

For me; because I'm awesome.

## **ACKNOWLEDGEMENTS**

As I sit, starting to write this dissertation in the gorgeous Bibliothèque Sainte Geneviève in Paris, I reflect on the past 4 years of my graduate career, and I can honestly say I look back on them fondly. I mean, come on, I'm writing my thesis in Paris!!! I must have done something right. Ergo, there will be no self-reflection here; however, don't think for a second that this acknowledgments section is going to be succinct. My ego will allow (this once) for acknowledgments of those that have helped me in my adventure.

I, of course, have to thank my research advisor, Sara Aton. Thanks for liking West Ham football and not batting an eye when a student with no lab background in neuroscience came up to you at the retreat in 2012 and asked if you were taking grad students. Thank you for allowing me to do my thing and be me – very few questions asked - for the past 4.5 years. It's hard to explain our mentor-student dynamic to people who haven't witnessed it, but it was/is a thing of beauty. I can go on forever, but I'll just say: Thank you. You know I appreciate all that you've done for me.

I need to next thank my family. As early as I can remember, education was of utmost importance. I don't think I so much chose to get a PhD, as it was something that was decided for me because of how much I came to love school. I know I was probably difficult and ridiculous much of my life; however, I can say that all I am now is

thanks to you. You rarely told me no – which provided me with a pretty solid work ethic. That and my dad's constant reminder of "Who's like you?" which I genuinely believe made me the person I am today. Who IS like me? I know how proud you are of me, and you know how much I appreciate EVERYTHING you've done for me over the years. The support both mentally and monetarily (grad school doesn't pay well enough for me to live as I do) have meant more than I can ever put into words. Thanks everyone for coming out to A<sup>2</sup> to eat out with me when I couldn't be bothered to travel the hour home. Especially thanks to Mom for always baking cookies. I didn't appreciate cookies enough as a kid, but as an adult- they are the best reminder of enjoying simple things. So, to everyone: Dad and Mom, Robert, and Gabby (and Gizmo can go here too!): Thank you so much.

To my extended family: I thank all of you all as well. Specifically: Ninka and Aja, Stephanie, Lorka, and Gregory thanks for the margaritas and wine at island parties. Thanks for indulging my crazy and letting me talk about all my hair-brained ideas on life and the world. Thanks to all my Babas and Dedos, who still probably think this degree is in neurosurgery and that I can help them with their medication. I would like to specifically acknowledge my Dedo Sofro, who was a professor in Yugoslavia, who always called me "dedo's prv student". I hope that getting this degree, the ultimate in academic achievement, makes him proud. I'd like to also acknowledge my Baba Milica, who, although didn't get to see the completion of this dissertation, attended my master's commencement and loved what a huge nerd I was. She also kept, for all these years, the walking stick that I used to climb a mountain when I was 9. So that was pretty dope of her. Specifically, because it's a kind of metaphor for my graduate career, as it

seemed like a daunting undertaking and people didn't think I could do it (the same way everyone told a 9 year old she couldn't climb a mountain). But hey I did (and 9-year old me did too). Ha.

I would definitely not have made it out of graduate school with all my mental capacities intact if it wasn't for my girlfriends. The Chain: I love you girls so much. Lauren, I'm glad you came back to Michigan to go to med school because that was a huge part of my being okay with staying at Michigan another 4 years. Thanks Nellie, Stacy, and Kim for letting me rant about everything besides science that happened to me the past 4 years. Meeting you all in college was the best thing to happen to me. Annalise and Vanessa: My travel companions, dinner daters, second families- I love you guys, and I think it's only fitting that I thank you together in this. Kristefer- my soul mate, co-selo-kid- thanks for being my therapist.

