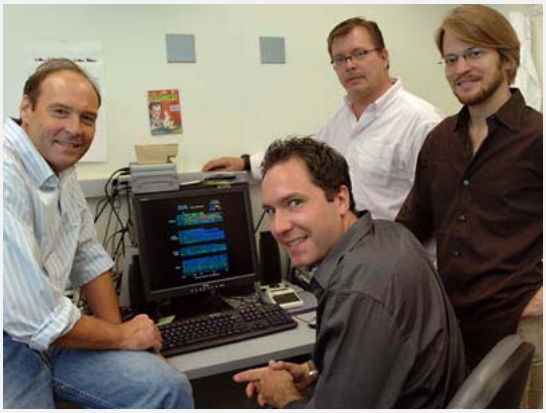
Learning Induces Long-Term Potentiation in the Hippocampus

Jonathan R. Whitlock, Arnold J. Heynan,
Marshall G. Shuler, & Mark F. Bear

Science (2006), 313: 1093-1097



Is LTP memory?

"Whether the intact animal makes use in real life of a property which has been revealed by synchronous, repetitive volleys to a population of fibers… is another matter". Bliss & Lomo

- "Strictly speaking … LTP is a "memory" only of having one's brain electrically stimulated"

Is LTP memory?

"1000s of papers … predicated on assumption that LTP reveals important mechanism for memory in the brain".

Hypothesis: LTP = memory

- Sufficiently long-lasting
  - but decays sooner than memory
- Appears quickly (within 5 min) and is induced by physiologically reasonable treatments
- Found in brain structures implicated in learning & memory
- Several pharmacological manipulations affect LTP and memory similarly

But, nobody has shown that learning induces LTP.

Why is that better than all the previous evidence?

Why no direct evidence that learning induces LTP?

1. Learning tasks require many training trials to form a memory
   – Variability in timing of memory may obscure changes

2. Synaptic changes may be sparse and widely-distributed

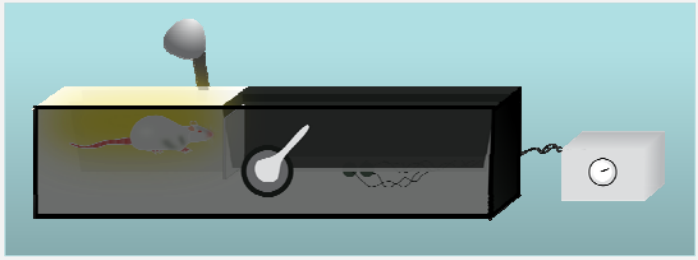
3. Simultaneous induction of LTP and LTD at different synapses may cancel each other out.
   • LTD could be memory, too

Discussion

- What are the hypotheses and predictions?
- Why did they do this?
- Strengths and weaknesses?
- Why is this important?
- How does is relate to what we've learned?
- Future directions?

Supplement Exp. Methods

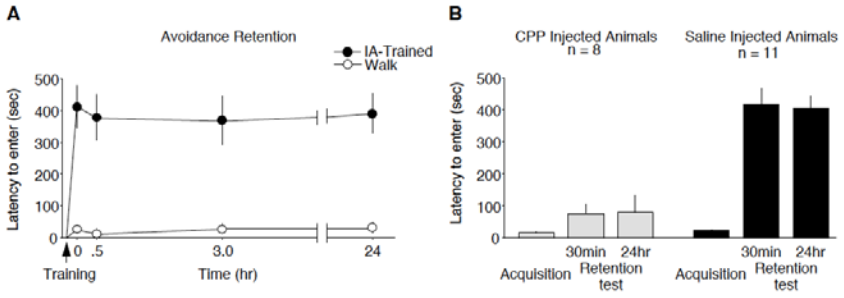
Groups:



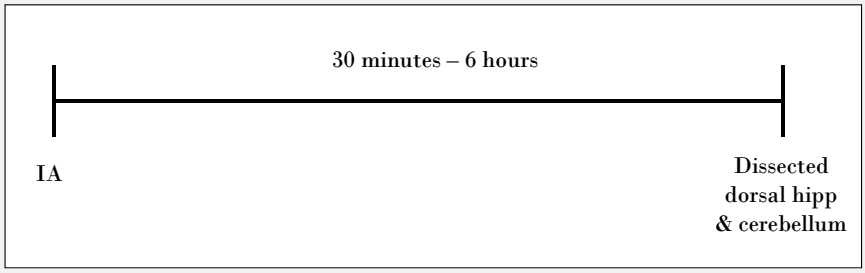
- 1 trial IA
- Walk-through control
- Saline
- CPP pretraining

