Physiological properties of entorhinal cortex and a model of Alzheimer's disease supporting treatment with NMDA receptor blockers and muscarinic M4 agonists.

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May 31, 2012 – Fields Institute Focus Program "Towards Mathematical Modeling of Neurological Disease from Cellular Perspectives."

Supported by:
NIMH R01 MH60013, NIMH R01 MH6149 (Program officer: Dennis Glanzman).
Office of Naval Research MURI grant N00014-10-1-0936 (Program officer: Tom McKenna)

Hasselmo lab members:

In vivo – unit (extracellular) recording in awake, behaving rats
Dr. Mark Brandon, Dr. Ehren Newman, Dr. Jake Hinman, Kishan Gupta, Jason Climer, Caitlin Monaghan, Andrew Bogaard

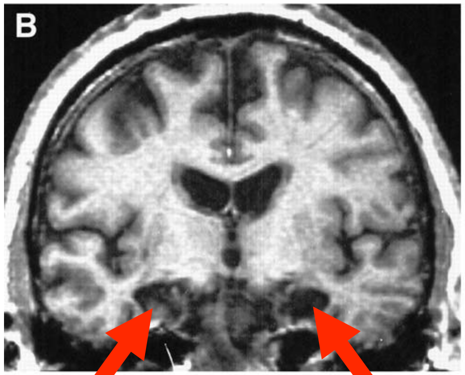
In vitro - whole cell patch (intracellular) recording in slice preparations
Jim Heys, Chris Shay, Dr. Lisa Giocomo, Dr. Nathan Schultheiss
Dr. Yusuke Tsuno

Computational modeling of grid cell firing, memory-guided behavior and dynamics of cortical structures
Dr. Murat Erdem, Dr. Eric Zilli, Dr. Vassilis Cutsuridis. Dr. Angela Onslow

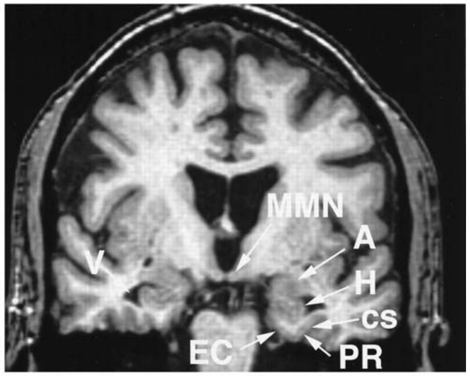
Undergraduates:
Chris Libby, Michael Connerney, Shea Gillet, Lauren Keller, Sven Eriksson, Owen Dean, Nathan Beer

Collaborators:
Prof. Chantal Stern – functional magnetic resonance imaging
Thackery Brown, Dr. Karin Schon
Prof. Erik Fransen – biophysical modeling of cortical function

Episodic memory involves hippocampus and parahippocampal structures



Patient HM



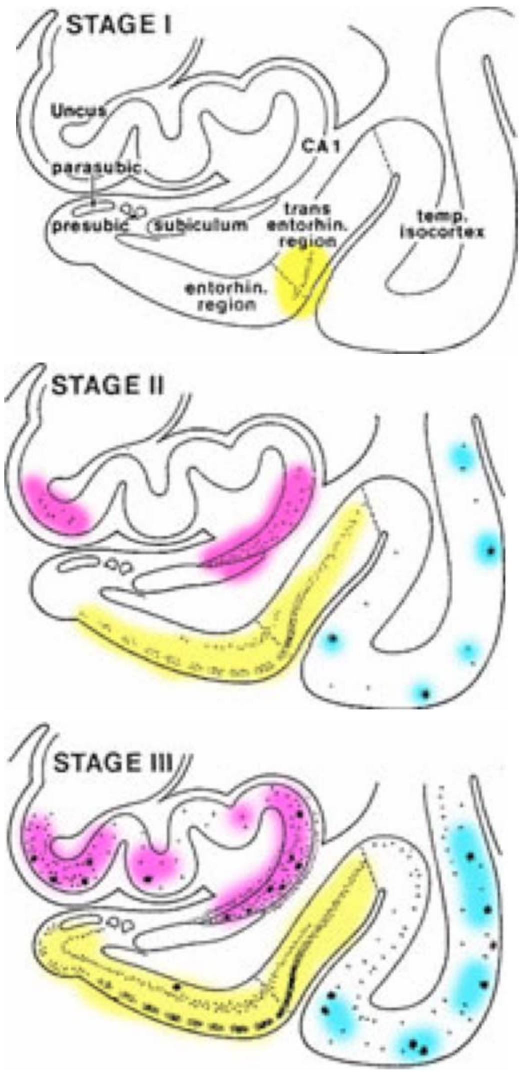
Control

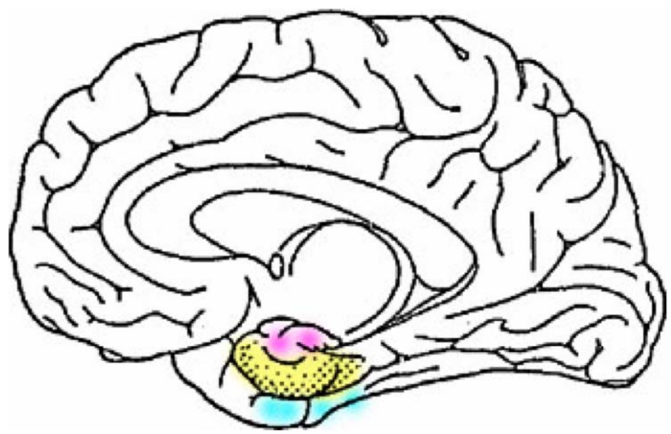
Scoville and Milner, 1957;
Corkin et al., 1997

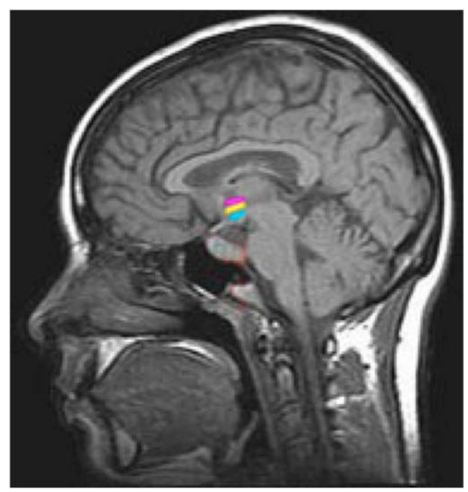
Lesions impair autobiographical recall
Steinvorth et al., 2006; Kirwan et al., 2008
… and also imagination of future
Hassabis et al., 2007; Schacter and Addis, 2007

Activation during temporal sequence recall
Ross et al., 2009 (faces); Lehn et al., 2009
… and autobiographical recall
Cabeza et al., 2004; Steinvorth et al., 2006

Neurofibrillary tangles start in entorhinal cortex







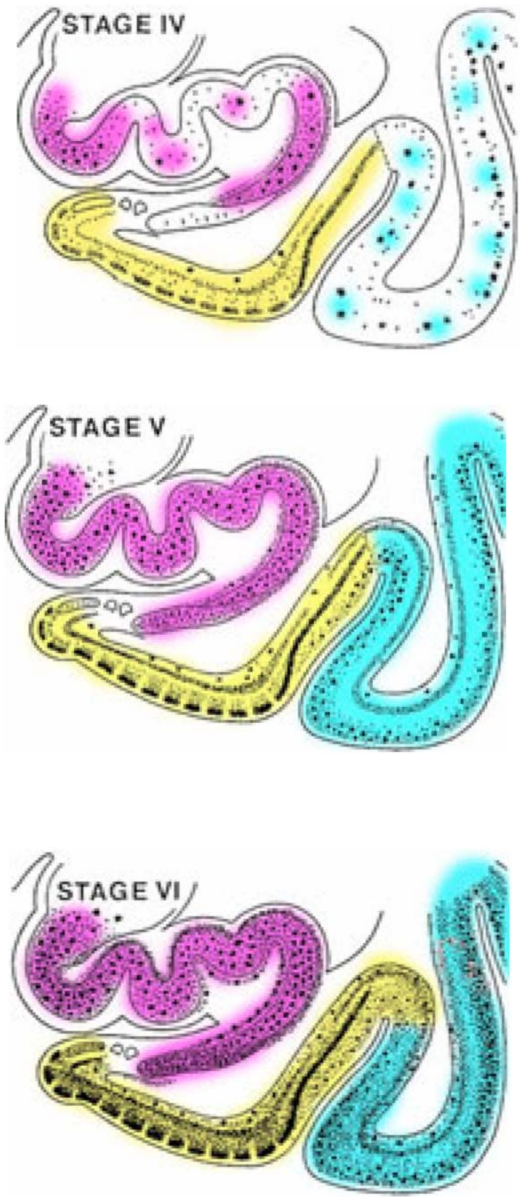
Tangles correlate with behavioral impairment

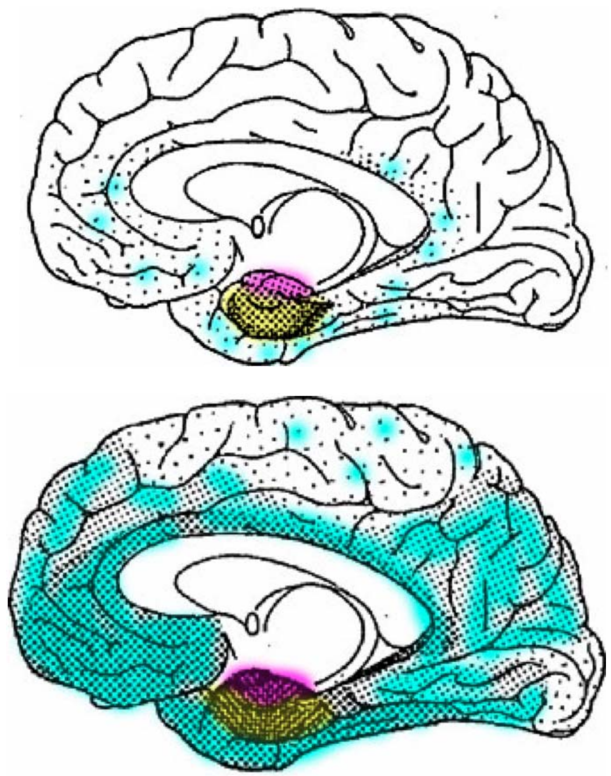
MCI
Braak stage 2–3
Mini Mental State Exam 26–30

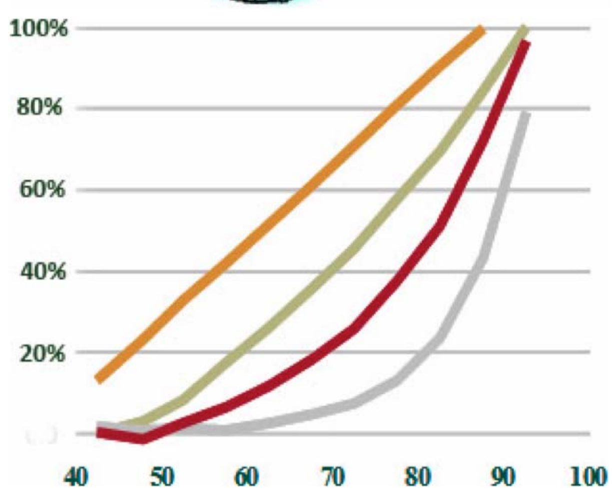
Mild AD
Braak stages 3–4
MMSE 20–26

Images taken from "Neuropathological stageing of Alzheimer-related changes", Braak and Braak, Acta Neuropathol (1991) 82:239-259.
Tangles start in lateral entorhinal border with perirhinal. Also at border of CA1 and subiculum.

Braak staging







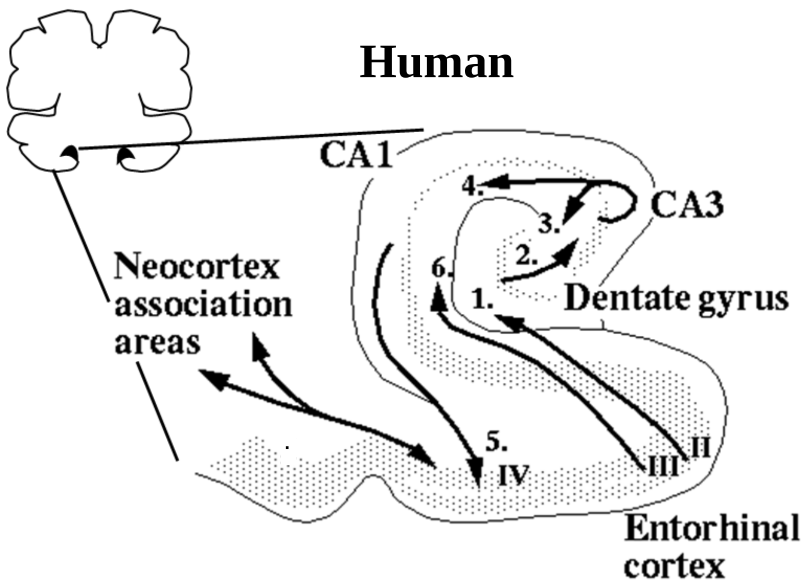
Moderate AD
Braak Stage 4–5
MMSE 11–19

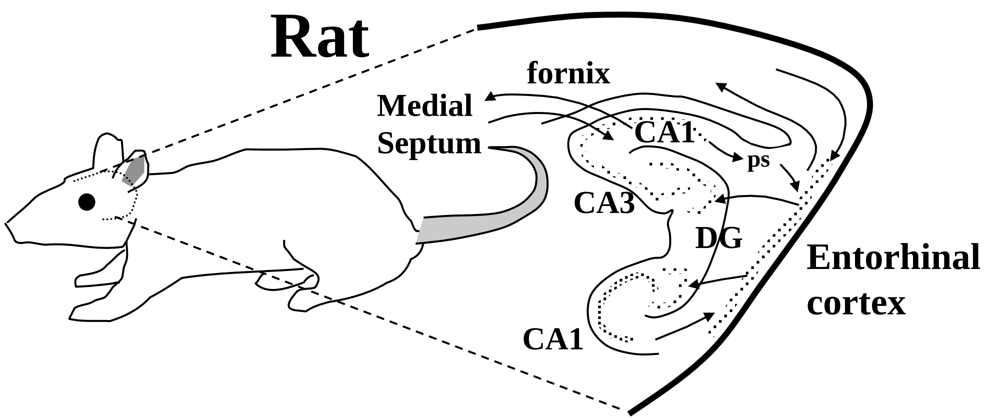
- **Progressive memory loss; confused thinking**
- **Agitation, paranoia**
- **Need for assistance in daily activities**

Severe AD
Braak Stage 5–6
MMSE 0–10

- **Severe memory loss and dementia**
- **Agitation, aggression, paranoia and delusions**
- **Loss of motor skills**
- **Hospitalization or long-term care**

Mechanisms of memory in entorhinal cortex and hippocampus

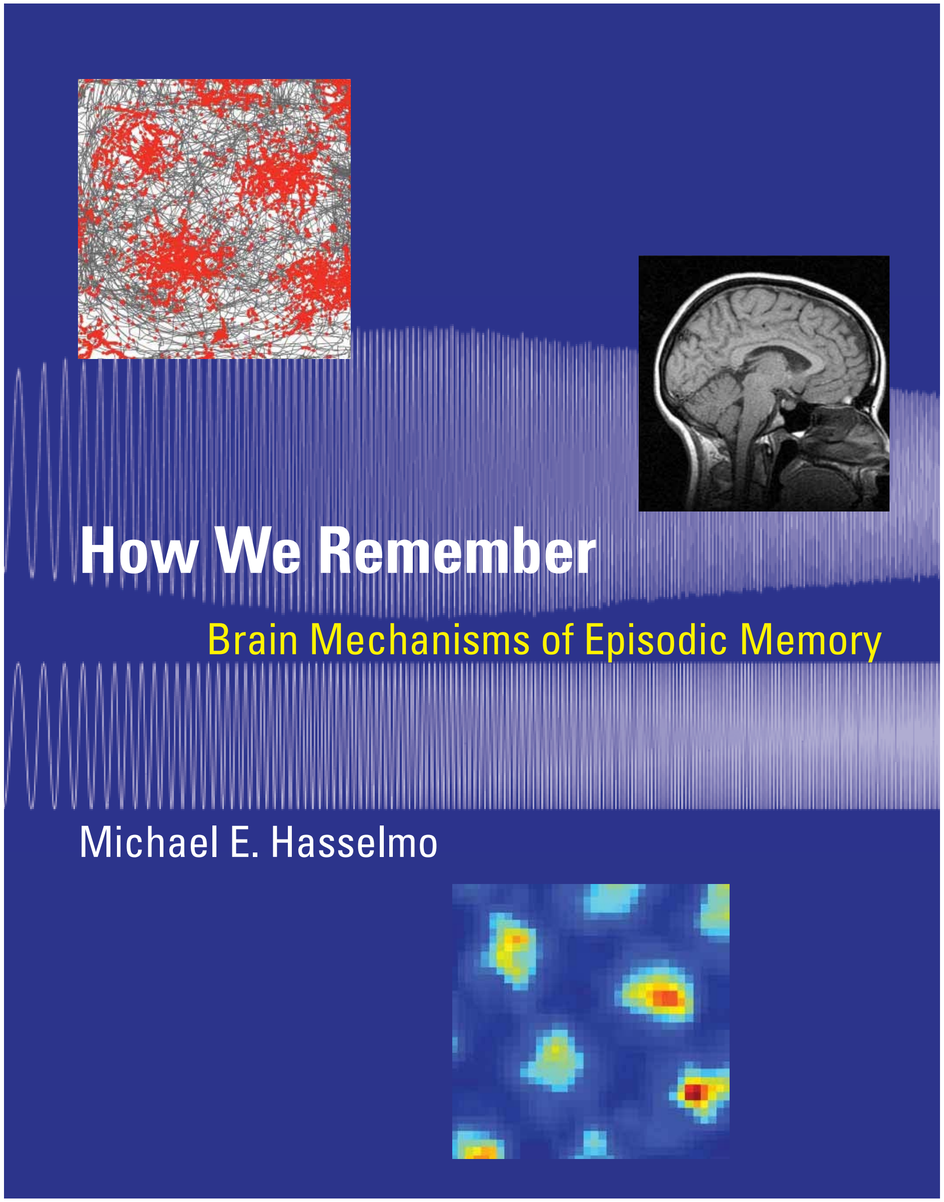




Behavior: Lesions impair memory for events at a specific time and location

Network mechanisms: Grid cells, Place cells and Head direction cells

Cellular mechanisms: Oscillations and resonance



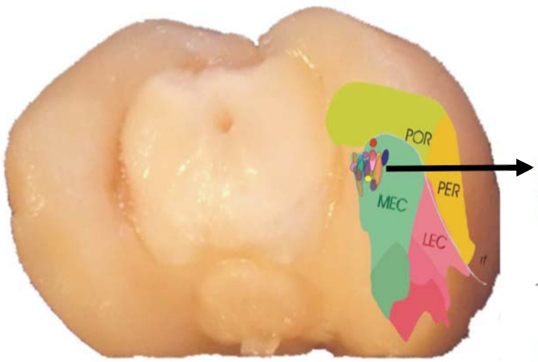
Episodic memories encoded as spatiotemporal trajectories

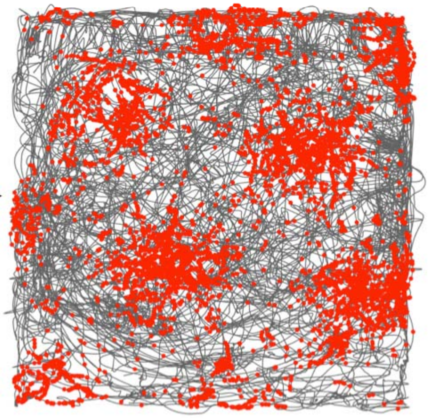
Hasselmo, M.E. (2012) How We Remember: Brain Mechanisms of Episodic Memory. MIT Press: Cambridge, MA

Talk outline:

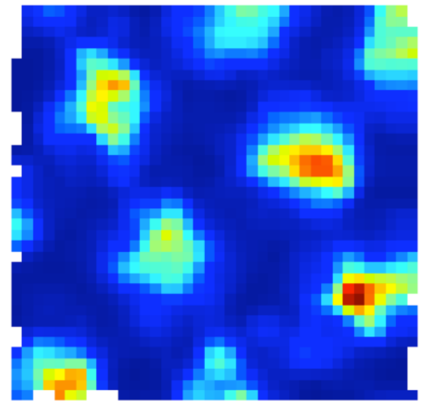
1. **Models of physiological properties in entorhinal cortex**
2. **Model of the initiation and progression of Alzheimer's disease**

Grid cells in entorhinal cortex – unit recording data

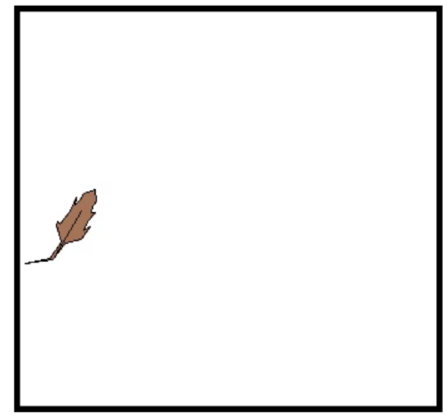




Trajectory plot



Firing rate plot

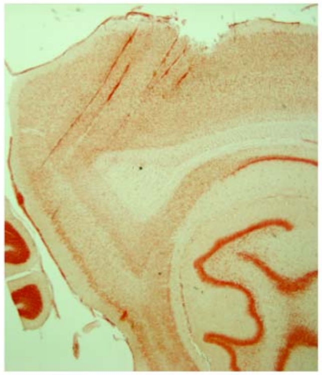


1 meter

Gray: Rat foraging trajectory

Red: Location when spike is fired

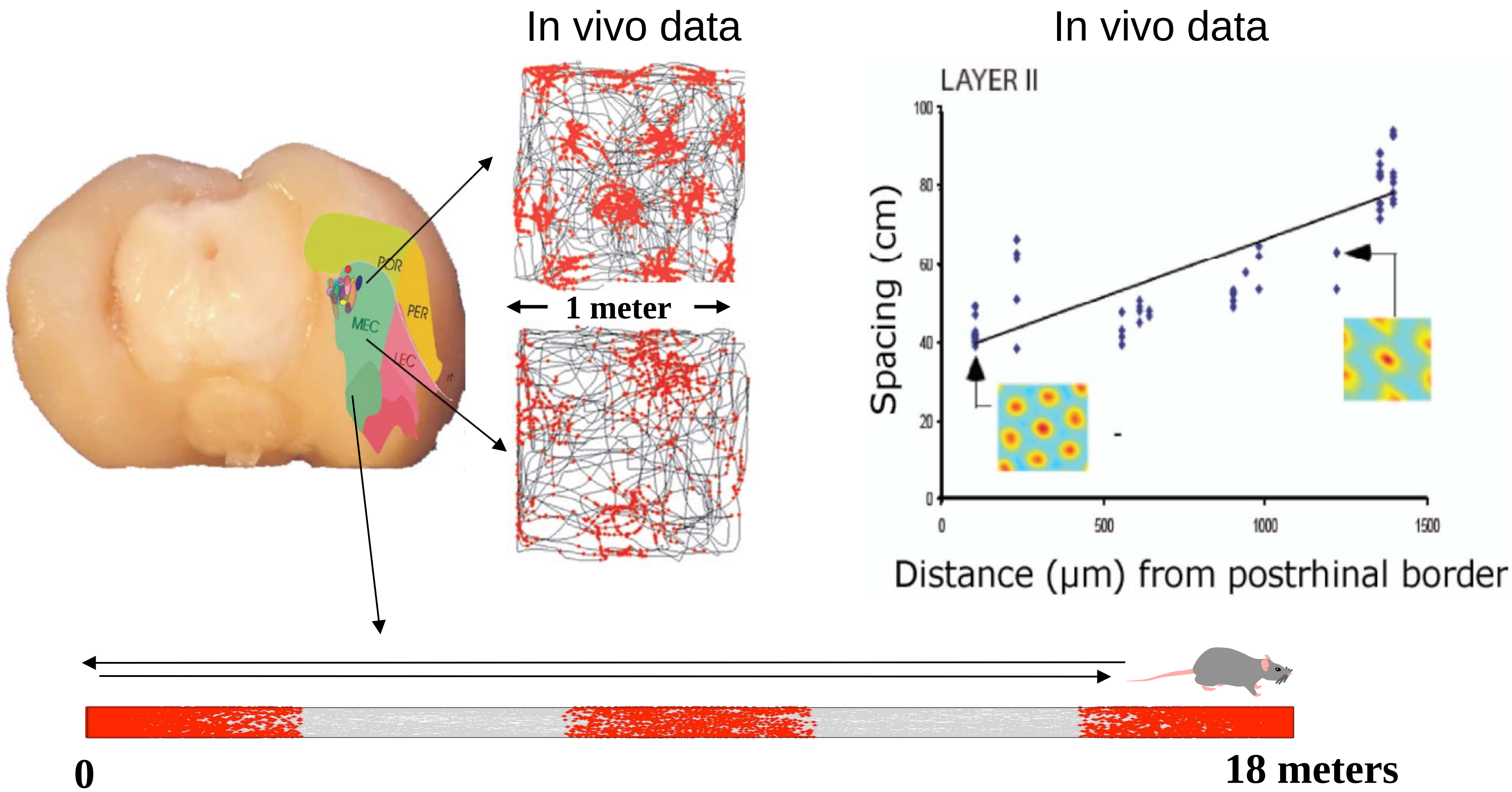
Anatomy



From: Brandon, Bogaard, Libby, Connerney, Gupta, Hasselmo, *Science*, 2011

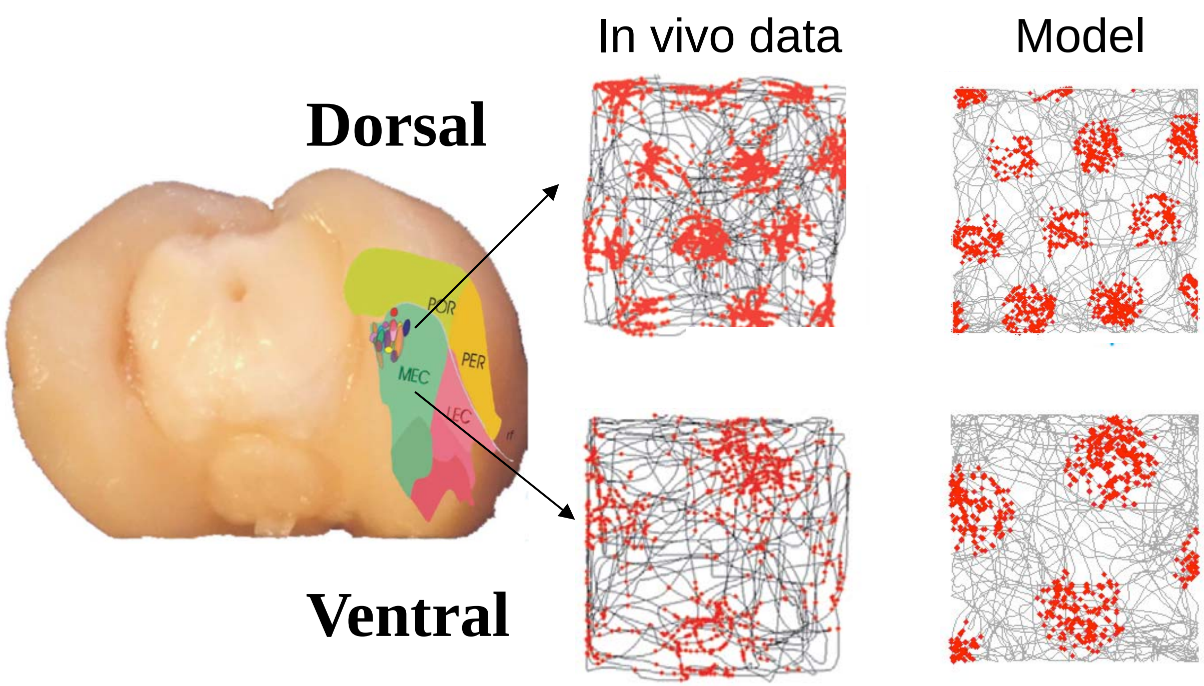
Grid cells discovered in Moser lab: Hafting, Fyhn, Molder, Moser, Moser (2005), *Nature*. Moser and Moser (2008) *Hippocampus*

