UNIVERSITÄT LEIPZIG

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Neuroplasticity in Multiple Sclerosis – Evidence from TMS

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Dept. of Neurology

University of Leipzig

RIMS 2012, Hamburg

Little correlation between functional deficit and lesion load

MRI T2 lesion burden in multiple sclerosis

A plateauing relationship with clinical disability

D.K.B. Li, MD; U. Held, PhD; J. Petkau, PhD; M. Daumer, PhD; F. Barkhof, MD, PhD; F. Fazekas, MD; J.A. Frank, MD; L. Kappos, MD; D.H. Miller, MD; J.H. Simon, MD; J.S. Wolinsky, MD; and M. Filippi, MD, for the Sylvia Lawry Centre for MS Research

NEUROLOGY 2006;66:1384–1389

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doi:10.1093/brain/awm329

Brain (2008), **131**, 808–817

Disability and T_2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis

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[1]NMR Research Unit, [2]Departments of Neuroinflammation, and [3]Brain Repair and Rehabilitation, Institute of Neurology, University College London, [4]Department of Neurology, Kings College Hospital, London, [5]Medical Statistical Unit, London School of Hygiene and Tropical Medicine, Keppel Street and [6]Department of Neuroradiology, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

Neuroplasticity Predicts Outcome of Optic Neuritis Independent of Tissue Damage

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Objectives: To determine whether lateral occipital complex (LOC) activation with functional magnetic resonance imaging (fMRI) predicts visual outcome after clinically isolated optic neuritis (ON). To investigate the reasons behind good recovery following ON, despite residual optic nerve demyelination and neuroaxonal damage.
Methods: Patients with acute ON and healthy volunteers were studied longitudinally over 12 months. Structural MRI, visual evoked potentials (VEPs), and optical coherence tomography (OCT) were used to quantify acute inflammation, demyelination, conduction block, and later to estimate remyelination and neuroaxonal loss over the entire visual pathway. The role of neuroplasticity was investigated using fMRI. Multivariable linear regression analysis was used to study associations between vision, structure, and function.
Results: Greater baseline fMRI responses in the LOCs were associated with better visual outcome at 12 months. This was evident on stimulation of either eye ($p = 0.007$ affected; $p = 0.020$ fellow eye), and was independent of measures of demyelination and neuroaxonal loss. A negative fMRI response in the LOCs at baseline was associated with a relatively worse visual outcome. No acute electrophysiological or structural measures, in the anterior or posterior visual pathways, were associated with visual outcome.
Interpretation: Early neuroplasticity in higher visual areas appears to be an important determinant of recovery from ON, independent of tissue damage in the anterior or posterior visual pathway, including neuroaxonal loss (as measured by MRI, VEP, and OCT) and demyelination (as measured by VEP).

ANN NEUROL 2010;67:99–113

Neuroplasticity in multiple sclerosis

Rapid onset plasticity

Interregional plasticity

Local network plasticity

Neuroplasticity in Multiple Sclerosis

Rapid onset plasticity

Interregional plasticity

Local network plasticity

Synaptic plasticity in multiple sclerosis

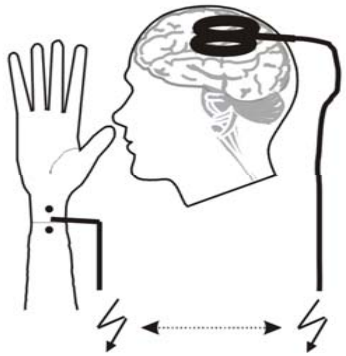
- Synaptic plasticity impaired by:
  - *demyelinating lesion: possibile loss of synchronicity*
  - *Atrophy of grey matter: (glial (-36%), neuronal (-10%), synaptic (-47%)): Wegner, Neurology, 2006; Sicotte, Brain, 2008)*

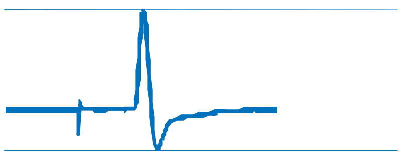
- Synaptic plasticity improved by:
  - *(EAN) T- and natural killer (NK) cells: Neurotrophins (z.B. BDNF, Hammarberg, J Neurosci., 2000)*
  - *Matrix-Metalloproteinase (Agrawal, Sem. Cell & Dev. Biol., 2008)*
  - *Ciliary neurotrophic factor (CNTF) signalling (Dutta, Brain, 2007)*
  - *Endocannabinoids? (Centonze, Brain 2006)*