Supplement 1

Figure S1

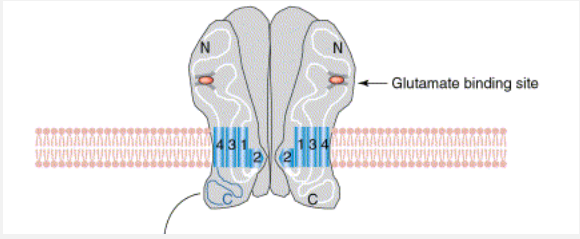


Exp II Methods



- Western blot to measure phosphorylated ser^{831} and ser^{845}
- Synaptoneurosome biochemical fractions

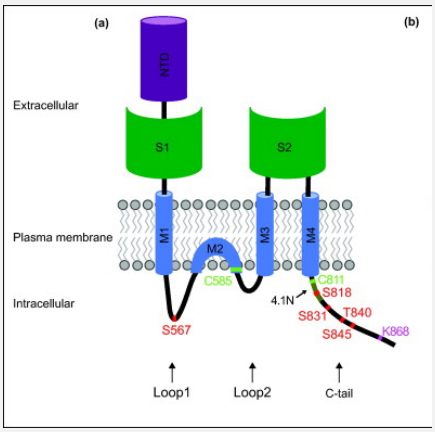
AMPA receptor



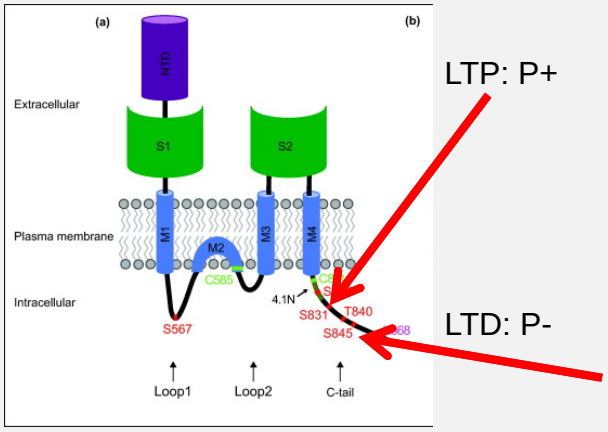
- **Four subunits: GluR1–4**
- **C-terminal domain**
  - **major intracellular domain of each subunit**
  - **allows subunit-specific regulation of AMPA receptors.**
  - **contains all of the known protein phosphorylation sites**

LTP & LTD biomarkers

- LTP: gluR1 serine 831 is phosphorylated
- LTD: gluR1 serine 845 is DEphosphorylated

