



Cortical Control of Swallowing in Health and Disease - Moving from Bench to Bedside

Rainer Dziewas

*Department of Neurology
University Hospital Münster, Germany*

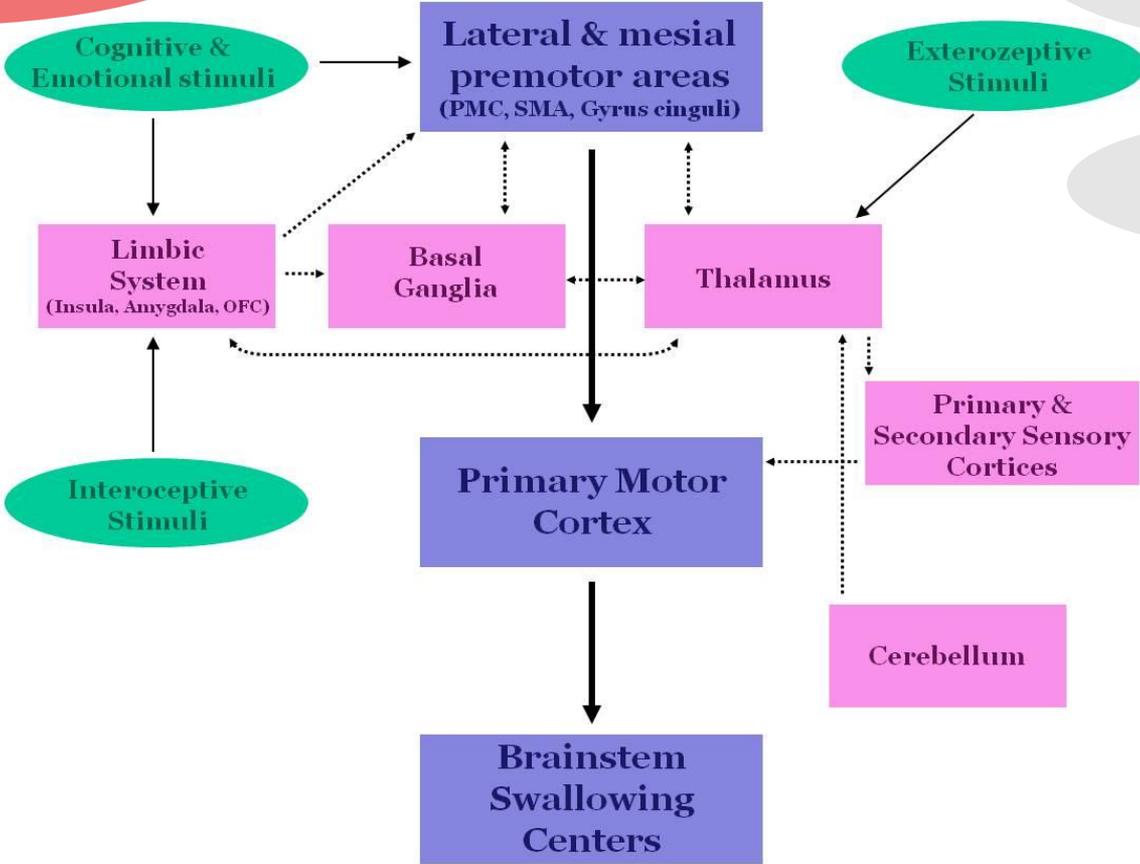
Outline

Hemispheric specialization?

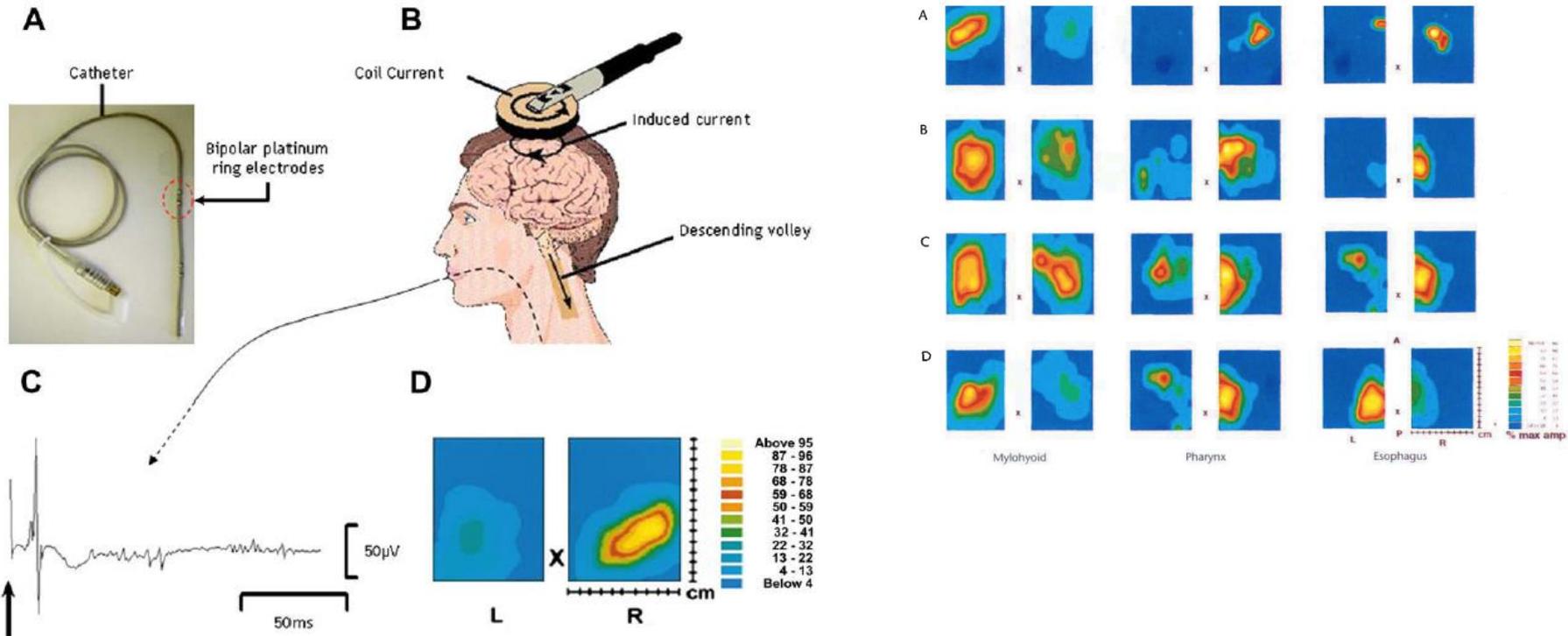
Modulation to external intervention?

Adaptive changes in the course of diseases?

Brain lesions & Dysphagia?



Swallowing Physiology Hemispheric Lateralization



- Interhemispheric asymmetry independent of handedness (10 right, 3 left, 7 bilateral)

Swallowing Physiology Hemispheric Lateralization

NeuroImage 76 (2013) 33–44



Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg



Functional connectivity of the cortical swallowing network in humans[☆]

Arash Babaei^a, B. Douglas Ward^b, Robert M. Siwiec^a, Shahryar Ahmad^a, Mark Kern^a,
Andrew Nencka^b, Shi-Jiang Li^b, Reza Shaker^{a,*}

Exp Brain Res (2012) 219:85–96
DOI 10.1007/s00221-012-3069-9

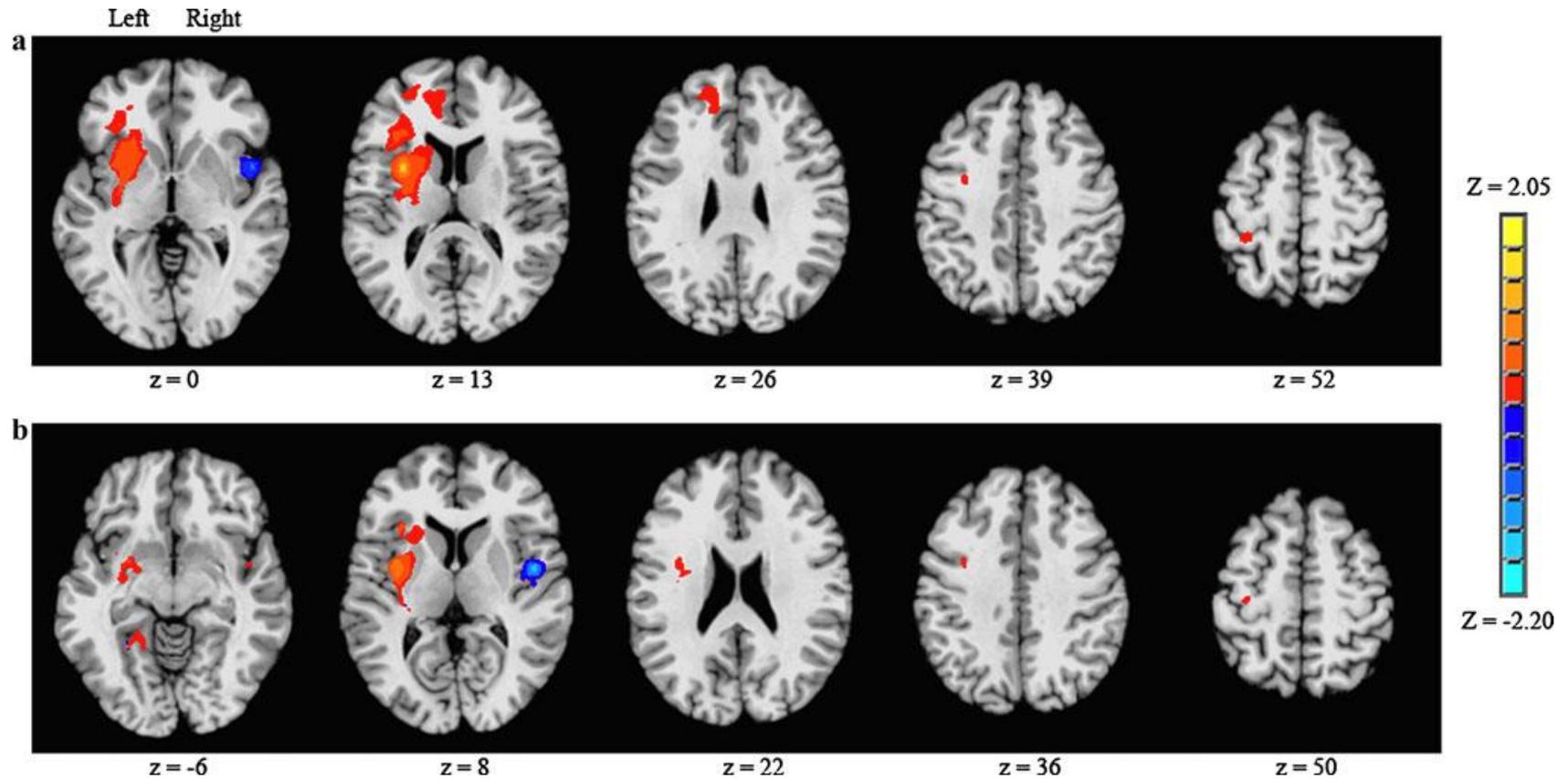
RESEARCH ARTICLE

**Functional connectivity and laterality of the motor and sensory
components in the volitional swallowing network**

Soren Y. Lowell · Richard C. Reynolds ·
Gang Chen · Barry Horwitz · Christy L. Ludlow

