DR. The neurodevelopmental hypothesis of schizophrenia: following a trail of evidence from cradle to grave. Dev Psychopathol. 2000 Summer;12(3):501-27.

McKee RD, Squire LR. Equivalent forgetting rates in long-term memory for diencephalic and medial temporal lobe amnesia. J Neurosci. 1992 Oct;12(10):3765-72.

McNeil TF, Cantor-Graae E, Weinberger DR. Relationship of obstetric complications and differences in size of brain structures in monozygotic twin pairs discordant for schizophrenia. Am J Psychiatry. 2000 Feb;157(2):203-12.

Miller, M. I., Banerjee, A., Christensen, G. E., Joshi, S. C., Khaneja, N., Grenander, U., and Matejic, L., 1997, Statistical methods in computational anatomy: Statistical Methods in Medical Research, v. 6, p. 267-299.

Milner B. The medial temporal-lobe amnesic syndrome. Psychiatr Clin North Am. 2005 Sep;28(3):599-611, 609.

Moser MB, Moser EI. Functional differentiation in the hippocampus. Hippocampus. 1998;8(6):608-19.

Murray EA, Mishkin M. Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. J Neurosci. 1998 Aug 15;18(16):6568-82.

Nairismägi J, Pitkänen A, Kettunen MI, Kauppinen RA, Kubova H. Status epilepticus in 12-day-old rats leads to temporal lobe neurodegeneration and volume reduction: a histologic and MRI study. Epilepsia. 2006 Mar;47(3):479-88.

Narr KL, van Erp TG, Cannon TD, Woods RP, Thompson PM, Jang S, Blanton R, Poutanen VP, Huttunen M, Lönnqvist J, Standerksjöld-Nordenstam CG, Kaprio J, Mazziotta JC, Toga AW. A twin study of genetic contributions to hippocampal morphology in schizophrenia. Neurobiol Dis. 2002 Oct;11(1):83-95.

Nelson MD, Saykin AJ, Flashman LA, Riordan HJ. Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: a meta-analytic study. Arch Gen Psychiatry. 1998 May;55(5):433-40.

Nestor PG, O'Donnell BF, McCarley RW, Niznikiewicz M, Barnard J, Jen Shen Z, Bookstein FL, Shenton ME. A new statistical method for testing hypotheses of neuropsychological/MRI relationships in schizophrenia: partial least squares analysis. Schizophr Res. 2002 Jan 1;53(1-2):57-66.

O'Driscoll GA, Florencio PS, Gagnon D, Wolff AV, Benkelfat C, Mikula L, Lal S, Evans AC. Amygdala-hippocampal volume and verbal memory in first-degree relatives of schizophrenic patients. Psychiatry Res. 2001 Aug 25;107(2):75-85.

Overman, W.H., Bachevalier, J., Sewell, F., and Drew, J. 1993. A comparison of children's performance on two recognition memory tasks: Delayed nonmatch-to-sample versus visual paired-comparison. Dev. Psychobiol. 26: 345–357.

Parkinson JK, Murray EA, MishkinM (1988) A selective mnemonic role for the hippocampus in monkeys: memory for the location of objects. J Neurosci. 8:4159–4167.

Pascalis O, Bachevalier J. Neonatal aspiration lesions of the hippocampal formation impair visual recognition memory when assessed by paired-comparison task but not by delayed nonmatching-to-sample task. Hippocampus. 1999;9(6):609-16.

Pascalis O, de Schonen S. Recognition memory in 3- to 4-day-old human neonates. Neuroreport. 1994 Sep 8;5(14):1721-4.

Pantelis C, Yücel M, Wood SJ, Velakoulis D, Sun D, Berger G, Stuart GW, Yung A, Phillips L, McGorry PD. Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. Schizophr Bull. 2005 Jul;31(3):672-96. Epub 2005 Jul 14.

Pegues MP, Rogers LJ, Amend D, Vinogradov S, Deicken RF. Anterior hippocampal volume reduction in male patients with schizophrenia. Schizophr Res. 2003 Apr 1;60(2-3):105-15.

Pimenta AF, Reinoso BS, Levitt P. Expression of the mRNAs encoding the limbic system-associated membrane protein (LAMP): II. Fetal rat brain. J Comp Neurol. 1996 Nov 11;375(2):289-302.

