Vascular conditions alter hippocampal neurophysiology and cortico-hippocampal communication

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Abstract

Vascular conditions alter hippocampal neurophysiology and cortico-hippocampal communication

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Vascular conditions such as stroke and diabetes are leading causes of disability worldwide. The incidence of these conditions increases dramatically with age, and as the global population increases, the prevalence of these conditions will continue to grow. Recently, a growing body of research has revealed a causal connection between vascular diseases and central nervous system injury, resulting in cognitive deficits and significantly increased risk for neurological conditions, such as dementia and depression. These conditions often increase the risk of further cognitive impairment, quickly accelerating debility and cognitive decline. These conditions have complex interactions with the neurophysiology underlying cognition. Electrophysiology is a powerful tool to understand the neural activity underlying cognitive function. In this work, I use extracellular field potentials recorded in rodent animal models to investigate two disease states associated with central nervous system vascular injury, type 2 diabetes mellitus (T2DM) and chronic ischemic

stroke, to better understand how these conditions affect neurophysiological function leading to mild cognitive impairment. In the first chapter, I will cover the necessary background information on T2DM, chronic ischemic stroke, and electrophysiology methods. In the second chapter, I present my findings on the interactions between age and T2DM in the neural activity of the hippocampus using a homozygous db/db mouse model, which is a genetic line that has a defective leptin receptor, a protein that regulates appetite and satiation. In the third chapter, I present my findings on how chronic stroke and a type of therapy called environmental enrichment which has been shown to improve behavioral outcomes interact in a rat model of stroke using distal middle cerebral artery occlusion. Finally, in the fourth chapter, I bring the results of both studies together to see what the broader implications are, and what future directions of this work may look like.

TABLE OF CONTENTS

LIST OF FIGURES

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Chapter 1. Vascular conditions that impact cognitive function and how to assess them

1.1 Introduction

Serious neurodegenerative disorders such as ischemic stroke and Alzheimer's disease are leading causes of disability. These conditions are highly heterogeneous disorders with many causes. Vascular health is a major risk factor for the development these conditions, therefore vascular diseases such as Type-2 Diabetes Mellitus (T2DM), hypertension, and atherosclerosis significantly increase the likelihood of developing neurodegenerative disorders (Reitz et al. 2007; Jacquin et al. 2014; Zilliox et al. 2016). The incidence of both upstream vascular diseases and downstream neurodegenerative conditions increases with age, and as the global population increases, the prevalence of these conditions will continue to grow (Kearney et al. 2004; Weiss and Sumpio 2006; Grysiewicz et al. 2008). Recently, a growing body of research has revealed a causal connection between these vascular conditions and cognitive deficits. For example, diabetes increases the risk of dementia by 50% (Biessels et al. 2006), and 30% of stroke survivors develop dementia within the first year (Cullen et al. 2007). The mechanisms of these conditions frequently interact and overlap, causing a downward spiral of debility and quality of life (Barrett-Connor and Khaw 1988; Tatemichi et al. 1994; Biessels et al. 2006).

Cognition and memory are complex processes whose neural substrate spans across multiple brain regions (Storm et al. 2015). One of these regions is the Hippocampus (HPC), a part of the temporal lobe that plays a critical role in memory formation and retrieval, which has long been studied to understand cognitive processes (Olton et al. 1979). Electrophysiology is a powerful tool to understand the neural activity underlying cognitive function. Noninvasive cerebral EEG recordings are widely used as a diagnostic tool for mild cognitive impairment in humans (Jackson and Snyder

2008), however animal models offer the ability to study neurophysiology at a more granular level, by allowing for invasive recording modalities of deep brain regions, genetic alterations, and histological analysis (Zakaria et al. 2021).

To better understand how vascular conditions affect neurophysiological function leading to mild cognitive impairment, this dissertation will use extracellular field potentials recorded in rodent animal models to investigate an upstream vascular condition: type 2 diabetes mellitus (T2DM), and a downstream neurodegenerative condition: chronic ischemic stroke to gain a deeper understanding of the neurophysiological basis underlying the cognitive deficits associated with those conditions.

1.1.1 Overview of vascular conditions that impact brain function

Vascular conditions can have a significant impact on brain function and health. These conditions can affect the brain through a variety of mechanisms, including inflammation, oxidative stress, changes in blood flow, and changes in blood sugar levels. Insulin resistance, as seen in T2DM, leads to chronic inflammation and oxidative stress which in turn damages neurons and blood vessels, ultimately causing changes in blood flow -also seen in hypertension- which reduces blood flow and oxygen to the brain (Zilliox et al. 2016). Changes in blood flow reduce the flow of oxygen to the brain, which can cause neuronal death, hyperexcitability, and seizure-like symptoms (Yang et al. 2018). One of the most common sequelae of these conditions is cognitive decline, which refers to a decline in memory, attention, and executive function, among others. Damage to blood vessels, atherosclerosis, and hypertension all increase risk of cerebrovascular disease such as transient ischemic attacks and ischemic stroke, where the blood supply to the brain is interrupted, resulting in cerebral infarction and brain injury. The severity and location of stroke is highly variable and depends on the location and size of the clot. Stroke is associated with a wide range

of symptoms, including weakness or paralysis on one side of the body, difficulty speaking or understanding speech, changes in vision or balance, and issues with cognition and memory (Grysiewicz et al. 2008).

Having discussed the general symptoms and consequences of vascular conditions on brain function, I will now focus specifically on the impact and mechanisms of T2DM, an example of upstream vascular disease, and stroke, an example of downstream neurodegenerative condition. Both T2DM and stroke are associated with a high risk of cognitive decline and dementia, and both have distinct mechanisms by which they affect the brain. In the following sections, we will delve deeper into the specific mechanisms of T2DM and stroke, as well as the ways in which they contribute to cognitive decline and dementia. Understanding the unique neurophysiological mechanisms of these two conditions is crucial for using electrophysiological recordings to understand how these conditions change neural activity underlying this cognitive decline.

1.2 Type-2 Diabetes

1.2.1 Overview of type-2 diabetes

T2DM, also known as adult-onset diabetes, is a chronic metabolic disorder characterized by high blood sugar levels. It occurs when the body is unable to use insulin effectively. Insulin is a hormone that regulates blood sugar levels, and when the body is unable to use insulin properly, it leads to an accumulation of glucose in the blood (Weiss and Sumpio 2006). T2DM is the most common form of diabetes, accounting for about 90-95% of all diabetes cases. Over half a billion people in the world had T2DM in 2018, and the global prevalence of T2DM over the next decade is rising (Kaiser et al. 2018).

1.2.2 The effect of type-2 diabetes in the brain

T2DM is associated with a number of structural changes in the brain, particularly in the HPC (Moran et al. 2013), which is particularly sensitive to changes in blood glucose (Djordjevic et al. 2015). Disrupted insulin signaling in the HPC impairs mitochondrial function, causing the mitochondria to overproduce reactive oxygen species (ROS) in the cell (Zilliox et al. 2016). Excess ROS in the HPC damages blood vessels, and causes neuronal death and chronic inflammation. This damage results in hippocampal atrophy in the gray matter and white matter tracts (Antal et al. 2022). Chronic hyperglycemia can also lead to microinfarcts (Guerrero-Berroa et al. 2014), though it has been shown that cortical atrophy is due to neurodegeneration rather than cerebrovascular lesion (Moran et al. 2013).

These changes in neurophysiology increase risk for the development of dementia by 50% (Biessels et al. 2006), particularly Alzheimer's disease. Work has shown a causative association between insulin resistance associated with T2DM and an accumulation of amyloid-β plaques and hyper phosphorylated tau microtubules (Rdzak and Abdelghany 2014). In addition to the microinfarcts, hypertension, inflammation, and oxidative stress, T2DM increases the risk of atherosclerosis, a condition in which fatty deposits build up in the blood vessels, narrowing them and making them more prone to thrombosis (Lonardo et al. 2018). These factors not only increase the risk of ischemic stroke but also can worsen the prognosis and recovery after stroke (Weiss and Sumpio 2006).

1.2.3 Cognitive impairment in humans and animal models as a result of type-2 diabetes

There is no definitive best neuropsychological test for impaired cognition, however, two common tests in the clinic are the mini-mental state examination (MME) and the Montreal Cognitive

Assessment (MOCA). These tests assess 7 cognitive domains such as abstract reasoning, immediate memory, learning rate, forgetting rate, information processing speed, attention and executive function. (Zilliox et al. 2016). T2DM patients have shown reduced information processing, impaired memory, attention, and executive function (Gregg et al. 2000; Kanaya et al. 2004; van den Berg et al. 2010). Interestingly, studies disagree on whether T2DM accelerated decline in cognitive function compared to controls. Some showed no significance (van den Berg et al. 2010), while others showed accelerated decline (Hassing et al. 2004).

Meanwhile, in rodent models of T2DM, there are multiple mechanisms of induced T2DM. The two most popular models for T2DM are the high fat diet (HFD) model (Lin et al. 2000), and genetic lines using disrupted leptin receptors (Guest & Rahmoune 2018). While HFD models are considered the most accurate to human T2DM, the development of insulin resistance and diabetes pathologies takes time, and animals often have weaker phenotypes. Genetic lines, though mechanistically unique from human T2DM, share similar characteristics, and display a much stronger phenotype. These models consistently show cognitive deficits assessed by tasks such as water maze or spatial-object learning (Lupien et al. 2003; Li et al. 2002).

One substantial caveat to note is that many of these studies use young or middle-aged animals, despite the majority of diabetic patients being elderly. In addition, the cognitive impairments associated with diabetes are most pronounced in the elderly (Biessels and Gispen 2005). The db/db (Considine et al. 1996) and Akita (Bugger et al. 2008) mouse, as well as the Otsuka Long-Evans Tokushima fatty (OLETF) rat (Dirkes et al. 2017), are models that require age as part of the diabetic mechanism, and therefore are better suited to understand the interaction between age and T2DM. In the following chapter, I analyze data that was collected from db/+ and db/db mice

at 200 days and 400 days of age to evaluate the interaction between effects that age and T2DM have on the neural activity within the hippocampus.

1.3 Ischemic Stroke

1.3.1 Overview of ischemic stroke

Stroke is a leading cause of neurological disability worldwide (Tsao et al. 2022). Ischemic stroke is the most common type of stroke and it occurs when a blood vessel that supplies blood to the brain is blocked. Permanent brain damage due to in part to hypoxia occurs within minutes to hours (Yang et al. 2018). The severity and symptoms of ischemic stroke vary widely depending on the size and location of the clot, but common symptoms include sudden weakness or numbness on one side of the body, difficulty speaking or understanding speech, vision problems in one or both eyes, trouble walking, and severe headache.

1.3.2 The effect of stroke in the brain

The brain is one of the most metabolically active organs in the body, therefore focal reductions in cerebral blood flow that restrict delivery of oxygen and glucose quickly cause a multitude of critical issues. Protein synthesis is inhibited (Markus 2004), ionic gradients across cell membranes collapse (Caplan and Liebeskind), and cellular metabolism is disturbed (Kunimatsu et al. 1999). Stroke progression is characterized by two opposing phases, both mediated by GABAergic and glutamatergic signaling. In the acute phase, hypoxia has a biphasic effect on extracellular concentration of glutamate, the primary excitatory neurotransmitter in the brain. In the first phase, presynaptic membranes rapidly depolarize causing an increase in extracellular glutamate before concentration drops due to reuptake in surrounding glia (Kunimatsu et al. 1999). If hypoxia persists, the surrounding glia will then undergo energy failure, leading to a second rise in

extracellular glutamate. Another facet of stroke pathology is a synchronized wave that propagates through the tissue leading to loss of transmembrane ion gradients, commonly referred to as spreading depression (Revah et al. 2016). These changes result in excitotoxic cell death (Carmichael 2012; Mayor and Tymianski 2018).

After cell death, surviving neurons begin to repair and reorganize in the chronic phase of stroke. Neurons in recovering peri-infarct areas of the brain experience enhanced tonic GABA currents and synaptic glutamate signaling is downregulated (Carmichael 2012). This is due to reduced GABA uptake in astrocytes (Clarkson et al. 2010). Blocking this increase in GABA current has shown to improve recovery following stroke (Clarkson et al. 2010). Besides the impaired GABA uptake in astrocytes, stroke also impairs the brain's glymphatic function (Sanchez-Bezanilla et al. 2019), causing an accumulation of neurotoxic proteins. These neurotoxic proteins, such as amyloid-β, cause inflammation and increase the risk of AD.

1.3.3 Cognitive impairment in humans and animal models

Cognitive impairment following stroke is extremely common, with 6-27% of survivors meeting the requirements for dementia within 3 months (Zhou 2006). Criteria for cognitive impairments for humans are detailed in the diagnostic manual of mental disorders V (DSM V), international classification of disease-10 (ICD 10), and national institute of neurological and communication disorders and stroke and the AD and related disorders association (NINCDS-ADRADA). These criteria measure learning and memory, language, executive function, complex attention, perceptual-motor, and social cognition impairments. If a patient does not meet these criteria, cognitive impairments are also observed using the MME and MOCA.

One issue with the quantification of cognitive impairments is that the majority of cognitive impairments as a result of stroke are associated with comorbidities and other confounding factors. Therefore, one avenue of studying stroke is to use animal models, which provide a valuable platform to examine the effect of ischemic stroke on cognition in isolation (Jiwa et al. 2010). The isolated environment comes at a cost however, because these homogenous animal models have been criticized for their inability to recreate the heterogeneity of human stroke characteristics, severely limiting their translational capability to clinical applications (Dirnagl 2010). Despite the criticisms, experiments using animal models to understand stroke pathophysiology remains an active and essential area of research.

