Brain Outcome after Cardiac Arrest Modifying working memory with non-invasive brain stimulation - A series of SCEDs

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Aim of the studyThis is a proof-of-concept study to investigate the effects of rTMS (iTBS protocol) on working memory of people with memory impairments after a cardiac arrest in the past. We propose a series of single case experimental design (SCED…

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON56290

Source
ToetsingOnline

Brief title
BROCA-NIBS

Condition

- Other condition
- Heart failures

Synonym
cognitive impairment, out of hospital cardiac arrest

Health condition

cognitieve stoornis

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Hartstichting

Intervention

Keyword: Cardiac arrest, rTMS, SCED

Outcome measures

Primary outcome

The main study outcomes are performance on the N-back task with regard to

accuracy.

Secondary outcome

Secondary study parameters:

-Reaction time in milliseconds.

-Changes in an individuals ability to detect signals expressed as sensitivity

(d*), where d* = z(false alarm rate) - z(hit rate).

Other study parameters include:

- Information regarding the cardiac arrest (date cardiac arrest, the cause,

length of hospital stay).

- personal information (sex, age, level of education, working hours and

profession).

- performance on the Stroop, Digit span, and trail making test during the

screening.

Study description

Background summary

Increasing number of cardiac arrest survivors with cognitive impairment
The worldwide incidence of out of hospital cardiac arrest (OHCA) is estimated at 50-55 events per 100.000 citizens a year (Berdowski, Berg, Tijssen, & Koster, 2010; Waalewijn, De Vos, & Koster, 1998). The survival rate of OHCA with attempted resuscitation lies between 10% and 25%, but differs a lot between regions (Dyson et al., 2019; Nichol et al., 2008; Yan et al., 2020). In the Netherlands, a large network of civilian volunteers with basic life support skills has been set up, the density of easily accessible automated external defibrillators has increased, and the healthcare system has been improved. Consequently, the survival rate of OHCA has increased in the past decades from 9.1% (1995) to 23% (2021) (Beesems, Stieglis, & Koster, 2012; Berdowski, Waalewijn, & Koster, 2006).

In sharp contrast with increased survival, neurological and cognitive outcome of cardiac arrest survivors have changed only marginally over the past twenty years. Still, approximately half of the people who survive a cardiac arrest have enduring cognitive impairments (Boyce & Goossens, 2017; V. Moulaert, Verbunt, van Heugten, & Wade, 2009; Zook et al., 2021). These impairments arise because of a temporary deprivation of oxygen- and glucose-rich blood to the brain during the arrest. This causes ischemic-hypoxic brain damage, which may lead to lasting cognitive impairment (Sandroni, Cronberg, & Sekhon, 2021). In cardiac arrest survivors, these impairments are most prevalent in the domains of memory, attention, and executive functioning (Cronberg et al., 2020; V. Moulaert et al., 2009).

Current treatment of OHCA
Currently, there are no treatments of proven benefit for cognitive impairment after cardiac arrest. Moulaert et al. (2015) showed that recognition of and attention for cognitive impairment after a cardiac arrest have a positive effect on the long-term quality of life of patients. Cognitive rehabilitation therapies or other treatments to improve cognitive functions could possibly enhance these positive effects. This implies a need for evidence of efficacy of treatments to improve cognitive functioning in this group of patients.

Non-invasive brain stimulation as treatment option
Promising new treatment options are arising in the field of non-invasive brain stimulation (NIBS). Repetitive transcranial magnetic stimulation (rTMS) is a form of NIBS that has been studied in a wide range of patient groups (Lefaucheur et al., 2020). rTMS is a non-invasive way to induce an electrical current in the brain through electromagnetic induction (Lefaucheur et al., 2020). A magnetic field generated by the TMS coil passes through the skull,

inducing an electric field. This electric field causes a current to flow within the brain. The presumed final common path of rTMS is modification of brain plasticity by stimulation of intrinsic plasticity mechanisms such as synaptic changes by promoting long-term potentiation (LTP) or long-term depression (LTD) (Klomjai, Katz, & Lackmy-Vallée, 2015). Faciliatory stimulation protocols, such as high-frequency rTMS, generally strengthens excitatory brain circuits. On the other hand, inhibitory protocols, such as low frequency rTMS, generally target inhibitory circuits and downregulate excitability and activity. In the last 15 years, a specific rTMS protocol called intermitted theta burst stimulation (iTBS) has been used a lot (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). Advantages of this protocol is that it is shorter than the regular rTMS protocol (190 seconds instead of 20 minutes). TBS paradigms have large effect sizes and acceptable interinvidusal variability compared with traditional rTMS paradigms (Huang et al., 2005).

TMS as a potential cognitive treatment

rTMS has been studied for, amongst other, motor and cognitive recovery after stroke (Corti, Patten, & Triggs, 2012; Zhang et al., 2021). Many studies show that rTMS can improve global cognitive functioning (Q.-M. Chen et al., 2021; H. Li et al., 2021; W. Li et al., 2022; Liu et al., 2020; Lu, Zhang, Wen, & Sun, 2015; Tsai, Lin, Tsai, Kuo, & Lin, 2020; Wang et al., 2021) and memory functions (J. Li et al., 2016; Lu et al., 2015; Yin et al., 2020) after stroke. RTMS also improved working memory and executive working performance compared to sham stimulation in traumatic brain injury patients (Ahorsu, Adjaottor, & Lam, 2021; Hoy et al., 2019). TMS has been used for almost 40 years and is a generally approved and accepted therapy by the FDA for treatment of psychiatric disorders (e.g. depression) (Cohen, Bikson, Badran, & George, 2022). Various TMS protocols have been developed and approved by the FDA. The dorsolateral prefrontal cortex (DLPFC), is related to working memory processes, and therefore a common target in those studies.

