The Cerebellum and Classical Conditioning

Acknowledgement:
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Auburn University

Classical Conditioning in Popular Culture

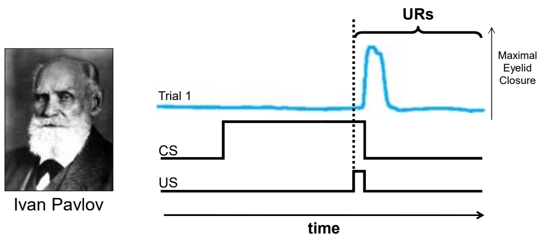
Why Classical Conditioning?

- 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

Basics of Eyeblink Classical Conditioning

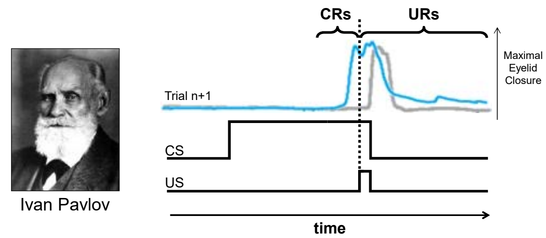


Conditioned stimulus (CS)
(tone)

Unconditioned stimulus (US)
(corneal airpuff)

Unconditioned response (UR)
(eyeblink)

Basics of Eyeblink Classical Conditioning



Conditioned stimulus (CS)
(tone)

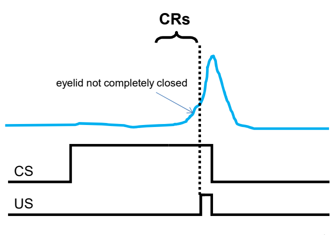
Unconditioned stimulus (US)
(corneal airpuff)

Unconditioned response (UR)
(eyeblink)

Conditioned response (CR)
(eyeblink)

Basics of Eyeblink Classical Conditioning

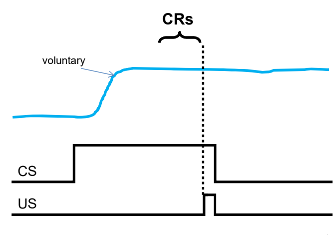
Characteristics of an adaptive CR
Amplitude



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

Basics of Eyeblink Classical Conditioning

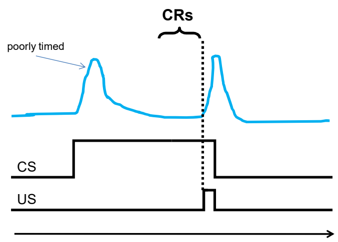
Characteristics of an adaptive CR
Duration



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

Basics of Eyeblink Classical Conditioning

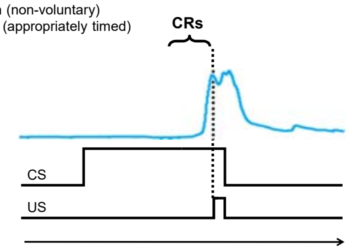
Characteristics of an adaptive CR
Latency (timing)



Gormezano (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)

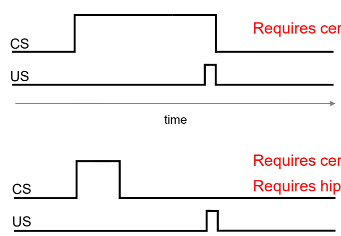


Gormezano (1966) *Experimental Methods and Instrumentation in Psychology (ed. Sidowski)*

Delay and Trace Conditioning

Delay Conditioning

Trace Conditioning

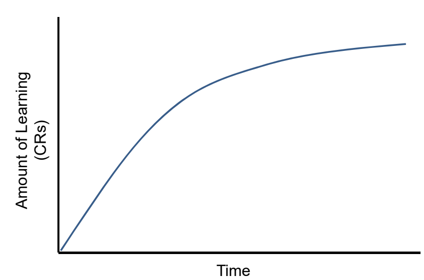


Delay: Requires cerebellum

Trace: Requires cerebellum, Requires hippocampus

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

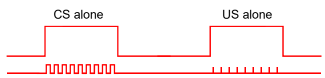


Basics of Eyeblink Classical Conditioning

Common Controls used in Classical Conditioning

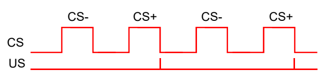
Pseudoconditioning

Unpaired CS and US presentation



Differential Conditioning

CS+ and CS- presentations



A Little History…..

