LINKING TOPIRAMATE EXPOSURE TO CHANGES IN ELECTROPHYSIOLOGICAL ACTIVITY AND BEHAVIORAL DEFICITS THROUGH QUANTITATIVE PHARMACOLOGICAL MODELING

A DISSERTATION

SUBMITTED TO THE FACULTY OF THE

UNIVERSITY OF MINNESOTA

BY

Samuel Paul Callisto

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

Dr. Susan E. Marino, Advisor

Dr. Angela K. Birnbaum, Co-advisor

May 2019

Acknowledgments

I could not have completed the monumental task of obtaining my doctorate without help from several individuals. First and foremost, I am so thankful for the support and guidance from my advisor Susan Marino. It is impossible to put into words how grateful I am for the flexibility and independence bestowed upon me by Dr. Marino in selecting my didactic coursework and directing my research into the areas which I was most interested in pursuing. I am also thankful for willingness to let me complete multiple summer internships, encouraging me to pursue various career development opportunities, and creating an environment in which creativity and experimentation was encouraged.

Many thanks are also due to my co-advisor Angela Birnbaum for continuously mentoring me in the art of conducting pharmacological research. Her insistence on developing well-rounded students provided me with the unique opportunity to experience nearly every aspect of a large-scale research project, including writing IRB applications, reviewing protocols, running samples on analytical instruments, and collaborating with scientists and physicians across the country. Dr. Birnbaum continually challenged me to think about the bigger picture and the context of my research, and in doing so helped me to become a better scientist.

I am forever grateful to Richard Brundage for encouraging me to sit in on his advanced pharmacometrics seminar during my first year in the PhD program. Although

initially I was completely lost, he lit a fire in my mind and showed me a way to combine my various interests and skills. Dr. Brundage has constantly amazed me with his insight into extremely complex topics such as NONMEM error codes, gradient descent algorithms, interpersonal relationships, and leading a fruitful article discussion.

Many thanks are also due to Christopher Barkley and his unending willingness to help me improve both my technical writing skills and my understanding of how the brain works. Dr. Barkley's mastery of crafting simple prose to illustrate complex ideas inspired me to think critically about each word before I even begin typing. My communication as not only a scientist, but also as a human, has been vastly improved through his patient correction of hundreds of pages of text.

As the sole biostatistician on my committee, a warm thanks is due to Mark Fiecas for his input on the many statistical analyses which went into this thesis. I came into his office with a research question, and no clue how to answer it, but he patiently helped me identify and test solutions. Through his generous donation of time and mental resources we were able to craft an analysis method that was both simple and insightful.

I would also like to thank members of our laboratory group for their contributions to my training, particularly Ilo Leppik for his insights into the patient experience and partially funding my trip to Uppsala University to receive pharmacometric training, and Rory Remmel for teaching me about medicinal chemistry and drug metabolism both in and out of the classroom. I would also like to thank Sai Praneeth Bathena for his assistance in developing the models presented in this thesis, and Taraswi Mitra Ghosh for

collaborating with me on pharmacogenomic research projects conducted in Dr. Birnbaum's lab. Finally, thanks to Michaela Roslawski, Alyssa Johnson, and Rachel Moniz for handling all the behind-the-scenes work involved in running the research laboratory.

The University of Minnesota College of Pharmacy is currently ranked the #2 pharmacy school in the country, and that is due in large part to the significant efforts of the amazing faculty. Thank you so much to all the professors who trained me through didactic and experiential learning opportunities. The training that I received during my time was better than anything I could have imagined prior to entering the program. A special thanks is due to Pamala Jacobson for allowing me to pursue pharmacogenomic research through wet laboratory experience during my first summer in the program and allowing me to assist in organizing the first two Precision Medicine Conferences hosted by the University of Minnesota College of Pharmacy. Her candor and enthusiasm for both research and social activities were a constant source of joy during my time in the program. I would also like to extend additional thanks to both L'Aurelle Johnson and Mahmoud Al-Kofahi, whose doors were always open. Their willingness to answer questions and help me to develop professionally and personally whenever I wandered in was greatly appreciated. Many thanks also to the administrative staff for the College of Pharmacy, especially Mary Moreno Lien, Dede Johnston, Becky Palapala, Carolyn Chase, Diane Blumenfeld, Susan Williford, Erin McGonagle, and Carol Ann Dickinson for all their support and help navigating the maze of graduate school.

Two deeply formational experiences during graduate school were the summer internship opportunities which I completed at OneOme and AbbVie. Thank you to Dione Bailey, Ross Higgins, Paul Owen, Sandy Goss, Megan Gibbs, Michael Casey, and everyone else who I was fortunate to work with during these summers. As mentioned previously, I am exceedingly appreciative to Susan Marino for allowing me to take time away from researching to intern with these companies as I attempted to discover the ideal path for my post-graduate school career.

Graduate school has been the most challenging yet rewarding five years of my life thus far. Very few individuals understand the 24/7 stressors; however, I am extremely thankful for the support of my fellow ECP graduate students. It is amazing how many great people have been part of this program, and I am humbled to have the experience of learning with and from all of them. I would like to especially thank my dear friend Natalie Schmitz, the only other student in the 2014 cohort. I could not have asked for a better person to spend most of my days with during the first few years of this program, and am continuously inspired by her determination, kindness, and humility. We did it! I would also like to thank Irene Vuu, whose unending positivity has always brightened my days even during the most difficult times. Her constant supply of sweets was always appreciated and usually necessary. I would also like to point out one senior student who played a humongous role in my professional development, Ali Al-Hadab. I am so thankful that we were able to experience coinciding summer internships in Chicago, and appreciative of his time spent teaching me how much can be accomplished using R and

helping me to understand the nuances of pharmacometrics. Many, many thanks are due as well for the mentorship that I received from Malek Okour, Chay Ngee-Lim, Ghada Ahmed, Mariam Ahmed, Kinjal Sanghavi, and Youssef Roman.

Many teachers encouraged the love of learning which drove me to devote 21 years of my life to the pursuit of knowledge through formalized education. In addition to the faculty members at the University of Minnesota College of Pharmacy mentioned previously, I would also like to specifically thank Lori Balza, Steve Provinzino, Bill Rahn, Roald Sateren, Rob Gordon, Deb Martin, and Jaime Mueller.

Finally, I would not have completed this arduous journey without the support of my family and friends. I have been blessed with such a wonderful network of people who have brought so much joy into my life. There are too many individuals to name, but you all know who you are. Thank you to my family for continued encouragement and support. My mother has been a role model of hard work throughout my entire life, and I am grateful for all the sacrifices which she made to allow me to be here today. Last but not least, thank you so, so much to my amazing wife Samantha. Since the day we met she has inspired me to reach for the stars and has supported me throughout this entire process. I am unable to express how grateful I am to be with such a supportive partner.

Abstract

Topiramate is a broad-spectrum anti-epileptic drug used to treat a variety of conditions, including epilepsy, migraine, substance abuse, mood, and eating disorders. We investigated the effects of topiramate on the working memory system using population pharmacokinetic-pharmacodynamic modeling and unsupervised machine learning approaches. Working memory is the capacity-limited neurocognitive system responsible for simultaneous maintenance and manipulation of information in order to achieve a goal. Behavioral and electrophysiological indices of working memory function were measured using data collected during a double-blind, placebo-controlled crossover study in healthy volunteers. Subjects completed a Sternberg working memory task, during which accuracy and reaction time were measured, while subjects' EEG was recorded.

A pharmacokinetic-pharmacodynamic model was constructed which demonstrated that accuracy decreased linearly as a function of plasma concentration, and that the magnitude of individual deficits was predicted by working memory capacity. A separate pharmacokinetic-pharmacodynamic model was developed which showed that spectral power in the theta frequency band (4-8 Hz) recorded during the retention phase of the Sternberg task increased as a function of plasma concentration. Furthermore, a mixture model identified two subpopulations with differential sensitivity in topiramate-induced theta reactivity. In the subpopulation defined by lower reactivity, reaction times were 20% slower than in the high theta reactivity subpopulation.

Principal component regression was used to quantify the relationship between changes in multiple measures of electrophysiological activity and behavioral deficits. Theta power during retention was found to be the best predictor of topiramate-related behavioral deficits. Performance on another working memory task, Digit Span Forward, was also predicted by theta power during retention, as well as alpha (8-12 Hz) power during encoding and retrieval stages.

In conclusion, two treatment-independent factors that predict differences in behavioral and electrophysiological responses to topiramate administration were identified: working memory capacity and theta reactivity. Future research will be needed to determine the utility of these demographic factors in predicting risk of cognitive side effects in patients eligible for treatment with topiramate.

Keywords: topiramate, working memory, pharmacokinetic-pharmacodynamic modeling, electrophysiology, cognition

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Chapter 1: Introduction

1.1 Adverse Drug Effects on Cognition

1.1.1 Impact of drug-induced cognitive impairment

Numerous drug classes impair cognition as a side effect, causing a significant negative impact on patient quality of life, decreasing adherence, and leading to treatment discontinuation (1, 2). Some drug classes commonly associated with cognitive side effects include anticholinergics (3, 4), benzodiazepines (5, 6), anti-cancer agents (7-10), and antiepileptic drugs (AEDs) (11-13). In this thesis, I focus specifically on the cognitive side effects caused by AEDs, with the ultimate goal of developing a methodological approach that can be applied to additional drug classes in the future.

Epilepsy pathophysiology is associated with neuropsychological dysfunction (14-16), and cognitive side effects of AEDs impose a significant burden on these already at-risk patients. The cognitive adverse event profile of a given medication is one of the strongest predictors of health-related quality of life for patients taking AEDs (17). The risk of side effects outweighs the benefits of seizure remission for many patients surveyed about AED preferences, with already-diagnosed patients citing memory problems as the side effect they are most concerned about (18). Moreover, when given the choice between two drugs with different side effect profiles, women of childbearing age ranked memory problems as a more important factor than seizure reduction or increased risk of fetal abnormalities (18). Cognitive side effects caused by AEDs can be

particularly debilitating for patients with epilepsy, who are at increased risk for cognitive impairment caused by epilepsy pathophysiology (19-21). Impairment of cognition can be especially problematic in vulnerable populations. For example, children with epilepsy may experience reduced learning ability due to AEDs, exacerbating academic underperformance relative to healthy peers related to their diagnosis (22). The potentially additive effects of cognitive impairments caused by pathophysiology and those associated with AEDs provide an explanation for why so many patients with epilepsy are concerned about the risk of medication-related side effects. As a consequence of this interaction between pathology and adverse drug effects, a great deal of research has investigated differences in the occurrence and severity of cognitive impairment within the AED class (23-34). I will focus on topiramate specifically in this thesis because it has consistently been shown to cause more intolerable adverse effects on cognitive than other AEDs, with a unique pattern of deficits in the language system (11, 23, 28-34).

1.2 Topiramate

1.2.1 Discovery and approved indications

Topiramate (TPM) is a second-generation AED developed in 1979 by Dr. Bruce Maryanoff while working at McNeil Laboratories (35). The base structure is a sulfamate derivative of D-fructose. Although the medicinal chemists were intending to develop a substituted carbohydrate that could inhibit fructose-1,6-bisphosphatase for diabetes management, neuropharmacologists in the company believed that the molecule may have

anticonvulsant properties due to its structural similarity to acetazolamide (35). It was approved by the U.S. Food and Drug Administration (FDA) in 1996 for adjunctive treatment of generalized tonic-clonic and focal impaired awareness (previously complex partial) seizures (36, 37). More recently topiramate has been approved for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome, and monotherapy treatment of generalized tonic-clonic and focal impaired awareness seizures (38). Topiramate is also approved by the FDA for migraine prophylaxis in adults and children over 12 years old (38), and is commonly used off-label for mood disorders (39, 40), substance abuse disorders (41-45), and weight loss (46). In 2012 a combination drug containing topiramate and phentermine was approved as a prescription anti-obesity treatment (47, 48).

1.2.2 Previous studies of topiramate-induced cognitive side effects

A subset of 10 to 40% of patients taking TPM experience some form of cognitive side effect, with the most common complaint described as "word-finding difficulties" (23, 49-52). The incidence of these impairments occurs disproportionately in patients taking TPM compared to other AEDs (28, 30, 31, 33), causing patients on the drug to discontinue treatment at a higher rate (28, 30). Topiramate administration negatively impacts multiple cognitive domains, including language, attention, perceptual motor function, and short-term and working memory (11, 33, 53). These impairments have been assessed using a variety of neuropsychological tests, including, but not limited to, the Trail Making Test (33, 54-56), Controlled Oral Word Association test (COWA) (23, 34,

53, 55-60), Symbol Digit Modalities Test (SDMT) (23, 34, 56, 60, 61), Digit Span (33, 53, 55-57), Token Test (53, 57), and Story Recall (53, 56, 59, 60). The effect of TPM on performance on two tests, the COWA and SDMT, have been previously modeled using a pharmacostatistical approach similar to the one described in detail later in this chapter. Therefore, I will provide more detail on previous studies incorporating these two neuropsychological tasks below.

The Controlled Oral Word Association Test, or COWA, is commonly used to assess verbal fluency, requiring subjects to spontaneously produce words in a defined category, such as words beginning with a certain letter or belonging to a specified semantic category such as animals (62-65). Studies have shown that performance on the COWA is significantly impaired by TPM administration, leading subjects to produce fewer correct responses in both healthy volunteers (28, 56, 58, 59) and epilepsy patients (23, 57).

The Symbol Digit Modalities Test (SDMT) is a task used to assess perceptual motor function, in which subjects substitute as many values as they can in 90 seconds using a provided decoding key which matches geometric figures to numbers (66). SDMT score is decreased after TPM administration in healthy volunteers at both low (56) and high doses (28) in a concentration-dependent (61) fashion, and a study comparing focal epilepsy patients receiving TPM to those receiving valproate found SDMT performance to be worse in patients taking TPM (23). The relationship between concentration and the

severity of impairment seen on the SDMT has been observed in many tasks, discussed further in the following section.

1.2.3 Factors known to affect the severity of TPM-induced cognitive impairment

Although it is currently impossible to accurately predict which individuals will experience cognitive deficits resulting from TPM administration, previous studies have identified various treatment-related factors which appear to be associated with the severity of side effects. Below, I review the literature for the three most commonly cited of these factors: titration rate, drug exposure, and concomitant medications.

Titration rate is a term that refers to the speed at which daily doses are increased to reach the amount necessary to provide therapeutic benefit, with various dose titration schedules recommended for several antiepileptic drugs (67). The recommended titration rate for patients taking TPM as monotherapy to treat epilepsy is a 50 mg/day starting dose increased by 50-100 mg/day each week to a target dose of 400 mg/day, while the titration rate for patients taking TPM for migraine prophylaxis is a starting dose of 25 mg/day increased by 25 mg/day each week to a target dose of 100 mg/day (38). An early study of the effects of TPM on cognition performed by Biton et al. compared the frequency of adverse cognitive events between the recommended titration schedule for epilepsy and a “fast” titration schedule, with an initial dose of 100 mg/day increased by 100-200 mg/day each week (68). Despite equivalent reductions in seizure frequency between the two groups, adverse effects were significantly more frequent in the fast titration group, with a greater proportion of patients withdrawing or discontinuing

compared to the patients being titrated at the recommended rate (68). These findings have been reproduced in a similar study looking at the recommended migraine prophylaxis titration rate (69), as well as in pediatric patients taking adjunctive TPM for refractory epilepsy (70), though these findings have not been consistently replicated (cf. (51, 71)). As a consequence of these failures to replicate, the influence of titration rate on the incidence of TPM-induced cognitive impairment remains unclear.

Another factor frequently reported to play a role in affecting the incidence and severity of TPM adverse effects is exposure, generally described by either the daily dose of the drug or plasma concentration. Studies have shown a relationship between TPM plasma concentration and the magnitude of deficits on tests of psychomotor speed (56, 61), verbal fluency (56, 58), and working memory (56, 59, 72) in healthy volunteers. However, studies in patients with epilepsy have found that the degree of impairment is not always associated with differences in plasma concentration (55, 57) or dose (33, 55). These seemingly contradictory findings on the relationship between exposure and behavior when comparing healthy volunteers and patients with epilepsy are clear indicators that exposure alone is not always a reliable predictor of TPM-induced deficits.

Finally, patients taking concomitant medications, especially other AEDs, are frequently shown to be at increased risk of experiencing TPM-induced cognitive impairment. In an observational study seeking to identify predictors of cognitive side effects of AED therapy, the two significant predictors identified during follow-up were lack of intellectual disability and polytherapy (11). Indirect evidence of this relationship

has also come from studies showing that patients taking concomitant AEDs may be more likely to discontinue TPM ((73), cf. (49)). A study in patients showed that individuals performed worse on a neuropsychological battery when taking the AED valproate in addition to TPM compared to patients taking TPM alone (57). Lastly, an indication that there may be an interaction between concomitant medications and exposure comes from a study which showed that decreasing the dose of concomitant AEDs when starting TPM, thereby lowering overall exposure, decreased discontinuation due to adverse events (74).

Although the previously discussed factors appear to play some predictive role, the inconsistencies across studies indicates that additional research is required. One potential source of these contradictory findings is the variability in test batteries used to assess cognitive function across studies. In this thesis I will be focusing specifically on the effect of TPM on working memory function, a cognitive system imperative for daily function which is profoundly impacted by TPM administration. Limiting my investigation to working memory is facilitated by a cognitive task which arguably reflects only activity in this system. Below I illustrate the importance of working memory in daily activities with the goal of motivating the choice of this specific cognitive system for my investigations into TPM's effects on cognition.

1.3 Working Memory

1.3.1 What is working memory?

Working memory (WM) is the limited-capacity neurocognitive system responsible for simultaneously maintaining and manipulating information in order to complete a task. A fundamental property of the WM system is that it is highly capacity-limited in terms of how much information can be stored simultaneously, and there is a large amount of variability in capacity between individuals. Crucially, these inter-individual differences are meaningful: measures of capacity correlate with fluid intelligence (75, 76), reasoning ability (77), processing speed (78), and predict academic attainment in both math and reading (79, 80). The association between WM and these other measures of high-level function illustrate the important role this system plays in daily activity; detrimental effects to this system could cause a variety of behavioral manifestations. Researchers investigating the capacity of WM originally argued for a consistent limit to the number of items retained regardless of modality, first thought to be seven (81), but later revised down to four (82). This revised estimate reflects the ability to "chunk" information together while stimuli are being stored (83, 84), with this ability dependent upon both the modality (85) and compressibility of information being stored (86). Common measures of capacity include, among others, reading span (87), operation span (88), Pashler's k (89), and Cowan's k (90), which each provide slightly different estimates of capacity. The differences in the method used for measuring WM function and capacity will be discussed in more detail in Chapter 2.

The WM system was initially described using a series of interconnected components, each specialized to complete a discrete task. In this model, the visuospatial sketchpad stores and manipulates visuo-spatial information, the phonological loop performs the same function for auditory information, and the episodic buffer serves to integrate complex information from various modalities including the two previously mentioned stores and long-term memory. These storage components were proposed to be managed and coordinated by a control system termed the central executive (91, 92). More recently, competing views of the structure of the WM system have emerged to describe in a more general, modality-independent way, how external information is processed (93). Rather than using modality-specific systems to store specific types of information, these models rely upon shifting attentional focus to information stored in long-term memory (82, 93-96). Although a consensus has not yet been reached regarding the architecture of WM, this discussion lies outside the scope of this thesis and will bear little impact on the outcomes described herein.

One of the many methods of assessing WM for an individual is the change detection task: individuals are shown some cue stimulus (e.g. a pattern of filled cells or a string of syllables) for a brief period of time, referred to as the "encoding" phase, as it is the point at which the stimulus is encoded into memory. The cue stimulus then disappears for a brief period, termed the "retention" phase. Shortly thereafter a probe appears, and subjects must respond whether the item has changed or is identical to the original cue. This final phase is called the "retrieval" stage, as the original cue stimulus must be

recalled from memory and compared to the probe stimulus. Throughout this thesis I will be referring to data collected using a variation of the change detection task, a modified Sternberg WM task, the structure of which enables investigation of these three phases, while enabling comparison of the effect of cognitive insult across multiple memory loads (97). This task is commonly used in WM studies, and will be described in detail in the second chapter of this thesis.

