Non-invasive cerebellar stimulation to rearrange disrupted functional networks

Kim van Dun, Mario Manto

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KNOWLEDGE IN ACTION

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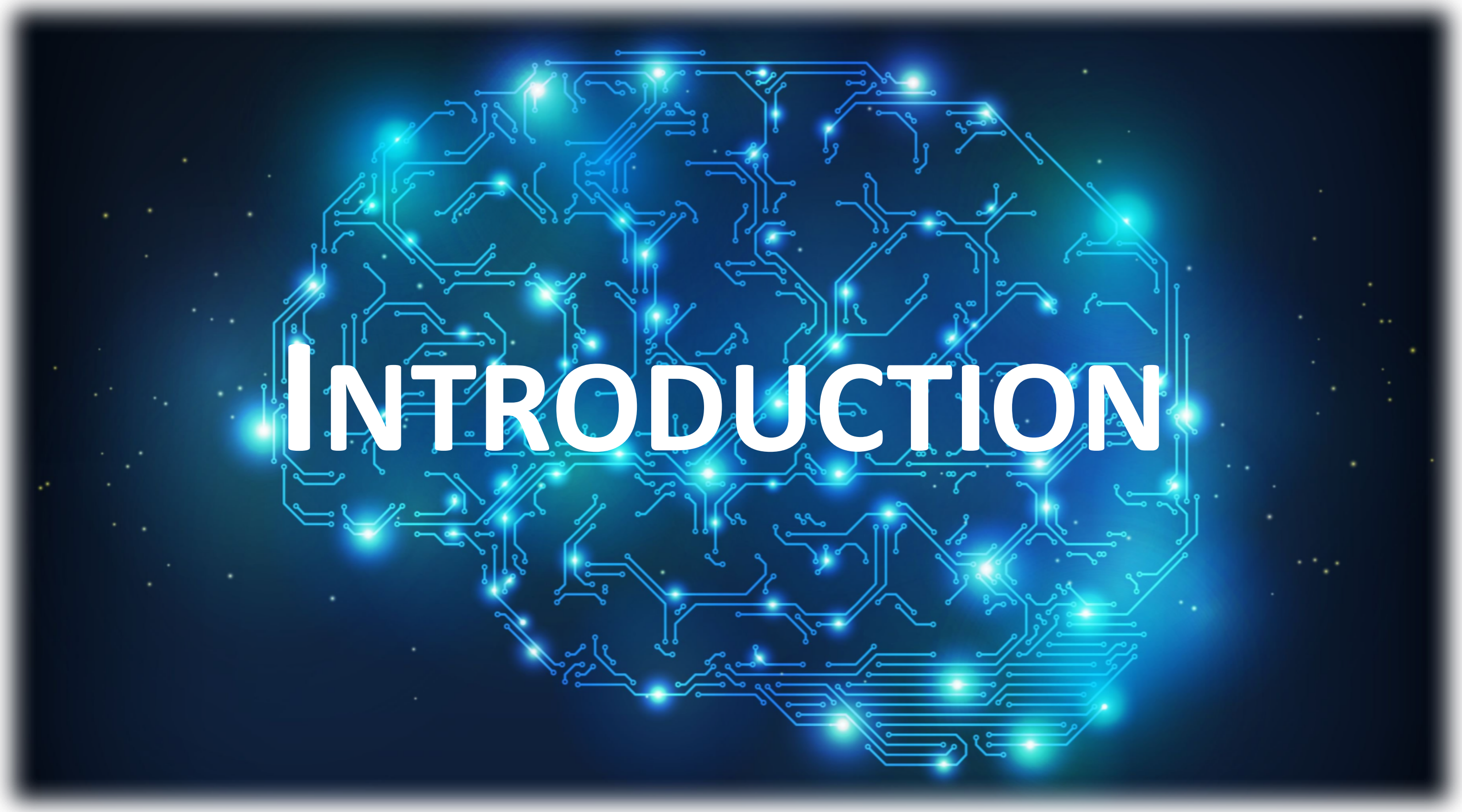

INTRODUCTION

The cerebellum:
The “little brain”

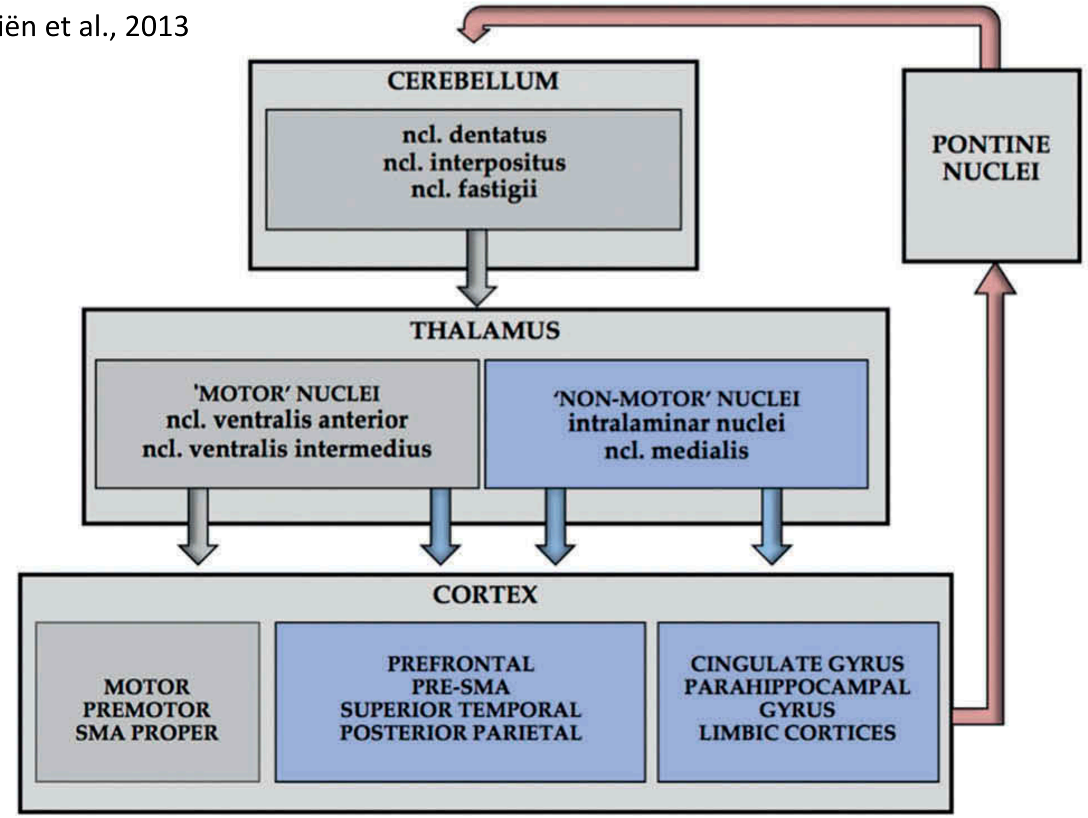
The cerebrum
= “Brain”
- 2 hemispheres
- 4 lobes

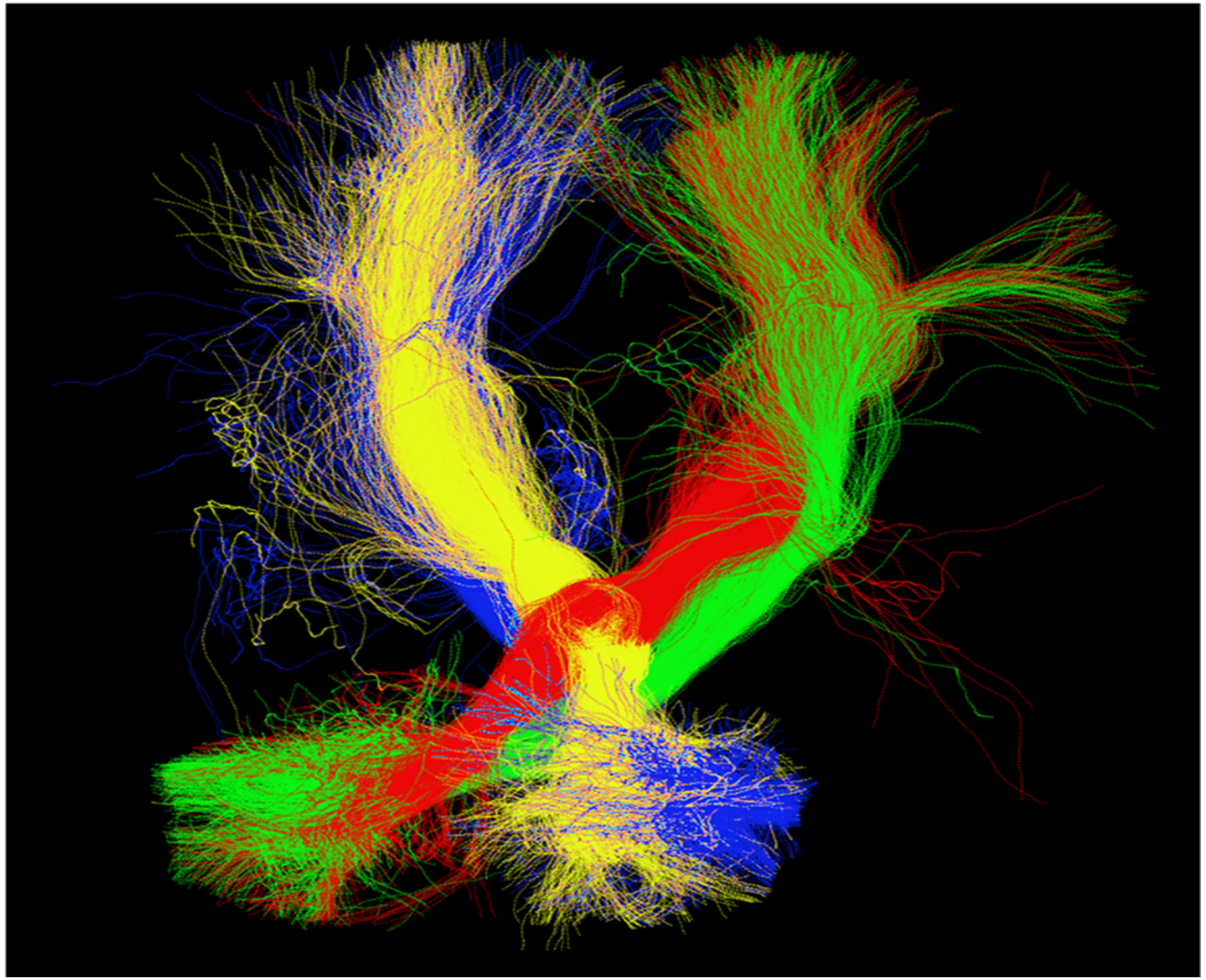
The cerebellum
= “Little brain”
- 2 hemispheres
- 3 lobes

