

Medizintechnik

Einführung Neurophysiologie /

General Introduction to Neurophysiology

Surjo R. Soekadar, MD

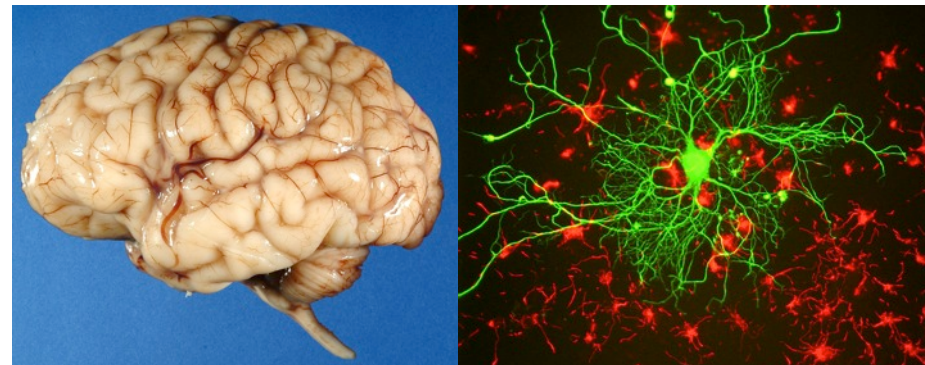
University of Tübingen, Germany

Overview

- Introduction: The Human Brain
- The Age of Neurotechnology
- US and EU Research Funding Initiatives
- Why now?
- Approaching New Frontiers: New Methods and Recent Breakthroughs
- Summary & Discussion

Some (rather superficial) facts about the human brain

- approx. 3 pounds
- 100.000.000.000 neurons (100 billion) linked and communicating through 1000-10.000 synapses
- 60% gray matter, 40% white matter
- 100.000 miles of blood vessels
- Generates 10-23 watts of **electricity!**



Ways to understand the brain...

- By observation of
 - Behavior
 - Single organisms
 - Behavior of groups, societies etc.
 - Physiology
 - E.g. electric, magnetic or metabolic activity
- Develop a “brain theory” that allows to test specific hypotheses (i.e. make predictions of behavior and physiology under specific experimental conditions)
- Direct manipulation of brain physiology (e.g. using drugs, brain stimulation)

Tools to measure brain activity



Magnetoencephalography (MEG)

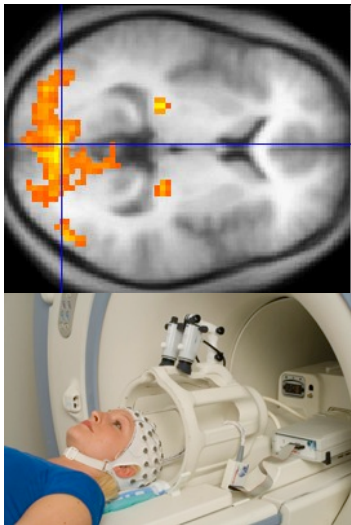


Electroencephalography (EEG)

Tools to measure brain activity

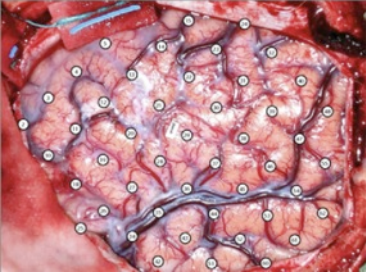


Near Infrared Spectroscopy (NIRS)

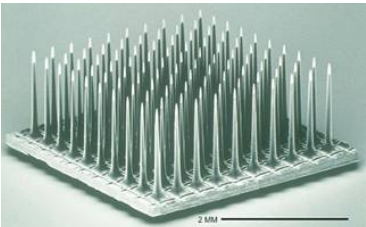


Magnet Resonance Imaging (MRI)
Functional MRI

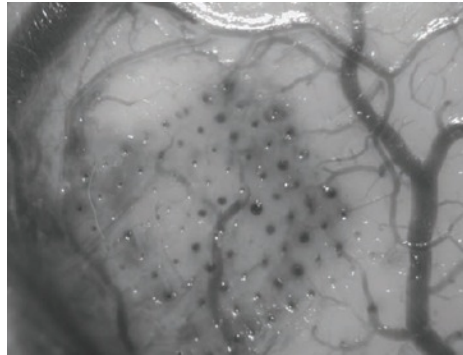
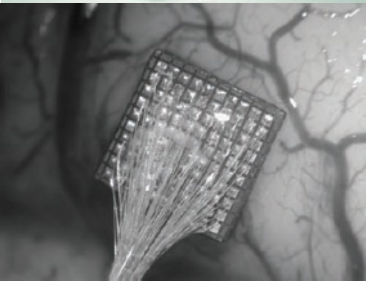
Tools to measure brain activity



