PROFESSOR L STAN LEUNG

Brain waves

In this discussion, **Professor L Stan Leung** outlines his work on hippocampal theta oscillations, which examines both their generation and the behavioural functions with which they are associated

What drew you to specialise in research of the hippocampus?

The initial choice of the hippocampus was made due to its rich patterns of neural activity. I did my PhD dissertation on the spatiotemporal patterns of evoked potentials in the hippocampus, in the laboratory of Professor Walter Freeman at the University of California, Berkeley. I was drawn to Freeman's laboratory because of his elegant engineering systems approach to oscillations in the olfactory system.

How much work has been done in the field to uncover the relationship between hippocampal theta oscillations and memory, sensory and motor functions?

Oscillations were considered epiphenomena, but as the relation between oscillation and brain function becomes better known, interest in the field has soared. Theoretically, oscillation provides both a means and an indication of interactions among neurons. In the hippocampus, functions of theta oscillations are strengthened by enhanced theta oscillations during active behaviours and memory tasks, discovery of theta oscillations in single neurons, and the participation of theta oscillations in neuronal coding of the spatial environment by place cells and grid cells. The mechanistic details of how theta oscillations facilitate neural coding, transmission and memory formation remain to be worked out. There is a general concept that normal theta (and gamma) oscillations in the hippocampus are necessary for sensorimotor integration and organisation of some behaviours.

Do your hypotheses depart from existing research, or expand upon it?

We try to look at research from different angles and disciplines. In one line of work, we try to integrate existing experimental data by theoretical biophysical models, and the models predict results and suggest avenues for further study. Most of our work is still experimentally-based, and our hypotheses are very much influenced by existing research. We try to create conditions for experimental observations that may lead to new findings.

You recorded spontaneous electroencephalography (EEG) evoked field potentials and neuronal firings in rats engaged in different behavioural states. What were the key differences between walking (active awake), awake immobility, slow-wave sleep and rapid eye movement sleep? Are hippocampal theta oscillations implicated in involuntary movements and spasms?

Hipppocampal theta activity is manifested during active awake behaviours and rapid-eye-movement sleep, but is low during involuntary movements such as licking, chewing and grooming in rats. Theta rhythm may be generated by cholinergic and atropine-sensitive inputs induced by sensory signals during immobility, and non-cholinergic, atropine-resistant inputs during voluntary movements. Many neurons fire in a rhythmic fashion, in phasic relation to the theta EEG. Awake-immobility and slow-wave sleep are characterised by irregular slow activity, with many neurons fired in bursts during the sharp waves.

To what extent can your findings in rats be applied to humans?

The theta EEG is not as high-amplitude in humans as compared to rats, and there are species-specific behavioural conditions for the observation of theta oscillations. However, in electrical recordings of the human hippocampus, theta oscillations have been shown to accompany memory tasks and during spatial navigation in real life or in virtual reality. Septal and other subcortical modulation of hippocampal synaptic transmission and plasticity is similar between humans and rats, and functional connections of the hippocampus to the nucleus accumbens and other subcortical structures likely mediate similar sensorimotor gating functions. Cholinergic and histaminergic modulation of consciousness through the hippocampus and neocortex is common among humans and animals.

Who have been your collaborators in this study, and how reliant have you been upon an integrated, multidisciplinary approach?

We have a relatively small laboratory of six to eight people. Our collaborators have been in complementary fields to expand our knowledge and technical horizons. We are currently collaborating with Dr Seyed Mirsattari in functional magnetic resonance imaging and epilepsy, Dr Nagalingam Rajakumar for schizophrenia animal models and functional anatomy, Dr Ian Herrick for anaesthesiology, and Dr Luis Colom at the University of Texas, Brownsville for the septal modulation of hippocampal function.

What are the primary benefits of working as a researcher in Canada?

I would rank stability as the primary benefit. My academic responsibilities have included teaching and administrative duties, but not needing to request my own salary through external grants is a benefit. While funding levels are somewhat limited in Canada, continuity in research funding is important, and I have managed to be continuously funded through the years. After some very lean research support in the past, it is encouraging to see more investment of the federal government in research in recent years.