1.3.2 Effects of topiramate on working memory

Multiple studies have shown that TPM negatively impacts performance on tasks that assess some aspect of working memory function, including digit span (33, 53, 55-57), Symbol Digit Modalities Test (SDMT) (23, 34, 56, 61), and the Trail Making Test (TMT) (33, 54-56). More recently it has been shown that TPM impairs performance on the Sternberg WM task (59, 72). These studies suggest that TPM causes severe WM impairments regardless of the task used to assess WM function. Investigation of electrophysiological indices of WM function, discussed in the next section, may lead to additional insights otherwise undetected by behavioral differences alone.

1.4 Electrophysiological Indices of Working Memory

1.4.1 Electrophysiology basics

Electroencephalography (EEG) is a method of recording the difference in electrical activity between two locations on the surface of the scalp which is commonly used as an index for underlying cognitive processes. These measurements reflect the

activity of a subset of the neuronal population adjacent to the electrode, with excitatory postsynaptic potentials in the cerebral cortex being the major contributor to electrical activity (98, 99). Specifically, the measurements from the surface of the scalp reflect the superposition of all extracellular activity, reflecting spatial alignment and temporal synchrony of neuronal firing. Memory processes occur in the span of milliseconds, leading many researchers to employ the millisecond temporal precision of the EEG technique to investigate these processes (98).

EEG data reflects changes in the electrical activity at a given electrode throughout the recording period, resulting in a time-ordered series of voltage measurements. Time-based analyses of EEG can be performed, such as event-related potentials; alternatively, the data can be converted into the frequency domain for analysis, the method applied in this thesis, using Fast Fourier transforms. The data is represented by the superposition of multiple oscillation frequencies following this transformation (100). EEG frequency-domain analysis is often split into five canonical nonoverlapping oscillation frequency bands: delta (0.1-3 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz), and gamma (>30 Hz), each of which has been associated with various cognitive or motor functions or with different states of arousal. A common measurement extracted from the power spectrum is the average band power, or simply “power,” calculated by taking the area under the power spectrum density curve (100). Power can be thought of as a measure of the sum of electrophysiological activity across multiple cells firing at different rates within a defined time window (101). Each individual has a peak frequency for a given

band, which is the frequency with the highest power in the defined frequency range. Each of these oscillations has an associated amplitude, the height of the waveform, as well as phase, the position of the oscillation at time zero. The work presented in this thesis will focus on power changes occurring in the theta and alpha band during performance on the Sternberg WM task. Associations between activity in these frequency bands and cognition, particularly WM function, is summarized in the following section.

1.4.2 Functional interpretation of theta and alpha band activity

Activity in the theta and alpha frequency bands are highly sensitive to WM function. During WM task performance, theta activity increases in areas involved in task performance, thought to reflect mental effort related to task completion; simultaneously, alpha activity decreases in these same areas involved in task completion and increases in task-irrelevant areas, hypothesized to correspond to suppression of extraneous neuronal activity which may interfere with memory processes (101-104). However, theta and alpha activity is not only observed during WM function.

Much research has been conducted on the role that theta oscillations (4 – 8 Hz) play in cognitive processes. Activity in the theta frequency range is related to memory processes in humans (101, 105-108), as well as spatial navigation (109-112) and internally-directed attention or meditation (113-116). During WM processes specifically, theta power changes are observed during the encoding (117, 118), retention (104, 117-120), and retrieval (118, 119) stages of a WM task. Increased power in the theta band has been shown to increase as a function of memory load during performance on Sternberg

WM tasks (121, 122), thought to reflect sustained mental effort (104, 123-125). In addition to the activity observed in the theta band, alpha band activity is also sensitive to WM function.

Activity in the alpha band (8 – 12 Hz) increases during eyes-closed resting conditions and decreases during mental activity and eyes-open resting conditions (126-128). Researchers have interpreted increased alpha activity as a marker for the "default mode network," the neuronal activity present in the brain when it is not focused on a task (129-131), as well as reflecting inhibition of cortical areas (132, 133). Tasks with lateralized stimuli illustrate this role of alpha activity, during which alpha power decreases in the hemisphere contralateral to the attended stimulus relative to the ipsilateral hemisphere for both visual (134) and sensorimotor (135) tasks. During WM tasks, alpha power decreases with memory load in posterior regions of the scalp, thought to correspond to release of inhibition of areas involved in task performance (136, 137). At the same time, increases in alpha power and amplitude increase with memory load over task-irrelevant regions, reducing extraneous, non-task-related processes (104, 124, 137-142). Due to their sensitivity to WM function, activity in the theta and alpha frequency bands seemed a likely target for TPM-induced cognitive impairment.

1.5 Population Pharmacokinetic-Pharmacodynamic Modeling

1.5.1 Population pharmacokinetic modeling

Population pharmacokinetic modeling is a pharmacostatistical approach which enables identification of parameters which quantify the time course of drug exposure in individuals within a population. Studies with an unbalanced design resulting in differing numbers of observations between patients can easily be analyzed using non-linear mixed effects models, a type of regression model that includes population-level parameters ("fixed effects"), and individual-level variability parameters ("mixed effects"). This facilitates the ability to leverage data at the population level to inform predictions for an individual. For the same reason these models can utilize both sparse and rich individual patient data within the same dataset, allowing more data to be included in analyses compared with other analytic techniques (143). Patient demographics can easily be included into these models to account for variability between individuals, such as drug metabolism differences due to weight, age, or altered kidney and liver function, among others. This approach is widely-used in drug development and has become an integral part of data contained in new drug applications by both the Food and Drug Administration (FDA) (144) and European Medicines Agency (EMA) (145). These models may also be combined with models of drug effect, or pharmacodynamics, which will now be described.

1.5.2 Pharmacokinetic-pharmacodynamic modeling

Population pharmacokinetic-pharmacodynamic (PK-PD) models combine population pharmacokinetic models with population-level descriptions of drug effects, or pharmacodynamics. This approach allows quantification of drug effect by predicting drug exposure at a specific time for each individual, including plasma concentration or AUC, even if patient samples were not obtained at that time. PK-PD models can be useful for assessing therapeutic effect across a range of drug exposures. In this thesis, I am applying PK-PD modeling to assess drug effects on working memory using behavioral and electrophysiological indices of cognitive function. Previous studies have used gross behavioral measures that reflect the sum of multiple cognitive systems, including sedative effects (146), measures of perceptual motor speed (147), and results of neuropsychological tests which can be interpreted to be measuring multiple cognitive domains (58, 61, 148). For example, the SDMT has been previously described as measuring cognitive processing speed (149, 150), motor speed (151), visuomotor coordination (152), working memory (152), and attention (150, 151). In contrast, this study uses the Sternberg WM task, a task which has been used for decades to measure WM function. Furthermore, electrophysiological correlates of impairment have not previously been used to quantify the exposure-response relationship between TPM plasma concentration and cognitive deficits.

Previous studies have utilized this approach to explore the exposure-response relationship between TPM and performance on tasks measuring verbal fluency and

perceptual motor speed/working memory, as measured by the COWA and SDMT neuropsychological tasks, respectively. A pharmacokinetic-pharmacodynamic model from a study performed in healthy volunteers found SDMT scores were on average reduced by 25% from baseline at the EC50 of 2.85 ug/mL in a group of healthy volunteers administered a single dose of either 50, 100, or 200 mg of TPM (61). Ahmed et al. used a population approach to investigate the effects of TPM on verbal fluency measured using COWA, with the model predicting a decrease of 14.5% score with each ug/mL of TPM, equating to a 27% reduction in score at the average observed maximum plasma concentration resulting from a 100 mg dose of TPM (58). The studies presented in this thesis build upon the findings from these previous studies by examining the effects of TPM specific to the WM system, as measured using behavioral and electrophysiological results from a modified Sternberg WM task. Previous studies using EEG measurements as a pharmacodynamic endpoint reveal mechanistic insights uniquely identified using electrophysiological data.

In chapter three of this thesis, measurements calculated from electroencephalogram (EEG) recordings are used as the pharmacodynamic endpoint in a PK-PD model. There are various methods for analyzing EEG data and converting it to a scalar value that is amenable to PK-PD modeling, with most studies using band power as the PD measure (153-161). Older studies more commonly relied upon measures of amplitude, possibly due to the computational burden associated with integrating across frequency ranges to calculate power (162-166); however, some contemporary studies still

use this measure (167, 168). A related measurement, waves per second in the beta frequency, was also utilized in multiple pharmaco-EEG studies (169-171). This research motivated the choice of amplitude or band power as the optimal EEG measurement to use as the pharmacodynamic endpoint in our PK-PD modeling approach. After demonstrating the relationship between concentration and changes to both behavior and electrophysiology, a third aim of this thesis was to link electrophysiological changes to behavioral changes, which will be accomplished using an adapted machine learning approach, detailed in the following section.

1.6 Machine Learning Approaches in Drug Research

1.6.1 Definition of Terms

The term "machine learning" was first defined as "the field of study that gives computers the ability to learn without being explicitly programmed" by Arthur Samuel in his seminal 1959 paper "Some studies in machine learning using the game of checkers" (172). A more contemporary definition was given by Tom Mitchell: "A computer program is said to learn from experience E with respect to some class of tasks T and performance measure P, if its performance at tasks in T, as measured by P, improves with experience E" (173). This term has enjoyed recent popularity with companies in various fields touting the power of machine learning to revolutionize their industry. In the area of precision medicine, this technique has been applied to predict susceptibility of cancers to novel therapeutics (174-176), empirically identify disease subtypes through biomarker

clustering (177-180), and develop individualized predictive models of disease progression (181-183). Despite its myriad applications, a simple idea underlies this approach: statistical models can generate predictions through the use of algorithms which can detect covert patterns in large data sets. Machine learning is divided into two broad categories: supervised algorithms, which use a predefined outcome to improve prediction accuracy, or unsupervised algorithms, which identify structure in a dataset through variable clustering when outcomes are undefined.

1.6.2 Justification for Machine Learning Approach

Although there are various methods of machine learning which could be applied to pharmaceutical research, one goal of this thesis is to identify electrophysiological indices associated with behavioral measures of cognitive impairment. Because there are innumerable measures which can be extracted from EEG data, the goal of using machine learning in this thesis is to find an empirical solution for identifying underlying structure in the EEG data, especially relations between measurements obtained at different stages of the memory process and in different frequency bands. To accomplish this task, an unsupervised machine learning algorithm, principal component analysis (PCA), was employed.

1.6.3 Principal Component Analysis

Principal component analysis (PCA) takes a set of possibly correlated datapoints and utilizes an orthogonal transformation to create weighted composites of the data called principal components (PCs). Use of these composite measures allows for reduction of

dimensionality by using a small set of composites, rather than every variable. Many disciplines utilize this statistical method for dimensionality reduction. Recently, this technique is in vogue in genetics under the alias “gene shaving”, where it is used to uncover latent associations in large microarray datasets (184). The variability explained by each component is maximized when generating the weighting applied to each variable, with the first PC describing the largest amount of variability. Each PC is orthogonal to the next, allowing interpretation of each PC independently. Once the PCs are generated, a subset of the PCs can be selected, which greatly reduces the number of variables used to describe a phenomenon. In addition to dimensionality reduction, PCA also identifies structure within a dataset by clustering variables which jointly explain a proportion of variability. These related outcomes illustrate the utility for this approach in selecting a subset of measurements derived from the EEG data collected during our study, while simultaneously identifying otherwise unseen relationships between measures.

1.7 Scope of Dissertation Work

The research outlined in this thesis utilizes PK-PD modeling to quantitatively link TPM exposure to various measures of cognitive side effects purportedly caused by this drug. The relationship between behavioral outcomes and electrophysiological responses will be characterized by creating a set of models that relate these changes both to each other and to TPM exposure, as measured by plasma concentration. Chapter 2 focuses on

development of a population PK-PD model of behavioral changes to performance on a modified Sternberg working memory task after topiramate administration. Chapter 3 discusses development of a population PK-PD model which includes theta band power as the pharmacodynamic marker for impairment. Finally, a machine learning algorithm is used in Chapter 4 to assess the relationship between these models by identifying composite electrophysiological measures associated with behavioral changes induced by TPM administration. Conclusions and proposed future directions of research are outlined in the final chapter.

1.8 References

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Chapter 2: Severity of Topiramate-Related Working Memory Impairment is Modulated by Plasma Concentration and Working Memory Capacity

2.1 Introduction

As mentioned in the introduction chapter, topiramate (TPM) administration is associated with deterioration in several cognitive domains including verbal fluency, verbal learning, and both short-term and working memory (1-3). Because of the prevalence of these impairments, patients discontinue topiramate at a higher rate than other AEDs, with many citing cognitive side effects as the primary reason for discontinuation (4-7). Although these patterns of TPM-related cognitive deficits have been described relatively well, we still lack a complete understanding of what makes certain individuals more susceptible to these side effects. Two potential factors, working memory capacity and drug exposure, have recently been identified to have a degree of predictive power with regard to the severity of TPM-related cognitive impairment.

Working memory (WM) is the capacity-limited neurocognitive system that functions to simultaneously store and manipulate information over short time intervals in order to achieve a behavioral goal (8, 9). Estimates of working memory capacity (WMC) positively correlate with complex cognitive functions such as fluid intelligence (10, 11), math and reading skills (12, 13), and reasoning and decision making (14, 15). Various

tasks have been employed in previous studies to estimate an individual's WMC, including, but not limited to, complex span (16-20) and change detection tasks (21-23). In this study we estimate individual WMC using a change detection task with three memory loads, allowing us to investigate differences in the severity of impairment occurring as a function of memory load.

A second factor which may play a role in modulating the severity of TPM-related cognitive deficits is drug exposure (24-27); however the relationship between exposure and performance has not been consistently replicated across all studies (28-30). Due to inability to measure concentrations at the site of action in the brain, plasma concentration is frequently used as a surrogate measurement of drug exposure. Other measures related to exposure are also associated with side effect severity, including titration rates (31-34) and concomitant AEDs (5); however, associations between drug exposure and side effects have not been consistently replicated (7, 35). These inconsistent findings indicate that treatment-related factors such as drug exposure are likely not the only variable driving individual susceptibility to TPM-related cognitive impairment.

Evidence from a recent study showed that both WMC and plasma concentration both make contributions to modulate the severity of TPM-related cognitive deficits. In that study, individuals with high WMC experienced more severe deficits which occurred as a function of plasma concentration, while low WMC individuals' impairments were not associated with plasma concentration (26). In the work presented here, we extend these findings by using a non-linear mixed effects model to better characterize the

relationship among WMC, drug concentrations, and the severity of TPM-related cognitive impairment. As such, the goal of this study was to determine the concentration-dependent impairment of WM function after accounting for differences in WMC between individuals.

2.2 Methods

2.2.1 Study design

Forty-six healthy volunteers completed a randomized, double-blind, placebo-controlled crossover study conducted at the University of Minnesota and approved by the University of Minnesota Institutional Review Board. Subjects provided written informed consent and then completed a modified Sternberg WM task (36) during the initial no-treatment baseline visit. Following completion of the baseline session, subjects were assigned to receive TPM, lorazepam, and placebo once each in one of six possible treatment sequences. On each subsequent visit the subject received a single dose of their assigned drug for that session, either TPM (100, 150, or 200 mg), inactive placebo, or lorazepam (2 mg; lorazepam results reported elsewhere). Visits were separated by at least two weeks to prevent carry-over effects from previous sessions, with an additional post-baseline session completed after the three treatment visits. All study drugs were stored at the University of Minnesota Investigational Drug Services pharmacy and administered by nurses trained on the study protocol. Blood samples were collected prior to dosing and approximately 0.5, 1.5, 2.5, 4, and 6 hours after dosing for quantification of TPM plasma

concentrations (37). Subjects returned for an additional blood draw after each treatment session which was randomly assigned to occur at 24, 48, 72, or 96 hours after dosing. Exclusion criteria included the following: cardiovascular, endocrine, hematopoietic, hepatic, neurologic, psychiatric, or renal disease; a history of drug or alcohol abuse within the past five years; the use of concomitant medications known to affect cognitive function (including antidepressants, anxiolytics, psycho-stimulants, analgesics, and antipsychotics); prior history of hypersensitivity to TPM, lorazepam, or related compounds; a positive pregnancy test (administered to all females before the start of each study visit); use of any investigational drug within the previous thirty days; a native language other than English; diagnosis of a speech and/or language impairment; uncorrected poor vision or hearing; and a dominant left hand (to control for brain lateralization of language). All subjects had normal kidney function (eGFR greater than 60 mL/min/1.73 m2), as assessed using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (38). Differences in distribution of demographic factors between TPM dose groups introduced by randomization were tested using Chi-squared tests for categorical variables and single factor ANOVAs for continuous variables.

2.2.2 Modified Sternberg working memory task

Four hours post-dose at each treatment session, subjects completed a modified version of the Sternberg WM task (36). In this task a pronounceable non-word string of either one, three, or five syllables (referred to hereafter as “memory load”) was displayed

on-screen for 1.5 seconds. After this initial encoding period, the string was replaced by a fixation cross for 5 seconds, followed by presentation of a probe string which either matched the cue string or differed by a single letter. Subjects indicated whether the probe was the same or different from the cue string via button press, with “yes” and “no” responses randomized to different hands for each subject. A practice block was administered at the beginning of each session, followed by six blocks of 60 trials, with short breaks between each block to reduce fatigue. There were 120 trials of each memory load per session, with trials randomized by memory load. Response accuracy, which was calculated as the number of correct responses divided by the total number of responses for each memory load, was used as the pharmacodynamic endpoint for the analysis reported here.

Each subject’s working memory capacity (WMC) was estimated independently for each memory load from the data collected during their placebo visit using Cowan’s k equation (39), where k = N * (hit rate + correct rejection rate – 1), and N equals the memory load (1, 3, or 5). The value of k can be interpreted as a measure of the amount of information that can be concurrently held in memory and is a commonly used estimate of working memory capacity (40-43).

The effect of placebo and TPM on modified Sternberg WM task performance was compared to baseline using two-sided paired t-tests for each memory load to determine if there was a significant difference in task performance between drug sessions. Familywise

error rate was controlled using Bonferroni correction for the six comparisons, yielding a cutoff for significance at 0.0083 ($\alpha = 0.05/6 = 0.0083$).

2.2.3 Pharmacometric model development

A population pharmacokinetic model was first developed, which included PK samples from all subjects who completed a treatment visit during which they received TPM (n=40). An additional 14 subjects were included from a previous clinical trial performed in a similar population that utilized both an oral and IV formulation of TPM (25), which allowed us to better characterize the drug's elimination phase. Allometric scaling was included on all clearances and volumes.

A sequential population pharmacokinetic-pharmacodynamic model was developed to fit the accuracy data from the modified Sternberg WM task. Only subjects who completed all study visits were included in this model (n=29). Linear, exponential, and Emax structural models were explored for drug effect, while an additive model was tested for placebo effect.

Models were implemented using nonlinear mixed effects modeling in NONMEM 7.3 (ICON Development Solutions, Hanover, MD). Data exploration and diagnostic plots were created using R (version 3.4.1). Competing models were compared using the likelihood ratio test for nested models (dOFV > 3.84), and Akaike/Bayesian information criteria (AIC/BIC) for non-nested models. Model fit was assessed using goodness of fit plots of observations vs. predictions and residual plots. Adequacy of the final model was determined using prediction-corrected visual predictive checks, while precision of

estimates was verified using 1000 sample bootstrap simulations, both performed using Perl speaks NONMEM (PsN, version 4.7.0).

The effects of covariates on both pharmacokinetic and pharmacodynamic parameters were explored after determining the best-fitting structural model. Covariates explored for pharmacokinetic parameters included age, sex, creatinine clearance, and race; additionally, age, education, sequence of treatment, and WMC were explored for pharmacodynamic parameters. Covariates were tested using combined forward selection ($p = 0.01$) and backward elimination ($p = 0.005$) implemented with the SCM function in PsN.

