The Cerebellum and Classical Conditioning

Acknowledgement:
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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)  Unconditioned stimulus (US)
(tone)  (corneal airpuff)

Unconditioned response (UR)  Conditioned response (CR)
(eyeblink)  (eyeblink)

Characteristics of an adaptive CR
Amplitude

Duration

Gormezano (1966), Experimental Methods and Instrumentation in Psychology (ed. Sidowski)
Characteristics of an adaptive CR

- **Latency (timing)**
  - Poorly timed

**Basics of Eyeblink Classical Conditioning**

**Delay and Trace Conditioning**

- **Delay Conditioning**
  - Requires cerebellum
- **Trace Conditioning**
  - 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 coterminal with US.

**Amplitude (eye must be fully closed)**

**Duration (non-voluntary)**

**Latency (appropriately timed)**

**Basics of Eyeblink Classical Conditioning**

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

- 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 eyelink conditioning
Neuronal activity appears to mirror development of CRs,
however for delay conditioning, lesions of hippocampus do not
affect conditioning

Desmond and Moore (1982) Physiology

First Reports of CR Disruption

Lesions of Nuc Interpositus Disrupt Conditioning

Recordings from Nuc Interpositus Show Conditioning-Related Activity

Desmond et al. (1981) Physiology

Desmond and Moore (1982) Physiology
J Neurosci  
Interpositus lesion prevents CR acquisition in eye ipsilateral to lesion  
Contralateral eye can still learn and make CRs  

Note: UCR = UR

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

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

Yeo et al. (1985)  
Exp Brain Res  
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Timing Normal
Essential Circuitry for Eyeblink Classical Conditioning

- Tone CS
- Auditory Nuclei
- Pontine Nuclei
- Mossy fibers
- Cerebellar Cortex
- Interpositus Nucleus
- Climbing fibers
- Inferior Olive
- Trigeminal Nucleus
- Corneal Airpuff US
- All other targets of the superior cerebellar peduncle
- Red Nucleus
- Cranial Motor Nerve
- Reticular Formation
- Eyeblink UR & CR

Electrophysiological recordings from the pons

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

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Electrophysiological recordings from the inferior olive

The inferior olive responds to airpuff to the eye

Thompson & Steinmetz (2009) Neuroscience

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Inferior Olive and Climbing Fibers

- Inferior Olive
- Climbing fibers
- Corneal Airpuff US
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- Reticular Formation

Electrophysiological recordings from the inferior olive

The inferior olive responds to airpuff to the eye

Sears and Steinmetz (1997) Braak Rev
Inferior Olive and Climbing Fibers

McCormick et al. (1985) Brain Res
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

Mauk et al. (1986) PNAS

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

Essential Circuitry for Eyeblink Classical Conditioning

Thompson & Steinmetz (2009) Neuroscience

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Reticular Formation
Eyeblink UR & CR

All other targets of the superior cerebellar peduncle

Essential Circuitry for Eyeblink Classical Conditioning

Thompson & Steinmetz (2009) Neuroscience
Human Memory Classification

Declarative
- Facts
- Events
- Procedural (Skills and Habits)
- Priming and Perceptual Learning

Nondeclarative
- Simple Classical Conditioning
- Nonassociative Learning

Medial Temporal Lobe
Diencephalon
Striatum
Neocortex
Amygdala
Cerebellum
Reflex Pathways

Squire (2004) Neurobiology of Learning and Memory

Human Memory Classification

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Nondeclarative
- Emotional Responses
- Skeletal Responses

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Squire (2004) Neurobiology of Learning and Memory

Behavioral Studies
- Cason (1922)

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

Neuroimaging Studies (PET and fMRI)
- Schneur et al. (1997, 2001); Parker et al. (2012)
- Ramnani et al. (2000); Knudtten et al. (2002); Cheng et al. (2008, 2014)

Neurostimulation Studies (TMS and tDCS)
- Hoffland et al. (2012)
- Kast et al. (2012)
- Zuchowski et al. (in press)
Patient Studies of Human Eyeblink Conditioning

Gerwig et al. (2003) - Brain

CR incidence

Affected = the affected eye, i.e., the one ipsilateral to the lesion.

Measuring Neural Activity Related to Learning

Gerwig et al. (2005) - J Neurosci
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

Conditioned Responses

Eyeblink Classical Conditioning Today
General Eyeblink Conditioning Methodology

1. **Delay Conditioning**: CS — US
2. **Trace Conditioning**: CS — US

What are some common and unique brain regions?

**Hippocampal Lesions Disrupt Trace but not Delay Conditioning**

- Cingulate and retrosplenial cortex receive outputs of hippocampus
- Hippocampus

**Diagram**

- A: Hippocampal lesions disrupt trace conditioning
- B: Hippocampal lesions do not disrupt delay conditioning

**Graph**

- X-axis: DAYS
- Y-axis: % score

- C+D Conditioned
- C+D Unoperated
- C+D Hip-trt

**Figure**

- Topography of Eyeblinks in the MRI Scanner
- The Gold Rush (Cheng et al. (2008) PNAS)
General Experimental Design

Delay Conditioning

Trace Conditioning

Pseudoconditioning

Acquisition

Behavioral Results

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

Imaging Results

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

Imaging Results

Greater hippocampal responding was measured during trace conditioning relative to delay conditioning
Transcranial Direct Current Stimulation (tDCS)


Zuchowski et al., (2014). Brain Stimulation

Zuchowski et al., (2014). Brain Stimulation

Zuchowski et al., (2014). Brain Stimulation