Office of Research Regulatory Affairs
4301 W. Markham, #813
Little Rock, AR 72205-7199
https://researchservices.uams.edu/

University of Arkansas for Medical Sciences

Study Title:	Pediatric Language and Memory Mapping in Refractory Epilepsy using Magnetoencephalography
Version:	4.0
Date:	1/13/2021
NCT#:	04888637

Study Title: Pediatric Language and Memory Mapping in Refractory Epilepsy using Magnetoencephalography

Principal Investigator:
Diana Escalona-Vargas, PhD
University of Arkansas for Medical Sciences
4301 W. Markham Street, Slot #518
Little Rock, AR 72205
Telephone: 501-364-3703
Email: DIEscalonavargas@uams.edu

Sub-Investigator:
Debopam Samanta, MD
University of Arkansas for Medical Sciences
1 Children's Way, Slot #512-15
Little Rock AR 72202
Telephone: 501-364-5281
Email: DSamanta@uams.edu

Linda J. Larson-Prior, PhD
University of Arkansas for Medical Sciences
4301 W. Markham St., Slot #568
Little Rock, AR 72205
Telephone: 501-526-4889
Email: LJLarsonPrior@uams.edu

Hari Eswaran, PhD
University of Arkansas for Medical Sciences
4301 W. Markham Street, Slot #518
Little Rock, AR 72205
Telephone: 501-526-4334
Email: EswaranHari@uams.edu

Medical Monitor:
Tara Johnson, MD
Telephone: 501-364-1850
Email: TJohnson9@uams.edu

Study location:
Arkansas Children's Hospital
MEG Laboratory
Arkansas Children's Hospital
1 Children's Way
Little Rock, AR, 72202

Sponsor: University of Arkansas for Medical Sciences

Table of Contents

Abbreviations

ACH	Arkansas Children's Hospital
ACMEGS	American Clinical Magnetoencephalography Society
AE	Adverse Event
AEF	Auditory Evoked Field
APR	Annual Progress Report
CFR	Code of Federal Regulations
CRF	Case Report Form
CT	Computerized Tomography
dB	Decibel
DOB	Date of Birth
ECD	Equivalent Current Dipole
ECG	Electrocardiogram
EEG	Electroencephalography
EOG	Electrooculogram
ERF	Evoked Response Field
FDA	US Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
HIPAA	Health Insurance Portability and Accountability Act
HPI	Head Position Indicator
kHz	Kilo Hertz
IAT	Intracarotid Amobarbital Test
ICF	Informed Consent Form
ICH GCP	International Council for Harmonisation Good Clinical Practice
IIR	Infinite Impulse Response
IRB	Institutional Review Board
ISI	Inter-Stimulus Interval
LCD	Liquid Crystal Display
MEG	Magnetoencephalography
MRI	Magnetic Resonance Imaging
MRN	Medical Record Number
MSR	Magnetically Shielded Room
nAm	NanoAmpere-Meter
msec	Millisecond
ORRA	Office of Research Regulatory Affairs
PET	Positron Emission Tomography
PI	Principal Investigator
s	second
SAE	Serious Adverse Event
SD	Standard Deviation
sLORETA	Standardized Low Resolution Brain Electromagnetic Tomography
SPL	Sound Pressure Level
SQUIDs	Superconducting Quantum Interference Devices
SSP	Signal-Space Projection
UADE	Unanticipated Adverse Device Effect
UAMS	University of Arkansas for Medical Sciences
UPIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
VSWM	Visuospatial Working Memory
WM	Working Memory

Background and Rationale

Pediatric epilepsy is the most common serious neurological disorder of childhood, affecting between 0.5-1% of children and young people under the age of 16 years [1]. Epilepsy is known to impair behavior, and adversely affect cognition and learning [2-4]. Antiepileptic drugs are effective medications available for epilepsy. However, many patients do not respond to this treatment and become resistant. Treatments such as the ketogenic diet, vagal nerve stimulators and resective and functional surgery have become available for these drug-resistant patients [5]. Surgery for removal of epileptogenic zone is the most effective treatment. The purpose of presurgical brain mapping is to facilitate surgical planning, prevent or reduce morbidity, and optimize the therapeutic effects of surgery. As part of the presurgical planning, assessment of hemispheric language and memory function is performed. The medical standard for determining the language dominant hemisphere and memory function prior to surgical resection is the intracarotid amobarbital test (IAT), also known as the Wada test [6]. It consists of an injection of sodium amobarbital into the left or right internal carotid arteries. This causes a temporary arrest of function in each hemisphere for approximately six to ten minutes, during which the unanaesthetised hemisphere is functionally assessed. A major drawback of this test is that it determines lateralization only, and does not allow intrahemispheric localization of language and memory functions. Moreover, because it is relatively invasive, this technique cannot be used with normal volunteers and is difficult to use with children. Additionally, the Wada test is associated with risks of stroke, infection, and hemorrhage [7]. Over the past decade, there is a significant discussion of the clinical utility of non-invasive brain imaging techniques (e.g. functional magnetic resonance imaging (fMRI)/ magnetoencephalography (MEG)) relative to the invasive Wada test for determination of hemispheric language and memory function. At present, while research has pointed to the better spatiotemporal resolution of both behavior and functional brain network organization available in brain imaging methods, the lack of language and memory tasks that map these functions in single individuals has reduced their clinical utility. The impact of epilepsy on language and memory are relevant not only from a clinical perspective but also because it sheds light on the underlying neurobiology of both processes. Identifying the patterns of language and memory organization prior to surgical intervention could therefore guide tailored resection and limit potential loss of function after surgery.

Advances in technology over the past decade have enabled researchers to study the functional development of the human brain with MEG, a novel and non-invasive technique with fine temporal and spatial resolution. While other modalities infer brain function indirectly (i.e. positron emission tomography (PET), computerized tomography (CT), MRI) by measuring changes in blood flow, cerebral metabolism and blood oxygenation, MEG records neuronal and synaptic function directly. MEG records the tiny biomagnetic fields generated by ionic currents generated by populations of synchronously activated neurons in the brain [8]. Evoked responses fields (ERF) measured with MEG, much like event-related potentials in electroencephalogram (EEG), are waveforms representing variations of brain activity across time following the onset of an external stimulus (auditory, visual, etc.). Early components of the ERF waveform (150-200 msec after stimulus onset) reflect neurophysiological activity in primary sensory cortices. On the other hand, neurophysiological activity represented by later components of the ERF waveform occurs primarily in association cortices. By estimating the regions that contribute to systematic variations in the late components of the ERF, we can study the brain circuits responsible for cognitive and linguistic functions. MEG signal arises from brain sources also seen using electrical signals recorded as the EEG. However, MEG is unaffected by scalp, skin and, to a large degree, brain tissue in homogeneities and is, therefore, an ideal technology to study brain development. MEG is one of several diagnostic techniques employed for the evaluation of patients with epilepsy and it is especially important for those patients being considered for epilepsy surgery [9, 10]. Resective

epilepsy surgery is performed mainly in the temporal and frontal lobes (selective amygdalohippocampectomies, anterior temporal lobectomies, or tailored temporal or frontal cortsicectomies). However, it must be previously determined that the resection will not have any substantial consequences on cognitive functions, such as language or memory.

