Passive Testing of Cognitive Function in Epileptic Children Unwilling or Unable to Cooperate: Comprehensive Summary of Non-Invasive Neurophysiological Approaches

Milena Korostenskaja1*, Ki H Lee1, James Baumgartner2 and Eduardo M Castillo1,3
1 MEG Lab, Florida Hospital for Children, Orlando, FL, USA
2 Functional Brain Mapping and Brain Computer Interface Lab, Florida Hospital for Children; Orlando, FL, USA
3 Comprehensive Pediatric Epilepsy Center, Florida Hospital for Children, Orlando, FL, USA
*Corresponding author: Milena Korostenskaja, Functional Brain Mapping and Brain-Computer Interface Lab, Florida Hospital for Children, Orlando, Florida, 601 E. Rollins St. Orlando, FL 32803, USA, Tel: 1-513-503-8026; Fax: 1-407-303-8197; E-mail: milena.korostenskaja@gmail.com

Abstract

Epilepsy surgery is a potentially curative option for children with intractable epilepsy. In order to avoid post-surgical deficits in language and cognitive functioning, the mapping of these brain functions must be performed. Neurophysiological techniques, such as Electroencephalography (EEG) and Magnetoencephalography (MEG) are non-invasive procedures that can be used to attain this goal. However, they often fail when used to perform functional mapping in uncooperative patients who are unwilling, or unable to communicate or follow the commands. Therefore, there is a need for a new functional mapping procedure that can be performed without active patient’s participation. The aim of this paper is to integrate and organize currently existing body of knowledge regarding passive testing of information processing and cognitive functioning in pediatric epilepsy patients. It is the first attempt to present a cohesive summary of literature regarding this topic. We will summarize results from currently available passive paradigms for neurophysiological assessment. There are a number of paradigms that could be used for passive evaluation of cognitive function in children with epilepsy. Examples include odd-ball paradigms eliciting Mismatch Negativity (MMN) and P3a responses, continuous word recognition paradigm, and story listening paradigms. In addition, resting state connectivity analysis with correlation to the cognitive testing/behavioral data can be used. Importantly, the majority of these paradigms can be performed during sedation.

Keywords: Electroencephalography (EEG); Epilepsy surgery; Event-Related Fields (ERFs); Event-Related Potentials (ERPs); Cognitive functions; Continuous word recognition task; Functional connectivity; Information processing; Magnetoencephalography (MEG); Mismatch Negativity (MMN); P3a; Pediatric epilepsy

Abbreviations: EEG: Electroencephalography; ERFs: Event-Related Fields; ERPs: Event-Related Potentials; fMRI: functional Magnetic Resonance Imaging; MEG: Magnetoencephalography; MMN: Mismatch Negativity; NES: Non-Epileptic Seizures; P3a: Involuntary attention switch; TLE: Temporal Lobe Epilepsy

Introduction

In the United States, epilepsy affects nearly 326,000 children under the age of 16 and it is estimated that 10-30% of these cases are resistant to antiepileptic medications [1]. The pediatric population with treatment-resistant epilepsy possesses a number of cognitive deficits in memory, attention and language domains [2] (within the context of our summary we will refer to these domains and subdomains (i.e. cognitive operations) as to cognitive functioning). While epilepsy surgery is a potentially curative option for these patients [3], it may not be given full consideration due to concerns regarding the potential impact on language and cognitive function [4,5].

In order to avoid post-surgical deficits in language and cognitive functioning, the mapping of these brain functions must be performed as part of a routine evaluation for epilepsy surgery [6-10]. The results from all neuroimaging modalities, outlining functional organization of cortical tissue, are integrated together and can be imported to neuronavigation system, which will be used by surgeon intra-operatively. Such approach allows surgeon to avoid resection of the areas, removal of which may lead to post-surgical morbidity.

Neurophysiological techniques, such as Electroencephalography (EEG) and Magnetoencephalography (MEG), are non-invasive procedures allowing the creation of functional brain maps with high temporal (both EEG and MEG) and spatial (MEG) resolution [11]. While these provide excellent clinical evaluation results in cooperative adults and children [12], they often fail in patients who are unwilling or unable to comply with the requirements of the neurophysiological procedures. Patients may have difficulty sitting still, following commands, and performing the required tasks [13]. For these patients, the probability of post-surgical morbidity is higher due to the lack of proper functional brain localization. Therefore there is a need to introduce neurophysiological procedures that allow mapping of cognitive brain function in children unwilling or unable to cooperate.