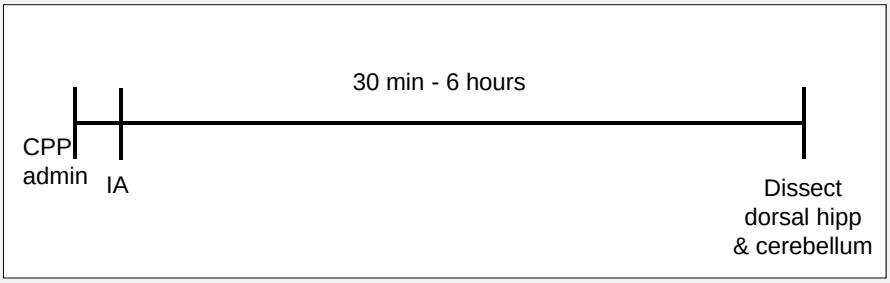


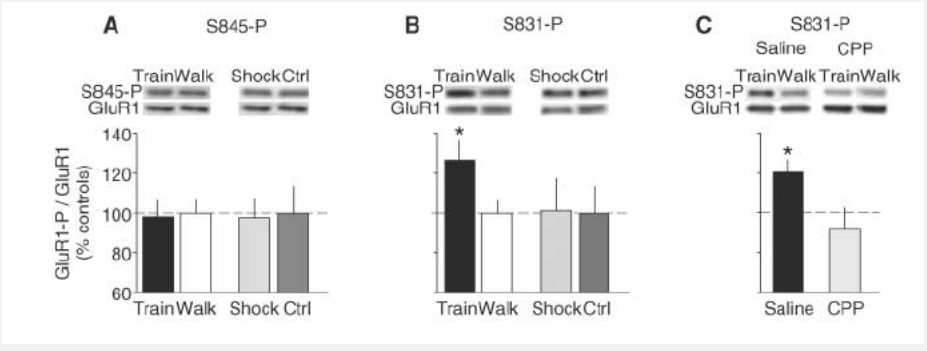
LTP & LTD biomarkers



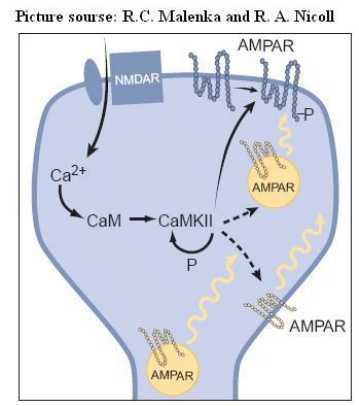
GluR1 subunit

Exp II Methods



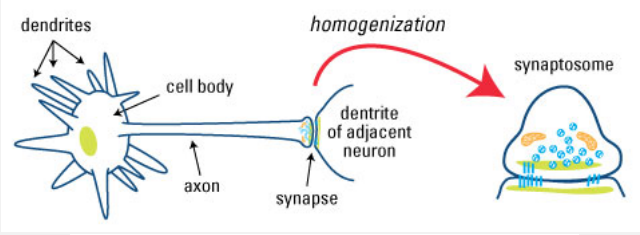


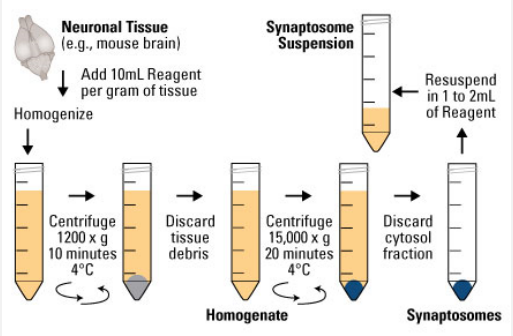
What do phosphorylation data predict about trafficking?



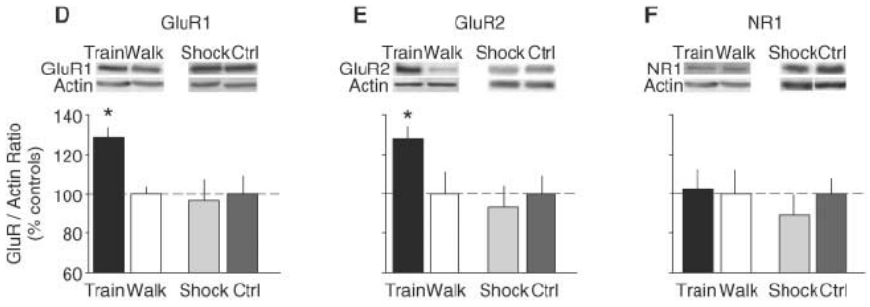
How can you measure trafficking?

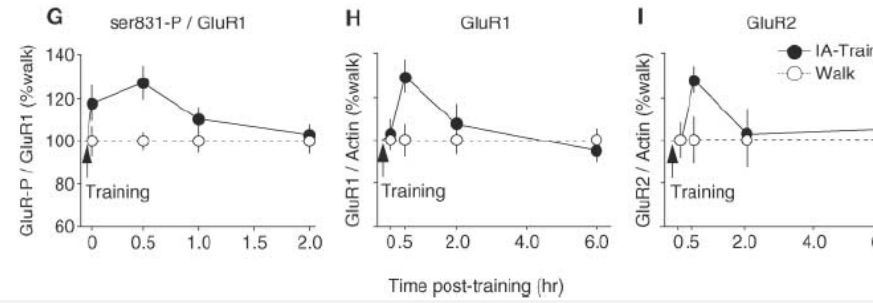
Synaptosome



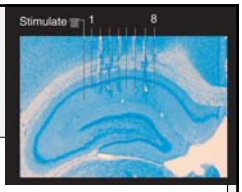


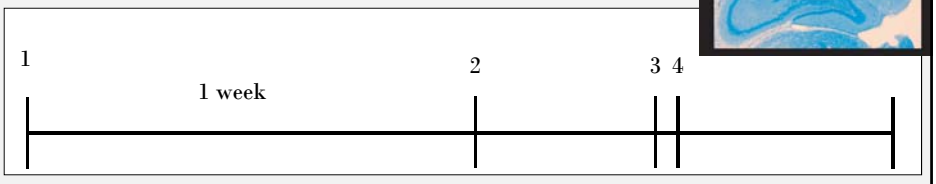
piercenet.com/previews/2012-articles/isolate-functional-synaptosomes/