Prasad KM, Patel AR, Muddasani S, Sweeney J, Keshavan MS. The entorhinal cortex in first-episode psychotic disorders: a structural magnetic resonance imaging study. Am J Psychiatry. 2004 Sep;161(9):1612-9.

Pravosudov VV, Lavenex P, Omanska A. Nutritional deficits during early development affect hippocampal structure and spatial memory later in life. Behav Neurosci. 2005 Oct;119(5):1368-74.

Pruessner M, Pruessner JC, Hellhammer DH, Bruce Pike G, Lupien SJ. The associations among hippocampal volume, cortisol reactivity, and memory performance in healthy young men. Psychiatry Res. 2007 May 15;155(1):1-10. Epub 2007 Mar 28.

Ragsdale CW, Grove EA. Patterning the mammalian cerebral cortex. Curr Opin Neurobiol. 2001 Feb;11(1):50-8.

Ranganath C, Yonelinas AP, Cohen MX, Dy CJ, Tom SM, D'Esposito M. Dissociable correlates of recollection and familiarity within the medial temporal lobes. Neuropsychologia. 2004;42(1):2-13.

Raz N, Gunning-Dixon FM, Head D, Dupuis JH, Acker JD. Neuroanatomical correlates of cognitive aging: evidence from structural magnetic resonance imaging. Neuropsychology. 1998 Jan;12(1):95-114.

Razi K, Greene KP, Sakuma M, Ge S, Kushner M, DeLisi LE. Reduction of the parahippocampal gyrus and the hippocampus in patients with chronic schizophrenia. Br J Psychiatry. 1999 Jun;174:512-9.

Rees S, Inder T. Fetal and neonatal origins of altered brain development. Early Hum Dev. 2005 Sep;81(9):753-61. Review.

Reiman EM, Uecker A, Caselli RJ, Lewis S, Bandy D, de Leon MJ, De Santi S, Convit A, Osborne D, Weaver A, Thibodeau SN. Hippocampal volumes in cognitively normal persons at genetic risk for Alzheimer's disease. Ann Neurol. 1998 Aug;44(2):288-91.

Reinoso BS, Pimenta AF, Levitt P. Expression of the mRNAs encoding the limbic system-associated membrane protein (LAMP): I. Adult rat brain. J Comp Neurol. 1996 Nov 11;375(2):274-88.

Reminger SL, Kaszniak AW, Labiner DM, Littrell LD, David BT, Ryan L, Herring AM, Kaemingk KL. Bilateral hippocampal volume predicts verbal memory function in temporal lobe epilepsy. Epilepsy Behav. 2004 Oct;5(5):687-95.

Ravizza T, Rizzi M, Perego C, Richichi C, Velísková J, Moshé SL, De Simoni MG, Vezzani A. Inflammatory response and glia activation in developing rat hippocampus after status epilepticus. Epilepsia. 2005;46 Suppl 5:113-7.

*Rio, C, Rieff HI, Qi P, Khurana TS, Corfas G. Neuregulin and erbB receptors play a critical role in neuronal migration. Neuron 1997; 19:39-50.

Rizzi M, Perego C, Aliprandi M, Richichi C, Ravizza T, Colella D, Velískŏvá J, Moshé SL, De Simoni MG, Vezzani A. Glia activation and cytokine increase in rat hippocampus by kainic acid-induced status epilepticus during postnatal development. Neurobiol Dis. 2003 Dec;14(3):494-503.

Rosen AC, Prull MW, Gabrieli JD, Stoub T, O'Hara R, Friedman L, Yesavage JA, deToledo-Morrell L. Differential associations between entorhinal and hippocampal volumes and memory performance in older adults. Behav Neurosci. 2003 Dec;117(6):1150-60.

Sahay A, Hen R. Adult hippocampal neurogenesis in depression. Nat Neurosci. 2007 Sep;10(9):1110-5.

Sanfilipo M, Lafargue T, Rusinek H, Arena L, Loneragan C, Lautin A, Rotrosen J, Wolkin A. Cognitive performance in schizophrenia: relationship to regional brain volumes and psychiatric symptoms. Psychiatry Res. 2002 Nov 30;116(1-2):1-23.