Swallowing Physiology Hemispheric Lateralization

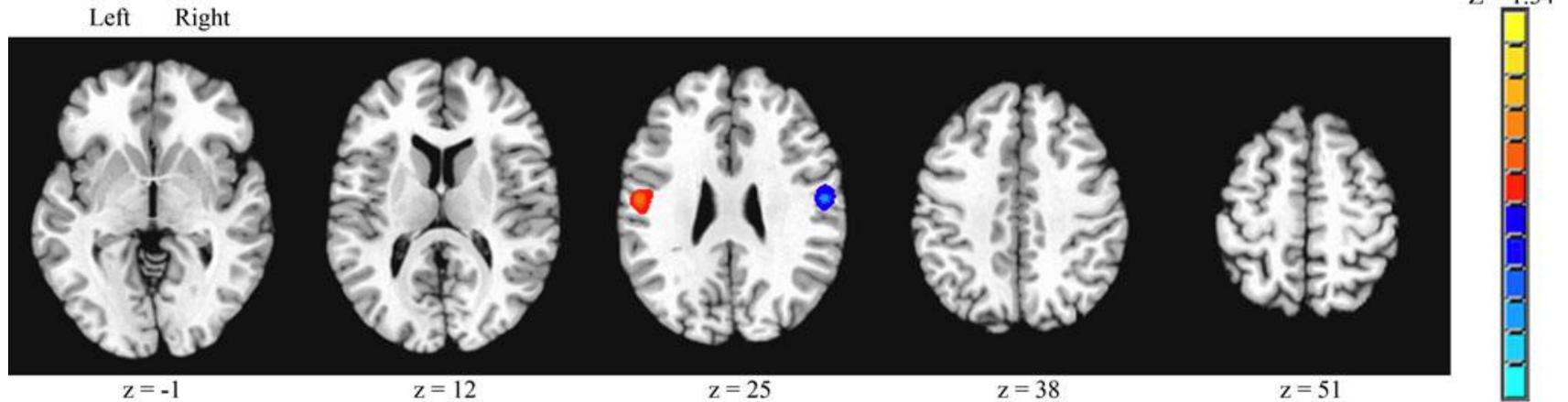
a=anterior insula; b= posterior insula



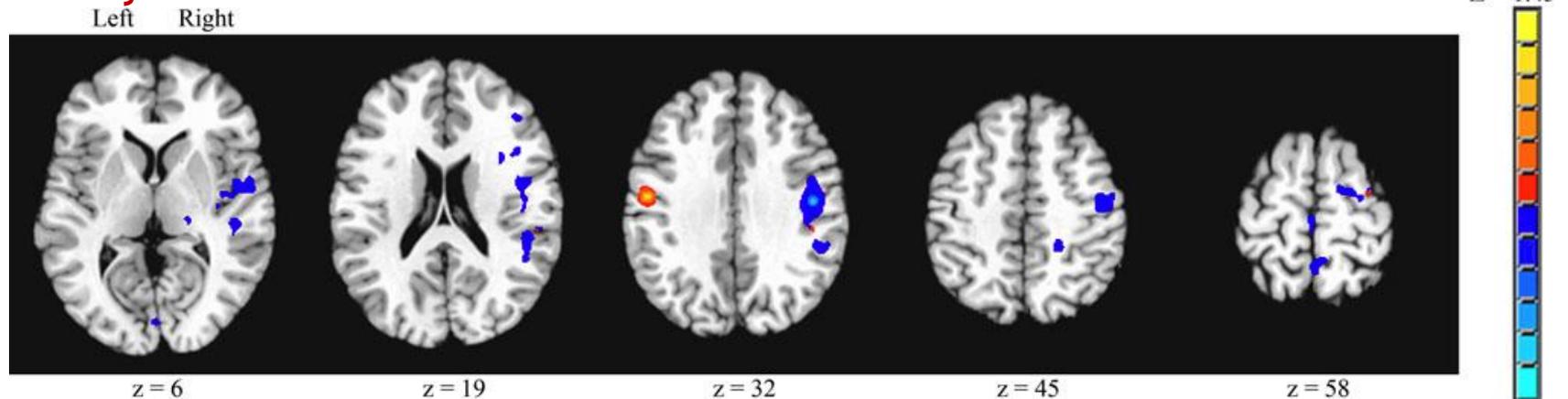
Swallowing Physiology

Hemispheric Lateralization

Primary sensory cortex

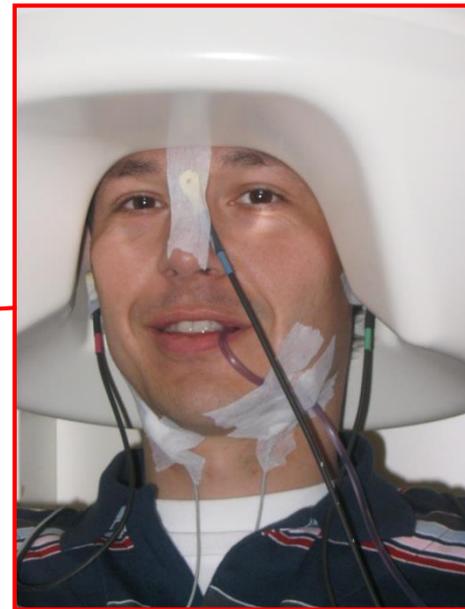
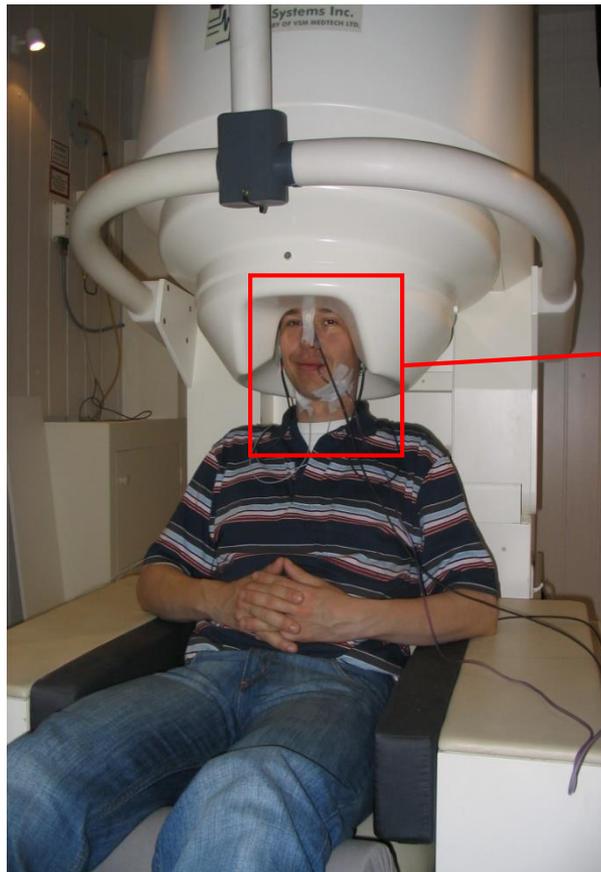


Primary motor cortex

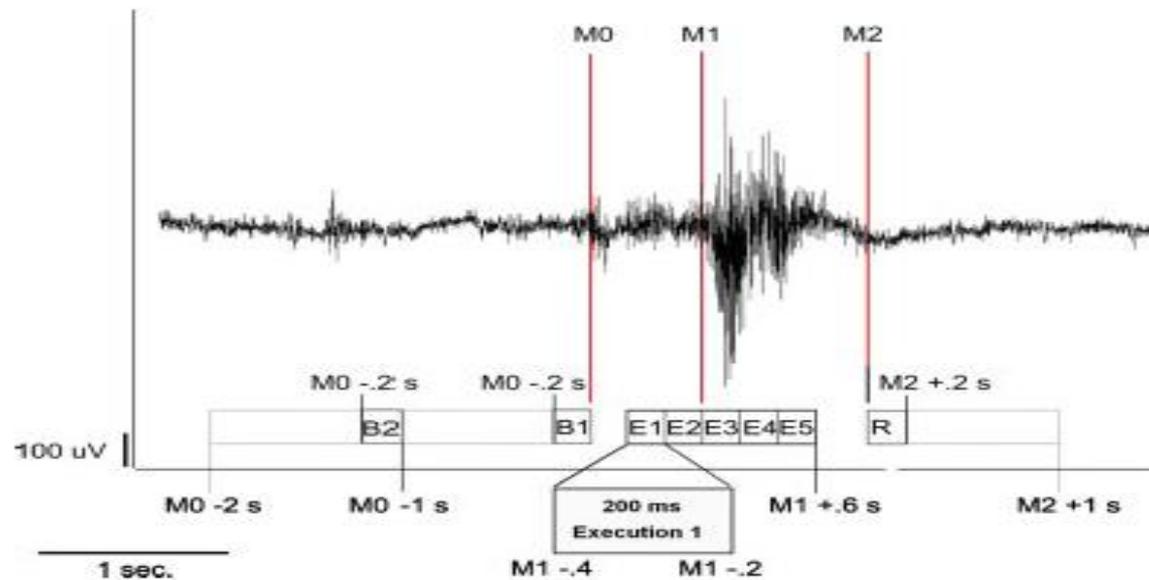
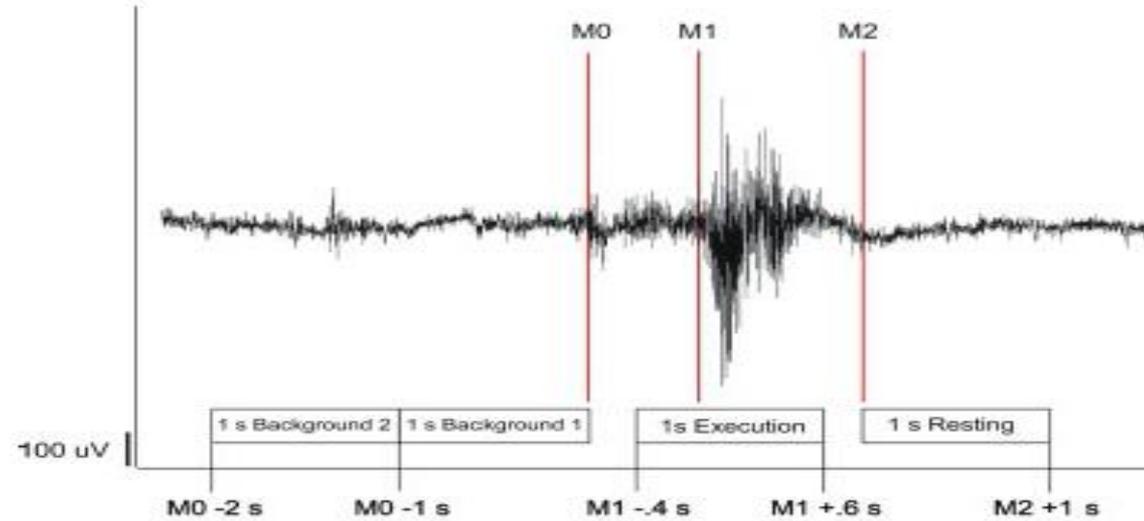


Magnetoencephalography (MEG)

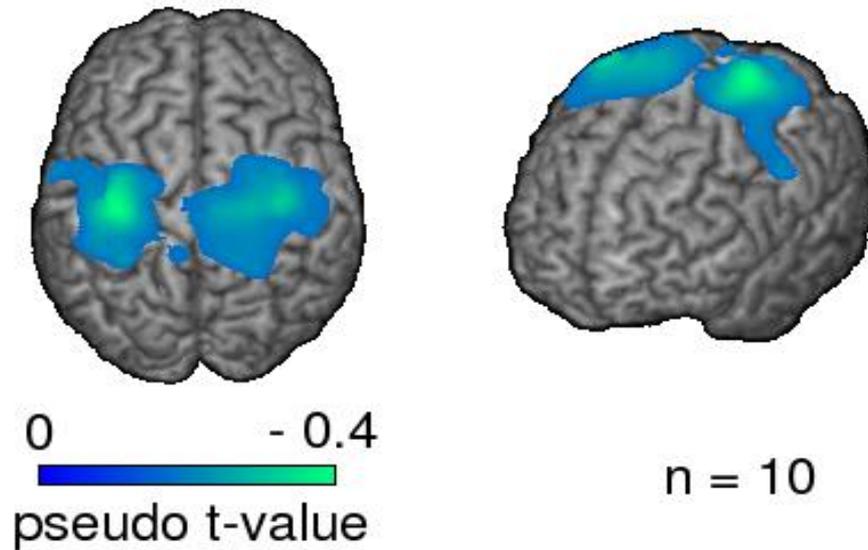
The experimental Set-up



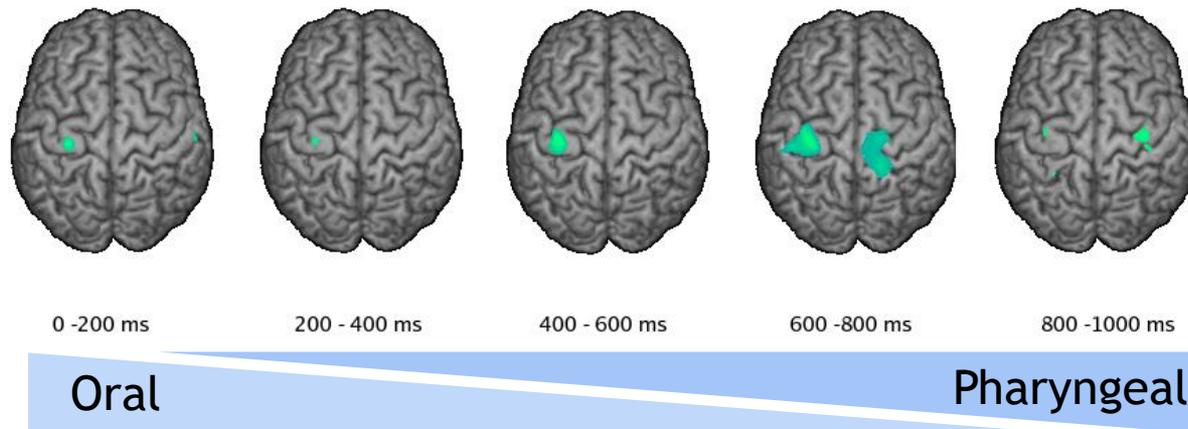
MEG sEMG signal



Time-dependent shift of activation



- „Early“ swallowing stage (= late orale phase?) => left-hemispheric dominance
- „Late“ swallowing stage (= pharyngeale phase?) => right-hemispheric dominance



Swallowing Physiology Hemispheric Lateralization

Sequential Evolution of Cortical Activity and Effective Connectivity of Swallowing Using fMRI

Human Brain Mapping 35:5962–5973 (2014)

Paul Glad Mihai,^{1*} Mareile Otto,² Thomas Platz,² Simon B. Eickhoff,^{3,4}
and Martin Lotze¹

“A repeated measure ANOVA revealed a significant activation over time in M1S1 starting in the left hemisphere and moving to the right hemisphere.”

