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To the Graduate Council:

I am submitting herewith a thesis written by Kerry Towler entitled "A study using the LORETA brain imaging technique : comparing Alzheimer's Dementia (AD) patients to normals during the counting stroop." I have examined the final electronic copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Arts, with a major in Psychology.

Joel Lubar, Major Professor

We have read this thesis and recommend its acceptance:

D. Baldwin, J. Malone

Accepted for the Council:
Carolyn R. Hodges

Vice Provost and Dean of the Graduate School

(Original signatures are on file with official student records.)

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A Study using the LORETA Brain Imaging Technique: Comparing Alzheimer's Dementia (AD) Patients to Normals During the Counting Stroop

A Thesis Presented for the Master of Arts Degree

The University of Tennessee, Knoxville

Kerry Towler

May 2002

Thesis
2002
.T69

DEDICATION

This project is dedicated to my family who faithfully is determined to allow me opportunities to grow and to reach for my dreams. To my husband, Tom, for the absolute steadfastness of his love, support and stubbornness. To my parents, Carl and Duane Sanders, whose faith in me and support of me props me up on many a day. Finally, to my girls, Adara and Kathryn, who show me their love everyday in all of their many ways and for being my daughters and my friends.

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ABSTRACT

This pilot study utilized (Low Resolution Electromagnetic Tomographic Analysis (LORETA), a brain-imaging alternative to classical QEEG, to evaluate early stage Alzheimer (AD) participants (n = 6) and healthy similar-aged (Controls) participants (n = 8) during the Counting Stroop. The Counting Stroop is a validated analog to the Color-Word Stroop that provides an attentional challenge and is demonstrated to activate cortical structures in the motor speech areas and the anterior cingulate. Two tasks were recorded and subsequently subtracted: the neutral stimulus (NS) in which animal words were presented multiple times on a single slide and the incongruent stimulus (IS) in which a number word was presented multiple times on a single slide. The NS was subtracted from the IS to create difference maps.

None of the within group T-tests that make up the group difference maps revealed statistically significant differences. However, several qualitative differences are evident between the two groups. The patterns of activation that differ between the AD and Control groups and description of trends that support cited literature references are worth reporting. Results include group relative power differences that clearly distinguish the two groups. Supporting the literature of relative power differences in eyes-closed baselines, the AD group produced greater relative power in the Delta, Theta and Alpha frequency bands while the Control group produced greater relative power in the Beta1 and Beta 2 bands. Other qualitative differences include differential activation at the insula. MRI data suggests that early damage occurs at the parahippocampal gyrus and the entorhinal cortex. The most rostral aspects of these neural locations abut the insula. Finally, the differences in group activation in the temporal lobes supports a possible early diagnostic to apply to those who will eventually develop clinical Alzheimer's disease.

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Chapter 1

INTRODUCTION

As the median age of the U.S. population increases and as medical costs become increasingly hard to contain, developing inexpensive methods of diagnosing and studying Alzheimer's disease (AD) becomes advantageous for all concerned. Approximately half of the over 85-age population are expected to be afflicted by AD. Census projections predict that by the year 2040, more than 14 million Americans will be in the over 85-age group; that means a staggering 7 million Americans may be in need of care and assistance for AD related issues. Without research and the development of innovative techniques to identify AD in the early stages so that treatments can begin early enough to postpone the onset of symptoms, millions of people and their families will face the devastation that accompanies AD with little hope for their future.

AD is a form of progressive dementia which in its early stages presents symptoms that are easily overlooked or explained away. In numerous cases, the earliest symptoms of the disease occur many years prior to pathological detection. Current techniques in diagnosis require identifying dementia apart from other possible conditions and determining the cause. Guidelines established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS/ADRDA) require the documentation of cognitive decline and identification of two or more cognitive deficits for people between the ages of 40 – 90 years for a specific AD diagnosis. New techniques in the area of diagnostics include sampling cerebral spinal fluid (CSF) for proteins differentially prevalent in AD

and identifying genetic influences. Genetic markers in particular might be a useful predictor for application of techniques designed to ameliorate the disease. Yoke these criteria with a neuroimaging technique such as magnetic resonance imaging (MRI) or quantitative electroencephalography (QEEG) and the diagnostic task becomes easier.

The preferred technology (i.e. MRI) for clinical neuroimaging provides many advantages. These techniques permit differentiation between types of tissues and identify brain structures, allowing the identification of patterns of atrophy and differential diagnosis apart from other types of pathology. Other forms of imaging (i.e. PET) allow for the detection of abnormal metabolism that is found in AD. However, all of these types of brain imaging techniques are not without weaknesses. Visual inspection relies heavily upon the skill of the interpreter and resolution can be variable. In addition, these techniques are very expensive and not easily accessible. A non-invasive, inexpensive alternative to the aforementioned imagining technologies is QEEG. This technique provides the clinician with a clear delineation between normal brain activity and abnormal activity associated with pathology. The EEG wave patterns follow a developmental progression into maturity. As people age normally, without pathology, the changes can be measured and used as comparators to the AD population. Indeed, most EEG research in AD operates from the assumption that the neural atrophy associated with the disease results in changes in the EEG spectrum (i.e. increases of slow wave activity and a gradual disappearance of the mean frequency).

Since the entire body of literature covering the neurophysiology underlying AD is so great, it is beyond the scope of this project. Instead, an overview of the affected

neural structures is provided to lend credibility for an examination of the use of EEG applied to the AD problem.

Finally, in the spirit of developing new research techniques for the study of AD, the major purpose of this investigation is to apply a promising new technique in QEEG application to cognitive tasks. Low Resolution Electromagnetic Tomographic Analysis (LORETA) applies an inverse solution to the activity recorded at the scalp. The technique shows promise in locating electrical source activity. The Stroop paradigm seems to be an ideal cognitive task to test the new technique upon. The Counting Stroop, a variant of the Color-Word Stroop test, is an attention demanding cognitive task that has been tested on normal and ADHD populations using the fMRI as the imaging technique. The neural structures targeted and shown to be activated by previous research with the Counting Stroop are the anterior cingulate (associated with attention/vigilance) and the dorsolateral prefrontal circuit or Brodmann's area 9 (associated with implementation of cognitive control). Both of these frontal lobe structures are implicated in the pathology associated with neural atrophy in AD. The successful application of the LORETA technique to EEG recordings of the AD population during the Counting Stroop tasks and comparison with established fMRI literature will further define a place for QEEG in AD research.

Chapter 2

REVIEW OF THE LITERATURE

Demographics on Alzheimer's Disease

As the median age of the U.S. population increases (U.S. Census Bureau Population Division Special Populations Branch, 2001) and as medical costs become increasingly hard to contain, developing inexpensive methods of diagnosing and studying Alzheimer's Disease (AD) becomes advantageous for all concerned. At a hearing before the Senate Subcommittee on Aging (Committee on Labor and Human Resources United States Senate: One Hundred and Fifth Congress: Subcommittee on Aging, 1997), Dr. Richard Hodes, the Director of the National Institute on Aging, National Institutes of Health, reported that approximately 3 percent of the population between the ages of 65 to 74 were afflicted with AD and that by the age of 85 the percentage increases to almost half of the population. The U. S. Census Bureau predicted that more than 4 million Americans would be age 85 or older by the year 2000 and more than 14 million Americans would be 85 or older by the year 2040 (U.S. Census Bureau, 2000).

In terms of health care, the over 85 group tends to be poorer in health than the younger old group [65 – 74] and its enlarging membership will produce an enormous impact upon the nation's health care system (Federal Interagency Forum on Aging-Related Statistics, 2000b). According to the Federal Interagency Forum on Aging-Related Statistics (2000), between 1992 and 1996, only a slight increase in healthcare spending was experienced across all over-65 populations, however, the 80 to 84 age group spent twice as much as the 65 to 69 group. Further, the over 85 age group spent three times as much as the 65 to 69 age group. The average cost of nursing home care for

older Americans in 1996 was $36,906 and represents approximately two-thirds of the total expenditures of the institutional population.

AD ultimately leaves its victims unable to care for themselves and home care becomes imperative. The baby-boomer population is growing older with as many as 70 million people predicted to be over the age of 65 by 2030 (Federal Interagency Forum on Aging-Related Statistics, 2000b). If the current percentages for prevalence of AD holds true in 30 years, as many as 7 million people could be in dire need of affordable diagnosis and care. Currently, an estimated 96 percent of the people over the age of 65 are covered by Medicare.

In 2000, Medicare reported spending $31.9 billion for AD care, $18.2 billion of it used for nursing home care. This care cost is expected to rise to $49.3 billion by 2010 with nursing home care to increase 81.3 percent, or approximately $33 billion (Federal Interagency Forum on Aging-Related Statistics, 2000a). By 2030, total costs including nursing home expenses paid by Medicare on behalf of AD patients have the potential to be debilitating to our nation's ability to provide for everyone's healthcare needs.

Despite the cost to the nation's health care system, the personal and financial burdens on the families with members afflicted with AD have tragic consequences on both the patient and the surviving family members. Current efforts to support AD need to provide easy, affordable access to treatment and long term care. In addition, research is important in providing innovative diagnostics, treatments, and understanding of the pathology involved with AD. Last year the National Institute on Aging (NIA) had funding for only 25 percent of viable AD research applications (Office of Legislative Policy and Analysis (OLPA) Hearing Report, 2001). Methods of research (i.e. QEEG)

that contain costs will provide better utilization of available funds and easier access for greater numbers of researchers.

Diagnosis of Alzheimer's Disease

The disease was first described by Dr. Alois Alzheimer. In 1907, he identified the neurofibrillary tangles and senile plaques, pathologic neural formations specific to this disorder, after microscopic examination in brain post-mortems of patients who suffered from the syndrome (Meeting the Challenges of Alzheimer's Disease: The Biomedical Research That Will Carry Us into the 21st Century, 1997; Allen, 2001). Today this form of identification is still the gold standard and can be accomplished only after the death of the patient (Jeffries & Burns, 2001). Other venues of identification and study show promise for early risk identification and intervention, as well as successful treatment of the disease in its various stages.

AD is a form of progressive dementia which in its early stages presents symptoms that are easily overlooked or explained away. Some research suggests that the earliest symptoms of the disease can occur many years prior to pathological detection (Folstein, 1998). Early recognizable symptoms include memory loss and confusion (Allen, 2001). Eventually, language and motor skills are affected and, in later stages, incontinence and gait disorders occur. Psychiatric symptoms frequently occur with AD: depression, hallucinations, aggression, wandering, paranoia ideation, (Jeffries & Burns, 2001) sleep disturbances and weight loss (Folstein, 1998). Treatment for the patient is often circumscribed by the occurrence of psychiatric comorbidity.

According to Suzanne Jeffries and Alistair Burns (2001), behavioral clinical assessment of AD occurs in two stages: first, identifying dementia apart from other

possible conditions and second, determining the etiology or its cause. Typically, the clinician identifies the syndrome by assessing three areas: neuropsychological, neuropsychiatric, and daily living. As stated in the preceding paragraph, memory loss is most often an early form of symptomology. Amnesia is only one of several possible cognitive deficits. Others include aphasia (loss of speech production or comprehension), apraxia (loss of normal motor function in typical tasks such as dressing oneself), and agnosia (losing the ability to recognize people such as family members or self).

Neuropsychiatric functioning involves symptoms of mental disturbance that often occur with AD. The symptoms of the non-AD related mental disturbance are not typically affected by the drugs used to alleviate AD cognitive symptoms and need to be approached from a different medical context. The last area assessed involves activities that an individual would normally undertake on a daily basis in the course of living. The early signs of pathology can be demonstrated by an individual's detrimental change in personal cleanliness or dressing habits while self-neglect can affect diet and produce weight loss. Toward the later stages of the disease, individuals may not be able to dress, eat, or go to the toilet without aid. Unfortunately, many types of dementias present symptoms that overlap those seen in AD patients, therefore a more specific criteria is applied to identify the disorder.

The specific AD diagnostic criteria identified by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS/ADRDA) (McKhann & Drachman, 1984) require documentation to support the clinical picture using a scale such as the mini-mental state exam. In addition, the identification of two or more cognitive deficits is

required and the patient's age must be between 40-90 years. A CT scan or other structural imaging technique is recommended plus blood testing in order to rule out other possible causes (Jeffries & Burns, 2001). Jeffries and Burns go so far as to state that identifying the presence of AD in patients from other dementia-types is a simple, straightforward process, as long as the clinician adheres to the diagnostic criteria.

Current researchers paint a hopeful picture in the neurobiological understanding of AD. Predicting who will get this disease is still not a refined art but identifying who does have the disease is becoming less difficult. Sampling the cerebral spinal fluid (CSF) for the combination of Tau and beta-amyloid proteins could be a useful diagnostic. Tau is a component of neurofibrillary tangles and has an increased presence in CSF of AD patients compared to other dementia patients and controls (Arai et al., 1995). One type of beta-amyloid (AB-42), which is a membrane protein, tends to have a decreased CSF presence even when total beta-amyloid subtypes are about the same as controls (Allen, 2001). Taken together, they may make a good marker for confirmation of diagnosis. Apparently, the CSF sampling process is risky and its benefits to the individual patient must be justified.