Electrocorticography (ECoG)



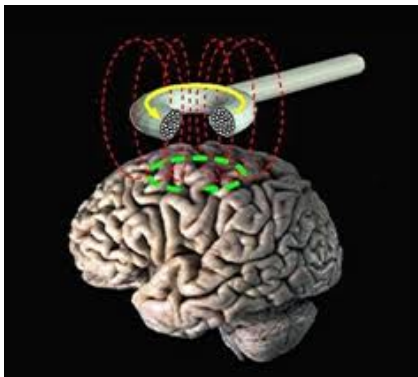
Single Spike Activity / Multi Unit Arrays
(*MUA*)



Non-invasive brain stimulation

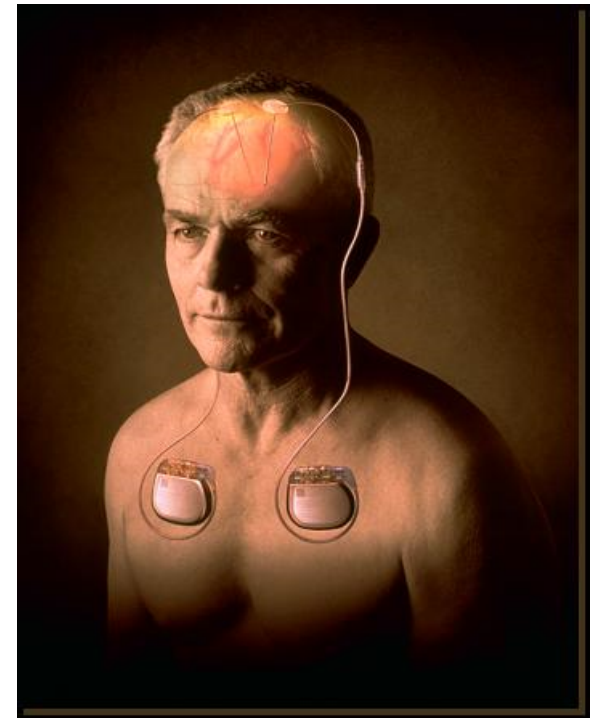
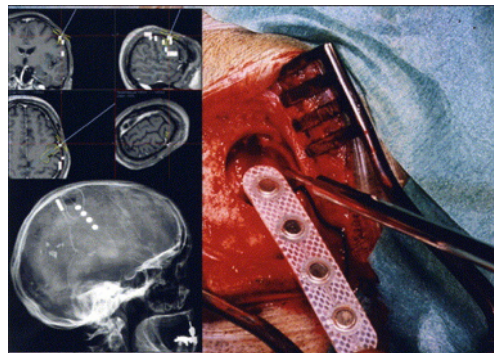


Transcranial direct current stimulation (tDCS)



Transcranial magnetic stimulation (TMS)

Established active brain implants for clinical applications



Neurotechnology

- Neurotechnology is defined as **any artificial measure** or method that **aims at interacting with brain activity**.
- This includes **technical and computational tools** that **measure** or analyze chemical or electrical neural signals in the peripheral or central nervous system (CNS).
- These tools can be used to **characterize the features** of these signals, **understand brain functions**, **diagnose** pathological states, or to **control** external devices or computers (brain-machine interfaces, BMI).
- Also, to **interact with the activity of the CNS** to modulate its activity, recover sensory capacities (cochlea implant) or **change pathological activity** (e.g. deep brain stimulation in Parkinson's).