*Saykin AJ, Gur RC, Gur RE, Mozley PD, Mozley LH, Resnick SM, Kester DB, Stafiniak P. Neuropsychological function in schizophrenia. Selective impairment in memory and learning. Arch Gen Psychiatry. 1991 Jul;48(7):618-24.

Saleem KS, Price JL, Hashikawa T. Cytoarchitectonic and chemoarchitectonic subdivisions of the perirhinal and parahippocampal cortices in macaque monkeys. J Comp Neurol. 2007 Feb 20;500(6):973-1006.

Schacter DL, Wagner AD. Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. Hippocampus. 1999;9(1):7-24. Review.

Schulze K, McDonald C, Frangou S, Sham P, Grech A, Toulopoulou T, Walshe M, Sharma T, Sigmundsson T, Taylor M, Murray RM. Hippocampal volume in familial and nonfamilial schizophrenic probands and their unaffected relatives. Biol Psychiatry. 2003 Apr 1;53(7):562-70.

Seidman LJ, Faraone SV, Goldstein JM, Kremen WS, Horton NJ, Makris N, Toomey R, Kennedy D, Caviness VS, Tsuang MT. Left hippocampal volume as a vulnerability indicator for schizophrenia: a magnetic resonance imaging morphometric study of nonpsychotic first-degree relatives. Arch Gen Psychiatry. 2002 Sep;59(9):839-49.

Selemon LD, Goldman-Rakic PS. The reduced neuropil hypothesis: a circuit based model of schizophrenia. Biol Psychiatry. 1999 Jan 1;45(1):17-25.

Sim K, DeWitt I, Ditman T, Zalesak M, Greenhouse I, Goff D, Weiss AP, Heckers S. Hippocampal and parahippocampal volumes in schizophrenia: a structural MRI study. Schizophr Bull. 2006 Apr;32(2):332-40. Epub 2005 Nov 30.

Sitskoorn MM, Aleman A, Ebisch SJ, Appels MC, Kahn RS. Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. Schizophr Res. 2004 Dec 1;71(2-3):285-95.

Smith MJ, Barch DM, Wolf TJ, Mamah D, Csernansky JG. Elevated rates of substance use disorders in non-psychotic siblings of individuals with schizophrenia. Schizophr Res. 2008 Dec;106(2-3):294-9. Epub 2008 Sep 5.

Sowell ER, Delis D, Stiles J, Jernigan TL. Improved memory functioning and frontal lobe maturation between childhood and adolescence: a structural MRI study. J Int Neuropsychol Soc. 2001 Mar;7(3):312-22.

Spoletini I, Cherubini A, Di Paola M, Banfi G, Rüsch N, Martinotti G, Bria P, Rubino IA, Siracusano A, Caltagirone C, Spalletta G. Reduced fronto-temporal connectivity is associated with frontal gray matter density reduction and neuropsychological deficit in schizophrenia. Schizophr Res. 2009 Mar;108(1-3):57-68. Epub 2008 Dec 18.

Squire LR, Stark CE, Clark RE. The medial temporal lobe. Annu Rev Neurosci. 2004;27:279-306.

Staal WG, Hulshoff Pol HE, Schnack HG, Hoogendoorn ML, Jellema K, Kahn RS. Structural brain abnormalities in patients with schizophrenia and their healthy siblings. Am J Psychiatry. 2000 Mar;157(3):416-21.

Stefansson H, Sigurdsson E, Steinthorsdottir V, Bjornsdottir S, Sigmundsson T, Ghosh S, Brynjolfsson J, Gunnarsdottir S, Ivarsson O, Chou TT, Hjaltason O, Birgisdottir B, Jonsson H, Gudnadottir VG, Gudmundsdottir E, Bjornsson A, Ingvarsson B, Ingason A, Sigfusson S, Hardardottir H, Harvey RP, Lai D, Zhou M, Brunner D, Mutel V, Gonzalo A, Lemke G, Sainz J, Johannesson G, Andresson T, Gudbjartsson D, Manolescu A, Frigge ML, Gurney ME, Kong A, Gulcher JR, Petursson H, Stefansson K. Neuregulin 1 and susceptibility to schizophrenia. Am J Hum Genet. 2002 Oct;71(4):877-92. Epub 2002 Jul 23.

