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Running head: PREFRONTAL THETA RESET

The Role of Prefrontal Theta Reset in Learning and Memory

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Abstract

Theta reset, in which the rhythmic firing of neurons stops and then restarts to the onset of a stimulus, is believed to improve encoding and retrieval of stimuli by causing stimuli to be time-locked to waves of depolarization in the HPC. Recent research by Williams et al. (in preparation) has demonstrated that, in rats, theta reset occurs 1) in several cortical areas including the anterior cingulate (AC), 2) occurs during different phases of a working memory task for different cortical areas, and 3) can be predictive of working memory task performance. In the current study, human participants received EEG recording of the AC while performing a working memory task. Participants viewed a picture of a random dot arrangement for four seconds (encoding), viewed a blank screen for eight seconds in which the dots disappeared (delay), and viewed a second picture that was either the same or slightly different from the previous picture (retrieval). Participants decided if the second picture was the same or different and then made a choice on a response box. While no significant main effects were revealed, several trends were present. Greater theta reset occurred during the encoding phase of the task for participants who were high in overall accuracy than those who were low in accuracy for midline recording. In contrast, greater theta reset occurred during the retrieval phase for those who were low in accuracy than those who were high in accuracy for midline recording. Greater theta reset occurred in the retrieval phase of the task for both left and right AC recording. It is possible that increased focus on encoding stimuli, visible by an increase in theta reset, caused better encoding and, consequently, better accuracy for these participants. Lower accuracy may have resulted from misplaced focus on the retrieval stimulus (as evidenced by an increase in theta reset) instead of the encoding stimulus. This study provides insight into the role of theta reset in the memory functioning of the AC of humans.

The Role of Prefrontal Theta Reset in Learning and Memory

Patient W.H.'s battle with memory impairment began in 1986 when he became unable to recollect the appearance of his desk at work or his employer's face. During the next few days he remained at home, often repeating himself and forgetting what he was doing after brief distractions. A week later patient W.H. was in the hospital and was unable to remember the month or current president. He was able to remember his home phone number and could still perform simple calculations, but could not remember four objects that were given to him just one minute before. His remote memory seemed intact despite his inability to recall recent events. Patient W.H. never exhibited intellectual or cognitive impairments other than memory. Cases such as W.H. have intensified efforts to find the neurophysiological basis of memory. The predominant focus on this research has been on the hippocampus (HPC), although other regions such as the prefrontal cortex have also gained prominence.

HPC History

During the last half of the nineteenth century, Sergei Korsakoff, a Russian psychiatrist, discovered that individuals who consume copious amounts of alcohol for a number of years can eventually suffer from anterograde and retrograde amnesia. Korsakoff patients have trouble learning new verbal and nonverbal information and have been noted to have trouble learning names of physicians and nurses and even the location of their beds. These deficits are believed to be a result of vitamin deficiencies affecting the thalamus and the mamillary bodies, structures important for the functioning of the HPC (Butters, 1985). The amnesia that these individuals exhibit resembles deficits following damage to the HPC itself, which research has demonstrated plays a large role in memory processing (Butters, 1985; Eichenbaum et al., 1994; Kesner et al., 1992; Olton, 1977; Squire et al., 1991).

This pattern is confirmed by more recent amnesic individuals. Autopsy revealed that

patient W.H. had extensive bilateral lesions of the HPC. Another specific case of memory disruption involving direct disruption of the HPC is that of H.M.. H.M. was an epileptic who received a bilateral medial temporal lobectomy resulting in the removal of his HPC. The procedure proved effective in reducing the severity of his seizures, but after the surgery, H.M. suffered from anterograde amnesia. He was unable to commit newly acquired information to long-term memory and lost some of the memory of the few years prior to the surgery (Schmolck et al., 2002). H.M.'s loss of HPC undoubtedly had a profound effect on his memory functioning.

The HPC's specific role in memory has been extensively researched and several theories have been developed to explain its role in both learning and memory. Theories by Kesner (1992), Olton (1977), Squire (1991), and Eichenbaum (1994) have attempted to explain the cognitive functioning of the HPC. Others (Bland, 1986; Brazhnik, 1999; Vertes, 1992; Vinogradova, 1995) have attempted to explain the functioning of the HPC from a physiological standpoint, paying particular attention to a specific wave pattern called the theta rhythm.

Cognitive Theories of HPC Memory Functioning

Attribute model of the HPC. Kesner's (1992) attribute model of HPC proposes that each individual memory is constructed by five attributes: time, space, affect, response, and sensory perception. Of these five attributes, the HPC is responsible for temporal attributes, which code the time order of individual events, and spatial attributes, which are the relationships between one or more place stimuli (Kesner et al., 1992).

To test his attribute theory, Kesner designed studies using a radial arm maze (which consists of several identical arms that extend from the center much like the spokes of a wheel) to assess temporal and spatial processing. In the temporal memory task, rats entered seven arms of a radial arm maze one at a time. In order to receive a food reward, rats had to remember the order

in which they visited specific arms of the maze. Rats with HPC lesioning were impaired on this task, having difficulty correctly recalling the order in which they had visited the arms.

In the spatial version of the radial-arm maze, rats were required to use allocentric, or external, maze cues to orient themselves and move throughout the maze. The HPC helps create cognitive spatial maps based on the external cues of the room in which the maze is located. For instance, objects in the room and on the walls such as globes or posters serve as spatial references for rats. When external cues were rearranged during the task, rats had difficulty orienting themselves correctly in the maze. If the rats had been using egocentric cues (personal orientation cues that arise because of previous left or right turns), manipulation of the external cues would not have had an effect because the external cues would not have been relevant to their orientation within the maze. HPC lesioned rats experienced difficulty navigating the maze when it was necessary to use external spatial cues, demonstrating that the HPC is important for spatial memory processing.

Working memory model of the HPC. David S. Olton (1977) also believes that the HPC is important for spatial memory. He demonstrated that animals use allocentric cues to solve spatial tasks in a radial arm maze, meaning they create cognitive spatial maps based on maze cues and external cues of the room in which the maze is located. In one experiment, rats searched for food located at the ends of the arms of the radial arm maze. After the rat consumed the food at the end of one arm, it was necessary for it to pass through the center of the maze and remember where it had been. While moving between arms, in search of food, the rat had to remember which arms it had previously visited to minimize the amount of time spent searching. HPC lesioned rats were significantly impaired in this task, returning to arms they had previously visited. Olton's work, like that of Kesner, demonstrates that the HPC is involved in working memory, specifically in the creation of spatial maps for navigation.

Unlike Kesner, Olton, however, does not believe that the HPC is solely restricted to spatial and temporal attributes. Instead, Olton proposed the “working memory model” of HPC memory storage, stating that the HPC is responsible for processing all short-term memory information, regardless of attribute. In working memory, information is stored as it is being worked on or processed and a limited amount of information can be stored in working memory at a time. In another radial-arm maze study by Kesner, HPC lesioned rats showed impairment in recalling the order in which they had previously visited arms. This study demonstrates that the HPC plays a significant role in temporal order memories of spatial locations (Chiba et al., 1994).

Declarative memory model of the HPC. While the majority of HPC memory research has involved rats, Squire (1991) extends the scope of the field by including human participants in his research. Further explaining the HPC’s involvement in memory functioning, Squire addresses the well-known distinction between declarative and non-declarative memory, claiming that amnesia, due to HPC system damage, impairs learning of facts and events but does not impair skill learning, priming, or certain types of conditioning. Study of patient W.H. revealed that while he had difficulty learning new facts and remembering everyday events, he was not impaired in his ability to perform certain tasks. Squire claims that many kinds of learning abilities, (e.g. skills, priming, and habit learning) lie outside the functioning of the HPC and its surrounding cortices. What the HPC is important for, according to Squire, is the acquisition of new information about facts and events. While Squire would agree with Olton that the HPC is important for working memory processing, he would be sure to make the distinction that the HPC is important for processing declarative working memory, not non-declarative.