fMRI is the most widely used of the minimally/non-invasive techniques for presurgical language mapping in children [11]. However, MEG is gaining increasing acceptance as a non-invasive method as an adjunctive part of the pre-surgical functional mapping procedure [12]. Especially for language identification in pediatric cases, the quiet environment of the MEG room and the head-motion-tracking methods available in recent MEG systems, increase the likelihood of success with language lateralization in young populations. Further, MEG allows examining both hemispheres simultaneously, which is especially useful in epileptic populations, in which language lateralization is more variable. MEG language localization studies have shown encouraging results with a wide variety of paradigms, especially in localization of receptive language areas that are well documented [13, 14] and validated [15, 16]. The suitability of MEG language lateralization protocols in adults as an alternative to the Wada procedure have been addressed with validation studies conducted using various methodologies and exhibit overall high concordance rates (about 86-92%) [17-20]. Language lateralization is calculated in both hemispheres by localizing dipole sources (equivalent current dipole, ECD model) accounting for late auditory evoked field (AEF) components (150-700 ms after stimulus onset). These late components localize to language-related areas (mainly within posterior temporal areas) of the brain regardless of the modality of stimulus presentation [21]. Depending on the activation task, the dipole sources can be used to identify the location of receptive (Wernicke's area) or expressive language-specific (Broca's area) cortex. The degree of hemispheric asymmetry in the duration or strength of activation can also be calculated as an index of hemispheric dominance for language functions. Estimations of language lateralization with MEG [22] have mainly been based on recognition memory tasks for spoken words [23] or by listening to synthesized vowel sounds [24]. Thus, most of the MEG language studies have focused on receptive language areas. However, other reports exist on frontal circuits in expressive language [25-27] and basal temporal areas during semantic language tasks (verb generation) [28, 29]. Recent MEG language studies have reported the feasibility of passive paradigms in children and adolescents under sedation [30] and during sleep [31]. A recent MEG study [32] uses a verbal memory and verbal fluency tasks showing activation of the left hippocampus and in Wernicke's area in favor of the left hemisphere. Authors found higher concordance rates between a verbal memory paradigm and language dominance in controls (using handedness as criterion) and in subjects with epilepsy (using fMRI or Wada as criterion), compared with a verbal fluency task. Only the concordance for verbal memory reached statistical significance, with 93% agreement. Previous studies in pediatric epilepsy have shown atypical language lateralization [33] and that the word recognition task is the only language comprehension task used in both children and adults that yields high concordance between MEG and the Wada test for language lateralization [22]. Despite all contributions of MEG in the assessment of language localization in typically developing individuals, studies in pediatric populations with epilepsy is still relatively small especially in single subjects, which is necessary for clinical utility.

Memory involves a network of interconnected anatomical brain structures - hippocampus, parahippocampal structures, temporal lobe neocortex, amygdala, and the frontal lobe [34, 35]. Medically intractable epilepsy may negatively affect cognition by disrupting cognitive processes through chronic and persistent seizures. Verbal memory declines in about 30-85% of epileptic patients undergoing left temporal lobe resection while non-verbal memory declines in about 30-50% of the patients when right temporal lobe resection is performed [36, 37]. The standard

procedure used to assess the risk of resection-induced loss in memory function prior to epilepsy surgery is with the invasive Wada Test together with language assessment. fMRI has been used to assess the risk of memory loss in epilepsy [38]. Usually, fMRI studies perform language protocols to predict memory outcome. However, this approach assumes collateralization of these functions, which has previously been studied, but dissociating these domains of function can be difficult, partly due to reorganization, and to overlapping and/or interconnectivity of regions involved during cognitive processing. Very few MEG studies exist for memory assessment, and most of them have been performed in adult epileptic subjects [39, 40] and less in children. Currently, there are insufficient available data to promote the use of MEG for assessment of pediatric memory function, as memory function is housed deep in the temporal lobes and is more difficult to accurately localize. However, previous studies have shown that it is possible to detect hippocampal activity with MEG [41] that will allow the study of deep sources involved in memory.

Working memory (WM) and executive functions are skills developed to deal with complexities in life and are necessary for effective and adaptive behaviors. WM is the cognitive system that entails maintaining information in mind over a short time to complete an activity. WM is one of the most important components of information processing. A dysfunction of the WM system may lead to problems in developing cognitive functions, including mental arithmetic, reading, decision making and reasoning. WM is constituted by three main components: the central executive, the phonological loop, and the visuospatial sketch pad. Each component works to store and manipulate information in a temporary short-term memory system that is essential to human memory [42]. Executive functions include the control and organization of complex cognitive operations that allow a person to plan strategies, solve problems, and modify behaviors as a result of new information. The frontal lobes play a crucial role in WM and epilepsy has an impact on working memory functioning [43]. Visuospatial working memory (VSWM) involves encoding, maintenance, and retrieval of object identity, particularly spatial position [44-47]. VSWM is especially important in children during letter/number recognition, reading, writing, and math by facilitating recall of shapes and colors as well as their positions and movements. Determination of hemispheric memory lateralization plays an important role in the presurgical epilepsy evaluation, and very few studies have been conducted in children. The comparisons between adults and children reveled a greater activation in large regions of the frontal, parietal and temporal lobes, basal ganglia, and cerebellum in adults, while children showed greater activity in several occipital regions [48]. In adults, verbal memory has been predominantly lateralized over the left temporal lobe and visual-spatial memory over the right hemisphere [49-51]. But in children with epilepsy, a clear pattern of hemispheric lateralization of visuospatial memory has not been thoroughly investigated and established, and more investigations are needed to further assess WM in epilepsy.

How epilepsy affects working memory performance is unclear but evidence suggest disruptions in the WM network [52]. MEG studies to examine the hemispheric lateralization of visuospatial memory circuitry prior to epilepsy surgery are severely lacking especially in children [53]. Importantly, visuospatial memory reorganization with seizure foci from the left and right hemispheres has not been investigated in detail. Although a significant role for the mesial temporal structure is suspected in visual-spatial memory, technological advances in MEG sufficient to detect hippocampal dynamics has become possible only recently [41]. Importantly, cortical stimulation and the Wada procedure cannot identify memory-specific circuitry or language circuit interactions whose activity patterns are developing in a non-typical brain environment due to on-going epileptic activity. Moreover, both cortical stimulation and the Wada are intimately related to the narrow time window and not suitable for delineation of neural pathways during complex tasks, and the repetition of these procedures to detect reliability cannot be performed.

