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Brain's compensatory response to drug-induced cognitive impairment

Immanuel Babu Henry Samuel^{#a}, Christopher Barkley^{#b}, Susan E. Marino^{#b}, Chao Wang^{#a}, Sahng-min Han^a, Angela K. Birnbaum^b, Jean E. Cibula^c, and Mingzhou Ding^{a,**}

^aJ Crayton Pruitt Family Department of Biomedical Engineering, University of Florida, Gainesville, FL, USA

^bCenter for Clinical and Cognitive Neuropharmacology, University of Minnesota, Minneapolis, MN, USA

^cDepartment of Neurology, University of Florida, Gainesville, FL, USA

[#] These authors contributed equally to this work.

Abstract

Topiramate (TPM), a frequently prescribed anti-seizure medication, can cause severe cognitive side effects. Though these side effects have been studied behaviorally, the underlying neural mechanisms are unknown. In a double-blind, randomized, placebo-controlled, crossover study of TPM's impact on cognition, nine healthy volunteers completed three study sessions: a no-drug baseline session and two sessions during which they received either TPM or placebo. Electroencephalogram was recorded during each session while subjects performed a working-memory task with three memory loads. Comparing TPM with baseline we found the following results. (1) TPM administration led to declines in behavioral performance. (2) Fronto-central event-related potentials (ERPs) elicited by probe-stimuli, representing the primary task network activity, showed strong memory load modulations at baseline, but the magnitude of these load-dependent modulations was significantly reduced during TPM session, suggesting drug-induced impairments of the primary task network. (3) ERP responses over bilateral fronto-temporal electrodes, which were not load-sensitive at baseline, showed significant memory load modulations after TPM administration, suggesting the drug-related recruitment of additional neural resources. (4) At fronto-central scalp sites, there was significant increase in response amplitude for low memory load during TPM session compared to baseline, and the amplitude increase was dependent on TPM plasma concentration, suggesting that the primary task network became less efficient under TPM impact. (5) At bilateral fronto-temporal electrodes, there were no ERP differences when comparing low memory load trials, but TPM administration led to an increase in ERP responses to high load, the magnitude of which was positively correlated with task performance, suggesting that the recruited neural resources were beneficial for task performance (compensatory). Placebo-TPM comparison yielded similar effects albeit with generally reduced significance and effect sizes. Our findings support the hypothesis that TPM

** Address correspondence and reprint requests to: Dr. Mingzhou Ding, mding@bme.ufl.edu

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impairs the primary task network by reducing its efficiency, triggering compensatory recruitment of additional resources to maintain task performance.

Keywords

topiramate; compensation; cognition; impairment; EEG

1. Introduction

Cognitive impairment is a frequently reported side effect of many commonly prescribed drugs. For epilepsy patients, who are prone to develop cognitive deficits (Motamedi & Meador, 2003), any additional cognitive side effects of pharmacological seizure control can be particularly debilitating. As a consequence, there has been more interest in how anti-seizure drugs (ASDs) affect cognition compared to agents from other drug classes. Topiramate (TPM), a second-generation broad spectrum ASD with formal indications for focal (partial) and generalized seizures, migraine and obesity (with phentermine), is a prime example of a drug that causes cognitive impairments that are often severe enough to lead to the discontinuation of an otherwise effective therapy (Berlant, 2004; Chengappa, Gershon, & Levine, 2001; S. Lee et al., 2003). It has been reported that chronic TPM regimens are associated with long-term side effects severe enough to lead to only a 70% retention rate after 4 years (Bootsma 2004). While not all patients on TPM treatment regimens report cognitive side effects (Bootsma et al., 2004), the incidence has been reported to be as high as 44% (H.-W. Lee, Jung, Suh, Kwon, & Park, 2006). The frequency and severity of adverse cognitive events appear to be related to the age of the patient population tested (Mohamed, Appleton, & Rosenbloom, 2000; Ramsay et al., 2008) and degree of drug exposure (Marino et al., 2012), but these factors do not account for all observed variability in patient responses to TPM. Despite widespread tolerability issues related to adverse cognitive events, because of TPM's efficacy in treating a wide range of conditions, including those outside of its formal indications such as pain, bipolar disorder, alcohol dependence and posttraumatic stress disorder (Berlant, 2004; Chengappa et al., 2001; Chong & Libretto, 2003; Coppola et al., 2008), it continues to be prescribed, even with increasing frequency.

