INTERNSHIP ARTICLE

Comparing Mathematical and Verbal Semantic Memory in Epileptic Patients Using Invasive Neurophysiologic Brain Mapping

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Abstract

Little is known about how memories are retrieved. Surgical removal of epileptic areas is an increasingly common method of treatment for seizures. However, patients undergoing surgery frequently suffer from post-operative memory defects. Mapping of the memory process is critical in preventing the removal of areas that may have a role in memory processing. Furthermore, an understanding of the relationship between arithmetic and verbal semantic memory processing could elucidate unknown aspects of the process of memory retrieval and potentially help patients to remember. Based on previous research, we hypothesize a wider distribution of activated cortical areas during verbal processing and a shorter retrieval period during arithmetic processing due to its factual nature. Twelve epilepsy patients were asked to answer basic arithmetic (e.g., "Seven times nine equals?") and verbal questions (e.g.,"Who is your favorite singer?") to map their arithmetic and verbal semantic memory areas. While answering these questions, the electrocorticographic (ECoG) brain activity was recorded focusing on gamma band power (70-100 Hz) because previous studies have shown that the gamma oscillations are effective at recording memory[1]. To locate active cortical areas, gamma band dynamics were compared to the latency of their answers (voice-onset time). Our hypothesis was confirmed that semantic memory activity was widely distributed over the frontal and temporal lobes, whereas brain activity during the arithmetic task was concentrated over the frontal lobe. Furthermore, the medial temporal lobe was active during both the verbal and arithmetic tasks while answering verbal and arithmetic questions did not activate the parietal episodic memory areas. Knowledge of the spatial distribution and temporal dynamics of neurophysiologic events during memory retrieval may allow a deeper understanding of this complicated and enigmatic human cognitive process.

Introduction

Epilepsy is a neurological disorder characterized by recurring and aberrant brain signaling commonly recognized as seizures. Although the specific causes of seizures are unknown, cerebral injuries, infections such as encephalitis and brain tumors are frequently associated with abnormal increases in brain activity that may trigger activations in nearby neurons. In addition, previous studies have shown that epilepsy rates are higher in children and the elderly[2]. By the age of 11, approximately 6.7% of the population will have experienced a seizure or related period of unconsciousness[3]. The recurring seizures that characterize epilepsy are classified by the regions of the brain they affect. Generalized seizures are described by the activation of almost all areas of the brain. They exhibit a variety of symptoms, such as a short period of unconsciousness that is characteristic of an absence seizure or a series of convulsions followed by unconsciousness in the classic grand-mal seizure[4]. Another category of epileptic seizures is localized on a particular area of the brain known as the epileptic focus. Focal seizures are further characterized into simple seizures, ones that result in brief motor impairment, and complex seizures, ones that result in involuntary activity. These complex focal seizures are most commonly exhibited in the temporal lobe, with occasional occurrences in the frontal and occipital lobes[5].

Treatment for focal seizures varies, depending on the condition of the patient. Most patients are first given antiepileptic drugs (AEDS), such as eslicarbazepine acetate, gabapentin, and oxcarbazepine[6] to correct brain signaling prior to surgical procedures. However, not only do a percentage of epileptic patients fail to respond to medication, but some AEDS may also be responsible for cognitive defects[7]. These patients must look for other methods, such as surgery. There are many types of epileptic surgery, one of the most common being temporal lobe resection, or the partial removal of the anterior and mesial temporal lobes. While temporal lobe resection theoretically reduces focal seizures in a long-term effort to make patients seizure-free, it has its disadvantages including the potential migration of epileptic foci over time in younger patients[8], a 20-60% seizure reoccurrence[9], and post-operative psychological, behavioral, and cognitive defects, especially those associated with memory processing.

Seminal research on post-operative memory-related impairments was produced after a 1953 medial temporal lobe resection on patient H.M. to treat intractable epilepsy. Patient H.M. exhibited normal short-term memory but severe Anterograde amnesia corresponding to long-term memory tasks. The damage done to both his ability to recount facts (semantic memory) and ability to recount his personal experiences (episodic memory) allowed researchers to realize the significance of the medial temporal lobe in memory function. Since his 1953 operation, various tasks administered to H.M., including motor training and maze tracing, have allowed researchers to better categorize memory and the location and timing of memory in the brain[10].