2.3 Results

2.3.1 Subject demographics

Forty-six healthy volunteers provided written informed consent and completed all five study visits. Seventeen subjects had missing data due to errors in data acquisition or storage. The remaining twenty-nine subjects were included in the analysis presented here. Stratifying subjects by TPM dose did not reveal bias resulting from random assignment to dose group for any demographic variables (Table 1).

2.3.2 Drug effects on working memory task performance

Administration of both placebo and TPM significantly reduced accuracy compared to baseline on the modified Sternberg WM task for all memory loads, with larger deficits produced by TPM administration (Figure 1). Performance on load one

trials was significantly ($\alpha = 0.0083$) decreased from the baseline accuracy of 96.1% by placebo administration (91.2%, $t_{28} = 3.9$, $p < 0.005$) and TPM administration (87.5%, $t_{28} = 7.7$, $p < 5e\text{-}5$). Similarly, load three accuracy was decreased from 91.4% during both placebo (86.8%, $t_{28} = 4.4$, $p < 0.0005$) and TPM sessions (80.9%, $t_{28} = 8.6$, $p < 0.0001$). Load five accuracy at baseline was 72.0%, which was significantly decreased by TPM administration (63.3%, $t_{28} = 5.1$, $p < 0.0001$), but not by placebo (69.0%, $t_{28} = 2.5$, $p > 0.008$).

2.3.3 Population pharmacokinetic model

The pharmacokinetic data were best fit by a two-compartment model (Table 2). Unlike previous models, a lag parameter was required to account for an absorption delay observed in approximately one-third of subjects. The NONMEM ALAG parameter with inter-individual variability was included in the model to obtain more accurate estimates of plasma concentrations at the hour four blood draw. Both C_{max} and t_{max} of TPM are historically reported to be affected by fed status (44), but including subject-reported fed status in the model resulted in poorer fit compared to models using the ALAG parameter. Pharmacokinetic parameters were not significantly influenced by any covariates after allometric scaling of clearance and volume terms.

2.3.4 Pharmacokinetic-pharmacodynamic model

The effect of TPM plasma concentration on WM task accuracy was best fit using a linear model with a unique intercept for each memory load. The following model

equation was used to predict accuracy on the modified Sternberg WM task after administration of TPM:

$$\mathrm{WMTaskAccuracy_{ijl}} = \mathrm{Intercept_{il}} * \left(\mathrm{WMC_{norm,il}}\right)^{\theta \mathrm{cov}} - \theta_{\mathrm{TPM}} * e^{\eta_i} * \mathrm{Cp_{ij}} - \theta_{\mathrm{PBO}} * \left(\mathrm{WMC_{norm,il}}\right)^{\theta \mathrm{cov}}$$

where $\mathrm{Intercept_{il}}$ refers to the predicted baseline accuracy without placebo or TPM administration for individual *i* at memory load *l*, $\mathrm{WMC_{norm,il}}$ refers to the normalized WMC of memory load *l* for individual *i*, and $\mathrm{Cp_{ij}}$ refers to the predicted plasma concentration for individual *i* at time *j*.

WMC was the only significant covariate identified, modulating subject performance for all three memory loads used in this WM task. These results show, as expected, that individuals with high capacity for larger memory loads outperformed all others (Table 3). The placebo effect was also modulated by WMC, with high capacity individuals exhibiting a smaller placebo effect than low capacity individuals (Table 3).

An additive placebo effect was included in the model to account for changes in accuracy during the placebo session relative to the baseline session. The magnitude of the effect was estimated to be a decrease of approximately 3% regardless of memory load for the typical subject, equivalent to the effect elicited at the predicted C_{max} of a 50 mg dose of TPM. The model predicted a 3.6% decrease in WM task accuracy for each μg/mL of TPM plasma concentration for the typical subject (Table 3). This TPM-related deficit was equivalent for all memory loads after accounting for individual differences in WMC. A decrease in accuracy of 9.0% would thus be expected independent of memory load for the mean observed hour 4 plasma concentration of 2.5 μg/mL.

2.3.5 Model evaluation

Goodness-of-fit plots from the final model showed the model fit both the PK (Figure 2) and the PD observations well (Figure 3). The prediction-corrected visual predictive check showed that model simulation fit the observed data well for each load independently (Figure 4).

2.4 Discussion

In this study we used a population modeling approach to better characterize the relationships between WMC, TPM exposure, and the magnitude of drug-related cognitive impairment. Whereas a previous study showed that high- and low-capacity individuals were differentially affected by TPM exposure (26), we showed for the first time that after accounting for differences in WMC and TPM exposure, cognitive side effects were equivalent for all individuals. We extended previous findings by developing a model capable of predicting the severity of an individual's WM deficits given their WMC and TPM dose. Additionally, we found that WMC also played a role in determining the severity of impairment resulting from placebo administration.

Our data revealed an association between TPM exposure and the extent of cognitive impairment, a finding that has not been consistently replicated (1, 27-30). A recent study showed that TPM exposure correlates with severity of cognitive side effects in individuals with high WMC, but not in those with low WMC, indicating that WMC may explain some of the inter-individual variability in sensitivity to TPM (26). Our

results show that impairment is equivalent amongst individuals with the same TPM plasma concentration after accounting for differences in WMC, consistent with these findings. By using a pharmacokinetic-pharmacodynamic modeling approach we were able to demonstrate the unique role of TPM exposure and WMC in determining the severity of cognitive side effects.

Including covariate effects is common practice in PK-PD modeling; however, using it to show that baseline cognitive function affects the degree of drug-related impairment is a novel application of this method. Previous studies have shown that baseline function plays a role in predicting disease progression in Alzheimer's disease (45-47), as well as cognitive impairment resulting from both aging and drug side effects (22, 26, 48, 49). However, this study marks the first time that covariate modeling has been used to quantify the role of baseline cognitive function in the severity of drug side effects. Unlike previous studies which show that TPM decreases performance on a neuropsychological task (24, 25), the results of this study show TPM's effect specific to WM function because of the use of the Sternberg task to accurately measure a single cognitive domain. Thus, our study design combined with a population modeling approach allowed us to characterize the effects of TPM exposure on a specific cognitive domain after accounting for differences in baseline cognitive function.

Placebo administration significantly reduced task performance for all memory loads. Our investigation of the placebo effect on WM function parallels alcohol research, which has shown that expectancy for intoxication causes physical, behavioral, and

cognitive changes (50-54). Thus, the observed placebo effect in our study may have been induced by the expectation that the administered drugs would cause impairment due to the description of side effects in the informed consent. When tested as a covariate affecting the placebo effect, treatment order was not found to be significant, implying that the observed placebo effect was not related to the randomized order in which drugs were administered. Additionally, a prior study showed that WM function was impaired by placebo when subjects were not told the expected effect of the substance they were being administered (55). Interestingly, subjects in our study with higher WMC experienced less severe placebo-related behavioral changes than those with low WMC. Parker et al. previously reported that WMC, as estimated by the operation span task, modulated the placebo effect in a study of the misinformation effect (56). Although alternate tasks were used in our study to estimate WM capacity and placebo effect, the association appears to be robust to these differences.

Our study has several limitations which may prevent generalizability of the results. Firstly, the pharmacodynamic endpoint utilized was obtained from a small sample of task-naïve subjects. While we were unable to quantify any learning effect which took place over the course of the experiment, this does not preclude the possibility that improvements took place in subsequent sessions. Secondly, as evidenced by the variability in absorption rate within our population sample and the limited range of concentrations observed at the time of WM task administration, having subjects complete the WM task only once at four hours post-drug-administration may reduce our ability to

capture the heterogeneity in side effects. While the use of a lag parameter helped increase precision of predicted concentrations, future studies should utilize multiple pharmacodynamic observations over the course of the elimination phase to further describe the temporal dynamics of TPM-related cognitive impairment. Finally, this single-dose study was unable to capture clinically-relevant concentrations such as those seen in patients taking chronic doses of TPM (57-60). It is unclear how these effects would extrapolate to patients receiving chronic doses of TPM. These limitations may be addressed by future studies to determine how this drug effect presents in a patient population.

2.5 Conclusions

This study demonstrated that the severity of TPM-related cognitive deficits depends partially on drug exposure and baseline cognitive function. By combining a unique study design with a population modeling approach, we were able to identify a concentration-dependent impairment which was equivalent across memory loads after accounting for differences in WMC. The results of this study indicate that consideration of both patient-related characteristics (such as WMC) and treatment-related factors (such as dose) may be important in developing individualized dosing algorithms which minimize TPM-related cognitive side effects.

2.6 Acknowledgments

The authors thank the subjects who participated in this trial, Characterizing and Predicting Drug Effects on Cognition (NCT01889602). Funding for this project provided by NINDS R01NS076665 awarded to S.E. Marino, NINDS P50NS16308 awarded to I.E. Leppik, and the Macmillan Innovation in Epilepsy Research and Education Fund.

Table 2-1. Baseline subject demographics stratified by topiramate dose assignment (mg)

Dose assignment group (mg)	100	150	200	p-value*
N	10	10	9	
Age [mean (SD)]	26.0 (8.2)	27.0 (9.7)	23.8 (6.3)	0.69
Sex = Male (%)	5 (50.0)	5 (50.0)	5 (55.6)	0.96
Height (cm) [mean (SD)]	169.6 (4.9)	175.0 (10.5)	172.1 (7.6)	0.35
Weight (kg) [mean (SD)]	78.7 (16.7)	77.6 (11.6)	78.5 (15.7)	0.98
WMC, load 1 [mean (SD)]	0.77 (0.26)	0.82 (0.17)	0.88 (0.06)	0.41
WMC, load 3 [mean (SD)]	2.13 (0.58)	2.12 (0.49)	2.38 (0.32)	0.43
WMC, load 5 [mean (SD)]	1.64 (1.15)	2.03 (0.92)	2.05 (0.95)	0.61
Education (%)				0.21
High school graduate or equivalent	1 (10.0)	0 (0.0)	0 (0.0)	
Some college/some university	6 (60.0)	6 (60.0)	6 (66.7)	
Completed vocational training	0 (0.0)	2 (20.0)	0 (0.0)	
Received bachelor's degree/university degree	1 (10.0)	2 (20.0)	3 (33.3)	
Any post-graduate education	2 (20.0)	0 (0.0)	0 (0.0)	
Race (%)				0.23
American Indian/Alaska Native	0 (0.0)	1 (10.0)	0 (0.0)	
Asian	0 (0.0)	0 (0.0)	2 (22.2)	
Asian & Black	0 (0.0)	0 (0.0)	1 (11.1)	
Black/African American	2 (20.0)	2 (20.0)	0 (0.0)	
White	8 (80.0)	7 (70.0)	6 (66.7)	

*: Chi-squared for categorial variables; ANOVA for continuous variables.

Table 2-2. Population pharmacokinetic model parameters

Parameter	Estimate	RSE (%)	Bootstrap Median	Bootstrap 95% CI	CV (%)	RSE (%)	Shrinkage (%)
CL (L/h)	1.1	7.3	1.1	(1.0, 1.2)	31.8	12.1	14.1
Vc (L)	51.1	4.8	50.8	(46.3, 56.5)	16.6	8.1	5.4
Vp (L)	12.9	13.1	13.0	(10.3, 19.0)			
Q (L/h)	1.2	34	1.2	(0.7, 2.3)			
Ka (h^{-1})	2.8	16.2	2.8	(2.1, 3.8)	136.3	12.9	18.3
ALAG1 (h)	0.4	7.1	0.4	(0.4, 0.5)	69.6	16.1	19.7
F1	1.1	2.9	1.1	(1.1, 1.2)			
Proportional RUV	0.01	22.5	0.009	(0.006, 0.014)			

Abbreviations used in table: *CL* = clearance; *Vc* = volume in central compartment; *Vp* = volume in peripheral compartment; *Q* = intercompartmental clearance; *Ka* = first-order absorption rate constant; *ALAG1* = absorption lag into the depot compartment; *F1* = oral bioavailability; *RUV* = residual unexplained variability; *RSE* = relative standard error, (standard error ÷ estimate) x 100; CV = coefficient of variation, $\sqrt{e^{\omega^2} - 1}$

Table 2-3. Pharmacokinetic-pharmacodynamic model parameters

Parameter	Estimate	RSE (%)	Bootstrap Median	Bootstrap 95% CI	CV (%)	RSE (%)	Shrinkage (%)
Intercept, Load 1 (%)	0.98	0.5	0.98	(0.97, 0.99)			
Intercept, Load 3 (%)	0.92	0.7	0.92	(0.91, 0.93)			
Intercept, Load 5 (%)	0.72	1.1	0.72	(0.70, 0.73)			
Drug Effect Slope (%/μg/mL)	0.036	12.6	0.036	(0.027, 0.045)	50.7	32.6	13.1
Placebo Effect (%)	0.036	19.8	0.034	(0.021, 0.050)			
CK_1 on Intercept, Load 3	-0.11	18.6	-0.12	(-0.30, -0.069)			
CK_3 on Intercept, Load 3	0.36	8.9	0.37	(0.28, 0.44)			
CK_1 on Intercept, Load 5	-0.29	16.5	-0.30	(-0.40, -0.17)			
CK_5 on Intercept, Load 5	0.21	8.1	0.21	(0.18, 0.26)			
CK_1 on Intercept, Load 1	0.099	38	0.10	(0.043, 0.23)			
CK_3 on Intercept, Load 1	0.091	43.5	0.080	(0.0068, 0.16)			
CK_1 on Placebo Effect	-0.99	11.3	-1.09	(-4.81, -0.82)			
Additive RUV	0.0015	10.5	0.0014	(0.0010, 0.0017)			

Abbreviations used in table: CK_n = Cowan's k estimate of working memory capacity for memory load n; *RUV* = residual unexplained variability; *RSE* = relative standard error, (standard error ÷ estimate) x 100; CV = coefficient of variation, $\sqrt{e^{\omega^2} - 1}$

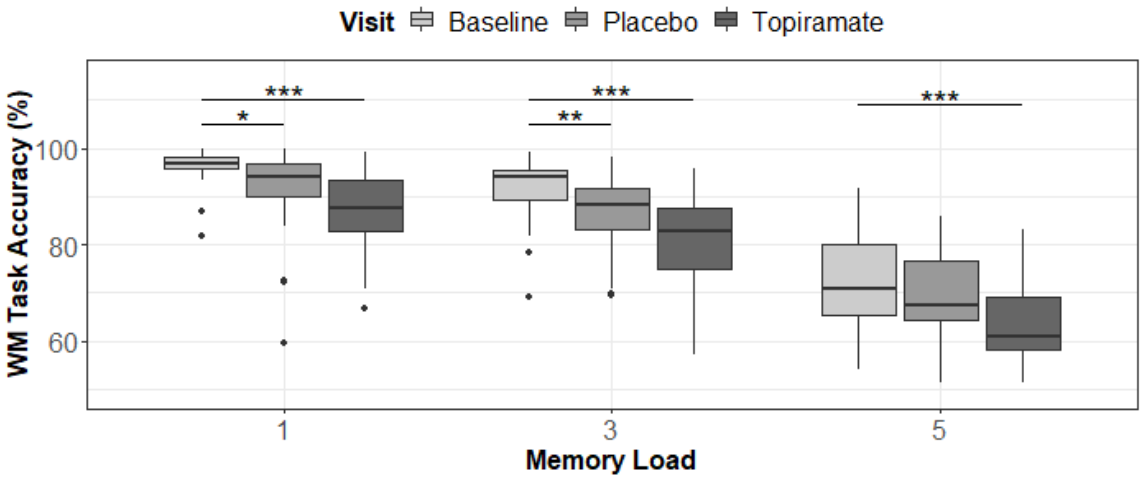

Figure 2-1. Accuracy results for the modified Sternberg working memory task from subjects who completed all study visits (n=29). Accuracy presented as percent correctly identified stratified by memory load. Memory load refers to the number of syllables in the remembered string. Points outside of the 1.5xIQR marked as individual points. Bonferroni correction for multiple comparisons was performed, resulting in an alpha of 0.0083. *:$p<0.005$, **:$p<0.0005$, ***:$p<0.00005$.

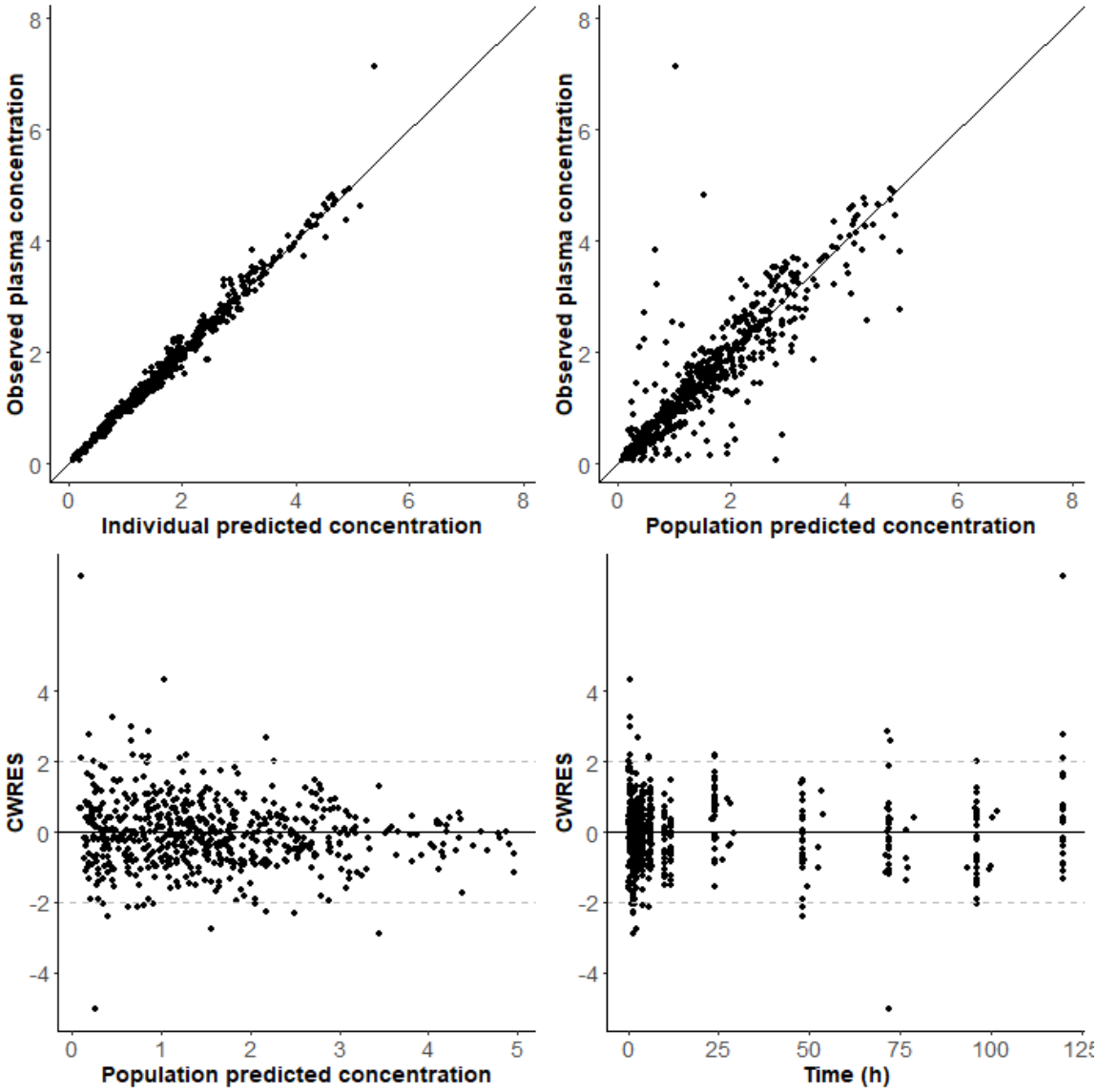

Figure 2-2. Goodness-of-fit plots for the final population pharmacokinetic model.Individual observations are denoted by closed circles, with trend lines indicated by the solid line. There were not any noteworthy trends which would indicate a problem with the model.