The cerebellum: Cerebello-cerebral reciprocal connections

Numerous crossed reciprocal connections between the cerebellum and cerebrum

Mariën et al., 2013



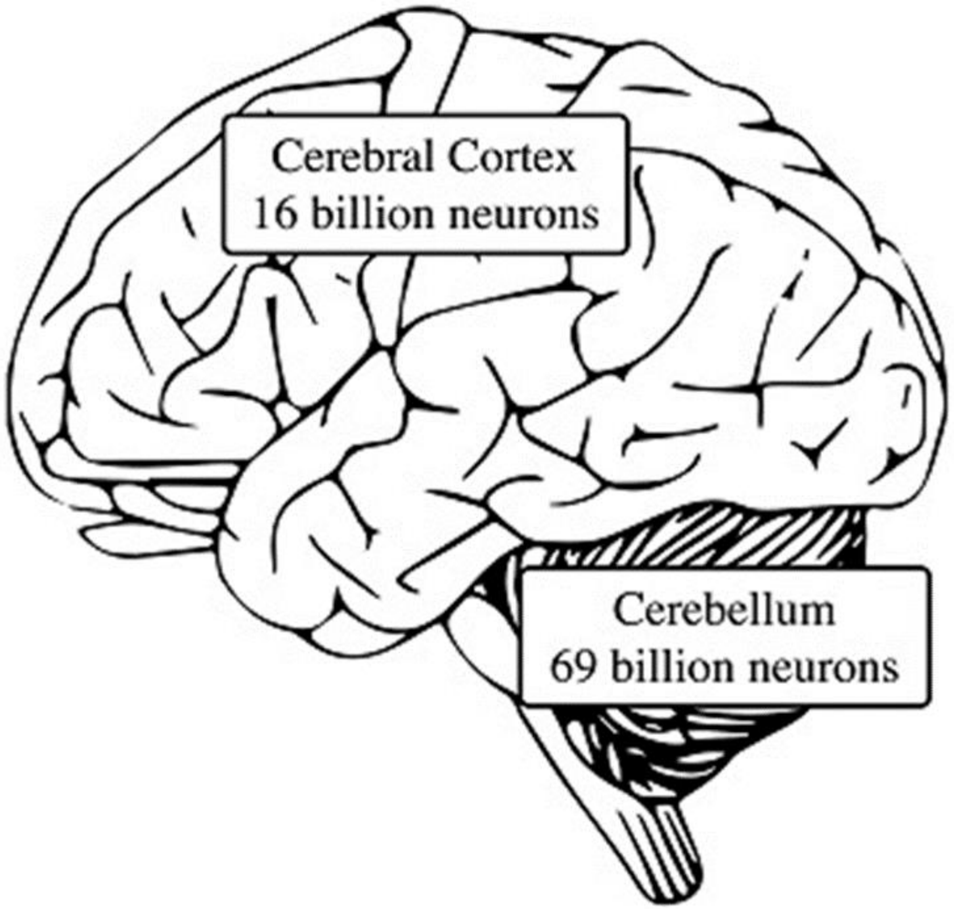


Pieterman et al., 2016

The cerebellum: Stimulation target

- Crossed connections between the cerebellum and the cerebrum
- Location of the posterior cerebellum right beneath the skull
- High concentration of neurons

Pieterman et al., 2016



Lent et al., 2012

Cerebellar neurostimulation: Types of stimulation

tES

= transcranial electrical stimulation

TMS

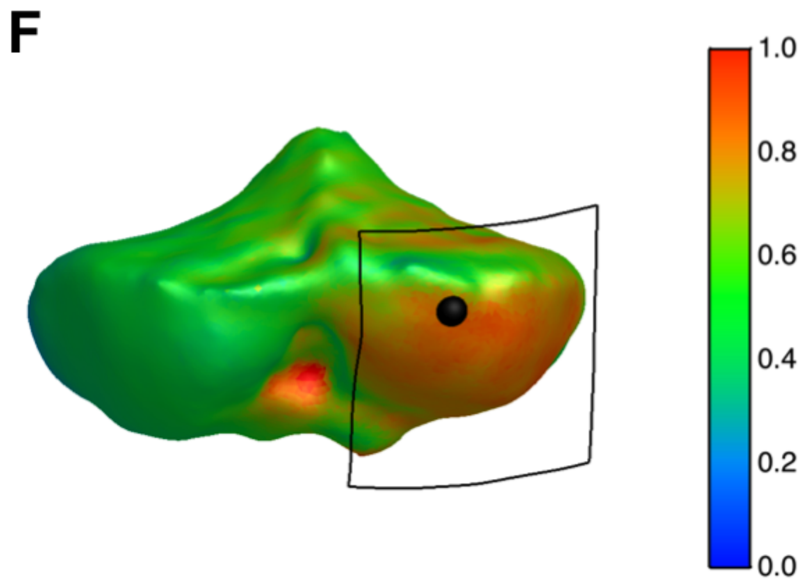
= transcranial magnetic stimulation

⇒ Capable of modulating (cerebellar) cortical excitability non-invasively

Cerebellar neurostimulation: Modeling

tDCS

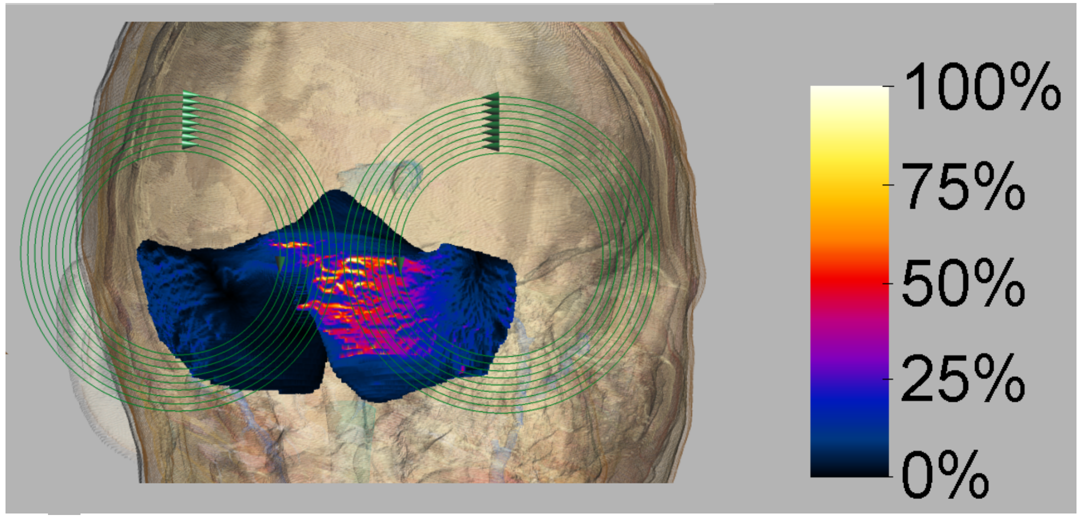
1mA
anode (5x5cm) over R CB
Cathode (5x5cm) over right cheek