Mind map

Innovative analyses of hippocampal theta rhythm are being conducted by an interdisciplinary team at the University of Western Ontario, Canada and an encouraging link with dysfunctions including schizophrenia may have been uncovered

HIPPOCAMPAL THETA RHYTHM is a strong oscillatory pattern which can be observed in a number of mammalian species including humans, and is particularly prominent during active behaviour. It is known that dysfunction in the hippocampus and its neural circuits underlies the abnormal physiology of Alzheimer's disease, schizophrenia and temporal lobe epilepsy. Despite this, the process by which theta rhythm provides for neural processing is still far from clear. Led by Professor L Stan Leung, a project is underway at the University of Western Ontario to investigate some of the phenomena surrounding the hippocampus and theta rhythms. The frequency of theta rhythm is between four and 10 Hertz, and is important for both synaptic transmission and synaptic plasticity, the latter being the ability of neurons to change the strength of their affiliation over time due to usage.

The objectives of the investigation are wide-ranging, but include both general questions such as how theta-frequency brain oscillations facilitate processing of single neurons and affect behavioural functions, and more specific aims such as examining the generation of the hippocampal rhythm both in time and space.

It seems that much of the rhythmic drive is provided by the medial septum, but oscillations intrinsic to the hippocampal neurons may also play an important role. Beyond this, questions of how hippocampal neural processing is modulated by its medial septal inputs and how sensorimotor functions are mediated by neural circuits involving the hippocampus must also be addressed. The examination of hippocampal neural circuits is integral to the study of a number of conditions, and may well have implications in the treatment of dysfunctions including Alzheimer's disease and behavioural comorbidity associated with temporal lobe epilepsy.

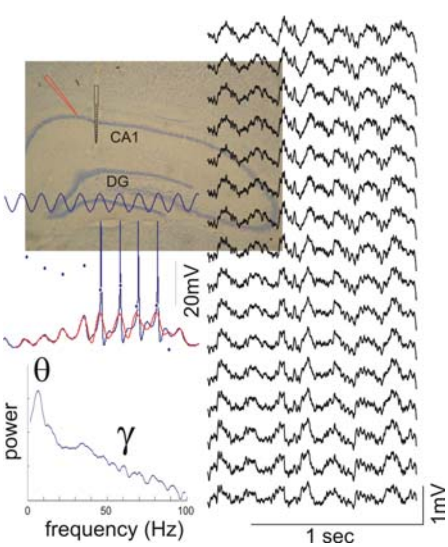
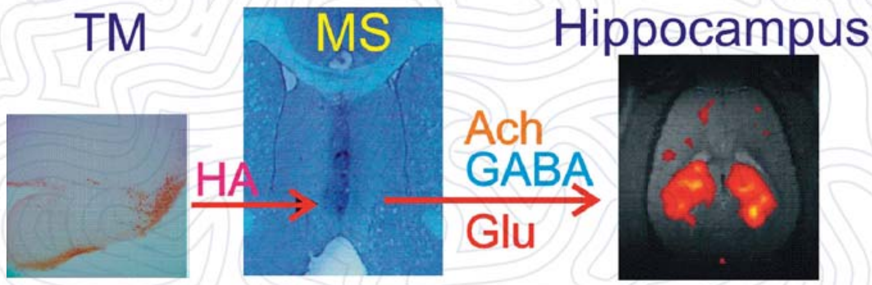


FIGURE 1. Hippocampal theta depth profile, spike phase precession and power spectral analysis..



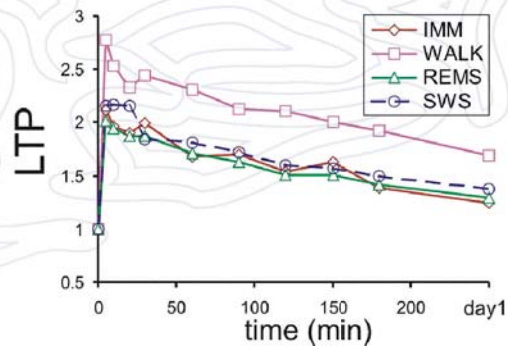


FIGURE 2. Histaminergic (HA) inputs from the thalamus tubermammillary nucleus (TM) and other inputs projecting to the medial septum (MS) affects long-term potentiation (LTP) in the hippocampus via cholinergic inputs during different behavioural states. Right panel shows bilaterally synchronous resting state functional magnetic resonance imaging in the hippocampus.