Paired associative stimulation

Paired associative

stimulation

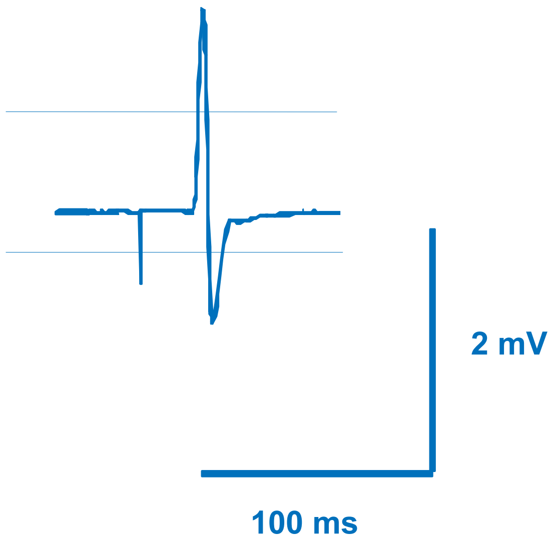




ISI=25 ms

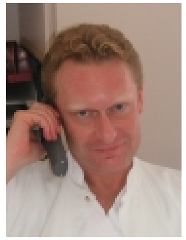
90 pairs

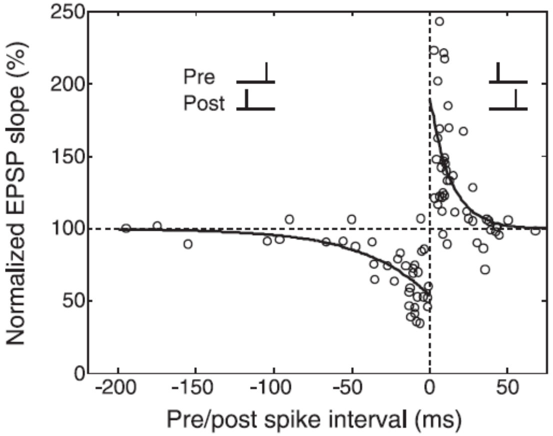
0.05 Hz



Stefan et al.. Brain. 2000

Temporally asymmetric Hebbian rule

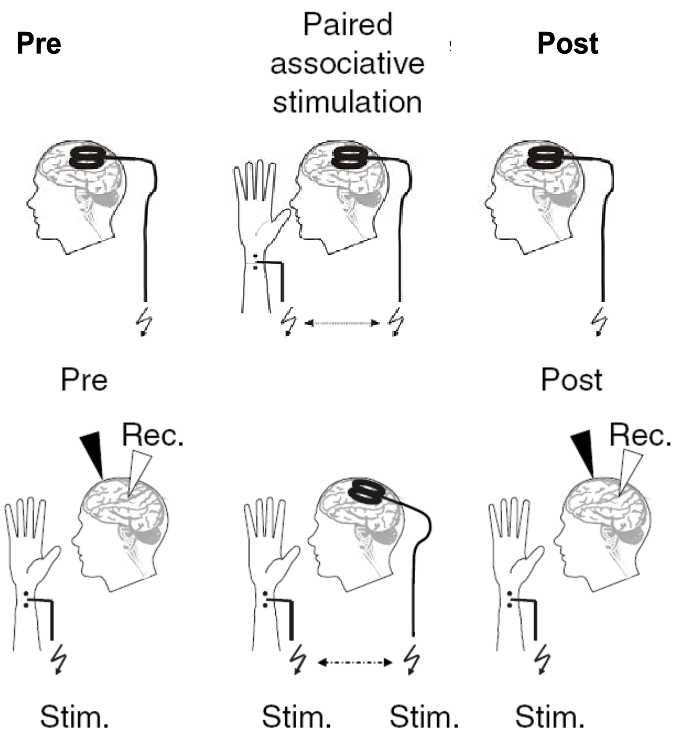




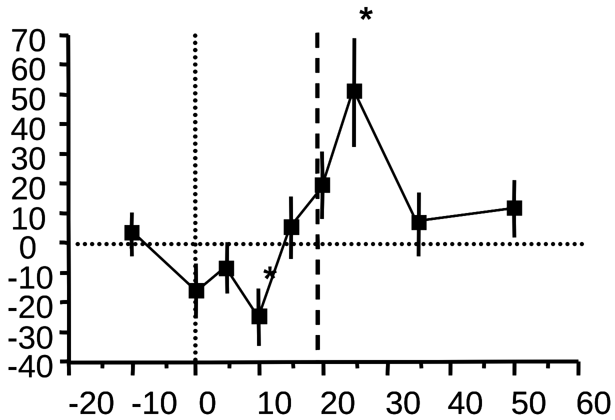
Dan. Physiol Rev. 2006

M1

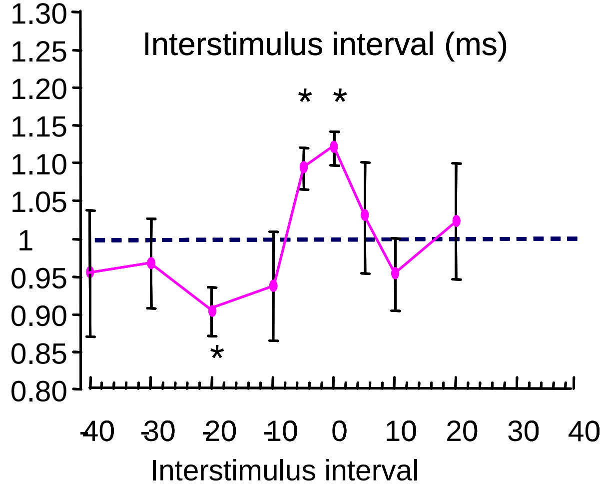
S1



Prozent des Ausgangs-wertes

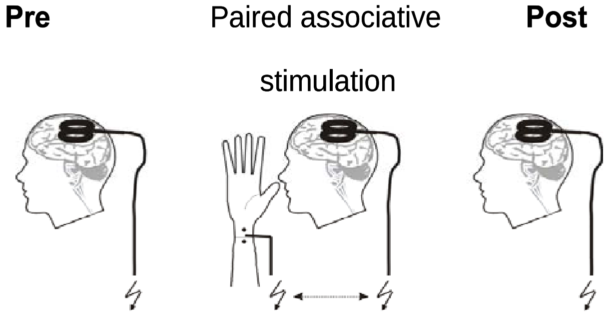


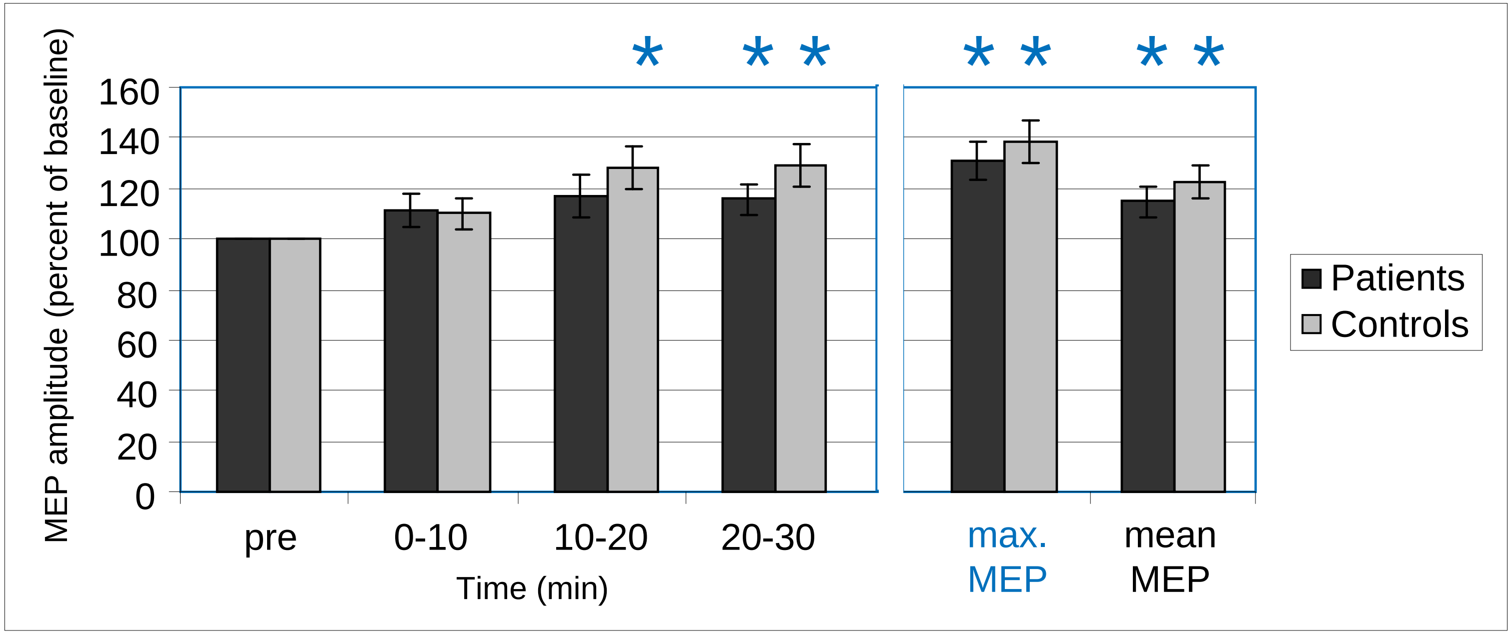
P25-Amplitude prä/post



Wolters. J. Neurophysiol.. 2003; J. Physiol.. 2005

Synaptic plasticity in multiple sclerosis

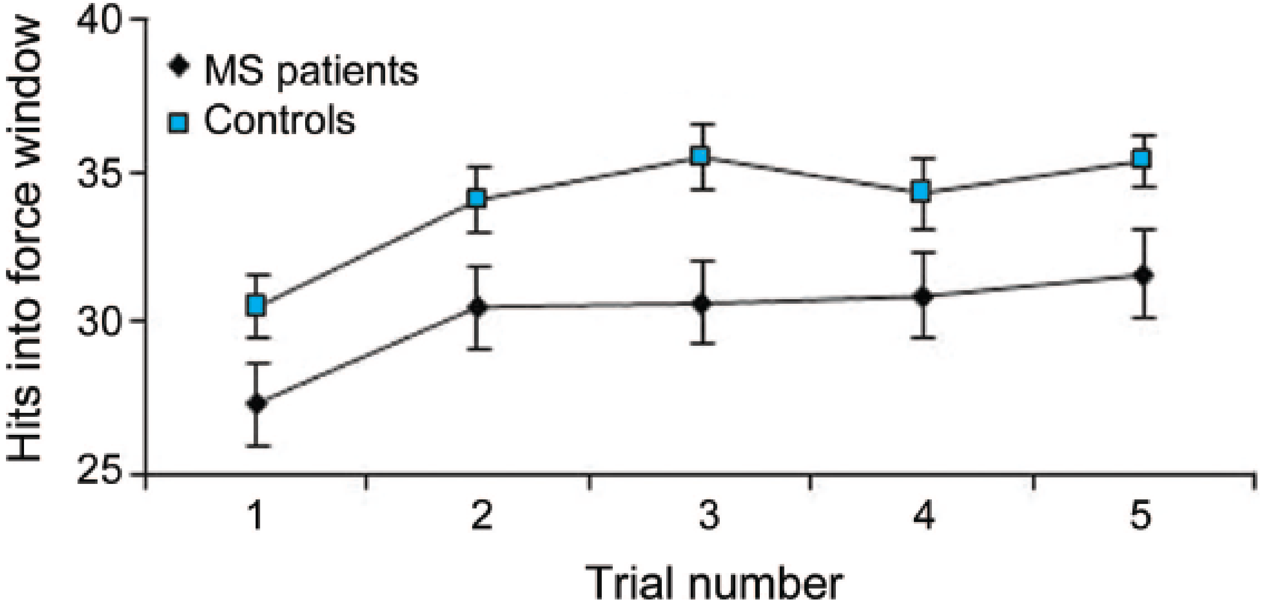




Zeller, aufm Kampe, Neurology, 2010

Motor learning in multiple sclerosis

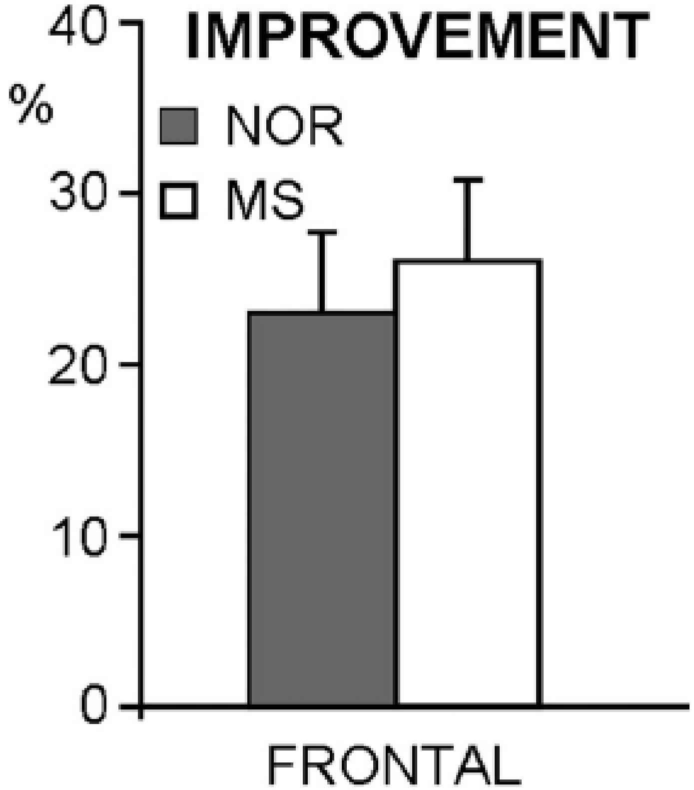
Figure 2 **Motor learning task**



Force window performance of 21 patients with multiple sclerosis (MS) and 22 matched control subjects over the course of the training. Each symbol refers to mean of 100 attempts (2 blocks of 50 each). Error bars indicate the SEM.

Zeller, aufm Kampe, Neurology, 2010

Normal baseline-normalized motor learning in a simple motor training task



Leocani et al., NeuroRehab NeurRepair, 2007

Brain (2002), **125,** 2646–2657

Functional brain reorganization for hand movement in patients with multiple sclerosis: defining distinct effects of injury and disability

H. Reddy,[1] S. Narayanan,[2] M. Woolrich,[1] T. Mitsumori,[1] Y. Lapierre,[2] D. L. Arnold[2] and P. M. Matthews[1]

