

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

		3. DATE RECEIVED BY STATE	State Application Identifier
1. TYPE OF SUBMISSION*		4.a. Federal Identifier MH107668	
<input type="radio"/> Pre-application <input checked="" type="radio"/> Application <input type="radio"/> Changed/Corrected Application		b. Agency Routing Number	
2. DATE SUBMITTED	Application Identifier	c. Previous Grants.gov Tracking Number	
5. APPLICANT INFORMATION			Organizational DUNS*: 046705849
Legal Name*: The Regents of the University of California Department: Office of Research Division: Street1*: 5171 California Avenue, Suite 150 Street2: City*: Irvine County: State*: CA: California Province: Country*: USA: UNITED STATES ZIP / Postal Code*: 92697-7600			
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6. EMPLOYER IDENTIFICATION NUMBER (EIN) or (TIN)*		195-2226406-A1	
7. TYPE OF APPLICANT*		H: Public/State Controlled Institution of Higher Education	
Other (Specify): <input type="checkbox"/> Small Business Organization Type <input type="radio"/> Women Owned <input type="radio"/> Socially and Economically Disadvantaged			
8. TYPE OF APPLICATION*		If Revision, mark appropriate box(es). <input type="radio"/> New <input checked="" type="radio"/> Resubmission <input type="radio"/> A. Increase Award <input type="radio"/> B. Decrease Award <input type="radio"/> C. Increase Duration <input type="radio"/> Renewal <input type="radio"/> Continuation <input type="radio"/> Revision <input type="radio"/> D. Decrease Duration <input type="radio"/> E. Other (specify):	
Is this application being submitted to other agencies?*		<input type="radio"/> Yes <input checked="" type="radio"/> No	What other Agencies?
9. NAME OF FEDERAL AGENCY* National Institutes of Health		10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER TITLE:	
11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT* Hippocampal contribution to cortical neurodynamics: a test of the memory index theory			
12. PROPOSED PROJECT Start Date* 09/01/2015		13. CONGRESSIONAL DISTRICTS OF APPLICANT Ending Date* 08/31/2019 CA-045	

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE**Page 2****14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION**

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15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	\$583,566.00
b. Total Non-Federal Funds*	\$0.00
c. Total Federal & Non-Federal Funds*	\$583,566.00
d. Estimated Program Income*	\$0.00

16. IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

- a. YES THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
 DATE:
- b. NO PROGRAM IS NOT COVERED BY E.O. 12372; OR
 PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

I agree*

* The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION

File Name:

19. AUTHORIZED REPRESENTATIVE

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Signature of Authorized Representative*

Wanda Kao

Date Signed*

03/12/2015

20. PRE-APPLICATION File Name:**21. COVER LETTER ATTACHMENT** File Name:1235-CoverLetter_Kim_Resub.pdf

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Project/Performance Site Location(s)

Project/Performance Site Primary Location

I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: The Regents of the University of California
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Project/Performance Site Congressional District*: CA-045

Project/Performance Site Location 1

I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

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Project/Performance Site Congressional District*: CA-049

File Name

Additional Location(s)

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* Yes No

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? Yes No

If YES, check appropriate exemption number: — 1 — 2 — 3 — 4 — 5 — 6

If NO, is the IRB review Pending? Yes No

IRB Approval Date:

Human Subject Assurance Number

2. Are Vertebrate Animals Used?* Yes No

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? Yes No

IACUC Approval Date: 05-02-2014

Animal Welfare Assurance Number A3416-01

3. Is proprietary/privileged information included in the application?* Yes No**4.a. Does this project have an actual or potential impact - positive or negative - on the environment?*** Yes No

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed?

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* Yes No

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* Yes No

6.a. If yes, identify countries: Canada

6.b. Optional Explanation:

Filename

7. Project Summary/Abstract*

1236-

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8. Project Narrative*

1237-

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9. Bibliography & References Cited 1238-Bibliography_Kim_Resub.pdf**10. Facilities & Other Resources**

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11. Equipment

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12. Other Attachments

1241-

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Summary

Memory is a fundamental cognitive process in which information from our experiences is encoded, consolidated, and later retrieved. The hippocampal formation (HF) has long been considered an essential brain structure supporting this function. One prominent view (*The Memory Index Theory*) holds that the HF generates an 'index' for each memory from experience, which is distributed among the many neocortical modules that store sub-attributes of each memory. Specifically, the HF helps 'consolidate' recent memories during sleep during which the memories become a HF-independent form of general knowledge. How exactly the HF index modulates neocortical neurodynamics during consolidation needs to be experimentally confirmed. The goal of the proposed study is to directly test the memory index theory and elucidate hippocampal-neocortical interaction underpinning memory consolidation. We propose to 1) evaluate the influence of HF output on cortical neurodynamics during memory consolidation process and 2) attempt restoration of memory by artificially applying hippocampal index code (weak, high-resolution, patterned stimulation) to the neocortex. To this end, we will use rodent models of hippocampal dysfunction, optical imaging and stimulation, electrical recording and stimulation, and behavioral approaches. The proposed study explores important research questions pertinent to mental health and disorders. Fulfilling the specific aims will provide important steps toward understanding the neuroscience of memory and toward developing potential clinical interventions for restoring memory function.

PUBLIC HEALTH RELEVANCE

The proposed work aims to investigate the fundamental neural mechanisms underlying how memory is acquired, and how it is consolidated into knowledge that could be later utilized for adaptive behavior, intelligence, and thought. Better knowledge about the mechanism will provide a foundation for development of effective clinical interventions where memory is impaired by neurodegeneration or brain injury.

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FACILITIES & OTHER RESOURCES

Laboratory at UCI:

Parts of the proposed studies will be carried out in Dr. Bruce McNaughton's laboratory at UCI. The laboratory is located in the Qureshey Research Laboratory in the Center for the Neurobiology of Learning & Memory, UCI (1st floor). The lab includes approximately 1900 sqft. of research, analysis, and workshop space. This laboratory space provides facilities for the high density electrophysiology work, including a high density electrophysiology recording suite (behavioral testing room and adjacent control room; Room 120C and 120B, respectively). In addition, a hyperdrive building station equipped with a stereoscope, manipulators for holding hyperdrives and tetrodes, and stimulating electrode electroplating and impedance testing station, and soldering stations are available (Room 111). There will be full time technicians available for assistance with building hyperdrives, printing circuit board design, surgery, and programming for data analysis. The laboratory is also equipped with a setup for optical imaging (Voltage-sensitive dye imaging) and high spatiotemporal resolution laser stimulation.

Office at UCI:

Dr. Kim has a desk space adjacent to the laboratory (Room 105). A common space including copying and fax facilities is also available nearby.

Vivarium at UCI:

Dr. Kim has access to a vivarium in the UCI animal facility. All facilities are fully accredited, are fully staffed by animal care technicians, and are under the supervision of a full time veterinarian. There is a surgical facility and a procedure room dedicated to the McNaughton laboratory for behavioral procedures and post-operative care.

Laboratory at INC (UCSD):

The Integrated Systems Neuroengineering Laboratory under direction of Prof. Gert Cauwenberghs in the Department of Bioengineering and the INC at UCSD and has ample facilities and instrumentation for design, validation, characterization, and functional testing of custom integrated circuits and systems in deep-submicron CMOS silicon technology. These include workstations running Cadence and Mentor Graphics computer aided-design tools, analog and mixed-signal test stations, function generators, oscilloscopes, and various other instruments and tools for circuit prototyping and characterization. The INC has received sufficient funding that is currently supporting the establishment of an animal laboratory. The neural recording and stimulating devices (e.g., ENIAC) tested in this laboratory will be used in the proposed study. Construction and equipment installation will be complete by the end of Year 2 of this award. Once complete, some of the operations under the proposed project will shift to this laboratory.

Other Resources:

Dr. Kim will have access to a computing cluster and multiple data storage servers for computationally demanding analyses.

The University of California systems (Irvine and San Diego) recognize the value of early stage investigators (postdoctoral associates, junior faculty) and provide a highly supportive environment for research and training. Counselors as well as career development specialists are available in the Career Center of UCI and in the Postdoctoral Office of UCSD. Through these offices numerous workshops and formal training opportunities are offered each month on a variety of topics, including research ethics, grant writing, leadership, and job search strategies.

Equipment

Surgical system at UCI

In Dr. Bruce McNaughton's laboratory, a rodent surgery system will be available for this project, including microscopes, stereotaxic frames (for both mice and rats), heating pads, and lamps.

Neural ensemble recording system at UCI

In McNaughton laboratory, a neural ensemble recording system is available for recording in freely behaving animals. This system includes a ceiling mounted automatically rotating commutator (Neuralynx, 128 channel) and Digital recording system (Neuralynx) setup for simultaneous recording from 128 channels. Each channel can simultaneously record local field potentials in addition to spike waveforms. Hardware is available to expand to 256 channels. A separate computer is in place for controlling and delivering precisely timed rewards and stimuli, including reinforcement (FPGA, National Instruments). The control systems can be programmed to either respond to keyboard input from the experimenter or to be triggered by specific behavioral or electrophysiological events recorded by the acquisition hardware, providing experimental flexibility.

Custom designed rodent virtual reality (VR) system at UCI

VR systems for rodent behavioral testing are also available (Figure E1).

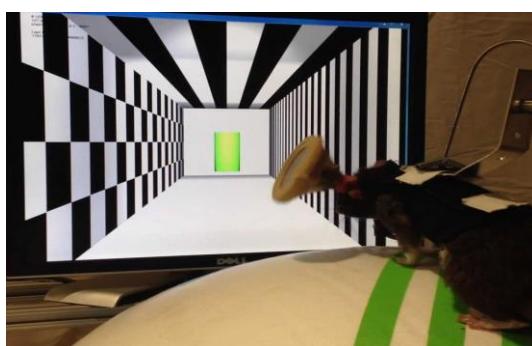
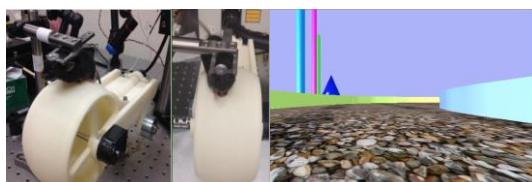


Figure E1. Top. A mouse VR system set up in McNaughton laboratory, in which the head-fixed mouse runs on a wheel with a curved surface (Left and middle) which allows rotation in 2 axes. The forward rotation (pitch axis) is translated into linear movement in the VR, whereas the lateral rotation (roll axis) is translated into rotation in the XY plane (yaw), permitting, for example the mouse to run around a virtual circular track (right) which is displayed on two video monitors placed at 90° to each other in front of the mouse and extending well into its lateral field of view. The wheel is rapidly interchangeable with the mouse in place, to insert wheels with different textures or local features in order to manipulate tactile input. Bottom. A rat VR system set up in McNaughton laboratory, in which the rat runs on a trackball that allows rotation in 2 axes. As in the mouse VR system, the forward rotation (pitch axis) is translated into linear movement in the VR, whereas the lateral rotation (roll axis) is translated into rotation in the XY plane (yaw).

Parallel computing cluster at UCI

McNaughton lab has access to a computing cluster (Hodgkin) with 64 blade servers containing 48 GB of RAM and two 6-core Intel Xeon processors. Hodgkin has 768 available computing cores and 3 TB (3072GB) of RAM. Each of the blade servers is running 64-bit Red Hat Enterprise Linux. The scheduler used on Hodgkin is Platform LSF, which is officially supported by MATLAB.

Data storage cluster at UCI

For the proposed work, vast quantities of data will be collected (~1TB/animal), requiring high data storage. The laboratory has access to a storage cluster, Huxley, equipped with 50TB of hard drive space with an extra 10TB volume for general use and 5TB of scratch space for temporary files. There is also a second dedicated data storage system with an additional 30TB of storage space. The contents of both systems are backed up every night to an off-site location. The off-site location has 80TB of storage for incremental backups. Data is backed up here for 6 months. Snapshots are kept for the most recent seven days, three weeks, and six months.

Optical imaging and stimulation system at UCI

An epi-fluorescent microscope for wide-field imaging is established in McNaughton laboratory. We can use dual CCD cameras to image both neuronal calcium (spiking) and voltage changes (membrane potential). The system also has fast scanning optogenetic lasers (473nm) that can be easily directed to many cortical regions with micro second precision for patterned sequence stimulation. The unique illumination design

allows concurrent insertion of microelectrodes or injecting compounds into the brain. The macro lenses possess exceptionally high numerical apertures which are designed specifically for observing small changes (~1% change) in fluorescence that form the basis of functional imaging techniques involving voltage sensitive dyes.

Equipment at INC

Data acquisition system for acquiring electrophysiological data from ENIAC recording is available. For stimulation, a multi-channel pattern stimulator has been constructed. The laboratory at INC (currently being established) will be equipped with a surgical setup as well as a virtual reality setup (duplicated from UCI). In the event there may be any delay in establishing the facility at INC, the proposed work will continue at UCI.

List of Referees

Dr. Larry R. Squire

Distinguished Professor

Departments of Psychiatry, Neurosciences, and Psychology

University of California, San Diego

Dr. Jeansok J. Kim

Professor

Department of Psychology

University of Washington

Dr. Robert E. Clark

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Department of Psychiatry

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RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator				
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PROFILE - Senior/Key Person				
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Attach Current & Pending Support:	1257-OtherSupport_McNaughton_Resub.pdf			

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Phone Number*: 858-534-6938	Fax Number:	E-Mail*: gert@ucsd.edu		
Credential, e.g., agency login: gcauwenberghs				
Project Role*: Other (Specify)	Other Project Role Category: Co-Mentor			
Degree Type: Ph.D.	Degree Year: 1994			
Attach Biographical Sketch*:	File Name 1258-Biosketch_Cauwenberghs_Resub.pdf			
Attach Current & Pending Support:	1259-OtherSupport_Cauwenberghs_Resub.pdf			

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.

Follow this format for each person. DO NOT EXCEED FOUR PAGES.

NAME Kim, Soyun	POSITION TITLE Assistant Project Scientist University of California, Irvine
eRA COMMONS USER NAME (agency login) SOYUNKIM	

EDUCATION/TRAINING

(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)

INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YYYY	FIELD OF STUDY
University of British Columbia	BS	05/2004	Biochemistry and Molecular Biology
University of Southern California, CA	PHD	05/2010	Neuroscience

A. PERSONAL STATEMENT

My scholarship has been grounded in memory research in both animals and humans. As a graduate student I investigated the neuronal circuitry and molecular bases supporting classical eyeblink conditioning in the laboratory of Richard Thompson. During the doctoral program, I developed expertise in behavioral experiment design, animal testing, surgical technique, and, neurohistochemistry. Upon completion of my Ph.D., I began postdoctoral training in the laboratory of Larry Squire. My most recent work, and the focus of my postdoctoral research, centered on the role of the human hippocampus and medial temporal lobe in memory, perception, and spatial cognition. Here I have worked with a group of memory-impaired patients with brain damage to the medial temporal lobe. I expanded my expertise in human neuropsychology, human behavioral testing, structural MRI, brain volume analysis, scientific presentation, and manuscript preparation. Combined training in animal and human memory research has prepared me well to utilize different approaches for the study of memory and memory disorders. My research projects have yielded 5 first-author publications in first-rate journals (6 authored publications total).

Building upon my previous training, my goal is to receive additional mentored training (in laboratories of Dr. Bruce McNaughton at UC Irvine and Dr. Gert Cauwenberghs at UC San Diego) from which I can acquire new sets of laboratory skills and advance my career to an independent research program. Specifically, I would like to acquire new expertise in neurophysiology combined with behavioral approach for investigating neural mechanisms (the hippocampal and neocortical interaction) supporting memory consolidation. I would like to receive training in innovative technology (e.g., optogenetics, optical imaging, electrical stimulation, cortical arrays) for study of rodent neuroscience that could be potentially linked to human neuroscience in the long end. Combining my previous experience on rodent and human behavioral research with new training on electrophysiology and neuromodulation will help me build groundwork for my future research program in translational neuroscience.

It should be noted that my Ph.D. mentor, Dr. Richard Thompson, has recently passed away (September 16, 2014). Dr. Bruce McNaughton has his reference letter on me and will happily forward the letter upon request.

B. POSITIONS AND HONORS

Positions and Employment

2015- current Assistant Project Scientist, University of California, Irvine

2010 – 2014 Postdoctoral Scholar, University of California, San Diego
2005 - 2010 Teaching Assistant, University of Southern California
2005 - 2010 Research Assistant, University of Southern California

Other Experience and Professional Memberships

2011 - Member, Cognitive Neuroscience Society
2007 - Member, American Korean Neuroscientists Association
2006 - Member, Society for Neuroscience
2004 - 2005 Research Associate, Seegene, Inc. South Korea

Honors

2009 Women in Science and Engineering Travel Grant, University of Southern California
2008 Women in Science and Engineering Travel Grant, University of Southern California
2004 University Scholarship Program, University of British Columbia
2003 Vancouver Korean Scholarship, Vancouver Korean Scholarship Foundation
2002 University Scholarship Program, University of British Columbia
2001 University Scholarship Program, University of British Columbia
2000 University Scholarship Program, University of British Columbia

C. SELECTED PEER-REVIEWED PUBLICATIONS

- Kim S, Borst G, Thompson WL, Hopkins RO, Kosslyn SM, Squire LR. Sparing of spatial mental imagery in patients with hippocampal lesions. *Learning & memory* (Cold Spring Harbor, N.Y.). 2013; 20(11):657-63. PubMed PMID: 24136183; PubMed Central PMCID: PMC3799416.
- Kim S, Sapiurka M, Clark RE, Squire LR. Contrasting effects on path integration after hippocampal damage in humans and rats. *Proceedings of the National Academy of Sciences of the United States of America*. 2013; 110(12):4732-7. PubMed PMID: 23404706; PubMed Central PMCID: PMC3606992.
- Kim S, Wang M, Lee AS, Thompson RF. Impaired eyeblink conditioning in 78 kDa-glucose regulated protein (GRP78)/immunoglobulin binding protein (BiP) conditional knockout mice. *Behavioral neuroscience*. 2011; 125(3):404-11. PubMed PMID: 21517144.
- Kim S, Jeneson A, van der Horst AS, Frascino JC, Hopkins RO, Squire LR. Memory, visual discrimination performance, and the human hippocampus. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2011; 31(7):2624-9. PubMed PMID: 21325530; PubMed Central PMCID: PMC3072247.
- Kim S, Thompson RF. c-Fos, Arc, and stargazin expression in rat eyeblink conditioning. *Behavioral neuroscience*. 2011; 125(1):117-23. PubMed PMID: 21319893.
- Pakaprot N, Kim S, Thompson RF. The role of the cerebellar interpositus nucleus in short and long term memory for trace eyeblink conditioning. *Behavioral neuroscience*. 2009; 123(1):54-61. PubMed PMID: 19170430; PubMed Central PMCID: PMC2751661.

