

Study on repetitive Transcranial Magnetic Stimulation (rTMS)

Bert van Zanten, Carlijn Hoekstra, Huib Versnel



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Utrecht

Overview



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- Tinnitus and MRI are introduced bij previous speakers
- Magnetic Stimulation and Transcranial Magnetic Stimulation
 - *Technical background*
 - *Earlier applications*
 - *Applied as tinnitus treatment*
- Literature reports on TMS in tinnitus
- The UMCU study on rTMS in tinnitus
- Summary.

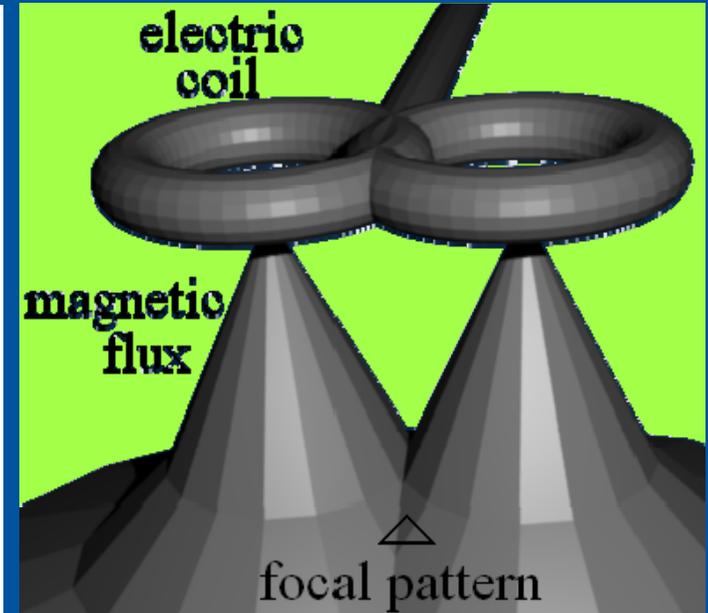
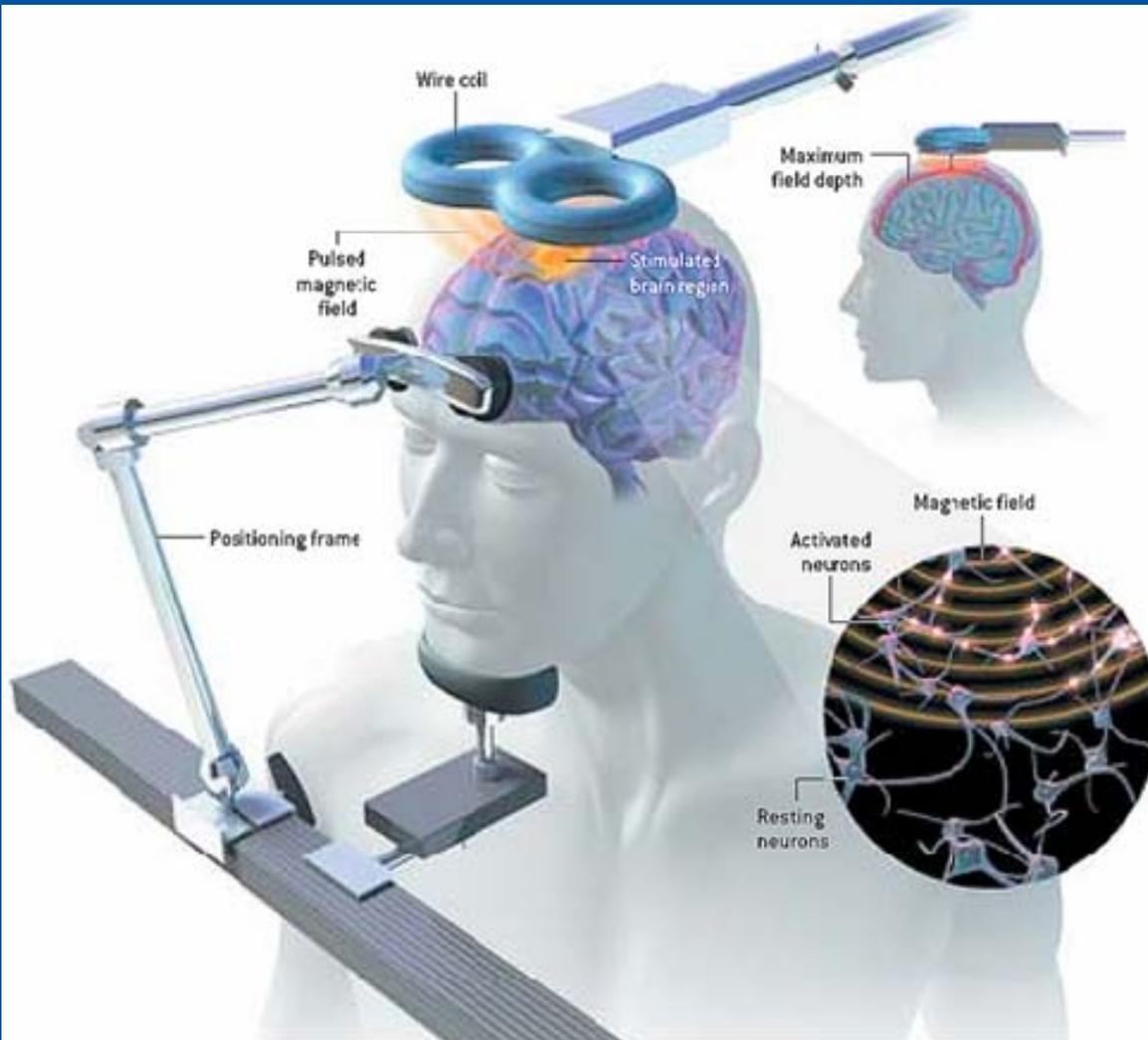
Magnetic Stimulation (MS) Technical Background



