様　式　Ｃ－１９、Ｆ－１９、Ｚ－１９　（共通）

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研究課題名（和文）Role of different ripples in memory encoding

研究課題名（英文）Role of different ripples in memory encoding

研究代表者
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交付決定額（研究期間全体）：（直接経費）　　3,000,000円

研究成果の概要（和文）：我々は海馬CA3からの出力が遮断されているとき、リップル波の周波数がコントロールマウスのそれよりも低下することを明らかにした。しかしながら、このミュータントマウスの場所細胞はマウスが現在占めている場所についての情報を問題なく記銘することができた。しかしながら、場所細胞のバースト活動（約125ミリ秒間）を通して動物の現在の場所だけではなく過去や未来の軌跡を海馬CA1神経細胞の集団が表現する現象であるθシーケンスは、このミュータントマウスにはみられなかった。この結果は、CA3が、CA1アンサンブルにおける空間記憶の分節化と時間的配置に必須であることを示している。

研究成果の概要（英文）：The project aim was to elucidate the role of ripples in memory. Since sharp wave ripples are generated in hippocampal area CA3, we used the transgenic CA3-tetanus toxin mouse line which allows blockade of CA3 output.
We recorded from both mutant and control mice performing a spatial navigation task. We found that when hippocampal area CA3 was blocked ripple frequency was lower than in control mice. However, place cells could still reliably encode the animals current position in space. Phase precession which is the progressive shift of spikes within a place field to earlier theta phases still occurred. However, surprisingly when we looked across the population of CA1 neurons, theta sequences, which are short bursts of place cell activity (lasting approximately 125ms) encoding the animals current position and previous and forward trajectories, were not detectable. This demonstrated that CA3 is key to the temporal ordering of spatial memory segments in the CA1 ensemble.

研究分野：Learning and memory

キーワード：CA3　Hippocampus　Ripples　Memory　Spatial coding

１．研究開始当初の背景

The hippocampus generates a variety of oscillations (varying in their frequency) which occur during specific behavioral states. These oscillations (large synchronized changes in extracellular current flow) have been shown to precisely regulate the output patterns of groups of neurons. This proposal focuses on a fast (>100 Hz) oscillation, termed ripples which occur during periods of rest or sleep in the hippocampus. These oscillations have been shown to be involved in the encoding and retrieval of memories.

２．研究の目的

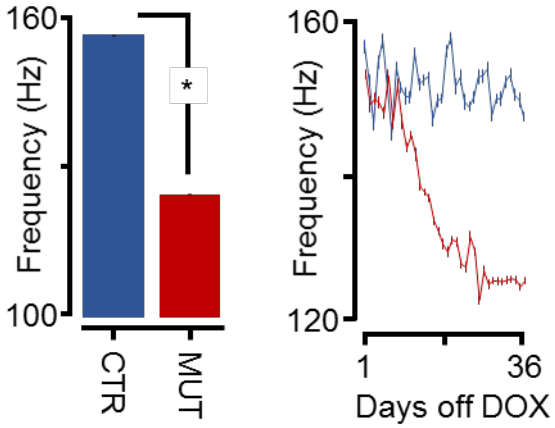
This project aimed to understand the relationship between hippocampal sharp wave ripples and memory encoding and retrieval in rodents. Since the hippocampus uses several different coding strategies, including rate coding, phase precession and temporal coding across the network, the project looked at all of these aspects and how they are affected by the removal of classical ripples, by using the CA3-TeTX transgenic mouse line.

３．研究の方法

In this project we used the CA3-TeTX transgenic mouse line, in which, CA3 output can be blocked by removal of doxycycline from the animals diet. We used microdrives with 10 independently adjustable tetrodes to perform *in vivo* hippocampal recordings from freely behaving mice, performing spatial navigation tasks. In addition we silicon probes with up to 64 linearly spaced recording sites to assess current flow throughout the hippocampal formation. As mice explored, local field potentials, individual pyramidal cell units and the mouse current position were all simultaneously recorded. This was done both in control and mutant mice, following CA3 shutdown. Post exploration sleep sessions, where ripples are present were also recorded.