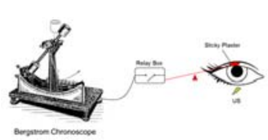
The first eyeblink conditioning studies were performed in humans (Cason, 1922).

Problems with humans:

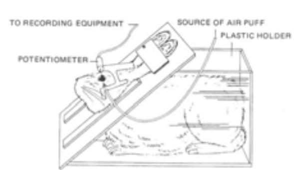
- measurement difficulties
- response variability
- voluntary responding
- cannot do invasive neuroscience research

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

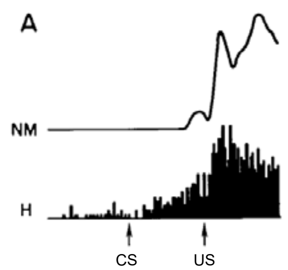
Gormezano (1962)


The Search for the Engram

RICHARD F. THOMPSON

- Mid 70's: CR had never been eliminated without affecting UR
- Engram = The hypothetical place where learned associations occurred
- Lashley: Memory is diffuse
- Scoville and Milner (1957): Hippocampus & memory (patient HM)
- Thompson: Engram likely to be in hippocampus

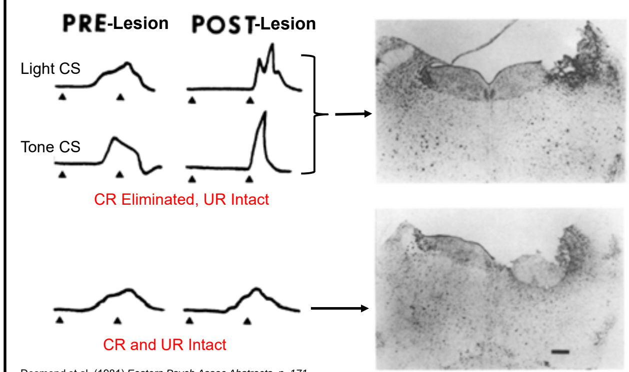
A Little History…..



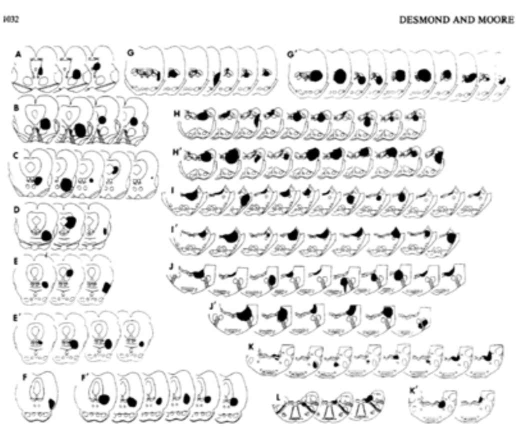
Recording in the hippocampus during rabbit eyeblink conditioning
Neuronal activity appears to mirror development of CRs,
however for delay conditioning, lesions of hippocampus do not
affect conditioning

Berger et al. (1976) *Science*

First Reports of CR Disruption

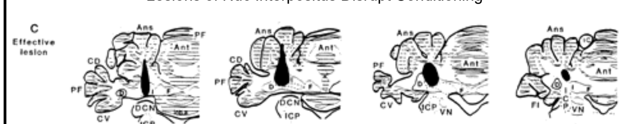


Desmond et al. (1981) *Eastern Psych Assoc Abstracts, p. 171*
Desmond and Moore (1982) *Physiol Behav*

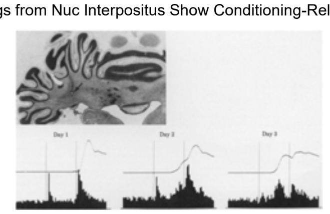


Desmond and Moore (1982) *Physiol Behav*

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. KETTNER, CHRISTINA E. RISING, and RICHARD F. THOMPSON
Stanford University, Stanford, California 94305

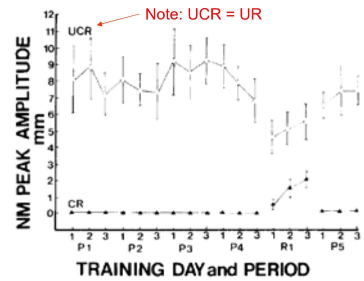
Electrophysiological recording of neural unit activity during paired training trials from the ipsilateral cerebellum in rabbits well trained in short-delay classical conditioning of the nictitating membrane (NM) and eyelid responses showed CS- and UCS-evoked responses and a pattern of increased neural activity that correlates with the learned behavioral response. Large ablations of the ipsilateral cerebellum completely and permanently abolished the conditioned response in well trained animals, as did more localized stereotaxic lesions. These lesions had no effect at all on the unconditioned reflex response. In marked contrast, conditioned responses were easily trained in the eye contralateral to the cerebellar lesion. We suggest that at least a part of the "engram," the essential neuronal plasticity that codes the learned response, may be localized to the cerebellum.