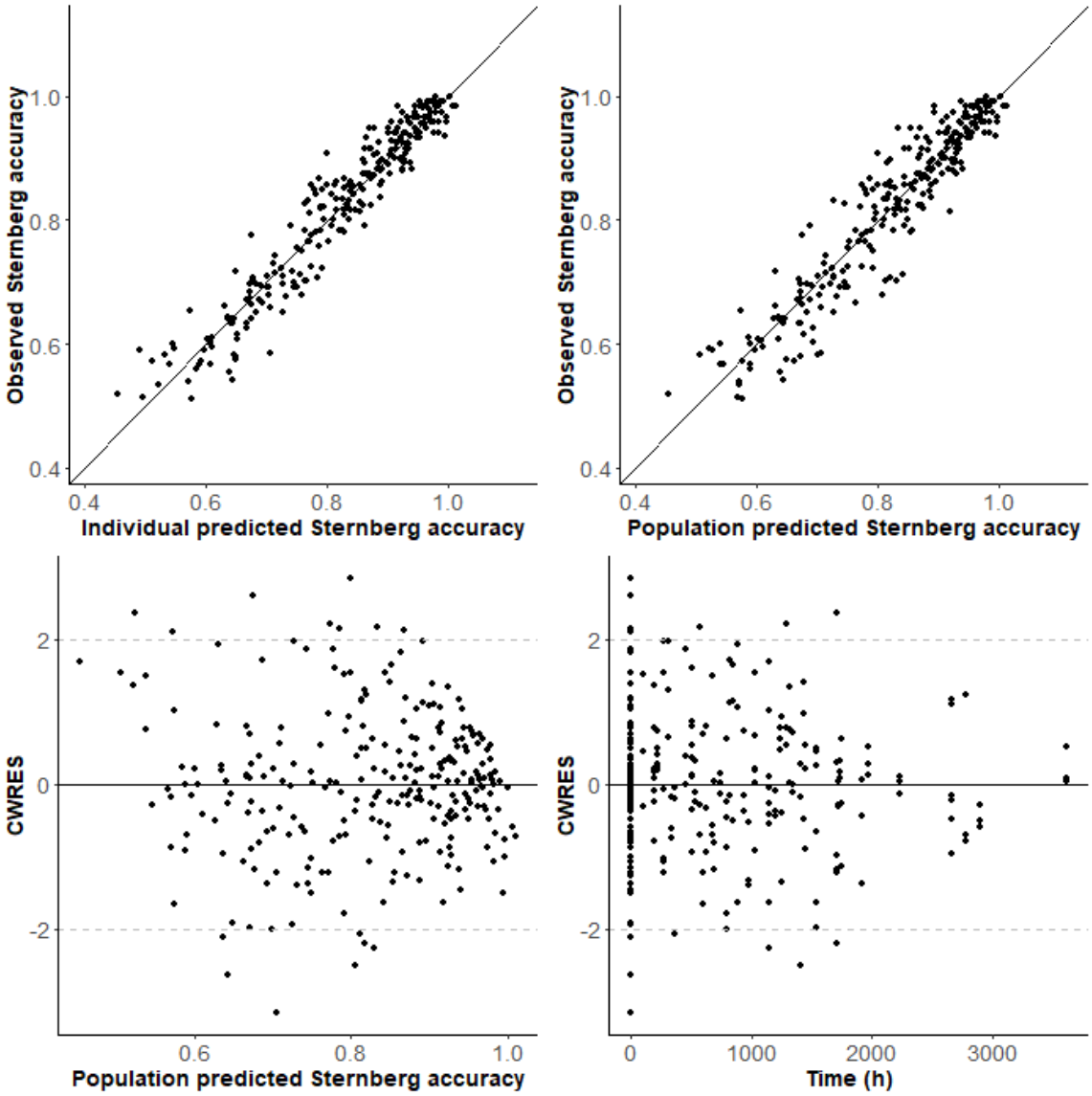

Figure 2-3. Goodness-of-fit plots for the final population pharmacokinetic-pharmacodynamic model.Individual observations are denoted by closed circles, with trend lines indicated by the solid line. There were not any noteworthy trends which would indicate a problem with the model.

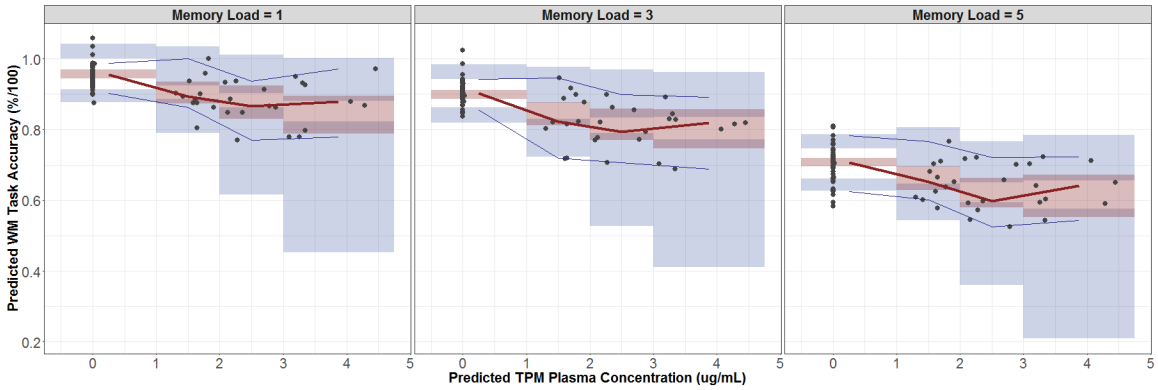

Figure 2-4. Prediction-corrected visual predictive check stratified by memory load for the final pharmacokinetic-pharmacodynamic model.Individual observations are represented by filled circles, with simulated prediction interval median denoted by a solid red line, and 5th & 95th percent simulated prediction intervals represented by solid blue lines. Ribbons represent the 95% confidence interval around the corresponding prediction intervals.

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Chapter 3: Topiramate Exposure Differentially Modulates Theta Power During Working Memory Retention in a Subset of Healthy Volunteers

3.1 Introduction

Topiramate (TPM) is a second-generation antiepileptic drug (AED) prescribed for migraine prophylaxis, treatment of epilepsy (1), obesity (2), substance abuse (3-7), and mood disorders (8, 9). Between 10 and 40 percent of patients taking TPM experience a variety of cognitive side effects (10-14), which can be severe enough to lead to discontinuation of treatment (15, 16). Studies have shown that multiple cognitive systems can be negatively impacted by TPM, including language, psychomotor function, and working memory (17-25). In the previous chapter we showed that performance on a Sternberg working memory task, which requires subjects to store varying amounts of information is working memory over short time intervals, was impaired by TPM in a concentration-dependent manner. However, additional insights into the nature of these deficits may be uncovered through investigation of TPM-related changes to electrophysiological activity.

Electroencephalography (EEG) is a commonly used neuroimaging technique with sufficient temporal precision to quantify changes in neural activity occurring on the scale of milliseconds (26). For a comprehensive review of this topic, readers can refer to the

Section 1.4.2 of this thesis. In this analysis, we aimed to quantify the effects of TPM exposure on spectral power in the theta band of the EEG recorded while healthy volunteers performed a modified Sternberg WM task. Electrophysiological activity in the theta frequency band has previously been shown to be a reliable index of WM function (27-31). In the Sternberg task specifically, theta power has been studied extensively during the retention phase of the Sternberg WM task (32-38) compared to the encoding and retrieval phases. As theta band power is known to be modulated by the amount of information retained in WM during Sternberg task performance, we hypothesized that TPM's known effects on WM function would be reflected in changes in theta power as a result of drug administration.

We employed a non-linear mixed effects modeling approach with the goal of determining whether there exists a concentration-dependent modulation of theta band power following TPM administration. Pharmacokinetic-pharmacodynamic modeling has previously been used to assess the concentration-dependent changes in electrophysiological activity associated with drug efficacy (39-45). The benefit of using this modeling approach is that it can account for differences between subjects and yield a model which can make predictions about impairment at a population-level as well as incorporating and quantifying between-subject variability. Here we apply this approach to determine if theta band power varies as a function of TPM concentration, and whether this EEG measure is a reliable index of TPM-related cognitive side effects.

3.2 Methods

3.2.1 Study population

Healthy volunteers were recruited from the University of Minnesota and surrounding communities. The study was approved by the University of Minnesota Institutional Review Board, and informed consent was obtained from subjects prior to enrollment in the trial. Subjects were at least 18 years old at the time of enrollment, right hand dominant, and native speakers of English. Women under 50 years old were required to be either post-menopausal or using an approved form of birth control and were administered a pregnancy test during the no-drug baseline visit and at each treatment visit. Subjects were excluded if they reported having any of the following conditions: previous diagnosis of cardiovascular, endocrine, hematopoietic, hepatic, neurologic, psychiatric, or renal disease; a history of drug or alcohol abuse; use of concomitant medications known to affect cognitive function; prior history of hypersensitivity to TPM, lorazepam, or related compounds; use of any investigational drug within the previous thirty days; diagnosis of a speech or language impairment; or uncorrected poor vision or hearing.

3.2.2 Study design

The study design has been reported in detail in chapter two of this thesis. Briefly, subjects were enrolled in a double-blind crossover study conducted at the University of Minnesota. Enrolled subjects completed a no-drug baseline visit during which their

electroencephalogram (EEG) was recorded while they completed a modified Sternberg WM task (46). Each individual was randomized to a treatment order for the subsequent three visits during which they received a single dose of either TPM (100, 150, or 200 mg), lorazepam (2 mg), or placebo (lorazepam results not included in the analyses reported herein). TPM plasma concentrations were quantified using a validated LC/MS assay (47) from blood samples obtained during each treatment session at approximately 0.5, 1.5, 2.5, 4, and 6 hours after dosing, and during a randomly assigned tail visit occurring either 24, 48, 72, or 96 hours post-dose. During each of the treatment sessions at approximately four hours after drug administration, subjects completed the modified Sternberg WM task described below.

3.2.3 Modified Sternberg Working Memory Task

Working memory function was assessed during the baseline session and at each treatment visit using a modified Sternberg WM task (46). This task is used to investigate three distinct memory processes that occur during WM task performance: encoding, retention, and retrieval. During the encoding phase individuals are shown a pronounceable non-word string (cue) for 1.5 seconds, followed by the retention phase, in which a blank screen appears for 5 seconds. The retrieval phase begins once the probe string appears, and subjects are required to respond whether the probe is the same as the cue via handheld buttons which were randomized to different hands for each subject. The subject's response, or lack of one within five seconds, triggers the onset of the next trial. Three memory loads, represented by strings of either one, three, or five syllables, were

used in the task. The experiment consisted of 360 total trials, comprised of 120 trials per memory load. Trials were randomized as a function of memory load and were presented in blocks of 60 with short breaks between blocks to prevent fatigue. Accuracy (the number of correct responses divided by the number of trials with responses) and reaction time (time between probe onset and a correct response) were recorded for each memory load.

3.2.4 EEG collection and analysis

High-density EEG data were recorded throughout the modified Sternberg working memory task by a trained technician in a soundproof and electrically shielded chamber using a 128-channel EGI System (Electrical Geodesics Inc., Eugene, OR, USA) with an online sampling rate of 1 KHz. As suggested by the manufacturer, impedances were kept below 50 KΩ. Stimulus presentation and recording of behavioral responses were controlled using E-prime software (Psychology Software Tools, Inc., Pittsburgh, PA, USA).

Data pre-processing was performed in MATLAB (version R2018b, The Mathworks, Natick, MA, USA) using the EEGLAB toolbox (48). Recording epochs from the retention phase of correct trials of the modified Sternberg task were first down-sampled to 250 Hz and high pass filtered at 1 Hz. Five second epochs were extracted time-locked to cue offset, incorporating 500 msec baseline and 5000 msec following cue offset. The data were cleaned in the following steps: bad channels were removed and subsequently re-interpolated, the data were re-referenced to the average of activity at all

electrodes, 60 Hz line noise and its' harmonics were removed using the CleanLine function (available from https://www.nitrc.org), and the resulting data were entered into independent components analysis (ICA). ICA was performed twice; artifactual components were rejected manually after both the first and second iterations of ICA. Fast Fourier transforms were then applied to the cleaned data in order to provide estimates of spectral power in the following traditional frequency bands: theta (4-8 Hz), alpha (8-13 Hz), lower beta (13-20 Hz), upper beta (20-30 Hz), and gamma (30-80 Hz). Power was calculated over regions of interest spanning six spatially contiguous electrodes over frontal (theta, lower & upper beta), central (gamma), and posterior (alpha) scalp sites.

Measures of absolute theta power obtained during the placebo and TPM sessions were converted to a change from baseline score using the following equation:

$$\frac{\theta_{TPMorPBO} - \theta_{baseline}}{\theta_{baseline}}$$

This transformation resulted in a continuous variable where zero represented no change from baseline, positive values a fractional increase in power from baseline, and negative values a fractional decrease in power from baseline. Using this approach to analyze the EEG data offered three distinct advantages: (i) controlling for baseline differences in power between subjects, (ii) permitting the detection of placebo effects through non-zero change scores observed during the placebo session, and (iii) reducing the number of outliers in the EEG data to be modeled by normalizing the distribution of the data.

Exploratory analysis using R (version 3.4.1) revealed larger theta power change scores with increasing TPM plasma concentrations, with all three memory loads

displaying a similar trend in this relationship (Figure 1). This pattern of results motivated the decision to deviate from the modeling approach used with the behavioral data in chapter two, in which each memory load was modeled separately. Instead, theta power change scores were averaged across all three memory loads, and the mean was used as the pharmacodynamic endpoint in the model described below.

3.2.5 Pharmacokinetic-pharmacodynamic model development

A sequential PK-PD model was developed to associate TPM plasma concentrations with theta power change scores using a nonlinear mixed-effects model implemented in NONMEM (version 7.4.3, ICON Development Solutions, Hanover, MD, USA). The estimates from the two-compartment population PK model (n=54) closely matched previously reported values in a similar population (49), and have been discussed in detail in the second chapter of this thesis. A linear model was used to approximate the relationship between TPM plasma concentration and theta power change scores. Though this likely over-simplifies the relationship between the two variables, an exploration of structural models other than a linear relationship was precluded by the sparsity of EEG recordings from each subject (one observation from the placebo session and one observation from the TPM session, both converted to a change from baseline score). This limitation prevented identification of any time lag effect, or exploration of more realistic relationships between plasma concentration and theta power change, including turnover, transduction, exponential, piecewise linear, or Emax models (50, 51).

During exploratory analysis of our dataset, we observed large variability in theta power change as a function of TPM plasma concentration (Figure 1). Motivated by this large variability, we attempted to identify a covariate which would correlate with sensitivity of theta power to TPM exposure but were unable to identify any useful correlates. Thus, we implemented a mixture model to assess the possibility of two distinct subpopulations with differing sensitivity to TPM-related theta power changes. A mixture model assigns individuals to one of multiple unique subpopulations, with each subpopulation characterized by different model parameters (52). The $MIX routine in NONMEM classifies individuals using an empirical Bayesian algorithm conditioned on the individual's data and *post hoc* population parameter estimates (52, 53). This unsupervised clustering algorithm assumes multiple populations exist within the observed dataset, and probabilistically assigns individuals to one of the subpopulations while also estimating the parameters defining the subpopulations (54). If multiple subpopulations do not exist in the dataset, there will be no significant difference between the parameter estimates for the two groups.

An Individual PK Parameters with Standard Errors (IPPSE) modeling approach was applied in this chapter. In this sequential modeling approach, conditional means and variance estimates for all PK parameters containing ETAs are obtained from the root.phi file output by the population pharmacokinetic run (52). Including this information in the PK-PD model allows propagation of PK parameter estimate uncertainty into the estimation of PD parameters. Parameter uncertainty may be a result of an unequal

number of observations between individuals, which may be important to the model presented here because individuals in the population PK analysis had between zero and two observations below the assay quantification limit of 0.375 ug/mL (47). Inclusion of the uncertainty from the PK parameters estimates increases PD parameter precision and decreases bias in a manner similar to simultaneous and Population PK Parameters and PK Data (PPP&D) modeling approaches, while also benefiting from run times ~60% shorter compared to the simultaneous approach (55). IPPSE allows increased parameter estimate precision with decreased bias compared to the Individuals PK Parameters (IPP) method used in chapter two, which assumes that the empirical Bayes estimates from the population PK model are estimated without error (55). Although the IPP and simultaneous methods are more commonly used, the IPPSE method is a useful compromise between the estimate precision offered by the simultaneous method and the shorter runtimes offered by the IPP method.

The existence of potential practice effects was explored by adapting an approach previously applied to practice effects on the SDMT (56). Number of previous tests administered (NPT) was included as a step function affecting the model intercept using the following equation:

$$Intercept_i = TVIntercept * I_{NPT \geq n} * \theta_{NPT \geq n}$$

where $I_{NPT \geq n}$ is a binary value indicating whether the number of previous tests is greater than or equal to the threshold n, and $\theta_{NPT \geq n}$ is the multiplicative effect on the intercept for visits meeting this criterion. Different values were tested for the threshold n

encompassing the three possible values in the study design (e.g. on the third visit $n = 2$, as the task has been completed twice previously). Lack of effect of subsequent visits is indicated by $\theta_{NPT \geq n}$ being equal to one.

All models during the model building process were evaluated using goodness-of-fit plots and compared using the likelihood ratio test (χ^2, $\alpha = 0.05$, df = 1, dOFV > 3.84) or Akaike/Bayesian information criteria (AIC/BIC) for nested and non-nested models, respectively. Covariate effects were explored using sequential forward selection (p = 0.01) and backward elimination (p = 0.005) implemented with the SCM function in Perl speaks NONMEM (PsN, version 4.7.0). The final model fit was evaluated using prediction-corrected visual predictive checks, and precision of final parameter estimates were evaluated using 1000 sample bootstrap simulations, both performed using PsN.

3.2.6 Behavioral differences between mixture populations

Significant differences between the two population mixtures, for both accuracy and reaction time, were tested using two-factor sequential analysis of variance (Type 1 ANOVA) which included an interaction term between memory load and population mixture estimate from the mixture model (described in PK-PD modeling section). Post hoc non-parametric Mann-Whitney U tests were also used to compare theta band power differences between population mixture estimates.

3.3 Results

3.3.1 Subject demographics

Forty-six subjects completed all visits in the protocol; however, due to data loss resulting from errors in either acquisition or storage, data from only twenty-seven subjects are reported here (Table 1).

3.3.2 Pharmacometric model results

Two distinct subpopulations were identified by the mixture model, with each subpopulation defined by a different relationship between theta power and TPM plasma concentration (Figure 1, Table 2). Unique slope parameters were estimated, significantly improving the model fit (dOFV = -16.662, $p < 0.0001$). The group exhibiting a stronger relationship between power and concentration (i.e. steeper slope) were referred to as the "theta-reactive" group because they showed a larger change in theta power for equivalent drug exposure relative to the "theta-unreactive" subpopulation, who showed a flatter slope. Eight individuals (37.5%) were predicted by the mixture model to be part of the theta-reactive subpopulation, while 19 individuals (62.5%) were predicted to be part of the theta-unreactive subpopulation (Table 2). Magnitude of theta power change in the theta-reactive group was eightfold more sensitive to TPM plasma concentrations compared to the theta-unreactive group (0.66 ug/mL vs. 0.082 ug/mL; Table 2). Stratifying subjects by mixture model subpopulation assignment did not reveal any significant demographic differences between the two groups (Table 1).

Differences were not observed between mixture populations on the PBO visit, so the same model intercept was used for both subpopulations. The intercept value shared between the two subpopulations, which indicates the change score from baseline on the placebo visit, was significantly different from zero (95% CI = 0.00047 - 0.325), indicating a slight placebo effect (Table 2, Figure 2).

Number of previous tests was found to be a significant covariate in the final model, with power in the typical subject 51% greater on visit three compared to the previous two visits (Table 2). Addition of this practice effect significantly improved the model (dOFV = -4.803, $p < 0.05$). Results from the bootstrap indicate that this effect was estimated with poor precision, as evidenced by the 95% CI crossing the null effect value of 1 (Table 2).