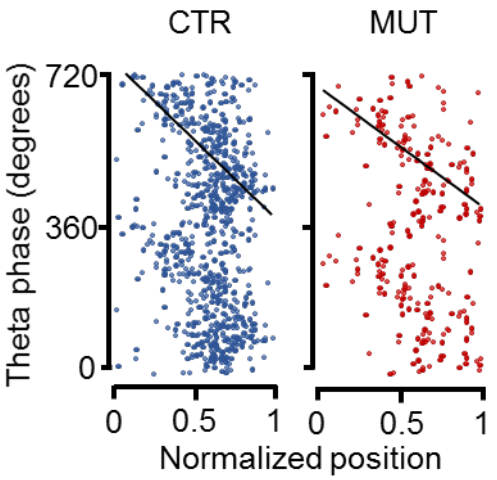
４．研究成果

We recorded from both mutant and control mice performing a spatial navigation task. We found that when hippocampal area CA3 was blocked the intrinsic frequency of CA1 ripples was lower than in control mice. This change is frequency occurred progressively which may be related to the progressive shutdown of the CA3 network.



1) Data showing the reduction in intrinsic frequency of CA1 ripples following shutdown of CA3 output (left). The time course of transition in ripple frequency following removal of doxycycline from the animals diet (right).

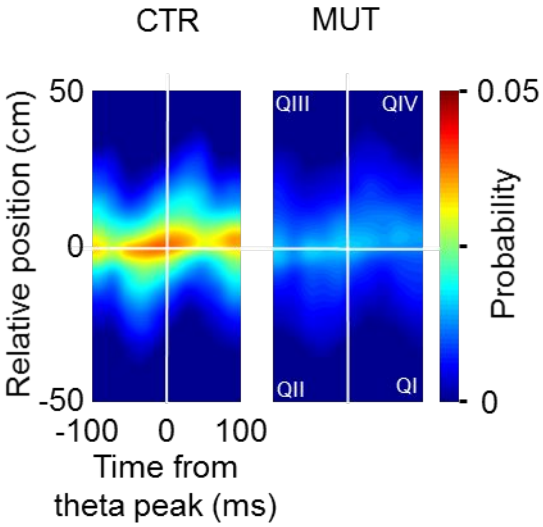
However, while exploring the environment individual place cells could still reliably encode the animals current position in space. Furthermore phase precession, the mechanism by which individual pyramidal cells display a progressive shift of spikes within a place field to earlier theta phases still occurred.



2) Examples of hippocampal phase precession for CA1 place cells both with (CTR), and without (MUT) input from area CA3.

However, surprisingly when we looked across the population of CA1 neurons,

theta sequences, which are short bursts of place cell activity (lasting approximately 125ms) encoding the animals current position and previous and forward trajectories, were not detectable. This demonstrated that CA3 is key to the temporal ordering of spatial memory segments in the CA1 ensemble.



3) Group data showing temporal coding (theta sequences) in CA1 with (CTR), and without (MUT) input from area CA3. In control animals ordered sequences of place cell activity sweep through the animals current position, with every theta cycle, this was absent in mutants.

These results have several implications, since to date, it was thought that phase precession and theta sequences were essentially the same process, with theta sequences simply representing an extension of phase precession across the neuronal ensemble. Our data challenged this theory, since following CA3 shutdown, we still observed phase precession in single neurons, but temporal ordering across a large population of cells was essentially absent.

Additionally we observed a reduction in the power of low gamma frequency oscillations. These oscillations are known to be a marker of CA3 to CA1 communication, and were associated with a reduction in the quality of spatial coding. This may be important in a clinical context, since reductions in these oscillations have been identified in various pathologies including Alzheimer's disease and schizophrenia.

Furthermore we have collected a large amount of data primarily from sleep sessions following behavior. Ripples from sleep data will be analyzed and related to the previous behavioral states of the animals. We also have *in vivo* data with pharmacological manipulation of ripples, which we are currently in the process of analyzing.

５．主な発表論文等
（研究代表者、研究分担者及び連携研究者には下線）

〔雑誌論文〕（計　1　件）

Steven J Middleton & Thomas J McHugh. Silencing CA3 disrupts temporal coding in the CA1 ensemble. *Nature Neuroscience*. Peer reviewed. 2016.
DOI: **10.1038/nn.4311** In press

〔学会発表〕（計　1　件）

Steven J Middleton & Thomas J McHugh. CA1 rate and temporal coding in the absence of CA3 input. Society for Neuroscience 2015. Chicago, USA.
2015 年 10 月 17 日～21 日

〔図書〕（計　0　件）

〔産業財産権〕
○出願状況（計　0　件）patent

名称：
発明者：
権利者：
種類：
番号：
出願年月日：
国内外の別：

○取得状況（計　0　件）patent

名称：
発明者：
権利者：
種類：
番号：
取得年月日：
国内外の別：

〔その他〕

ホームページ等
http://cbp.brain.riken.jp/publications.php

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