Rampersad et al., 2014

TMS

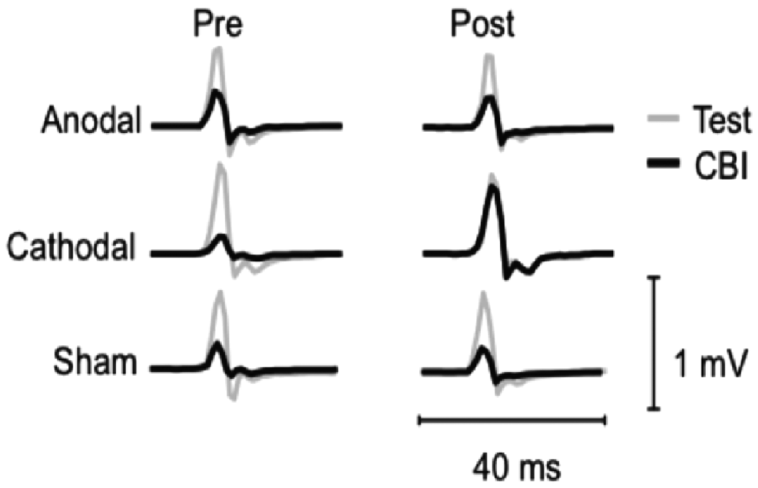
Figure-of-eight coil
MMO



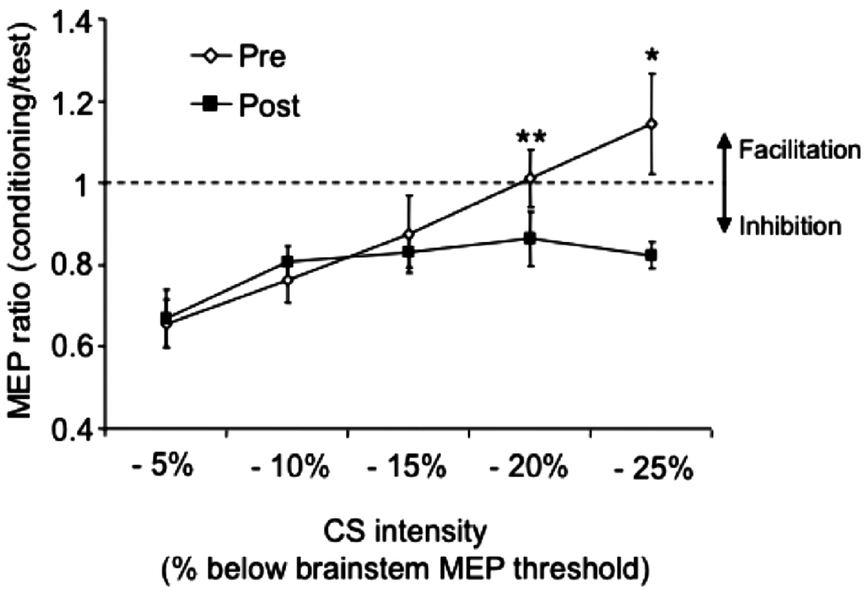
Bijsterbosch et al., 2012

Cerebellar neurostimulation: Effectiveness

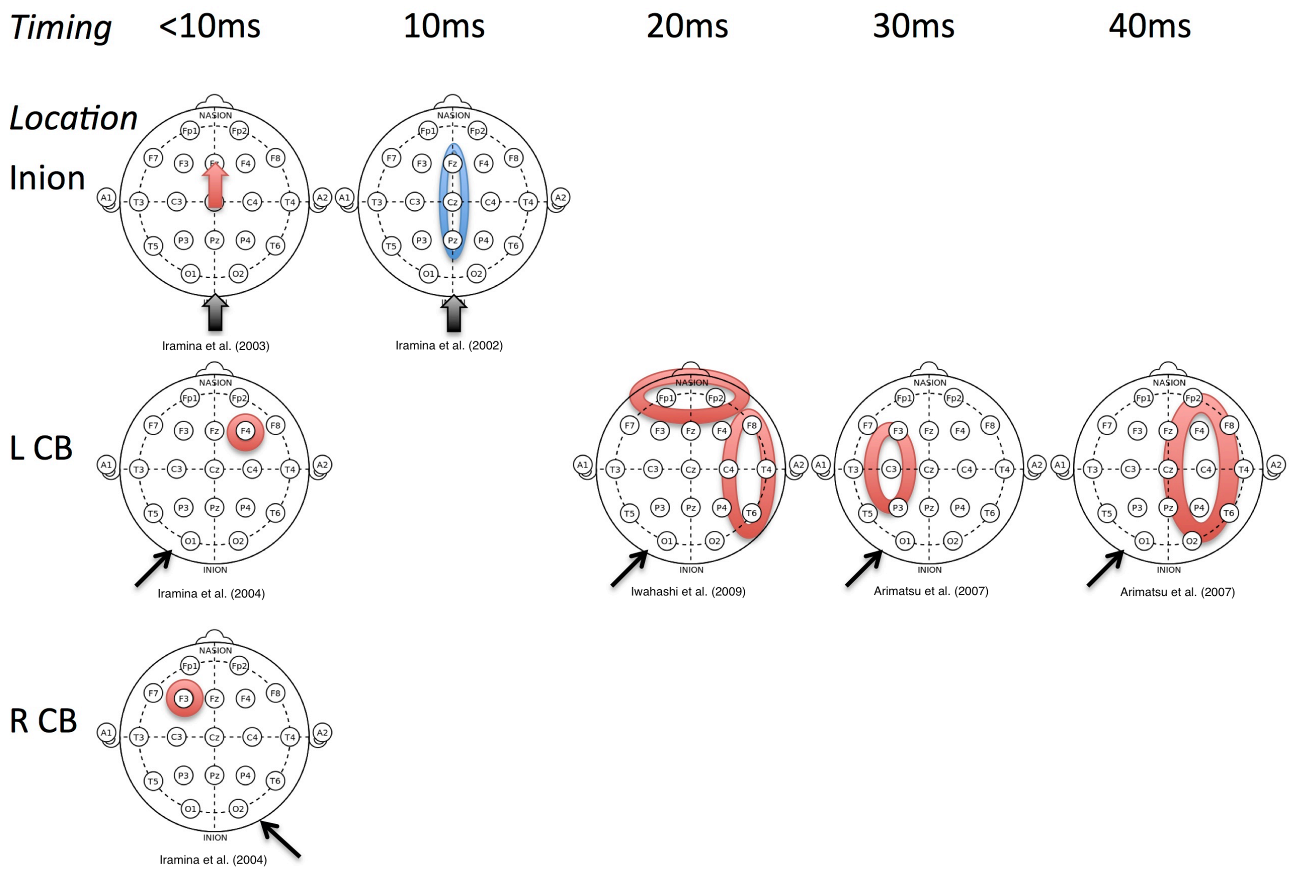
tDCS (CBI)



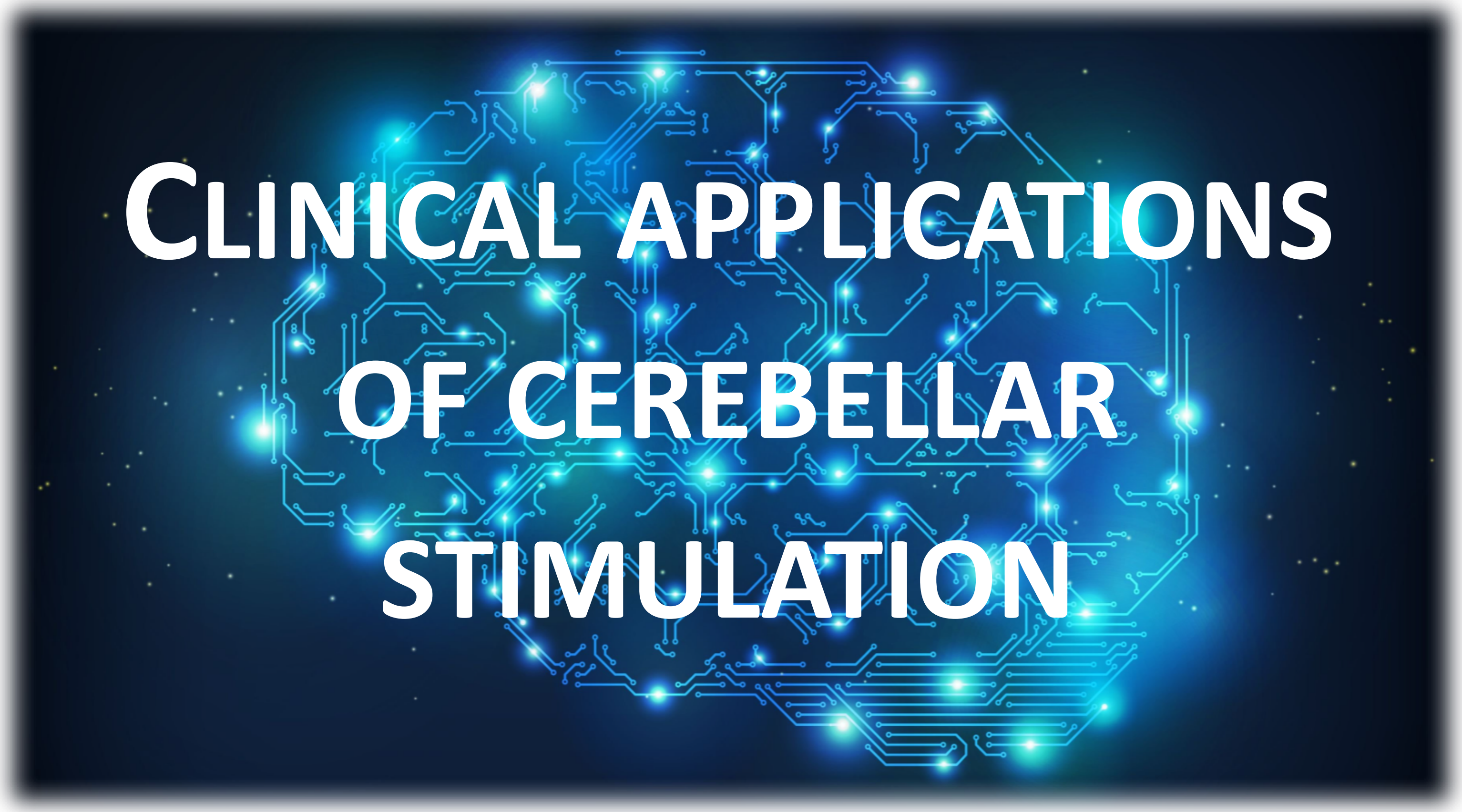
Galea et al., 2009



TMS (EEG)



van Dun et al., 2017



Clinical applications of cerebellar stimulation

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Clinical applications of cerebellar stimulation

