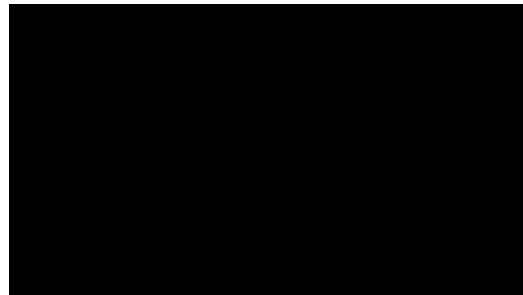


The Cerebellum and Classical Conditioning

Acknowledgement:
Dominic T. Cheng, Ph.D.
Auburn University

Classical Conditioning in Popular Culture



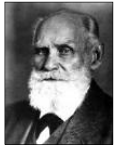
Why Classical Conditioning?

- A model for a fundamental form of memory
- One of the most studied forms memory
- Tight experimental control
- Clinical relevance

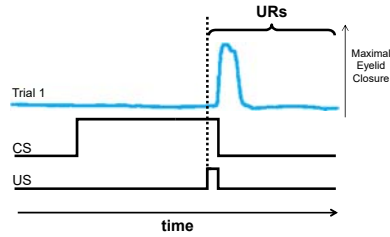
Outline

- Classical Conditioning Terminology
 - CS, US, CR, UR
- Animal Evidence
 - basic neural circuitry
 - mice, rats, rabbits, cats, dogs
 - lesion, recordings, stimulation
- Human Evidence
 - taxonomy of memory
 - patient, neuroimaging, stimulation
- Summary

Basics of Eyeblink Classical Conditioning



Ivan Pavlov

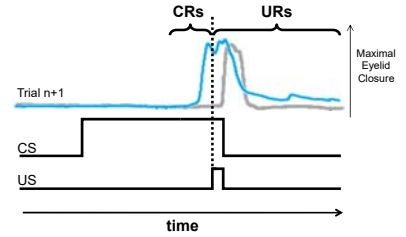


Conditioned stimulus (CS) (tone) Unconditioned stimulus (US) (corneal airpuff)
 Unconditioned response (UR) (eyeblink)

Basics of Eyeblink Classical Conditioning



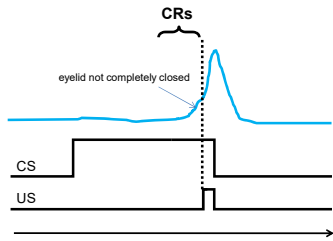
Ivan Pavlov



Conditioned stimulus (CS) (tone) Unconditioned stimulus (US) (corneal airpuff)
 Unconditioned response (UR) (eyeblink) Conditioned response (CR) (eyeblink)

Basics of Eyeblink Classical Conditioning

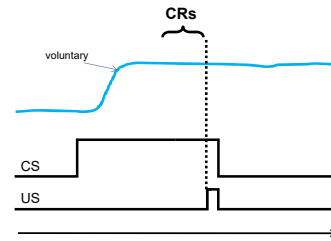
Characteristics of an adaptive CR
 Amplitude



Gomezano (1966) *Experimental Methods and Instrumentation in Psychology* (ed. Sidowski)

Basics of Eyeblink Classical Conditioning

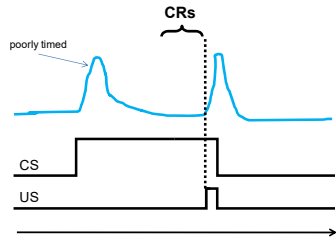
Characteristics of an adaptive CR
 Duration



Gomezano (1966) *Experimental Methods and Instrumentation in Psychology* (ed. Sidowski)

Basics of Eyeblink Classical Conditioning

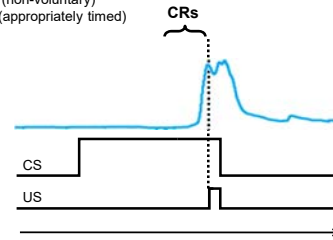
Characteristics of an adaptive CR
 Latency (timing)



Gomezano (1966) *Experimental Methods and Instrumentation in Psychology* (ed. Sidowski)

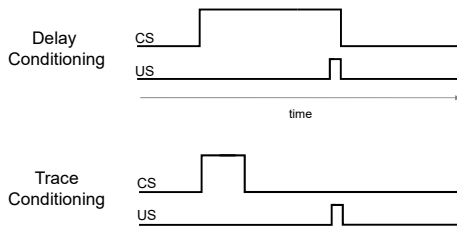
Basics of Eyeblink Classical Conditioning

Characteristics of an adaptive CR
 Amplitude (eye must be fully closed)
 Duration (non-voluntary)
 Latency (appropriately timed)



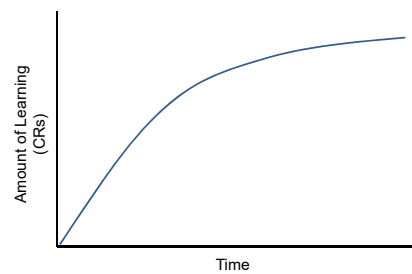
Gomezano (1966) *Experimental Methods and Instrumentation in Psychology* (ed. Sidowski)

Delay and Trace Conditioning



In trace conditioning there is a gap between CS offset and US onset. In delay conditioning there is no gap and CS typically coterminates with US

Basics of Eyeblink Classical Conditioning



Basics of Eyeblink Classical Conditioning

Common Controls used in Classical Conditioning

Pseudoconditioning

Unpaired CS and US presentation



Differential Conditioning

CS+ and CS- presentations



A Little History.....

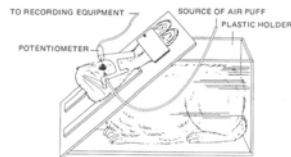
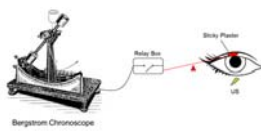
The first eyeblink conditioning studies were performed in humans (Cason, 1922).

