Third congress on
NeuroRehabilitation and Neural Repair

From Science to Evidence-based Practice
22-23-24 May 2019 | Maastricht, the Netherlands

Neuronavigated Theta Burst Stimulation (TBS) in Chronic post-Stroke Aphasia

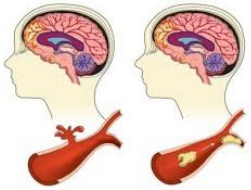
Anastasios M. Georgiou, PhD, Maria Kambanaros, PhD, Ioannis Phinikettos, PhD

Department of Rehabilitation Sciences, Cyprus University of Technology, Cyprus

Aphasia

- acquired language disorder

❑ injury to the brain – most typically **stroke** in the left hemisphere



haemorrhage **ischemia**

Overall, more than 1/3 of post stroke patients

1/3: improvement within the first 4 weeks

1/2: improvement within the first **6 months**

(Heiss & Thiel, 2016)

- Spoken expression
- Spoken comprehension
- Reading
- Writing

Mild → **Severe**

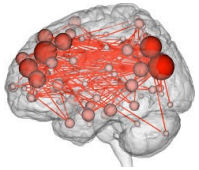
non-fluent: **reduced speech output**

fluent: **speech output is not reduced, but speech is incoherent**

Transcranial Magnetic Stimulation (TMS)

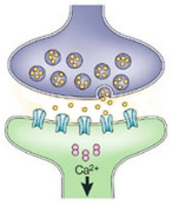
- ✓ non-invasive
- ✓ safe (Rossi et al., 2009)

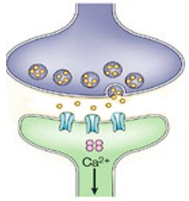
- ✓ investigation of brain areas responsible for specific functions (e.g. language)



- ✓ stimulation of areas of interest for treatment

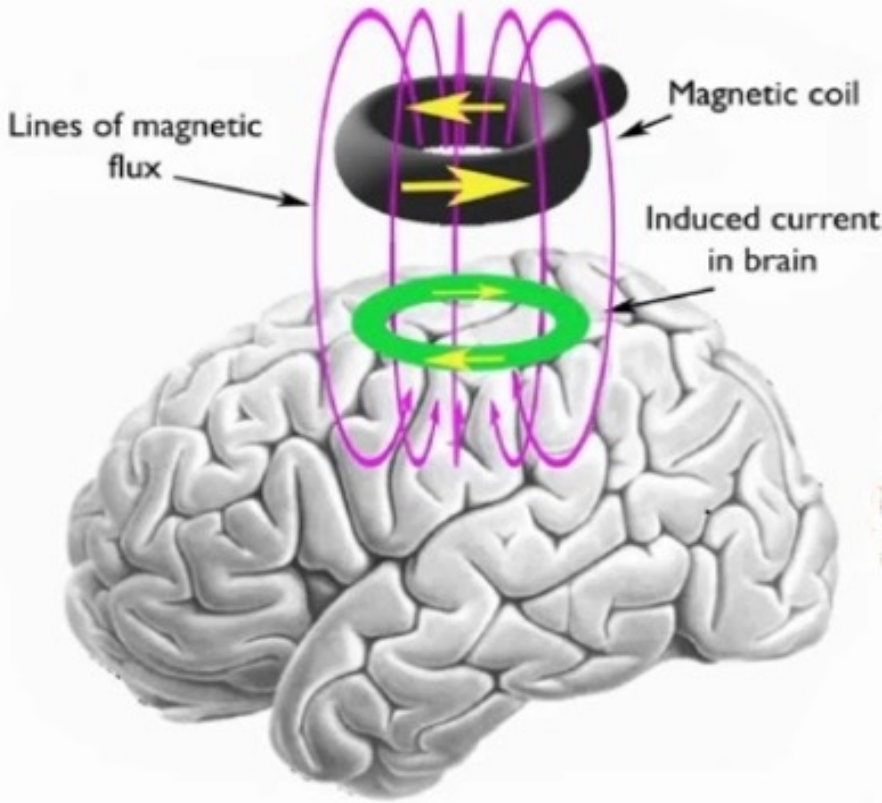
✓enhancement of neuroplasticity
✓TMS after-effects represent changes in synaptic efficacy (LTP/LTD)





Basic Principles

electromagnetic induction (1831)

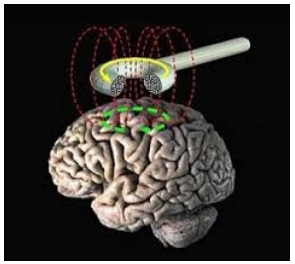


- **time-varying current (value/direction) → magnetic field → electric field and hence a secondary <u>current within nearby conductors</u>**
  - there is always electric current flowing through neurons
    - **TMS stimulates neurons that act as conductors !**

- **the more current in the coil, the stronger the magnetic field**

TMS with Speech & Language Therapy (SLT) leading to language gains in post stroke aphasia

- Naming (e.g. Hu et al., 2018; Rubi-Fessen et al., 2015)
- Repetition (e.g. Barwood et al., 2013; Seniow et al., 2013)
- Comprehension (e.g. Hu et al., 2018)
- Naming reaction time (e.g. Waldowski et al., 2012)
- Spontaneous speech (e.g. Hu et al., 2018)
- Aphasia profile (Rubi-Fessen et al., 2015; Heiss et al., 2013)



- **significant inconsistencies between studies regarding type & intensity of SLT and TMS**
  - 30-minute SLT, post-TMS, focusing on **naming** (Hu et al., 2018)
  - 45-minute SLT, post-TMS, focusing on **word retrieval** (Rubi-Fessen et al., 2015)
  - 60-minute SLT, post-TMS, twice a week focusing on **expressive skills** (Wang et al., 2014)

TMS as a standalone treatment for aphasia post-stroke

No SLT given

English speakers with chronic aphasia post-stroke

Barwood et al. (2013)

- 6 participants
- 10 sessions of TMS
  - **Improvement**
    - ✓ Naming
    - ✓ Repetition
    - ✓ Length of utterances
    - ✓ Picture description tasks (i.e. picture description complexity and length of utterance)
      - **Up to 12 months post-treatment**

Standardized language measures

Medina et al. (2012)

- 5 participants
- 10 sessions
  - ✓ **Improvement**
    - ✓ closed-class words of discourse productivity
  - ✓ **Trends**
    - ✓ unique words, unique nouns, unique verbs, open-class words and correct information units
      - **2 months post-treatment**

Functional communication outcome measure

Objectives

To investigate the effectiveness of Transcranial Magnetic Stimulation (TMS) as a standalone treatment for chronic aphasia post-stroke

Methods

Single Subject Experimental Design (SSED)

- ✓ small sample sizes + heterogeneous participants
- ✓ no control group → each participant provides their own control for purposes of comparison
  - **2 pre-treatment assessments (baseline)** for performance on language and cognition (problem solving skills) → level of performance prior to treatment & rule out spontaneous recovery (Howard, Best & Nickels, 2015)