There are many modalities of inducing stroke, including global, focal, chronic, and transient hypoperfusion models, injected and photo-activated embolic models, hypertensive models, and vasculopathy models. These models vary widely in invasiveness, size, and variability of size of infarct, mortality, and vascular impact (Dirnagl 2010). Focusing only on the focal ischemic models, there are two major factors to consider: craniectomy or non-craniectomy procedure, and permanent or transient ischemia. In general, craniectomy models are more invasive and induce numerous confounds such as skull trauma, and change in brain temperature and intracranial pressure. These factors increase inflammation in the brain and lead to longer recovery times and greater brain damage. Non-craniotomy models generally use an endovascular approach, and access cerebrovasculature via common carotid artery. Though less invasive, this technique does have the potential to damage the vascular endothelium (Dirnagl 2010). Models with permanent ischemia closer mimic strokes without reperfusion, while transient models reflect stroke with medically induced or spontaneous reperfusion, which reflect the majority of stroke cases (Dirnagl 2010). One final element to consider is how distal or proximal to place the occlusion. The more

proximal the occlusion is placed, the larger the amount of neural tissue will be affected; however, proximal occlusions also benefit from increased collateral circulation, which may mitigate some effects. Proximal occlusions are risky procedures with higher variability and mortality due to unpredictability in infarct size and location. More distal occlusions conversely, have much smaller and more consistent affected areas. In the following study, I analyze data that was collected using a distal middle cerebral artery occlusion (dMCAO), which is a chronic procedure that requires a craniotomy. Despite the drawbacks, this model provides consistent infarct size and location and maintains hippocampal integrity without insult.

Rodent models utilize tasks such as the Morris water maze, radial arm maze, novel object recognition test, and passive avoidance tests to test the cognitive impairment following stroke. More sophisticated tests have been developed for non-human primates, which have been based on human neuropsychiatric tests (Moss and Jonak 2007). While comparing and contrasting the differences in cognitive impairment between these models is beyond the scope of this section, these models all show impaired working memory, and impaired reference memory and learning are also common outcomes (Jiwa et al. 2010).

1.4 Brain areas involved in memory and cognitive function

Cognitive function requires the coordination of many subprocesses, such as perception, attention, and memory (Storm et al. 2015). Memory is a complex phenomenon that itself is composed of many interdependent subprocesses, such as semantic, episodic, procedural, emotional, and non-associative memory (Deiana et al. 2011). These processes are distributed widely across many areas of the brain.

Memory is stored in multiple stages. The frontal lobe is an area that is responsible for executive function, attention, processing, and immediate working memory (Bero et al. 2014). After an experience, the episodic memory is encoded in the HPC, a brain region in the temporal lobe that acts as an intermediary nexus between working and long-term memory. Then, in a process called memory consolidation, memories are gradually retrieved and distributed to long-term storage across the neocortex (Squire et al. 2015).

1.4.1 Hippocampal anatomy

The HPC is a complex brain structure that is located in the medial temporal lobe and is critical for the formation and retrieval of long-term declarative memories (Buzsaki 2011). The HPC has a distinct primary and secondary structure. The primary structure can be divided into several subregions, or fields, including the dentate gyrus (DG), subiculum, CA3, and CA1. The secondary structure has a distinct laminar structure, and is composed of multiple layers, such as the pyramidal, radiatum, and stratum lacunosum moleculare (SLM). Specific areas of the HPC are denoted by both primary and secondary signifiers, for example, the CA1 field pyramidal layer.

The HPC primarily interfaces with the entorhinal cortex (EC), which is strongly and reciprocally connected with many cortical areas (Buzsaki 2011), and the perirhinal cortex, which provides input to the HPC related to object recognition and memory (Deshmukh et al. 2012). The EC then sends output to the septal nuclei, the hypothalamus, the mediodorsal thalamic nucleus, the cingulate cortex, and the parietal cortex.

Hippocampal fields are functionally and anatomically distinct (Fanselow and Dong 2010). The DG is a part of the HPC and is located at the front of the structure. The subiculum is a transition zone, linking the DG and HPC (Fogwe et al.). The granule cells in the DG and pyramidal neurons in the

CA3 and CA1 region work together to form the trisynaptic circuit (Andersen 1975). The DG is the start of the circuit, and has high levels of neurogenesis (Gozel and Gerstner 2019). The CA3 region is considered the "pacemaker" of the trisynaptic circuit (Buzsaki 2011), and has been shown to be essential to memory consolidation. The CA1 region completes the trisynaptic circuit, feeding back into the EC.

The layers of the HPC are also functionally and anatomically distinct. The stratum pyramidale contains the cell bodies of pyramidal neurons, the principal excitatory neuron in the HPC. Stratum radiatum contains mostly septal and commissural fibers along the trisynaptic circuit, though some interneurons can be found here. Stratum lacunosum is very thin and often combined with stratum moleculare, referred to as stratum lacunosum moleculare (SLM). Here, perforant path fibers form synapses onto the dendrites of Pyramidal cells. Finally, in stratum oriens the cell bodies of inhibitory basket cells and horizontal trilaminar cells are located (Buzsaki 2011).

1.5 Electrophysiological assessment of neural activity

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1.5.1 Neural activity observed through electrophysiology

The firing of neurons within neural tissue generates ionic field potentials. By placing an electrode at a specific location in the brain, the activity of the local population of neurons can be measured. These changes in electrical activity reflect the synchronized activity of large groups of neurons and can provide important information about the neural processes underlying memory formation,

storage, and retrieval. In humans, these field potentials can be gathered non-invasively using the electroencephalogram (EEG), which records electrical activity from the scalp. EEG presents certain limitations, such as high levels of noise from muscles, low temporal specificity, and is limited to measuring low frequency activity. In animals, one of the most widely used field potentials is the local field potential (LFP), which can be measured from the surface of the brain or using penetrating electrodes to reach deeper brain areas. Recording coherent signals from the brain is an extremely delicate task, which requires significant signal processing and preprocessing before understanding can be gleaned from recordings.

1.5.2 Electrophysiology signal processing and data analysis

Although the techniques of neural signal processing continue to evolve, the principles behind signal recovery, representation and control have remained unchanged (Chen 2017; Alam et al. 2020). Recent advances in nanofabrication technologies have enabled the development of multi electrode arrays with growing density that allow simultaneous recording from multiple brain areas with rich biological information. Some examples include the micro-ECoG that has high spatial and temporal resolution (Griggs et al. 2021), and the advanced linear depth electrode arrays that can simultaneously record from cortical and subcortical areas (He et al. 2020). These advanced technologies in combination with awake animal recordings have created unprecedented opportunities to study the brain and its networks in complex behavioral settings, and require robust and scalable methods to process the ever-increasing size of recorded data.

One caveat to note is that frequency bands are isolated from the raw electrophysiology via signal recovery techniques that remove noise and artifact using methods such as deconvolution and filters. Careful consideration must be taken when designing filters, as it is possible to introduce contamination into the signal if the filter characteristics are not designed properly (de Cheveigné

and Nelken 2019). For example, artificial features such as response peaks or oscillations may be created de novo by filters in response to some feature or noise of the signal (de Cheveigné and Nelken 2019). Furthermore, it is relevant to note that the different recording modalities -such as EEG, field potentials, and single unit recordings are not directly comparable as they represent neural data at different scales.

Following signal recovery, signal representation techniques then can create interpretable insights from neural data. Common methods of signal representation include spectral analysis, which involves estimating the frequency components of signal oscillations in a set of sequenced data (Rayner 2001); dimensionality reduction, which uses linear or nonlinear transformations of high dimensional data into a lower dimensional space which can be more easily interpreted (Sorzano et al. 2014); and current source density analysis (CSD) (Kenan-Vaknin and Teyler 1994), which uses a surface Laplacian of the field potentials recorded from multi-electrode arrays to estimate the current flow between the recording sites. With respect to spectral analysis, although multiple studies have validated the correlation between narrow-band Power Spectral Density (PSD) and stroke outcome, the classic narrow-band spectral analysis method conflates the periodic and aperiodic features of the signal (Donoghue et al. 2020; Lanzone et al. 2022). One important reason is that band-power measures of the EEG fails to take into account of the aperiodic 1/f-like component that defines the shape of the PSD (Bédard et al. 2006; He et al. 2010), i.e. the exponentially decreasing power with increasing frequency. The spectral slope, or the slope of the PSD in log-log coordinates, was recently proposed to reflect the neuronal balance between excitation and inhibition (Gao et al. 2017). A steeper PSD slope suggests overall EEG slowing, since it reflects an overall change of the PSD shape, rather than changes in narrowband power.

Because the relation of phase and amplitude governs large-scale brain networks, other metrics inferred from field potentials have also been developed to analyze phase synchrony in the frequency domain, providing insight about functional connectivity between and within areas. For instance, coherence, ranges from 0 to 1, measures the consistency of a phase relationship between two signals averaged across all electrodes and computed separately for each frequency band; this is the frequency domain equivalent to the time domain cross-correlation function (Pesaran et al. 2018; Bastos and Schoffelen 2015). A recent scalp EEG study detected decreased and increased coherence in Down Syndrome patients with Alzheimer's dementia compared to those without dementia (Musaeus et al. 2021), attesting the sensitivity and utility of frequency specific coherence in sensing neural synchrony and cognitive function. Changes in network coherence derived from EEG signals are also often used to reflect the rate of activation of the lesioned hemisphere following rehabilitation therapy (Dubovik et al. 2012). Granger causality, another advanced parameter measures how a field potential affects the ability to predict future values or "forecast" another field potential. Cross frequency coupling (Tort et al. 2010), is another frequently used analysis method that has recently revealed critical insight to the pathophysiology of stroke (He et al. 2020; Ip et al. 2021), Parkinson's disease (Devergnas et al. 2019), Alzheimer's disease (Zhang et al. 2016) and Schizophrenia (Barr et al. 2017). This type of analysis reveals the interactions between brain oscillations at different frequency bands, to assess the functional connectivity between and within brain areas.

Finally, neural signals can be used to develop signal prediction and control algorithms. Recently, advances in computational power have recently made brain-machine interfaces (BMIs) a viable platform to leverage these algorithms, where neural signals must be processed in real-time. BMIs consist of two phases, open loop prediction and closed loop control. For example, therapeutic

closed-loop BMIs have been designed to apply deep brain stimulation for Parkinson's patients in real-time based on the intent to perform a motor task (Fleming et al. 2020) . Another advance that is revolutionizing neural signal processing is machine learning and artificial neural networks (ANNs). ANNs use a series of layers of simulated neurons and weights which can transform the input signal into an output signal. Poetically, ANNs have been designed which perform signal representation and signal control feats that traditional methods have failed to match (Shen et al. 2019). These are merely some examples of modern signal processing techniques that are applied to neural data and by no means an exhaustive list.

Chapter 2: Type-2 Diabetes reduces hippocampal neural activity and disrupts functional connectivity between hippocampus and sensori-motor cortex

This chapter is representative of work which is in progress and nearing completion. I plan to submit a revised version of this chapter to a peer-reviewed journal.

2.1 Abstract

Type 2 diabetes mellitus (T2DM) increases the risk of neurological diseases, yet how brain oscillations change as age and T2DM interact and alter underlying neurophysiology is not well characterized. To delineate the age and diabetic effect on brain oscillations, we recorded local field potential with multichannel electrodes spanning the cortex and hippocampus (HPC) under urethane anesthesia in diabetic and normoglycemic control mice, at 200 and 400 days of age. We analyzed the strength of brain oscillations, properties of theta state and sharp wave associate ripples (SPW-Rs), and functional connectivity between the cortex and HPC. We found that while both age and T2DM were correlated with a breakdown in long-range functional connectivity, and reduced neurogenesis in the dentate gyrus and subventricular zone, T2DM slowed brain oscillations and reduced theta-gamma coupling. Counter intuitively, both age and T2DM prolonged the duration of SPW-Rs, increased gamma power and current flow during SPW-R. Our results show for the first time potential electrophysiological substrates of cognitive deficit that occur as a result of T2DM-induced hippocampal atrophy. The neural activity in the hippocampus and synchrony between the hippocampus and cortex which are crucial for cognitive function are

disrupted by age and T2DM. The disturbed brain oscillation features and diminished neurogenesis may underlie T2DM-accelerated cognitive impairment.

2.2 Introduction

Over half a billion people in the world had T2DM in 2018, and the global prevalence of T2DM over the next decade is rising (Kaiser et al. 2018). Type 2 diabetes mellitus (T2DM) is a condition characterized by chronic hyperglycemia caused by insulin resistance. T2DM is a significant risk factor for a wide spectrum of neurological diseases including ischemic stroke, depression, dementia, and Alzheimer's disease (AD) (Yu et al. 2020). T2DM accelerates normal brain aging by increasing gray matter atrophy 26% ± 14% faster than seen with normal aging, and a decrease in white matter integrity (Wang et al. 2020) thus T2DM patients displayed a more rapid rate of cognitive decline than typically associated with natural aging (Antal et al. 2022).

Like diabetes, age has profound effects on the brain, including neuronal and white matter atrophy, which has complex implications on neural activity and functional connectivity (Dorsemans et al. 2017). However, how T2DM and age interact to affect network activity that underlies cognitive dysfunction remains unclear. Cerebral EEG rhythms are widely used as a diagnostic tool for mild cognitive impairment (MCI) due to their accessibility and noninvasive attributes (Jackson and Snyder 2008). In humans, T2DM causes cortical oscillatory power to shift from higher to lower frequencies and reduce neural synchrony, albeit to a lesser extent than other pathological cognitive aging disorders, such as AD (Dauwels et al. 2011; Benwell et al. 2020). Animal models offer the opportunity to study neurophysiology at a more granular level, allowing for invasive recording modalities and histological analysis of deeper brain regions like the hippocampus, an area critical to memory and cognitive function (Zakaria et al. 2021). Further, due to challenges in

evaluating behavioral performance in T2DM models, electrophysiology methods provide complementary information to reflect cognitive function.

To better understand the impact of T2DM on brain function, in this study we investigated key features of underlying network neurophysiology that have shown to represent cognitive processes using field potentials recorded simultaneously in the sensorimotor cortex and HPC of a mouse model of T2DM. To better understand the impact of T2DM on neurophysiology, we recorded field potentials in the sensorimotor cortex and HPC in two age groups of diabetic and normoglycemic mice under urethane anesthesia. We measured the relative strength of slow and fast brain oscillations using signal power, slowing score, and spectral exponent. We determined brain state using the theta/delta ratio. Within periods of low theta state, we measured characteristics of SPW-Rs. Finally, we examined functional connectivity using coherence, phase-locking index, and network communication with theta-gamma coupling.

