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Non-invasive brain stimulation improves neglect and functional outcome after stroke

Submission date
25/04/2018

Recruitment status
No longer recruiting

Registration date
14/05/2018

Overall study status
Completed

Last Edited
15/04/2019

Condition category
Circulatory System

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Neglect, which is defined as a failure to attend to the side opposite a brain lesion, frequently occurs after stroke. Neglect severely impairs recovery after stroke, i.e. the outcome is worse than without neglect. The aim of this study is to find out whether non-invasive brain stimulation compared to placebo/sham stimulation can accelerate neglect recovery and thereby improve functional outcome.

Who can participate?
Stroke patients who have suffered from a right hemispheric stroke with and without left sided neglect

What does the study involve?
All participants receive standardized neurorehabilitation. Participants are randomly allocated to one of three different groups to receive either sham stimulation, 8 trains of non-invasive brain stimulation, or 16 trains of non-invasive brain stimulation within a period of 4 weeks. Before and after non-invasive brain stimulation several tests are performed to measure neglect and recovery after stroke.

What are the possible benefits and risks of participating?
A faster neglect and functional recovery is expected in participants who receive non-invasive brain stimulation compared to sham stimulation. No negative side effects are expected from the non-invasive brain stimulation.

Where is the study run from?
Luzerner Kantonsspital (Switzerland)

When is the study starting and how long is it expected to run for?
April 2014 to February 2017

Who is funding the study?
Swiss National Science Foundation

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
320030

Study information

Scientific Title
cTBS reduces disability by ameliorating neglect – a randomized, sham controlled and double-blind study

Study objectives
In the present study the trialists aimed to clarify the role of the undamaged hemisphere in neglect recovery by inhibiting the PPC which is a critical node of the dorsal attentional network (e.g. Corbetta and Shulman, 2011). They hypothesized that if the undamaged PPC plays indeed a compensatory role, one would expect a worsening of neglect recovery after inhibition of the PPC, at least in some outcome measures and/or in some patients

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Kantonale Ethikkommission Bern (KEK), 14/04/2014, KEK Nr. 076/12
2. Ethikkommission Nordwest- und Zentralschweiz (EKNZ), 14/04/2014, EKNZ 11011

Study design
Single-center randomized double-blind sham-controlled design

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Right hemisphere stroke patients with neglect

Interventions
All patients received, besides neurorehabilitation, a 4-week standardized training protocol which included a daily smooth pursuit training, which is a specific effective neglect training (Hopfner et al. 2015). After randomisation, three different groups received either a sham stimulation, 8 trains of cTBS, or 16 trains of cTBS intervention within a period of 4 weeks. Continuous theta burst stimulation (cTBS) is an inhibitory repetitive transcranial magnetic stimulation (rTMS) protocol. The target region for stimulation is the left posterior parietal cortex (PPC). Thirty patients without neglect serve as a control group.

Intervention Type
Behavioural

Primary outcome measure
Neglect measured using the Catherine Bergego Scale (CBS) was chosen as a primary outcome measure since the ecological validity in a rehabilitation facility is high (Azouvi, 2016). It quantifies the influence of spatial neglect-related deficits in the ADL. The CBS consists of 10 items, such as grooming, etc. Items are scored on a 0-to-3 scale, with 0 indicating no neglect and 3 indicating severe neglect (range, 0–30). The CBS was completed by nurses, who were blinded to the protocol, observing a patient performing different ADL. Primary and secondary outcomes are all measured at admission to and discharge from inpatient neurorehabilitation (mean length of stay 50 days). The primary outcome (neglect) is additionally measured 3 months after discharge from inpatient neurorehabilitation, to analyse whether post-stroke time and length of stay is a predictive factor for the positive cTBS effects.

Secondary outcome measures
Measured at admission to and discharge from inpatient neurorehabilitation (mean length of stay 50 days):
1. Body representational neglect tested by means of the Fluff Test (Cocchini et al. 2001). Hereby,