Relatively new to the diagnosis of AD is the use of biological markers. The prospect of understanding how genetics is integrated into the causality behind AD leaves a short path to predicting who will be afflicted and, perhaps, to methods that ameliorate the disease's impact on neurological functioning. Research is focusing on genetic causes and in identification of proteins found in cerebral spinal fluid (CSF) and in serum. Investigations have identified several chromosomes that contain alles which express proteins used in neural membranes and intracellular structures. Mutations on

chromosomes 1, 14 and 21, which contain alles responsible for producing presenilins and over producing amyloid, are associated with early onset of the disease and are considered causative factors in disease development (Kamino et al., 1998). Typically, the disease presents after the age of 80, but the disease can occur as early as the 20's (Folstein, 1998). Mutations on chromosomes 9, 12, 14, and 19 produce products such as apolipoprotein E (APOE) and low density lipoprotein-related protein (LRP) that create a susceptible environment (Kamino, et al., 1998). Kamino and colleagues have presented a hypothesis that suggests that early-onset AD is caused by the genetic component combined with pathogenic substances and that late-onset AD occurs primarily because the body produces more beta-amyloid, a membrane protein, than the immune system can clean up. The first part of that statement would seem to find support in research in that early onset AD is associated with greater spectral abnormalities achieved at a faster rate than late onset (Pucci, Belardinelli, Cacchio, Signorino, & Angeleri, 1999), more widespread neurotransmitter deficits (Davies, 1979), and a greater prevalence of senile plaques and neurofibrillary tangles (Terry, Peck, DeTeresa, Schechter, & Horoupian, 1981). One challenge to their proposal is that not everyone who has the AD genetic components present with the disease. For example, Allen (2001) reports that 16% of the elderly would test positive for the APOE susceptibility gene while presenting no AD symptoms. Another challenge is research that suggests the real culprit of cognitive deficits in AD is in the change of dendritic density. Concomitant with the change in dendritic density are the plaques and neurofibrillary tangles. However, because they are not found predominantly in the neocortex they are considered by-products of the the density change not causal (Terry et al., 1991).

Neuroimaging used in Diagnosis of AD

While identifying cognitive and behavioral aspects of the disease is the primary mechanism for diagnosis, clinicians also rely upon neuroimaging techniques to assist in differential diagnosis of dementia. Structural imaging techniques such as magnetic resonance imaging (MRI) are thought to be more sensitive and specific to diagnosis than functional imaging techniques like positron emission tomography (PET) (Allen, 2001). They permit differentiation between types of tissues and identification of brain structures. Computed Tomography (CT) and MRI are structural imaging techniques that allow for differential diagnosis of atrophy, ischemic changes, tumors, hydrocephalus, and subdural hematoma. Their value in dementia diagnosis comes from identifying patterns of atrophy and excluding other forms of brain pathology. Functional imaging techniques, functional MRI (fMRI), PET, Single Photon Emission Computed Tomography (SPECT), all detect changes in metabolism (Allen, 2001). The detection of hypometabolism may indicate the presence of a degenerative process that can exist without the appearance of structural changes or, on the contrary, may be complementary to them. Pairing the imaging technique to a qualitative clinical assessment increases the accuracy of diagnosis.

Electroencephalography (EEG) and quantitative EEG (QEEG) are techniques also used in clinical protocol. These forms easily allow for often complex statistical manipulations of recorded scalp activity. EEG/QEEG is often utilized in clinical aspects of ADD/ADHD, epilepsy and mood disorders and has promise as a tool for researching and diagnosis of dementias. EEG measures electrical brain activity derived from the top layers of the cerebral cortex. The waveforms studied in this form of brain activity

include delta (i.e. 1 to 4 Hz; slow wave activity), theta (i.e. 4 to 7 Hz activity; square-topped waveforms), alpha (i.e. 8 to 12 Hz activity; often associated with a vigilant resting state), and Beta (13 Hz and above; low power small waves associated with cognitive acitivities).

The current methods of EEG analysis include evaluation of power band ratios (Bennys, Rondouin, Vergnes, & Touchon, 2001), spectral analysis, discriminant analysis (Zappoli et al., 1995), and brain mapping (Dierks et al., 2000; Knott, Mohr, Mahoney, & Ilivitsky, 2001). There are varying opinions about the value of this type of clinical analysis. Many clinicians see little diagnostic value in this method by itself (Nuwer, 1995; Zappoli et al., 1995; Nuwer, 1997). The technique is plagued by artifacts and inconsistencies among research studies. However, Jonkman (1997) rates EEG as equal or higher in sensitivity to MRI, CT, SPECT or PET. He recommends that because of the cheap availability, the relative comfort of the patient, and the quality and type of information provided by the technique (i.e. extra information such as epileptic activity, metabolic activity, etc.) that MDs utilize EEG at least once in the diagnostics and continuing evaluation process. In addition, he recommends that MRI be used along with EEG because of the difference in clinical information provided by the technique (i.e. ventricular enlargement). Finally, Duffy et al. (1984) suggests that visual inspection may not be the best method of interpreting EEG, because too much information may be present for accurate visual interpretation. This method relies heavily on the skills of the electroencephalographer. QEEG methods can help to tease out the complex information and increase visualization of the data present.

Neurophysiology

The neurophysiology underlying Alzheimer's disease has a great body of literature, but it is largely beyond the scope of this presentation. The information provided in this section is designed to give an overview of the neural structures affected and to lend credibility for an examination of the use of EEG.

The limbic system may be among the first neural tissues to be affected: the amygdala, the nucleus basalis of Meynert, locus caeruleus and raphe nuclei. As a result, a depletion of acetylcholine, norepinephrine, and serotonin occurs. The parietal and frontal cortical lobes become involved next (Folstein, 1998). MRI study methods have proved to be very useful in demonstrating which cortical regions are first affected in early stage AD. The initial cortical area to be affected is the entorhinal cortex. As a portion of the anterior parahippocampal gyrus, it provides major excitatory input into the hippocampus and can lose from 40 percent to 60 percent of neuronal cells in some layers before pathological memory impairments are measured (Killiany et al., 2000). In AD pathology, gray matter in the hippocampus, subiculum and the entorhinal cortex frequently contain great numbers of neurofibrilary tangles which no doubt contribute to the atrophy and malfunction (Terry et al., 1991). The superior temporal sulcus region, which is a multimodal association area of cortex, loses cellular volume a little later than the entorhinal cortex. Kaye, et al. (1997) suggest that temporal lobe volume loss may be a good marker to predict disease as many as six years in advance of dementia onset. In their study of healthy subjects above the age of 84 years, participants who eventually developed pre-clinical dementia (pre-D) were distinguished best by the greater rate of atrophy of the temporal lobe. Interestingly, the rate of hippocampal and parahippocampal

volume loss between healthy and pre-D groups was about the same though the pre-D group presented with smaller hippocampal volume at the beginning of the study. Another study found the hippocampal volume rate of change over time to be very different between healthy and pre-D equivalent groups (Jack et al., 2000). The amygdala, parahippocampal gyrus and medial temporal lobes are all neural structures implicated in episodic memory (Dolan, Paulesu, & Fletcher, 1997) which is selectively lost during the progression of the disease. The caudal portion of the anterior cingulate (Brodmann area 24) is also affected at about the same time as the superior temporal gyrus (Killiany et al., 2000). The anterior cingulate has been associated with attention processes. Brodmann area 24, the caudal portion of the anterior cingulate has importance in emotional and cognitive behaviors (Devinsky, Morrell, & Vogt, 1995). This area is spliced into parts that access autonomic functions and the amygdala, and parts that access motor activity, executive functions, and participate in nociception.

The EEG is sensitive to dipole electrical activity thought to originate from the apical dendrites organized in the topmost layer of the neocortex. When the tissue supporting the activity changes, due to damage or disease, the expectation is that the EEG spectrum should change too. Alzheimer's disease affects the cortex by reducing the volume of cortical tissue over time. This is explained in a couple of ways: first, the neuritic plaques, which are the residue of neural cells that have died and the second is the loss of dendritic volume. Terry, et al. (1991) posit that the density of the plaques is not the major cause of cognitive deficits. In their research, plaque density did not correlate with the severity of dementia. However, loss of dendritic density in the neuropil, away from neuritic plaques, correlates better with cognitive decline. In their opinion, the

plaques are a useful diagnostic post-mortem, but the drop in cortical volume is a better predictor of severity of dementia. Along those lines, research measuring CSF volume adds some support (Shear et al., 1995). Comparing early onset-type AD, late onset AD and healthy controls, the researchers found a strong positive correlation between the volume of CSF and AD severity. In particular, the cerebral ventricles and the sylvian fissures showed greater abnormal changes in the late onset AD group, and marked change in the frontal sulci was noted. The early onset-type showed a more rapid progression not only in the ventricular region, but also in the frontal sulcal regions. The CSF volume changes were significantly and negatively correlated to the Mini-Mental State Examination scores. As CSF volume increases, the cognitive ability declines. As Kaye, et al. (1997) suggested above and is supported by both Terry, et al. (1991) and Shear, et al. (1995), the temporal lobe atrophy may well be an excellent method of predicting who will acquire AD. However, until current neuroimaging methods are made available and affordable to asyptomatic patients, prediction with this method is a merely a dream. However, measuring the change in the EEG spectrum as it relates to global or focal cortical atrophy is easily in the domain of accessible affordability.

Normal Aging and EEG

One of the biggest challenges to identifying neuropathology with neuroimaging and EEG techniques is defining normal as compared to defining abnormal. "In order to be clinically useful any method needs to distinguish mild AD from normal ageing and ideally from other causes of cognitive impairment" (Fox, Scahill, Hogh, & Rossor, 2001). To make this distinction with CT, MRI and PET, visual inspection of the brain image is generally performed. Visual inspection alone demonstrates how the subjectivity between

evaluators can cloud issues by being entirely reliant upon the skill and abilities of the radiologist reading the images. MRI images have more resolution than do CT images, but even MRI images when evaluated by applying atrophy rating scales vary in sensitivity from 40 percent to 95 percent. They also are not uniformly sensitive to atrophy from a global brain perspective with the entorhinal cortex and temporal lobes tending to be best represented (Fox et al., 2001). EEG has been routinely used in evaluation of dementia and other types of neurological disfunction by visual inspection (Nuwer, 1995). Nuwer (1997) is of the opinion that this form of EEG analysis is very sensitive to moderate to severe dementias and the degree of abnormality present in the EEG trace record is indicative of degree of disease progression. Again, the sensitivity and the degree of usefulness relies heavily on the skill of the interpreter, in this case the electroencephalographer. Duffy and colleagues (1984) argue that the subjective nature of the visual inspection of the EEG tracings opens the door for the collaborative use of QEEG.

In the past, the general opinion of clinical encephalographers regarding the use of EEG with the elderly was that the spectral power bands change somewhat as people age past 60 years old. The delta and theta bands become slightly more prominent as alpha and beta bands decrease. The alpha frequency band is also affected by aging in that the peak frequency and amplitude decreases with age, and there is a reduction in a related phenomenon called alpha blocking. Frank Duffy and colleagues published a study in 1984 with results that heralded a change to that body of research literature. Reporting research drawn from a group of men age 30 to 80 years old in an eyes-closed resting condition, not only did they not find an increase in normalized (mV) delta and theta

bands, but their results indicated a relative decrease in the low bands. Also, normalized beta was positively correlated with age; in other words, desychronization increased with age. Also, Koyama, Hirasawa, Okubo and Karasawa (1997) found significantly higher relative beta in their elder group. Duffy et al. (1984) noted no significant change in alpha except that alpha reactivity was positively correlated with age which is in keeping with more current understanding of alpha blocking and reactivity (Van Sweden, Wauquier, & Niedermeyer, 1993).

Subsequent study involving both men and women have found similar results in the lower bands for men, but women showed no significant decline suggesting a gender effect (Williamson et al., 1990). Using a smaller age range and a participant pool that had a disproportionate number of women (1.6: 1, Female to male ratio) researchers found no significant correlation between age and QEEG variables (Pollock, Schneider, & Lyness, 1990). A follow-up study with octogenarians found a slight drop in posterior alpha frequency and intermittent focal slowing in the left temporal and left frontal areas in 9 of 13 and 8 of 13 participants, respectively (Shigeta et al., 1995). No indication of sex differences was available in the Pollock, Schneider and Lyness (1990) study, however, the purpose of this study was to investigate the distribution of the EEG amplitude bands in a normal elderly population. Logarithmic transformation resolved most issues of non-normality in all but the eyes-opened (EO) and eyes-closed (EC) Theta band and in the EO alpha band. Interestingly, Pollock's team found a between groups difference with the distribution of theta amplitude. The distribution of theta for the youngest group had a light skew and no kurtosis. In other words, the EO and EC spectral amplitude distribution though not normal in the younger group, had few differentiating

features from the norm. The older group demonstrated 60 percent more skew and 68 percent more kurtosis in the EC condition with the EO condition demonstrating similar but lesser results. Theta amplitude did not convert readily into a normally distributed curve due to among other things, the variability observed. In this study, the theta amplitude variability in the older group was greater than that of the younger group.

In summary, QEEG current research on age related changes in spectral bands reflect disparate results. Areas of focus between studies include finding an increase in relative beta with age (Duffy, et al., 1984; Koyama, et al., 1997), decrease in absolute delta and theta (Duffy, et al., 1984; Williamson et al., 1990; Hartikainen, Soininen, Partanen, Helkala E.L., & Reikkinen, 1992) with focal slowing in extreme age (Shigeta et al., 1995) and a slight decrease in peak frequency (Hartikainen et al., 1992; Shigeta, et al., 1995). In addition, spectral variability increases with age (Dustman, LaMarche, Cohn, Shearer, & Talone, 1985; Pollock et al., 1990). Focus on alpha band research reveals quite a variety of results; a decrease in relative alpha power (Koyama, et al., 1997), a decrease in mean alpha frequency with age (Giaquinto & Nolfe, 1986; Van Sweden et al., 1993) though Duffy et al (1984) saw only a weak relationship, and alpha blocking/reactivity decreases with age (Duffy, et al, 1984; Van Sweden et al., 1993). To confuse the issue even more, Pollock, et al. (1990) found no statistical correlation between age and QEEG variables. A couple of sex differences were reported. Hartikainen, et al. (1992) found women had increased beta activity, while Williamson, et al. (1990) reported no decrease in delta and theta, but a decrease in beta activity in the frontal leads. However, they reported sex differences in beta activity in two frontal leads and four posterior leads with women having significantly more beta activity. The age

range for women was greater; much younger and older women were admitted to the study than the men. Also, only small but statistically significant correlations were reported for age related group differences implying a linear application. No age grouping was indicated. The age discrepancy and comparative age group procedure might account for differences particularly if extreme age has a different etiology.