We found that both aging and T2DM disrupted functional connectivity between the cortex and hippocampus, and led to increases in sharp-wave ripple duration, current flow, and gamma power. These changes were correlated with reduced neurogenesis in the hippocampus. However, in contrast to the impact of aging on neural activity, T2DM additionally caused increased slowing scores and aperiodic spectral exponent in the hippocampus, as well as reduced signal power in the beta band in both the cortex and hippocampus. These results suggest that T2DM has a unique impact on brain oscillations and functional connectivity, beyond the effects of aging alone. The combination of these changes may contribute to the accelerated cognitive decline seen in individuals with T2DM.

2.3 Materials & Methods

2.3.1 Animals and housing

Diabetic *db/db* mice (B6.BKS(D)-Lepr*<db/db>*/J) carrying a point mutation in the leptin receptor gene were used as the model of obesity-induced T2DM, while heterozygous *db/+* mice (B6.BKS(D)-Lepr*<db/+>*/J) were used as normoglycemic controls (Akamatsu et al. 2015; Kanoke et al. 2020). Male and female db/+ and db/db mice at 200 or 400 days of age were housed in the institutional standard cages (5 mice per cage) on a 12-h light/12-h dark cycle, with ad libitum access to water and food. All animal experiments were conducted in accordance with the *Guide for Care and Use of Laboratory Animals* issued by the National Institutes of Health *and approved by* San Francisco Veterans Affairs Medical Center Institutional Animal Care and Use Committee. The identity of each mouse subject was blinded to investigators who conducted the experiments and data analysis.

2.3.2 Electrophysiological recording

Recordings were performed using 16-channel extracellular silicon electrodes (A1x16-5mm-100-703, NeuroNexus Technologies) under urethane anesthesia (Sigma, 15 mg/kg i.p.) for one hour (He et al. 2020; Ip et al. 2021). Following craniotomy and resection of the dura mater, 2 electrodes were each inserted into left and right hemispheres to target the dorsal hippocampus at [AP: -1.84 mm; ML: +/- 1.2 mm] via a stereotaxic frame (David Kopf Instruments, Tujunga, CA, USA). Real-time data display and an audio aid were used to facilitate the identification of proper recording location while advancing electrodes until characteristic signals from stratum pyramidale and stratum radiatum were detected and recorded (He et al. 2020). A 1-hr multi-channel recording from bilateral sensorimotor cortex and dorsal hippocampus was collected from each mouse. Data were stored at a sampling rate of 32 kHz after band-pass filtering (0.1-9 kHz) with an input range

of ± 3 mV (Digital Lynx SX, Neuralynx, USA). Data were down sampled to 1250 Hz for further analysis. A total of 23 mice were successfully recorded and subjected to data processing. The groups had the following counts: db/+ 200 d (*n* = 7), db/db 200 d (n = 6), db/+ 400 d (n = 5), db/db 400 d (n = 5). Mortality rate was about 15% due to reaction to urethane anesthesia.

2.3.3 Electrophysiology data analysis

Spectral power analysis: Local field potentials from the pyramidal layer and stratum lacunosum moleculare (SLM) of the CA1 hippocampus and the deep cortical layer of the sensorimotor cortex were used in our analysis. Brain waves were filtered from the LFPs according to the following frequency ranges: delta (0.1–3 Hz), theta (4–7 Hz), gamma (30–58 Hz), and high-gamma (62–200 Hz). For each layer, signal power was calculated as described previously (Zachary Ip et al., 2019). A slowing score was calculated, defined as the ratio between low frequency (1-8 Hz) and high frequency oscillations (9-30 Hz), where higher values of the slowing score correspond to a shift in spectral power from high to low frequencies (Laptinskaya et al. 2020). Theta state in the brain was estimated using a ratio of theta / delta (TD) signals in the pyramidal layer of the hippocampus. The theta and delta signals were smoothed with a Gaussian kernel (σ = 1 s, 8 s window), and the TD was further smoothed with a second Gaussian kernel (σ = 10 s, 80 s window), to stabilize changes of state and reduce noise. The smoothed ratio was then split by a manual threshold set by visual assessment to define two states, high theta/delta (HTD) and low theta/delta (LTD) (Barth and Mody 2011; Lockmann et al. 2016; Wolansky et al. 2006).

Estimation of the spectral exponent from the PSD background: To estimate the balance of inhibitory and excitatory networks, the spectral exponent was isolated from the aperiodic component of the signal (Lanzone et al. 2022). The spectral exponent (SE) measures the

steepness of the decay of the power spectral density (PSD) background. PSD is assumed to decay according to the inverse power-law $PSD(f) \sim 1/f^{\alpha}$, therefore we define the spectral exponent to be $\beta = -\alpha$. The SE therefore is equivalent to the slope of the linear regression resulting from the log of the PSD (Colombo et al. 2019). We estimated the PSD using Welch's method (2s window, 50% overlap). SE was calculated between the 1-40 Hz range.

Sharp wave associated ripples detection and characterization: SPW-Rs were identified from the pyramidal layer during LTD periods (Ip et al. 2021). To isolate SPW-Rs, the LFP of the pyramidal layer was filtered (150–250 Hz), squared, and *Z*-scored. When the signal exceeded 6 standard deviations for a period longer than 20 ms, a SPW-R event was registered. When the signal subsequently dropped below one SD, the event was considered to have ended. Multiple characteristics of SPW-Rs were calculated. Pyramidal gamma LFP power during SPW-R was estimated in the same manner detailed in *spectral power* analysis for periods during SPW-R events. Duration and inter-ripple interval (IRI) were calculated using the start and end timings of SPW-R events. The flow of current during SPW-Rs was estimated using CSD analysis (Baskaran et al. 2013). Laminar CSD is defined as the second derivative of voltages across the recording sites. CSD was calculated across windows of time temporally aligned to the onset of a SPW-R with half a second preceding onset, and one second after. The CSD was spatially centered on the pyramidal layer. Strength of current flow was estimated by calculating the dipole amplitude between the source in the pyramidal layer, and the sink in the radiatum before, during, and after SPW-R occurrence.

Functional connectivity: Functional connectivity between the cortex and HPC areas was estimated using three methods. Phase locking index (PLI), coherence, and cross regional phase amplitude coupling (xPAC). PLI is an index of asymmetry of the distribution of phase differences between

measured signals (Stam et al. 2007; Vinck et al. 2011). In other words, PLI is a measure of the consistency in the distribution of instantaneous phase differences between two signals. If the phase differences between two time series are $\triangle\phi(t_k)(k = 1 \ldots N)$, PLI is defined as:

$$PLI = |\langle sign[\triangle\phi(t_k)]\rangle|$$

where $\langle\cdot\rangle$ is the mean value operator. PLI values range from 0 - 1, where a value of 0 indicates no coupling or coupling with a phase difference centered around 0 mod pi, while a value of 1 reflects complete synchrony between signals. Coherence measures the degree of correlation between two signals. Coherence was calculated pairwise between cortex, CA1 pyramidal and CA1 SLM layer of the hippocampus for each of the frequency bands. The coherence between signals x and y is defined as the square of the cross-spectrum of the channels divided by the product of the power spectra of the individual channels:

$$C_{xy}(f) = \frac{|G_{xy}(f)|^2}{G_{xx}(f)G_{yy}(f)}$$

where G_{xx} and G_{yy} refer to power spectral density of channels x and y respectively, and G_{xy} refers to their cross-spectral density (Bendat and Piersol 2011). Finally, xPAC was measured between the pyramidal layer and the cortex as described previously (He et al. 2020; Ip et al. 2021). To estimate xPAC we bandpass-filtered the LFP between 0.1 and 200 Hz, extracted the instantaneous phase from the pyramidal layer and instantaneous amplitude from the cortical layer using the Hilbert transform. A composite phase-amplitude time series then determined the amplitude distribution across phase. The modulation index (MI) was then calculated from the divergence of the amplitude distribution from a uniform distribution (Berdugo-Vega et al. 2020). MI was compared between groups by averaging the MI across a window of frequencies pertaining to canonical

frequency bands. A data driven threshold was found using Otsu's method (McIntyre et al. 2010) to determine the window of significant coupling.

2.3.4 Statistical analysis

We expressed data as mean ± standard deviation and performed two-way analysis of variance (ANOVA) to assess the main effects of age or T2DM, followed by a post-hoc Tukey test to determine between-group differences in which the adjusted *p* values less than 0.05 were considered as significant.

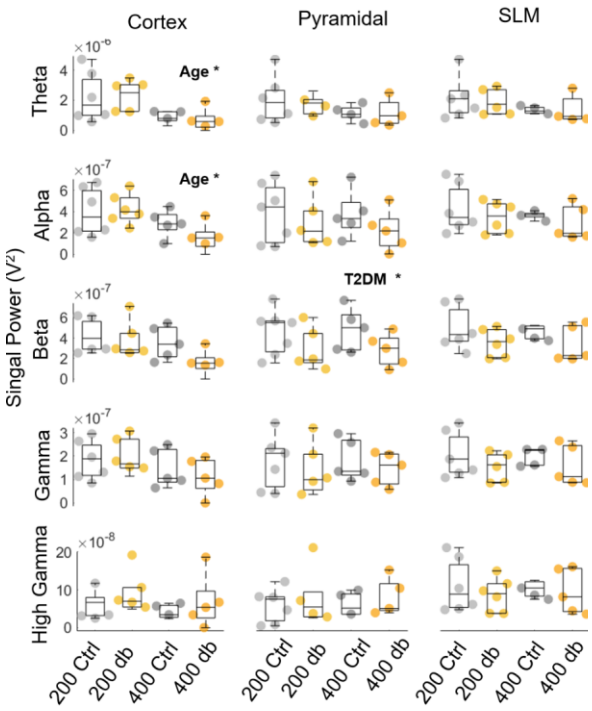

Figure 2.1. Signal power between treatment groups. The first column measures power in cortex, pyramidal, and SLM respectively. Frequency bands from top to bottom are theta, alpha, beta, gamma, and high gamma. Two-way ANOVA test with post-hoc Tukey's test. 200: 200 days old, 400: 400 days old. Significant differences ($p < 0.05$, $p < 0.01$, and $p < 0.001$ are demarcated with $*$, $**$, or $***$ respectively).

2.4 Results

2.4.1 Age broadly decreased signal power while T2DM only decreased beta signal power

To gain a deeper insight into the functional changes in neural activity that may underlie T2DM associated cognitive impairment, we examined the relative signal powers within the deep layers (layers 4-6) of sensorimotor cortex, CA1 field pyramidal layer, and SLM layer in the hippocampus. We found that signal power decreased as a function of age across theta ($p < 0.05$) and alpha ($p < 0.05$), while T2DM was associated with reduced beta power in the pyramidal ($p < 0.05$) layer (Fig 2.1).

2.4.2 T2DM slowed neural rhythms in the hippocampus

We assessed the slowing score, defined by the ratio of low frequencies (1-8 Hz) over high frequency oscillations (9-30 Hz) within the cortex or hippocampus. We found that T2DM significantly increased the slowing score in both pyramidal ($p < 0.05$) and SLM ($p < 0.001$) layers of the hippocampus (Fig. 2.2).

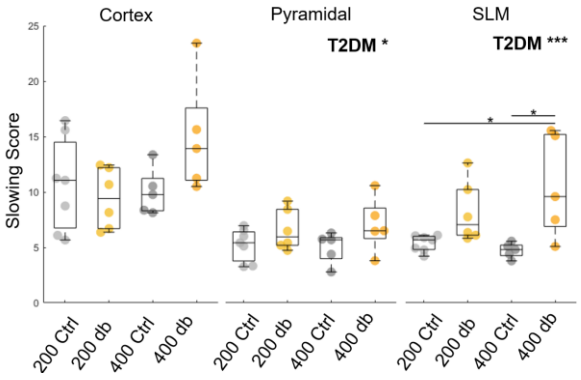

Figure 2.2. Measurement of slowing score in cortex and hippocampus. Two-way ANOVA test with post-hoc Tukey's test. 200: 200 days old, 400: 400 days old. Significant differences ($p < 0.05$, $p < 0.01$, and $p < 0.001$ are demarcated with $*$, $**$, or $***$ respectively).

2.4.3 The spectral exponent of the aperiodic signal

We next analyzed the aperiodic spectral exponent of the signals. T2DM exponentially reduced power with increasing frequency in the SLM layer of the hippocampus, reflecting a diabetes-associated increase in inhibition in the hippocampus, which was more prominent in the aged group (Fig. 2.3).

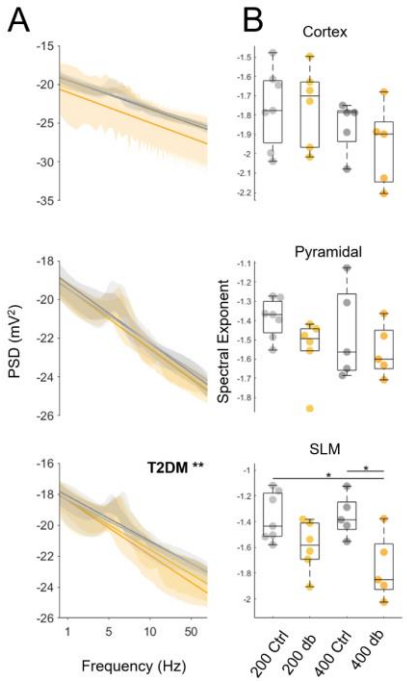

Figure 2.3. Comparison of Spectral exponent. (A) Display of linear best fit to PSD. (B) Comparison of Spectral exponent. Two-way ANOVA test with post-hoc Tukey's test. 200: 200 days old, 400: 400 days old. Significant differences ($p < 0.05$, $p < 0.01$, and $p < 0.001$ are demarcated with $*$, $**$, or $***$ respectively).

2.4.4 Age decreased time spent in high theta state

We determined the effect of age and T2DM on brain states by investigating the relative time spent in theta and delta brain state. Theta state is defined by the ratio of theta/delta in the pyramidal layer and reflects resting brain state. We found that age significantly

decreased the ratio of HTD to LTD ($p < 0.05$) indicating that age reduces time spent in HTD (Fig. 2.4).