Stefansson H, Steinthorsdottir V, Thorgeirsson TE, Gulcher JR, Stefansson K. Neuregulin 1 and schizophrenia. Ann Med. 2004;36(1):62-71.

Suzuki, W.A., Zola-Morgan, S., Squire, L.R., and Amaral, D.G. 1993. Lesions of the perirhinal and parahippocampal cortices in the monkey produce long-lasting memory impairment in the visual and tactual modalities. J. Neurosci. 13: 2430–2451.

Suzuki WA, Amaral DG. Perirhinal and parahippocampal cortices of the macaque monkey: cortical afferents. J Comp Neurol. 1994 Dec 22;350(4):497-533.

Suzuki WA. The anatomy, physiology and functions of the perirhinal cortex. Curr Opin Neurobiol. 1996 Apr;6(2):179-86.

Szeszko PR, Lipsky R, Mentschel C, Robinson D, Gunduz-Bruce H, Sevy S, Ashtari M, Napolitano B, Bilder RM, Kane JM, Goldman D, Malhotra AK. Brain-derived neurotrophic factor val66met polymorphism and volume of the hippocampal formation. Mol Psychiatry. 2005 Jul;10(7):631-6.

Takahashi LK, Turner JG, Kalin NH. Prolonged stress-induced elevation in plasma corticosterone during pregnancy in the rat: implications for prenatal stress studies. Psychoneuroendocrinology. 1998 Aug;23(6):571-81.

Tan YL, Zhou DF, Cao LY, Zou YZ, Wu GY, Zhang XY. Effect of the BDNF Val66Met genotype on episodic memory in schizophrenia. Schizophr Res. 2005 Sep 15;77(2-3):355-6.

Tepest R, Wang L, Miller MI, Falkai P, Csernansky JG. Hippocampal deformities in the unaffected siblings of schizophrenia subjects. Biol Psychiatry. 2003 Dec 1;54(11):1234-40.

Thoma RJ, Hanlon FM, Petropoulos H, Miller GA, Moses SN, Smith A, Parks L, Lundy SL, Sanchez NM, Jones A, Huang M, Weisend MP, Cañive JM. Schizophrenia diagnosis and anterior hippocampal volume make separate contributions to sensory gating. Psychophysiology. 2008 Nov;45(6):926-35. Epub 2008 Sep 24.

Tisserand DJ, Visser PJ, van Boxtel MP, Jolles J. The relation between global and limbic brain volumes on MRI and cognitive performance in healthy individuals across the age range. Neurobiol Aging. 2000 Jul-Aug;21(4):569-76.

Tsuang M. Schizophrenia: genes and environment. Biol Psychiatry. 2000 Feb 1;47(3):210-20.

Torres IJ, Flashman LA, O'Leary DS, Swayze V 2nd, Andreasen NC. Lack of an association between delayed memory and hippocampal and temporal lobe size in patients with schizophrenia and healthy controls. Biol Psychiatry. 1997 Dec 15;42(12):1087-96.

Tulving E. Episodic memory and common sense: how far apart? Philos Trans R Soc Lond B Biol Sci. 2001 Sep 29;356(1413):1505-15.

Turetsky BI, Moberg PJ, Roalf DR, Arnold SE, Gur RE. Decrements in volume of anterior ventromedial temporal lobe and olfactory dysfunction in schizophrenia. Arch Gen Psychiatry. 2003 Dec;60(12):1193-200.

Van Erp TG, Saleh PA, Rosso IM, Huttunen M, Lönnqvist J, Pirkola T, Salonen O, Valanne L, Poutanen VP, Standertskjöld-Nordenstam CG, Cannon TD. Contributions of genetic risk and fetal hypoxia to hippocampal volume in patients with schizophrenia or schizoaffective disorder, their unaffected siblings, and healthy unrelated volunteers. Am J Psychiatry. 2002 Sep;159(9):1514-20.

Van Erp TG, Saleh PA, Huttunen M, Lonnqvist J, Kaprio J, Salonen O, Valanne L, Poutanen VP, Standertskjold-Nordenstam CG, Cannon TD. Hippocampal volumes in schizophrenic twins. Arch Gen Psychiatry. 2004 Apr;61(4):346-53.

van Haren NE, Picchioni MM, McDonald C, Marshall N, Davis N, Ribchester T, Hulshoff Pol HE, Sharma T, Sham P, Kahn RS, Murray R. A controlled study of brain structure in monozygotic twins concordant and discordant for schizophrenia. Biol Psychiatry. 2004 Sep 15;56(6):454-61.