D
GluR1
Train Walk Shock Ctrl
GluR1
Actin
GluR / Actin Ratio (% controls)
140
120
100
80
60
*
Train Walk Shock Ctrl
E
GluR2
Train Walk Shock Ctrl
GluR2
Actin
*
Train Walk Shock Ctrl
F
NR1
Train Walk Shock Ctrl
NR1
Actin
Train Walk Shock Ctrl

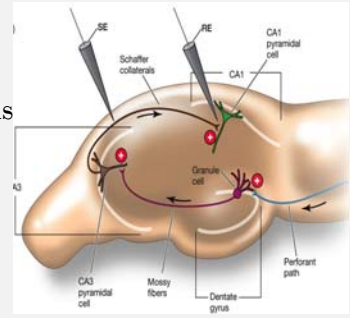

G
ser831-P / GluR1
GluR-P / GluR1 (%walk)
140
120
100
80
60
Training
0 0.5 1.0 1.5 2.0
H
GluR1
GluR1 / Actin (%walk)
Training
0.5 2.0 4.0 6.0
I
GluR2
IA-Trained
Walk
GluR2 / Actin (%walk)
Training
0.5 2.0 4.0 6.0
Time post-training (hr)

Exp III Methods



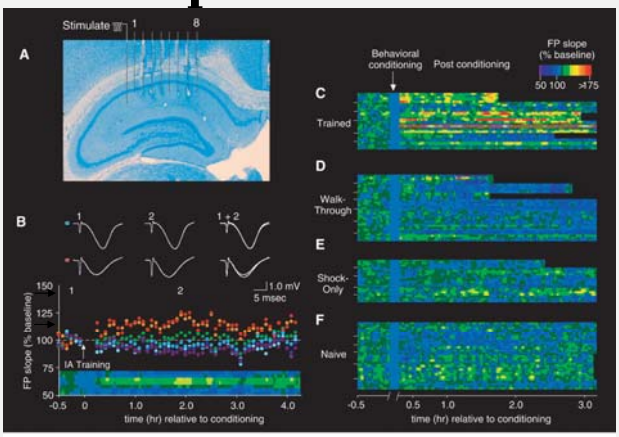


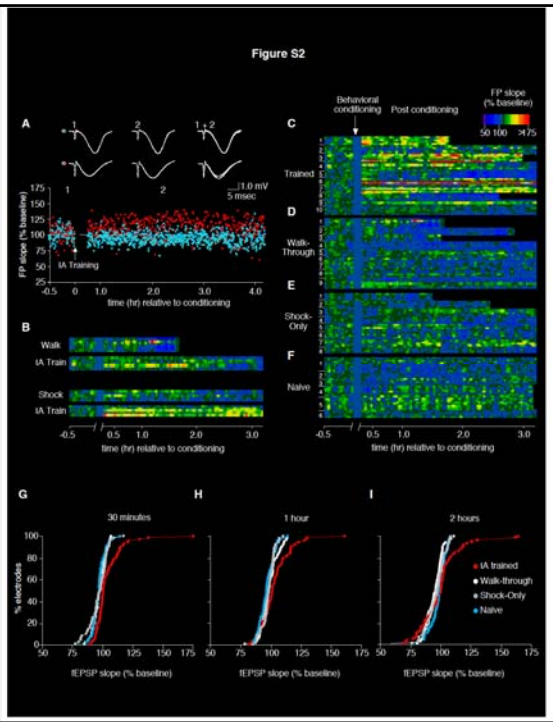
1. Surgically implant multielectrode recording array apical dendritic layer of CA1
2. Baseline fEPSPs in freely moving animals in recording box
   - Stimulate Schaffer collaterals
   - Animals previously habituated
3. IA training (no recording)
4. Return to recording box & measure fEPSPs