Memory can be categorized into short-term and long-term. Short-term memory is essential for retaining recent

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information so that the frontal lobe of the brain can perform the necessary manipulations for its use or the temporal lobe can initiate short to long-term memory conversion. Also known as working memory, this short-term memory is crucial to an individual's ability to retain immediate information and learn. A typical short-tem memory can hold up to seven items for 10-15 seconds. The information learned can be converted to long-term memory by the hippocampus through repetition and association with previously known facts. Long-term memory is categorized into declarative (explicit) and nondeclarative (implicit) memory. Declarative memory is named as such because it encompasses facts that are consciously retrieved. On the other hand, non-declarative memory describes skills that are unconscious and learned through repetition, such as riding a bicycle or spinning a locker combination. This type of memory is frequently associated with priming, which describes altered memory functions as a result of prior exposure or repetition. Declarative memory can be further divided into semantic and episodic memory. Semantic memory is the ability of the individual to recall facts that are highly impersonal and not linked to a particular time and experience. Thus, a patient suffering from a loss in semantic memory would probably be unable to answer questions such as, "What is the capital of France?" Patients suffering from episodic memory, or a recollection of personal experiences, would probably be unable to answer questions such as, "What did you eat for breakfast?" Semantic memory can be roughly divided into verbal and arithmetic. Verbal semantic questions are presented as sentences (e.x. What is the color of your house?) whereas arithmetic questions are presented as computations[11].

Many different task protocols have been designed to test the functionality of various types of memory. Most prominently, these tasks include maze tracing, the Boston naming test, and long-term memory inventory. The Boston naming task requires patients to identify images with words[12], testing their association whereas maze tracing evaluates the effects of repetition in procedural tasks. The typical long-term memory inventory requires patients to memorize a list of words, usually tangible and conceptual nouns. Patients, after a period of time, are required to recall as many words as they can. Later, they are given a list of mixed words and asked to identify which ones were originally presented to them. Such long-term memory assessments usually compare the effects of auditory and visual stimuli.

The current memory pathway is largely modeled after the work of Atkinson and Shriffon, who proposed a multi-store model in 1968, which classifies memory as signal, storage, and retrieval. Based on these stages, Atkinson and Shriffon further divided memory into sensory, short-term, and long-term. Sensory memory, lasting 1 to 3 seconds, relayed essential signals to the short-term memory. After rehearsal, a portion of short-term memory is relayed to long-term memory, which can last any time from one minute to a lifetime[13]. After information is solidified in the long-term memory system, it can be retrieved with recall, without the help of external stimuli, or recognition, with the help of external stimuli. Furthermore, today's memory process model, which evaluates a patient's response to a question, follows psychologist McClelland's 1979 cascade theory[14]. McClelland proposed that the patient's retrieval process be divided into a series of steps that are not time-locked. For example, processes could occur simultaneously. His theory developed into the contemporary model for memory retrieval, which consists of a stimulus, activation of the audio cortex, Wernicke's area responsible for language processing, executive function responsible for preparation, the actual memory retrieval, Broca's speech area, the motor cortex, and then the response. The response is commonly measured by voice onset time (VOT) or the time between the end of the question and when the patient first begins speaking.

Because of the expanse of memory functions that are controlled in the brain and the number of epileptic patients who suffer from post-operative memory defects, it is imperative to map the brain for critical areas. To avoid amnesia as a result of temporal lobe resection, it is necessary to achieve a better understanding of how exactly memory is relayed in the brain.

The specific performance of the patients is documented through two popular invasive methods, direct electrical cortical stimulation (ECS), where neurons are directly stimulated with electricity, and electrocorticography (ECoG), where the activity of the brain during different memory tasks is transferred from electrode grids. ECoG presents numerous advantages over ECS such as less possible damage to the patient's brain and a greater span of recordings due to electrode grid placements. ECoG also has more than 4000 times temporal resolution than functional magnetic imaging (fMRI), providing specific time measurements that correspond to the gamma activations. Data from ECoG is typically analyzed through averaging gamma, theta, or alpha activations. The activations for trials are overlapped in event-related band power (ERBP) so that patterns can be observed.