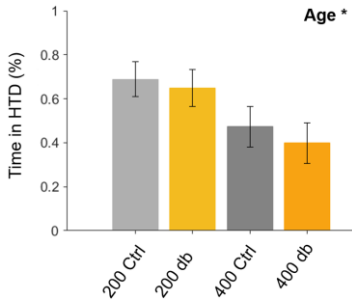

Figure 2.4. Age altered brain state by reducing theta/delta (T/D) ratio. Two-way ANOVA test with post-hoc Tukey's test. 200 d: 200 days old, 400 d: 400 days old. *p < 0.05.

2.4.5 Age and T2DM reduced cortico-hippocampal coherence and phase synchrony

We determined functional connectivity between brain networks in the frequency domain by coherence and phase synchrony. We found that coherence significantly decreased as a function of age between cortex and pyramidal layer in theta, alpha, beta, gamma ($p<0.05$) and high gamma ($p<0.01$) frequency bands (Fig. 2.5A). Meanwhile, coherence reduced as a function of T2DM in alpha ($p < 0.05$), beta ($p < 0.001$), and high gamma ($p < 0.05$) frequency bands between cortex and SLM layer (Fig. 2.5B).

By measuring how stable the phase difference varies over a period of time between two regions independent of the amplitude of oscillations, we found that the phase synchrony represented as phase-locking index (PLI) decreased as a function of age in theta, alpha, beta, gamma, and high gamma frequencies between cortex and CA1 ($p<0.05$) (Fig. 2.6A), while it decreased as a function of T2DM in beta and gamma ($p<0.05$) frequencies between cortex and SLM layers (Fig. 2.6B).

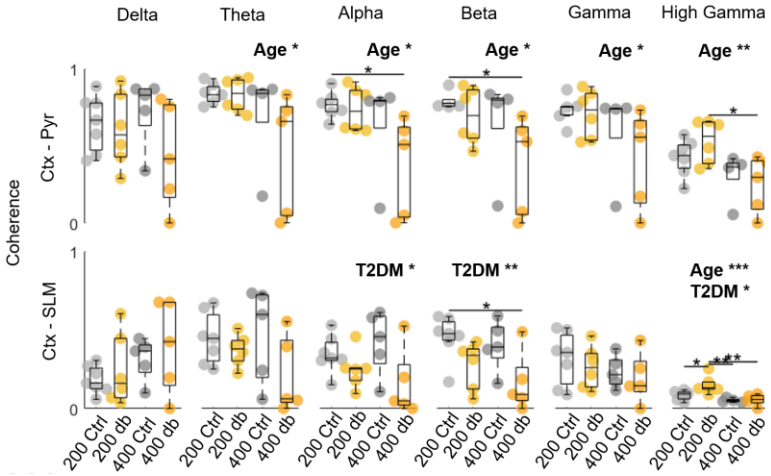

Figure 2.5. Comparison of coherence between Cortex and CA1 layers (pyramidal and SLM). Two-way ANOVA test with post-hoc Tukey's test. 200 d: 200 days old, 400 d: 400 days old. *p < 0.05, **p < 0.01, ***p < 0.001.

2.4.6 Both age and T2DM showed dynamic effects on cross regional phase-amplitude modulation between cortex and hippocampus

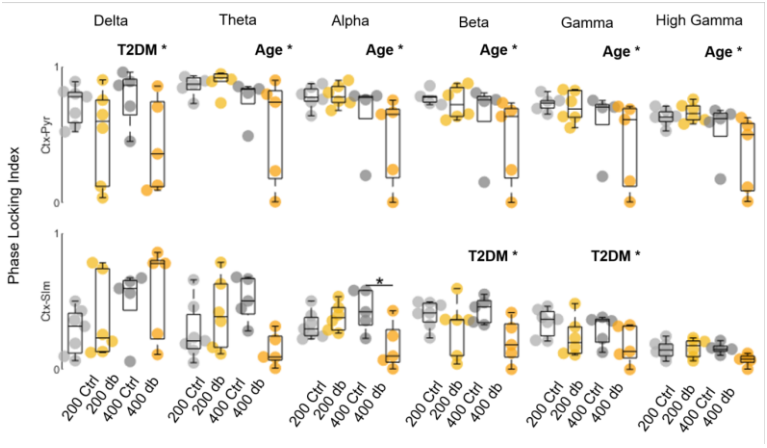

Figure 2.6. Comparison of PLI between cortex and CA1 layers (pyramidal and SLM). Two-way ANOVA test with post-hoc Tukey's test. 200 d: 200 days old, 400 d: 400 days old. *p < 0.05.

A third approach to assess functional connectivity is via cross regional phase-amplitude coupling in different frequency bands between cortex and pyramidal or SLM layers of the hippocampus using phase amplitude coupling analysis. We found that both age and T2DM increased delta-gamma phase amplitude coupling between the HPC and cortex as shown by the modulation index (MI), while T2DM decreased theta-gamma coupling (Fig. 2.7).

2.4.7 Age and T2DM affected the duration and current flow of SPW-Rs and gamma power during SPW-Rs

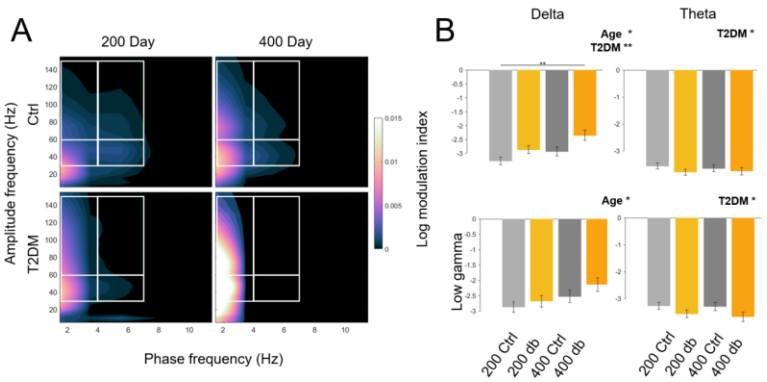

Figure 2.7. Cross regional phase-amplitude coupling between cortex and pyramidal or SLM layer of the hippocampus. (A) Comodulograms of cortex-pyramidal areas demonstrating delta-high gamma (upper left), theta-high gamma (upper right), delta-low gamma (lower left), and theta low-gamma (lower right) coupling area by white boxes. (B) Quantified average log modulation index within areas of interest. Two-way ANOVA test with post-hoc Tukey's test. 200 d: 200 days old, 400 d: 400 days old. *p < 0.05, **p < 0.01.

We next examined how age or T2DM affects the properties of SPW-Rs and their emergence, a hippocampal specific oscillation resulting from the dynamical interaction between pyramidal

cells and GABAergic interneurons within the local hippocampal circuit. We first examined the amount of network activation in CA1 during SPW-Rs by measuring gamma signal power. We found that both age and T2DM affected gamma power during SPW-Rs firing and interaction between two factors existed. At 200 days, T2DM gamma power was significantly higher at 200 days ($p < 0.0001$; Fig. 2.8B) yet lower at 400 days than control ($p < 0.0001$; Fig. 8B). We then found that the both age and T2DM prolonged ripple duration ($p < 0.0001$; Fig. 2.8C). Specifically, older db/db mice had reduced IRI compared to younger ones (Fig. 2.8D), likely due to increased ripple duration.

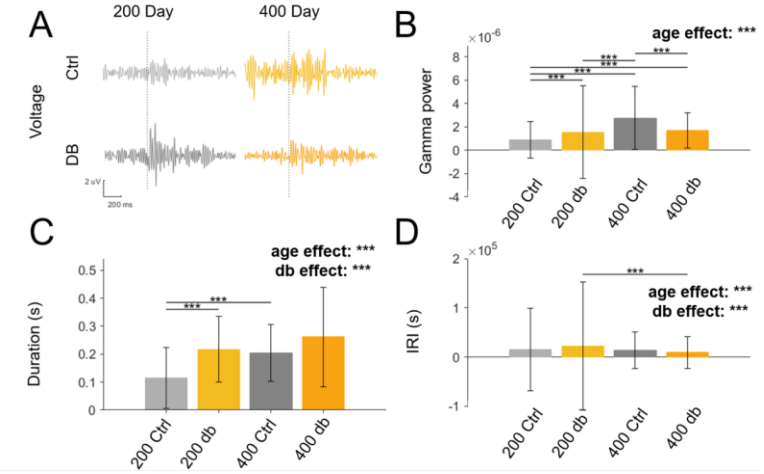

Figure 2.8. Characteristics of SPW-Rs. A, Average ripple waveform in 200 ms clips. B, Comparison of gamma signal power during SPW-Rs. C, Comparison of duration of SPW-Rs. Age and T2DM increased ripple duration and gamma power during ripples. D, Comparison of inter-ripple intervals (IRI). Two-way ANOVA test with post-hoc Tukey's test. 200 d: 200 days old, 400 d: 400 days old.. $^{**}p < 0.01$, $^{***}p < 0.$, $^{****}p < 0.0001$.old. $^{*}p < 0.05$, $^{**}p < 0.01$.

2.4.8 Current source density (CSD) analysis

Finally, we analyzed the strength of current flow through the hippocampus during SPW-Rs

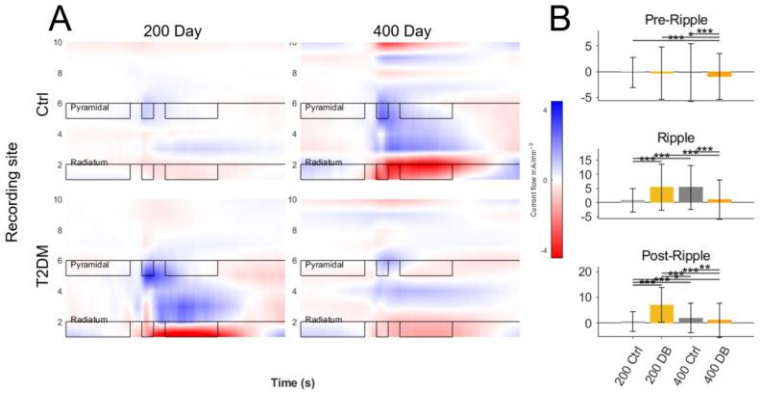

Figure 2.9. Current source density analysis during SPW-Rs. A, CSD plots showing average current of all ripples in each group. The pre- during- and post-ripple windows of interest were defined with rectangle areas. B, Dipole amplitude was calculated by finding the maximum and minimum current along the recording site in the specified phase windows. Two-way ANOVA test with post-hoc Tukey's test. 200: 200 days old, 400: 400 days old. Significant differences ($p < 0.05$, $p < 0.01$, and $p < 0.001$ are demarcated with $*$, $**$, or $***$ respectively).

events using CSD analysis. The CSD analysis revealed alterations in dipole amplitude as a function of age during, pre- ($p < 0.05$), and post-ripple ($p < 0.0001$) phases and also as a function of T2DM in pre- ($p < 0.001$) and post-ripple ($p < 0.0001$) phase (Fig. 2.9).

2.5 Discussion

While systematic changes in neural oscillations are known to occur under normal and pathological aging, (Rossini et al. 2007; Vlahou et al. 2014; Voytek and Knight 2015; Neto et al. 2016; Marshall and Cooper 2017) how cognitive aging risk factors alter or accelerate these natural progressions is unclear. Here we investigate the electrophysiological effect of T2DM and aging on neural oscillations in the hippocampus and neural synchrony between brain regions. We estimated changes to the relative strength of neural oscillations using signal power, slowing score, and spectral exponent, which indicates changes to the balance of excitatory and inhibitory networks. We estimate changes to theta state by measuring the amount of time spent in theta-delta states. Theta states represent the "online" status of the hippocampus, and are critical for temporal coding/decoding of neuronal ensembles and synaptic plasticity (Buzsáki 2002). We measured changes to SPWR-Rs, which have been shown to encode memories and play a role in memory consolidation. Finally, we estimated functional connectivity between the sensori-motor cortex and HPC using coherence, PLI, and xPAC, which has been shown to support memory encoding (Wang et al. 2021). We found that age strongly reduced theta brain state and low frequency cortical EEG power, while T2DM significantly reduced signal power of beta band. Age and T2DM both increased SPW-RS duration, gamma power during ripple firing and ripple dipole amplitude. With respect to neural synchrony, age and/or T2DM reduced phase-locking index and coherence between cortex and HPC. Both age and T2DM increased delta-gamma coupling while T2DM reduced theta-gamma coupling between HPC and cortex. Although T2DM is widely accepted as an accelerated aging

with known effect on cortical atrophy, the electrophysiological manifestation of T2DM is more prominent in the HPC as reflected by the increased SPW-Rs as well as reduced signal power and neural synchrony between cortex and HPC.

Reduced amplitude and peak frequency of the alpha-band was often reported during normal cognitive aging in humans (Mierau et al. 2017; Marshall and Cooper 2017; Knyazeva et al. 2018). Our study in mice showed a clear age effect on diminishing signal power in all EEG bands in the cortex, in addition to reduced hippocampal theta and gamma power. Compared to age effect, T2DM only significantly decreased signal power in the beta frequency range both in the cortex and SLM, which has been associated with alertness, attention, and cognitive control. We have also detected an T2DM-associated increase in slowing score in the HPC. Apart from changes seen in the periodic component, recent work has suggested that the aperiodic component of LFP signals can infer the balance between excitatory and inhibitory networks (Haegens et al. 2014; Mierau et al. 2017). Our results showing a T2DM-associated increase in the spectral exponent of the aperiodic signal and slowing score not only reflect reduced signal power, but also indicate that brain oscillations slow down as a result of T2DM, caused by an increase in the relative activity of inhibitory neurons in the hippocampus (Gao et al. 2017).

We estimated functional connectivity using PLI and coherence analysis. PLI is a measure of neuronal synchrony between two recorded signals and an electrophysiological proxy of functional connectivity between brain regions. A reduction in PLI globally across the neocortex has been reported in T2DM (Zeng et al. 2015) and mild cognitive impairment(Youssef et al. 2021; Kuang et al. 2022). In our study we have also detected a decrease in PLI between cortex and HPC over various frequency bands as a function of T2DM and age, showing that the decrease in PLI extends to connections between the neocortex and the temporal lobe in diabetic or aged mice.

Unlike PLI which measures the consistency of the instantaneous phase difference between two signals, coherence determines the ratio of the cross spectral density and the individual auto spectral densities. Coherence has been shown to be altered by neurodegenerative disorders such as stroke (Cassidy et al. 2020), depression (Khan et al. 2022), AD (Rodinskaia et al. 2022) and Down syndrome with AD (Musaeus et al. 2021). Similar to the PLI, we detected a decrease in coherence due to age and diabetes.