Exp III Results

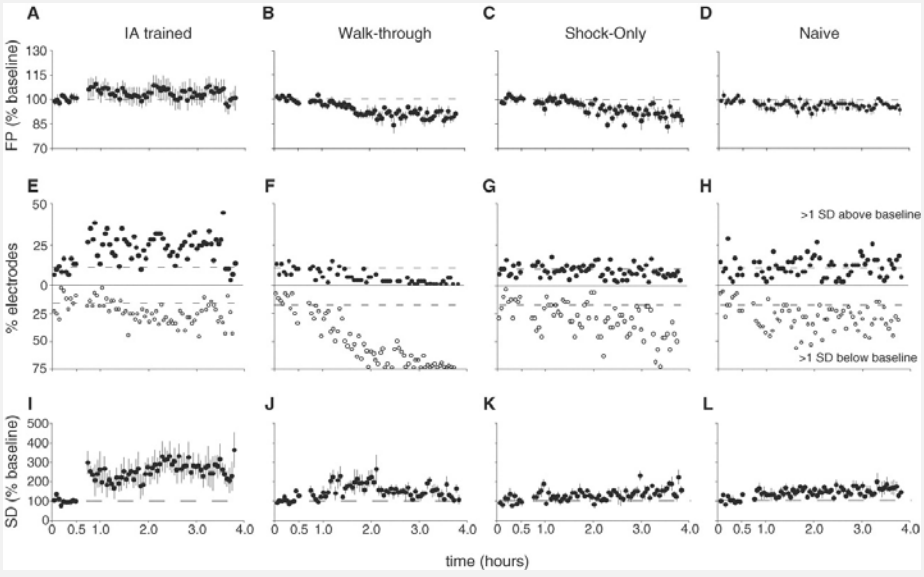
Mark electrode tip location w lesions





>10% enhancement following IA training. **(C-F)** Color plots representing fEPSP slope measures obtained from all animals in the study, including those subjected to a second behavioral condition (white tick-marks indicate individual animals in each group). Whereas 16 of 71 recording electrodes showed average fEPSP slope measures >10% above baseline following IA training, no electrodes showed such an enhancement following any of the control behavioral conditions (totaling 174 electrodes). Of the 10 trained animals (T_1-T_{10}), 4 had undergone prior control behavioral conditioning; T_4 & T_5 were used as walk-through controls (W_1 & W_2), and T_7 & T_{10} were used earlier as shock-only animals (S_6 & S_8). Walk-through animals W_3 & W_7 were used previously as shock-only controls (S_5 and S_7). Shock-only animals S_1, S_9 & S_{10} were used previously as walk-through animals (W_8, W_9 & W_{10}). **(G-I)** Cumulative probability distributions of fEPSP

Exp III Results



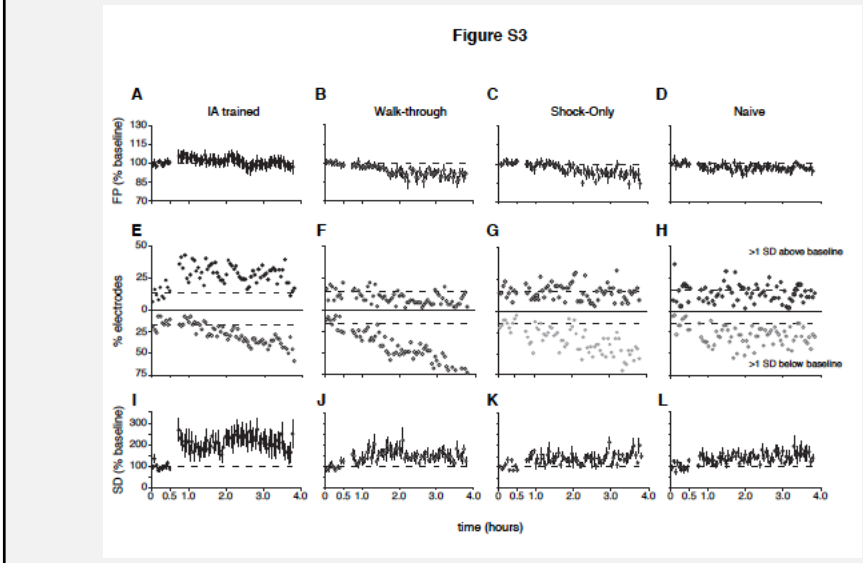


Figure S3
A
IA trained
B
Walk-through
C
Shock-Only
D
Naive
FP (% baseline)
E
F
G
H
>1 SD above baseline
% electrodes
>1 SD below baseline
I
J
K
L
SD (% baseline)
time (hours)