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- Physics: if a magnetic field in an electrically conductive medium (body tissue) changes, then in this medium electric loop currents are generated (eddy currents) during the change. This phenomenon is widely used, for instance in cooking by induction. Here it is applied for generating electric potential field and current in body tissues.
- MS was developed in electro-neurophysiology for stimulation non-invasively nerves in extremities, in order to activate muscles.
- From 1985 this was also used for Transcranial stimulation in the motor cortex (TMS). The stimulus gives a local electro-schock that causes excitation or inhibition of nerve cells and tracts.

TMS set up.



TMS application



- The 8-shaped coil is positioned over the skull. A very short (2-5 ms) and very strong electric current (4000 A) is fired through the wires in the 8-shaped coil.
- When fired the short magnetic field pulse generates electric potential fields and currents in the brain tissue.
- This can lead to excitation or inhibition of nerve cells and nerve tracts.
- Which has been used for therapy in patients suffering from depression, auditory hallucinations and/or tinnitus, post-traumatic stress syndrome and for supporting recovery of stroke,



Literature in TMS in general

- Review: Wassermann EM & Zimmermann T. Transcranial magnetic brain stimulation: Therapeutic promises and scientific gaps. *Pharmacology & Therapeutics* xxx (2011) xxx–xxx. Behandelresultaten:
 - *Depression (+)*
 - *Schizophrenic Auditory Hallucination & Tinnitus (-+)*
 - *Anxiety Disorders (OCD and PTSD) (+-)*
 - *Neurodegeneration (Parkinson and Alzheimer) (-+)*
 - *Neurorehabilitation (in acquired brain damage like stroke) (+-)*
 - *Migraine and chronic pain (+)*
- *“Nevertheless, we expect TMS to continue attracting the interest of innovative clinicians and scientists and to continue to advance. There are many potential opportunities to improve TMS treatment, in addition to those mentioned above.”*