D. RESEARCH SUPPORT

Ongoing Research Support

N/A

BIOGRAPHICAL SKETCH

NAME Bruce L. McNaughton eRA COMMONS USER NAME: McNaughton	POSITION TITLE Distinguished Professor, Department of Neurobiology and Behavior, University of California, Irvine
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EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Carleton University, Ottawa, Canada	B.Sc.	09/1972	Biology
Carleton University, Ottawa, Canada	M.Sc.	09/1975	Biology
Dalhousie University, Halifax, Canada	Ph.D.	09/1978	Psychology

A. Personal Statement:

My research involves is the physiological and computational basis of cognition, with particular focus on memory and memory disorders, and the dynamic interactions among neuronal populations and synaptic plasticity mechanisms that underlie these phenomena. I have made significant contributions to understanding central synaptic plasticity mechanisms, spatial information processing in hippocampus and cortex, cortico-hippocampal interactions and memory consolidation, and brain aging. My current interest is the role of hippocampal outflow to neocortex in memory replay and memory consolidation and the extraction of knowledge from episodic memory. Throughout my career I have been involved in the development and application of new conceptual approaches and innovative technologies to my research questions. The following list highlights some of these research achievements :

- (1978) The first demonstration of Hebbian associative synaptic plasticity (long-term potentiation).
- (1981) The first successful application of quantal analysis methods to cortical neurons. I introduced the method of minimal stimulation to identify unitary synaptic responses in brain slices.
- (1983) I introduced the concept of separating the extracellular spike signals on the basis of a 'triangulation' operation, in which signals from the same cluster of cells were recorded from two or more points in space. I outlined the principle of 'tetrode' recording, which is arguably the most important advance in single unit recording technology since the invention of the microelectrode.
- (1983) Introduced the use of automated video tracking to quantify the relationship between hippocampal neural activity and spatial location, and demonstrated the first evidence that place cells are also modulated by external sensory input.
- (1989) Laid the foundation for our modern understanding of the role of self-motion information (path-integration) in updating neural representations of space in the brain.
- (1989) We provided the first evidence that the hippocampus might be able to reconstruct complete activity patterns from partially degraded input, a sine qua non of an associative memory network.
- (1991) Introduced the concept that hippocampal neurons might use an attractor-like neural network architecture to integrate angular and linear displacements to keep track of heading and location.
- (1993) First recordings from large ensembles of neurons (100 or more) in behaving animals and decoding of neural ensemble activity in real-time.
- (1994) First study to show that patterns of neural interaction expressed during learning are recreated in the brain during sleep, thus opening a new era in the study of the physiological basis of memory consolidation.
- (1995) Laid out a computational framework for understanding memory consolidation. One of the 15 most highly cited papers in psychology in the decade since its publication.
- (1997) Proposed a large scale neural net model for path integration based cognitive mapping which forms the basis of current understanding of the process.
- (1997) First demonstration of the formation of Hebb's phase sequences during sequential spatial behavior.
- (1998) First application of Bayesian statistics to the decoding of neural ensemble activity.

Program Director/Principal Investigator (Last, First, Middle):

- (1998) Outlined conceptual framework for identification of memory related activity in neural recordings.
- (1999) First demonstration that immediate early gene activation dynamics can be used to identify the precise neural ensembles that were activated in two different specific epochs of behavior, thus opening the way for large scale decoding cortical activity patterns at the level of individual neurons.
- (2000) First successful neural ensemble recordings from conscious mammals in space flight, during the Neurolab mission of the space shuttle Columbia.
- (2002) I developed a high density neural ensemble recording array for use in awake non-human primates, capable of recording simultaneously from 576 independently adjustable microelectrodes. We confirmed a central prediction of the trace reactivation theory of memory consolidation.
- (2004) Development of an automated image analysis for using IEG activation to decode cortical activity.
- (2005) Demonstration that the superficial neocortical laminae, which receive hippocampal output, exhibit strong sensitivity to spatial context, whereas the deeper layers of neocortex are strictly domain specific (i.e., context insensitive). This forms a basis for the development of a memory prosthesis device.
- (2005) We showed that the scale at which space is represented in the activity of 'place' cells in the brain is determined by an afferent signal about how fast the animal is moving in space. Systematic variation in the strength of this signal leads to a corresponding variation in spatial scaling.
- (2007) Demonstration of 'fast forward' playback of recent memory patterns in medial prefrontal cortex.
- (2008) Demonstration that the mnemonic code for a simple memory is reprocessed and altered over a 'consolidation' period of several weeks without reinstatement of the memory or context.
- (2010) A classical theory for the function of the hippocampus is that it is a general purpose autoassociative memory. We showed that this theory is incorrect and that only codes for spatial location exhibit the signature of autoassociative recall.
- (2012) Published a major theoretical review paper concerning the role of the rodent prefrontal system.
- (2013) We showed that memory traces can be formed by repetitive sensory stimulation under anesthesia if the cortex is induced to a desynchronized state by pharmacological manipulation.
- (2014) We established a method and statistical framework for reliable detection of weak excitatory-excitatory interactions among cortical neurons using spike-train correlation analysis, thus providing a critical missing technology for developing functional connection maps at synaptic scales.

B. Positions and Honors

Positions

- 1980 NATO Postdoctoral Fellow, Institute of Neurophysiology, Oslo, Norway
- 1981 Medical Research Council Postdoctoral Associate, University College London, United Kingdom
- 1982 - 1987 Research Associate, Department of Psychology, University of Colorado, Boulder
- 1987 - 1990 Associate Professor (tenure), Department of Psychology, University of Colorado, Boulder
- 1990 - 2008 Professor, Departments of Psychology and Physiology, University of Arizona, Tucson
- 1990 – 2008 Research Scientist, ARL Division of Neural Systems, Memory and Aging, Univ. Arizona.
- 2004 – 2008 Director, Program in Neuroscience, University of Arizona, Tucson
- 2008-Present Professor, Dept. Neuroscience, The University of Lethbridge and director Polaris Brain Dynamics Research Group
- 2014-Present Distinguished Professor, Department of Neurobiology and Behavior, UC Irvine

Honors and Awards

- 2000 Jacob Javits Award, National Institutes of Neurological Disorders and Stroke, NIH
- 2000 MERIT Award, National Institute of Mental Health, NIH
- 2004 Elected Norwegian Royal Society of Sciences and Letters
- 2005 Visiting Professor, Swammerdam Institute for Life Sciences, Univ. of Amsterdam
- 2006 Bass Award for Excellence in Science, The Society of Neurological Surgeons
- 2008 AHFMR Polaris Award
- 2013 Linda and Jack Gill Foundation Distinguished Research Award

C. Selected Peer-reviewed Publications (from over 215)

Program Director/Principal Investigator (Last, First, Middle):

- McNaughton, BL, O'Keefe, J, & Barnes, CA (1983) The stereotrode: A new technique for simultaneous isolation of several single units in the central nervous system from multiple unit records. *Journal of Neuroscience Methods*, 8:391-395 PMID: 6621101
- Wilson, MA & McNaughton, BL (1994) Reactivation of hippocampal ensemble memories during sleep. *Science*, 265:676-679 PMID: 8036517
- McClelland, JL, McNaughton, BL & O'Reilly, RC (1995) Why there are complementary learning systems in the hippocampus & neocortex: insights from the successes & failures of connectionist models of learning & memory. *Psychological Review*, 102:419-457 PMID: 7624455
- Skaggs, WE & McNaughton, BL (1996) Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. *Science*, 271:1870-1873 PMID: 8596957
- Zhang, K, Ginzburg, I, McNaughton, BL & Sejnowski, TJ (1998) Interpreting neuronal population activity by reconstruction: Unified framework with application to hippocampal place cells. *Journal of Neurophysiology*, 79:1017-1044 PMID: 9463459
- Kudrimoti, HS, Barnes, CA & McNaughton, BL (1999) Reactivation of hippocampal cell assemblies: effects of behavioral state, experience & EEG dynamics. *Journal of Neuroscience*, 19:4090-4101
- Hoffman, KL & McNaughton, BL (2002) Coordinated reactivation of distributed memory traces in primate neocortex. *Science*, 297:2070-2073 PMID: 12242447
- Leutgeb, S, Leutgeb, JK, Barnes, CA, Moser, EI, McNaughton, BL & Moser, M-B (2005) Independent codes for spatial & episodic memory in hippocampal neuronal ensembles. *Science*, 309:619-623 PMID: 16040709
- Tatsuno, M, Lipa, P, & McNaughton, BL (2006) Methodological considerations on the use of template matching to study long-lasting memory trace replay. *The Journal of Neuroscience*, 26:10727-10742 PMID: 17050712
- Euston, DR, Tatsuno, M, & McNaughton, BL (2007) Fast-forward playback of recent memory sequences in prefrontal cortex during sleep. *Science*, 318:1147-1150 PMID: 18006749
- Takehara-Nishiuchi, K & McNaughton, BL (2008) Spontaneous changes in neocortical code for associative memory during consolidation. *Science*, 322:960-963 PMID: 18988855
- Johnson LA, Euston DR, Tatsuno M, & McNaughton, BL (2010) Stored-trace reactivation in rat prefrontal cortex is correlated with down-to-up state fluctuation density. *The Journal of Neuroscience*, 30:2650-2661 PMID: 20164349
- McNaughton, BL (2010) Cortical hierarchies, sleep, and the extraction of knowledge from memory. *Artificial Intelligence*, 174:205-214.
- Bermudez Contreras, E., Gomez Palacio Schjetnan, A., Muhammad, A., Bartho, P., McNaughton, B.L., Kolb, B., Gruber, A., Luczak, A.* (2013) Formation and reverberation of sequential neural activity patterns evoked by sensory stimulation is enhanced during cortical desynchronization. *Neuron*, 79(3):555-566. PMID: 23932001 PMID: 23932001
- Schwindel, CD, Ali, K, McNaughton, BL, Tatsuno, M (2014) Long-Term Recordings Improve the Detection of Weak Excitatory–Excitatory Connections in Rat Prefrontal Cortex. *J. Neurosci*, 34:5454-5467. PMID: 24741036

D. Research Support

Natural Sciences and Engineering Research Council of Canada. Role, PI. Grant period 2012-2015. The main question is whether both the spatial and the non-spatial ("rate remapped") components of hippocampal activation are expressed during post trial sleep, to determine how well subiculum outputs of hippocampus to neocortex orthogonalize spatial context, and to determine the coding sparsity of neocortical cells in layer II-III, which are the main recipients of the hippocampal formation output.

European Union FP7 program. Role, Co-PI. Grant period 2012-2015. The main goal is to develop a closed loop optogenetic stimulation and ensemble recording system which can detect cell assemblies in real time and provide patterned optogenetic stimulation to modify these assemblies.

Alberta Innovates-Health Solutions. Polaris Award Role, PI. Grant period. 2008-2018. This is mainly an infrastructure grant that has supported the salary and start-up expenses for 5 independent faculty working in the general field of brain dynamics and memory.

Pending R01: "The memory index theory: hippocampal impact on cortical neurodynamics and plasticity" University of California Irvine Start-up fund.

BIOGRAPHICAL SKETCH

NAME Gert Cauwenberghs	POSITION TITLE Professor		
eRA COMMONS USER NAME gcauwenberghs			
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
University of Brussels, Belgium California Institute of Technology California Institute of Technology	Eng. Degree M.S. Ph.D.	1988 1989 1994	Applied Physics Electrical Engineering Electrical Engineering

A. Personal Statement

One of the greatest challenges in neuroengineering, whether towards new therapies for neurological diseases or towards new means of human-computer interaction, is to advance our fundamental understanding of how the brain functions to the point where we may effectively interface the human brain with engineered systems.

My group has pioneered the design and implementation of highly energy efficient, massively parallel microchips that emulate function and structure of adaptive neural circuits in silicon. A main focus of our current work is on extending integrated sensing and actuation to dynamical interfaces to neural and brain activity. Recent developments include implantable and wireless microelectrode arrays for distributed recording of electrical and chemical neural activity, and biopotential sensor arrays and integrated signal processing for electroencephalogram and electrocorticogram functional brain imaging. These dynamical interfaces between living and artificial nervous systems offer tremendous opportunities for transformative, integrative neuroscience and neuroengineering that are the focus of continued research in our laboratory, in collaboration with partners in academia, industry, and the clinical sector.

B. Positions and Honors

Positions and Employment

- 1/94-6/98 Assistant Professor, Department of Electrical and Computer Engineering, The Johns Hopkins University, Baltimore MD 21218
- 7/98-6/02 Associate Professor, Department of Electrical and Computer Engineering, The Johns Hopkins University, Baltimore MD 21218
- 6/98-8/99 Visiting Professor, Center for Biological and Computational Learning, Department of Brain and Cognitive Science, Massachusetts Institute of Technology, Cambridge MA 02142, (sabbatical leave from Johns Hopkins University)
- 7/02-6/05 Professor, Department of Electrical and Computer Engineering, The Johns Hopkins University, Baltimore MD 21218
- 7/05-6/09 Professor, Neurobiology Section, Division of Biological Sciences, University of California San Diego, La Jolla CA 92093
- 7/09-present Professor, Department of Bioengineering, Jacobs School of Engineering, University of California San Diego, La Jolla CA 92093

Other Experience and Professional Memberships

9/08-present Co-Director, Institute for Neural Computation, University of California San Diego, La Jolla CA 92093

Editorial Boards

2011-present Editor-in-Chief, IEEE Transactions on Biomedical Circuits and Systems
2004-present Senior Editor, IEEE Sensors Journal
2011-present Senior Editor, IEEE Journal of Emerging Topics in Circuits and Systems
1999-2003 Associate Editor, IEEE Transactions on Circuits and Systems II: Analog and Digital Signal
2004-2008 Processing Associate Editor, IEEE Transactions on Circuits and Systems I: Regular Papers
2006-present Associate Editor, IEEE Transactions on Neural Systems and Rehabilitation

Honors

1988 Francqui Fellow, Belgian American Educational Foundation
1997 Career Award, National Science Foundation
1999 Young Investigator Award, Office of Naval Research
2000 Presidential Early Career Award for Scientists and Engineers (PECASE)
2003-04 Distinguished Lecturer, IEEE Circuits and Systems Society
2011 Fellow, IEEE

C. Selected Peer-reviewed Publications

1. R.J. Vogelstein, U. Mallik, J.T. Vogelstein and G. Cauwenberghs, "Dynamically Reconfigurable Silicon Array of Spiking Neurons With Conductance-Based Synapses," *IEEE Trans. Neural Networks*, vol. 18 (1), pp. 253-265, 2007.
2. M. Stanacevic, K. Murari, A. Rege, G. Cauwenberghs and N.V. Thakor, "VLSI Potentiostat Array With Oversampling Gain Modulation for Wide-Range Neurotransmitter Sensing," *IEEE Trans. Biomedical Circuits and Systems*, vol. 1 (1), pp. 63-72, 2007.
3. R. Karakiewicz, R. Genov, and G. Cauwenberghs. "480-GMACS/mW Resonant Adiabatic Mixed-Signal Processor Array for Charge-Based Pattern Recognition," *IEEE J. Solid-State Circuits*, vol. 42 (11), pp. 2573-2584, 2007.
4. M. Mollazadeh, K. Murari, G. Cauwenberghs, and N. Thakor. "Micropower CMOS Integrated Low-Noise Amplification, Filtering, and Digitization of Multimodal Neuropotentials," *IEEE Transactions on Biomedical Circuits and Systems*, vol. 3 (1), pp. 1-10, 2009.
5. M. Mollazadeh, K. Murari, G. Cauwenberghs, and N. Thakor. "Wireless Micropower Instrumentation for Multimodal Acquisition of Electrical and Chemical Neural Activity," *IEEE Trans. Biomedical Circuits and Systems*, vol. 3 (6), pp. 388-397, 2010.
6. T. Yu and G. Cauwenberghs. "Analog VLSI Biophysical Neurons and Synapses with Programmable Membrane Channel Kinetics," *IEEE Trans. Biomedical Circuits and Systems*, vol. 4 (3), pp. 139-148, 2010.
7. Y.M Chi, T.P. Jung, and G. Cauwenberghs. "Dry-Contact and Noncontact Biopotential Electrodes: Methodological Review," *IEEE Reviews in Biomedical Engineering*, vol. 3, pp. 106-119, 2010.
8. T. Yu, T.J. Sejnowski, and G. Cauwenberghs. "Biophysical Neural Spiking, Bursting, and Excitability Dynamics in Reconfigurable Analog VLSI," *IEEE Transactions on Biomedical Circuits and Systems*, vol. 5 (5), pp. 420-429, 2011.
9. J.D. Driscoll, A.Y. Shih, S. Iyengar, J.J. Field, G.A. White, J.A. Squier, G. Cauwenberghs, and D. Kleinfeld. "Photon Counting, Censor Corrections, and Lifetime Imaging for Improved

- Detection in Two-Photon Microscopy," *J. Neurophysiology*, vol. 105 (6), pp. 3106-3113, 2011.
10. G. Indiveri, B. Linares-Barranco, T.J. Hamilton, A. van Schaik, R. Etienne-Cummings, T. Delbruck, S.C. Liu, P. Dudek, P. Hafnerger, S. Renaud, J. Schemmel, G. Cauwenberghs, J. Arthur, K. Hynna, F. Folowosele, S. Saighi, T. Serrano-Gotarredona, J. Wijekoon, Y. Wang, K. Boahen. "Neuromorphic Silicon Neuron Circuits," *Front. Neuroscience*, vol. 5 (73), 2011.
11. Y.M. Chi, Y.-T. Wang, Y. Wang, C. Maier, T.-P. Jung, and G. Cauwenberghs, "Dry and Noncontact EEG Sensors for Mobile Brain-Computer Interfaces," *IEEE Trans. Neural Systems and Rehabilitation Engineering*, vol. 20 (2), pp. 228-235, 2012.
12. Y.M. Chi, P. Ng, and G. Cauwenberghs, "Wireless Noncontact ECG and EEG Biopotential Sensors," *ACM Trans. Embedd. Comput. Syst.*, vol. 12 (4), pp. 103:1-19, 2013.
13. E. Neftci, S. Das, B. Pedroni, K. Kreutz-Delgado, and G. Cauwenberghs, "Event-Driven Contrastive Divergence for Spiking Neuromorphic Systems," *Frontiers in Neuroscience*, doi: 10.3389/fnins.2013.00272, vol. 7, pp. 272:1-14, 2014.
14. S. Ha, C. Kim, Y.M. Chi, A. Akinin, C. Maier, A. Ueno, G. Cauwenberghs, "Integrated Circuits and Electrode Interfaces for Noninvasive Physiological Monitoring," *IEEE Trans. Biomedical Engineering*, vol. 61 (5), pp. 1522-1537, 2014.
15. F.D. Broccard, T. Mullen, Y.M. Chi, D. Peterson, J.R. Iversen, M. Arnold, K. Kreutz-Delgado, T.P. Jung, S. Makeig, H. Poizner, T. Sejnowski, and G. Cauwenberghs, "Closed-Loop Brain-Machine-Body Interfaces for Noninvasive Rehabilitation of Movement Disorders," *Annals of Biomedical Engineering*, vol. 42 (8), pp. 1573-1593, 2014.

D. Research Support

Ongoing Research Support

NSF ENG-1137279 (Cauwenberghs, PI) 9/11-9/15
EFRI-M3C: Distributed Brain Dynamics in Human Motor Control
Towards non-invasive remediation of Parkinson's through EEG-EMG force neurofeedback.

DARPA and SAIC (Cauwenberghs, UCSD PI) 10/11-9/15
Cognitive Radio Low Power Signal Analysis ICs
RF analog circuit design of adaptive beamforming and signal classification systems for cognitive radar.

Completed Research Support

NIH/NIA 1R01AG029681 (Cauwenberghs, PI) 9/06-6/10
CRCNS: Imaging and Modeling of Cortical Microvascular Dynamics
Development and application of high-resolution functional imaging techniques to study the interaction between bloodflow and neural activity in cortex at micrometer and millisecond resolution.