Van Petten C. Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. Neuropsychologia. 2004;42(10):1394-413.

Velakoulis D, Pantelis C, McGorry PD, Dudgeon P, Brewer W, Cook M, Desmond P, Bridle N, Tierney P, Murrie V, Singh B, Copolov D. Hippocampal volume in first-episode psychoses and chronic schizophrenia: a high-resolution magnetic resonance imaging study. Arch Gen Psychiatry. 1999 Feb;56(2):133-41.

Venkatesan, R., and Haacke, E., 1997, Role of high resolution in magnetic resonance (MR) imaging: Applications for MR angiography, intracranial T1-weighted imaging, and image interpolation: Int J Imaging Syst Technol, v. 8, p. 529-543.

Waddington JL, O'Callaghan E, Buckley P, Larkin C, Redmond O, Stack J, Ennis JT. The age dependencies of MRI abnormalities in schizophrenia suggest early ventricular enlargement but later prominence of cortical atrophy. Schizophr Res. 1991 Oct;5(3):188-9.

Wang L, Joshi SC, Miller MI, Csernansky JG. Statistical analysis of hippocampal asymmetry in schizophrenia. Neuroimage. 2001 Sep;14(3):531-45.

Wang L, Mamah D, Harms MP, Karnik M, Price JL, Gado MH, Thompson PA, Barch DM, Miller MI, Csernansky JG. Progressive deformation of deep brain nuclei and hippocampal-amygdala formation in schizophrenia. Biol Psychiatry. 2008 Dec 15;64(12):1060-8.

Weickert TW, Goldberg TE, Gold JM, Bigelow LB, Egan MF, Weinberger DR. Cognitive impairments in patients with schizophrenia displaying preserved and compromised intellect. Arch Gen Psychiatry. 2000 Sep;57(9):907-13. Erratum in: Arch Gen Psychiatry 2000 Dec;57(12):1122.

Wheeler MA, Stuss DT, Tulving E. Toward a theory of episodic memory: the frontal lobes and autonoetic consciousness. Psychol Bull. 1997 May;121(3):331-54.

Whitworth AB, Honeder M, Kremser C, Kemmler G, Felber S, Hausmann A, Wanko C, Wechdorn H, Aichner F, Stuppaeck CH, Fleischhacker WW. Hippocampal volume reduction in male schizophrenic patients. Schizophr Res. 1998 May 25;31(2-3):73-81.

Wiegand LC, Warfield SK, Levitt JJ, Hirayasu Y, Salisbury DF, Heckers S, Dickey CC, Kikinis R, Jolesz FA, McCarley RW, Shenton ME. Prefrontal cortical thickness in first-episode psychosis: a magnetic resonance imaging study. Biol Psychiatry. 2004 Jan 15;55(2):131-40.

Witter MP, Wouterlood FG, Naber PA, Van Haeften T. Anatomical organization of the parahippocampal-hippocampal network. Ann N Y Acad Sci. 2000 Jun;911:1-24.

Wood SJ, Yücel M, Velakoulis D, Phillips LJ, Yung AR, Brewer W, McGorry PD, Pantelis C. Hippocampal and anterior cingulate morphology in subjects at ultra-high-risk for psychosis: the role of family history of psychotic illness. Schizophr Res. 2005 Jun 15;75(2-3):295-301.

Yonelinas AP. Components of episodic memory: the contribution of recollection and familiarity. Philos Trans R Soc Lond B Biol Sci. 2001 Sep 29;356(1413):1363-74.

Zola SM, Squire LR, Teng E, Stefanacci L, Buffalo EA, Clark RE. Impaired recognition memory in monkeys after damage limited to the hippocampal region. J Neurosci. 2000 Jan 1;20(1):451-63.

Zola-Morgan S, Squire LR, Amaral DG. Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. J Neurosci. 1986 Oct;6(10):2950-67.

Zola-Morgan, S., Squire, L.R., Clower, R.P., and Rempel, N.L. 1993. Damage to the perirhinal cortex exacerbates memory impairment following lesions to the hippocampal formation. J. Neurosci. 13: 251–265.