Grid cell spatial coding: increasing spatial scale along dorsal to ventral axis of medial entorhinal cortex



Figures from Hafting, Fyhn, Molder, Moser, Moser (2005), *Nature*
Sargolini, Fyhn, Hafting, McNaughton, Witter, Moser, Moser (2006), *Science*
Brun, Solstad, Witter, Moser, Moser (2008), *Hippocampus* (special issue on grid cells)

Oscillatory interference model links grid field spacing to intrinsic oscillation and resonance frequencies in neurons



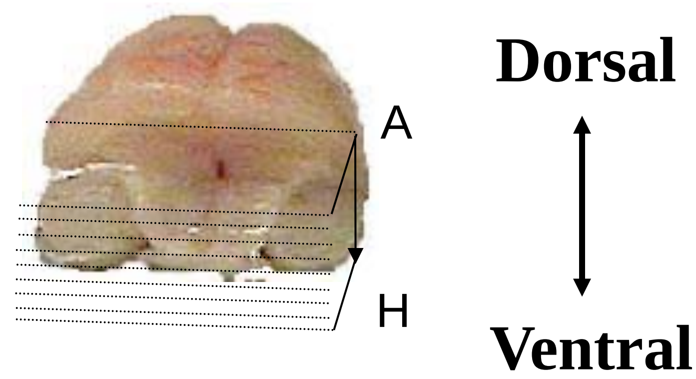
Prediction: Spacing of grid fields could arise from dorsal to ventral differences in intrinsic frequency of entorhinal neurons

In vivo data from Hafting, Fyhn, Molder, Moser, Moser, *Nature*, 2005

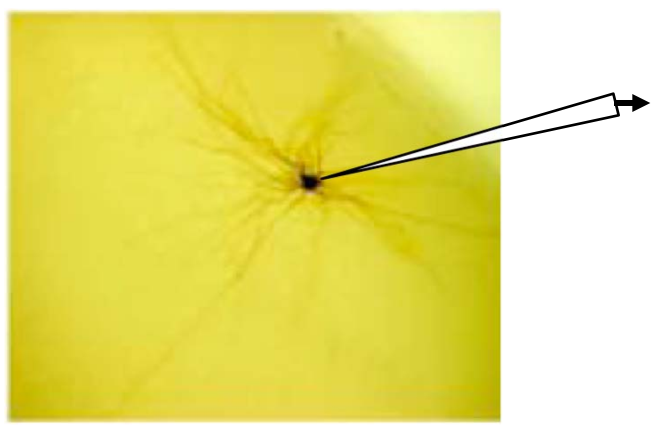
Simulation from Hasselmo, Zilli, Giocomo, *Hippocampus*, 2007
Using model from Burgess, Barry, O'Keefe, 2007

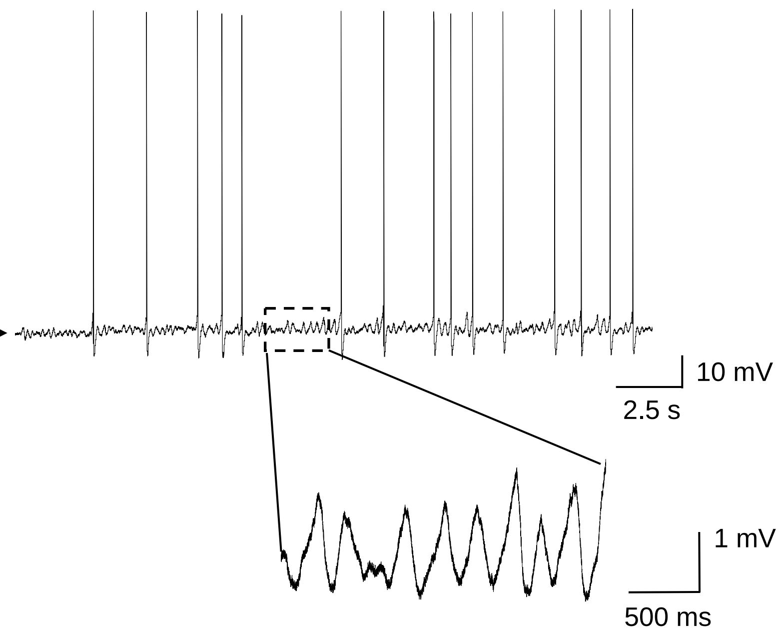
Whole cell patch recording of membrane potential oscillations

Giocomo, Zilli, Fransen, Hasselmo (2007) *Science* 315: 1719-22



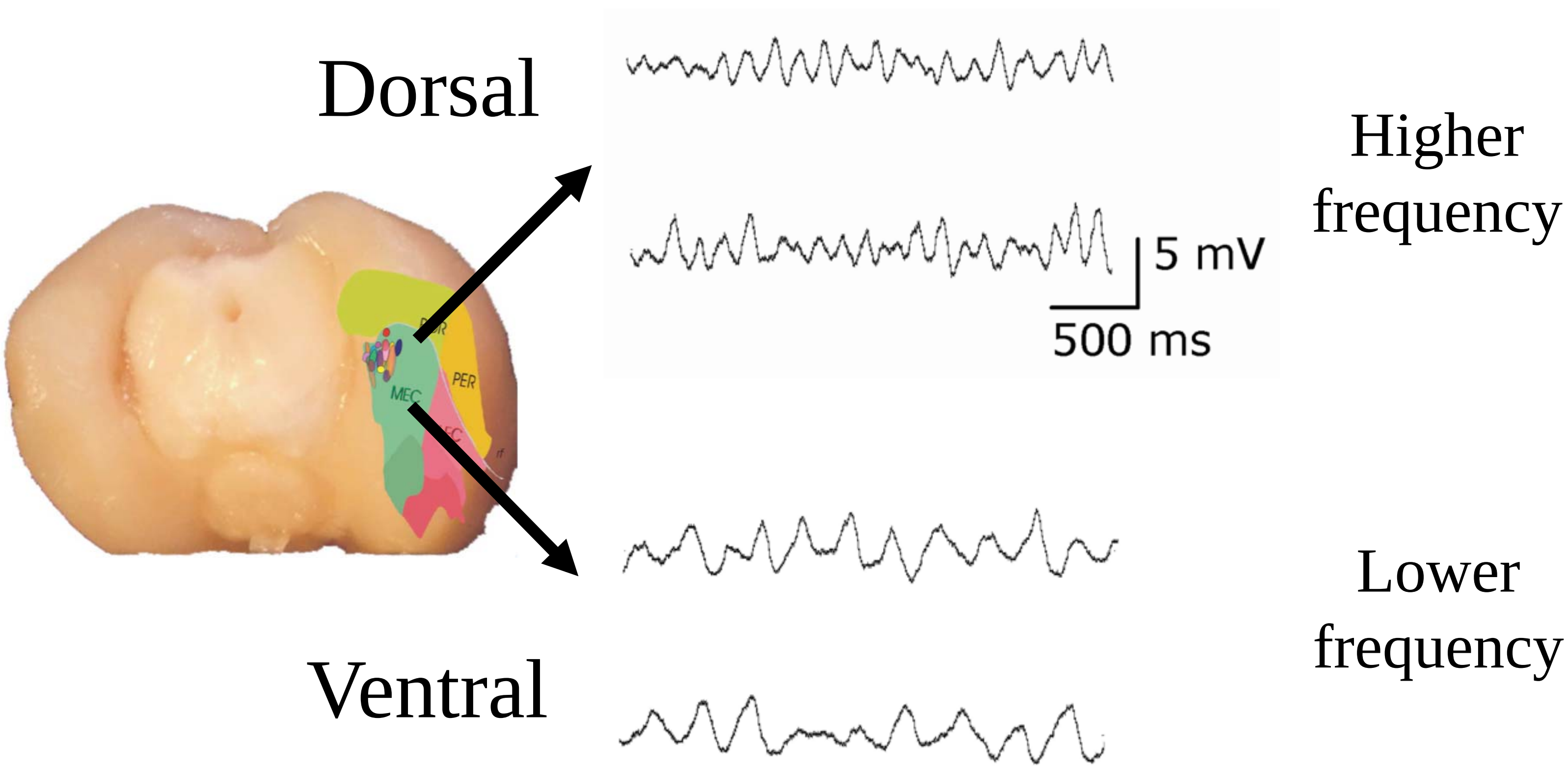
Entorhinal slices at different distances from dorsal surface





Dr. Lisa Giocomo

Membrane potential oscillations and resonance differ in frequency along dorsal to ventral axis



Giocomo, Zilli, Fransen, Hasselmo (2007) *Science* 315: 1719-22

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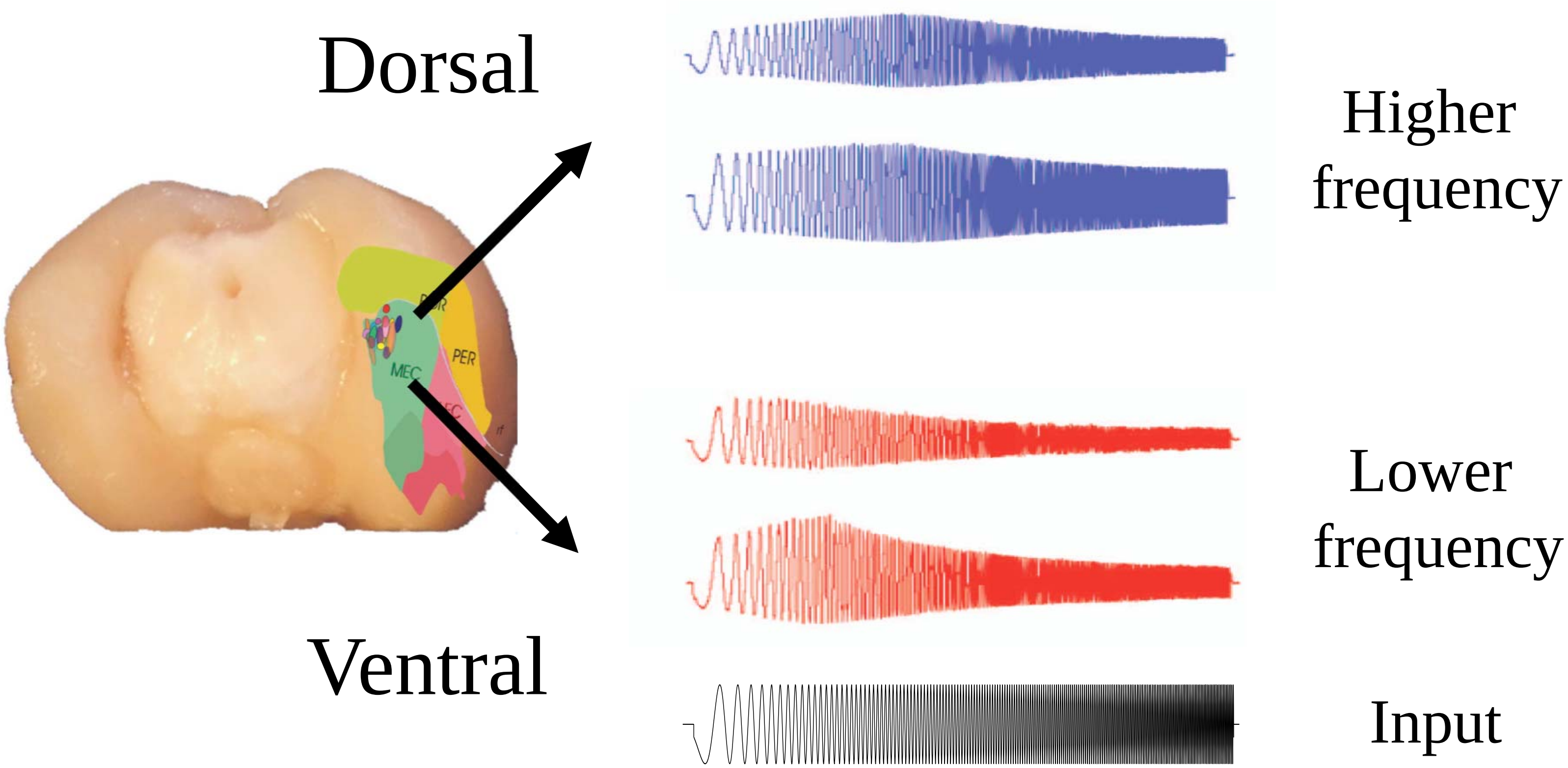

Giocomo, Zilli, Fransen, Hasselmo (2007) *Science* 315: 1719-22

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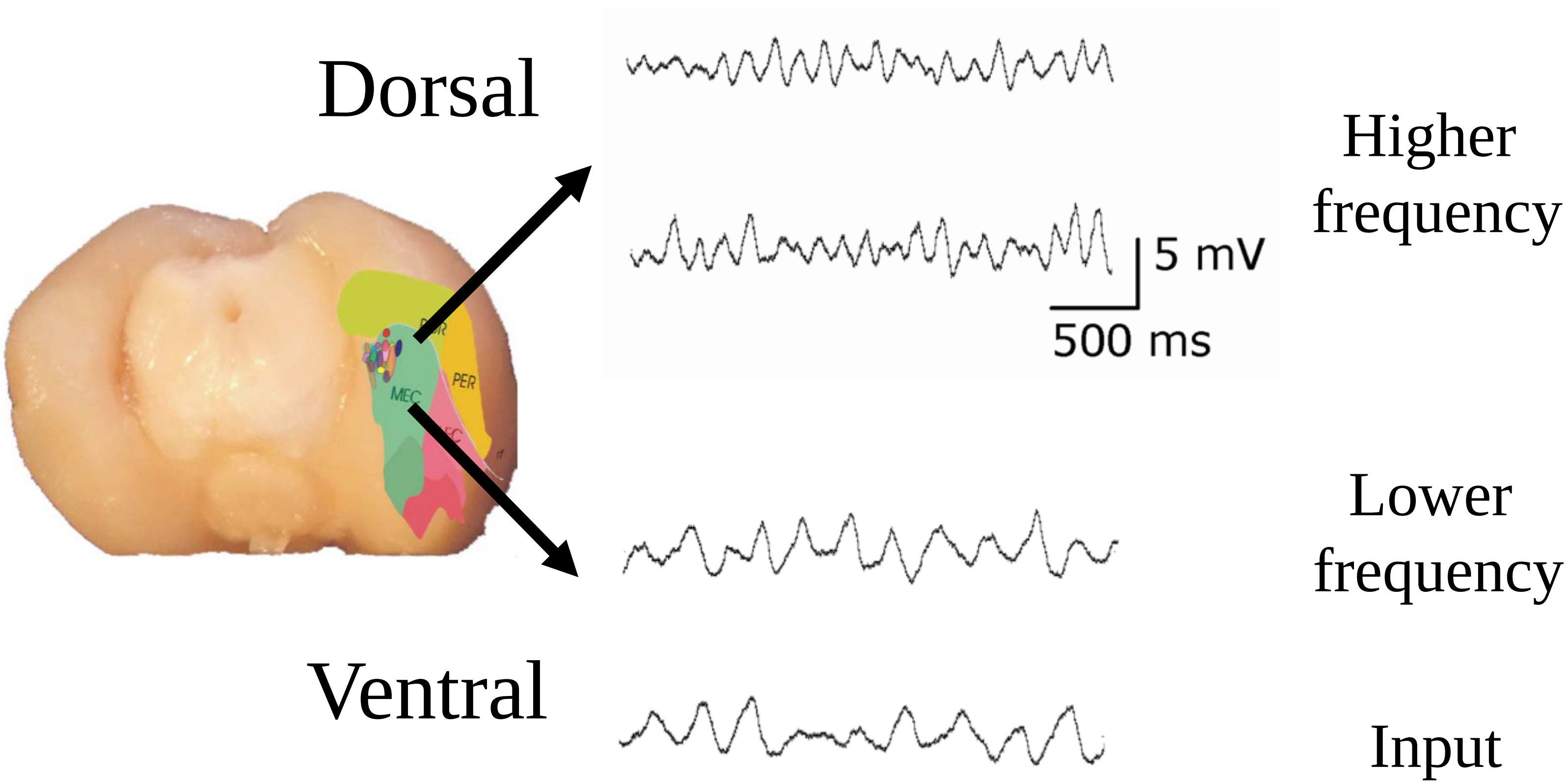
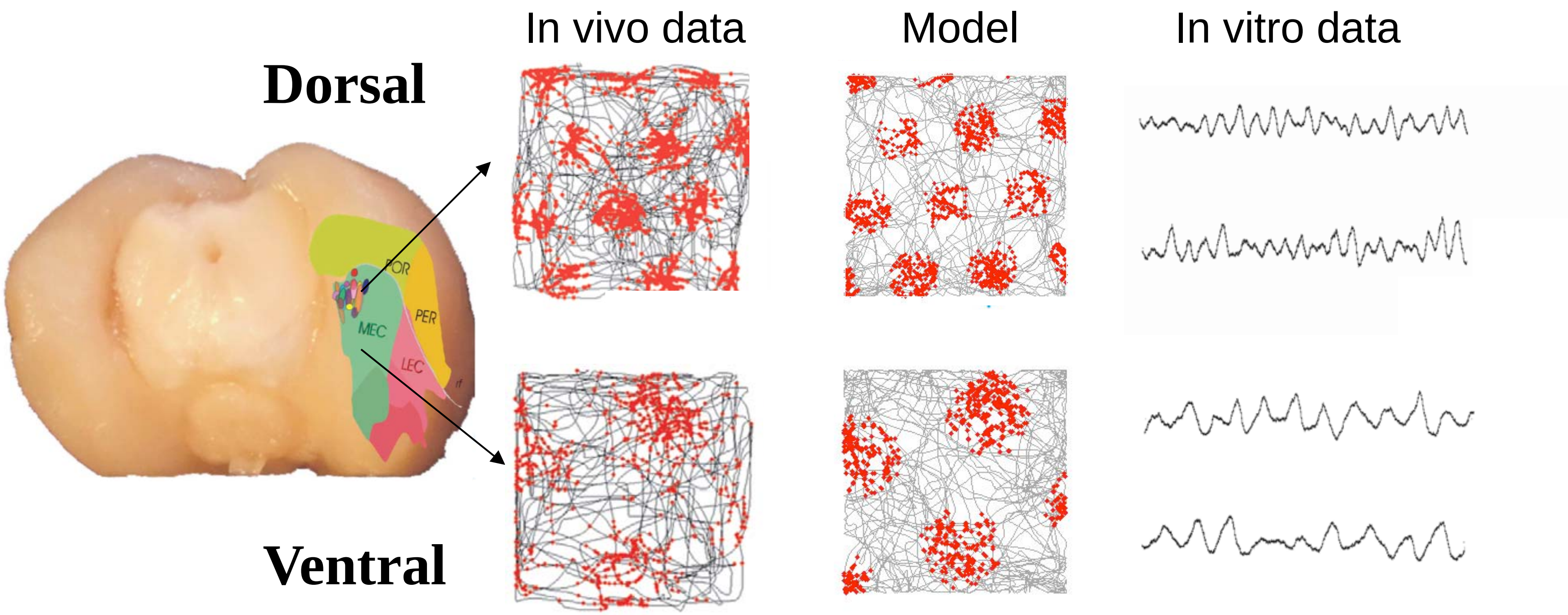


Giocomo and Hasselmo (2008) J. Neurosci. 28(38):9414-25
Giocomo and Hasselmo (2009) J. Neurosci. 29(23):7625-30
Boehlen, Heinemann and Erchova (2010) J. Neurosci. 30(13):4585-9
Dodson, Pastoll, Nolan (2011) J. Physiol. 589: 2993-3008
Yoshida, Giocomo, Boardman, Hasselmo (2011) J. Neurosci. 31: 12683-12694

Oscillatory interference model links grid cell spacing to different intrinsic oscillation frequencies of entorhinal neurons



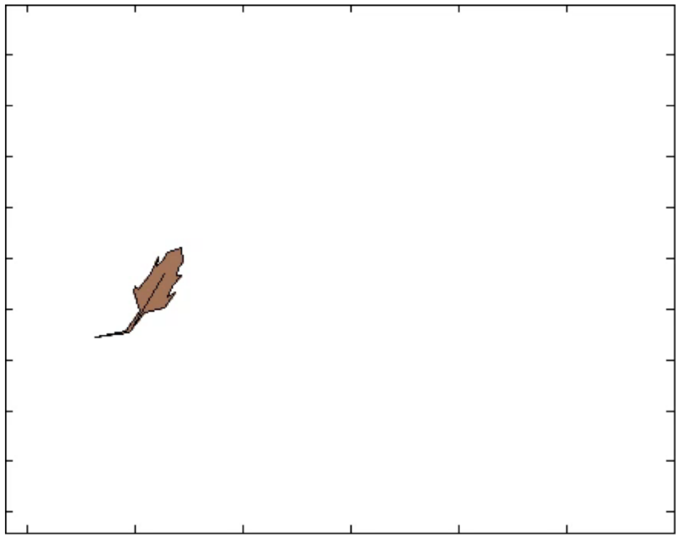
In vivo data from Hafting, Fyhn, Molder, Moser, Moser, *Nature*, 2005

Simulation from Hasselmo, Zilli, Giocomo, *Hippocampus*, 2007
Using model from Burgess, Barry, O'Keefe, 2007

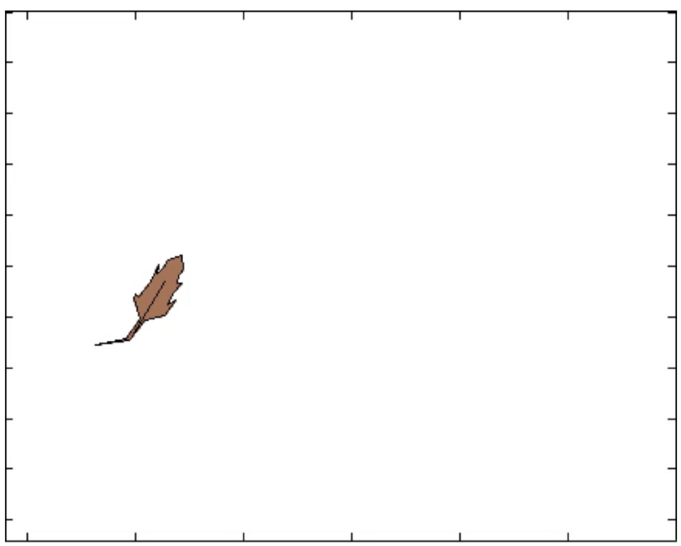
In vitro data from Giocomo, Zilli, Fransen, Hasselmo, *Science*, 2007