To achieve this goal, it is possible to record automatic brain responses that do not require active patient participation [14,15]. These automatic brain responses can be recorded in patients who are conscious [16], sleeping [17], uncommunicative [18,19], or under sedation [20]. We will discuss possible recording approaches by summarizing existing paradigms, such as procedures that evoke the desired brain response. These paradigms may help evaluate processing of external information (i.e., primary auditory processing) [21], sensory memory trace formation [22-25], involuntary attention switch [26], and language [27]. In particular, we will focus on automatic auditory evoked responses,
such as Mismatch Negativity (MMN) [28], involuntary attention switch (P3a) [29], as well as functional connectivity studies [30]. Then we will discuss literature related to the use of automatic brain responses during anesthesia and sedation [31]. Finally, we will summarize studies where these paradigms were used with epilepsy patients to provide evidence for mapping of cognitive function in unwilling and uncooperative patients [32].

Methods

Literature search

A literature search was conducted in PubMed (years 1970–2013) using the following key words: epilepsy and: information processing; auditory information processing; cognitive function, event-related potentials, ERPs; event-related fields, ERFs; change detection, mismatch negativity, MMN; P300, P3a, novelty detection; language function; connectivity; resting state; functional mapping. In addition, we searched the reference lists of our located papers in order to manually find other pertinent studies. We were able to identify 96 relevant articles.

Inclusion and exclusion criteria

For inclusion in our summary of the existing paradigms and procedures, a study had to meet following criteria: (1) to represent Neurophysiological approach of testing cognitive function and information processing; (2) to represent neuroimaging approach that has a potential to be translated into neurophysiological approach for testing information processing and cognitive functioning in children with epilepsy as a part of pre-surgical evaluation.

Neurophysiological Indices

The objective detection of changes in human brain activity with millisecond temporal resolution can be achieved with non-invasive neurophysiological techniques such as EEG and MEG [11]. Moreover, signal averaging and other event-related algorithms help to extract Event-Related Potentials (ERPs) and Event-Related Fields (ERFs), which reflect cognitive events related to a particular stimulus, from general spontaneous brain activity [33]. There are a number of paradigms (described in the following sections within the rest of this paper: 6.1 Testing auditory sensory memory (MMN), 6.2 Testing Involuntary Attention Switch (P3a), 6.3 Testing Language Function and 6.4 Resting State Functional Connectivity) that can be used to passively test cognitive functions in healthy people [16], and may have potential application for the pediatric epilepsy population [21]. These indices of passive cognitive processing may yield valuable information in uncooperative children [34]. In addition, passive paradigms adapted for neurophysiological recordings from other imaging modalities, such as functional Magnetic Resonance Imaging (fMRI), may provide additional necessary information [35].

Testing Auditory Sensory Memory (MMN)

An event-related brain response that reflects brain activity resulting from change in stimulus features (such as duration, frequency, intensity, etc.) was termed the Mismatch Negativity (MMN) [36,37]. It can be recorded both electrically and magnetically (MMNm). An example of an MMNm response is shown in Figure 1. The auditory MMN response peaks at about 100–240 ms and is elicited by any detectable change in some repetitive aspect of auditory stimulation, such as a change in sound frequency, duration, intensity, or location [38]. It is thought to represent auditory echoic memory formation [39] as well as passive deviance detection in the auditory domain [40]. It is suggested that dysfunction reflected by the MMN can hinder language and other complex cognitive development [38,41].

MMN in uncooperative patients: The most valuable feature of the MMN for investigating the clinical patient population is that it can be recorded without requiring the subject's active response or attention to sounds. A number of studies have demonstrated the potential for recording MMN response in premature newborns [42]; neonates [43,44] (EEG recordings); and fetuses [45–47] (MEG recordings). A recent study found increased MMN-like response to deviant sounds compared to standard stimuli, suggesting the potential use of MMN as

Figure 1: Event-Related Field (ERF) responses in healthy 12-yo male elicited during: (left) “oddball” paradigm with one standard and one frequency deviant tone; (right) “novelty odd-ball” paradigm with one standard, one frequency deviant, and one novel (unexpected) sound. Please, note higher P3am response elicited during “novelty odd-ball” paradigm. Responses from three MEG sensors located in the right temporal areas are presented for each condition: paired sensors – gradiometers; single sensor – magnetometer.
a biomarker of cognition in newborn infants [48]. Moreover, patients in a coma or vegetative state were able to produce distinguishable MMN responses [49,50].