2013: The year of the large funding initiatives for brain research based on neurotechnology

- BRAIN Initiative (Brain Research through Advancing Innovative Neurotechnologies Initiative) – **USA**
 - The BRAIN initiative aims at accelerating the development and application of new technologies that allow scientists to investigate how individual cells and more complex neural networks interact.
 - The BRAIN initiative was estimated to sum up to **4.5 billion USD** over 10 years and is coordinated by the **National Institutes of Health (NIH)**, the **Defense Advanced Research Projects Agency (DARPA)** and the **National Science Foundation (NSF)**.
- Human Brain Project - **Europe**
 - The Human Brain Project includes over **80 European** and international research institutions aiming at integrating existing knowledge about the human brain to realize a super-computer based simulation of the brain. Such digital brains should have the capacity to simulate the processes of single neurons and within whole brains.
 - The HBP has a volume of over **1.3 billion Euros over 10 years**.

Neuroscience

A few numbers

- 100.000 publications per year
- 7 billion USD p.a. worldwide
- HBP, BRAIN initiative = 1.6%

Examples of recent **methodological innovations** to investigate and simulate neural activity

PNAS

Synthesizing cognition in neuromorphic electronic systems

Emre Neftci^{a,1}, Jonathan Binas^a, Ueli Rutishauser^b, Elisabetta Chicca^{a,c}, Giacomo Indiveri^a, and Rodney J. Douglas^a

Author Affiliations

Edited* by Terrence J. Sejnowski, Salk Institute for Biological Studies, La Jolla, CA, and approved June 10, 2013 (received for review July 20, 2012)

Significance

Neuromorphic emulations express the dynamics of neural systems in analogous electronic circuits, offering a distributed, low-power technology for constructing intelligent systems. However, neuromorphic circuits are inherently imprecise and noisy, and there has been no systematic method for configuring reliable behavioral dynamics on these substrates. We describe such a method, which is able to install simple cognitive behavior on the neuromorphic substrate. Our approach casts light on the general question of how the neuronal circuits of the brain, and also future neuromorphic technologies, could implement cognitive behavior in a principled manner.



Bakkum et al. 2013

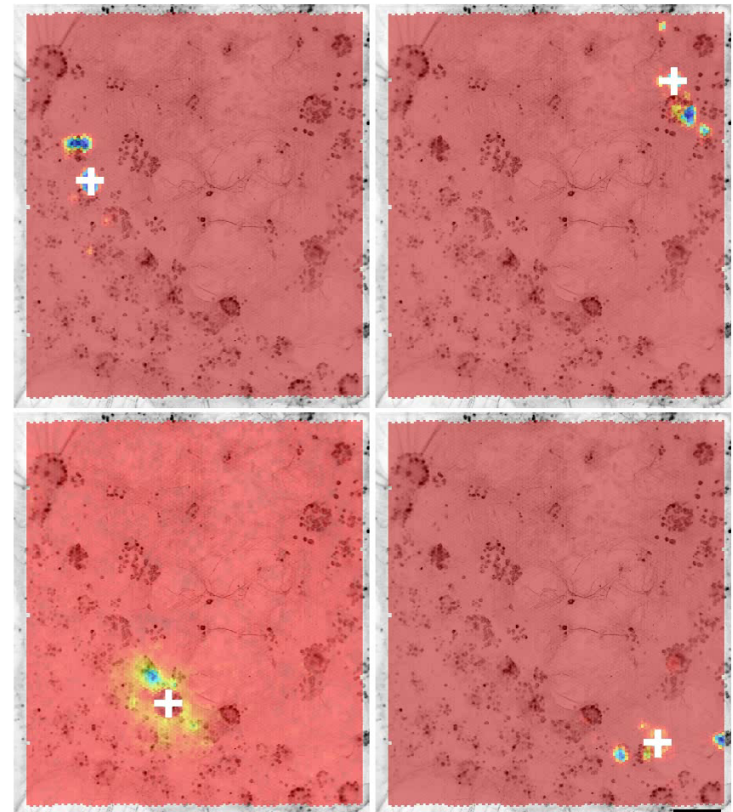
Supplemental Video S1

Somatic and propagating action potentials evoked by electrical stimulation at 4 sites in the same culture.