The data from these experiments since H.M's operation have already provided substantial information as to the key areas of the brain associated with memory. The primary location for all memory processes is the temporal lobe, which contains the hippocampus that is used in the transfer of short-term memory to long-term memory. However, the frontal, parietal, and occipital lobes all are involved in memory processing. The frontal lobe is strongly associated with the analysis that is necessary for arithmetic tasks and is also the site of Broca's area, a critical region used for speech formation[15] named after its discoverer, neurosurgeon Paul Broca, who in 1861, studied a patient who could only say one syllable-tan-tan. More importantly, the frontal area is associated with executive function, a top-down preparation process of the brain for answering the question. Previous research has noted activations in the frontal lobe prior to the end of a question. Although initially confused with memory retrieval, researchers have been able to separate this function as a preparation process. However, executive function has not been observed in other areas of the brain. Another key region that is frequently studied in memory research is Wernicke's area, an area used for language processing whose high activation is seen as a peak lasting a short duration but with a large change in magnitude on ERBP. Wernicke's area originated from an 1871 discovery by scientist Carl Wernicke when he studied the nonsensical responses of the patients to speech. Both Broca's and Wernicke's theories, along with an appreciation of more recently discovered concepts like executive function make up today's memory processing models.

Because of what is known about cortical areas and their roles

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in the memory process, semantic verbal memory processing is hypothesized to create higher activations in Wernicke's (temporal-parietal lobe boundary) and Broca's area (frontal-temporal lobe boundary) while arithmetic processing is hypothesized to create higher activations in the frontal lobe. A short preparation process (executive function) is predicted to occur only in patients performing the arithmetic task. However, the relationship between arithmetic and verbal semantic memory processing is still unclear. Electrocorticography (ECoG) will be used to measure the magnitude, latency, and location of brain activations to evaluate the validity of these hypotheses.

Materials and Methods

Memory processing analysis was performed on twelve patients with intractable epilepsy. These patients represented both males and females from ages eight to 48 (average= 25 years) and a variety of educational backgrounds. Electrodes were implanted over the frontal, parietal, and temporal cortex according to each patient's needs to record electrical stimulation through electrocorticography. After implantation, these patients were given an inventory of [memory related tasks that tested both their short term and long term memory functions. These tasks specifically include cued, repeat, questions, noun-verb, and arithmetic sections. The cued section and the repeat section focused on the patient's ability to recognize and repeat, rather than understand the stimulus. The noun-verb, questions, and arithmetic sections documented the effectiveness of the patient's long term memory. A microphone and a pulse channel were recorded to establish the timing of the question and the patient's response. All memory tests were also recorded on video. Data were collected in the form of an inventory packet on which were documented each patient's response to the questions asked and the voice-onset time (VOT), or the time interval between the end of the question and the beginning of the patient's response. Specific data were collected through the activity of the electrodes and analyzed through digital recording using Neuroscan 4.3, an analysis system (Compumedics, Inc., El Paso, Texas). IRB approval was required and written consent was obtained from all patients prior to experimentation. Data on long-term memory was collected through the noun-verb, arithmetic, and questions tasks. The noun-verb task consisted of 40 questions along with a three-question practice for patients to become familiar with the procedure. A set of auditory instructions was given immediately preceding the task. Each of these 40 questions was a common object such as "chair" or "ears." The goal for the responders was to answer with a verb that is normally associated with the noun such as "sit" or "hear." The noun-verb task tested for the understanding of language, particularly the activation of Wernicke's area for language processing, rather than simple repetition. Each question was read by a female voice and preceded by a tone (auditory stimulus) so that each patient was aware of when a question started. Both the electrode activity and the verbal response of each patient were recorded. Patients were also given an arithmetic task that consisted of three trials of ten questions. Each trial was staggered between a verbal long-term memory task as to reduce the effects of repetition and familiarity on the patient's response. The arithmetic task featured elementary computations (e.g. "3 times 5 equals?") featuring addition, subtraction, and multiplication. A set of instructions was given before the arithmetic task. A signal, or tone, was also given one second before the beginning of each question. All questions were read clearly in a female voice. The patients could only respond based on the speaker's question since no visual signals were given. The arithmetic trial was designed initially as a way to reduce the effects of familiarity for patients taking the verbal long-term memory retrieval and recall task. It is currently used to arithmetic semantic memory, or the ability of the patient's to recall basic facts such as "What is twenty times two?" Patients were also given a conversational task that focused primarily on their verbal semantic memory. The questions task is a set of nine questions that ask the patients to recall verbal facts such as "What color is your house?" or "What is the name of your favorite singer?" A set of auditory instructions were given to each patient before the task began. Each question asked was preceded by a tone and read in a female voice. The questions task was designed to test the patient's ability to function normally in a simulated real-life setting. Instead of asking generic "laboratory" questions such as "What is the capital of France?", these questions were similar to what the patients would encounter in their daily conversations. Thus, this task also had the ability of testing to see the practical results of the laboratory's memory tasks. The timing of the voice onset time for each patient was recorded and analyzed. The electrode activities for the patients were transferred to a continuous recording file on Neuroscan 4.3. The microphone channel of the continuous file was labeled so that the activity of the electrodes could be analyzed. The continuous file for each patient's inventory of memory tasks was broken into specific sections that correspond to a certain task. A system of labels was developed to mark the tone, pulse, each question's beginning, end, and the beginning of the response time for the patient. Code numbers corresponded individually to each type of task. The labels for the end of the question and for the beginning of the patient's response were most intensively studied. These numbers would be selected and analyzed even further on EEG, which displays the activation of each electrode on the brain for all trials. The trials that contain square peaks or abnormally high activation indicated the presence of a seizure, and therefore these trials were rejected. In addition, many steps were made to the continuous file to eliminate contaminated data known as "noise." This unnecessary data could be due to the epileptic peaks in the patients or to adjustments of the microphone during surgery. Such data needed to be cleaned before it could be used for analysis. The separation of significant waves and insignificant waves were sometimes difficult to differentiate. Attempts at separation were made through changing the "gain" or magnitude of the graph, creating a band pass, and the elimination of signals at much too high or low frequencies (outliers), and creating filters. After the EEG was created, a complete trial must be eliminated if any of its electrodes displayed abnormal brain signaling. A gamma band- related power (event related band power) was used to average the data for the remaining EEGs. This averaging technique allowed the creation separation of each trial into a line graph that displayed clear activation patterns. A brain model and animation of observed patterns was created using ITKSnap, EEGView, Loc3DJr , and Procrustes. Thirteen critical fiducial points were located in both MRI and CT on ITKSnap to locate the positioning of the brain. Electrodes were added from the Loc3DJr program and combined through a Procrustes code to EEGView, a specialized analysis software. EEGView allowed an easy viewing of brain models and electrode activations. A red-yellow color range was applied to match the intensity of the activation. Slices of