**MMN during sedation:** For practical purposes, it is important that the responses related to cognition in uncooperative epilepsy patients can be detected under anesthesia or sedation. In epilepsy patients, propofol is the most commonly utilized anesthetic. However, studies investigating the effect of propofol on MMN are not comprehensive and have shown conflicting results. For example, one study found no MMN response to change in stimuli frequency and duration with low dosage of propofol [51]. Other studies have found identifiable, but MMN differences were found comparing reduced MMN responses during propofol induced sedation [52,53]. Alternatively, another study found no changes in MMN response in children with benign rolandic epilepsy [58].

**MMN in epilepsy:** MMN seems to be particularly suitable for studying temporal and frontal lobe epilepsy, as the main sources of MMN activity are located in the temporal cortex with subsequent activation in the inferior frontal gyri [55,56]. The number of reported epilepsy-related MMN changes is limited (Table 1). Nevertheless, altered MMN responses were demonstrated in epilepsy patients when compared with healthy controls (Figure 2). For example, an EEG study showed delayed latency of MMN response [57], and absence of MMN response was found in children with benign rolandic epilepsy [58]. Alternatively, another study found no changes in MMN response in medication-free patients with centrotemporal spikes [59], thus implying the possible effect of medication on the parameters of MMN response.

**Impairment of the auditory change detection was also observed in patients with Mesial Temporal Lobe Epilepsy (MTL), as demonstrated by longer MMNm latencies in these patients when compared to healthy control subjects [60]. Significant delay of MMN response to sound stimuli in both frontal and mastoid sites was found in patients with Temporal Lobe Epilepsy (TLE) compared to healthy controls [61]. Interestingly, in the same group of TLE patients, the MMN response to speech sounds was reduced only at fronto-central sites but not over the mastoids [62].**

Unlike studies utilizing the classic odd-ball paradigm to elicit MMN response, a recent study on epilepsy patients employed a "multi-feature" paradigm [21]. This "multi-feature" paradigm ("Optimum-1") [63], enables the recording of MMN for five deviant sound types in the same amount of time that MMN can be obtained for only 1-2 deviant types in the traditional oddball paradigm. The "multi-feature" paradigm is extremely useful for studies of clinical and pediatric

### Table 1: Mismatch Negativity (MMN) and P3a changes in epilepsy.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of epilepsy</th>
<th>Type of stimuli used with “Novelty odd-ball” paradigm</th>
<th>Observed MMN change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boatman et al. (2008) [57]</td>
<td>Benign rolandic epilepsy</td>
<td>“Odd-ball” MMN to tone frequency change and to speech stimuli (phoneme change)</td>
<td>↑ MMN latency</td>
</tr>
<tr>
<td>Liiasis et al. (2006) [58]</td>
<td>Benign rolandic epilepsy with centrotemporal spikes</td>
<td>“Odd-ball” MMN to speech stimuli (syllable change)</td>
<td>Absence of MMN response</td>
</tr>
<tr>
<td>Duman et al. (2008) [59]</td>
<td>Epilepsy with centrotemporal spikes</td>
<td>“Odd-ball” MMN to tone frequency change</td>
<td>No changes</td>
</tr>
<tr>
<td>Lin et al. (2007) [60]</td>
<td>Mesial temporal lobe epilepsy</td>
<td>“Odd-ball” MMN to tone frequency and duration change</td>
<td>↑ MMN latency</td>
</tr>
<tr>
<td>Miyajima et al. (2011) [61]</td>
<td>Temporal lobe epilepsy</td>
<td>“Odd-ball” MMN to tone frequency change</td>
<td>↑ MMN latency in both frontal and mastoid sites</td>
</tr>
<tr>
<td>Hara et al. (2012) [62]</td>
<td>Temporal lobe epilepsy</td>
<td>“Odd-ball” MMN to speech (vowel) sounds change</td>
<td>↓ MMN amplitude at fronto-central sites, but not mastoids</td>
</tr>
<tr>
<td>Korostenskaja et al. (2010) [21]</td>
<td>Intractable epilepsy</td>
<td>“Multi-feature” MMN to change in tone duration, frequency, intensity, location, and gap</td>
<td>↓ MMNm amplitude</td>
</tr>
<tr>
<td>Honbozy et al. (2006) [64]</td>
<td>Landau-Kleffner syndrome</td>
<td>“Odd-ball” MMN to ‘phoneme-deviant’ and a ‘stress-deviant’</td>
<td>Absence of MMN to phoneme deviant; presence of MMN to stress deviant</td>
</tr>
<tr>
<td>Gene-Cos et al. (2005) [65]</td>
<td>Epileptic vs non-epileptic seizures</td>
<td>“Odd-ball” MMN to tone frequency change</td>
<td>↑ MMN latency in epilepsy patients</td>
</tr>
<tr>
<td>Borghetti et al. (2007) [66]</td>
<td>Epilepsy treated with vagus nerve stimulation</td>
<td>“Odd-ball” MMN to tone frequency change</td>
<td>Improvement of MMN parameters after treatment</td>
</tr>
<tr>
<td>Hara et al. (2013) [67]</td>
<td>Epilepsy with cavernous angioma</td>
<td>“Odd-ball” MMN to speech (vowel) sounds change</td>
<td>Improvement of MMN parameters after surgery (recovery of MMN response, ↑ amplitude, ↓ latency)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of epilepsy</th>
<th>Type of stimuli used with “Novelty odd-ball” paradigm</th>
<th>Observed P3a change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kotz et al. (2007) [77]</td>
<td>Primary lesions in the anterior portion of the left (ATL) and right (ATR) temporal lobe</td>
<td>2 pure tones (deviating in frequency) and 1 novel stimuli (sound categories: meaningful and non-meaningful)</td>
<td>Differentiation of meaningful and non-meaningful sounds at midline sites (healthy controls had effect at posterior lateral and midline electrode sites)</td>
</tr>
<tr>
<td>Friedman et al. (2011) [76]</td>
<td>Intractable epilepsy patients that had unilateral anteromedial resection of the medial temporal lobe (ATML)</td>
<td>2 pure tones (deviating in frequency) and 1 novel stimuli (sound categories: animal, bird, human, musical instrument, environmental, and electronic)</td>
<td>Lack of P3a habituation (compared to healthy controls)</td>
</tr>
</tbody>
</table>