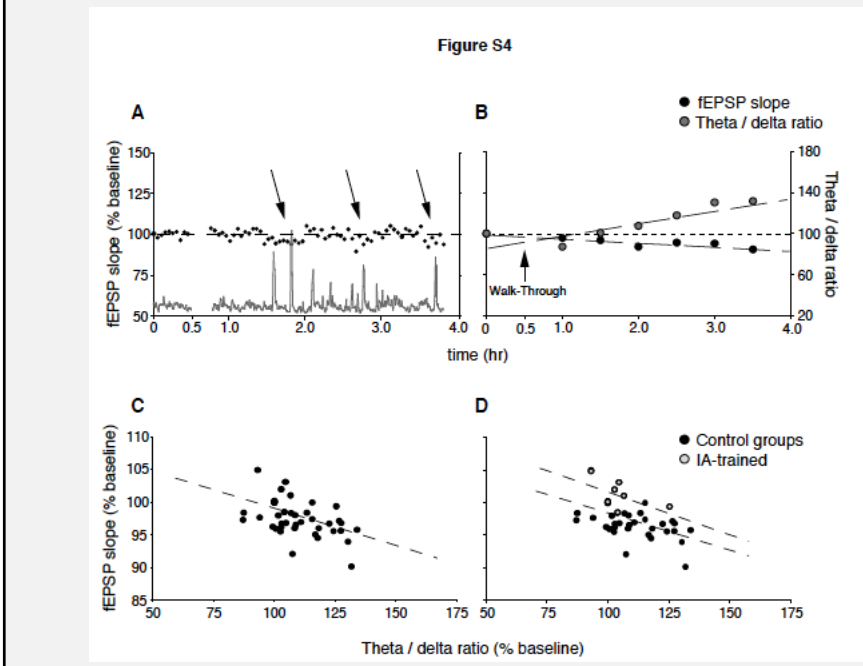
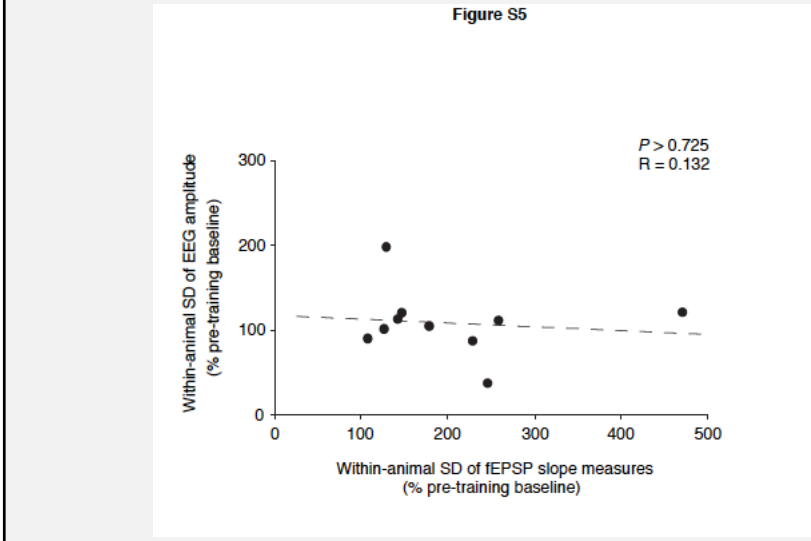
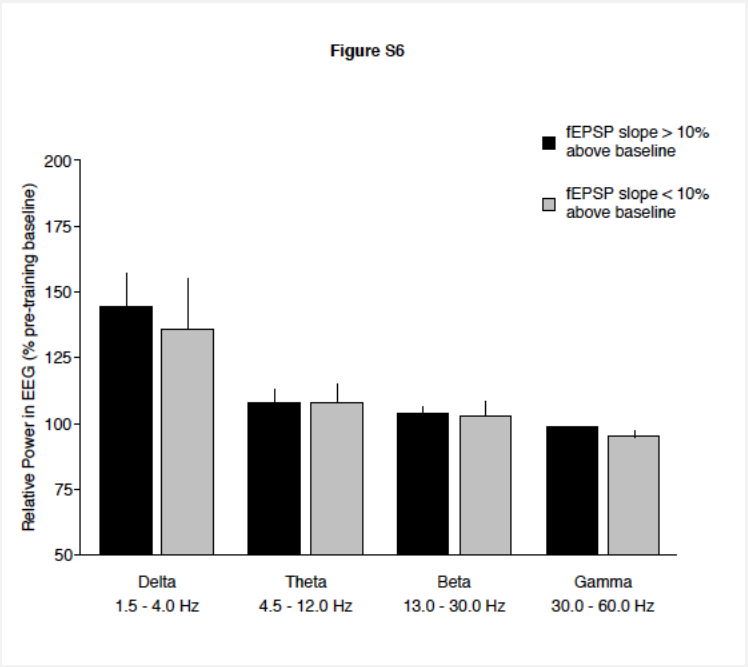


Figure S4
A
B
fEPSP slope
Theta / delta ratio
fEPSP slope (% baseline)
Theta / delta ratio
Walk-Through
time (hr)
C
D
Control groups
IA-trained
fEPSP slope (% baseline)
Theta / delta ratio (% baseline)



Are the changes they see really LTP?