The final model predicted theta power change from baseline using the following equation:

$$ThetaPower_{i,j,m} = \theta_{intercept} * \theta_{visit,j} * (1 + \theta_{etascale} * \eta_1) + \theta_{slope,m} * Cp_{pred,i,j} * (1 + \eta_1) + \epsilon_{i,j}$$

where $\theta_{intercept}$ is the predicted theta power change score for the placebo session in the typical subject (which should be zero if no placebo effect is present), θ_{visit} refers to the multiplicative increase in theta power at visit 4 compared to prior visits, $\theta_{etascale}$ refers to the difference in scale between inter-individual differences in intercept and slope (included due to correlation near 1 when separate etas for slope and intercept were used), $\theta_{slope,m}$ refers to the slope for mixture *m*, $Cp_{pred,i,j}$ refers to the predicted plasma concentration for individual *i* at time *j*, and $\epsilon_{i,j}$ refers to residual unexplained variability for individual *i* at time *j*.

Visual predictive checks revealed that the model adequately described the data for both subpopulations (Figure 2). Goodness-of-fit plots confirmed that no consistent bias due to model misspecification was present (Figure 3).

3.3.3 Behavioral differences between empirically identified subpopulations

Differences in behavioral performance of the two subpopulations identified by the mixture model were compared for each of the three memory loads independently using two-factor ANOVA. Although the two groups did not differ in their response accuracy, there was a statistically significant difference in their reaction time (Figure 4). Theta-unreactive individuals on average responded 276 msec slower (1614 +/- 61.0 msec vs. 1338 +/- 94.1 msec) than the theta-reactive individuals after adjusting for differences due to memory load, a difference of approximately 20% compared to the theta-reactive response time ($F_{1,75} = 6.05$, $p < 0.05$). The interaction between memory load and population mixture estimate was not significant ($F_{2,75} = 0.08$, $p > 0.05$). *Post hoc* Mann-Whitney U tests were used to compare groups for each memory load because the data violated the assumption of equal variance. Reaction time differences were not significant in the non-parametric analysis for any of the three memory loads. This inconsistency is likely due to the lack of a non-parametric equivalent to two-factor ANOVA which can account for differences in reaction time due to memory load.

Mann-Whitney U tests were implemented to determine whether baseline differences in theta power existed between mixtures (Figure 5). At baseline, theta-reactive individuals exhibited significantly lower theta power than theta-unreactive

individuals ($p < 0.05$); this pattern was reversed at the TPM visit, with the theta-reactive group showing significantly higher theta power ($p < .0001$). There were no significant differences in theta power between the two subpopulations observed during the placebo visit.

3.4 Discussion

In this study we showed that oscillatory power in the theta frequency band recorded during the retention phase of a modified Sternberg task increased linearly as a function of TPM plasma concentration. Using a mixture model, we identified two distinct subpopulations who differed eightfold in their sensitivity of theta power to TPM concentrations. These electrophysiological differences also mapped onto differences in behavior on the Sternberg WM task, with reaction time being significantly different between the two groups after adjusting for differences due to memory load. An electrophysiological correlate of practice, manifesting as increased band power as a function of the number of previous times the subject performed the task, was observed in both groups. A small placebo effect was also observed, as was the case with the behavioral results reported in chapter two.

The mixture model identified two subpopulations defined by sensitivity of an electrophysiological measure to TPM. The existence of varying levels of sensitivity to TPM-related side effects is in line with previous reports of high variability in side effects within the population taking the drug (10-13, 20, 23); however, the extent to which theta

activity and the incidence of cognitive side effects is related is unclear. Stratifying behavioral results by the subpopulations defined by electrophysiological sensitivity showed that the theta-unreactive group responded significantly slower than the theta-reactive group on the modified Sternberg WM task. Interestingly, there was no population-level effect of TPM on reaction time in a previous analysis of these data (18). This implies that the slowing effect present in the theta-unreactive group is masked by the patients who experience minimal TPM-related impairment.

One possible explanation for the difference in behavioral response between these groups may be that the theta-reactive group is increasing their mental effort following TPM administration in order to overcome TPM-induced cognitive insult. Mental effort has been previously defined by Paas et al. as “the aspect of cognitive load that refers to the cognitive capacity that is actually allocated to accommodate the demands imposed by the task” (57). Overcoming performance impairment resulting from stressors such as noise, sleep deprivation, or a cognitive insult, may be accomplished by increasing mental effort (58, 59). Theta power is frequently cited as an index of mental effort (60-64), as evidenced by its consistent increase with memory load during the Sternberg task, for example (32-36, 38). According to this interpretation, the large theta power increases in reaction time in response to TPM exposure in the theta-reactive group may reflect increased mental effort, allowing these individuals to maintain similar performance levels as in drug-free sessions. This behavioral pattern is contrasted with subjects in the theta-

unreactive subpopulation, who exhibit minimal changes in theta power in response to TPM exposure, and thus are unable to overcome TPM's negative impact on cognition.

An alternative explanation for the behavioral differences between the theta-reactive and theta-unreactive groups is that they differ in terms of neural efficiency. The neural efficiency hypothesis states that high-functioning individuals show less brain activation than low-functioning individuals while completing the same task (65, 66). Theta power at baseline was lower in the theta-reactive group than the theta-unreactive group (Figure 5), consistent with the idea that theta-reactive individuals have a greater degree of neural efficiency. In response to TPM exposure, theta power increases in the theta-reactive group, while reaction times on the Sternberg task remain similar to those observed during drug-free conditions. Meanwhile, neural resources are being used less efficiently by the theta-unreactive group, resulting in an inability to increase resource allocation to overcome the TPM-related cognitive insult, which results in slower response times on the Sternberg task. This hypothesis is supported by a previous study which showed that TPM impairs neural efficiency as manifested in larger mid-latency ERP component amplitudes and recruitment of additional neural resources following TPM administration while holding memory load constant (67). Thus, it may be the case that the behavioral differences between subpopulations are due to a ceiling effect which prevents the theta-unreactive group from allocating additional resources to maintain optimal task performance following TPM exposure.

A neurophysiological correlate of a practice effect was observed in both subpopulations which manifest as a 51% increase in theta power on the fourth completion of the task relative to power measurements during previous visits. This increase in theta power as a result of multiple test administrations was not sufficient to cause differences in accuracy on the Sternberg task, as evidenced by a lack of practice effect observed in the behavioral pharmacokinetic-pharmacodynamic model presented in Chapter 2. One plausible interpretation of these findings is that individuals have learned the structure of the Sternberg task trials after completing 1080 trials over the course of the previous three study visits. The probe stimulus is presented once the retention phase ends after exactly five seconds, and the increased activity is occurring just prior to probe stimulus display in preparation for comparison with the cue stimulus. To determine if this hypothesis is correct one might look at the EEG data as event-related potentials (ERP) to visualize the temporal dynamics underlying the increase in theta power change during the retention phase of the Sternberg task. Previous studies of this phenomenon have termed it the contingent negative variation (68-70), and it has been reported during the retention phase of the Sternberg task (71-73). Alternatively, theta power has also been described as an index of attention and cognitive control (74-77). This increased theta power on the final visit may reflect an increased burden on attentional resources resulting from subject boredom. Therefore, increased theta may reflect the subject's attempt to stay attentive to a 90-minute task which they have previously completed three times. Further research

must be completed to determine whether increased theta power may reflect a practice effect.

Theta power increased by an average of 12.6% following placebo administration (Table 2). A placebo effect was also observed in behavioral measures of the modified Sternberg WM task (see Chapter 2), which showed that placebo administration resulted in a 3.6% decrease in accuracy; however, the relationship between the electrophysiological and behavioral indices is unclear at this point. Although few studies have investigated electrophysiological indices of the placebo effect, there is some evidence that both theta and alpha power (78, 79) are affected by placebo administration.

One limitation of this study is the exclusion of EEG measures obtained during incorrect trials of the Sternberg task. Although these trials were not analyzed because there are many reasons why a subject may give an incorrect response (e.g. not paying attention, errors in either encoding or retrieval of the cue stimulus, misreading either the cue or probe stimuli, etc.), using only electrophysiological measurements during correct trials leaves us unable to characterize changes taking place during incorrect trials. Inclusion of all measurements coded as correct/incorrect may allow a more accurate representation of the differences in behavior between individuals, for example looking at power change differences within a treatment session between correct and incorrect trials. Furthermore, this data censoring is especially impactful for load five observations, resulting in a loss of up to 48% of observations for poorly-performing individuals. Another limitation is the use of healthy volunteers taking a single dose of TPM. Although

these are clinically relevant doses, steady-state concentrations will be higher during chronic dosing. Patients taking the drug may exhibit different electrophysiological responses to TPM, especially activity related to the condition for which the drug was prescribed. Patients may adjust to the presence of the drug over time, and compensatory mechanisms may manifest during chronic dosing. There is also potential for drug interactions to play a role in cognitive side effects in patients taking multiple medications.

In conclusion, our results show that two distinct subpopulations existed which differed in their change in theta band power as a function of TPM exposure by a factor of ten, with changes in electrophysiological activity correlating with performance on a modified Sternberg WM task. Further studies are necessary to determine if the electrophysiological changes exhibited may provide insight into the mechanism through which TPM-related cognitive impairment occurs.

3.5 Acknowledgments

A sincere thanks to Dr. Cornelis Smit for his assistance in data exploration and suggestions regarding EEG analysis methods for creating a more interpretable pharmacometric model.

Table 3-1. Population demographics

	Mix 1 (Theta-reactive)	Mix 2 (theta-unreactive)	p-value
N	8	19	
TPM Dose (%)			0.099
100 mg	1 (12.5)	8 (42.1)	
150 mg	2 (25.0)	7 (36.8)	
200 mg	5 (62.5)	4 (21.1)	
Age (years) (mean (sd))	24.00 (6.16)	26.63 (9.00)	0.459
Education (%)			0.734
Some college/some university	5 (62.5)	12 (63.2)	
Completed vocational training	0 (0.0)	2 (10.5)	
Received bachelor's degree/university degree	2 (25.0)	4 (21.1)	
Any post-graduate education	1 (12.5)	1 (5.3)	
Sex = Male (%)	5 (62.5)	9 (47.4)	0.767
Weight (kg) (mean (sd))	76.39 (15.31)	80.14 (14.36)	0.549
eGFR (mL/min/1.73 m^2) (mean (sd))	78.48 (3.39)	79.60 (6.89)	0.669
Race (%)			0.301
American Indian/Alaska Native	0 (0.0)	1 (5.3)	
Asian	2 (25.0)	1 (5.3)	
Black/African American	0 (0.0)	3 (15.8)	
White	6 (75.0)	14 (73.7)	

Table 3-2. PK-PD model results

Parameter	Estimate	RSE (%)	Bootstrap Median	Bootstrap 95% CI
Theta Intercept	0.126	71.8	0.129	(0.00047, 0.325)
Population 1 Slope $(\mu g/mL)^{-1}$	0.664	10.4	0.674	(0.489, 0.866)
Population 2 Slope $(\mu g/mL)^{-1}$	0.0821	39.0	0.0796	(0.0163, 0.173)
Population 1 Mix Fraction	0.358	31.6	0.370	(0.132, 0.629)
Eta Scale Factor	12	66.8	12.2	(3.5, 1613.7)
Visit ≥ 3 Practice Effect	1.51	15.9	1.46	(0.444, 2.04)
IIV Intercept & Scaled-Slope	0.758	46.3	0.806	(0.0062, 0.283)
Additive RUV	0.0499	31.3	0.0403	(0.174, 0.084)

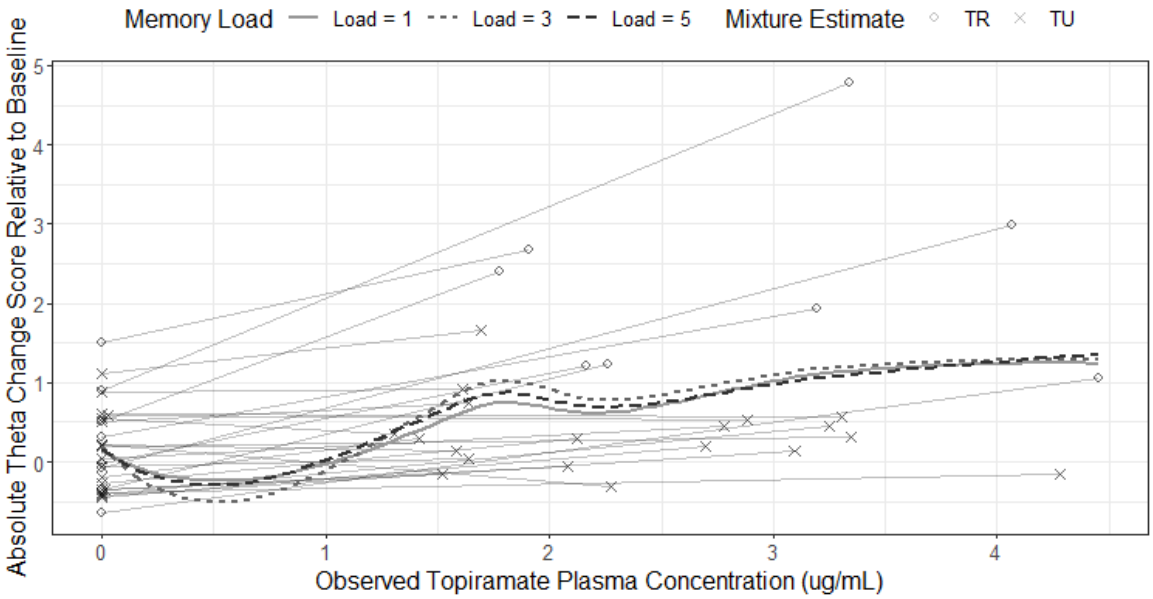

Figure 3-1: Change in EEG power as a function of topiramate plasma concentration for all subjects (n=27).Loess smooth lines use a smoothing parameter of 0.75, with memory loads 1, 3, and 5 represented by solid, short-dashed, and long-dashed lines, respectively. Thin solid lines connect mean observations from individuals during their placebo and topiramate sessions, with observations labeled according to mixture estimate of Theta-Reactive (x) or Theta-Unreactive (o).

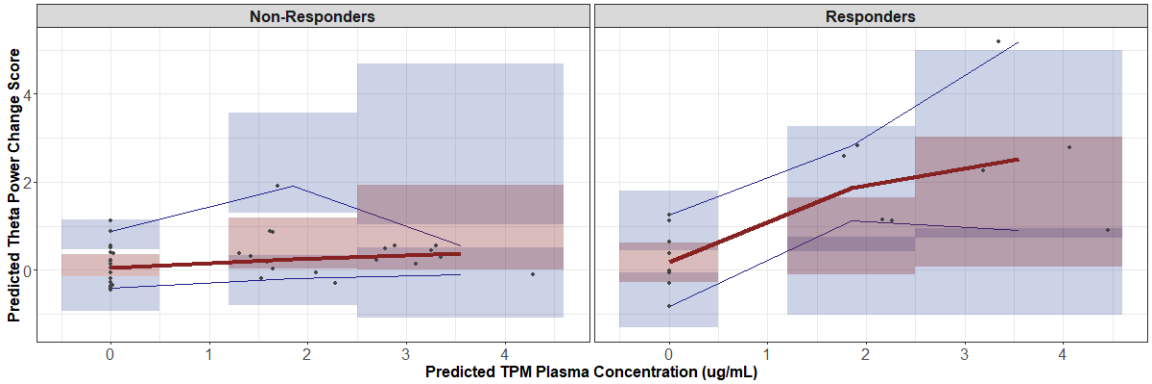

Figure 3-2. Prediction-corrected visual predictive checks for the two subpopulations. Filled circles represent observed theta power change score relative to baseline vs. model-predicted TPM plasma concentrations. Solid and dashed lines represent median and 5^{th}/95^{th} percentile, respectively. Colored ribbons depict 95% confidence interval about the 90% prediction interval and median.

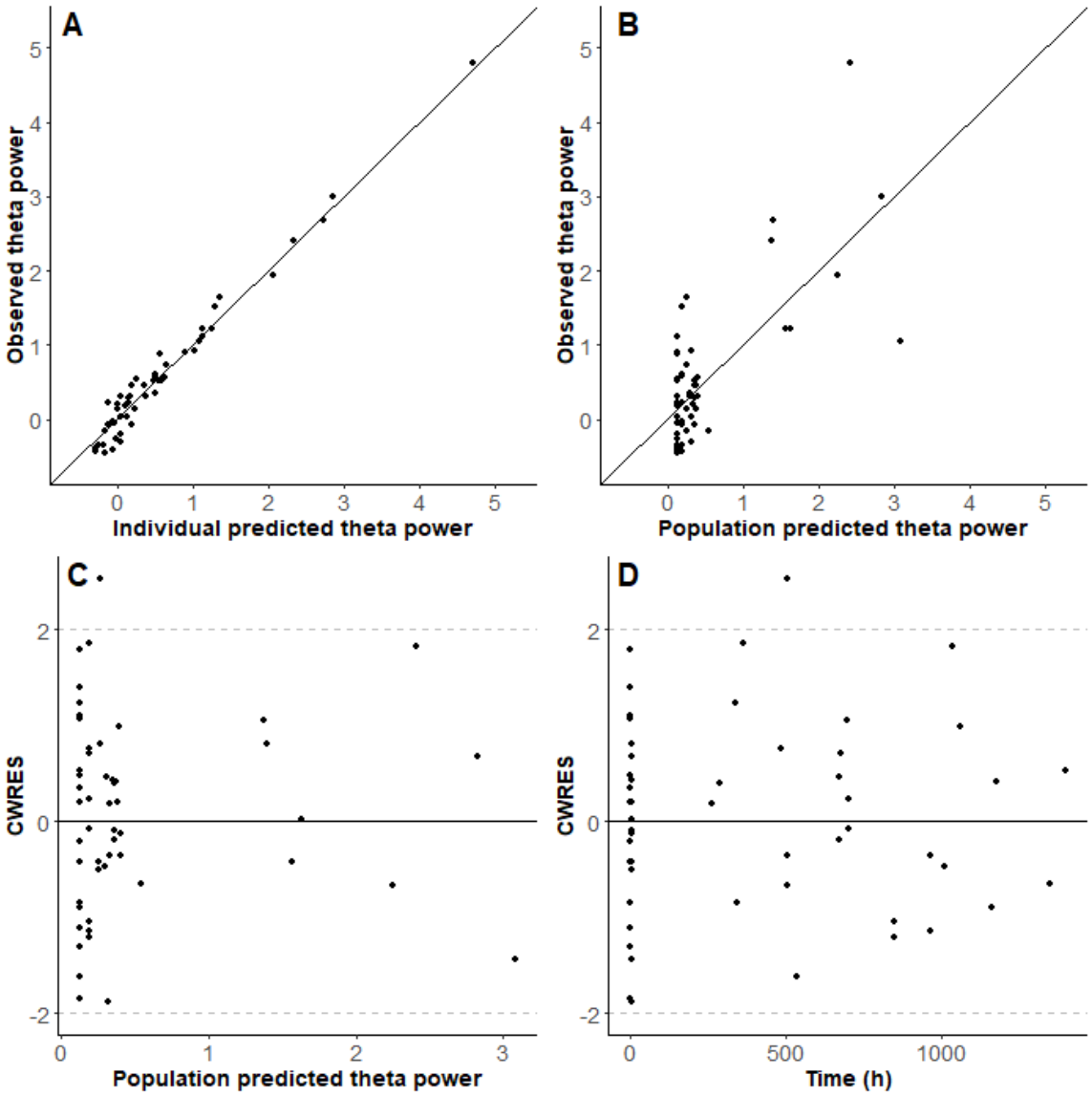

Figure 3-3. Goodness-of-fit plots for final population pharmacokinetic-pharmacodynamic model.Individual observations are denoted by closed circles, with trend lines indicated by the solid line. There were not any noteworthy trends which would indicate a problem with the model.