TMS co-effects



- The strong magnetic pulse
 - *passes through muscle and nervous tissue on the outside of the skull, thereby activating them*
 - *Deforms the casing of the coil. This shrinks and subsequently expands a little, which generates a strong click sound*
- So the treated patient feels the muscle activity and hears the click sound. This makes it not simple to blind the treatment for the patient.
- In patients with a history of epilepsy, TMS might cause an insult (<20 cases described in the literature)

TMS parameters, most important ones



- The exact position over the skull. Where to position the coil, in order to stimulate the patient's auditory cortex. This is done by neuronavigation in many studies, also in the UMCU-study
- The current in the coil, or the magnetic field strength. Maximum field strengths of 1-3 T are used. The strength for the individual patient is referenced to the "motor threshold". This is the current that evokes a hand muscle contraction 50% of the times if fired in a position over the motor cortex controlling the hand. The commonly used strength is 100-120% of the motor-threshold.
- Is the stimulation given once or more? Pulse repetition rates of 1-50 Hz are used. The number of pulses given is between 1 and 3000, repetitive-TMS, rTMS

The motor threshold



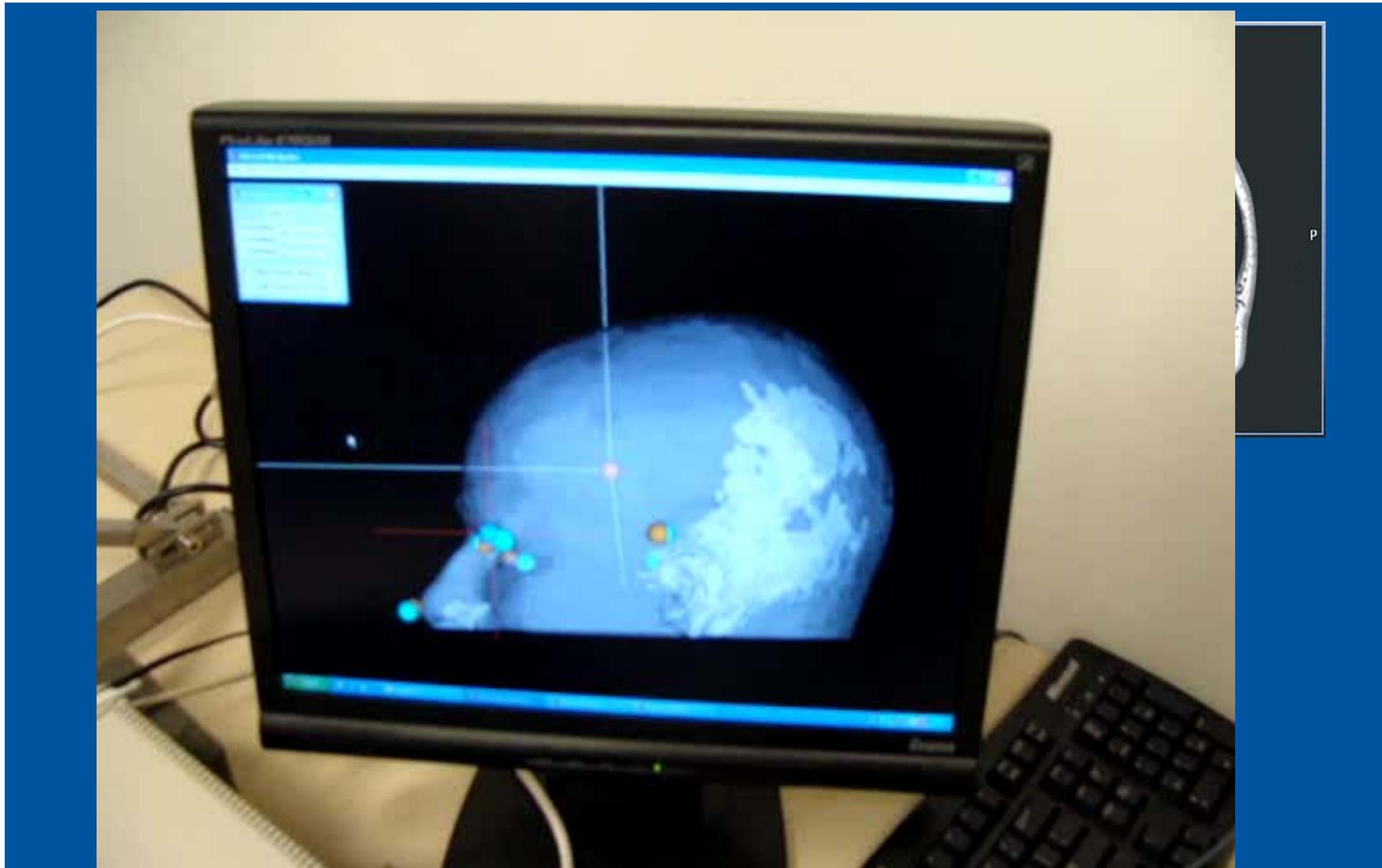
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NeuroNavigation: NeNa [Neggers et al., 2004]