To date, the cognitive side effects of TPM have been mainly characterized using behavioral assessments. Studies have shown that it has a more pronounced adverse effect than other ASDs on a wide range of cognitive domains (Javed et al., 2015), including verbal fluency (Marino et al., 2012), language comprehension (Fritz et al., 2005), working memory (Jung et al., 2010), attention (De Araujo Filho, Pascalicchio, Lin, Sousa, & Yacubian, 2006), and short-term memory (Gomer et al., 2007), although other functions such as inhibitory control (assessed by the Stroop test) are not affected (Cirulli et al., 2012). However, simply mapping the behavioral manifestations of these side effects is not sufficient. It is only when the nature of the neural mechanisms underlying these impairments is established will it be possible to develop methods that will enable us to predict the occurrence and severity of cognitive side effects and subsequently tailor treatment regimens to the needs of individual patients.

There is an extensive literature examining the brain's responses to the cognitive impairments caused by normal aging and brain disorders (Yaakov Stern, 2012). This research has uncovered a general pattern: impairment leads to increased activity within the brain networks responsible for performing a given task ("primary" task networks), reflecting a decrease in neural processing efficiency (Rypma et al., 2006). When cognitive demand is high, and resources within the primary task network are fully engaged, additional brain networks are recruited to maintain task performance, a phenomenon referred to as neural compensation (Reuter-Lorenz & Cappell, 2008). This type of neural compensatory response has been studied in aging (Cabeza, 2002; Grady et al., 1994; Reuter-Lorenz et al., 2000) and in various brain disorders such as mild cognitive impairment (MCI) (Clément & Belleville, 2010; Hämäläinen et al., 2007), Alzheimer's disease (Becker et al., 1996; Grady et al., 2003; Y. Stern et al., 2000; Woodard et al., 1998), and multiple sclerosis (Bonnet et al., 2010; Hillary, Genova, Chiaravalloti, Rypma, & DeLuca, 2006). Recent work has also described compensatory responses to cognitive fatigue (Wang, Trongnetrpunya, Samuel, Ding, & Kluger, 2016), and to chronic use of recreational drugs such as alcohol (Berre et al., 2014). Although the specific patterns of recruitment vary depending on the specific tests and the cognitive system that is impaired, the principle above appears to be general. The aim of the current research was to determine whether the same types of compensatory responses are observed during periods of cognitive impairment induced by the acute administration of TPM (Wandschneider et al., 2017).

We employed a double-blind, randomized, placebo-controlled, crossover design. Nine healthy volunteers completed three study sessions on three separate visits; a no-drug baseline session and two drug sessions during which they received either a 100 mg oral dose of TPM or a placebo (PBO). On each visit, subjects performed a Sternberg working memory task in which the level of cognitive demand was systematically varied by manipulating the amount of information to be held in memory (1, 3 or 5 digits). High-density scalp electroencephalogram (128-channel EEG) was recorded while subjects performed the task. We hypothesized that TPM administration would (1) reduce neural efficiency within the primary task network leading to an increase in the amplitude of responses under low levels of cognitive demand, and (2) trigger the compensatory recruitment of additional networks when cognitive demand was high.

2. Method

2.1 Participants

The experimental protocol was approved by the Institutional Review Board of the University of Florida. Exclusion criteria included: significant 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, psychostimulants such as Ritalin, prescribed analgesics, and antipsychotics; prior history of hypersensitivity to TPM or related compounds; a positive pregnancy test (administered to all females before the start of each test session); use of any investigational drug within the previous thirty days; non-native

speakers of English; diagnosis of a speech and/or language impairment; uncorrected poor vision; and a dominant left hand (to control for brain lateralization of language).

Eleven healthy right-handed volunteers gave written informed consent and participated in the study. Two participants were excluded from analysis: one did not finish all of the required experimental sessions and the other was suspected of having a history of drug abuse. Data from the remaining nine participants (age: 21 ± 2 years, 2 females) were included in the analyses reported here. All participants were asked to refrain from consuming alcoholic beverages for at least 48 hours prior to testing.