Problems with humans:

- measurement difficulties
- response variability
- voluntary responding
- cannot do invasive neuroscience research

Isidore Gormezano developed the rabbit preparation "to remedy long-term deficiencies and difficulties in the study of classical conditioning (Gormezano et al., 1983, p. 202)."

From Humans to Rabbits



- Measurement difficulties
- Response variability
- Voluntary responses
- Lack of physiological manipulations

- Tolerate restraint well (60-90 min)
- Show low spontaneous blink rates
- Gradual acquisition
- Few alpha (orienting) responses
- Eyes can be conditioned independently

Gormezano (1962)

The Search for the Engram

MICHAEL F. THOMPSON University of California, Irvine
 Graduate: Michael M. Newman, Richard A. Gray,
 Timothy J. Coles, and Richard A. Yung

1. Introduction: In studying the engram, the localization of the memory trace, that the memory continues to live having just been recalled.

2. The engram: The engram is the physical-chemical process in the nervous system that links the kind of learning, learning is ultimately not a variety phenomenon. Usually considered, it is a change in the structure of the nervous system, a change in the way that the nervous system may be made to respond to particular stimuli, and "neuronal" events which involve changes in the structure of the nervous system.

3. Experimental studies of the engram and its localization: The engram is a physical-chemical process in the nervous system that links the kind of learning, learning is ultimately not a variety phenomenon. Usually considered, it is a change in the structure of the nervous system, a change in the way that the nervous system may be made to respond to particular stimuli, and "neuronal" events which involve changes in the structure of the nervous system.

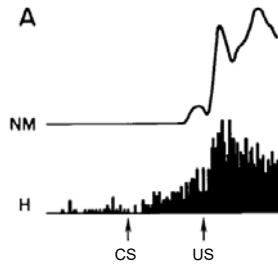
4. The search for the engram: The search for the engram is a search for the physical-chemical process in the nervous system that links the kind of learning, learning is ultimately not a variety phenomenon. Usually considered, it is a change in the structure of the nervous system, a change in the way that the nervous system may be made to respond to particular stimuli, and "neuronal" events which involve changes in the structure of the nervous system.

5. The search for the engram: The search for the engram is a search for the physical-chemical process in the nervous system that links the kind of learning, learning is ultimately not a variety phenomenon. Usually considered, it is a change in the structure of the nervous system, a change in the way that the nervous system may be made to respond to particular stimuli, and "neuronal" events which involve changes in the structure of the nervous system.

about the engram: The engram is the physical-chemical process in the nervous system that links the kind of learning, learning is ultimately not a variety phenomenon. Usually considered, it is a change in the structure of the nervous system, a change in the way that the nervous system may be made to respond to particular stimuli, and "neuronal" events which involve changes in the structure of the nervous system.

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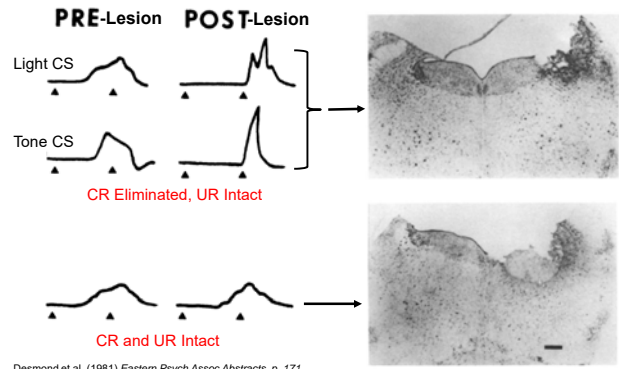
A Little History.....



Recording in the hippocampus during rabbit eyeblink conditioning
Neuronal activity appears to mirror development of CRs,
however for delay conditioning, lesions of hippocampus do not
affect conditioning

Berger et al. (1976) *Science*

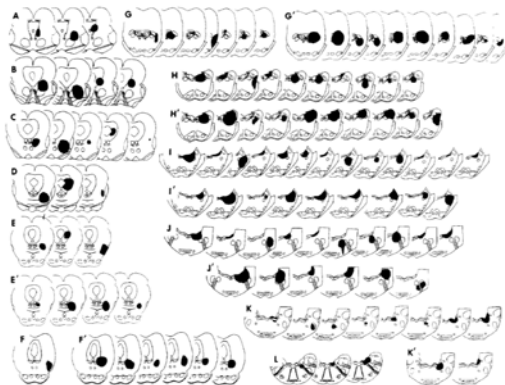
First Reports of CR Disruption



Desmond et al. (1981) *Eastern Psych Assoc Abstracts*, p. 171
Desmond and Moore (1982) *Physiol Behav*

H832

DESMOND AND MOORE

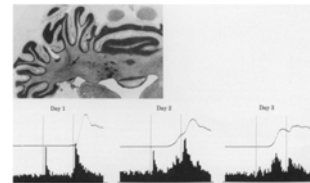


Desmond and Moore (1982) *Physiol Behav*

Lesions of Nuc Interpositus Disrupt Conditioning



Recordings from Nuc Interpositus Show Conditioning-Related Activity



The engram found? Role of the cerebellum in classical conditioning of nictitating membrane and eyelid responses

DAVID A. MCCORMICK, DAVID G. LAVOND, GREGORY A. CLARK, RONALD E. KEYSER, CHRISTINA E. BUNING, and RICHARD F. THOMPSON
Dartmouth University, Hanover, Colorado 80521

Electrophysiological recording of neural unit activity during paired training trials from the deep cerebellar nucleus (DCN) and eyelid responses showed CR and UCS-related responses and a pattern of neuronal activity that correlates with the learned behavioral response. Large ablation of the ipsilateral cerebellum completely and permanently abolished the conditioned response to well-trained stimuli, or did more localized ablations. These lesions had no effect at all on the unconditioned reflex response. In marked contrast, conditioned responses were nearly normal in the eye contralateral to the cerebellar lesion. We suggest that at least a part of the "engram," the neuronal information that under the learned response, may be localized in the cerebellum.