The initial goal in the analysis of the "engram," the essential neuronal plasticity that codes learning and memory, is to determine the location of the engram in the brain, if such exists. To date, 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, short-delay classical conditioning of the nictitating membrane (NM) and eyelid responses in the rabbit, is at least in part localized to the cerebellum. Because this result is of considerable potential importance, we are taking the somewhat unusual step of reporting preliminary results from experiments still in progress.

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

It is important to emphasize the nature of the CR. Investigators typically record either extension of the NM, which is a largely passive consequence of eyeball retraction (Cegavske, Thompson, Patterson, & ...

Nuc Interpositus Lesion Prevents CR Acquisition

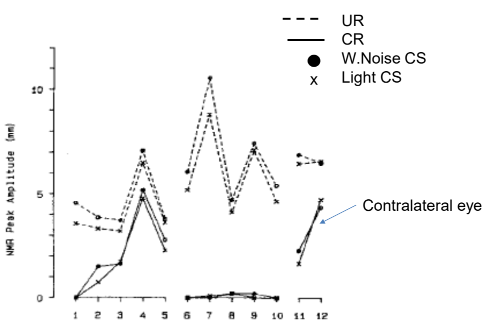


P: Eye ipsilateral to lesion
R: Eye contralateral to lesion

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)

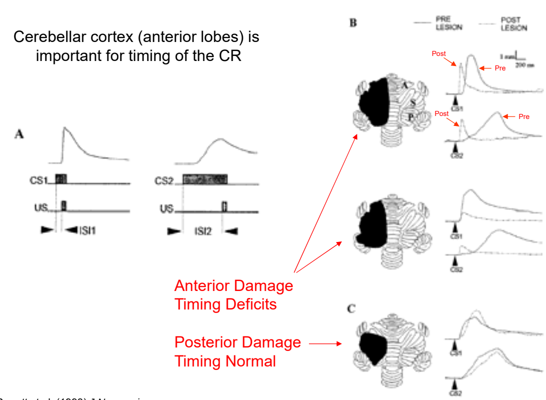


Lesions to the Lobule H VI in cerebellar cortex
Disrupt CRs to ipsilateral but not contralateral eye
URs are intact

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

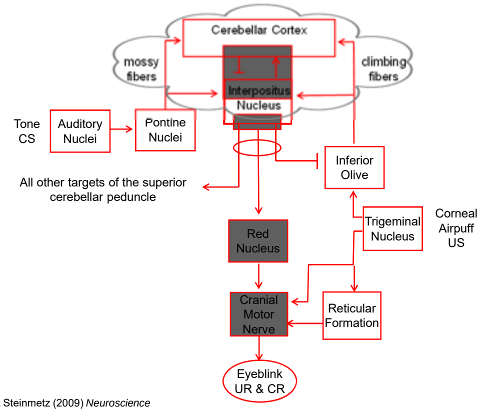
CR timing and the cerebellar cortex

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



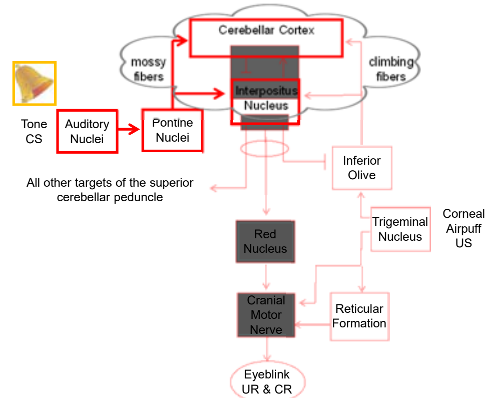
Perrett et al. (1993) *J Neurosci*

Essential Circuitry for Eyeblink Classical Conditioning



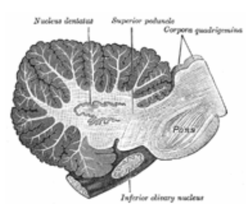
Thompson & Steinmetz (2009) *Neuroscience*

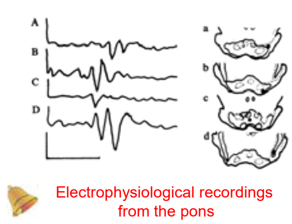
Essential Circuitry for Eyeblink Classical Conditioning



