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The Dostoyevsky effect: epileptogenesis and memory enhancement after kindling stimulation in the primate basolateral amygdala

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Abstract— **Kindling is an electrical stimulation technique used to lower the threshold for epileptogenic activity in the brain. It can also be used as a tool to investigate electrophysiologic alterations that occur as a result of seizures. Epileptiform activity, like seizures and after-discharges (AD; evoked epileptiform activity), commonly cause memory impairment but rarely, can elicit vivid memory retrieval. We kindled the basolateral amygdala of a non-human primate (NHP) once weekly and had him perform a spatial memory task in a 3D virtual environment before, during and after kindling. AD were associated with an initial average performance increase of 46.6%. The enhancement which followed AD persisted up to 2 days. Memory task performance enhancement was accompanied by significant resetting of hippocampal theta oscillations and robust hippocampal potentiation as measured by field evoked potentials. However, neither lasted throughout the duration of performance enhancement. Sharp-wave ripples (SWR), a local field event that supports episodic memory, were generated more often throughout the period of enhancement. SWR rate increased from 14.38 SWR per min before kindling to 24.22 SWR per min after kindling on average. Our results show that kindling can be associated with improved memory. Memory function appears to depend on the particular induction circuit and the resultant excitation/inhibition ratio of the mesial temporal lobe network. Investigating the electrophysiologic underpinnings of this observed memory enhancement is an important step towards understanding the network alterations that occur after seizures and stimulation.**

Clinical Relevance— **Our findings provide new insight into the effects of kindling stimulation in the primate brain. Kindling can cause increase MTL synchrony and the frequency of spontaneous seizures in a primate. This work highlights important considerations for therapeutic deep brain stimulation.**

I. Introduction

Deep brain stimulation (DBS) can enhance declarative memory in humans when delivered below the threshold for eliciting epileptiform activity [1]–[4]. In contrast, events like seizures and after-discharges (AD; subclinical, electrographic seizures which begin after termination of the stimulus) are commonly associated with memory impairment [5]–[7]. While this is generally true, not all seizures impair memory. The natural history of benign epilepsy is largely unknown in our time because of the availability of anti-epileptics and surgery. Historical cases of untreated epilepsy describe clinical presentations that we don't commonly see, including vivid memory retrieval. One of the most interesting of these cases was the famed author Fyodor Dostoyevsky. His epilepsy presented with auditory hallucinations but his seizures became generalized and persisted throughout his adulthood [8]. Dostoyevsky was described as one of the greatest novelists of all time. He had a unique ability to depict the conditions of 19th-century Russia with a tendency towards incredibly detailed autobiographical descriptions of events and thoughts. His enhanced episodic memory was attributed to the seizures originating from his mesial temporal lobe (MTL) and his prominence helped destigmatize epilepsy [9].

We kindled AD in the basolateral amygdala of a non-human primate (NHP) and noticed a robust enhancement in memory task performance. AD were followed by a performance increase that persisted up to 2 sessions (separated by 24 h). To investigate the mechanisms of this enhancement we compared our post-kindling, neural data to data from humans that experienced enhancement after DBS. In humans phase resetting of the theta rhythm on hippocampal EEG was associated with enhancement after DBS [1], [4]. We found a significant change in hippocampal theta phase resetting between baseline and stimulation. Theta resetting did not persist throughout the period of enhancement. We therefore investigated two other signatures of memory function: Long term potentiation (LTP) and sharp-wave ripples (SWR).

LTP is considered an electrophysiologic model for the basic mechanisms involved in learning and memory formation [10], [11]. We used field evoked potentials to determine whether kindling caused potentiation. We found that stimulation caused hippocampal potentiation but that this also did not persist throughout the period of enhancement. SWR are a local field potential event that has previously been linked to episodic memory [12], [13]. Their selective disruption by electrical stimulation was shown to impair memory task performance [14]–[16]. We found that increased SWR generation during task performance persisted throughout the period of enhancement. SWR generation also returned to baseline in concordance with memory task performance.