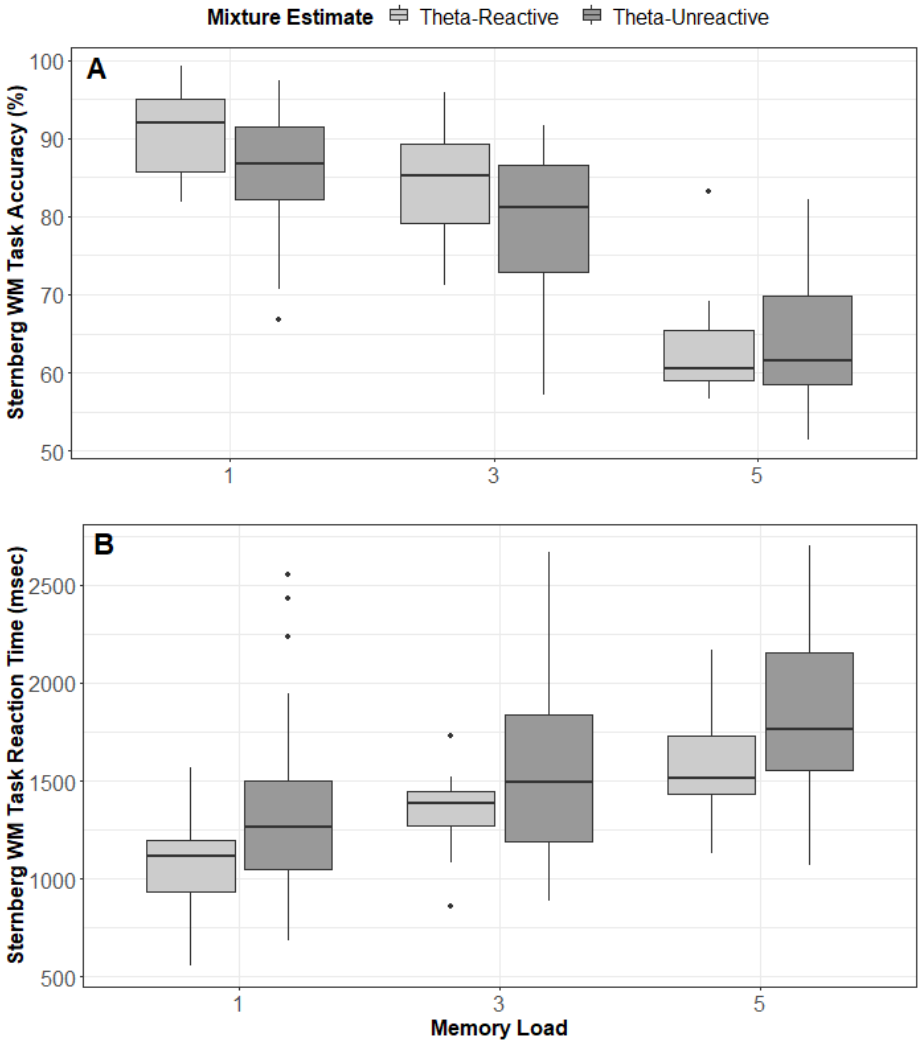

Figure 3-4. Comparison of Sternberg task accuracy (A) and reaction time (B) for three memory loads stratified by mixture population estimate. Population 1 (theta-reactive) group is shown in light gray, and population 2 (theta-unreactive) is shown in dark gray. Outliers, as defined by observations > 1.5*inter-quartile range, are represented by closed circles. A statistically significant difference between subpopulations was identified for WM task reaction time when stratified by memory load (B), but not for accuracy (A).

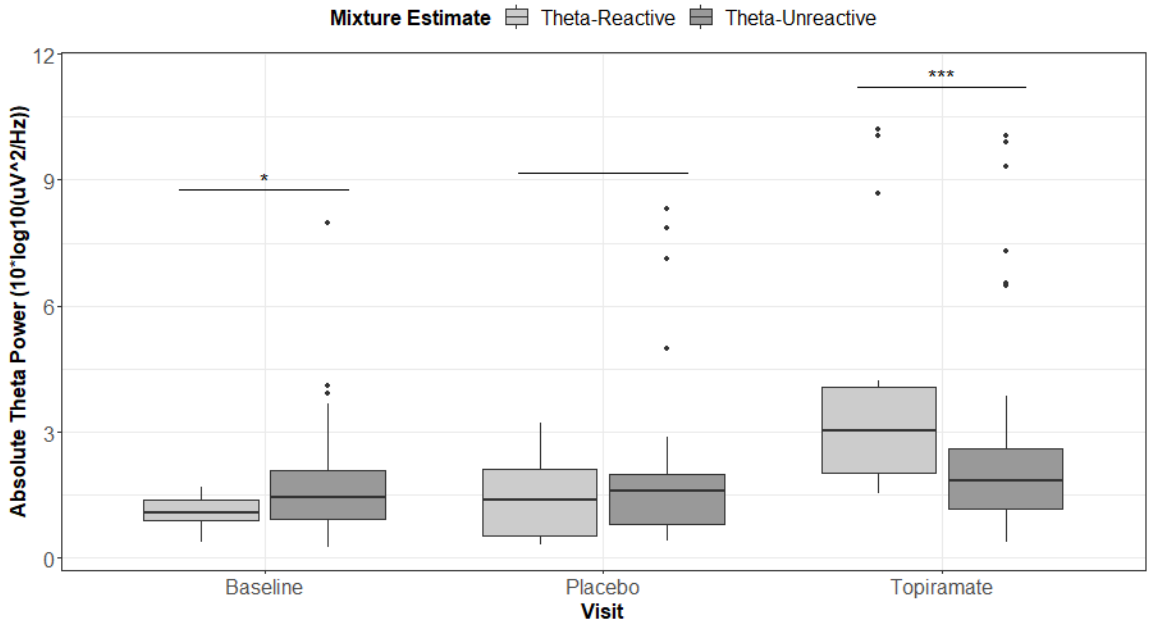

Figure 3-5. Comparison of theta power for each visit between mixture population estimates.Population 1 (theta-reactive) group is shown in light gray, and population 2 (theta-unreactive) is shown in dark gray. *: $p < 0.05$, ***: $p < 0.0005$

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Chapter 4: Application of an Empirical Approach to Identifying Electrophysiological Correlates of Topiramate-Related Working Memory Impairment

4.1 Introduction

When modeling drug-induced changes to physiological processes, there are two options available for selecting indices of drug effect: relying on indices identified by previous research, or using a data-driven approach to empirically select an optimal measure. Application of a literature-driven approach may result in selection of sub-optimal indices of drug effects when investigating previously under-studied phenomena. Investigations into the effects of topiramate (TPM) on WM function are an ideal case for the application of a data-driven approach, as limited research has been conducted into the possible indices of impairment. In the previous chapter, we showed that theta power observed during the retention phase of a modified Sternberg WM task increases linearly as a function of TPM plasma concentration. In this case, we based our selection of spectral power in the theta frequency band on the rich literature illustrating how this electrophysiological activity is positively correlated with the amount of information held in WM (1-7). However, there are additional electrophysiological indices of WM function that may be sensitive to TPM exposure, including (i) theta power seen during the encoding and retrieval stages of the Sternberg WM task (8-10), and (ii) power in the

alpha frequency band observed during encoding, retention, and retrieval processes (1, 3, 5, 7, 11-19). Although these measures are plausibly sensitive to TPM-related WM impairment, the dearth of existing research investigating the effects of TPM on any of these measures made it difficult to determine whether this would in fact be the case. As a result, we relied on existing literature and investigated the relationship between retention-related theta power and TPM exposure. We therefore applied a *post hoc* data-driven approach to investigate whether theta power observed during retention in WM was the optimal marker for TPM-induced WM impairment, and better understand how results from a data-driven selection of electrophysiological endpoints would differ from a literature-driven selection.

Principal component analysis (PCA) is an unsupervised machine learning algorithm primarily used for dimensionality reduction in large datasets. This technique takes a set of possibly-correlated variables and uses a linear combination of these variables to form principal components (PCs), such that each PC maximizes explained variability and is orthogonal to the other PCs. The motivation for this transformation is to explain as much of the variability in the data using as few variables as possible. This approach yields PCs that can replace the original variables while minimizing the amount of information lost and reducing degrees of freedom for predictive modeling. PCA has been applied in biomedical research in a number of ways, including identifying latent factors in medical records (20), determining therapeutic sensitivity of tumors subtyped

using genomic markers (21), and clustering expression patterns in microarray assay results (22).

One limitation of PCA is that variable weights for each PC are typically nonzero, resulting in a linear combination of all input variables in each PC. PCs composed of loadings of all variables in the original data set are often difficult to interpret. However, this limitation may be overcome through application of shrinkage methods, which facilitate empirical selection of subsets of data. Variable shrinkage is not a primary result of standard PCA, but a modified version of PCA called "sparse principal component analysis" (SPCA) uses a combination of ridge regression and least absolute shrinkage selection operator (LASSO) to shrink loadings of variables toward zero (23). Thus, PCs identified by SPCA retain weights on only a subset of the variables, facilitating a more straightforward interpretation of which aspects of the data are meaningfully reflected in each PC. SPCA has been previously applied to dense electroencephalography (EEG) data in brain-computer interface applications as a method of component selection and feature extraction (24).

In this analysis, we applied a SPCA-based analysis with the goal of identifying the EEG-derived measures obtained during a modified Sternberg task that would be most sensitive to TPM administration. Although theta power observed during the retention phase of the Sternberg task was found to be modulated by TPM exposure (see Chapter 2), our aim was to assess whether this was the optimal index of TPM-related cognitive deficits. It is possible that a linear combination of EEG-derived measures

identified by SPCA would be a better indicator of impairment and that this type of composite measure would provide additional insights into the mechanism(s) underpinning TPM-related cognitive side effects.

4.2 Methods

4.2.1 Study design

The electroencephalography (EEG) data included in this analysis is identical to the data modeled in Chapter 3, which was collected during the clinical protocol first described in Chapter 2. Briefly, healthy volunteers were recruited for a crossover study of TPM's negative impact on cognition. A modified Sternberg WM task (25) and a neuropsychological battery were administered at a drug-free baseline visit. Subjects were randomly assigned to receive a single dose of either TPM (100 mg, 150 mg, or 200 mg), lorazepam (2 mg), or inactive placebo on three subsequent treatment visits. Subjects completed the neuropsychological battery at approximately 0.5, 2.5, and 6 hours after dosing, and during a tail visit randomly assigned to occur either 24, 48, 72, or 96 hours after dosing on each treatment visit, while the Sternberg task was administered approximately 4 hours after dosing at each treatment visit.

4.2.2 Digit span task

In addition to the Sternberg WM task, the digit span forward and backward tasks (DSF and DSB, respectively) are also commonly used to assess WM function (26-29). These tasks were administered multiple times for each subject as part of the

neuropsychological battery (see Chapter 2 for protocol details). DSF is a simple span task, evaluating the storage component of WM, while DSB is a complex span task, evaluating both storage and manipulation of objects in WM (27, 30). In both tasks, subjects are verbally presented a three-digit long string of random numbers. In the DSF task, the subject repeats back the numbers verbatim, whereas in the backward task the subject repeats back the numbers in reverse order. After two successfully recalled strings of a given length, the length of the string was increased by one, up to a maximum string length of nine for DSF and eight for DSB. Each correct response is worth one point when scoring the tasks. If the subject does not correctly recall a string of digits for a given string length, a second string of the same length was given. Two sequential failures to repeat a string of a given length results in the task being terminated by the test administrator. The mean t_{max} in our pharmacokinetic data was 2.49 +/- 1.42 hours, motivating our choice of analyzing DSF/DSB scores from the hour 6 post-dose neuropsychological battery instead of hour 2.5 results. TPM concentrations at hour 6 should be most similar to hour 4, when the Sternberg task was administered, because the majority of subjects are past the absorption phase, resulting in a smaller change in concentration over time.

4.2.3 Electroencephalogram recording and analysis

EEG recordings from correct trials of the modified Sternberg WM task were analyzed separately for each stage of the task. One second encoding epochs were time-locked to cue stimulus onset, including 200 msec prior to onset and 1000 msec

following onset. Five second retention epochs were time-locked to cue stimulus offset, including 500 msec prior to offset and 5000 msec following offset. Three second retrieval epochs were time-locked to probe stimulus onset, including 500 msec prior to onset and 3000 msec following onset. These data were analyzed using an identical method as that described in detail in Section 3.2.4 of this thesis. Absolute spectral band power for both the frontal theta (4 – 8 Hz) and posterior alpha (8 – 12 Hz) frequency bands from each of the encoding, retention, and retrieval phases of the Sternberg WM task were calculated separately for each of the three memory loads, resulting in a total of 18 EEG measurements per visit per individual. All EEG measurements were then converted to a change from baseline score using the following equation:

$$\frac{\theta_{TPM} - \theta_{baseline}}{\theta_{baseline}}$$

This transformation simplifies interpretation as positive values indicate an increase in power from baseline after TPM administration, and negative values a decrease. Furthermore, standardizing the data using this approach increases validity of the results of subsequent analyses by converting measures to the same scale (31). A correlation matrix was calculated for all power change scores in order to determine the correlation structure within and across frequency bands.

Multivariate regressions using spectral power change scores from the theta and alpha frequency bands as regressors were constructed to quantify the extent to which electrophysiological measurements predicted performance on the modified Sternberg

task, and to assess the interpretability of these results. Accuracy and reaction time were each regressed separately on theta and alpha power change scores.

4.2.4 Principal component analysis

Sparse principal component analysis (SPCA) was implemented to handle the small sample size and to facilitate interpretation of PCs. This technique uses the elastic net, a penalized least-squares method commonly used in multiple linear regression as a variable selection technique to drive regressor loadings to zero when possible (23). Elastic net combines two different penalty terms to allow correlated predictors: 1-norm LASSO (least absolute shrinkage and selection operator (32)) penalty and a quadratic ridge penalty. LASSO and ridge penalty are both shrinkage methods which minimize regression coefficients; however, only LASSO results in zero loadings on variables. These shrinkage methods are both driven by selection of a tuning parameter, a penalty term which shifts weights of a fraction of the predictors to zero. The number of nonzero predictors is negatively correlated with the tuning parameter, which is typically chosen using a cross-validation approach. The result of SPCA is that variables which make minimal contributions to explaining variability are excluded. According to the "elbow method" for determining the number of PCs to retain (33), only one PC was recommended to be retained; however, five total PCs were retained to maximize the potential for identifying meaningful relationships between electrophysiological measures and behavior in the subsequent regression analyses (described in the following

section). SPCA was implemented using the spca() function in the elasticnet R package (34) in R (version 3.4.1) (35).

Five-fold cross validation was performed to determine the optimal tuning parameters for both the ridge regression penalty and LASSO penalty in the SPCA analysis. The spca() function uniquely implements the 1-norm LASSO tuning parameter in a way that allows a specified number of predictors to be retained within each PC, with the remaining regressor weights driven to zero. Competing tuning parameters were compared during the five-fold cross validation using a residual sum of squares as the cost function.

Behavioral measures from the Sternberg task were regressed on the first five PCs generated by SPCA in order to determine whether these linear combinations of EEG-derived measures would provide improved prediction of task performance compared to simple spectral power change scores. DSF score was also regressed on the first five sparse PCs to investigate whether electrophysiological measures obtained during the Sternberg task would be predictive of performance on a separate task assessing WM function. Statistical significance for the regression models was set at $p < 0.05$.

4.3 Results

4.3.1 Multivariate regression of theta and alpha power change scores

Four multivariate regression models examining relationships between spectral power change scores and performance on the modified Sternberg WM task were

analyzed: i) theta power regressed on accuracy, ii) theta power regressed on reaction time, iii) alpha power regressed on accuracy, and iv) alpha power regressed on reaction time. Although theta power during the encoding and retention phase was predictive of accuracy, regression coefficients were not consistent between loads within a task phase (Table 1, Figure 1A). Likewise, some theta power measures from the retention phase were predictive of reaction time, but not all (Table 2, Figure 1B). No alpha band power regression coefficients were significantly different from zero when used to predict accuracy or reaction time on the Sternberg task (results not shown).

Correlations between EEG measures were calculated in order to determine the suitability of multivariate regression analysis for this data (Figure 2). High correlations between independent regressors may cause regression coefficients to be unstable, motivating the need to use a dimensionality reduction technique such as PCA (31). Within a given phase of the WM task and frequency band (e.g. theta power during the retention phase), spectral power change scores were highly correlated ($r \geq 0.8$) across memory loads. High correlation was also observed across phases of the WM task in both the theta ($0.22 \leq r \leq 0.72$) and alpha ($0.84 \leq r \leq 0.98$) bands. Theta power during the retention phase was correlated with alpha power across all phases of the WM task and for each memory load ($0.42 \leq r \leq 0.68$). These high correlations show that the data were did not meet the statistical assumptions required for a multivariate regression analysis.

4.3.2 Principal components analysis

SPCA was conducted to reduce the dimensionality of the dataset (Table 3). PCA was also applied to the data but offered limited interpretability, further motivating use of SPCA (results not shown). The optimal LASSO tuning parameter identified during the five-fold cross validation retained nine variables in each PC, decreasing the number of retained regressors by 50% while maintaining a similar percent of variability explained by each of the first five PCs (Figure 3). The first principal component, comprising activity in the alpha band for all loads and all phases of the WM task, explained more than 80% of the variability in theta and alpha spectral power (Figure 3).

4.3.3 Sternberg behavioral measures regressed on principal components

Accuracy and reaction time data collected during the modified Sternberg WM task were regressed on the five PCs identified by SPCA. In the accuracy model, none of the slopes of the five PCs were significantly different from zero, with a coefficient of determination less than 11% (results not shown). In the reaction time model, PC 4, primarily comprised of activity in the theta band during the retention period, was the only regressor trending toward significance (Table 4, $p < 0.1$). Goodness-of-fit plots showed the model comprised of the five PC regressors fit the reaction time data well (Figure 4).

4.3.4 Digit Span score regressed on principal components

Score on DSF and DSB were tested as outcome variables in models using the SPCA-derived PCs as regressors. In the model in which DSF score was regressed on the five sparse PCs, the third component was found to be a significant regressor (Table 5, $p < 0.05$). PC 3 was primarily defined by activity in the alpha band during the encoding and retrieval phases of the Sternberg task. The measure associated with reaction time on the Sternberg task, PC 4, also trended toward significance in the DSF model (Table 5 $p < 0.1$). In the model constructed to account for the relationship between PCs and DSB performance, none of the PC regressors reached statistical significance (results not shown). Goodness-of-fit plots revealed that DSF scores were fit well by the regression model (Figure 5).

4.4 Discussion

In this chapter, we demonstrated the application of a data-driven approach to selecting electrophysiological indices of TPM-related WM impairment. The results are consistent with the endpoint selected based on a limited amount of previous research. Although it explained less than 3% of the variability in the electrophysiological data, theta activity observed during the retention period (PC 4) predicted both reaction time on the modified Sternberg task and score on the DSF task. SPCA showed that over 80% of variability in the electrophysiological data collected was explained by activity in the alpha band across stages of the Sternberg WM task (PC 1), but that this activity was not

predictive of performance. However, a combination of alpha activity recorded during the encoding and retrieval stages (PC 3) of this task was the best predictor of score on the DSF task.

Few previous studies have been conducted to determine the electrophysiological indices of drug-induced WM impairment, so in order to determine which measures were likely to be modulated by TPM exposure, we turned to activity in the theta (1-10) or alpha (1, 3, 5, 7, 11-19) frequency bands because of their sensitivity to memory load effects. Theta power during the retention phase of the Sternberg task was selected as the pharmacodynamic endpoint in Chapter 3 based on the extensive literature which showed that this measure was sensitive to memory load changes in studies involving no pharmacological manipulation. However, it was unknown whether theta power was the optimal marker of TPM-related impairment due to the lack of existing literature on this phenomenon. Interestingly, the unsupervised machine learning algorithm presented here showed that theta band power during WM retention was in fact the optimal electrophysiological index of impairment. Application of SPCA showed that alpha power observed at each stage of the WM task was the most variable of the electrophysiological measures analyzed here. Despite this, the first PC, defined entirely by alpha activity at all stages of the modified Sternberg WM task, was not a significant predictor of performance on the Sternberg task. This illustrates that, though widely variable between individuals, alpha power variability does not influence task performance.