- Alternative interpretations?



ELSEVIER

Behavioural Brain Research 71 (1995) 11–18

RESEARCH

Research report

Learning-related changes in hippocampal field potentials

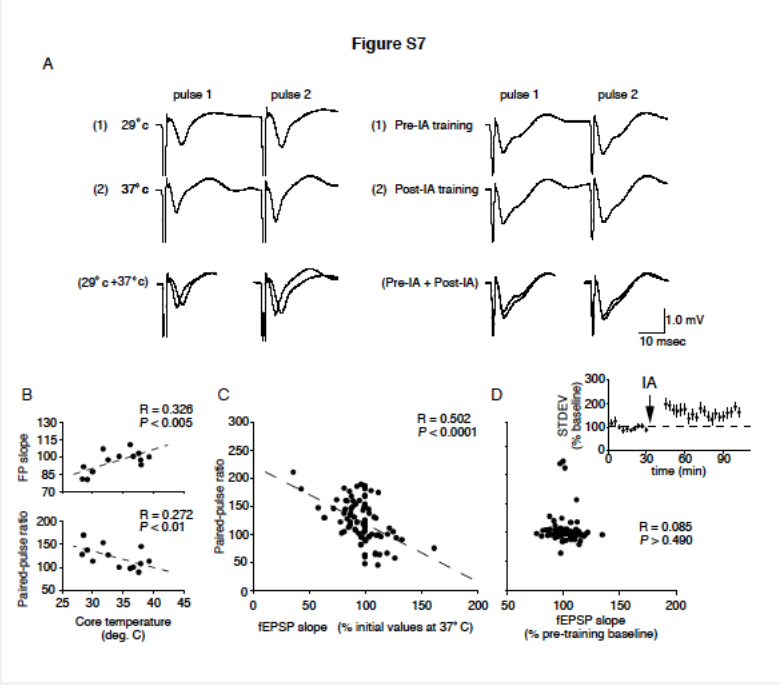
Edvard I. Moser *

Centre for Neuroscience, University of Edinburgh, Crichton Street, Edinburgh EH8 9LE, UK

Abstract

It is commonly believed that learning is based on modifications of synaptic strength. Much of the evidence for this comes from the observation that blockade of processes necessary for induction of long-term potentiation in the hippocampus also blocks certain forms of learning. As such correlations may have many causes, an understanding of the mechanisms for memory formation might also profit from direct recording of cellular activity in learning tasks. Field potential recording represents one such approach. Although changes in field potentials are unlikely to uncover modifications in synaptic strength related to the storage of memory, any general facilitation (or reduction) of synaptic transmission taking place in populations of neurons during the acquisition stage might be picked up by a field measure. One problem related to the approach is that field potentials are heavily affected by non-learning factors. It is shown that field potentials in the hippocampus are highly sensitive to changes in brain temperature and that a significant part of the increase in field excitatory postsynaptic potentials (f-EPSPs) during learning reflects warming of the brain. Temperature-related changes in synaptic transmission do not affect the efficiency of spatial learning, as the acquisition of a water-maze task is equally efficient at low (30–32°C) and high (37–39°C) brain temperatures. Subtraction of the temperature component of the field potential alterations during learning in an exploration task shows that exploration is accompanied by a temperature-independent synaptic potentiation as well. Both the f-EPSP and the population spike are increased, and both decay gradually within 15–20 min. It is important to find out whether this potentiation reflects learning-related processes and whether such a potentiation is useful to the brain given the apparent 'noise' caused by temperature–related physiological changes.

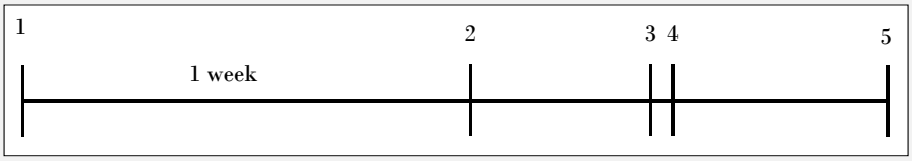
Keywords: Hippocampus; Dentate gyrus; Field potential; LTP; Learning; Brain temperature; Water-maze; Exploration



How can you more definitely show the changes are LTP?