This work adds important clarification to the narrative that subthreshold stimulation is therapeutic because it helps to synchronize memory networks. Subthreshold stimulation is may seem beneficial to patients because it improves memory performance [1]–[4] but we show this can also occur after kindling. Subthreshold stimulation induces network changes that overlap with overt epileptogenic activity. An electrophysiologic description of the processes underpinning memory enhancement, namely the increase in SWR, may help to refine future therapeutic intervention.

II. Methods

All animal care and experimental procedures were approved by either the Queen's University Animal Care Committee or the McGill University Animal Care Committee and were conducted in accordance with the Canadian Council on Animal Care guidelines on the care and use of laboratory animals.

A. Subjects

Experiments were performed on a healthy male rhesus NHP Macaca mulatta; NHP L (9 years old;15.2 kg) NHP. NHP L was single housed and trained to transfer into the laboratory using our methodology and equipment which has been described previously [17].

B. Behavioral setup and task

The NHP used a two-axis joystick (M212, PQ Controls, Bristol, CT) to navigate a 3D world displayed on 3 video monitors. This 3D world was built with an open-source library running a freely available videogame engine (Unreal Engine 4, Epic Games, Inc., Potomac, NC) [18]. A control computer ran an experimental suite programmed in MATLAB (Mathworks Inc., Natick, MA), called NIMH MonkeyLogic [19]. The tasks took place in an X-maze, which is similar to the double-ended Y- choice maze [20]. Spatial tasks in this X-maze have been used to quantify hippocampal activation during navigation [21]. The spatial task required the NHP to find an invisible target which is always in the same one of the four maze arms. Target location was learned by trial and error. After steering into any one of the 4 maze arms, or after a 60 second time-out, the NHP was teleported to the maze center. A time-out was considered an incorrect trial. The NHP had to use context (trees and mountain placed outside the maze walls) to orient himself and remember the target location.

C. Stimulation

Ascending series threshold testing was performed once weekly. Kindling stimulation consisted of a 2-second train of biphasic, charge-balanced, 60 Hz, square wave pulses with a 1 ms phase width and 0.5 ms interphase [22]. We use biphasic, charge-balanced stimulation to prevent brain tissue damage [23]. The stimulation was delivered in a bipolar configuration by contacts separated by 250 μm. Pulses were initially delivered at an amplitude of 1 μA which was increased stepwise to 700 μA every 2 min or until an AD was evoked. If no AD was evoked at 700 μA, the surface area of the stimulated region was increased by increasing the number of active anodal and cathodal linear microelectrode array (LMA) contacts. Even after maximally increasing amplitude and surface area, still no AD was evoked for 4 weeks. Those stimulation responses were categorized as subthreshold.

We also used single pulse (mapping) stimulation daily, to probe excitability before and after kindling. Mapping stimulations were all square wave pulses with 100 μs phase width, 55 μs interphase and 25 μA amplitude. We delivered 20 pulses per stimulated contact per daily recording session. On the threshold-testing day we delivered 10 before kindling and 10 after. Each pulse was separated by a minimum of 10 seconds and adjacent electrode contacts were not stimulated within the same day.

D. Data collection and processing

Neural data was recorded at 10 kHz using a neural data acquisition system (Cerebus®, Blackrock Microsystems UT, USA) interfaced with a neural stimulator (CereStim R96; Blackrock Microsystems, UT, USA). The stimulator was controlled by our custom software programmed in MATLAB (Mathworks Inc., Natick, MA).

To measure theta resetting, 5-second periods before and during the onset of stimulation were averaged for each session [4]. Phase resetting results in increased synchrony of oscillatory activity across neural populations and a greater amplitude in the local field potential [24]. We chose to examine the power of low theta (3-5 Hz) because it predominates in the anterior human hippocampus [25].

To detect SWR, signals were band-pass filtered (100-300Hz), rectified and low-pass filtered (cut-off 20 Hz) [26]. We used a custom peak detection algorithm that detects peaks with SWR-specific features [27]. Our algorithm captures peaks with a prominence of at least 3 SD from the event-free baseline and for which the peak duration has a minimum duration of 50 msec beginning and ending at 1 SD above event-free baseline [28], [29]. To assess significance a one-way analysis of variance was performed [30]. A p-value of < 0.05 was considered significant.

