The Cerebellum and Classical Conditioning

Acknowledgement:
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Why Classical Conditioning?
- A model for a fundamental form of memory
- One of the most studied forms of 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

Classical Conditioning in Popular Culture
Basics of Eyeblink Classical Conditioning

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

Ivan Pavlov

Characteristics of an adaptive CR
Amplitude

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

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)

CS
US
CRs
poorly timed

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)

CS
US
CRs

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 cotermimates with US

Amount of Learning

Time
Basics of Eyeblink Classical Conditioning

Common Controls used in Classical Conditioning

**Pseudoconditioning**
Unpaired CS and US presentation

**Differential Conditioning**
CS+ and CS- presentations

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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 (80-90 min)
- Show low spontaneous blink rates
- Gradual acquisition
- Few alpha (orienting) responses
- Eyes can be conditioned independently

Gormezano (1962)
A Little History…

Berger et al. (1976) Science

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

First Reports of CR Disruption

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

Lesions of Nuc Interpositus Disrupt Conditioning

Recordings from Nuc Interpositus Show Conditioning-Related Activity
Lincoln et al., (1982) *Brain Res*

Interpositus lesion prevents CR acquisition in eye ipsilateral to lesion

Contralateral eye can still learn and make CRs

Nuc Interpositus Lesion Prevents CR Acquisition

Cerebellar Cortex (H VI)

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

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

CR timing and the cerebellar cortex

Perrett et al. (1993) *J Neurosci*

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

Anterior Damage Timing Deficits

Posterior Damage Timing Normal
Essential Circuitry for Eyeblink Classical Conditioning

Thompson & Steinmetz (2009) Neuroscience

Pons and Mossy Fibers

Steinmetz et al. (1987) PNAS

Electrophysiological recordings from the pons

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

Steinmetz et al. (1987) PNAS

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Pons and Mossy Fibers

Steinmetz et al. (1986) Beh Neuro

Essential Circuitry for Eyeblink Classical Conditioning

Thompson & Steinmetz (2009) Neuroscience

Electrophysiological recordings from the inferior olive

Sears and Steinmetz (1991) Brain Res
Inferior Olive and Climbing Fibers

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

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

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

McCormick et al. (1985) Brain Res.

Mauk et al. (1986) PNAS

Inferior Olive and Climbing Fibers

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

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

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

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

McConnell et al. (1985) Brain Res.

Mauk et al. (1986) PNAS

Essential Circuitry for Eyeblink Classical Conditioning

Tone CS Auditory Nuclei

All other targets of the superior cerebellar peduncle

Mossy fibers

Cerebellar Cortex Interpositus Nucleus

Climbing fibers

Red Nucleus

Reticular Formation

Eyeblink UR & CR

Thompson & Steinmetz (2009) Neuroscience

Essential Circuitry for Eyeblink Classical Conditioning

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Eyeblink UR & CR

Thompson & Steinmetz (2009) Neuroscience
Tone
CS
Auditory
Nuclei
All other targets of the superior
cerebellar peduncle

Essential Circuitry for Eyeblink Classical Conditioning

Red Nucleus

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

Cooling
Normal

Neural CR in
Cerebellum

Clark & Lavond (1993) Behav Neurosci

Essential Circuitry for Eyeblink Classical Conditioning

Red Nucleus

Electrophysiological recordings from red nucleus


Essential Circuitry for Eyeblink Classical Conditioning

Red Nucleus

Cooling of RN
prevents neural CR here
and prevents
Behavioral CR

Clark & Lavond (1993) Behav Neurosci
Summary so far.....

- Eyeblink Classical Conditioning
  - Terminology
  - Adaptive Responses

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

Human Memory Classification

- Declarative
  - Facts
  - Events
- Nondeclarative
  - Medial Temporal Lobe
  - Diencephalon
  - Striatum
  - Neocortex
  - Amygdala
  - Cerebellum
  - Reflex Pathways

Squire (2004) Neurobiology of Learning and Memory
**Human Eyeblink Classical Conditioning**

**Behavioral Studies**
Cason (1922)

**Patient Studies (MTL and Cerebellar Lesions)**
Woodruff-Pak et al. (1990, 1993, 1996)
Gabriel et al. (1995)
Braiche et al. (1997)
Clark and Squire (1998)

**Neuroimaging Studies (PET and fMRI)**
Mitchell et al. (1994); Logan & Grafman. (1995); Blaunet et al. (1996)
Schneiders et al. (1997, 2001); Parker et al. (2012)
Ramnani et al. (2000); Knutti et al. (2002); Cheng et al. (2008, 2014)

**Neurostimulation Studies (TMS and tDCS)**
Hoffland et al. (2012)
Katic et al. (2012)
Zuchowski et al. (in press)

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**Patient Studies of Human Eyeblink Conditioning**

**CR incidence**

**CR timing**

*Gerwig et al. (2003) Brach*
Measuring Neural Activity Related to Learning

PET Studies of Human Eyeblink Conditioning

Learning-related cerebellar cortical activation during EBC

Mishkin 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

Cheng et al. (2008) PNAS
**Eyeblink Classical Conditioning Today**

**Conditioned Responses**

**Topography of Eyeblinks in the MRI Scanner**

**General Eyeblink Conditioning Methodology**

**Delay and Trace Conditioning**

What are some common and unique brain regions?

Cheng et al. (2008) PNAS

The Gold Rush
Hippocampal Lesions Disrupt Trace but not Delay Conditioning

**General Experimental Design**

- **Delay Conditioning**
  - CS
  - US

- **Trace Conditioning**
  - CS
  - US

- **Pseudoconditioning**
  - Delay CS alone
  - Trace CS alone
  - Airpuff alone

- **Acquisition**
  - Delay Block
  - Trace Block

**Behavioral Results**

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

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<tr>
<th></th>
<th>Early Acquisition</th>
<th>Late Acquisition</th>
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<tbody>
<tr>
<td>Pseudo-conditioning</td>
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<tr>
<td>Delay Conditioning</td>
<td><img src="image" alt="Graph" /></td>
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<td>Trace Conditioning</td>
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**Imaging Results**

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

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<th>Delay</th>
<th>Trace</th>
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<tr>
<td>Cerebellar Activity</td>
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Greater hippocampal responding was measured during trace conditioning relative to delay conditioning.

Cheng et al. (2008). PNAS

**Imaging Results**

**Transcranial Direct Current Stimulation (tDCS)**

Transcranial Direct Current Stimulation (tDCS)