2.2 Study design

We employed a double-blind, randomized, placebo-controlled crossover experimental design. Each participant completed three experimental sessions on three separate visits. The first visit involved no treatment and will be referred to as the baseline session. At each session, participants performed a Sternberg working memory task with three memory loads while their brain activity was recorded using high-density EEG. As it was difficult to predict the severity of acute drug-induced cognitive impairment, we selected this task because at low memory loads, it has previously been shown to be simple enough for individuals with chronic cognitive impairment to perform (Kerr, Vitiello, Calogero, Wilkie, & Prinz, 1998), whereas at high memory loads, it is sufficiently difficult to reveal impaired cognition. During the second (one week after the first visit) and third (one week after the second visit) sessions, after a vitals check, participants randomly received either a single oral dose of 100 mg TPM (TPM session) or an inactive placebo (PBO session). The drugs were dispensed by the University of Florida Research Pharmacy and the labels were blind to both the researchers and the subjects. One and a half hours after drug administration, participants completed the working memory task while their EEG was recorded. Blood samples were drawn immediately after testing to establish TPM plasma concentration levels. See Figure 1A for an illustration of the study design.

It is important to note that at the time that this protocol was designed and implemented, the mean half-life of TPM was reported to be 21 hours (Doose & Streeter, 2002). As it takes approximately 5 half-lives for a drug to be totally cleared from the body, a one-week washout period, which is the time separating the third visit from the second, was deemed to be sufficient for full TPM clearance. However, in a more recent study, carried out in a population and at a dose similar to that employed here, it was found that the mean half-life of TPM was 42 hours (Clark et al., 2013). This implied that, when the participants in this study were randomized to receive TPM prior to PBO, behavioral performance, and especially brain activity during these PBO sessions, may have been impacted due to the presence of residual TPM.

Given the foregoing, we chose to mainly focus on presenting TPM-baseline comparison results, because baseline is the ideal condition for defining normal brain operations and for providing a platform for interpreting the impairing effects of TPM. However, given the importance of placebo (PBO) control in drug studies, identical analysis was also carried out to compare TPM and PBO; the results were presented alongside the results from the TPM-baseline comparison.

2.3 Working memory paradigm

As shown in Figure 1B, at the beginning of each trial, a string of one, three, or five digits, corresponding to memory load of 1, 3 and 5, was displayed on a CRT monitor for 1 second (encoding phase). This was followed by a three-second retention phase, during which participants were instructed to retain the digit set in memory. At the end of the retention period, a single probe digit was presented on the screen and subjects were instructed to press a “yes” (right index finger) or “no” (right middle finger) button to indicate whether or not the probe digit belonged to the set of digits presented at the beginning of the trial (retrieval phase). The entire experiment consisted of 7 blocks of 60 trials each. There were an equal number of trials (140) for each memory load, and trials were randomized as function of memory load within each block. To reduce the effects of fatigue, there were brief breaks between blocks. Subjects first completed a practice block in order to become familiarized with the task.

2.4 Data acquisition and preprocessing

EEG data was recorded in an acoustically and electrically shielded chamber using a Biosemi Active Two high-density EEG system (128-channel) at a sampling rate of 1024 Hz. An Experimental Run-Time System (ERTS) was used to present visual stimuli and to record responses. Off-line data preprocessing was performed using BESA 6.0, EEGLAB and custom scripts written in MATLAB. Raw data from each subject were first visually inspected. Data segments contaminated by large head-movement-induced artifacts were rejected and electrodes with poor signals were replaced by spherical spline interpolation implemented in BESA 6.0. The data were then band-pass filtered between .1Hz and 30Hz, down-sampled to 250Hz, and epoched between –200ms to 1000ms relative to probe onset (0ms). Artifacts including eye blinks, horizontal eye movements and temporal muscle activity occurring in these epochs were removed by independent component analysis (ICA) based on a SOBI algorithm implemented in EEGLAB (Delorme & Makeig, 2004). After performing ICA, epochs containing activity with amplitudes greater than 100 μ V at any scalp channel were removed. Trials with incorrect responses were also excluded from further analyses. The remaining trials (~120 for each memory load) were re-referenced to the average of the activity at the two mastoid electrodes.