E. Surgery and intracranial hardware

NHP L underwent 2 surgeries under general anesthesia to implant a halo for head-fixation [31] and cranial hardware, including the custom recording implant and LMA (Microprobes, MD USA) for recording. Chronic LMA were implanted in NHP L using a custom NHP stereotactic arc-radius frame adapted from human neurosurgery [32]. Standard coordinates, from Paxinos' atlas [33], preoperative MRI (1 sequence, 0.6 mm isotropic pixels, 3.0 T Siemens TimTrio) and our custom neuronavigational system were used to plan surgical trajectories. Implants were positioned over the right prefrontal cortex and trajectories were chosen to minimize damage to brain tissue blood vessels. All chronic LMA were implanted unilaterally on the right side. Each LMA was fabricated using 37.5 μm platinum/iridium microwires (Microprobes) threaded through polyimide guide tubes for MRI compatibility. The 16 contacts on the LMA were spaced 250 μm apart and span 3.75 mm. LMA were implanted in the anterior hippocampus, basolateral amygdala and medial entorhinal cortex. Both humans and macaques have anatomical connections between these regions. Specifically, the amygdala (lateral, medial and basal nuclei) indirectly project to the hippocampus (CA1, CA3, Dentate Gyrus and the subiculum) [34]–[36].

III. Results

We recorded 124 behavioral sessions, with sub- and suprathreshold stimulation and 27 of which followed AD. Example raw traces with and without AD are shown in Fig 1. Together, behavioral sessions included a minimum of 40 trials. On days where kindling stimulation was delivered, the NHP showed an average task performance increase of 46.6% between baseline and kindling. Due to the difficulty of the task, the mean and standard deviation of baseline performance before kindling was 36.72 $\pm$ 13.1% (*25% = chance*), performance after kindling was 83.32 $\pm$ 6.4% on the same day and 51.86 $\pm$ 17.1% 1 day after (Fig 1). The enhancement lasted for 1 session in all weeks but 2 where enhancement persisted for 1 and 2 additional sessions on

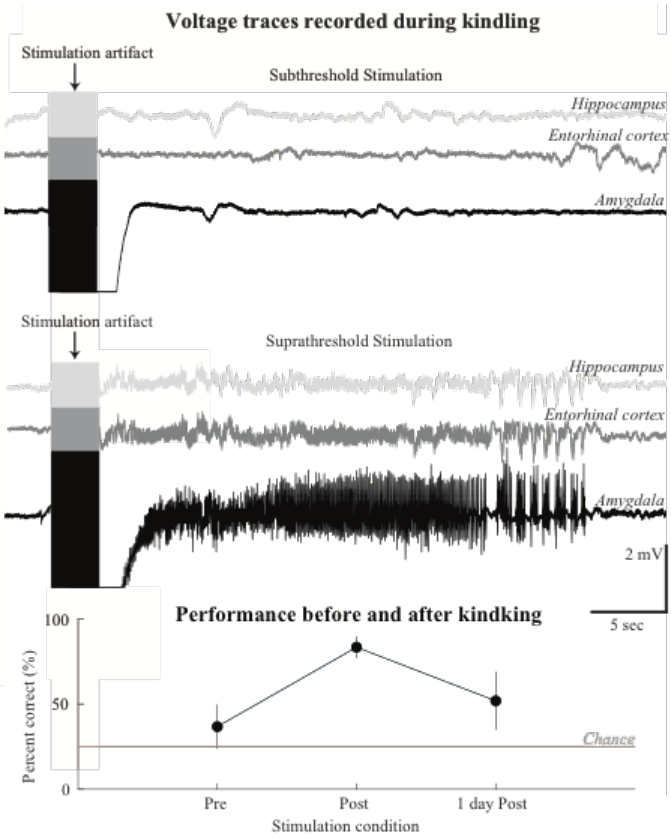

Figure 1. Voltage traces and behavioral results. Traces are recorded from the hippocampus, entorhinal cortex and amygdala simultaneously. The first 3 traces show subthreshold stimulation (400 μA on kindling day 1). The next 3 traces show suprathreshold stimulation (25 μA on kindling day 9). In both conditions, the amygdalar trace is from the stimulated LMA (*top*). Average behavioral performance in the session before kindling (Pre), immediately after kindling (Post) and in the following session (1 day Post).