Summary (1)

Summary (1):

- High intraindividual variability
- Different brain regions show different lateralization
- Time-dependent hemispheric shift within the primary sensorimotor cortex
 - „early“ => left
 - „late“ => right

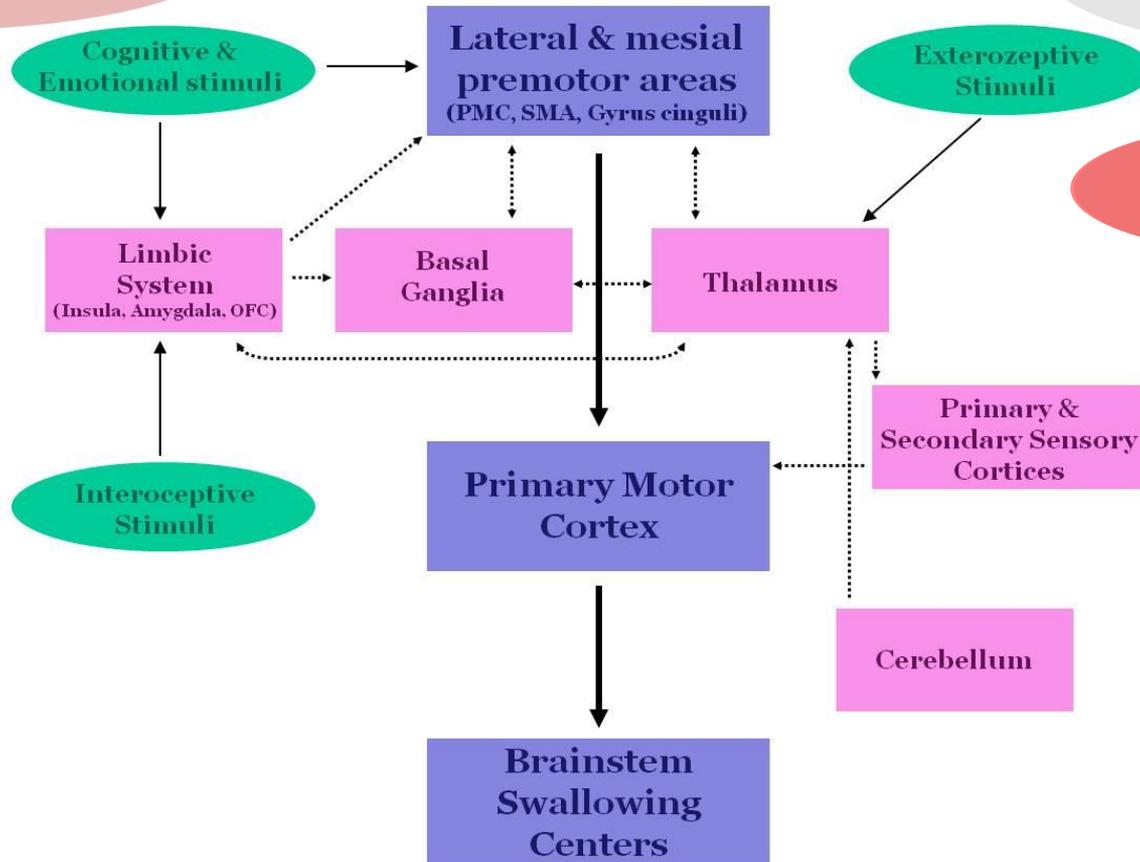
Outline

Hemispheric specialization?

Modulation to external intervention?

Adaptive changes in the course of diseases?

Brain lesions & Dysphagia?



Stroke&Dysphagia - Lesion studies

Back to the roots

Dysphagia 3:11-17 (1988)

Dysphagia
© Springer-Verlag New York Inc. 1988

Swallowing After Unilateral Stroke of the Cerebral Cortex: Preliminary Experience

JoAnne Robbins, Ph.D. and Ross L. Levine, M.D.
Departments of Neurology and Radiology, University of Wisconsin Clinical Science Center
and William S. Middleton Veterans Administration Hospital, Madison, Wisconsin, USA

Arch Phys Med Rehabil Vol 74, December 1993

Swallowing After Unilateral Stroke of the Cerebral Cortex

JoAnne Robbins, PhD, Ross L. Levine, MD, Andrea Maser, MS, John C. Rosenbek, PhD, Gail B. Kempster, PhD

Lesion Site in Unilateral Stroke Patients with Dysphagia

Journal of Stroke and Cerebrovascular Diseases, Vol. 6, No. 1, 1996: pp 30-34

Stephanie K. Daniels, MS, Anne L. Foundas, MD, Gregory C. Iglesias, MD,
and Michael A. Sullivan, MD

- Left-hemispheric stroke:
 - Premature spillage
 - Oral residues
 - Oral dyscoordination
- Right-hemispheric stroke:
 - Delayed swallowing reflex
 - Impaired pharyngeal motility
 - Higher incidence of penetration and aspiration

Stroke&Dysphagia - Lesion studies

A new approach

The impact of lesion location on dysphagia incidence, pattern and complications in acute stroke. Part 1: Dysphagia incidence, severity and aspiration

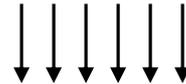
The impact of lesion location on dysphagia incidence, pattern and complications in acute stroke. Part 2: Oropharyngeal residue, swallow and cough response, and pneumonia

S. Suntrup-Krueger^{a,*} , A. Kemmling^{b,*}, T. Warnecke^a, C. Hamacher^a, S. Oelenberg^a, T. Niederstadt^c, W. Heindel^c, H. Wiendl^a and R. Dziewas^a

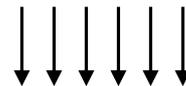
- 200 patients with acute Stroke
 - Mean age 73,7 years (30-96 years); ♀ 99, ♂ 101
 - NIH 9,7 (0-22)
 - First-ever strokes, no preexisting dysphagia
- FEES within 96h from admission
- Correlation of clinical findings with lesion topology as seen in CT or MRI (24-48h)

Stroke&Dysphagia - Lesion studies Methods

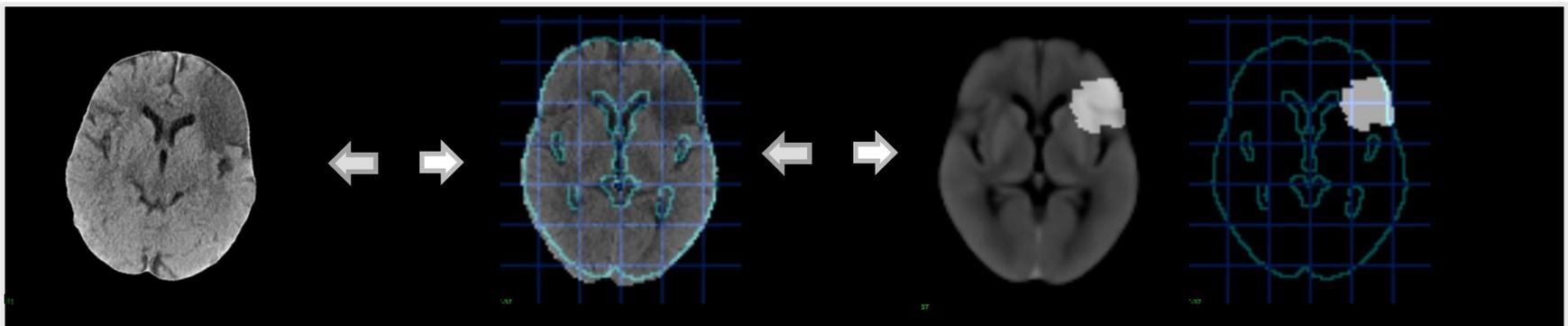
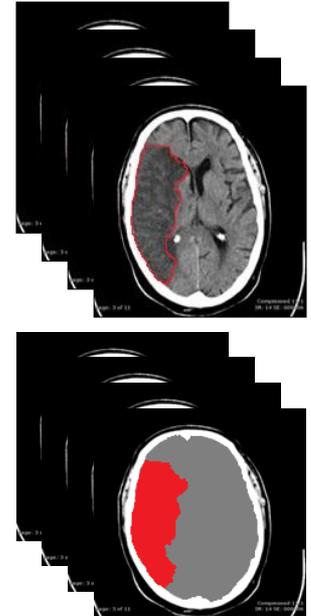
- Manual lesion segmentation in CT/DWI/FLAIR (24-48h from admission)



- binary lesion mask



- Registration to MNI standard space optimized by non-linear refinement



Stroke&Dysphagia - Lesion studies Methods

- Region-specific Odds Ratio (OR) for dichotomized variables (present vs. not present):
 - Dysphagia
 - Mild (FEDSS 1-3) vs. severe dysphagia (FEDSS 4-6)
 - Penetration/aspiration
 - Delayed/absent swallow reflex
 - Missing/insufficient cough reflex
 - Development of Pneumonia until discharge

$$OR_{Region\ i} = \frac{Dysphagia^+ \left\{ \left(\frac{\%Vol_{Infarct}}{\%Vol_{no-Infarct}} \right)_{Region\ i} \right\}}{Dysphagia^- \left\{ \left(\frac{\%Vol_{Infarct}}{\%Vol_{no-Infarct}} \right)_{Region\ i} \right\}}$$

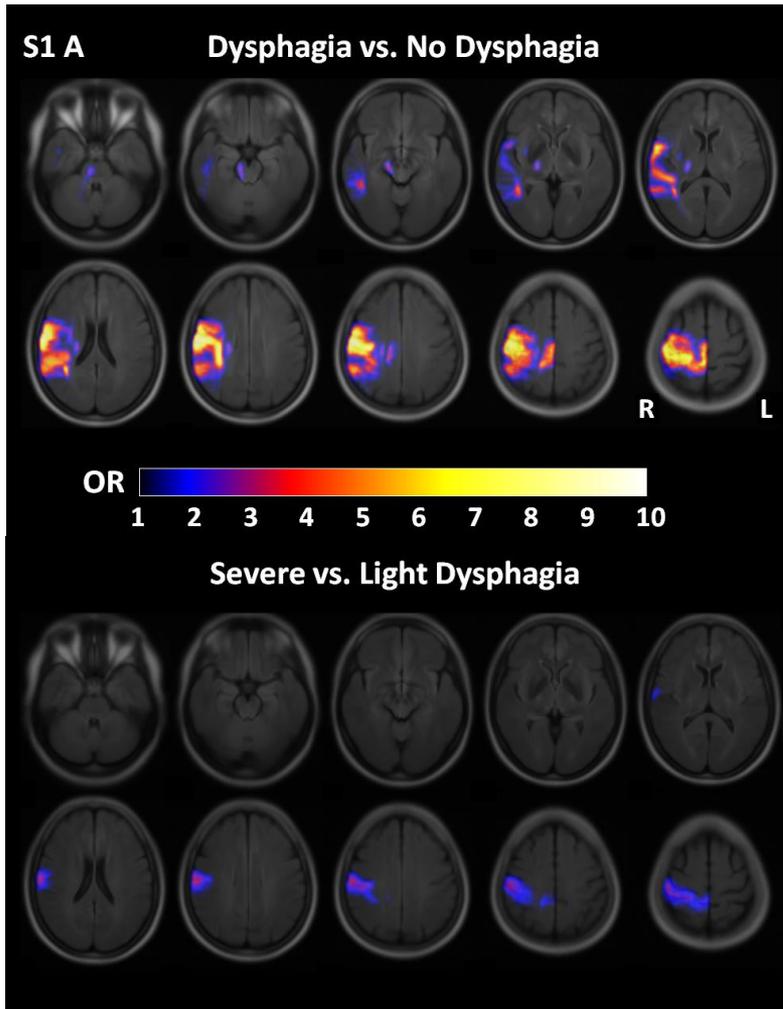
Stroke&Dysphagia - Lesion studies Results

	Yes, ml	No, ml	p-value
Dysphagia	101.9 ± 127.9	59.3 ± 97.1	0.032*
Severe Dysphagia	94.4 ± 150.7	86.6 ± 99.9	0.013*
Penetration/Aspiration	108.2 ± 131.6	62.4 ± 97.6	0.008*
Absent/delayed swallow reflex	113.0 ± 142.5	81.0 ± 95.6	0.058
Absent/insufficient cough reflex	129.0 ± 168.0	86.7 ± 97.2	0.021*
Pneumonia	127.0 ± 174.0	93.8 ± 105.0	0.067

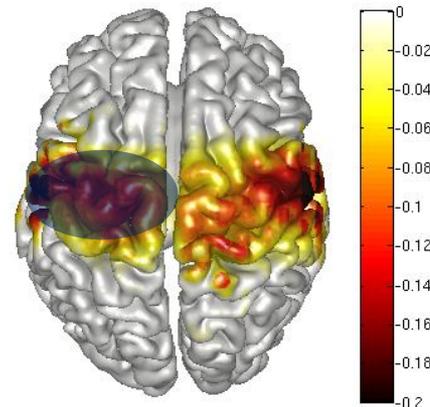
=> Size matters!