- the optimal number of pre-therapy probes is currently not clear
  - 2 probes are sufficient to provide an estimate of both **level of performance** and **rate of change** (Howard, Best & Nickels, 2015)

Participant selection

Inclusion Criteria

- 18-75 y.o.
- Native speakers of (Cypriot) Greek
- First ever stroke (ischemic/haemorrhagic) in the left hemisphere
- Chronic aphasia (>6 months post-stroke) of any type & severity
- Right handed
- Abstinence from Speech & Language Therapy

Exclusion Criteria

- Prior stroke
- TMS and MRI exclusion criteria (e.g. aneurysm clips or coils)
- Severe dysarthria affecting intelligibility

Language Measures

- **Boston Diagnostic Aphasia Examination-Short Form (BDAE-SF) (Messinis, Kastellakis, Panagea & Papathanasopoulos, 2013)**
  - ✓ **Language skills in adults suspected of having aphasia**
    - **comprehension – expression – naming – reading**

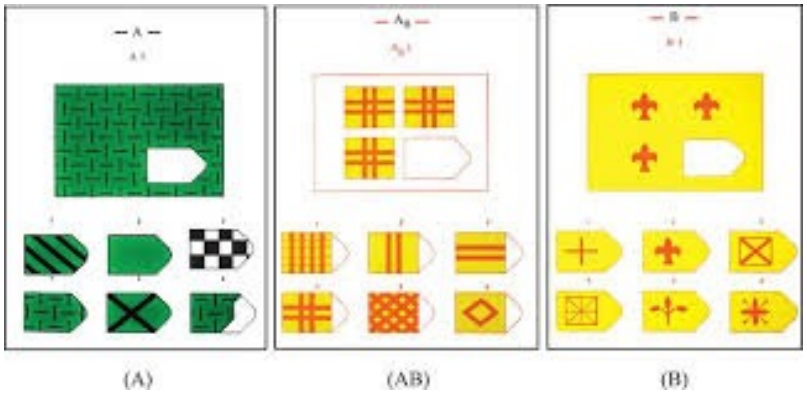
- Peabody Picture Vocabulary Test-Revised (**PPVT-R**) (Simos, Sideridis, Protopapas & Mouzaki, 2011)
  - ✓ receptive vocabulary at the word level

- Greek Object and Action Test (**GOAT**) (Kambanaros, 2004)
  - ✓ naming of single nouns and verbs

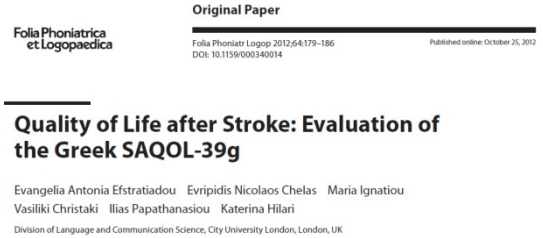
- Multilingual Assessment Instrument for Narratives (**MAIN**) (Gagarina et al., 2012)
  - ✓ narrative skills → functional communication

Cognitive Assessment & Quality of Life Measurement

- Raven's Coloured Progressive Matrices (RCPM) (Raven, Raven & Court, 1998) → cognition (problem solving skills)



- Stroke and Aphasia Quality of Life scale-39 item (SAQOL-39g) for Greek → quality of life
  - comprehension problems in 2 participants
    - common policy adopted for all → proxies' reports


Folia Phoniatrica et Logopaedica

Original Paper

Folia Phoniatr Logop 2012;64:179–186
DOI: 10.1159/000340014

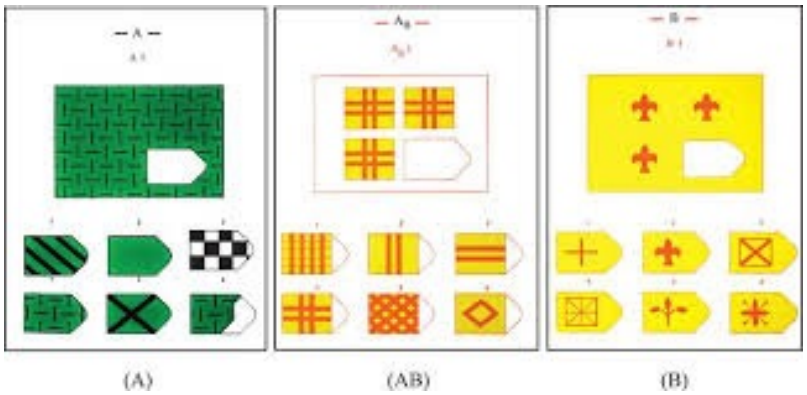
Published online: October 25, 2012

Quality of Life after Stroke: Evaluation of the Greek SAQOL-39g

Evangelia Antonia Efstratiadou Evripidis Nicolaos Chelas Maria Ignatiou Vasiliki Christaki Ilias Papathanasiou Katerina Hilari

Division of Language and Communication Science, City University London, London, UK

Cognitive testing – problem solving (control variable)



- 2 pre-therapy probes

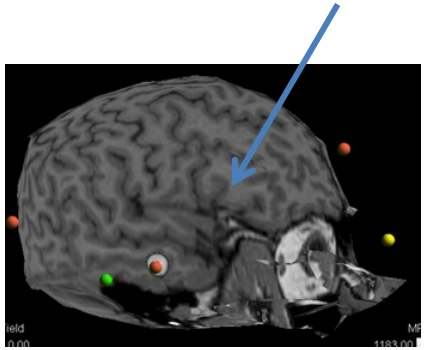
if a change in language skills is noticed but the control variable (i.e. **problem solving**) remains stable ➔

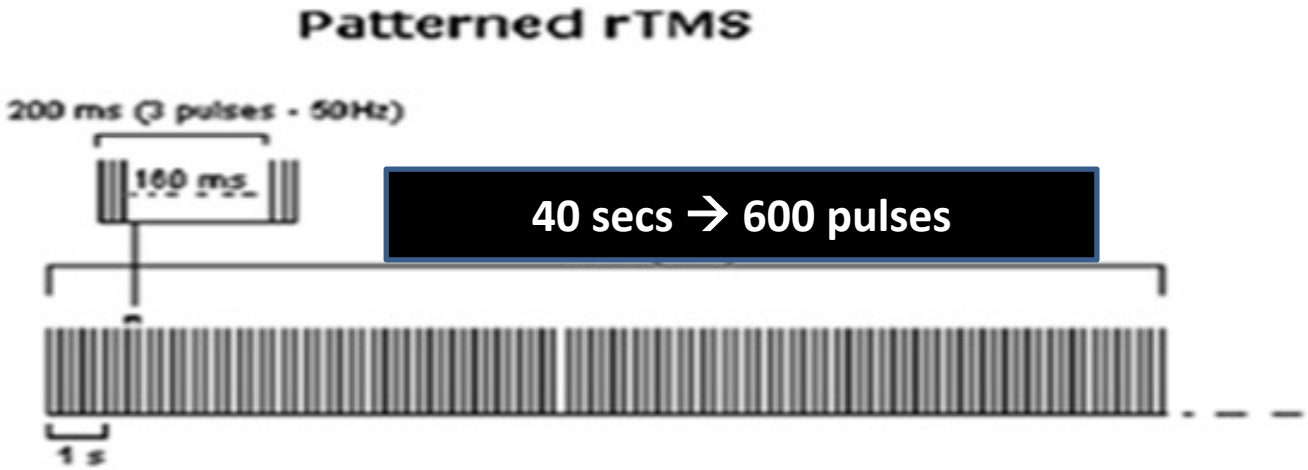
✓the chances that TMS leads to language specific gains are increased