According to Ernst Niedermeyer (1993), the ideal guide for evaluation of the EEG of an aged individual is in the absence of pathology. People age at different rates and variability of what is normal for the aged individual increases with advancing age so applying a statistical norm to this group as is often done to younger ages is not reasonable. Therefore, the absolute qualifier for the normal aging population sample is good health. Duffy, et al. (1984) suggests that the reason they reported differences from other studies of long standing was that the careful screening of subjects in their study excluded people with developing chronic illnesses with potential EEG impact such as diabetes, chronic hypertension, and arteriosclerosis. They suggest that if the presence of these diseases were not recognized, then any results would be biased. Their participants had been part of a larger study for 18 years or more and as such had their health followed meticulously. This degree of quality scrutiny is in keeping with Niedermeyer's (1993) interpretation of the definition of normal functioning in the elderly.

Dementia and EEG

Most EEG research in AD operates from the assumption that the pathological neural degeneration underlying the disease results in the behaviors seen in progressive dementia and must also show evidence of pathology in spectral profile changes from the

norm. A great amount of research is available that shows distinctions between the aging, healthy population and the AD population with people in varying stages of the disease.

Generally, when assessing resting background EEG activity, theta appears to distinguish between controls and moderate AD (Coben, Danziger, & Storandt, 1985; Rodriguez, Copello, Vitali, Perego, & Nobili, 1999; Rodriguez, Copello, Vitali, Perego, & Nobili, 1999; Jelic et al., 2000) and an increase in Delta tends to be associated with greater severity of the disease (Coben et al., 1985; Szelies et al., 1992; Schreiter-Gasser, Gasser, & Ziegler, 1994; Rodriguez et al., 1999; Pucci et al., 1999; Jelic et al., 2000). Other measures that share the distinction of discriminating AD patients involve several different aspects of Alpha. In some cases, it is as simple as reduced power (Pucci et al., 1999), percent power (Coben et al., 1985), or coherence measures (Locatelli, Cursi, Liberati, Franceschi, & Comi, 1998; Jelic et al., 2000) that reflect global cortical atrophy which marks AD progression. Peak or mean frequency tends to be negatively correlated with the severity of AD. As AD progresses to its later stage, the mean frequency shifts to the lower frequencies (Coben et al., 1985; Rodriguez et al., 1999) or it disappears all together leaving a flat spectral profile (Pucci et al., 1999).

Since the purpose of doing research with clinical QEEG is to validate its usefulness in accurate as well as early diagnositics or prediction of pathology, several studies found a combination of spectral variables that tend to identify early stage AD. Jelic, et al. (2000) found that a combination of alpha and theta relative power were successful at distinguishing controls from those with mild cognitive impairment. Another found that peak frequency in the central electrodes was a strong discriminating factor between controls and early AD participants as groups (Zappoli et al., 1995). However,

the individual variation made discriminating between participants who were healthy and pathological problematic. Generally, the success rate of prediction or discrimination using spectral variables as a group in a regression formula is somewhere around 80 percent (Besthorn et al., 1997; Jelic et al., 2000). Thus supporting researchers' like Zappoli, et al. (1995) skepticism in the usefulness of EEG/QEEG as a stand alone clinical diagnostic tool. However, nowhere in the literature nor in recommended clinical practice is any neuroimaging tool used as a solitary designator of pathology. The best success rates for diagnosis come from utilizing clinical assessment tools, blood sampling and neuroimaging methods. Some studies have demonstrated that the predictive accuracy of QEEG only improved a few percentage points when using it with screeners like the Mini-Mental State Examination (Jelic et al., 2000) or contributed to a very high correct classification; 97 percent (Zappoli et al., 1995). It is therefore reasonable to consider the cost-effective utility of quantitative analysis with the readily available EEG.

LORETA

A new technique in the quantitative application of EEG is Low Resolution Electromagnetic Tomographic Analysis (LORETA). Whereas traditional EEG attempts to measure electrical activity confined to the scalp, LORETA estimates current density of the brain tissue and applies a mathematical inverse solution in an attempt to find the generators of the electrical activity in three dimensional space (Pascual-Marqui, 1999). The technique is most valid in proximity to the recording electrode and tends to blur deeper into cortex. In other words, the deeper layers of cortical tissue demonstrate less resolution than the layers closer to the source electrodes. However, the technique has been used successfully in AD research attempting to identify EEG generator correlates to

spatial indices of glucose metabolism during a resting state (Dierks et al., 2000). This is important because, glucose metabolism and neuroelectric activity are related to synaptic activity. The cortical neurodegeneration in AD reflects a change in metabolism that is measured by PET. Localizing the EEG generator correlates to the same areas of metabolism opens the door to greater clinical application of EEG.

Research Rationale

The U. S. population is ageing. As the population ages, the numbers of people who will be afflicted by Alzheimer's dementia will increase, causing future problems with affordable diagnosis and healthcare. Current methods of diagnosis for AD include expensive neuroimaging techniques. A potentially acceptable and inexpensive substitute to MRI and PET techniques is QEEG.

EEG and QEEG have been used to study selective attention in ADD/ADHD and other types of clinical disorders. However, these techniques are limited to localization in the upper most layers of the neocortex. A new method of brain imaging, LORETA, overcomes that limitation. It makes use of EEG data by calculating an inverse solution to uncover 3-demensional activation sources deeper into cortical areas than traditional EEG is designed to disclose. This study looks at the activation paradigm of the Counting Stroop comparing AD patients to age-matched controls.

The Stroop Color-Word test has been used effectively to demonstrate activation in the caudal portion of the anterior cingulate (Brodmann area 24). In normal participants, MRI studies suggest that greater activation in the anterior cingulate during the performance of the incongruent task (word color and color of word are different) is indicative of performance monitoring (MacDonald , Cohen, Stenger, & Carter, 2000).

The increased activation of the dorsolateral prefrontal cortex (Brodmann area 9) during the congruent task (word color and color of word are the same) is consistent with the implementation of control during the task. In keeping with this interpretation of the Stroop-paradigm, the Counting Stroop has been demonstrated with fMRI to show increased anterior cingulate activity during the incongruent task (Bush et al., 1998). In the Counting Stroop incongruent paradigm, two cognitive processes are placed in competition with each other; reading and counting. A number word is presented a conflicting number of times: for example, the word 'ONE' is printed on a slide three times. The participant's task is to count the number of words seen. The cognitive interference experienced by study participants due to the conflicting aspects of the stimulus generates greater cingulate activity.

The purpose of using LORETA to evaluate the paradigm is to compare EEG generator correlates to the body of Stroop-type research supported by MRI and fMRI activation data. Both neural structures, the anterior cingulate and the dorsolateral prefrontal circuit, are implicated in the frontal lobe atrophy associated with AD pathology. Following the logic described in the Dementia and EEG section, a change in EEG spectral correlates should accompany the cortical tissue atrophy. If EEG generator correlates are present but at different levels of activation between the healthy and AD participants, then LORETA will represent a promising paradigm as an inexpensive method to evaluate and study AD in its early stages. To that end, this study proposes to evaluate early stage AD patients and age-matched controls during the Counting Stroop paradigm.

Chapter 3

METHODS

Participants

The Cole Neuroscience Center, under the direction of John Dougherty, Jr. M.D., provided AD patients (n = 6) and control participants (n = 8) and funding for this project. Screening was performed by Mattea de Leonni Stanonik, M.A. as a part of her dissertational research project. See Table 1 for demographic profiles of the groups (all tables are located in Appendix A). Each participant was screened with the Mini Mental State Exam (MMSE) and the Self Test. To meet criteria for early stage AD, patients' scores on the MMSE were 20 to 24 and Self Test scores were 13 to 16. Controls performed at or above 24 on the MMSE and above 16 for the Self Test. In addition, all participants were screened for and free of other neurological pathologies (i.e. depression, stroke, etc). A second screener was applied prior to EEG recording to verify age, education, medicines, and other types of pertinent personal information that could impact the participant's value to the research project. All participants were required to read and sign a consent form prior to taking part in the research. Storage of consent forms and confidentiality of all data has been explicitly provided for by locked storage in the research lab.

All AD participants were recorded while taking Aricept, an ACh esterase inhibitor, and other drugs such as Zoloft, an SSRI, that were prescribed by their attending physician for their condition. See Table 2 for a list of medications.

Measures

EEG recordings were conducted with Lexicor's V4.1E software. Utilizing the 10-20 international electrode placement system and a 19-channel electrode cap by Electro Cap Inc. with ear referencing, Electrode impedance, a measure of signal interference, was kept below 5kΩ. Relative power bands are defined as delta (2 Hz – 3.5 Hz), theta (4 Hz – 7.5 Hz), alpha (8 Hz – 12.5 Hz), beta 1 (13 Hz – 21.5 Hz), and beta 2 (22 Hz – 30.5 Hz). At a sampling rate of 128 samples per second, 100 two-second epochs were recorded per baseline condition: eyes-opened baseline, eyes-closed baseline. In addition, recordings were made during active cognitive tasks. Participants' EEGs were recorded while computerized stimuli were presented utilizing the Counting Stroop incongruent (IS) and neutral stimuli (NS) paradigms. For stimuli examples, see Table 3. In some cases, a 1 Hz high pass filter was used to remove the largest forms of muscle artifact.

Artifact rejection was accomplished with the EEG Editor 2.0, developed by University of Tennessee Brain Research and Quantitative EEG laboratory colleagues Marco Congedo, M. A. and Leslie Sherlin, B.A. of NOVATECH. EEG spectral filtering and group analysis was accomplished with the LORETA Wizard, a statistical software facilitation program developed for use with LORETA-KEY by Marco Congedo, M. A.. LORETA-KEY was used to provide 3-dimensional images of the intracerebral EEG-data (Pascual-Marqui, Michel, & Lehman, 1994; Pascual-Marqui et al., 1999). The image computations utilize the human head model as it corresponds to the Talairach brain atlas (Talairach & Tournoux, 1988) with a cross registration of

electrode postions onto the Talairach scalp. Within group data were subjected to non-parametric T-tests.

A computer program was developed for this project by Keith Jones, Ph.D. of Axciom Corporation in Conway, Arkansas. The program combined timing of the stimulus presentation, stimulus access and the output of simple reaction time responses. Counting Stroop stimuli (see Table 3) were placed in a text file from which the program selected the stimuli and created a picture on screen according to the file parameters. For example, in the incongruent stimulus (IS) paradigm (interference blocks), a number word ('ONE' through 'TEN') is presented in a multiple fashion (one to four times) on the computer screen. Contained within the text file is the number word (i.e. 'NINE') and instructions for the multiple for that stimulus presentation. A numerical three (3) in the text file would indicate that the word 'NINE' be placed on the screen three times, 'NINE NINE NINE', in a vertical arrangement. An example slide is provided in Figure 1 (all figures are located in Appendix B). The neutral stimulus (NS) paradigm matched word names of animals ('FISH', 'CAT', etc.) with the one to four multiple vertical presentation. Another example is provided in Figure 2. The versatility of the program allowed for the timing of the stimulus presentation to be automated or responsive to the mouse click to forward the next stimulus. In this data set, the participants controlled the speed of stimulus presentation by using the mouse button.

Procedure

Consent forms were acquired at the time of recruitment into the study by the investigator in the Cole Neuroscience Center. Immediately upon arriving for the EEG session, participants were screened for state of health, current medications and other

personal considerations prior to recording. The recording sessions lasted from two hours to two hours and thirty minutes. Capping required approximately twenty minutes and then instruction for the baseline measures helped the participants to settle comfortably into the procedure.

After baseline measures were recorded, participants were provided instruction for the Counting Stroop via a Powerpoint presentation with sample stimuli responsive to the click of the mouse. To prepare the participant for the actual task, the Powerpoint slide presentation was activated on the computer screen while the participant was being familiarized with the mouse. The investigator facilitated the use of the mouse by placing the participants fingers on the correct button and encouraged practice until the participant was comfortable and ready to continue with the stimulus practice program. The slide presentation utilized the same stimuli as in the active task. Prior to the first practice, the participant was given the verbal instruction, "Count the number of words that you see on the screen and then click the mouse with your pointer finger one time only." Verbal responses were encouraged during the first practice so that the investigator could measure the participant's understanding of the task. A second practice occurred with the added instruction, "Now count the number of words you see on the screen with your inside voice. Do not speak out loud." Practices continued until the participant indicated a comfortable familiarity with the task. The AD participants generally required more practice than the healthy participants did. Indeed, the AD patients often required retraining during the active task. This was accomplished by suspension of recording, verbal reinforcement of the practice instructions and the AD participant verbally

reiterating the task requirements. Recording resumed when the participant indicated readiness.

The tasks were recorded after training. The participant's job was to look at the stimulus presented on the computer screen, count the number of words on the screen and then respond by pushing the left mouse button one time.

Training and recording of the total tasks accounted for approximately one and a half hours of the session time. Participants were encouraged to stand and stretch between recording sessions. In addition, the investigator made an active effort to engage the participants between recordings to ensure alertness and decrease drowsiness.

Chapter 4

RESULTS

Table 1 illustrates group differences. The AD group age range is 72 – 84 with a mean age of 76.8. The Control group age range is 64 – 78 with a mean age of 72.6. Sex composition is lopsided between groups with the majority of AD participants being male (4:2) and the majority of healthy control participants being female (2:6).

The digitized spectral values were normalized and log-transformed. The NS data (easy task) was subtracted from the IS data (hard task) within groups with non-parametric, paired T-tests performed on the data that make up the difference maps. Difference images that are compared between groups are scaled equally in order to illustrate the differential use of waveforms. The color on the images reflects the within groups activation of waveforms. Red color indicates that the activation level during the IS task is stronger than during the NS task, while the blue color indicates that the activation level of the NS task is stronger than that of the IS task.