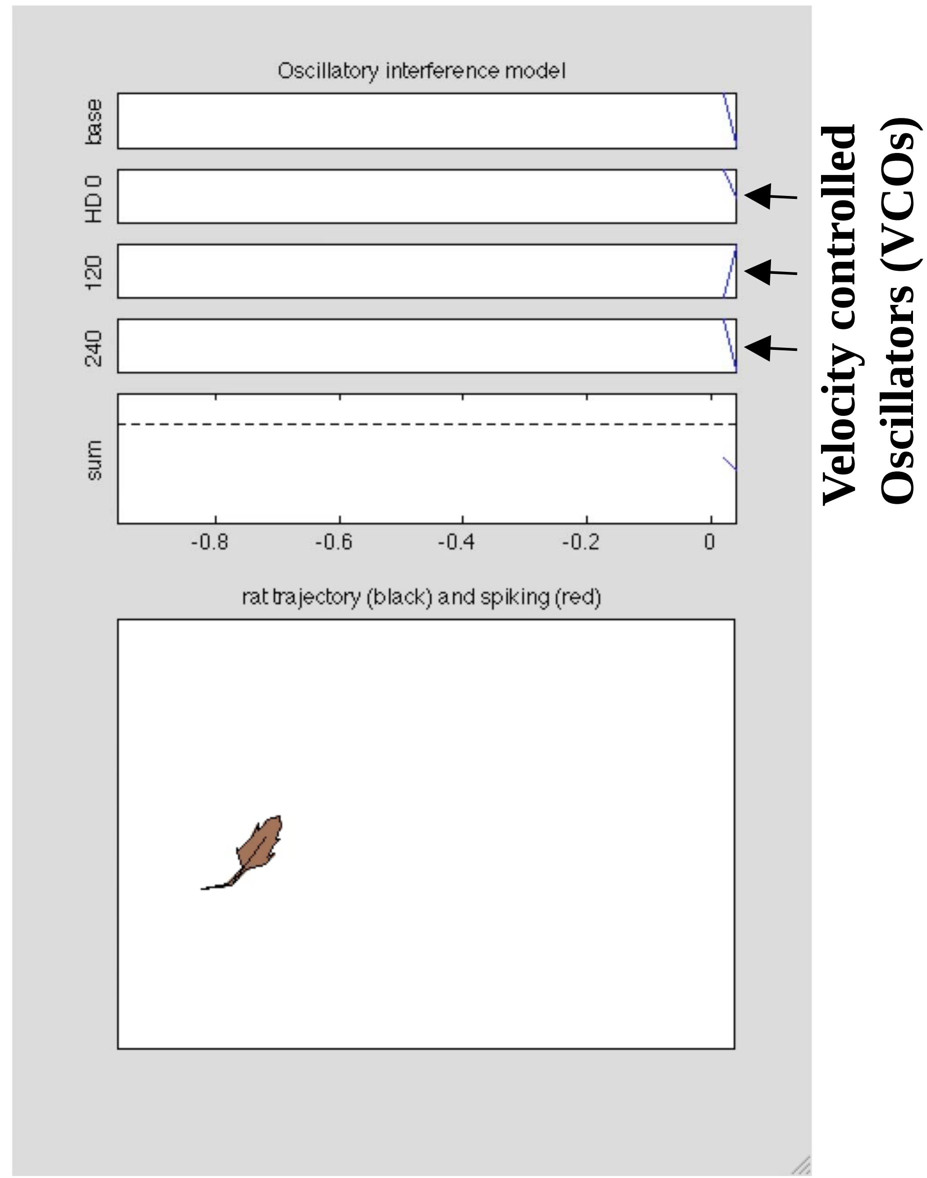
Oscillatory interference model of grid cells

DATA



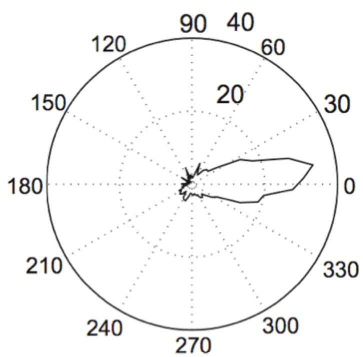
MODEL

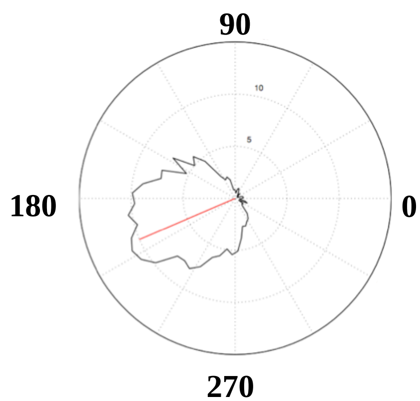


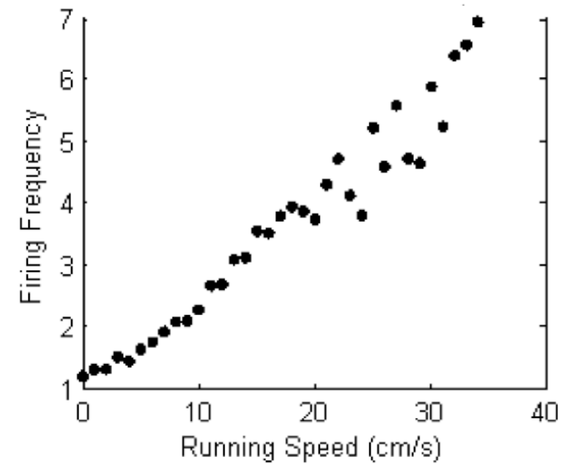


Velocity input from cells responding to head direction and speed

Example of head direction cells







10 degrees = preferred direction

200 degrees = preferred direction

Firing rate with head direction

Brandon, Bogaard, Andrews Hasselmo, 2011

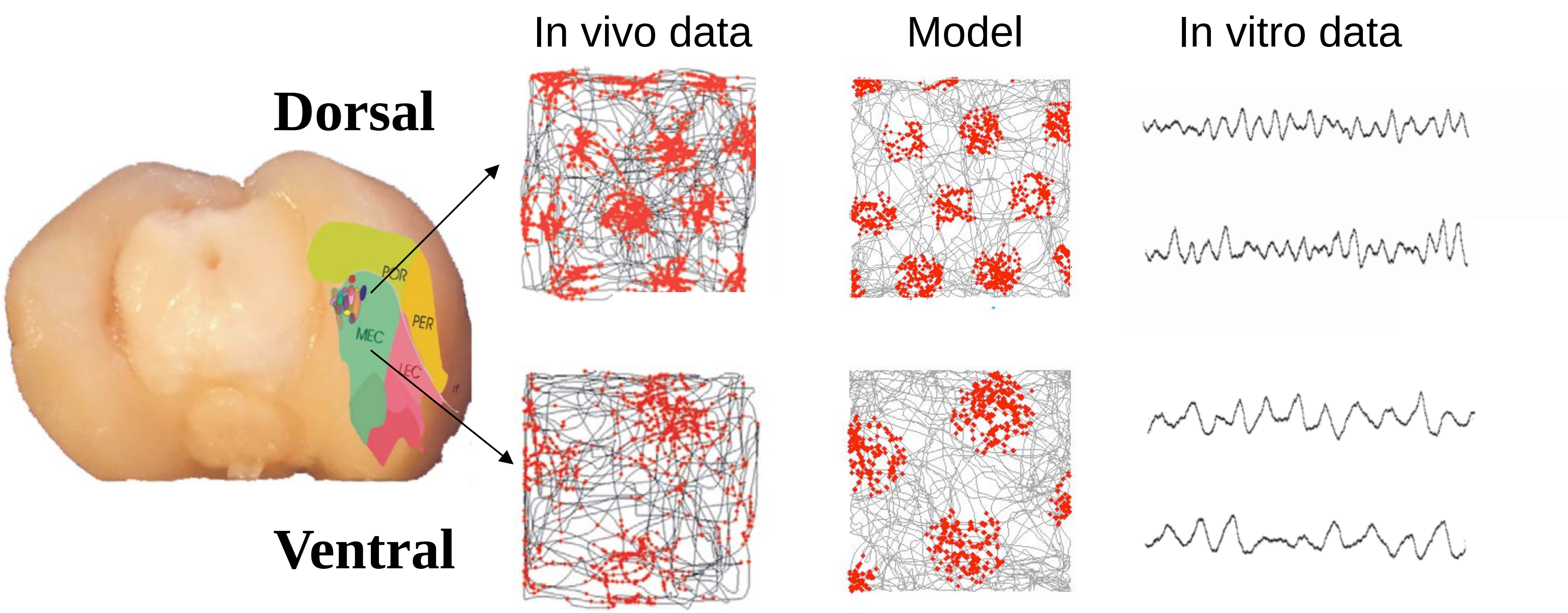
Previous: Taube, Muller, Ranck, 1990

Rate with running speed

Brandon, Bogaard, Libby, Connerney, Gupta, Hasselmo, 201`

Previous: O'Keefe et al., 1998

Oscillatory interference model links grid cell spacing to different intrinsic oscillation frequencies of entorhinal neurons



In vivo data from Hafting, Fyhn, Molder, Moser, Moser, *Nature*, 2005

Simulation from Hasselmo, Zilli, Giocomo, 2007 Using model from Burgess, Barry, O'Keefe, 2007

In vitro data from Giocomo, Zilli, Fransen, Hasselmo, *Science*, 2007

Strengths of oscillatory interference model:

1. Predicted dorsal-ventral frequency difference (Giocomo et al., 2007; Giocomo and Hasselmo, 2008)
2. Predicts loss of grid cell periodicity with loss of theta (Brandon et al., 2011)
3. Predicted theta phase precession in entorhinal cortex (Hafting et al., 2008; Climer et al., in review)
4. Resonance distribution matches grid cell distribution (Shay et al., 2012)
5. Predicted spiking frequency change with field size and running speed (Jeewajee et al., 2008)
6. Predicts theta cell interburst frequency (Blair et al., 2008; Welday et al., 2011)
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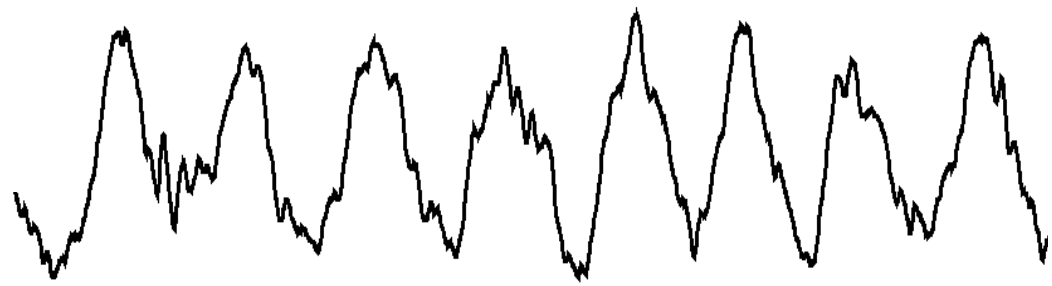
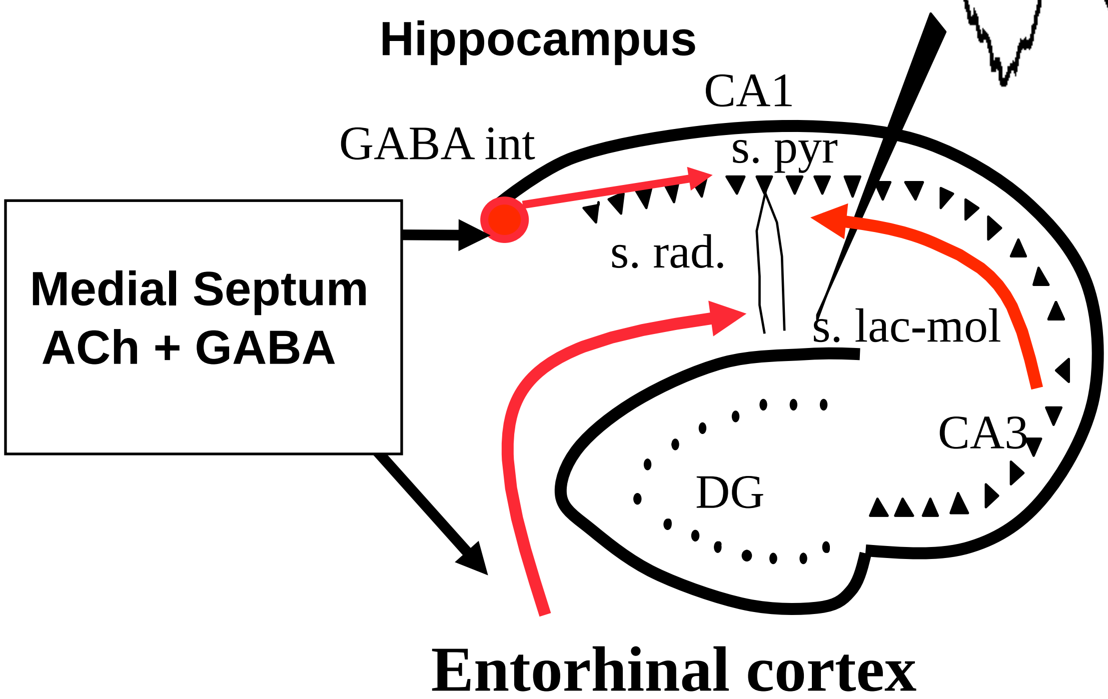




Theta rhythm in entorhinal cortex and hippocampus
7-8 Hz oscillation
(human EEG 4-7 Hz)

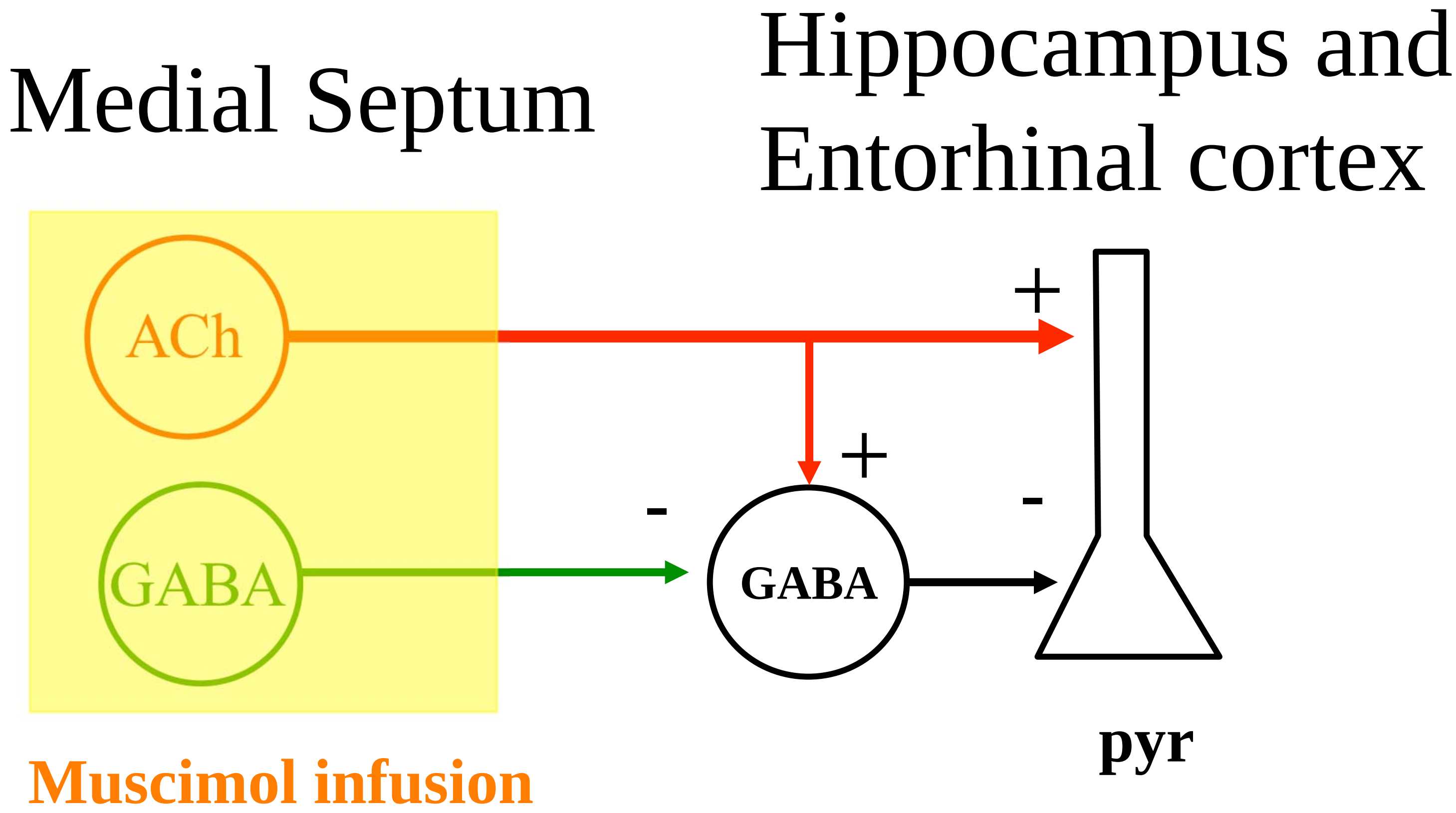
Appears during running and orienting

Reduced during grooming, eating, drinking

Theta rhythm correlates with learning and memory performance:
Winson, 1978; Mitchell et al., 1982; Mizumori et al., 1990;
Givens and Olton, 1994; Berry and Thompson, 1978; Seager et al., 1997

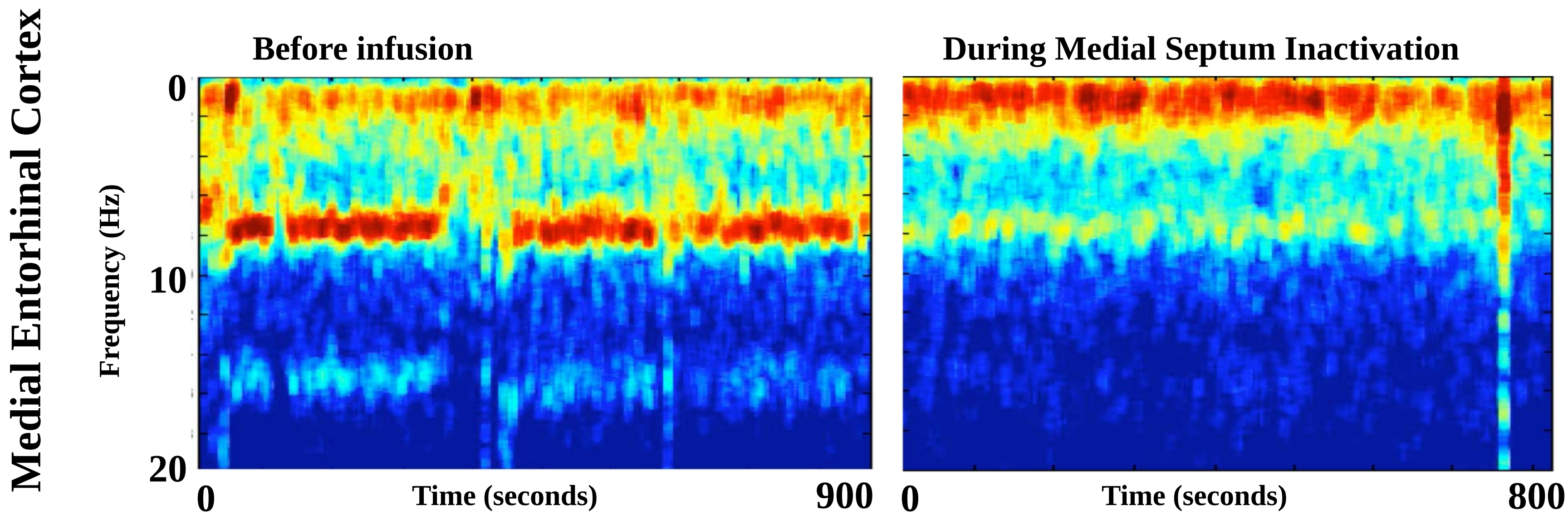
Rhythmic activity in medial septum drives theta rhythm

Block theta rhythm – test grid cells



Mark Brandon (Hasselmo lab) Brandon et al., 2011.
Muscimol infusions also cause memory impairments (Chrobak et al., 1989; Brioni et al., 1990)

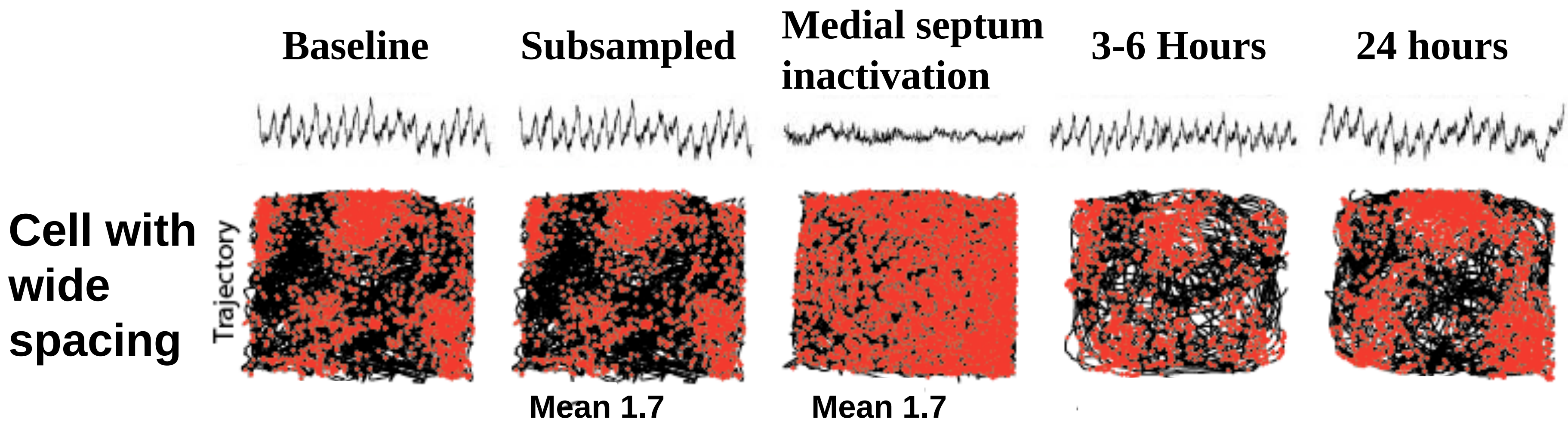
Medial septum inactivation disrupts theta oscillations in the medial entorhinal cortex



Brandon, Bogaard, Libby, Connerney, Gupta, Hasselmo (2011) Reduction of theta rhythm dissociates grid cell spatial periodicity from directional tuning. ***Science*, 332: 595-599.**

With lidocaine:, Koenig, Linder, Leutgeb, Leutgeb (2011)

Loss of grid cell periodicity during loss of theta rhythm



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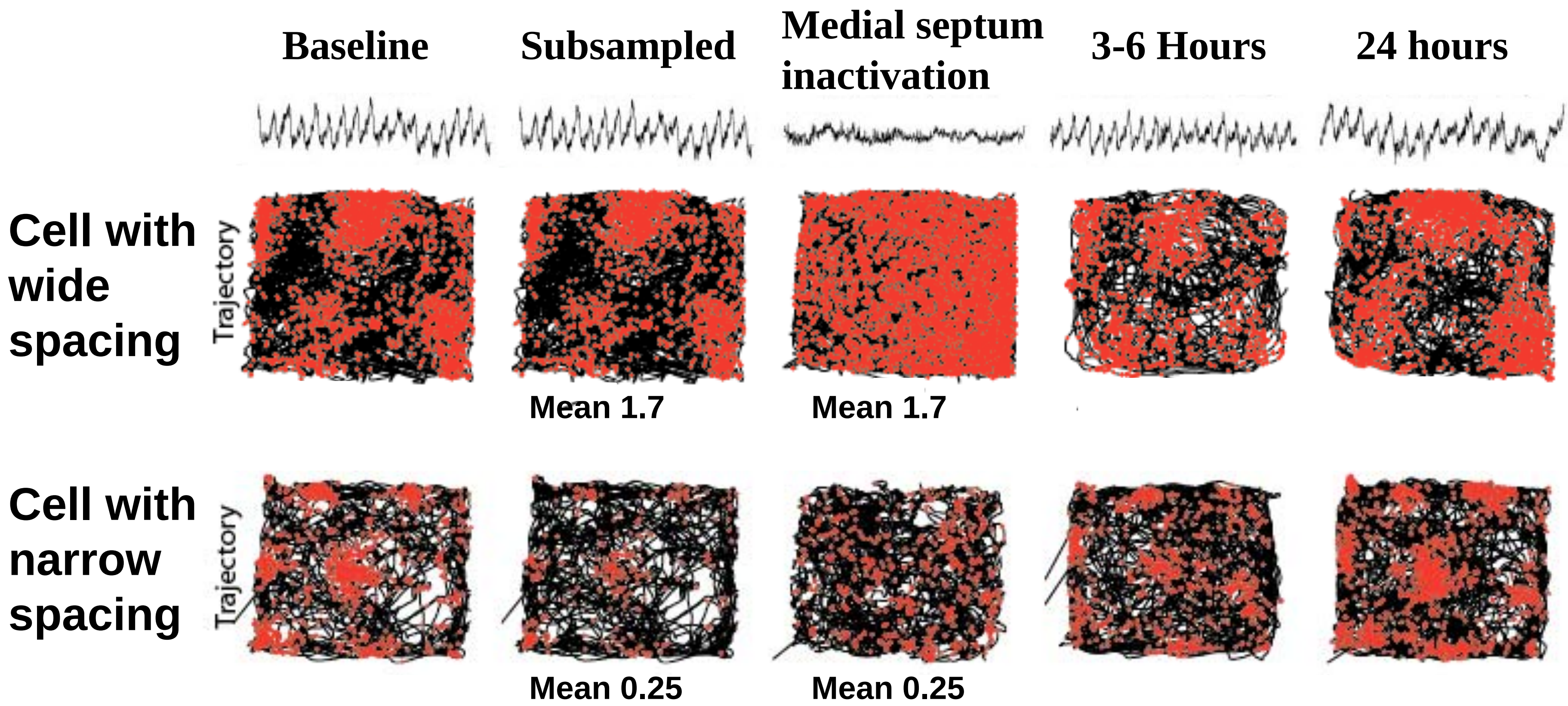