✓the possibilities for the placebo and training effects are reduced

Neuronavigated Continuous Theta Burst Stimulation (cTBS)

- 10 consecutive days over the right pars triangularis (pTr)
  - Language performance in chronic post-stroke aphasia
    - 1-day (short-term) post-treatment
    - 2 months (long-term) post treatment

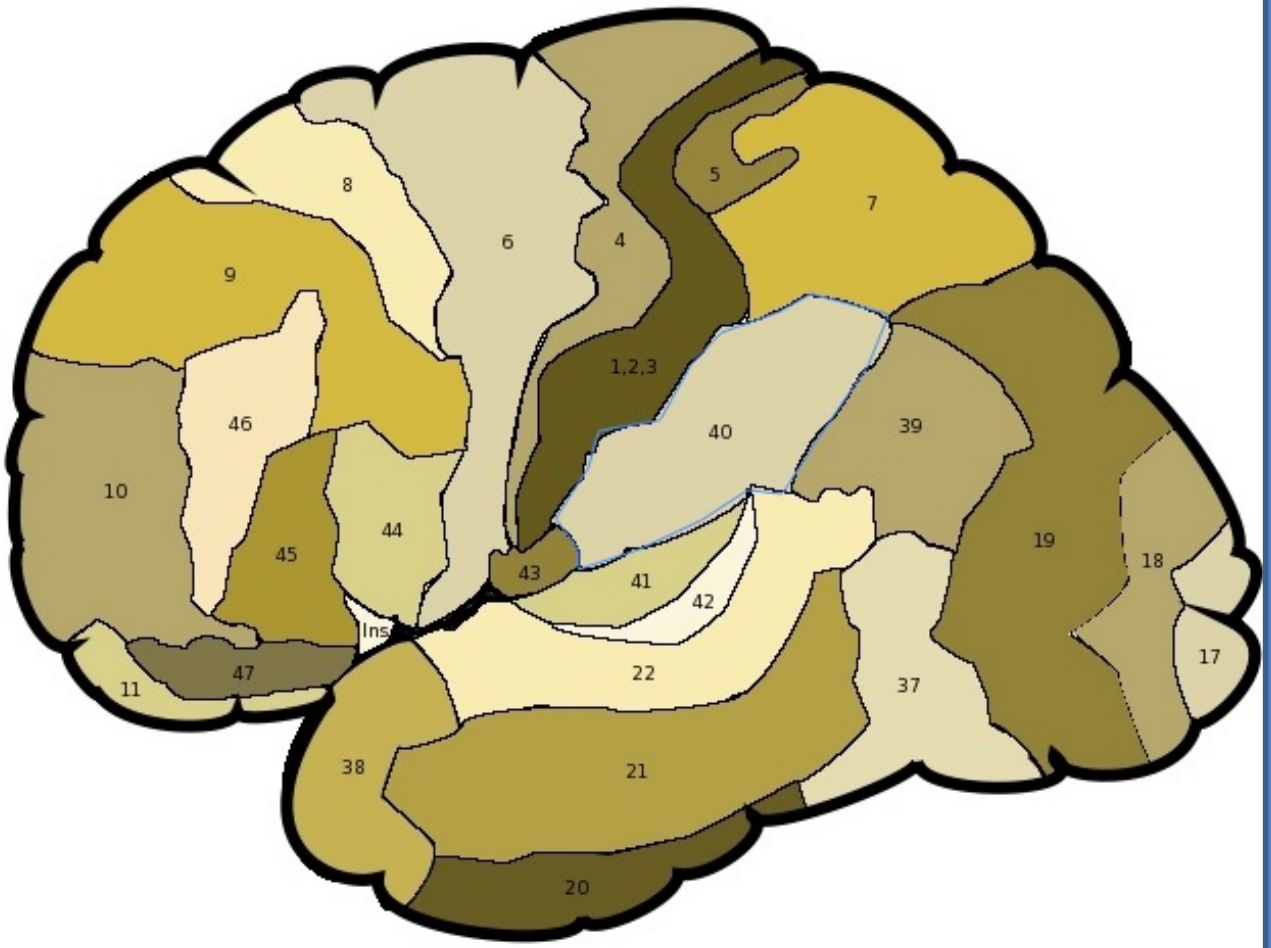




Broca's Area (BA45)

BA4: primary motor cortex
BA6: pre-motor cortex

Pars Triangularis: BA45
Pars Opercularis: BA44



BA45

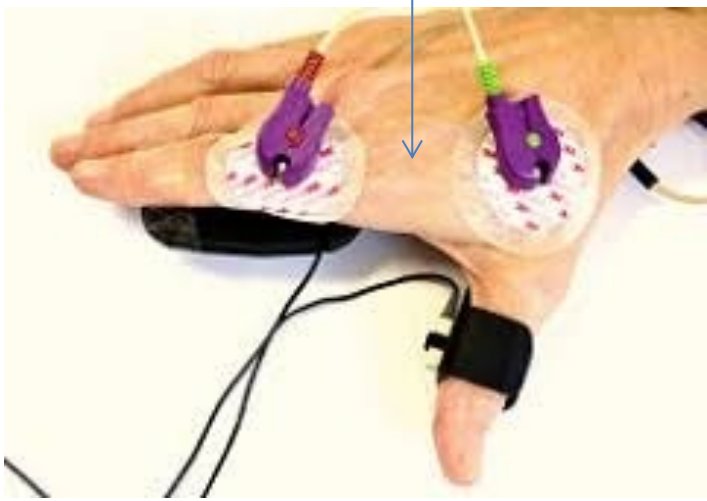
Language

- ✓Semantic > phonological processing (Gold et al., 2005)
- ✓Internally specified word generation (Tremblay & Gracco, 2006)
- ✓Verbal fluency (Abrahams et al., 2003)
- ✓Lexical search (Heim et al., 2005)
- ✓Phonological processing (Heim et al., 2005)
- ✓Grammatical processing (Sahin, Pinker & Halgren, 2006)
- ✓Semantic memory retrieval (Duzel et al., 2001)
- ✓Selective attention to speech (left) (Vorobyev et al., 2004)
- ✓Sign language (Horwitz et al., 2003)
- ✓Affective prosody comprehension (Wildgruber et al., 2005)
- ✓Lexical inflexion (Sahin, Pinker & Halgren, 2006)
- ✓Reasoning (Goel et al., 1998)
- ✓Processing of metaphors)(Rapp et al., 2004)
- ✓Generation of melodic phrases (Brown, Martinez & Parsons, 2006)