None of the within group T-tests revealed statistically significant differences. However, several qualitative differences are evident between the two groups. The patterns of activation that differ between the AD and Control groups and description of trends that support cited literature references are worth reporting.

The image color intensity in delta, theta and alpha is greater in the images of the AD group. The Control group images demonstrate greater color intensity in beta 1 and beta 2 bands. See Figures 3 through 12. Each case implies that the relative power for each frequency is more pronounced as the intensity of the color increases. In other words, the implication is that the AD group demonstrates greater delta, theta, and alpha

relative power than the Controls, while the Controls demonstrate greater relative power in the beta 1 and beta 2 bands.

Figures 3 through 12 display temporal lobe differences and Figures 13 through 17 show differences around the area of the insula. See Table 4 for a summary of activations by frequency and neural location. The delta band demonstrates group bilateral differences at the level of the orbital gyrus, moving upwards through the insula and the fronto-temporal junction to just above the level of the superior temporal gyrus. The AD group is activating delta during the IS task on the left side while the controls present the opposite pattern of NS activation in the left hemisphere. In addition, theta reveals differential bilateral activation between the groups (IS activity is more prominent as evidenced by the intensity level for the AD group) at the insula and the temporal lobe locations in the control group show NS activation. Alpha activity at the insula shows the Control group with bilateral activation that for the most part represents equal use of Alpha during both tasks and the AD group with heavily right sided IS activation. At the temporal lobe (inferior, medial and superior gyrus) the both groups demonstrate right sided IS activity and the Controls with left-sided activation during the NS task. In the Beta 1 band, the Control group bilaterally activated the insula the hard task (IS) and temporal lobe during the easy task (NS). The AD group activated the right insula during the IS task while bilaterally activating the temporal lobes during the IS task. Finally, a different pattern of activation in Beta 2 was evident with the IS task being prominent in the Control group on the right side of the insula and the AD group brought out the NS activity on the left side. The temporal lobe activity for both groups in Beta 2 was rather mixed.

Chapter 5

DISCUSSION

The non-statistically significant patterns seen in the LORETA images hint at future research possibilities for Alzheimer's Disease. Currently, the number of participants in this study is not enough to provide statistical power for the results discussed herein. While it is wise to view the following interpretations with caution, it's also important to see the results for their potential.

A very prominent feature of the entire image set is the intensity differences observed in all frequency bands. The AD group demonstrated more intense colors in the three lowest frequency bands while the Control group revealed more intense color in the highest two frequencies. One way to interpret intensity is as greater activation. If intensity is interpreted as greater relative power, then the AD group produced more Delta, Theta and Alpha frequency. The QEEG literature in AD demonstrates the global increased presence of relative Delta and Theta wave forms during eyes-closed conditions as the disease progresses (Coben, Danziger, & Storandt, 1985; Szelies et al., 1992; Schreiter-Gasser, Gasser, & Ziegler, 1994; Pucci et al., 1999; Rodriguez, Copello, Vitali, Perego, & Nobili, 1999; Jelic et al., 2000). As a result, since lower wave forms become prevalent, relative alpha and beta bands tend to diminish. This effect in the AD group could be due to the existing pathology that underlies the disease process. As cortical atrophy progresses, the increased presence of the lower waveforms observed in the resting condition may very well underlie all cognitive states.

Another interesting result involves that differential activity at the insula. The insula, which is Brodman's area 21, is only one of the neural structures found in the

encircled area of Figure 13. Also found in close proximity are limbic structures such as the amygdala and the parahippocampal gyrus. This result is interesting because of the Killiany et al. (2000) report that the entorhinal cortex, an anterior part of the parahippocampal gyrus, is affected very early in the progression of AD and that these structures and the medial temporal lobe are all implicated in episodic memory (Dolan, Paulesu, & Fletcher, 1997). Bush, et al. (1999) studied adults with ADHD during the Counting Stroop. The controls in this study activated the anterior cingulate, the lateral prefrontal cortex (Brodmann area 9), and superior parietal cortex (Brodmann area 7). The ADHD group bilaterally activated the insular cortex and the lateral prefrontal cortex (Brodmann 45) and a number of the striatal nuclei. The investigators reasoned that either of two possibilities may be occurring, 1) the use of a less efficient compensatory attentional circuit or 2) a frustration/anxiety response due the difficulty of the task. As Table 4 attests, not only did the AD and Control groups differ in the type of activation between tasks at the insula, but the frequency bands were not uniformly activated. Theta and Delta were bilateral for the AD group, Alpha and Beta 1 were not, and so on. Because the frequency activation differences are complex and the numbers of participants are so small, attempting an interpretation is risky at best. However, because the AD group strongly activated left sided Delta during the hard task and the left sided Beta 1 during the easy task at the insula, the implication could be that the cells that produce these two wave forms are at odds in the AD group when stressed during a cognitive task. During a stressful task the Delta waveform becomes prominent because the Beta 1 waveform cannot be accessed efficiently. Since the activation of the insula is not bilateral across frequencies and between groups, equating the AD performance to the ADHD

performance is problematic. However, the fact that both studies focus about this neural structure makes it worthy of a second look with the AD population.

The other standout group difference in the images is the Delta and Theta activity at the temporal lobe. This cortical area is among the first to suffer atrophy. According to Kaye, et al. (1997), the temporal lobe volume (measured without the hippocampal tissue or parahippocampal gyrus regions) in preclinical dementia participants changed more overtime (decreased) than that of the healthy participants. Their supposition is that the disease process may be in motion, as evidenced by temporal volume loss, as much as six years prior to the onset of dementia. The group of AD participants in this pilot study has been diagnosed in the early stages of the disease. The group activation differences in Delta and Theta at the temporal lobes are remarkable when viewed in light of the literature that suggests that cortical volume loss may be responsible for the onset of symptoms (Kaye, et al., 1997; Shear, et al., 1995; Terry, et al.,1991).

Admittedly, this is a very small group upon which to base strong conclusions. However, the patterns discussed open directions for future research investigations. A useful examination of a dementia population involves the nature of the use of insular cortex during complex cognitive activity to identify an inferior attentional pathway or an anxiety reaction. Also, the results of this study reveal differential temporal lobe activity which offers support for the literature that suggests this cortical area should be investigated as an early predictor of those who will develop clinical dementia.

A final note of caution is required regarding the preceding discussion. This is simply a pilot study. The small group of participants made this more an exercise in creative thinking than an application of new information to the field. Another caution is

the reality of the LORETA inverse solution technique. It's resolution declines in imaging the lower cortical layers. The resolution at the level of the insula, a neural structure which figured prominently in the discussion, makes interpretation of activity challenging. For statistical power to counter-act the resolution, a greater number of subjects needs to be evaluated in the paradigm.

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APPENDICES

APPENDIX A

Table 1

Demographics			
Group membership	Age	Sex	Education (completed)
AD			
	84	M	Ph. D.
	77	M	Ph. D.
	72	M	Ph. D.
	72	M	< 1 year HS
	81	F	HS
	75	F	GED/2 yrs college
Control			
	78	M	< MS
	76	F	HS
	73	F	B.S.
	72	F	HS
	78	F	MSW
	64	F	HS
	70	M	HS
	70	F	1 yr college

Note. The < indicates some study at identified education level, but not completion. HS indicates High School; BS indicates Bachelor's Degree; MS indicates Master's of Science; MSW indicates Master's of Social Work; Ph. D. indicates doctorate

Table 2

Medicines of AD patients during recording

Drug Name
Aricept
Exelon
Zyprexia
Topol XL
Zoloft
Prilosec
Synthroid
Antidiuretics

Note. This list is an example of the types of medications taken by the AD group. Medication types varied between individuals.

Table 3

Counting Stroop Stimuli

Incongruent Stimuli	Neutral Stimuli
ONE	DOG
TWO	CAT
THREE	PIG
FOUR	CHICKEN
FIVE	TURTLE
SIX	BIRD
SEVEN	HORSE
EIGHT	FISH
NINE	BUTTERFLY
TEN	DUCK

Table 4

Between Group Spectral Differences

	Insula		Temporal Lobe	
	LH	RH	LH	RH
AD Group				
Delta	IS	IS	IS	IS
Theta	IS	IS	IS	IS
Alpha	mixed	IS	mixed	IS
Beta 1	NS	IS	IS	IS
Beta 2	NS	IS	NS	mixed
Control Group				
Delta	NS	IS	NS	NS
Theta	IS	IS	NS	NS
Alpha	IS = NS		NS	IS
Beta 1	IS	IS	NS	NS
Beta 2	mixed	IS	mixed	mixed

Note. The locations represent differential activation between the IS (Incongruent Stimuli) and NS (Neutral Stimuli) cognitive tasks. NS activation data is subtracted from IS activation data. RH indicates Right Hemispheric location. LH indicates Left Hemispheric location. Color is used to represent the activation effect seen on the figures.

APPENDIX B

Figure B-1: Example of the Incongruent Counting Stroop. An example of the Counting Stroop paradigm Incongruent Stimulus that is responsible for the cognitive interference recorded in several MRI studies.

FISH

FISH

FISH

Figure B-2: Example of the Neutral Counting Stroop. An example of the Counting Stroop paradigm Neutral Stimulus.

AD Group: IS - NS Delta Pattern

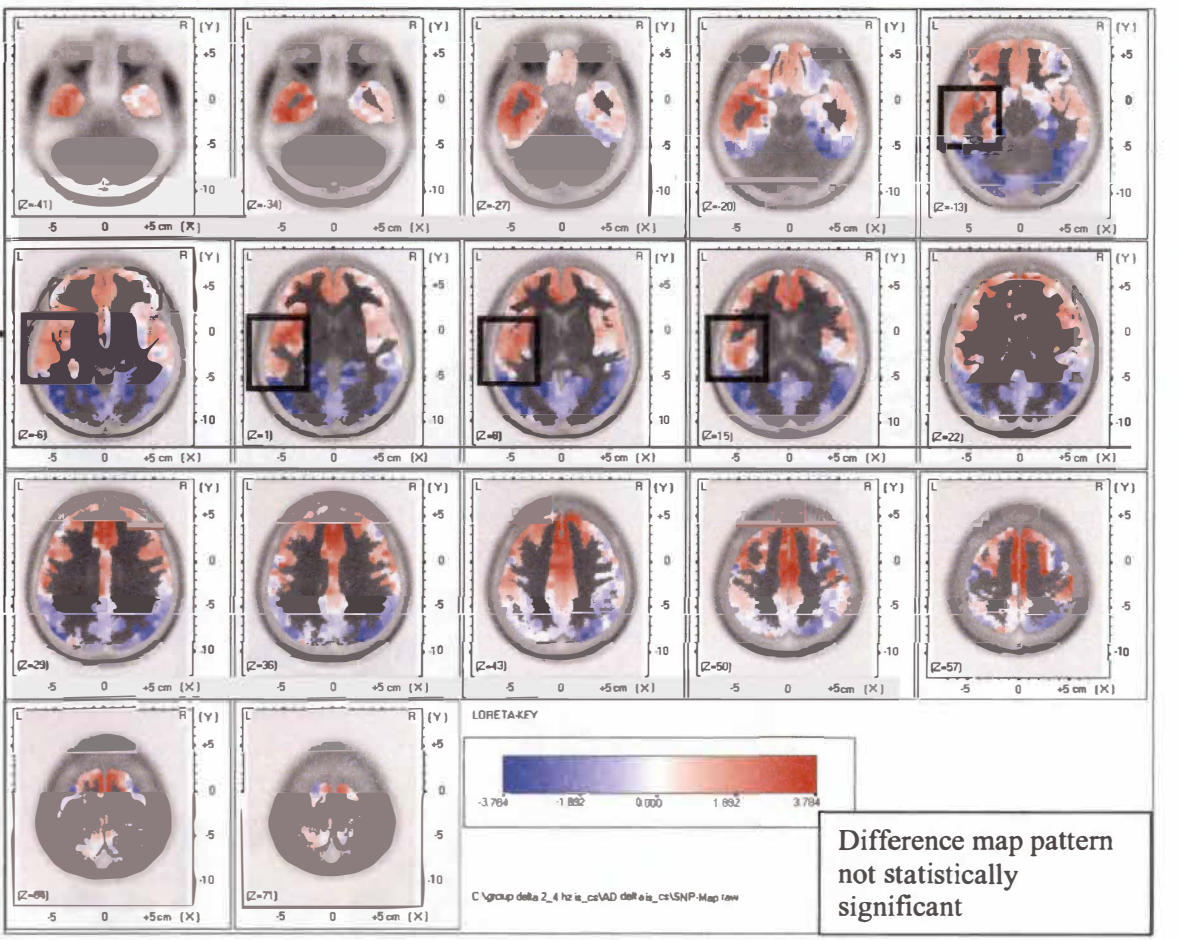


Figure B-3. The black square is highlighting the right temporal lobe. The red color indicates activity that predominates during the IS task. Similar, but less activity also occurs in the left temporal lobe.