It has been suggested that cortical areas surrounding the HPC may also play a role in memory functioning. Squire (1991) was able to take a closer look at the areas of the HPC system

responsible for different degrees of impairment and discovered that combined damage to the HPC and adjacent cortical areas produced more impairment than just damage to the HPC itself. Lesions to the amygdala, perirhinal, and entorhinal cortices caused more severe impairment on spatial and non-spatial tasks than just damage to the HPC itself (Squire & Zola-Morgan, 1991). Squire effectively demonstrates that the integrity of the HPC system, not just the HPC itself, is important for maintaining the maximum level of memory processing.

Task specific model of the HPC. In an attempt to unite the theories of Olton, Kesner, and Squire, Eichenbaum (1994) suggests that the memory task that is being performed is just as important in revealing the nature of HPC memory processing as the specific areas that have experienced lesioning. Eichenbaum's theory involves aspects of each of the previously reviewed theories. Like Kesner, Eichenbaum demonstrated that the HPC is involved in spatial processing and that rats likely create spatial cognitive maps using allocentric cues. He also suggests that the HPC has a temporal component but that the HPC's processing of temporal stimuli is dependent on the specifics of the task being performed. The combined functioning of the HPC in the processing of temporal and spatial information results, according to Eichenbaum, from the fact that specific HPC areas contributing to declarative memory have different processing functions. Also, Eichenbaum's research supports Olton's claim that the HPC is specifically involved in working memory by demonstrating that the HPC is necessary for continually processing external stimuli in radial arm maze tasks. Finally, Eichenbaum's theory supports the work of Squire in that both theories demonstrate that the HPC is important for declarative memory but not important for skill learning. He further supports Squire's work by demonstrating, as Squire previously has, that all HPC system components contribute, in some degree, to memory functioning.

Drawing on aspects of these previous theories, Eichenbaum claims that the HPC memory

system mediates the storage of “relational representations,” which result from comparisons between information. Relational representations create scenes and events that are organized into an already existing memory system. This system is very flexible and provides a way in which individuals can quickly handle a novel experience by comparing available stimuli. Eichenbaum predicts that damage to the HPC will result in problems performing tasks that require relational comparisons. In a spatial learning task set in a radial arm maze, rats with HPC damage were impaired when external cues were spread out, but showed no impairment when the cues were clustered. When the cues were spread apart, rats attempted to orient themselves by comparing their relation to two or more stimuli, creating a relational representation. HPC lesioned rats could not orient themselves correctly, supporting Eichenbaum’s claim that damage to the HPC results in an inability to create relational representations.

The Role of Theta Activity in HPC Memory Functioning

The theta rhythm. While the precise role of the HPC is unclear, most researchers agree that the HPC is involved in memory formation and processing and, therefore, much effort has been directed at understanding the neurophysiology of these cognitive processes. Of particular interest to memory research is the theta rhythm. This is a particular wave pattern of neuronal activity whose presence has been detected in the HPC as well as an increasing number of other cortical areas involved in memory. Much effort has been directed at characterizing both the physiology behind theta activity in the HPC and several other cortical areas and investigating theta activity’s general relationship to memory and other cognitive processes.

Theta rhythms are characterized by a distinct, slow-wave, rhythmic waveform pattern that is typically visible between 4 - 8 Hz in humans (Jensen & Tesche, 2002). Theta rhythms are detected and recorded through electroencephalography (EEG) which provides a continuous recording of brain activity in the areas of interest. Different behavioral states produce different

patterns of EEG recordings and, consequently, through the use of EEG, it is possible to record the presence or absence of theta activity while an individual performs a particular task (Gazzaniga et al., 1998).

The integrity of the pathways between the medial septal area (MSA) and the HPC has been shown to be important for the presence of theta activity in the HPC (Bland, 1986), with the MSA serving as the “pacemaker of the theta rhythm” (Brazhnik, 1999). Disruption of the MSA - HPC pathway leads to an overall decrease in theta activity and stimulation of the MSA results in increased theta activity in the HPC, further demonstrating the direct relationship between the MSA and the HPC (Brazhnik, 1999; Vinogradova, 1995).

Several brain areas have been identified as possible loci of theta activity generation. Bland (1976) identified two generators of HPC theta activity, in the basal part of CA1 and the stratum moleculare of the fascia dentata of rats. CA1 pyramidal cells and dentate granule cells were found to be rhythmically coupled with theta activity, meaning that their firing patterns were linked. These theta rhythms may be modulated by brainstem areas including the nucleus pontis oralis, which travels from the pontine reticular formation through the midbrain, eventually exerting influence on the HPC formation via the medial septum-diagonal band complex (Vertes, 1982).

Role of theta in cognitive functioning. Theta rhythm activity has been linked to motor as well as memory functioning and has been regarded as a “correlate” of arousal, orientation, exploration and attention (Vinogradova, 1995). Oddie and Bland (1998) detected the presence of two types of theta rhythms in rats which are present during different motor activities. Type 1 theta has been linked to voluntary motor activity while type 2 theta is present during automatic behaviors. Type 2 theta rhythms are believed to be important for involuntary motor decision making and their presence has been detected in rats preparing to jump to avoid a foot shock (Oddie & Bland, 1998). Beyond motor functioning, theta activity has also been noted during

visual, auditory, and tactile stimulation, as well as memory storage and retrieval, further demonstrating the extent to which theta activity is involved in cognitive processes. Research by Givens (1996) has specifically demonstrated that theta activity increases during certain memory tasks.

Theta Reset

While it is clear that theta plays an important role in cognitive and motor functioning, its precise role in memory remains unclear. The connection between theta and memory may lie in a phenomenon called theta reset, which has been closely linked to working memory. Research has demonstrated that the presentation of sensory stimuli during a working memory task causes a resetting of MSA - HPC rhythmic activity, resulting in a phase-locking to the onset of the sensory stimulus. This occurrence, termed “theta reset,” (Givens, 1996) is an actual interruption of the ongoing theta rhythm. Cells that are firing in this rhythmic pattern cease their ongoing firing pattern and reset their firing to the presentation of certain relevant stimuli. Recent research has investigated the role of theta reset in a variety of brain areas during working memory.

Working memory. Givens (1996) investigated the theta rhythm reset phenomenon by analyzing neural activity in rats performing a working memory task. Rats were trained to perform a continuous conditional discrimination (CCD) working memory task in which a stimulus was presented at the beginning of each trial and, after a brief delay, a second stimulus was presented. If the second stimulus was the same as the first, the rat was required to press the “match” lever. If the second stimulus was different, the rat was required to press the “non-match” lever. Theta rhythm reset occurred in the HPC of rats performing the working memory task. Givens suggests that for accurate hippocampal processing of working memory stimuli to occur, theta reset may be advantageous. Williams, Johnson, and Givens (in preparation) have recently demonstrated that an increase in theta reset in certain cortical areas is positively

correlated with accuracy on a working memory task. Theta reset is believed to be advantageous for working memory processing because of its tie to the strengthening of synapses during long term potentiation (LTP), (Bliss, 1993).

Long term potentiation. LTP induction leads to a stronger postsynaptic response. During normal transmission, glutamate enters the synaptic cleft from the presynaptic dendrite and binds to the receptors on the NMDA and AMPA gates of the post-synaptic cleft. This binding opens the AMPA gate and sodium and magnesium cations enter the postsynaptic dendrite, resulting in a single pulse. The NMDA gate, however, remains blocked by magnesium. Trains of stimuli then occur and an influx of cations into the postsynaptic dendrite through the open AMPA gate cause a depolarization that leads to the expulsion of the magnesium block on the NMDA gate. Now cations can freely flow through both NMDA and AMPA gates resulting in a stronger postsynaptic response when information arrives (Bliss & Richter-Levin, 1993).