The initial goal in the analysis of the "engram," the neuronal information that under the learned response, is to determine the location of the engram in the brain. For this, this has not been done for any instance of associative learning in the mammalian brain. We report here evidence suggesting that the engram for a simple form of associative learning, shown in daily classical conditioning of the nictitating membrane (NM) and eyelid responses in the rabbit, is at least partially localized in the cerebellum. Because this is not an unconditioned generalization, we are taking the structural removal of any of repeating preliminary results from experiments with the engram.

A number of brain regions are involved even in a "simple" conditioned response (CR) to NM and eyelid conditioning, both the neocortex (Maguire & Baran, 1970; Poppel, Lavond, & McCormick, 1975) and the hippocampus (Thompson, Berger, Berry, Hoshino, Katsura, & Wain, 1982) necessarily play important roles in the case of the hippocampus, this is particularly so when greater demands are placed on the memory system, as in trace conditioning or latent inhibition (Shikama & Mizusawa, 1975; Wain, Shikama, & Thompson, 1982). However, rabbits with ablation more than above the level of the dentate nucleus showed no effect on the short-delay classical conditioning of the response (Clayton, Berry, & Vilhjálmsson, 1975). These results suggest that there is a neuronal engram located in the cerebellum that under the short-delay CR.

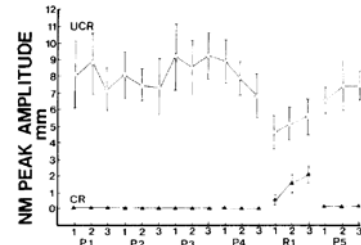
Our initial approach to identification of this circuit. This work was supported in part by a research grant from the National Science Foundation (DMS-8106444). We thank Jan Laska for assistance in typing.

has been to map the entire brain area is already treated already by recording neural unit activity. In the course of this mapping, we discovered a clear pattern of neuronal unit activity in portions of the cerebellum that corresponds closely with the learned behavioral response. We then conducted two types of brain studies, large ablations and more localized microstimulation, in well-trained animals. All these results will be reported here.

It is important to emphasize the nature of the CR. Although typically viewed as an extension of the NM, which is a largely passive consequence of eyelid movements (Clayton, Thompson, Parsons, & McCormick, 1975), or direct of the eyelid. However, with standard conditioning simultaneously and independently, together with some degree of coactivation of the periorbital facial musculature (Lavond, Katsura, & Thompson, 1982; McCormick & Thompson, 1982). The major components are NM extension (eye-blink) and eyelid closure. Both were measured in the CR below, we report both the NM and eyelid. All effects reported here occur equally for both.

Preliminary results from these experiments are reported here in 1) electrophysiological recordings from the ipsilateral cerebellum and 2) ablation studies in well-trained animals. (3) Effects of well-trained animals, and (4) effects of localized ablation in response to the ipsilateral cerebellum in well-trained animals. Standard statistics were used for analyzing the NM and eyelid responses (Clayton, Thompson, 1975). A cluster analysis system that groups neurons according to timing of response, or to specific activity, was a

Nuc Interpositus Lesion Prevents CR Acquisition



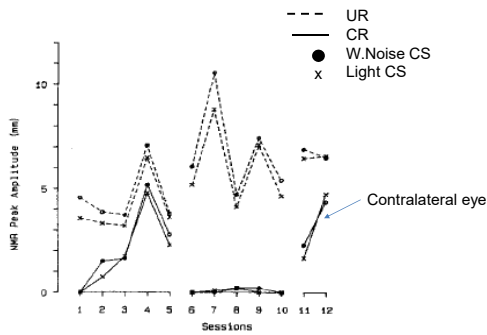
TRAINING DAY and PERIOD

P: Eye ipsilateral to lesion
R: Eye contralateral to lesion

Interpositus lesion prevents CR acquisition in eye ipsilateral to lesion
Contralateral eye can still learn and make CRs

Lincoln et al., (1982) *Brain Res* and McCormick and Thompson (1984) *J Neurosci*

Cerebellar Cortex (H VI)

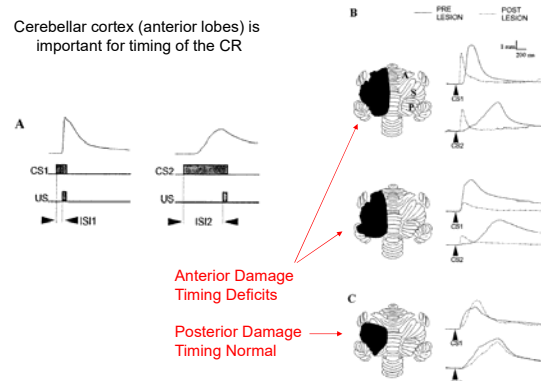


Lesions to the Lobule H VI in cerebellar cortex
Disrupt CRs to ipsilateral but not contralateral eye
URs are intact