- **Cerebellar motor disorders**
- **Cerebellar stroke**
- **Subcortical stroke**
- **Cerebello-cerebral network disorder**
- **Neurodevelopmental disorders**

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Clinical applications of cerebellar stimulation

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CEREBELLAR MOTOR DISORDERS

- **Cerebellar ataxia (CA)**
  - e.g. Significant alleviation of truncal ataxia in spinocerebellar degeneration after cerebellar TMS (Shiga et al., 2002)

- **Essential tremor (ET)**
  - Acute or subacute tremor effect demonstrated in most studies (van Dun et al., 2018)

- **Dystonia**
  - Mixed results after a single session => Studies with consecutive sessions needed (Ferrucci et al., 2016)

- **Dyskinesia in Parkinson's Disease (PD)**
  - Promising effect of cerebellar atDCS (Ferrucci et al., 2016)

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Clinical applications of cerebellar stimulation

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CEREBELLAR STROKE

Cerebellar stroke

Bonnì et al. (2014)
6 (5M, 1F) patients with posterior circulation stroke (9m-7y poststroke)
2 weeks of iTBS over the lesioned cerebellar hemisphere

Behavioral results:
- Posture and gait significantly improved

CEREBELLAR STROKE

Cerebellar stroke

Kim et al. (2014)
32 (17M, 15F) patients with posterior circulation stroke (~15days poststroke)
1 week of 1Hz rTMS over the lesioned cerebellar hemisphere
Randomized sham-controlled study

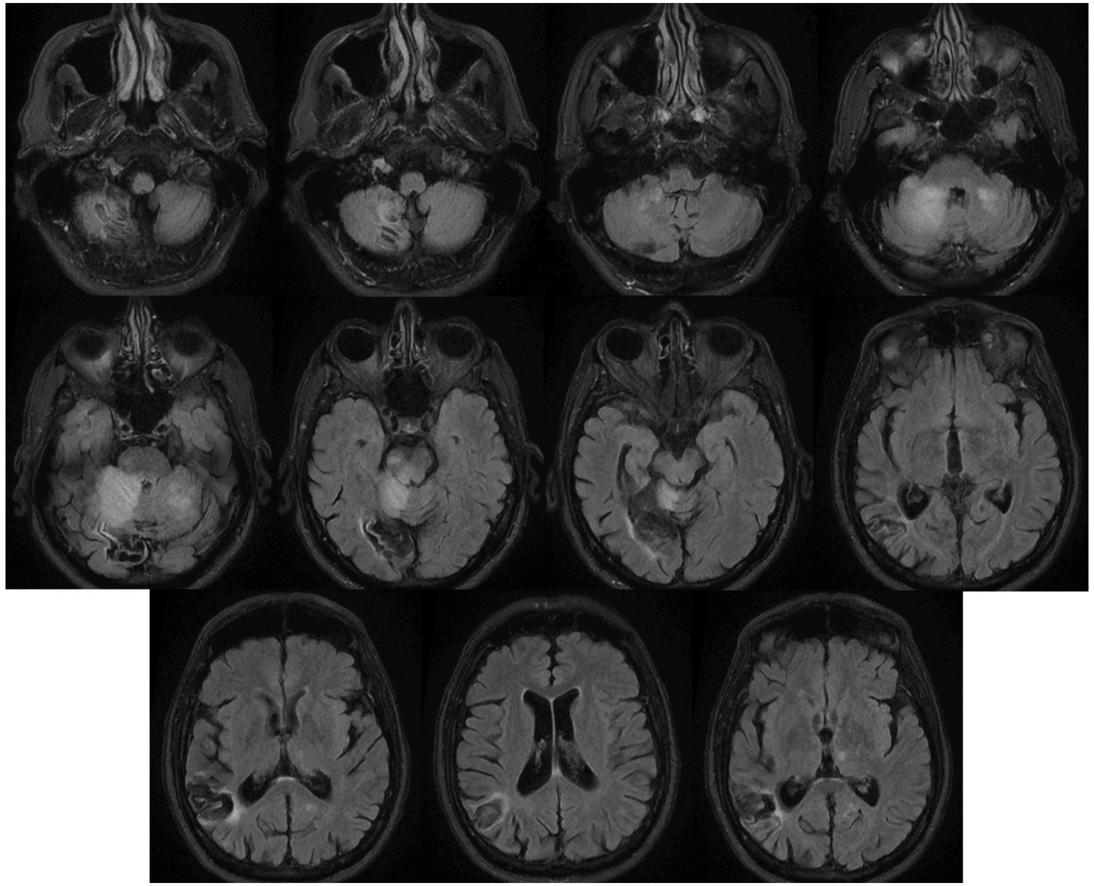
Behavioral results:
- Overall walking significantly improved in the active group
- Balance improved in both groups

CEREBELLAR STROKE: case study

Cerebellar stroke

66-year-old right-handed man
- Cerebellar infarct
- Lesions in bilateral posterior lobes + mesencephalon/pons
- R occipital and L thalamic damage

- Cerebellar dysarthria



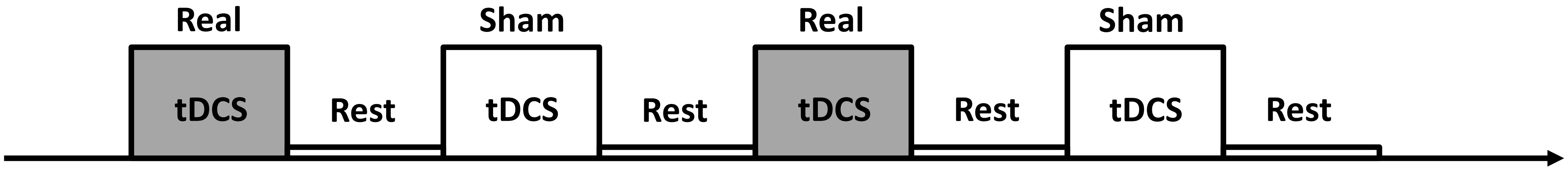
van Dun, 2017

CEREBELLAR STROKE: case study

Cerebellar stroke

tDCS protocol:

- Anode over R insula
- Cathode over L insula
- 1.5mA, 20min, online (speech therapy)
- 3 weekly sessions, 16 weeks in ABAB design



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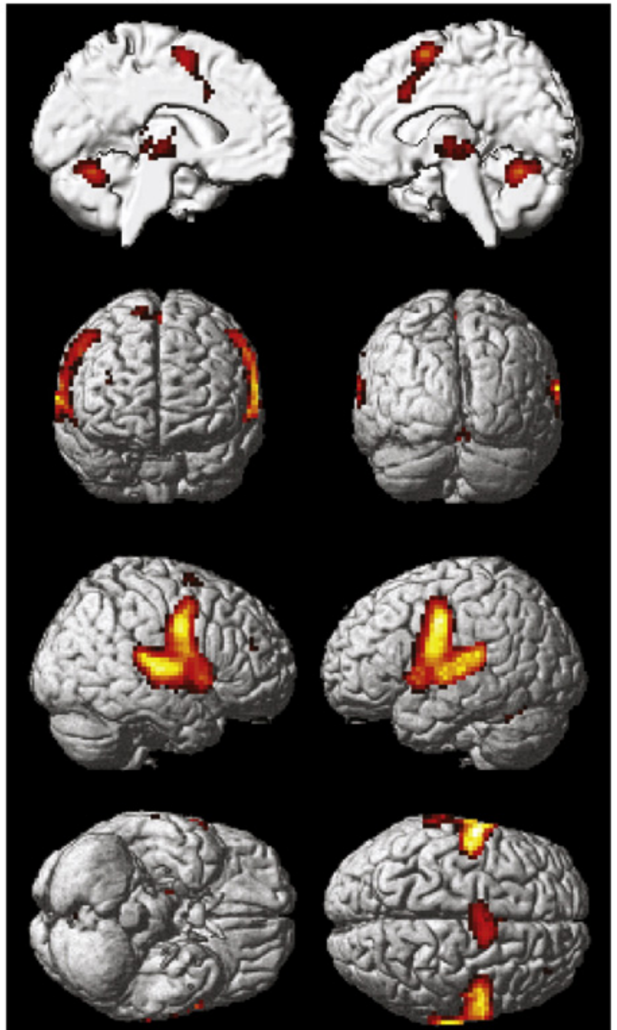
CEREBELLAR STROKE: case study

Cerebellar stroke

fMRI: Speech protocol (pataka/tatata compared to rest)
~ Brendel et al. (2010)