2.5 ERP analysis

ERPs elicited by probe-stimuli were computed by averaging the preprocessed single-trial EEG data. For a given time period of interest, the extent to which ERP responses were modulated by memory load was estimated using a linear regression method in which the ERP response and memory load (L) was fitted to the model, $ERP_{amp}(L) = \beta L + \alpha$. The value of $|\beta|$ measures the linear change in amplitude as a function of memory load increase, and will henceforth be referred to as the Load Modulation Index (LMI). A larger LMI reflects stronger modulation of neural activity by memory load.

Neural response of the primary task network was indexed by an ERP component identified in a previous study (Kotchoubey, Jordan, Grözing, Westphal, & Kornhuber, 1996). To explore impaired processing and compensatory recruitment triggered by TPM administration, LMIs were computed for each electrode as a function of time using a 300ms

moving time window with 100ms increments; the use of a 300ms window was because (1) compensatory processes are known to be slow to develop (Voytek et al., 2010) and (2) sufficient window length was needed to obtain a stable ERP estimate from which LMIs could be calculated. The number of channels with significant LMIs ($p < .05$) was then plotted as a function of time to map load-dependent activity during the baseline session, the PBO session and the TPM session. Significant declines in LMI values at electrodes following TPM administration were taken to reflect TPM-induced disruptions to the functioning of the primary task network, and significant load-dependent modulations observed during the TPM session, but not at baseline or PBO, were taken to index compensatory recruitment.

2.6 Relationship between ERPs and task performance

Load modulation in networks external to the primary task network would indicate its involvement in the task and suggests neural recruitment. If the amplitude of the ERP responses observed over recruited regions were positively associated with task performance, this provides further evidence supporting the notion that the function of the recruited networks was compensatory in nature. To assess the relationship between TPM-related changes in neural response and task performance, trials were sorted according to reaction time (RT) within each participant. ERP amplitudes on fast ($RT < 30$ th percentile) and slow ($RT > 70$ th percentile) trials were subsequently compared.

2.7 Relationship between ERPs and TPM plasma concentration

In addition to behavioral and EEG data, a single blood sample was also collected into EDTA-containing tubes immediately following the working memory task. TPM plasma concentration levels were assessed using a simultaneous liquid chromatography–mass spectrometry (LCMS) assay developed by Subramanian et al. (Subramanian, Birnbaum, & Rummel, 2008). The effect of TPM plasma concentration on changes in ERP amplitudes was assessed by correlating the magnitude of the difference in the amplitude of ERP responses between TPM and baseline sessions and between TPM and PBO with TPM plasma concentration across subjects.

2.8 Statistical analysis

For behavioral data statistical analysis was carried out using a nonparametric mixed effects model (Kay & Wobbrock, 2016; Wobbrock, Findlater, Gergle, & Higgins, 2011); nonparametric Wilcoxon tests were used for neural data. In addition to calculating p values, which signified statistical significance, effect sizes were also reported where appropriate in terms of Cohen's d. Effect size was considered *small* ($.2 < d < .5$), *medium* ($.5 < d < .8$) and *large* ($d > .8$), according to established definitions (Rosenthal & Rosnow, 1991).

3. Results

3.1 Behavioral analysis

Subjects responded more slowly for higher memory loads during both TPM and baseline sessions (main effect of memory load: $p < .01$, $d = 2.99$, Figure 2A; TPM-PBO main effect of memory load: $p < .01$, $d = 2.01$). TPM administration led to an increase in RT for each

memory load compared to baseline (main effect of treatment: $p < .01$, $d = 1.33$; TPM-PBO main effect of treatment: $p < .01$, $d = 1.95$). There was no interaction between the two factors ($p = .47$, $d = .09$; TPM-PBO no interaction between the two factors: $p = .33$, $d = .19$). Similarly, subjects responded less accurately for higher memory loads during both baseline and TPM sessions (Figure 2B; main effect of memory load: $p = .02$, $d = 1.58$; TPM-PBO main effect of memory load: $p = .01$, $d = 1.29$). TPM administration also led to a decrease in accuracy compared to baseline (main effect of treatment: $p < .01$, $d = 2.09$; TPM-PBO main effect of treatment: $p < .01$, $d = 2.66$). The interaction between memory load and treatment was not statistically significant but it reached a *medium* effect size ($p = .23$, $d = .64$; TPM-PBO interaction between the two factors: $p = .21$, $d = .54$). These data demonstrate that TPM impairs performance on the working memory task, manifesting in both increases in RT and decreases in accuracy (Marino et al., 2012).