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EEGView were then converted to a movie that can be played to visualize brain activity during one question. To analyze the data, a two sample T-test assuming equal variances was used to compare measurements of separate memory activations in different patients for the two different conditions: the questions and the arithmetic task. Equal variances was assumed because the sample size for each task was similar (13= questions, 12= arithmetic).

Results

Figure 1 shows the electrodes implanted over the frontal, parietal, and temporal cortex. Figures 2 and 3 illustrates psychologist McClelland's 1979 cascade theory, which evaluates a patient's response to a question[14].

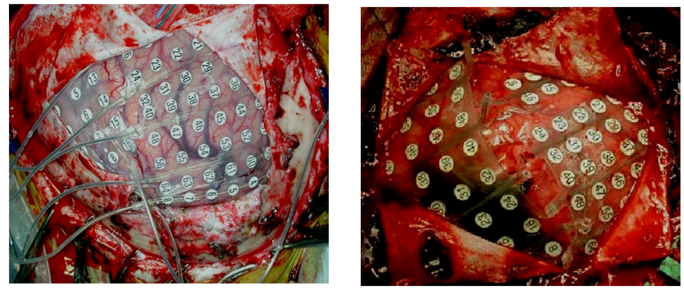

Figure 1. Electrode implantation. Electrode grids on the parietal, frontal, and temporal lobes were implanted on epileptic patients according to their needs (Towle Lab).

Figure 4 shows an elevated or increased change in magnitude of gamma activation was observed for the questions section as opposed to the arithmetic section on parietal electrodes (PG 15, 23, 45, 46, 47), frontal electrodes (IT 1, 2, 20, 50 63, SF 6, 7) and temporal electrodes (LPT 3, 4, 5) (2-sample t-test, $p=0.018$, $t= 2.67$). The magnitude of the activation was calculated using a baseline, correct to compare unlike results. After averaging, the gamma band power at the highest activation was recorded. Patients responding to the conversational task displayed an average gamma power of 7.74 µv2 whereas patients responding to the arithmetic task displayed an average gamma power of 3.96 µv2

Figure 5 demonstrates that activations for verbal semantic memory in the conversational questions task were more widely distributed throughout the cortex compared to the activations for arithmetic semantic memory. This distribution can be shown by the activation of the frontal, parietal, and temporal electrode grids. As can also be shown by the heated object color scale in EEGView, it is apparent that activations for verbal semantic tasks are higher.