Thompson & Steinmetz (2009) *Neuroscience*

Pons and Mossy Fibers

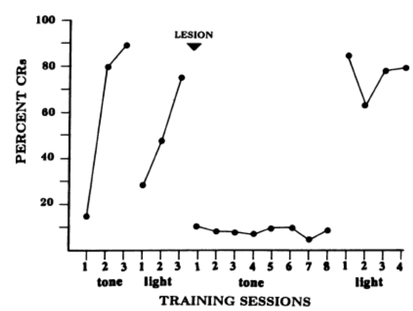




Electrophysiological recordings from the pons

Steinmetz et al. (1987) *PNAS*

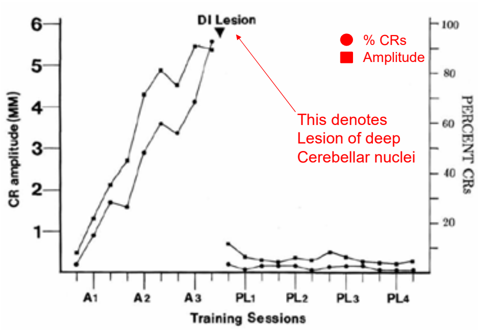
Pons and Mossy Fibers



Lesions to the auditory-responsive pontine nuclei
Eliminates CRs to auditory CS but not to light CS

Steinmetz et al. (1987) *PNAS*

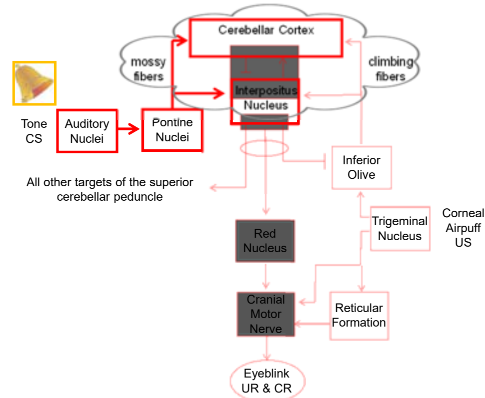
Pons and Mossy Fibers



Pontine and mossy fiber stimulation
Can be used as a CS to support conditioning

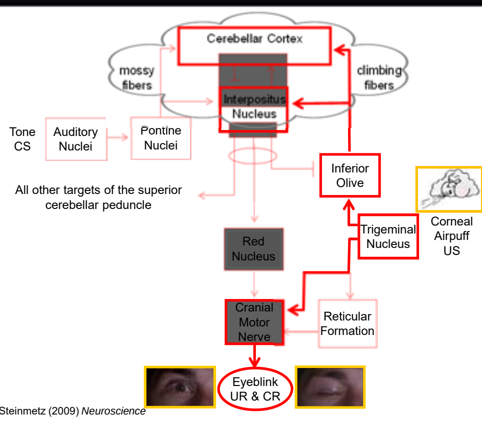
Steinmetz et al. (1986) *Beh Neuro*

Essential Circuitry for Eyeblink Classical Conditioning



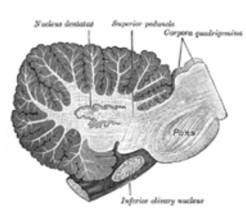
Thompson & Steinmetz (2009) *Neuroscience*

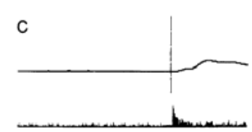
Essential Circuitry for Eyeblink Classical Conditioning



Thompson & Steinmetz (2009) *Neuroscience*

Inferior Olive and Climbing Fibers



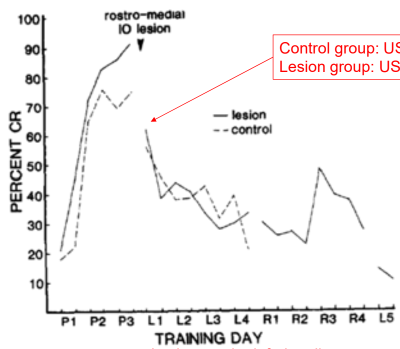


Electrophysiological recordings
from the inferior olive

The inferior olive responds
To airpuff to the eye

Sears and Steinmetz (1991) *Brain Res*

Inferior Olive and Climbing Fibers



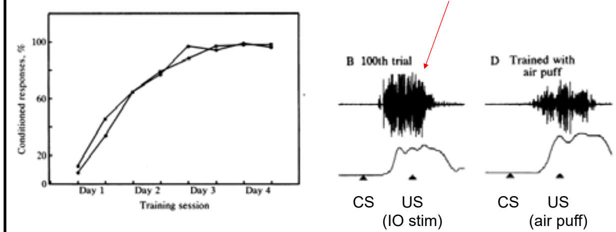
Control group: US turned off
Lesion group: US stays on, IO lesioned