3.2 The impact of TPM on the primary task network

Figure 3A shows ERP responses at electrode Cz for each of the three memory loads during both TPM and baseline sessions. In agreement with prior literature (Kotchoubey et al., 1996), a mid-latency component (300ms to 400ms) was modulated by memory load, with higher loads eliciting larger responses. Defining 300ms to 400ms as the time period of interest, we examined the relationship between the magnitude of ERP responses and memory load. A linear regression model was fit to the data, and the absolute value of the slope, referred to as Load Modulation Index (LMI), was taken to indicate the degree of memory load modulation (see an illustration of *large* versus *small* LMI in Figure 3B). Based on prior literature (Kotchoubey et al., 1996) and the topographic distribution of the LMIs shown in Figure 3C, we defined a fronto-central region of interest (ROI), which included Cz and adjacent electrodes (Figure 3D left). The memory load-dependent activity observed at these electrodes at baseline suggests that they reflect the activity of the primary task network engaged during working memory task performance.

Following TPM administration, the magnitude of LMIs within the fronto-central ROI decreased ($p = .02$, $d = .57$; for TPM-PBO comparison: $p = .11$, $d = .69$), Figure 3D right, suggesting that the function of the primary task network was impaired. Furthermore, as shown in Figure 3E, the amplitude of the mid-latency ERP component for Load 1 trials increased during the TPM session compared to baseline ($p = .03$, $d = .27$; for TPM-PBO comparison: $p = .05$, $d = .26$). For Load 5, however, no significant differences between treatments were observed ($p = .11$, $d = .19$; for TPM-PBO comparison: $p = .16$, $d = .12$), consistent with the notion that the primary task network was fully engaged for the cognitively demanding Load 5 condition even at baseline.

3.3 Compensatory recruitment of additional neural resources

The extent of load-modulated neural activity external to the primary task network was explored by computing the temporal profile of the total number of electrodes with significant LMIs ($p < .05$) using a 300ms moving time window with 100ms increments. This analysis enabled us to identify electrodes that were sensitive to memory load during the TPM session but were not modulated by memory load at baseline. The results showed that the total number of electrodes with significant memory load modulations increased after TPM

administration between 300ms - 600ms (Figure 4A). The scalp distribution of load-sensitive electrodes is shown in Figure 4B. As can be seen, bilateral fronto-temporal electrodes exhibited increased task involvement during the TPM session, whose LMI were significant only during the TPM session but not during the baseline session. Defining two ROIs, right fronto-temporal ROI (Figure 4C right) and left fronto-temporal ROI (Figure 4D right), the ERP waveforms from these two ROIs for Load 1 and Load 5 are shown in Figures 4C and 4D, respectively. In the low memory load condition (Load 1), there were no significant ERP differences observed at either the left or right fronto-temporal ROIs after TPM administration (right fronto-temporal: $p = .38$, $d = .10$; for TPM-PBO comparison: $p = .43$, $d = .04$; left fronto-temporal: $p = .30$, $d = .11$; for TPM-PBO comparison: $p = .30$, $d = .19$). For Load 5, however, the amplitude of the ERP responses in both left and right fronto-temporal ROIs increased significantly during the TPM session compared to baseline (right fronto-temporal: $p = .02$, $d = .38$, for TPM-PBO comparison: $p = .13$, $d = .28$; left fronto-temporal: $p = .02$, $d = .33$, for TPM-PBO comparison: $p = .22$, $d = .28$). Thus, in contrast to the TPM-induced decline in the strength of memory load modulations over the primary task network (Figure 3), electrodes in the bilateral fronto-temporal ROIs showed increased memory load modulations during the TPM session. That the activity over these ROIs was increased for the Load 5 condition but not for the Load 1 condition during the TPM session suggests that these networks were recruited when cognitive demand was high.

