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Childhood Absence Epilepsy And Varied Effect On Performance On Attention And Motor Tasks, With Correlation To Eeg And Fmri

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Childhood absence epilepsy and varied effect on performance
On attention and motor tasks, with correlation to
EEG and fMRI

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Jose Luis Gonzalez

2012

Abstracts of M.D. Thesis

Childhood absence epilepsy is characterized by a distinct 3-4 Hz spike and wave discharge seen on EEG that is usually associated with a brief loss of consciousness. It is a general form of epilepsy believed to affect the entire brain. We studied children with childhood absence epilepsy with simultaneous fMRI/EEG while they were doing a behavioral test, either continuous performance task (CPT), or repetitive tapping task (RTT). We were interested in the effect seizures would have on their performance on the CPT and RTT task, an attention and motor task respectively. We found that children would be affected earlier or even before seizure onset during the CPT task, while they would be affected later on in the seizure during the RTT task. There was also worse interictal performance in runs where a seizure was recorded. When correlating this with the imaging we found there to be greater power in the frontal leads of the EEG when a child was unable to perform during a seizure, and there was decreased signal in the frontal lobe with fMRI in similarly impaired performance during seizure. This leads us to believe that the frontal lobes, through corticothalamic networks, are more greatly affected during seizure with increased impairment.

Acknowledgements

I would first like to thank Yale for giving me the opportunity and the resources to be able to successfully complete this thesis. I would also like to thank all the members of the Blumenfeld lab that have worked on this project over the years. I would like to give a specific thank you to Jennifer Guo as she was a great lab coworker and someone to bounce ideas off of, XiaoXiao Bai, for all the fMRI and EEG analysis, and Stephen Jhun for helping me query and organize the behavioral data from the database. Most importantly, I could not thank enough Dr. Hal Blumenfeld, for all the encouragement, the great mentorship, being a superb role model, and someone from whom it has truly been an honor to learn.

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Introduction:

The first description of absence seizures, also known as petit mal, was in 1705 by the French physician Francis Poupart. The renowned Johns Hopkins history of medicine professor Owsei Temkin, in his book “The falling sickness: A history of epilepsy from the Greeks to the beginnings of modern neurology” translates the original French article where Poupart describes a patient he had: ‘If she has begun to talk and the attack interrupts her, she takes it up again at precisely the point at which she stopped, and she believes she has talked continuously.’ He offered this description to contrast absence seizures’ short, brief episodes with loss of consciousness, from the loss of consciousness following a larger convulsive seizure (1). These stereotypical absence seizures were later better characterized by the Swiss physician Samuel Tissot in 1770, who termed the seizure episodes *petits*. The first mention of “absence” was by French physician Louis-Florentin Calmeil in 1824, who called the brief loss of consciousness with seizures, “epileptic absence (2).” Shortly thereafter, in 1838, the French psychiatrist Jean-Etienne Esquirol termed this milder form of epileptic seizure episodes ‘petit mal,’ which was the term used for over a century to distinguish it from the more severe or grand mal seizures. He described petit mal seizures as short, lasting a couple of seconds, with loss of consciousness and uniquely non-convulsive (3)(4). It was not until 1935 that Gibbs, Davis and Lennox were able to show the associated EEG findings with the typical 3 Hz

spike and wave discharge, which at that time they proposed had an 'egg and dart' shape (5). With the aid of EEG, they were able to differentiate seizures electrographically, instead of purely behaviorally, and therefore added an extra criterion to the classification for petit mal seizures (6). This was important because petit mal, or absence epilepsy, was made worse with common seizure medications and alternate treatments proved beneficial to reducing absence epilepsy if properly diagnosed (7).

With the invention of EEG, many physicians started relying more on the EEG, but video monitoring of seizures showed that although many seizures may look electrographically similar, there were characteristically different behavior phenomena (8). In 1981, the International League Against Epilepsy, attempted to classify petit mal, or absence seizures, between primary, or idiopathic form of generalized epilepsy, from the secondary, or symptomatic, generalized epilepsies. They later in 1989 recognized the heterogeneity of the petit mal, idiopathic generalized epilepsies, and separated them into three different characteristic types: childhood absence epilepsy, juvenile absence epilepsy, and juvenile myoclonic epilepsy (2). Childhood absence epilepsy was defined by the International League Against Epilepsy as: "occurs in children of school age (peak manifestation age 6 to 7 years), with a strong genetic predisposition in otherwise normal children. It appears more frequently in girls than in boys. It is characterized by very frequent (several to many per day) absences. The EEG reveals bilateral, synchronous symmetrical

spike and waves, usually 3 Hz, on a normal background activity. During adolescence, generalized tonic-clonic seizures often develop. Otherwise, absences may remit or, more rarely, persist as the only seizure type (2).”

Despite this bold attempt to better classify seizures, there was controversy over these classifications and some researchers felt that there could have been more inclusion and exclusion criteria to ensure that researchers are studying the same patient population (9). They argued that it was too broad a definition, and certain exclusion criteria should be created such as: myclonia, (except for very mild myoclonia of the eyelids), mild or no loss of consciousness during the seizure, spike and wave discharges of less than 4 seconds, and photic stimulation bringing about the seizure (2)(9).

With a better working international definition for epilepsy, there have been multiple epidemiological studies on obtaining the prevalence of childhood absence epilepsy in children. A study in 205 Swedish children with seizures between one month and 16 years of age found the prevalence to be 5.9% (10). In a prior Swedish study, they found that the highest incidence of diagnosing absence epilepsy was between the ages of six to seven years of age. While the mean annual incidence was 7/100,000 and the five- year incidence was 34.8/100,000 (11). In a study conducted in Spain, of 191 children less than 15 years old diagnosed with epilepsy, 7.9% had absence, with the majority of the cases diagnosed between the ages of six to ten years of age. No children

under one year of age, or above ten years of age, were diagnosed with childhood absence epilepsy (12). A Dutch study of 462 children between the ages of one month and 16 years old found a prevalence of 10%. They also found that 17% of patients had a positive family history of some sort of seizure (13). In a Connecticut study of 613 children between 0 and 15 years of age, there was a prevalence of 12.4% (14). As one can see the range is quite variable from 5.9% all the way to 12.4%, which can be partially attributed to the inclusion criteria used for each study.