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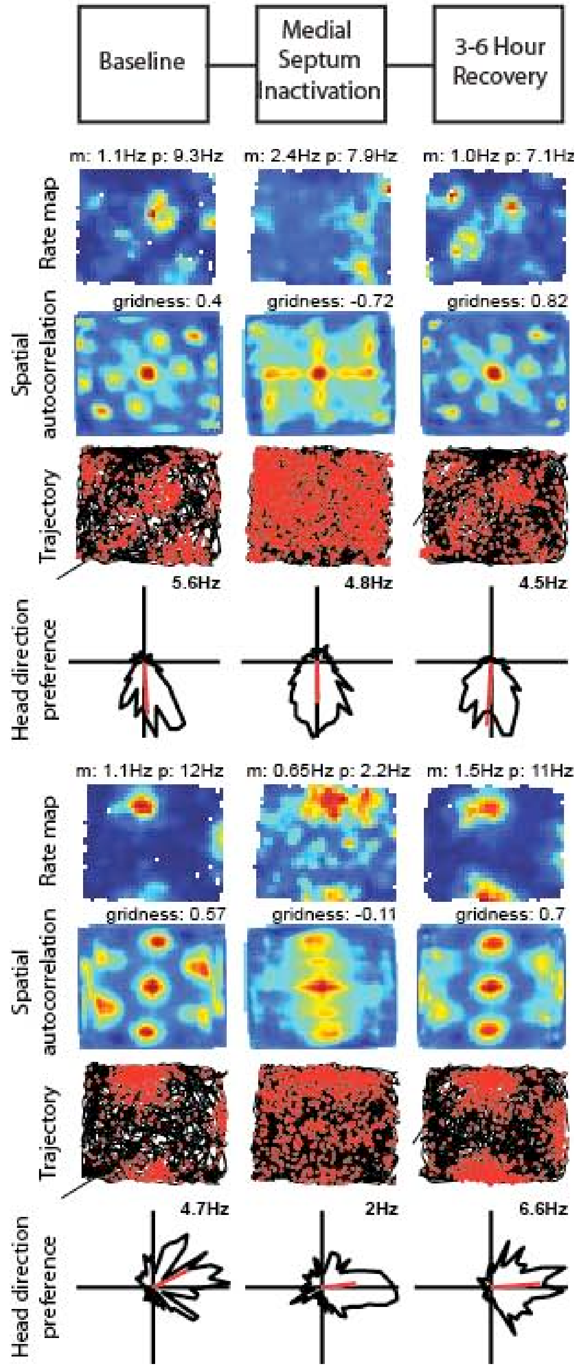
With lidocaine:, Koenig, Linder, Leutgeb, Leutgeb (2011)

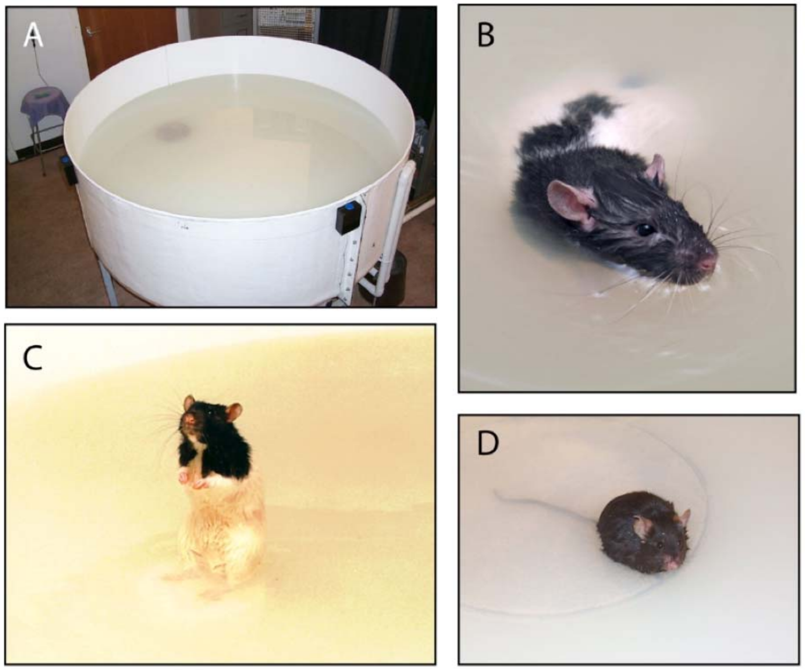
Conjunctive cells lose grid cell periodicity but not head direction selectivity

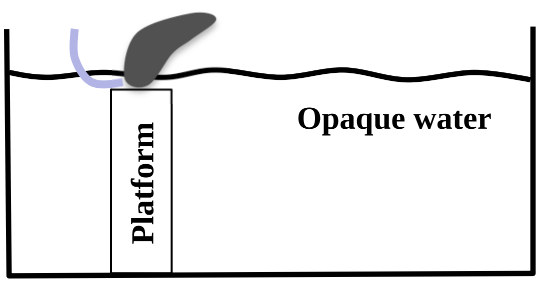
Brandon, Bogaard, Libby, Connerney, Gupta, Hasselmo, (2011). *Science*, 332: 595-599.



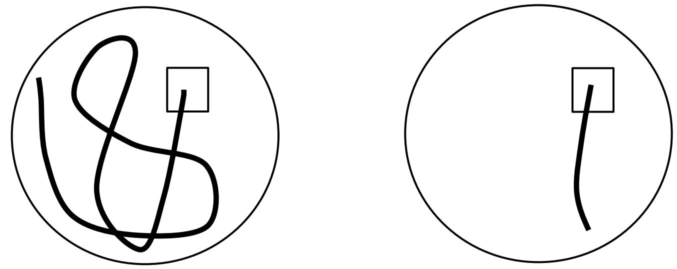
Memory impaired by inactivation of medial septum

Morris water maze





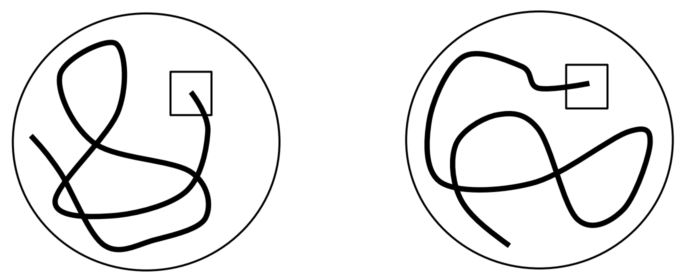
Control



First trial

Later trials

Inactivation of the medial septum



First trial

Later trials

Inactivation of medial septum: Chrobak et al., 1989; Brioni et al., 1990

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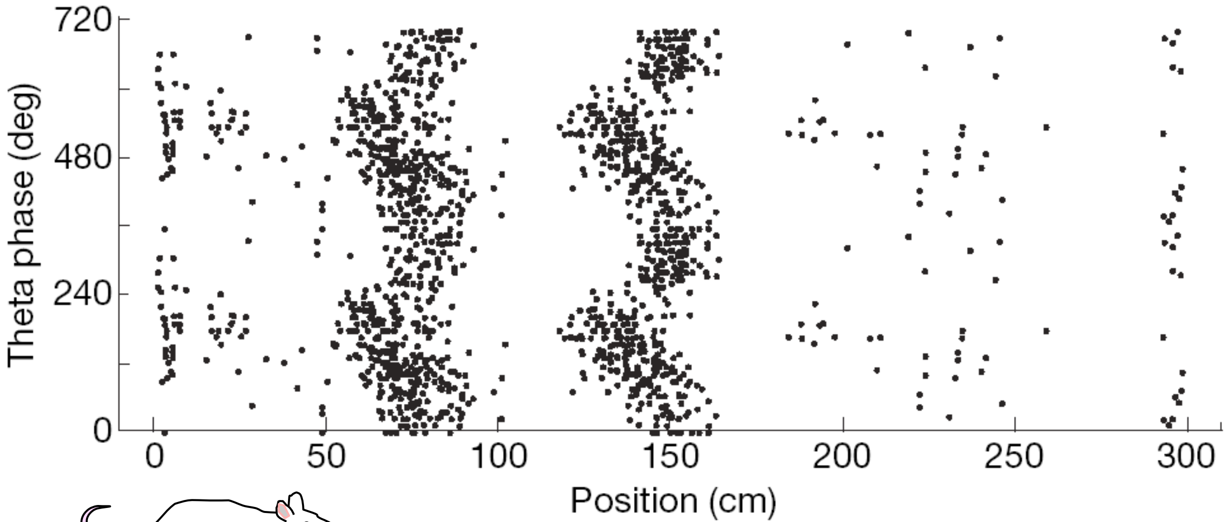
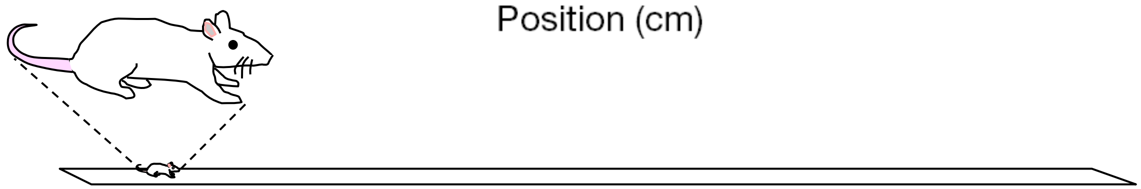
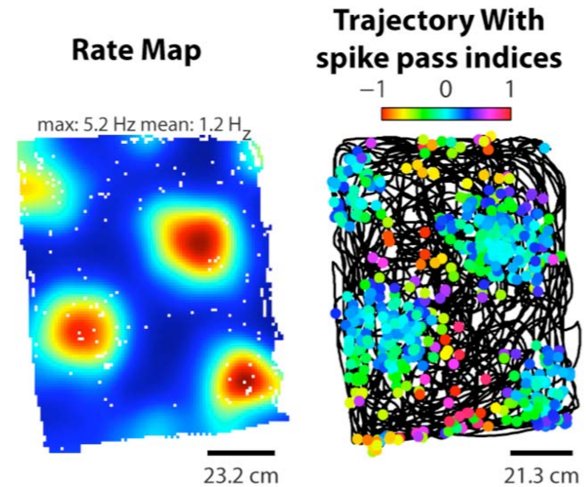
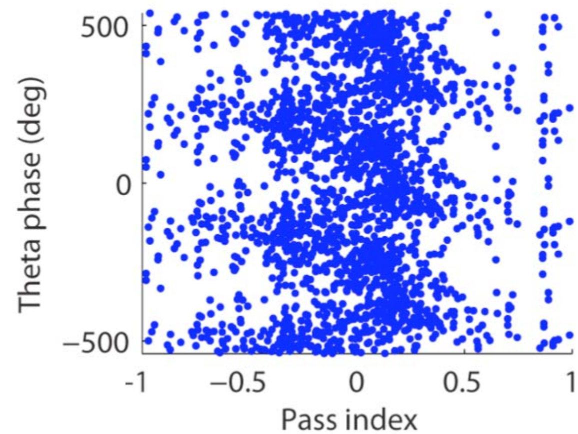
Grid cells: theta phase codes position

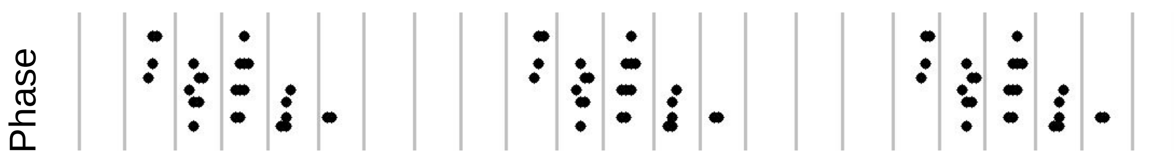








Hafting, Fyhn, Bonnevie, Moser, Moser (2008)



Oscillatory interference model
Burgess, Barry, O'Keefe (2007)
Burgess (2008); Hasselmo (2008)

Climer, Newman, Brandon, Hasselmo

Strengths of oscillatory interference model:

1. Predicted dorsal-ventral frequency difference (Giocomo et al., 2007; Giocomo and Hasselmo, 2008)
2. Predicts loss of grid cell periodicity with loss of theta (Brandon et al., 2011)
3. Predicted theta phase precession in entorhinal cortex (Hafting et al., 2008; Climer et al., in review)
4. Resonance distribution matches grid cell distribution (Shay et al., 2012)
5. Predicted spiking frequency change with field size and running speed (Jeewajee et al., 2008)
6. Predicts theta cell interburst frequency (Blair et al., 2008; Welday et al., 2011)
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Grid cell firing field spacing

↑

Membrane potential resonance and oscillation frequency

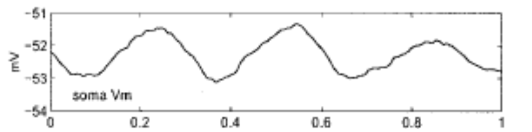
↑

Properties of h current

h current and intrinsic freqeuncy

h current: Hyperpolarization activated cation current (depolarizing)

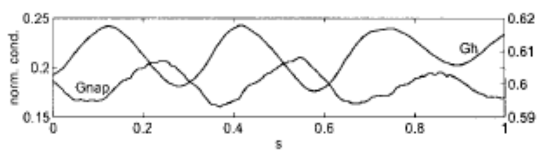
Membrane potential



Fransen, Alonso, Dickson, Magistretti, Hasselmo, 2004

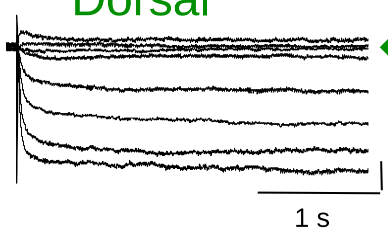
Dickson et al., 2000

h current

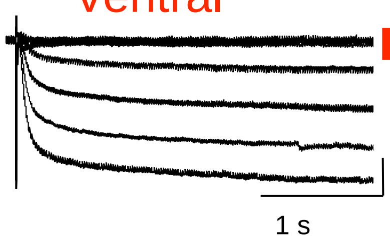


h current time constant differs in voltage clamp

Dorsal



Ventral



Biophysical model using voltage clamp data

Dorsal

Ventral

Giocomo and Hasselmo (2008) J. Neuroscience 28:9414-25
Heys, Giocomo, Hasselmo, (2010) J. Neurophysiology
Heys, Hasselmo, 2011, SFN poster ZZ 25, 730.09.

Grid cell firing field spacing

↑

Membrane potential resonance and oscillation frequency

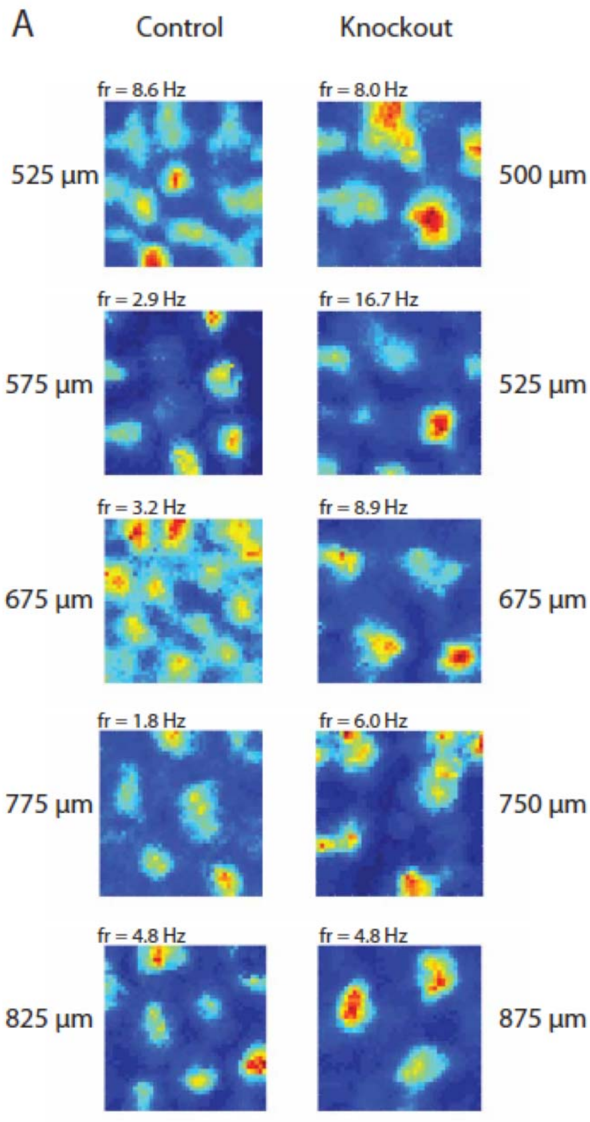
↑

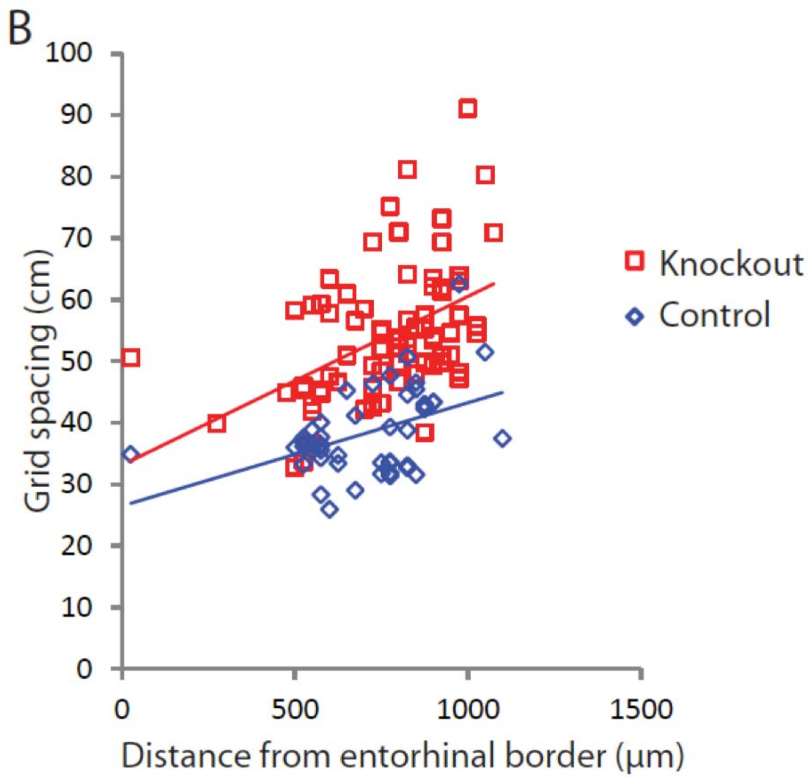
Time constant of h current

↑

Expression of HCN1 subunit of h current

Wider spacing with HCN1 knockout
Giocomo et al., 2011





Data from: Giocomo, Hussaini, Zhang, Kandel, Moser, Moser, (2011) Increased spatial scale of grid cells of HCN1 knockout mice. *Cell*, 147: 1159-1170.

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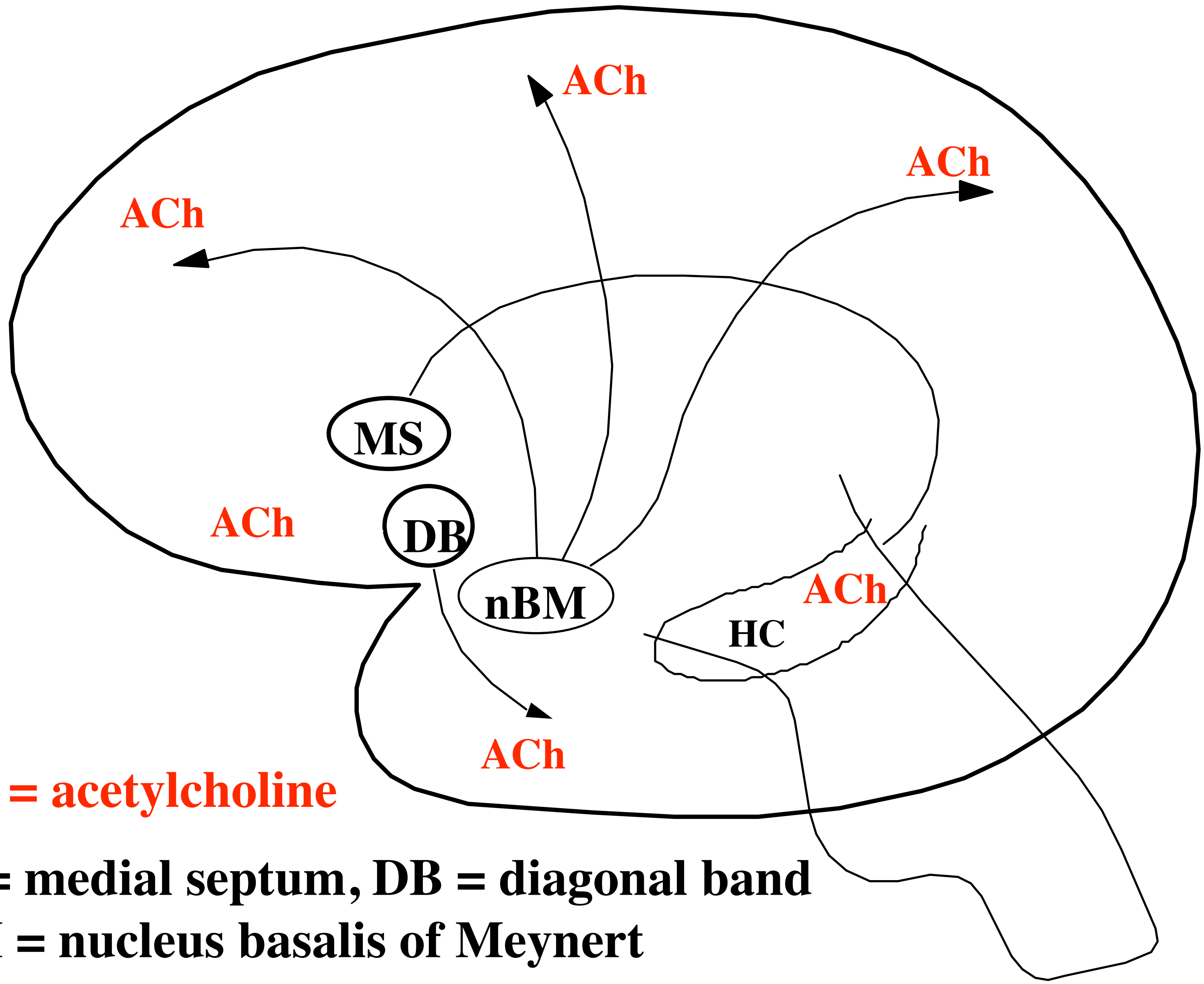
Talk outline:

1. Models of physiological properties in entorhinal cortex
2. Model of the initiation and progression of Alzheimer's disease

Central question

Why do the molecular mechanisms of Alzheimer’s disease start in entorhinal cortex and spread to connected cortical regions?



ACh = acetylcholine

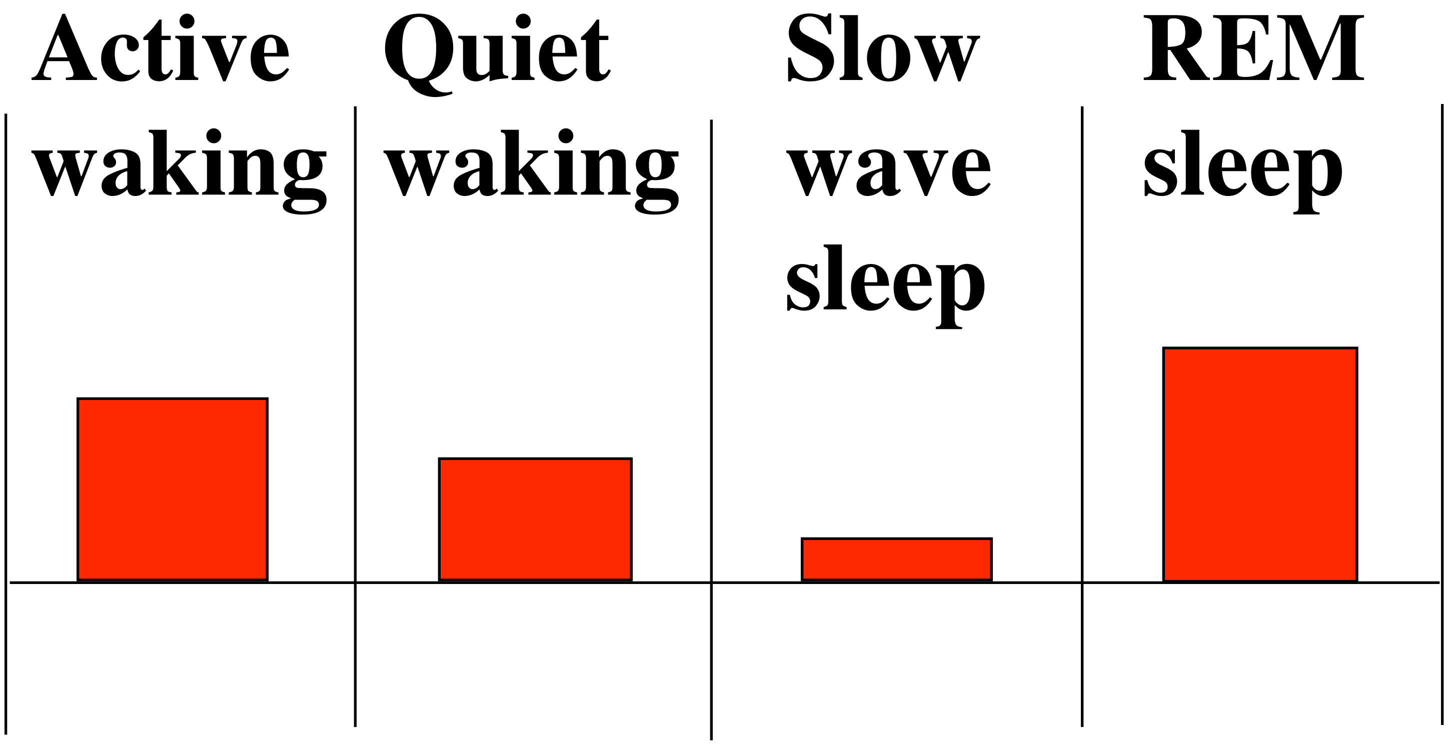
MS = medial septum, DB = diagonal band

nBM = nucleus basalis of Meynert

HC = hippocampus

Reviewed in:
Hasselmo (1999) Trends in Cognitive Science 3: 351-359.