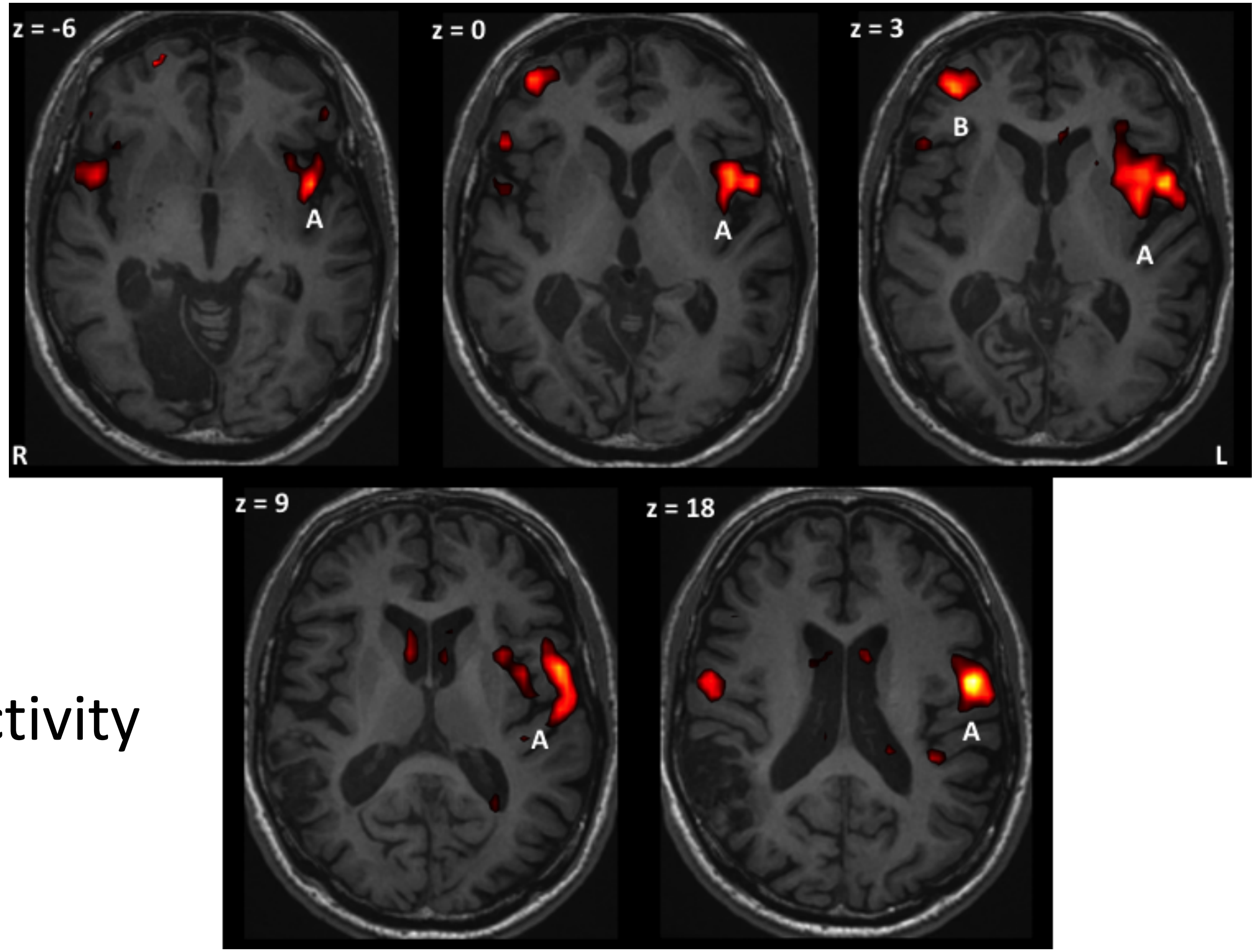


CEREBELLAR STROKE: case study

Cerebellar stroke

tDCS protocol:
- Anode over R insula
- Cathode over L insula

⇒ Goals:
- Restore insular equilibrium
- Restore cerebello-cerebral connectivity



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CEREBELLAR STROKE: case study

Cerebellar stroke

Behavioral results:

Test	Baseline	**2 weeks of real tDCS**	2 weeks of rest	2 weeks of sham tDCS	2 weeks of rest	**2 weeks of real tDCS**	2 weeks of rest	2 weeks of sham tDCS	2 weeks of rest
HN									
Fonation	5s (-12.9SD)	**7s (-11.4SD)**	9s (-9.8SD)	8s (-10.6SD)	10s (-9.1SD)	**10s (-9.1SD)**	9s (-9.8SD)	9s (-9.8SD)	-
NSVO words	76%	**80%**	84%	78%	84%	**88%**	86%	90%	88%
NSVO sen-tences	86%	**94%**	91%	88%	93%	**94%**	93%	95%	93%
SHI	20/60	**21/60**	22/60	22/60	21/60	**20/60**	23/60	22/60	21/60
Physical	9/20	**10/20**	10/20	10/20	9/20	**9/20**	11/20	11/20	12/20
Emotional	6/20	**6/20**	6/20	6/20	7/20	**6/20**	6/20	6/20	5/20
Functional	5/20	**5/20**	6/20	6/20	5/20	**5/20**	6/20	5/20	4/20

Legend: tDCS = transcranial direct current stimulation; MFT = maximal phonation time; NSVO = Dutch speech comprehensibility investigation; SHI = Speech handicap index.

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CEREBELLAR STROKE: case study

Cerebellar stroke

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Test	Baseline	**2 weeks of real tDCS**	2 weeks of rest	2 weeks of sham tDCS	2 weeks of rest	**2 weeks of real tDCS**	2 weeks of rest	2 weeks of sham tDCS	2 weeks of rest
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Emotional	6/20	**6/20**	6/20	6/20	7/20	**6/20**	6/20	6/20	5/20
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CEREBELLAR STROKE: case study

Cerebellar stroke

Behavioral results:

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Physical	9/20	**10/20**	10/20	10/20	9/20	**9/20**	11/20	11/20	12/20
Emotional	6/20	**6/20**	6/20	6/20	7/20	**6/20**	6/20	6/20	5/20
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CEREBELLAR STROKE: case study

Cerebellar stroke

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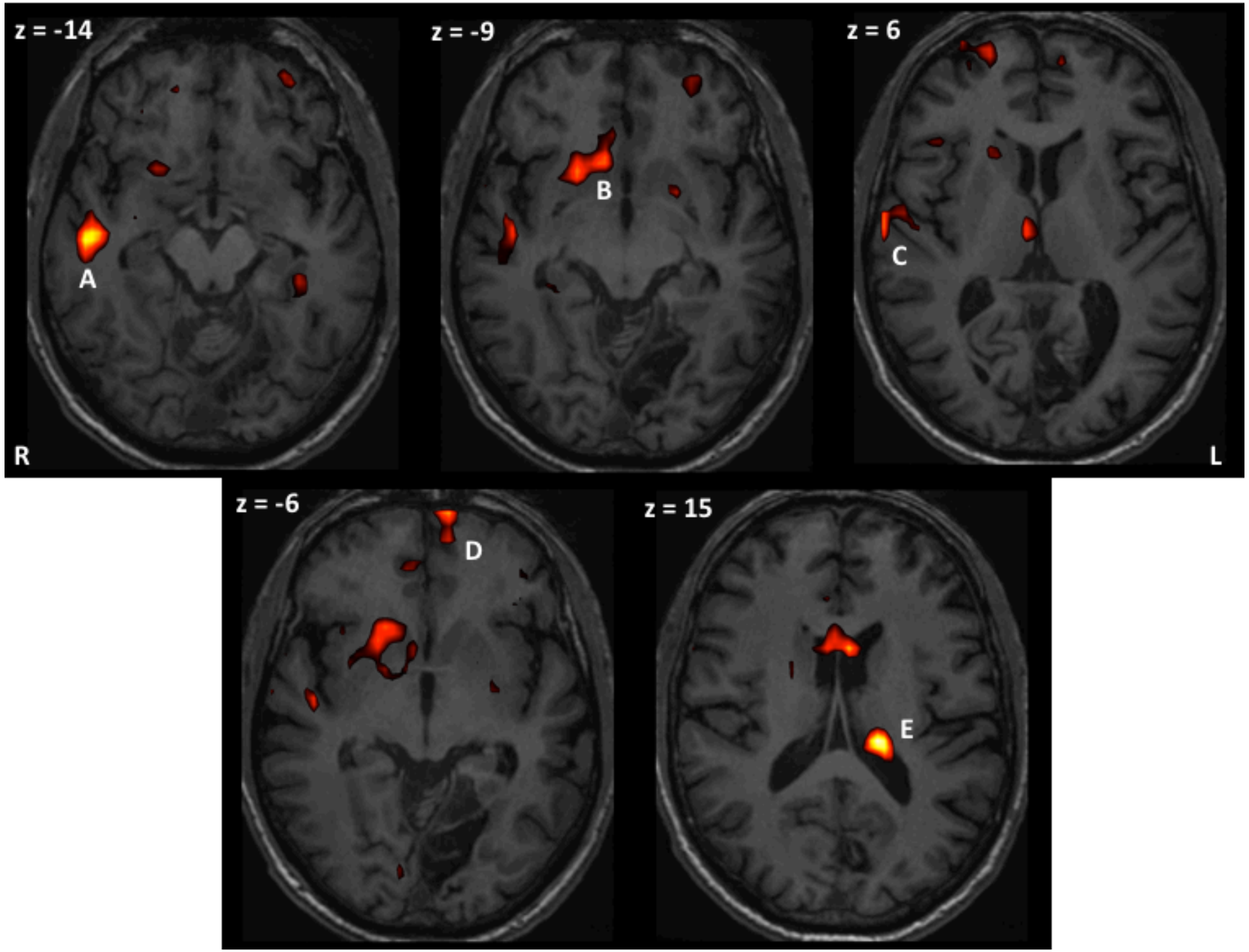
CEREBELLAR STROKE: case study

Cerebellar stroke

fMRI results:
- After > Before tDCS



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CEREBELLAR STROKE: case study