Function of theta reset. While the exact function of theta reset is still under investigation, there are several theories as to its purpose. A consistent relationship between LTP and theta activity has been observed. The optimal level of LTP induction occurs when there is a gap between stimuli of about 200 ms which corresponds to the frequency of naturally occurring theta rhythms (Greenstein et al., 1988). It is believed that resetting of theta rhythms provides a way in which stimuli may become time-locked to waves of depolarization in the HPC so that sensory representation can be stored more sufficiently for later retrieval. Theta reset, therefore, may be responsible for an increased intensification of sensory processing after the presentation of a stimulus (Givens, 1996). Since priming stimuli activate postsynaptic depolarization during LTP, a reset of theta activity to these stimuli improves the chance that these stimuli will be adequately stored (Greenstein et al., 1988). Simply put, being time-locked to depolarization causes input of stimuli to occur at a critical point of LTP induction, resulting in a strengthening of memory

storage for stimuli. Specifically, since LTP causes a stronger postsynaptic response, having a stimulus tied to that event, through theta reset, is advantageous for storage of that memory.

Theta reset may simply be a mechanism by which an individual can successfully process relevant stimuli (Williams & Givens, 2003).

Theta reset in other cortical areas. While the influence of theta reset in the HPC has been consistently documented, recent research has turned to other brain areas that may also exhibit theta rhythms. If theta reset is a mechanism for enhanced memory processing, then it should be evident in other brain regions, such as the anterior cingulate (AC), that are involved in memory. Early research has alluded to the possible presence of a theta generator in the cingulate cortex because of the presence of rhythmic properties that resembled hippocampal theta cells (Bland et al., 1986). In addition, Vinogradova (1995) observed low level expression of rhythmic theta-modulation in the anterior limbic cingulate cortex, the posterior limbic and retrosplenial cortex, and the medial entorhinal cortex. Theta-modulation of neuronal activity is present in the anterior and posterior cingulate cortices as well as the entorhinal cortex. Also, previous MEG and EEG studies have localized frontal theta activity to the anterior cingulate cortex (Jensen and Tesche, 2002). Finally, Fuster (1984) observed that recording of single-cells demonstrated that prefrontal neurons were involved in short-term memory.

Bland (1986) has also extended theta research beyond the HPC proper, investigating the roles of the cingulate and entorhinal cortices in the maintenance of HPC theta activity. Removal of the cingulate cortex was found to be partially effective in reducing HPC theta activity. Montoya and Sainsbury (as cited in Bland, 1986), in studying guinea pigs, discovered that entorhinal cortex lesions were effective in reducing the occurrences of type 2 theta in the HPC. In summary, there exists significant evidence that theta rhythm activity exists in other cortical areas and that these areas are linked to hippocampal theta (Bland, 1986).

Investigating the presence of theta activity beyond the HPC, Jensen and Tesche (2002) focused on frontal theta activity in humans during a working memory task. Participants performed a working memory task while theta activity of the frontal brain areas was recorded. The goal of the study was to determine whether frontal theta activity is dependent on memory load. Each participant was presented with a list of digits and, following a delay, asked to determine if a second digit was among the first set. The power of theta activity was found to be significantly stronger during the memory task than the control task. Theta power also increased with memory load indicating that theta rhythms were active during this working memory task. While this study was effective in demonstrating that theta rhythms are present during working memory tasks, it is unclear whether the increases in theta were a result of encoding, retention, or recall.

Recent developments in theta research. It thus appears that frontal theta activity, specifically the anterior cingulate, is clearly related to cognitive processing. The present study builds upon the previous research of Williams et al. (in preparation) in which theta reset in the AC was identified during a working memory task. This prior study focused on three main objectives. These objectives were to 1) determine whether theta reset occurs during the encoding and/or retrieval phases of a working memory task, 2) determine whether theta reset differs between the entorhinal cortex, the hippocampus, and the anterior cingulate, and 3) to determine whether correct task performance is predicted by theta reset. Rats were trained to perform a delayed non-match to position task in which the reward for a correct response was a small amount of water. Rats were presented with a light above either the left or right of three levers. The rats pressed the lever beneath the encoding stimulus for a reward. Following a delay of either five or ten seconds, a light above the center lever was presented. The rats were then to press the lever opposite the lever in the encoding phase for a water reward. The pressing of the

second lever represented the retrieval phase of the task (Williams et al., in preparation).

Recording electrodes were placed into several brain areas of each rat. Electrodes were placed bilaterally into the dentate hilus, unilaterally into the right anterior cingulate region of the medial prefrontal cortex, and unilaterally into the right prefrontal cortex. EEG activity was recorded one second before and after onset of both the sample light and the choice light.

Theta reset occurred in the hippocampus, entorhinal cortex, and anterior cingulate in accordance with the working memory task. Reset, however, occurred during different stages of the memory task for each area. In the entorhinal cortex, theta reset was present during the encoding phase but not the retrieval phase of the task. Theta reset in the hippocampus occurred during both the encoding and retrieval phases of the task. Anterior cingulate theta reset was only observed during the retrieval phase of the working memory task. Theta reset in the entorhinal cortex during the encoding phase was predictive of correct response. This suggests that theta reset in the entorhinal cortex may improve the encoding of the relevant stimuli. Theta reset in the HPC was also correlated with correct response in the choice phase of task. However, for the anterior cingulate, theta reset occurred to choice light stimuli regardless of response accuracy, suggesting that the anterior cingulate may prime the animal for the possibility of a necessary behavioral response (Williams et al., in preparation).

The results of this study answer many current questions in the field. The success of this study is apparent in that it demonstrates that theta reset occurs consistently in areas beyond the HPC and that in each of these areas theta reset is present during different aspects of working memory. It also reveals that theta reset predicts trial success differently for each brain area studied, supporting the hypothesis that theta reset can enhance mnemonic processing.

To date, no studies have examined theta reset in human participants and, therefore, there are many questions to be answered. First, will EEG analyses reveal distinct theta reset in the AC

area of humans? Second, will there be an increase in theta reset associated with encoding stimuli, retrieval stimuli, or motor response to retrieval stimuli? Third, will bilateral recording reveal hemispheric differences in theta reset activity? And, if so, will there be differences in theta activity directly before presentation of stimuli and motor responses as compared to directly after stimuli and motor responses?

There are also several questions to be answered in regards to Williams's (in preparation) previous work. Theta activity of the right AC was recorded to see if right hemispheric recording of humans mirrored previous results. Also, since bilateral recording of the anterior cingulate was not possible in the previous study because of simultaneous recording of several brain areas, it was advantageous to compare theta activity of the left and right AC areas in the present study. It is presently unknown whether theta reset detected in the right AC accurately reflects the theta activity of both hemispheres. It is possible that no theta reset will be detected in the left AC, suggesting that only the right AC is involved in theta reset. A second possibility is that theta reset will be detected in the same phases of the working memory task for both the left and right AC. If theta reset is detected during the retrieval phase in the right AC, theta reset may also be detected during the retrieval phase in the left AC. A third possibility is that theta reset is detected in different phases of the working memory task for the left and right AC, suggesting that the left and right AC work somewhat independently during working memory processing.

The current study involves the recording of frontal lobe activity while performing a working memory task. Human participants performed a computer-based task that consisted of an encoding phase and a retrieval phase as well as a motor response to the retrieval phase. Continuous EEG data was collected and the resulting EEG data and responses were analyzed to determine if and when theta reset was occurring.