---

**Reference Type of epilepsy MMN type Observed MMN change**

- **Boatman et al. (2008) [57]** Benign rolandic epilepsy “Odd-ball” MMN to tone frequency change and to speech stimuli (phoneme change) ↑ MMN latency
- **Liiasis et al. (2006) [58]** Benign rolandic epilepsy with centrotemporal spikes “Odd-ball” MMN to speech stimuli (syllable change) Absence of MMN response
- **Duman et al. (2008) [59]** Epilepsy with centrotemporal spikes “Odd-ball” MMN to tone frequency change No changes
- **Lin et al. (2007) [60]** Mesial temporal lobe epilepsy “Odd-ball” MMN to tone frequency and duration change ↑ MMN latency
- **Miyajima et al. (2011) [61]** Temporal lobe epilepsy “Odd-ball” MMN to tone frequency change ↑ MMN latency in both frontal and mastoid sites
- **Hara et al. (2012) [62]** Temporal lobe epilepsy “Odd-ball” MMN to speech (vowel) sounds change ↓ MMN amplitude at fronto-central sites, but not mastoids
- **Korostenskaja et al. (2010) [21]** Intractable epilepsy “Multi-feature” MMN to change in tone duration, frequency, intensity, location, and gap ↓ MMNm amplitude
- **Honbozy et al. (2006) [64]** Landau-Kleffner syndrome “Odd-ball” MMN to ‘phoneme-deviant’ and a ‘stress-deviant’ Absence of MMN to phoneme deviant; presence of MMN to stress deviant
- **Gene-Cos et al. (2005) [65]** Epileptic vs non-epileptic seizures “Odd-ball” MMN to tone frequency change ↑ MMN latency in epilepsy patients
- **Borghetti et al. (2007) [66]** Epilepsy treated with vagus nerve stimulation “Odd-ball” MMN to tone frequency change Improvement of MMN parameters after treatment
- **Hara et al. (2013) [67]** Epilepsy with cavernous angioma “Odd-ball” MMN to speech (vowel) sounds change Improvement of MMN parameters after surgery (recovery of MMN response, ↑ amplitude, ↓ latency)