However, a more important factor leading to such variability is the subtle features of absence. Unlike other seizures, there are no auras or overt behavioral manifestations. Their staring spells are usually mistaken for daydreaming, and because of the loss of consciousness they are not aware they have had an episode. Finally because it occurs in children, absence may go unrecognized for years (15).

What is driving these short bursts of 3-4 Hz spike and wave discharges consistently seen in absence epilepsy is still an ongoing area of research. Some of the first evidence that it may be originating in the thalamus was from the 1950's when intraoperative recordings from the thalamus of patients with petit mal seizures were made. The EEG recordings showed the rhythmic 3 Hz spike and wave activity beginning in the leads inserted in the thalamus before appearing on the scalp leads recording from the cortex. They also found that the spike and wave discharges are gone from the cortex leads before the seizure activity

stops in the thalamus (16)(17). The spike, which is believed to be necessary for continuing the 3 Hz spike and wave discharges, is thought to originate in the deep cortex, which travels to the thalamus, and then back to the cortex in a corticothalamic circuit. More specifically the primary somatosensory cortex area coinciding with the peri-oral region has been implicated (15). Data has shown that focal increases of sodium channel expression in this area may be contributing to its hyperexcitability or intense epilepsy activity (18). Although the cortex has been implicated in initiating and synchronizing the spike and wave discharges, the thalamus is mainly involved in maintaining it (15)(17). This model lends evidence to the fact that electrographically the seizure is generalized, or seen throughout all leads on the cortex, as well as its synchronicity (17). Although, power analysis on the EEG has shown to have the maximum amplitude in the medial frontal cortex (20)(21). Low threshold voltage gated Ca^{2+} channels have been shown to be involved based on genetic models of animals (15)(19). The GABAergic neurons which make up most of the nucleus reticularis of the thalamus appears to be playing a role because potentiating their function makes slow wave discharges more frequent, and blocking the GABA receptor results in a reduction in seizure activity (15)(18)(19). A proposed model is that the increase firing of the cortex causes increase release of GABA within the thalamus, which slows the frequency down to the 3 Hz seen in absence epilepsy (18). There also appears to be some effect from the dopamine

system as well. Dopamine agonists induce a dose-dependent decrease in spike and wave discharges, while dopamine antagonists exacerbate experimental absence seizures. How dopamine neurons are causing this effect is unclear. The unifying mechanism that is currently one of the working models of generalized absence seizures is that an NMDA mediated excitatory post synaptic potential, followed by inhibition from GABA receptors, triggers the low voltage gated calcium channels in nucleus reticularis thalamic neurons, leading to the 3 Hz spike and wave activity (19). There is no mechanism proposed for how the 3 Hz burst abruptly stops but it was shown that the increase of the spike-to-spike interval may cause the 3 Hz “circuit” to break (17). There does appear to be a trend that patients had a propensity to have seizures of the same duration (8). So there appears to be an individual intrinsic mechanism ending the seizure activity. How absence can rarely become generalized tonicclonic seizures still remains to be explained (19).

Armed with the EEG as the gold standard to diagnose childhood absence epilepsy, researchers have tried to better characterize the heterogeneous behavioral impairments seen during absence epilepsy. Some of the first studies were done by Schwab in 1939 where he found an increase in reaction time during an absence seizure, which was shown in many subsequent studies as well (22)(23). Reaction time, though, has a component of attention and of motor inherent in its measure, thus future studies tested different behaviors, trying to better

separate attention from motor tasks. A more purely attention task is considered to be a continuous performance task, where patients are shown a string of letters and told to only push when they see a specific letter. A more purely motor task is considered to be a repetitive tapping task. This is where a patient was asked to push a button repetitively at a fixed, comfortable interval. Mirsky and Van Buren were able to better categorize patients from those that are able to perform during a seizure and those that were not able to perform during a seizure. In the continuous performance task they found that a difference in the organization of the EEG was significant between the two groups, with a more organized EEG leading to poorer performance, the length of the seizure affected performance, with longer seizures leading to more errors, and the burst-stimulus interval, or when the letter was presented in respect to the seizure also affected performance, with a shorter burst-stimulus interval leading to greater error. In the repetitive tapping task, or motor task, they found that the difference between responders and non-responders was correlated also with the organization of the EEG, as well as the length of the seizure, with longer seizures causing more impairment in performance. When looking at the data closer they were able to find that in the continuous performance task the errors, if there was an omission, usually occurred a couple of seconds before an electrographic seizure or at the beginning of the seizure. While in the repetitive tapping task, if they stopped performing, it was usually after

the onset of the electrographic seizure (22)(24). Little has been done to correlate behavior during seizures with any other modality of brain function other than the EEG, until the recent advancement of non-invasive neuroimaging that could capture brain activity in the frequency and time scale needed for absence epilepsy. There have been multiple attempts with different methodologies, but many of them are not suited for the short duration and unexpected timing of absence seizures. Therefore the best method to capture brain function during absence seizures is fMRI (20). Evidence from fMRI studies has shown both cortical and subcortical areas involved during the seizure. The thalamus shows increased signal during seizures, and there is a decrease in signal seen in the prefrontal cortex, parietal cortex, and posterior cingulate (21). Our group is interested in correlating neuroimaging changes with behavior performance. In a paper published in 2011, we saw that each subjects' performance on a continuous performance task and a repetitive tapping task were similar to prior reported studies, where worse performance was seen in the continuous performance task compared to the repetitive tapping task (22)(25). The study showed that there were differences in brain regions between individual subjects that were not able to perform during the task, and those that were able to perform (26). For my current research, I will better characterize the performance of children with childhood absence epilepsy on the continuous performance task and the repetitive tapping task, now that we have a larger sample

size, and will correlate this with both EEG changes and fMRI signal changes.

Hypothesis:

We expect to find, like previous behavioral studies have shown, the performance on the continuous performance task, a measure of attention, will be affected more, with greater omissions, than on the repetitive tapping task, a more purely motor task, during an absence seizure. There should be a difference in the EEG power and fMRI signal in brain regions that correlates with performance. We anticipate that having had a seizure will continue to affect the interictal performance in the continuous performance task as well.