Method

Participants

Thirty-one male (N=17) and female (N=14) student volunteers from the General Psychology (Psychology 100) courses at Illinois Wesleyan University in Bloomington, Illinois served as participants in the study. These students consented to participate in the study by signing up for a testing date and time. American Psychological Association ethical guidelines were followed and students were aware that their participation in the study was of their own free will and that they could discontinue participation at any time. Volunteers received two hours of research credit in their General Psychology course through their participation.

Procedure

Testing was performed in a psychology research laboratory in the Center for Natural Science at Illinois Wesleyan University (Bloomington, IL) and lasted approximately one hour and twenty minutes. To begin, each participant was fully informed of the study's objectives and experimental procedures. Each participant was again made aware that he or she could discontinue participation if he or she so desired. Testing of the participants was conducted by myself and five trained research assistants who were skilled in participant preparation and data collection.

Preparation of the participant. Participants were seated in a low-back armchair positioned in front of a computer monitor in the corner of the testing room. EEG and motor response recording wires passed through the wall into an adjacent room where the data was collected by computer.

Preparation for EEG recording followed the specific instructions provided by Electro-Cap International, Inc. (Eaton, OH). Measurement of the head was performed using a special Color-Coded Head Measuring Tape. The circumference of the head at the points one inch above the nasion (bridge of the nose) and one inch above the inion (the bony protrusion at the base of the

skull) was recorded. Based on this measurement, a medium- or large-sized electro-cap was used.

Next, a measurement was taken to ensure correct placement of the cap electrodes. Using a measuring tape, the distance from the nasion to the inion, across the top of the head, was taken. This measurement, recorded in centimeters, was divided by ten. The resulting distance was measured using calipers. Using the calipers, the distance was then measured up from the nasion and three horizontal dashes were placed on the participant's forehead at this distance using a washable marking pen.

Two adhesive sponges were applied to the two forward-most electrodes on the cap. The participant was then asked to tilt his or her head back so that these electrodes could be lined up with the reference marks on his or her forehead. The experimenter fixed the adhesive sponges to the scalp and slid the cap over the head. Before securing the cap, a clip-style grounding electrode was placed on the left ear lobe of the participant. A blunted needle attached to a syringe was then inserted into the disk cavity of the electrode. A small amount of Electro-Gel was then injected into the cavity to insure conductivity. A velcro strap was fastened under the participant's chin so that the cap was snug but not uncomfortable. A pad was placed between the participant's skin and the strap to add comfort. The experimenter made sure that the participant was comfortable before he or she continued.

Participants were randomly assigned to one of two groups. EEG data of group one participants was recorded from one electrode on the midline of the frontal lobe (FZ) and one electrode on the left hemisphere of the frontal lobe (F3). EEG data of group two participants was recorded from the same electrode (FZ) on the midline of the frontal lobe as group one and one electrode on the right hemisphere of the frontal lobe (F4). These specific electrodes are located above the prefrontal cortex and were chosen because they provide the best possible recording of medial and bilateral anterior cingulate activity (Yordanova & Kolev, 1998). Since the

available equipment only allowed recording from two electrodes at a time, it was decided that each participant would receive recording from the FZ electrode since it has been reported to be the best AC recording site.

Based upon the group to which the participant was assigned, the appropriate electrodes were prepared for recording. The midline electrode was moved back and forth against the scalp to get it as close to the scalp as possible. Holding the syringe in one hand and the electrode in the other, the blunt needle was placed into the electrode cavity. The syringe was gently moved back and forth against the scalp to move as much hair away from the electrode as possible. The needle was then lifted slightly off the scalp and a small amount of Electro-Gel was injected into the electrode cavity. The needle was then pressed back against the scalp and the needle was gently rocked back and forth to make sure that the electrode was properly abraded. Electro-Gel was again injected into the electrode so that the cavity was completely full. This procedure was then repeated with the left or right electrode (see Figure 1).

Once both electrodes were properly abraded, the working memory task was explained in full to the participant. They were told the number of trials in the task and approximate length of time that the task would take. The experimenter then handed the participant the response box that he or she would use to make choices in the working memory task. The participant was allowed to hold the box however he or she liked. The experimenter asked the participant if he or she had any questions and answered any that were asked. The experimenter then went into the next room to begin EEG recording. If the signals were poor, inconsistent, or if there was excessive noise on the recording lines, recording was stopped and the electrodes were reabraded. If good signals were present, the experimenter returned to the participant and started the working memory task.

The working memory task. The computer-based working memory task administered in this

study was created using the program “SuperLab” (Cedrus Corporation, Phoenix, AZ). Each trial consisted of an encoding phase and a retrieval phase. The encoding phase consisted of the presentation, via computer monitor, of one square (positioned in the center of the screen) containing a random arrangement of approximately 23 one centimeter black dots arranged in rows and columns. The encoding stimulus was present on the computer screen for four seconds. Following the presentation of the encoding stimulus, the program presented a blank screen for eight seconds. After this delay period, the retrieval phase, consisting of one more dot arrangement box, was presented for five seconds. This second box was either exactly the same as the previous box or differed by the addition or subtraction of one or more dots. Examples are shown below (see Figure 2).

Responses were made by pressing the appropriate button on the response box. If the participant believed the second stimulus to be the same as the first, he or she pressed the “match” button. If the participant believed the second stimulus to be different from the first, he or she pressed the “non-match” button. Participants had five seconds from the onset of the retrieval phase stimulus to make a choice on the response box. After five seconds, the screen went blank and the program went on to the next trial. At this point a response on the response box could not be recorded. At the beginning of each trial, before the presentation of the encoding stimulus, the words “Next Trial” appeared on the screen so that participants always knew which phase of the trial they were in. Participants performed one hundred trials which took approximately fifty minutes.

Data collection. EEG data was collected through a Biopac Systems interface. Continuous EEG data was collected on two analog channels, one for midline recording and one for left or right recording. The resulting waveform outputs could be analyzed separately. In addition to the two analog channels, three digital channels were also used to record the times at which stimuli

were presented and motor responses were made. Every time that a stimulus was presented or a motor response was made, a peak was created in the data record to serve as a reference for data analyses (see Figure 3). Based on the location of the peaks, sample intervals of EEG data were taken before and after the onset of stimuli and motor responses.

Analyses. The EEG data was digitally filtered to include only EEG records between 4 and 12 Hz., the frequency of the theta rhythm being investigated in this study. Using the AcqKnowledge 3.73 software from Biopac (Santa Barbara, CA), the EEG records of each participant were broken down into one second intervals. One second intervals of the EEG record were taken before and after 1) encoding stimuli onset, 2) retrieval stimuli onset, and 3) motor responses for all 100 trials. A waveform averaging was then performed on each of these samplings. For example, midline EEG data one second before all one hundred encoding stimuli was averaged. This process was repeated so that a waveform averaging was performed on all one hundred one second interval samples before and after encoding, retrieval, and motor response of both midline and non-midline EEG data. The result was twelve waveform averages for each participant. A Fast Fourier Transformation (FFT) was then performed on each waveform average and from the FFT the maximum power and frequency from the 6 to 10 Hz. range was recorded. The 6-10 Hz. frequency range was chosen because it represents the more cognitive end of the theta range (Bland, 1986). The maximum power and frequency for all twelve averages was recorded for all thirty-one participants.

The percent change in maximum power from one second before to one second after both encoding and retrieval stimuli was calculated for all participants. Theta reset was defined as a significant increase in theta power in the post-waveform average relative to the pre-waveform average. Waveform averaging produces an average waveform of all included EEG samples. When theta reset is not present, averaging will produce a fairly flat line because peak amplitudes are

canceled out. Consequently, the maximum power of this waveform average will not be very large. When theta reset is present, neurons are firing in a rhythmic pattern. Therefore, an averaging of EEG samples in which theta reset is present, will not result in an canceling out of peak amplitudes because wave peaks are occurring at the same time (see Figure 4).