* statistically significant

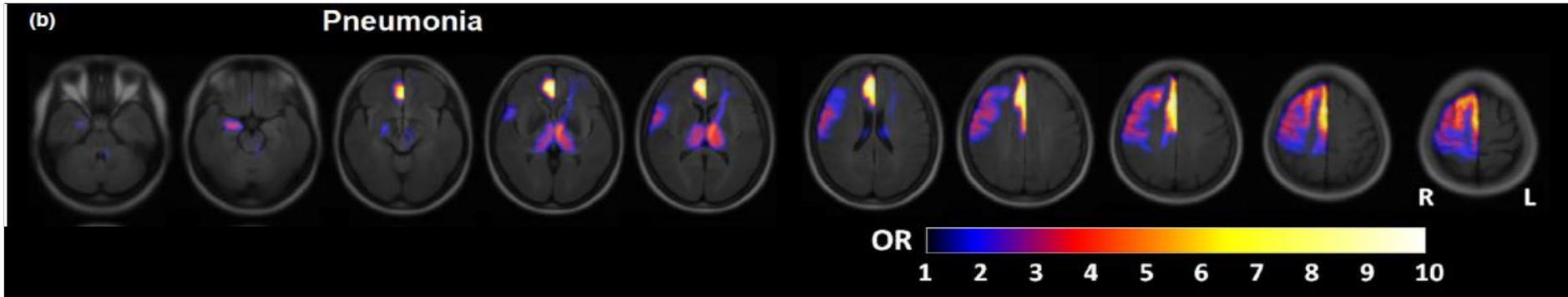
Stroke&Dysphagia - Lesion studies Results



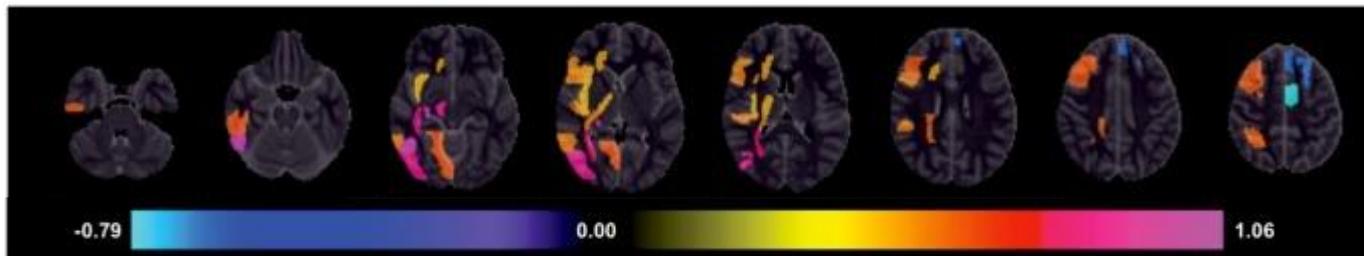
Brain region	Dysphagia +	Dysphagia -	p-value	OR
Postcentral gyrus, r	5.2 ± 15.9	0.5 ± 2.8	0.043	10.68
Precentral gyrus, r	5.1 ± 15.3	0.8 ± 3.1	0.048	6.88
Supramarginal gyrus, r	8.0 ± 2.2	1.6 ± 7.3	0.043	5.27
Planum temporale, r	9.9 ± 25.5	2.2 ± 10.0	0.041	4.88
Parietal operculum cortex, r	11.0 ± 27.2	2.7 ± 14.3	0.041	4.45
Sup. longitudinal fasciculus, r	8.5 ± 19.3	2.2 ± 5.3	0.028	4.17
Corticospinal tract, r	5.4 ± 11.3	2.0 ± 5.2	0.044	2.79



Stroke&Dysphagia - Lesion studies Results



- Cohort study
- 215 stroke patients with pneumonia vs. 215 stroke patients without pneumonia
- Right-hemispheric lesions significantly more frequent in stroke patients with pneumonia



Lesion Study II

NeuroImage: Clinical 22 (2019) 101685

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl



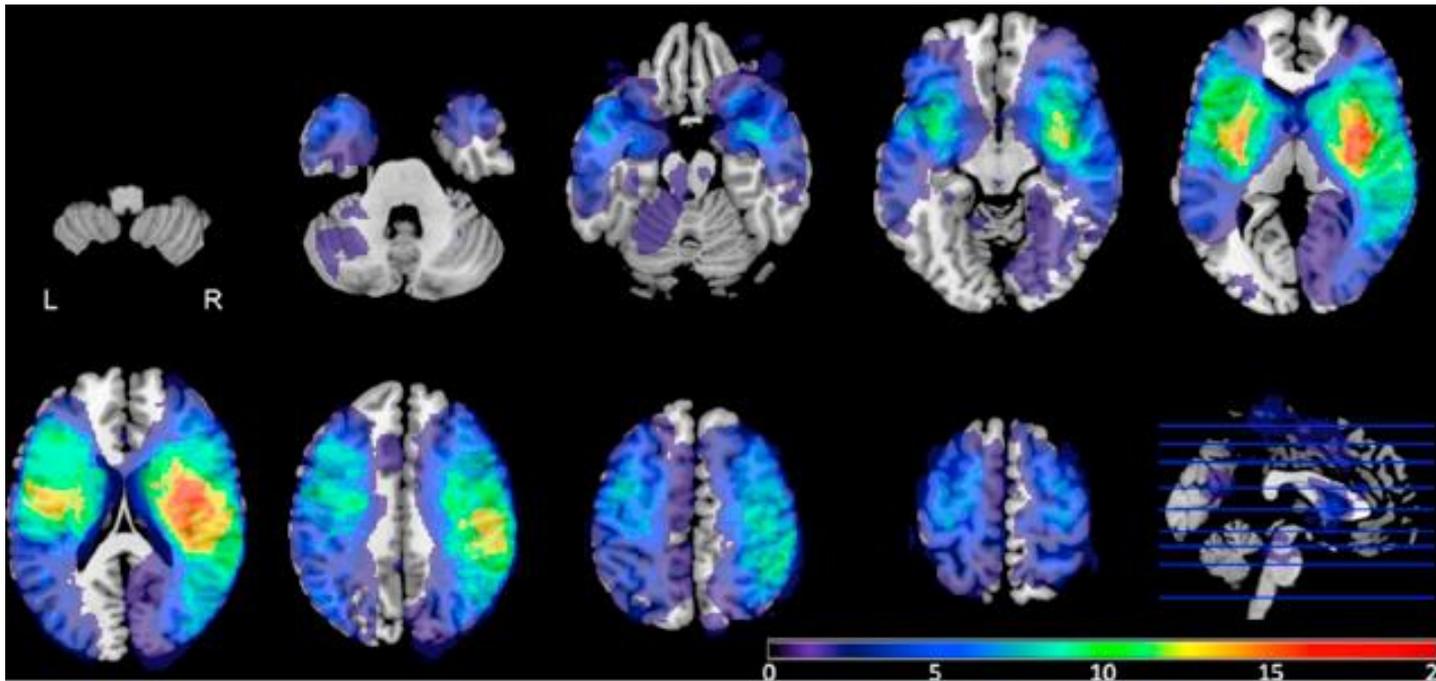
ELSEVIER



Mapping acute lesion locations to physiological swallow impairments after stroke

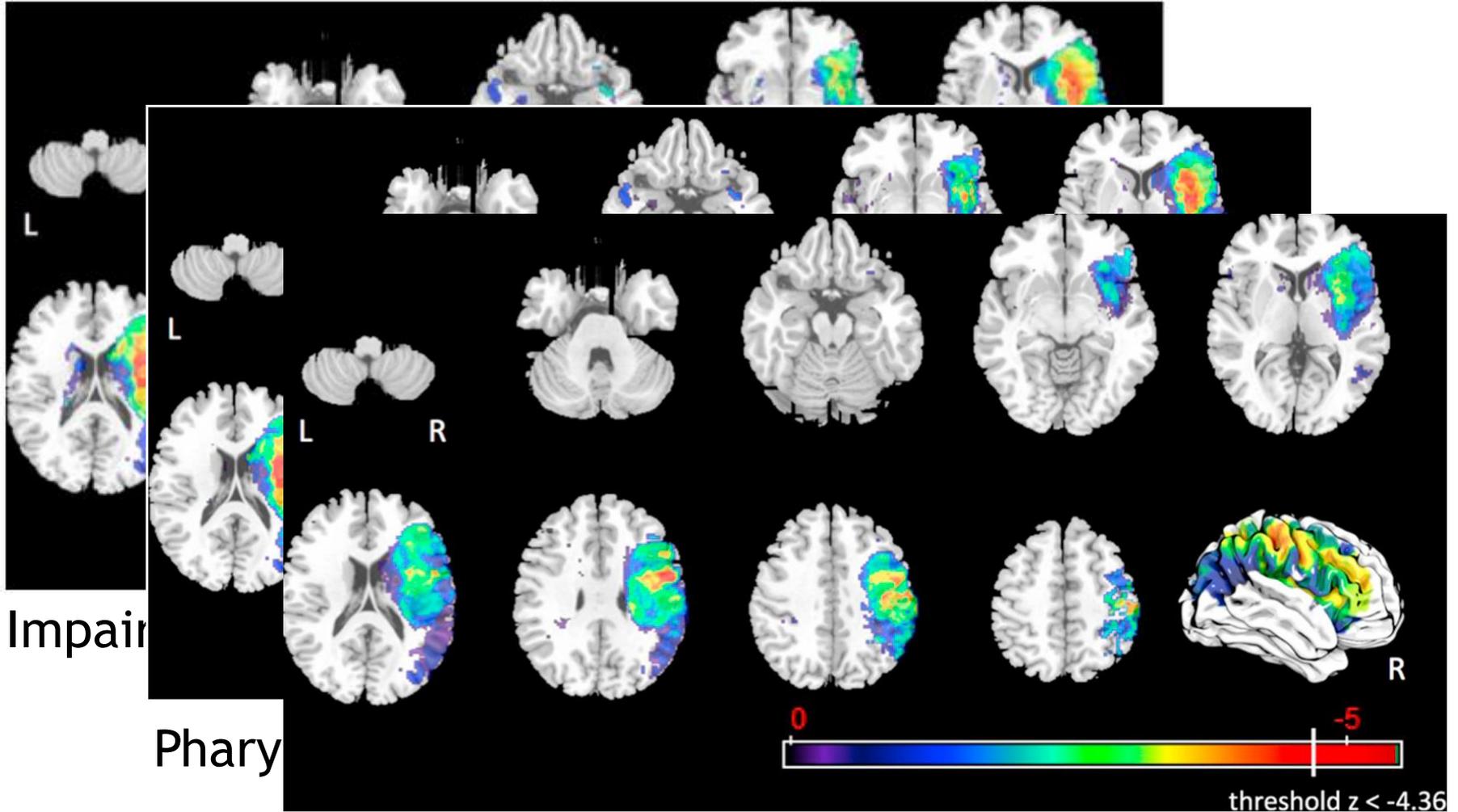


Janina Wilmskoetter^{a,b,*}, Leonardo Bonilha^b, Bonnie Martin-Harris^c, Jordan J. Elm^d, Janet Horn^a, Heather S. Bonilha^{a,e}



Lesion distribution in total cohort (N=68)

Lesion Study II



Impair

Phary

Penetration-Aspiration Score

Stroke&Dysphagia - Lesion studies

What about left-hemispheric lesions?