Several tasks exist to assess memory such as n-back task, the Sternberg Item Recognition task and others [54]. Some of these tasks require extended periods of time to complete the test or require verbal knowledge, which may impede the subject's ability to complete the test due to age or education. Our project proposes the use of an established working memory task that is an n-back paradigm that has been widely used to investigate working memory processes in neuroimaging research in children [55] and it is a simple task that kids can performed [56-59]. An n-back task consist of the presentation to participants with a sequence of stimuli and asked to answer when a stimulus matches another stimulus "n" trials back. Previous studies in memory assessment has shown extensively that n-back tasks are able to find memory disruptions in children [60-63] and some studies have noted particular aspects of memory to be more at risk. For example, Hershey et al. [61] shows that children with epilepsy scored lower than normative scores on measures of spatial tasks with high memory load or long delays, but not on short delay memory tasks which were within the normal range. Lindgren et al [62] showed that the percentage of children with epilepsy scored lower on visuospatial memory and learning (4%). Children with epilepsy appear to be at significant risk for memory impairment. It is not clear what particular aspects of memory are more likely to be affected or whether particular syndromes are more likely to be associated with particular impairments. Further research is needed to identify the extent and nature of the difficulties in children with epilepsy.

To address these knowledge gaps, our study will evaluate the utility of ~~an~~a well-established and validated ~~existing clinical~~ MEG protocol that is used to ~~localize~~ study language function in children [23, 30, 64]. ~~s and~~ In addition, we will use a widely deployed ~~a new~~ memory protocol [55-59] ~~that we have designed~~ to ~~localize~~ assess memory functions in children and young adults with epilepsy. The research study itself will be conducted immediately following the standard-of-care MEG evaluation, which currently includes the language task. For all consenting subjects, this standard language clinical protocol will be supplemented by the addition of the experimental memory task and a resting-state MEG acquisition, which will only add an estimated 20-30 minutes to the standard protocol time. No treatment/intervention will be performed or evaluated in this pilot research study. As accurate localization requires co-registration with an MRI, this additional procedure will be required for any study subjects who do not already have an existing MRI scan of sufficient quality to be used in the current research study. Our project will improve our understanding of the dynamic brain network mechanisms underlying memory and language.

Specific Aims

Aim 1

Feasibility of measuring language and memory functions in pediatric epilepsy with MEG brain signals.

Aim 2

Characterize language and memory circuitry in pediatric epilepsy subjects with seizure focus from the right or left hemispheres.

Study Design and Procedures

This is a pilot research study where we will ~~design, develop and implement~~use language and working memory tasks to study brain activities from children with epilepsy. ~~Specifically F~~for language assessment, a well known MEG language protocol will be used and novel signal processing techniques will be applied. We will use a ~~design and implement a new~~widely utilized paradigm to study memory function and adapt signal-processing techniques from previous literature for the processing and analysis of MEG signals collected during memory task. We will perform a MEG scan and collect data from ten pediatric subjects with drug-resistant focal epilepsy

under evaluation for resective surgery. If a MRI scan is available from medical records and images have the appropriate characteristics for MEG (see more specifications at MRI section) analysis, we will use MRI for MEG source reconstruction. If MRI is not available, we will perform one scan. MRI is necessary to obtain brain anatomy for high quality MEG source reconstruction. Quantitative parameters will be extracted from MEG data for evaluating language and memory functions. This is a pilot research study where we will test the feasibility of the recording of both standard language and ~~experimental~~ well-known memory task in patients with epilepsy. This research is important to investigate, by a non-invasive means, possible patterns of language and memory organization that may in future guide surgery and limit potential loss of these functions.

Study Population

A total of fifteen (15) pediatric patients with drug-resistant focal epilepsy under evaluation for resective surgery will be recruited from the comprehensive epilepsy program of the Arkansas Children's Neuroscience Center. If the patient is eligible, they will be informed about this study during their routine clinic visits by their clinician, and asked if they are interested in participating. Those who express an interest will be provided with the informed consent form (ICF) approved by the UAMS Institutional Review Board (IRB). If they agree to participate, they will be scheduled for the research visit. Subjects will be compensated with a gift card of $40 which will be given to the parent or guardian (for subjects under 18) or to the subject (if over 18) after completion of study procedures.

Inclusion Criteria

- 8 to 21 years old
- Drug-resistant focal epilepsy
- Enrolled in the Arkansas Children's Neuroscience Center Comprehensive Epilepsy Program
- Under evaluation for resective surgery
- English speakers. This is not a treatment/intervention study.

Exclusion Criteria

- Previous resective surgery for epilepsy
- Presence of progressive neurodegenerative disorders
- Presence of significant magnetic artifacts; electronic, magnetic or metallic implants (e.g. pins, screws, shrapnel remains, surgical clips, artificial heart valves, cochlear implants, vascular stents pacemakers); or permanent make-up or tattoos made with metallic dyes
- Presence of seizures within 24 hours of the MEG
- Use of sedation during the MEG acquisition
- Inability to be in a seated or supine position during the tasks
- Major medical disorders (e.g. HIV, cancer)
- Significant visual or auditory disabilities
- Physical disabilities that interfere with accomplishment of study tasks (when applicable)
- Claustrophobia, or fear of cramped or confined spaces
- Pregnancy or suspected pregnancy
- Any condition that the investigator feels might put the patient at risk

MEG Acquisition

Each subject will have one MEG session with the recordings of baseline resting state, language and memory protocols. Subjects will have a break period between the language and memory tasks. MEG recordings will be acquired for approximately 35 minutes. The subject will be allowed to practice the language and memory tasks before the MEG recording to feel familiar with them. This practice phase will be a short version of the task administered by a computer and will take approximately 6 minutes.

MEG System Equipment

Arkansas Children's Hospital (ACH) hosts the only one of its kind in the state and latest-generation whole-head MEG system (TRIUX™ neo, see Fig. 1A) with helium recycling technology for zero helium boil-off. MEG system is a clinical device with Food and Drug Administration (FDA) approval. The MEG system consists of 306 (see Fig. 1C) Superconducting Quantum Interference Devices (SQUIDs). The MEG scan is located inside of a magnetically shielded room (MSR, see Fig. 1D) to reduce environmental noise to a level compatible with the brain signals. The MEG system is equipped with a specially designed bed (Fig. 1A) and chair (Fig. 1B) for supine and seated measurements (reclined and upright). MEG laboratory is equipped with an audio-video surveillance and communication system, and additional electronics to design specific protocols to record MEG in response to external stimuli. Because exact information about the relative position of the head with respect to the sensor array is necessary for post-analysis, MEG laboratory is equipped with "head position indicator" coils and digitization system to determinate this relative position. The 3-dimensional (3D) digitization system is used in the preparation phase before MEG measurements to digitize the positions of the coils as well as the landmarks on the head. The locations of the landmarks are used to establishing a coordinate transformation between MEG and the anatomical information.