Consequently, the maximum power of this waveform average will be significantly larger than the maximum power of a waveform average in which theta reset is not present. Therefore, a significant positive change power from pre-stimulus to post-stimulus demonstrates that theta reset to the stimulus is occurring.

Based on their percent accuracy on the working memory task, participants were placed in one of three accuracy groups: high accuracy, medium accuracy, and low accuracy. Williams et al. (in preparation) found that theta reset in different phases of a working memory task can be predictive of task accuracy. Therefore, it was desirable to be able to compare theta reset to performance on the task. The average percent change in power of the participants in each of these groups was calculated. It could then be determined whether an increase in power, demonstrating an increase in theta reset, was correlated with performance on the working memory task.

Within our analyses there were two dependent variables: working memory task accuracy and theta reset. Because of the study design, variables were either between-subject or within-subject variables and this distinction had a direct bearing on the type of analyses that were performed. Between-subject variables were accuracy group (high, medium, or low), sex, and left/right recording. These are considered between-subject variables because for each of these variables participants can only be in one category. Therefore, analyses must be performed between participants in these categories. Within-subject variables are the different phases of the task (encoding, retrieval, and motor response). Each person participates in all three of these

phases of the task so, therefore, analyses can be performed within participants for these variables.

Results

Accuracy

Participants performed at an average of 78.75% accuracy on the working memory task. An analysis of variance (ANOVA) using choice accuracy as a dependent variable revealed no significant main effects or interactions by between-subjects variables gender and hemisphere. Results demonstrated that there was no overall gender effect for accuracy. Mean accuracy was 75.2% correct for males and 78.8% correct for females, $F(1, 27) = 1.40, p > .05$. In addition, no differences in performance level as a function of hemisphere were found, $F(1, 27) = 0.20, p > .05$. Participants who received recording of the right prefrontal area had a mean accuracy of 77.69% correct and those who received recording of the left prefrontal area had a mean accuracy of 75.16% correct. Participants in the high accuracy group had a percent accuracy range of 92.9% to 83.7%. Those in the medium accuracy group had a percent accuracy range of 81.8% to 73.2%. Those in the low accuracy group had a percent accuracy range of 72.4% to 61%.

Midline Recording

Differences in theta reset as a function of accuracy and task phase was investigated. Within this analysis, the dependent variable is the degree of theta reset. The between-subject variable is accuracy group (high, medium, low) and the within-subject variable is the specific phase of the task (encoding, retrieval, motor response). ANOVA demonstrated that there was no overall main effect for accuracy group, $F(2, 28) = 1.19, p > .05$, or task phase, $F(2, 56) = 0.03, p > .05$, on the dependent variable theta reset. However, an interaction between performance level and task phase revealed a trend towards significance, $F(2, 56) = 2.13, p = .09$. This trend is most

likely due to differences in theta reset between the high and low performance groups. T-tests revealed significant differences in theta reset between the high and low performance groups during both encoding and retrieval phases. More specifically, high accuracy group individuals had a significantly greater amount of theta reset during encoding than low accuracy group individuals, $t(8) = 3.12, p < .05$, (see Figure 5). In contrast, individuals in the high accuracy group had a near significantly *lower* degree of theta reset than individuals in the low accuracy group during retrieval, $t(8) = -2.21, p > .05$, (see Figure 6).

Lastly, there was no gender difference for these comparisons. Midline theta reset did not vary by gender, $F(1, 29) = 0.70, p > .05$, as males and females exhibited a similar degree of theta reset in prefrontal recording.

Left/Right Recording

While a small sample size prohibits inferring too much from hemisphere differences at the present time, it remains advantageous to report interesting trends. ANOVA reported that there was no main effect for gender on left/right theta reset, $F(1, 19) = 0.00, p > .05$. Males and females exhibited a similar degree of theta reset for left and right prefrontal recording.

Again, the differences in theta reset as a function of accuracy and task phase was investigated for left and right recording. ANOVA demonstrated that there was no overall main effect for performance level, task phase, or hemisphere on the dependent variable theta reset. There was no significant effect for performance level on left/right theta reset $F(2, 19) = 1.19, p > .05$. Also, there was no significant effect for task phase on left/right theta reset, $F(2, 38) = 1.36, p > .05$. Finally, there was no significant effect for left versus right recording on left versus right theta reset, $F(1, 19) = 0.22, p > .05$.

While there was no significant main effect in non-midline theta reset, an interesting trend was present. Combined left and right participants had a near significantly greater theta reset

during the retrieval phase compared to the encoding phase (see Figure 7).

Discussion

Gender

Most previous studies have involved male rats and, therefore, little research has examined a gender difference in theta reset. Because theta reset was hypothesized as a general, universal mechanism for mnemonic processing, it was predicted that males and females would show similar degrees of theta reset if their task performance was equal. Although studies report some gender differences in cognitive performance, such as gender differences in linguistic (Shaywitz et al., 1995) and spatial (Gazzaniga, 1998) task performance, no gender differences were expected in this study on our visually-oriented working memory task. The present study supports this hypothesis as there was no significant difference in task performance by gender. Given the equal task performance across gender, it was predicted that there would be no gender differences in degree of theta reset. The present study supported this hypothesis as no significant gender difference in theta reset was observed.

Midline Theta Reset

While there was no significant main effect on midline theta reset by performance level and task phase, some interesting relationships did exist within this analysis. First, participants who had the highest performance accuracy on the task exhibited significantly greater theta reset during the encoding phase than participants who had the lowest performance accuracy. An increase in theta reset during the encoding phase of the trial may have improved encoding of the stimulus and, subsequently, may have led to higher accuracy on the task, perhaps through an LTP-like mechanism (Greenstein et al., 1988). However, this is in opposition to the findings of Williams et. al (in preparation) in which increased theta reset of the anterior cingulate (AC) occurred during

the retrieval phase of the task, but not during the encoding phase.

There are several possible explanations as to why this difference exists. First, recording of the AC differed in the two studies. In the Williams et al. study, electrodes were placed directly in the midline AC of rats. In the current study, recording occurred more laterally and it is possible that different areas of the AC were recorded. The functional role of cortical areas is often not uniform, suggesting that this may be true of the AC (Baudena et al., 1995). Evidence exists that the AC may have different roles in both encoding and retrieval across the anterior-posterior axis. If different areas of the AC were recorded, this might explain why theta reset was present in both the encoding and retrieval phases of working memory in the current study but only the retrieval phase in the previous study. It is also possible that differences in the working memory task might explain differences in theta reset. In the previous study, rats performed a more spatially oriented task requiring the rat to make a motor response based on the location of stimuli. The current study only involved visual discrimination of two stimuli; spatial location was not a factor. It is possible that this slight difference could have caused the difference in theta reset. Lastly, it is also possible that this difference is a result of species differences. The AC of humans may simply function in memory differently than the AC of rats. However, this is unlikely, as cognitive deficits as a result of prefrontal cortex lesioning have been consistent across species (Birrell & Brown, 2000).

Like theta reset during the encoding phase, theta reset during the retrieval phase of the working memory task was also predictive of task accuracy. However, during this phase of the task, participants who had the lowest performance accuracy had greater theta reset than high accuracy participants. There exists a possible explanation as to why, in this study, increased theta reset in the retrieval phase was correlated with low accuracy on the working memory task. If participants are intensely focused on the retrieval stimulus, an increase in theta reset to that

stimulus is likely to occur. It is possible that participants focused a great amount of attention on the retrieval stimulus but not on the encoding stimulus which is more important for choice accuracy. If they did not pay an adequate amount of attention to the encoding stimulus, they would be less likely to be able to recall it and, consequently, make more incorrect responses. Therefore, higher theta reset to the retrieval stimulus for participants who performed poorly on choice accuracy may mean inadequate attention to the more relevant encoding stimulus.