Theta oscillations in the hippocampus provide a temporal reference for gamma oscillations through theta-gamma coupling (Buzsáki 2015), which can be measured using xPAC as means to modulate the amplitude of a high frequency oscillation by a low frequency signal (Berdugo-Vega et al. 2020). Theta-gamma coupling within the hippocampus supports memory processes during HTD (Buzsáki 2002; Fernández-Ruiz et al. 2019) and it has also been observed between brain regions such as the prefrontal and entorhinal cortex (Lloyd et al. 2010; Pan et al. 2010). Recent work has revealed that the hippocampus and cortical areas utilize xPAC to support memory encoding (Wang et al. 2021). Our data showed that theta-gamma xPAC was reduced between cortex and hippocampus by T2DM, similar to the effect of chronic ischemic stroke in rats (He et al. 2020; Ip et al. 2021). These results suggest that T2DM acts to accentuate decreases in functional connectivity correlated with age, potentially caused by the increase in inhibitory activity, preventing signals from propagating as widely.

Some hippocampal electrophysiological features are correlated with memory, such as the ratio of theta to delta (TD) band signal power of the CA1 pyramidal layer within the hippocampus, which defines brain states relevant to memory function (Benwell et al. 2020). High theta/delta (HTD) ratio during sleep, also known as rapid eye movement sleep (REM), is correlated with memory performance (Knyazeva et al. 2018). Manipulation of hippocampal HTD alters cognition, further

supporting the role of HTD in cognition (Benwell et al. 2020; Mierau et al. 2017). Meanwhile, low theta/delta (LTD) ratio, also known as slow wave state, is associated with immobility and memory consolidation, during which sharp-wave associated ripples (SPW-Rs) occur (He et al. 2020). We found that aging altered brain state by proportionally prolonging the LTD periods, and necessarily shortening HTD periods. The balance and duration of brain states has been shown to be essential to proper memory function (Buzsáki 2002), and thus, may be an indicator of disrupted learning, memory, and cognitive function.

SPW-Rs serve to reactivate neurons encoding episodic memories such as place cells to promote memory consolidation and also contribute to the planning of future actions by generating ordered neuronal firing sequences (Buzsáki 2015). Increased SPW-R power is associated with higher fidelity replay of past experiences and of place cell trajectories (Carr et al. 2011), while disruption of SPW-RSs and/or gamma oscillation in the HPC-EC of experimental animals and humans causes severe memory impairment (Van Quyen et al. 2010; Jadhav et al. 2012; Fernández-Ruiz et al. 2019; Hollnagel et al. 2019; Jones et al. 2019; Mendes et al. 2021; Fernández-Ruiz et al. 2021). For the first time our study has revealed that age and T2DM increased the duration of hippocampal SPW-Rs and gamma power during SPW-Rs, while age reduced inter-ripple interval. Age and T2DM also altered the strength of current flow through the hippocampus during SPW-Rs complex. The increased gamma power and current flow during SPW-Rs suggest that neurons firing during SPW-RSs become more excitable as a function of age or T2DM. These paradoxical changes in dipole amplitude by age and T2DM as revealed by CSD analysis suggest that there was a significant interaction between age and T2DM status. Our finding is consistent with a recent study demonstrated that by reversing age-associated decline in neurogenesis with CDk4/cyclinD1 overexpression, ripple duration was shortened and inter-ripple intervals lengthened possibly by

promoting the activity of CA3 and CA1 inhibitory interneurons (Berdugo-Vega et al. 2020). However, our findings might not seem intuitively compatible with an earlier study showing that the longer duration of ripples was found to be related to mnemonic demand and performance (Fernández-Ruiz et al. 2019). A few factors might have contributed to the discrepancy between findings. We previously reported increased power and duration of SPW-Rs as a transient effect during the recovery of the chronic stroke condition (Ip et al. 2021). The pathophysiology of stroke is characterized in part by transient hyperexcitability succeeded by chronically decreased activity levels. While motivated by significantly different mechanisms, T2DM causes a related pathophysiology in the hippocampus. Insulin signaling is essential for proper memory function (Skeberdis et al. 2001), which when disrupted by T2DM, can lead to both increased excitability (Florez et al. 2015), and hippocampal atrophy (Milne et al. 2018), caused by increases in oxidative stress (Zilliox et al. 2016). In addition, SPW-Rs have been shown to modify glucose levels in the hippocampus (Tingley et al. 2021), which may be able to explain the possibility of increased ripple power and duration while measures like global signal power is decreased and slowing score is increased. Additionally, the average duration of SPW-Rs detected in our T2DM or older mice was more than 250 msec, which was significantly longer than the physiological ripples ranging 1-200 msec, which may further indicate the underlying cause of these increases to be aberrant hyperexcitability. Finally, one more factor to consider is that the SPW-Rs detected in our study are not related to task, and recorded under urethane anesthesia.

These electrophysiological changes begin to untangle the complex interactions between age and T2DM, however, a growing body of research is showing that diabetes mellitus (DM) and major depressive disorder (MDD) share a bi-directional relationship(Lloyd et al. 2010; Pan et al. 2010; Khaledi et al. 2019; Kan et al. 2013). Not only is depression a common comorbidity of type 1 DM

(T1DM) and type 2 DM (T2DM) (Zhu et al. 2022), but also the depressive symptoms have been found to be associated with a higher incidence of diabetes (Demakakos et al. 2010; Chien and Lin 2016). Preclinical data linking T2DM to depression is relatively scarce due to limited means in assessing rodent depression behavior. Besides, decreased locomotor activity often associated with diabetes may confound the behavioral performance in these animals. Nevertheless, depression-like behavior was already evident in db/db mice in forced swim test accompanied by thigmotaxis behavior and hypo-locomotion at a relatively young age of 10-11 weeks (Sharma et al. 2010). Evidence also supported a role of impaired leptin production or signaling in depression since treatment of diabetic mice with leptin reversed the depressive-like behavior in the tail suspension test as reported in another study (Hirano et al. 2007). However, the pharmacology and pathophysiology of leptin signaling defect in causing depression is not well understood. It is possible that leptin defect could cause depression by modulating the firing and downstream signaling of monoaminergic neurons in the forebrain. This is in line with the evidence that leptin receptors are expressed in the serotonergic raphe nuclei (Finn 2001), and the leptin deficient db/db mice have reduced serotonin transporter expression in raphe nucleus (Collin et al. 2000). Leptin also increased the production of forebrain 5-hydroxyindoleacetic acid, a breakdown product of serotonin (Calapai et al. 1999). In addition, systemic leptin treatment reversed the hedonic-like deficit induced by chronic stress and produced an antidepressant-like effect in the forced swim tests in rats(Lu et al. 2006). Interestingly, the authors found that the targeted brain regions of leptin intervention happened to be in the hippocampus and amygdala including the dentate gyrus as mapped by Fos expression (Lu et al. 2006).

Shared abnormal neurophysiological features between patients with DM and depression are well documented including elevated power in delta and theta band, and impaired response to task-

oriented stimulation such as increased P300 latency in EEG (Baskaran et al. 2013). Most EEG studies in diabetes failed to find consistent support towards the role of low blood glucose level in event related potential and EEG spectral power abnormalities, instead they point to an impairment in cognitive dysfunction. Apart from neurocognitive deficits, DM patients exhibit regional abnormalities in both cortical and subcortical brain structures including the hippocampus and amygdala by brain volumetric analysis. Interestingly, overlapping pathology such as the pattern of volumetric abnormality and neurocognitive deficits was also found between diabetic patients and those with depressive disorder (McIntyre et al. 2010). With respect to structural abnormality, reduced hippocampal neurogenesis is also common to pathological conditions with cognitive decline, such as T2DM and depression, apart from aging.

Among preclinical models of diabetes, reduced neurogenesis was reported in STZ-induced- or NOD mouse model of T1DM. Zucker rats and rodents fed with high-fat diet were shown to have reduced neurogenesis, although Goto-Kakizaki rats had increased neurogenesis (Beauquis et al. 2010; Ho et al. 2013). Depending on the age studied, db/db mice have been shown to have increased or reduced neurogenesis (Dorrance et al. 2006; Ramos-Rodriguez et al. 2014). In our study we found that neurogenesis at the hippocampus and SVZ was reduced in db/db mice of both age groups, which correlated with changes in neurophysiology. Although stress impairs neurogenesis and neurogenesis is required for some of the behavioral effects of antidepressants, the relationship between neurogenesis and depression still remains unclear (Sahay and Hen 2007). Regarding the role of hippocampal neurogenesis in maintaining the balance of excitatory and inhibitory activity and proper cognitive function, established evidence suggests that newborn neurons project monosynaptic inhibitory input onto granule cells, producing a feed-forward inhibition of CA3 neurons (Luna et al. 2019). This process is crucial in maintaining remote memory

(Guo et al. 2018), but is weakened by age (Oh et al. 2016), resulting in hyperexcitability of the CA3 auto-associative network that has been proposed to lead to memory rigidity during aging (Wilson et al. 2006; Leal and Yassa 2015). Increased neurogenesis by Cdk4/cyclinD1 overexpression triggered an overall inhibitory effect on the trisynaptic hippocampal circuit and reversed age-associated CA3 hyperactivation, resulting in decreased occurrence, duration and internal frequencies of SPW-ripples (Berdugo-Vega et al. 2020). Thus, increased neurogenesis might counteract the changes in excitability of the aged hippocampus, which drives up ripple firing.

This study reveals many effects and interactions between age and T2DM within the hippocampus. However, there are multiple limitations that warrant further study to gain a deeper understanding and to develop causal associations toward the eventual development of therapeutics. The dataset developed in this study consists of single time point recordings recorded under urethane anesthesia. While general anesthetics are known to reduce spike activity (Guo et al. 2018), urethane anesthesia preserves brain rhythms of interest, in particular, hippocampal rhythms (Leal and Yassa 2015). Besides, urethane generates naturalistic sleep patterns (Oh et al. 2016; Wilson et al. 2006). However, a single recording time point prevents assessment of neurophysiology over time and limits our observations to between-group analysis of different animals. Limited recording sites are another major weakness of our study. Although cognitive dysfunction is recognized as a disconnection syndrome, previous studies point to a heterogeneous disruption of functional networks. To strengthen the recording of hippocampal rhythms we chose the high signal quality linear array over the conventional EEGs. However, lacking globally distributed recording sites limits our assessment of functional connectivity to only restricted cortical and hippocampal networks. Another weakness of this study is a lack of awake-behaving recordings. An Awake-behaving experimental setup is difficult to use with a mouse model because T2DM animals are difficult to

train, and it is difficult to determine whether change in behavior is due to cognitive deficit or apathy.

T2DM causes complex changes to brain, which cause cognitive deficit, and significantly increases risk for other severe complications, such as depression, Alzheimer's Dementia, and stroke (Biessels et al. 2006; Weiss and Sumpio 2006; Baskaran et al. 2013) which can lead to a downward spiral of cognitive function, health, and quality of life. To develop effective therapies for these disorders, a deeper understanding of how these seemingly unrelated conditions interact and impact each other. Understanding the changes to both the neurophysiology and the electrophysiological functions is essential to the development of therapeutics, and to understand how potential therapeutics affect and ameliorate these conditions. Here we have shown that T2DM causes slowing in the hippocampus, disrupts functional connectivity, and reduces neurogenesis, however, establishing a causal link between these changes and cognitive behavior requires further study. Understanding these changes to brain oscillations and neurogenesis following T2DM can uncover insights that may translate to many neurological disorders; for example, recent work has uncovered a bi-directional link between depression and T2DM, and T2DM increases risk for dementia. This understanding will open the door for more targeted therapies as well. Recently we have shown that brain oscillations can be induced through optogenetic stimulation (Yazdan-Shahmorad et al. 2018), which allows for the potential to recover brain oscillations in disease models.

Chapter 3: Local field potentials identify features of cortico-hippocampal communication impacted by stroke and environmental enrichment therapy

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3.1 Abstract

Objective. Cognitive and memory impairments are common sequelae after stroke, yet how middle cerebral artery (MCA) stroke chronically affects the neural activity of the hippocampus, a brain region critical for memory but remote from the stroke epicenter, is poorly understood. Environmental enrichment (EE) improves cognition following stroke; however, the electrophysiology that underlies this behavioral intervention is still elusive. Approach. We recorded extracellular local field potentials simultaneously from sensorimotor cortex and hippocampus in rats during urethane anesthesia following MCA occlusion and subsequent EE treatment. Main results. We found that MCA stroke significantly impacted the electrophysiology in the hippocampus, in particular it disrupted characteristics of sharp-wave associated ripples (SPW-Rs) altered brain state, and disrupted phase amplitude coupling (PAC) within the hippocampus and between the cortex and hippocampus. Importantly, we show that EE mitigates stroke-induced changes to SPW-R characteristics but does not restore hippocampal brain state or PAC. Significance. These results begin to uncover the complex interaction between cognitive deficit following stroke and EE treatment, providing a testbed to assess different strategies for therapeutics following stroke.

3.2 Introduction

Stroke is a leading cause of adult disability, with the most common occurrence in the middle cerebral artery (MCA) region in humans. Unfortunately, there are few effective treatment options for disability following stroke. In addition to the impairment of high level sensorimotor functions, a common outcome of stroke is cognitive and memory deficit (Khedr et al. 2009). The hippocampus is highly involved in the encoding and retrieval of memories, but hippocampal and parahippocampal areas are rarely directly affected by MCA stroke because hippocampal blood flow is supplied by the posterior circulation (Bederson et al. 1986). Animal models represent this phenomenon, displaying cognitive impairment following stroke in the absence of hippocampal injury (Wang et al. 2011; Sun et al. 2013). However, a thorough understanding of the mechanisms underlying cognitive and memory impairment caused by MCA stroke remains poorly understood.