In grad school you spend a lot of time in lab. I owe thanks to my lab mates for listening to my ludicrous stories and telling me I'm smart and pretty even when I'm being insufferable. Specifically, I'd like to thank Sha, my lab mom, who keeps the lab running. We (I) would be so lost without you. Your kindness and supportive words everyday are so warming to my heart. Also, you are the single greatest cook I've ever encountered. All the lunches you made me while I was locked in the basement doing laser experiments were so appreciated. Jackie (my back-to-back) you are a radiant sunflower, and I am so grateful that I moved all your stuff to the desk behind me. I wouldn't have wanted to spend these past 3 years absentmindedly massaging anyone else's hair. I truly appreciate the serenity I got from talking with you and need you to know that you're gorgeous inside and out. Brittany- thanks for making sure I made it out

of Prague alive. You are such a ball of energy. Stress less though, remember how much fun Bougie and Bruggie had in Europe- except Zizkov, forget that place. James, I guess you're cool. Additionally, I had the pleasure of having the two most ABSOULELY WONDERFUL undergrads during my time in the lab, Nora Lashner and Sammy Schaeffer- you girls were so awesome! I couldn't have completed  $\frac{1}{2}$  (literally) of my thesis without you two.

I also have to thank all of my collaborators at the University of Michigan over the years. To Dr. Michal Zochowski and his students, Dan, Sima, Quinton, and Jiaxing, I have learned more and become more excited about math than I ever thought I would in grad school. Your expertise and guidance helped make my thesis as beautiful as it is. Additionally, I would like to thank Christopher Broussard, Igor Belopolsky, and Abbey Roelofs at the University of Michigan for their technical assistance and helping me with all the MatLab scripts (Stractor, Spectral, NapMapper) I needed for data analysis.

To all the friends, domestic and foreign, I've made in grad school and the fun times we had: BROadtrips, PBRs, nights at 8-Ball, Fleetwood, grad lounge parties, and numerous other shenanigans. You know who you all are. We had some fun 😊

Sleep peeps... ugh... I don't even know how to put into words how many different ways I feel about you. Allison, Jimmy, Zoltan, and Allen- Never leave me.

At this point people usually thank lovers/significant others. I don't have those, so I'll thank the 2 things I've loved most during my time in Ann Arbor: Ashley's and my cat, Shakira. One offers me tons of love and attention, the other sits in front of the TV when I'm trying to watch soccer.

I also have to thank the hospitality of the people of France, Germany, Switzerland, Italy, Slovenia, Croatia, Montenegro, Serbia, Macedonia, Morocco, Spain, the Dominican Republic, England, the Czech Republic, the Netherlands, and Belgium for providing me with mental respite and beauty. My semiannual escapes from my work were so vital to my ultimate success.

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## LIST OF ABBREVIATIONS

<b>CFM</b>	Contextual Fear Memory
<b>CFC</b>	Contextual Fear Conditioning
<b>CA1</b>	Cornu Ammonis area 1
<b>REM</b>	Rapid Eye Movement Sleep
<b>NREM</b>	Non Rapid Eye Movement Sleep
<b>SWS</b>	Slow Wave Sleep
<b>SPWR</b>	Sharp-wave Ripple Complexes
<b>PV</b>	Parvalbumin
<b>FS</b>	Fast-Spiking
<b>EMG</b>	Electromyographic
<b>LFP</b>	Local Field Potential
<b>EPSP</b>	Excitatory Post-synaptic Potential
<b>PC</b>	Principal Cells
<b>GABA</b>	Gamma-Aminobutyric Acid
<b>CA3</b>	Cornu Ammonis area 3
<b>FCA</b>	Functional Clustering Algorithm
<b>LTP</b>	Long Term Potentiation
<b>mTOR</b>	Mammalian Target of Rapamycin
<b>EEG</b>	Electroencephalogram
<b>GC</b>	Granger Causality
<b>TE</b>	Transfer Entropy
<b>AMD</b>	Average Minimum Distance
<b>MPC</b>	Mean Phase Coherence