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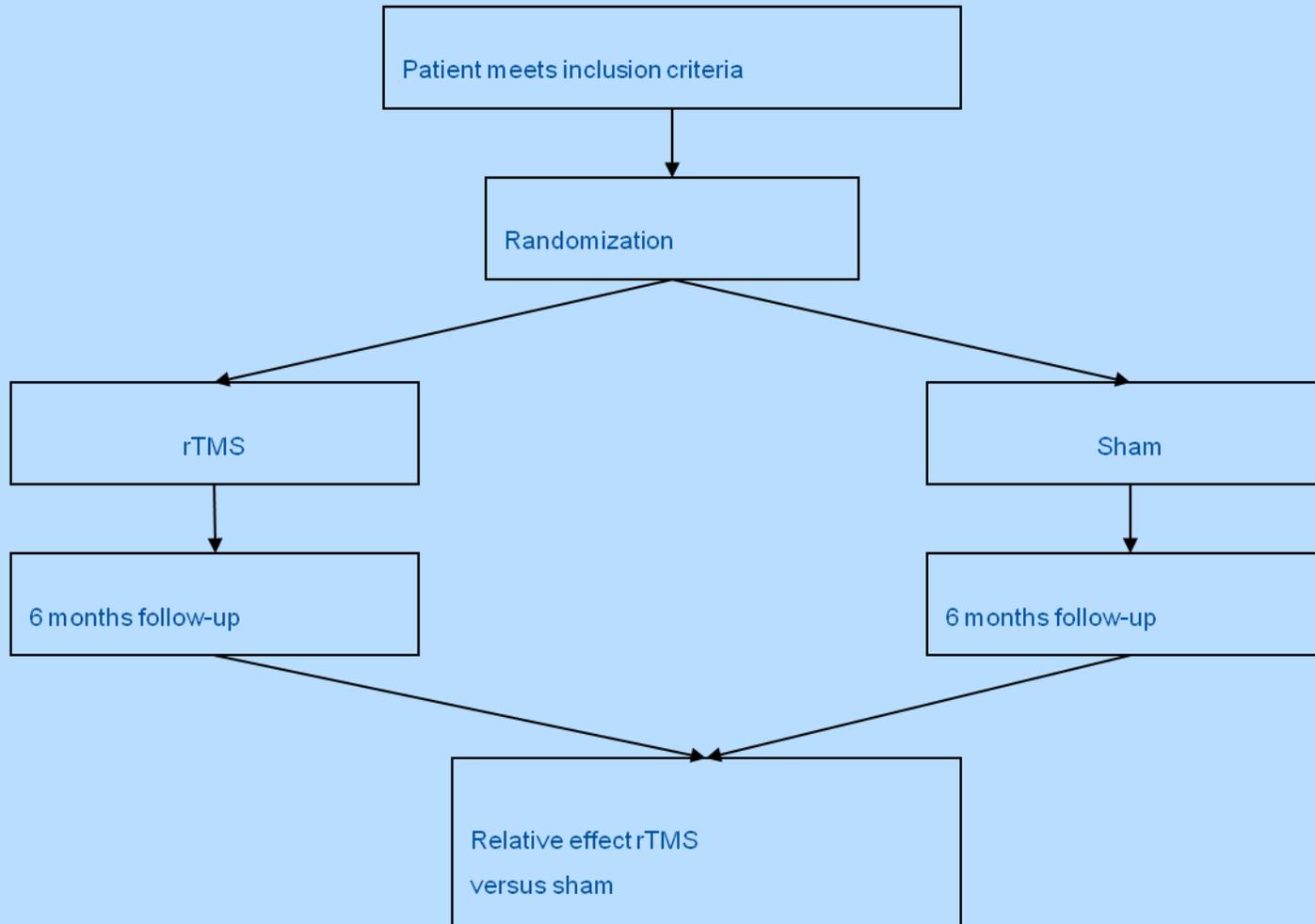