**P3a**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of epilepsy</th>
<th>Type of stimuli used with “Novelty odd-ball” paradigm</th>
<th>Observed P3a change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kotz et al. (2007) [77]**</td>
<td>Primary lesions in the anterior portion of the left (ATL) and right (ATR) temporal lobe</td>
<td>2 pure tones (deviating in frequency) and 1 novel stimuli (sound categories: meaningful and non-meaningful)</td>
<td>Differentiation of meaningful and non-meaningful sounds at midline sites (healthy controls had effect at posterior lateral and midline electrode sites)</td>
</tr>
<tr>
<td>Friedman et al. (2011) [76]**</td>
<td>Intractable epilepsy patients that had unilateral anteromedial resection of the medial temporal lobe (ATML)</td>
<td>2 pure tones (deviating in frequency) and 1 novel stimuli (sound categories: animal, bird, human, musical instrument, environmental, and electronic)</td>
<td>Lack of P3a habituation (compared to healthy controls)</td>
</tr>
</tbody>
</table>
populations, since it facilitates evaluation of the patient’s cortical discrimination accuracy for multiple sound features such as duration, frequency, intensity, location, or silent gap with a minimal recording time. Compared to healthy controls, patients with intractable epilepsy had reduced amplitude in all magnetic MMN responses to 5 deviant sounds [21].

It is important to note that there seems to be a specific pattern of MMN changes in patients with a certain type of epilepsy. For example, specific MMN changes related to language impairment were found in patients with Landau-Kleffner syndrome [64]. MMNs were recorded in response to phoneme and stress differences; however authors were able to identify MMN responses only to the phoneme, but not the stress differences [64]. This was in agreement with neuropsychological examination that showed dissociation between verbal and nonverbal functions. Because the source of epileptic activity was localized, it was assumed that a limited brain region was affected. Combined with results of specific MMN deficiency, this may suggest dissociation between intact phonemic and defective higher-level language processing.

Subjects with epileptic seizures had longer MMN latencies than subjects with Non-Epileptic Seizures (NES) [65]. This suggests that patients with epilepsy may have difficulty with auditory change discrimination. Moreover, the significantly different distribution of MMN responses in the NES group compared to healthy controls suggests an abnormal generation of MMN responses in the NES group.

Changes in MMN parameters following epilepsy treatment were observed in a study of MMN data from epilepsy patients before and after one year of treatment with implanted vagus nerve stimulation [66]. Two of those patients show clearly identifiable improvement, through an increase in amplitude and decrease in latency, for abnormal baseline MMN parameters despite no improvement in seizure density. This was interpreted as an improvement in automatic attention processes in those patients. Moreover, recovery of MMN response and improvement in MMN parameters were observed after surgical resection in epilepsy patient with temporal lobe epilepsy [67].

Changes in MMN parameters following epilepsy treatment were observed in a study of MMN data from epilepsy patients before and after one year of treatment with implanted vagus nerve stimulation [66]. Two of those patients show clearly identifiable improvement, through an increase in amplitude and decrease in latency, for abnormal baseline MMN parameters despite no improvement in seizure density. This was interpreted as an improvement in automatic attention processes in those patients. Moreover, recovery of MMN response and improvement in MMN parameters were observed after surgical resection in epilepsy patient with temporal lobe epilepsy [67].

The literature on MMN epilepsy studies is limited in size and scope. Additional studies are needed that explore the cognitive correlates, clinical, and predictive ability of this neurophysiological response before it can be fully incorporated into the clinical assessment of cognition. The relationship between abnormalities in MMN response and language function also needs to be investigated. Nevertheless, the application of MMN to the study of epilepsy is very promising and could give new insight into the pathophysiology of the disorder.

Summary of MMN: MMN can potentially be a valuable tool, providing a reliable index of auditory sensory memory formation in pediatric epilepsy patients that are unwilling or unable to cooperate. Future studies are needed to evaluate the effect of light sedation in this challenging population.

Testing Involuntary Attention Switch (P3a)

The P3a in EEG recordings is a positive response, peaking around 250-350 ms after stimulus onset [29]. P3a is elicited by a novel unexpected stimuli ("distractor") and has been associated with the reorienting of involuntary attention towards the novel event following the processes reflected by MMN [68]. The frontal lobes seem to be necessary for P3a generation, as P3a amplitude was significantly diminished in the presence of distracting stimuli in patients with frontal lobe lesions [69]. Similar to MMN, the P3a response can be recorded with Magnetoencephalography (P3am) [70,71] (Figure 1).