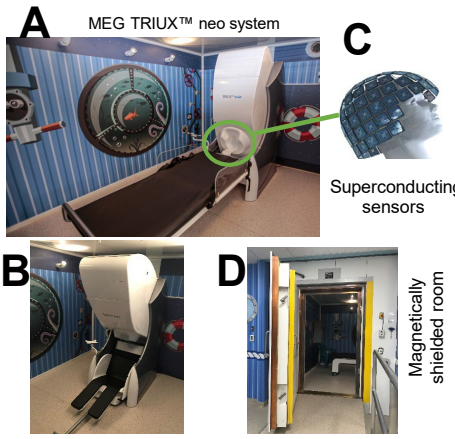

Figure 1: ***(A-B)*** *Whole-head MEG system with a specially designed bed and chair for measurements.* ***(C)*** *SQUID sensors.* ***(D)*** *Magnetically shielded room (MSR) to reduce environmental noise.*

MEG Preparation Phase

The subject will be first seated in a chair outside of the MSR. One pair of electrooculogram (EOG) electrodes will be attached to the lower corner of the left eye and upper corner of the right eye to measure eye blinks. Electrocardiogram (ECG) electrodes will be attached to the chest. Five head position indicator coils will be attached to the head. Three landmarks (left and right preauricular points, and nasion) and the five HPI coils will digitize along with ~200 additional points of the head surface with an electromagnetic 3D digitizer (Polhemus Fastrak®). We will take pictures with an ACH camera (e.g. standalone camera, tablet or phone device) of the three landmarks and MEG coils. Pictures will be used to guide the coregistration between MRI and MEG for source analysis and to know precisely where each of the MEG coils and points are located in relation to the head. Next, the subject will be placed under the MEG helmet.

Resting State Measure

Baseline brain activities will be measure for 5 minutes. The subject will be asked to remain still with eyes closed and rest.

Tasks

Receptive Language Task

We will follow the standard protocols according to the American Clinical Magnetoencephalography Society (ACMEGS) [64]. The language task corresponds to an adapted version [30] of the continuous auditory word recognition protocol previously described by Papanicolaou [23] for determining hemispheric dominance of language function. The subject will perform a practice session where they will be instructed to "try to remember" a set of five audibly spoken English words, deemed targets. Target words are as follows: *jump, little, please, drink, and good*. Depending on the subject's overall verbal memory capacity, the target words will be presented once or twice during the practice phase. Subsequently, during the MEG recording, the five target words will repeat in a different random order, mixed with a different set of 40 distractors (non-repeating words) in each of three blocks of stimuli. Words will be presented for 1 s, one at a time, and randomly varied with an interstimulus interval between 2 s and 3 s. The auditory stimuli will be delivered binaurally through two long plastic tubes terminating in ear inserts at an intensity of 60 dB sound pressure level (SPL) at the 'subject's outer ear. Target words correspond to four monosyllabic and one disyllabic word with a mean frequency in the G6-7 corpus of 158 occurrences per million (range: 32-194 occurrences) [65]. For distractors, 40% of words will be disyllabic and the remaining will be monosyllabic with a mean frequency of occurrence of 150 words per million in the same corpus (range: 18-820). The subject's task will be to listen to the words and lift their index finger of the dominant hand whenever they hear a repeated target word (one of the five). After the language task, the subject will be given a break.

Memory Task

In this project, we will ~~develop~~ use a widely deployed~~new~~ procedure to study memory function using a visuospatial working memory (VSWM) task that will manipulate working memory (WM) load by using visual-stimulus complexity [55-59]. The task will be composed of a two-dimensional visual grid plane (see Fig. 2) segmented into nine regular squares, each of which might contain a symbol "○" or "+", otherwise empty. Only two symbols will be displayed in the grid. We will manipulate the WM load and congruency as follows: a) low WM load will only have one type of symbol with two apparitions in the grid (i.e., circles); b) high WM load will have two types of symbols with six apparitions in the grid (i.e., circles and crosses). Congruency will be manipulated by matched or unmatched encoding and retrieval stimuli. A total of 96 stimuli will be designed: 24 low-WM load-congruent; 24 low-WM load-incongruent; 24 high-WM load-congruent; and 24 high-WM load-incongruent.

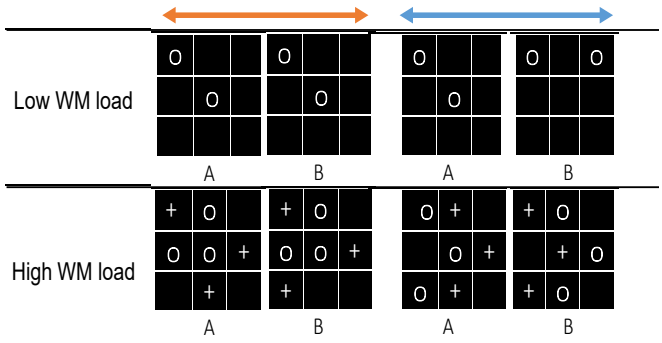

Figure 2: Memory task; examples of experimental conditions. A: encoding stimulus; B: retrieval stimulus

The symbols and grid plane will be white on a black background. The type font will be Arial with 80pp size. Each trial will begin with a central fixation cross-displayed for 300 ms, followed by encoding, maintenance, and retrieval phases. The symbols and grid will appear for 1 s (encoding phase), then a blank inter-stimulus interval (ISI) will display for 1.5 s (maintenance phase). Next, the symbols and grid will appear for 1 s (retrieval phase). The subject will be tasked with indicating whether the encoding stimulus matched the retrieval stimulus using two buttons; one for "congruent" and the other for "incongruent" response. Button type will be counterbalanced among subjects. The task will take around 16 minutes. The visual stimuli will be projected through an LCD projector onto a white screen located about 0.5 m in front of the subject and subtending 1.0-4.0 and 0.5 degrees of horizontal and vertical visual angle, respectively. A MEG compatible keyboard will be used to measure the subject's responses for "congruent" and "incongruent". The subject will practice the memory task before going to the MEG system using a computer from MEG laboratory. This practice phase will consist of a short version of the memory task with duration of approximately 4 minutes.

MRI

MRI will be used to obtain individual anatomical brain information for MEG source reconstruction. MRI characteristics for MEG is a fast T1 scan containing tip of nose, both ears, and top of the head. If a previous MRI is available from medical records, we may use if it has the appropriate characteristics for MEG and if subject did not have any neurosurgery after this specific MRI. Otherwise, if no MRI is available, the subject will have an MRI scan of the brain.

Subject Withdrawal

Participants may withdraw at any time for any reason, without penalty. No data will be collected about the subject following withdrawal from the study. Any subject withdrawing their consent to participate in the study or their authorization to use their protected health information will be withdrawn from the study. Additionally, the investigator may choose to remove subjects from the study for any reason.