Literature on rTMS in tinnitus patients

- 4 research regions active with 2 or more papers
 - 13 Germany (*Kleinjung, Langguth, Schlee, Plewniak, ...*)
 - 9 Belgium (*De Ridder, Vanneste, ...*)
 - 3 Arkansas (*Mennemeier, ...*)
 - 2 New York
- Low rate rTMS, 1 Hz repetition, can inhibit overactive brain regions, like found in the auditory cortex of tinnitus patients. BUT it can work for a short period only, weeks to months
- It is difficult to blind the patient and impossible to blind the therapist
- There is a lack of prospective placebo controlled blinded studies
- The best designed study (Khedr et al 2010) –contralateral stimulation in unilateral tinnitus– did not show the low rate preference.

The UMCU rTMS study design 1



The UMCU rTMS study: inclusion criteria



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- Patient having gone through the UMCU-tinnitus group's diagnostic protocol (multidisciplinary – ENT/Audiology/Psychology/Social Work)
- Chronic non-fluctuating tinnitus (for over 2 months)
- > 18 yrs of age

The UMCU rTMS study: exclusion criteria



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- Treatable possible causal conditions (like high blood pressure)
- Positive relation with epilepsy, also in the family, or use of drugs that might lower the seizure threshold
- Active migraine
- Structural brain changes (whole brain MRI)
- Psychiatric disease
- Severe internal or heart disease
- Non-removable metal objects in or at the body
- Pregnancy
- Abuse of substances (alcohol, drugs)
- Prior TMS treatment

The UMCU rTMS study: outcome measures



Evaluation method		Day							Week							
		0	1	2-4	5	6-11	12	13-90	5	9	13	17	21	25		
	Diagnostic phase															
Self assessment scales		X	X	X	X	X	X	X	X		X	X	X	X	X	X
TQ, THI		X			X		X		X		X					X
HADS		X			X		X		X		X					X
Clinical characteristics	X															
Tinnitus analysis: (PM + LM)		X			X		X				X					X
Tinnitus analysis: (MML + RI)		X														X
Audiometry	X				X		X		X		X					X

The UMCU rTMS study: treatment



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The UMCU rTMS study: present status



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- All patients included and rTMS/sham treated
- Follow-up period runs through november 2011
- Than blinding will be broken for the main investigator

Summary



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- rTMS can induce temporarily plastic changes in the brain and thereby alleviate the burden due to depression, migraine and may be some other conditions
- The scientific evidence that rTMS can temporarily alleviate the tinnitus burden is still not very strong, due to lack of well designed studies
- The UMCU-study is designed to provide the evidence that the rTMS-treatment-effect is stronger than the placebo-effect, or not.
- The final results will be presented in a coming NVA-meeting