P3a for uncooperative patients: Although P3a studies are not

---

Figure 2: Example of reduced magnetic MMN and P3a responses in adult epilepsy patient when compared with healthy control subject. Importantly, MRI-integrated MEG results on top demonstrate interictal epileptiform discharges localized in the left temporal lobe – the area of reduced amplitudes of MMNm and P3am responses.
as common in young children and uncooperative patients as MMN studies, there is sufficient data to suggest that the novelty ("distraction") paradigm can be used in this targeted group of subjects. It can provide a measure of frontal lobe function, as well as attention switch from pre-attentive change detection. The P3a was successfully recorded in children aged 6-8 and 10-12 years old [72]. Moreover, P3a differences were demonstrated between 5 year olds born premature or full-term [73]. P3a-analogue was recorded with EEG in 2 year olds and newborns [74]. In addition, novelty-related responses in newborns were recorded with MEG [75]. P3a has also been recorded in patients with disorders of consciousness [15, 49].

**P3a during sedation:** The literature on the effect of sedation and/or anesthesia on novelty processing, especially processing as indexed by P3a, is relatively scarce. There is, however, evidence suggesting brain regions are affected differently by type and dose of anesthetic. For example, while temporal brain regions can be active even during deep sedation, frontal brain regions are more sensitive to the effects of anesthetics and tend to switch off earlier than the temporal ones. A study using fMRI showed language-related activation in temporal and frontal regions during wakefulness, but only temporal area activation during the unresponsiveness due to propofol anesthetic induction [54]. Similar results were shown in a study in which ERPs were recorded in patients undergoing anesthesia with propofol [20]. This has a direct impact on the ability to observe P3a under different levels of anesthesia, as frontal lobes play an important role in its generation. This differs from MMN, the main generators for which are localized in the auditory cortices. Therefore, it is expected that while MMN responses can still be detected, P3a responses may be diminished or absent. Similar to MMN responses, a study found indexed P3a attention reorientation processes to be functional during deep sedation [52], although these findings need to be replicated. It is possible to speculate that during light sedation, P3a responses can be successfully recorded. However, additional studies are needed to evaluate the effect new sedation drugs, such as dexmedetomidine, have on this response.

**P3a in epilepsy:** Limited studies have examined the change in novelty detection for patients with epilepsy. To our knowledge, only two studies were carried out in this regard (Table 1). One study demonstrated the importance of both left and right intact hippocampi in the detection of repetitive novel stimuli [76]. The other showed that both left and right intact anterior temporal lobes are imperative for lexical-semantic processing of novel sounds [77].

**Summary of P3a.** Overall, P3a appears to be a potential tool for evaluation of frontal lobe function in children with epilepsy. For these patients, the novelty paradigm may assess the functionality between the left and right temporal lobes. There is evidence to suggest that uncooperative children can be studied with the novelty paradigm during anesthesia.

**Testing language function**

Functional mapping of eloquent language cortex is one of the most broadly utilized MEG tests and is approved for clinical use. A variety of different paradigms are employed to test language function. MEG is used to localize the Wernicke’s areas located in temporal and temporoparietal regions that are responsible for receptive language function [78]. The inherent sensitivity of MEG to tangentially oriented sources of brain magnetic activity (as opposed to radial sources) makes this instrument ideal to characterize language-specific activity arising from posterior temporoparietal structures. Examples of the paradigms utilized for such localization include the recognition memory task for spoken words (“continuous word recognition task”) [79], semantic decision task, and general reading task [80]. However, paradigms assessing expressive language function have also been proposed [81]. They include, but are not limited to, picture naming and verb generation [82,83], action word stem completion, action naming, and verbal fluency tasks [80].

MEG has been used to characterize the contribution of posterior temporoparietal structures to word comprehension in patients with Landau-Kleffner syndrome [84] (Figure 3) and in children with reading disorders [85]. The reorganization of linguistic functions that takes place following brain surgery [78] and the effects of intensive speech therapy following a stroke have been as well documented [86].