This trend is contrary to the results of the Williams et al. (in preparation) study in which theta reset of the AC during the retrieval phase was not predictive of correct response on the task. In that particular study, theta reset in the AC occurred during both correct and incorrect response trials. One explanation for the difference in the predictive quality of theta reset between these two studies may be the different data analysis techniques that were used. In the previous study, the relationship between theta reset and task accuracy was determined slightly differently than in the current study. In the previous study, theta reset was compared to rats' accuracy on individual trials, not their average accuracy of all the trials. In the current study, theta reset was compared to the overall accuracy level of participants. This may explain why in the current study theta reset was predictive of task accuracy and in the previous study it was not. Another possible explanation, again, is the possible functional differences between the AC of humans and the AC of rats. However, there is no empirical data to support this claim.

Left/Right Theta Reset

No hemispheric differences were found for AC theta reset. Prior research by Williams et al. (in preparation) was only able to record EEG from the right AC so the theta functioning of the left AC remained inconclusive. Due to the small sample size in this study these results are only speculative. Additional participants may or may not reveal hemispheric differences in theta activity.

While there was no overall effect in non-midline theta reset by accuracy level and task phase, there existed a trend of greater theta reset in the retrieval phase of the task. In the previous study by Williams et al. (in preparation), it was reported that theta reset of the AC was only present during the retrieval phase of the task. While in this study midline theta reset of the AC was present in both encoding and retrieval phases of the task, the trend that a greater amount of non-midline theta reset occurred in the retrieval phase supports the previous finding that AC theta reset is more likely to occur during retrieval. The recording site in the previous study was in the right AC which is more similar to the present non-midline recording. It is possible that the non-significance of this trend is a result of a small sample size. While the previous study analyzed eighty data sets, the current study was only able to include thirty one. It is possible that an increase in sample size would reveal an overall significant effect in non-midline theta reset by accuracy level and task phase. However, it is also possible that there truly is no effect in this comparison and an increase in sample size would reveal that no difference in theta reset by task phase exists.

Summary

This study builds upon the previous work in the area of theta reset. It both supports aspects of previous studies and brings to light new possibilities. While results did not fully support the findings of the previous study, they were consistent with several current trends in the field. Theta reset has been found to be present in both encoding and retrieval phases of working memory tasks. The results of this study demonstrate that, in humans, AC theta reset may be involved in both encoding and retrieval of stimuli, as it was correlated with task performance in both phases. While no significant main effects were revealed, two interesting trends were revealed. Greater theta reset during the encoding phase was correlated with higher task accuracy, while greater theta reset during the retrieval phase was correlated with lower task

accuracy. Though inconsistent with the results of the previous study in which AC theta reset was not predictive of task accuracy, these trends demonstrate that theta reset in the AC of humans may function as a mechanism for improved encoding and retrieval of stimuli. A near significant trend, revealed in analysis of non-midline EEG, further supports the findings of the previous study in that the greatest degree of theta reset was found in the retrieval phase of the task. Minimal theta reset research has been performed on humans, especially in the prefrontal area. Results of this study demonstrate the presence of theta reset in the AC but subsequent research must be performed to further understand its specific role. A true understanding of AC theta reset may supplement the ever growing knowledge base of memory formation and processing.

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Figure Captions

Figure 1: Participant hooked up to EEG recording equipment and ready to perform the working memory task.

Figure 2: Example of a “non-match” trial. Participants viewed the encoding stimulus for four seconds and after an eight second delay viewed the retrieval stimulus.

Figure 3: An example of the EEG data record showing waveforms from the midline electrode and the left hemisphere electrode as well as retrieval and motor response signal tags

Figure 4: A visual representation of theta reset to the onset of a stimulus. Before the stimulus, when theta reset was not present, amplitudes of peaks averaged out. After the stimulus, when theta reset is present, amplitudes of peaks do not average out.

Figure 5: Greater midline theta reset in high accuracy participants during encoding

Figure 6: Greater midline theta reset in low accuracy participants during retrieval

Figure 7: Mean theta reset during encoding, retrieval, and motor response of combined left and right participants