NSF SBE-0847752 (Cauwenberghs, PI) 10/08-9/10
SGER: Wireless EEG Brain Interface for Extended Interactive Learning
Design and implementation of a mobile EEG headset for monitoring and augmenting learning function.

DARPA and Evolved Machines (Cauwenberghs, UCSD PI) 6/10-12/11
Neovision2: Neuromorphic Modular and Evolvable Vision Systems
Large-scale neuromorphic silicon implementation of neocortical vision systems.

Current and Pending Support

Dr. Bruce McNaughton Current Support

Alberta Heritage Foundation for Medical Research (AHFMR) Polaris Research Prize 08/1/2008 – 07/30/2018, \$20 million CAD

Title: The Development of an Understanding of Basic Brain Mechanisms of Memory and Animal Models for Use in Applied Studies The aim of this project is to form a research group and support state of the art research facilities at the Canadian Centre for Behavioural Neuroscience in the field of brain dynamics. The main focus of the laboratory's research will be in the physiological and computational basis of cognition. In particular, focus will be directed on memory and memory disorders, and the dynamic interactions among neuronal populations and synaptic plasticity mechanisms that underlie these phenomena. Role on Project: Principle Investigator

Natural Sciences and Engineering Research Council of Canada (NSERC) Collaborative Research and Training Experience Program (CREATE) 4/1/12 – 3/31/18 \$1.65 million CAD

Title: Information Processing in Biological Systems The vision of this program is that the most productive and exciting frontier of life science will be in a multidisciplinary region of overlap between cell biology and computational science. The essence of this training program is to conjoin cell biology, dynamic neuroimaging, and computational methods. The proposed program will enable the establishment of a world-class training environment for students and post-doctoral trainees in the field of systems neuroscience, integrating three subdisciplines: cell biology, dynamic imaging, and neural computation. Role on Project: Collaborating Investigator

Natural Sciences and Engineering Research Council of Canada (NSERC) 4/1/12 – 3/31/17 \$570,000 CAD

Title: Hippocampal Indexing Theory The central theme and long-term goal of this research program is to elucidate how hippocampal formation back-projections actually affect neocortical dynamics and information storage and retrieval. To accomplish this, we will take advantage of some of the most advanced genetic, molecular, optical and electronic technologies in the toolkit of modern neuroscience. Role on Project: Principle Investigator

University of California, Irvine Departmental Start-up fund, \$1,200,000

The purpose of this grant is to set up the laboratory and to fund preliminary studies needed to be competitive for extramural research support.

Multicampus Research Programs and Initiatives (MRPI) Multi-Year Program Award, University of California Research Initiatives 1/1/2015-12/31/2018 \$2,166,225

Title: Memory Prosthetics

This project aims to establish a world-leading research center devoted to understanding the neuroepigenetic processes governing cognitive capacity and adaptation, within the context of healthy living and in relation to neuropsychiatric disorders that emerge across the lifespan, which complements the NIH Epigenetic Roadmap initiative to "to identify fundamental epigenetic changes or epigenetic mechanisms underlying specific diseases; conditions of development or aging; or response to exposures (physical, chemical, behavioral, and social factors)".

Role: Lead PI

Pending/Overlapping Support

None

Dr. Cauwenberghs Current and Pending Support

ACTIVE

NSF 9/15/2011 – 8/31/2015, \$1,296,415

EFRI-M3C: Distributed brain dynamics in human motor control

The major goals of this project are to advance science and engineering towards non-invasive remediation of Parkinson's through EEG-EMG force neurofeedback.

Research Grant 7/24/2012 – 3/24/2015, Texas Instruments, \$240,000

Event-driven sensory analog processing

The major goal of this project is to advance the engineering of low-power sensory processing systems inspired by neural computation and communication.

NSF CCF-1317407 (Narayanan) 10/01/2013 – 9/30/2018, \$110,930

Collaborative Research; Visual cortex on silicon

The major goals of this project are to make progress towards reverse engineering of the mammalian visual cortex in silicon integrated circuits.

Multicampus Research Programs and Initiatives (MRPI) Multi-Year Program Award, University of California Research Initiatives 1/1/2015-12/31/2018 \$2,166,225

Title: Memory Prosthetics

This project aims to establish a world-leading research center devoted to understanding the neuroepigenetic processes governing cognitive capacity and adaptation, within the context of healthy living and in relation to neuropsychiatric disorders that emerge across the lifespan, which complements the NIH Epigenetic Roadmap initiative to “to identify fundamental epigenetic changes or epigenetic mechanisms underlying specific diseases; conditions of development or aging; or response to exposures (physical, chemical, behavioral, and social factors)”.

Role: Co-PI

PENDING

R01 (Khraiche) 04/01/2015 – 03/31/2020, NIH/NEI, \$149,546

High density optoelectronic nanowire platform for retinal prosthesis

The major goals of this project are to advance the science and technology of nano-scale retinal prostheses for restoration of high-resolution vision in patients with retinal degenerative disease.

CalBrain Seed Grant (Mercier) 02/01/2015 – 01/31/2016, \$108,835

ENIAC: An Encapsulated Neural Interfacing and Acquisition Chip

The principal aim of this research is to develop a new neural interfacing system that can electrically read from and stimulate the brain at groundbreaking scales – upwards of 10,000 channels and beyond.

CalBrain Seed Grant (Dayeh) 02/01/2015 – 01/31/2016, \$104,592 no salary

Neural Probes for *in-vivo* Intracellular recording and stimulation

The goal of this project is to develop and test a nanowire probe for intracellular recording and stimulation of single-unit neural activity in scalable fashion, without the use of glass pipettes.

OVERLAP

None.

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: 0467058490000

Budget Type*: ● Project ○ Subaward/Consortium**Enter name of Organization:** The Regents of the University of California

Start Date*: 09-01-2015

End Date*: 08-31-2016

Budget Period: 1

A. Senior/Key Person												
Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . Dr.	Soyun		Kim		Ph.D	PD/PI	59,004.00	12.00		59,004.00	21,241.00	80,245.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:										Total Senior/Key Person		80,245.00

B. Other Personnel											
Number of Personnel*	Project Role*	Calendar	Months	Academic	Months	Summer	Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*	
Total Number Other Personnel										Total Other Personnel	
										Total Salary, Wages and Fringe Benefits (A+B)	80,245.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1**ORGANIZATIONAL DUNS*:** 0467058490000**Budget Type*:** Project Subaward/Consortium**Organization:** The Regents of the University of California**Start Date*:** 09-01-2015**End Date*:** 08-31-2016**Budget Period:** 1**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item**Funds Requested (\$)*****Total funds requested for all equipment listed in the attached file****Total Equipment****Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)***

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost**E. Participant/Trainee Support Costs****Funds Requested (\$)***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees**Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1**ORGANIZATIONAL DUNS*:** 0467058490000**Budget Type*:** ● Project ○ Subaward/Consortium**Organization:** The Regents of the University of California**Start Date*:** 09-01-2015**End Date*:** 08-31-2016**Budget Period:** 1

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	50,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
	Total Other Direct Costs
	50,000.00

G. Direct Costs	Funds Requested (\$)*
	Total Direct Costs (A thru F)
	130,245.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . Modified Total Direct Costs		8.00	130,245.00	10,420.00
				Total Indirect Costs
				10,420.00
Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)	Not Applicable			

I. Total Direct and Indirect Costs	Funds Requested (\$)*
	Total Direct and Indirect Institutional Costs (G + H)
	140,665.00

J. Fee	Funds Requested (\$)*

K. Budget Justification*	File Name: 1234- BUDGETJUSTIFICATION_K01Kim.pdf (Only attach one file.)
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*: 0467058490000

Budget Type*: ● Project ○ Subaward/Consortium**Enter name of Organization:** The Regents of the University of California

Start Date*: 09-01-2016

End Date*: 08-31-2017

Budget Period: 2

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . Dr.	Soyun		Kim		Ph.D	PD/PI	60,184.00	12.00		60,184.00	22,088.00	82,272.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	82,272.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Total Number Other Personnel				Total Other Personnel		

Total Salary, Wages and Fringe Benefits (A+B) **82,272.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2**ORGANIZATIONAL DUNS*:** 0467058490000**Budget Type*:** Project Subaward/Consortium**Organization:** The Regents of the University of California**Start Date*:** 09-01-2016 **End Date*:** 08-31-2017 **Budget Period:** 2**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	<hr/>
	Total Equipment

Additional Equipment: File Name:

D. Travel

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Funds Requested (\$)*

Total Travel Cost**E. Participant/Trainee Support Costs**

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Funds Requested (\$)***Number of Participants/Trainees****Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2**ORGANIZATIONAL DUNS*:** 0467058490000**Budget Type*:** ● Project ○ Subaward/Consortium**Organization:** The Regents of the University of California**Start Date*:** 09-01-2016**End Date*:** 08-31-2017**Budget Period:** 2

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	50,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
	Total Other Direct Costs
	50,000.00

G. Direct Costs	Funds Requested (\$)*
	Total Direct Costs (A thru F)
	132,272.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . Modified Total Direct Costs		8.00	132,272.00	10,582.00
				Total Indirect Costs
				10,582.00
Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)	Not Applicable			

I. Total Direct and Indirect Costs	Funds Requested (\$)*
	Total Direct and Indirect Institutional Costs (G + H)
	142,854.00

J. Fee	Funds Requested (\$)*

K. Budget Justification*	File Name: 1234- BUDGETJUSTIFICATION_K01Kim.pdf (Only attach one file.)
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: 0467058490000

Budget Type*: ● Project ○ Subaward/Consortium**Enter name of Organization:** The Regents of the University of California

Start Date*: 09-01-2017

End Date*: 08-31-2018

Budget Period: 3

A. Senior/Key Person												
Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . Dr.	Soyun		Kim		Ph.D	PD/PI	64,397.00	12.00		64,397.00	23,634.00	88,031.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:										Total Senior/Key Person		88,031.00

B. Other Personnel											
Number of Personnel*	Project Role*	Calendar	Months	Academic	Months	Summer	Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*	
Total Number Other Personnel										Total Other Personnel	
										Total Salary, Wages and Fringe Benefits (A+B)	88,031.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3**ORGANIZATIONAL DUNS*:** 0467058490000**Budget Type*:** Project Subaward/Consortium**Organization:** The Regents of the University of California**Start Date*:** 09-01-2017**End Date*:** 08-31-2018**Budget Period:** 3**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item**Funds Requested (\$)*****Total funds requested for all equipment listed in the attached file****Total Equipment****Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)***

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost**E. Participant/Trainee Support Costs****Funds Requested (\$)***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees**Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3**ORGANIZATIONAL DUNS*:** 0467058490000**Budget Type*:** ● Project ○ Subaward/Consortium**Organization:** The Regents of the University of California**Start Date*:** 09-01-2017**End Date*:** 08-31-2018**Budget Period:** 3

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	50,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
	Total Other Direct Costs
	50,000.00

G. Direct Costs	Funds Requested (\$)*
	Total Direct Costs (A thru F)
	138,031.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . Modified Total Direct Costs		8.00	138,031.00	11,042.00
				Total Indirect Costs
				11,042.00
Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)	Not Applicable			

I. Total Direct and Indirect Costs	Funds Requested (\$)*
	Total Direct and Indirect Institutional Costs (G + H)
	149,073.00

J. Fee	Funds Requested (\$)*

K. Budget Justification*	File Name: 1234- BUDGETJUSTIFICATION_K01Kim.pdf (Only attach one file.)
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS*: 0467058490000

Budget Type*: ● Project ○ Subaward/Consortium**Enter name of Organization:** The Regents of the University of California

Start Date*: 09-01-2018

End Date*: 08-31-2019

Budget Period: 4

A. Senior/Key Person												
Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . Dr.	Soyun		Kim		Ph.D	PD/PI	65,685.00	12.00		65,685.00	24,106.00	89,791.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:										Total Senior/Key Person		89,791.00

B. Other Personnel											
Number of Personnel*	Project Role*	Calendar	Months	Academic	Months	Summer	Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*	
Total Number Other Personnel										Total Other Personnel	
										Total Salary, Wages and Fringe Benefits (A+B)	89,791.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4**ORGANIZATIONAL DUNS*:** 0467058490000**Budget Type*:** Project Subaward/Consortium**Organization:** The Regents of the University of California**Start Date*:** 09-01-2018**End Date*:** 08-31-2019**Budget Period:** 4**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item**Funds Requested (\$)*****Total funds requested for all equipment listed in the attached file****Total Equipment****Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)***

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost**E. Participant/Trainee Support Costs****Funds Requested (\$)***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees**Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4**ORGANIZATIONAL DUNS*:** 0467058490000**Budget Type*:** ● Project ○ Subaward/Consortium**Organization:** The Regents of the University of California**Start Date*:** 09-01-2018**End Date*:** 08-31-2019**Budget Period:** 4

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	50,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
	Total Other Direct Costs
	50,000.00

G. Direct Costs	Funds Requested (\$)*
	Total Direct Costs (A thru F)
	139,791.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . Modified Total Direct Costs		8.00	139,791.00	11,183.00
				Total Indirect Costs
				11,183.00
Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)	Not Applicable			

I. Total Direct and Indirect Costs	Funds Requested (\$)*
	Total Direct and Indirect Institutional Costs (G + H)
	150,974.00

J. Fee	Funds Requested (\$)*

K. Budget Justification*	File Name: 1234- BUDGETJUSTIFICATION_K01Kim.pdf (Only attach one file.)
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

BUDGET JUSTIFICATION

Personnel

Soyun Kim, Ph.D. Candidate (Years 1-4:12 cal mos)

During the phase of this award, Dr. Kim will perform the proposed experiments, collect and analyze data, prepare manuscripts upon completion of the studies, and present the findings in scientific meetings. In addition, she will be submitting grant applications to continue her research.

Salary is escalated by 2% yearly for cost of living increase and an additional 5% for merit increase in Year 2. Fringe benefits are calculated using the composite benefit rate of 36% in year and 36.7% in yrs 2-4.

Mentor and other significant contributors

Bruce McNaughton, Ph.D. (Mentor, no salary support is requested). Dr. McNaughton is a Distinguished Professor of Neurobiology and Behavior at the University of California, Irvine. He is a systems neuroscientist, recognized as an expert in the mechanisms that underlie memory and in advanced high density recording and imaging techniques. As the co-mentor for the candidate, Dr. McNaughton will provide guidance on career development and supervision of the proposed training and research plan.

Gert Cauwenberghs, Ph.D. (Co-Mentor, no salary support is requested). Dr. Cauwenberghs is the Professor of Bioengineering at the University of California, San Diego, and co-director of the Institute for Neural Computation at UCSD. He pioneered the design and implementation of highly energy efficient, massively parallel microchips that emulate function and structure of adaptive neural circuits in silicon. As a mentor for the candidate, Dr. Cauwenberghs will coordinate with Dr. McNaughton to provide guidance on career development and supervision pertaining to his expertise for the proposed training and research plan.

Other Program Related Expenses

TBN, Laboratory Technician (Yrs 1-2: 3.0 cal mos; Yr 3:3.6 cal mos; Yr 4: 4.8 cal mos)

Technician effort will be shared between the PI and mentors for managing supplies, animal stocks, animal training, data acquisition, and perform surgeries for electrophysiological and imaging experiments, histology, and data analysis.

Salary is escalated by 2% yearly for cost of living increase. Fringe benefits are calculated using the composite benefit rate of 36% in year and 36.7% in yrs 2-4.

All salaries and wages were estimated using UCI's academic and staff salary scales.

Fringe benefit composite rates are escalated each year based on University guidelines due to the resumption of employer contributions to the UC Retirement Plan (UCRP) for academic and staff personnel.

Materials and Supplies

Funds are also requested for transgenic mice and non-transgenic rats. The species are required at any given time during all years for the experiments proposed. Estimated average costs based on historical usage are \$2,614 per budget year.

Funds are requested for project-specific computers and computing devices (e.g., tablets) in year 1 for data analysis and presentation. Estimate costs are \$5,151.

Funds are requested for surgical supplies (e.g., skull screws, isoflurane, injectors, tubing) and electrophysiological research supplies for yrs 2 - 4. The proposed project require use of custom-designed, built, plated and tested stimulators and cortical arrays that are critical for neural probing and neuromodulation. Estimated average cost per budget year is \$4,618.

Travel

Funds are requested for PI to attend an annual research conference (Society for Neuroscience). Costs are estimated based on historical rates including airfare, lodging, transportation, registration fees, and meals and

incidentals. Estimated costs are \$2197 in yr 1 with a 3% inflationary increase in years 2 and 3. In year 4, estimated costs are \$1597.

Funds are also requested for PI to travel to the University of Lethbridge for essential short term training in years 1 and 2 (see Plan for Career Development and Training Activities). These visits will offer essential training and resources for acquiring new set of skills (e.g., MATLAB for data processing and data analyses, optical imaging, electrical device instrumentation) as well as for initiating collaborative projects that could potentially develop to the PI's independent research program. Costs are estimated based on historical rates including airfare, lodging, transportation, meals and incidentals. Estimated costs are \$5,400 in year 1 with a 3% inflationary increase in year 2.

Funds are requested for private auto mileage for PI traveling between UCI and INC at UCSD several times a year (see Plan for Career Development and Training Activities). Estimated costs are an average of \$473 per budget year for the 140 miles round trip).

Other Direct Costs

Funds are requested breeding and housing transgenic mice and housing rats. We estimate approximately 70 cages per year throughout the project. Rates are calculated based on per diem rate published by University Laboratory Animal Resources. The estimated daily rate per cage for FY 2015-16 is \$0.84 with a 3% inflationary increase per year. Estimated average costs are \$21,040 per budget year.

Funds are also requested for publications costs to publish the result of the research in yrs 3 and 4. Estimated costs are \$2,000 in year 3 and \$1900 in year 4.

Total Direct Costs \$540,339

Indirect Costs \$43,227

Per the guidelines, for all K applications, F&A/indirect costs are reimbursed at 8% of modified total direct costs (exclusive of tuition and fees and expenditures for equipment) rather than on the basis of a negotiated rate agreement. This indirect cost rate is effective from 9/1/2015-8/31/2019.

Total Funds Requested \$583,566

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals (\$)
Section A, Senior/Key Person	340,339.00
Section B, Other Personnel	
Total Number Other Personnel	
Total Salary, Wages and Fringe Benefits (A+B)	340,339.00
Section C, Equipment	
Section D, Travel	
1. Domestic	
2. Foreign	
Section E, Participant/Trainee Support Costs	
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other	
6. Number of Participants/Trainees	
Section F, Other Direct Costs	200,000.00
1. Materials and Supplies	200,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other 1	
9. Other 2	
10. Other 3	
Section G, Direct Costs (A thru F)	540,339.00
Section H, Indirect Costs	43,227.00
Section I, Total Direct and Indirect Costs (G + H)	583,566.00
Section J, Fee	

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OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix: Dr.
 First Name*: Soyun
 Middle Name:
 Last Name*: Kim
 Suffix: Ph.D

2. Human Subjects

Clinical Trial? No Yes
 Agency-Defined Phase III Clinical Trial?* No Yes

3. Permission Statement*

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

Yes No

4. Program Income*

Is program income anticipated during the periods for which the grant support is requested? Yes No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

Budget Period*	Anticipated Amount (\$)*	Source(s)*
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5. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?* No Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): Specific stem cell line cannot be referenced at this time. One from the registry will be used.