Linear combinations of theta and alpha power recorded during the modified Sternberg WM task correlated with performance on the DSF task, another test commonly used to evaluate WM function. In the DSF task, subjects have to retain, but not manipulate, a string of digits. Likewise, during the retention phase of the Sternberg task, subjects are tasked with maintaining representations of the string of syllables and are not manipulating or comparing this information. It is therefore unsurprising that electrophysiological activity during the retention phase of a modified Sternberg task would correlate with performance on the DSF task.

Regression using sparse PCs also found that PC 3, primarily defined by alpha activity during the encoding and retrieval phases of the Sternberg task, was predictive of performance on the DSF task. Recall that PC 3 is separate from and orthogonal to PC 1, which is defined by alpha activity at all stages of the Sternberg task and accounts for over 80% of the variability in the electrophysiological data. Results of the regression showed that increased alpha power during encoding predicted higher DSF scores, while increased alpha power during the retrieval phase predicted lower DSF scores. Increased alpha power during memory encoding has previously been associated with increased memory performance in healthy volunteers (36, 37), consistent with the results presented here. WM retrieval processes have received less attention in the literature compared to the encoding and retention phases; however, one previous study also found alpha power during retrieval was negatively correlated with memory performance (37). There are numerous differences between the DSF and Sternberg tasks, which may

explain why alpha activity predicts performance on DSF, but not on the Sternberg task. It is possible that the lack of correlation between alpha power and reaction time is due to the dual speed-accuracy requirements of the Sternberg task, commonly termed the speed-accuracy trade-off (38), through which behavioral deficits can manifest as either decreased accuracy or increased reaction time. Furthermore, there is an impetus for subjects to respond quickly in DSF, due to the rapid degradation of memory representations. Finally, the to-be remembered stimuli are presented differently between these two tasks: verbally in DSF and visually in the modified Sternberg, a difference that has consequences for all WM functions. Because of the many differences in these two tasks, it is unsurprising that they are not defined by identical electrophysiological correlates of performance.

There were several limitations to our study. Spectral power in the theta and alpha band were selected due to the large literature describing their relation to WM function; however, a multitude of electrophysiological measures are also known to correlate with WM , such as P2 amplitude (39), P300 amplitude (40), theta-gamma amplitude coupling (41, 42), alpha-gamma coupling (17, 43), alpha phase (14, 43) and alpha peak frequency (4). These measures were not analyzed here due to an inability to reliably extract these variables from the type of noisy EEG data associated with drug administration, but it may be advantageous to incorporate some of these additional electrophysiological indices of WM function in future studies. Additionally, the cross-validation method used to identify the optimal number of nonzero variables in the sparse PCA assumed the same

number of variables should be included in each PC. This simplification was adopted due to the exponential increase in computational time if the number of retained variables in each PC can vary independently. For example, imposing this limitation allowed for minimization of tuning parameters across a two-dimensional surface, rather than the six-dimensional surface which would exist had each of the five retained PCs been allowed to vary independently. Although it did not affect interpretation of PCs, the inadequacy of this assumption can be seen in PC 4, which has large weights on the retention phase measures, and near zero measures for four of the remaining six retained variables.

In conclusion, this analysis demonstrated the utility of an unsupervised machine learning algorithm for the identification of electrophysiological markers of TPM-related cognitive side effects, especially because of the limited research previously conducted in this area. Although the optimal measure identified using this novel method matched the measure previously selected after surveying the existing literature (see Chapter 2), agreement between these two approaches was not a foregone conclusion. This type of analysis may be productive in future studies during early stages of the drug development process when investigating a novel therapeutic with multiple possible drug effect biomarkers, and the results may also have downstream applications in pharmacokinetic-pharmacodynamic modeling.

Table 4-1. Multivariate regression of accuracy (%/100) on a modified Sternberg working memory task as a function of absolute midline theta power change score.

	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	-0.059	0.019	-3.119	0.007*
Theta$_{\text{encoding, load 1}}$	-0.150	0.094	-1.595	0.131
Theta$_{\text{encoding, load 3}}$	0.028	0.042	0.685	0.504
Theta$_{\text{encoding, load 5}}$	0.113	0.045	2.500	0.025*
Theta$_{\text{retention, load 1}}$	-0.082	0.044	-1.867	0.082†
Theta$_{\text{retention, load 3}}$	-0.095	0.057	-1.658	0.118
Theta$_{\text{retention, load 5}}$	0.157	0.067	2.345	0.033*
Theta$_{\text{retrieval, load 1}}$	0.068	0.051	1.320	0.207
Theta$_{\text{retrieval, load 3}}$	-0.005	0.078	-0.071	0.945
Theta$_{\text{retrieval, load 5}}$	-0.060	0.068	-0.880	0.393

R-squared = 55.01%. †: $p < 0.1$, *: $p < 0.05$

Table 4-2. Multivariate regression of reaction time (msec) on a modified Sternberg working memory task as a function of absolute midline theta power change score.

	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	0.138	0.047	2.928	0.010*
Theta$_{\text{encoding, load 1}}$	0.245	0.235	1.043	0.313
Theta$_{\text{encoding, load 3}}$	-0.215	0.104	-2.075	0.056†
Theta$_{\text{encoding, load 5}}$	0.060	0.113	0.528	0.605
Theta$_{\text{retention, load 1}}$	0.191	0.109	1.747	0.101
Theta$_{\text{retention, load 3}}$	0.327	0.143	2.289	0.037*
Theta$_{\text{retention, load 5}}$	-0.632	0.167	-3.778	0.002*
Theta$_{\text{retrieval, load 1}}$	0.071	0.128	0.552	0.589
Theta$_{\text{retrieval, load 3}}$	0.140	0.193	0.723	0.481
Theta$_{\text{retrieval, load 5}}$	-0.216	0.170	-1.270	0.223

R-squared = 67.26%. †: $p < 0.1$, *: $p < 0.05$

Table 4-3. Principal component weights for sparse principal component analysis.

Frequency	Memory Stage	Load	PC 1	PC 2	PC 3	PC 4	PC 5
Theta	Encoding	1	-	-0.2555	0.0094	-	-
Theta	Encoding	3	-	-0.5288	0.0816	-0.1059	-
Theta	Encoding	5	-	-0.3911	0.022	-	0.0976
Theta	Retention	1	-	-0.0476	-	0.3368	-
Theta	Retention	3	-	-	-	0.6608	-
Theta	Retention	5	-	-	-	0.6413	-
Theta	Retrieval	1	-	-0.4462	-0.1027	0.1576	-0.1097
Theta	Retrieval	3	-	-0.3465	-	-	-
Theta	Retrieval	5	-	-0.4228	-	-	-
Alpha	Encoding	1	0.3288	-	-0.1425	-	-
Alpha	Encoding	3	0.2922	-	-0.7833	-0.0368	-0.1218
Alpha	Encoding	5	0.1505	-	-0.4206	0.0259	-
Alpha	Retention	1	0.1937	0.0089	-	-	0.4221
Alpha	Retention	3	0.1667	-	-	-	0.4624
Alpha	Retention	5	0.0696	-	-	0.0224	0.603
Alpha	Retrieval	1	0.6247	-	0.3561	0.0003	-0.2062
Alpha	Retrieval	3	0.5344	-	0.2114	-	-0.1918
Alpha	Retrieval	5	0.1947	-0.0433	-	-	0.3587

Table 4-4. Multivariate regression of reaction time (msec) on a modified Sternberg working memory task as a function of sparse principal components.

	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	0.106	0.062	1.723	0.101
PC 1	0.004	0.010	0.366	0.718
PC 2	-0.027	0.031	-0.847	0.408
PC 3	-0.049	0.043	-1.142	0.268
PC 4	-0.082	0.043	-1.925	0.069†
PC 5	-0.025	0.053	-0.461	0.650

R-squared = 23.64%. †: $p < 0.1$, *: $p < 0.05$

Table 4-5. Multivariate regression of digit span forward as a function of sparse principal components.

	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	-0.319	0.044	-7.185	0.000*
PC 1	-0.001	0.007	-0.074	0.942
PC 2	-0.012	0.023	-0.531	0.602
PC 3	-0.075	0.031	-2.410	0.026*
PC 4	-0.055	0.031	-1.770	0.093†
PC 5	-0.029	0.038	-0.762	0.455

R-squared = 36.67%. †: $p < 0.1$, *: $p < 0.05$

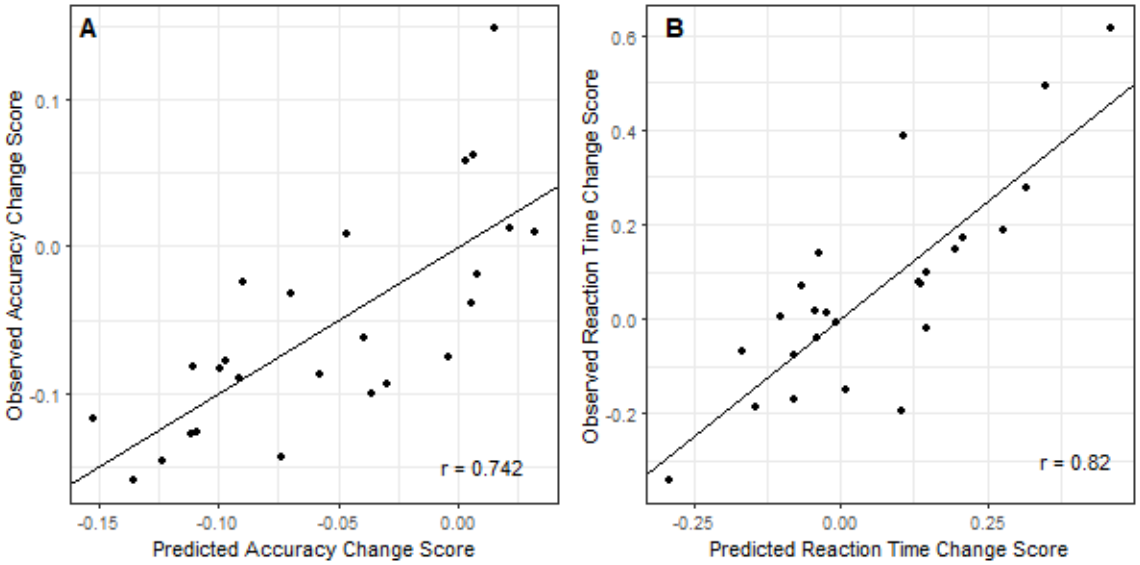

Figure 4-1. Goodness-of-fit plots for multivariate regression models of theta power band vs Sternberg behavioral results.Observed vs predicted accuracy (a) and reaction time (b) plots include line of unity for reference. r = Pearson's correlation coefficient.

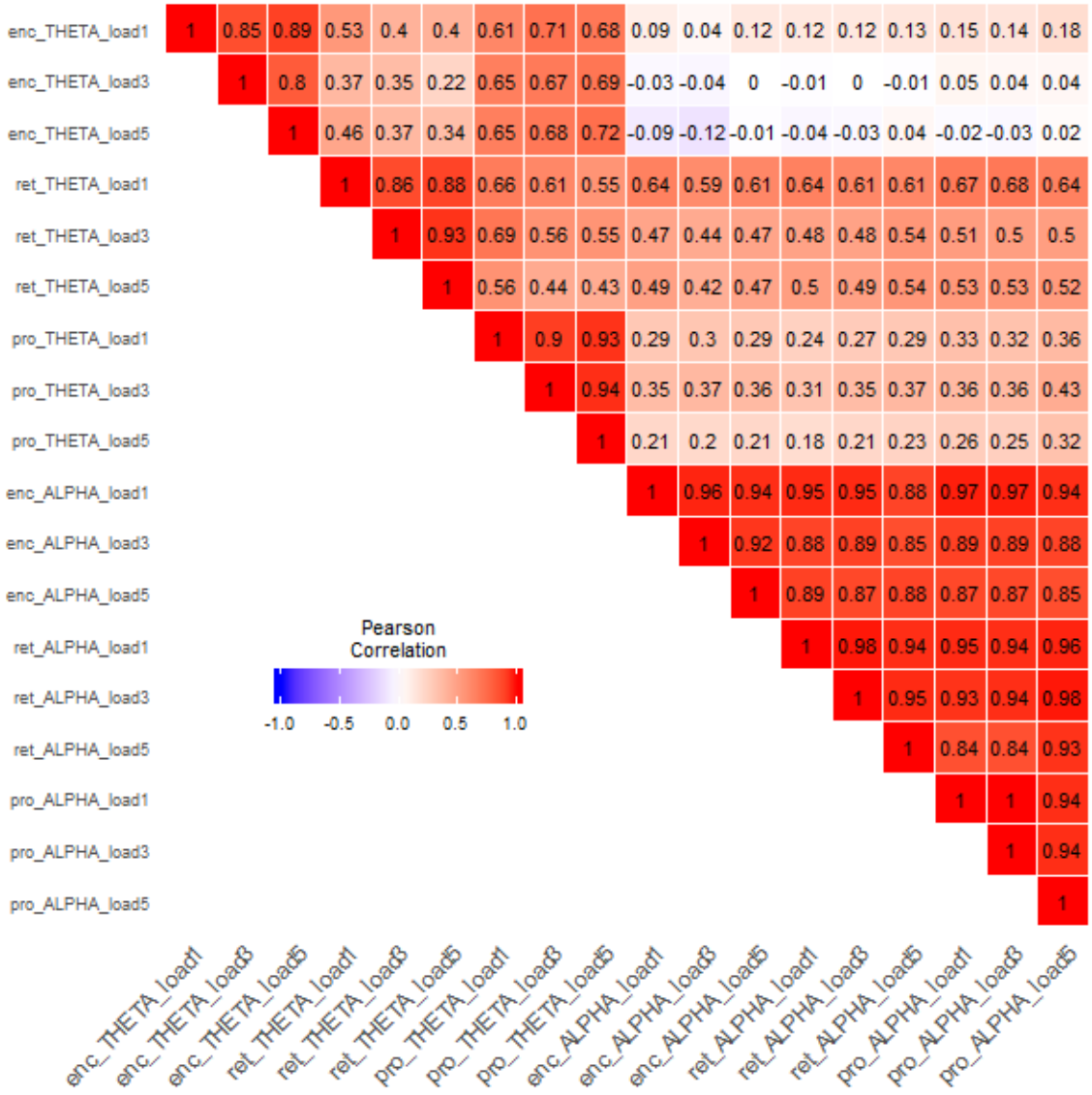

Figure 4-2. Correlation between EEG absolute power change in theta and alpha bands during the encoding, retention, and probe phase of a modified Sternberg working memory task separated into three memory loads.Plot created using Dr. Julian Wolfson's CorHeatmap() function available on GitHub.

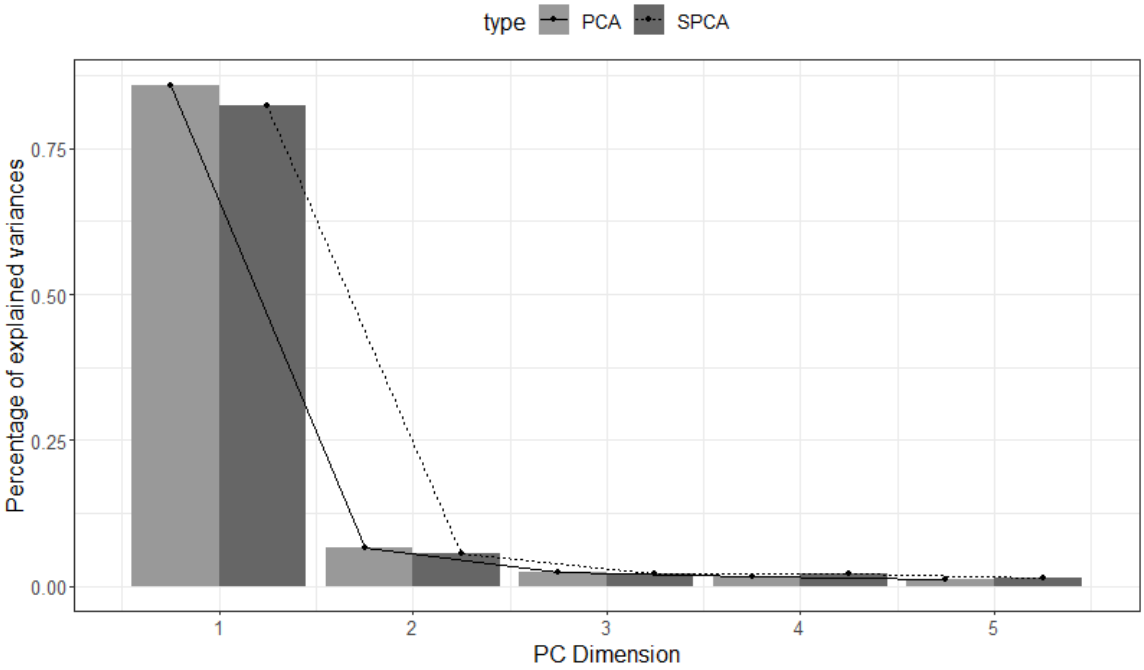

Figure 4-3. Scree plot comparing explained variances of principal component analysis and sparse principal component analysis.

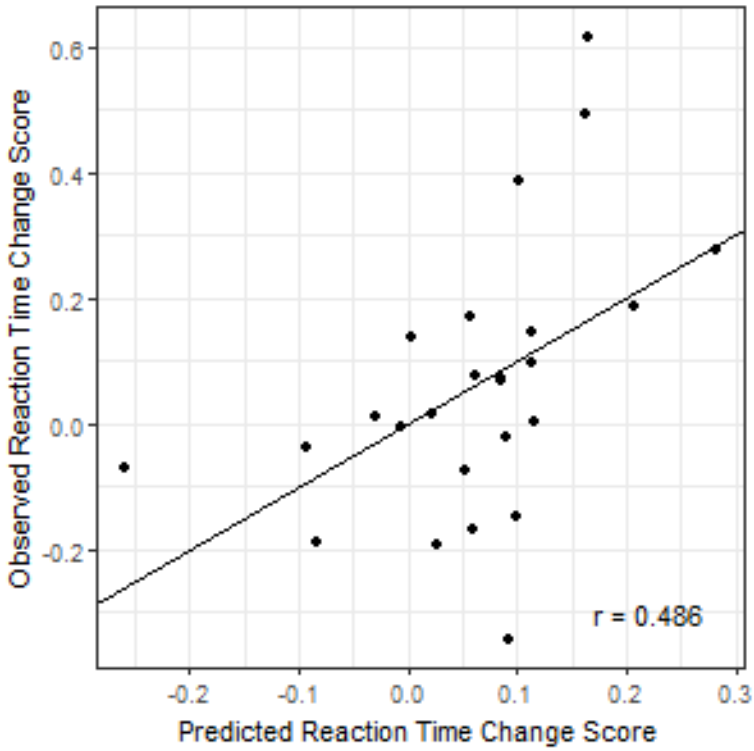

Figure 4-4. Goodness-of-fit plot for multivariate regression models of sparse principal components vs Sternberg reaction time (msec) results.Observed vs predicted plot includes line of unity for reference. r = Pearson's correlation coefficient.

