Research in Blepharospasm:
Modulating the Blink Response

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Disclosure

• All material presented is independent of and unrelated to industry

• I will be discussing off-label uses for FDA-approved magnetic and electrical stimulators
Blink reflex is hyper-excitable in blepharospasm

- Blink reflex recovery (BRR) curves
  - Uses paired-pulse trigeminal nerve stimulation
  - Disinhibition of BRR

- Long-term potentiation (LTP)-like response in blink response is exaggerated
  - Uses spike-timing and burst stimulation to test a LTP response of the trigeminal nerve
Blink reflex recovery (BRR) more excitable (less inhibition) in blepharospasm
Spike-timing plasticity of blink reflexes shows exaggerated LTP-like response in blepharospasm

Mao & Evinger 2001

Can we reduce excess excitability in blepharospasm?
Types of neuromodulation to probe or shape plasticity

High-frequency stimulation (LTP)
Presynaptic stimulation: 100 Hz, 1 s
Postsynaptic activity: not controlled, not measured

Low-frequency stimulation (LTD)
Presynaptic stimulation: 1 Hz, 900 s

Theta-burst stimulation (LTP)
Presynaptic stimulation: 100 Hz bursts at 5 Hz
Postsynaptic activity: not controlled, not measured

Timed-spike stimulation
Presynaptic stimulation: \( \frac{\Delta t}{f} \)
Postsynaptic activity: not controlled, not measured

(a) Repetitive TMS (rTMS)
Low-frequency rTMS (~1 Hz) 2 s
High-frequency rTMS (5 Hz) 2 s

(b) Theta-burst stimulation (TBS)
Continuous TBS (40 s) 2 s
Intermittent TBS every 10 s

(c) Paired associative stimulation (PAS)
Given every 3 to 20 s
ISI of ~10 ms
ISI of ~25 ms

(d) Transcranial direct-current stimulation (TDCS)
Cathodal TDCS
Given continuously for >5 min
Anodal TDCS

Shouval et al, Front Comput Neurosci 2010
Quartarone et al, TINS 2010
Can LTD be induced in the blink reflex at the brainstem level?

- Low-frequency stimulation
- Spike-timing burst stimulation (Mao & Evinger 2001)
- Trigeminal nerve stimulation (TNS)
LTD with low-frequency trigeminal nerve stimulation

- Trigeminal nerve stimulation does provide evidence of LTD-like effects
- Stimulation at 300% pain threshold at 1 Hz for 20 minutes
- Note habituation depression over time without LFS

Yekta et al, EBR 2006
Can we show LTD-like effects with low-frequency trigeminal nerve stimulation at tolerable intensities?

- Low-frequency 1 Hz stimulation at 2x blink threshold for 20 minutes (not painful)
- Habituation is prominent!
Habituation confounds blink reflex assessments

- Habituation (especially to low-frequency stimulation) prevents assessment of stimulation blink reflex changes

Esteban 1999
sensory inputs
sensory states (trigeminal, auditory, visual, pain)

LOCAL BRAINSTEM BLINK CIRCUIT

Brainstem afferent input

Blink GAIN

LTD(-)/LTP(+)?

Brainstem efferent output

Basal ganglia & frontal ctx

HABITUATION

Cerebellum

(-)habituate  (+)dishabituate

(+)(+)adapt/inc gain [decondition/dec gain (-)]
Blink reflex habituation may be another pathophysiologic feature of blepharospasm (another loss of inhibition)

Dishabituation methods
- high-frequency stimulation
- brain stimulation
- startle
- forced activation
- between-session assessments

http://graulab.tamu.edu
Can LTD be induced in the blink reflex at the brainstem level?

- Low-frequency stimulation
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Mao & Evinger 2001

Zeuner et al, PLoS 2010
Can LTD be induced in the blink reflex at the brainstem level?

- Low-frequency stimulation
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- Trigeminal nerve stimulation (TNS)

DeGiorgio et al, Epilepsia 2006
Trigeminal nerve stimulation (TNS)

- High-frequency cyclic trigeminal nerve stimulation (hf-cTNS)
  - TENS units applied daily over the trigeminal nerve has been tested in epilepsy
    (DeGiorgio et al 2006, 2009)
  - TNS is being studied in a phase 3 study for both epilepsy and depression.
  - Devices should be used under supervision within a clinical trial
  - Mechanism presumed an ascending inhibitory influence from the brainstem

DeGiorgio, et al, Epilepsia 2006
Can we reduce excess excitability in blepharospasm?
Transcranial magnetic stimulation noninvasively probes corticomotor excitability

MEP (motor evoked potential)
Cingulate motor area controls orb. oculi

Types of neuromodulation to probe or shape plasticity

<table>
<thead>
<tr>
<th>Type</th>
<th>Details</th>
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(a) **Repetitive TMS (rTMS)**
- Low-frequency rTMS (~1 Hz)
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(b) **Theta-burst stimulation (TBS)**
- Continuous TBS (40 s)
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- Given every 3 to 20 s
- ISI of ~10 ms
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(d) **Transcranial direct-current stimulation (TDCS)**
- Cathodal TDCS
- Anodal TDCS
- Given continuously for >5 min

Shouval et al, Front Comput Neurosci 2010
Quartarone et al, TINS 2010
• Neuromodulatory method
  – rTMS (0.2 Hz)
  – continuous theta-burst stimulation TBS
  – cathodal TDCS

• Locations
  – M1 (primary motor cortex)
  – PMC (lateral premotor cortex)
  – SMA (suppl motor area)
  – CMZ (cingulate motor region)
Low frequency-rTMS (0.2 Hz) over cingulate motor region shows trends for blepharospasm improvement.
Low frequency-rTMS (0.2 Hz) over cingulate motor region shows trends for blepharospasm improvement

Future of neuromodulation for plasticity disorders

- TMS (transcranial magnetic stimulation)
- TNS (trigeminal nerve stimulation)
  - spinal cord stimulation, other nerve stimulation
- TDCS (transcranial direct-current stimulation)
- Motor cortex stimulation
- DBS (deep brain stimulation)
- VNS (vagal nerve stimulation)
- Vibration, exercise/re-training, botulinum toxin
Conclusions

• Neuromodulation for disorders of plasticity is a currently active field

• Blink reflex
  • Promising target for neuromodulation for blepharospasm patients
  • Useful to measure brainstem excitability

• Blink reflex modulation
  • Must account for habituation in studies of plasticity
  • Optimal parameters for modulation not yet known
  • Trigeminal nerve stimulation is a new promising system being used in epilepsy for which we are planning to continue to study
  • Effects of botulinum toxin not yet known
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