6. Inventions and Patents (For renewal applications only)

Inventions and Patents*: Yes No

If the answer is "Yes" then please answer the following:

Previously Reported*: Yes No

7. Change of Investigator / Change of Institution Questions

Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name*:

Middle Name:

Last Name*:

Suffix:

Change of Grantee Institution

Name of former institution*:

PHS 398 Career Development Award Supplemental Form

OMB Number: 0925-0001

Introduction (if applicable)	
1. Introduction to Application (for RESUBMISSION applications only)	1242-IntroductiontoApplication_Kim_Resub.pdf
Candidate Information	
2. Candidate's Background	1243-CandidateBackground_Kim_Resub.pdf
3. Career Goals and Objectives	1244-CareerGoalsandObjectives_Kim_Resub.pdf
4. Career Development/Training Activities During Award Period	1245-CareerDevelopmentandTrainingActivities_Kim_Resub.pdf
5. Training in the Responsible Conduct of Research	1246-ResponsibleConductofResearch_Kim_Resub.pdf
6. Candidate's Plan to Provide Mentoring (as applicable)	
Statements of Support	
7. Plans and Statements of Mentor and Co-Mentor(s)	1247-StatementsofSupport_Kim_Resub.pdf
8. Letters of Support from Collaborators, Contributors, and Consultants	1248-LettersofSupport_Kim_Resub.pdf
Environment and Institutional Commitment to Candidate	
9. Description of Institutional Environment	1249-InsitutionalEnvironment_Kim_Resub.pdf
10. Institutional Commitment to Candidate's Research Career Development	1250-InsitutionalCommitment_Kim_Resub.pdf
Research Plan	
11. Specific Aims	1251-SpecificAims_Kim_Resub.pdf
12. Research Strategy*	1252-ResearchStrategy_Kim_Resub.pdf
13. Progress Report Publication List (for RENEWAL applications only)	
Human Subject Sections	
14. Protection of Human Subjects	
15. Inclusion of Women and Minorities	
16. Inclusion of Children	
Other Research Plan Sections	
17. Vertebrate Animals	1253-VertebrateAnimals_Kim_Resub.pdf
18. Select Agent Research	
19. Consortium/Contractual Arrangements	
20. Resource Sharing Plan(s)	1254-ResourcesSharingPlan_Kim_Resub.pdf
Appendix (if applicable)	
21. Appendix	
Citizenship*:	
U.S. Citizen or noncitizen national	
Non-U.S. Citizen with temporary U.S. visa	
● Permanent Resident of U.S. (If a permanent resident of the U.S., a notarized statement must be provided by the time of award)	
Permanent Resident of U.S. Pending	

Introduction to the revised application

I thank the reviewers for their very helpful comments on the proposal, which was admittedly developed on a short time schedule and was consequently somewhat overambitious and lacking in details. Below I outline how I addressed the specific concerns. Significant changes have been made to the Research Strategy. Other changes in response to reviewers' comments are now marked with vertical bars in the right margin. I have included some preliminary data in support of the revised experimental approach. I have limited the scope of the research to the animal studies, but will receive informal exposure to related ongoing human studies through discussions with the advisors, in particular Dr. Halgren. Finally, the proposal is now being submitted through UCI (to which I have formally transferred), where all the experimental work will take place. Extensive mentoring will take place during the course of ENIAC technical developments, for which the mentors have recently received a joint grant.

The proposal now focuses on fewer techniques, and has been divided into two specific aims, both of which address the fundamental question of how hippocampal dysfunction affects memory related neocortical dynamics, and whether memory function can be artificially restored using patterned neocortical stimulation designed to substitute for hippocampal 'index code' output. Aim 1 will use optical methods in a mouse model, whereas Aim 2 will use electrophysiological methods in a rat model. The optical approach is currently established at UCI, so I will be able to start immediately on this. It also provides the highest spatiotemporal resolution for both optical recording (VSDI) and optogenetic stimulation. The stimulation will be achieved using a high-speed, scanning laser currently installed in the McNaughton lab, and commercially available CHR2 mice. I apologize for not making this clear in the initial proposal, which led one reviewer to conclude that we "cannot provide sequence stimulation": with this method we can provide sequence stimulation with high spatiotemporal complexity. For VSDI, I will use externally applied voltage sensitive dye (RH 1691) since this method is established in the lab, and we have preliminary data with it. For Aim 2, the electrophysiological approach will provide a link to the ENIAC device under development which uses electrical stimulation and recording. I will use proven technology, at least initially, pending successful development of the ENIAC chips. Thus, the studies do not depend on the success of the ENIAC developments. The reasons for the choice of animal models are mainly technical, since the optical methods are best suited to mice, whereas the electrical methods are best suited for rats. I have also eliminated the use of DREADD technology since this is unproven in our hands. I will use conventional neurotoxic lesions instead, in both species.

The reviewer pointed out that virtual reality (VR) has some issues; however, those issues pertain mainly to 2-D environments where the head direction system, which normally ensures that the hippocampal map is consistent, is likely offline or not updating virtual direction. On linear tracks, virtual place fields are highly consistent (see preliminary data). The main role of the VR is to provide reproducible hippocampal output to associate with the external stimuli, and this can be achieved with these methods. Whether VR is a good model for spatial cognition *per se* is a separate issue not of concern in these studies.

For stimulation, weak patterned stimuli will be delivered during the learning phase, to establish the index pattern in the cortex and associate it with the task-related cortical representation, and again during slow-wave sleep and/or quiet wakefulness. The latter states are accompanied by neocortical slow waves (up-down states, k-complexes) and hippocampal SPWR activity. These are the states associated with robust memory trace reactivation and which have been shown to be necessary for both memory consolidation and neocortical structural plasticity. Thus, we will record neocortical slow wave activity during all stimulation experiments and time the stimulation to these epochs. The hypothesis is that the latter will reinstate the complete cortical memory traces, allowing consolidation to take place.

Alternative plans: the revised plans now rely on proven techniques, and so the concern over backup plans are mitigated somewhat. Nevertheless I now outline some possible failure points and possible backup solutions. For example, I will focus on "place" learning in VR. Place learning is well established to be dependent on hippocampus and very rapid, but has not been clearly demonstrated in VR. Trace conditioning, which also depends on hippocampus (but requires a lot more trials), will be a backup used only in the event that animals fail to learn the "place" task in VR. It is well established that head restrained animals exhibit trace conditioning. For the reviewer's information, although this is no longer included as a variable, trace eyeblink conditioning actually has been shown to be spatial context dependent by the mentor (Science, 2008, 322:960).

Finally, a question was raised about Dr. McNaughton time at UCI vs Lethbridge. By agreement between institutions, he spends half of his time at each, generally partitioned into two, scheduled 4-month blocks at each, plus variable blocks depending on ongoing operations. During his absence, Dr. McNaughton maintains communication with trainees and collaborators electronically (email, skype).

CANDIDATE'S BACKGROUND

My goal of applying for the Mentored Research Scientist Development Award is to acquire new essential training from an established, collaborative team of mentors and build upon my previous research training in memory research. The award for my research and career development plan will help me broaden my expertise in both animal and human neurophysiology and behavior, providing a critical foundation for transitioning into an independent research career.

In 2004, I received a B.Sc in Biochemistry and Molecular Biology Honors from the University of British Columbia, Canada. A major strength of the honors program was its emphasis on mentored research training in the final year of the program. In fulfilling this requirement, I had an opportunity to work in Dr. Natalie Strynadka's laboratory, where I focused on resolving structures of bacterial proteins implicated in antibiotic resistance. During training, I acquired hands on experience in experimental design, biochemical preparation, x-ray crystallography, and data analysis. My undergraduate training was essential for me not only to establish solid knowledge basis on molecular biology, but also gain scientific research experience.

I furthered my pre-doctoral training in Biochemistry by pursuing doctoral training in Behavioral/Cognitive Neuroscience. In 2005, I was admitted to the doctoral program in Neuroscience in the University of Southern California, where I had a privilege of working in Dr. Richard Thompson's laboratory. The dissertation topic reflected my original interest of understanding molecular mechanisms related to behavior. Specifically, my thesis focused on investigating the neuronal circuitry and molecular bases supporting classical eyeblink conditioning. I combined behavioral, neuroanatomical, and neurohistological approaches to probe the changes in essential molecules (e.g., plasticity-related proteins) in Purkinje cells and the Interpositus Nucleus in the cerebellum, regions which have been identified to be critical for mediating associative learning and forming memory traces. The end result of this pursuit was produced in the form of doctoral dissertation as well as three publications (Pakaprot et al., 2009; Kim et al., 2011; Kim and Thompson, 2011; *Behav Neurosci*).

In 2010, I joined Dr. Larry Squire's laboratory at UCSD to expand the scope of my research to human memory research. Here, I explored the role of the hippocampus and the medial temporal lobe in human memory, perception, and spatial cognition. Completed projects include a study on visual perception (Kim et al., 2011, *J Neuroscience*), a study on path integration in humans and rodents (in collaboration with Dr. Robert Clark at UCSD, Kim et al., 2013, *PNAS*), and a study on spatial mental imagery (Kim et al., 2013, *Learn & Mem*). The article on path integration was particularly featured in the In This Issue section of the journal. During the postdoctoral program, I developed experience working with memory-impaired patients with brain lesions limited to the bilateral hippocampus or medial temporal lobe. Furthermore, I gained experience in human neuropsychology and behavior, experimental design and analyses, and neuroimaging (structural MRI, brain volumetric quantification) technique.

My postdoctoral program Dr. Squire's laboratory concluded with three additional projects remaining for publication. One project focused on the post-mortem neuropsychological analysis of a patient with hippocampal lesion. I have completed preparing a manuscript on the neuropsychology of this patient and am waiting for results from neurohistology analysis (will be prepared by Dr. David Amaral, a distinguished neuroanatomist at UC Davis). Another project explored the issue of hippocampal role in spatial cognition (scene construction, spatial imagery), and the manuscript is in press in *PNAS*. The last project is about spatial navigation behavior in memory-impaired patients. This project is complete with a manuscript in preparation.

Overall, I have had a unique opportunity to pursue training across intersecting disciplines: biochemistry, animal neuroscience, and human neuroscience. Importantly, the overarching theme of my research programs was the organization of memory in the brain and neurobiology of memory disorders. I value the experience that covered a broad range of analysis from molecules to systems and behavior (high-order cognitive functions). My new position in Dr. McNaughton's laboratory at UC Irvine formally started from January 2015. I highly expect that additional training from this laboratory, in combination with training from Dr. Cauwenberghs's laboratory, will give me a well rounded, multi-level basis for future work, and thus will support me to achieve an independent position where I can continue to carry out translational research on the neuroscience of learning and memory.

CAREER GOALS AND OBJECTIVES

Career goals

My previous research in animal and human neuroscience, with emphasis on studies of memory, has focused on memory impairment following lesions to specific parts of the brain (the medial temporal lobe). My career goal is to build on this previous body of work by acquiring new set of experimental skills from an established team of mentors and applying the expertise to the study of learning and memory in animal models and translate to humans. The Mentored Research Scientist Development Award would essentially support me to achieve these goals and objectives.

Objectives

Specific objectives are to complete the proposed studies while acquiring new laboratory skill sets, publish in impactful journals, apply for additional funding and academic positions, and to develop independent research programs on study of memory and memory disorders. During the phase of this award (Year 1 – 4), I would require additional training and mentoring in the following areas:

(1) Acquire new technique and skill sets

- Learning experimental technique for probing neural activity and dynamics (Year 1 – 2)
- Training in biomedical engineering for utilizing neuromodulation device (Year 3 -4)
- Informal training on clinical application of memory prosthesis (Year 3 – 4)

(2) Attend didactic courses and Technical Workshops

- Responsible conduct of research training (Year 1, and additional years if needed)
- Workshops offered in the University of Lethbridge Brain Dynamics Group (Year 1 - 2)

(3) Evaluation

- Obtain formal evaluation and feedback from mentors and advisors (Year 1 – 4)

(4) Career development and preparation for independence

- Attend meetings, seminars, conferences (Year 1 – 4)
- Presentations (Year 1 – 4)
- Reviewer/Editorial service (Year 1 – 4)
- Apply for grants (Year 3 – 4)
- Apply for tenure-track positions (Year 3 – 4)

CAREER DEVELOPMENT AND TRAINING ACTIVITIES

Throughout my pre-doctoral and postdoctoral research program, I have had exposure to animal and human memory research. Although my training provided a broad understanding of behavioral studies in both species, I will need additional formal training to successfully develop my own research project and carry out the proposed experiments. During the grant period, I will need to acquire training in high density electrophysiology for recording neuronal activities and neural ensemble codes in rodents. I would also need to acquire training in wide-field optical imaging (voltage-sensitive dye imaging), which will be useful in monitoring cortical activity with high spatiotemporal resolution. In addition, I will need to acquire training in neuromodulation (optical stimulation and electrical stimulation) technique in rodents.

New Techniques and Skills Acquired:

(1) Learning experimental technique for probing and modulating neural activity and dynamics.

Dr. McNaughton (at UCI) will provide essential training in high density electrophysiology, behavioral experiment design (in vivo recording), optical imaging, and neuromodulation (neocortical stimulation) for experimental evaluation of the memory index theory. Although high-density ensemble may not be utilized in the proposed work, I will be collaborating with other colleagues in the lab who runs relevant projects (e.g., sequence learning in a maze with hyperdrive recording). I will obtain co-authorship if the work gets published.

(2) Training in biomedical engineering for developing neuromodulation device (i.e., memory prosthesis).

This specific goal will be supervised by Dr. Cauwenberghs (at UCSD). He will provide training in utilization of memory prosthesis (instrumentation, fabrication). He will also provide training in neural computation also with other advisory members (Drs. Mercier, Gilja, and Sejnowski).

(3) Informal training on clinical application of memory prosthesis.

As the memory prosthesis project makes progress (the mentors are closely collaborating on this project and have recently been awarded a joint grant), Dr. Halgren (at UDSD) will be able to provide introductory, informal training in human electrophysiology. I will participate in the designing of human application and sit on human recording studies under his guidance. This way I would be able to become an independent member of the team and gradually merge into clinical domain. Specifically, my postdoctoral training on memory-impaired patients will be helpful in pursuit of this long-term goal.

Didactic Coursework/Technique Workshop:

In Spring 2015, I plan to attend a formal course offered at UCI about Responsible Conduct of Research. In addition, I plan to attend other formal courses provided by the university (e.g., grant writing skills, leadership, job search strategy) occasionally throughout the year.

One major activity of my training plan is to attend workshops and short-term training provided by the Brain Dynamics group at the University of Lethbridge, Canada in the first two years of the grant period. The group offers world-class training programs and facilities for excellent and unique learning environment for new and experienced neuroscientists. I will visit the group every year for workshops and intensive training on MATLAB (electrophysiological data processing and data analyses), optical imaging, and behavioral experiments. This group is highly collaborative and encourages multidisciplinary approaches for studying population neuronal activity and relevant behavior (including learning and memory). Thus, it will be a critical component of my training that I dedicate time (2-4 weeks) visiting this institute to learn new technique and collaborate with leading investigators in the field of my research.

Evaluation:

During training, I plan to organize formal meetings with my mentors either individually or as a team as much as needed. The two campuses are located within 1-hr driving distance, allowing round trip possible within a day. Informal meetings and skype meetings will be organized as many times as needed.

Career development and preparation for independence

In addition to research training, I plan to attend seminars and symposium that are relevant to my research. Different departments at UCI and UCSD (Neuroscience, Psychology, Neurobiology and Behavior) as well as institutes (Institute for neural computation) usually offer weekly seminar series. If given a chance, I will present my work in one of the seminar series or symposiums. This will improve my presentation and

communication skills. I could also use this opportunity to practice my future job talk.

Training will be also provided in manuscript preparation, peer review and editorial role, and grant writing. I have been invited to review for *Frontiers in Behavioral Neuroscience*, and I am currently an associate editor of protocol-based journal, *Bioprotocol*. During the proposed training, I will assist my mentors with manuscript review in prestigious journals, particularly on topics relevant to my research. In parallel, I will develop an independent research program upon which I can construct job application packages. I will also continuously apply for additional funding to support my transitioning to independence.

The table below summarizes my plans for research training and career development.

Award Year	Research Training	Career Development
Year 1	<ul style="list-style-type: none"> ▪ Acquire laboratory skills (Neurophysiology, Optical imaging, Data processing and analysis, Virtual reality system) ▪ Course/Workshop (Training in Responsible Conduct of Research, at UCI; Summer course at the University of Lethbridge Brain Dynamics for MATLAB) ▪ Meet with mentors and advisors 	<ul style="list-style-type: none"> ▪ Attend seminars ▪ Presentation in lab meetings and seminars ▪ Review manuscripts
Year 2	<ul style="list-style-type: none"> ▪ Acquire laboratory skills (Neurophysiology, Optical imaging, Optogenetic stimulation) ▪ Workshop (University of Lethbridge Brain Dynamics for data processing and analysis) ▪ Meet with mentors and advisors ▪ Set initial plan for an independent research program 	<ul style="list-style-type: none"> ▪ Attend seminars ▪ Presentation in lab meetings and seminars ▪ Attend and present at scientific meetings ▪ Review manuscripts
Year 3	<ul style="list-style-type: none"> ▪ Acquire laboratory skills (Optogenetic Stimulation, Electrophysiology, Electrical stimulator instrumentation) ▪ Meet with mentors and advisors 	<ul style="list-style-type: none"> ▪ Attend seminars ▪ Presentation in lab meetings and seminars (job talk) ▪ Attend and present at scientific meetings ▪ Prepare/publish manuscripts ▪ Apply for grants
Year 4	<ul style="list-style-type: none"> ▪ Acquire laboratory skills (Introduction to human electrophysiology, Neural computational modelling, Electrical stimulation) ▪ Meet with mentors and advisors 	<ul style="list-style-type: none"> ▪ Attend and present at scientific meetings ▪ Apply for tenure-track positions ▪ Publish manuscripts ▪ Apply for grants

RESPONSIBLE CONDUCT OF RESEARCH

Previous training

In the 5th year of my graduate school (University of Southern California), a 3-hr workshop on Ethical Research was organized by Dr. Michael Quick (Executive Vice Provost and Vice President for Academic Affairs and Professor of Biological Sciences). The workshop covered several practical issues, including data collection and management, attribution of credit, plagiarism, peer review, and conflicts of interest. The topics were explained with sample cases, followed by group discussion.

In September, 2014, I attended a course entitled “Introduction to the Ethical Challenges of Research”. The course was taught by Dr. Mary Devereaux, Assistant Director of the UC San Diego Research Ethics Program. Discussed topics included: data management; bias and negative results; authorship; and the definition of misconduct.

During my postdoctoral training I have also completed online training courses required by the Veterans Affairs San Diego Healthcare System. The training was specifically designed for researchers working with human subjects (e.g., Information Security, Privacy & HIPAA, Human Subjects Protection & Good Clinical Practices).

Plan for training

I plan to maintain up-to-date training status throughout the time of the award. Training will include both formal and informal instructions.

Subject Matter: Training will cover topics on animal and human welfare/rights, data management and sharing, authorship practices, workplace obligations, conflicts of interest, whistle blowing, and research misconduct.

Frequency of Instruction: I plan to take a formal course (MMG 250, “Responsible Conduct in Research”) offered at UCI in Spring 2015. Informal instructions will be provided by the mentors through individual meetings.

Duration of Instruction: MMG 250 is offered across 10 sessions (1.5hr/session). Informal instruction (by mentors and advisors) will take place as much as needed (minimum of 12hr/year).

Format: Unless training is provided online, face-to-face meetings will take place for both formal (MMG 250) and informal instruction. If needed, I will contact relevant staffs at UCI and UCSD to seek for advice.