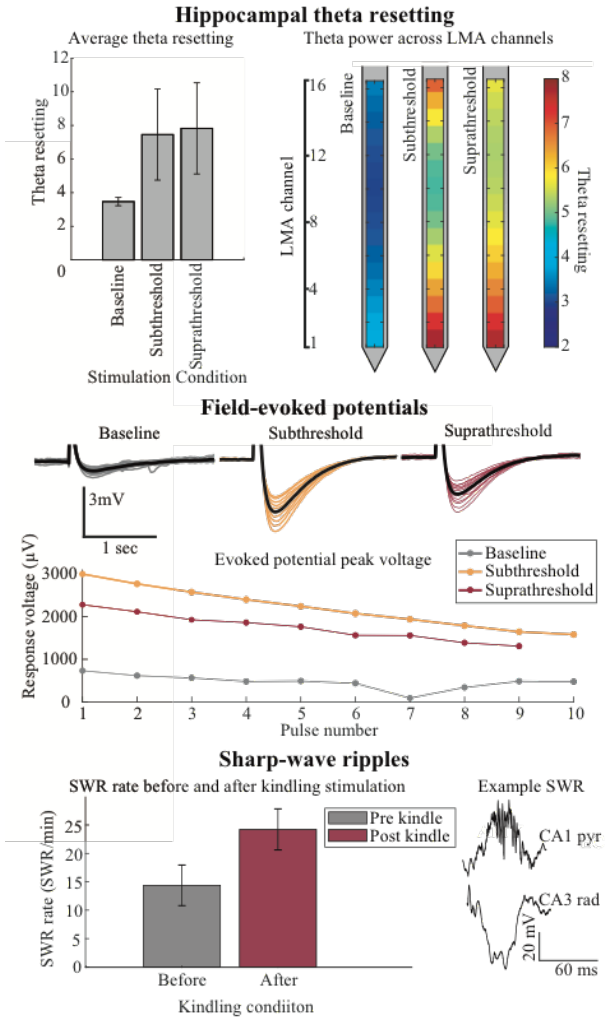

Figure 2. Hippocampal theta resetting, potentiation and sharp-wave ripples (SWR). Hippocampal theta power averaged across all sessions (*top left*) and theta power distribution across 16 channels of the hippocampal LMA in 3 example sessions: before stimulation (Baseline), after stimulation with no AD (Subthreshold), and with AD (Suprathreshold) (*top right*). A series of extracellular voltage traces showing sets of 20 responses to 25 μA stimulation and their peak amplitude. Responses were recorded before kindling (Baseline); after kindling, no AD (Subthreshold); and with AD (Suprathreshold) (*center*). SWR rate before and after kindling shows the number of SWR per min in sessions before and after kindling. An example SWR is shown to the right (*bottom*).

consecutive days. Hippocampal theta resetting occurred after both sub- and suprathreshold stimulation. The mean average theta power was 3.46 ± 0.2 before kindling. Theta power increased to 7.45 ± 2.4 and 7.82 ± 2.7 for sub- and suprathreshold stimulation respectively (Fig 2). Power increases were not distributed uniformly; the 3 schemata of the hippocampal LMA in Fig 2 show how theta power was distributed across channels in 3 example sessions, power returned to baseline on the following day. Kindling produced robust hippocampal potentiation after sub- and suprathreshold stimulation as measured by field evoked potentials. The mean amplitudes of the hippocampal responses were 551.81 ± 31.9 μV before kindling (n = 101) and 1492.4 ± 87.5227 μV after kindling (n = 75) (p = 2.80e-22; *1-way ANOVA*). There wasn't a significant difference between sub- and suprathreshold conditions (Fig 2). SWR rate in the session was 14.38± 3.57 SWR/min before kindling and 24.220 ± 3.615 SWR/min after kindling (p = 0.0314; *1-way ANOVA)* (Fig 2).