Methods:

All human research subject procedures and forms were approved by the institutional review board at Yale University School of Medicine and by the Yale Magnetic Resonance Research Imaging Center. Children between the ages of 6 and 18 years of age with typical childhood absence epilepsy were referred to our study by their pediatric neurologist or self-referral. I helped with recruitment and obtaining patient histories over the phone to ensure they were good candidates for the study. Informed written consent was obtained from all research subjects participating in our study. To be able to participate in the study children had to have a clinical diagnosis of childhood absence epilepsy based on the International League Against Epilepsy criteria (2), send a copy of an EEG report that states typical 3-4 Hz generalized spike and wave discharges with a normal background activity, they could not have a history of any other additional seizure types like myoclonic, tonic-clonic, or partial seizure, they could not have any known structural brain abnormality, and the subjects could not have any other known neurological disorder.

Research subjects underwent a training session on a separate day prior to the day of the scan, which I also assisted in. During the training, the children were placed inside a mock-scanner where they familiarized themselves with the sounds of an MRI machine, and practiced the behavioral task, while they were encouraged to keep their head as still as possible. We also administered a Weschler Abbreviated Scale of

Intelligence test to research subjects and one of their parents, usually maternal, to obtain a rough intelligence quotient score. We also obtained socioeconomic status variables based on the Hollighshead Four Factor scale (28). I helped with coding for both of these variables.

The two behavioral tasks, continuous performance task (CPT) and repetitive tapping task (RTT), were already established as the behavioral measures for the study. Research subjects were asked to do both tasks on each given day, and they were randomly assigned as to what order the task would appear. All the tasks were previously generated using E-Prime, and they consisted of a total of 640 seconds. There were 10 blocks of 32 seconds of fixations, used to be able to obtain a baseline for the fMRI. Then there were 10 blocks of 32 seconds for the task. Letters were presented for 250ms at one-second consistent intervals for the entire task blocks. In the CPT, one quarter of the letters were X's, the remainder of the letters were random, and the subject was asked to push a button with their right thumb only when they saw the letter X. In the RTT, subjects were presented with random letters, the letter X was not used, and they were instructed to push the button with their right thumb every time they saw a letter (See Figure 1). The letter presentation and the button push response were being recorded by the E-Prime program and by a separate channel on the continuous EEG recording. I assisted with the review of the behavioral data. If the subject was not performing the task for more than half a block, and it was not due to a

seizure, then that block was excluded. In addition, if the subject did not perform in five or more blocks then that whole run was removed from the behavioral analysis.

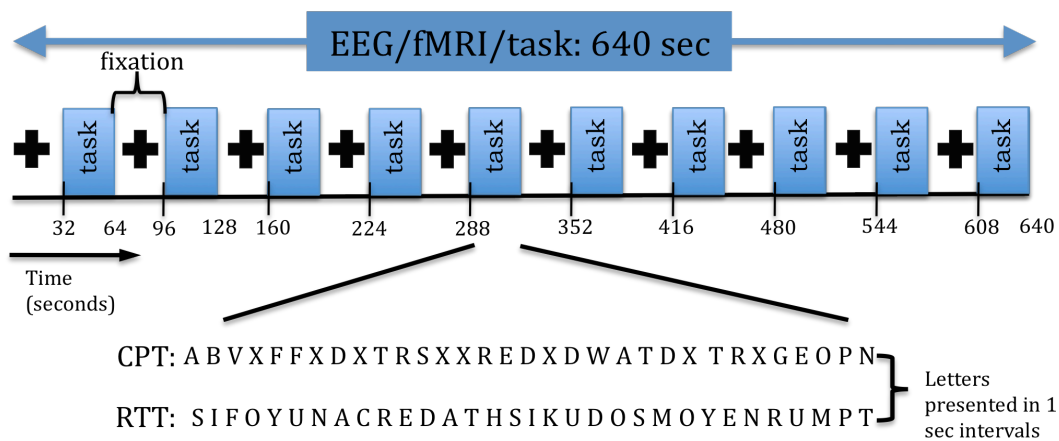


Figure 1. Task design.

640 seconds long simultaneous EEG and fMRI recordings while completing the task. There was only one task per run, but there would be multiple runs in one scanning session/day, and the order in which the task was administered was randomly assigned. For the continuous performance test (CPT) one quarter of the 32 letters per block were X's, and the subjects were instructed to push only when they saw an X. For the repetitive tapping task (RTT), random letters were presented at 1 sec intervals, and the subjects were instructed to push the button every time they saw a letter.

On the day of the scan we acquired simultaneous EEG and fMRI data. I helped during the scanning sessions of the patients, which usually occurred on weekends given the medication withdrawal and convenience for the parents and child. The only means we employed to be able to increase the probability of obtaining a seizure was medication withdrawal. If a patient was on medications, the principal investigator

and the patient's parent and neurologist would have a discussion about medication withdrawal, and usually an agreement was reached where medications were held for up to 48 hours before the last day of the scan. While the patients were off their medication, the parents were advised to never leave them alone nor allow them to do things that may endanger themselves like ride a bike, or cross the street. This method was successfully undertaken without any adverse events. Although hyperventilation is known to trigger absence seizures, this method was not implemented because it has been previously shown to affect cerebral blood flow and therefore the BOLD response from fMRI, which would have made interpretation of the fMRI data more difficult (25).

The continuous EEG data obtained from the subjects were recorded using an EEG cap with silver/silver-chloride electrodes (modified from Quik-Cap Carolina, U.S.A.), 21 channel (international 10–20 system), 32 carbon wire EEG electrodes (in-house) and a pre-amplifier (in-house) were used at 125 Hz analog low pass butterworth filter (in-house), and the signals were digitized at 1000 Hz. An in-house temporal principal component analysis software was used for filtering the MRI artifact (27).

All patients were scanned using a 3 Tesla Magnetom Trioscanner (Siemens Medical Systems, Erlangen, Germany). During scanning, foam padding was used to help secure the EEG leads, reduce motion artifacts, and improve patient comfort. Earplugs and headphones were also

provided to the subject to offer them additional comfort and to be able to communicate with them while in the scanner, respectively. Prior to the task, AC-PC aligned axial T1 anatomical images (spin echo, repetition time=300 ms, echo time=2.47ms, matrix size=256Å~256, 25 slices per image, slice thickness=6 mm, field of view=22 cm) were acquired in the same image planes as the functional MRI data. Functional images were acquired with an echo-planar imaging BOLD sequence (repetition time=1550 ms, echo time=30 ms, flip angle=80, matrix size=64Å~64, other parameters were the same as the T1 anatomical images). BOLD fMRI was obtained in 640-second runs. At the beginning of each fMRI run, a transistor-transistor logic pulse from the MRI scanner was supplied to one EEG channel in order to accurately match the fMRI, EEG and behavioral task time series. The letters were presented on a screen to the subjects by a projector, and the subjects viewed the screen through a mirror attached to the headcoil. The subjects usually completed four to five runs but could go up to seven fMRI runs per day as long as the subject tolerated the session (previously described in 28).