**Language function in uncooperative patients:** Although a variety of different tasks for assessing language function have been proposed, only a limited number of these tasks can be applied to young children, and even fewer can be used passively for uncooperative patients. Several researchers have developed neurophysiological tools to assess language function without active subject participation, such as speech sound

---

**Figure 3:** Integrated individual patient’s MRI and MEG-derived activation map obtained during a continuous word recognition task in a 10 yo male patient with Landau-Kleffner syndrome. Notice that MEG localized the sources of interictal discharges (yellow triangles) in close proximity to the language-specific cortex (red dots).
discrimination. The stimuli for these tests are presented in "odd-ball" fashion – similar to those for eliciting passively MMN-like responses. Such paradigms for vowel discrimination (/a/ versus /ai/) were tested in healthy adults [87], as well as adults evaluated for tumor surgery [88]. Moreover, it was demonstrated that it is possible to study speech–sound discrimination even in neonates [89]. A recent study showed that a "multi-feature" paradigm utilizing changes in syllables (in current study Finnish syllables - /tec/ and /pi/) can be successfully used for assessing speech–sound discrimination in newborns in a relatively short period of time [90]. Another study found that a "multi-feature" MMN paradigm with changes in pseudo-words was an effective tool for studying speech development in children from 7 to 12 years of age [16].

Passive listening paradigms with words have yielded favorable results in populations of healthy adults, and are potentially applicable to young patients [91-96]. A recent study proposed a new paradigm, inducing both MMN and P3a responses, for studying involuntary language processing in the brain [27]. Investigators observed a clear P3a peak to spoken stimuli around 240 ms after stimulus onset, suggesting an involuntary shift of attention to spoken (as opposed to tone) stimuli. They suggest that this paradigm can help with assessing the language comprehension process, especially in uncooperative patients [27].

Other paradigms, such as "story listening", have been used to passively assess receptive language function. This paradigm originally came from fMRI studies [97,98] and was successfully applied to functional mapping with intracranial electrodes by calculating power changes in the gamma frequency band [6]. During testing, the subject is presented with a short story; for comparison, a modulated sound is then presented for the same amount of time. Differences between the activities elicited by these tasks are evaluated and are considered to be a reflection of language comprehension. However, to our knowledge, no MEG studies to date have used this task for passive evaluation of receptive language function. MEG data showing newborns' responses to prosodic clues in continuous speech has been used to evaluate speech processing in newborns [99].

Language function during sedation: The examination of language function during anesthesia was performed more often in fMRI studies than neurophysiological recordings. For example, a different pattern of BOLD signal activation with the passive "story listening" paradigm was demonstrated in 1 year old infants after administration of pentobarbital and propofol [100]. A distinct effect of anesthesia was found on language activation in frontal and temporal areas of the brain [54]. An fMRI case study in a 4 year old autistic patient indicated that it is possible to elicit activation of brain areas responsible for word recognition during propofol sedation [101]. Neurophysiological studies of language during anesthesia need to be performed.

Language function in epilepsy: There are a relatively large number of studies related to evaluation of language function in adult epilepsy patients [12], compared to studies of uncooperative adults or young patients. Generally, children 5 years of age and younger require anesthesia during MEG evaluation for epilepsy surgery [102]. To our knowledge there has only been one study to date on reported MEG language mapping in sedated epilepsy patients. The authors of this study reviewed successful functional language mapping results obtained during passive continuous word recognition task from patients under propofol sedation [32]. In three patients evaluated for epilepsy surgery, the language evaluation with MEG enabled avoidance of post-surgical language deficits.

Summary of language function: There are a number of paradigms currently available that allow passive testing of language function. However, they need to be transferred to clinical settings, validated, and applied to pediatric patients undergoing evaluation for epilepsy surgery with sedation.

Resting state functional connectivity

Studies of resting state functional connectivity with fMRI [103,104] triggered an interest from neurophysiologists working with EEG and MEG. As a result, a number of studies investigated functional connectivity with neurophysiological techniques in different clinical populations, such as patients with traumatic brain injury [105], multiple sclerosis [106,107], and schizophrenia [108]. The impetus behind the resting state functional connectivity studies is the hope that identification of correlations between the activities in different brain regions during resting state may reveal functional neural networks, which are imperative for proper cognitive functioning. Studies of healthy subjects showed that changes in different parts of functional networks in the developing brain are associated with cognitive performance on a number of domains, such as executive function and processing speed [109]. Moreover, it was demonstrated that disruption of functional networks may produce specific cognitive dysfunction. For instance, in a study of resting state connectivity in patients with agenesis of the corpus callosum to matched healthy controls, interruption of the functional network involving the corpus callosum produced very specific cognitive changes [110]. Because tests involving resting state connectivity measurements do not require active participation, they can be performed in both uncooperative and very young participants.

Functional connectivity in uncooperative patients: There are several studies that have demonstrated the possibilities of functional connectivity evaluation in very young children, as well as in challenging patient populations such as children with autism spectrum disorder. For example, EEG was used to study functional brain network organization in children between 2 and 5 years of age, demonstrating a correlation between functional connectivity and age [111]. Another study showed significant increase in functional excitation from occipital to frontal areas of the brain in youth with autism spectrum disorders, as assessed with MEG [112].