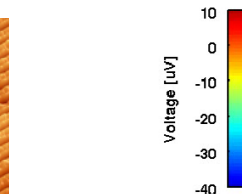
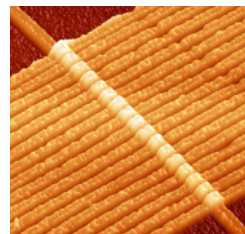
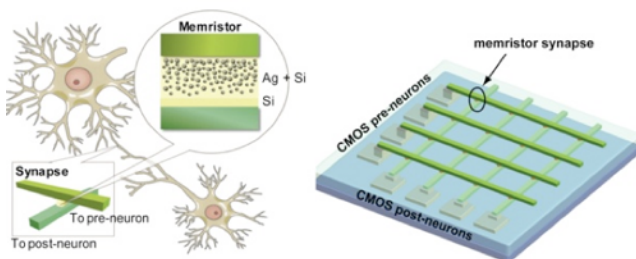
A series of rectangular recording configurations were scanned across the 1.8mm x 2.0mm array. The median voltage per electrode (colored pixels) in response to stimuli applied to a single electrode (white plus) 40 times per configuration show action potentials evoked in a subset of somas (blue). The color scale was clipped in order to observe propagating action potentials (yellowish). Scale bar: 250 μ m.

A black and white image of MAP2, marking soma and dendrites, underlies each voltage plot.

Time since stimulation: 1.00 msec. Sample: 81



Innovative Chipdesign: Memristor



LB. BAKKUM

Examples of recent **methodological innovations** to investigate and simulate neural activity

Creating a False Memory in the Hippocampus

Steve Ramirez,^{1*} Xu Liu,^{1,2*} Pei-Ann Lin,¹ Junghyup Suh,¹ Michele Pignatelli,¹ Roger L. Redondo,^{1,2} Tomás J. Ryan,^{1,2} Susumu Tonegawa^{1,2†}

Memories can be unreliable. We created a false memory in mice by optogenetically manipulating memory engram-bearing cells in the hippocampus. Dentate gyrus (DG) or CA1 neurons activated by exposure to a particular context were labeled with channelrhodopsin-2. These neurons were later optically reactivated during fear conditioning in a different context. The DG experimental group showed increased freezing in the original context, in which a foot shock was never delivered. The recall of this false memory was context-specific, activated similar downstream regions engaged during natural fear memory recall, and was also capable of driving an active fear response. Our data demonstrate that it is possible to generate an internally represented and behaviorally expressed fear memory via artificial means.

Neuroscience aims to explain how brain activity drives cognition. Doing so requires identification of the brain regions that are specifically involved in producing internal mental representations and perturbing their activity to

see how various cognitive processes are affected. More specifically, humans have a rich repertoire of mental representations generated internally by processes such as conscious or unconscious recall, dreaming, and imagination (1, 2). However,

whether these internal representations can be combined with external stimuli to generate new memories has not been vigorously studied.

Damage to the hippocampus impairs episodic memory (3–8). Recently, using fear conditioning in mice as a model of episodic memory, we identified a small subpopulation of granule cells in the dentate gyrus (DG) of the hippocampus as contextual memory-engram cells. Optogenetic stimulation of these cells is sufficient to activate behavioral recall of a context-dependent fear memory formed by a delivery of foot shocks. This finding provided an opportunity to investigate how the internal representation of a specific context can be associated with external stimuli of high valence. In particular, a hypothesis of great interest is

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Neuroethics...

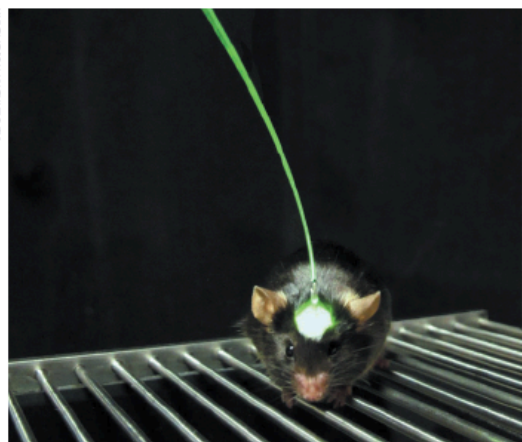
NEWS IN FOCUS

RUSSIA Hopes pinned on elite tech campus to fight brain drain **p.262**

PHYSICS Romania dreams of 'laser valley' to light up economy and science **p.264**

PHARMACEUTICALS India takes a stand over cancer-drug patents **p.266**

PSYCHOLOGY Elizabeth Loftus, maven of malleable memory **p.268**



Optical stimulation of light-responsive neurons in engineered mice can be used to create false memories.

NEUROSCIENCE

US brain project puts focus on ethics

Unsettling research advances bring neuroethics to the fore.