Yeo et al. (1985) *Exp Brain Res*

CR timing and the cerebellar cortex

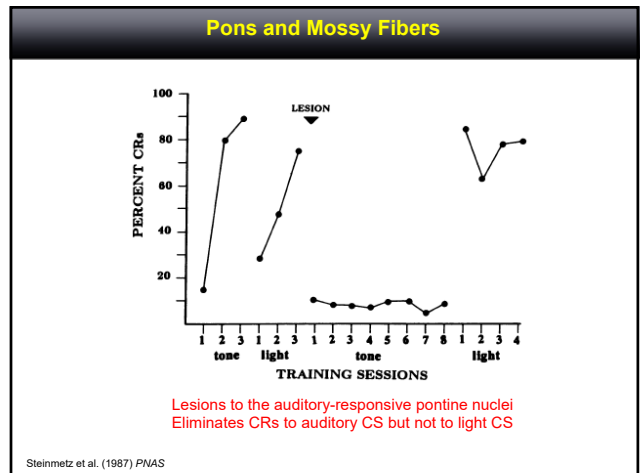
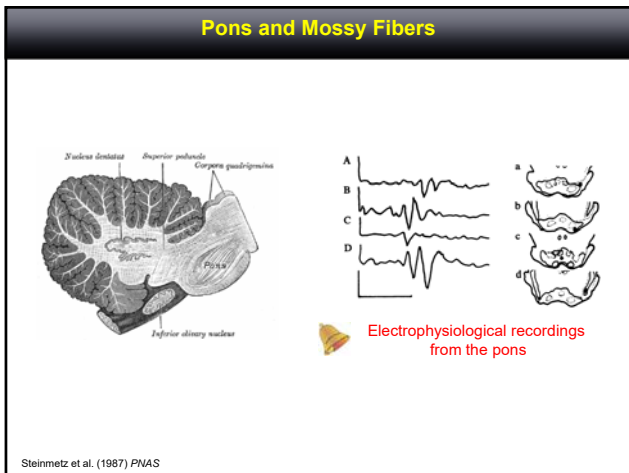
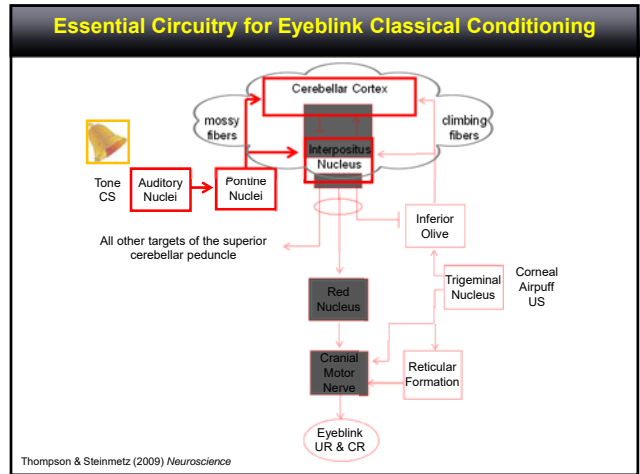
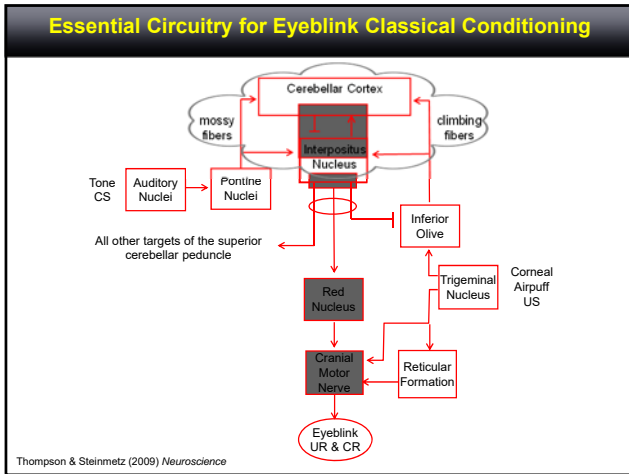
Cerebellar cortex (anterior lobes) is important for timing of the CR



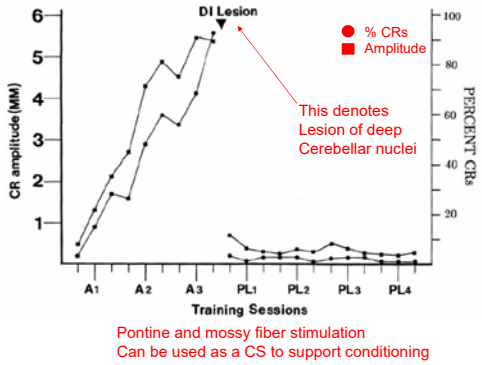
Anterior Damage
Timing Deficits

Posterior Damage
Timing Normal

Perrett et al. (1993) *J Neurosci*

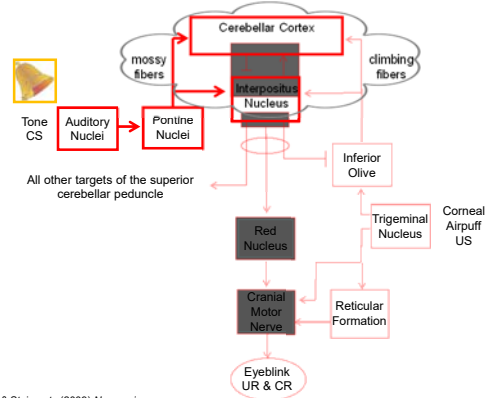


Pons and Mossy Fibers



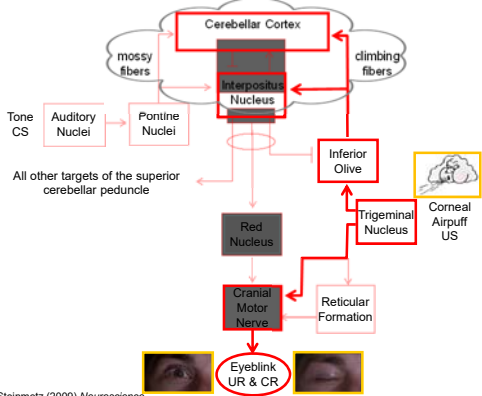
Steinmetz et al. (1986) *Beh Neuro*

Essential Circuitry for Eyeblink Classical Conditioning



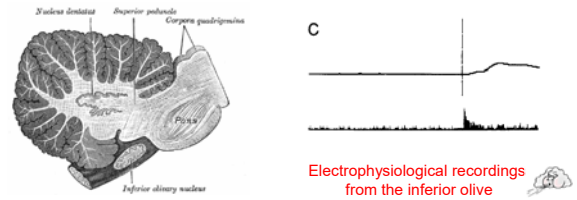
Thompson & Steinmetz (2009) *Neuroscience*