Control Group: IS - NS Delta Pattern

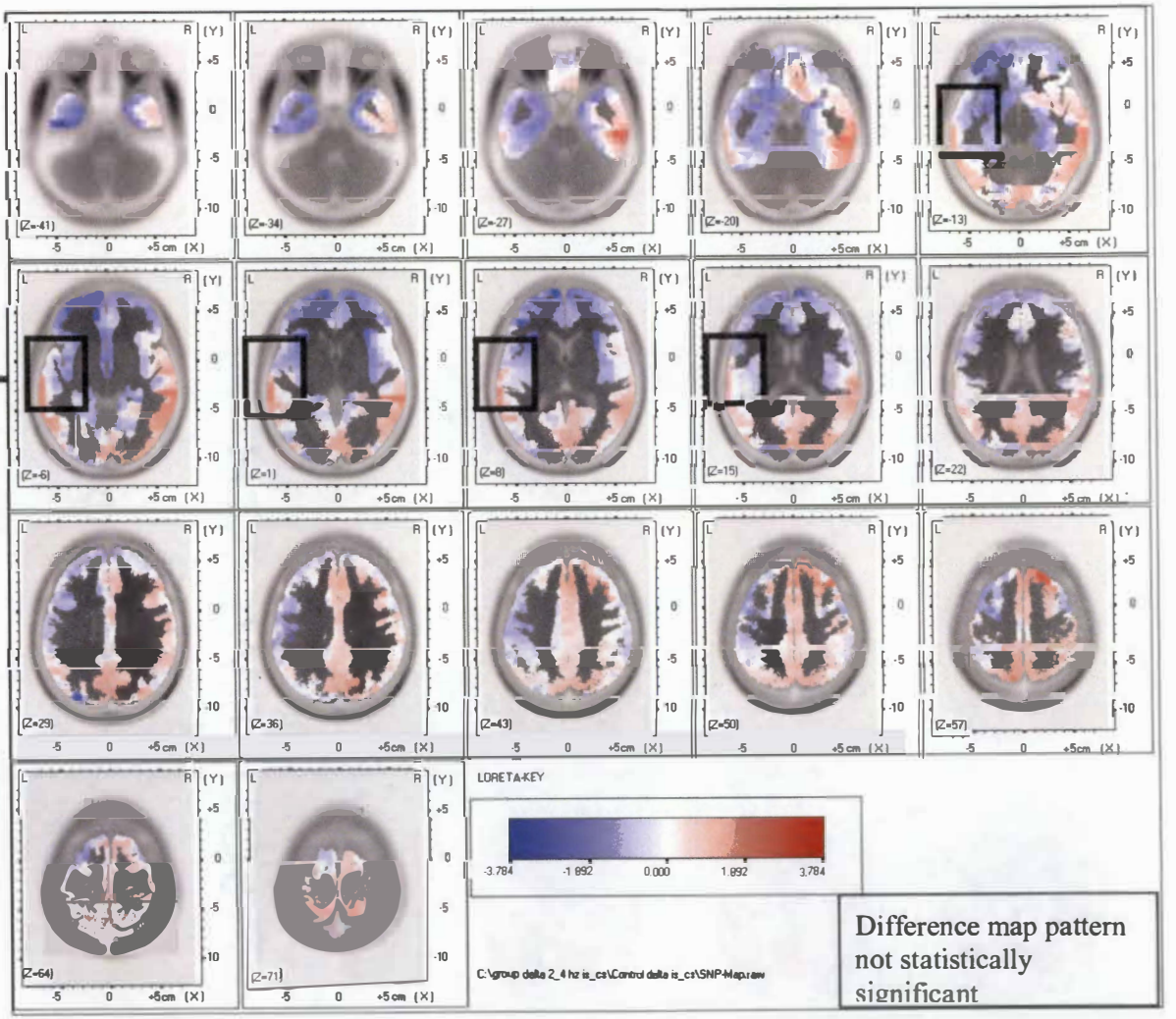


Figure B-4. The black square is highlighting the left temporal lobe. The blue color indicates activity that predominates during the NS task. Similar, but less activity also occurs in the right temporal lobe.

AD Group: IS - NS Theta Pattern

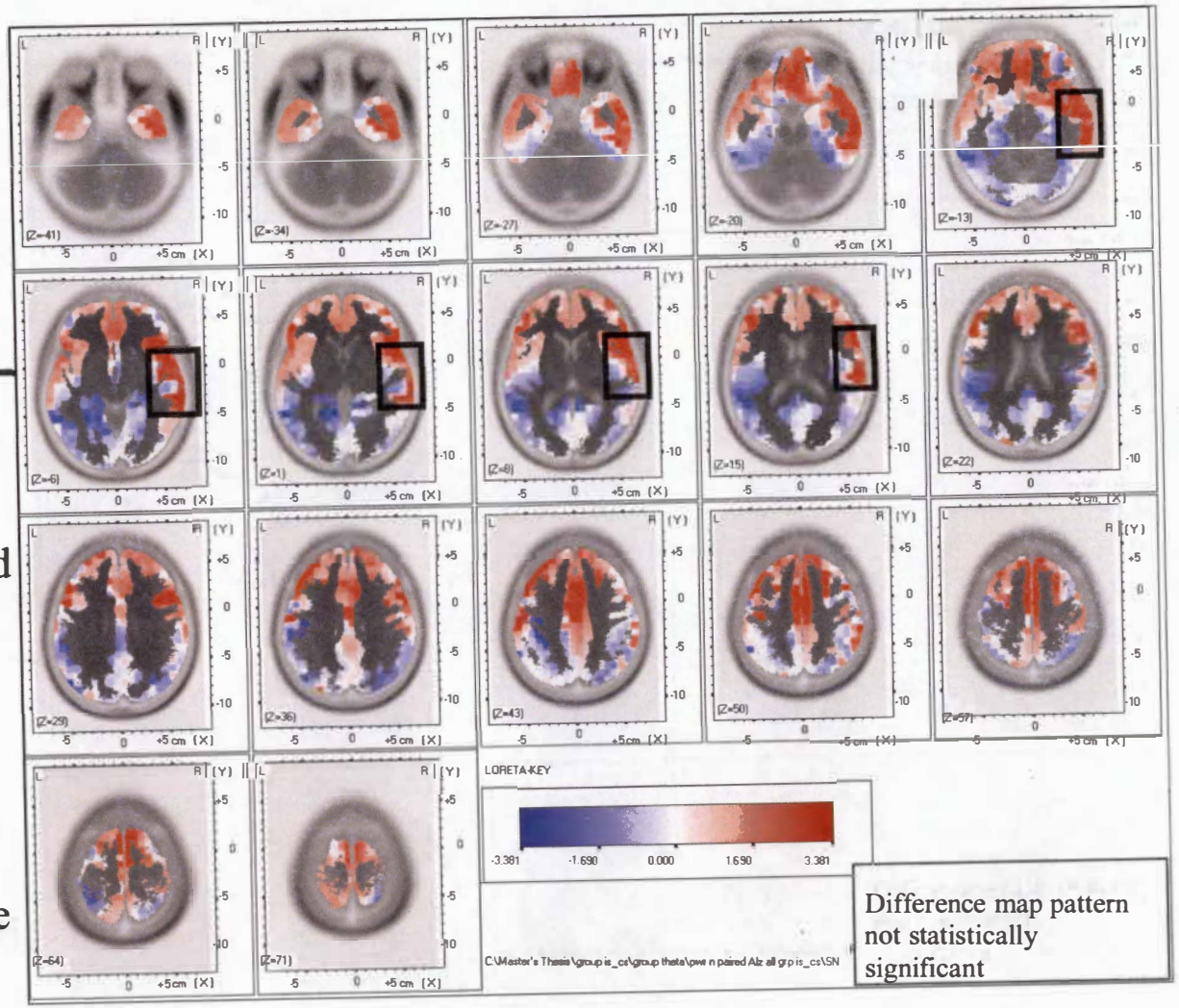


Figure B-5. The black square is highlighting the right temporal lobe. The red color that dominates particularly in the inferior portion (*) indicates that IS activity predominates. A similar activation pattern is present in the left temporal lobe.

Control Group: IS - NS Theta Pattern

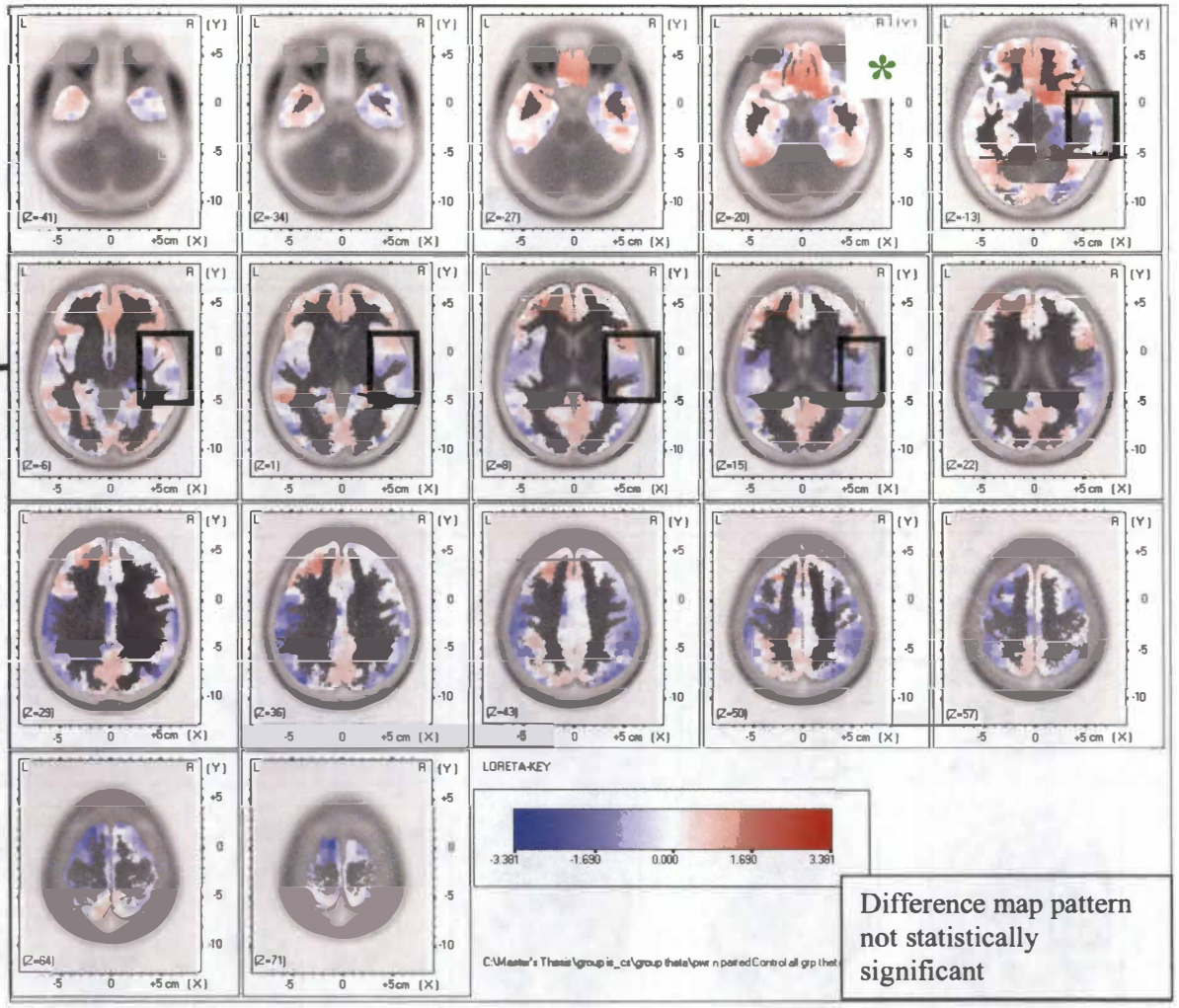


Figure B-6. The black square is highlighting the right temporal lobe. The blue color that dominates particularly in the superior portion (*) indicates that NS activity predominates. A similar activation pattern is present on the left temporal lobe.

AD Group: IS - NS Alpha Pattern

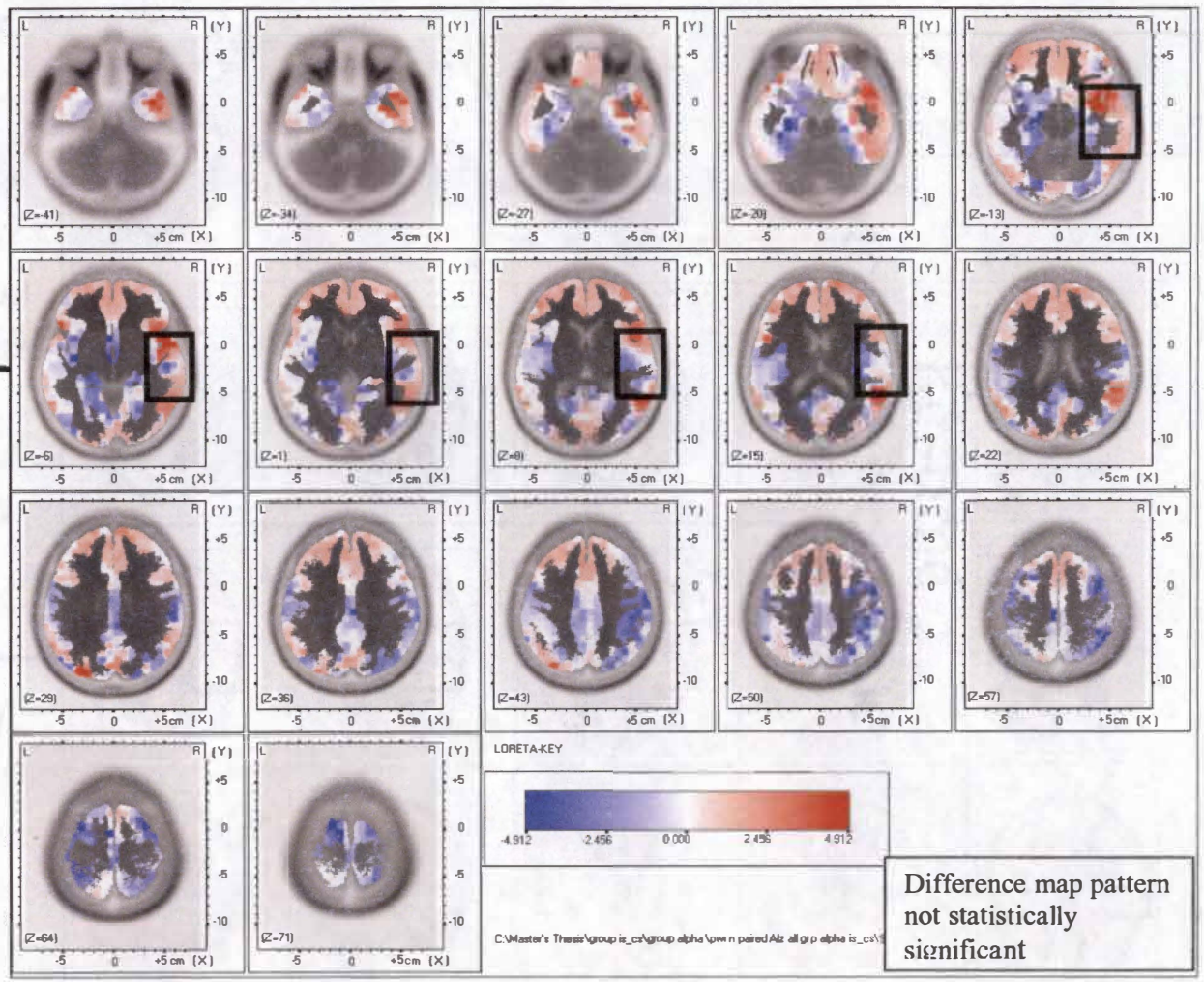


Figure B-7. The left and right temporal lobe activity is mixed. The black box follows the predominant right sided IS activity inferiorly (*) upward to mixed activity in the superior temporal lobe.