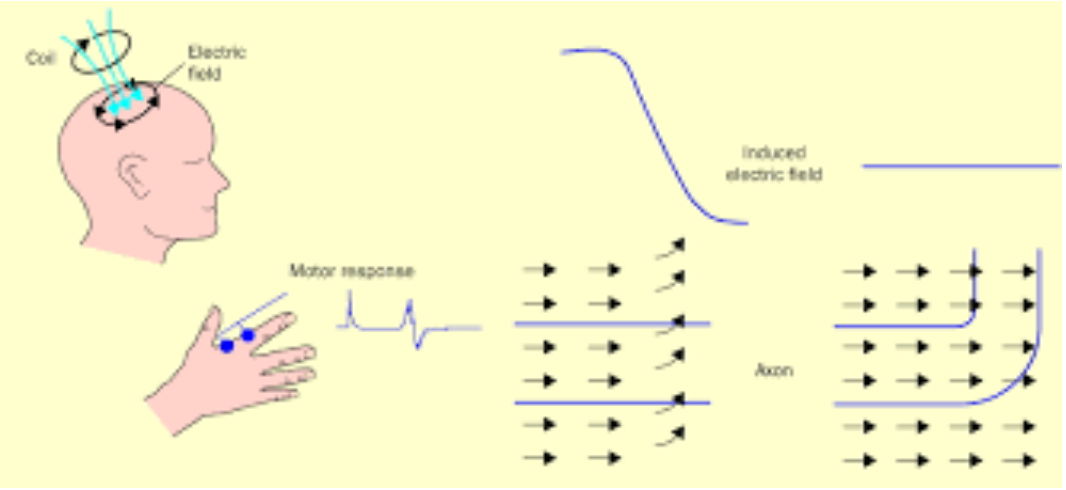
Memory – movement – others (e.g. music enjoyment)

Intensity

- EMG of the FDI



➢ Brain area controlling the FDI identified through neuronavigated TMS → 80% of the minimum TMS intensity output resulting in FDI contraction of a **specific value** (50 μV) defined as the intensity value used in **all subsequent TMS sessions**



Timeline

Pre rTMS sessions	rTMS sessions (10 consecutive days)	Post rTMS sessions
• Background measures • MRI scan • Linguistic testing (BDAE-SF; PPVT-R; GOAT) • Functional communication (MAIN) • Cognitive testing (RCPM) • QoL assessment (SAQOL-39g)	50 Hz neuronavigated cTBS at 80% RMT applied at right pTr	• Linguistic testing (BDAE-SF; PPVT-R; GOAT) • Functional communication (MAIN) • Cognitive testing (RCPM) • QoL assessment (SAQOL-39g)
Time (relative to start of treatment)		
– 12 & – 1 days (baseline 1 & 2)	0 days (rTMS therapy)	+ 1 day & + 2 months (post rTMS)

cTBS

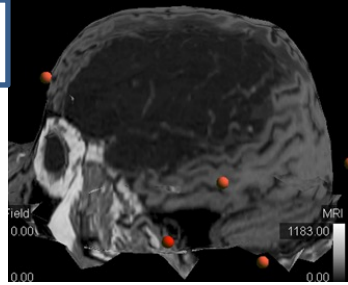
Participant	Sex	Age (years)	Handedness	Education (years)	Type of stroke	Months post stroke	Lesion site (left hemisphere)	Type of Aphasia	Severity of Aphasia	SLT prior to enrolment	Termination of SLT
1	F	74	right	6	ischemic	48	diffuse frontal, parietal and temporal (middle and superior gyri) lobes; insula; basal ganglia	global	severe	20 months – 2 times per week – 45 min of SLT	2 years before enrolment
2	M	61	right	12	ischemic	9	Broca's and Wernicke's areas; arcuate fasciculus; insula; inferior precentral gyrus; temporal pole	anomic	moderate-severe	6 months – 2 times per week – 45 min of SLT	2 months before enrolment
3	M	48	right	15	ischemic	11	IFG; internal capsule; insula; caudate nucleus; putamen; inferior precentral gyrus	Broca's	moderate-severe	8 months – 4 times per week – 45 minutes	10 days before enrolment

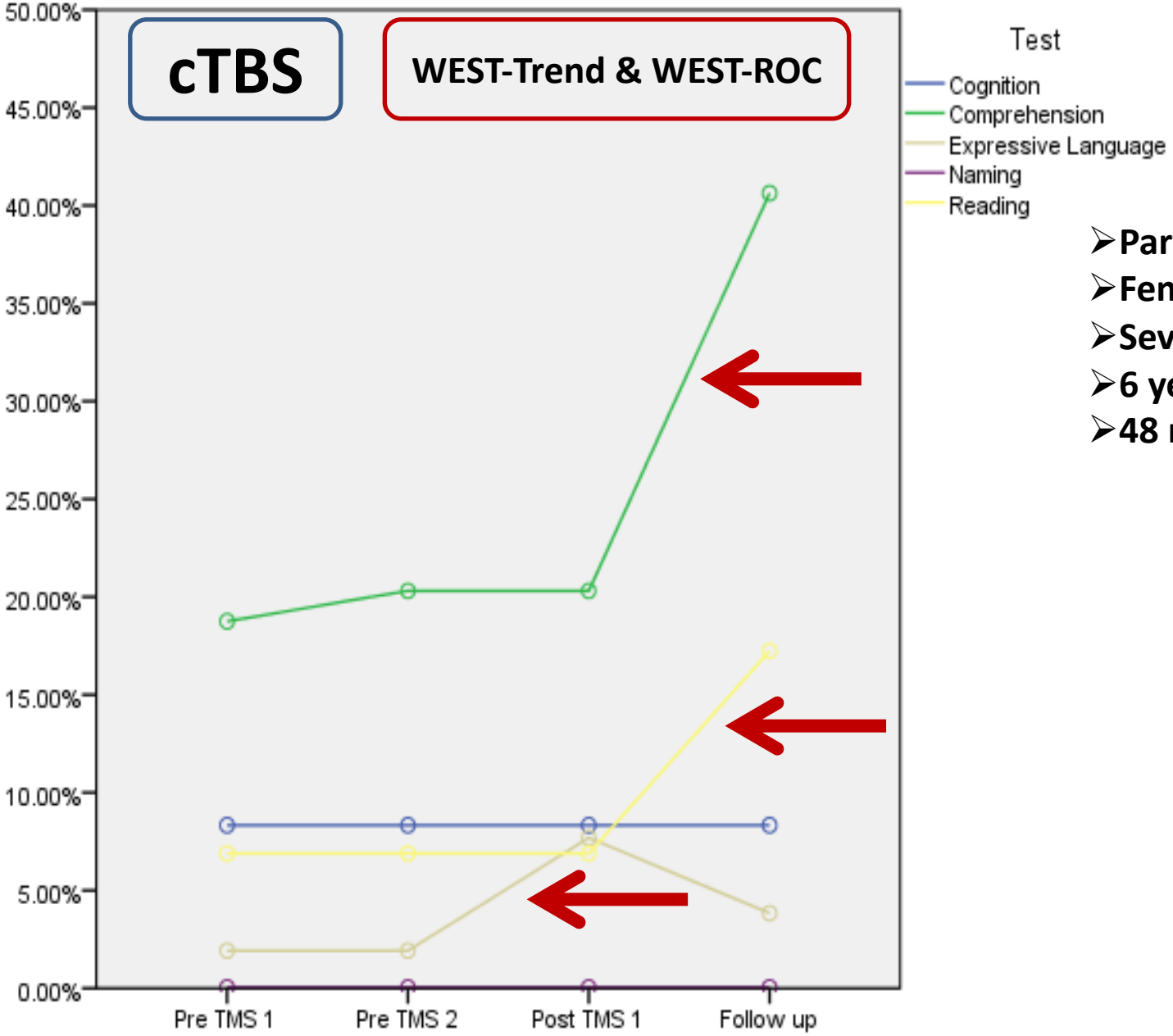
Data analysis

- **Weighted Statistics (WEST)** (Howard, Best & Nickels, 2015)
  - WEST-Trend → is there is an upward linear trend for improvement?
  - WEST-ROC → analyses the amount of change in
    - treated vs the untreated period
    - long - vs short-term

