For me; because I’m awesome.

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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.

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LIST OF ABBREVIATIONS

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

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

ABSTRACT

Hippocampal Network Mechanisms Underlying Sleep-Dependent Memory Consolidation

by

Nicolette Nevena Ognjanovski

Chair: Sara J. Aton

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. Optogentically 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.