Figure 1

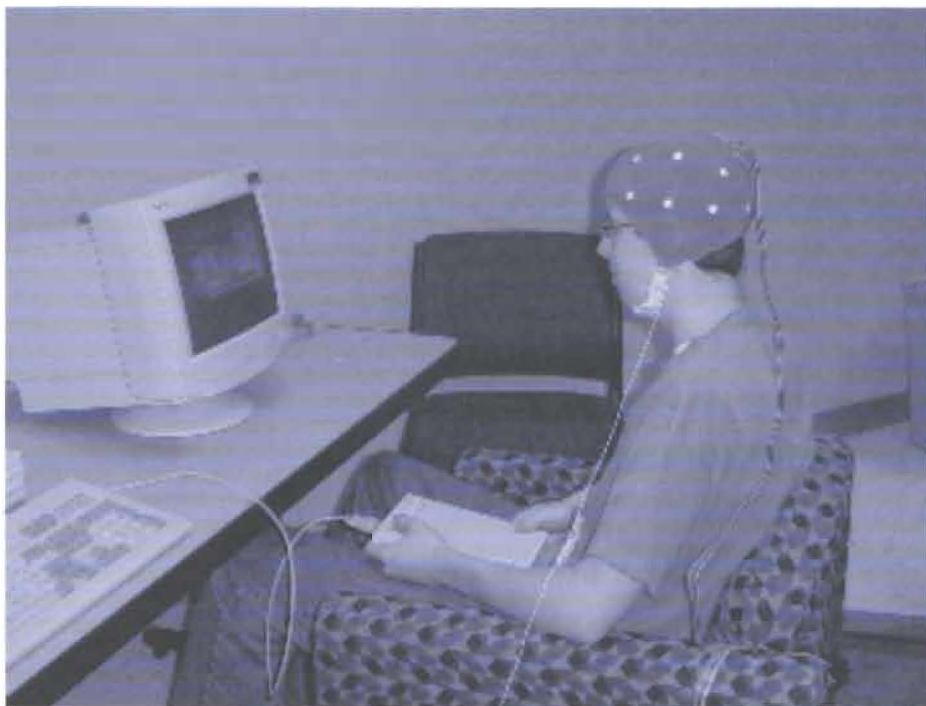


Figure 2

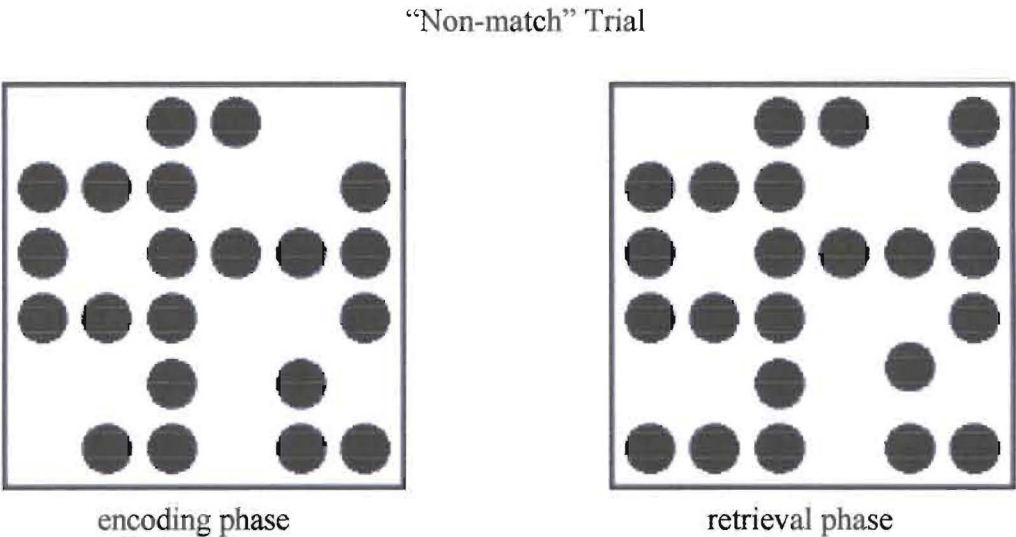


Figure 3

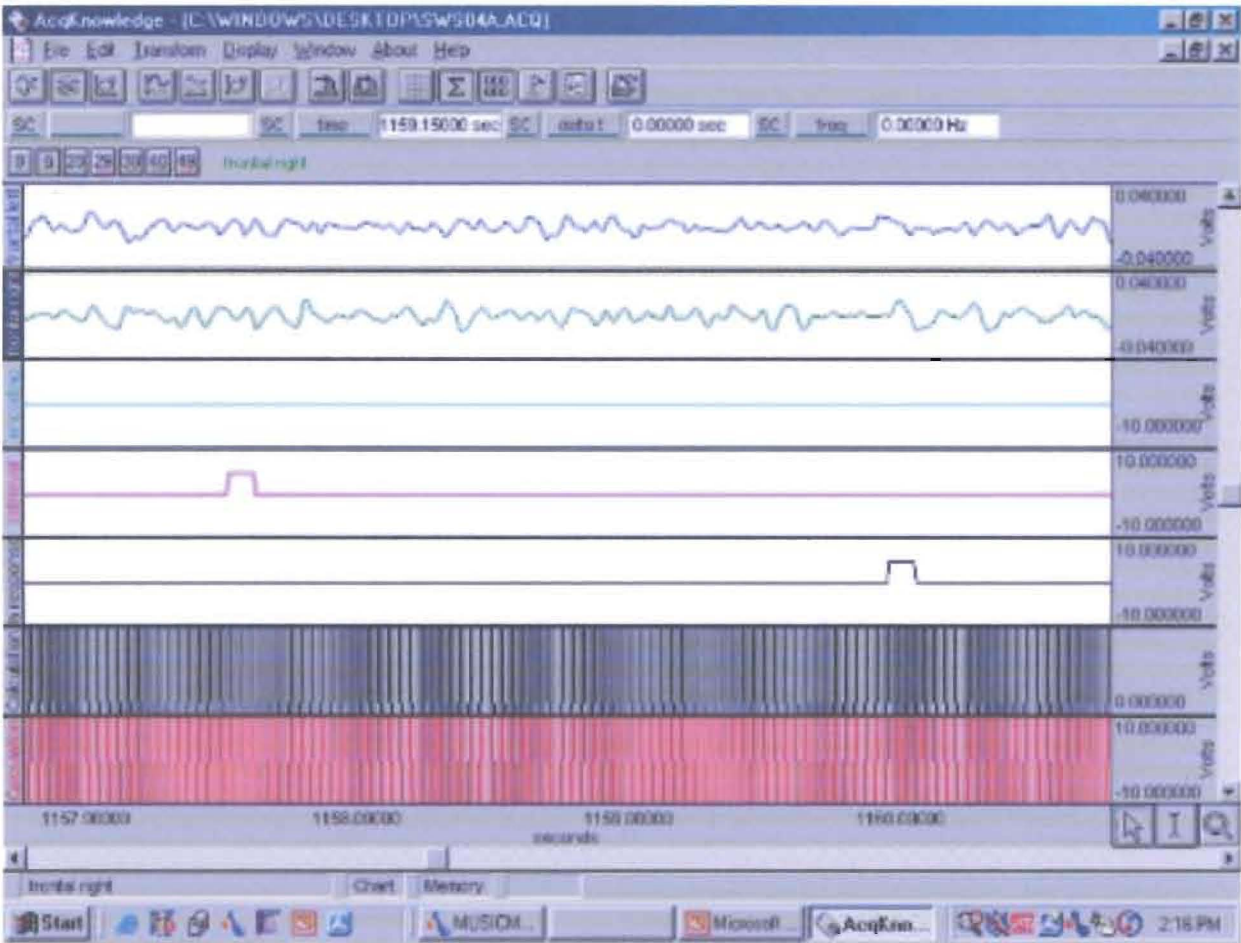


Figure 4

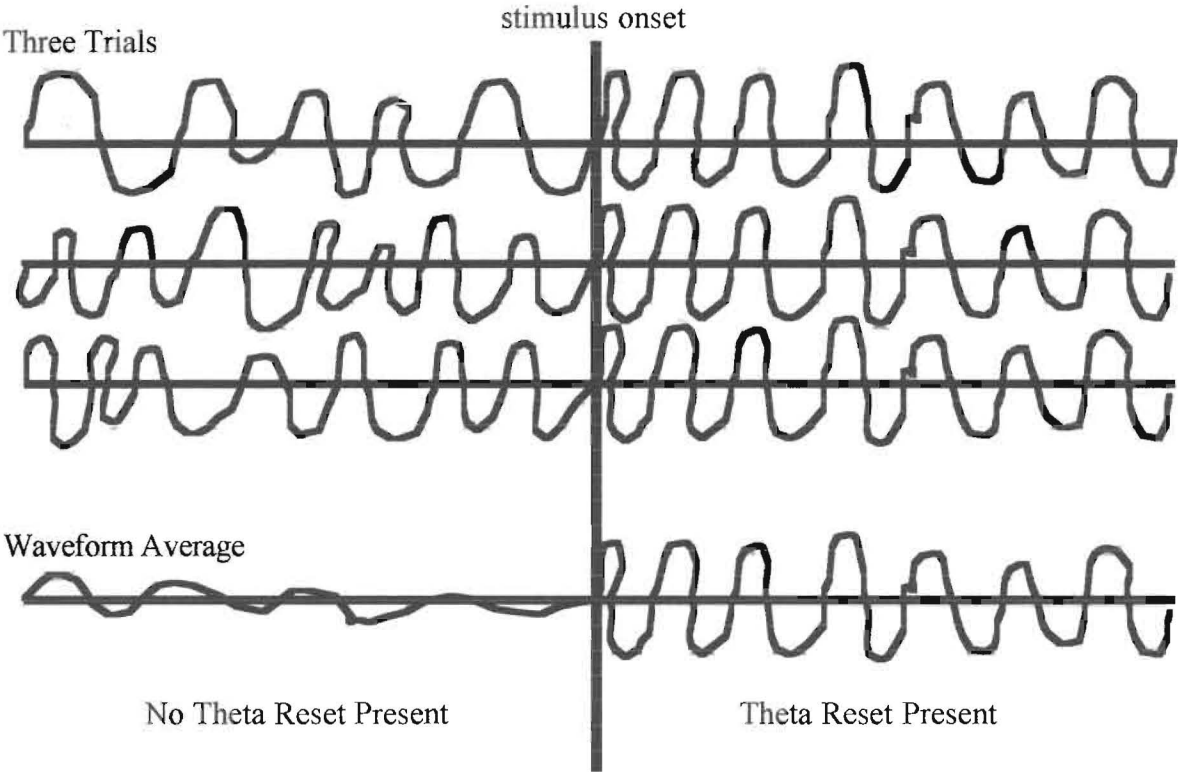


Figure 5

Greater Midline Theta Reset in High Accuracy Participants During Encoding