Essential Circuitry for Eyeblink Classical Conditioning

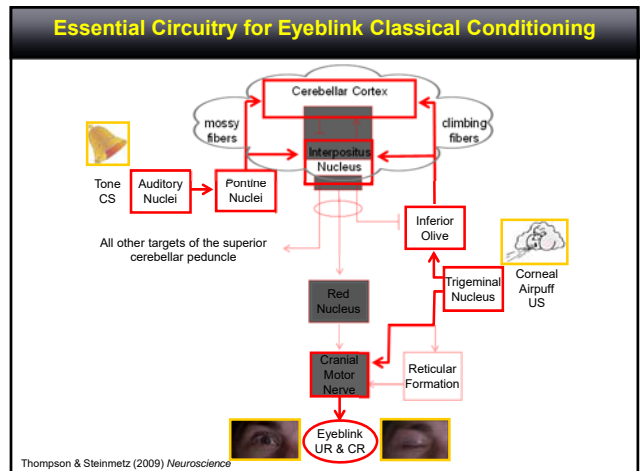
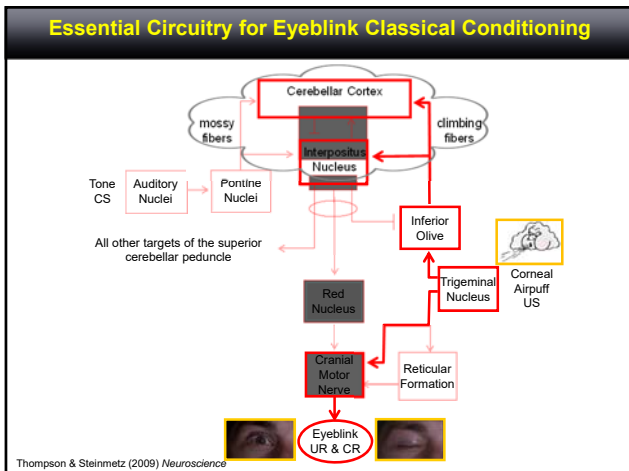
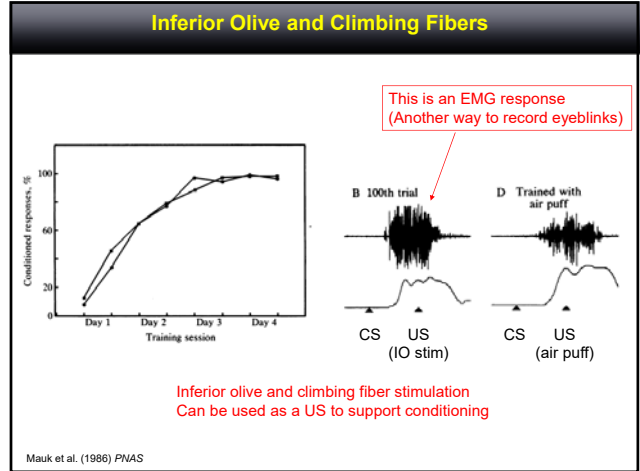
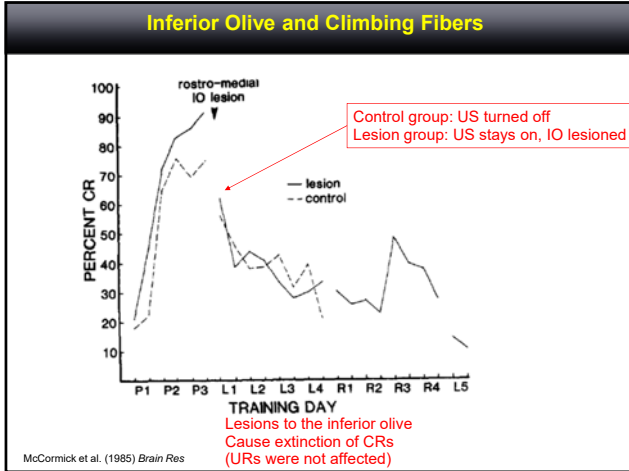