We tracked the kindling threshold throughout the course of these experiments and found that after 4 weeks of sub-threshold stimulation, the threshold was lowered to 200 μA (from above 700 μA). It continued to fall and remained at 20 ± 5 μA for the remaining 27 weeks of kindling. Kindling was stopped after the NHP developed spontaneous seizures.

IV. Discussion

Kindling has been a useful technique for investigating electrophysiologic alterations that occur as a result of seizures. No other study has reported performance improvements following AD. AD, kindled in the hippocampus of rats, seem to consistently impair memory task performance in both rats and humans [6], [37], [38] but extra-hippocampal kindling did not appear to affect performance (except for transient behavioral arrest during AD) [39]. It is important to highlight that behavioral testing after extra-hippocampal kindling was conducted on animals that had reached a performance ceiling (100% accuracy) and so if enhancement occurred, it would not have been be detectable. Rodent models of epilepsy have likely been used to quantify the post-ictal memory impairment because it is so prevalent.

LTP is accepted as a basic mechanism for learning and memory [10], [11]. Potentiation following kindling, and behavioral changes caused by potentiation without kindling, have been reported separately and are consistent with our results. In rats, extrahippocampal (e.g. perforant path [40] and amygdala [41]) kindling produced a potentiation as measured by the population response. Dentate gyrus kindled rats on the other hand, show a net depression of the hippocampal population evoked potential [37]. LTD caused by hippocampal kindling correlated with memory impairment [42]. Our results indicate that hippocampal potentiation induced by extrahippocampal stimulation boosts memory performance. Kindling causes transfer effects [22], [43] so it is reasonable to assume that amygdalar kindling could alter hippocampal circuit function in a way that increases LTP and improves memory.

Exaggerated hippocampal LTP has also been measured in animal models of aging and memory loss [44]–[46]. This is inconsistent with the classical view, that increased LTP magnitude correlates with memory improvement. There is convincing evidence to support that the increased LTP observed in aged animals or those with memory related disorders is a compensatory phenomenon [47]. Amygdalar kindling may activate compensatory mechanisms in the primate model and, when introduced into a healthy functioning brain, produce memory enhancement. Kindling stimulation in a brain that is not healthy (i.e., does not have a neurologic reserve) may not have an enhancing effect.

The SWR is a strongly synchronous event observed in all studied mammals, including humans [28]. If kindling increases MTL network synchronicity (to generate epileptic activity), then it makes sense that SWR generation would also increase. SWR-related firing was previously shown to increase in animal models of temporal lobe epilepsy (after intra-amygdalar kainite injection) [48]. Pathological high frequency oscillations have been recorded in animal models and in humans with temporal lobe epilepsy [49]. Increases in SWR rate was the only measured feature which lasted the duration of enhancement. However, the body of previous work relating increases in high frequency activity to memory impairment suggest that this may be a feature of early, benign epileptic activity generated through kindling. Still, these results suggest that further research into the relationship between synchronicity, SWR generation and memory could help us understand and improve the memory loss experienced by patients with epilepsy. Our study is limited in that it is about one NHP. In future studies a larger subject pool will allow us to draw stronger conclusions and rule out variables specific to this individual.

Electrical stimulation is an emerging technique for treating memory related disorders.[50] Our results provide an interesting case of kindling accompanied by memory enhancement. The association of kindling-induced AD with the development of disorder symptoms suggest that enhancement may result from compensatory processes. The same process may occur in the case of DBS induced memory enhancement. This may provide insight into the lack of success in using DBS to treat Alzheimer's disease [50]. Compensatory processes, in brain afflicted with a degenerative disorder, may be exhausted.

Our work highlights the need to further examine the electrophysiologic differences between those with degenerative disorders and those with available neurologic reserve. Parsing out these differences may help us improve the efficacy of therapeutic stimulation. Dostoyevsky's memory deteriorated later in life [8], but early on they allowed him to re-experience autobiographical events which he detailed in Notes from Underground among many works. An understanding of compensatory mechanisms which occur in primate brain after kindling may tell us something about memory and epilepsy.

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