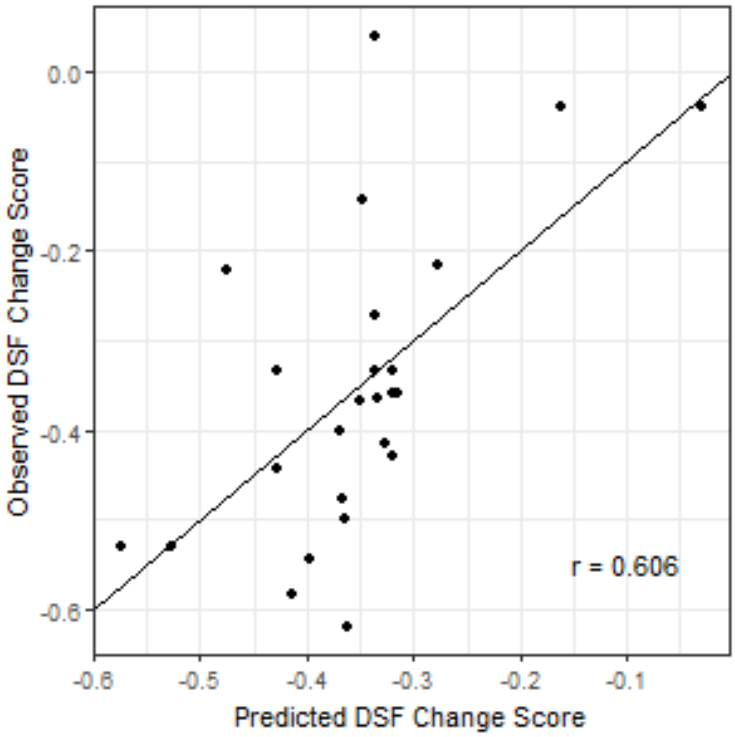

Figure 4-5. Goodness-of-fit plot for multivariate regression models of sparse principal components vs digit span forward.Observed vs predicted plot includes line of unity for reference. r = Pearson's correlation coefficient.

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Chapter 5: Conclusion

The analyses presented in this thesis demonstrate the multifaceted effects of topiramate (TPM) on working memory (WM). The major goals of this thesis were to characterize the changes to behavioral and electrophysiological indices of WM processes resulting from TPM exposure and to determine how these indices are related to one another. To achieve this goal, a combination of non-linear mixed effects models and machine learning algorithms were constructed to determine i) the effects of TPM on behavior, ii) the effects of TPM on brain responses, and iii) how electrophysiological and behavioral changes in response to TPM are associated with one another.

5.1 Effects of topiramate on behavior

We identified a concentration-dependent relationship between TPM exposure and the severity of performance deficits on a modified Sternberg WM task. As stated throughout this thesis, the Sternberg task has been used for decades to quantify WM function. This specificity allowed us to understand the effects of TPM on this neurocognitive system in particular, rather than being limited to broad statements regarding its effect on subjects' performance on tasks that simultaneously assess multiple aspects of cognition. Our motivation for focusing on the WM system is its correlation with numerous measures of high-level cognitive processes, including math skills (1, 2), reading comprehension (2, 3), fluid intelligence (4, 5), and verbal fluency (6-9). In the

results reported here, we showed that the magnitude of TPM-related impairment was partially determined by both WM capacity (WMC) and TPM plasma concentration, but independent of the amount of information held in WM after accounting for differences in WMC. Although this is not the first time that WMC has been associated with the severity of TPM-induced cognitive deficits (10), we improved upon previous findings by developing a tool which can make predictions about the severity of WM deficits prior to drug administration given an individual's WMC and TPM dose.

5.2 Effects of topiramate on brain responses

We showed for the first time that the magnitude of spectral power observed during the retention phase of the Sternberg WM task increased linearly as a function of TPM plasma concentrations. Even though subjects were exposed to TPM levels much lower than would be expected from chronic dosing in patients with epilepsy (11), significant changes in electrophysiology were still observed in response to drug administration. Furthermore, a subset of individuals was particularly sensitive to the electrophysiological effects of TPM, showing eightfold greater increases in theta power as plasma concentration increased. Reaction times on the Sternberg task differed significantly between these two subpopulations, indicating that sensitivity to TPM affected not only electrophysiology, but also behavioral measures of task performance.

5.3 Relationship between electrophysiological and behavioral changes

Some of the most compelling findings presented in this thesis are those that showed that brain and behavioral responses are not always linked in predictable ways as one might expect; changes in brain responses do not always co-occur with observable changes in behavior. Although over 80% of the variability in the EEG data was explained by differences in alpha power, we did not find alpha power to predict performance on the Sternberg task. Alpha power varies widely between individuals depending on age, mental state, and the task being performed (12-14). Although previous studies show that alpha power correlates with WM function (15-20), our approach demonstrated that it is not sensitive to TPM-induced impairment of WM function. In contrast, less than three percent of the variability in the EEG data was explained by differences in theta power during the retention phase of the WM task. Although much less variable than alpha power, this narrow range of variability was the best predictor of task performance. Characterizing the interaction between activity in the theta and alpha bands following TPM administration and their association with behavioral outcomes remains a topic for future research.

We observed a practice effect in the electrophysiological data (Chapter 3), while there was no evidence of a behavioral practice effect (Chapter 2). The electrophysiological index of this practice effect was an increase in theta power during the retention stage of the Sternberg task when comparing the final study visit to previous visits. We hypothesized that this increased activity reflects anticipation of the time-locked

display of the probe stimulus: after completing over 1000 trials of the task, individuals developed an ability to predict the occurrence of the probe stimulus onset which occurred, consistently and exactly, five seconds after cue stimulus offset. The lack of a practice effect observed in the accuracy results may imply that this electrophysiological index of a practice effect is either i) not related to task performance, or ii) related to reaction time on the Sternberg task rather than accuracy.

Though not consistently, there were also instances in which changes in electrophysiology *were* mirrored by behavioral changes. Although at the population level it was shown that there is no effect of TPM on reaction time in the Sternberg task (10), analysis of subgroups based on sensitivity of theta power to TPM did show an effect (Chapter 3). The group defined by lower theta reactivity as a function of TPM exposure performed the Sternberg task slower than their high sensitivity counterparts. These subpopulations were not visible in the pharmacokinetic-pharmacodynamic model of the accuracy data, indicating that analyzing the Sternberg accuracy and reaction time results may be necessary because deficits can manifest through either measure.

A negative effect of placebo administration on task performance, or a "nocebo effect," was observed in both the behavioral (Chapter 2) and electrophysiological measures (Chapter 3) collected during Sternberg task performance. The ability to quantify the effect of placebo administration in a novel way was made possible by the crossover study design, which allowed us to separate the impairments occurring as a function of TPM exposure, and those corresponding to the nocebo effect. We

hypothesized that the nocebo effect was due to an expectancy bias resulting from the informed consent process, during which subjects were told that the goal of the study was to understand the negative impact of drugs on cognition. Interestingly, the magnitude of the nocebo effect was predicted by individual WMC in a manner similar to that seen in the drug effect. Limited research has been conducted into predictors of individual vulnerability to the placebo effect; however, one study found that expected improvement in cognition following placebo administration was modulated by WMC (21). Our results show that this relationship holds for negative placebo effects as well, highlighting the important role that expectancy plays in the effects of drugs on cognitive function.

The electrophysiological response to placebo exhibited large interindividual variability in magnitude and direction. Unlike the placebo effect observed in the behavioral results, the magnitude of these changes were not predicted by WMC. Due to the existence of distinct subpopulations with differing sensitivity to TPM, it is difficult to compare the TPM-related changes to electrophysiology with placebo-related changes. However, theta band power showed small increases following placebo administration, similar to those observed in the theta-unreactive group following TPM administration, with behavioral deficits observed in both instances. A possible interpretation of this result is that an electrophysiological measure not analyzed here is associated with behavioral deficits on the Sternberg task, while theta power plays a complementary role in overcoming these deficits. This would explain why the TPM-sensitive theta-reactive

group did not exhibit large behavioral differences with their large changes in theta power. One possible measure, which would also explain the observed association between behavioral measures of the placebo effect and WMC, is P300 amplitude, which has been previously shown to correlate with WMC (22, 23). Although there are limited studies on electrophysiological indices of the placebo effect, these results clearly indicate that there exists a relationship between spectral power and placebo-induced behavioral deficits.

5.4 Future directions and concluding statements

The application of sparse principal component analysis (SPCA) in this thesis offers a unique proof of concept for investigations where physiological drug effect research is lacking. Prior to this research, there were limited published accounts of the effect of TPM on electrophysiological indices of WM function. Spectral power in the theta frequency band during the retention period of the Sternberg task was selected as the measure to be analyzed in Chapter 3 simply because of the previously reported sensitivity of theta power to manipulations of memory load; however, it was unknown if it would also be an index of the well-studied WM deficits caused by TPM. The results of the SPCA empirically confirmed theta power during retention to be the best predictor of TPM-related impairment, consistent with existing work. Although we completed the pharmacokinetic-pharmacodynamic modeling and the SPCA sequentially, SPCA could also be completed prior to modeling to inform variable selection in circumstances when there is a lack of clarity regarding the measure that should be used as the

pharmacodynamic endpoint. Moreover, linear combinations of multiple endpoints (i.e. PCs) identified by SPCA could be used as composite endpoints sensitive to the multifaceted effects of a drug on behavior and electrophysiology in downstream applications such as pharmacokinetic-pharmacodynamic models.

In summary, the quantitative pharmacological approach developed throughout this thesis provides a blueprint for future explorations into drug-induced cognitive impairment. Using this framework, I showed that TPM impairs behavioral performance on a WM task, and the magnitude of impairment is predicted by individual WMC. TPM also modulates an electrophysiological index of WM function, and certain individuals are more sensitive to TPM's effect on electrophysiology. Furthermore, the electrophysiological measure modulated by TPM exposure predicted WM impairments. Two treatment-independent factors were identified using this approach, WMC and TPM sensitivity, which predict the magnitude of TPM-induced impairment. Future research can build upon these findings to develop a clinical tool using these measures to predict which patients are most likely to experience cognitive side effects prior to TPM administration, thus improving patient experience by avoiding prescribing of TPM in patients likely to experience cognitive side effects.

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Chapter 7: Appendices

7.1 Chapter 2: Population Pharmacokinetic Model Control Stream

```
$PROBLEM Topiramate 2-compartment PK Model with absorption lag
$INPUT C ID TIME NTIME DV AMT RATE DRUG CMT MDV EVID WT AGE HT
    SEX BSA LBM IBW BMI RACE0 RACE1 RACE2 RACE3 RACE4
    RACE5 TSB FED1 FED15 FED2 FED25 FED3 FED35 FED4

$SUBROUTINES ADVAN4 TRANS4

$PK
; shared iv/oral pk parameters
TVCL = THETA(1) * (WT/70)**0.75
CL = TVCL * EXP(ETA(1))
TVV2 = THETA(2) * (WT/70)
V2 = TVV2 * EXP(ETA(3))
TVV3 = THETA(3) * (WT/70)
V3 = TVV3
TVQ = THETA(4) * (WT/70)**0.75
Q = TVQ

; oral pk parameters
IF(DRUG.EQ.1) THEN
TVALAG1 = THETA(6)
ALAG1 = TVALAG1 * EXP(ETA(4))
TVKA = THETA(5)
KA = TVKA * EXP(ETA(2))
TVF1=THETA(7)
F1=TVF1
ELSE
; iv pk parameters
ALAG1=0
KA=0
F1=1
ENDIF

S2 = V2
S3 = V3

$ERROR
IPRED = F
Y = F * (1 + EPS(1))

$THETA
```

```
(0, 1)            ; CL
(0, 40)     ; VC
(0, 20)     ; VP
(0, 5)            ; Q
(0, 0.5)    ; KA
(0, 0.2)  ; ALAG1
(0, .8)   ; F1

$OMEGA
0.1 ; IIV CL
0.1 ; IIV KA
0.1 ; IIV V2
0.1 ; IIV ALAG1

$SIGMA
0.01 ; Proportional CV

$ETAS FILE=output.phi
$EST METHOD=1 INTERACTION MAXEVALS=9999 POSTHOC NOABORT NSIG=3
SIGL=9 MCETA=1

$COV UNCONDITIONAL SIGL=12 PRINT=E
```

7.2 Chapter 2: Population Pharmacokinetic-Pharmacodynamic Model Control Stream

```
$PROBLEM  Topiramate Direct Response PK-PD Model of Sternberg WM
Task Accuracy
$INPUT   C ID DATE=DROP CTIME=TIME DV SESSION VISIT LOAD AMT FLAG
      AGE SEX HT WT EDU CKDEPI MDRD CG ETH RACE0 RACE1 RACE2
      RACE3 RACE4 RACE5 CLI V2I V3I QI KAI ALAG1I F1I TAD MDV
      EVID COMPLETE SEQ CK1 CK3 CK5
$SUBROUTINE ADVAN4 TRANS4

$PK
; sequential PK parameter assignment
CL = CLI
V2 = V2I
V3 = V3I
Q = QI
ALAG1 = ALAG1I
KA = KAI
F1 = F1I

S2 = V2
S3 = V3

; covariate model from SCM (PsN)
  PBOEFFECTCK1 = ((CK1/0.88)**THETA(12))
PBOEFFECTCOV=PBOEFFECTCK1

  INTERCEPTCK3 = ((CK3/2.3)**THETA(11))
  INTERCEPTCK1 = ((CK1/0.88)**THETA(10))
INTERCEPTCOV=INTERCEPTCK1*INTERCEPTCK3

  INT5CK5 = ((CK5/1.75)**THETA(9))
  INT5CK1 = ((CK1/0.88)**THETA(8))
INT5COV=INT5CK1*INT5CK5

  INT3CK3 = ((CK3/2.3)**THETA(7))
  INT3CK1 = ((CK1/0.88)**THETA(6))
INT3COV=INT3CK1*INT3CK3

; PD model parameters
TVINTERCEPT = THETA(1)

TVINTERCEPT = INTERCEPTCOV*TVINTERCEPT
TVINT3 = THETA(2)
```

```
TVINT3 = INT3COV*TVINT3
TVINT5 = THETA(3)

TVINT5 = INT5COV*TVINT5
TVDVSLOPE = THETA(4)
TVPBOEFFECT = THETA(5)

TVPBOEFFECT = PBOEFFECTCOV*TVPBOEFFECT

$ERROR
CP = F

;;;;;; LOAD-specific Variable definition
; LOAD 1
IF(LOAD.EQ.1) THEN
INTERCEPT = TVINTERCEPT
DVSLOPE = TVDVSLOPE * EXP(ETA(1))
ENDIF

; LOAD 3
IF(LOAD.EQ.3) THEN
INT3 = TVINT3
INTERCEPT = INT3
DVSLOPE = TVDVSLOPE * EXP(ETA(1))
ENDIF

; LOAD 5
IF(LOAD.EQ.5) THEN
INT5 = TVINT5
INTERCEPT = INT5
DVSLOPE = TVDVSLOPE * EXP(ETA(1))
ENDIF

;;;;;;;;; Drug Effect Model Subcomponent
; Linear DVSLOPE
DVS = CP*DVSLOPE

;;;;;;;; Full Model
EFF = INTERCEPT - DVS

PBOEFFECT = TVPBOEFFECT
; subtract placebo effect on placebo visit
IF(SESSION.EQ.1) THEN
EFF = EFF - PBOEFFECT
ENDIF

; Save Effect prediction as IPRED for graphing
IF(FLAG.EQ.2) THEN
IPRED=EFF
```

```
ENDIF

;;;;;; Residual Unexplained Variability
Y = EFF + EPS(1) ; PD additive error

$THETA
; PD model parameters
(0,0.9) ; Load 1 Intercept
(0,0.9) ; Load 3 Intercept
(0,0.7) ; Load 5 Intercept
(0,0.1) ; Load 1,3,5 Drug Effect slope
(0,0.1) ; Placebo Effect
; covariate effects
(-0.1) ; CK1 on Intercept Load 3
(0.3)  ; CK3 on Intercept Load 3
(-0.3) ; CK1 on Intercept Load 5
(0.2)  ; CK5 on Intercept Load 5
(0.1)  ; CK1 on Intercept Load 1
(0.1)  ; CK3 on Intercept Load 1
(-1.2) ; CK1 on Placebo Effect

$OMEGA
0.1   ; IIV on Load 1,3,5 DVSLOPE

$SIGMA
0.1   ; PD additive error

$ESTIMATION METHOD=1 INTERACTION MAXEVALS=9999 POSTHOC NOABORT
NSIG=3 SIGL=9

$COVARIANCE UNCONDITIONAL SIGL=12 PRINT=E
```

7.3 Chapter 3: Population Pharmacokinetic-Pharmacodynamic Control Stream

```
$PROBLEM  Topiramate EEG Indirect PK-PD Model
$INPUT   C ID DATE=DROP TIME DV SESSION VISIT LOAD AMT FLAG
      AGE SEX HT WT EDU CKDEPI MDRD CG ETH RACE0 RACE1 RACE2
      RACE3 RACE4 RACE5 CLI V2I V3I QI KAI ALAG1I F1I TAD MDV
      EVID COMPLETE SEQ CK1 CK3 CK5 CKA SECL SEKA SEV2 SEALAG1

$SUBROUTINE ADVAN4 TRANS4

$PK
CL = CLI*EXP(ETA(2)*SECL)
V2 = V2I*EXP(ETA(3)*SEV2)
V3 = V3I
Q = QI
ALAG1 = ALAG1I*EXP(ETA(4)*SEALAG1)
KA = KAI*EXP(ETA(5)*SEKA)
F1 = F1I

S2 = V2
S3 = V3

$ERROR
;---- Drug Effect Model
; assign Cp for drug effect model
CP = F
; save system variable
EST = MIXEST
; create CK mean variable
CK = (CK1 + CK3 + CK5) / 3

VISITEFF = 1
IF(VISIT.GE.3) THEN
VISITEFF = THETA(6)
ENDIF

; shared baseline
BL_tPower = THETA(1) * VISITEFF * (1 + THETA(5) * ETA(1))

; mixture model for drug slope
IF(MIXNUM.EQ.1) THEN
TVSLOPE1 = THETA(2)
SLOPE = TVSLOPE1 * (1 + ETA(1))
ELSE
TVSLOPE2 = THETA(3)
```

```
SLOPE = TVSLOPE2 * (1 + ETA(1))
ENDIF

; effect = slope * concentration
EFF= SLOPE*CP

;---- Full Model
tPower = BL_tPower + EFF
IPRED = tPower

;---- Residual Error Model
Y = tPower + EPS(1)

$MIX
P(1) = THETA(4)
P(2) = 1-THETA(4)
NSPOP=2

$THETA
0.5 ; BL tPower
(0, 2); SLOPE POP1
(0, 0.5)    ; SLOPE POP2
(0, 0.5, 1) ; MIX POP1
(1)    ; ETA-SCALE
(1)   ; VISIT4

$OMEGA
0.1 ; IIV BL
1 FIX ; SECL
1 FIX ; SEV2
1 FIX ; SEALAG1
1 FIX ; SEKA

$SIGMA
0.5 ; AddRUV

$ESTIMATION METHOD=1 INTERACTION MAXEVALS=9999 POSTHOC NOABORT
NSIG=3 SIGL=9
$COVARIANCE UNCONDITIONAL SIGL=12 PRINT=E
```

7.4 Chapter 3: Spectral Power Calculation EEGLAB Script

```
function f = powerCalc(EEG)

  % multiple channel locations
  [spectra1,freqs1] = spectopo(EEG.data([19 10 12 5 11],:,:), 0,
EEG.srate);
  thetaSpec = mean(spectra1); % frontal theta
  [spectra2,freqs2] = spectopo(EEG.data([61 79 67 78 68],:,:), 0,
EEG.srate);
  alphaSpec = mean(spectra2); % posterior alpha
  [spectra3,freqs3] = spectopo(EEG.data([7 107 32 81 129],:,:), 0,
EEG.srate);
  gammaSpec = mean(spectra3); % central gamma
  [spectra4,freqs4] = spectopo(EEG.data([19 10 12 5 11],:,:), 0,
EEG.srate);
  betaSpec = mean(spectra4); % frontal beta

  thetaIdx = 5:9;
  alphaIdx = 9:13;
  beta1Idx = 13:21;
  beta2Idx = 21:31;
  gammaIdx = 31:81;

  % compute power specific to each frequency ROI
  thetaPower = mean(10.^(thetaSpec(thetaIdx)/10));
  alphaPower = mean(10.^(alphaSpec(alphaIdx)/10));
  beta1Power = mean(10.^(betaSpec(beta1Idx)/10));
  beta2Power = mean(10.^(betaSpec(beta2Idx)/10));
  gammaPower = mean(10.^(gammaSpec(gammaIdx)/10));


  f = [thetaPower alphaPower beta1Power beta2Power gammaPower];
end
```