Leung's research is making progress in a densely complex field. In order to maximise their success, he has ensured the team is comprised of complementary expertise in functional imaging, epilepsy, schizophrenia, anatomy, and anaesthesiology. The approach his group has taken, based on recording hippocampal electrical activity using linear arrays of electrodes in anaesthetised and freely behaving rats, is proving to be successful, and they have made a number of significant findings. These include demonstrating that a cholinergic input to the hippocampus is involved in sensory processing, cognitive function and synaptic plasticity, and also discovering a link of medial septal modulation of the hippocampus in behavioural responses to psychoactive drugs and general anaesthetics. Further results so far have demonstrated that inputs into the hippocampus are important for the expression of certain dysfunctions, notably causing behaviours of a schizophrenic type.

LINKS WITH DYSFUNCTIONS

A major reason that the study of hippocampal theta rhythm is of such importance is because of the impact it may have on dysfunctional neural circuits in the physiology of Alzheimer's disease, schizophrenia and temporal lobe epilepsy. The team began with the operation in normal behaving animals of acetylcholine's modulation of hippocampal neural plasticity and synaptic transmission. From this, they were able to infer that a loss of cholinergic modulation of the hippocampus would adversely affect both hippocampal neural circuits and synaptic plasticity in Alzheimer's disease. This links with the idea that neuron loss in the basal forebrain, in particular the medial septum that projects into the hippocampus, affects the hypnotic and stimulant response to a range of drugs, including psychoactive drugs and general anaesthetics. There have also been interesting discoveries made in schizophrenic behaviours in animal models, including locomotor hyperactivity, loss of automatic filtering (gating) of sensory signals and sensory gating of motor response (prepulse inhibition). All of these were connected with septal modulation in the hippocampus, and are thought to be expressed through septal GABAergic neurons. Finally, whilst temporal lobe epilepsy models are associated with changes in excitatory and inhibitory synaptic transmissions in the hippocampus, the scientists also found that the subcortial spread of seizures to the nucleus accumbens is responsible for the hyperactive behaviours immediately after a temporal lobe seizure.

UNCOVERING POSSIBLE TREATMENTS

The connection through many of the above dysfunctions is that the altered behaviours

INTELLIGENCE

HIPPOCAMPAL THETA OSCILLATIONS - GENERATION AND BEHAVIOURAL FUNCTIONS

OBJECTIVES

The project seeks to investigate synaptic transmission and synaptic plasticity in the hippocampus of behaving animal, in relation to the ongoing hippocampal electrical activity (electroencephalogram, EEG).

KEY COLLABORATORS

Dr Luis Colom, University of Texas, Brownsville (septal modulation of hippocampal function)

From the University of Western Ontario:

Dr Seyed Mirsattari (functional magnetic resonance imaging and epilepsy) • **Dr N Rajakumar** (schizophrenia animal models and functional anatomy) • **Dr Ian Herrick** (anaesthesiology)

Leung's Laboratory team:

Dr J Ma (schizophrenia and epilepsy), research associate • **Dr MC Kuo** (theta rhythm and synaptic plasticity), postdoctoral fellow • **SK Tai**, PhD graduate (septal modulation of hippocampal physiology) • **RM Hutchison**, PhD candidate (resting state functional magnetic resonance imaging)

FUNDING

Canadian Institutes of Health Research

Natural Sciences and Engineering Research Council

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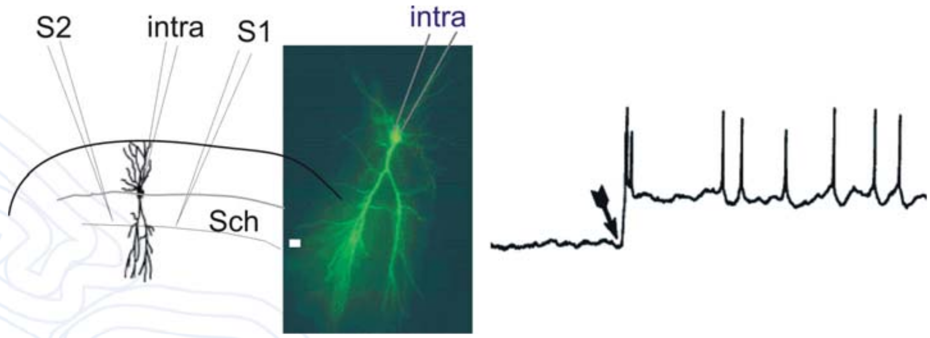

FIGURE 3. Intracellular recording of intrinsic theta oscillations in hippocampal neurons *in vitro*.

observed are accompanied by abnormal neural oscillations in the hippocampus. This suggests potential treatments of such conditions may be related to restoration of the normal oscillations in the hippocampus. While there are known treatments that enhance or suppress septohippocampal function, other possibilities that emerged from the research being conducted at the University of Western Ontario remain to be explored.