Lesions to the inferior olive
Cause extinction of CRs
(URs were not affected)

McCormick et al. (1985) *Brain Res*

Inferior Olive and Climbing Fibers

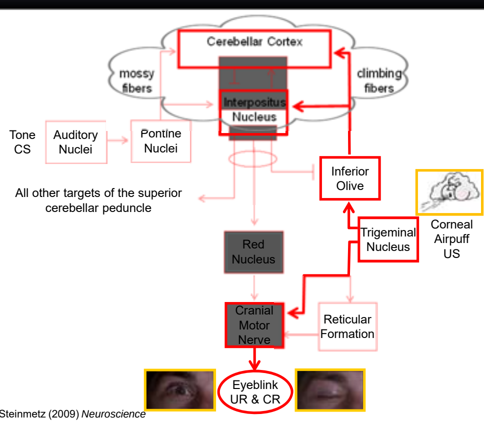
This is an EMG response
(Another way to record eyeblinks)



Inferior olive and climbing fiber stimulation
Can be used as a US to support conditioning

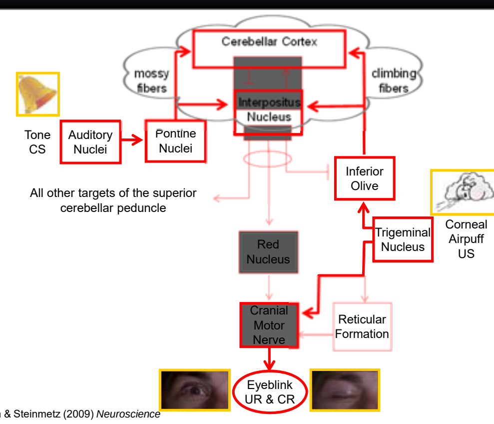
Mauk et al. (1986) *PNAS*

Essential Circuitry for Eyeblink Classical Conditioning



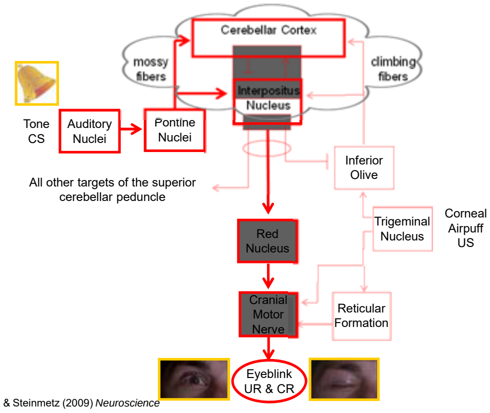
Thompson & Steinmetz (2009) *Neuroscience*

Essential Circuitry for Eyeblink Classical Conditioning



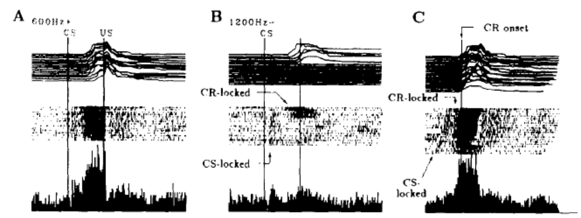
Thompson & Steinmetz (2009) *Neuroscience*

