Transcranial Magnetic Stimulation
Session 3 – Repetitive TMS Protocols

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Today's Schedule

Repetitive TMS Protocols
- Introduction into rTMS Protocols
- Safety issues
- Experimental treatment of major depression and tinnitus: A brief overview
“Classical” rTMS protocols
- Pioneered by Pascual-Leone, Hallett and colleagues (1994)
- Usually consisting of several hundred pulses having a constant temporal spacing
- 1Hz rTMS reduces motor cortex excitability (Chen et al. 1997)
- “High-frequency” rTMS (typically ≥ 5Hz) increases motor cortex excitability

Theta-burst stimulation (Huang et al. 2005)
- Consisting of pulse triples (50Hz), repeated every 200ms
- Facilitatory or inhibitory, depending on the exact temporal structure of the protocol

Paired-pulse rTMS (Thickbroom et al. 2006; Khedr et al. 2004)
- Consisting of pulse pairs at I-wave periodicity (1.5ms or 3ms spacing), repeated at a low frequency (<1Hz)
- Facilitatory or inhibitory, depending on the exact temporal structure of the protocol

Paired associative stimulation (PAS) (e.g. Wolters et al. 2003)
- Specific to the motor cortex
- Median nerve is stimulated either 25ms (facilitatory) or 10ms (inhibitory) before a TMS pulse is delivered to the motor cortex
- Effects are thought to be similar to spike-timing-dependent plasticity effects seen in LTP/LTD-experiments → Maybe a protocol to study LTP/LTD in humans

RTMS with ischemic nerve block (Ziemann et al. 1998)
- Specific to the motor cortex
- Transient “deafferentation” probably causes GABAergic disinhibition in M1
- As a consequence, rTMS at 0.1Hz results in a reduced SICI and enhanced MEP amplitudes

I make no claims that this list is complete!
In the following, we will focus on “classical” rTMS and theta-burst stimulation
1Hz rTMS

- One of the most commonly used rTMS protocols
- Moderate effect size: 1Hz rTMS (15min, 115% rMT) decreases MEP amplitude by ~20% (e.g. Heide et al. 2006); the effect lasts for ~15min
- High interindividual variability (e.g. Maeda et al. 2000a)
- High intraindividual variability (at least when using only 240 pulses; Maeda et al. 2000b)

4min (240pulses) 90%rMT

1Hz rTMS: Optimizing Its Efficiency

- Effect size & duration increases with number of stimuli
- Voluntary contraction abolishes the effect → Make sure that the muscle is relaxed
- Monophasic is more efficient than biphasic; shown for motor system (Sommer et al. 2002) & visual system (Antal et al. 2002); effect strength for monophasic stimulation strongly depends on the current orientation
- No good data on the dependency on stimulation intensity

10min at 100% phospene threshold

lowered contrast sensitivity after optimal monophasic stimulation

(Touge et al 2001)
1Hz rTMS: Physiology

A mixture of different effects resulting in a net inhibition of the MEP amplitude:

- H-reflex remains unchanged (e.g. Touge et al 2001): Intracortical effects
- Axonal excitability: Some studies report increases in rMT (e.g. Muellbacher et al. 2000), others don’t (e.g. Heide et al 2006)
- SICI remains unchanged (e.g. Heide et al. 2006)
- Divergent findings for ICF (e.g. Heide et al. 2006 vs. Bagnato et al 2005)
- GABA agonist lorazepam and NMDA antagonist dextromethorphan both abolish the effect of 1Hz rTMS, suggesting that it affects both GABA and NMDA receptor systems

To summarize, the physiological mechanisms of 1Hz rTMS are poorly understood up to now

1Hz rTMS: Effects on the Non-stimulated Side

- MEP amplitude in the non-stimulated motor cortex is enhanced
- Interhemispheric Inhibition is reduced (e.g. Gilio et al 2003):
  - IHI is measured by two stimuli, CS is applied to the opposite motor cortex than TS (ISI usually ~8ms)
  - MEP due to TS is reduced by preceding CS
  - After 1Hz rTMS, the effect of the CS is smaller
- SICF in the non-stimulated motor cortex is enhanced (Heide et al. 2006)
  → Interpreted as disinhibition of the non-stimulated side

(Heide et al. 2006)

(Gilio et al. 2003)
High-frequency rTMS

- rTMS at 5-20Hz increases the MEP amplitude; the effect lasts "for some minutes"
- High interindividual variability
- Effectiveness seems to increase with frequency, with the total number of stimuli, and with stimulation intensity
- Mono- is more efficient than biphasic stimulation (only tested for short trains for 3Hz & 5Hz; Arai et al 2005; Tings et al 2005)