One example of an effective treatment strategy is to treat Alzheimer's disease with a cholinesterase inhibitor, which also enhances theta oscillations and hippocampal functions of both animals and humans. Interesting findings have also been made linking schizophrenic symptoms with septohippocampal GABAergic pathways. These links may well open the way for the development of drugs which can be used for the treatment of schizophrenia or attention deficit hyperactivity disorder, through the targeted suppression of the septohippocampal GABAergic neurons.

MODEL DEVELOPMENT

One of the ways in which the project is moving forwards is through the development of a theoretical biophysical model that will integrate the experimental results. The current model shows that different dendritic and somatic compartments are depolarised by rhythmic proximal somatic and distal dendritic synaptic inputs. Additionally, it shows that theta frequency waves travel in a longitudinal direction in the pyramid cell, which is the principal cell type in the hippocampus. Whilst currently in its early stages, it is hoped that the model will soon be able to predict how different drugs or lesions may affect the theta rhythm and how the theta rhythm modulates neural processing.

Another area Leung's group intends to investigate in the future is the notion that shifts in synaptic weight (strength of neuronal connections) depend on the timing of a synaptic input in relation to the theta rhythm, or the idea that there is a phase of the rhythm at which optimal synaptic plasticity will be induced for particular dendritic connections. These will be explored by collecting electrophysiological data using electrode arrays that simultaneously record somatic and dendritic hippocampal responses, thus following the various synaptic inputs to the pyramidal cell dendrites. As the project continues to investigate the theta rhythm in the hippocampus, it is likely that many more questions will be uncovered, opening up new possibilities of research into this under-investigated area of neurophysiology.

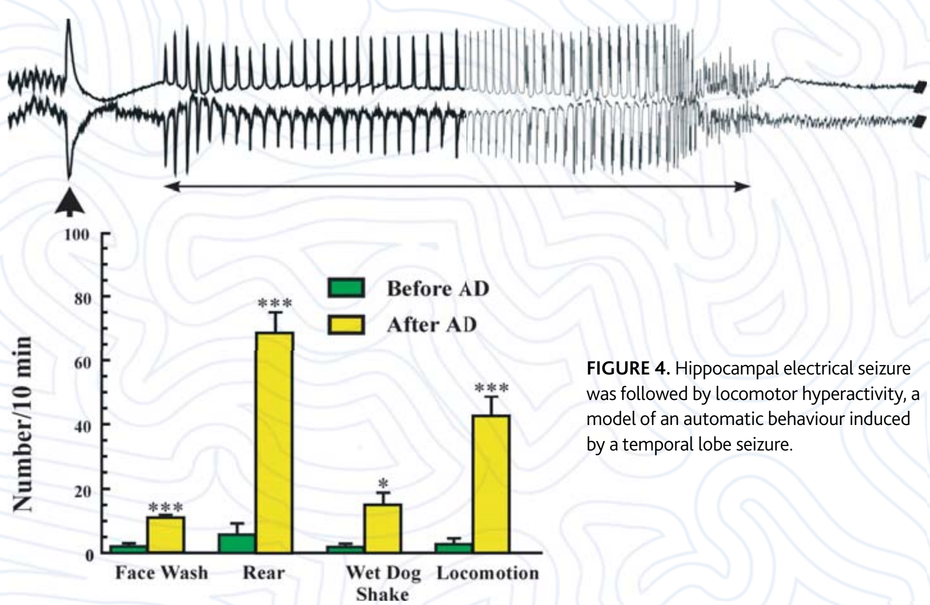

FIGURE 4. Hippocampal electrical seizure was followed by locomotor hyperactivity, a model of an automatic behaviour induced by a temporal lobe seizure.