Faculty Participation: MMG250 is taught by Dr. Al Goldin (Associate Dean for Graduate Studies, UCI School of Medicine). The course is also taught by other faculty member of the department on some sections. My mentors and advisors will ensure that my conduct of research is complying to ethical standards. Topics on research ethics and responsible conduct will be also covered in weekly lab meetings in addition to individual instructions.

STATEMENT BY MENTOR AND CO-MENTOR

It is with great pleasure that we serve as mentors for Dr. Soyun Kim's research and career development training. In January, 2015, Dr. Kim joined Dr. McNaughton's laboratory with strong recommendations from her former mentors. Dr. Kim has recently completed her post-doctoral training at UCSD in the laboratory of Dr. Larry Squire and formally transferred to Dr. McNaughton's laboratory in January 2015.

According to her former mentors (Dr. Richard Thompson and Dr. Larry Squire), Dr. Kim is careful, hard working, and highly motivated, and has had no trouble coming up to speed on learning new skills (note her transition from animal laboratory to human laboratory). In addition, she is very good at organizing her thoughts on research topics, and she is meticulous and careful in every step of research, from design of experiment to interpretation of data. She is confident in her own abilities, yet listens to the advice of others. During both doctoral and postdoctoral training, she demonstrated her ability to lead independent projects and focus on important issues in cognitive neuroscience. With strong assets in memory research, Dr. Kim wanted to pursue further training where she could acquire new set of skills and prepare for an independent scientist career.

Both of us have demonstrated solid mentorship in research training and career development, and several of our past trainees have landed tenure-track positions in major universities. Some of Dr. Cauwenberghs' trainees currently hold full professorships at University of Toronto and Washington University in St. Louise, and a recent trainee secured a tenure-track position at UCI. Dr. McNaughton also has an outstanding list of trainees who successfully transitioned to independent academic positions, including a recent recipient of the K99 award (Dr. Aaron Wilber).

More importantly, we have been collaborating for about the past 2 years on the technical and conceptual developments that underlie Dr. Kim's proposal and have established a highly functional training environment for behavioral, cognitive, or computational neuroscientists in two UC campuses (UCSD and UCI).

Specifically, we were in search of a trainee with strong background in the neurobiology of memory mechanisms, paralleled with substantial expertise in working with both rodent models and humans. Dr. Kim has been trained in both animal and human neuroscience, with emphasis on a common topic: learning and memory. Dr. Kim has a dual interest in basic and translational neuroscience research, and her interest complements the scope of our research that lies at intersections of basic neuroscience and clinical neuroscience. The major directions that our team and collaborators are heading to is to conduct tests in rodents of a major theory of memory consolidation and in parallel to develop a memory prosthesis, based on the animal work, for clinical populations with devastated memory function. Dr. Kim's long-term career plan suits this agenda, and both her PhD training with Richard Thompson (neurobiology of classical conditioning) and her postdoctoral training with Larry Squire (she worked with memory-impaired patients with brain lesions) will be important assets for this kind of translational work.

We both agree that by all indications, Dr. Kim, exhibits all the critical attributes for becoming a successful independent neuroscientist who will contribute substantively to both basic and applied understanding of brain function, and we think her chosen project will produce provocative and highly impactful data. In summary, we emphatically and enthusiastically support Dr. Kim's mentored research and transition to an independent research career. This statement of plans will help us guide and structure our support during the phase of the award.

1. Plan for Training and Research Career Development

Research. Dr. Kim comes from a strong molecular, behavioral, and neuropsychological background. She has spent her five-year doctoral program mastering rodent behavioral experiments (both mice and rats), neurohistochemistry, and neuroanatomy. Specifically, she already had solid foundation on molecular biology (her undergraduate major), which enabled her to link behavior and molecular analyses in study of memory. Dr. Kim also has strong background in human research, including human neuroanatomy, structural neuroimaging, and neuropsychology. She also carried out behavioral experiments testing spatial memory and computation of humans.

However, she has had very little exposure to other kinds of tools for probing neural correlates and interactions that underlie mnemonic or spatial behaviors. Her proposal will offer technical training in our laboratories on rodent models of hippocampal damage (Aim 1, 2), optical imaging and stimulation (Aim 1), and electrical recording and stimulation (Aim 2). The new training she will acquire during this award phase will be essential to pursuing her research interests in learning and memory, filling the gap between the rodent and human literatures.

In order to achieve research independence with these newly learned techniques in the later stages of the award period, the mentors will meet with Dr. Kim at least weekly, and the three of us will meet together at least bi-monthly. Further, we have assembled an advisory team (Letters of support attached) that includes Drs. Eric Halgren (human neurophysiologist), Vikash Gilja (biomedical engineer), Patrick Mercier (biomedical engineer), and Terrance Sejnowski (computational neuroscientist). Drs. Majid Mohajerani and Shadi Dayeh will be also available for technical support on the proposed studies. The training objective has the additional benefit of extending Soyun's interactions to these same scientists. Thus, by completing the proposed research, she will learn increasingly sophisticated neurophysiological and neuromodulation techniques (primarily in rodents and later extended to humans), which she can utilize for her own research program.

Finally, in order to ensure research independence at the conclusion of the award phase, we designed this proposal so that:

- 1) Dr. Kim will utilize a variety of techniques needed for both Aim 1 and Aim 2. For example, she will learn about wide-field optical imaging in mice (voltage-sensitive dye imaging, data analysis) during Aim 1. Further, we will train her in electrical recording using cortical arrays during Aim 2 to evaluate the neocortical dynamics in rats. This will permit us to fully train Soyun on all of the neural probing tools needed for Aim 1 and 2.
- 2) For Dr. Kim's proposed experiments (hippocampal effects on neocortical neurodynamics), we will utilize a virtual reality preparation with head-fixed rodents. This enables simultaneous application of optical imaging (Aim 1), laser scanning stimulation (Aim 1), cortical array recording (Aim 2), and electrical stimulation of the cortex (Aim 2). We have constructed a parts list for installing rodent VR setups and will support Dr. Kim in future in building a duplicate system in her own laboratory. Thus, Dr. Kim will have all the necessary training to utilize this approach in her later career by the onset of Aim 1.
- 3) Dr. Kim will be also trained on breeding optogenetic mice and optogenetic stimulation (during Aim 1), which are the most current innovations in the field. Thus, by the completion of the award phase, Dr. Kim will be fully trained in all research methods and analysis techniques for Aims 1 and 2 and be well prepared for carrying out her independent research.

Didactic Training. We will address a career goal related to Dr. Kim's longstanding interest in connecting her electrophysiological and behavioral findings from rodent models to understanding neurobiology of memory disorders. Therefore, didactic training will focus on providing training relevant to these topics, specifically Dr. Kim will:

- 1) Attend the course Responsible Conduct of Research (MMG250), provided at UCI in Spring 2015 (Year 1). This is a graduate level course that covers all subject areas in which NIH mandates training.
- 2) Dr. Kim will attend a 2-week summer course at the University of Lethbridge, Brain Dynamics Group (Year 1 – 2). The course will teach MATLAB-based data processing and data analyses methods for electrophysiological data, instrumentation and fabrication of experimental devices used for the proposed study, and optical imaging methods (voltage-sensitive dye).

There are a variety of local courses that can be used to provide similar training; however, we feel that the experience of summer school training, including the networking that occurs at such meetings, is preferable and crucial. Therefore, we will complete as much of this training as possible via external courses.

Training in the Responsible Conduct of Research. For details regarding the ethical training, see the *Training in Responsible Conduct of Research* of this application. Responsible conduct of research training is standard for all trainees in our laboratories and is often discussed in depth at lab meetings. Dr. Kim will receive the training by attending a formal course provided by the University of California, Irvine in year 1 of

the award and will receive additional informal training in laboratory meetings at least once every semester, with additional training specific to her project during our one-to-one meetings (at least once every month).

Seminars. The University of California, San Diego (UCSD) and the University of California, Irvine (UCI) complement Dr. Kim's transition goals both within and outside of her home department (Neurobiology and Behavior at UCI and Institute for Neural Computation at UCSD). There is also a core emphasis on the neurobiology of learning and memory, including annual conferences both locally (UCI) and regionally (UCLA) on this topic. Dr. Kim will be encouraged to regularly attend these seminars and symposium in order that she can be exposed to diverse training and interdisciplinary approaches.

Scientific Meetings. Dr. Kim has had limited experience in electrophysiological or neural engineering research previously, so it is important that she acquires the breadth of research in the area and begin networking with other investigators in the field. Therefore, we will encourage Dr. Kim to attend major conferences every year (e.g., Society for Neuroscience or similar conference) to update and expand her understanding of brain system dynamics. The conferences typically cover all neuroscience-related topics (from molecular neuroscience to systems neuroscience), so she will have opportunity to interact with neuroscientists from diverse background as well.

Presentations. Dr. Kim has been trained on presentation skills. She will continue to gain training on this skill. She will regularly attend a variety of seminars at the University of California, Irvine or San Diego that are relevant to her training offered through various departments in both campuses (e.g., department of Neurobiology and Behavior at UCI, department of Neuroscience at UCSD). This will expand the breadth of her knowledge and ability to communicate science. Further, Dr. Kim will attend the weekly lab meetings and regularly present her past and present work at these meetings to refine her skills in a controlled but feedback-intensive setting. Finally, Dr. Kim will annually present at the neurobiology of learning and memory journal club (UCI), the departmental research seminar series, and the MIND seminar series. At UCSD, she will have a chance to present at the INC Chalk Talk Series. These are excellent opportunities to polish presentation skills in preparation for delivering a job talk.

Publications. The philosophy in both of our laboratories is to teach how to do innovative and sound research. Trainees spend several years working initially independently, then with support as they demonstrate that they have truly mastered an innovative approach to a problem. An added benefit to this training approach is that trainees have a complete understanding of their research methodology, which is critical when it is time to set up their own laboratory. Part of this process requires developing a novel approach to research problems, but also being productive in publication. Dr. Kim's publication record is competitive as is now, but we will maintain her productivity such that she could make a strong candidate for job applications.

Research Direction for Independence. Dr. Kim will be allowed to take any follow-up experiments from the proposed study and prepare her own research program. Further, Dr. Kim will be allowed to maintain access to all data collected in our laboratories, software and technical documentation for all projects in which she was involved, and any apparatus she built in the laboratory. We feel that these independent directions will significantly enhance the independent research skills that Dr. Kim will begin to develop from our training. We are confident that Dr. Kim will be highly successful in her independent research career and will fundamentally enrich our understanding of the memory systems in normal and diseased brains.

2. Source of Anticipated Support for Research Project

The majority of the financial support for conducting the proposed experiments including space and equipment will come from both mentors' laboratories. We have recently been awarded a joint grant on development of memory prosthetics device, which is of particular relevance to Dr. Kim's proposal. In the initial stage of the K01 award, Dr. McNaughton will take the lead on orchestrating this training plan and will coordinate with Dr. Cauwenberghs. Dr. Kim has also requested funds for research materials, supplies, individual salary and fringe benefits. Still, it is likely that this amount will not fully cover the costs required for research purposes. Dr. McNaughton recently relocated his laboratory from Canada to the University of California, Irvine. Before moving to Canada in 2008, he had continuous funding from NIMH and NINDS for almost 25 years, and had received both the MERIT award (NIMH) and the Jacob Javitz Award (NINDS) for

research excellence. This funding terminated when Dr. McNaughton left the United States in 2008; however, he currently has a substantial start-up grant from UCI that can provide the funds for additional K01 expenses. Both of us are continuously applying major grant proposals for memory related research.

3. Mentoring Plan

We have developed a transition plan for Dr. Kim so that she could use research and technical innovation to significantly extend scientific knowledge.

Advisory Committee. To ensure that training is well rounded and encompasses a variety of perspectives and approaches we have developed an advisory committee for Dr. Kim:

1. Dr. Eric Halgren (UCSD) will offer introductory training in human neurophysiology and application of memory prosthesis (tested in rodents in the proposed study) to clinical patients.
2. Dr. Vikash Gilja (UCSD) will offer training in large cortical array experiments and analysis. Dr. Gilja is relatively early in his career and thus will provide an important perspective for job application.
3. Dr. Patrick Mercier (UCSD) will offer training in biomedical engineering aspect of neuromodulation device.
4. Dr. Terrance Sejnowski (Director of INC, UCSD) will offer training in computational neuroscience and modeling of neuronal systems underlying learning and memory. Dr. Sejnowski has previously mentored many successful independent scientists.

Dr. Kim will formally meet with her advisory committee as a group at least every 6 months; however, we expect substantial informal interactions as well, because of the shared, collaborative goals of the entire mentoring group. This career development plan will structure a presentation that she will prepare prior to each meeting. Dr. Kim will also maintain an updated 'project log' for her work in the form of a Powerpoint presentation so that her mentors can easily track her experimental and training progress.

Lab Meetings. We have weekly lab meetings attended by all members of our laboratories. Training comes in a variety of forms including individual interactions with us; however, we also foster professional development by encouraging trainees to interact with each other and other faculty, to collaborate on research projects and to discuss their work and interests at weekly meetings. We both regularly present at laboratory meetings to provide didactic training in our area of expertise.

One-on-one Training. Within our laboratories the training is based on individual meetings with trainees on an ad hoc basis, usually at least once a week but often more frequently based on needs. We will discuss research plans and results, career training related issues, and career development. We will also use this opportunity to discuss laboratory management, preparation for job searches, assess progress and provided guidance to ensure Dr. Kim gains training in both research and career development. We occasionally receive information about career opportunities from colleagues and will use these meetings to share these opportunities. In addition, we will regularly communicate as needed in person and via email and video conference.

Manuscript Review. We will often ask Dr. Kim to assist us with manuscript reviews, in which she will prepare written comments and meet with us before finalizing the review. Dr. Kim is currently serving as a reviewer for the Frontiers in Behavioral Neuroscience. She is also an associate editor for the journal Bioprotocol. She will continue to serve on any other editorial/reviewer role as it becomes available.

Further professional skills development. To supplement the informal training in grant preparation, Dr. Kim will attend at least one formal training workshop offered at the University of California, Irvine on grant writing and editing. She will be also encouraged to talk to the Program Officers prior to applying for any future grants. When Dr. Kim has completely developed the next proposal for her independent research program, both of us as well as the full advisory committee will review and comment on the proposal.

4. Commitments Other Than Research

We designed this training plan to focus on research related career development, consistent with the objective of a NIMH K01 proposal. During the award phase, Dr. Kim will not be required to teach, serve on committees, or hold any administrative assignments. Though not required and entirely up to Soyun, we will

offer her the opportunity to teach up to 2 relevant lectures per semester for our courses (e.g., She is scheduled to lead two lectures in May 2015 in Dr. McNaughton's class on Neural computation [N174]). This could be used to ease her transition to a combined independent research and teaching career.

5. Transitional Plan from Mentored to Independent Stage

Career Advising

A critical component of this plan is supporting Dr. Kim's job application preparation and transition to an independent career. We will actively assist Dr. Kim in her job search both by providing suggestions for jobs openings and reaching out through our personal network of colleagues. We will review Soyun's drafts on teaching, research statement, and cover letter when she is ready to apply for independent positions. We will also assist Dr. Kim on preparing her job talks, phone and on-site interviews, and job negotiation.

Grant Preparation

Another critical component of this plan is to support Dr. Kim's transition to independence. As she makes progress during the phase of the award, we will encourage her to develop an independent research program and apply for additional grants. We will meet regularly (at least once a month) to discuss about this topic as Dr. Kim acquires new training.

Lab and Grant Management

Training in grant management will take place throughout the entire period of this award. Dr. Kim will work with us in grant management to get an idea of how to prepare budgets, track expenditures, and prepare progress reports (she also has some experience in writing progress reports from her postdoctoral program). She will be also advised on strategies to maintain research direction.



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March 1, 2015

Re: Soyun Kim K award application

Dear Soyun,

I am pleased to offer my advisory support to your K01 proposal, titled "*Hippocampal contribution to cortical neurodynamics: a test of the memory index theory*". Your proposed projects are closely linked to my research interests, and could have implications for the ultimate development of a prosthesis for memory-impaired patients.

My laboratory is focused on the neurophysiology of distributed cortico-thalamo-limbic functions in humans, with a long-standing interest in declarative memory. I have experience in intracranial recordings of human medial temporal lobe neurons and field potentials, laminar recordings in humans, and Utah array recordings in humans during cognitive tasks or sleep. Your mentored training in tests of a memory prosthesis in rodents, coupled with your previous experience working with memory-impaired patients, will prepare you with a strong skill set for making the transition to an independent position. I will be available for consultation on any technical or conceptual queries that may arise during or after the period of this proposal.

I have been actively involved in the introduction of several technologies for microelectrode array recordings in humans, and am co-PI of the grants which are supporting the initial development of the ENIAC device. I will help guide you through the testing that is expected for regulatory approvals by the FDA and IRB, and collaborate with you and our engineering colleagues in the initial human acute and semi-chronic recordings.

Your proposed training will uniquely prepare you to play a central role in the introduction of novel diagnostic and therapeutic technologies for currently intractable neurological and psychiatric diseases in the coming decades. I commit my time and my laboratory's resources to helping you achieve your goals.

Sincerely,

A handwritten signature in black ink, appearing to read "Eric Halgren".

Eric Halgren, Ph.D.

Distinguished Professor, Vice Chair for Basic Research, Department of Neurosciences, UCSD.

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Terrence Sejnowski
INSTITUTE FOR NEURAL COMPUTATION
TEL: (858) 534-7207
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9500 GILMAN DRIVE MC 00523
LA JOLLA, CALIFORNIA 92093-0523
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March 12, 2015

Soyun Kim, Ph.D.
Department of Neurobiology & Behavior
University of California Irvine

Dear Dr. Kim,

I write to fully support your proposed research and training activities outlined in your K01 proposal about evaluation of the *Memory Index Theory*. With pleasure I agree to facilitate your project by consulting with you about neuromodulation with cortical arrays as well as about your career development.

The support will come from my expertise in computational neuroscience. The approaches I use combine both computational and experimental tools to understand the function of neural systems. We are specifically interested in how neural circuits generate behavior and how learning and sleep adaptively modify underlying neural circuits. These interests complement what you proposed for this award. Thus, I am highly supportive of your training. I have trained numerous scientists who have achieved independent careers. In this regard, I am also pleased to provide useful advice on your career development.

Regards,

A handwritten signature in black ink that reads "Terrence J. Sejnowski".

Terrence Sejnowski, Co-Director
Institute for Neural Computation
University of California, San Diego

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March 1, 2015

Dear Soyun Kim,

I am writing this letter to express my interest and support for the work outlined in your proposal, "Hippocampal contribution to cortical neurodynamics: a test of the memory index theory."

My relevant experience is within the field of brain machine interface (BMI), which draws upon experimental techniques from systems neuroscience and engineering methods from statistical signal processing, machine learning, and embedded systems. I study BMI both in animal model and with human participants, including clinical trial study participants.

At UCSD my lab focuses on developing new techniques and paradigms for studying human neuroscience in the clinical setting and for testing novel neural interface technologies. As part of this effort, I am setting up a shared space (approximately 300 sq. ft) within the Electrical and Computer Engineering Department to facilitate rapid *in vivo* testing and validation of neural interface technologies in rodent to optimize device parameters and surgical technique. My dedicated lab space occupies approximately 430 sq. ft in. I am also developing a shared clinical mockup lab (approximately 200 sq. ft), which will be used for prototyping experiments intended for the clinic.

I look forward to being a member of your advisory committee and to supporting your work through our interactions and access to my lab.