<b>ISI</b>	Inter Spike Interval
<b>FuNS</b>	Functional Network Stability
<b>AAV</b>	Adeno-associated Virus
<b>CNO</b>	Clozapine-N-oxide
<b>DMSO</b>	Dimethyl-sulfoxide
<b>PSD</b>	Power Spectral Density
<b>DB</b>	Davies-Bouldin validity index
<b>GFP</b>	Green Fluorescence Protein
<b>ChR2</b>	Channelrhodopsin
<b>FSM</b>	Functional Similarity Matrix
<b>SD</b>	Sleep deprivation



# ABSTRACT

## Hippocampal Network Mechanisms Underlying Sleep-Dependent Memory Consolidation

by

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Sleep is thought to play a critical role in promoting various forms of learning and memory, and is also thought to regulate plasticity in brain circuits *in vivo*. In many human neuropathologies (e.g. Alzheimer's disease, schizophrenia, and epilepsy) there exist both cognitive deficits as well as disrupted sleep patterns, suggesting that sleep is critically linked to cognitive function. However, the mechanisms underlying this relationship are poorly understood.

The focus of this dissertation is to explore how sleep-associated effects on neural network activity affect the consolidation of contextual fear memory (CFM) in mice. In a contextual fear conditioning (CFC) paradigm, a single training trial pairs exposure to a novel environment with a foot shock. Proper consolidation of CFM (a sleep-dependent process) leads to long-lasting fear memory exemplified as stereotyped freezing behavior when a mouse is put back into the same context 24 hours later. Using a combination of behavioral analysis, electrophysiological recordings, new computational methods, and pharmacogenetic and optogenetic tools, I have investigated the role of sleep-associated CA1 network dynamics in promoting CFM.

To characterize how activity patterns in CA1 during rapid eye movement (REM) sleep and non-REM (NREM) sleep might promote memory, I first recorded ongoing neuronal and network activity in CA1 during CFM consolidation. I found that during this time, there are multiple changes occurring in the network: increases in neuronal firing rate, increases in delta (0.5-4 Hz), theta (4-12 Hz), and sharp-wave ripple (SPWR, 150-250 Hz) oscillations, and increasingly stable functional communication patterns between neurons during NREM sleep. Because I also observed that fast-spiking (FS) interneurons show greater firing coherence with CA1 network oscillations during CFM consolidation, I next aimed to test whether these specific cells play a critical role in controlling sleep-specific oscillations and memory formation. Using pharmacogenetics to transiently inhibit parvalbumin-expressing (PV+) FS-interneurons after learning, I found that these neurons are critical for the changes in CA1 associated with CFM

consolidation. Mice treated in this way show an absence of CFM. This effect is associated with loss of three network changes associated with normal consolidation: 1) augmented sleep-associated delta, theta, and SPWR oscillations, 2) long-lasting stabilization of CA1 neurons' functional connectivity patterns and, 3) consistent NREM specific reactivation of ensembles of neurons in CA1.

To further clarify the state-specific role of PV+ interneurons in CFM consolidation, I employed targeted optogenetic manipulations in CA1 following learning. I found that theta-frequency optogenetic stimulation of PV+ interneurons drives frequency-specific, rhythmic activity in the CA1 LFP associated with enhanced neuronal spike-field coherence. Optogenetically induced coherent firing stabilized functional communication between CA1 neurons. Critically, rhythmic stimulation of CA1 PV+ interneurons is sufficient to rescue CFM from deficits caused by sleep deprivation. To test whether PV+ interneuron-mediated oscillations during sleep are specifically required for CFM, I optogenetically silenced these cells in a state-specific manner. I found that PV+ interneuron activity during NREM sleep, but not wake or REM sleep, is critical for CFM consolidation. This suggests that PV+ interneurons amplify NREM sleep-associated CA1 network oscillations to regulate spike timing in a manner that could promote systems-level memory consolidation.

Together, this work sheds light on how sleep contributes to long-term memory formation, which has been a long-standing mystery in neuroscience. An understanding of these mechanisms may lead to targeted interventions for the multitude of neuropathologies where sleep quality and cognitive function are impaired.