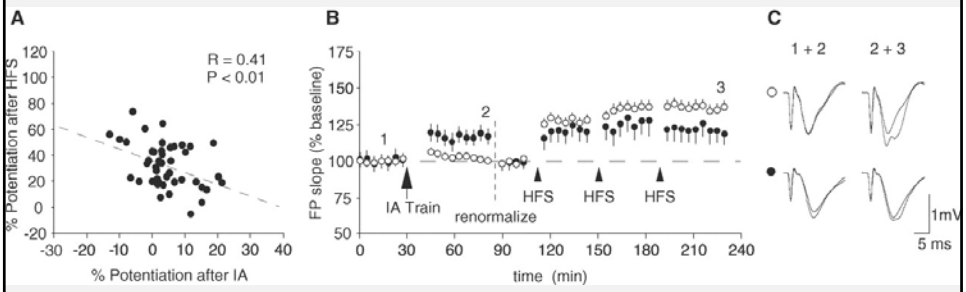
- Occlusion

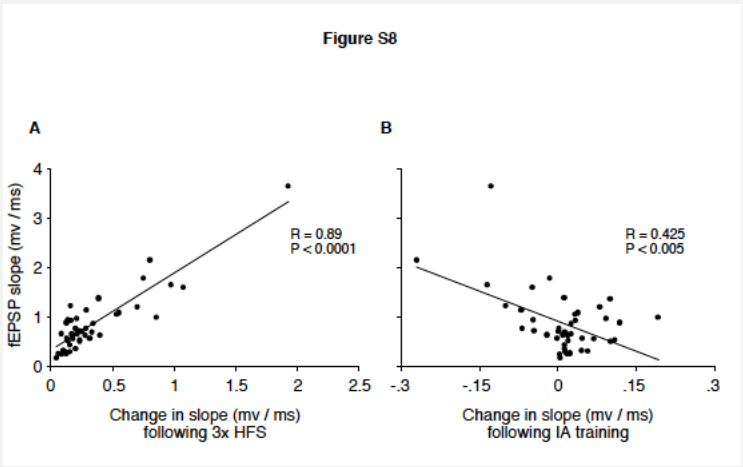
Exp IV Methods



1. Implanted multielectrode recording array in apical dendritic layer of CA1
2. Measure fEPSPs in freely moving animals in recording box
   - Stimulate Schaffer collaterals
   - Animals previously habituated
3. IA training (no recording)
4. Return to recording box & measure fEPSPs
5. High frequency stimulation (HFS) to saturate LTP

Exp IV Results





Questions

- Why do responses decrease in trained, walk-through and shock-only over time? (see also S3)
- Why do naïve animals have the least tendency for gradual reduction in slope?
  - Reflect changes in behavioral state and/or LTD?
- Why is synaptic transmission enhanced in some electrodes? (spatially restricted)
  - Distributed memory?

Strengths

- Positive and negative controls
- 2 criteria to conclude LTP & Memory (or any other two events) share common mechanism:
  1. Mimicry
  2. Occlusion

Mimicry

- IA mimics effects of HFS
  - Immediate NMDA-dependent increase in GluR1 phosphorylation at Ser^{831}
    - No effect on Ser^{845}
  - Delivery of AMPA GluR1 and GluR2 to synapse
    - Not NR1
  - Increases fEPSP slope
    - No effect on paired pulse facilitation

Occlusion

- IA-induced increases in evoked fEPSP partially occlude subsequent HFS-induced LTP

Conclusions

- "We therefore conclude that IA training induces LTP in CA1".

Questions

- Why are AMPA events rapid and transient but IA-induced increase in fEPSPs stay elevated up to 3 hr?
  - Could it be a shift to presynaptic mechs?
    - What argues against that? (S7)
  - Cumulative probability curves says only some synapses stay potentiated for long (Fig 2 and S2)
    - maybe below biochemical threshold of detection

Questions

- How do you know it's not due to change in blood flow and hippo temperature?
  - IA potentiation only at some synapses
  - Paired pulse ratio is sensitive to temp but not affected by IA (S7)
  - Occlusion

Questions

- How do you know occlusion isn't just due to generalized inhibition of plasticity?
  - Only saw occlusion at IA potentiated synapses
  - Best evidence that LTP and learning are operating at the same mechanism

Questions

- Why not compare "LTP" with memory (i.e. correlate with retention latencies)?
- Why wasn't LTD observed?
  - Maybe see bidirectional shifts in with memories less basic to survival
- Stimulate through recording electrodes specifically at enhanced synapses to disrupt?

- Would you expect the IA training to induce LTP in other areas of the brain?
- Other types of memory?
- Working memory?

Discussion points

- Contribution to the field?
  - Does it change thinking?
  - Historical context