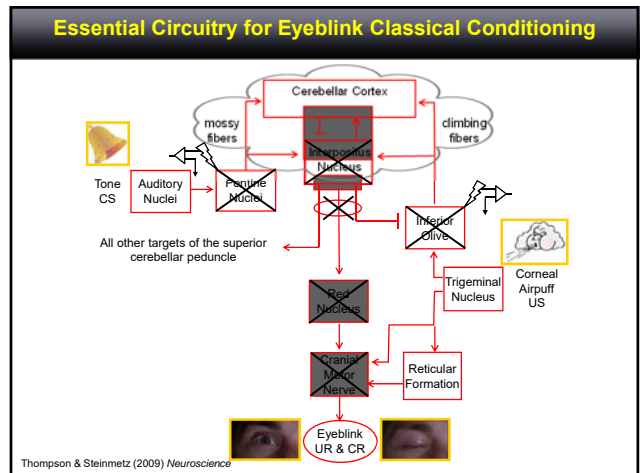
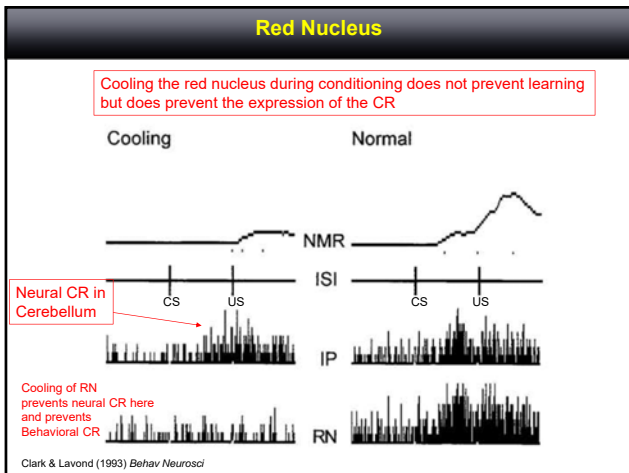
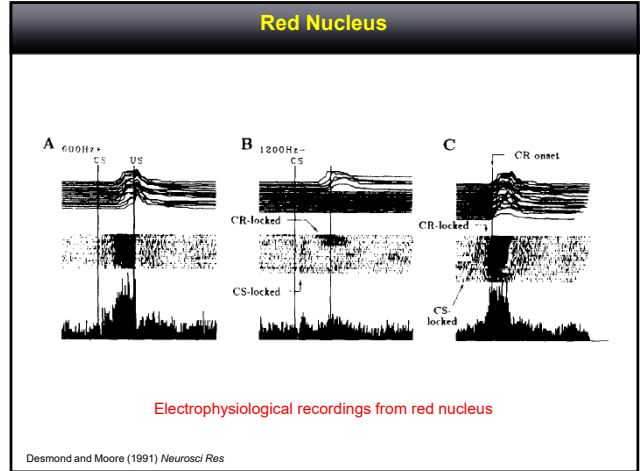
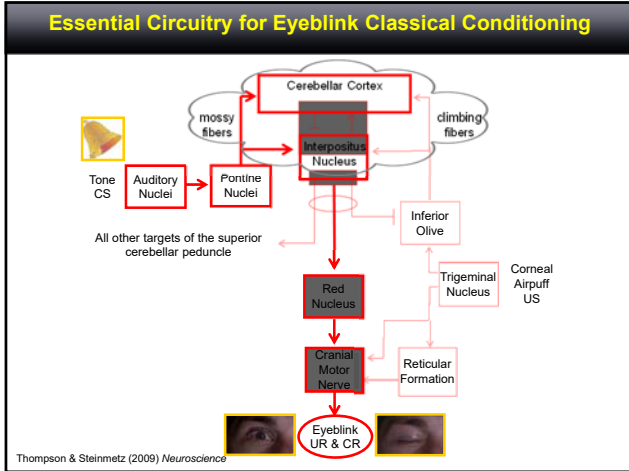
Thompson & Steinmetz (2009) *Neuroscience*

Inferior Olive and Climbing Fibers



Sears and Steinmetz (1991) *Brain Res*



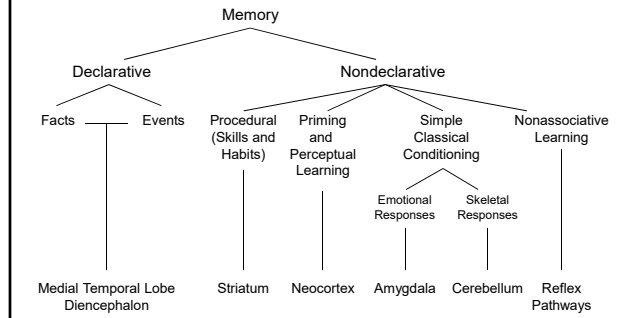


Summary so far.....

- **Eyeblink Classical Conditioning**
 - Terminology
 - Adaptive Responses

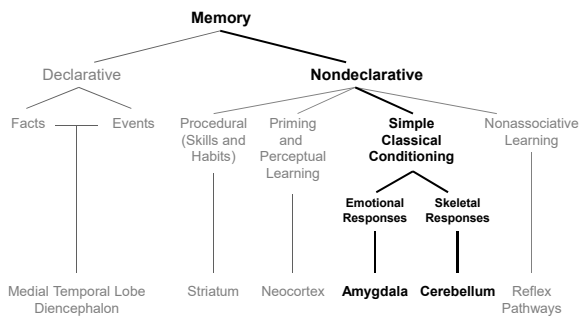
- **Animal Evidence** (lesions, electrophysiology, stimulation)
 - Pons and Ollives
 - Red Nucleus
 - Cerebellum
 - Cortex (Lateral Lobule VI)
 - Interpositus Nucleus

Human Memory Classification



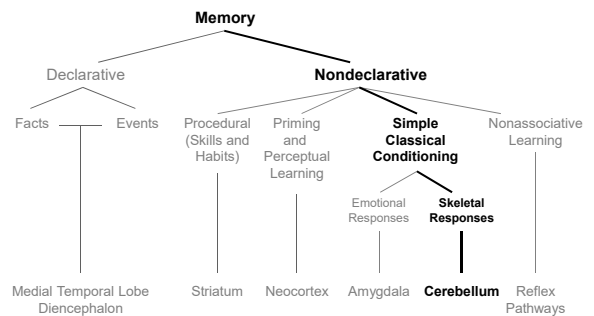
Squire (2004) *Neurobiology of Learning and Memory*

Human Memory Classification



Squire (2004) *Neurobiology of Learning and Memory*

Human Memory Classification



Squire (2004) *Neurobiology of Learning and Memory*

Human Eyeblink Classical Conditioning

Behavioral Studies

Cason (1922)

Patient Studies (MTL and Cerebellar Lesions)

Daum et al. (1989, 1991, 1992, 1993)
 Woodruff-Pak et al. (1990, 1993, 1996)
 Gabrieli et al. (1995)
 Bracha et al. (1997)
 Clark and Squire (1998)
 Gerwig et al. (2003, 2005, 2006, 2008, 2010)