Synaptic plasticity retained also in high brain injury

Table 3 Paired associative stimulation-induced plasticity and motor learning performance in patients with multiple sclerosis with good hand function, stratified into those with high and low CNS injury according to corticomuscular latency or NAA/Cr spectra

Hand function and CNS injury	9-Hole peg board test, s	Tapping	n	CNS injury index	Maximum MEP% after PAS	*p* Value (vs PHF)	Force production performance increment	*p* Value (vs PHF)
PHF	45.1 ± 51.8	64.9 ± 14.5	6		123.2 ± 31.8	—	5.3 ± 4.4	—
GHF	19.0 ± 3.2	104.3 ± 19.2	16		133.6 ± 35.7	0.537	3.9 ± 5.0	0.578
				CML				
GHF-LBI	20.8 ± 2.9	99.1 ± 18.8	4	18.9 ± 1.1	119.3 ± 8.4	0.823	0.5 ± 4.0	0.121
GHF-HBI	18.5 ± 3.2	106.0 ± 19.8	12	22.9 ± 1.1	138.3 ± 40.2	0.433	5.2 ± 4.8	0.977
				NAA/Cr				
GHF-LBI	18.7 ± 3.4	95.6 ± 10.7	7	1.6 ± 0.1	126.0 ± 28.1	0.869	3.2 ± 4.9	0.451
GHF-HBI	21.2 ± 4.7	106.7 ± 21.4	3	1.4 ± 0.1	113.6 ± 2.3	0.630	5.3 ± 7.8	0.984

Abbreviations: CML = corticomuscular latency; Cr = creatine; GHF = good hand function; HBI = high CNS injury; LBI = low CNS injury; MEP = motor evoked potential; NAA = *N*-acetyl aspartate; PAS = paired associative stimulation; PHF = poor hand function.

Zeller, aufm Kampe, Neurology, 2010

Long-term potentiation-like plasticity and rapid motor learning of a simple motor task are not compromised in MS.

In mild-to-moderately affected patients, rapid-onset plasticity does not appear to be a factor determining good hand function in the presence of variable degrees of brain injury.