Essential Circuitry for Eyeblink Classical Conditioning



Thompson & Steinmetz (2009) *Neuroscience*

Red Nucleus

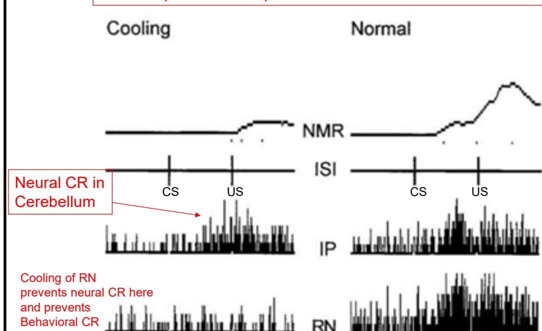


Electrophysiological recordings from red nucleus

Desmond and Moore (1991) *Neurosci Res*

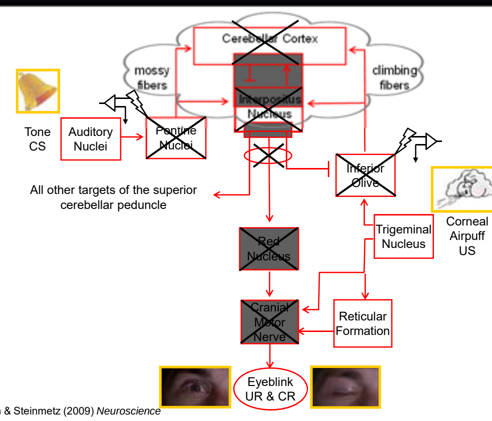
Red Nucleus

Cooling the red nucleus during conditioning does not prevent learning but does prevent the expression of the CR



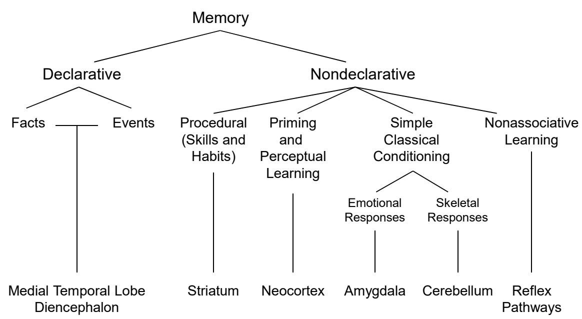
Clark & Lavond (1993) *Behav Neurosci*

Essential Circuitry for Eyeblink Classical Conditioning



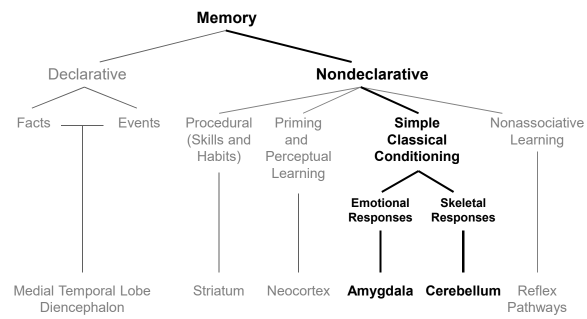
Thompson & Steinmetz (2009) *Neuroscience*

Human Memory Classification



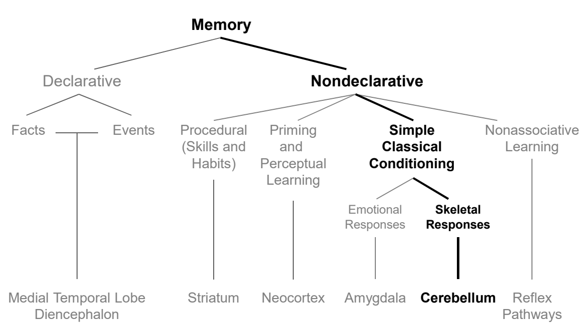
Squire (2004) *Neurobiology of Learning and Memory*

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)

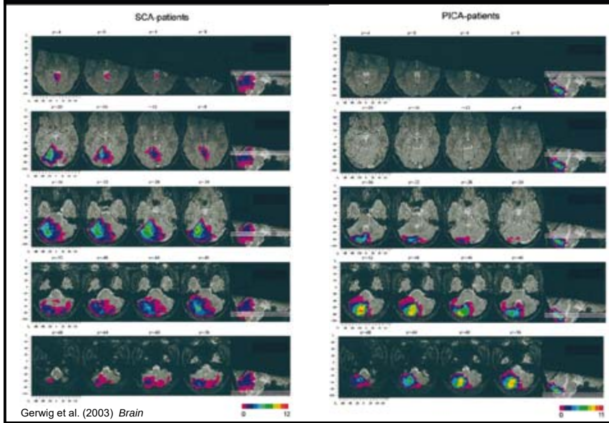
Molchan et al. (1994); Logan & Grafton, (1995); Blaxton et al. (1996)
Schreurs et al. (1997, 2001); Parker et al. (2012)

Ramnani et al. (2000); Knuttinen 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)