Figure 6 shows that executive function is observed for both tasks (1-sample t-test, $p<0.001$, $t= -5.61$). There is some evidence supporting that the executive function in the arithmetic section begins earlier than executive function in the questions section.

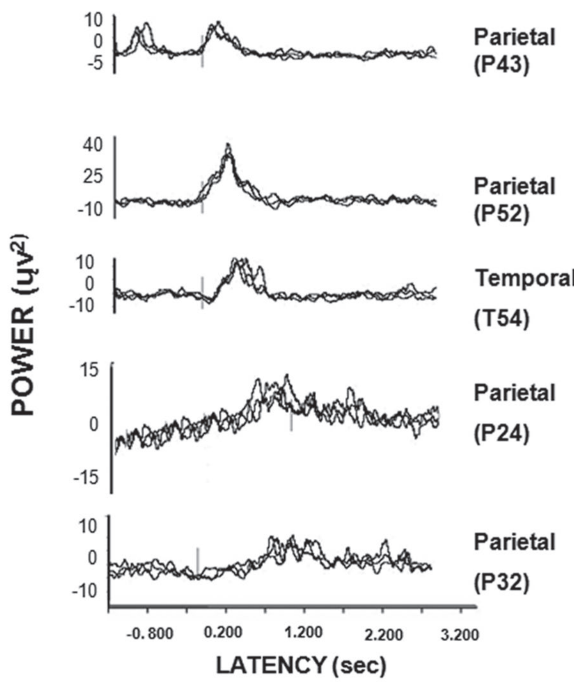

Figure 2. Event related band power. Event related band power at gamma frequencies showing brain activity from the parietal and temporal lobes. The activations are presented over a timing of between the end of the question and the beginning of the patient's response (latency). This graph is representative of the McClelland model in Figure 3.

Discussion

Following the predictions of previous researchers, we observed that memory activation during verbal semantic processing is more widespread throughout the frontal, parietal, and temporal lobes. The wide distribution of verbal semantic memory activation may be a result of the wide range of questions asked, branching from "What is your telephone number?" to "Do you have any pets?" to "What is the name of your favorite singer?" In contrast, the arithmetic task design was highly focused and concentrated on repetitive, computational skills. These findings matched the initial hypothesis about the relative distributions of verbal and non-verbal semantic memory. For future study, the distribution of brain activations in a noun-verb task may be investigated because, similar to the conversational questions task, it also tests for the patient's verbal processing. However, this task can also evaluate the patient's ability to understand language and whether this comprehension causes a wider range of activations.

More importantly, the changes in the magnitude of activation in verbal semantic tasks were greater than the respective changes in the arithmetic semantic tasks. This could be due to an element of surprise as the patient is forced to answer a highly variable set of conversational questions that differed from the consistency of the arithmetic trial. The greater activation may represent a greater postoperative response to verbal tasks. This could be due to alterations in language control, commonly in the temporal area, after surgical resections. Following these conclusions, patients responding to verbal tasks are hypothesized to exhibit a higher activation than those responding to the arithmetic trial.

This study confirmed earlier findings on the widespread nature of verbal semantic memory, verifying our hypothesis. This study also associated greater gamma band activation with postoperative epileptic patients responding to verbal semantic tasks compared to those responding to arithmetic semantic tasks. Moreover, executive function, the top-down preparation process closely associated with frontal lobe activity and previously documented for the arithmetic task has also been exhibited in other areas of the brain, including the parietal