  - studies with small sample sizes, heterogeneous participants
  - does not exclude any participant from receiving treatment
  - **novelty in small-scale TMS aphasia research**

Language & Cognition (problem solving) results





- **Participant 1**
- **Female 74 y.o.**
- **Severe global aphasia**
- **6 years education**
- **48 months post-stroke**

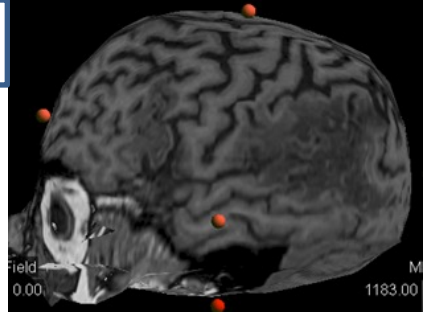
<u>Short-term effects</u>

improvement in expressive language ($t(25) = 1.79$, $p = .04$) → not higher in the treated versus the untreated period ($t(25) = .90$, $p = .19$).

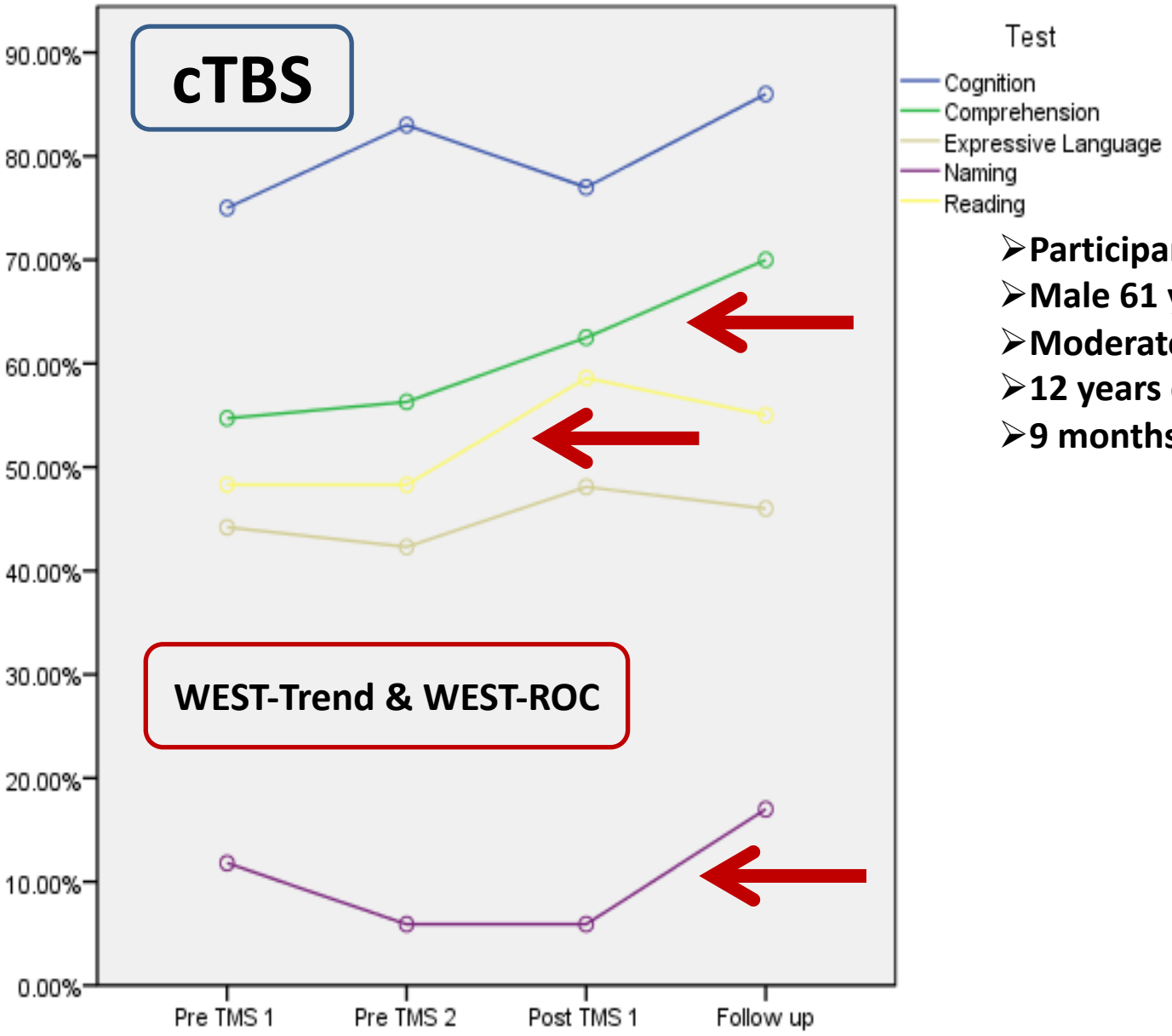
<u>Long-term effects</u>

improvement in comprehension ($t(63) = 3.66$, $p < .001$) and reading ($t(28) = 1.79$, $p = .04$) → greater during the follow up period compared to short term for both comprehension ($t(63) = 2.61$, $p < .01$) and reading ($t(28) = 1.79$, $p = .04$).