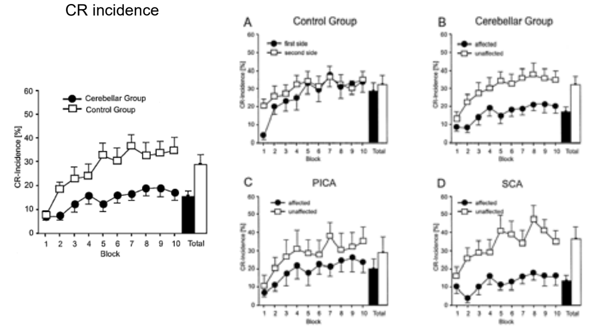
Patient Studies of Human Eyeblink Conditioning



Gerwig et al. (2003) *Brain*

Patient Studies of Human Eyeblink Conditioning

CR incidence

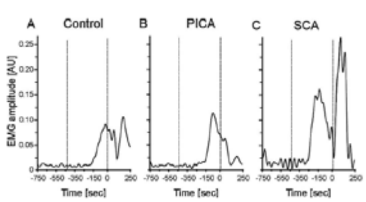


Gerwig et al. (2003) *Brain*

Affected=the affected eye, ie, the one ipsilateral to the lesion

Patient Studies of Human Eyeblink Conditioning

CR timing



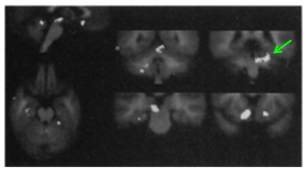
Gerwig et al. (2005) *J Neurosci*

Measuring Neural Activity Related to Learning

PET Studies of Human Eyeblink Conditioning

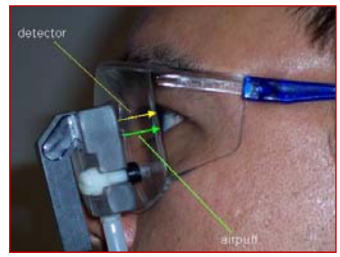
Learning-related cerebellar cortical activation during EBC

Molchan et al. (1994) *PNAS*



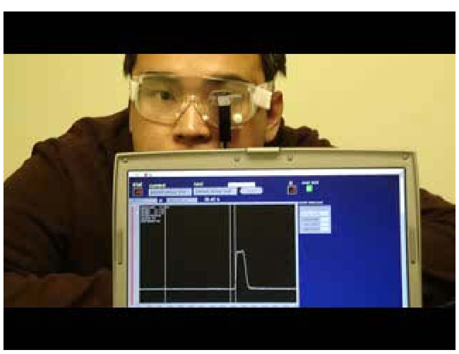
Logan and Grafton (1995) *PNAS*

Eyeblink Classical Conditioning in the MRI Scanner



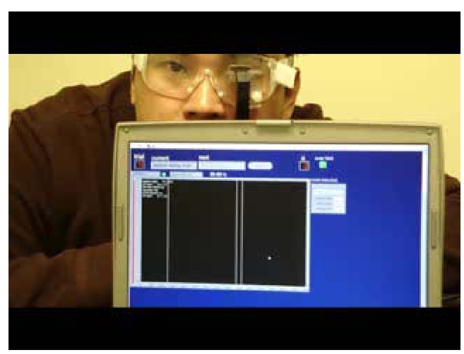
Cheng et al. (2008) *PNAS*

Eyeblink Classical Conditioning Today



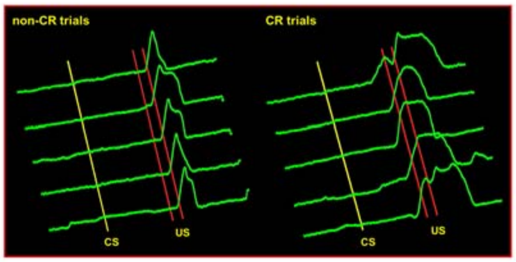
Unconditioned Responses

Eyeblink Classical Conditioning Today



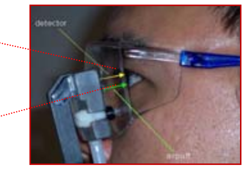
Conditioned Responses

Topography of Eyeblinks in the MRI Scanner



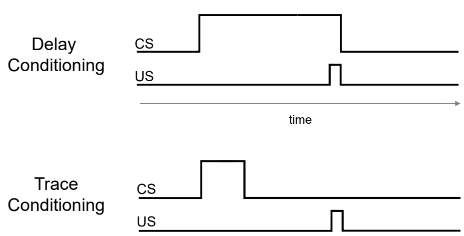
General Eyeblink Conditioning Methodology

The Gold Rush



Cheng et al. (2008) *PNAS*

Delay and Trace Conditioning



What are some common and unique brain regions?