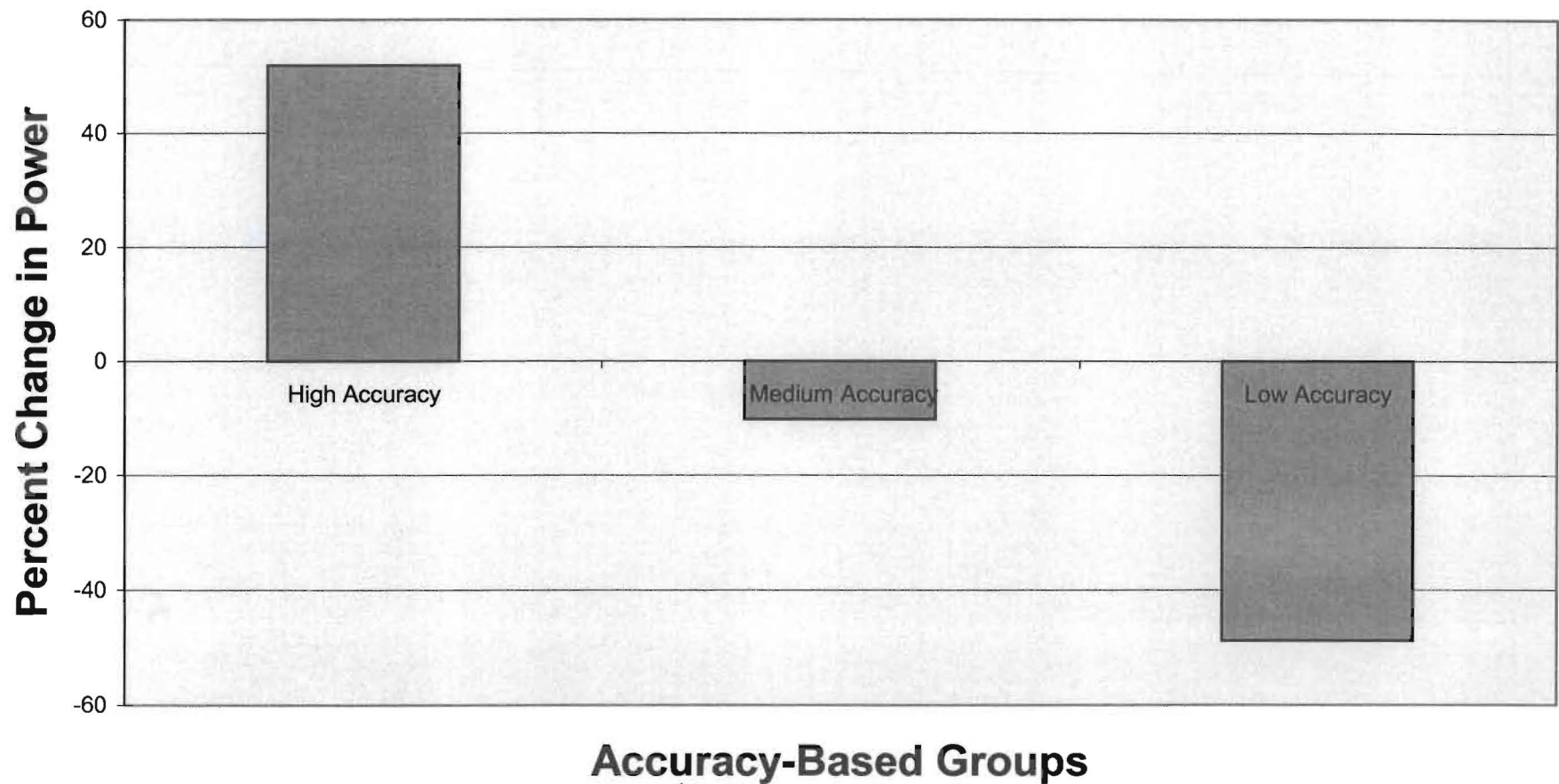


Figure 6

Greater Midline Theta Reset in Low Accuracy Participants During Retrieval

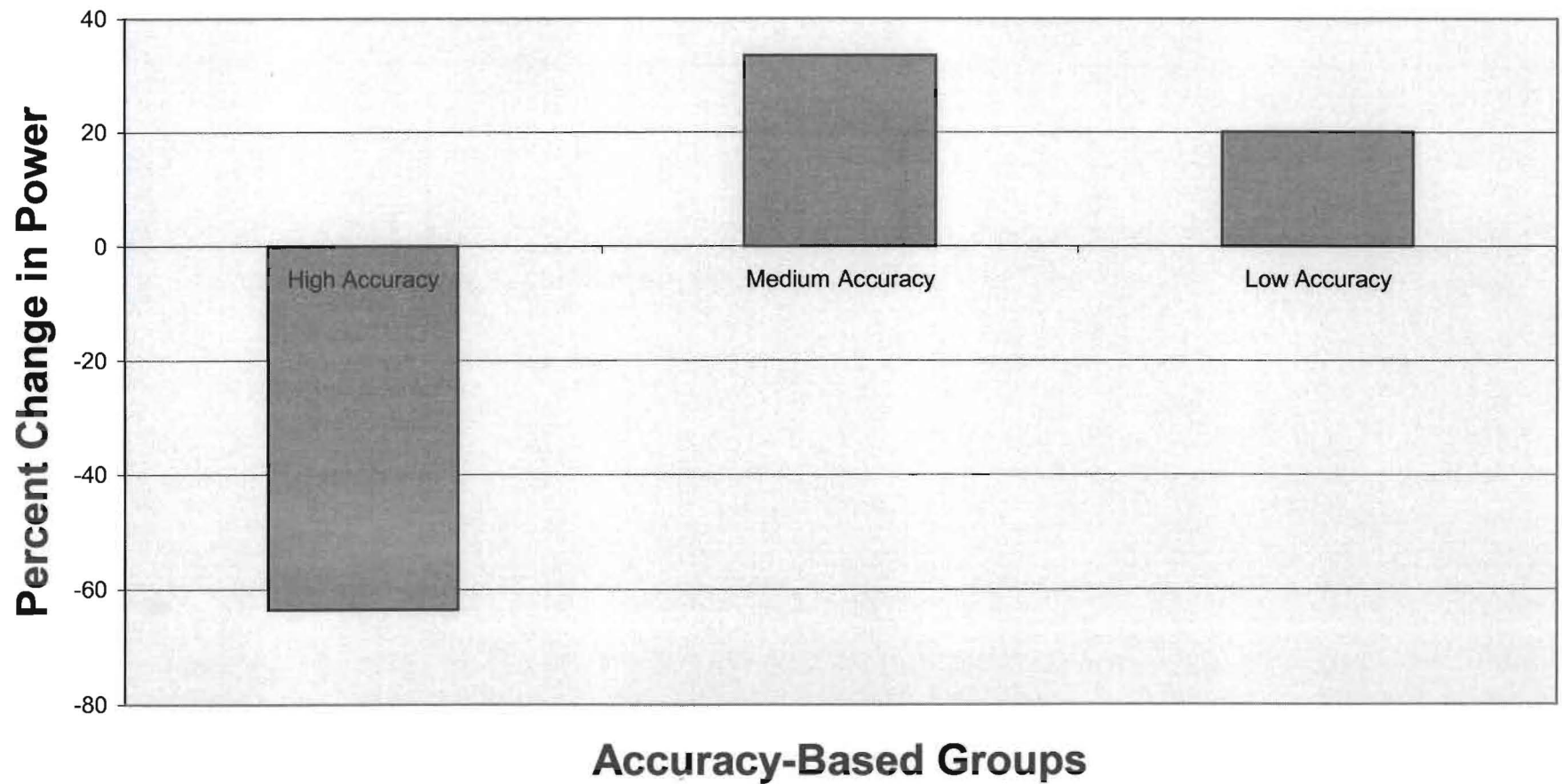


Figure 7

Mean Theta Reset During Encoding, Retrieval, and Motor Response of Combined Left and Right Participants