Control Group: IS - NS Alpha Pattern

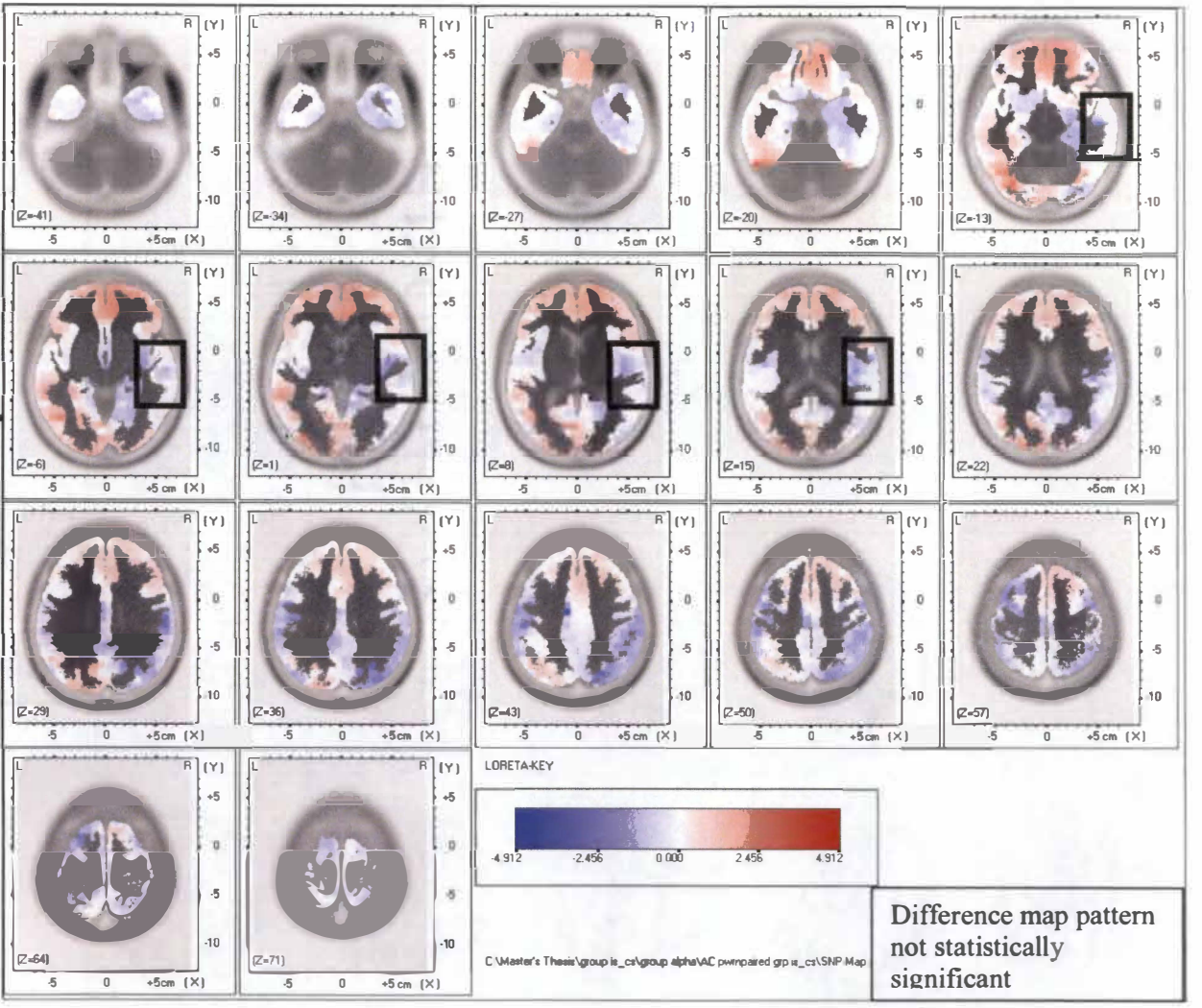


Figure 8. The black box shows very weak bilaterally differential activation. The right temporal lobe tends toward the blue or NS activation while the left side tends toward the red or IS activation.

AD Group: IS - NS Beta 1 Pattern

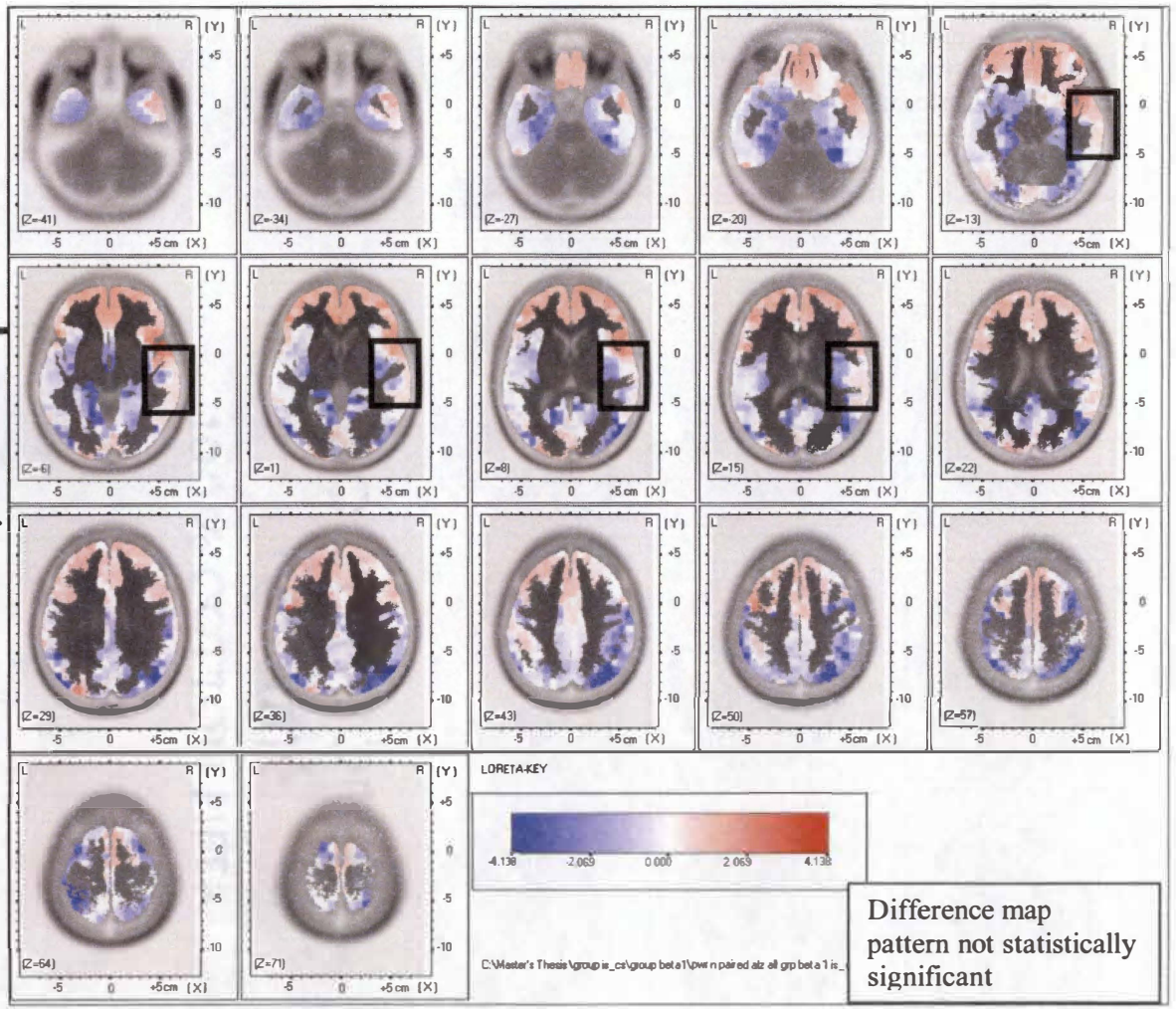


Figure B-9. The AD group produces less power in Beta 1 band demonstrated by a lesser color intensity. In addition, the black boxes reveal an activation mixture at the temporal lobes; red is mixed with blue as move from left to right in the top row to the second row.

Control Group: IS - NS Beta 1 Pattern

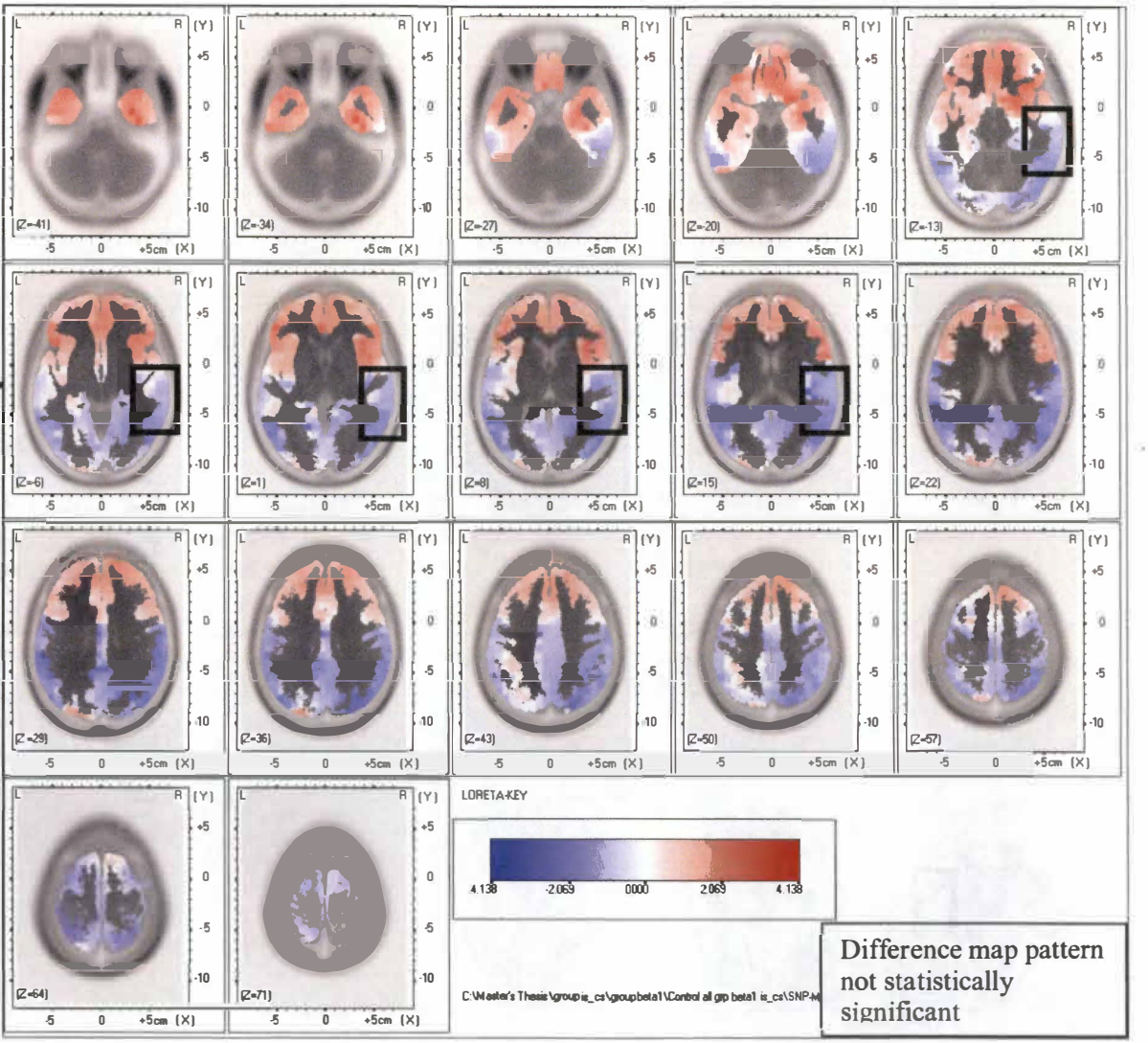


Figure B-10. The Control group produces greater power demonstrated by the intensity of color. In addition, the black box indicates that activity in the right temporal lobe is predominantly resulting from the NS task; the color is blue.