Best regards,

A handwritten signature in blue ink that reads "Vikash Gilja".

Vikash Gilja, PhD
Asst. Prof. of Elect. & Comp. Eng.

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Dear Dr. Kim,

I am writing to offer my full support to your research training and career development as proposed in your K01 award application (Hippocampal contribution to cortical neurodynamics: a test of the memory index theory). I consider this proposal as novel and am very interested in your plans to perform high-density recordings, optical imaging, and neural stimulation on transgenic mouse models to investigate the mechanisms underlying learning and memory.

The central theme of my research is building low-power and energy-efficient analog, digital, and power management integrated circuits for biomedical electronics (e.g., memory prosthesis, neural stimulation device), as well as designing short-range wireless applications. I believe the scope of my research and my expertise will be helpful for design and implementation of your proposed project on cortical array stimulation of hippocampal index code in mice.

I look forward to working with you should your project be funded. You are very welcome to contact me for consultations about research or career planning.

Sincerely,

A handwritten signature in blue ink that reads "Patrick Mercier".

Patrick Mercier
Assistant Professor, Electrical and Computer Engineering
Associate Director, Center for Wearable Sensors
University of California, San Diego



University of Lethbridge

Department of Neuroscience, 4401 University Dr W, Lethbridge AB Canada
Phone: +1(403)394-3950 Email: mohajerani@uleth.ca

Lethbridge, March 02, 2015

Dear Soyun,

I write with enthusiasm to collaborate with you on your project (*Hippocampal contribution to cortical neurodynamics: a test of the memory index theory*) proposed for the NIMH- K01 grant. In the past few years I have been working closely with Dr. Bruce McNaughton at the University of Lethbridge, Canada, and have recently assisted him in establishing a voltage-sensitive dye imaging and laser stimulation equipment in his laboratory at UC Irvine. I would happily continue this collaboration, with extra support for your training on optical imaging and stimulation technique. As we discussed, I am happy to have you visit my laboratory in Lethbridge for an extended (1-2 month) training period on VSD imaging and in our analytic approaches. I will also be able to provide technical advice on generating optogenetic mice models.

My research focuses on the physiological and computational basis of sensory perception and associative learning at the level of individual neurons and their synaptic interactions within complex neural circuits. We use *in vivo* optical methods (including two-photon microscopy and voltage sensitive dye imaging) to study neural activity on the subcellular, cellular, and circuit level in real-time, which might be an essential tool for your proposed project. The topic of your proposed work on hippocampal-neocortical interaction underpinning memory consolidation is important and also complements my research interest. I look forward to seeing meaningful results from this promising collaboration.

Sincerely yours,

Majid Mohajerani, PhD

Campus Alberta for Innovation Program Chair

Canadian Centre for Behavioural Neuroscience

The University of Lethbridge

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Shadi Dayeh, Assistant Professor
Department of Electrical & Computer Engineering
La Jolla, California 92093-0407

Phone: (858) 534-5171
Fax: (858) 534-0556
Email: sdayeh@ece.ucsd.edu

Dear Dr. Soyun Kim:

I am delighted to provide this letter of support for your K01 grant application (Hippocampal contribution to cortical neurodynamics: a test of memory index theory). During our collaboration I will provide full technical support for using the thin film electrocorticographic array, a high-performing flexible and cortex-conformal neural probing device fabricated and characterized in my laboratory, in your rodent models.

My laboratory develops hybrid integration schemes for high fidelity bio-interface devices with nanoscale resolution for probing dynamic processes in biological tissues, brain activity mapping, and better accuracy in controlling prosthetic limbs. The advanced monolithic and hybrid integration schemes our group masters in solid-state devices are currently being applied for solving critical problems in electrophysiological interfaces, where we are developing bio-compatible nanoscale capacitive probes for high resolution sensing from neural tissue.

I look forward to our collaboration and testing the arrays in an interesting way.

Sincerely,

A handwritten signature in blue ink, appearing to read "Shadi Dayeh".

Shadi Dayeh
Assistant Professor
Department of Electrical and Computer Engineering
University of California San Diego
Phone: 858 534 5171
e-mail: sdayeh@ece.ucsd.edu

Institutional Environment

Numerous training opportunities as well as resources for career development and research are offered at the University of California, Irvine (UCI) and at the Institute of Neural Computation (INC, University of California, San Diego).

The Department of Neurobiology and Behavior (home department of Dr. Bruce McNaughton's laboratory) and the UCI Center for the Neurobiology of Learning and Memory (CNLM, whereby Dr. McNaughton has an appointment) is ideal resources for conducting the proposed research. There is a strong sense of collaboration across labs at the department of Neurobiology and Behavior and at the CNLM, with many of the researchers having expertise in multiple neuroscience techniques that span varying levels of analysis. McNaughton laboratory consists of adequate space and supplies for optical imaging/optogenetic stimulation in mouse and electrical recording/electrical stimulation in rats. Space is authorized for rodent *in vivo* experiments. There is a mouse breeding and rodent housing facility available for use as well as office and workstation space for project personnel and staff.

The mission of the INC is to bring together research community from different backgrounds (basic sciences, medical, and engineering) for advancing and promoting a new science of computation and learning. Because the scope of the proposed project lies at the intersection of cognitive neuroscience and biomedical engineering, it will be well supported by the prominent investigators and resources available at INC. The INC is well equipped with the necessary instrumentation and provides dynamic and stimulated scientific environment to conduct the proposed study.

There will be significant external support from my mentors, who are internationally recognized experts in the field, and resources for the proposed research program. Dr. Cauwenberghs has pioneered the design and implementation of highly energy efficient, massively parallel microchips that emulate function and structure of adaptive neural circuits in silicon. His current work focuses on application of neural interfaces (e.g., wireless microelectrode arrays) for recording neural activities. The proposed study complements Dr. Cauwenberghs expertise and research interests. Dr. Bruce McNaughton is perfectly suited to mentor this research training and career development plan. He is a pioneer in the development and application of new conceptual approaches and innovative technologies in exploration of the physiological and computational basis of cognition. Dr. McNaughton's focus is on memory and memory disorders, and the dynamic interactions among neuronal populations and synaptic plasticity mechanisms that underlie these phenomena. Dr. McNaughton has a long history of training postdoctoral fellows and placing them in faculty positions at major research institutions, and my training with him will facilitate me advance toward an independent research career.

The consortium of mentors and advisors has been working together on several grants that are related to the theme of this project and have done extensive planning and preparation for this proposed work. I will be joining a highly functional team environment, which will ensure the success of this project. Indeed, it's hard to imagine a better training situation.

Finally, both institutes offer a variety of conferences, seminars, colloquia, journal clubs, and workshops. These include monthly colloquia hosted by the departments of Neurobiology and Behavior and Cognitive Sciences; the annual UCI MIND Distinguished Lecture Series on Brain, Learning, and Memory; the annual UCI Neuroscience Symposium; the bi-monthly CNLM Colloquium Series; CNLM's annual Conference on the Neurobiology of Learning and Memory; and a bi-weekly Medial Temporal Lobe journal club; the INC Chalk Talk series.



MARCELO WOOD, PH.D.

Chancellor's Fellow and Chair
Department of Neurobiology and Behavior
University of California, Irvine

GERT CAUWENBERGHS, PH.D

Co-Director, Institute for Neural Computation
University of California, San Diego

March 2, 2015

Re: Institutional support for the K01 proposal of Dr. Soyun Kim

Dear Reviewers:

As Chair of the Department of Neurobiology and Behavior at the University of California Irvine, and as Co-director of the Institute for Neural Computation at the University of California, San Diego, we enthusiastically support Dr. Soyun Kim's Mentored Research Scientist Development Award (K01) application, "**Hippocampal contribution to cortical neurodynamics: a test of the memory index theory**". This application represents a collaborative effort between UCI and UCSD, which we strongly encourage, and we will provide the Institutional Support for a major component of Dr. Kim's work and emerging career.

The NIMH/NIH's Mentored Research Scientist Development Award is intended for early-stage investigators to obtain additional mentored research experience from established mentors and pioneers and to facilitate transition to independence. Through her previous training, Dr. Kim has already shown potential to succeed as an independent young investigator. Thus, we are enthusiastic to commit to this K01 grant to support Dr. Kim's training and transition to independent research that combines her strengths in rodent and human behavioral neuroscience with new training in *in vivo* electrophysiology, optical neural imaging, and neuromodulation. We specifically commit to Dr. Kim's advancement through the following: 1) Providing the resources necessary to complete the proposed research and to advance to independence during the award phase, including career training through presentations, departmental seminars, career seminars, and didactic training, 2) Our strategic plan supports precisely this kind of research through our major program for research involving the neuroscience of memory, 3) We expect that positions will come open in this field and, Dr. Kim will be a strong candidate who we will actively recruit. We will support and encourage her applying for such a position, as would many of our faculty. If Dr. Kim instead chose to seek a position elsewhere, we would advise her in all aspects of the application, interview, and negotiation process, 4) While we cannot guarantee a faculty position without a job search, Dr. Kim has been offered a non-tenure track Assistant Project Scientist position at the Institute for Neural Computation, where she will receive training in the later phase of this award. Please note, this appointment is *not* contingent upon receiving a K01 award.

We will ensure that she continues as a full-time research employee with all pertaining rights, privileges and salary, and that at least 85% of time will be protected for research, and that any remaining time will be reserved for career development purposes. Thus, the institutes will not require any teaching, committee or administrative assignments, although such activities may occur for the purposes of career development as outlined in Dr. Kim's development plan. In addition, Dr. Kim will have a structured research career development experience with access to office and laboratory space and experienced administrative support as described in the proposed Career Development Plan, for research and grant management, including support from the identified key persons and any faculty capable of productive collaboration. The research proposal, with mentorship and resources from Drs. Cauwenberghs and McNaughton, fits well with the mission and capabilities of our department and institute, and we would highly support it.

Sincerely,

A handwritten signature in black ink, appearing to read "M W".

Marcelo Wood, PhD

A handwritten signature in black ink, appearing to read "Gert Cauwenberghs".

Gert Cauwenberghs, PhD

Specific Aims

How are memory and semantic knowledge organized in the brain? One well supported view is that, during wakeful behavior, the brain encodes and responds to sensory inputs on the basis of current knowledge, and stores the new data in raw form ('episodic memory'), which is distributed widely over neocortical (NC) modules. The Memory Index Theory holds that the unique pattern generated by the hippocampal formation (HF), the highest module in the cortical hierarchy, provides a tag that links together attributes of a given experience that are independently stored in weakly interacting modules throughout the NC. Spontaneous reactivation of index patterns from HF during sleep would enable retrieval of recent experiences stored in NC and the gradual extraction of 'semantic' knowledge from them by gradual rewiring of both short and long-range connections. This process then enables NC to encode regularities in the input as a compact, flexible model of the internal world (i.e., semantic knowledge). Thanks to the development of high-density electrophysiological technique, we now have a general understanding of how HF works, what kinds of information it transmits to NC, and the dynamics of HF and NC memory reactivation during sleep. But we know almost nothing about how NC activity is actually changed by the HF index codes. The central goal of the proposed work is to understand the interaction between the HF and NC in learning and memory reactivation. The fundamental questions are: how does the HF output (index) influence the NC neurodynamics? Can we replace the index in HF-inactivated brain so that impaired memory function can be restored? We aim to address both questions in two studies.

Aim 1: A test of memory index theory using optical imaging and optical stimulation in mice.

We aim to investigate how NC dynamics change with or without the HF index output during learning behavior and during subsequent sleep. The hypothesis is that hippocampal-dependent learning and NC activity patterns will be altered in the absence of HF output. Using voltage-sensitive dye imaging, we will assess the superficial layer of the NC in behaving (spatial learning in virtual reality, which is presumed to generate HF index output) mice and in lightly anesthetized mice. A range of NC dynamic parameters will be considered, including effective synaptic connectivity, coding sparsity, speed of memory replay, and complexity of resting state network. We also aim to investigate whether memory can be restored by replacing the HF index code in mice with HF lesion. According to the memory index theory, superficial NC contains a conjunctive representation of the HF index code, which is associated in each module with raw data stored in lower neocortical layers. The index code is essentially a random 'hash code', which implies that (in principle) the pattern could be replaced by artificial patterned stimulation of superficial NC. We will directly test this possibility using optogenetic (laser) stimulation delivered to NC in behaving and lightly anesthetized animals.

Aim 2: A test of memory index theory using electrical recording and electrical stimulation in rats.

We aim to evaluate the same hypothesis as in Aim 1, but using electrical methods in rats. We will again address the question of HF influence on the NC neurodynamics during learning behavior and during subsequent sleep. High-density microelectrode arrays and thin film cortical arrays will be used for recording cortical neurodynamics in behaving (spatial learning in virtual reality) rats and in lightly anesthetized rats. We then aim to investigate whether memory can be restored by replacing the HF index code by electrical stimulation through the arrays. The multi-channel arrays will serve as a prototype of a memory prosthetic device (ENIAC, under development by the mentors) that allows both stimulation and recording local field potentials (e.g., gamma power). Ultimately, the findings from this study will lay the groundwork for developing a memory prosthetics used for probing and modulating neural activities in clinical population.

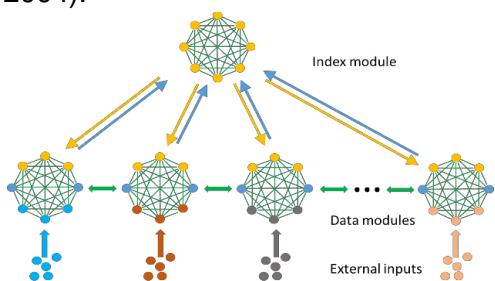
Research Strategy

Significance

The Memory Index Theory: Cortical hierarchies and the hippocampal-neocortical “dialogue”.

How memory is organized in the brain has been a continuing topic of interest in the history of neuroscience. During behavior, the brain responds to sensory inputs on the basis of current knowledge and stores the new data in raw form known as 'episodic memory'. During slow-wave sleep (when external sensory input is gated out), the brain re-processes the episodes to self-reorganize its own synaptic matrix, to compress (both spatially and temporally) and categorize the raw data into 'semantic' and meaningful knowledge. This self-organization involves repeated, interleaved reactivations of recent and older memories, and gradual adjustment of inter-modular cortical synaptic weights (McClelland et al., 1995). An influential theory (*The Memory Index Theory*) holds that the hippocampal formation (HF) plays a central role in orchestrating this process, referred to as 'memory consolidation'. Specifically, the theory posits that the unique pattern generated by the hippocampus provides a tag or 'index' that links together components of a given experience that are independently stored in weakly interacting modules throughout the neocortex (NC).

The average synaptic connectivity within NC is too low ($\sim 10^{-6}$) to support arbitrary associations if connectivity were random (O'Kane and Treves, 1992). Evolution may have solved this problem by creating a modular, hierarchical NC, with locally dense connectivity but very sparse intermodular connectivity (Fig.1). The densely connected individual modules are capable of storing arbitrary associations within their input domain. However, this leaves few connections to support sparse intermodular associations. Critically, lower-level modules are reciprocally connected, via Hebbian synapses, with higher-level modules. Thus, a given set of patterns encoded in separate low-level modules would generate a unique pattern in the next higher one. The higher-level pattern would be both stored associatively at that level and fed back to the lower-levels via modifiable synapses at the time of initial encoding. The top-down pattern thus would add an extra dimension to the lower level, which would serve to "index" (Teyler & Discenna, 1986; Squire et al., 1984; O'Kane & Treves, 1992; Paller, 1997; McNaughton et al., 2003) the corresponding event represented in the low-level modules. The HF is thought to create the index codes. Activation of a few sub-events in lower-level modules would result in associative retrieval of the index codes in higher modules, which would then enable associative retrieval of the complement sub-events in the other low-level modules. Moreover, repeated, spontaneous, retrieval of the index codes would provide opportunity for selection of the specific intermodular connections necessary to sustain the corresponding association, without the need for exhaustive intermodular connectivity (e.g., Wang et al., 2009). Gradual rearrangement of connections would also enable NC to extract regularities in the input to create compact, flexible representations (i.e., semantic knowledge) (Marr 1971, Alvarez & Squire, 1994; McClelland et al., 1995; Murre, 1997; Kali and Dayan, 2004).



*Fig. 1. The essential components of the **Memory Index Theory**. The NC memory system consists of hierarchically arranged modules (for simplicity only two levels are shown). Each module has dense internal connectivity and sparse connectivity with other modules. Each module acts like a Hopfield Net (autoassociative memory) capable of pattern storage in the domain of its inputs. The index module (the highest located in the HF) generates a code unique to each distribution of patterns (context) in the data modules and adds that code to the stored patterns during acquisition. Data in lower modules can then be retrieved either bottom-up or top-down. Gradual rearrangement of inter- and intramodular connections (during slow-wave sleep) results in encoding of 'semantic' knowledge. Among the implications of this theory are that some neurons in lower modules are modulated by the HF output*

(Burke et al., 2005), and the index module can (in theory) be replaced by artificial activation of the index recipient cells in lower modules (see Barnes & Wilson, 2014).

Abundant evidence (e.g., Bhatt et al., 2009) supports the idea that NC synapses are constantly being rearranged as a result of experience, and this rearrangement occurs primarily during sleep (Yang et al., 2012). The rodent HF exhibits two dynamic states; theta occurs during externally-directed wakeful behavior and during REM sleep, whereas large irregular activity (LIA; Vanderwolf et al., 1975) occurs during rest, consummatory behaviors, and slow-wave sleep. LIA is characterized by large, 50-100 msec, fluctuations in total activity that occur during sharp-wave-ripple (SPWR) events. (O'Keefe and Nadel, 1978; Buzsaki, 1986). SPWRs are semi-synchronous over the HF, but are locally variable in amplitude and duration. Reactivation of recent patterns is predominantly a correlate of the SPWR (Kudrimoti et al., 1999).

This is important because the SPWR is initiated in the CA3 field (Chrobak and Buzsaki, 1994) consistent with the theory that CA3 is the main autoassociator of the HF (Marr 1971; McNaughton & Morris, 1987; Treves & Rolls, 1992), and because widespread modulations of NC excitability ("up" and "down" states) during SWS are correlated with the peak of SPWRs in both rodents (Battaglia et al., 2004) and humans (Logothetis et al., 2012). Also, the most robust memory reactivation in NC takes place during periods of SWS in which there are frequent up-down transitions (Johnson et al., 2010). Yet, how memory reactivation during sleep contributes to memory consolidation and how the HF acts to integrate and support memories that are distributed across different modules remain to be clarified experimentally.

The theoretically optimal strategy for an indexing system would be to allocate an arbitrary, random pattern to each event. This pattern separation would optimize the indexing capacity and minimize interference. An indexing system, however, has two incompatible requirements: it must be noise tolerant and capable of pattern completion from an appropriate sub event, yet it must also create distinct patterns for similar events (i.e., pattern separation). Recordings from HF neurons suggest that this system satisfies these conflicting constraints (reviewed in McNaughton, 2010; Leutgeb et al., 2005; Frank et al., 2006; Navratilova et al., 2012); 'place' cells exhibit complete or partial 'remapping' with sufficient changes in external inputs or in internal state variables, such as behavioral context or the orientation of the head-direction system; yet, under some conditions, HF is able to retrieve the index codes from partial or degraded input (Colgin et al, 2010). These properties lead to the conclusion that the 'meaning' of an HF activity pattern can only really be understood in terms of the retrieval of activity patterns that it induces in lower NC modules. It is the latter modules which store the actual data. Therefore, it is theoretically possible to create artificial index codes (Barnes and Wilson, 2014).