Dysphagia
DOI 10.1007/s00455-017-9856-5



ORIGINAL ARTICLE

Lesions Responsible for Delayed Oral Transit Time in Post-stroke Dysphagia

Hyun Im Moon¹ · Seo Yeon Yoon¹ · Tae Im Yi¹ · Yoon Jeong Jeong¹ ·
Tae Hwan Cho¹

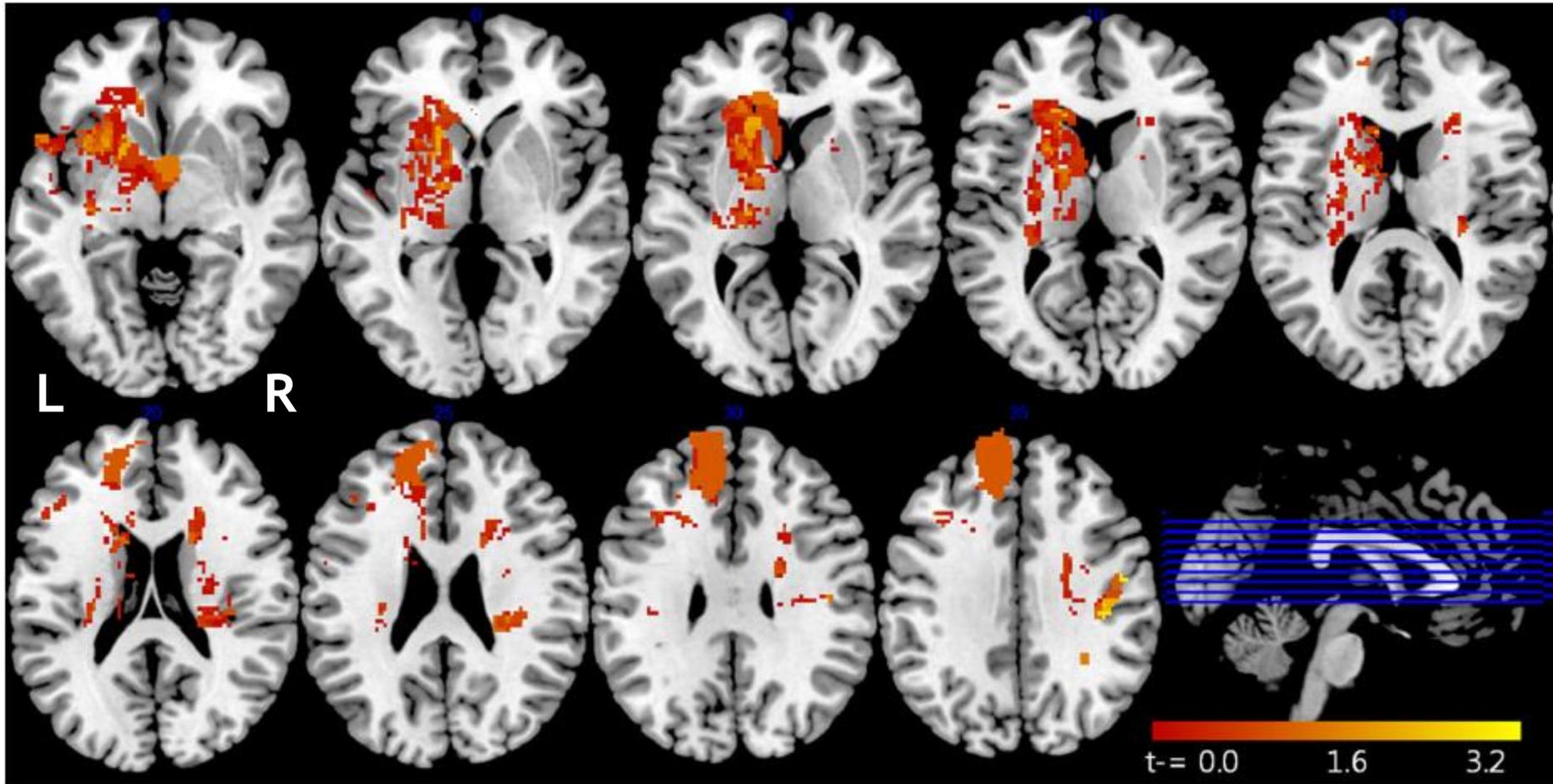
Table 1 General characteristics of subjects ($N = 90$)

Characteristics		
Age, years (range)		68.02 ± 13.21 (40–97)
Gender, n (%)	Male	57 (63.3%)
Lesion side, n	Right/left/bilateral	50/35/5
Lesion location, n	Supratentorium/infratentorium	74/16
Stroke type, n	Ischemic/hemorrhagic	64/26
Lesion volume, mm ³		29248 ± 3612
Interval between stroke onset and VFSS, days		18.9 ± 6.2
K-MMSE		17.71 ± 8.45
FIM		52.76 ± 19.85
Feeding status, n	Regular diet	21
	Soft diet	30
	Nasogastric tube	37
	PEG	0
	NPO	2

K-MMSE Korean version of the Mini Mental Status Exam, *FIM* functional independence measure, *PEG* percutaneous endoscopic gastrostomy, *NPO* none per oral

Stroke&Dysphagia - Lesion studies

What about left-hemispheric lesions?



Summary (2)

- Right hemispheric stroke:
 - Increased risk of pharyngeal stage dysphagia
- Left hemispheric stroke:
 - Increased risk of oral stage dysphagia

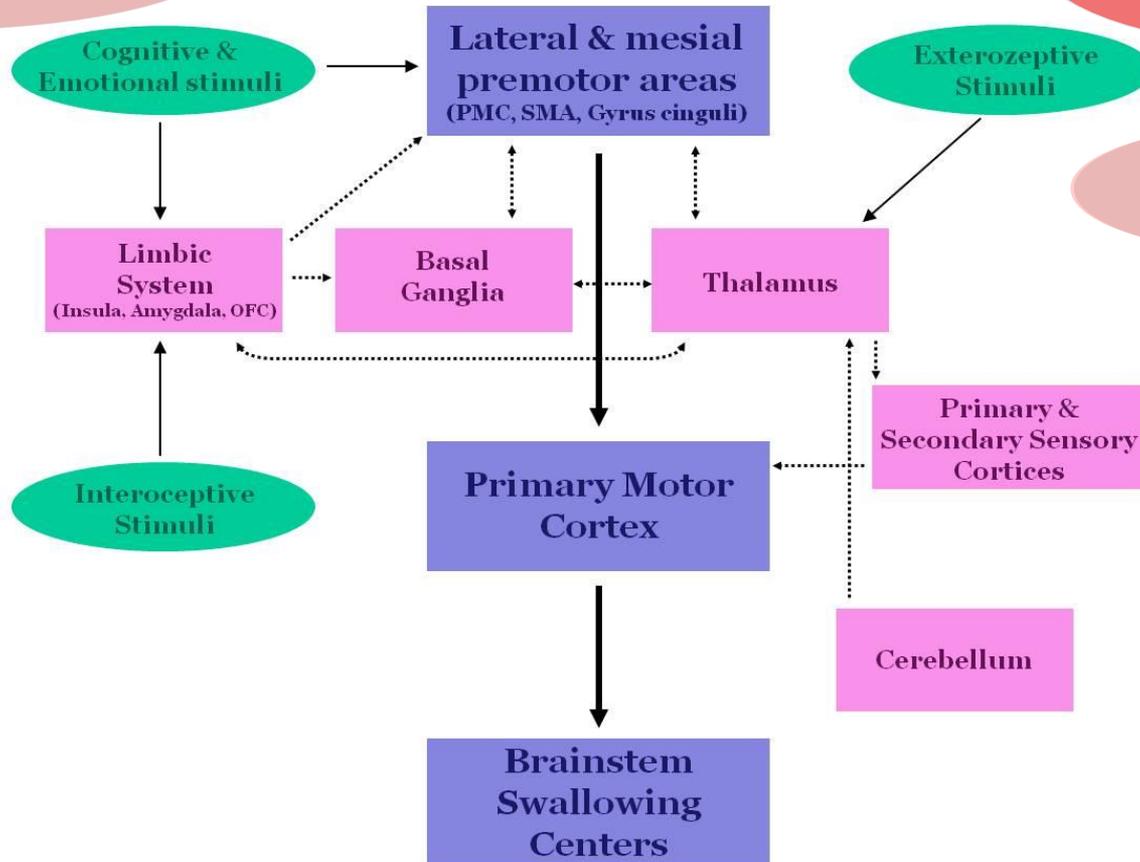
Outline

Hemispheric specialization?

Modulation to external intervention?

Adaptive changes in the course of diseases?

Brain lesions & Dysphagia?



Stroke & Dysphagia Functional Connectivity

Altered Resting-State Functional and White Matter Tract Connectivity in Stroke Patients With Dysphagia

Neurorehabilitation and
Neural Repair
2014, Vol. 28(3) 260–272
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DOI: 10.1177/1545968313508227
nrr.sagepub.com



Shasha Li, MD^{1,2}, Zhenxing Ma, MD¹, Shipeng Tu, MS³, Muke Zhou, MD¹,
Sihan Chen, MS¹, Zhiwei Guo, MS³, Qiyong Gong, PhD^{1,4}, Li He, MD¹,
Xiaoqi Huang, PhD¹, Dezhong Yao, PhD³, Su Lui, PhD¹, Bo Yu, MD⁵,
Xiaotong Wang, MS², Dong Zhou, MD¹, and Chengqi He, MD¹

J Rehabil Med 2014; 46: 126–131

ORIGINAL REPORT

ALTERED DEFAULT MODE AND AFFECTIVE NETWORK CONNECTIVITY IN
STROKE PATIENTS WITH AND WITHOUT DYSPHAGIA

Shasha Li, MD^{1,2}, Muke Zhou, MD³, Bo Yu, MD⁴, Zhenxing Ma, MD³, Sihan Chen, MS³,
Qiyong Gong, PhD^{5,6}, Li He, MD³, Xiaoqi Huang, PhD⁵, Su Lui, PhD⁵, Xiaotong Wang, MS⁷,
Dong Zhou, MD³ and Chengqi He, MD¹

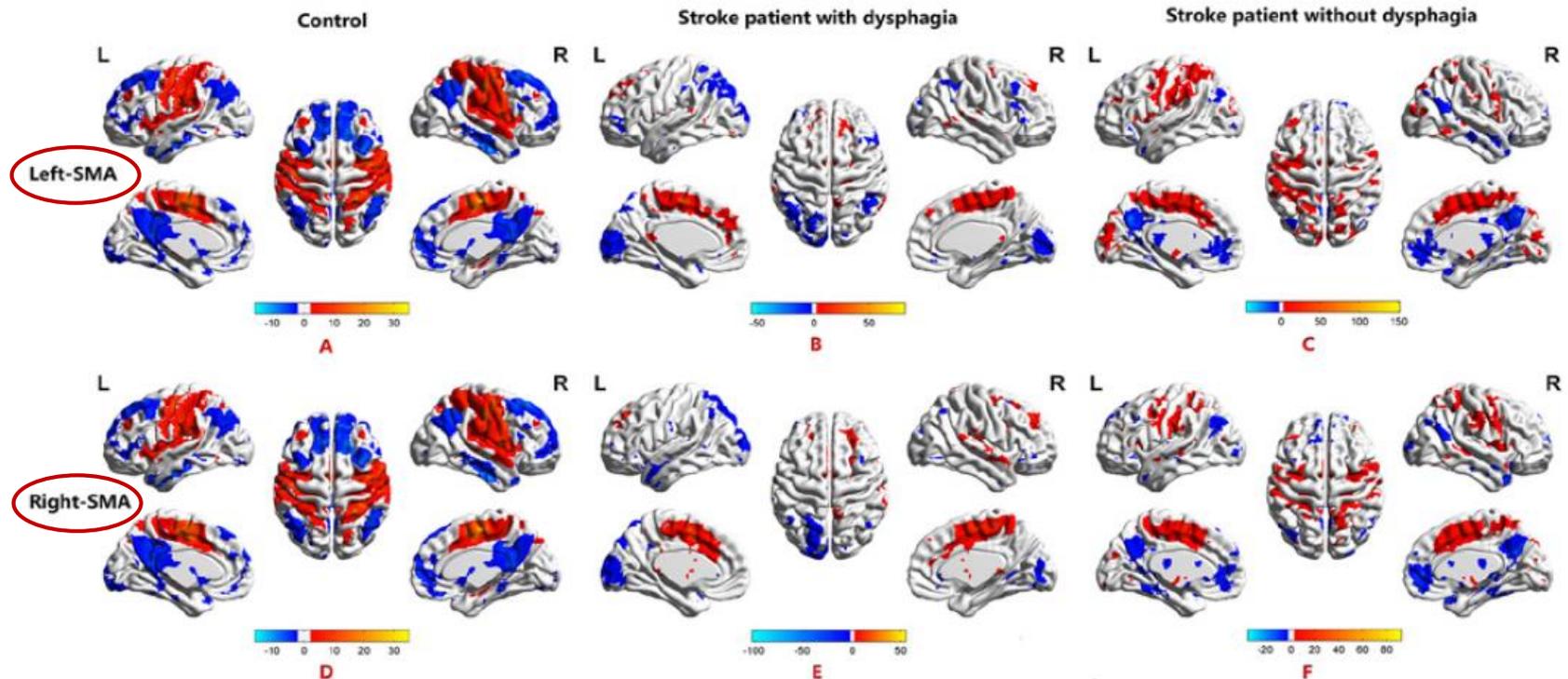
Stroke & Dysphagia Functional Connectivity

- Patients:

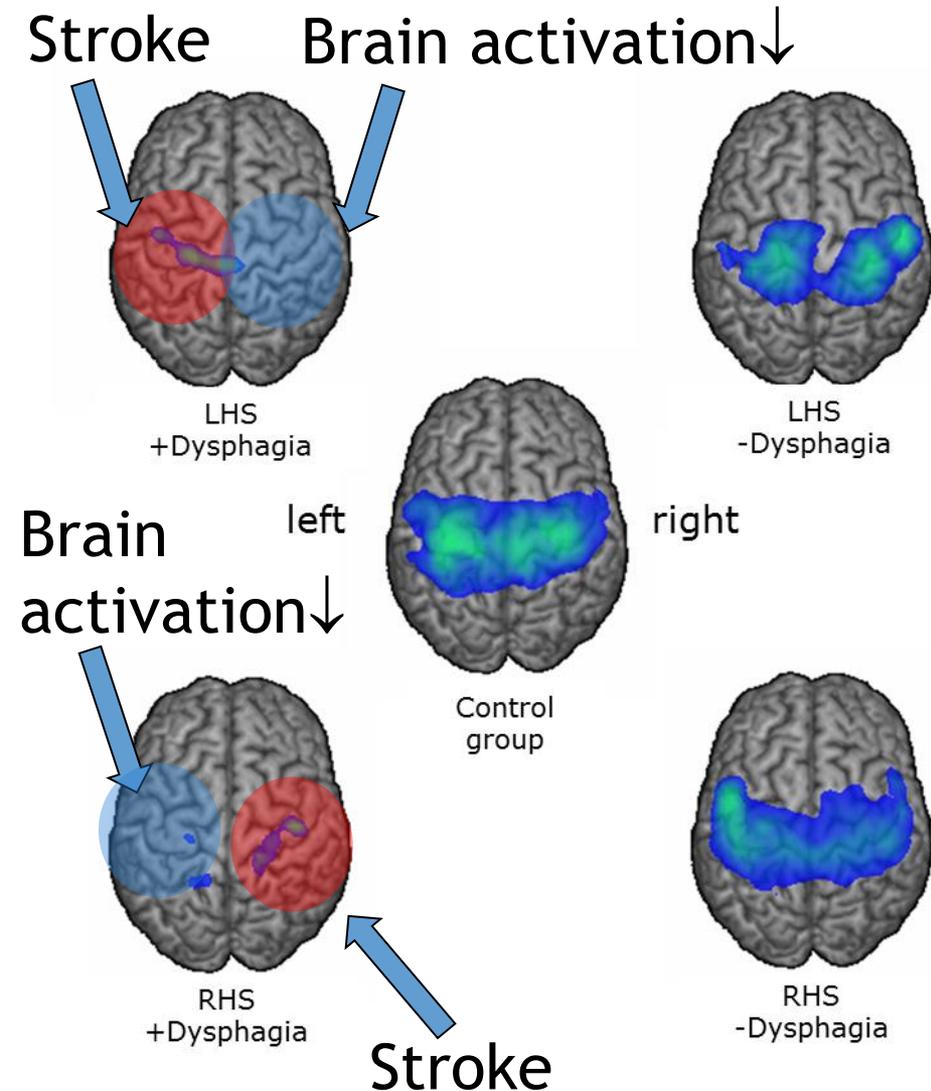
- 12 acute dysphagic stroke patients
- 12 acute nondysphagic stroke patients
- 12 healthy controls

- Methods:

- Resting-state connectivity analysis with different seed regions



Stroke & Dysphagia Functional Imaging



- **Methods:**

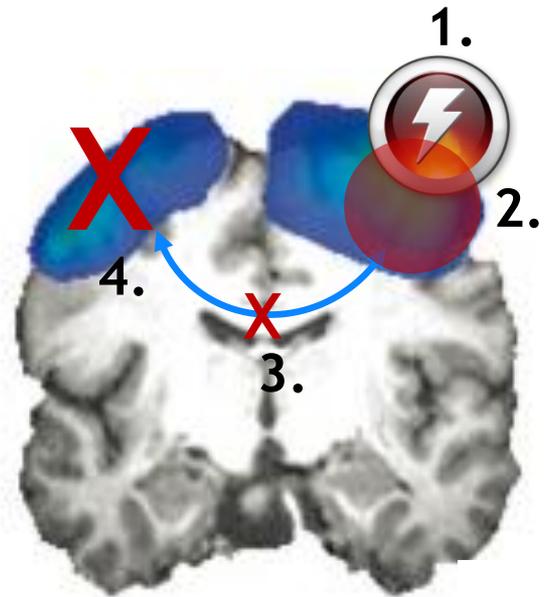
- MEG-recording during self-paced swallowing
- 7 acute stroke patients in each group

- **Results:**

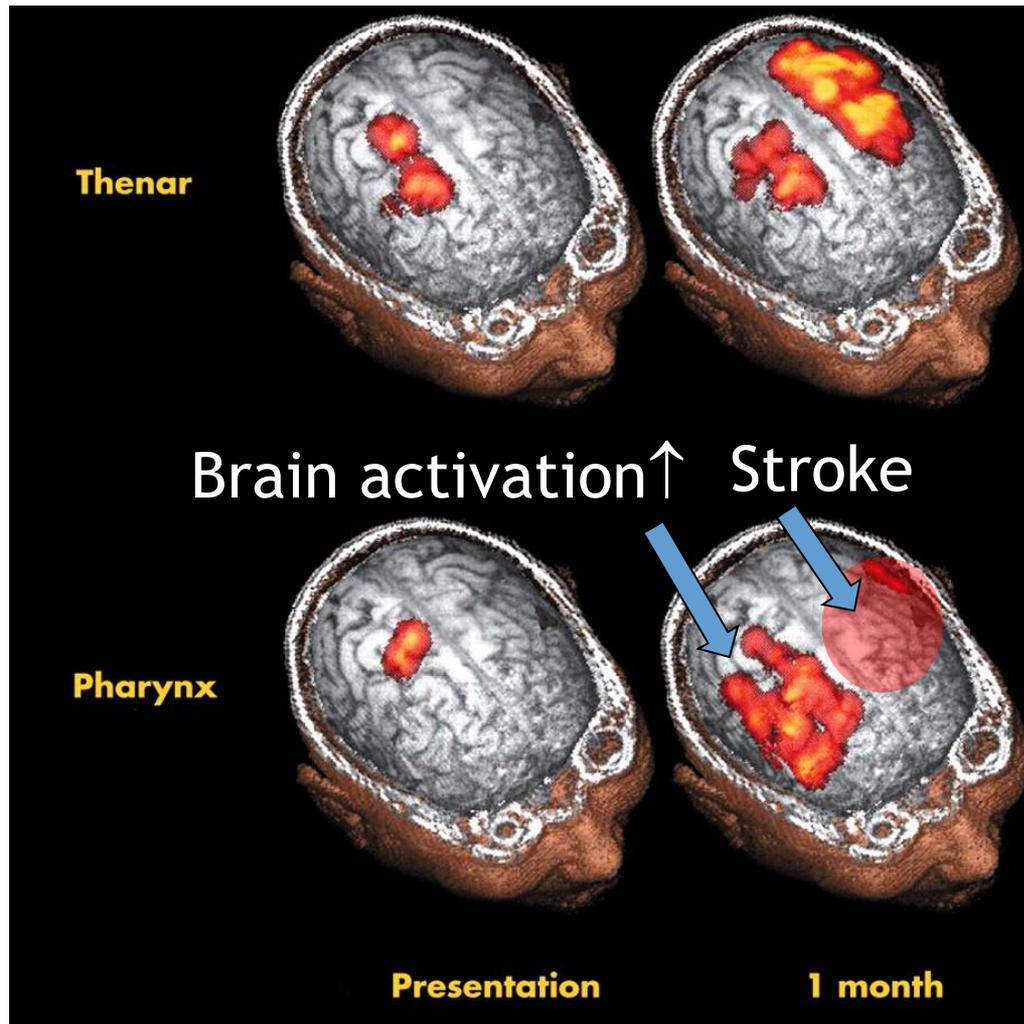
- Dysphagic stroke:
- Reduction of ipsilateral and deficiency of contralateral activation
- Non-dysphagic stroke:
- Nearly normal activation pattern

Stroke & Dysphagia Functional Imaging

1. Stroke
2. Reduced ipsilateral activation
3. Impaired transcallosal communication
4. Strongly reduced contralateral activation (diaschisis)



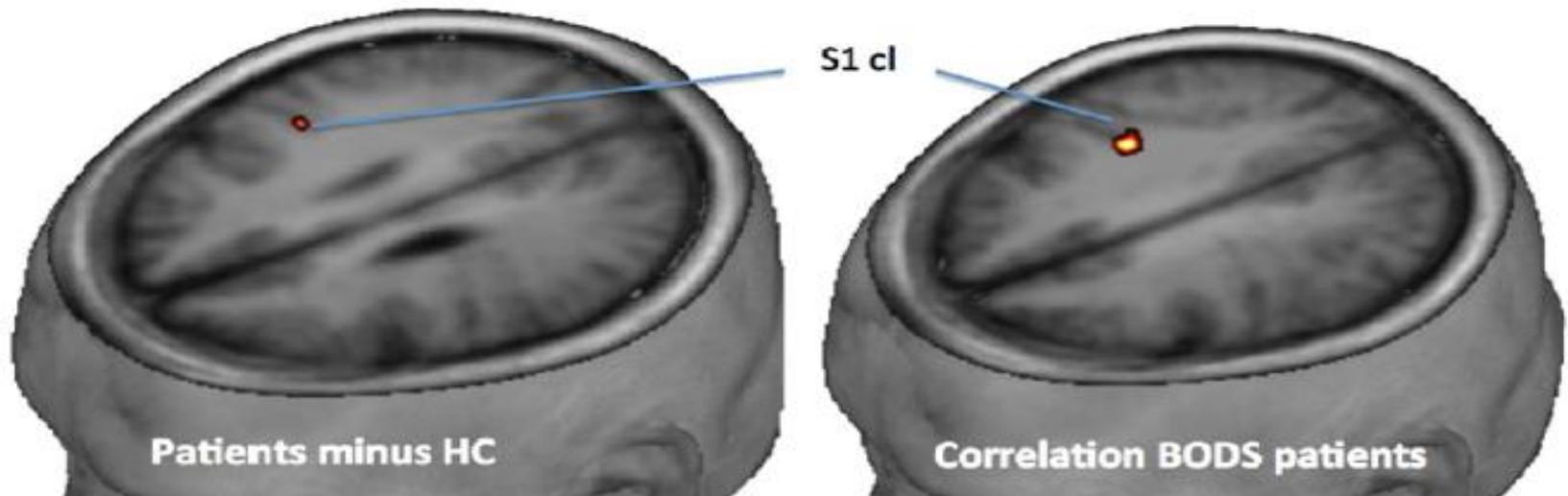
Stroke & Dysphagia Functional Imaging



- Left hemispheric stroke:
- TMS-mapping of pharyngeal constrictors and thenar muscles
- Thenar: Increase of the ipsilateral motor representation
- Pharynx: Increase of the contralesional pharyngeal motor representation

Stroke & Dysphagia Functional Imaging

- 18 chronic stroke patients having recovered from post-stroke dysphagia
- fMRI > 4 weeks post stroke



- Increased activation of contralesional S1 compared to HC
 - Contralesional S1 activation related to initial severity of PSD
- **Increased recruitment of contralesional resources**

Summary (3)

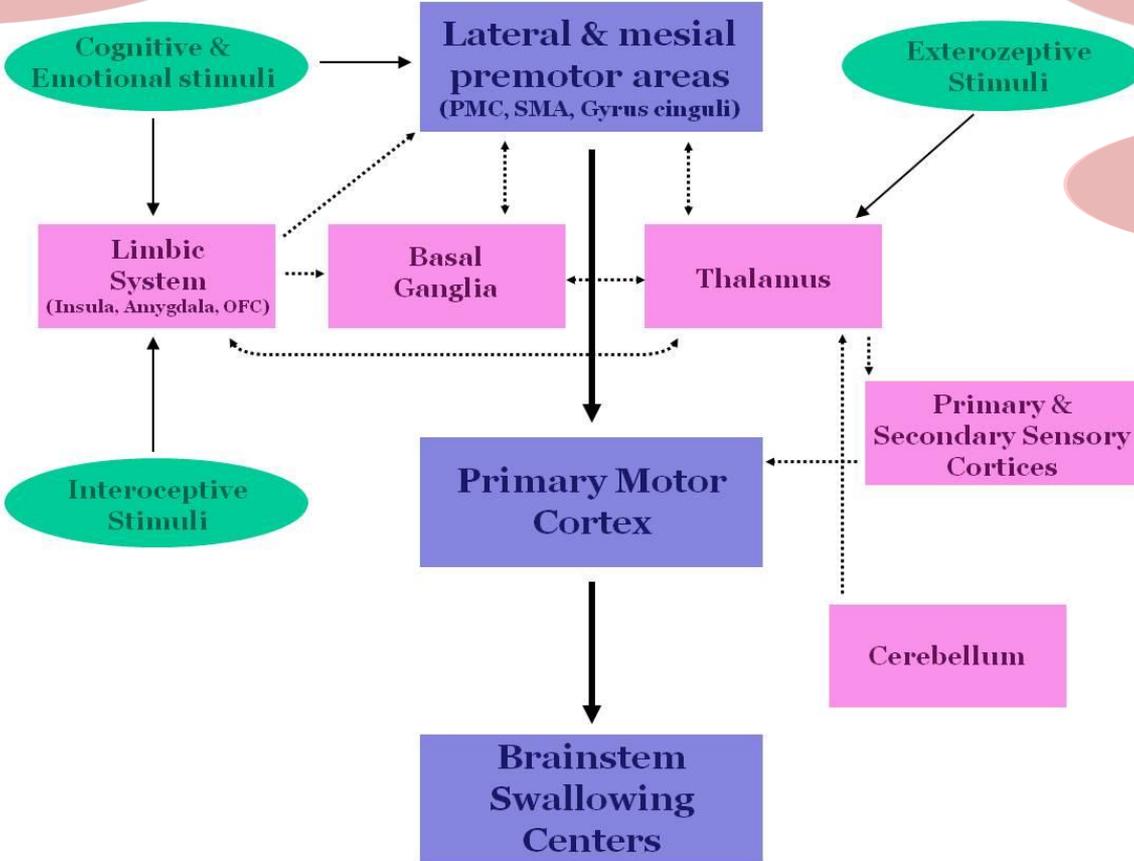
- Dysphagic stroke:
 - Decreased activation of the lesioned hemisphere
 - Extinct activation of the unlesioned hemisphere
- Recovery:
 - Increase of contralesional activation
 - Ipsilesional activation unchanged

Outline

Hemispheric specialization?