3.4 Relationship between ERP responses and behavior

To determine whether the additional activity observed at left and right fronto-temporal ROI aided in compensating for TPM-induced deficits, we examined the relationship between the magnitude of ERP responses over these two ROIs and task performance for the Load 5 condition. Figure 5 shows the ERP responses for the fast RT trials and the slow RT trials. Over the right fronto-temporal ROI, as shown in Figures 5A and 5B, larger ERP amplitudes were associated with faster RT ($p = .03$, $d = .41$; for TPM-PBO comparison: $p = .01$, $d = .81$), consistent with the notion that these responses reflect the activity of a network recruited to maintain task performance. No statistically significant effects were observed for the left fronto-temporal ROI ($p = .26$, $d = .16$, Figure 5C and 5D; for TPM-PBO comparison: $p = .34$, $d = .27$).

3.5 Association with TPM plasma concentration

ERP amplitude differences between TPM and baseline sessions were correlated with TPM plasma concentration (Figure 6). In the fronto-central ROI (Figure 6A), there was a significant negative correlation between TPM plasma levels and the amplitude of ERP responses with a *large* effect size ($p = .05$, $r = -.67$, $d = 1.79$; for TPM-PBO comparison: $p = .11$, $r = -.57$, $d = 1.41$). This correlation did not reach significance in either of the two fronto-temporal ROIs, but the effect size was *medium* in the right fronto-temporal ROI (Figure 6B, $p = .39$, $r = -.33$, $d = .70$; for TPM-PBO comparison: $p = .40$, $r = -.32$, $d = .67$), and *large* in left fronto-temporal ROI (Figure 6C, $p = .17$, $r = -.50$, $d = 1.15$; for TPM-PBO comparison: $p = .08$, $r = -.61$, $d = 1.54$). These results suggest a differential sensitivity to TPM between the primary task network and the secondary recruited network although the TPM-baseline comparison and TPM-PBO comparison differed on which network was being more affected.

4. Discussion

In this study, we investigated the brain's compensatory response to drug-induced cognitive impairment. Comparing TPM and baseline, we demonstrated that a single 100mg oral dose of TPM impairs working memory function, leading to performance decrements in healthy young adults performing a Sternberg working memory task. These behavioral performance deficits manifested as TPM-induced increases in RT and decreases in accuracy for all three memory loads tested (Figure 2). In addition, ERP results showed that TPM caused a reduction in memory load modulations over fronto-central electrodes, supporting our hypothesis that TPM negatively impacts the function of the primary task network (Figure 3D). The observation that the response to Load 1 was larger after TPM administration (Figure 3E) provided support for our hypothesis that TPM impairs the primary task network by reducing neural efficiency, evidenced by the fact that TPM led to increased neural activity even when cognitive demand is held constant. For the more difficult condition (Load 5), fronto-central ERP responses during the TPM session were not distinguishable from baseline (Figure 3E), consistent with the notion that all resources within the task-related network were fully engaged when the cognitive demand is high even during the baseline session (ceiling effect). However, in response to these demanding Load 5 trials, we observed compensatory recruitment of additional bilateral fronto-temporal regions. Electrodes in these regions were task-irrelevant at baseline but becoming task-relevant by showing strong memory load modulations following the administration of TPM (Figure 4). The observation that activity over the recruited regions was positively associated with behavioral performance (Figure 5) is further evidence supporting the compensation hypothesis. Furthermore, unlike the fronto-central electrodes, the amplitude of the recruited fronto-temporal responses was less associated with TPM blood plasma levels (Figure 6), suggesting that these regions were less impacted by the drug and thus could be recruited to fulfil the compensatory function.

Comparing TPM and PBO, similar results were found, to a large extent, but with generally reduced statistical significance and effect sizes. The TPM-PBO comparison can be seen as providing corroborative evidence in support of the main findings derived from TPM-baseline comparison. In the meantime, the reduced statistical significance and effect sizes of TPM-PBO comparison analysis also demonstrate that PBO likely introduced additional variability not present at baseline, and that larger sample sizes are essential to provide sufficient power to overcome such variability.