Risks and Benefits

The measurement principles of MEG have no harmful effects on subjects. It does not expose the subject to any medication, radiation, or magnetic fields. It non-invasively measures the magnetic fields produced by the human brain.

There is no loud noise generated during acquisition, hence the MEG environment is generally considered as relatively comfortable to subjects, including young children. A possible risk from MEG is the spontaneous boil-off (evaporation) of the liquid helium used for refrigeration of the superconducting sensing system. Although very unlikely, boil-off can occur with minimal risk to subjects. The MEG instrument has safety valves to prevent pressure from building inside the helium reservoir, and if helium is released, the air ventilation inside the MSR has been designed to rapidly exhaust the extremely volatile helium gas out of the MSR. Although helium is inert, there is a risk of oxygen depletion inside the MSR, in case of massive helium boil-off. It would take only seconds for the attending personnel to open the MSR door, which would immediately resolve the situation. Overall, the risk and potential harm from spontaneous helium boil-off in the MEG is minimal and much lower than that from MRI quenching, for instance. This study will include a MEG scan of language and memory testing. There are no known risks of language and memory testing, although some subjects may become frustrated by the tasks or uncomfortable. If this

occurs, breaks will be offered in which subjects may move or change their position until comfortable. The measures of MEG, uses standard clinical tape to stick the coils and EOG/ECG electrodes to the subject's head and chest that may produce mild skin irritation.

Besides the MEG measurements, a structural MRI may be obtained if the subject does not have one with appropriate characteristics for MEG in the medical record. There are also no adverse side effects known for MRI, although some subjects may experience temporary claustrophobia, anxiety, or dizziness. Ferromagnetic artifacts may heat, twist or pull in the MRI. The effect of the strong magnetic fields on fetuses is not well known. Therefore, as is typical with MRI research, subjects with ferromagnetic implants and pregnant women will be excluded from the study. Subjects will be carefully screened and required to complete the ACH's MRI safety questionnaire. If they qualify for scanning, they will change in a gown, and all magnetic parts have to be removed.

Another potential risk to subjects is the potential for loss of confidentiality. Measures to protect the confidentiality of subjects will be implemented as described in the Data Handling and Recordkeeping section below.

The standard-of-care clinical MEG protocol includes the language task, but the ~~experimental~~ memory task has not been approved by the FDA or ACMEGS [43]. As such, this data will not be utilized in presurgical planning and will be used only for research purposes. Accordingly, there are no guarantees that participation will yield direct benefits to the subjects; however, the knowledge gained from the study could potentially benefit patients in the future. There will be no financial charges to the subject as a result of participation in this study.

Adverse Events

Definitions

Adverse Event: An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. For the purposes of this study, AEs will be collected from the time of consent through the end of the MEG tasks, or following the MRI scan if one is required. Intercurrent illnesses or injuries should be regarded as AEs.

Serious Adverse Event: A serious adverse event (SAE) means any untoward medical occurrence with the device: An event is "serious" if it involves considerable detriment or harm to one or more persons (who may or may not be subjects), or required intervention to prevent one or more persons from experiencing considerable detriment or harm. SAEs include:

- Death
- Life-threatening experience - Disease or condition where the likelihood of death is high unless the course of the disease/condition is interrupted or diseases/conditions with potentially fatal outcomes where the end point of the clinical trial analysis is survival
- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in subject's offspring
- Any other important medical event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, the development of drug dependency or drug abuse, suicidal ideation or attempts, or the unintentional revealing of some genetic information to insurers.

Although an event may be considered "serious" based on previous criteria and should be reported to ORRA immediately, not all SAEs meet IRB or FDA Expedited Reporting criteria.

To avoid confusion, as the terms "serious" and "severe" are not synonymous, the following clarification is given: The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction); the event itself; however, may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious", which is based on subject/event outcome or action usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. [ICH-E2A(II)(B)]

Unanticipated Adverse Device Effects (UADEs): A UADE is defined as "any serious adverse effect on health or safety, or any life-threatening problem, or death caused by, or associated with, a device; if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or application (including supplementary application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects." If an unanticipated adverse effect occurs, the investigator will promptly notify the sponsor of such an event within 24 hours of first learning of the event using the FDA MedWatch 3500A form.

Related: An event is "related" if more likely than not it was caused by the research activity.

Unexpected: An event is "unexpected" when its specificity, nature, severity or incidence is not accurately reflected in the ICF, protocol, or investigator's Device Manual previously reviewed and approved by the IRB. Examples include a lower rate of response to treatment or a side effect that is more severe than initially expected.

Study Period: All AEs will be recorded from the time of consent through the end of the study procedure. All AEs will be captured in the electronic medical record and recorded on the Case Report Forms (CRFs) and AE log.

Monitoring, Recording and Reporting of AEs

All AEs occurring during the study period as previously defined must be recorded. All relevant historical medical conditions (as determined and documented by Investigator/Clinician that are known/diagnosed prior to the start of the study are to be recorded as medical history. Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates or exacerbates at any time during the study, it will be recorded as an AE. Pre-existing conditions should be recorded as adverse events only if the frequency, intensity, or the character of the condition worsens during the study.

The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. SAEs that are still ongoing at the end of the study period must be followed for up to 30 days to determine the final outcome. Any SAE that occurs after the study period and is considered to be possibly, probably, definitely, or related to the study treatment or study participation should be recorded and reported immediately to the Sponsor.

All subjects will be monitored for AEs during the study. Assessments may include monitoring the subject's clinical symptoms; laboratory, pathological, radiological, or surgical findings; physical examination; or other appropriate tests and procedures.

AE data collection and reporting, which are required as part of every study, are done to ensure the safety of subjects enrolled in the studies and those who will enroll in future protocols. AEs are to be reported in a routine fashion at scheduled times during the trial, such as with the annual continuing review to the IRB. Certain AEs must be reported in an expedited fashion to allow for timely monitoring of subject safety and care.

The reporting of these events depends on the characteristics of the event:

1. Seriousness (grading of event)
2. Relatedness to use of the investigational device or study procedure
3. Expectedness

Steps to Determine if the Event Requires Expedited Reporting:

1. Identify the type of event
2. Grade the event using
3. Determine whether the adverse event is related to the investigational device. Attribution categories are as follows:
   - Unrelated
   - Unlikely
   - Possible
   - Probable
   - Definite
4. Determine expectedness of event. Expected events are those previously identified resulting from administration of the investigational device. An adverse event is considered unexpected when the type or severity of the event is not listed in:
   - Protocol
   - Device Manual
   - ICF

Note: This includes all events that occur within 30 days of the last protocol procedure (2nd IPA procedure). Any event occurring more than 30 days after the last protocol procedure that is possibly, probably, or definitely attributable to the investigational device must be reported according to the instructions above.