Cortical dysfunction following MCA stroke is well described by histological and electrophysiological methods (Oliveira et al. 2014; Hazime et al. 2021). Hippocampal functional impairment following MCA stroke has been demonstrated using behavioral assessment (Wang et al. 2011), however how hippocampal electrophysiology changes following stroke is largely unknown. There are many hippocampal electrophysiological features correlated with memory such as the ratio of theta to delta (TD) band signal power of the CA1 pyramidal layer within the hippocampus which defines brain states relevant to memory function (Aminov et al. 2017). High theta/delta ratio (HTD) during sleep, also known as rapid eye movement sleep, is correlated with memory performance (Buzsáki 2002). Manipulation of hippocampal HTD alters cognition, further supporting HTD's role in cognition (Williams et al. 2003; Aminov et al. 2017). Meanwhile, low theta/delta ratio (LTD), also known as slow wave state, is associated with immobility and memory consolidation. Sharp-wave associated ripples (SPW-Rs) are short, high frequency oscillations that

represent memory recall and encoding (Buzsáki 2015), which occur during LTD and in the awake state during consummation and immobility (Kay et al. 2016).

Theta oscillations in the hippocampus provide a temporal reference for gamma oscillations through theta-gamma coupling (Heusser et al. 2016) which can be measured using phase amplitude coupling (PAC) (Tort et al. 2010). Theta gamma coupling within the hippocampus supports memory processes during HTD (Heusser et al. 2016; Tort et al. 2009). PAC has been observed between brain regions such as the prefrontal and entorhinal cortex (Tamura et al. 2017; Bandarabadi et al. 2019). Manipulating theta has been shown to alter cognition (McNaughton et al. 2006), further supporting theta oscillation's causative role in cognition.

Chronic stroke leads to a complex cascade of effects within the brain such as the loss of functional connectivity (Schmitt et al. 2017) and changes in local oscillations (Rabiller et al. 2015; Ip et al. 2019), which can affect remote brain areas such as the hippocampus. EE is an effective non-invasive therapy that has long been studied as a potential treatment for improving cognition (Cooper and Zubek 1958) by increasing exposure to novelty, social contact, and physical activity. Cognitive and behavioral deficit following stroke is consistently improved by environmental enrichment (EE) (Hamm et al. 1996; Matsumori et al. 2006; Fan et al. 2007; Wang et al. 2011). However, the underlying electrophysiological mechanisms are still largely unknown.

We have previously shown that an MCA occlusion acutely disrupts the electrophysiology of the hippocampus, which we observed through increases in SPW-R frequency and theta-gamma coupling between hippocampus and cortex within the first hour of ischemia (He et al. 2020). Here we seek to understand the changes in hippocampal electrophysiology during the chronic phase of MCA stroke to understand the underlying mechanisms of cognitive impairment following stroke and cognitive improvement following EE.

3.3 Materials and Methods

3.3.1 Animals

We conducted all experiments in accordance with the animal care guidelines issued by the National Institutes of Health and by the San Francisco VA Medical Center Institutional Animal Care and Use Committee. We used adult male Sprague–Dawley rats approximately 2.5 months of age weighing 250 g (Charles River Laboratories, Wilmington, MA) housed in institutional standard cages (two rats per cage) on a 12 h light/12 h dark cycle with ad libitum access to food and water before the experimental procedures. Only male rats were used to avoid potential effect of sex hormones on stroke injury. The identity of the test subject was blinded to investigators who performed the stroke surgery and recording.

3.3.2 Experimental stroke

Stroke was induced unilaterally in rats by the distal MCA occlusion method in combination with supplemental proximal artery occlusion of the bilateral common carotid arteries under isoflurane (1.5%)/O2 (30%)/N2O (68.5%) anesthesia as described previously (He et al. 2020; Sun et al. 2011), producing cortical infarct restricted to the somatosensory cortex (Wang et al. 2011). Core temperature was maintained at 37 ± 0.5 ◦C with a heating blanket and rectal thermistor servo loop throughout the procedure. Mortality due to stroke was approximately 12%–15%.

3.3.3 Environmental enrichment

Immediately following MCA occlusion, we randomly assigned rats into EE or standard housing groups. One week after surgery, we transferred the EE group rats to EE cages (dimensions: 76 × 56 × 77 cm; two story cage equipped with a running wheel, a three dimensional labyrinth, bedding, a ladder, a house, chains, a hammock, wooden blocks, and nylon bones; ten rats per cage) for 3

weeks of residence. Similarly, non-stroke control animals assigned to EE treatment were placed in EE cages for 3 weeks before recording. We changed the arrangement of movable objects once a week to maintain novelty (Wang et al. 2011; Matsumori et al. 2006). Rats assigned to the standard housing groups remained in institutional standard cages.

3.3.4 Recording

We performed electrophysiological recordings using two 16-site extracellular silicon probes (NeuroNexus Technologies) under urethane anesthesia for 2 h (Sigma, 15 mg kg−1i.p.). Following craniotomy, two electrodes (A1x16-5 mm-100-703) were inserted into each hemisphere after the dura mater was pierced to target the dorsal hippocampus at AP: −3.3 mm; ML: ±2 mm via a stereotaxic frame (David Kopf Instruments, Tujunga, CA, USA) (figure 3.1). Realtime data display and an audio aid were used to facilitate the identification of proper recording location while advancing electrodes until characteristic signals from stratum pyramidal and stratum radiatum were detected and recorded. We collected a 2 h multi-channel recording from bilateral sensorimotor cortex and dorsal hippocampus from each rat. Data were stored at a sampling rate of 32 kHz after band-pass filtering (0.1–9 kHz) with an input range of ±3 mV (Digital Lynx SX, Neuralynx, USA). We down sampled all recordings to 1250

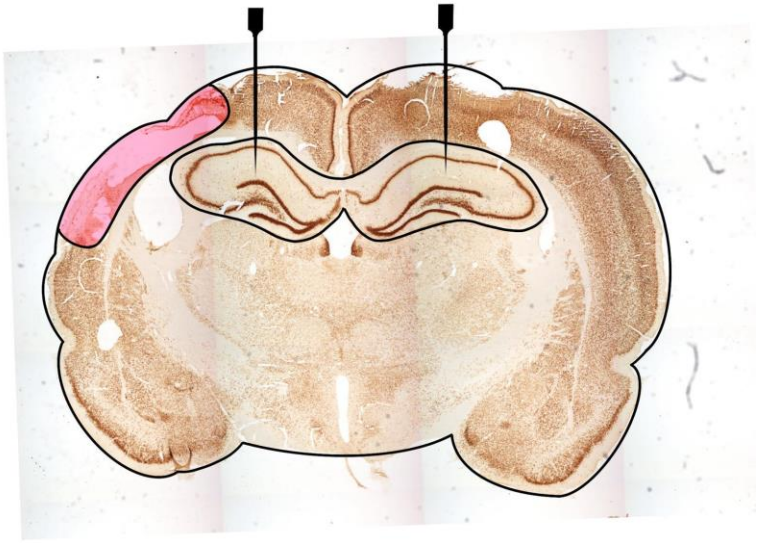

Figure 3.1. Schematic of infarct area and probe locations. Probes are inserted to cover sensorimotor cortex and hippocampus. Approximate infarct and peri-infarct areas from stroke indicated by pink shading intervals (IRI). Two-way ANOVA test with post-hoc Tukey's test. 200 d: 200 days old, 400 d: 400 days old. **p < 0.01, ***p < 0., ****p < 0.0001.old. *p < 0.05, **p < 0.01.

Hz (Matlab, MathWorks, USA) prior to analysis. Approximately 7%–10% of rats were excluded due to excessive bleeding occurred during craniotomy surgery or insertion of recording or reference electrodes.

3.3.5 Tissue preparation and infarct assessment

After recording, rats were perfused transcardially with 4% paraformaldehyde in 0.1 M phosphate buffer, pH 7.4. The brains were collected, post fixed overnight in 4% PFA, and placed in 30% sucrose solution for 24 h. Brains were cut coronally in 40 m thick sections and stored at 4 ◦C. Serial coronal sections were stained using the hematoxylin and eosin method. Infarct volume was measured by subtracting the difference between intact tissue in the ipsilesional side from the contralesional side using Stereoinvestigator software (Microbrighfield, VA). We determined both the infarct volume and the ratio of infarct to intact tissue volume (Sun et al. 2013).

3.3.6 Data analysis

We used local field potentials (LFP) from deep cortical layers and four layers from CA1 field hippocampus (stratum oriens, pyramidal, radiatum and lacunosum-moleculare) in our analysis. We isolated brain waves from the LFPs by band-pass filtering the following frequency ranges: delta (0.1–3 Hz), theta (4–7 Hz), alpha (7–13 Hz), beta (13–30 Hz), gamma (30–58 Hz), and high-gamma (62–200 Hz). A total of 52 rats were successfully recorded and subjected to data processing. We further excluded the data from ten rats after screening for bad channels and recordings where individual layers could not be discerned. The groups had the following counts: control (n = 8), enriched control (EEC) (n = 10), 2 week stroke (2WS) (n = 6), 1 month stroke (1 MS) (n = 9) and enriched 1 month stroke (EES) (n = 9). To analyze changes to signal power we normalized data by

subtracting the mean and dividing by the standard deviation to account for impedance differences between individual electrodes.

To estimate LTD and HTD brain states we calculated the ratio of spontaneous signal power between theta band and delta band from the pyramidal layer. The threshold defining LTD and HTD states was defined manually for each animal by visual assessment (Kay et al. 2016; Bódizs et al. 2001). The ratio of HTD/LTD was calculated by dividing the total time spent in each state for each recording.

SPW-Rs were identified when a pyramidal ripple and radiatum sharp wave co-occurred as described previously (Kay et al. 2016). To detect pyramidal ripples, the LFP of the pyramidal layer was bandpass filtered (150– 250 Hz), then squared and Z-scored. When the signal exceeded 6 standard deviations for a period longer than 20 ms, an event was registered. When the signal subsequently dropped below one SD, the event was considered to have ended. To identify radiatum sharp waves, a similar process was used, however the bandpass filter was from 8 to 40 Hz, and the standard deviation threshold was 3.

We performed laminar current-source density (CSD) analysis (Kenan-Vaknin and Teyler 1994) along each electrode, temporally aligning the LFP to the onset of a SPW-R, and spatially centering each recording on the pyramidal layer. We used windows of time before during and after ripple to examine local current flow in relation to the timing of ripple firing. Dipole amplitude was calculated by finding the maximum and minimum current along the probe from the specified time window and taking the difference. We analyzed PAC within the hippocampus and between the layers of the hippocampus and the cortex as a metric of functional connectivity and communication. PAC was calculated as described in (Heusser et al. 2016). Briefly, we bandpass filtered the LFP between (0.1–200 Hz), extracted the instantaneous phase and amplitude using the Hilbert transform. A

composite phase-amplitude time series then determined the amplitude distribution across phase. The modulation index (MI) is then calculated from the divergence of the amplitude distribution from a uniform distribution (Tort et al. 2010). MI was compared between groups by averaging the MI across a window of frequencies pertaining to canonical frequency bands. A data driven threshold was found using Otsu's method (Otsu 1979) to determine the window of significant coupling.

3.3.7 Statistical analysis

We expressed data as mean ± standard error. We performed one-way ANOVA to assess changes in stroke progression, and two-way ANOVA to assess changes between the effect of stroke and the effect of EE. We used post-hoc Bonferroni's to control for multiple comparisons between treatment groups. We performed between-group comparisons for each neural feature independently. We performed paired t-tests to assess changes between hemispheres. For nonnormal distributions, we performed Kruskal–Wallis with post-hoc Bonferroni's to control for multiple comparisons. We considered p values less than 0.05 as significant.

3.4 Results

We analyzed the absolute infarcted volume and the ratio of infarcted volume to intact tissue volume, confirming there was no hippocampal lesion and determining whether lesion size was affected by the chronicity of stroke or by exposure to enrichment. There was no apparent morphological difference in the hippocampus as revealed by hematoxylin and eosin staining between the stroke and non-stroke groups, suggesting that experimental MCA did not compromise hippocampal structural integrity. Both analyses revealed that lesion size did not significantly differ between groups (ANOVA; $p < 0.460$) (supplemental figure 3.1 (available online

at stacks.iop.org/ JNE/18/046001/mmedia)). We verified probe location through histology, spanning from −3 mm to −3.72 mm AP and 2.5 mm to 3 mm laterally (figure 3.1).

We analyzed normalized signal power within the cortex and hippocampus as a simple metric of activity levels within the tissue. Surprisingly, there were sparse significant differences between groups. Delta power in 2WS and 1MS tended to be lower than control in both cortex and hippocampus, though interestingly, theta, gamma and high gamma signal power tended to be higher in both 2WS and 1MS compared to control (figure S3.2).

3.4.1 Brain state stability is disrupted following

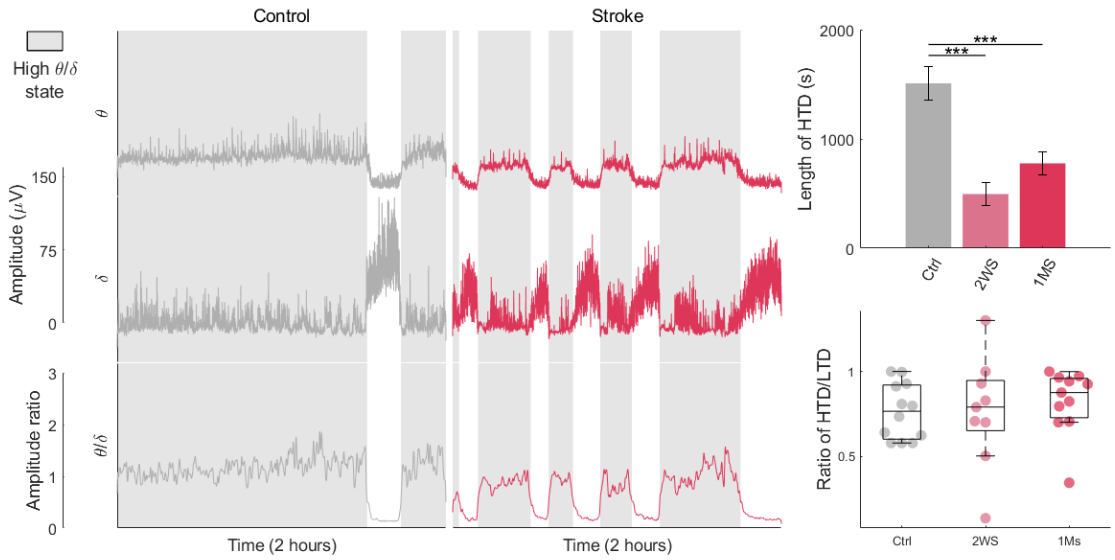

Figure 3.2. Detecting HTD and LTD states. (A) The columns show examples of LFP traces for a control and stroke sample. The rows are: 1—spontaneous amplitude of theta, 2—spontaneous amplitude of delta, 3—ratio of theta/delta. (B) Comparison of the average duration of ipsilateral HTD state. (C) Comparison of the proportion of ipsilesional HTD to LTD. Significant differences ($p < 0.001$, are demarked with $***$). © [2019] IEEE. Reprinted, with permission, from (Ip et al., 2019).