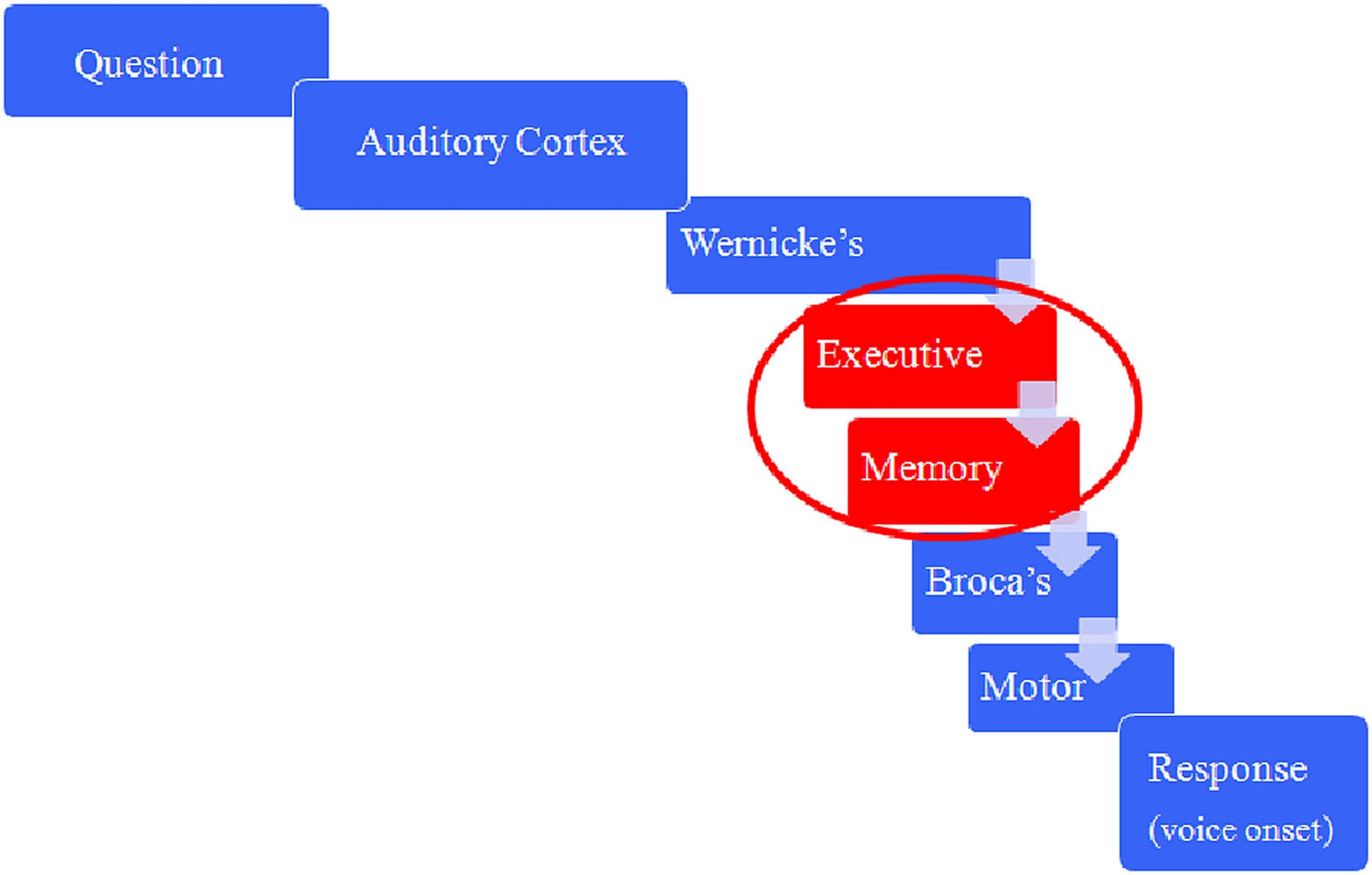

Figure 3. Contemporary variation of McClelland's Cascade model. McClelland proposed a memory mechanism in 1979 that documented a series of steps that document memory. The highlighted area, the executive function and the memory retrieval process, document the main focus of the research.