Acetylcholine levels



Marrosu et al. (1995) Brain Res. 671: 329-332

Reviewed in:
Hasselmo (1999) Trends in Cognitive Science 3: 351-359.

Blockade of acetylcholine impairs encoding not retrieval

Ghonheim and Mewaldt, 1975; Peterson, 1977

Learn list #1.

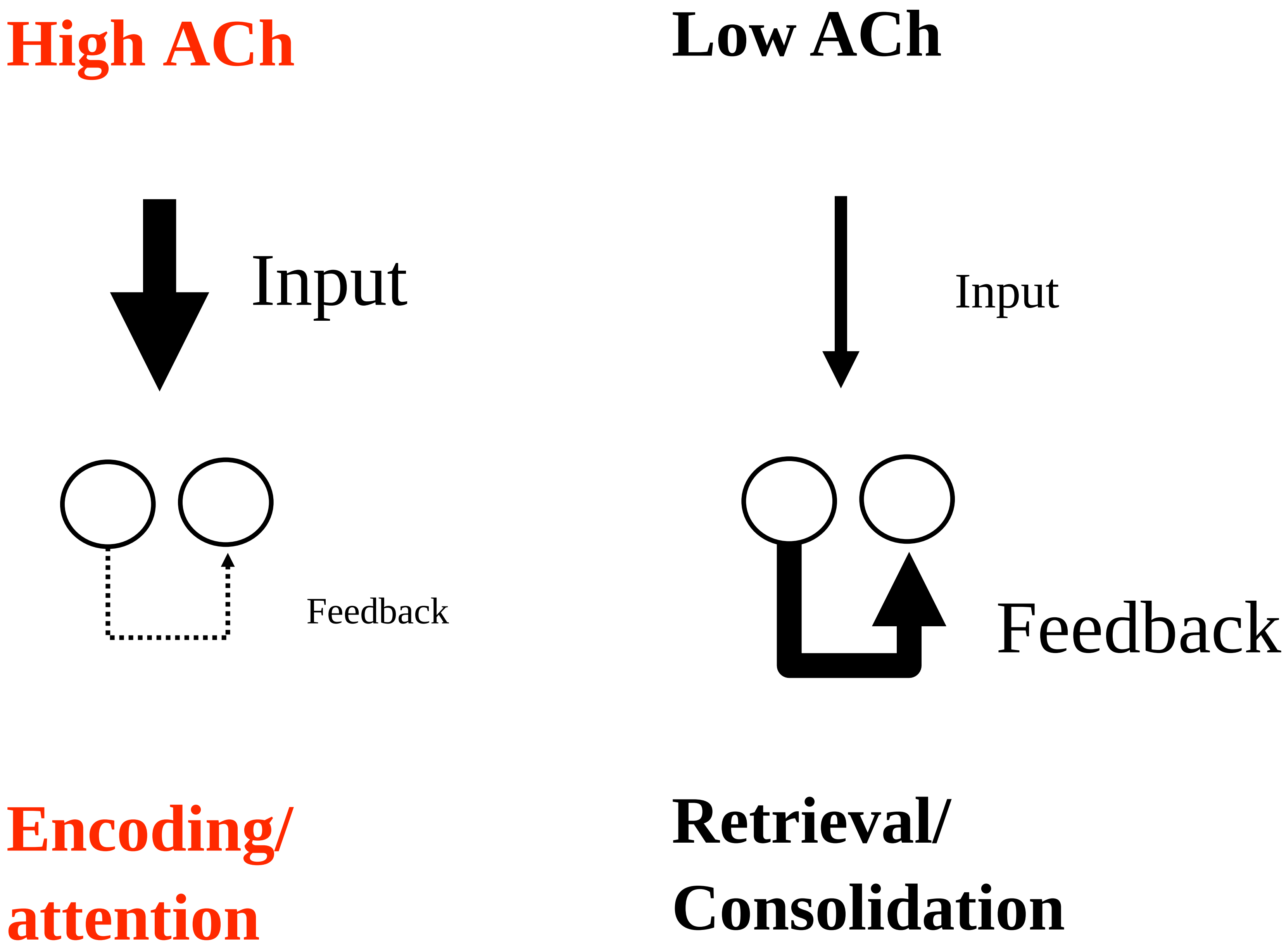
Scopolamine injection (muscarinic antagonist)

Recall list #1 (no effect)

Learn list #2

Recall list #2 (strong impairment)

Hasselmo (1999) Trends in Cognitive Science 3: 351-359.



Hasselmo (1999) Trends in Cognitive Science 3: 351-359.

ACh effects in cortex

Input strong

Depolarization of pyramidal cells

Decreased spike frequency accomodation

Feedback weak

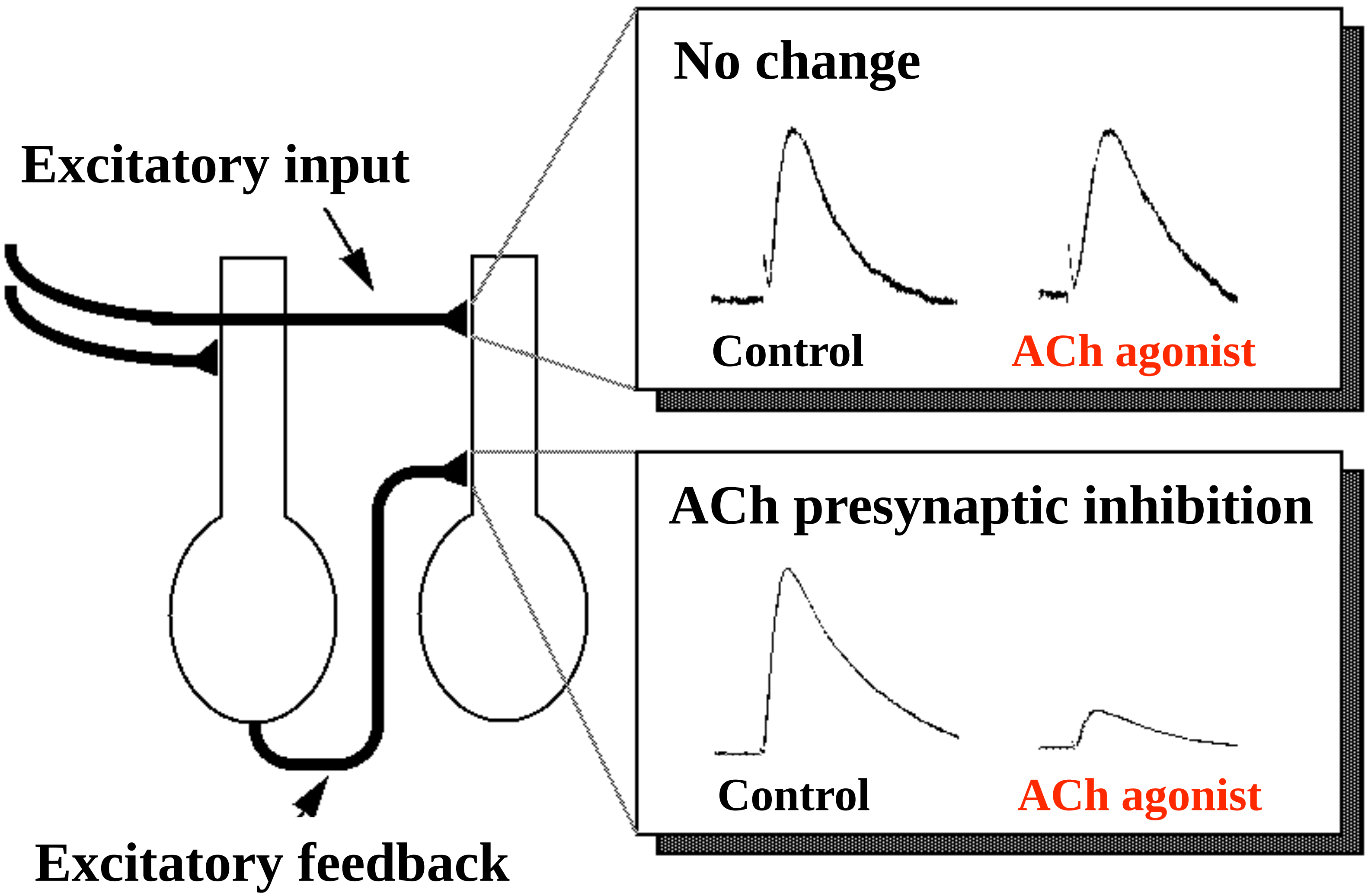
Decreased excitatory feedback transmission

Memory enhanced

Increased LTP

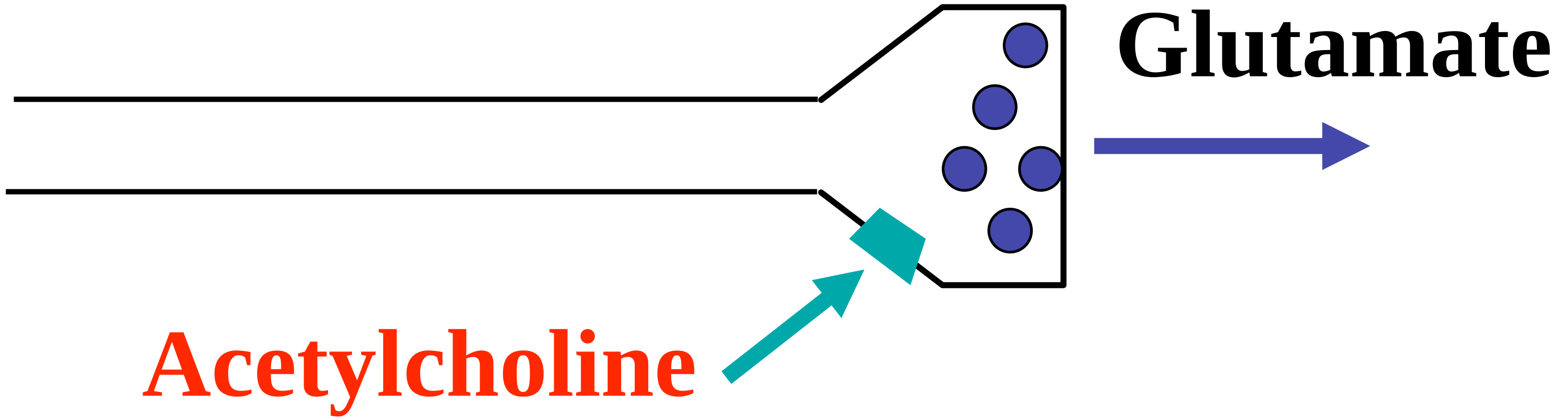
Hasselmo (1999) Trends in Cognitive Science 3: 351-359.

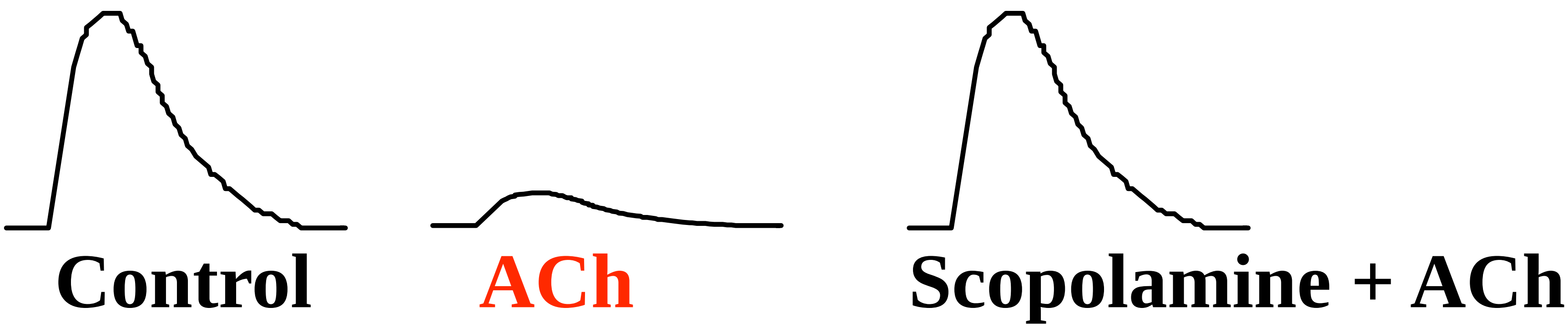
Cholinergic presynaptic inhibition of glutamate transmission: Selective for feedback



Hasselmo and Bower (1992) J. Neurophysiology
Hasselmo (1999) Trends in Cognitive Science 3: 351-359.

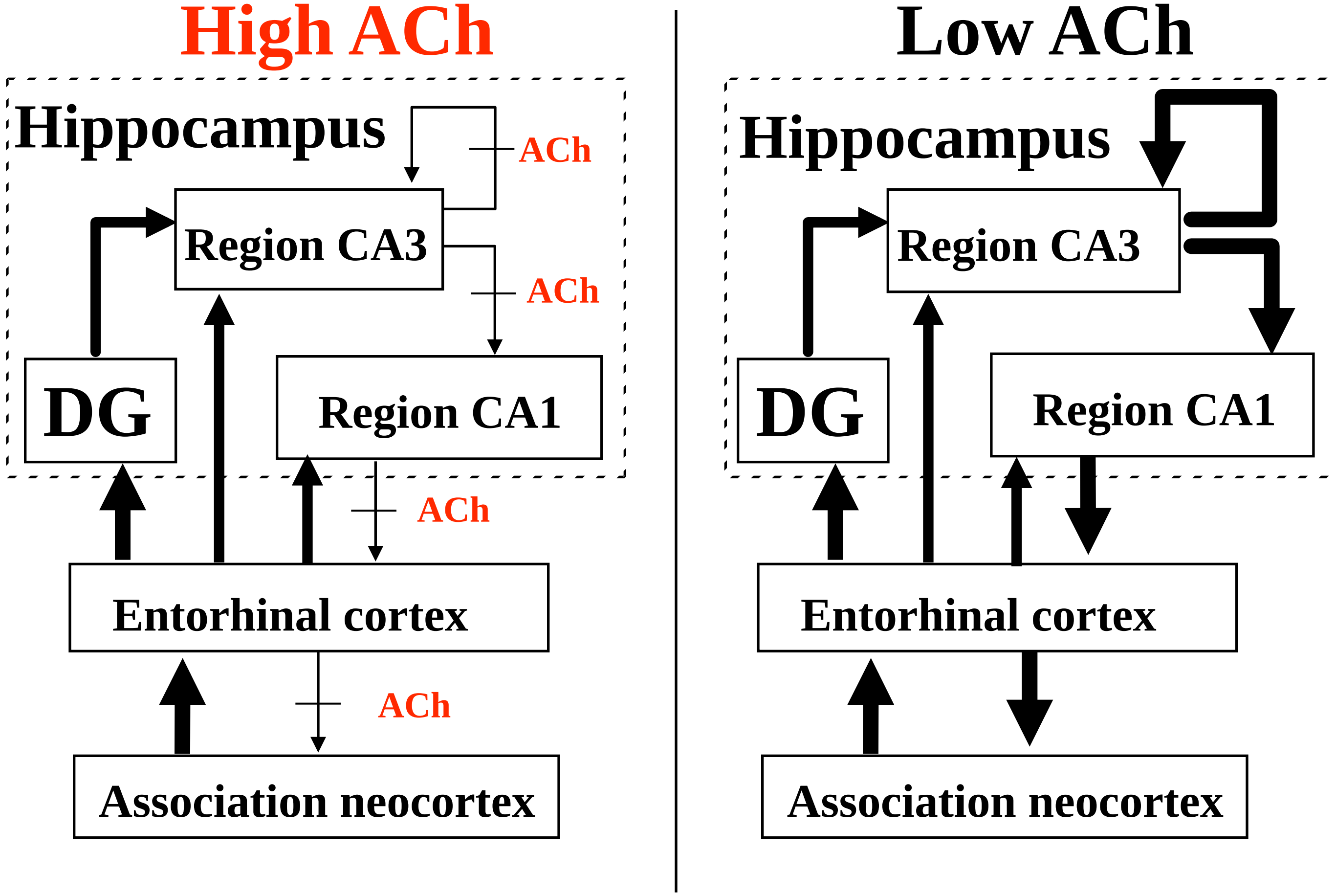
Muscarinic M4 receptors cause presynaptic inhibition of glutamate release





Hasselmo (1999) Trends in Cognitive Science 3: 351-359.
Dasari and Gulledge (2011) J. Neurosci. 105: 779-792

High ACh | Low ACh

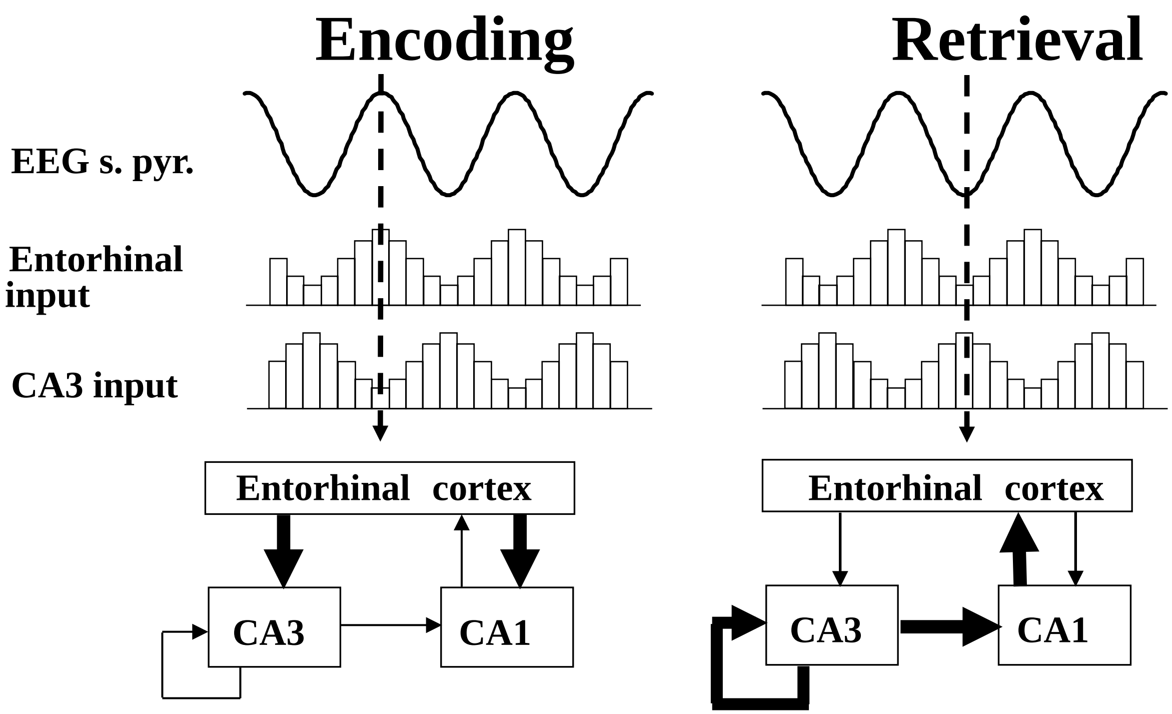


Encoding/ Attention

Retrieval/ Consolidation

Hasselmo (1999) Trends in Cognitive Science 3: 351-359.

Encoding and retrieval on different phases of theta



Hasselmo et al., 2002
Cutsuridis and Hasselmo, 2012

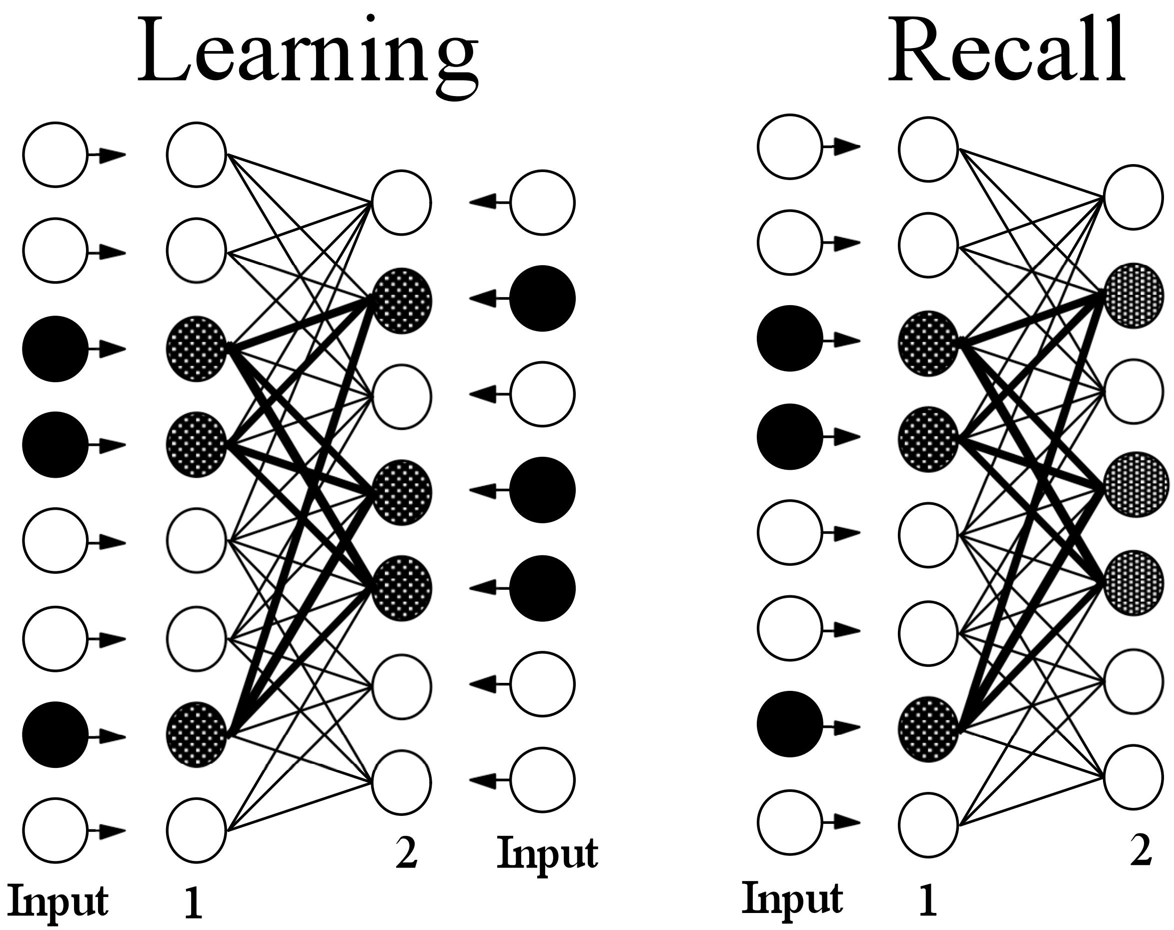
ACh effects in cortex

Decreased excitatory feedback transmission

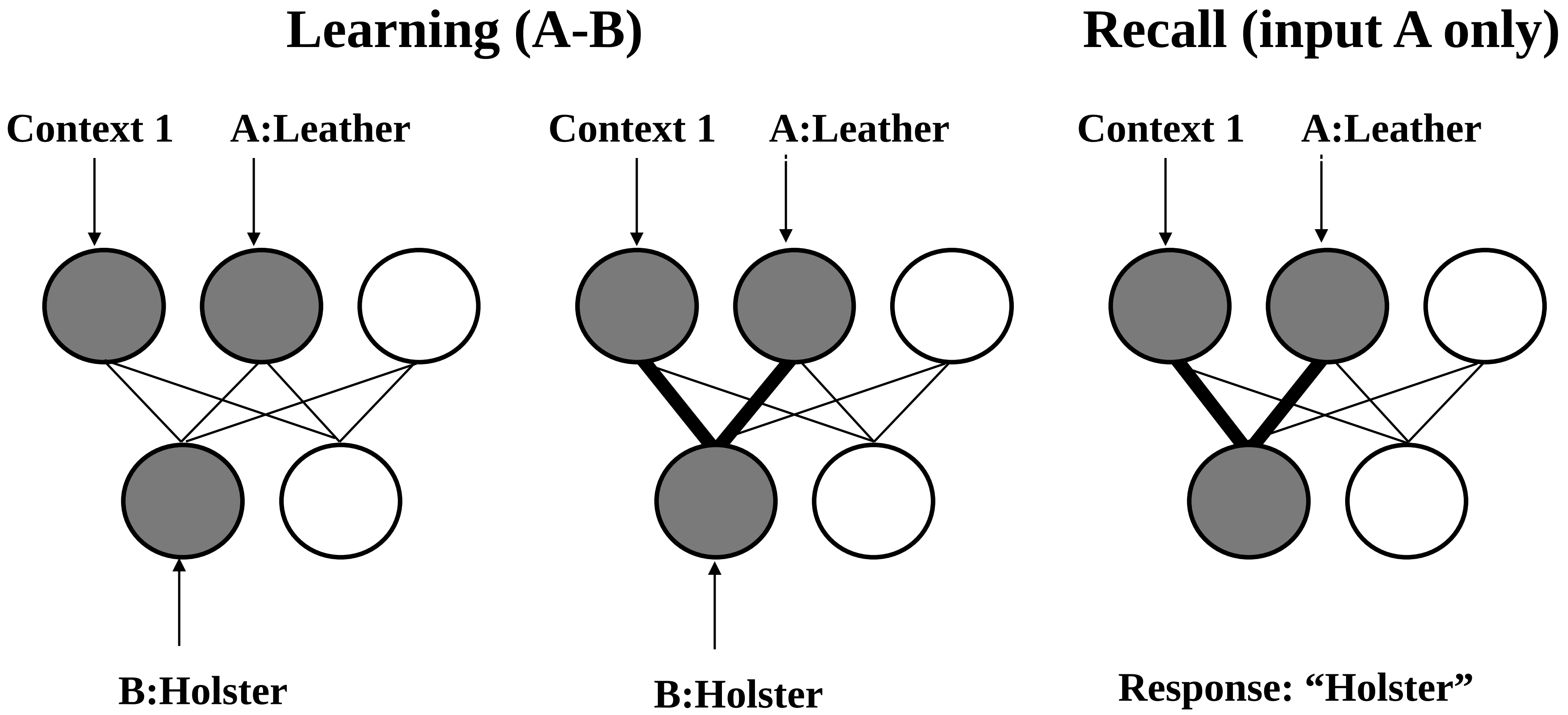
Increased LTP

Why does acetylcholine inhibit glutamate release at the same synapses that show enhanced LTP?