Stroke We analyzed the stability of TD states under anesthesia by analyzing the duration of HTD state (figure 3.2(A)). Surprisingly, we found that TD state stability is disrupted following stroke

despite no direct lesion to the hippocampus, with a significant decrease in the duration of HTD brain state bilaterally for both stroke groups compared to control (ANOVA; $p < 3.33 \times 10{-}4$) (figures 2(B) and S3(A)). However, the disruption of state stability does not alter the overall proportion of HTD to LTD as evidenced by the HTD/LTD ratio (figures 3.2(C) and S3(B)) (ANOVA; $p > 0.21$). This shows that stroke chronically disrupts the stability of brain states defined within the hippocampus, but does not disrupt the proportion of HTD to LTD.

3.4.2 SPW-R characteristics change following stroke

SPW-Rs occur within the CA1 pyramidal layer of the hippocampus during LTD and represent memory encoding. We quantified characteristics of SPW-Rs following stroke. There was an increase in SPW-R signal power of both ipsilesional and contralesional hemispheres in 2WS and 1MS compared to control (Kruskal Wallis; $p < 9.97 \times 10{-}4$) (figures 3(A) and S4(A)). The duration of SPW-Rs was also significantly different; SPW-Rs at 2WS were significantly longer than control (ANOVA; $p = 5.41 \times 10{-}5$), while SPW-Rs at 1MS were significantly shorter (ANOVA; $p = 5.41 \times 10{-}5$) (figure 3.3(B)). These results indicate that stroke significantly affects both power and duration of SPW-Rs. Both the signal power and duration of SPW-Rs at 2WS significantly increased compared to 1MS in both hemispheres (Kruskal Wallis; $p < 4.03 \times 10{-}9$,). These results indicate that there is some compensatory mechanism occurring at 2WS.

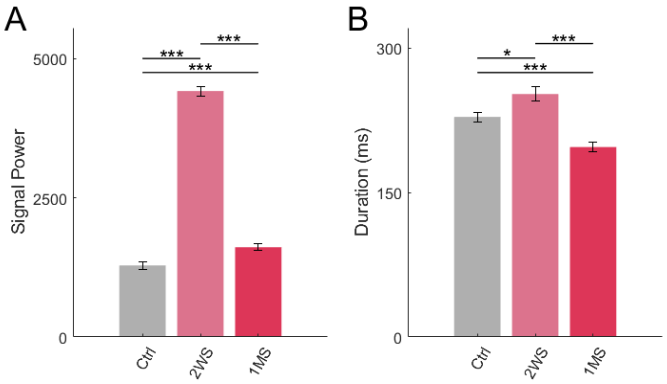

Figure 3.3. Comparison of ipsilesional (A) SPW-R power and (B) SPW-R duration. Significant differences ($p < 0.05$, $p < 0.01$, and $p < 0.001$ are demarcated with *, **, or *** respectively).

3.4.3 Current flow surrounding SPW-Rs is disrupted following stroke

We performed laminar CSD aligned to the onset of SPW-R to evaluate current flow through the hippocampus during SPW-Rs. The control group revealed pairs of dipoles with the apparent source centered in the pyramidal layer with the sink centered in the radiatum as expected. After SPW-R, the dipole reverses at a lower amplitude, with the sink in pyramidal and the source in the radiatum (figure 3.4(A)). This post-SPW-R phase lasts approximately 0.6 s before dissipating. To analyze these changes to this current flow, we calculated the amplitude of current within windows of interest before, during, and after SPW-R.

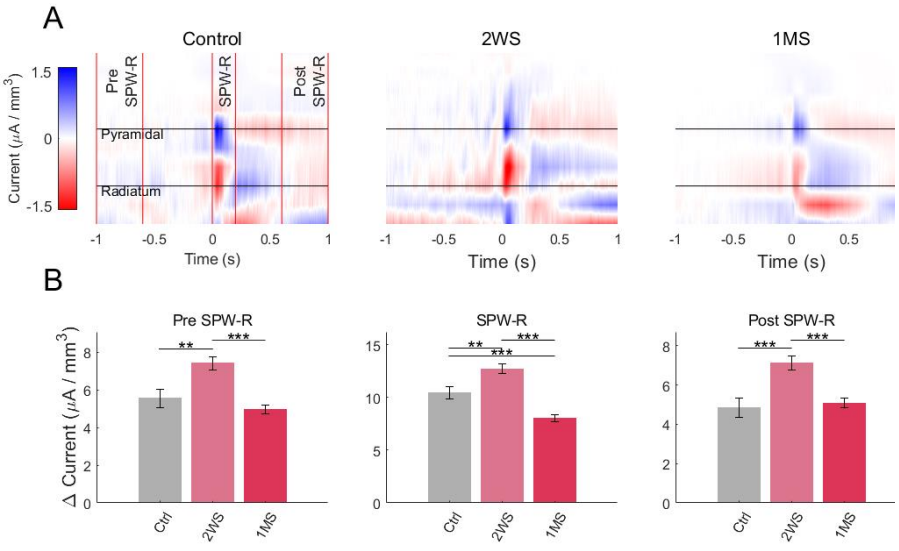

Figure 3.4. Comparison of ipsilesional CSD during and following SPW-R. (A) CSD plots of ipsilesional hemisphere, displaying average current of all ripples for all animals within a particular group. Windows of interest are demarcated with red lines. (B) Change in current was measured using difference between the minimum and maximum amplitudes with the demarcated windows. *Significant differences: p<0.01 and p<0.001, are demarcated with **, or *** respectively.*

In both hemispheres, the dipole amplitude before, during, and after SPW-R was significantly higher at 2WS compared to control (ANOVA; $p < 0.0077$) (figures 3.4(B) and S5) while the amplitude of 1MS is significantly lower compared to control (ANOVA; $p < 6.78 \times 10-4$) (figure 3.4(B)). Like SPW-R power and duration, the dipole amplitude at 1MS is significantly lower than

2WS before, during and after SPW-R (ANOVA; $p < 4.72 \times 10^{-5}$). These results show that stroke causes significant change in current flow, while the decrease of dipole amplitude from 2WS to 1MS support our SPW-R previous observations that there is some compensatory activity at 2WS.

3.4.4 Theta-gamma coupling between hippocampus and cortex is reduced following stroke

Theta rhythms coordinate high frequency gamma activity within the hippocampus during HTD and supports memory processes. We used PAC to detect theta-gamma coupling within the hippocampus, and to determine whether coupling existed between cortex and hippocampus. During HTD, theta-gamma coupling, and delta-high gamma coupling was present bi-directionally within the hippocampus as expected, however we also detected coupling between cortex and hippocampus in the control group. Coupling within the pyramidal layer and between pyramidal theta and cortical gamma are shown as examples (figure 3.5(A)). Although the majority of coupling is captured by the theta frequency band, some coupling extends to the border between theta and delta (figure S6), however

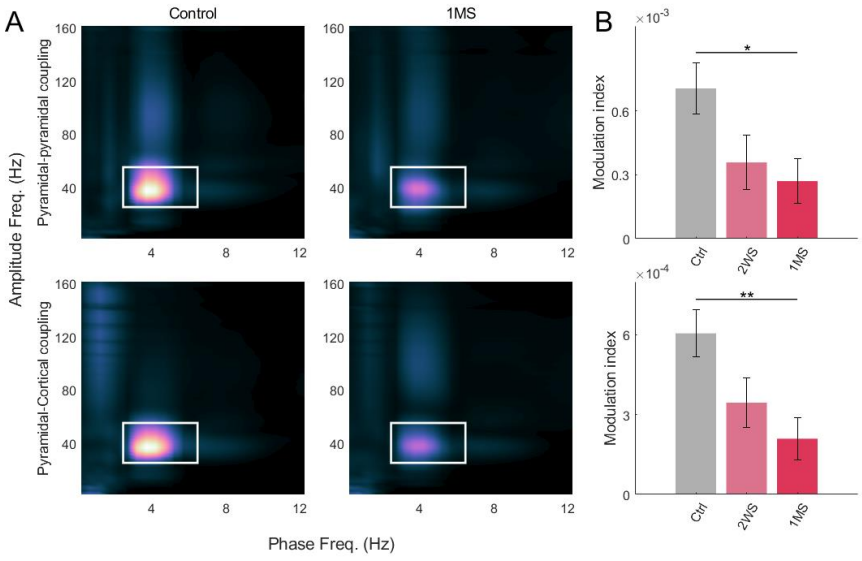

Figure 3.5. Coupling between theta and gamma. (A) Phase amplitude comodulograms displaying modulation within the pyramidal layer (top), and between cortex and hippocampus (bottom). Theta-gamma coupling demarcated by white rectangle. (B) Comparison of average modulation index between theta and gamma. Ipsilesional and contralesional hemispheres are compared separately. Significant differences ($p<0.05$ and $p<0.01$, are demarcated with * and ** respectively).

for the rest of the analysis we are focusing on theta-gamma coupling. Ipsilesional coupling within the pyramidal layer was significantly lower at 1MS compared to control. Interestingly, ipsilesional coupling between hippocampus and cortex at 1MS was also significantly lower than control for all hippocampal layers in compared to control (figure 3.5(B)) (ANOVA; $p < 0.0356$). Coupling within the hippocampus and between cortex and hippocampus is lower than control at 2WS, though not significantly. This could be due in part to the compensatory mechanisms observed in SPW-Rs. During LTD, theta-gamma coupling was not present within the cortex or between cortex and hippocampus as expected. Instead, only delta-high gamma coupling was present during LTD, which did not change following stroke. The breakdown in PAC between hippocampal theta and cortical gamma implies that MCA stroke, which does not cause infarct to the hippocampus, breaks down coordination of oscillations between theta and gamma within the hippocampus, and the coordination of cortical gamma by hippocampal theta.

3.4.5 The effect of EE on stroke

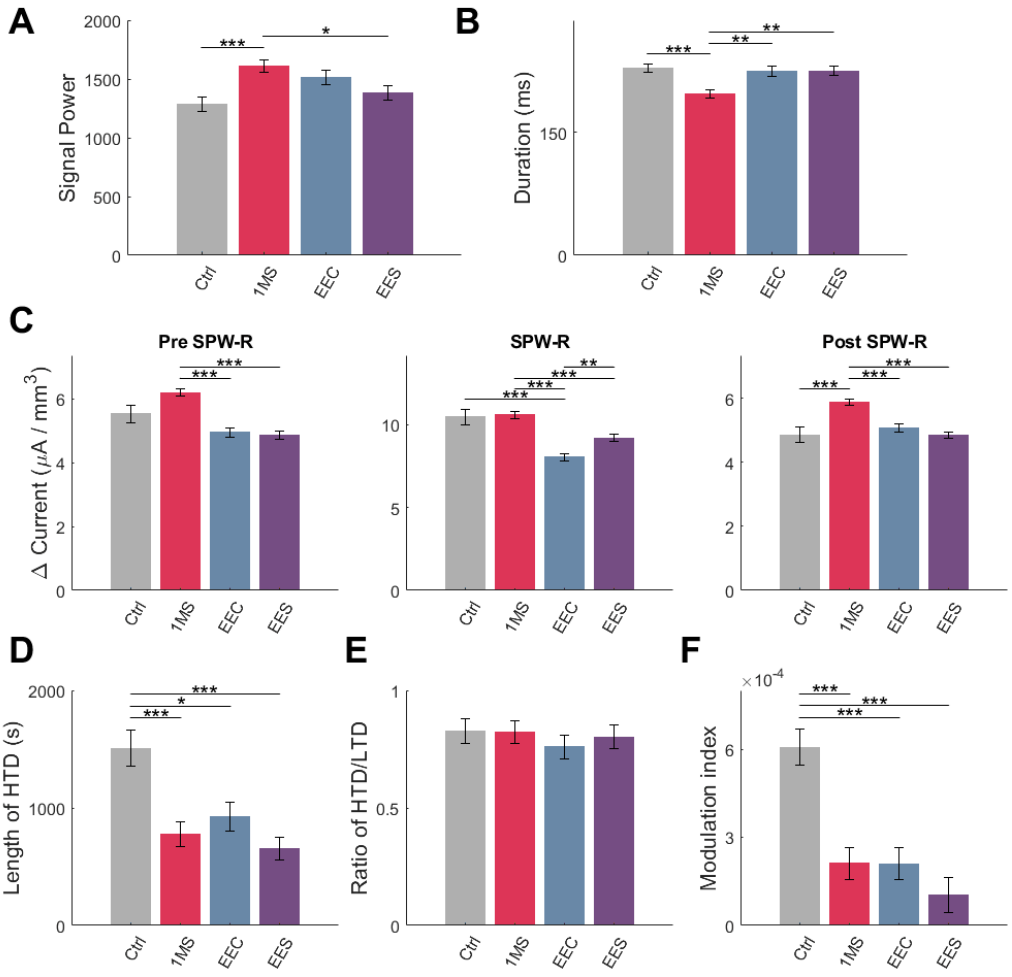

Figure 3.6. Summary of the effects of EE following stroke using 2-way ANOVA comparisons on ipsilesional hemisphere. (A) Changes in SPW-R power (B) Changes in SPW-R power. (C) Changes in CSD dipole amplitude surrounding SPW-R. (D) Change in average HTD state (E) Change in HTD/LTD ratio. (F) Changes in theta-gamma coupling between cortex and pyramidal. *Significant differences: p<0.05, p<0.01 and p<0.001, are demarcated with *, **, or *** respectively.*

Following our analysis of stroke progression, we investigated the effect of EE on the hippocampal electrophysiological features involved in memory using a two-way ANOVA. EE had two main interactions with these features affected by stroke. Characteristics of SPW-Rs, which were increased by stroke, were mitigated by EE. Interestingly, features that were disrupted by stroke, such as TD state and PAC, were further disrupted by EE.