Front



Language & Cognition (problem solving) results



- **Participant 2**
- **Male 61 y.o.**
- **Moderate-severe anomic aphasia**
- **12 years education**
- **9 months post-stroke**

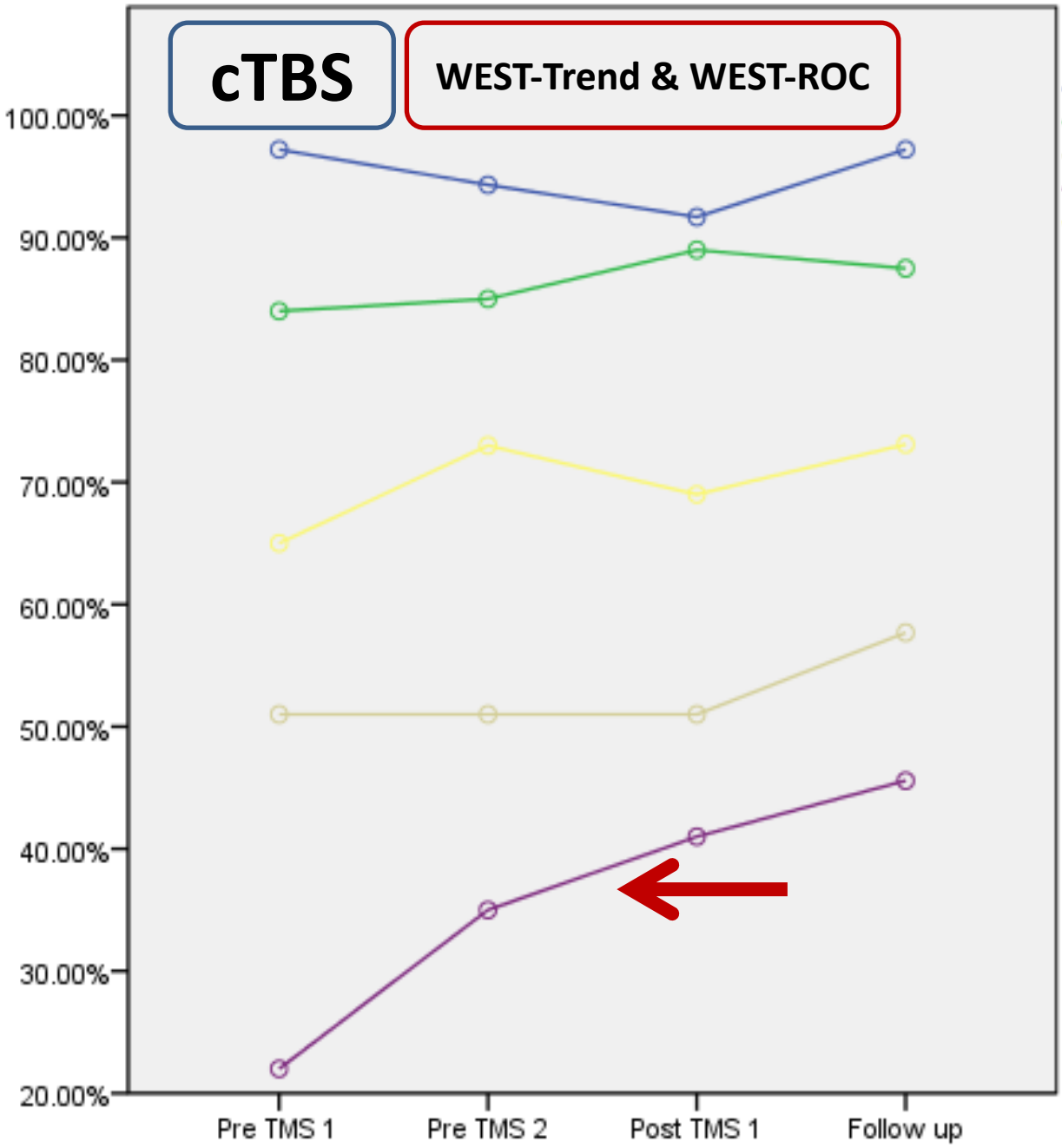
<u>Short-term effects</u>

improvement in reading ($t(28) = 1.79$, $p = .04$) → not higher in the treated versus the untreated period ($t(28) = 0.91$, $p = .187$).

<u>Long-term effects</u>

improvement in comprehension ($t(63) = 1.76$, $p = .041$) and naming ($t(33) = 1.75$, $p = .04$) → not higher in the follow-up stage compared to the short-term for either comprehension ($t(63) = 0.12$, $p = .45$) or naming ($t(33) = 1.07$, $p = .14$).

Language & Cognition (problem solving) results



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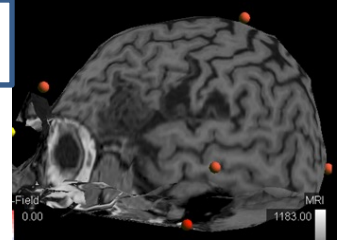


- **Participant 3**
- **Male 48 y.o.**
- **Moderate-severe Broca's aphasia**
- **15 years education**
- **11 months post-stroke**

<u>Short-term effects</u>

improvement in naming ($t(33) = 3.01$, $p < .01$) → not higher in the treated versus the untreated period ($t(33) = -.55$, $p = .71$).