Expedited Reporting of AEs

Only adverse events meeting the UPIRTSO (Unanticipated Problem Involving Risks to Subjects or Others) will need to be reported to the UAMS IRB within the required 10-day allotment of being notified of the event. UPIRTSO requires that an unanticipated problem meet the following qualifications: a) unanticipated or unexpected; b) related to the research; and c) involves new or increased risk to the subject(s). All other adverse events should be recorded and reported to the UAMS IRB at continuing review.

The Sponsor will be promptly notified of all potential SAEs/UADEs by the investigator/study staff using the FDA MedWatch 3500A. The Sponsor will evaluate all potential SAEs/UADEs and report these evaluations in accordance with 21 CFR 812. All other SAEs/UADEs not expeditiously reported will be reported to the Sponsor and IRB in the Annual Progress Report (APR).

Report all deaths to the Sponsor (ORRA) as soon as possible, preferably within 24 hours, but no later than 48 hours, of learning of the subject's death, regardless of whether it is related or unrelated to the investigational device. A death due to a terminal condition of the research subject would be considered anticipated and not related to the research.

The Sponsor will report deaths in accordance with 21 CFR 812.

Clinical Site Monitoring

Clinical site monitoring will be conducted by the UAMS Office of Research Regulatory Affairs (ORRA) to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable from source documents, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), ICH GCP, and applicable regulatory requirements.

Monitoring specialists from ORRA will conduct periodic on-site, comprehensive monitoring as determined by a protocol specific monitoring plan, which will be provided by the ORRA Monitoring Unit to the Investigator.

Deviations and Violations

Protocol Deviation: A deviation is any unintentional change, divergence, or departure from the study design or procedures defined in the protocol. Protocol deviations will be tracked and compiled in a Protocol Deviation Log. Deviations that potentially cause concern for the subject health, safety, or rights will be reported to the Sponsor as soon as possible for guidance on reporting.

Protocol Violation: A violation is a change to, or non-compliance with, the IRB-approved procedures without prior Sponsor and IRB approval (excluding changes made to eliminate apparent immediate hazard to subjects). A violation may affect health, safety, or rights of a subject. Any violation will be reported immediately to the Sponsor for guidance on reporting.

If the protocol deviation/protocol violation does not represent a significant alteration in the approved protocol and/or affect the safety or welfare of the subject, it will be reported to the UAMS IRB at the time of Continuing Review. If the protocol deviation/violation represents a significant alteration in the approved protocol and/or if it affects the safety or welfare of the subject, it must be reported to the Sponsor and UAMS IRB immediately.

Data Handling and Recordkeeping

The Principal Investigator will carefully monitor study procedures to protect the safety of research subjects, the quality of the data, and the integrity of the study. All study subject material will be assigned a unique identifying code or number. The key to the code will be kept in a password-protected file on a secure, password-protected computer in the principal investigator's office. Only the Principal Investigator (PI) will have access to the code and information that identifies the subject in this study. Clinical data and medical evaluation information will be obtained from the ACH Electronic Medical Record.

- Medical record information to be collected will include the subject's name, address, telephone number, age, sex, race, ethnicity, head circumference, education, medical history - especially related to epilepsy such as epilepsy duration, results of routine EEG and imaging tests.

At the conclusion of the study, the secure file containing linkages between the study ID and any subject identifiers (e.g., MRN, DOB) will be deleted, while the data will be stored for no more than 10 years or until the last subject reaches the 23rd birthday. If consent was granted by the subject for future research then their data will be retained for an unspecified amount of time for use in future research which will be limited to future IRB-approved studies evaluating brain activity. All stored data will be de-identified. Data will be stored in the ACH MEG Center and only study personnel authorized to view the data will have access. Subjects may request to withdraw from the study by calling the PI at the number listed in the ICF or withdraw their data for future research use by writing a letter to the PI at the address specified in the HIPAA Authorization of the ICF.

Data Analysis

Preprocessing

MEG data will be exported for further analysis from the acquisition computer to the signal processing research software, Brainstorm [66] (https://neuroimage.usc.edu/brainstorm/), which is an open-source application dedicated to the analysis of brain recordings. Next, data will band-pass filtered between 0.5Hz to 100Hz and a notch filter will be applied for power-line noise removal (60Hz, 2nd order IIR notch filter with zero-phase lag). We will perform visual inspection to mark bad channels and segments. Data will be preprocessed for eye-blink and electrocardiogram reduction using a signal-space projection (SSP) technique [67]. The corresponding triggers recorded during acquisition will be used to import MEG epochs in the time window ranging from -200s to +800s with respect to the trigger [68, 69]. Baseline correction will be applied on the 200s before the trigger. Next, we will average across epochs to obtain an ERF waveform per subject for the language and memory tasks. Resting state data will use for baseline source imaging.

Source Imaging

To obtain the subject's anatomical information for source modeling, native-space structural MRI data will be segmented using the research software, BrainSuite [70] (http://brainsuite.org/), to generate a cortical surface with a resolution of ~15,000 triangular vertices and imported into Brainstorm for further analysis. We will estimate empirical covariance statistics from the empty-room recordings, to characterize instrument and environmental noise. The noise covariance estimates will use for subsequent inclusion into the imaging estimator of distributed cortical currents. Source analysis will utilize a boundary element model to compute the forward model with lead fields determined from elementary current dipoles distributed perpendicular to each individual's segmented and tessellated cortical surface. We will apply the source modeling method, the minimum norm imaging (sLORETA) algorithm, to the ERFs. To obtain the most meaningful dipoles only source amplitudes of >=3.2 nanoAmpere-meter (nAm) will be selected. Dipoles meeting the above selection criteria will place on the subject's MRI coregistered to the anatomic landmarks recorded during MEG collection.

Statistical Analysis

Overall: MEG and clinical parameters will be summarized as means, SD and ranges (for continuous and count data), as proportions (for binary and nominal data), or as proportions supplemented with mean scores (for Likert-scaled or other ordinal data). We will export the MEG

source analysis parameters for further statistical analysis. This is a pilot study that will provide the preliminary sample size estimates to support future research.

Hemispheric dominance: Estimation of hemispheric dominance for language [69] and memory [68] will be calculated as the degree of activation of each hemisphere during performance of the task. We will derive an estimate of hemispheric dominance by calculating the difference in activation levels between the hemispheres.

Group level: For this pilot research study, we will perform a preliminary statistical analysis by comparing MEG source activations between hemispheres (left vs. right) with $\alpha=0.05$ significance level using a research statistical software.

Ethical Considerations

This study will be conducted in accordance with all applicable government regulations and ACH-UAMS research policies and procedures. This protocol and any amendments will be submitted and approved by the UAMS IRB to conduct the study.

The formal consent of each subject, using the IRB-approved ICF, will be obtained before that subject is submitted to any study procedure. All subjects for this study will be provided an ICF describing this study and providing sufficient information in language suitable for subjects to make an informed decision about their participation in this study. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and requirements of the study.