The behavior was analyzed by in-house code written on Matlab that incorporated the E-prime file and EEG data. For the CPT runs, a correct response was considered if the subject pushed the button to an X between 120 milliseconds after the letter presentation, but before 1000ms, or the onset of the next letter presentation. The cutoff of greater than 120 milliseconds after letter presentation was decided based on

prior work that showed that to be able to perform a conscious action from a visual cue, it took at least that long for the visual stimulus to be processed and a response initiated (29). For the RTT runs, a response was considered correct if the button push occurred anytime after the letter presentation and 1000 milliseconds, or the onset of the next letter.

I assisted with the EEG processing to remove the fMRI artifact, then I was present when it was carefully reviewed by an experienced epileptologist for any seizures. Start and end times for each seizure were recorded to facilitate behavior analysis. For the behavioral analysis, a colleague in the lab helped with querying much of the data from the database and also helped with some of the calculations. The EEG power and fMRI analysis were performed on Matlab with in house code by a post-doc in our lab. As I was not involved in this process, I will direct you to the paper that describes the methods in detail (26).

Results:

We define “good performance” as a subject with less than 25% omission rate, and “bad performance” as greater than 75% omission rate. The omission error rate was calculated by taking the number of correct responses and dividing it by the total number of responses. All seizures were normalized to six seconds. In figure 2, we show the difference between the good versus bad performers during seizure for CPT. The bad performers appear to be severely impaired, even before seizure onset, but they quickly recover after the seizure, performing on par with the good performers. Due to the low probability of obtaining an X during a seizure, there was no data available for a correct response during CPT for the first two seconds of the normalized seizure.

Given the increased response during RTT, there was a larger sample size for the performance during seizure. In figure 3, the seizure effect on RTT performance has been divided into good versus bad performers, similar to CPT. The graph shows that the bad performers are still performing similar to the good performers on RTT before the onset of the seizure. There is then a sharp decline in performance with the seizure, with a fairly quick recovery of performance, comparable to the good performers, by the end of the seizure.

Seizure effect on Continuous Performance Task

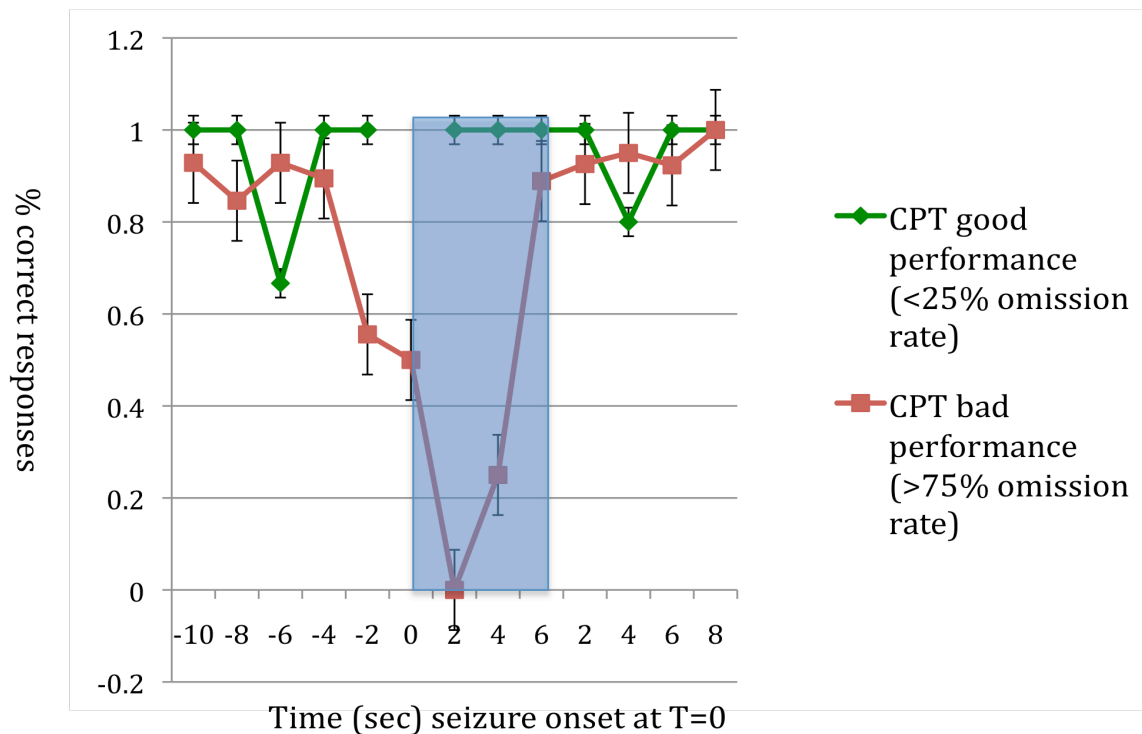


Figure 2. Seizure effect on CPT. Seizures were normalized to six seconds, with start time at T=0. Data includes ten seconds before and after the seizure and is shown in two-second intervals. There were no data points for the beginning of the seizure with good performance. The subjects affected the most by the seizures appear to begin having omission errors even before the electrographic onset of the seizure, with a sharp decline in performance, but an equally quick recovery back to baseline by the end of the seizure. Sample size varied between 0-6 samples within the normalized seizure. Data points are shown with standard error bars.

We then decided to take all performance during seizures for both CPT and RTT, irrespective of how they did on the task. There appears to be worse performance on the CPT task, as compared to the RTT task, during the seizure initially (figure 4). The performance on CPT appears to improve quicker, even during seizure, while performance on RTT remains impaired through the end of the seizure.