Neuroplasticity in Multiple Sclerosis

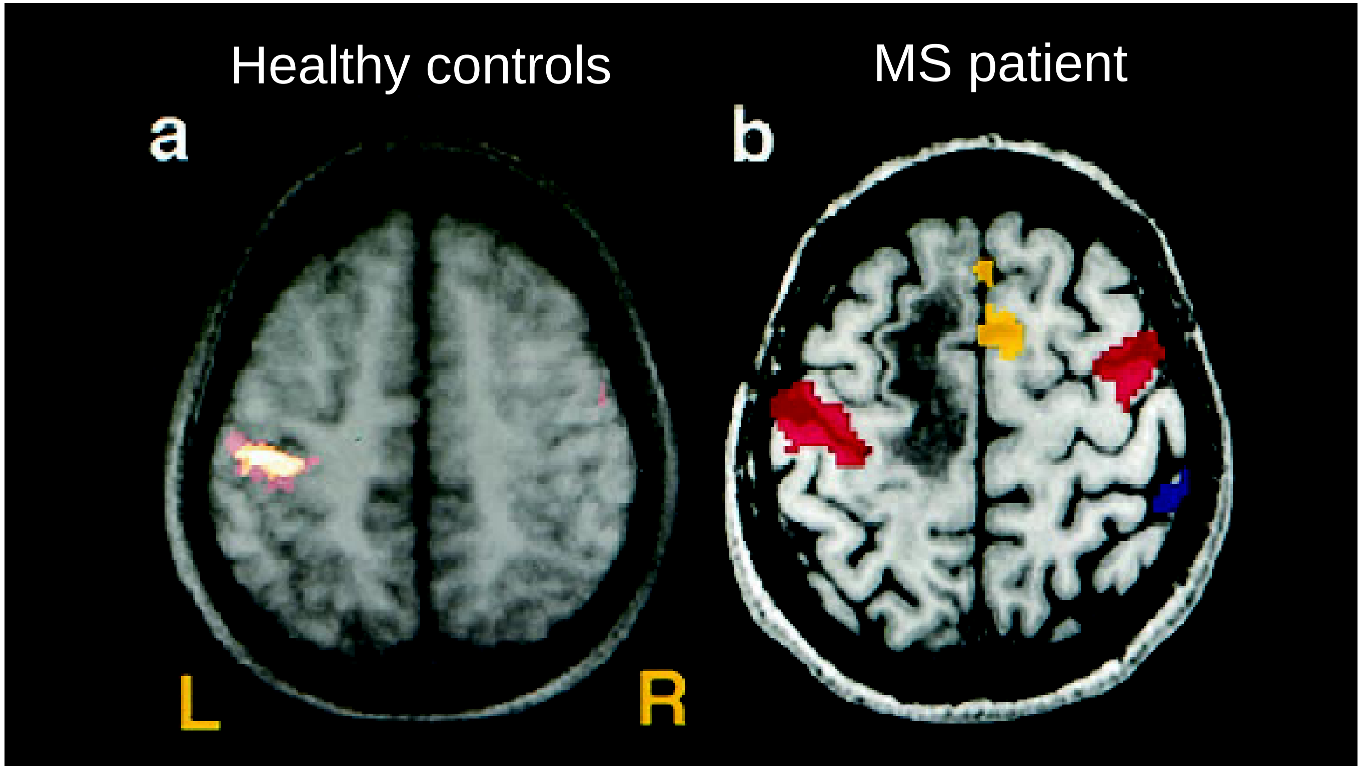
Rapid onset plasticity

Interregional plasticity

Local network plasticity

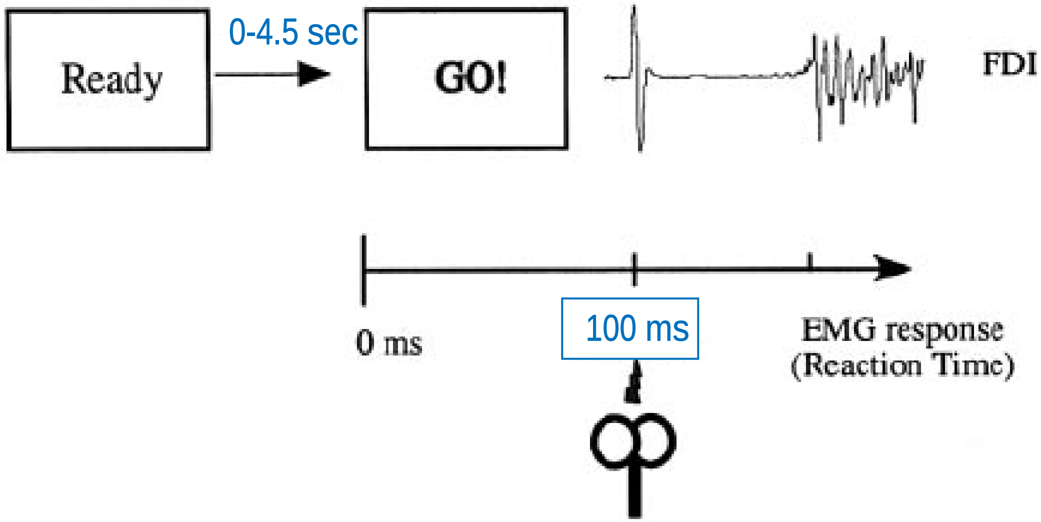
MS patients without impairment of hand function

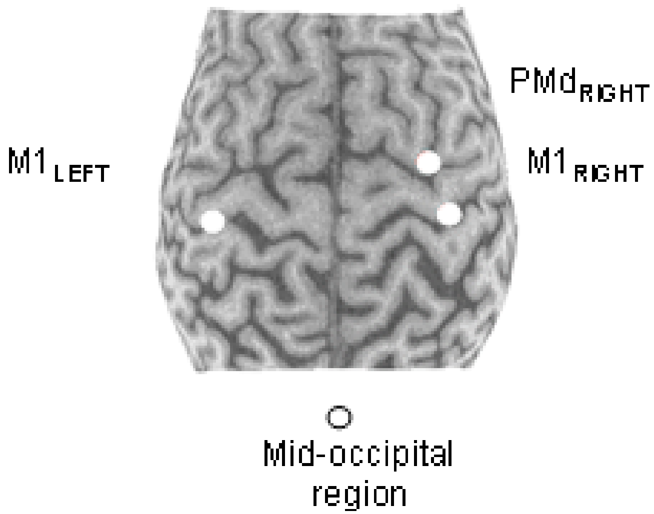
– Activation of ipsilateral sensorimotor cortex (Reddy, Brain 2000).

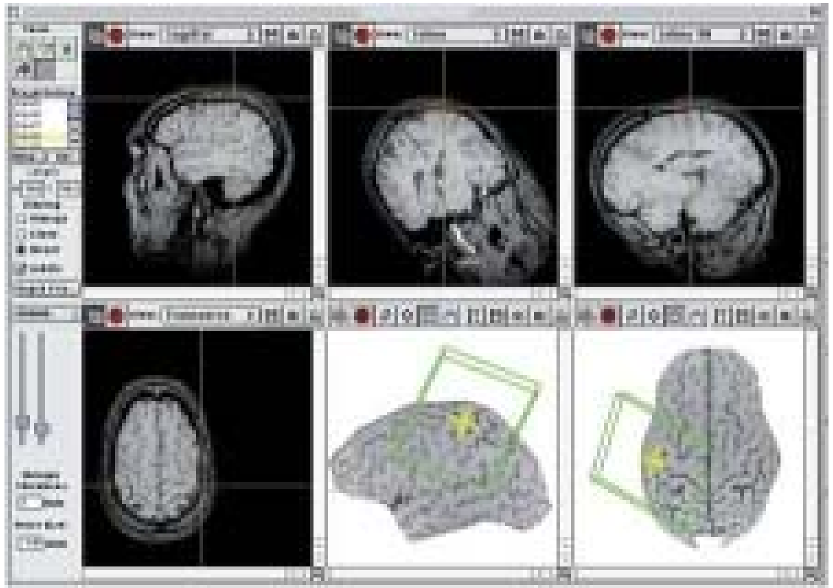


Reddy, Brain, 2000

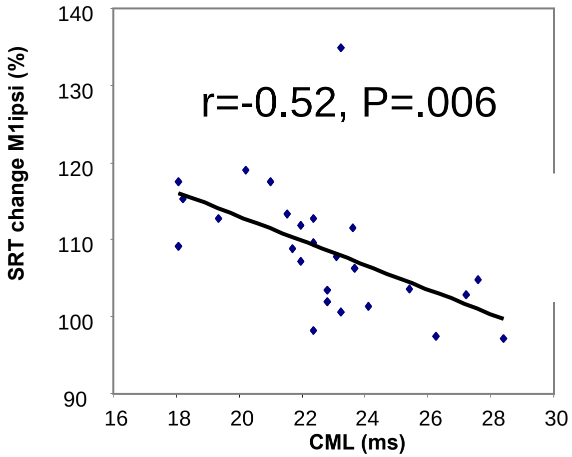
Exploring interregional plasticity by neuronavigated TMS