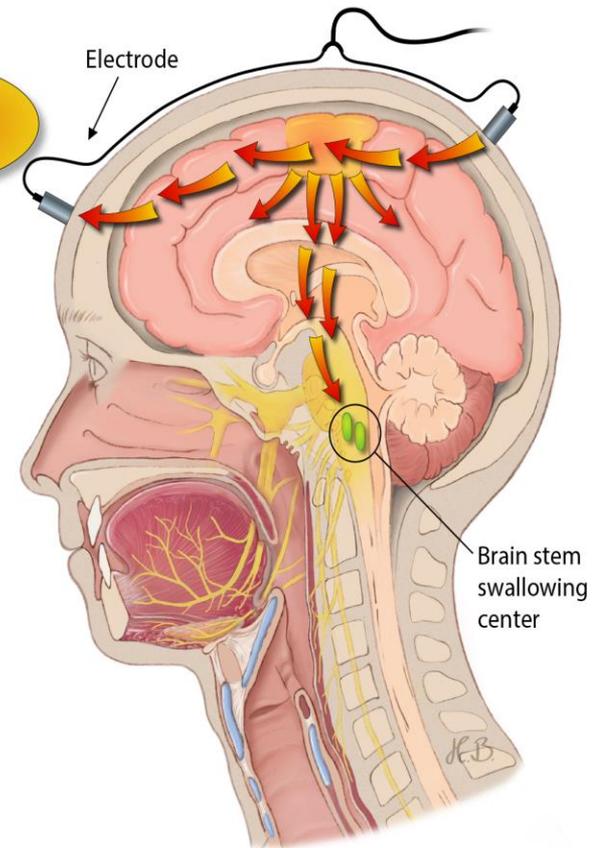
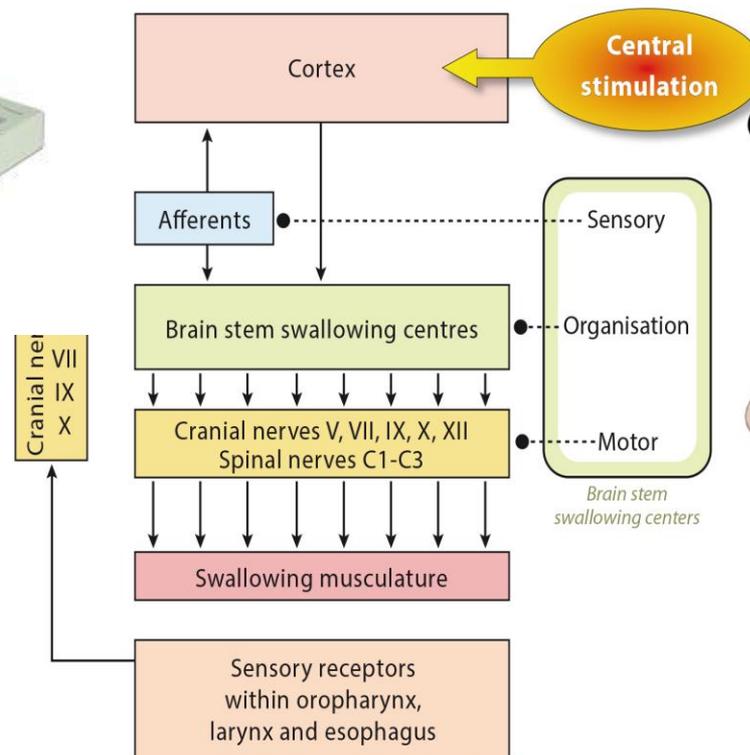
Modulation to external intervention?

Adaptive changes in the course of diseases?



Brain lesions & Dysphagia?

tDCS to treat post-stroke dysphagia



Cortical representation of swallowing

Where is the target?

Clinical Neurophysiology 127 (2016) 956–968

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

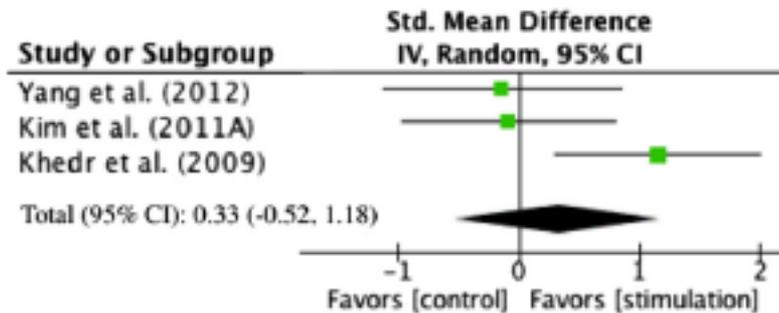


Effects of non-invasive brain stimulation on post-stroke dysphagia: A systematic review and **meta-analysis of randomized controlled trials**

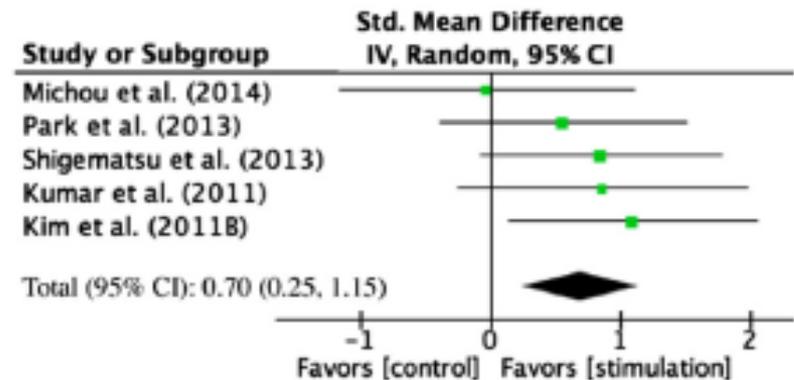


Jessica M. Pisegna^{a,b,*}, Asako Kaneoka^{a,b}, William G. Pearson Jr.^c, Sandeep Kumar^d, Susan E. Langmore^{a,b}

Affected hemisphere



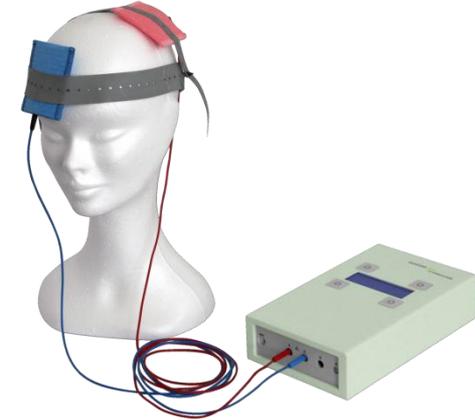
Unaffected hemisphere



tDCS Study Outline

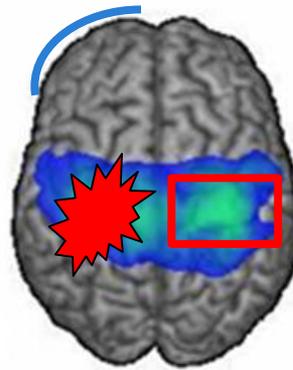
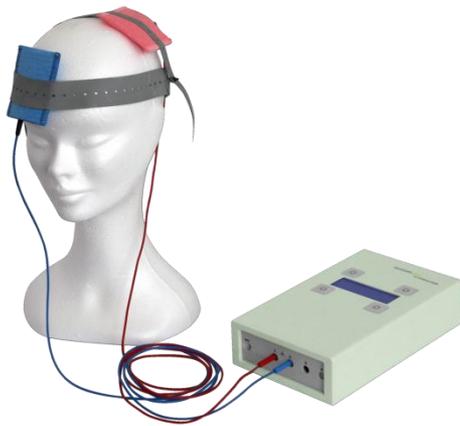
Randomized Trial of Transcranial Direct Current Stimulation for Poststroke Dysphagia

Sonja Suntrup-Krueger, MD,^{1,2} Corinna Ringmaier,³ Paul Muhle, MD,^{1,2}
Andreas Wollbrink,² Andre Kemmling, MD,⁴ Uta Hanning, MD,⁵
Inga Claus, MD,¹ Tobias Warnecke, MD,¹ Inga Teismann, MD,¹
Christo Pantev, PhD,² and Rainer Dziewas, MD¹



- Purpose:
 - to investigate the therapeutic effect of tDCS in dysphagic stroke patients
 - on swallowing function
 - on cortical reorganization of the swallowing network
 - to identify predictors of treatment success
- RCT (NCT01970384)
 - real vs. sham tDCS (anodal tDCS, 20 min, 1 mA, once daily, 4 consecutive days)
- Measurement of cortical swallow-associated activation by 275-channel magnetoencephalography (MEG)

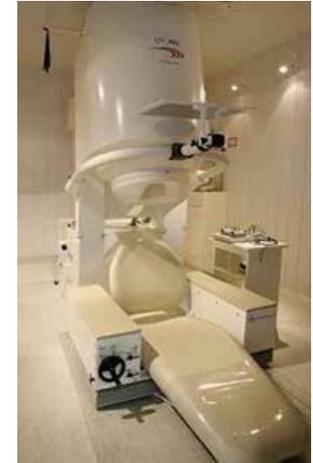
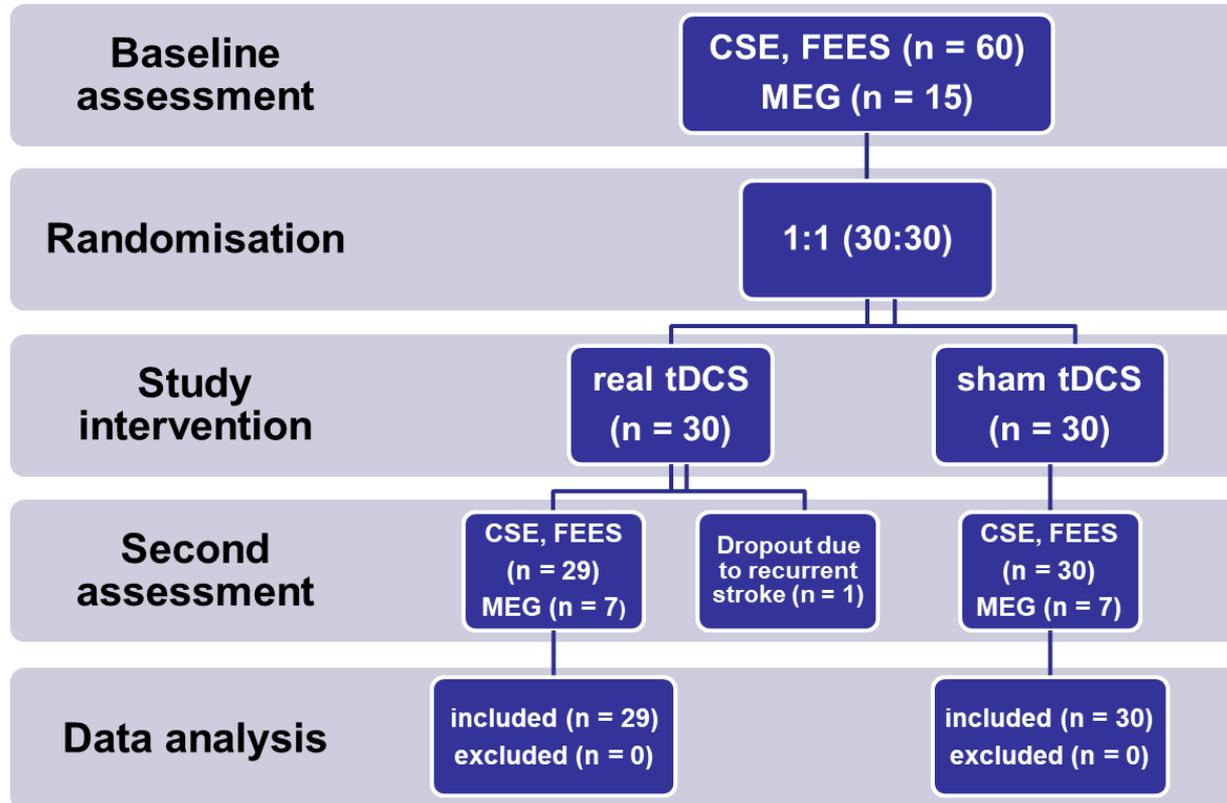
tDCS Study Outline