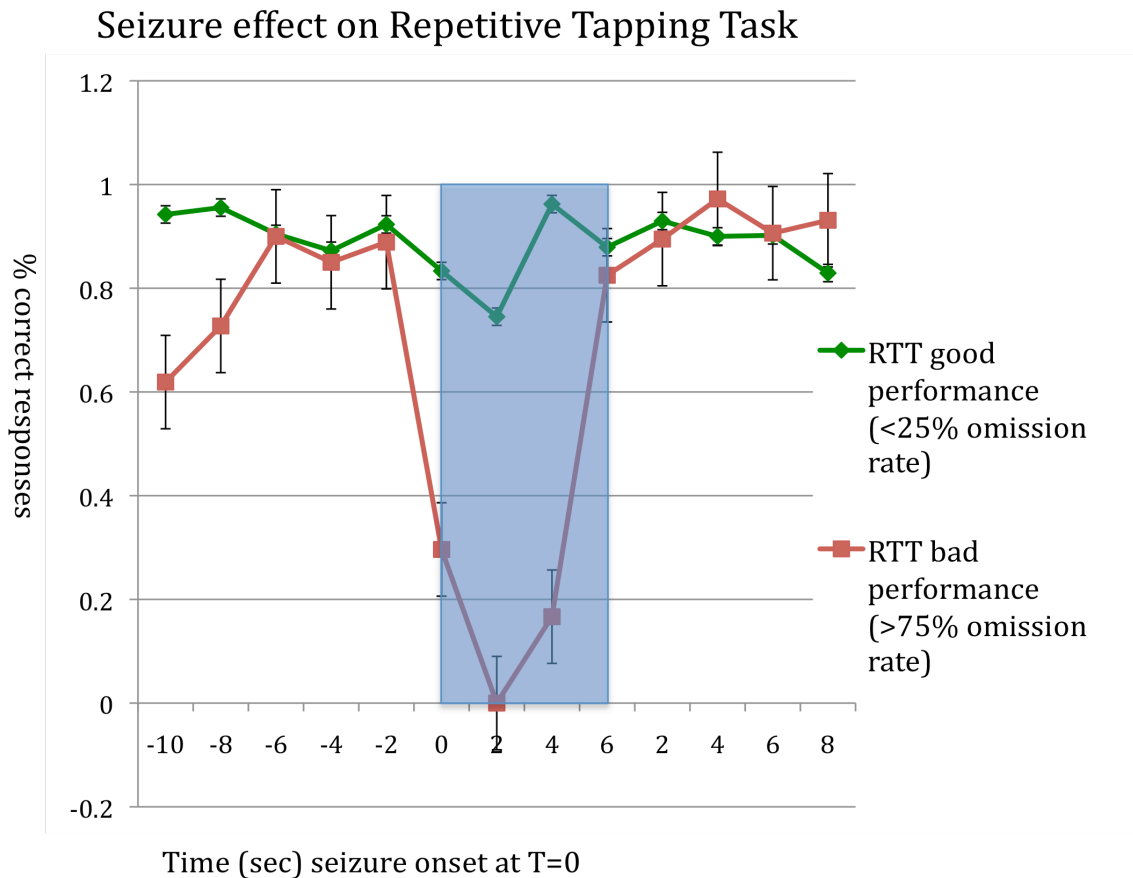


Figure 3. Seizure effect on RTT. Seizures were normalized to six seconds, with start time at T=0. Data includes ten seconds before and after the seizure and is shown in two-second intervals. Here good and bad performance are the same before seizure onset, and drops quickly for bad performers during the seizure, but recovers to similar values to the good performers by the end of the seizure. Sample size varied from 13-32 data points within the normalized seizure. Data points are shown with standard error bars.

In figure 5 we show the CPT performance during seizure in a different previously calculated manner, where we looked at the burst-stimulus interval (22). For this figure only ictal performance was used. The location where the correct response occurred was divided by the length of the seizure to get a percentage of the location within the total seizure, or burst-stimulus interval. For instance, if a correct response

occurred at three seconds into a seizure that lasted six seconds it received a value of .5, if on the other hand the correct response occurred at three seconds into a ten second long seizure, then it received a score of .3. The results of the graph show that most of the correct responses tended to occur at the end of the seizure rather than in the beginning.