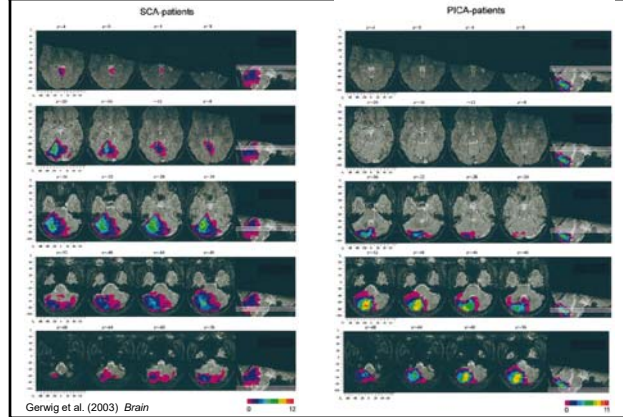
Neuroimaging Studies (PET and fMRI)

Molchan et al. (1994); Logan & Grafton, (1995); Blaxton et al. (1996)
 Schreurs et al. (1997, 2001); Parker et al. (2012)
 Ramnani et al. (2000); Knutinen et al. (2002); Cheng et al. (2008, 2014)

Neurostimulation Studies (TMS and tDCS)

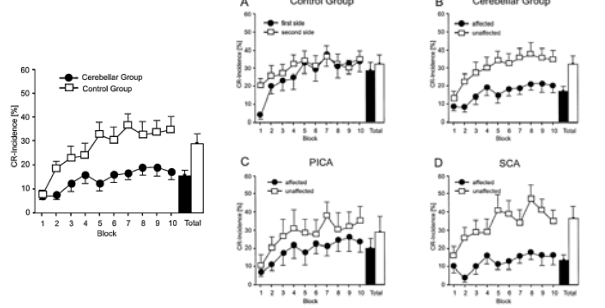
Hoffland et al. (2012)
 Kaski et al. (2012)
 Zuchowski et al. (in press)

Patient Studies of Human Eyeblink Conditioning



Patient Studies of Human Eyeblink Conditioning

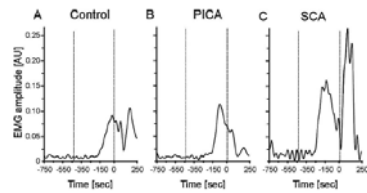
CR incidence



Gerwig et al. (2003) Brain

Patient Studies of Human Eyeblink Conditioning

CR timing



Gerwig et al. (2005) J Neurosci

Measuring Neural Activity Related to Learning

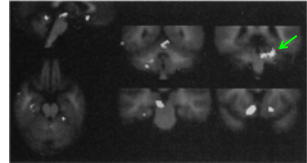


PET Studies of Human Eyblink Conditioning

Learning-related cerebellar cortical activation during EBC

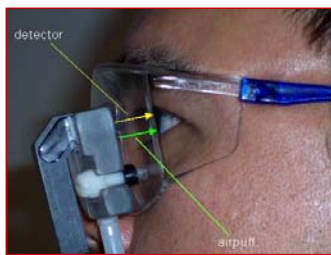


Molchan et al. (1994) *PNAS*



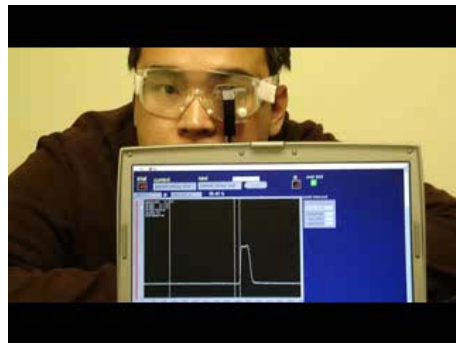
Logan and Grafton (1995) *PNAS*

Eyblink Classical Conditioning in the MRI Scanner



Cheng et al. (2008) *PNAS*

Eyblink Classical Conditioning Today



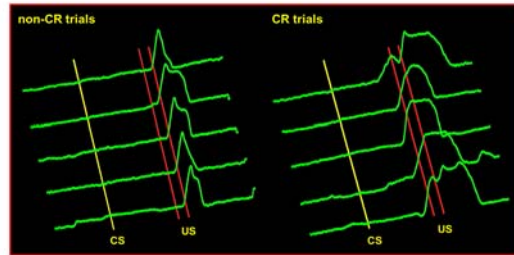
Unconditioned Responses

Eyblink Classical Conditioning Today



Conditioned Responses

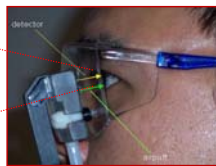
Topography of Eyeblinks in the MRI Scanner



General Eyblink Conditioning Methodology

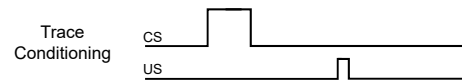
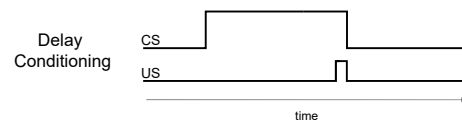