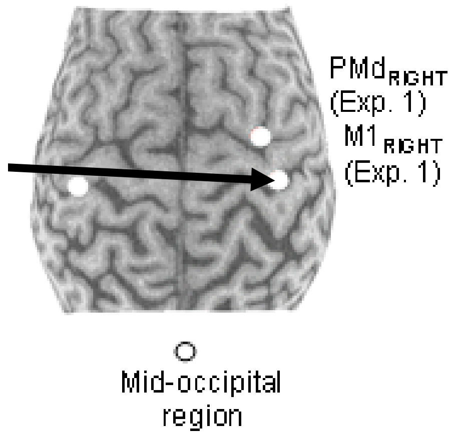


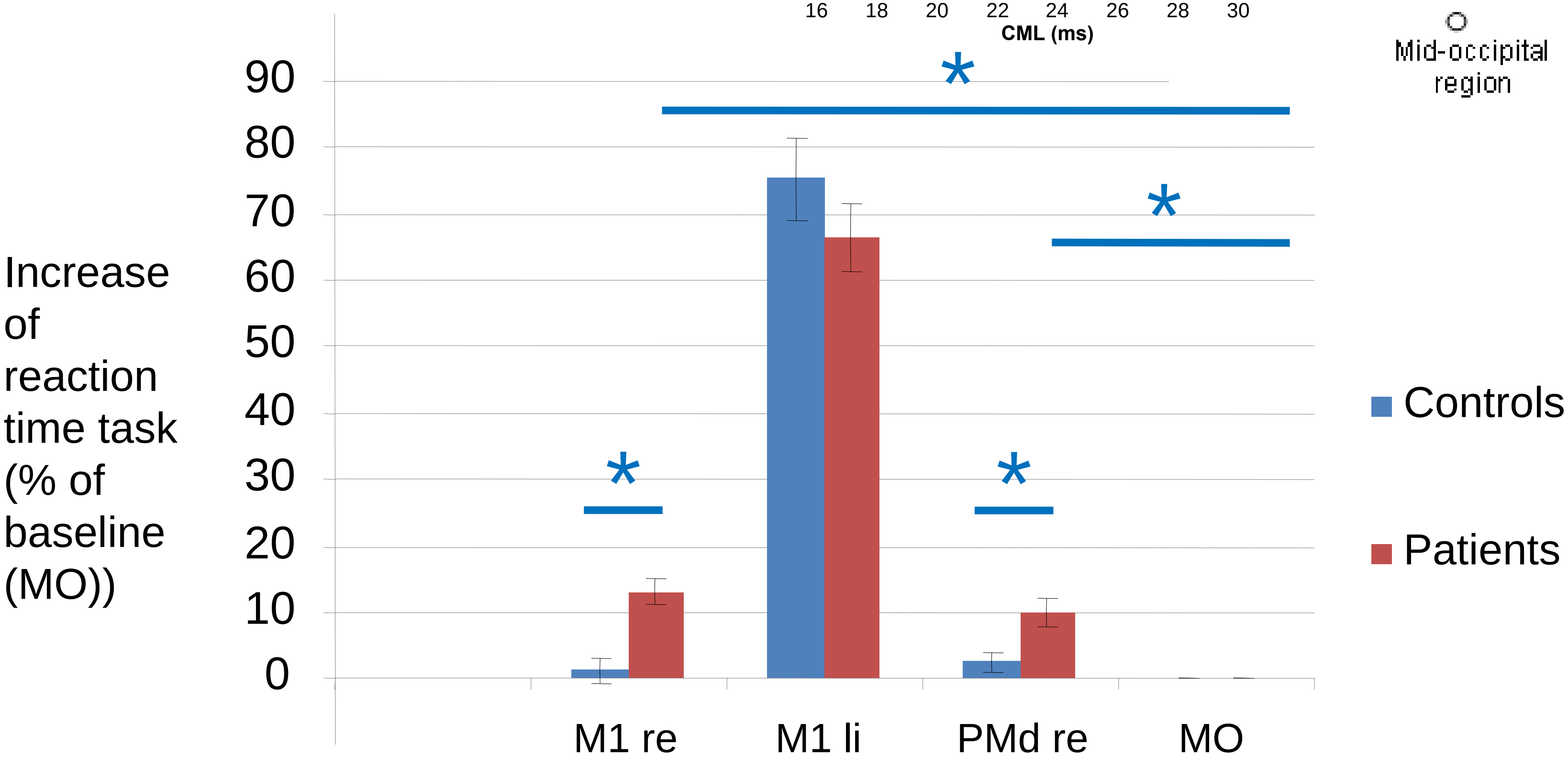




Regional plasticity in MS - reaction time task







Zeller, Dang, JNNP, 2011

Non-canonical (motor) brain regions are involved in the execution of simple motor tasks in MS.

Activation of these regions is functionally relevant, but compensation likely is limited by disease-related brain injury.

Neuroplasticity in Multiple Sclerosis

Rapid onset plasticity

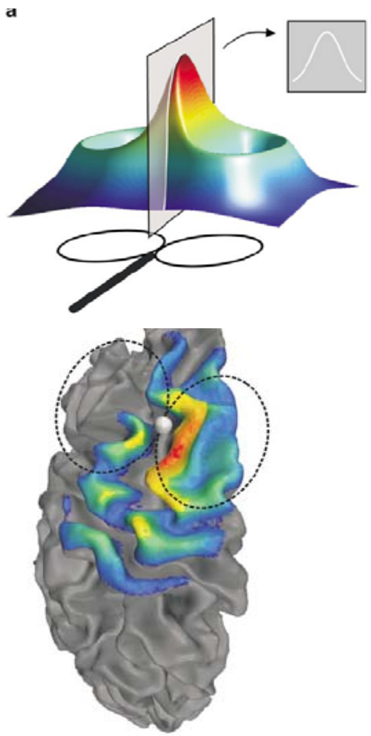
Interregional plasticity

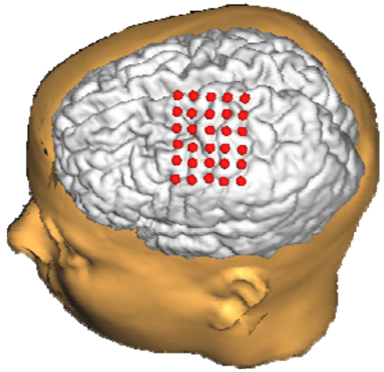
Local network plasticity

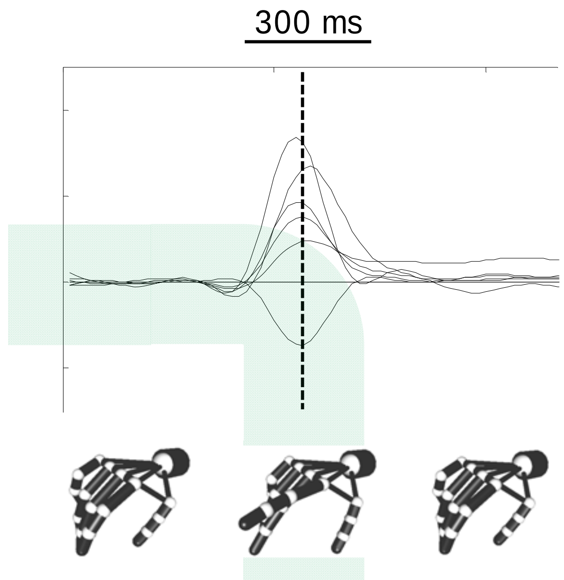
Extracting complex parameters of motor control by TMS-mapping of finger movements