Safety

The safety of rTMS is well studied and the overall safety profile is good (Loo, McFarquhar, & Mitchell, 2008). The study of Bakker et al. (2015) did not encounter any seizure or other serious adverse event in over 7912 runs of stimulation (4274 rTMS and 3638 iTBS runs). A recent meta-analysis reported that a seizure has only occurred once with TBS to date, and it accounts for the crude risk of seizure per session of 0.02%. The overall crude risk of mild adverse events was estimated to be 1.1%, and these findings were comparable with high frequency rTMS protocols (Oberman, Edwards, Eldaief, & Pascual-Leone, 2011).

rTMS and working memory assessed with the N-back task

The N-back task is a commonly used and valid task to assess working memory. In the N-back task a subject is presented with a sequence of stimuli, and the task

consists of indicating when the current stimulus matches the one from n steps earlier in the sequence. The load factor n can be adjusted to make the task more or less difficult. Outcome variables of the N-back task include accuracy, reaction times, and working memory accuracy (d*). D* is the standardized difference between the means of the signal present and signal absent distributions. The advantage of d* is that it is robust to the response bias.

rTMS studies assessing n-back performance in healthy controls and patient populations have shown mixed results (Boggio et al., 2006; Esslinger et al., 2014; Teo, Hoy, Daskalakis, & Fitzgerald, 2011), Brunoni and Vanderhasselt (2014) conducted a systematic review and meta-analysis on working memory improvement, based on the n-back task, with non-invasive brain stimulation of the dorsolateral prefrontal cortex. Based on 14 experiments they found that participants (healthy and people with schizophrenia) after receiving active rTMS compared to those receiving sham stimulation, were faster and more accurate on the N-back task with a medium effect size. They also found that non-invasive brain stimulation techniques showed superior improvement in clinical populations on the N-back task.

Single Case Experimental Design
Patients with cognitive impairment after OHCA are a heterogeneous population. This means that they differ on many characteristics, such as baseline cognitive functioning and severity and type of cognitive impairment. A classical clinical trial comparing groups of patients is therefore not an ideal study design. First, because of the heterogeneity it is not expected that one outcome measure is suitable for all included patients. Secondly, large numbers of patients would be needed for sufficient statistical power in a group-design trial, limiting the feasibility of the study.

A promising study design that is increasingly used in the field of rehabilitation is the single case experimental design (SCED). In this design the unit of intervention and data analysis consists of a single or a few cases that provide their own intervention and control data. A main characteristic of this design is that the outcome

Study objective

Aim of the study
This is a proof-of-concept study to investigate the effects of rTMS (iTBS protocol) on working memory of people with memory impairments after a cardiac arrest in the past. We propose a series of single case experimental design (SCED) studies to study the causal relationship between a manipulated independent variable (iTBS yes or no) and our outcome variable (working memory) in a relatively small number of participants.

Primary objective

The primary objective of the present study is to test whether iTBS over the left dorsolateral prefrontal cortex enhances the accuracy of working-memory performance, defined as the percentage hits minus the percentage false alarms, on the N- back task, in participants with working memory impairment after a cardiac arrest.

Secondary Objectives
- To estimate iTBS effects on reaction time (RT).
- To estimate iTBS effects on an individual*s ability to detect signals expressed as changes in sensitivity (d*)

Study design

This study will consist of single blinded replicated randomized SCED withdrawal designs in nine participants at the NIBS laboratory at Maastricht University. The intervention contrast will be iTBS versus sham stimulation. The reason for adding sham stimulation is to minimize placebo effects of rTMS. The study will be split up in two days. During the first day the eligibility of the potential participant will be determined, which takes approximately 1 - 1,5 hour. On the second day the experiment will be conducted, which takes approximately 200 minutes.

Intervention

The participant will receive sham iTBS. The participant is not aware what type of stimulation he/she receives. Directly after stimulation the participant is asked to perform the N-back task on a computer for 8-12 minutes, with a small break of 30 seconds after every 2 minutes. After this, the participant can rest for approximately 45 min (making sure there is at least 50 minutes between stimulation and the next N-back session). The participant can do his / her personal relaxing activity during this break. Then the same procedure is repeated with active, sham, and active iTBS. The total time of the experiment session will be approximately 200 minutes.

Study burden and risks

Potential risk: The potential risks are the side effects of TMS, including common side effects: headache, scalp discomfort, tingling or twitching of the facial muscles, and light-headedness. Serious side effects are very rare and may include: seizures.

Potential benefit: Working memory performance may be enhanced.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- You are between 18 and 75 years old
- You have had a cardiac arrest from three months to five years before the start of the study

Exclusion criteria

-being pregnant
-A medical history of a neurological condition that may affect memory beyond cardiac arrest
-Having a metal implant in or close to the head
- Have a medical history with epilepsy or a family member who has it.

- Have a pacemaker or ICD

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	18-01-2024
Enrollment:	9
Type:	Actual

Medical products/devices used

Generic name:	transcranial magnetic stimulator
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	28-09-2023
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL84433.068.23
Other	The study will be registered at Clincaltrials.gov

Study results

Date completed: 13-06-2024

Summary results
Trial ended prematurely