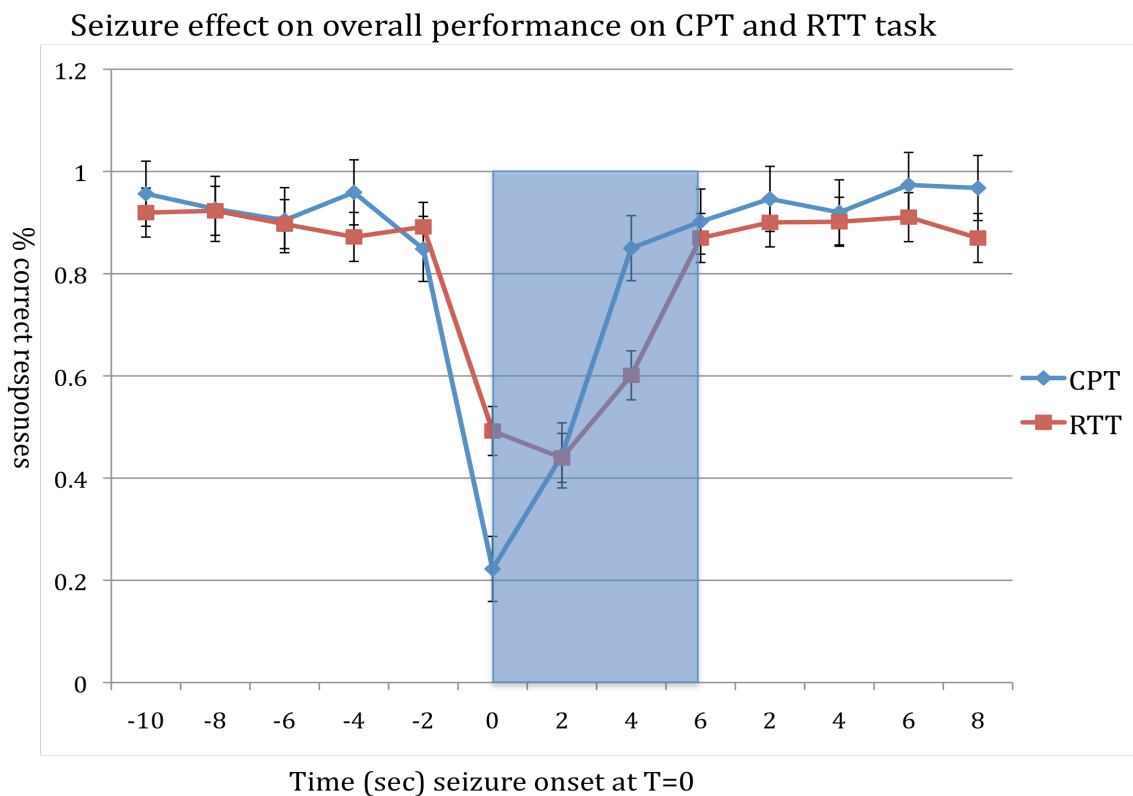


Figure 4. Seizure effect on overall performance for CPT and RTT. Seizures were normalized to six seconds, with start time at T=0. Data includes ten seconds before and after the seizure and is shown in two-second intervals. CPT appears to be affected greater earlier on in the seizure, but recovers quicker than RTT. The performance on both tasks appears to be similar after the seizure. Sample size varied from as low as 3 data points for CPT up to 102 samples for RTT. Data points are shown with standard error bars.

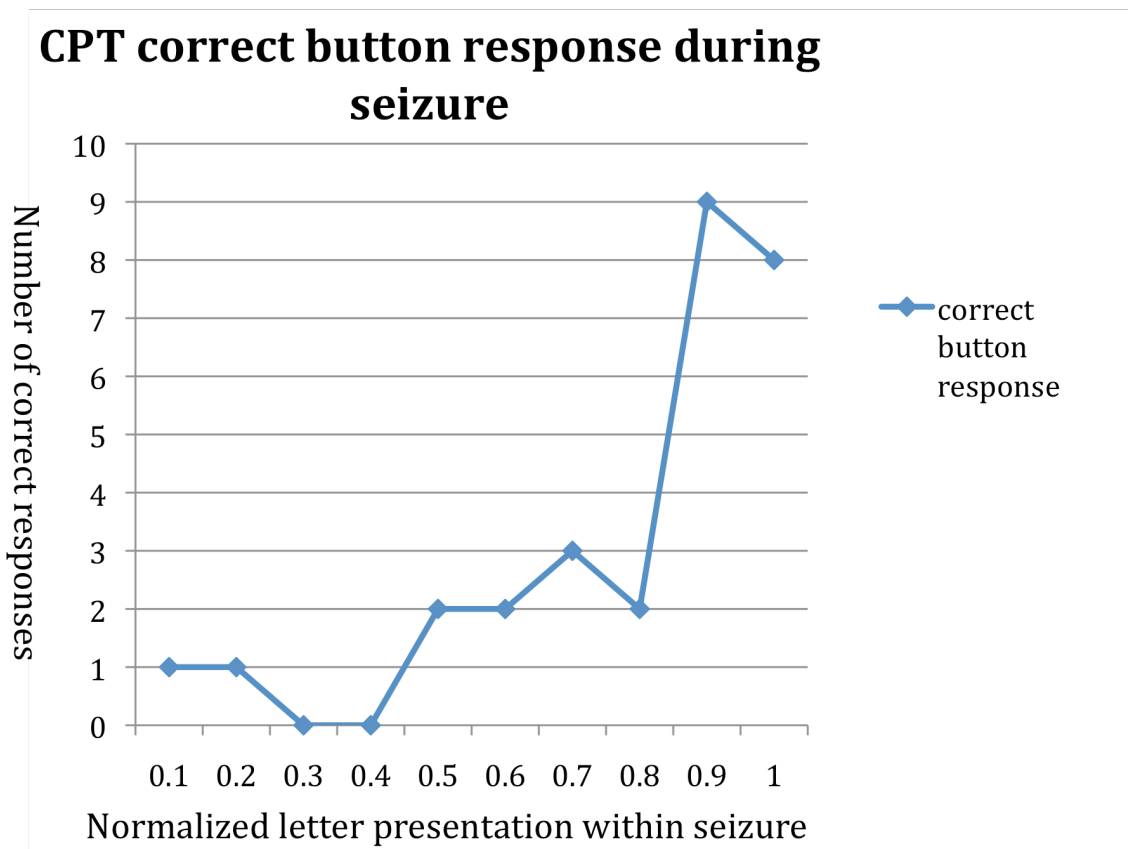


Figure 5. Correct CPT response during seizure based on seizure burst- stimulus interval. The graph shows that most of the correct responses tended to occur at the end of the seizure as opposed to the beginning of the seizure.

After separating the behavioral data between good and bad performance, we wanted to see if there were EEG changes we could correlate with the performance on CPT during seizure (figure 6). The good performance EEG was subtracted from the bad performance EEG, and it showed that there was greater 3-4 Hz power seen mainly in the medial frontal leads of the bad performers. The fMRI signal was also studied in one subject on CPT runs where she was able to continue performing and where she was not able to perform (figure 7). Here, the subject appears to have more decreased signal in the medial and lateral frontal cortex in the

bad performance seizure, which is not seen in the seizure with good performance.

Seizures with poor performance on CPT show greater amplitude in 2.5-4 Hz range

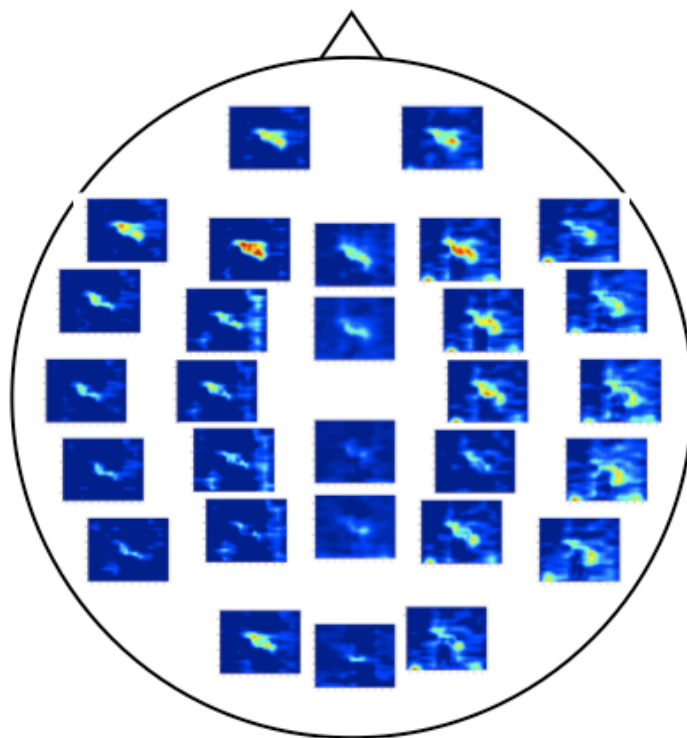


Figure 6. EEG power frequency analysis of good versus bad performance. Greater signal is seen in the medial frontal leads in the subjects that performed worse. This is a top down view, where left is the patient's left and right is the patient's right, and the front of the patient is at the top of the image.