Model of memory as Hebbian associations between patterns of neural activity

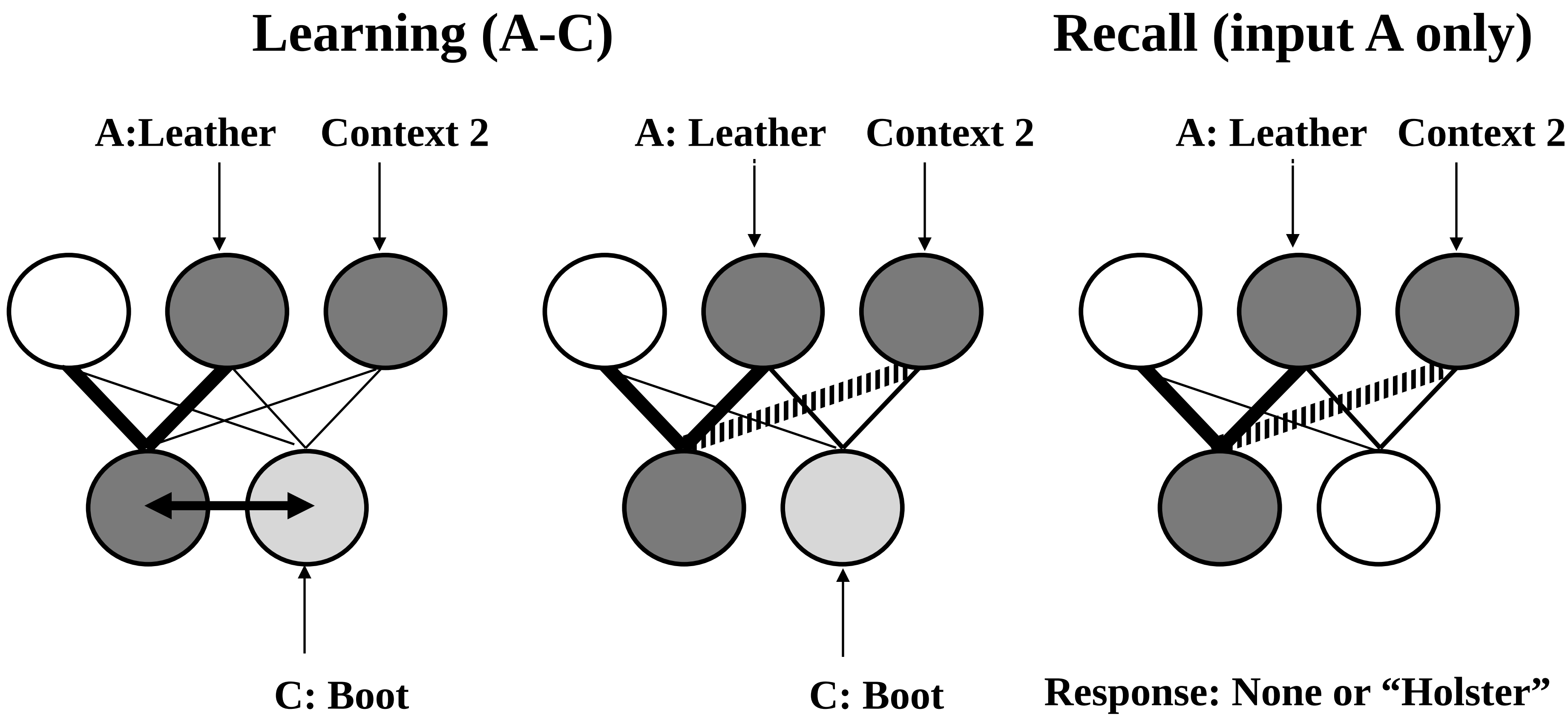


Learning 1st word pair



Hasselmo, M.E. (2012) How We Remember: Brain Mechanisms of Episodic Memory. MIT Press: Cambridge, MA

2nd word pair (no ACh - scopolamine)



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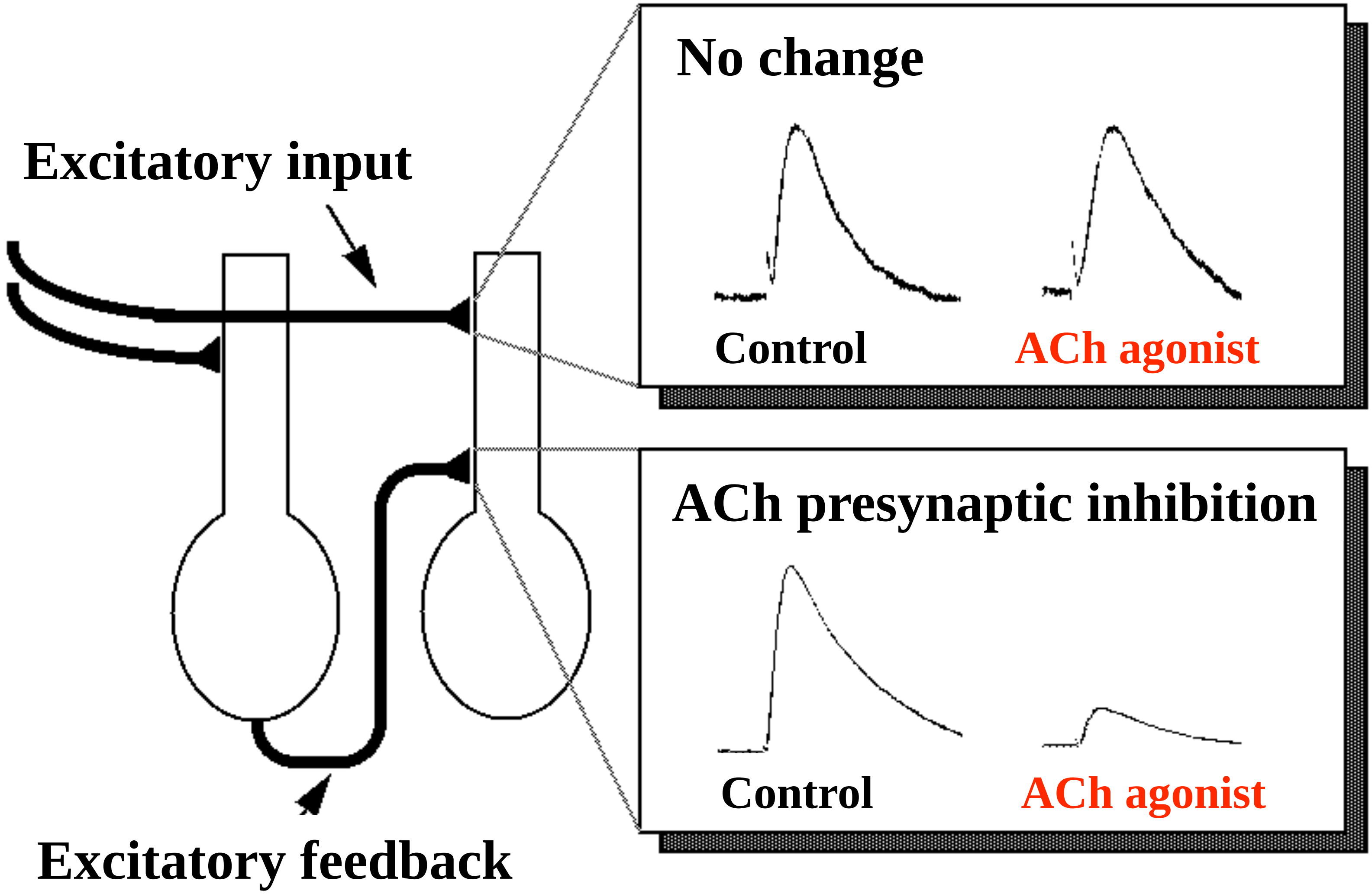
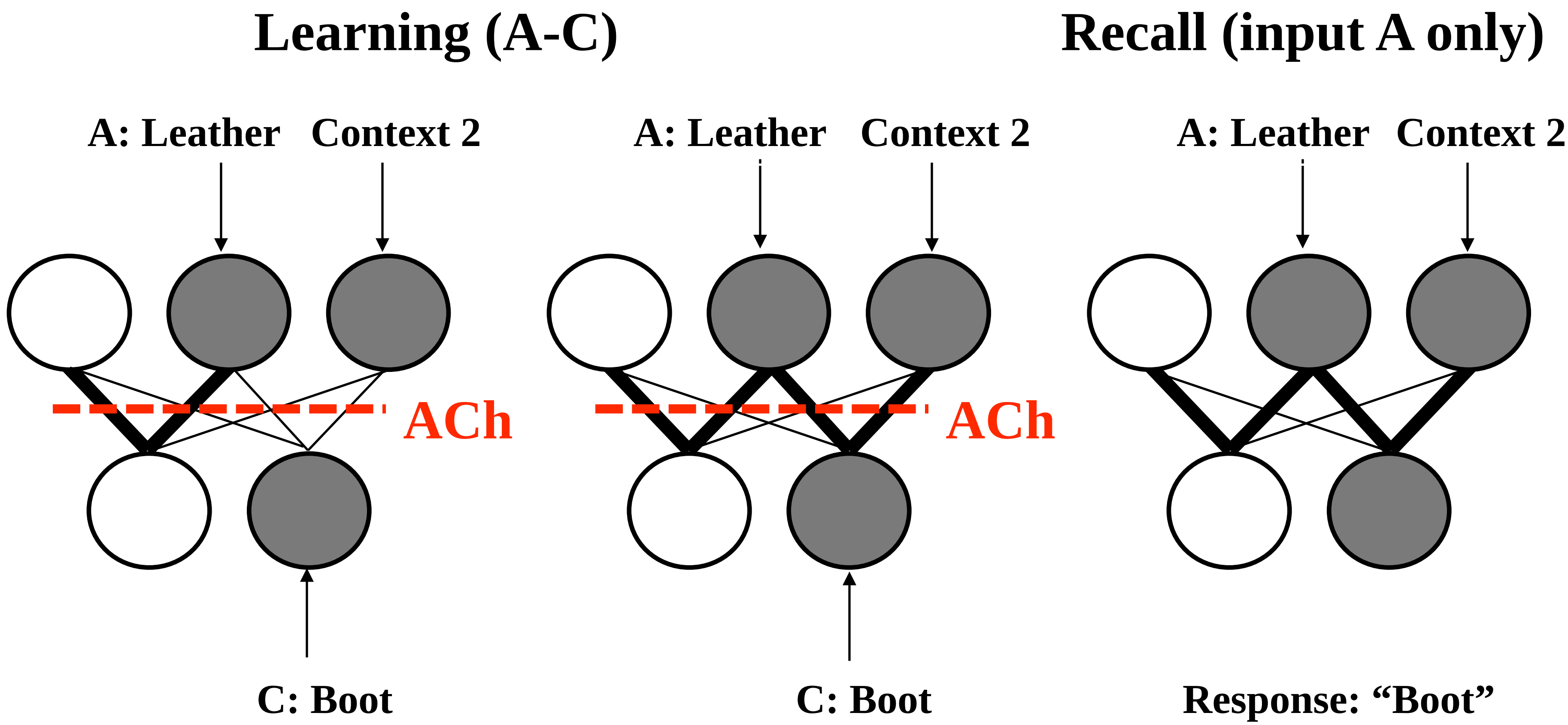


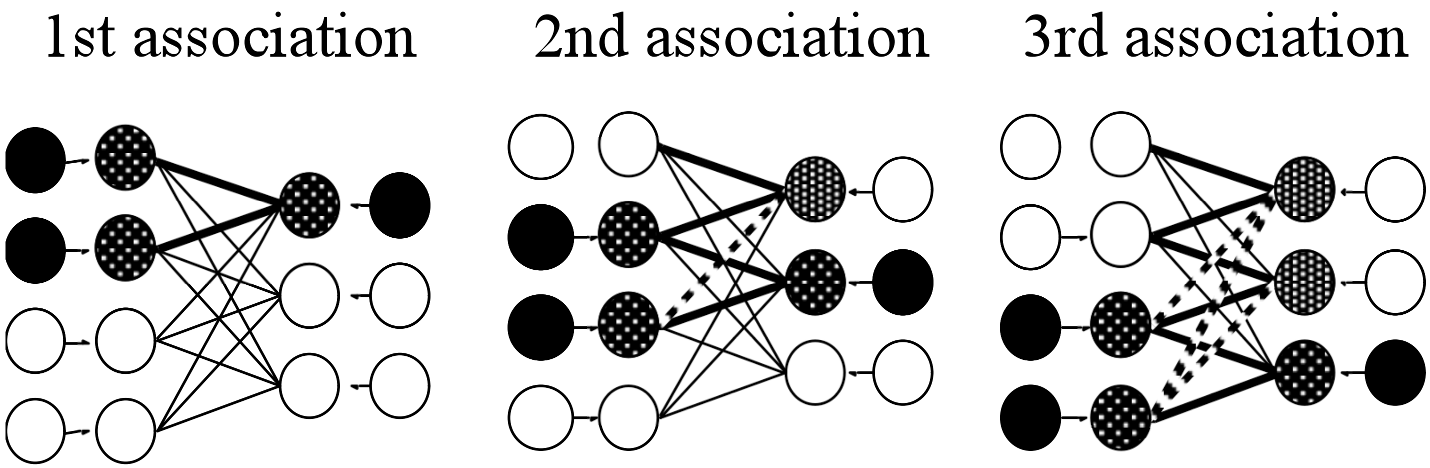
Hasselmo and Bower (1992) J. Neurophysiology
Hasselmo (1999) Trends in Cognitive Science 3: 351-359.

2nd paired associate (with ACh)



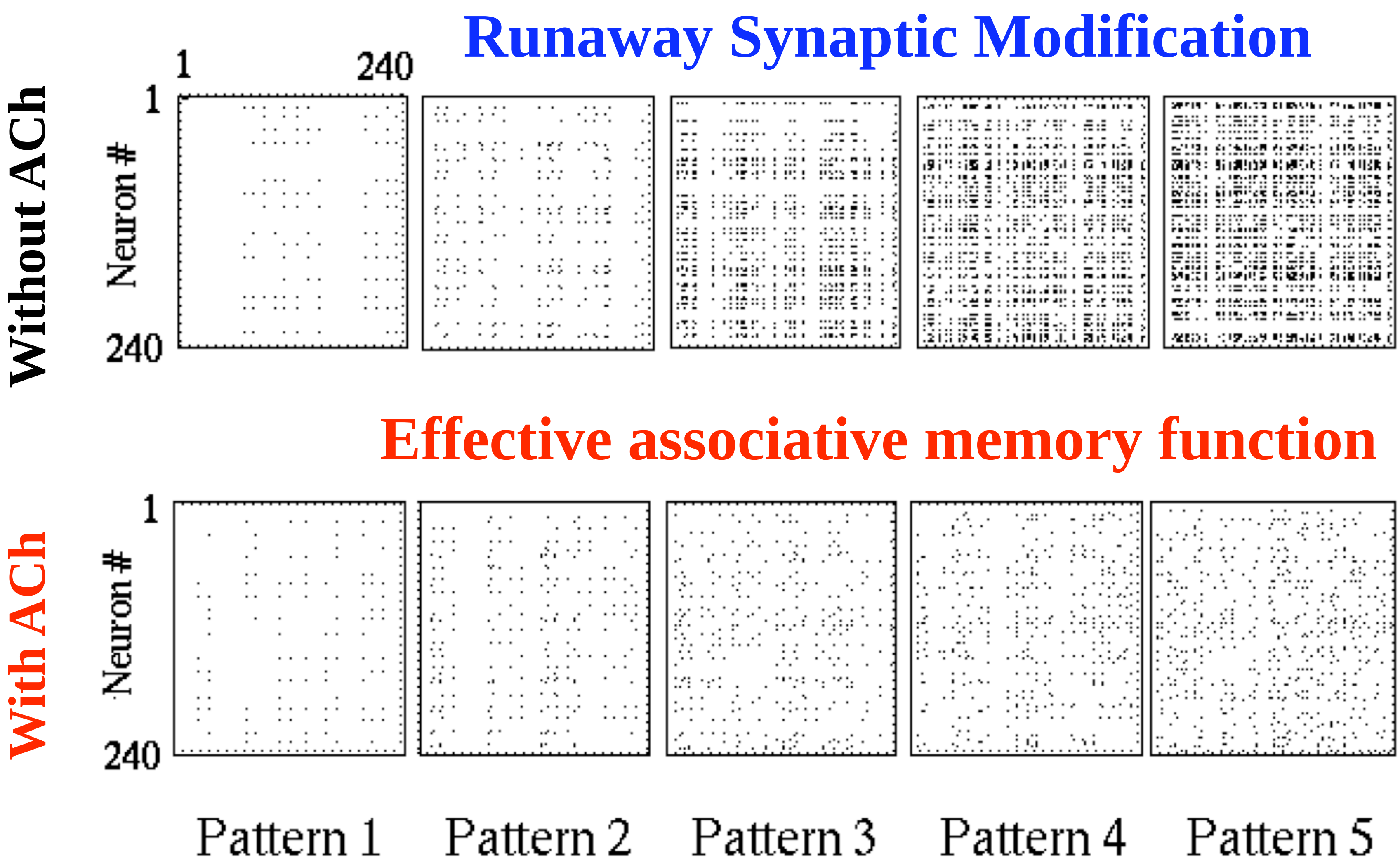
Hasselmo, M.E. (2012) How We Remember: Brain Mechanisms of Episodic Memory. MIT Press: Cambridge, MA

Theory of Alzheimer’s disease:
Runaway Synaptic Modification



Hasselmo M.E. (1994) Runaway synaptic modification in models of cortex: Implications for Alzheimer’s disease. *Neural Networks* 7(1): 13-40.

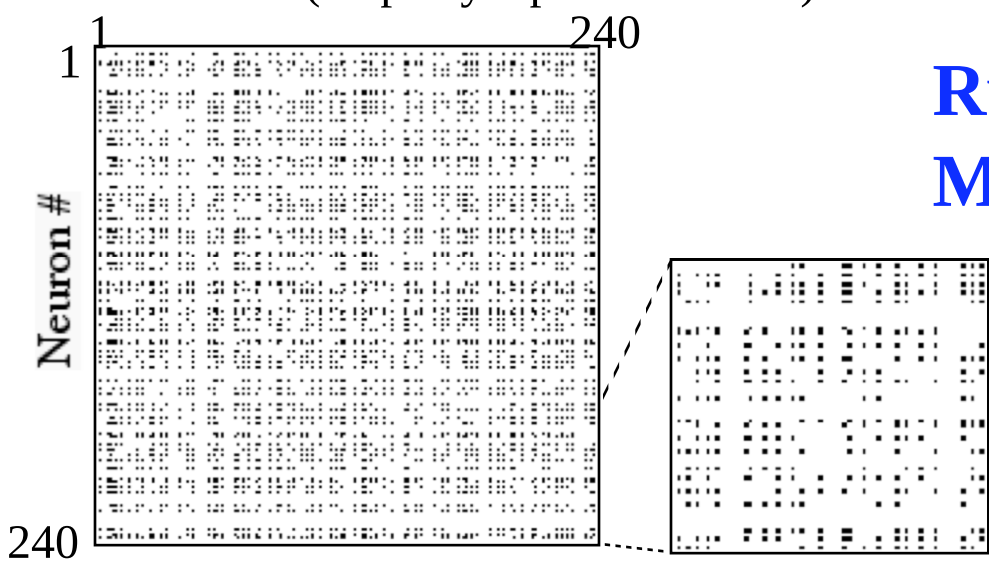
Hasselmo, M.E. (1997) A computational model of the progression of Alzheimer's disease. *M.D. Computing* 14: 181-191.



Hasselmo M.E. (1994) *Neural Networks* 7(1): 13-40.

Hasselmo, M.E. (1997) *M.D. Computing* 14: 181-191.

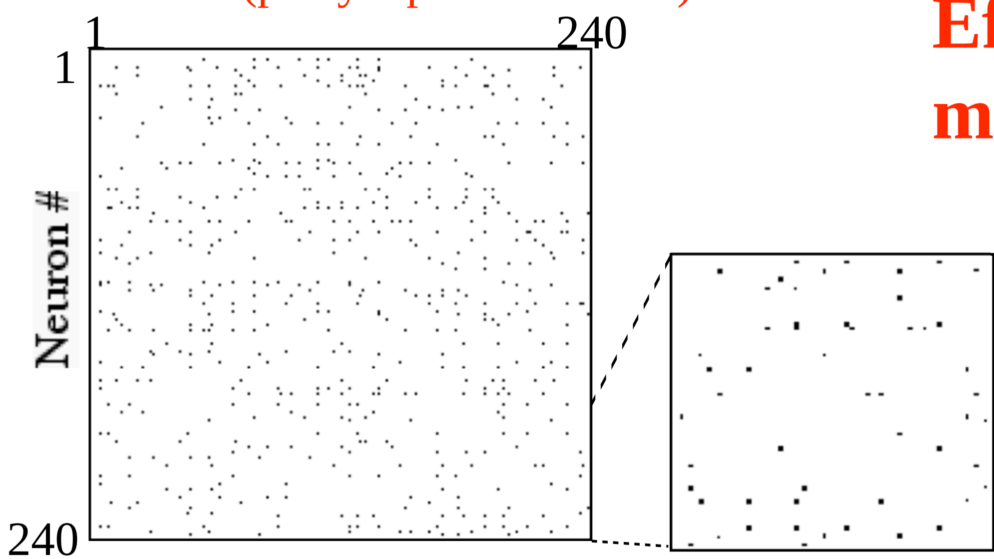
Without ACh (no presynaptic inhibition)



Runaway synaptic modification

Runaway Synaptic Modification

With ACh (presynaptic inhibition)