- •Somatotopical representation

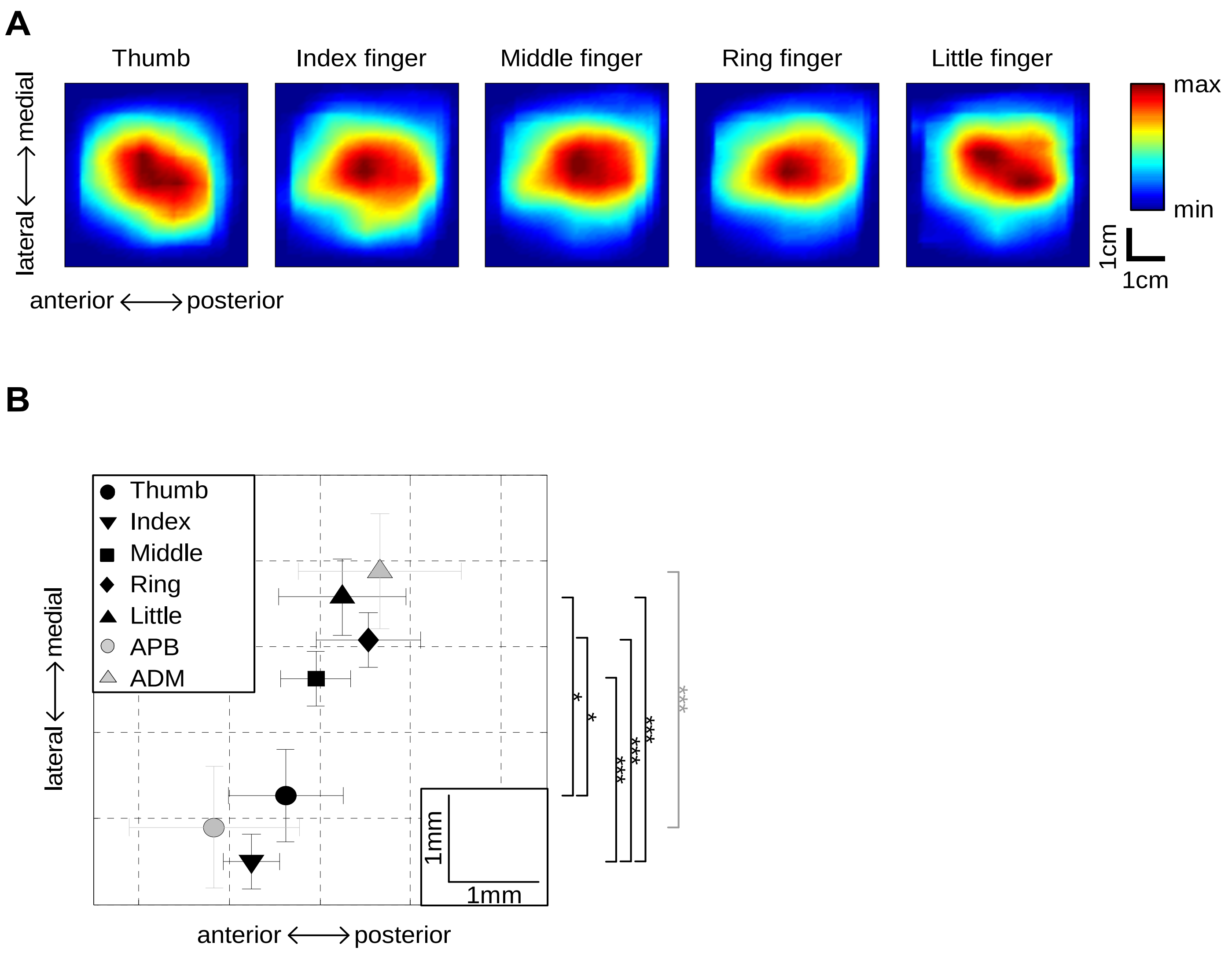
- •Efficiency of motor control







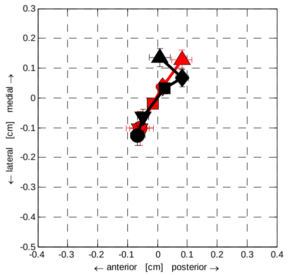
Somatotopical organisation of finger movements as revealed by TMS



Gentner, Neuron, 2006

Homuncular finger movement representation

Healthy control



▲ Little

◆ Ring

■ Middle

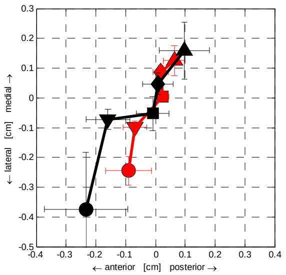
▼ Index

● Thumb

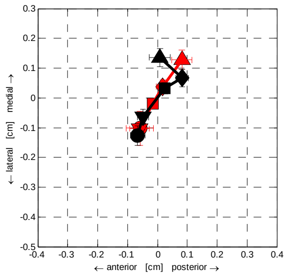
Nagel, Gentner

Expansion of homuncular representation in professional musicians – mapping finger movts. = plasticity paradigm

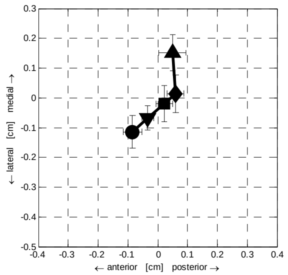
Violinists (red=right M1)



Healthy control



Dystonia



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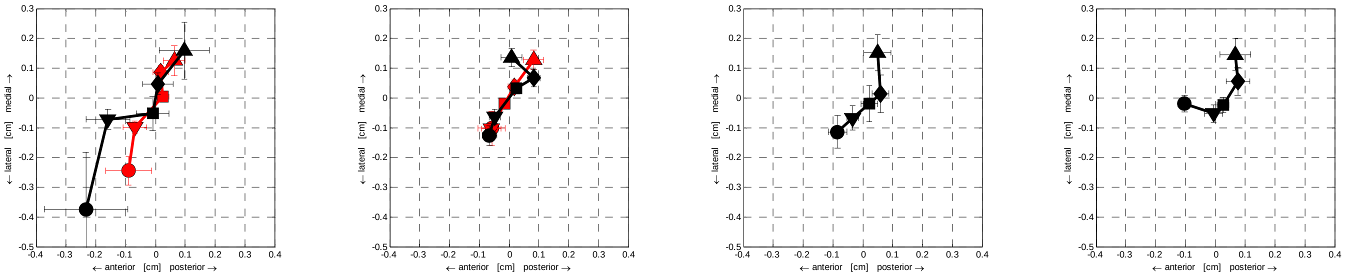
Nagel et al., in preparation