Hippocampus

Hippocampal Lesions Disrupt Trace but not Delay Conditioning

Cingulate and retrosplenial cortex receive outputs of hippocampus

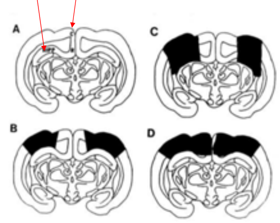
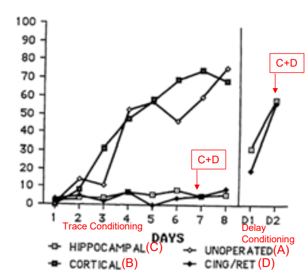
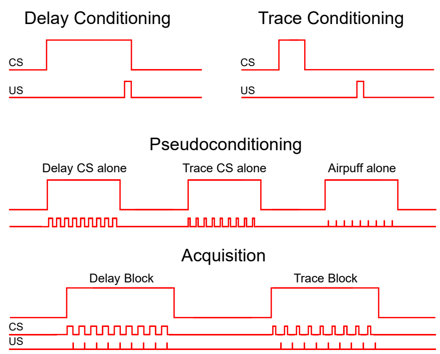


Figure 2 Reconstructions of typical lesions. (C: Hippocampal lesion; B: Neocortical lesion that spared the cingulate/retrosplenial [C-R] cortex; D: Neocortical lesions that included the cingulate/retrosplenial cortex.)



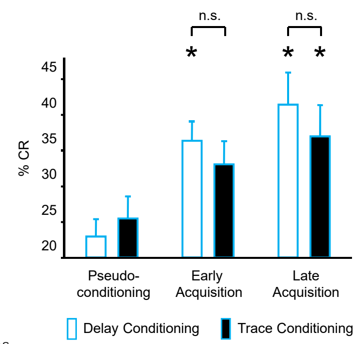
General Experimental Design



Cheng et al. (2008) *PNAS*

Behavioral Results

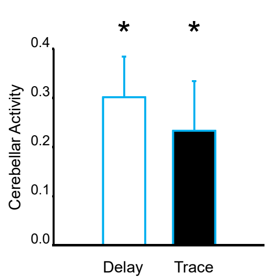
Subjects were able to learn both delay and trace paradigms in parallel



Cheng et al. (2008) *PNAS*

Imaging Results

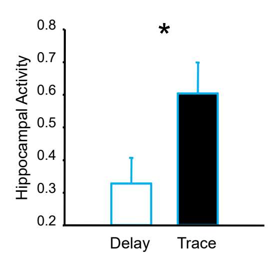
Both delay and trace trials elicited significant activity in the left cerebellar cortex (Lobule HVI)



Cheng et al. (2008) *PNAS*

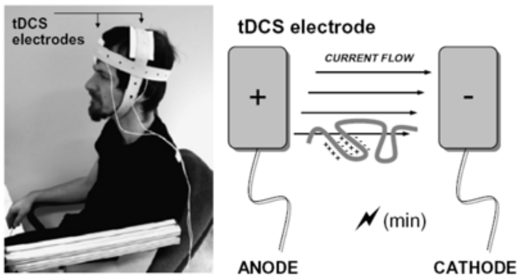
Imaging Results

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



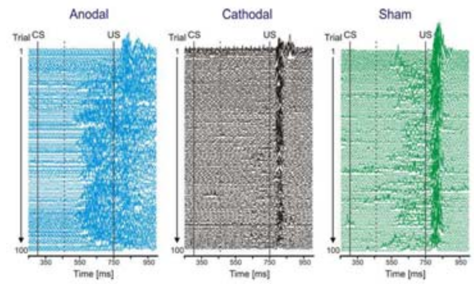
Cheng et al. (2008) *PNAS*

Transcranial Direct Current Stimulation (tDCS)



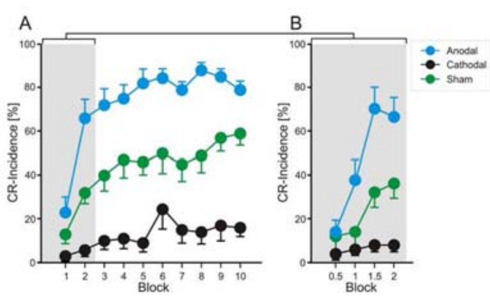
Sparing & Mottaghy (2008) *Methods*

Transcranial Direct Current Stimulation (tDCS)



Zuchowski et al., (2014) *Brain Stimulation*

Transcranial Direct Current Stimulation (tDCS)



Zuchowski et al., (2014) *Brain Stimulation*