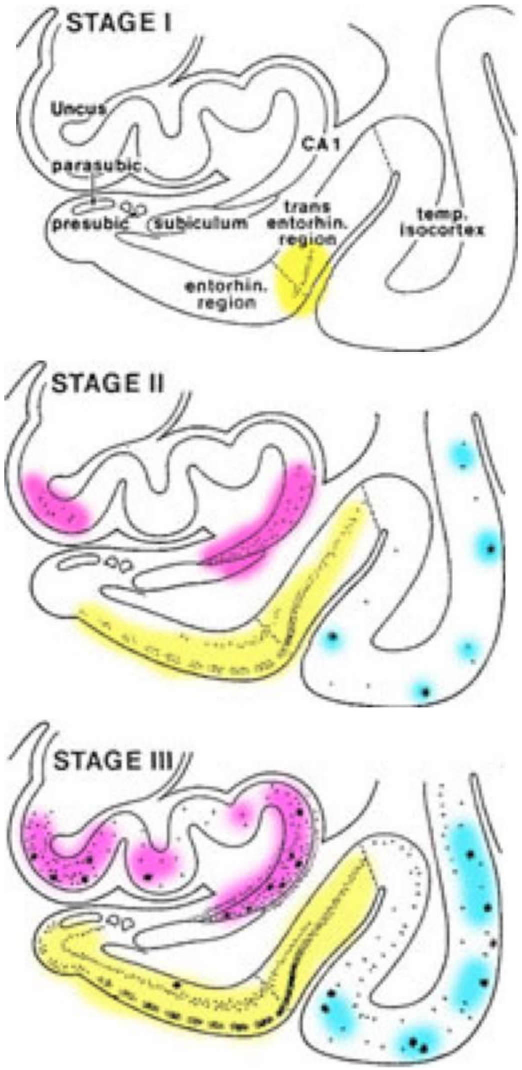


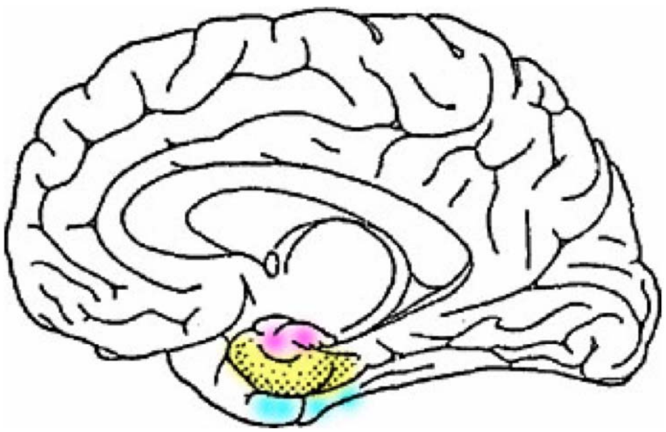
Effective associative memory function

Hasselmo M.E. (1994)
Neural Networks **7(1): 13-40.**

Hasselmo, M.E. (1997)
M.D. Computing **14: 181-191.**

Neurofibrillary tangles start in entorhinal cortex





Tangles correlate with behavioral impairment

MCI
Braak stage 2–3
Mini Mental State Exam 26–30

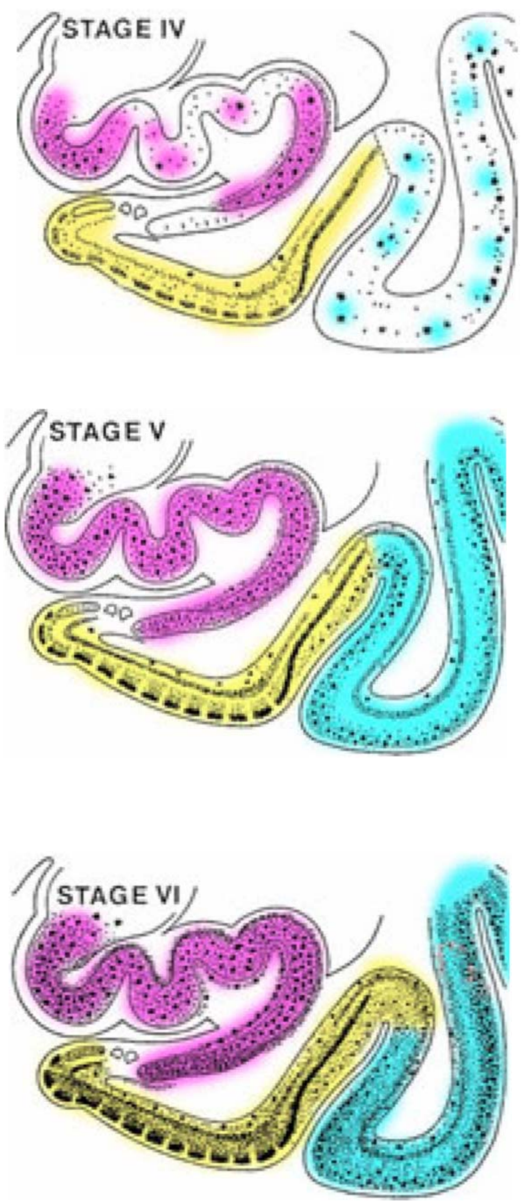
Mild AD
Braak stages 3–4
MMSE 20–26

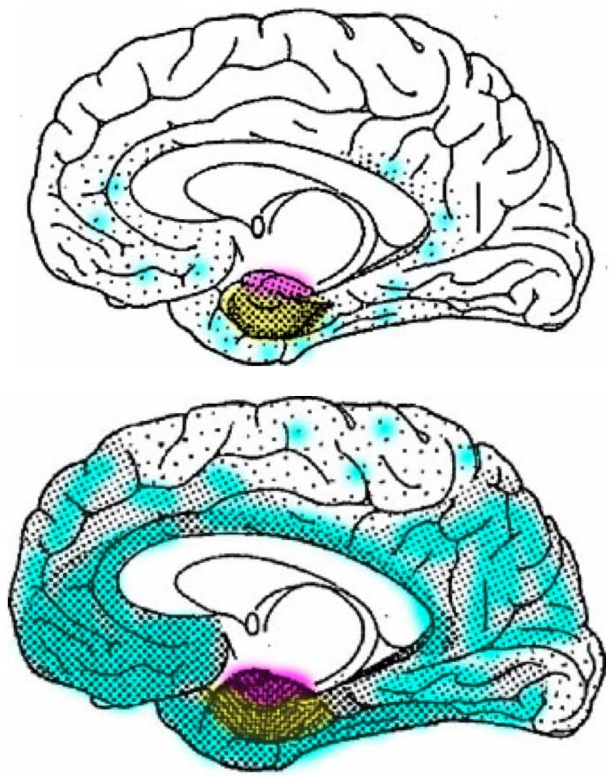
Images taken from "Neuropathological stageing of Alzheimer-related changes", Braak and Braak, Acta Neuropathol (1991) 82:239-259.
Tangles start in lateral entorhinal border with perirhinal. Also at border of CA1 and subiculum.

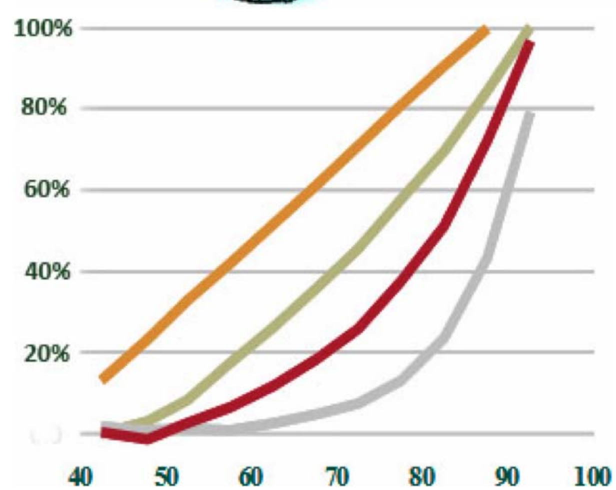
Basic summary:

1. **Runaway synaptic modification puts demands on role of APP in synaptic regulation that cause build-up of Abeta and amyloid plaques**
2. **Redistribution of synaptic resources puts demands on axonal transport that causes neurofibrillary tangles in cells of origin (initially lateral entorhinal cortex and CA1/subiculum border)**
3. **The functional effect of runaway synaptic modification causes a spread from one region to another.**
4. **The normal progression of runaway synaptic modification can cause sporadic Alzheimer's disease in the absence of mutations.**
5. **The progression of runaway synaptic modification should cause initial hyperactivation followed by eventual hypoactivation**
6. **The model accounts for cognitive features of the disease including hyper-priming and superordinate category use.**

Braak staging





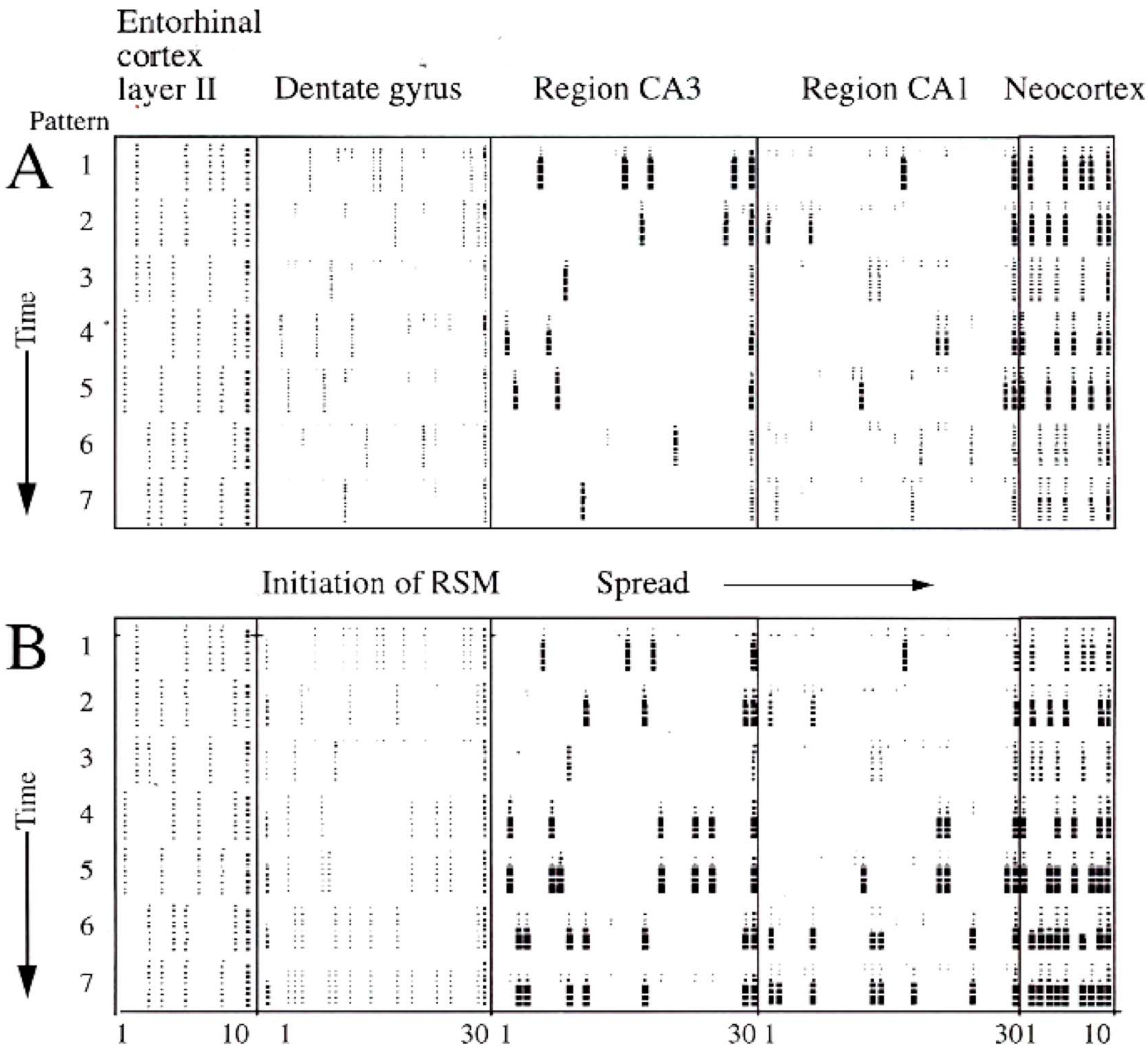


Moderate AD
Braak Stage 4–5
MMSE 11–19

*** Progressive memory loss; confused thinking**
*** Agitation, paranoia**
*** Need for assistance in daily activities**

Severe AD
Braak Stage 5–6
MMSE 0–10

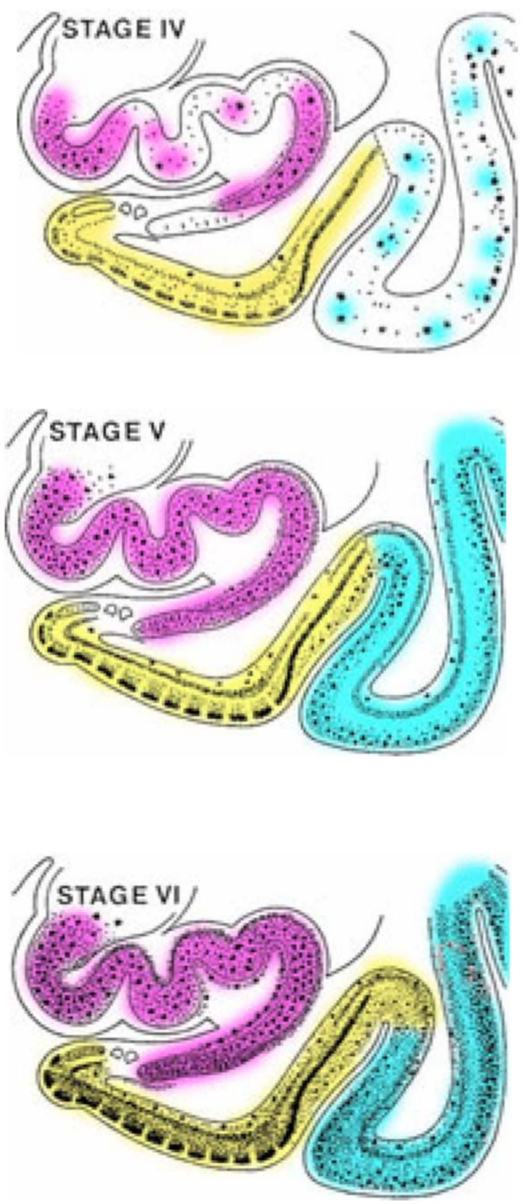
*** Severe memory loss and dementia**
*** Agitation, aggression, paranoia and delusions**
*** Loss of motor skills**
*** Hospitalization or long-term care**

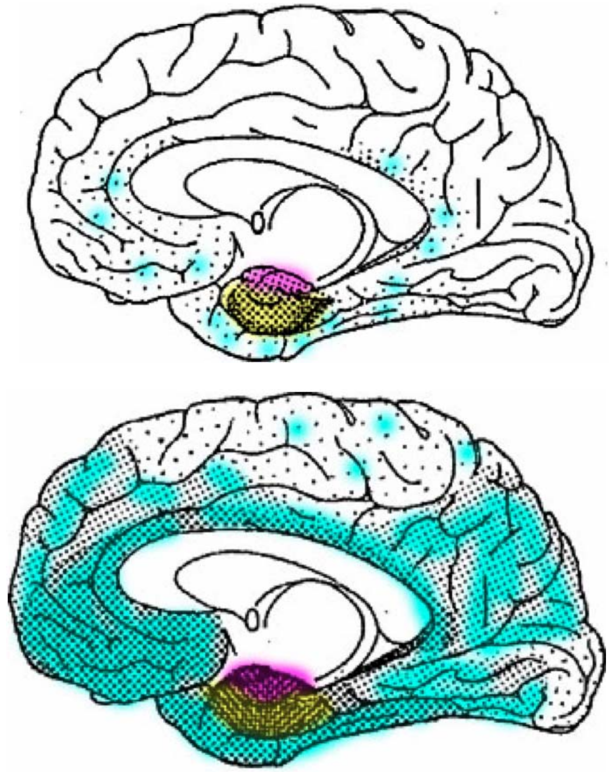


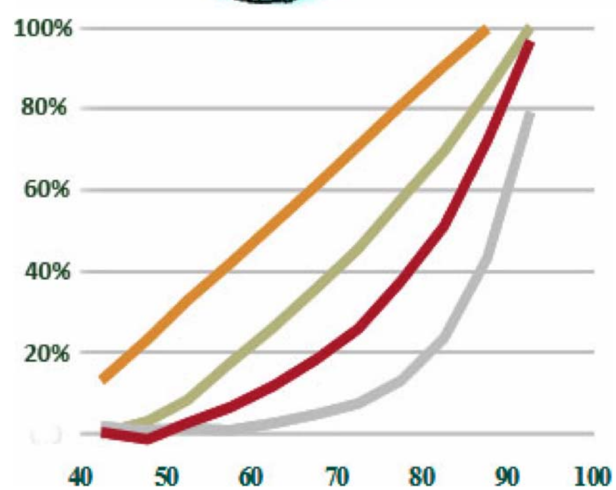
Effective memory

Spread of Runaway Synaptic modification

Braak staging







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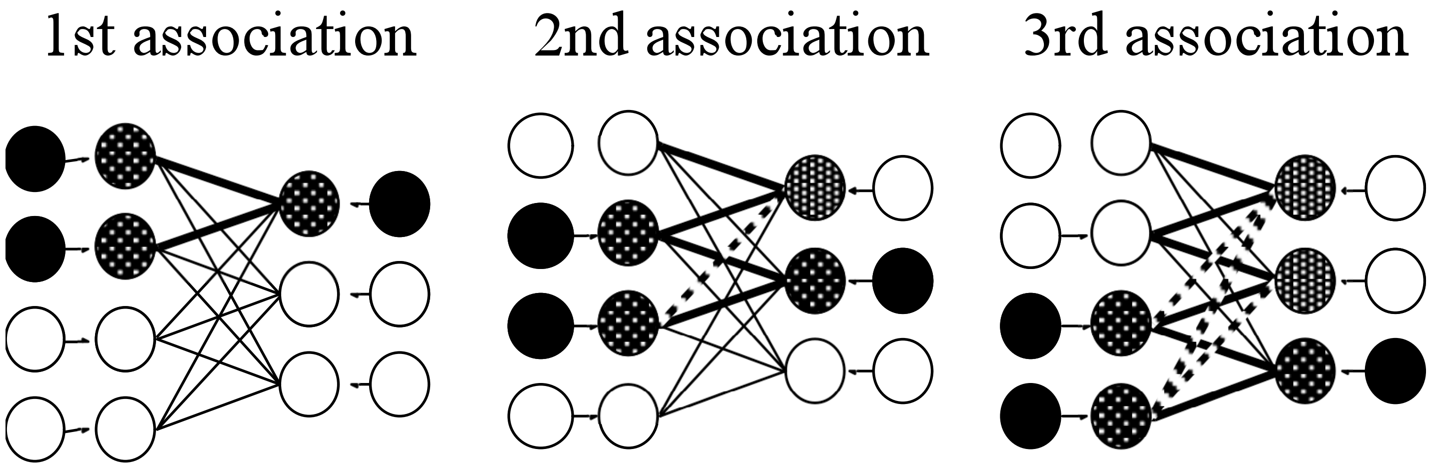
Theory of Alzheimer's disease: Runaway Synaptic Modification



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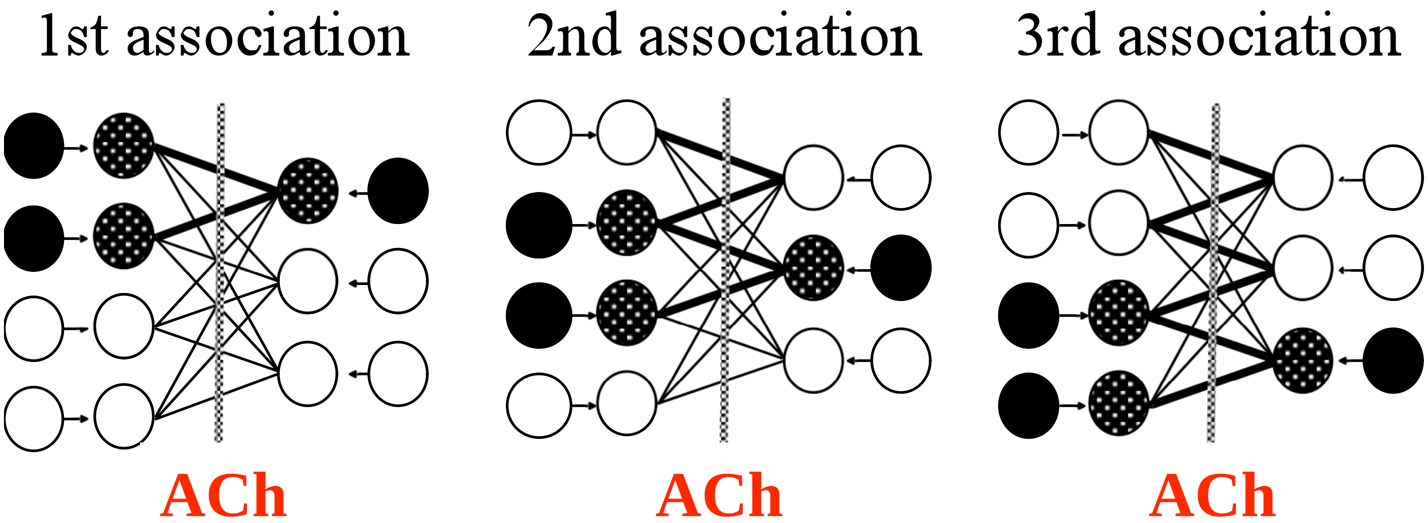
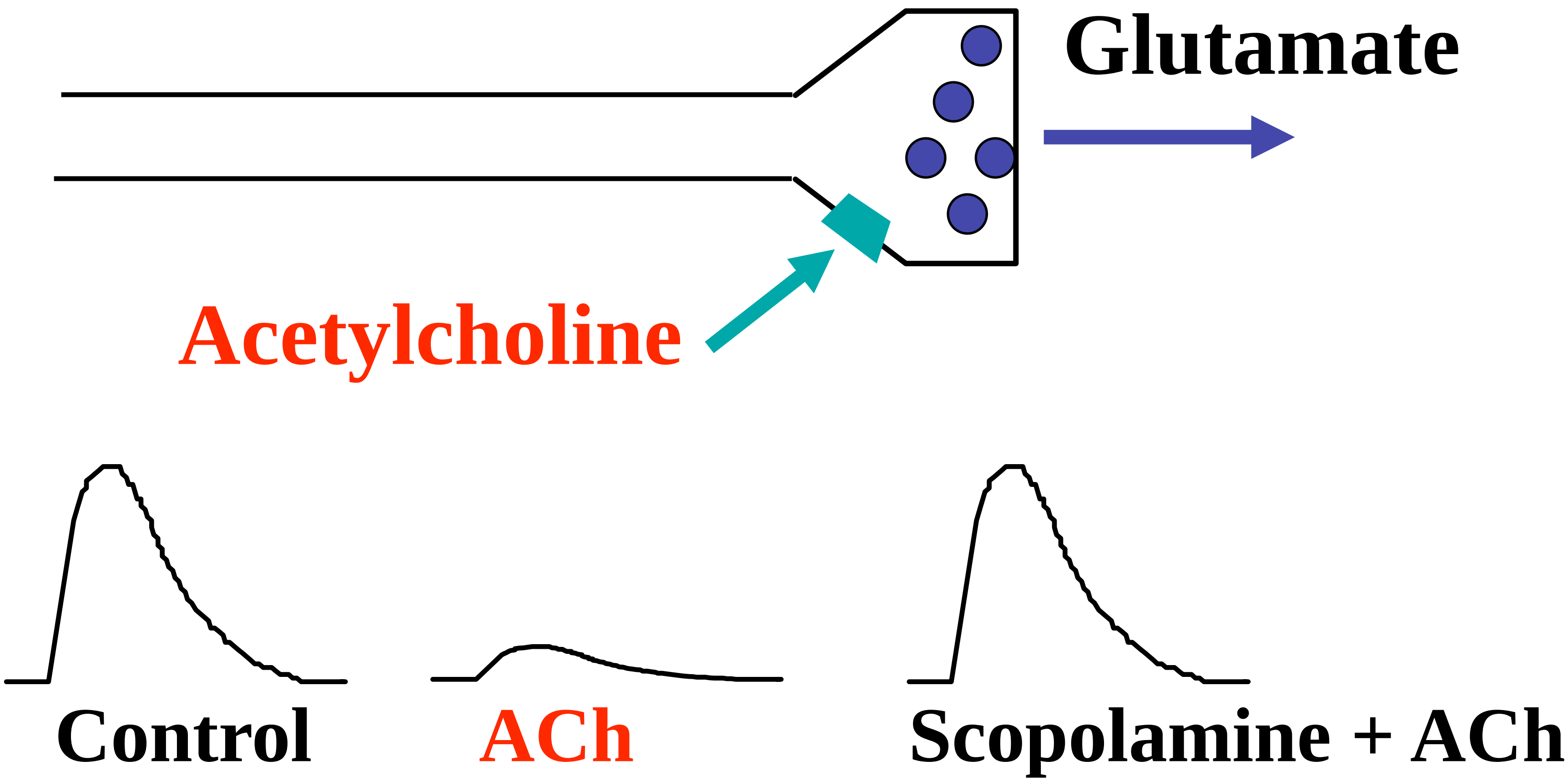


Selective agonists for M4 muscarinic ACh receptors
Cause presynaptic inhibition of glutamate release
Could prevent runaway synaptic modification

Hasselmo M.E. (1994) *Neural Networks* 7(1): 13-40.

Hasselmo, M.E. (1997) *M.D. Computing* 14: 181-191.

Muscarinic M4 receptors cause presynaptic inhibition of glutamate release



Hasselmo (1999) Trends in Cognitive Science 3: 351-359
Shirey et al., (2008) Nat. Chem. Biol. 4: 42-50
Dasari and Gulledge (2011) J. Neurosci. 105: 779-792

Pharmacological treatments of Alzheimer's disease

donepezil (Aricept) – acetylcholinesterase (AChE) blocker used for treatment of Alzheimer's disease. Increases central acetylcholine levels . Decreases memory problems (Howard et al., 2012). However, disease still progresses.

rivastigmine (Excelon) - slowly reversible AChE blocker.

galantamine (Reminyl) - AChE blocker, nicotinic agonist

Pharmacological treatments of Alzheimer’s disease

memantine (Namenda) - noncompetitive antagonist of NMDA receptors. Improves cognition in Alzheimer's disease. Some studies suggest that it slows progression of the disease. Could block runaway synaptic modification via blockade of Hebbian synaptic modification.