Disruption of homuncular motor representation in multiple sclerosis patients

Violinists (red=right M1) | Healthy control | Dystonia | MS patients



Little

Ring

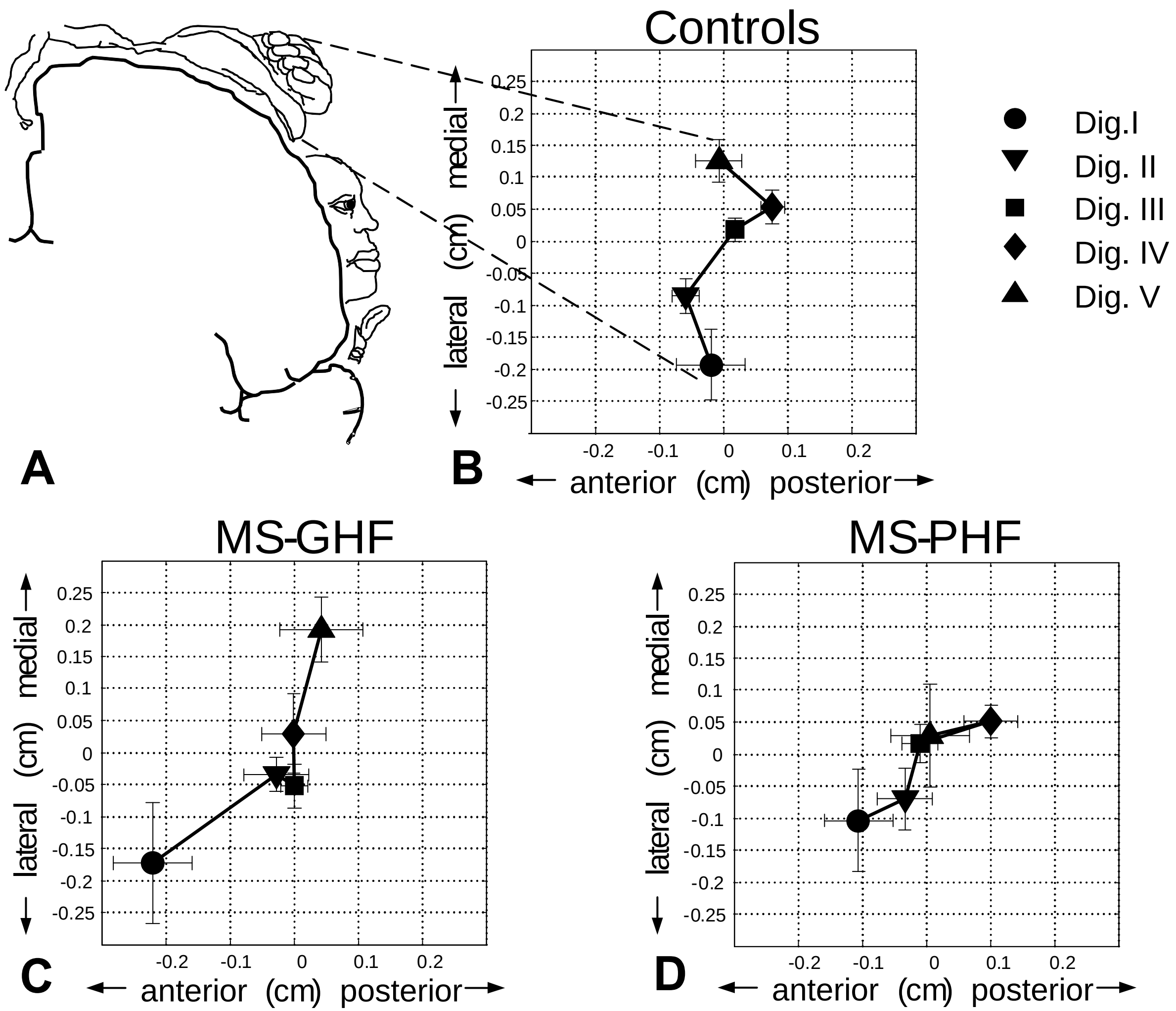
Middle

Index

Thumb

Nagel et al., in preparation

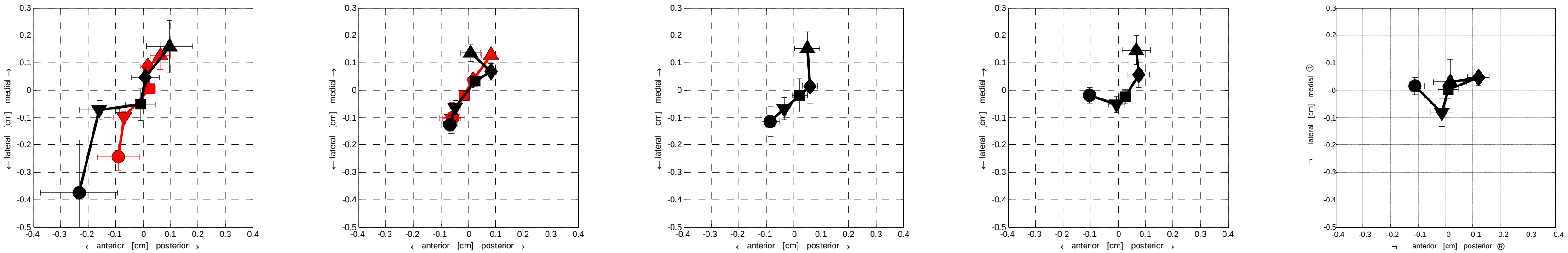
Disruption of homuncular motor representation covaries with hand function in multiple sclerosis patients

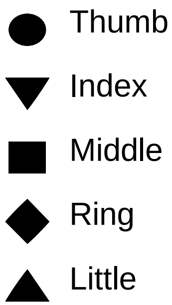


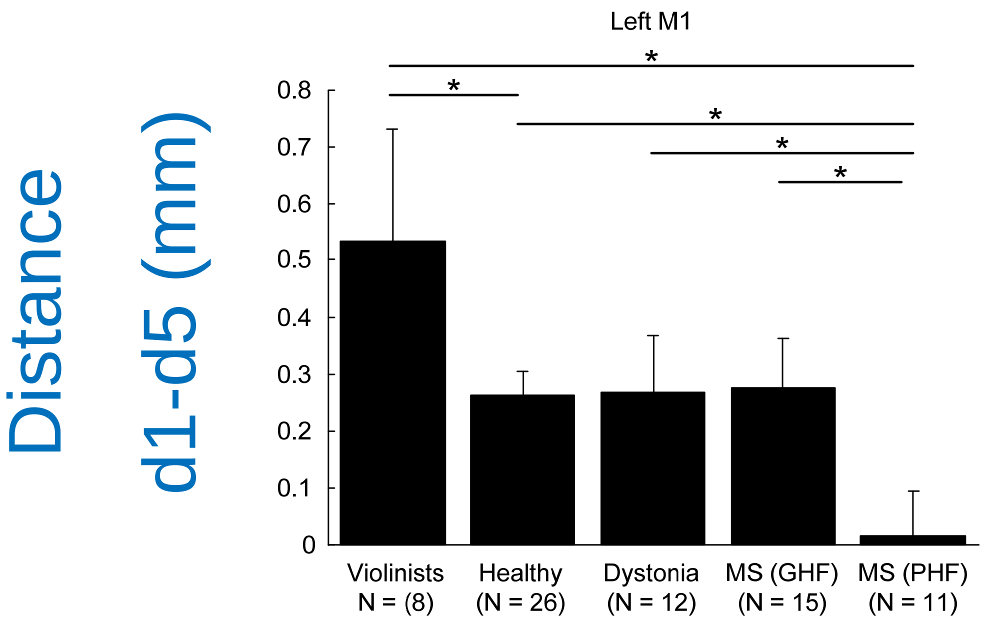
Nagel et al., in preparation

Disruption of homuncular motor representation covaries with hand function - in multiple sclerosis patients

Violinists (red=right M1) | Healthy control | Dystonia | MS (all) | MS (poor HF)