(Q uartarone et al. 2005)

High-frequency rTMS: Physiology

- For higher stimulus numbers, spinal effects are likely to contribute to the overall facilitation
- Axonal excitability: rMT, aMT unaffected
- SICI is reduced
- 1st peak of SICF is enhanced
- ICF is enhanced (Wu et al. 2000)

- Modulations of SICI and ICF exhibit different time courses, hinting to a mixture of different facilitatory mechanisms that contribute to the MEP enhancement (Wu et al. 2000)

600 pulses 90%rMT
Theta-burst stimulation

Huang et al 2005:

- Basic building block: Pulse-triples (2 x 20ms pause) that are repeated at 200ms intervals (i.e., at EEG-theta-frequency)
- Continuous TBS: Triples are continuously repeated for e.g., 20s or 40s
- Intermittent TBS: Triples are arranged in 2s blocks with 8s gaps in between
- Stimulation intensity: 80% aMT
- Biphasic PA-AP (i.e., non-optimal current orientation)
- Phosphene threshold: Increased by cTBS, unaffected by iTBS (600 pulses at 80% PT) (Franca et al. 2006)

MEP changes after TBS (600 pulses)

Theta-burst stimulation: Optimizing Its Efficiency

- Effect increases with the number of stimuli
- Changing the current direction to biphasic AP-PA (i.e., optimal):
  - cTBS is not effective for 80% aMT, again effective for 100% aMT
  - iTBS is not effective for 80% & 100% aMT
- Voluntary contraction can reverse the effect of cTBS (Huang et al. 2008) → Make sure that target muscle is relaxed all the time!
Theta-burst stimulation: Physiology

- H-reflex unaffected: Intracortical origin
- Axonal excitability: cTBS slightly enhances rMT, leaves aMT unaffected
- cTBS reduces SICI, and enhances ICF (even though it reduces MEP amplitude)
- iTBS enhances SICI (even though it is facilitatory)
  - Likely explanation: cTBS reduces mainly I1-wave, while SICI&ICF test changes of the later I-waves
- NMDA antagonist memantine blocks the effects of cTBS & iTBS (Huang et al. 2007)

Safety of TMS (Wassermann 1998)

Contraindications
- Absolute: metal in cranium, increased intracranial pressure, intracardiac lines
- Relative: pregnancy, childhood, heart disease, cardiac pacemaker, medication pump, medications lowering the seizure threshold, epilepsy (or family history of), history of major head injury or stroke, brain neurosurgery, neurological & major psychiatric disorders
  - People with relative contraindications are normally excluded from studies targeting basic neuroscientific questions. However, they are sometimes included in clinical trials.

“Classical” rTMS protocols
- Depending upon the protocol and the targeted area, some studies reported transient impacts on neuropsychological, mood and motor test scores, hormone serum levels & lymphocyte concentrations
- Coil click is short, but intense: Transient increase in the auditory threshold may occur (use foam earplugs in case of doubt)
“Classical” rTMS protocols (cont’d)

- Relatively frequent side effects are local pain near the TMS coil, and transient headaches
- Main concern: Induction of seizures (7 reported cases up to 1996; all with >1Hz)
- After revising the safety guidelines, no new cases have been reported.
- Note: Maximal stimulation intensity for rTMS is given relative to MT, even for non-motor areas (exception: some studies targeting occipital areas defined the intensity relative to the phosphene threshold)

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>100</th>
<th>110</th>
<th>120</th>
<th>130</th>
<th>140</th>
<th>150</th>
<th>160</th>
<th>170</th>
<th>180</th>
<th>190</th>
<th>200</th>
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<tr>
<td>1</td>
<td>&gt;1800</td>
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<td>360</td>
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<td>27</td>
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<td>5</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>76</td>
<td>5.2</td>
<td>3.6</td>
<td>2.6</td>
<td>1.6</td>
<td>1.4</td>
<td>1.0</td>
<td>1.2</td>
<td></td>
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<tr>
<td>10</td>
<td>&gt;5</td>
<td>&gt;5</td>
<td>&gt;5</td>
<td>&gt;5</td>
<td>4.2</td>
<td>2.9</td>
<td>1.3</td>
<td>0.8</td>
<td>0.9</td>
<td>0.8</td>
<td>0.6</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>20</td>
<td>2.65</td>
<td>1.6</td>
<td>1.6</td>
<td>0.65</td>
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<td>0.25</td>
<td>0.15</td>
<td>0.2</td>
<td>0.24</td>
<td>0.24</td>
<td>0.12</td>
<td>0.12</td>
<td>0.08</td>
</tr>
<tr>
<td>25</td>
<td>1.28</td>
<td>0.84</td>
<td>0.4</td>
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<td>0.12</td>
<td>0.08</td>
<td>0.08</td>
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</table>

Numbers preceded by > are the longest durations tested. No after discharge or spread of excitation has been encountered with single trains of rTMS at these combinations of stimulus frequency and intensity.