M4 agonists – selective activation of presynaptic muscarinic receptors. Cause presynaptic inhibition of glutamate release (Shirey et al., 2008; Dasari and Gulledge, 2011) without enhancing Hebbian modification. Could block runaway synaptic modification

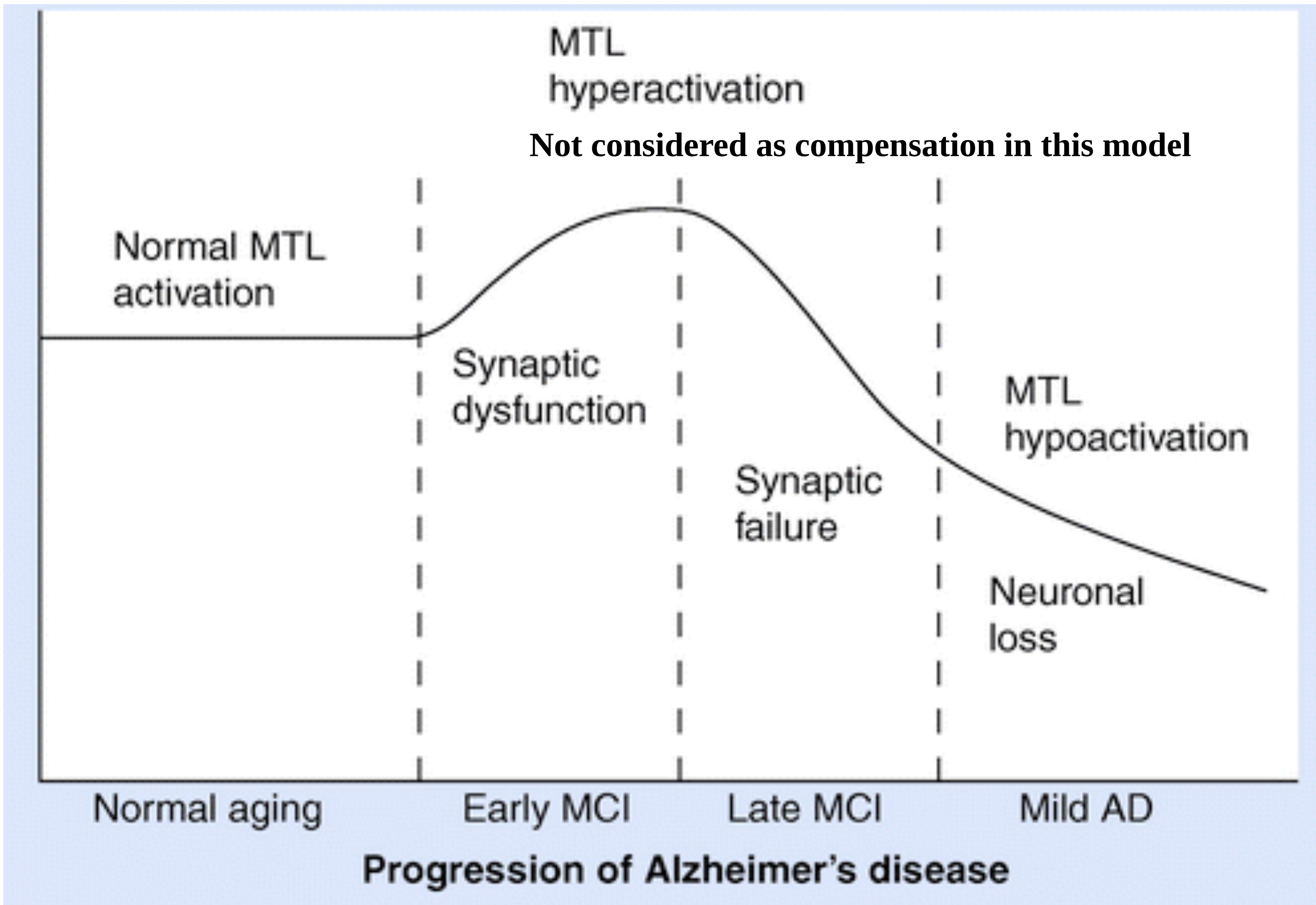
Talk outline:

1. **Models of physiological properties in entorhinal cortex**
2. **Model of the initiation and progression of Alzheimer's disease**

Implications of model

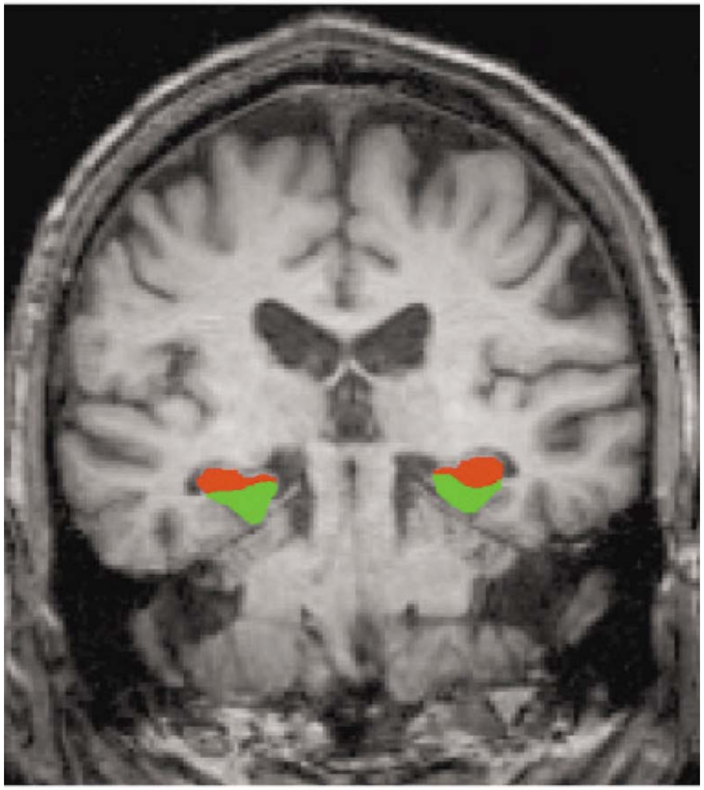
- Model predicts early hyperactivation preceding later hypoactivation – supported by fMRI data

MTL activity across time in MCI

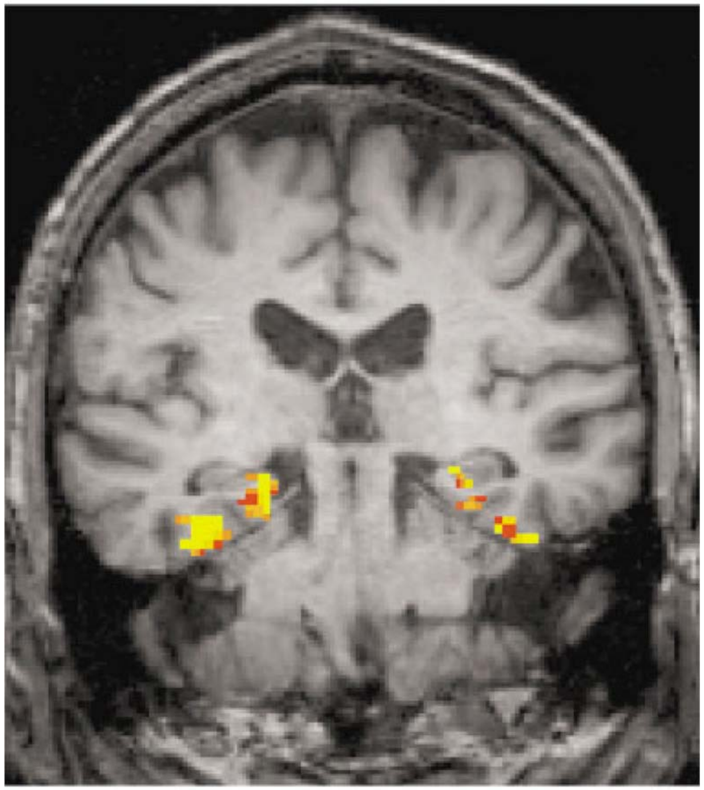


Stern et al., 1996

MTL Hyperactivation in MCI



Red: Hippocampus
Green: Parahippocampus

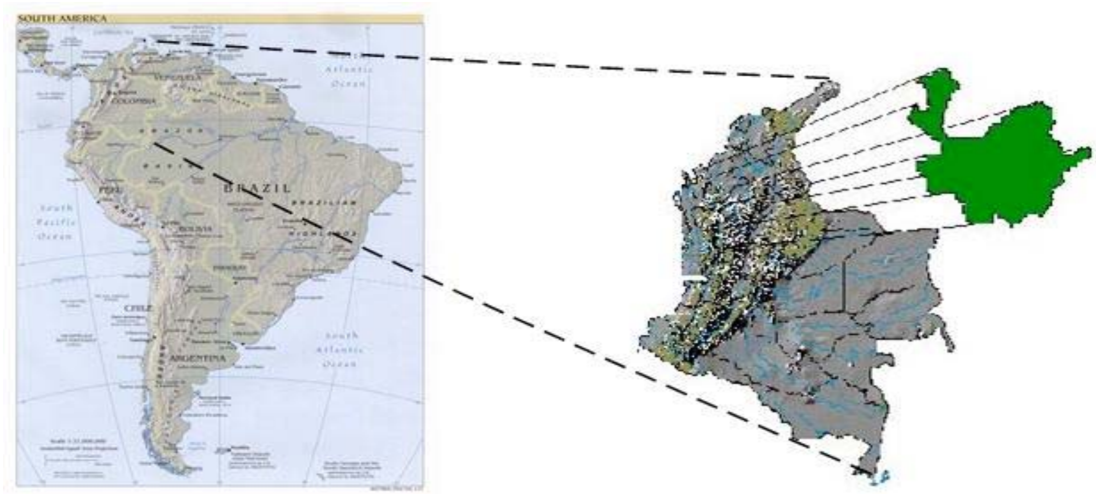


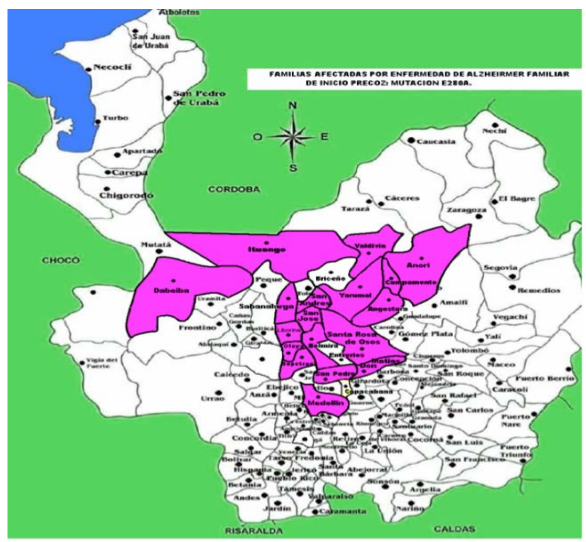
MTL Activity Novel>Repeating

Dickerson et al., Ann Neurol. 2004

Antioquia (Colombia), a genetically isolated Region, has the largest population in the World with Familial Alzheimer´s Disease

Paisa Mutation E280A in PSEN1





Yakeel Quiroz

Francisco Lopera

Chantal Stern

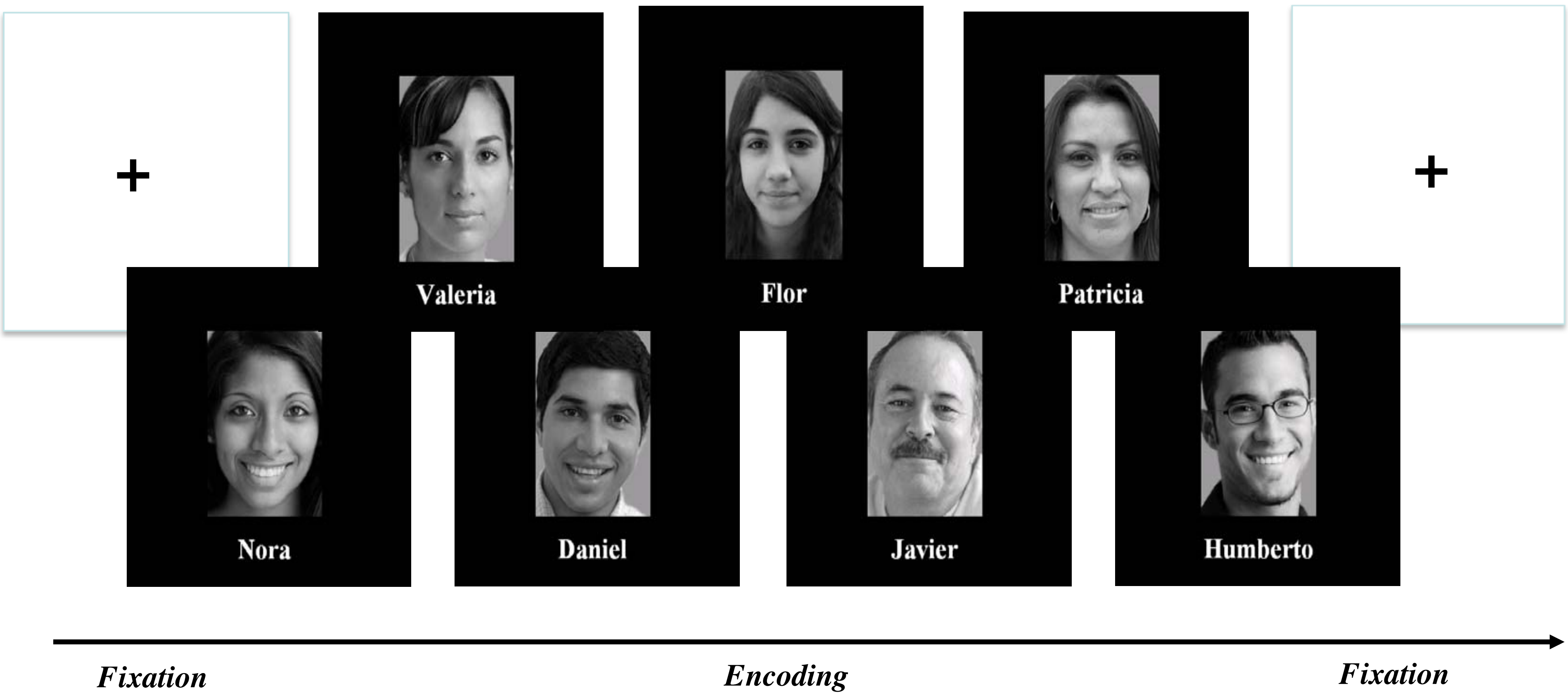
Colombian Early-Onset AD due to E280A Presenilin-1 Mutation

Alzheimer's Stalks a Colombian Family

http://www.nytimes.com/2010/06/02/health/02alzheimers.html?emc=eta1

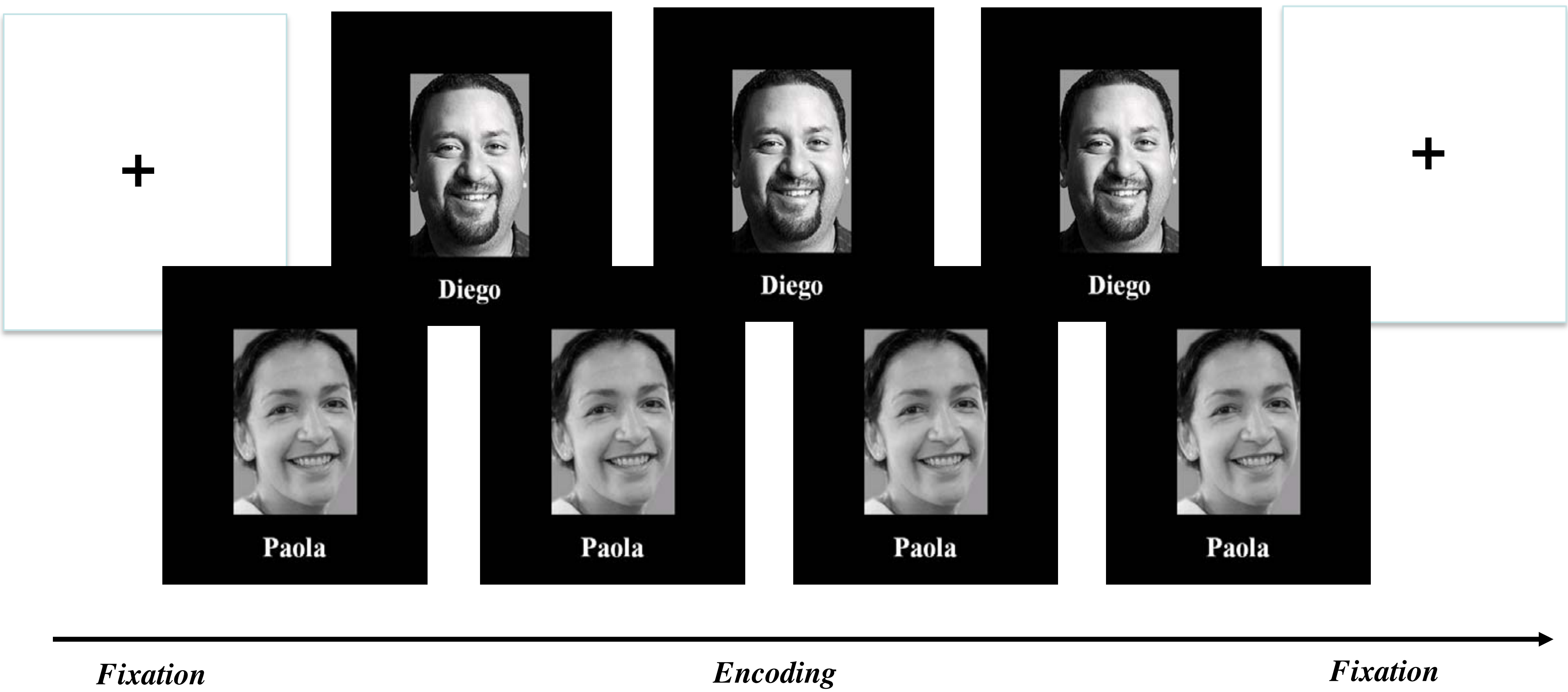
Face-Name Associations

<u>Novel Blocks</u>



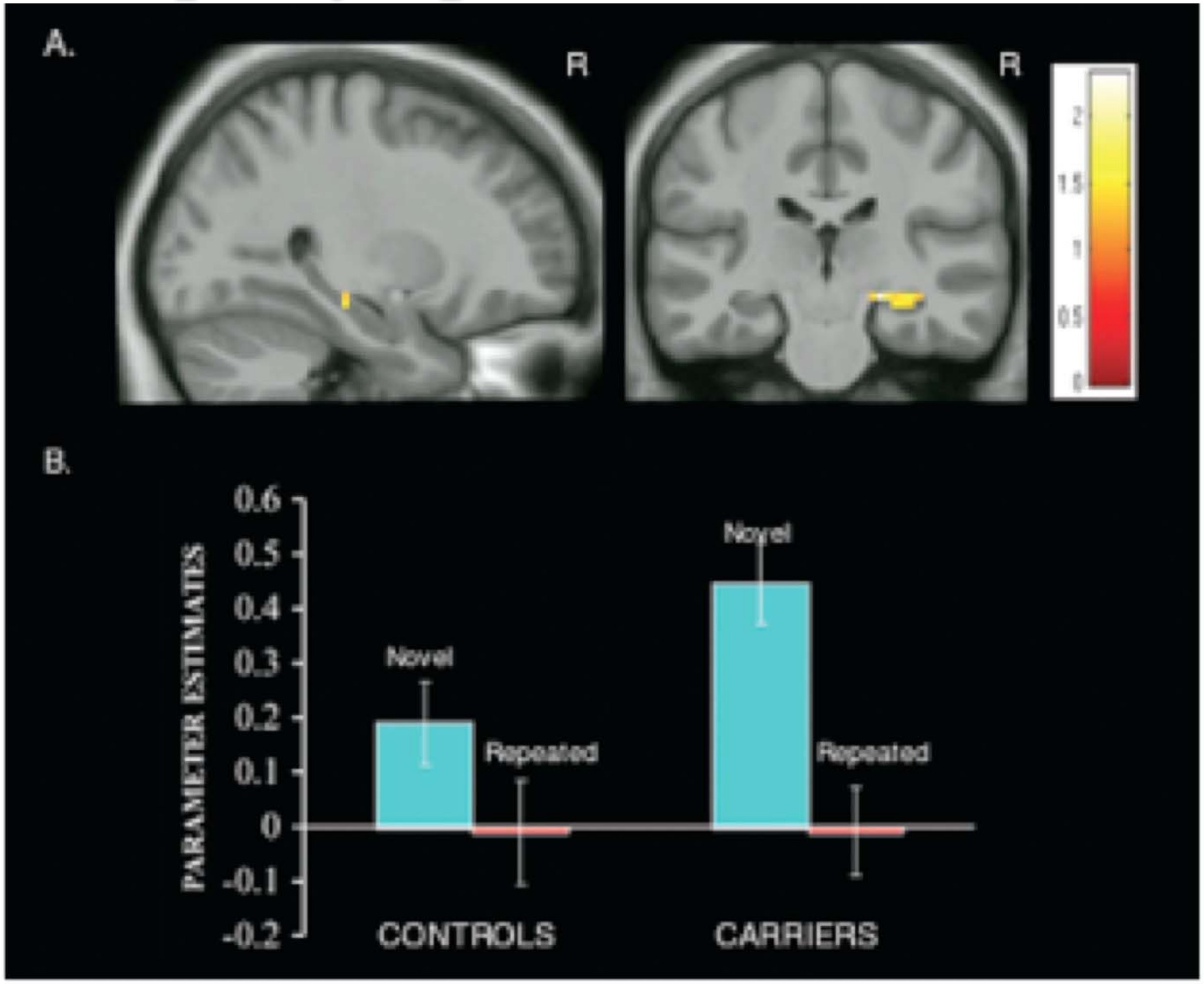
Adapted from Sperling et al., 2001

Repeated Blocks



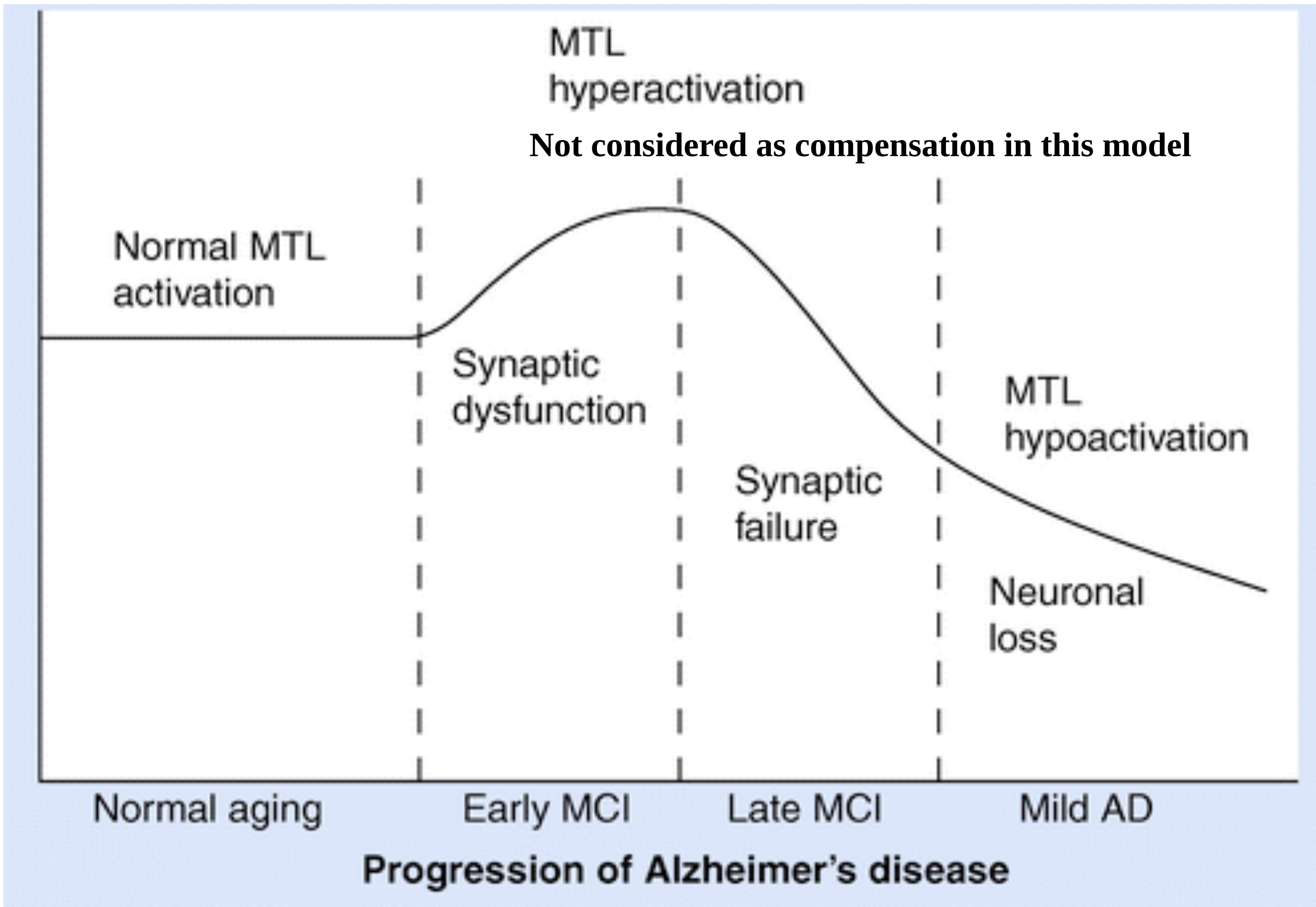
Adapted from Sperling et al., 2001

Hippocampal Hyperactivation in presymptomatic carriers



Quiroz, Budson, Celone, Ruiz, Newmark, Castrillon, Lopera, Stern (2010) Hippocampal hyperactivation in presymptomatic familial Alzheimer's disease, Annals of Neurology 68: 865-875

MTL activity across time in MCI



PSEN1 pre-symptomatic carriers showed differential activation in hippocampus compared to non-carriers.

◆**Carriers show hyperactivation in the right anterior hippocampus during the presymptomatic stages of AD**

◆**Changes in hippocampal function are detectable with fMRI years before clinical onset**

◆**This finding is consistent with studies of Mild Cognitive Impairment**

◆**Our results suggest that the PSEN1 mutation, leading to AD pathology, may impact the efficiency of the hippocampus**

Quiroz et al., Annals of Neurology 2010)

Talk outline:

1. **Models of physiological properties in entorhinal cortex**
2. **Model of the initiation and progression of Alzheimer's disease**