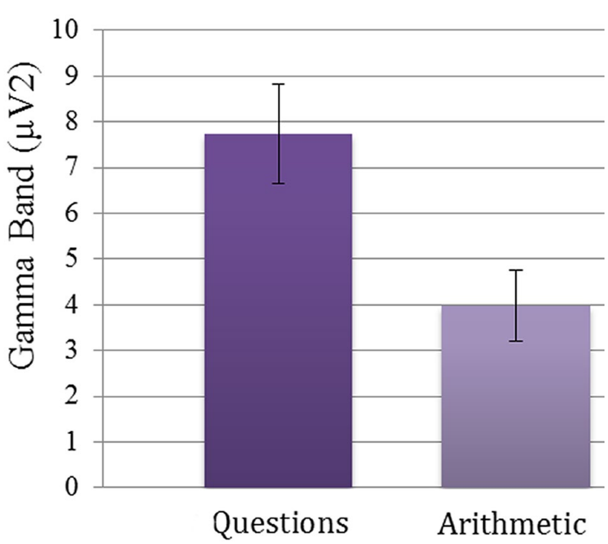

Figure 4. Gamma band power of verbal and arithmetic tasks. Significant memory trials for the "questions" conversations task displayed an average gamma power of 7.74 μv2 whereas the arithmetic task displayed an average gamma power of 3.96 μv2 (2-sample t-test, N=16, t=2.67, p<0.02).

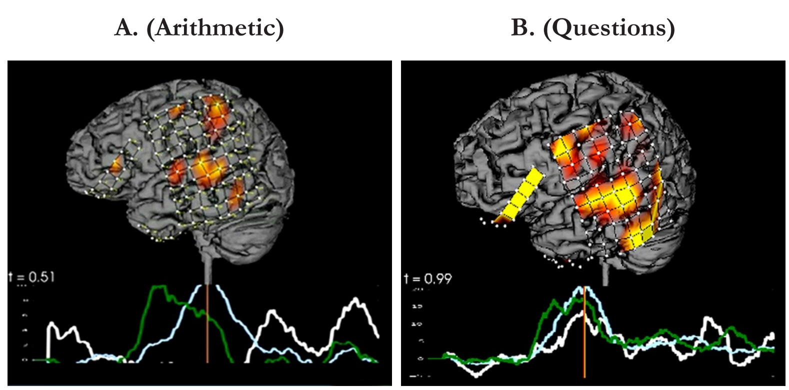

Figure 5. Comparison between spread of brain activation in verbal and arithmetic semantic memory tasks. The highest points of activation were much more synchronized in (B) and displayed greater gamma power. Visually, verbal semantic memory (B) is seen as more spread out in the brain compared to arithmetic semantic memory (A), which has concentrated activations in the temporal and frontal lobes. White, green, and blue lines refer to three individual trials of long-term memory task. Activation in the somatosensory and motor cortex support Pulvermullër's model of active perception that points to a link between action and perception circuits[17].

and temporal lobes. The data suggests that this process may begin approximately 0.3 seconds earlier in the arithmetic section.

Surprisingly, this study countered previous findings documenting the frontal lobe as the only location for executive function[16]. This investigation showed that executive function is exhibited by the frontal, temporal, and parietal lobes. Because executive function is a top down preparation process, it is usually associated with analytical thinking and thus seen as a significant factor in only arithmetic trials. Possible sources of error in this experiment can be attributed to individual differences among patients due to their ages and backgrounds and the possible appearance of noise even after the elimination of contaminated data. These conclusions took a step in both confirming and countering previously known information in the field of epileptic neuroscience. This study helped the community gain a better understanding of what memory processes are and how areas of the brain, previously unknown to perform certain functions, actually play a major role in memory retrieval.

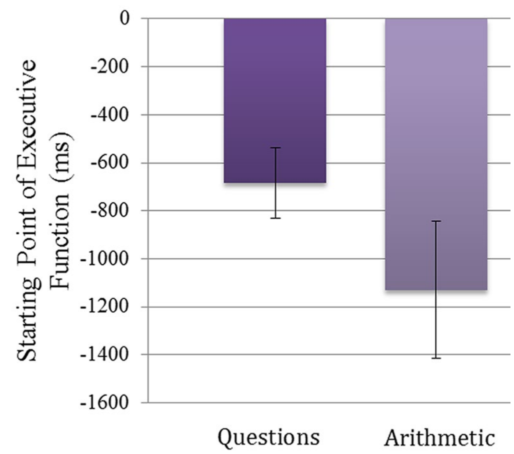

Figure 6. Onset of executive function for "questions" and "arithmetic" tasks. Patients performing both tasks exhibited executive function (1-sample t-test, N=25, t= -5.6, p<0.0001). The average onset of executive function for arithmetic semantic tasks was approximately 1.01 s. before the beginning of the question whereas the average onset of executive function for the verbal semantic tasks was approximately 0.7 s.

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