AD Group: IS - NS Beta 2 Pattern

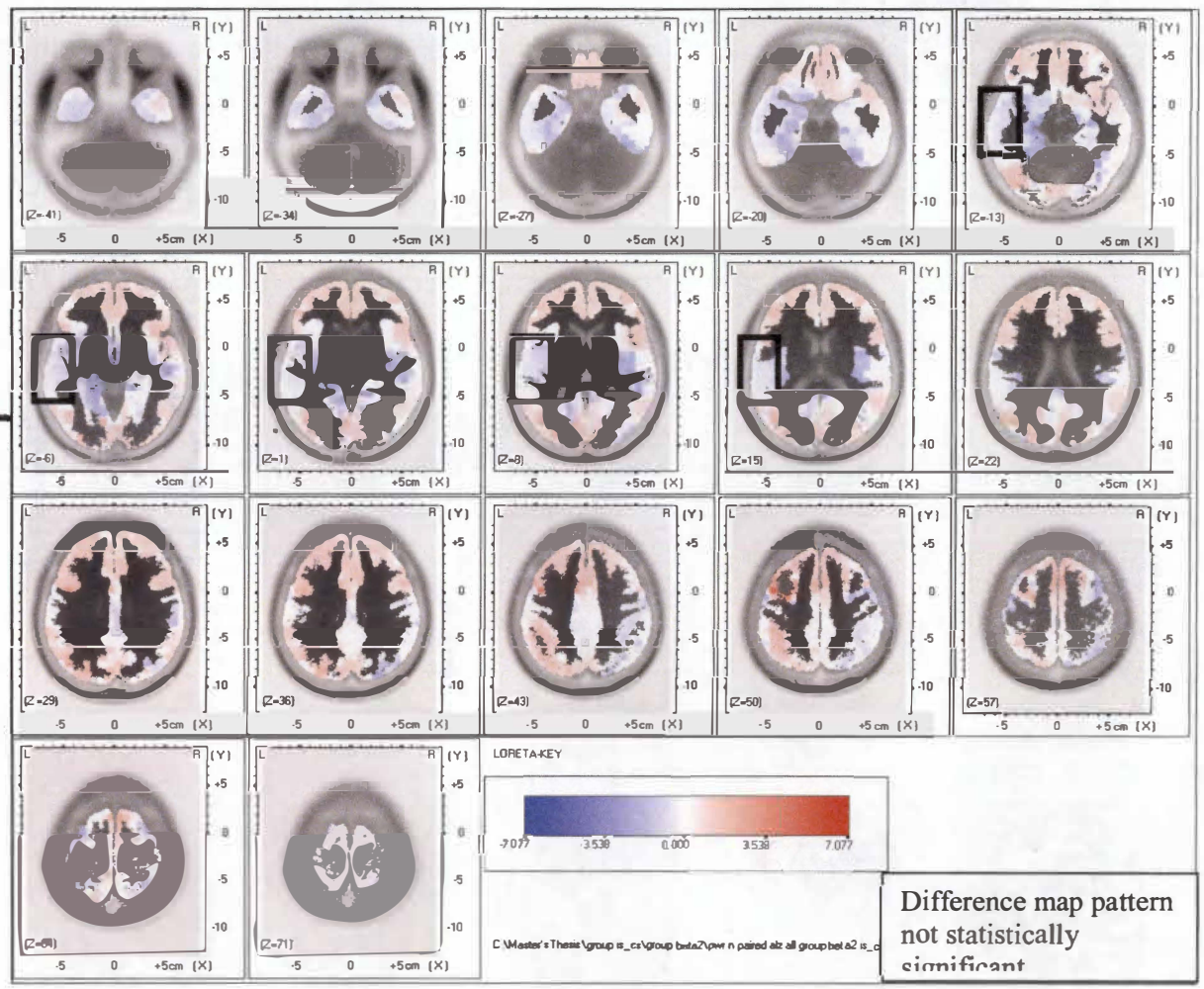


Figure B-11. The square highlights a very light NS activation (blue color) in the left temporal region. The right temporal lobe demonstrates a mixture of IS and NS activity.

Control Group: IS - NS Beta 2 Pattern

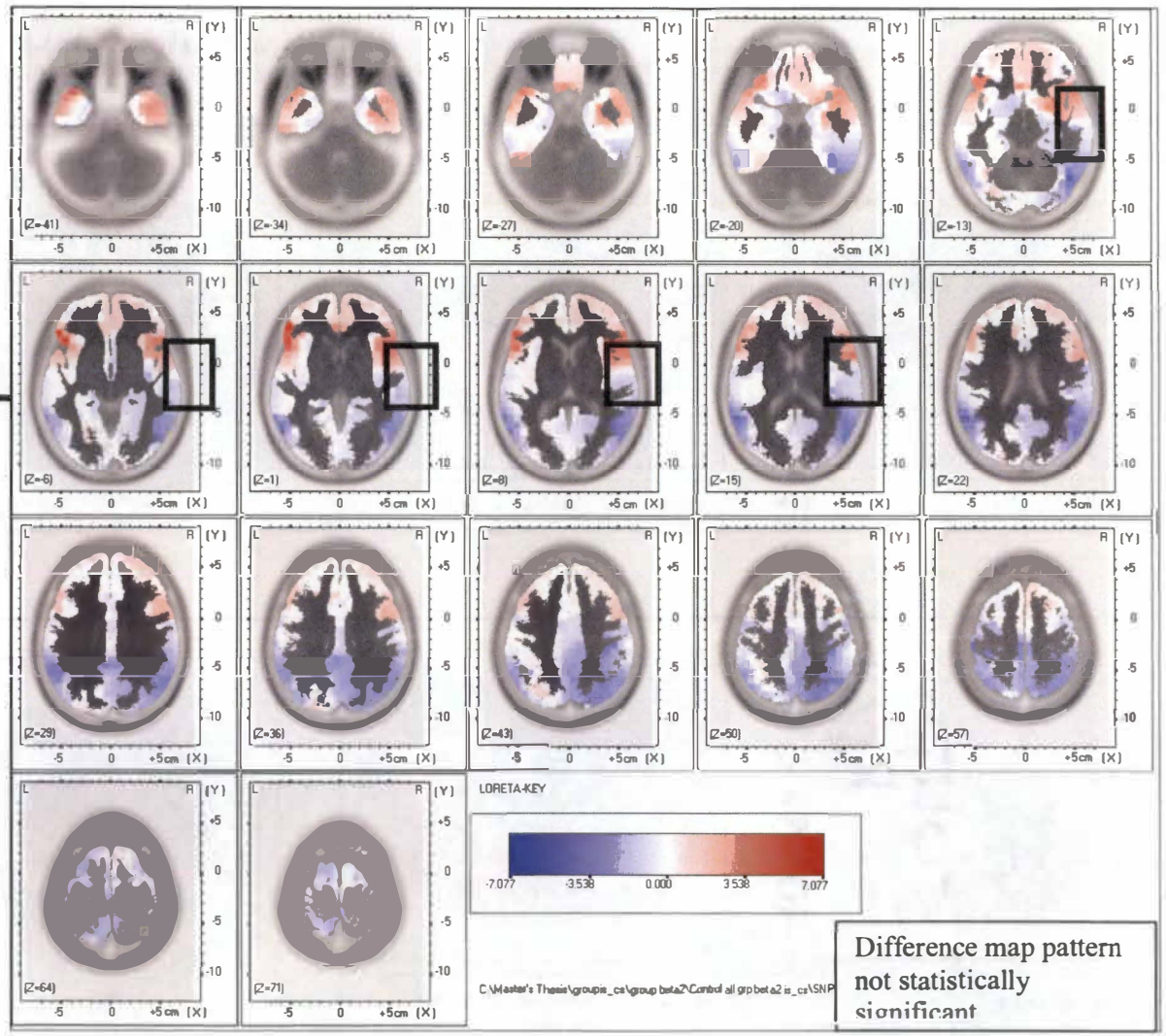
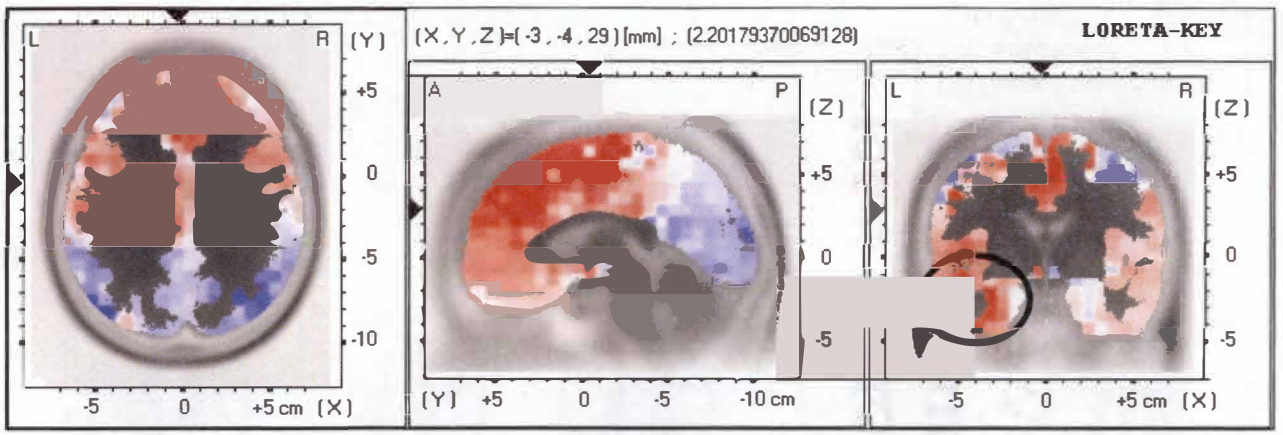
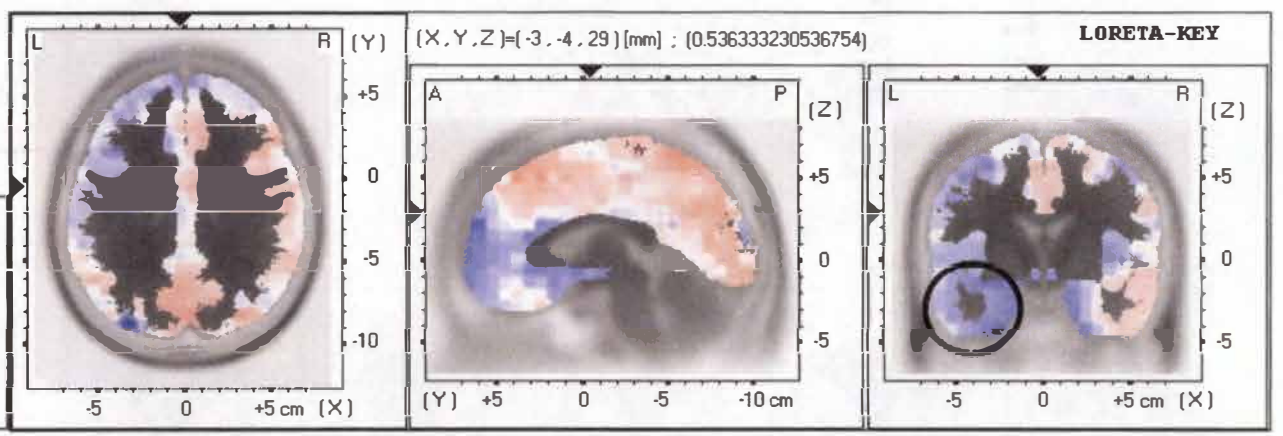


Figure B-12. Both temporal lobes are exhibiting a mixture of IS and NS activity. The red color (IS) is in the most raustral section of the temporal lobe, approximately at the fronto-temporal junction.

AD Group



Control Group



Note: The black circle highlights the insula and the most rostral portions of the amygdala and the parahippocampal gyrus.