If our Specific Aims are successfully achieved, the findings will advance our conceptual understanding of how neural systems interact during memory consolidation. Moreover, the study on neocortical stimulation of artificial index code will lay pre-clinical groundwork to develop a human prosthetic device for restoring memory.

Innovation/Approach

The proposed work is founded upon many years of theoretical and empirical work by the co-mentor in the field of memory research. Nevertheless, the theoretical question of how HC output contributes to NC function at the neural dynamics level remains to be elucidated. Answers to this question will clarify how the brain organizes memory to construct an adaptive representation of the world from experience.

The proposal aims to evaluate the index theory using innovative tools, including behavioral tests and recording in virtual reality, wide-field optical imaging of cortical neurodynamics, optical (laser) stimulation, and instrumentation for multi-site (up to 240 channels) cortical stimulation and electrophysiological recording. Virtual reality (VR) offers a unique experimental paradigm for spatial learning (in which the HF plays a critical role). In VR, animals can exhibit spatial memory while expressing virtual place-specific activity in the HF (see Fig. 5). While neural ensemble recording permits long-term and high-temporal resolution recording of neurons, wide-field optical imaging permits assessments of neuronal dynamics across wide cortical surfaces. For instance, voltage-sensitive dye imaging (VSDI) provides an overview of the subthreshold membrane potential activity (spontaneous or evoked) of the underlying superficial cortical neurons. In addition to high-density electrophysiological recording, McNaughton's laboratory is equipped with a VSDI rig combined with a high-spatiotemporal resolution resonance laser for optical stimulation of NC with complex patterns (see Preliminary data). All of these tools are essential for our test of the memory index theory (i.e., recording NC activity and delivering the HF index code to the NC).

In addition, the mentors have been collaborating on development and test of a wireless, power-efficient, bio-compatible neural interface that will permit 2-way communication between the host computer and NC. The Encapsulated Neural Interfacing & Acquisition Chip (ENIAC; Fig. 9) is designed for concurrent stimulation and recording of the NC and will consist of an implantable array containing several thousand contacts. The first prototype is under test, and a usable device for my experiments is expected within 1-2 years. The ENIAC will enable precision mapping and induction of cortical electrical activity, significantly changing the therapeutic possibilities for control of epilepsy, restoration of sensory, motor, and cognitive function after neurological injury. Although the proposed studies do not depend on the implementation of ENIAC, they will be greatly enhanced by it if the device is successfully completed in time.

We plan to combine these novel approaches with pre-established tools (e.g., cortical surface arrays available in the mentors' laboratories) and evaluate the hippocampal influence on neocortical

neurodynamics (Aim 1 and Aim 2). The general strategy is to assess cortical neural dynamics during awake behavior and during slow-wave sleep in animals with or without a functional HF. Then, on different cohorts of animals, we will stimulate the NC with 'virtual' index codes to see whether the stimulation restores memory in brains without the HF. We will use a VR-based learning paradigm, either combined with optical recording and stimulation in a mouse model (Aim 1) or combined with electrophysiological recording and stimulation in a rat model (Aim 2). We choose different animal models mainly for technical reasons; the optical methods are best suited for mice, whereas the electrical methods are best suited for rats.

Preliminary Data

The proposed work extends from approaches that have been proven to work in the co-mentor's laboratory. The optical approach (VSDI and laser stimulation), for example, provides the highest spatiotemporal resolution for both imaging and stimulating the superficial cortical neurons. Preliminary data from the co-mentor's laboratory (Fig. 2) shows that we can optically record cortical slow wave (k-complex) activity under urethane anesthesia.

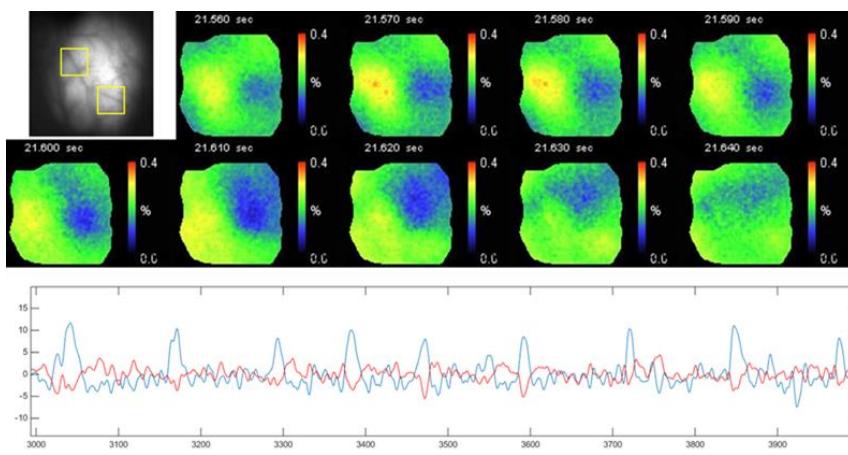


Fig. 2. Spontaneous dynamics of rat cortex under urethane anesthesia imaged with VSDI (unpublished data from mentor's lab). Colored plots are successive frames at 10 ms intervals from window shown in upper left, illustrating the complex spontaneous dynamics observable with this method. Bottom traces are mean activity from two small patches of cortex indicated in yellow over 10 s illustrating spatially restricted cortical slow oscillations (K-complexes). As can be seen in the figure, and as has been shown by others, the slow oscillations are actually spreading dynamic waves. We know that cortical memory reactivation occurs during these periods (Johnson et al., 2010), and we hypothesize that the VSDI signal patterns will recapitulate patterns observed during salient behavioral

events. Dr. Mohajerani has already demonstrated specific reactivation of sensory evoked responses (see Fig. 6) and has shown that the VSDI signal contains functional connectivity information (Mohajerani et al., 2013).

Using a 144-channel microelectrode array (available in McNaughton laboratory; See also Fig. 8), we recorded local field potentials from anesthetized rat cortex and stimulated through a few channels (Fig. 3). The preliminary data and analysis implies that a cortical surface array may be used for testing a prototype of ENIAC, for electrical recording of NC activity (e.g., local field potential) and stimulating the NC.

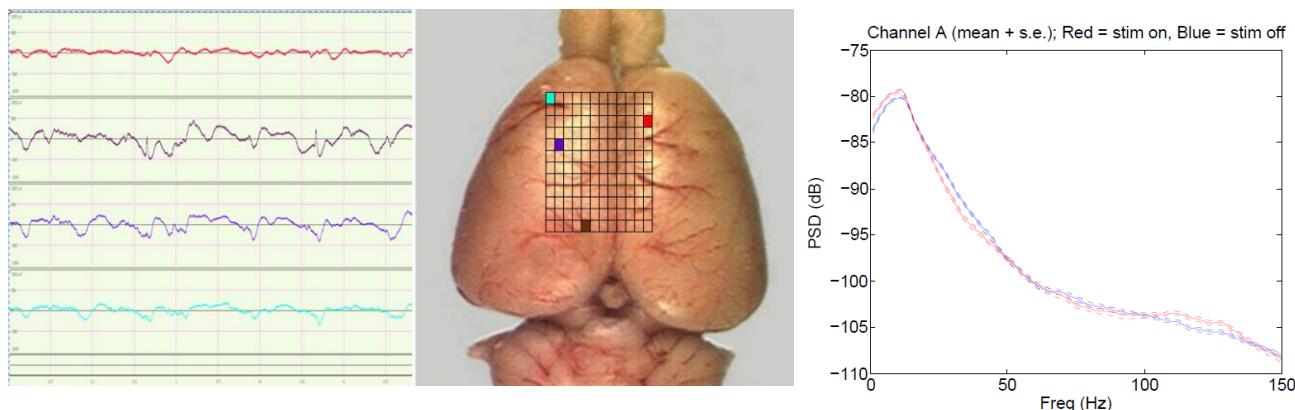


Fig. 3. (Left) Electrocorticogram of surface LFPs recorded by a 144-channel microelectrode array. Recordings from 4 representative channels are shown. (Middle) The position of the array is shown on a real brain image. Colored squares represent the position of 4 of 96 electrodes (currently we can only sample 96 channels simultaneously, but 128 channels will soon be implemented). Periodic electrical stimulation was delivered through two of the right hemisphere channels. (Right) Preliminary analysis suggests that stimulation reduced traditional gamma band activity and increased activity in the high gamma range.

Preliminary data from the co-mentor's laboratory shows that animals can learn to eyeblink at spatial locations (e.g., on a circular maze), and presumably the HF generates context-specific index patterns (Fig. 4).

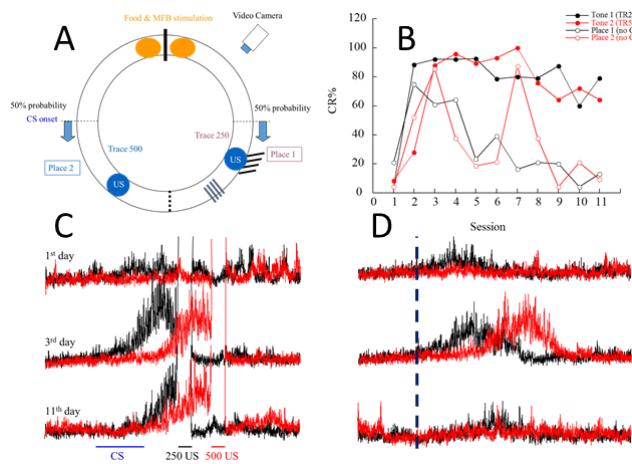


Fig. 4. Preliminary data for the behavioral task. These data were obtained by Dr. S. Kawahara in the McNaughton Lab in 2002 in an experiment designed to test whether rats could use spatial context (location on a circular track to discriminate two different CS-US intervals (250 vs 500 msec)(A), in a trace conditioning paradigm. However, the interval was confounded with the place at which the USs were delivered due to relatively constant running speed. The animal rapidly learned to blink at the associated places as shown by the fact that they blinked in the absence of the CS at those spots (open circles in (B) and EMG traces in (C and D)). Eventually they stopped responding to place alone and responded only when the CS was present; however, it was unclear whether they were actually using space to discriminate the interval, or merely using the cue to set the context for the place response (from Kawahara et al, SfN 2003). This experiment was never submitted for publication because Dr. Kawahara had to return to Japan for personal reasons and was therefore unable to collect the necessary additional data

from additional animals. Nevertheless, the data clearly show that rodents can learn to blink at fixed locations on the track, which is the essential parameter for the proposed studies.

Aim 1. Test of memory index theory in mice using optical imaging and stimulation.

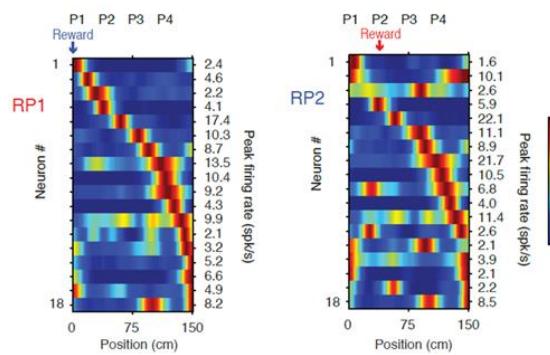
Rationale: The memory index theory suggests that memory reactivation in the NC should be disrupted without the HF index output. To test this idea, I will compare NC activities between mice with and without the hippocampus during behavior (when the HF index pattern is generated) and during subsequent sleep (when the HF index pattern is re-activated) (Experiment 1). The theory also suggests that superficial NC contains a conjunctive representation of the HF index code which is associated in each module with raw data stored in lower layers. This also implies that the index code is essentially a random ‘hash code’, which could be (in principle) replaced by artificial patterned stimulation of superficial NC at the time of encoding and be used to retrieve the stored items during sleep for consolidation. We should be able to test this by applying weak, random pattern stimulation to the NC during behavior and during sleep, and ask whether memory reactivation or consolidation is restored by this neuromodulation (Experiment 2). Note that the purpose of stimulation is not to attempt to “recreate” memories directly through cortical patterns that represents the memory itself; rather, it is to test the index theory by merging weak, random patterns, delivered to the superficial layers of the cortex, with ongoing activity representing the event.

Animals: Optogenetic mice will be used for Experiment 1 and 2, particularly because optical stimulation (using fast-scanning laser) will be used for replacing hippocampal index pattern. Although Experiment 1 alone would not necessarily require optogenetic mice (i.e., imaging without any stimulation), we would still need the same strain of mice to serve as specific control for optically stimulated mice in Experiment 2. We will cross two commercially available mouse lines (Rasgrf2-2A-dCre and Ai32, The Jackson Laboratory) and acquire offsprings that express channelrhodopsin-2/EYFP fusion protein mainly within the pyramidal neurons of cortical layer II and III. Although unlikely, if breeding is not successful, we will use a direct viral transfection method to generate similar type of optogenetic mice expressing ChR2 in superficial cortical layers.

In Experiment 1, animals will be divided into two groups: 1) control ($n = 10$) and 2) HF lesioned ($n = 10$). We will use the conventional neurotoxic method (NMDA infusion) for lesioning bilateral hippocampi. In Experiment 2, animals will be divided into three groups: 1) control ($n = 10$) with stimulation, 2) HF lesioned with stimulation ($n = 10$), and 3) HF lesioned with stimulation representing different index pattern ($n = 10$).

Behavior: We will use a hippocampal-dependent spatial learning paradigm carried out in the mouse VR system (Fig. 5). All animals will be handled, water deprived, and pre-trained before testing to run on a continuous circular track in VR for water rewards. In addition, an aversive stimulus (e.g., airpuff) will be delivered at a particular location in the VR. This way we will train animals to eyeblink by associating airpuffs with spatial location. Dr. McNaughton's group has previously established that rats learn this very quickly on a real circular track (Fig.4). Eyeblink response will be captured by camera under infrared illumination. We have shown that animals can learn to pause for water at a specific VR location, so we expect the spatial eyeblink response can similarly be learned in VR. As a backup, we may revert to the trace eyeblink

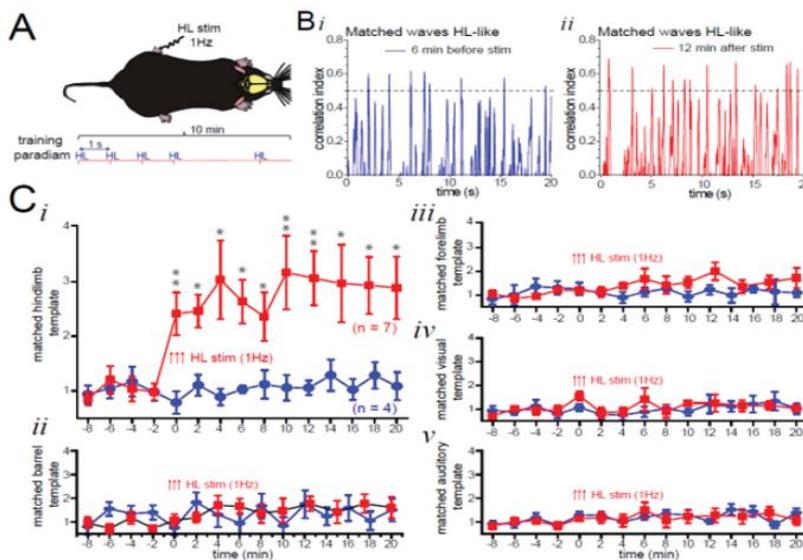
conditioning paradigm (albeit requiring a greater number of training trials than spatial learning) in head-fixed mice.



and the animals express normal looking place fields in the hippocampus (right). Airpuffs will be delivered to the eye to condition the mouse to eyeblink at a specific location. Eyeblink responses will be monitored by camera under infrared illumination. This system does not interfere with the VR display. (Right) Preliminary data showing reliable place fields in VR recorded by the mentor's group (courtesy of Dun Mao, Ph.D. Student). Mice were running on a simple VR apparatus (continuous circular belt in which the spatial cues repeat periodically) while CA1 pyramidal cells were recorded using a silicon probe.

Experiment 1: Voltage-sensitive dye imaging during VR learning and during sleep state

The VR apparatus allows us to assess NC dynamics in appropriate behavioral contexts and is compact enough to be compatible with VSD imaging. All animals will undergo headplate implantation and craniotomy before behavioral training. The headplate has a large cranial window (7 mm x 6 mm) covering the mouse cortex (bregma 2.5 to - 4.5 mm, lateral 0 – 6 mm), allowing both wide-field imaging and optogenetic stimulation across different cortical areas. Data acquisition and analysis will be performed as previously completed by the collaborator's laboratory (Fig. 6).



will be added to the cranial window 1 – 2h before VR testing. During imaging, the dye will be excited at 630nm. To reduce potential VSD signal distortion caused by large blood vessels, we will focus into the cortex to a depth of ~1 mm. VSD fluorescence will be obtained at 673 - 703nm (bandpass optical filter). Twelve-bit images will be captured at 6.67-ms temporal resolution with a CCD camera and an EPIX E4DB frame grabber with XCAP 3.1 imaging software. To reduce regional bias in VSD signal caused by uneven dye loading or brain curvature, all VSD responses will be expressed as a percentage change relative to baseline VSD responses ($\Delta F/F_0 \times 100\%$) using custom-designed Matlab program (courtesy of Dr. Mohajerani).

Following VSDI during VR running, we will conduct additional VSDI during subsequent slow-wave sleep to test whether cortical memory traces reemerge during this period with or without the HF. Mice do exhibit periods of slow-wave activity and hippocampal SPWRs in VR when the ability to virtually move is suspended (McNaughton group, unpublished), but, if necessary, to establish a prolonged SWS-like state we

Fig. 5. (Left) A reproducible 2-D virtual reality (VR) system for mice used in Aim 1. Mice are head fixed while running on a treadmill for water reinforcement. The animal runs unidirectionally on a linear (but repeating) track or on a circular track. Under these conditions, head direction updating is not required to maintain consistent place fields (which is a problem in fully 2-D VR when vestibular input is absent; Ravassard et al., 2013),

Fig. 6. Reactivation of recent sensory experience in a rodent model. (A) Hindlimb (HL) was stimulated for 10 min. Cortical spontaneous activity was measured with VSDI before and after stimulation. (B) Effect of stimulation on regional patterns of spontaneous activity was assessed by measuring the correlation index between HL sensory-evoked VSD template and spontaneous signals before (blue trace) and after (red trace) stimulation. (C) HL stimulation specifically increased the spontaneous expression of somatosensory response patterns compared to either no sensory stimulation to patterns induced by other stimuli. X axis is time in minutes (Mohajerani et al., unpublished).

A voltage-sensitive dye (RH-1692, Optical Imaging, New York, NY)

will lightly sedate the animals with urethane after running (urethane produces a SWS like state; Clement et al., 2008; also see Fig. 2).

Experiment 2: Hippocampal index replacement by optical stimulation during VR learning and during sleep state

We will optogenetically apply weak, random stimulations to establish the index pattern in the cortex, associated with the task-related cortical representation (Fig. 7). A different cohort of mice with and without the HF will be tested. On another group of mice with HF lesion, stimulation representing a different index pattern (e.g., index coded at a non-learned location in VR) will be applied. Animals will undergo surgery and behavioral training as in Experiment 1, and high spatiotemporal resolution resonance laser (473nm) stimulation (Lim, Mohajerani et al., 2012) will be applied during initial acquisition of learning in the VR and during ‘off-line’ (resting) periods. The entire dorsal cortex will be stimulated while cortical neurodynamics are measured by VSDI. We will also assure that the stimulation does not actually interfere with spatial learning.