+



tDCS Study Outline



- Primary Endpoint: Severity of Dysphagia
- Secondary Endpoints: Pneumonia, LOS, FOIS,...
- Physiologica Endpoint: Changes of the Swallowing Network

tDCS Study Cohort

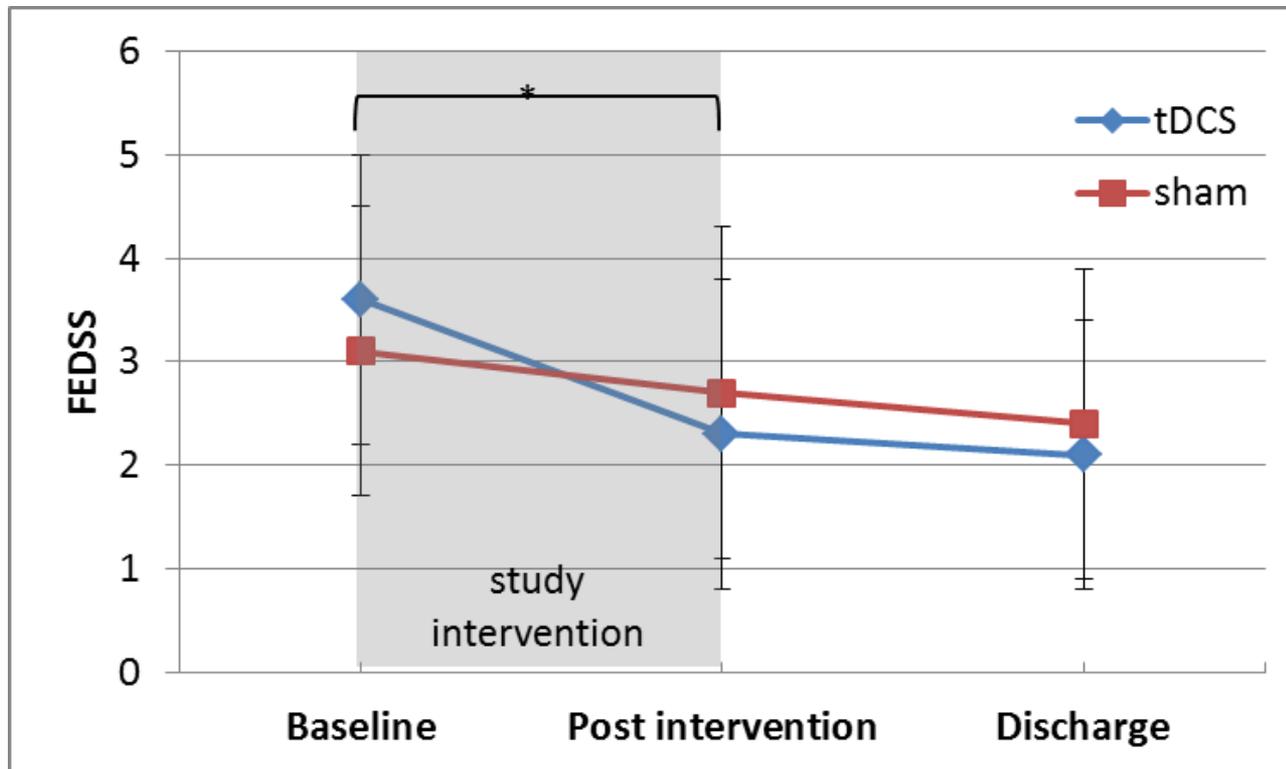
TABLE 1. Baseline Characteristics of the Stimulation and Control Groups

Characteristic	Stimulation Group, n = 29	Control Group, n = 30	Difference of Means/ Proportions (95% CI)	<i>p</i>
Age, mean yr ± SD	68.9 ± 11.5	67.2 ± 14.5	1.7 (−5.1 to 8.5)	0.802
Female, No. [%]	12 [41.4]	13 [43.3]	2.0 (−24.3 to 28.2)	0.879
NIH-SS on admission, mean ± SD	11.5 ± 7.0	13.2 ± 8.5	1.7 (−5.8 to 2.4)	0.425
Site of stroke, No. [%]				
Supratentorial {left/right}	21 [72.4] {12/9}	24 [80.0] {14/10}	7.6 (−14.9 to 30.1)	0.493
Infratentorial	8 [27.6]	6 [20.0]		
Ischemic stroke etiology, No. [%]				
Large-artery atherosclerosis	8 [27.6]	7 [23.3]	4.3 (−18.8 to 27.3)	0.708
Cardioembolism	11 [37.9]	14 [46.7]	8.7 (−34.8 to 17.4)	0.497
Small-vessel occlusion	1 [3.4]	2 [6.7]	3.2 (−14.8 to 8.4)	1.000
Other determined etiology	3 [10.3]	4 [13.3]	3.0 (−20.1 to 14.1)	1.000
Unknown etiology	6 [20.7]	3 [10.0]	10.7 (−8.2 to 29.6)	0.299
Acute stroke treatment				
None, No. [%]	16 [55.2]	13 [43.3]	11.8 (−14.5 to 38.2)	0.363
i.v. thrombolysis only, No. [%]	5 [17.2]	5 [16.7]	0.6 (−19.3 to 20.5)	1.000
With mechanical recanalization, No. [%]	8 [27.6]	12 [40.0]	12.4 (−37.3 to 12.5)	0.314
With orotracheal intubation, No. [%]	6 [20.7]	12 [40.0]	16.7 (−17.5 to 50.9)	0.107
Duration of artificial ventilation, mean days ± SD	1.0 ± 0.9	1.85 ± 2.2	0.8 (−2.6 to 0.9)	0.280
Time from stroke onset to study inclusion, mean h ± SD	116.3 ± 98.9	116.8 ± 64.9	0.6 (−44.0 to 42.9)	0.404
Swallow training during intervention, No. [%]	17 [58.6]	20 [66.7]	8.0 (−33.6 to 17.5)	0.523

CI = confidence interval; i.v. = intravenous; NIH-SS = National Institutes of Health Stroke Scale; SD = standard deviation.

tDCS Results

- Primary endpoint: FEDSS



tDCS Results

- **Secondary endpoints:**

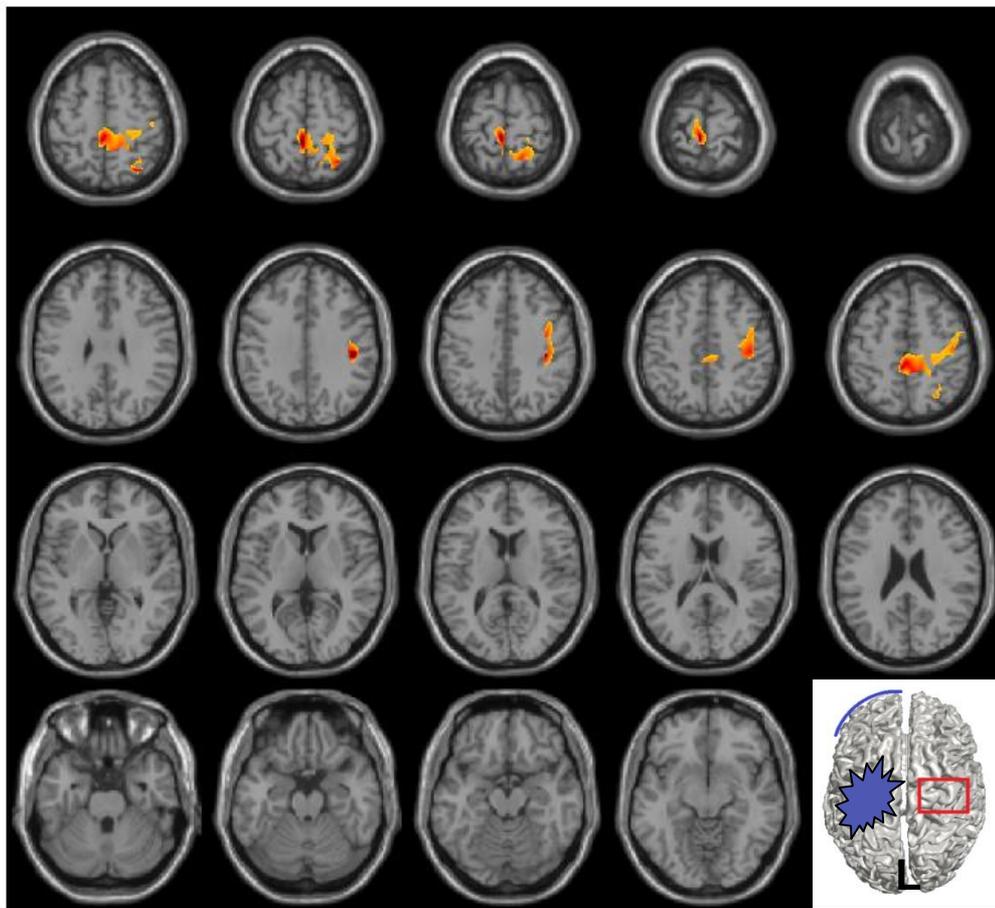
	Stimulation Group (N=29)	Control Group (N=30)	p-value
FOIS			
at baseline, mean (SD)	3.2 ± 1.8	3.8 ± 1.9	0.186
Improvement in FOIS, mean (SD)	1.8 ± 1.6	1.0 ± 1.4	0.041*
DSRS			
at baseline, mean (SD)	8.5 ± 3.4	6.9 ± 3.8	0.107
Improvement in DSRS, mean (SD)	4.0 ± 2.8	1.5 ± 1.6	0.001*
Dysphagia limit (ml) tested, n (%)	23 (79.3)	22 (73.3)	0.590
at baseline, mean (SD)	5.7 ± 5.7	7.3 ± 7.2	0.506
Improvement, mean (SD)	5.0 ± 5.6	1.9 ± 4.8	0.018*
Pneumonia rate, n (%)	11 (37.9)	16 (53.3)	0.235
Length of Stay (LOS), mean (SD)	16.2 ± 6.8	13.4 ± 5.1	0.080
LOS on Stroke Unit/ICU, mean (SD)	6.7 ± 4.4	7.0 ± 3.3	0.783

tDCS to treat post-stroke dysphagia

	Change in FEDSS	Change in FOIS	Change in DSRS	Change in Dysphagia limit
Age	$r = -0.115 (0.55)$	$r = 0.038 (0.85)$	$r = -0.084 (0.67)$	$r = -0.028 (0.88)$
pre treatment NIH-SS	$r = 0.151 (0.43)$	$r = 0.067 (0.73)$	$r = 0.307 (0.11)$	$r = 0.060 (0.76)$
Baseline FEDSS	$r = 0.223 (0.24)$	$r = -0.020 (0.92)$	$r = -0.218 (0.26)$	$r = -0.235 (0.22)$
Time to treatment	$r = -0,350 (0.06)$	$r = -0,336 (0.08)$	$r = -0.398 (0.03)^*$	$r = -0.399 (0.03)^*$



tDCS Results



Significant increase of
swallowing network
activation after real tDCS!

No significant effects
after sham tDCS.

Figure:
Areas with significant
activation increase post
real tDCS as compared
to baseline
(pre vs post contrast)

13-30 Hz (beta)
n = 5 (cortical strokes only)
p = 0.038

Summary (4)

- Consistent findings across 30 years of research applying different methods.
- In the pathophysiology of post-stroke dysphagia lesion site and size do matter!
- PSD in supratentorial stroke is caused by disruption of the swallowing network.
- Impaired activity of the unlesioned is pathophysiologically particularly important.
- From bench to bedside: successful application of tDCS to the unlesioned hemisphere in acute stroke.

Thank you!



dziewas@uni-muenster.de

Dysphagia Research Group

Sigrid Ahring

Inga Claus

Rainer Dziewas

Bendix Labeit

Thomas Marian

Paul Muhle

Stephan Oelenberg

Sonja Sauer

Jens Schröder

Sonja Suntrup-Krüger

Inga Teismann

Marion Thomas

Tobias Warnecke

Christina Wüller

Institute for Biomagnetism & Biosignalanalysis

Joachim Groß

Christo Pantev

Andreas Wollbrink

Carsten Wolters