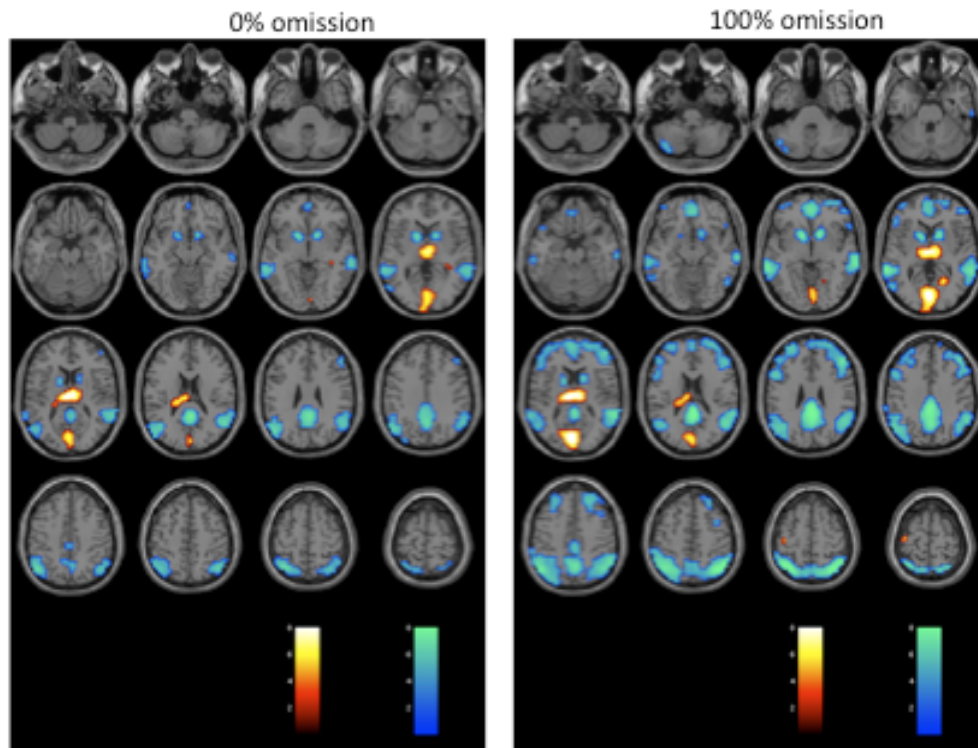


Figure 7. fMRI analysis in one patient between good performance, or 0% omission, and bad performance, or 100% omission. It appears that there is more decrease in signal seen in the medial and lateral frontal lobes in the bad performance that is not seen in the good performance. Image shown in radiological convention, where right side of image is the patient's left.

Given that there is differing effect on performance during seizure, we wanted to see if there was any lasting effect on the omission rate interictally for CPT. We separated the subjects into those that had a seizure during the 640 second scan block, and those that did not have a seizure during the scan. The statistics showed that having had a seizure during the scan causes the subject to have a significant increase in interictal omission rate, $p=.0011$ (table 1).

Effect of seizure on interictal CPT performance

Seizure recorded in run (n= 84)	No seizure recorded in run (n=141)	Two tail T-Test p value
interictal omission rate: .1648 +/- .1438	interictal omission rate: .1032 +/- .1155	.0011

Mean +/- stdv

Table 1. Effect of seizure on interictal CPT performance based on whether the subject had a seizure during the run or not.

Discussion:

Our results show that during a seizure there is an impairment of performance for both tasks with more omissions occurring during the continuous performance task, at least early within the seizure, as compared to the repetitive tapping task, which is very similar to many prior studies (22)(20)(26). In order to correctly identify a letter and push a button, one must consider that there are multiple steps from the input of the information, to the motor output, to the mental processing of whether or not to push the button. Which of these steps is being impaired during the seizure is difficult to assess (22). We can say with some confidence that the motor response is at least initially spared during the seizure. For the repetitive tapping task, most of the omissions did not occur until after the seizure onset time. While in the continuous performance task there were omissions that would occur even a couple of seconds before the seizure onset time. To explain why subjects are impaired differently while doing these different tasks, there are two crucial pieces of information that are needed. First, what are the neural structures responsible for each individual task? And what neural structures have been shown to be affected by seizures? The overlapping structures between the tasks and seizure can then be implicated in the impairment seen with the task during seizure. Fortunately these topics have been researched, and I will present the data for each.

Recent studies have shown the neural networks involved in the continuous performance and repetitive tapping task. Using data from fMRI on the continuous performance task versus fixation, results showed greater activation in the frontal, anterior cingulate cortex located within the cingulate motor area, parietal, temporal and occipital cortices and in the cerebellum. All these areas are involved in attention, visual processing, and planning and execution, which are expected with a more involved task like this (30). Using EEG and magnetoencephalogram, different brain regions were found to be important in the repetitive tapping task. Somatosensory feedback is necessary to be able to synchronize a repetitive behavior. It has been shown that in finger tapping there is a strong association in the contralateral rolandic fissure, correlating with the somatosensory area. Approximately 100 ms before a movement, there was activity in the motor cortex, most likely as anticipatory for the movement to come. At the time of the tapping, there was activity within the primary somatosensory cortex, but this could be the normal electrical activity expected from the somatosensory feedback from pushing the button. What was interesting is that they found an area inferior, or deeper, to the primary somatosensory cortex that had activity up to 80 ms before tapping, and this primary somatosensory inferior region was crucial for the evaluation of the temporal distance between repetitive tapping tasks (31).