The consent process will take place in a quiet and private room, and subjects may take as much time as needed to make a decision about their participation. Privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. This ICF must be signed by the subject or legally authorized representative and the person obtaining the consent. A copy of the signed ICF will be given to the subject, and the informed consent process will be documented in the research record.

Dissemination of Data

The results of this study may be used for presentations, posters, or publications. The publications will not contain any identifiable information that could be linked to a subject.

References

1. Shinnar, S. and J.M. Pellock, *Update on the epidemiology and prognosis of pediatric epilepsy.* Journal of Child Neurology, 2002. **17**(1_suppl): p. S4-S17.
2. Dunn, D.W. and K. Walsh, *Anxiety in Children and Adolescents with Epilepsy.* Journal of Pediatric Epilepsy, 2018. **7**(03): p. 097-102.
3. Schraegle, W.A. and J.B. Titus, *The relationship of seizure focus with depression, anxiety, and health-related quality of life in children and adolescents with epilepsy.* Epilepsy & Behavior, 2017. **68**: p. 115-122.
4. Hunter, M.B., et al., *Neurobehavioral problems in children with early-onset epilepsy: A population-based study.* Epilepsy & Behavior, 2019. **93**: p. 87-93.
5. Feindel, W., R. Leblanc, and A.N. De Almeida, *Epilepsy surgery: historical highlights 1909–2009.* Epilepsia, 2009. **50**: p. 131-151.
6. Wada, J. and T. Rasmussen, *Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance: experimental and clinical observations.* Journal of neurosurgery, 1960. **17**(2): p. 266-282.
7. English, J. and B. Davis, *Case report: Death associated with stroke following intracarotid amobarbital testing.* Epilepsy & Behavior, 2010. **17**(2): p. 283-284.
8. Baillet, S., J. Mosher, and R. Leahy, *Electromagnetic brain mapping.* IEEE Signal Processing Magazine, 2001. **18**(6): p. 14-30.
9. Bagic, A.I., et al., *American Clinical Magnetoencephalography Society Clinical Practice Guideline 1: recording and analysis of spontaneous cerebral activity.* Journal of Clinical Neurophysiology, 2011. **28**(4): p. 348-354.
10. Hari, R., et al., *IFCN-endorsed practical guidelines for clinical magnetoencephalography (MEG).* Clinical Neurophysiology, 2018. **129**(8): p. 1720-1747.
11. Rodin, D., et al., *Language dominance in children with epilepsy: concordance of fMRI with intracarotid amytal testing and cortical stimulation.* Epilepsy & Behavior, 2013. **29**(1): p. 7-12.
12. Pang, E.W., et al., *Localization of Broca's area using verb generation tasks in the MEG: Validation against fMRI.* Neuroscience letters, 2011. **490**(3): p. 215-219.
13. Papanicolaou, A.C., et al., *Functional neuroimaging with MEG: normative language profiles.* Neuroimage, 2006. **33**(1): p. 326-342.
14. Foley, E., et al., *MEG Assessment of Expressive Language in Children Evaluated for Epilepsy Surgery.* Brain topography, 2019. **32**(3): p. 492-503.
15. Knecht, S., et al., *Handedness and hemispheric language dominance in healthy humans.* Brain, 2000. **123**(12): p. 2512-2518.
16. Breier, J.I., et al., *Atypical language representation in patients with chronic seizure disorder and achievement deficits with magnetoencephalography.* Epilepsia, 2005. **46**(4): p. 540-548.
17. Papanicolaou, A.C., et al., *Is it time to replace the Wada test and put awake craniotomy to sleep?* Epilepsia, 2014. **55**(5): p. 629-632.
18. Abou-Khalil, B., *An update on determination of language dominance in screening for epilepsy surgery: the Wada test and newer noninvasive alternatives.* Epilepsia, 2007. **48**(3): p. 442-455.
19. Schevon, C.A., et al., *Pediatric language mapping: sensitivity of neurostimulation and Wada testing in epilepsy surgery.* Epilepsia, 2007. **48**(3): p. 539-545.

20. Hirata, M., et al., *Determination of language dominance with synthetic aperture magnetometry: comparison with the Wada test.* Neuroimage, 2004. **23**(1): p. 46-53.
21. Papanicolaou, A.C., et al., *Magnetoencephalographic mapping of the language-specific cortex.* Journal of neurosurgery, 1999. **90**(1): p. 85-93.
22. Pirmoradi, M., et al., *Language tasks used for the presurgical assessment of epileptic patients with MEG.* Epileptic Disorders, 2010. **12**(2): p. 97-108.
23. Papanicolaou, A.C., et al., *Magnetocephalography: a noninvasive alternative to the Wada procedure.* Journal of neurosurgery, 2004. **100**(5): p. 867-876.
24. Szymanski, M.D., et al., *Magnetic source imaging of late evoked field responses to vowels: toward an assessment of hemispheric dominance for language.* Journal of Neurosurgery, 2001. **94**(3): p. 445-453.
25. Bowyer, S.M., et al., *Language laterality determined by MEG mapping with MR-FOCUSS.* Epilepsy & Behavior, 2005. **6**(2): p. 235-241.
26. Castillo, E.M., et al., *Mapping of expressive language cortex using magnetic source imaging.* Neurocase, 2001. **7**(5): p. 419-422.
27. Kamada, K., et al., *Expressive and receptive language areas determined by a non-invasive reliable method using functional magnetic resonance imaging and magnetoencephalography.* Neurosurgery, 2007. **60**(2): p. 296-306.
28. Bowyer, S.M., et al., *Magnetoencephalographic localization of the basal temporal language area.* Epilepsy & Behavior, 2005. **6**(2): p. 229-234.
29. Breier, J.I., et al., *Lateralization of cerebral activation in auditory verbal and non-verbal memory tasks using magnetoencephalography.* Brain topography, 1999. **12**(2): p. 89-97.
30. Rezaie, R., et al., *Assessment of hemispheric dominance for receptive language in pediatric patients under sedation using magnetoencephalography.* Frontiers in human neuroscience, 2014. **8**: p. 657.
31. Van Poppel, M., et al., *Passive language mapping with magnetoencephalography in pediatric patients with epilepsy.* Journal of Neurosurgery: Pediatrics, 2012. **10**(2): p. 96-102.
32. Pirmoradi, M., et al., *Verbal memory and verbal fluency tasks used for language localization and lateralization during magnetoencephalography.* Epilepsy research, 2016. **119**: p. 1-9.
33. Yuan, W., et al., *fMRI shows atypical language lateralization in pediatric epilepsy patients.* Epilepsia, 2006. **47**(3): p. 593-600.
34. Sparrow, S.S. and S.M. Davis, *Recent advances in the assessment of intelligence and cognition.* The Journal of Child Psychology and Psychiatry and Allied Disciplines, 2000. **41**(1): p. 117-131.
35. Nolan, M., et al., *Memory function in childhood epilepsy syndromes.* Journal of paediatrics and child health, 2004. **40**(1-2): p. 20-27.
36. Bonelli, S.B., et al., *Imaging memory in temporal lobe epilepsy: predicting the effects of temporal lobe resection.* Brain, 2010. **133**(4): p. 1186-1199.
37. Gleissner, U., et al., *Memory outcome after selective amygdalohippocampectomy: a study in 140 patients with temporal lobe epilepsy.* Epilepsia, 2002. **43**(1): p. 87-95.
38. Duncan, J.S., et al., *Brain imaging in the assessment for epilepsy surgery.* The Lancet Neurology, 2016. **15**(4): p. 420-433.