Cognitive compensation, defined as recruitment of resources external to primary task network in response to cognitive impairment, has been studied extensively in aging and brain disorders (Solé-Padullés et al., 2009; Steffener, Brickman, Rakitin, Gazes, & Stern, 2009; Yaakov Stern, 2012). From these studies a general principle has emerged (see Introduction). This general principle appears to generalize to cognitive impairment induced by central nervous system drugs such as TPM. When cognitive demand is low, increased activity within the primary task network under TPM is observed, suggesting that neural processing efficiency has been reduced by the drug's adverse effects; more activation is required to achieve the same function relative to the unimpaired brain. When task difficulty increases, and the primary task network becomes fully engaged even when unimpaired,

additional brain networks are recruited to meet the increased cognitive demand and maintain task performance under TPM impairment (Bootsma et al., 2004). Because past studies on aging and brain disorders has been cross-sectional in nature, namely comparing across age groups or comparing healthy controls to patient populations, the developmental time course of compensatory mechanisms has yet to be described. Here, we extend the current literature on neural compensation by showing that this mechanism can be triggered by a single acute dose of TPM.

The Sternberg paradigm used in this study is a widely used paradigm to study working memory related neural responses (Sternberg, 1966, 1969). Previous studies identified a component termed the N300 (300ms-400ms) which showed high level of modulation by memory loads at the Cz electrode (Kotchoubey et al., 1996). In our study, we confirmed this finding, and further identified a fronto-central topography underlying greater memory modulation during baseline or PBO than after TPM administration (Figure 3D). Since the amplitude of this component was thought to reflect the amount of resources utilized to perform the task (Kotchoubey et al., 1996), TPM induced increase of the ERP amplitude in Load 1 trials (Figure 3E), suggests that more resources were utilized to perform the same task under TPM. This increase in resource utilization after TPM administration even when task difficulty remained constant suggests a reduced efficiency of the primary task network (Rypma et al., 2006). In Load 5 condition, the lack of increase in ERP amplitude after TPM administration reflects the maximal engagement of the resources of the primary task network even at baseline for the cognitively demanding condition, and the need for additional resources to maintain task performance may then be satisfied through compensatory recruitment of neural resources external to the primary task network.

Although, as indicated earlier, there are many drugs that can negatively impact cognition, the choice of TPM for the present study was based on several considerations. First, TPM's pharmacokinetic-pharmacodynamic profiles make it an ideal candidate for testing whether the brain can acutely recruit resources to overcome drug-induced cognitive impairments. Specifically, TPM is rapidly absorbed (1–4hr) into the bloodstream (Easterling, 1988; Perucca, 1997) but not extensively metabolized (Langtry, Gillis, & Davis, 1997; Rosenfeld, Doose, Walker, & Nayak, 1997). The peak plasma concentration occurs about two hours after oral dosing (Sachdeo et al., 1996). Its protein binding is low (15%), and there is a close correlation between plasma and cerebro spinal fluid (CSF) total and unbound concentrations, where total TPM concentration in CSF is 85% of that in the plasma (Christensen, Højskov, Dam, & Poulsen, 2001). Moreover, the onset of TPM's effects on cognitive function is relatively rapid. In a previous study in healthy volunteers, we found significant concentration-dependent performance declines on verbal fluency and working memory tasks 1.5–4 hours after oral drug administration (Marino et al., 2012). Therefore, given the sound assumption that reported plasma levels obtained shortly after drug administration are a good approximation of TPM brain concentrations, it is not surprising that higher TPM plasma levels are associated with greater impairment of the primary task network. Second, while TPM is known to affect some cognitive functions such as language and verbal working memory (Marino et al., 2012), it appears to spare others, such as inhibition as measured by the Stroop test (Cirulli et al., 2012). It then becomes possible for the neural substrates of spared cognitive functions to be recruited to fulfil task demands,

making TPM an ideal pharmacological probe into compensatory processes (Thompson, Baxendale, Duncan, & Sander, 2000). This pattern of selective sparing of certain cognitive systems may explain the pattern of compensatory recruitment observed in response to Load 5 condition. In particular, the stronger involvement of the right fronto-temporal electrodes is consistent with the previous finding that some right-hemisphere-mediated functions such as inhibition (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Aron, Robbins, & Poldrack, 2014) are spared by TPM. In addition, given that our subjects were all right handed, and that TPM significantly impairs language function, it is not surprising that the networks underlying the left fronto-temporal sites demonstrate a weaker involvement in compensating for TPM-induced cognitive impairment than those on the right.