Cerebellar stroke

Bilateral damage in the cerebellum resulting in cerebellar dysarthria

↓

Asymmetrical insular activations (L > R)

↓

R anodal stimulation over insular region, cathode over L insular region

↓

More activation directly under anode and subcortically

Some improvement in speech intelligibility

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Clinical applications of cerebellar stimulation

- Cerebellar motor disorders
- Cerebellar stroke
- **Subcortical stroke**
- Cerebello-cerebral network disorder
- Neurodevelopmental disorders

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SUBCORTICAL STROKE: case study

Subcortical or extensive bilateral cerebral cortical damage

68-year-old right-handed man

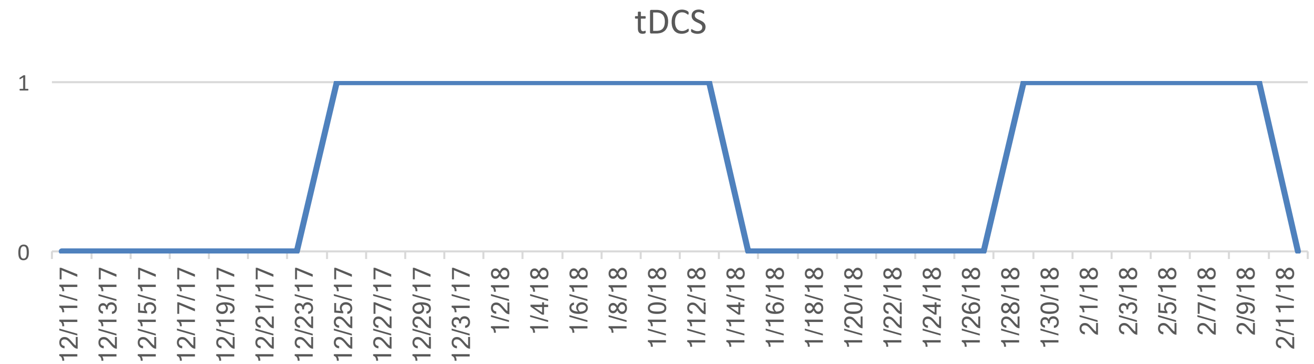
- Subcortical hemorrhage in left basal ganglia
- Hypokinetic dysarthria

- Old extensive lesion in right frontal and left parietal area

SUBCORTICAL STROKE: case study

Subcortical or extensive bilateral cerebral cortical damage

tDCS protocol:
- Anode over L CB
- Cathode over R CB
- 2mA, 20min, online (speech training)
- 3 weekly sessions, 9 weeks

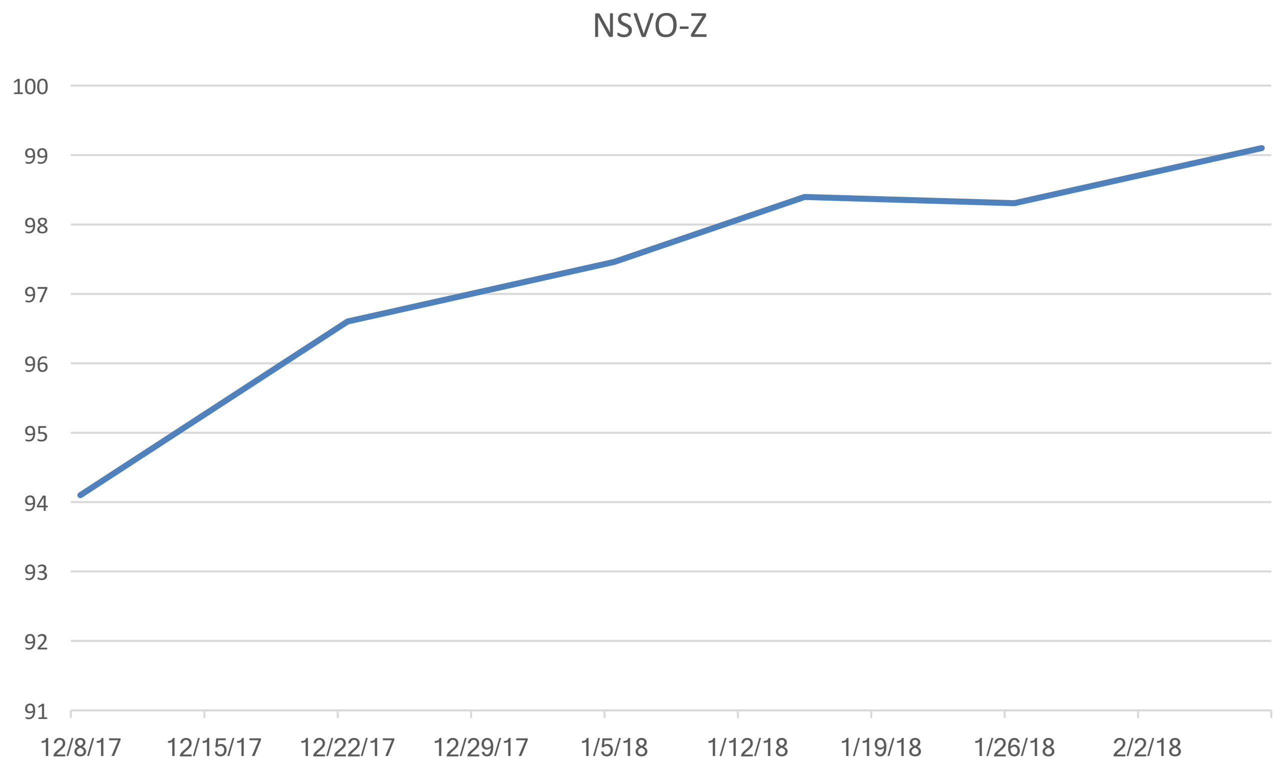


SUBCORTICAL STROKE: case study

Subcortical or extensive bilateral cerebral cortical damage

Results:

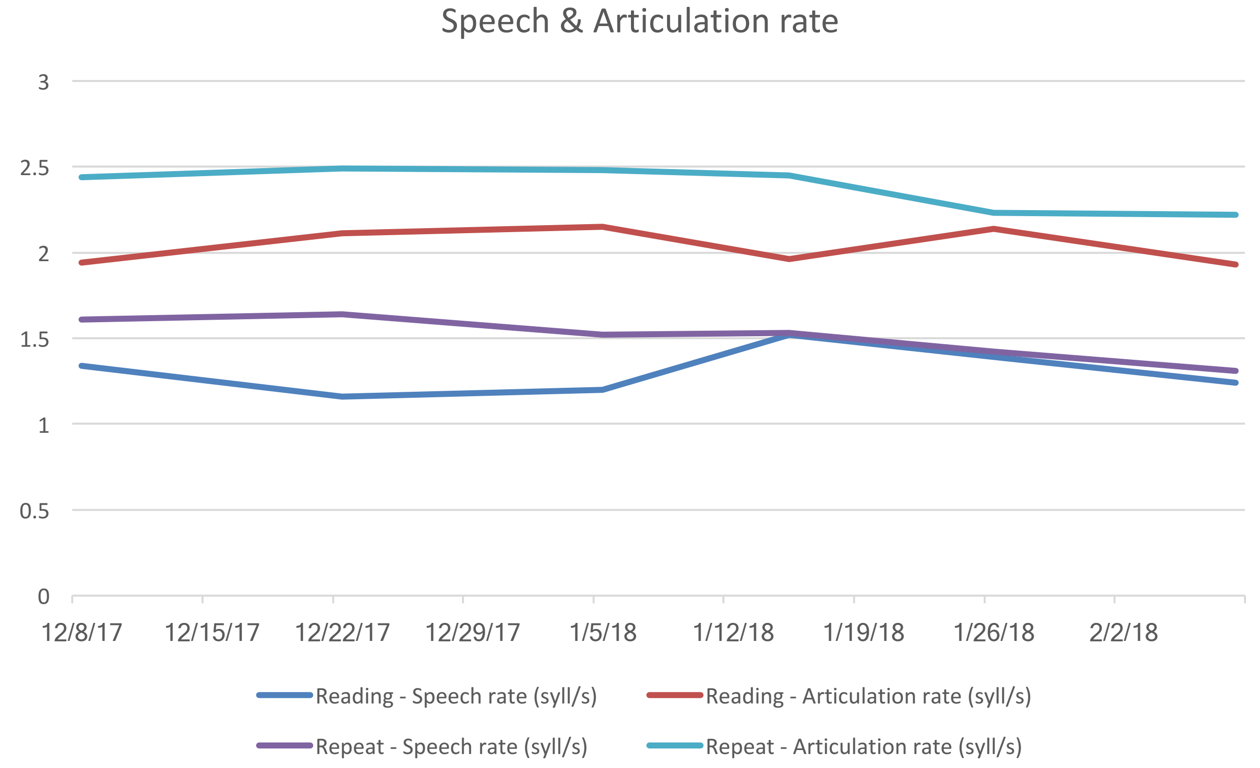
- Speech intelligibility

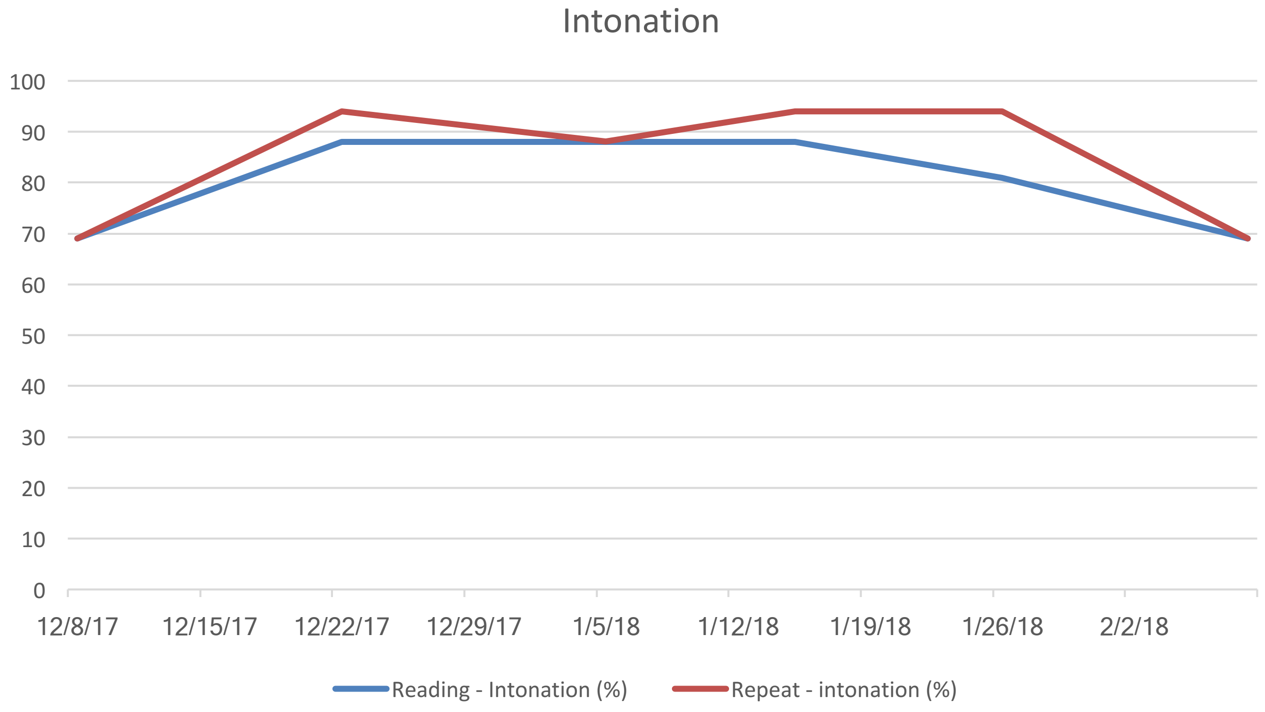


SUBCORTICAL STROKE: case study

Subcortical or extensive bilateral cerebral cortical damage

Results:





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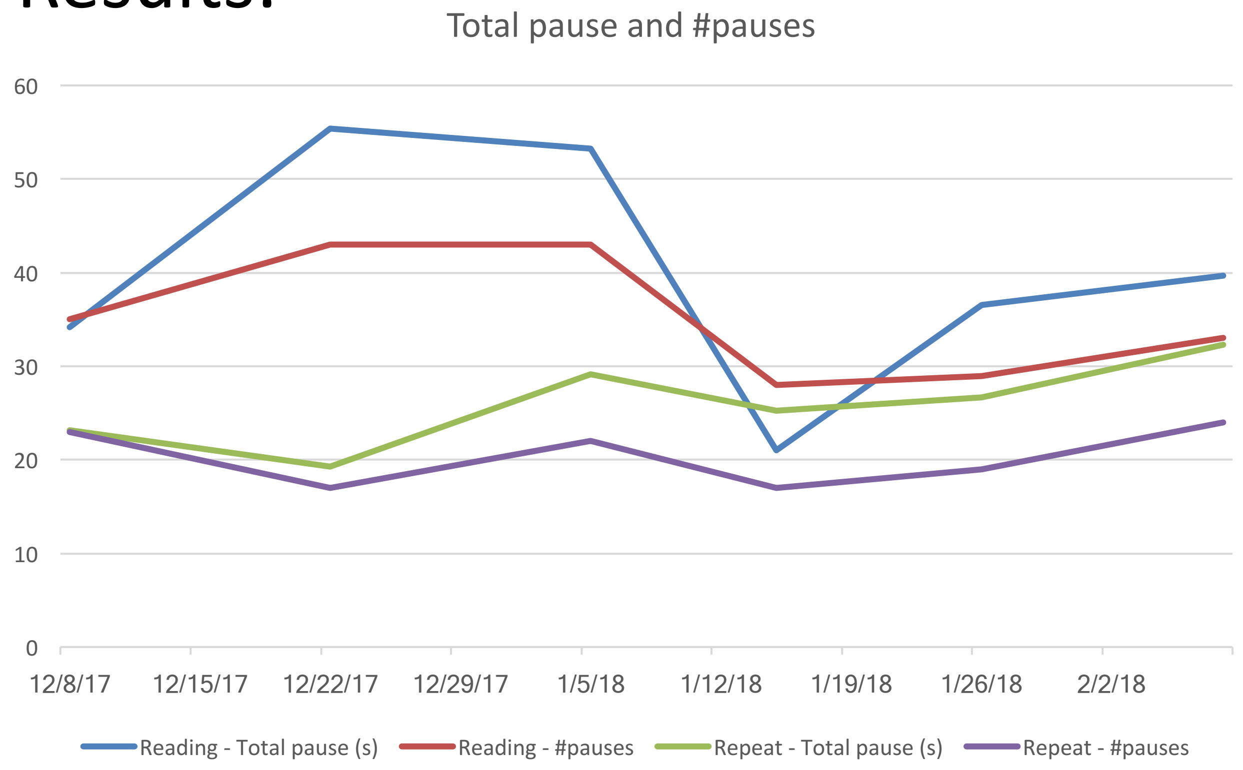
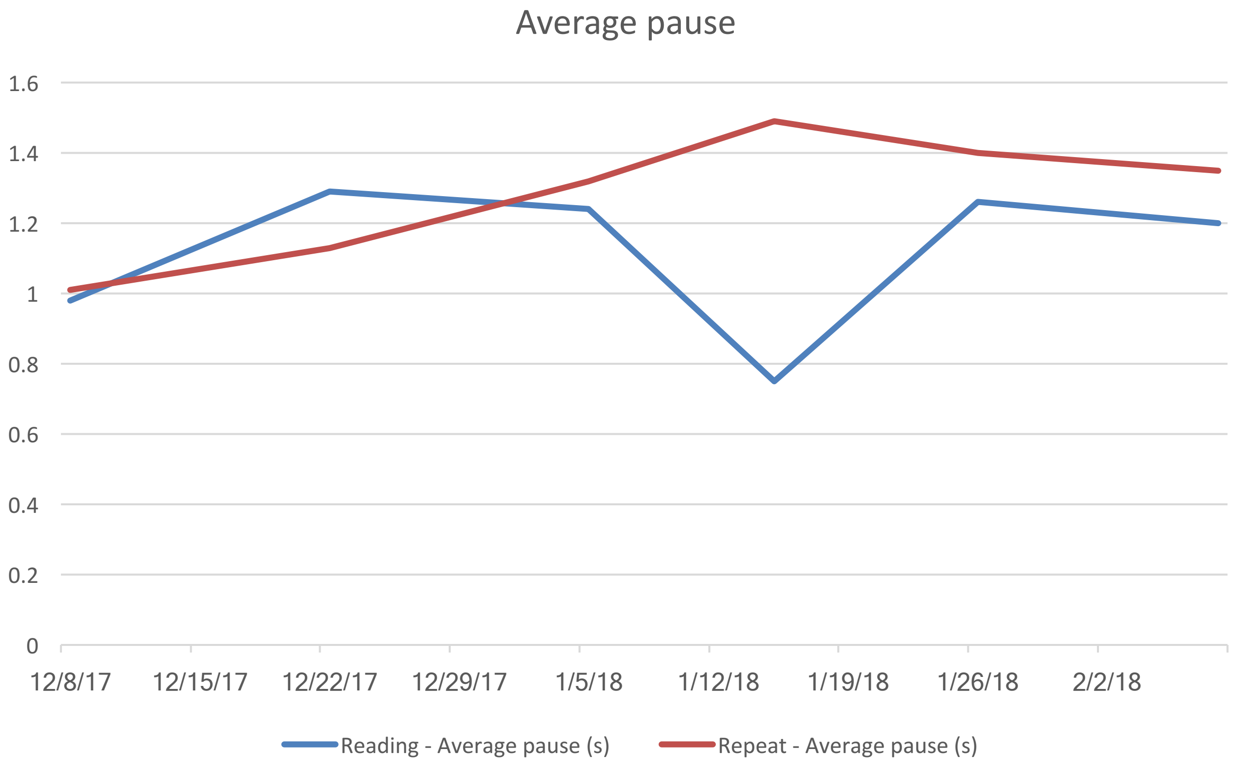
Results:





SUBCORTICAL STROKE: case study

Subcortical or extensive bilateral cerebral cortical damage

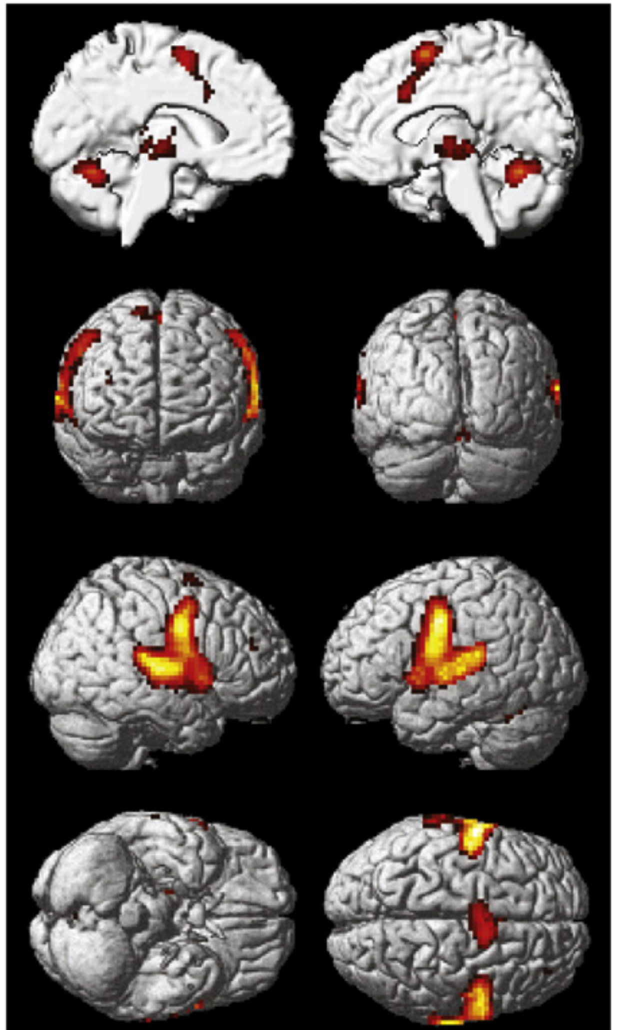
Speech:

- Speech intelligibility markedly improved but no clear indication for the added value of tDCS
- No change in intonation or speech/articulation rate
- Possible effect on pauses during reading after 3 weeks of tDCS

SUBCORTICAL STROKE: case study

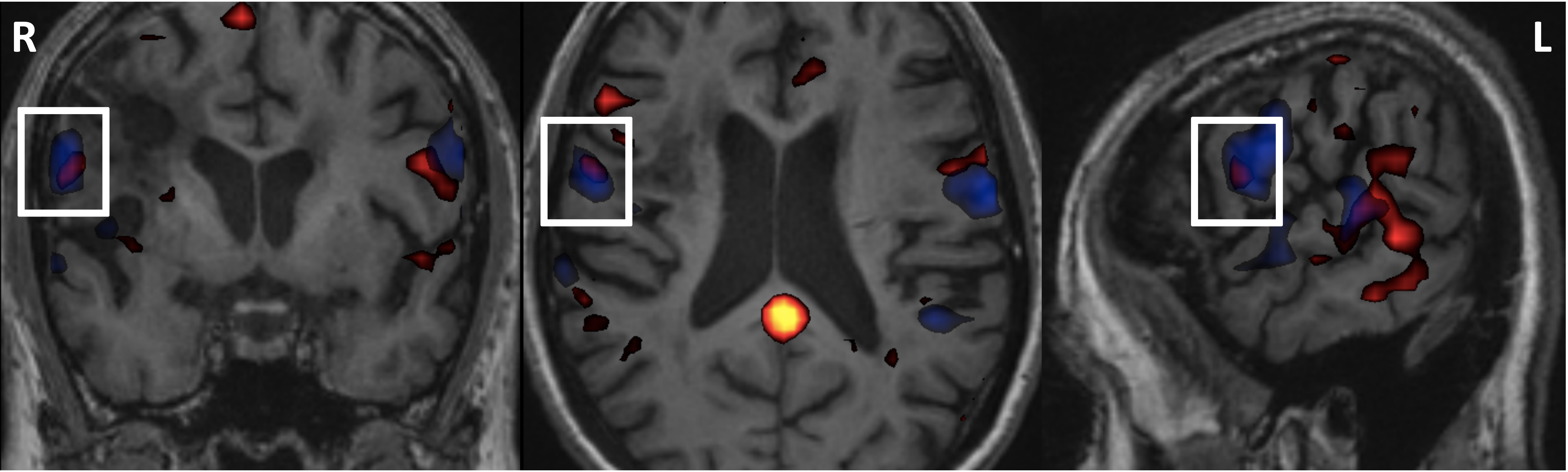
Subcortical or extensive bilateral cerebral cortical damage

fMRI: Speech protocol (pataka/tatata compared
to rest)
~ Brendel et al. (2010)



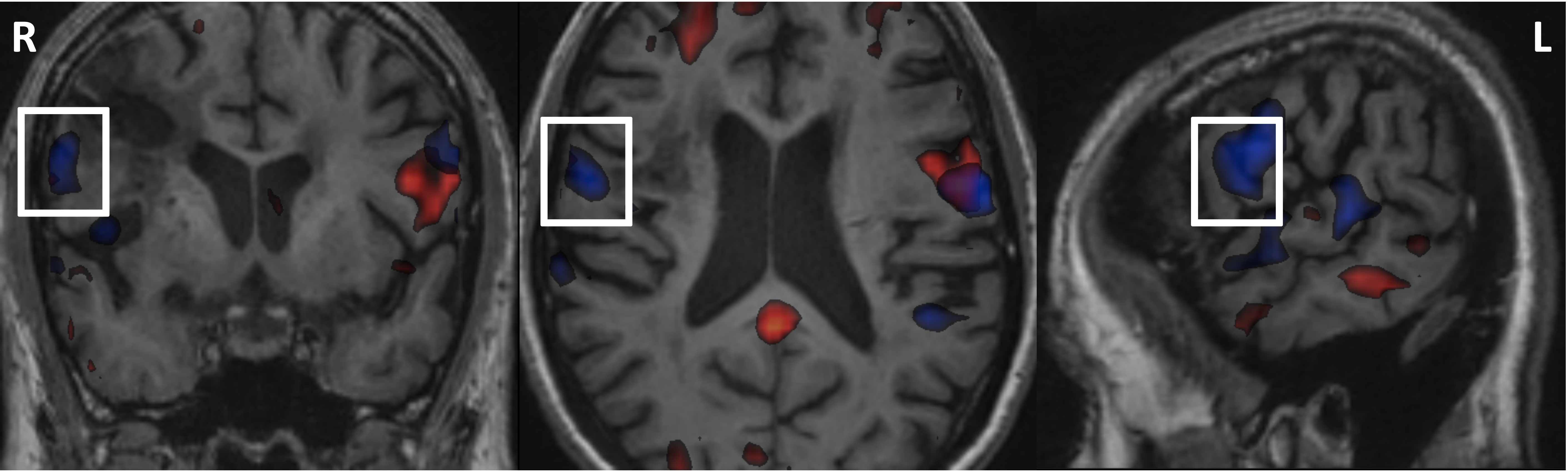
SUBCORTICAL STROKE: case study

fMRI pre stimulation



SUBCORTICAL STROKE: case study

fMRI post stimulation



SUBCORTICAL STROKE: case study

Subcortical or extensive bilateral cerebral cortical damage

fMRI:
- Left anodal stimulation appeared to inhibit right motor activations during speech
- Right cathodal stimulation appeared to excite left motor activations during speech
- Cerebellar stimulation primarily affected bilateral prefrontal areas

⇒ Neurophysiological mechanisms of cerebellar stimulation still poorly understood

Clinical applications of cerebellar stimulation

- Cerebellar motor disorders
- Cerebellar stroke
- Subcortical stroke
- **Cerebello-cerebral network disorder**
- Neurodevelopmental disorders

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CEREBELLO-CEREBRAL NETWORK DISORDER

Disorders caused/accompanied by cerebello-cerebral network anomalies

- Neuropsychiatric diseases (Schizophrenia, bipolar disorder)
- Neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, …)

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Clinical applications of cerebellar stimulation

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Why cerebellar stimulation?
NEURODEVELOPMENTAL DISORDERS

CEREBELLUM implicated in

- Developmental Coordination Disorder (DCD)
- Dyslexia
- Autism
- Attention Deficit Hyperactivity Disorder (ADHD)

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Why cerebellar stimulation?
Adults vs Children

CEREBELLAR DAMAGE

Adults:
- Subtle effect on acquired skills
- Most pronounced in acquisition/learning process

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Why cerebellar stimulation?
Adults vs Children

CEREBELLAR DAMAGE

Adults:
- Subtle effect on acquired skills
- Most pronounced in acquisition/learning process

Children (acquired and developmental damage):
- Great impact on cognitive and behavioral functions
- Rare improvement with conventional therapy

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Cerebellar stimulation: Future directions

Systematic studies needed to investigate the specific impact of

<u>Different stimulation parameters</u>

- Type, timing, and area of stimulation
- Intensity/duration/…

<u>Difference TMS and tDCS/tACS</u>

- Different working mechanisms

<u>Cerebellar involvement in neuroplasticity and functional networks</u>

- How exactly is the cerebellum involved in spontaneous recovery and the functional network

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CONCLUSION

Conclusion

- TMS and tDCS over the cerebellum are capable of modulating cortical functions through cerebello-cerebral connections, which might be useful to restore functional connectivity in a stroke population (e.g. case study of patient with subcortical stroke)

- Cerebellum is involved in several neurodegenerative, neuropsychiatric, and neurodevelopmental disorders, which makes it an interesting target for stimulation as a therapeutic aid

HOWEVER

- More research is needed to investigate the specific impact of cerebellar stimulation parameters on cerebellar excitability and cortical functions, and, more specifically, on functional connectivity

Thank you for your Attention

Questions:
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