39. Collinge, S., et al., *Pre-surgical mapping of eloquent cortex for paediatric epilepsy surgery candidates: Evidence from a review of advanced functional neuroimaging.* Seizure, 2017. **52**: p. 136-146.
40. Kemp, S., et al., *Concordance between the Wada test and neuroimaging lateralization: Influence of imaging modality (fMRI and MEG) and patient experience.* Epilepsy & Behavior, 2018. **78**: p. 155-160.
41. Pu, Y., et al., *Non-invasive investigation of human hippocampal rhythms using magnetoencephalography: a review.* Frontiers in neuroscience, 2018. **12**: p. 273.
42. Baddeley, A., *Working memory: looking back and looking forward.* Nature reviews neuroscience, 2003. **4**(10): p. 829-839.
43. Myatchin, I., et al., *Working memory in children with epilepsy: an event-related potentials study.* Epilepsy research, 2009. **86**(2-3): p. 183-190.
44. Wager, T.D. and E.E. Smith, *Neuroimaging studies of working memory.* Cognitive, Affective, & Behavioral Neuroscience, 2003. **3**(4): p. 255-274.
45. Awh, E., L. Anllo-Vento, and S.A. Hillyard, *The role of spatial selective attention in working memory for locations: Evidence from event-related potentials.* Journal of Cognitive Neuroscience, 2000. **12**(5): p. 840-847.
46. Kübler, A., et al., *Co-ordination within and between verbal and visuospatial working memory: network modulation and anterior frontal recruitment.* Neuroimage, 2003. **20**(2): p. 1298-1308.
47. Postle, B.R., M. D'Esposito, and S. Corkin, *Effects of verbal and nonverbal interference on spatial and object visual working memory.* Memory & cognition, 2005. **33**(2): p. 203-212.
48. Thomason, M.E., et al., *Development of spatial and verbal working memory capacity in the human brain.* Journal of cognitive neuroscience, 2009. **21**(2): p. 316-332.
49. van der Ham, I.J., et al., *Categorical and coordinate spatial relations in working memory: An fMRI study.* Brain research, 2009. **1297**: p. 70-79.
50. Lamp, G., et al., *Mapping of the underlying neural mechanisms of maintenance and manipulation in visuo-spatial working memory using an n-back mental rotation task: a functional magnetic resonance imaging study.* Frontiers in Behavioral Neuroscience, 2016. **10**: p. 87.
51. Champod, A.S. and M. Petrides, *Dissociation within the frontoparietal network in verbal working memory: a parametric functional magnetic resonance imaging study.* Journal of Neuroscience, 2010. **30**(10): p. 3849-3856.
52. Stretton, J. and P. Thompson, *Frontal lobe function in temporal lobe epilepsy.* Epilepsy research, 2012. **98**(1): p. 1-13.
53. Canuet, L., et al., *Working memory abnormalities in chronic interictal epileptic psychosis and schizophrenia revealed by magnetoencephalography.* Epilepsy & Behavior, 2010. **17**(1): p. 109-119.
54. Chai, W.J., A.I. Abd Hamid, and J.M. Abdullah, *Working memory from the psychological and neurosciences perspectives: a review.* Frontiers in psychology, 2018. **9**: p. 401.
55. Yaple, Z. and M. Arsalidou, *N-back working memory task: Meta-analysis of normative fMRI studies with children.* Child development, 2018. **89**(6): p. 2010-2022.
56. Mürner-Lavanchy, I., et al., *Visuospatial working memory in very preterm and term born children—Impact of age and performance.* Developmental cognitive neuroscience, 2014. **9**: p. 106-116.

57. Song, W., et al., *A simple spatial working memory and attention test on paired symbols shows developmental deficits in schizophrenia patients.* Neural plasticity, 2013. **2013**.
58. Klingberg, T., H. Forssberg, and H. Westerberg, *Increased brain activity in frontal and parietal cortex underlies the development of visuospatial working memory capacity during childhood.* Journal of cognitive neuroscience, 2002. **14**(1): p. 1-10.
59. Olesen, P.J., et al., *Brain activity related to working memory and distraction in children and adults.* Cerebral cortex, 2007. **17**(5): p. 1047-1054.
60. Bechtel, N., et al., *Attention-deficit/hyperactivity disorder in childhood epilepsy: A neuropsychological and functional imaging study.* Epilepsia, 2012. **53**(2): p. 325-333.
61. Hershey, T., et al., *Short-term and long-term memory in early temporal lobe dysfunction.* Neuropsychology, 1998. **12**(1): p. 52.
62. Lindgren, Å., et al., *Development of cognitive functions in children with rolandic epilepsy.* Epilepsy & Behavior, 2004. **5**(6): p. 903-910.
63. Viggedal, G., et al., *Cognitive development from two to ten years after pediatric epilepsy surgery.* Epilepsy & Behavior, 2012. **25**(1): p. 2-8.
64. Burgess, R.C., et al., *American Clinical Magnetoencephalography Society Clinical Practice Guideline 2: presurgical functional brain mapping using magnetic evoked fields.* Journal of Clinical Neurophysiology, 2011. **28**(4): p. 355.
65. Zeno, S., et al., *The Educator's Word Frequency Guide [CD-ROM, DOS version].* Brewster, NY: Touchstone Applied Science Associates, 1996.
66. Tadel, F., et al., *Brainstorm: a user-friendly application for MEG/EEG analysis.* Computational intelligence and neuroscience, 2011. **2011**: p. 8.
67. Nolte, G. and G. Curio, *The effect of artifact rejection by signal-space projection on source localization accuracy in MEG measurements.* IEEE transactions on biomedical engineering, 1999. **46**(4): p. 400-408.
68. Ver Hoef, L.W., et al., *Left mesial temporal sclerosis and verbal memory: a magnetoencephalography study.* Journal of Clinical Neurophysiology, 2008. **25**(1): p. 1-6.
69. Papanicolaou, A.C., *Clinical magnetoencephalography and magnetic source imaging*. 2009: Cambridge University Press.
70. Shattuck, D.W. and R.M. Leahy, *BrainSuite: an automated cortical surface identification tool.* Medical image analysis, 2002. **6**(2): p. 129-142.

Study Flow Diagram