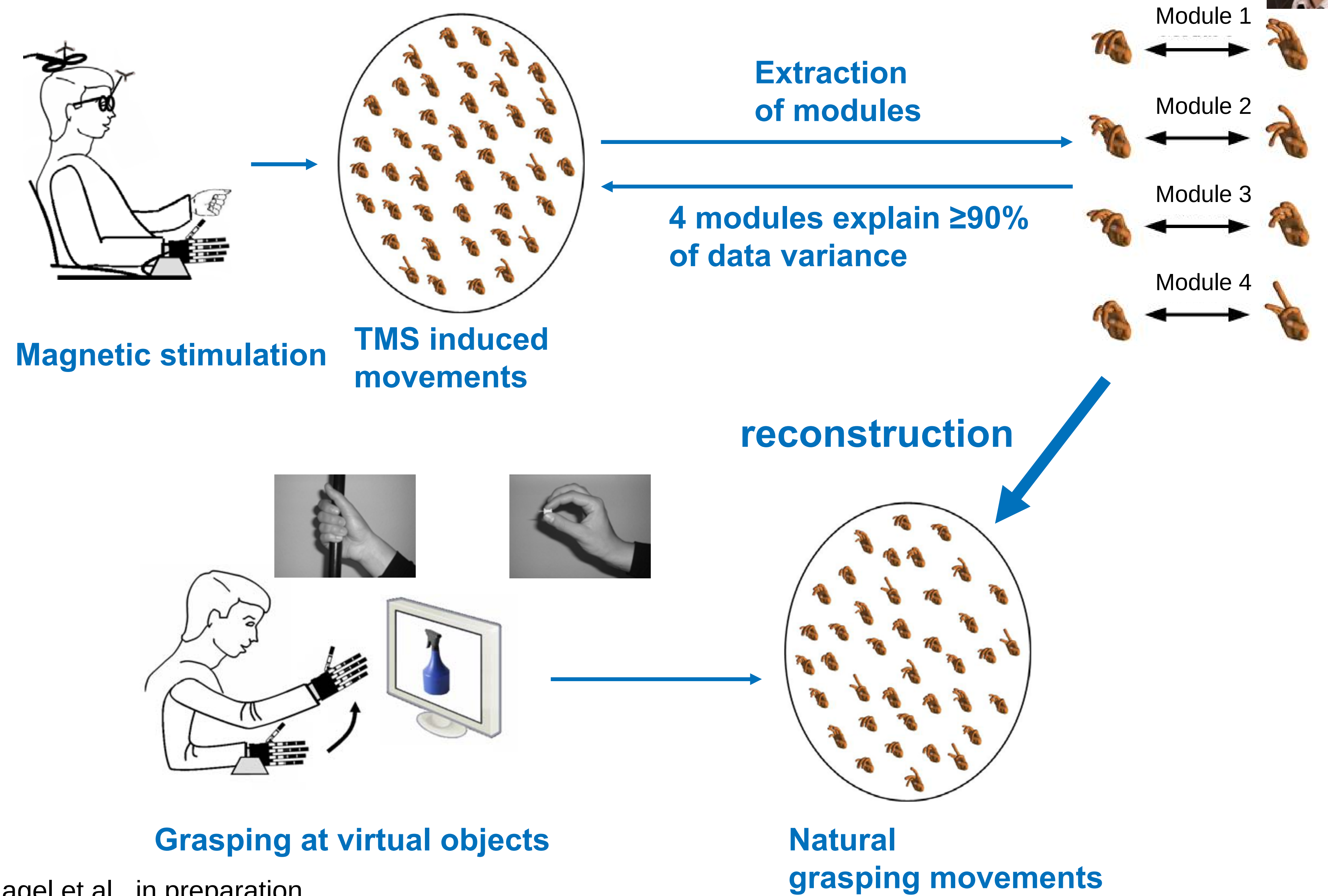






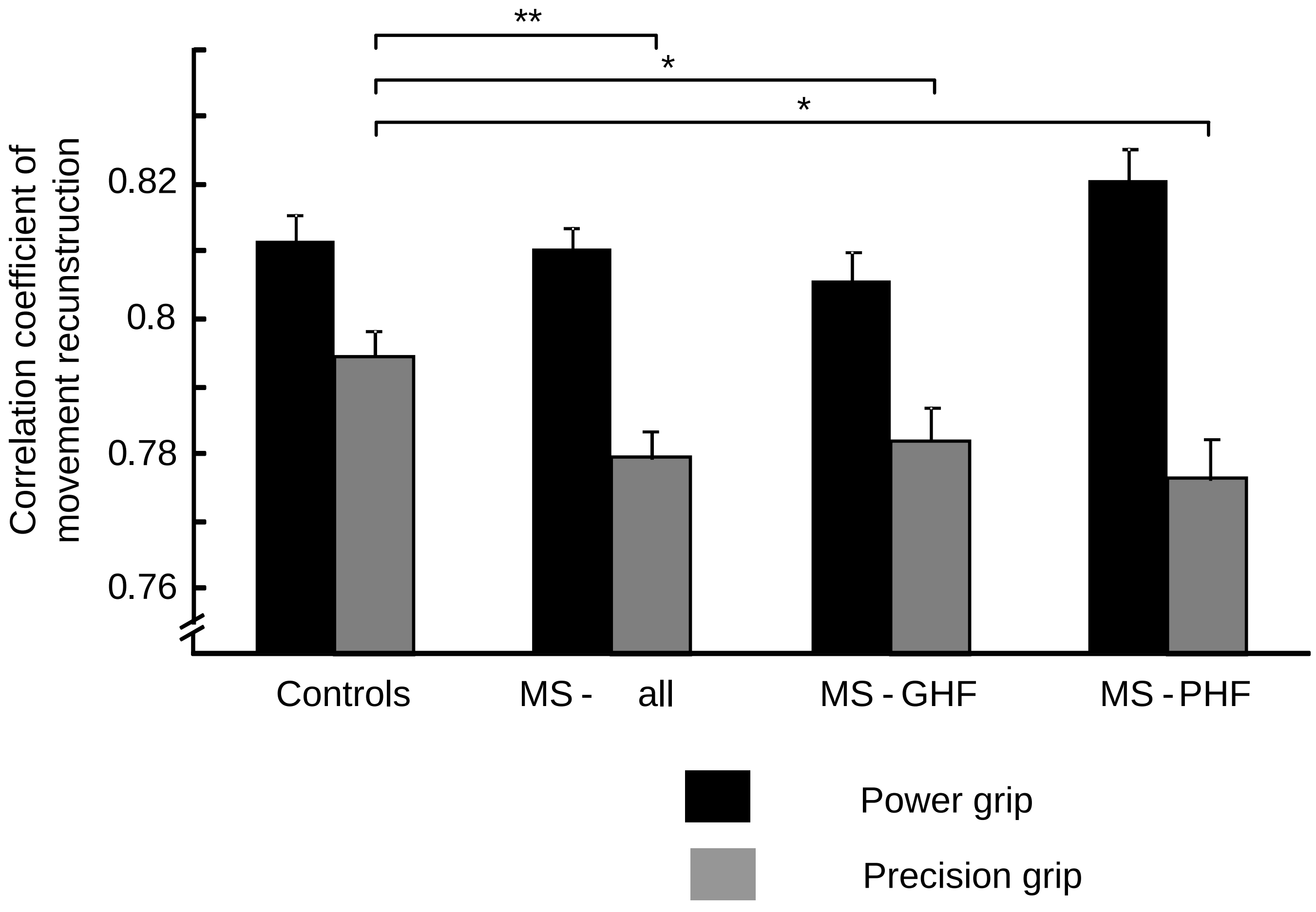
Nagel et al., in preparation

Modular control of precision and power grip



Nagel et al., in preparation

Impairment of modular control of precision movements in MS – independent of hand function in timed motor tests



Nagel et al., in preparation

Increased functional connectivity indicates the severity of cognitive impairment in multiple sclerosis

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Edited by Marcus E. Raichle, Washington University, St. Louis, MO, and approved October 19, 2011 (received for review June 22, 2011)

Short-term plasticity, resembling long-term potentiation of excitatory neuronal synapses is was **not compromised**, in patients with mild-to-moderate MS.

Activation of **non-canonical brain regions** is functionally relevant.

Reduced efficiency of motor control of dexterous movements may provide a pathophysiological model for impairment of behavioral control beyond that detectable in conventional functional assessments.

Daniel Zeller

Reinhard Gentner

André Nagel

Suyin Dang

Kristin aufm Kampe

Deutsche Forschungsgemeinschaft DFG

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