Figure B-13: Delta activity at the insula

AD Group

Control Group

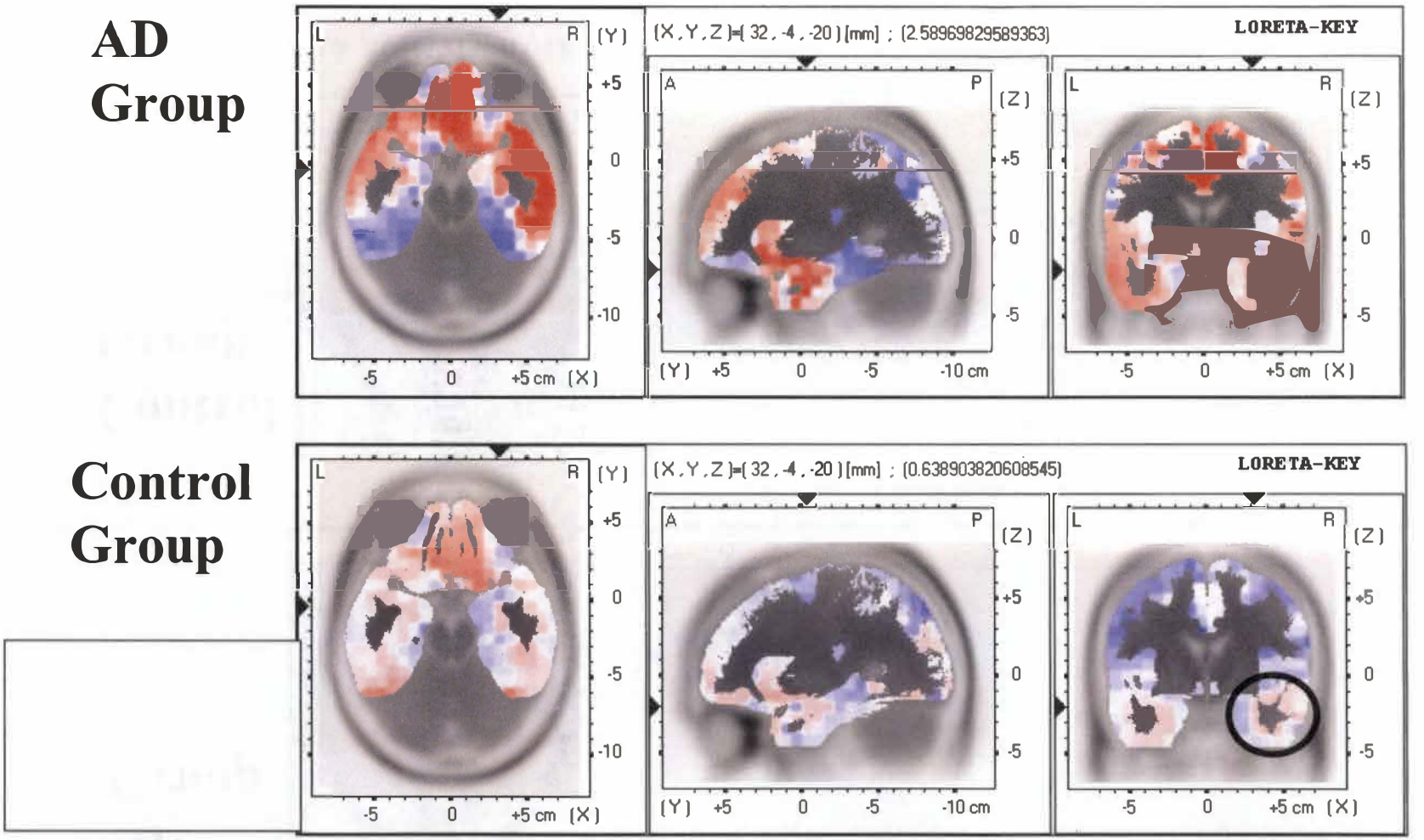
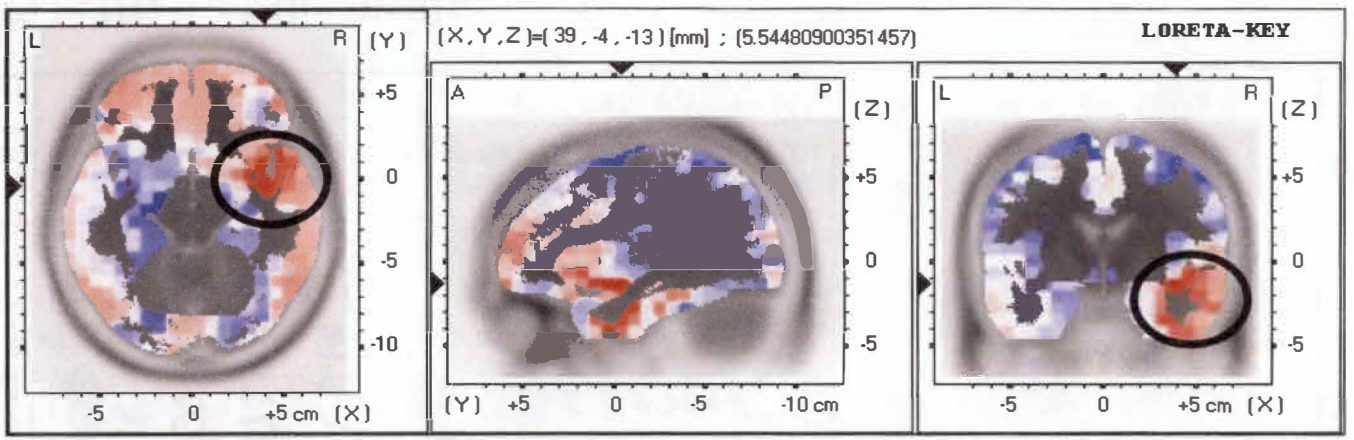


Figure 14: Theta activity at the insula

AD Group



Control Group

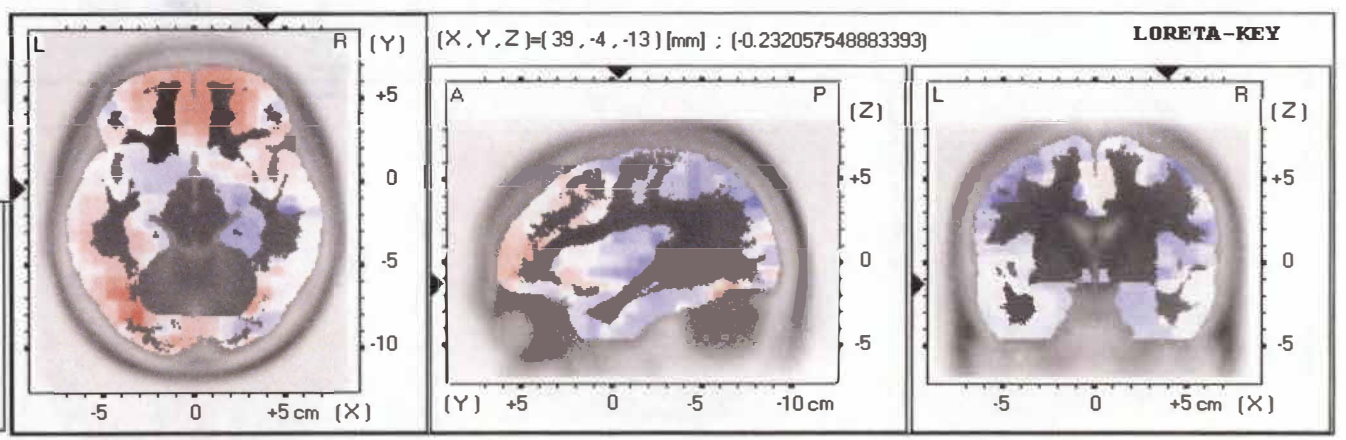


Figure 15: Alpha activity at the insula

AD Group

Control Group

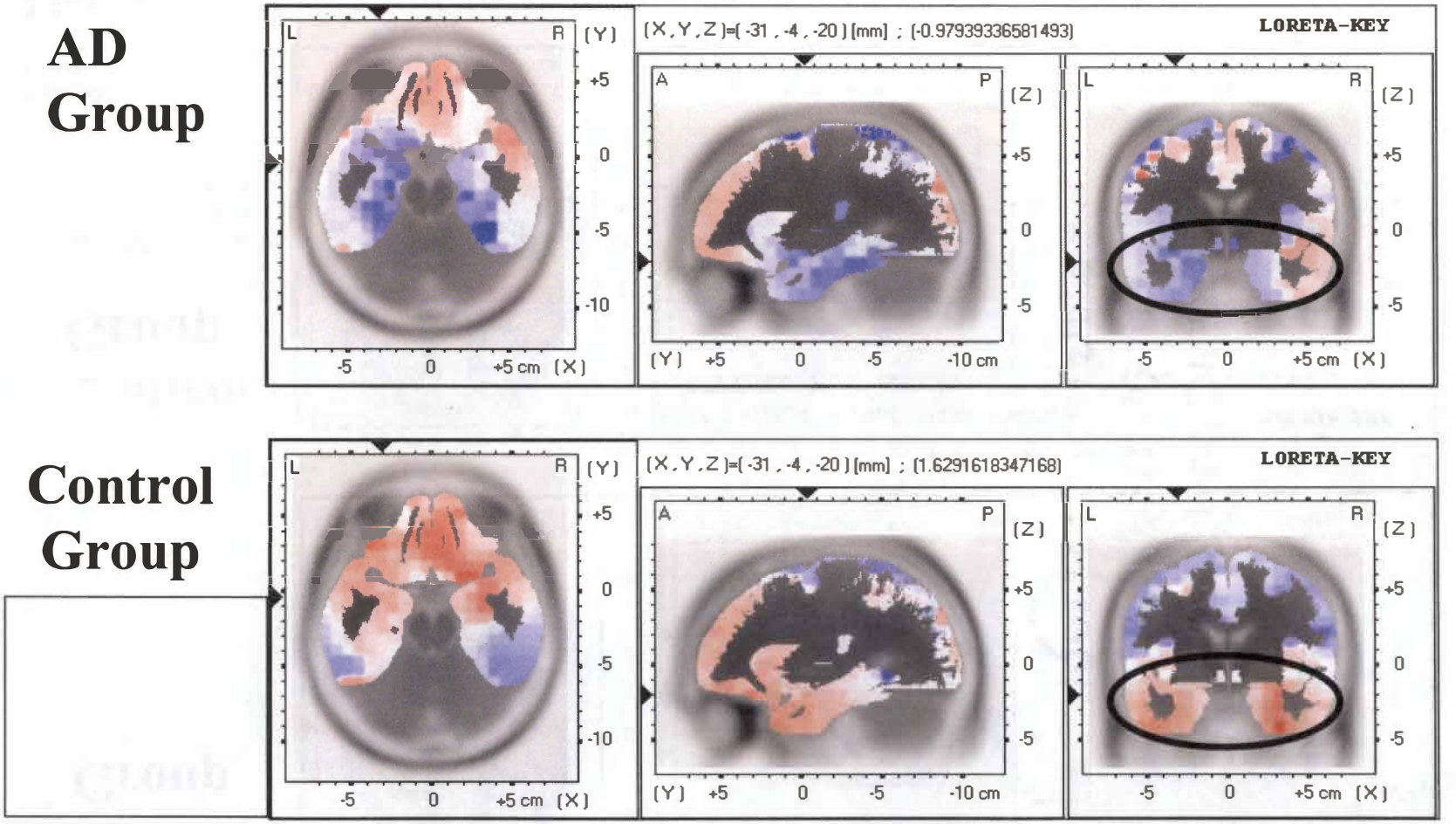
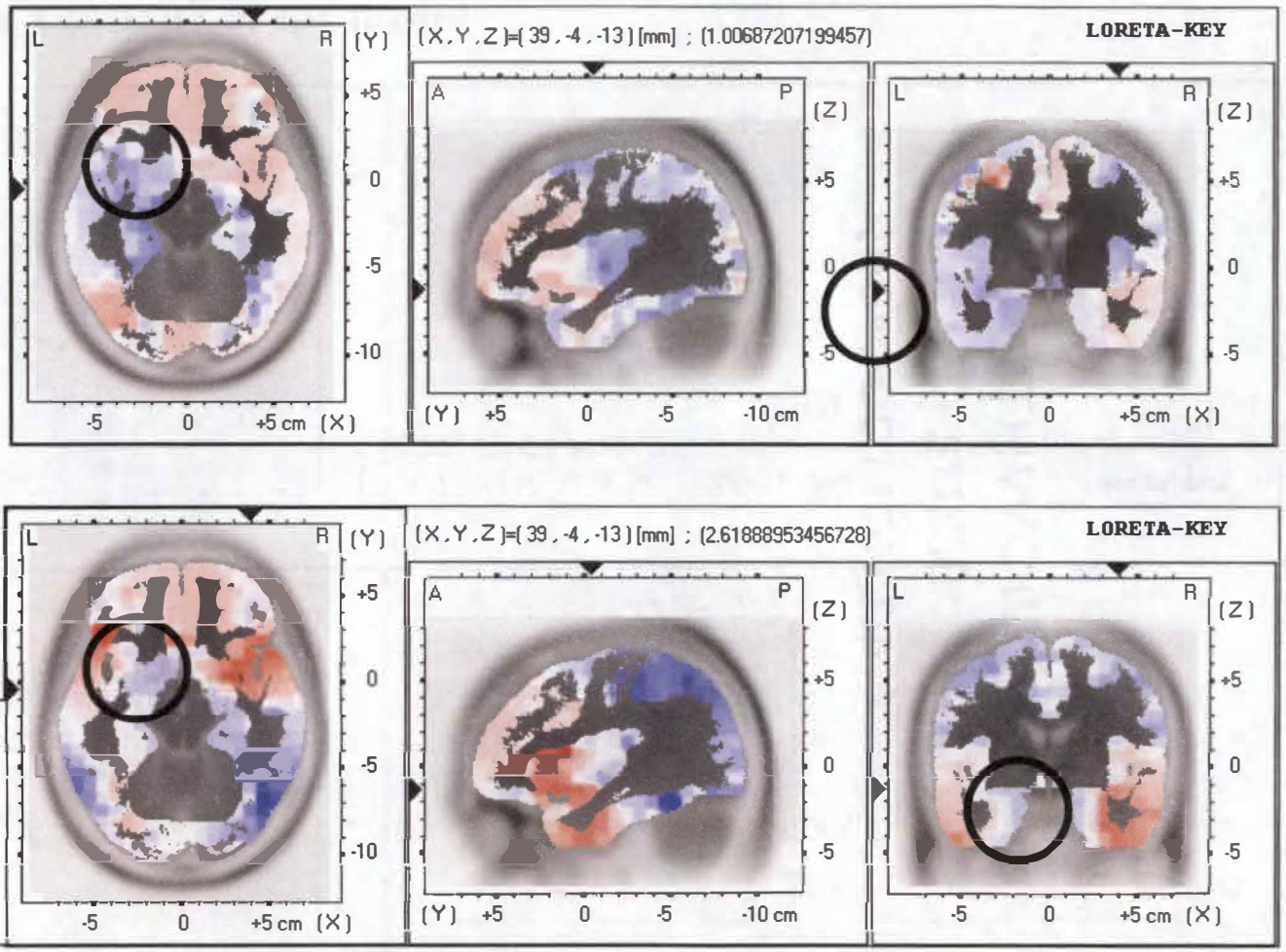


Figure 16: Beta 1 activity at the insula

AD Group

Control Group



Note: The black circle highlights the insula and the most rostral portions of the amygdala and the parahippocampal gyrus.

Figure 17: Beta 2 activity at the insula

VITA

Kerry Towler was born in Fayetteville, AR on April 25, 1962. She was raised in Fort Smith, AR and graduated from Southside High School in 1980. Her undergraduate career culminated in graduating Magna Cum Laude from the University of Central Arkansas in 1998 with a B.S. degree in psychology and a minor in chemistry. She attended the University of Tennessee, Knoxville for graduate study where she received her M.A. in Psychology, with an emphasis in Experimental.

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