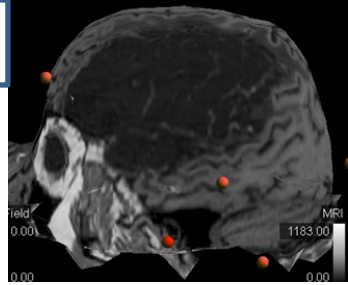
<u>Long-term effects</u>

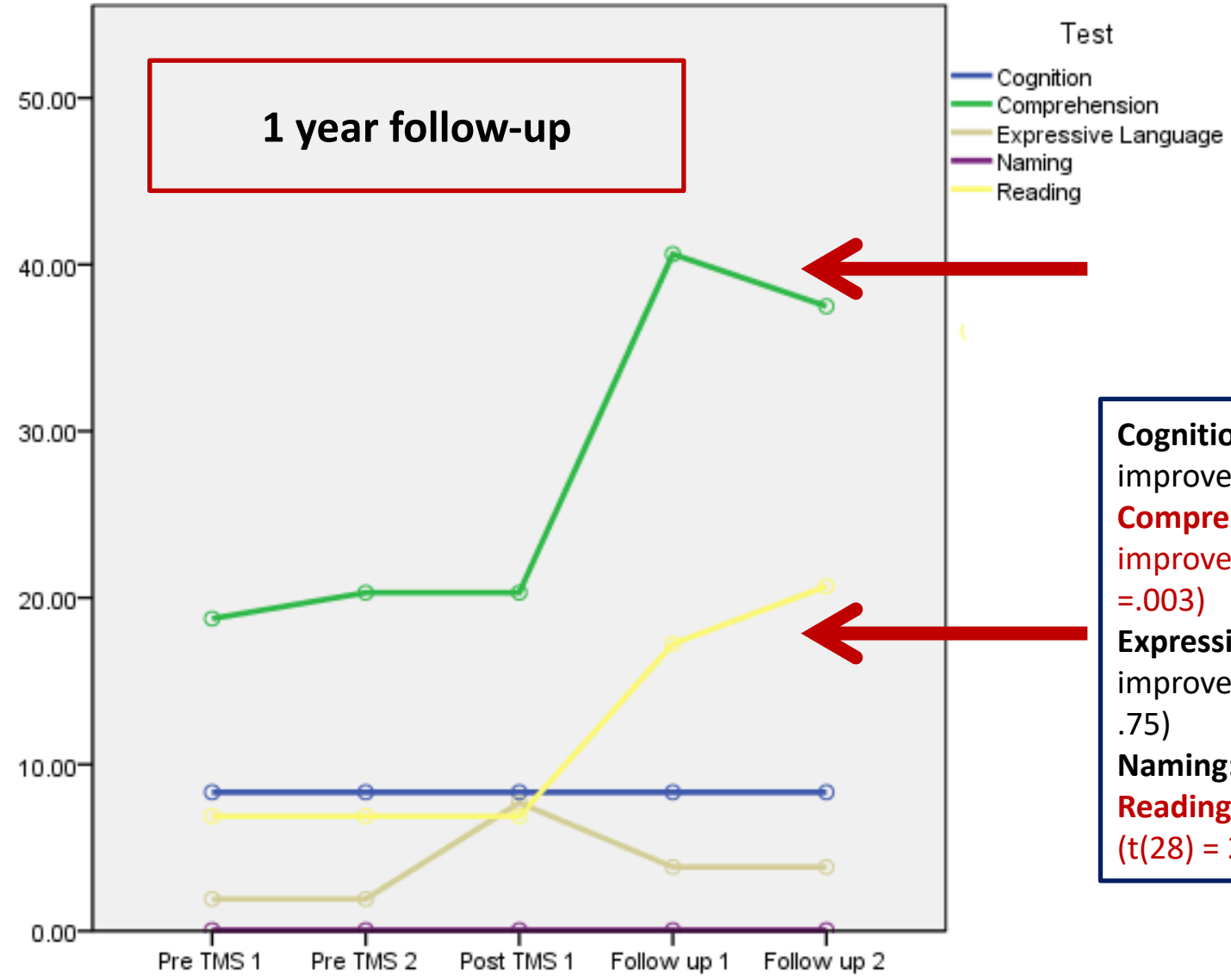
no improvement in any domain

Language & Cognition (problem solving) results

cTBS

WEST-Trend & WEST-ROC





- **Participant 1**
- **Female 74 y.o.**
- **Severe global aphasia**
- **6 years education**
- **48 months post-stroke**

Cognition: no overall improvement
Comprehension: overall improvement (t(63) = 2.80, p =.003)
Expressive Language: no overall improvement (t(25) = 0.76, p = .75)
Naming: no overall improvement
Reading: overall improvement (t(28) = 2.11, p =.02)

Conclusions (1)

- First of its kind conducted in Cyprus on aphasia and TMS

- First TMS aphasia study that used
  - Single subject experimental design (SSED)
    - Weighted statistics (WEST)

- standardized language measures to assess language skills
- thorough analyses of narrative skills as an index of functional communication skills → number of narrative words increased i) in the short-term in 1 participant and ii) in the long-term in 1 participant
- QoL measure → no change

Conclusions (2)

- Problem solving skills (control variable)
  - ➢ stable in all participants

- Language skills (several domains):
  - ➢ trends for improvement in all participants in the short and/or long-term
  - ➢ significant improvement in 1 participant up to 1 year post-treatment
    - oldest participant
    - **severe** global aphasia resulting from diffuse brain lesions
    - 48 months post-stroke

- ➢ **based on the present preliminary data, it seems that lesion location and extent does not predict cTBS efficacy**
- ➢ **the chances that the change in language performance was attributable to TMS treatment are increased**
- ➢ **the possibilities for the placebo and training effects are reduced**

Implications

Even small in sample size, this research adds to existing literature

rTMS (cTBS) over the right pTr

has the potential to drive changes in

- ✓ **Comprehension**
- ✓ **Expression**
- ✓ **Naming**
- ✓ **Reading**
- ✓ **retrieval of narrative words**

in Chronic Aphasia post-Stroke

regardless of severity and type of aphasia

Variability (failure/success) in response to TMS attributed to:

- aphasia type
- aphasia chronicity
- site of stimulation
- TMS stimulation parameters
- SLT
- age
- gender
- genetics & epigenetics
- …

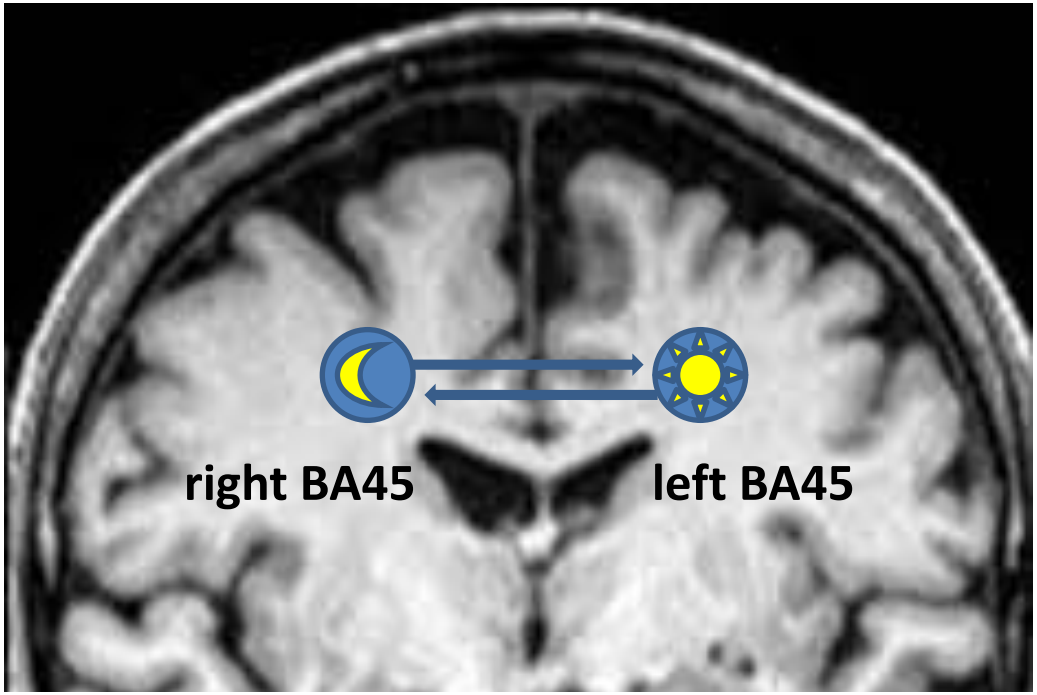
(Coslett, 2016; Lefaucheur, 2014)

Need for:

➢ **biomarkers of good responders and non-responders**

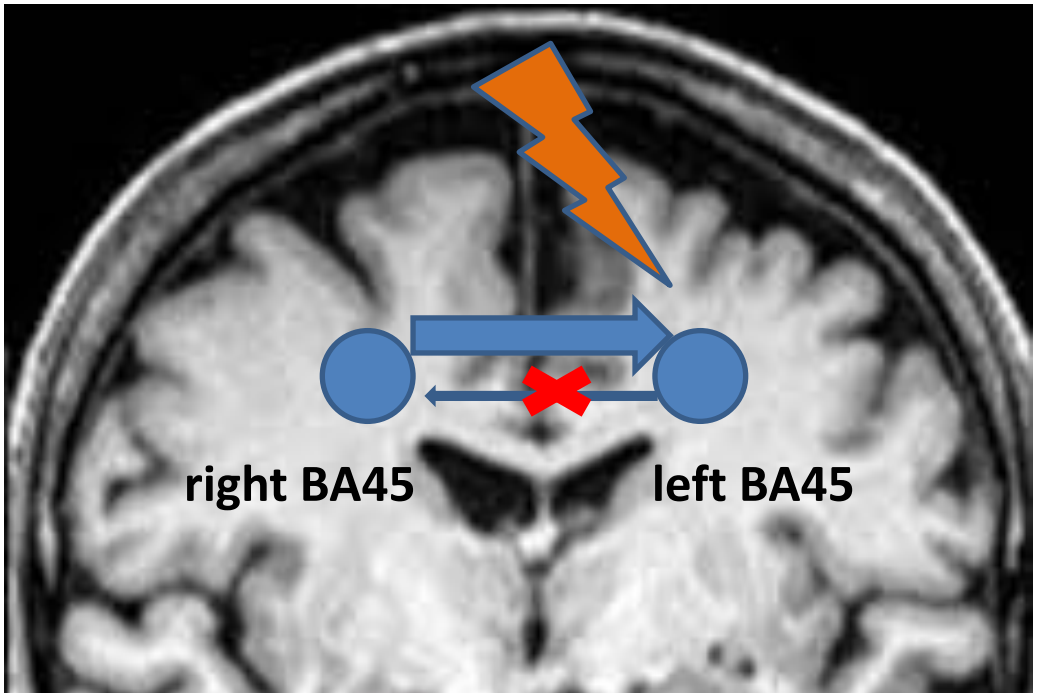
Backup slides

How the suppression of the right BA45 leads to language gains in post-stroke aphasia?

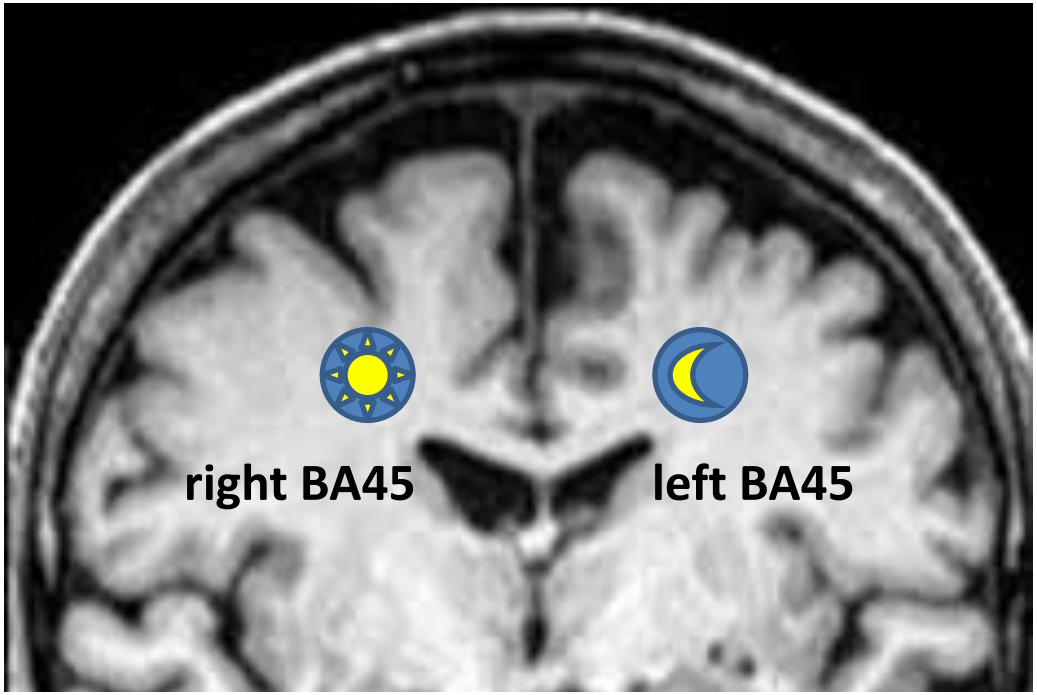


This protocol is based on a theoretical model for language networks reorganization in the lesioned brain, called “mutual and balanced transcallosal inhibition”

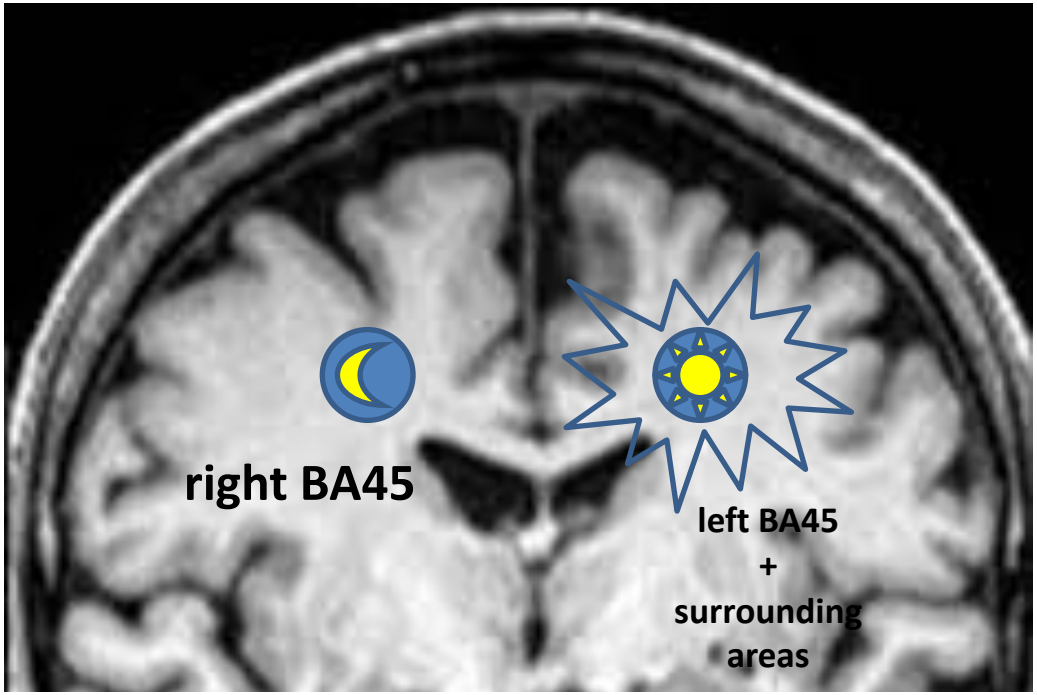
How the suppression of the right BA45 leads to language gains in post-stroke aphasia?

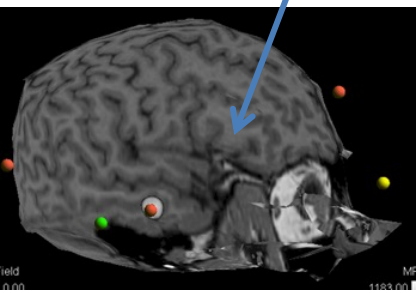


How the suppression of the right BA45 leads to language gains in post-stroke aphasia?



How the suppression of the right BA45 leads to language gains in post-stroke aphasia?





Larger shift of network activity towards the left ipsilesional hemisphere (Heiss et al., 2013; Thiel et al., 2013; Weiduschat et al., 2011)