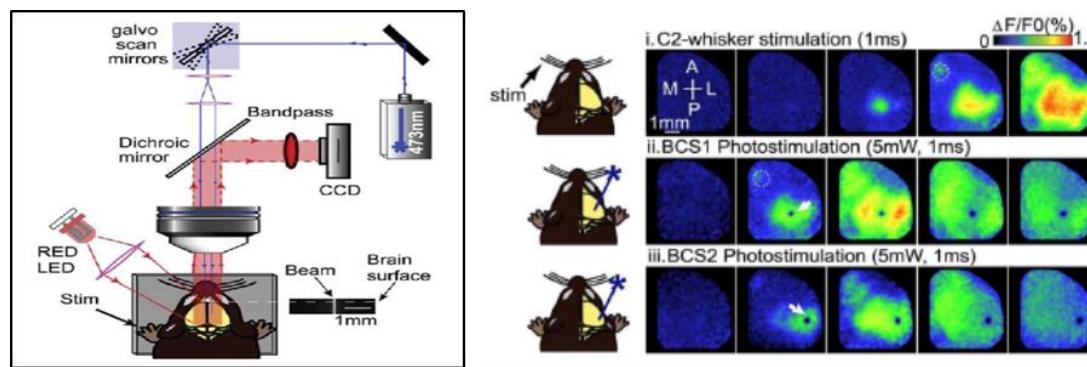


Fig. 7. (Left) An illustration of the setup for simultaneous VR training, ChR2-photostimulation and optical imaging (courtesy of Dr. Majid Mohajerani, who will provide technical advice and training for this method; see Letters of Support). (Right) Reproduced image from Lim, Mohajerani et al., (2012) showing how laser stimulation can elicit cortical activity similar to simple sensory stimulation. Our experiments will use substantially weaker stimuli in animals expressing ChR2 in layer II-III pyramidal cells, and the stimuli will consist of rapidly changing spatiotemporal patterns covering large areas of cortex. The laser frequency (473 nm) does not encroach on the VSDI fluorescence signal (673-703 nm bandpass). Laser location can be modulated at high speed (e.g., for illustration, it could write ~1000 alphanumeric characters per sec over the cortex surface) and the spot size collimated to 100 μ m.

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Predicted and alternative outcomes: We will assess the data in the first cohort of mice (Experiment 1) with and without intact hippocampus to investigate hippocampal influence on learning and memory during behavior and on reactivation during slow-wave sleep. I expect that performance on VR as well as various parameters of NC neurodynamics (e.g., coding sparsity, speed of memory reactivation, and complexity of resting state network) will be altered in the absence of HF output. This would implicate an important role of the HF in indexing of memories that are distributed across different modules. The data from Experiment 2 will be particularly useful in determining whether the HF index could be replaced by artificial index and whether the treatment restores learning and persistence of memory (during sleep) that have been impaired by hippocampal dysfunction. I expect that HF lesioned animals receiving the “virtual” index codes induced during learning will perform better in VR and exhibit reactivation during sleep. Alternatively, HF lesioned animals receiving a different pattern of index codes (i.e., index patterns representing a non-learned location) will not improve with respect to the parameters. Whether the stimulation alters behavior or NC dynamics in control mice remains less clear, although one may expect that the artificial index code (which is weak and random) may interfere with the patterns of original HF index code.

Timeline: I have learned the head-post surgeries for mice, and started behavioral training of mice in VR. I participated in setting up and testing the VSDI rig in Dr. McNaughton's lab with the supervision of Dr. Mohajerani. In April 2015, I will spend one month in Dr. Mohajerani's lab in Canada receiving detailed training on the surgeries and VSD image analysis protocols. Thus, I will be fully prepared to begin the imaging and optical stimulation experiments by summer 2015 and fully expect to complete them during the first two years of the grant period.

Aim 2. Test of memory index theory in rat using electrical recording and stimulation.

Rationale: As described in Aim 1, Aim 2 will test the same hypothesis that the HF plays a critical role in “indexing” attributes of experience and driving off-line reactivation during sleep. To test the hypothesis, I will compare NC activity between rats with and without the hippocampus during behavior and during

subsequent sleep (Experiment 1). Assuming that the index code could be (in principle) replaced by artificial patterned stimulation of superficial NC at the time of encoding and be used to retrieve the stored items during sleep for consolidation, I will deliver weak, random patterned stimulation to the NC during behavior and during sleep, and ask whether memory reactivation is restored by this neuromodulation (Experiment 2). Note that the ultimate goal of Aim 2 is to lay the foundational work for developing the ENIAC device which is based on electrical stimulation and recording. Thus, rats will be used instead of mice, because the high-density cortical surface arrays (i.e., prototype of ENIAC device) are more compatible with rats than with mice.

Animals: Fischer 344 Brown Norway F1 Hybrid rats will be used. Animals will be handled prior to any surgery. In Experiment 1, the animals will be divided into two groups: 1) control ($n = 8$) and 2) HF lesioned ($n = 8$). We will use the conventional neurotoxic method (NMDA infusion) for lesioning bilateral hippocampi. In Experiment 2, animals will be divided into three groups: 1) control ($n = 8$) with stimulation, 2) HF lesioned with stimulation ($n = 8$), and 3) HF lesioned with stimulation representing different index pattern ($n = 8$). Craniotomy will be performed to fix the cortical array on the surface of the dura matter.

Behavior: Behavior: Similar to Aim 1, rats will be trained for eyeblink conditioning in spatial location in the VR system (see Fig. E1). All animals will be handled, water-deprived, and pre-trained on the setup before testing. Animals will learn to navigate in the VR (i.e., explore toward goal locations at which water rewards are given). Airpuffs will be delivered at certain locations in the VR. Eyeblink response will be captured by camera under infrared illumination. Alternatively, if we have any problems with VR learning in rats, we may revert to real maze-based spatial eyeblink conditioning (using electrical stimulation and EMG recording) in freely moving rats as illustrated in Fig. 4 (a circular maze with video-tracking system has been set up in Dr. McNaughton's laboratory).

Experiment 1: Cortical neural ensemble recording during VR learning and during sleep state

The rat VR apparatus allows us to assess NC dynamics in appropriate behavioral contexts. Rats will be restrained in vests while navigating on a trackball, allowing relatively stable recording. We will use two types of cortical arrays: a custom-designed 144- or 240- channel array and a thin-film multi-channel ECoG array (provided by Dr. Shadi Dayeh, see Letters of Support) (Fig. 8). Data will be acquired and amplified by a PC board connected to low-noise, low-power, and low-input bias current Op-amps. Cautions will be taken to reduce output impedance and minimize signal distortion. We will also make use of 3D-printed plastic headstages, which conforms to the rat skull and enables precise and secure implantation of electrodes and screws (printed by ProJet 1200, 3D Systems). The printer uses micro-SLA technology (stereo-lithography) and has an effective resolution of 43 micron (XY plane) and 30 micron (Z plane). We will conduct further recording during subsequent slow-wave sleep (in lightly anesthetized animals) and test whether cortical memory traces are replayed in the presence or absence of the HF.

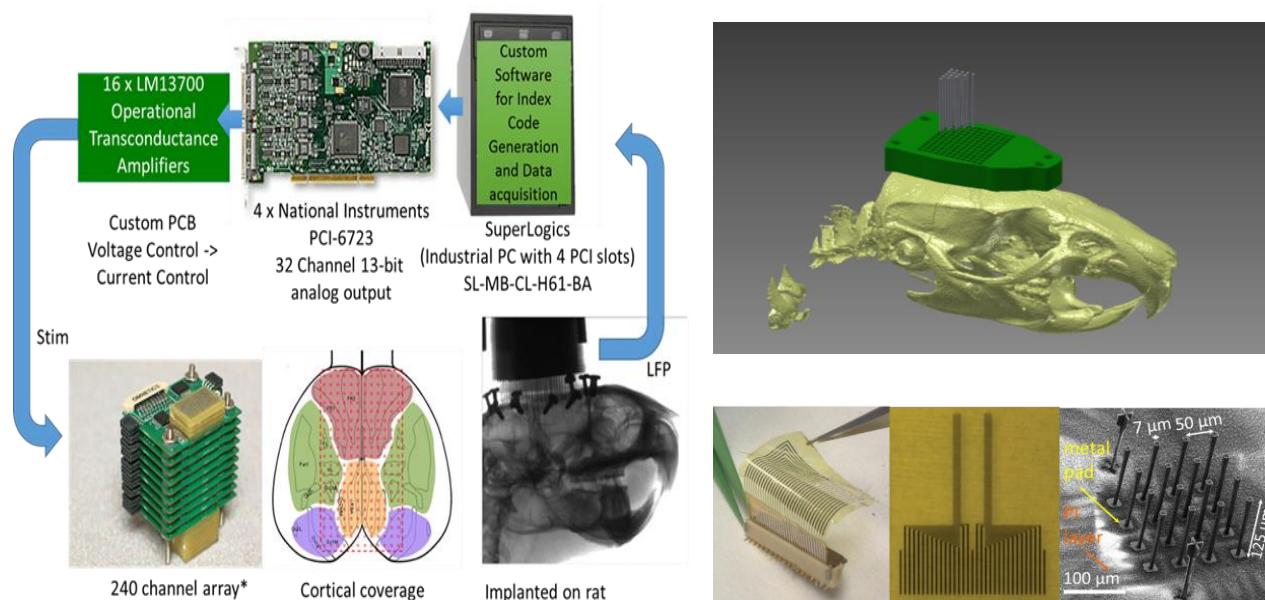


Fig. 8. (Left) A prototype of ENIAC array. We will use off-the-shelf components and an electrode array already in use in the mentor's lab (Hoffman & McNaughton, 2002; Battaglia et al., 2004; Tatsuno et al., 2006). The array consists of a set (144 or 240) of

30 ga cannula tubes on a 700 micron lattice. Each tube is individually connected to a separate channel of a set of PC boards which in turn can be connected to either recording op-amps or to a stimulus channel. In this array, we can use either all channels for stimulation, all channels for recording or a mixture. The published version allows individual positioning of 240 single microelectrodes in depth in the cortex; however, for the initial studies I will focus on cortical surface LFP recording. (Right, Top) An illustration of a 3D-printed headstage (green) placed on top of a rat skull image (rendered from a CT scan). (Right, Bottom) I will also have access to thin film multi-channel ECoG arrays under development at UCSD (by Dr. Shadi Dayeh; see Letters of Support) which will enhance cortical LFP recording and stimulation through nanoscale protrusions that extend 125 μ m into the cortex.

Experiment 2: Hippocampal index replacement by electrical stimulation during VR learning and during sleep state

Weak, random-patterned stimulation will be delivered via the cortical arrays used for recording. Thus, we will replace the original hippocampal index pattern in the cortex, associated with the task-related cortical representation. We will first determine important stimulation parameters (e.g., pulse duration, current density) and record spontaneous and evoked local field potentials (LFPs) of stimulated cortical neurons.

For stimulation, a different cohort of rats with and without the HF will be tested. On another group of rats with HF lesion, stimulation representing a different index pattern (e.g., index coded at a non-learned location in VR) will be applied. Stimulation will be delivered during initial acquisition of learning in the VR and during 'off-line' (resting) periods. Utilizing the LFP data (e.g., spindle, sharp-wave ripple), I will assess gross measures of replay (e.g., explained variance) and replay of sequences of neuronal activity across the cortex (e.g., population cross-correlation). The cortical arrays may be replaced by the ENIAC once it becomes available (Fig. 9).

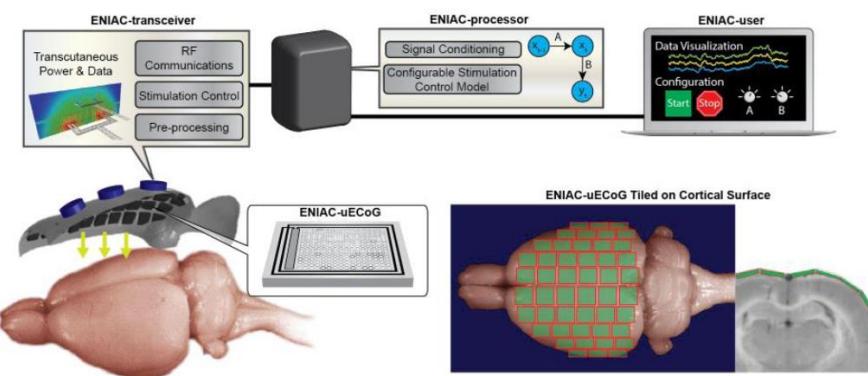


Fig. 9. Schematic of ENIAC array embedded in an artificial skull cap generated by 3-D printing, and mounted on one hemisphere of a rat cortex. About 24 ENIAC chips, each with 256 channels could be mounted on each hemisphere, for a total of 12288 contacts. The first prototype of the ENIAC has been produced at UCSD and I participated in the initial testing in a rat. The prototype is not yet encapsulated for capacitative interface with the brain, but when interfaced with the electrode array shown in Fig 8, it was able to wirelessly record

and deliver stimulus pulses at up to 60 μ A.

Predicted and alternative outcomes: It is expected that the NC activity pattern will be observed during learning (tagged by the HF index) and then will reappear during SWS in rats with intact hippocampus but not in the other. Rats with HF lesion will be impaired in VR spatial learning. Also, various NC activity parameters (e.g., spontaneous population activity, spatiotemporal decorrelation times) will be perturbed in the brains with damaged HF. Electrical stimulation (replacing the HF index output) delivered to the superficial layers of the NC will restore memory function and memory reactivation in rats without functional HF, only when the patterned stimulation is relevant to the original index. Alternatively, electrical stimulation representing non-learned context will not restore memory in HF lesioned rats. If our approach of electrical stimulation works, the findings would specifically be a prelude to the development of a closed loop system (the ENIAC) for replacing normal HF input to cortex in brain with HF damage.

Timeline: I have learned surgical skills (e.g., craniotomy) for rats for placing the cortical surface array. Experiment 1 will start in year 2 and continue with Experiment 2 in the remaining years of the grant period.

Both Aim 1 and Aim 2 address a common research question of memory index theory, yet different types of approaches will be employed. Thus, the success of each project will not completely depend on the other. Regardless of the outcome from the proposed experiments, I will have been extensively trained in novel skillsets for probing and modulating neural activities by the end of the grant period. The overall results from this grant will allow me to conceive an independent proposal to assess the interaction between the hippocampus and specific cortical areas (e.g., medial prefrontal cortex, retrosplenial cortex) underpinning high-order cognitive functions. Furthermore, the collaborative work (with mentors and advisors) on development of clinically acceptable memory prosthetic will help me broaden the scope of my research into translational neuroscience, to which my previous experience with memory-impaired patients (post-doctoral training in human neuroscience) will become more relevant and useful.

VERTEBRATE ANIMALS

Proposed Animal Usage

All experiments involving animals are performed in strict accordance with the NIH Guide for the Care and Use of Laboratory Animals and are reviewed and approved by the University of California, San Diego IACUC and University of California, Irvine IACUC before studies begin. All mice (C57BL/6J background) will be male and 21 days – 4 months of age at the onset of the experiment. All rats (Brown Norway/Fischer 344) will be male and 1 – 4 months of age at the onset of the experiment. Animals will be handled prior to any procedures, including survival surgery, behavioral testing, optical imaging and stimulation, and electrical recording and stimulation. The total number of animals used should not exceed 400. This estimation is based upon successful completion of all possible experiments outlined in the Research Strategy.

Justification for use of animals

The use of animals in the proposed studies is essential as we are examining neocortical neurodynamics with and without a functional hippocampus. All animals proposed for this study are well characterized strains for behavioral studies. For this study rodents are the most appropriate model systems due to the following reasons: 1) a great deal is known about the spatial information processing circuitry, classical conditioning, and memory reactivation in rodents; 2) rodents are especially useful for assessing the relationships among neural variables that cannot be assessed experimentally in humans; and 3) much relevant background research on this approach has been performed in rodents, providing for a rich base for next critical steps.

Veterinary Care

All animals will be group housed in the vivarium facilities of UCI or UCSD, where animal care is provided by the staff under the supervision of the campus veterinarians who routinely check the health of the laboratory animals and the quality of their care and quarters. The veterinary and vivarium staff has extensive experience working with these animals and established protocols are in place for the care of rodents. The facilities are operated under guidelines set forth by the NIH and is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC).

Assurance of Minimal Discomfort

All surgical procedures will be conducted under aseptic conditions that have been approved by the IACUC committee. All recovery surgical procedures will be accomplished via isoflurane induced at a concentration of 4-5% isoflurane (oxygen at 2 L/min) and maintained at 2-3% isoflurane (oxygen at 0.5-1 L/min) for the remainder of the procedure. Depth of anesthesia will be assessed in all animals prior to the commencement of procedures via observation of respiration, tail, and toe pinch. Respiration and heart rate will be monitored regularly throughout surgery. Animals will be kept warm with heating pads and monitored until full recovery from anesthesia before return to the animal colony room. Following surgery the animals' condition, including electrode stabilization, will be monitored 2-3 times a day for 2-4 days and analgesic will be administered 1x day. Euthanasia will be consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. Animals will be maintained on a 12 h light/12 h dark cycle, and have access to food and water ad libitum. For behavioral experiments animals will be food or water deprived to 85-90% of their body weight.

Method of Euthanasia

Animals will be euthanized under deep Euthasol (100 mg/kg of sodium pentobarbital) anesthesia, in some cases followed by perfusion with phosphate-buffered saline and formalin. This method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association.

RESOURCES SHARING PLAN

Data Sharing Plan

Intellectual property and data generated under this project will be administered in accordance with both University and NIH policies, including the NIH Data Sharing Policy and Implementation Guidance of March 5, 2003.

Ownership of sole or joint inventions developed under the project will be owned by the institution(s) employing the inventor(s). Inventors shall be determined by U.S. Patent law, Title 35 SC. University and Participating investigators/institutions will disclose any inventions developed under the project and such inventions will be reported and managed as provided by NIH policies. Sole inventions will be administered by the institution employing the inventor. Joint inventions shall be administered based on mutual consultation between the parties. Similar procedures will be followed for copyrights.

Materials generated under the project will be disseminated in accordance with University/Participating institutional and NIH policies. Depending on such policies, materials may be transferred to others under the terms of a material transfer agreement.

Access to databases and associated software tools generated under the project will be available for educational, research and non-profit purposes. Such access will be provided using web-based applications, as appropriate.

Publication of data shall occur during the project, if appropriate, or at the end of the project, consistent with normal scientific practices. Research data that documents, supports and validates research findings will be made available after the main findings from the final research data set have been accepted for publication. Such research data will be redacted to prevent the disclosure of personal identifiers.

Sharing model organisms

If needed, we will share materials and our management of intellectual property, adhering to the NIH Grant Policy on Sharing of Unique Research Resources including the Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources issued December 23, 1999. All 'model organisms' (e.g., optogenetic mice) by this project will be distributed widely or deposited into a repository/stock center making them available to the broader research community, either before or immediately after publication, in accordance with University policies. If we assume responsibility for distributing the newly generated model organisms, we will fill requests in a timely fashion. In addition, we will provide relevant protocols and published genetic and phenotypic data upon request. Material transfers will be made with no more restrictive terms than in the Simple Letter Agreement (SLA) or the Uniform Biological Materials Transfer Agreement (UBMTA) and without reach through requirements. Should an intellectual property arise which requires a patent, we will ensure that the technology (materials and data) remains widely available to the research community in accordance with University policies and the NIH Principles and Guidelines document.

Genome Wide Association Studies

N/A