Despite the significant findings reported above this study also has limitations. First, the small sample size is a major limitation. As a consequence, it is possible to overlook important effects by relying solely on statistical significance as assessed by p values. We thus also reported effect size to complement the results of statistical significance testing. The underpowered nature of this study is also apparent in the TPM-PBO comparison where PBO introduces an additional source of variability along with learning and order effects. It is essential that larger sample sizes be employed in future studies to test the robustness of the findings reported here. Second, this study involved three visits, and the same working memory task was performed on each visit. Learning is thus an important consideration when comparing performance across different treatments and sessions. In the behavioral data, we observe that, although not statistically significant, reaction times during the PBO session were faster than during the baseline session, albeit the effect size was *small* ($p = .12$, $d = .39$). These learning effects actually make the TPM induced cognitive decline even more pronounced, as the TPM session always occurred after the baseline session. In other words, the negative effect of TPM was strong enough to manifest through the positive learning effects. Third, TPM is known to induce fatigue (Siniscalchi, Gallelli, Russo, & De Sarro, 2013), and fatigue can negatively impact cognitive performance. To what extent the observed impairment in task performance was attributable to fatigue cannot be assessed in this study because fatigue level was not measured. Fourth, studying the cognitive effects of TPM in patients on chronic regimens is the ultimate goal. Characterizing TPM's effects in healthy controls is a starting point: in a healthy population it is possible to disentangle the cognitive effects of drug administration and underlying pathology (Perucca, 1997).

5. Summary and outlook

Our data, while preliminary, shed important light on the brain's ability to compensate during periods of acute impairment, which appears to proceed via similar mechanisms as have been observed in states of chronic/long-term impairment. Characterizing individual variability in susceptibility, which we are not able to do due to small sample size, raises the possibility that the research described here can inform clinical practice and aid in the development of personally-tailored treatment regimens. Whether or not the pattern of compensation demonstrated in healthy adults is mirrored in a patient population remains an open question. To address this issue, we are planning a large study of both acute and chronic administration of TPM in patients with temporal lobe epilepsy.

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6. References

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Figure 1.

Study design and the working memory task. (A) Temporal sequence of the three visits: baseline and placebo (PBO)/Topiramate (TPM). (B) The working memory paradigm where a trial of memory load 5 is shown.

Figure 2.
 Behavioral data: (A) RT as a function of memory load for TPM and baseline. (B) Accuracy as a function of memory load for TPM and baseline.

Figure 3.

ERP responses to probe-stimuli. (A) ERP waveforms at Cz for three memory loads during TPM and baseline sessions. (B) Examples of *large* and *small* load modulation index (LMI). (C) Topography of LMIs of the mid-latency ERP response (300ms to 400ms) identified in (A) for TPM and baseline sessions. (D) Fronto-central ROI where LMI during the baseline session was higher compared to TPM. (E) ERP waveforms of Load 1 and Load 5 trials at fronto-central ROI during both treatment sessions.

Figure 4.

Compensatory recruitment in response to TPM administration. (A) Number of electrodes modulated by working memory load after TPM administration is maximal between 300ms and 600ms. (B) Topography of the electrodes showing significant memory load modulations during the time period of interest. (C) ERP waveforms from the right fronto-temporal ROI for Load 1 and Load 5. (D) ERP waveforms from the left fronto-temporal ROI for Load 1 and Load 5.

Figure 5.

Association between the magnitude of fronto-temporal ERP responses to Load 5 condition and behavioral performance during the TPM session. ERP waveforms on fast and slow RT trials in (A) right fronto-temporal ROI and (C) left fronto-temporal ROI. Statistical comparison of ERP amplitude between fast and slow trials in (B) right fronto-temporal ROI and (D) left fronto-temporal ROI.

Figure 6. Correlation between ERP responses and TPM plasma concentration. (A) fronto-central ROI, (B) right fronto-temporal ROI, and (C) left fronto-temporal ROI.