Functional connectivity during sedation: It appears that resting state functional connectivity can be studied without conscious subject participation. Several studies have reported functional connectivity results during anesthesia. A study of functional connectivity used fMRI in healthy volunteers at several levels of consciousness during propofol sedation: "awake", "sedated", and "unresponsive" [113]. They observed the relationship between changes in the pattern of functional connectivity, a reduction in the connectivity between putamen and other brain regions, and extinguishing of auditory responsiveness. The effect of sevoflurane in "awake", "deep" and "light" states of healthy adult volunteers was examined by studying BOLD response changes [114]. It is interesting to note that there was a significant reduction in functional connectivity during deep anesthesia, and the amount of the reduction depended on the anesthesia level. To date, there are no published studies that relate brain functional connectivity measures under anesthesia with a subject's cognitive characteristics. Furthermore, to our knowledge there are no neurophysiological studies to date on functional connectivity in the brain during anesthesia.

Functional connectivity in epilepsy: Several Neurophysiological studies have investigated functional connectivity in patients with epilepsy and were able to: (1) delineate networks of functional connectivity in this challenging patient cohort [115]; and (2) demonstrate changes in connectivity pattern associated with the active
state of childhood benign rolandic epilepsy with sharp waves and with its remission [116]. Interestingly, functional brain connectivity findings in patients with intractable epilepsy were more consistent when derived from EEG data rather than from MEG [117]. However, to our knowledge only one study to date has explored the relationship between connectivity measures and the cognitive status of epileptic patients. The study reported that functional network characteristics correlated with cognitive performance in epileptic glioma patients [118]. A decrease in global integration and synchronization in theta frequency band was associated with cognitive decline in those patients [118]. More studies are needed to expand existing data in this field, as well as to evaluate the relationship between functional connectivity and cognition in children with epilepsy.

Summary of resting state functional connectivity: Studies investigating the functional state of brain networks are relatively new in the field of neurophysiology. Although existing studies show promising results and indicate the potential for applying functional connectivity methodology to the study of cognition in children with epilepsy, there is a need for more data to advance this approach and make it available for clinical use.

Reliability and Validity

Verification with electrocorticography

Existence and generation of a number of cognitive evoked potentials, that can be elicited passively, was confirmed by a recognized golden standard of neurophysiological recordings – electrocorticography (ECoG) [119-128]. This method allows the recording of brain signals directly from the cortical surface and is performed as a routine procedure during invasive evaluation for epilepsy surgery. By utilizing ECoG, for example, the origins of auditory MMN generation in superior temporal and frontal lobes [119] as well as hippocampus [125] were confirmed.

Relationship with cognitive functioning

The relationship between passive ERP/ERF responses and cognitive functions was demonstrated. For example, Foster, Kisley [129] showed that verbal memory and executive functions (i.e., planning and conditional inhibition) were excellent predictors of variance in the frequency MMNm amplitude had significant correlation with the behavioral improvement of verbal memory and focused attention in stroke patients. Finally, Mikkola, Kushnerenko [130] demonstrated that frequency MMN was larger in the preterm than in control children. This recorded MMN to frequency change correlated well with verbal intelligence quotient (Verbal IQ) (r=0.43, p=0.03) and with NEPSY verbal fluency subtest scores (r=0.5, p<0.04) in preterm children at 5 years of age.

Reliability of ERPs/ERFs

Reliability of ERP/ERF responses was explored in several studies [131,132]. For example, Hall et al. [132] showed that high reliabilities for both amplitude and latency of P300 response and amplitude of MMN response. Later study by Paukkunen et al. [131] demonstrated that the measurement error may affect reliability of repeated MMN measures. However, these effects can be minimized. These results can be applicable to both actively and passively registered ERP/ERF responses.

Conclusion

In our paper, we have summarized possible paradigms to study cognition in uncooperative epilepsy children using neurophysiological techniques (EEG, MEG). The main approaches that we have discussed involved “odd-ball” paradigms, allowing examination of auditory information processing. It is important to note that brain responses elicited during these paradigms can be essential for learning, memory, as well as language function. We believe that further development of currently available paradigms and techniques, and external clinical validation of the results, can have a positive impact on surgical outcomes in patients undergoing resection of seizure focus.

References