twenty-four sticky notes (12 left, 12 right) are attached to the participant's body (trunk and thighs) and have to be removed with one's eyes closed. In the present study, the performance was measured by the total number of removed sticky notes on the left side of the body.
2. Free visual exploration measured by the Two Part Picture Tests in the near and far space. The Two Part Picture Test is a commonly used detector for screening of visuospatial neglect (Brunila et al., 2003). In this assessment two simultaneously presented pictures have to be described. In both pictures a room is shown containing 10 items each (10 items in the left picture and 10 in the right picture). Correctly named items were scored one point each. Asymmetry-Score was calculated using the number of correct items on the left divided by the total number of correct items (Asymmetry Score= ((correct items left)/(correct items total)); Brunila et al., 2003). The test was conducted twice: once in the near space and once in the far space. For the near space the pictures were shown in reading distance on an A3 landscape format paper. Hereby, the test was placed on the table centrally to the patient's midsagittal axis. For the far space the same pictures were presented on a 685 cm x 1215 cm flat screen (LED) monitor at a distance of two meters.
3. Visual search behaviour assessed by the bird cancellation task (Hopfner et al. 2015). 64 targets (birds displayed as flying straight to the participant) and 96 distractors (birds displayed as flying in other direction) were shown on a 685 cm x 1215 cm touch screen (Hopfner et al. 2015). The patient was seated comfortably in 0.5 meter distance to the screen. Targets had to be identified by tapping them with an arm extension consisting of a stick with a rubber tip. The center of mass of the spatial distribution of correct identified targets was used to calculate the Center of Cancellation (CoC) (Rorden & Karnath, 2010). Since the inter-individual as well as an intra-individual variability in neglect tests is high (Lundervold et al., 2005) and a battery is more sensitive than any single test alone (Azouvi et al., 2002) a composite score was derived from these neglect tests. Consequently, the patient's individual performance for each test was calculated between admission and discharge of hospital. The mean out of these four test performances was calculated resulting in an individual composite score.
4. General functional outcome measured by the Functional Independent Measurement (FIM) which is a standardized assessment for ADL, including 18 items rated on a 7-point scale: 1 = total assistance; 2 = maximal assistance; 3 = moderate assistance; 4 = minimal contact assistance; 5 = supervision or set-up; 6 = modified independence; and 7 = complete independence (Keith et al. 1987). The FIM consists of 13 motor (or physical) items and 5 cognitive items. The scores range from 13 to 91 for the motor subscale and from 5 to 35 for the cognitive subscale.
5. Functional outcome assessed using the Lucerne ICF based Multidisciplinary Observation Scale (LIMOS). The reason why LIMOS was included as an additional measure was that it's has been shown to be more responsive than FIM (Vanbellingen et al. 2016). The LIMOS include 7 chapters incorporating 45 domains: 1) Learning and applying knowledge, 2) General tasks and demands, 3) Communication, 4) Mobility, 5) Self-care, 6) Domestic life and 7) Interpersonal interactions and relationships (for more details see Ottiger et al. 2015, Vanbellingen et al. 2016). Every item is rated on a 5-point scale (1 -5), so that total scores can range from 45 to 225. The 5-point scale for the LIMOS is defined as follows: 1 = patient is not able to fulfil a task or need assistance up to 75 % (corresponding to "complete"); 2 = patient is able to fulfil tasks with assistance of 25 % to 75 % (corresponding to "severe"); 3 = patient is able to fulfil tasks with assistance less than 25 % or under supervision (corresponding to "moderate"); 4 = patient is able to fulfil tasks independently but needs more time and/or with auxiliary materials, aids (corresponding to "slight"); 5 = patient is able to fulfil tasks independently (corresponding to "none"). A major advantage of the LIMOS is that upper limb in ADL is assessed. Consequently, we were able to validate a modified upper limb LIMOS score, LIMOS upper limb, which consists of 5 items, i.e.: lifting up and carrying objects, fine hand use, hand and arm use, washing the upper body, putting on and taking off clothes in the upper body. Score ranges from 5 (totally dependent) to 25 (independent).

Overall study start date
01/04/2014

Completion date
01/02/2017

Eligibility

Key inclusion criteria
Sixty patients (aged between 27 - 86 years, mean = 66.4, SD = 14.2; 24 women) with a first, right-hemispheric stroke (RHS) participated in this study:
1. Thirty neglect patients entered the randomisation procedure
2. Thirty patients without neglect served as a control group

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
30

Total final enrolment
60

Key exclusion criteria
1. Patients suffering from major psychiatric diseases and other comorbidities (drug and alcohol abuse)
2. For the patients participating in the TMS study a history of epilepsy and metallic implants were further exclusion criteria (Rossi et al. 2009)

Date of first enrolment
01/04/2014

Date of final enrolment
01/01/2017

Locations

Countries of recruitment
Switzerland

Study participating centre

Luzerner Kantonsspital
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Sponsor information

Organisation
Swiss National Science Foundation

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Sponsor type
Research organisation

ROR
https://ror.org/00yjd3n13

Funder(s)

Funder type
Research organisation

Funder Name
Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung

Alternative Name(s)
Schweizerischer Nationalfonds, Swiss National Science Foundation, Fonds National Suisse de la Recherche Scientifique, Fondo Nazionale Svizzero per la Ricerca Scientifica, Fonds National Suisse, Fondo Nazionale Svizzero, Schweizerische Nationalfonds, SNF, SNSF, FNS

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Switzerland

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal.

Intention to publish date
01/10/2018

Individual participant data (IPD) sharing plan
Participant data will be available upon request to researchers who provide a methodologically sound proposal, beginning 9 months and ending 36 months following article publication. Proposals should be directed to thomas.nyffeler@gmail.com.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/04/2019	15/04/2019	Yes	No