Event-related TMS (single pulses, ppTMS or short rTMS trains)

- Known side effects: Local pain near the TMS coil, transient headaches, transient increase in auditory threshold (rarely)
- Considered to be “safe” in healthy subjects
- Note: Maximal stimulation intensity is usually not restricted by the safety guidelines for rTMS

New rTMS protocols (TBS, pp-rTMS)

- The safety guidelines for classical rTMS do not necessarily hold for new, more efficient protocols!
- e.g., Huang et al 2005: Stepwise increase of stimulation intensity & frequency to make sure that protocol is safe and the changes are transient.
- e.g., Thickbroom at al 2006: repetitive ppTMS (1.5ms spacing, repeated every 5s): Safe or not?
rTMS in the Treatment of Major Depression

- Experimental therapeutic applications of rTMS include the treatment of major depression, bipolar disorder, schizophrenia, anxiety disorders, movement disorders, tinnitus and pain.

Up to now, most studies (~37) have targeted **major depression**

- Most commonly, high-frequency rTMS is delivered to the left dorsolateral prefrontal cortex (IDLPC) repeatedly on a daily basis for several weeks.
- Hypothesis: rTMS normalizes prefrontal hypoactivity (e.g. Speer et al. 1999) and/or neurotransmitter release in connected subcortical areas (e.g. increased dopamine release in the striatum; Pogarell et al. 2007).
- Results up to now: rTMS has probably a moderate antidepressant effect (Loo 2008; in Wassermann et al. 2008); Note: A recent study with 127 patients didn’t find any effect (Herwig et al. 2007).

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**Table 40.1 (Cont.): Summary of sham-controlled studies of repetitive TMS for the treatment of depression**

<table>
<thead>
<tr>
<th>Publication</th>
<th>Study design</th>
<th>Sham method</th>
<th>n</th>
<th>Medication resistant</th>
<th>Repetitive TMS treatment parameters</th>
<th>Mean % change, HRSD*</th>
<th>No. of responders*</th>
<th>Adverse events*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herwig et al. 2006</td>
<td>Add-on to venlafaxine or mirtazapine. Parallel: L active L sham</td>
<td>Active coil at 45° over L temporal cortex, 90% MT</td>
<td>127</td>
<td>No</td>
<td>10 Hz, 112%, 15 days x 2000 stim</td>
<td>Active: 40%</td>
<td>Active: 20/69</td>
<td>Active: headache (3/62), scalp pain (1/62), nausea (1/62), Sham: headache (1/65), dizziness (1/65), scalp pain (2/65)</td>
</tr>
<tr>
<td>O’Reardon et al. (2007)</td>
<td>Parallel: L active L sham Antidepressants added during 3 week taper</td>
<td>Placebo coil</td>
<td>303</td>
<td>Yes</td>
<td>10 Hz, 89±4, 120%, 30 days x 1000 stim, 32 weeks over 3 week taper</td>
<td>End 6 weeks: Active: 23%</td>
<td>Sham: 13%</td>
<td>End 6 weeks: Active: 29%</td>
</tr>
</tbody>
</table>

adapted from (Loo 2008; in Wassermann et al. 2008)
Localization of the target area for rTMS

- Cortical area showing tinnitus-related hyperactivity was determined by $^{15}$O]H$_2$O PET using 2 scans: rest (‘tinnitus-ON’) vs. injection of lidocaine (‘tinnitus-OFF’)

Testing the immediate effects of 1Hz-rTMS (120% rMT, max. 30min) in a placebo-controlled crossover design (n=8):

- **Sham condition**: Stimulation at the lower occiput; Coil-ear distance individually matched to result in equal noise levels; Aversive sensations comparable for verum & sham

- **Result**: Subjective ratings indicated a sign. decrease in tinnitus intensity for verum, but not for sham stimulation

Testing the effects of 20 days of 1Hz-rTMS (120% rMT, 30min per session) in a placebo-controlled crossover design (n=8):

- Tinnitus-related distress was assessed using tinnitus questionnaire (TQ) scores

- **Result**: Sign., but moderate reduction in TQ scores immediately after the 20 days; all except one patient returned to baseline within 2 weeks after stimulation end