The Gold Rush

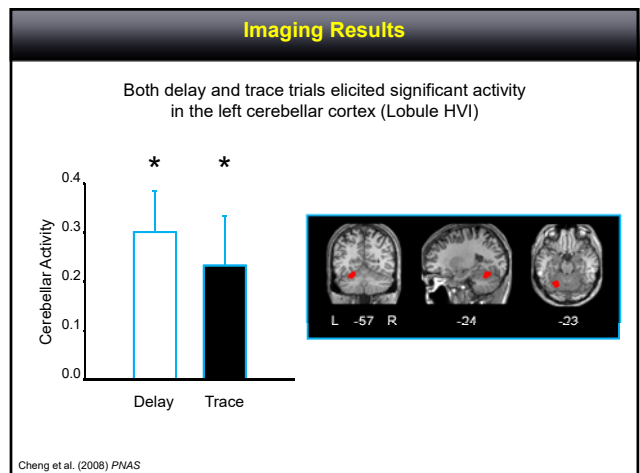
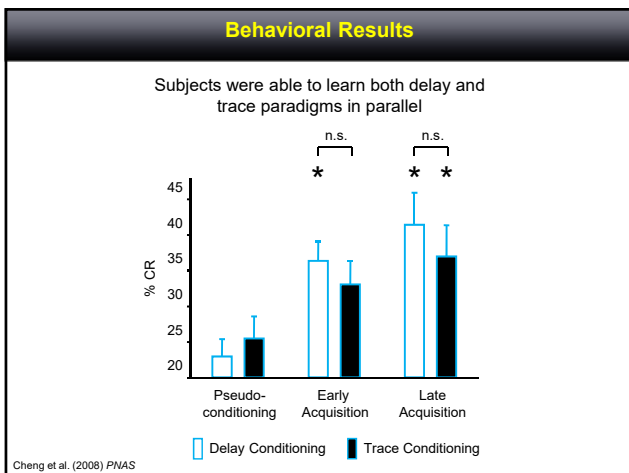
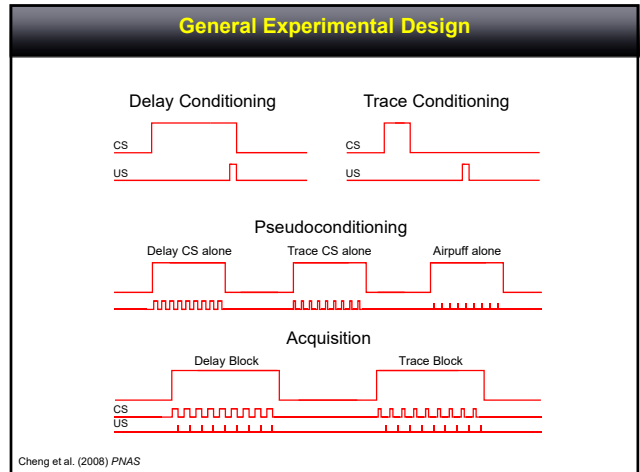
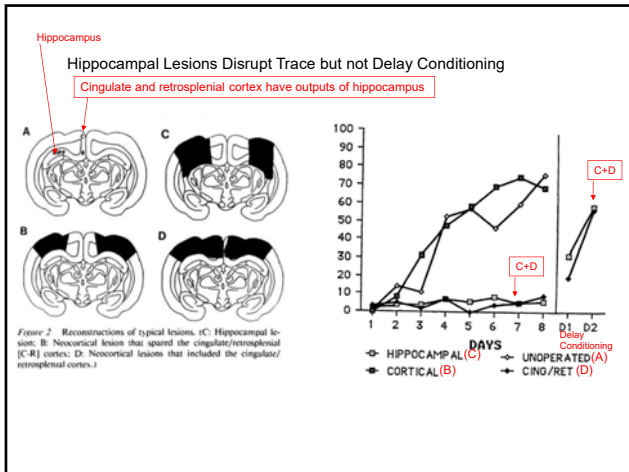


Cheng et al. (2008) PNAS

Delay and Trace Conditioning

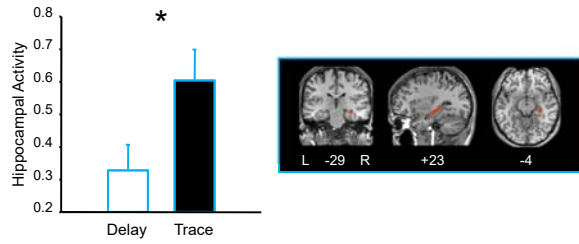


What are some common and unique brain regions?



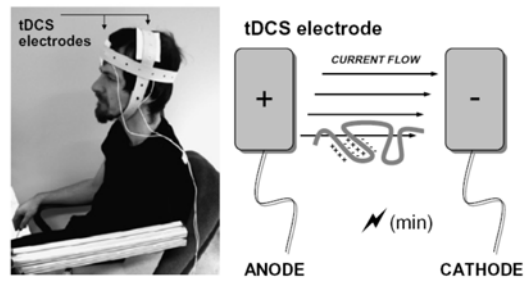
Imaging Results

Greater hippocampal responding was measured during trace conditioning relative to delay conditioning



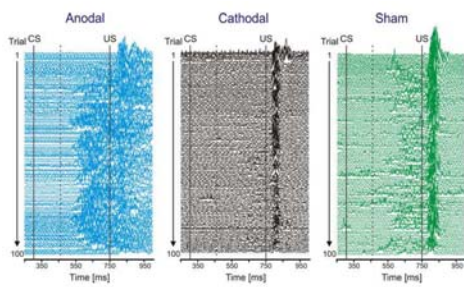
Cheng et al. (2008) PNAS

Transcranial Direct Current Stimulation (tDCS)



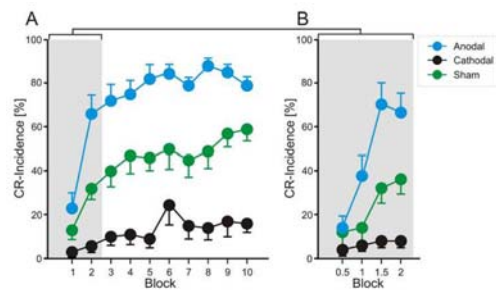
Sparing & Mottaghy (2008) Methods

Transcranial Direct Current Stimulation (tDCS)



Zuchowski et al., (2014) Brain Stimulation

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Zuchowski et al., (2014) Brain Stimulation