In a time course fMRI analysis of childhood absence epilepsy, there is evidence to show that up to 14 seconds before seizure onset there was increase signal in the orbital frontal cortex, as well as in the medial and less pronounced signal increase in the lateral parietal cortex. This increase signal persisted during seizure, with extension to the lateral frontal region and temporal lobe, with greater signal in the lateral parietal cortex. After the seizure ended there was increase signal in the thalamus and occipital lobe as well as global decrease signal in the cortex, with greater decrease seen in the frontal and parietal lobes continuing for up to 20 seconds after the electrographic end of the seizure (32). The thalamus not showing early increased signal is in stark contrast to some of the first intraoperative EEG recordings where it was shown that the thalamus had the spike and wave activity before seen in the cortex (16)(17). This difference can be reconciled if the abnormal activity begins in the cortex, predominantly in the frontal cortex, and through corticothalamic connections, spreads to the thalamus, initiating the spike and wave discharge, but given the extensive blood supply of the thalamus the fMRI signal does not change immediately. Using these results and the ones from the behavioral task, it appears that the frontal cortex is implicated in the worse performance seen in the continuous performance task, with omissions occurring even before seizure onset similar to the fMRI signal increase seen before seizure onset. The later

increased fMRI signal seen in the parietal cortex, can be affecting the sensory input necessary for the repetitive tapping task.

Given these global changes in fMRI signal seen during an absence seizure, it is not surprising that many other behavioral measures previously studied are also affected during seizures. One large criticism of many of these studies is that it requires a subject to attend to a visual cue and then respond. It is well noted that there are eye deviations and gaze shifts during absence seizures (24). This confounds the results because it is not clear whether a subject did not respond because they did not see a stimulus, they did not perceive the stimulus, or could not respond to the stimulus. In a study on primates, it was shown that there was a decrease in the evoked potential in the visual system while enhancement in non-visual system during an induced seizure (24). In an early study there was a significant association between the laterality of the EEG and the kind of behavior affected. Wilkins et al. found that left-sided discharges were associated with errors in a verbal task, and right-sided discharges with impairment in non-verbal tasks. This suggests that behavior impairment is not necessarily a consequence of impairment in attention but a reflection of the disruption of “specific psychological functions located in regions of epileptiform activity (33).” In another study where subjects were given a test phrase during an absence seizure, many of them could not recall what the test phrase was when it was given to them during a seizure, but were able to recall it if given right

after the electrographic end of the seizure. It is important to note that even though the performance was impaired, it was better than on the continuous performance task (8). In an interesting study, it was found that a seizure could be terminated if a loud external stimulus was provided (20). All this taken together lends evidence that sensory input is being received, with some modalities more affected than others, but the cognitive process of the information appears to be the most impaired. Based on our results, it is reasonable to conclude that the sensory, or input pathways, and cognitive processing are likely affected greater and earlier than the motor, or output pathways.

Another behavioral measure commonly studied in childhood absence epilepsy is reaction time. It has been shown in many studies that reaction time is increased during spike and wave discharges (22)(20)(23)(34)(35). Although this can be explained by motor inhibition, there have been studies to tease apart the difference. It was shown that the length of the seizure had a direct correlation with the reaction time, where longer seizures cause increased reaction time. Also the fact that a motor response is not initially impaired in the repetitive tapping task, lends evidence that the increase in reaction time is more a result of a cognitive process than a motor response (23). Activation of the anterior cingulate cortex, not part of the primary motor cortex, in normal subjects was also shown to have the strongest positive correlation with reaction time (30). Reaction time appears to not only be affected during seizure,

but during interictal periods as well. Compared to matched controls, children with childhood absence epilepsy had an increase in mean reaction time interictally (28). To account for why these subjects have worse performance even when not having a seizure, researchers have looked at the implications of the default mode network in childhood absence epilepsy (30)(35)(36)(37).

The default mode network is thought to involve the medial prefrontal cortex, medial and lateral parietal cortex, and posterior cingulate, and is constantly activated at rest and deactivated during goal-directed behavior. Its role is believed to be one of constant awareness and alertness, needed to be able to respond to external stimuli (36). Reviewing the ictal imaging data, there appears to be an increase in default mode network areas of orbital frontal, lateral parietal and posterior cingulate even before the electrographic seizure onset, which may implicate the default mode network and impaired performance during seizure. This is followed by a profound decrease in signal in these default mode network areas, which is thought to be an undershoot due to the recovery from the early activation (36). Vigilance plays a large role in order to respond correctly and quickly in the continuous performance task. It has been shown that reaction time is negatively correlated with several regions of the default mode network (30). This may explain why there is an increased omission rate seen in our data in the runs where subjects had a seizure. A study has found

there to be smaller grey matter volumes in the left orbital frontal cortex of patients with childhood absence epilepsy compared to control, while at the same time there appears to be a significant increase in resting connectivity between the left and right orbital frontal cortex (37)(38).

Further implicating medial frontal lobe dysfunction in childhood absence epilepsy, a recent study on the background EEG of patients with absence epilepsy compared to control found there to be a significant difference in the interictal medial frontal cortex leads (39)(40).

There are more global cognitive, linguistic, and behavioral impairments in childhood absence epilepsy interictally than just what occurs during a seizure (37)(41)(42). Children with childhood absence epilepsy were found to be more inattentive and hyperactive when compared to age and IQ matched controls (44). It is not surprising then that they are significantly more likely to also be diagnosed with attention deficit hyperactivity disorder (ADHD) and suffer more from anxiety, although only about 23% of the children are treated for these disorders (41). Verbal fluency, abstract thinking, and cognitive flexibility, all thought to rely on frontal lobe function, has also been shown to be more affected in children with absence epilepsy compared to normal controls (42)(43). It is important to keep in mind that children are suffering from all these neurocognitive deficits during their school years, so even though the seizures may remit, the long-lasting implications of these deficits extend well into adulthood. Although childhood absence epilepsy is

thought of as a generalized form of epilepsy the recent discovery of the default mode network and its likely involvement in childhood absence epilepsy may be the unifying idea as to why there is not only impairment during a seizure, but also why there are significant impairments interictally. As puzzling as childhood absence epilepsy develops, the majority of them mysteriously disappear around puberty; “fortunately the healing forces of nature usually bring spontaneous cure (7).”

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