To analyze the effect of EE on hippocampal features of memory, we first looked at characteristics of SPW-Rs. We started with SPW-R power. At 1MS SPW-R power is significantly higher than control in both hemispheres, (figure 3.6(A)) (ANOVA; $p < 2.16 \times 10{-}4$), while there is no significant difference between control, EES, and EEC (ANOVA; $p > 0.058$). SPW-R power shows that EE mitigates the effects following stroke.

We then analyzed the duration of SPW-Rs. At 1MS the duration of SPW-Rs is significantly shorter than control ipsilesionally (ANOVA; $p = 5.65 \times 10{-}5$), while control, EES, and EEC are not significantly different (ANOVA; $p = 1$) (figure 3.6(B)). Contralesionally, the duration of 1MS, EEC, and EES are all significantly shorter than control (figure S8(B)) (ANOVA; $p < 2.61 \times 10{-}10$), though 1MS is also significantly shorter than EES. Like SPW-R power, SPW-R duration results show that EE mitigates the decrease in duration following stroke. These results support our findings in SPW-R power that EE tends to reduce the severity of the effects of stroke.

As for the effects on the CSD surrounding SPW-Rs, we see that stroke generally causes an increase in dipole amplitude, while EE generally causes a decrease in dipole amplitude. Leading up to SPW-R, there is a between-subjects effect in both the ipsilesional and contralesional hemisphere for stroke (ANOVA; $p < 2.09 \times 10{-}6$) (table S1). The dipole amplitude ipsilesionally at 1MS is significantly higher than EEC and EES before, during, and after SPW-R (ANOVA; $p < 1.77 \times 10{-}5$), while there is no significant difference between control, EEC, and EES (ANOVA, $p > 0.15$) (figure 6(C)). These changes support our findings that EE mitigates the effects of Stroke.

Investigating the effect of EE on TD states revealed a between-subjects effect that both stroke and EE significantly decrease the length of ipsilesional HTD state (ANOVA; $p < 0.0041$), though contralesionally, only stroke significantly changed HTD state (ANOVA; $p = 3.01 \times 10{-}6$) (table S1). This was shown in our post-hoc analysis as well, where the length of ipsilesional HTD in 1MS, EEC,

and EES were all significantly lower than control (ANOVA; $p < 0.021$) (figure 3.6(D)). Neither stroke nor EE had any significant effect on the ratio of HTD/LTD (figure 3.6(E), table S1). These results show that both EE and stroke can disrupt the stability of TD states, while leaving the ratio of HTD/LTD intact.

Contrary to its known benefit on synaptic plasticity and cognition, EE unexpectedly lowered the levels of theta-gamma coupling during HTD. The between-subjects effects show both stroke and EE significantly lower ipsilesional and contralesional thetagamma coupling. Additionally, stroke and EE showed significant interaction ipsilesionally, meaning that the change in PAC seen in EES compared to control was significantly different than could be expected from the additive effects of stroke and EE combined (ANOVA; $p < 0.017$) (figure 3.6(F), table S1). Our post-hoc analysis revealed that coupling in 1MS, EEC, and EES are all significantly lower than control ipsilesionally (ANOVA; $p < 2.10 \times 10{-}4$), while contralesionally coupling in 1MS and EES are significantly lower than control (ANOVA; $p < 0.0022$) (figure S8(F)). These results additionally show a reduction of information flow between cortico-hippocampal networks for both stroke and EE groups.

3.5 Discussion

While impairment of memory after dMCAO is well reported, (e.g. poor performance in the Barnes Maze test and hippocampal hypoactivation following spatial exploration [3]), the electrophysiological substrates of cognitive deficit in the hippocampus have not been established. There are no direct projections between the sensorimotor cortex and hippocampus. However, we recently showed that cortical lesion following dMCAO stroke acutely affects the electrophysiology of the hippocampus. We saw counterintuitive effects, such as an increase in SPW-Rs, an increase in theta-gamma coupling, and a persistent increase in LTD state (He et al. 2020). These results showed that MCA stroke strongly affects remote regions like the hippocampus. With these neural

features, we sought to understand the underlying changes to hippocampal electrophysiology that drive the cognitive deficit observed during chronic phase of stroke, and how EE interacts with these effects.

We found that EE mitigates the stroke induced changes to SPW-R characteristics, like SPW-R power, duration, and CSD. This shows that although the anatomy of the hippocampus is not compromised, SPW-Rs, which are well known and thoroughly studied for their role in memory and cognition, are disrupted throughout stroke progression. Crucially, we show that EE stabilizes the characteristics of SPWRs throughout stroke progression, revealing that EE impacts features related to cognition. These results begin to uncover the complex interaction between stroke and EE, providing a testbed to assess different strategies for therapeutics following stroke. Our recordings allowed analysis of other features as well. For features such as TD brain state and PAC, EE compounded the disruptions caused by stroke. These neural features may be areas of interest to further understand the network imbalances caused by stroke and to investigate future therapeutic interventions.

PAC has been characterized within the hippocampus in previous work [14–16]. Interestingly, the frequency range defining theta in these studies has been inconsistent (e.g. 7–12 Hz (Tort et al. 2009), 4–12 Hz (Tamura et al. 2017), and 6–10 Hz (Bandarabadi et al. 2019)). Crucially, the coupling that we are seeing in our results here is the lower than these frequencies (3–5 Hz) (figure S6). The neural activity from previous studies were recorded during awake behaving sessions; therefore, the coupling at lower frequencies that we observe here maybe due to urethane anesthesia. To our knowledge this is the first time PAC is being reported between cortex and hippocampus where we also see coupling of gamma to lower frequencies (3–5 Hz) consistent with the range we see within the hippocampus.

Current literature describes stroke progression as two opposing phases. The first phase lasts approximately three days after onset, characterized by increased activity and plasticity, and excitotoxic cell death. Following this, neuronal activity is chronically suppressed (Carmichael 2012). Our results show that SPW-Rs, which encode memories within the hippocampus, remain upregulated up to 2 weeks before partially returning to baseline levels, while TD state and PAC are chronically disrupted.

The chronic changes to hippocampal electrophysiology differ drastically from the acute effects occurring in the hour after infarct, detailed in (He et al. 2020). The frequency of SPW-Rs increases in the acute setting, while in the chronic setting SPW-R power increases at 2WS. PAC also differs between acute and chronic settings, where theta gamma coupling is increased in the acute setting and disrupted in the chronic setting.

SPW-Rs are well-known for their causative role in memory performance: disruption on SPW-Rs interferes with memory formation (Kay et al. 2016). The marked increase in SPW-R power, duration, and current flow at 2WS may be correlated with the increased cortical plasticity or disinhibition during stroke progression. This suggests some compensatory activity at 2WS. The decrease in SPW-R power, duration, and current flow at 1MS could represent stabilization of the network. Long-duration SPW-Rs are correlated with increased memory function (Fernández-Ruiz et al. 2019), which may imply that shorter SPW-Rs impair memory. Our current results as well as our previous findings (He et al. 2020) agree with this interpretation.

The other neural features that we analyzed, TD states and PAC, were disrupted at 2WS and further disrupted at 1MS compared to controls. Disrupted TD states have been shown to cause neuroinflammation and have been associated with impairment of learning and memory (Williams et al. 2003; Aminov et al. 2017; Ip et al. 2019), which may be a contributing mechanism to post-

stroke cognitive impairment. PAC within the hippocampus has been shown as a mechanism for memory processing during sleep (Rasch and Born 2013; Staresina et al. 2015; Bergmann and Born 2018), and the breakdown of hippocampal theta rhythms, which are known to coordinate oscillations in many regions, such as entorhinal cortex and prefrontal cortex, may be a contributing factor to cognitive impairment following stroke.

EE has been shown to consistently improve behavioral measures of cognitive recovery following stroke (Hamm et al. 1996; Matsumori et al. 2006; Wang et al. 2011). We show that EE stabilizes the characteristics of SPW-Rs throughout stroke progression. However, TD state and PAC are further disrupted by EE following the stroke. TD states, though measured in the hippocampus, are an indicator for functions of many areas of the brain. Theta-gamma coupling, which we observed within the hippocampus and between cortex and hippocampus, has also been reported between prefrontal cortex and entorhinal cortex. Therefore, the features which are further disrupted by EE are indicators of a more global effect on the brain compared to SPW-Rs, which occur locally. Interestingly, we rarely observed interaction effects between EE and stroke. This indicates that the effect that EE has on these neural features remains consistent regardless of stroke condition.

This study is limited in that our dataset consists of single time point recordings that were done under urethane anesthesia. While general anesthetics are known to reduce spike activity (Suzuki and Smith 1988), urethane anesthesia preserves brain rhythms of interest and generates naturalistic sleep patterns (Hara and Harris 2002; Pagliardini et al. 2013). Urethane anesthesia is widely used both in hippocampal (Klausberger and Somogyi 2008) and stroke (Srejic et al. 2013; Rabiller et al. 2015) studies. However, a single recording time point prevents assessment of neurophysiology over time and limits our observations to between-group analysis of different animals. An awake behaving recording setup will allow for a more complete understanding of how

stroke affects hippocampal electrophysiology across time. Another limitation of unconscious recordings is they do not provide real-time correlates to spatial encoding or recall. An awake-behaving set-up would allow us to record electrophysiology during these events and pair them with behavioral readouts.

Stroke causes complex changes to remote regions of the brain beyond the direct infarct. Similarly, many neurological disorders have far reaching effects in remote brain regions. To create effective therapies for these disorders, a deeper understanding of how these remote regions interact is needed. Furthermore, a greater understanding of how existing therapies like EE affect these interactions is essential to developing and translating these therapies to clinical settings. Here we have shown how EE impacts SPWRs following stroke which may explain the cognitive improvement previously reported, however the effects on other features such as PAC require further study. PAC specifically may uncover insights that translate to other neurological disorders; for example, abnormal PAC has been implicated in Parkinson's disorder (Devergnas et al. 2019), Alzheimer's Disease (Zhang et al. 2016), and schizophrenia (Barr et al. 2017). This understanding will open the door for more targeted therapies as we have shown that PAC can be induced through optogenetic stimulation (Yazdan-Shahmorad et al. 2018), which allows for the potential to recover PAC between regions in disease models.

Chapter 4. Summary and future directions

4.1 Electrophysiological changes as a result of vascular disease

In the previous two chapters I have presented findings on the electrophysiological effects of an upstream vascular condition, T2DM and a downstream neurodegenerative disorder, ischemic stroke, both of which have a significant impact on neurophysiology. These conditions have been shown to disrupt the balance of excitatory and inhibitory networks in the hippocampus, causing changes in neural activity (Goutagny and Krantic 2013). The electrophysiology revealed both diverse differences and striking commonalities between disease states. The power and duration of SWRs, which are typically associated with better recall, were found to be increased in both T2DM and two weeks post-stroke. T2DM is characterized by hyper excitability (Zilliox et al. 2016), which is also seen transiently during stroke (Carmichael 2012), In this context, the increase in power and duration could imply that these SWRs are aberrantly stronger, or indicate that the brain is attempting to reorganize itself in response to neurodegeneration. Another measure that was consistent in both studies was disruption of cross regional theta-gamma coupling between the hippocampus and cortex. This long-range communication was disrupted not only by T2DM and stroke, but also by EE, a therapy that is related to a wealth of neuroprotective benefits (Young 2013). This result may be interpreted multiple ways, one possible hypothesis is that there are multiple mechanisms that disrupt theta-gamma coupling, not all of which may be deleterious, and coupling is not a sensitive enough measure to distinguish between underlying causes. Another hypothesis could be that EE has a more complicated and heterogeneous profile of effect in neurophysiology compared to the net positive benefit in the cell markers and behavior. EE is associated with increases in neurogenesis, synaptogenesis, expression of Brain-derived neurotrophic factor (Young 2013); these changes may uncouple hippocampal activity from the

activity of remote brain regions. This could imply that while the EE may improve functions in the HPC, the signals may not be coordinated with the rest of the brain. The consistency of disruption to theta-gamma coupling suggests that functional connectivity may be one of the earliest mechanisms affected. These results show that the interactions between memory, T2DM, and stroke are complex and may react in surprising and unintuitive ways.

While these two conditions may seem unrelated, these similarities seem to suggest that within the scope of cognitive function, age, T2DM, stroke, dementia, even AD all lie along a continuum of cerebrovascular health. Dementia is merely a clinically diagnosable level of cognitive impairment, and while AD is a specific form of dementia marked by the presence of amyloid-β plaques and hyperphosphorylated tau, a growing body of research suggests that these markers may be symptoms rather than the underlying cause (Perez Ortiz and Swerdlow 2019). Further, many conditions correlated with cognitive impairment share some form of disrupted metabolism and increased oxidative stress. The highly sensitive nature of the hippocampus to changes in blood flow, blood glucose, and inflammation make flagging vascular health a domino effect to neural atrophy and cognitive impairment. Therefore, developing a more comprehensive understanding of the commonalities between vascular conditions and their effects on neurophysiology is essential to developing effective translational therapies which understand the brain as a complex heterogeneous system rather than a series of isolated systems with independent problems.

4.2 Future directions

While these contributions to our understanding of the interactions between vascular disease and hippocampal function are notable, this is merely the first step to providing translatable results for therapeutic interventions. These exploratory studies have revealed electrophysiological measures

that are robust to animal model and disease state. Importantly, these studies have also revealed that these features have surprising and unintuitive interactions, providing both valuable insight and a promising testbed for further research into the complicated dynamics between vascular disorders and cognitive impairments. An obvious next step would be to observe these electrophysiological metrics such as SWRs and cross regional theta-gamma coupling on recordings during cognitive behavioral tasks such as a maze or novel object recognition. To further our understanding of the relationship between vascular disease and hippocampal function, it would be beneficial to study the effects of cognitive behavioral tasks and pharmacological interventions on electrophysiological measures such as SWRs and cross regional theta-gamma coupling.

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