BY HELEN SHEN

The false mouse memories made the ethicists uneasy. By stimulating certain neurons in the hippocampus, Susumu Tonegawa and his colleagues caused mice to recall receiving foot shocks in a setting in which none had occurred. Tonegawa, a neuroscientist at the Massachusetts Institute of Technology in Cambridge, says that he has no plans to ever implant false memories into humans — the study, published last month, was designed

just to offer in sight into memory formation. But the experiment has nonetheless alarmed some neuroethicists. "That was a bell-ringer, the idea that you can manipulate the brain to control the mind," says James Giordano, chief of neuroethics studies at Georgetown University in Washington DC. He says that the study is one of many raising ethical concerns, and more are sure to come as an ambitious, multi-year US effort to parse the human brain gets under way.

The BRAIN (Brain Research through

Advancing Innovative Neurotechnologies) Initiative will develop technologies to understand how the brain's billions of neurons work together to produce thought, emotion, movement and memory. But, along with the discoveries, it could force scientists and society to grapple with a laundry list of ethical issues: the responsible use of cognitive-enhancement devices, the protection of personal neural data, the prediction of untreatable neurodegenerative diseases and the assessment of criminal responsibility through brain scanning.

On 20 August, US President Barack Obama's commission on bioethics will hold a meeting in Philadelphia, Pennsylvania, to begin to craft a set of ethics standards to guide the BRAIN project. There is already one major mechanism for ethical oversight in US research: institutional review boards, which must approve any studies involving human subjects. But many ethicists say that as neuroscience discoveries creep beyond laboratory walls into the marketplace and the courtroom, more comprehensive oversight is needed. "The long-term consequences of more brain knowledge — whether it's good for an ethnic group or threatens your personal identity — there's sort of no one in charge of that," says Arthur Caplan, director of medical ethics at New York University's Langone Medical Center.

Tonegawa's study adds to the growing evidence that memories are surprisingly pliable. In the past few years, researchers have shown that drugs can erase fearful memories² or disrupt alcoholic cravings in rodents³. Some scientists have even shown that they can introduce rudimentary forms of learning during sleep in humans⁴. Giordano says that dystopian fears of complete human mind control are overblown. But more limited manipulations may not be far off: the US Defense Advanced Research Projects Agency (DARPA), one of three government partners in the BRAIN Initiative, is working towards 'memory prosthetic' devices to help soldiers with brain injuries to regain lost cognitive skills.

Deep brain stimulation (DBS), in which implants deliver simple electrical pulses, is another area that concerns neuroethicists. The devices have been used since the 1990s to treat motor disorders such as Parkinson's disease, and are now being tested in patients with psychiatric conditions such as obsessive-compulsive disorder and major depression. Giordano says that applying DBS technology more widely ▶

THE WHITE HOUSE
WASHINGTON

July 1, 2013

The Honorable Amy Gutmann, Ph.D.
Commission Chair
Presidential Commission for the Study of Bioethical Issues
Washington, D.C. 20005

Dear Dr. Gutmann:

As I noted in my announcement of the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative on April 2, 2013, developments in neuroscience hold great potential to help individuals and society. New technologies to better visualize the brain and understand how it works promise to speed the discovery of new ways to treat and prevent brain disorders, including those caused by disease and traumatic injury, and to shed light on the neural components of memory and learning, among other benefits.

Advances in neuroscience can also raise ethical and legal issues that require reflection and analysis. In keeping with my Administration's strong commitment to rigorous research ethics in all fields, I want to ensure that researchers maintain the highest ethical standards as the field of neuroscience continues to progress. As part of this commitment, we must ensure that neuroscientific investigational methods, technologies, and protocols are consistent with sound ethical principles and practices.

Equally important, we should consider the potential implications of the discoveries that we expect will flow from studies of the brain, and some of the questions that may be raised by those findings and their applications—questions, for example, relating to privacy, personal agency, and moral responsibility for one's actions; questions about stigmatization and discrimination based on neurological measures of intelligence or other traits; and questions about the appropriate use of neuroscience in the criminal-justice system, among others. It will also be important to consider these types of questions as they relate to different life stages, from infancy through old age.

I request that the Presidential Commission for the Study of Bioethical Issues engage with the scientific community and other stakeholders, including the general public, to identify proactively a set of core ethical standards—both to guide neuroscience research and to address some of the ethical dilemmas that may be raised by the application of neuroscience research findings.

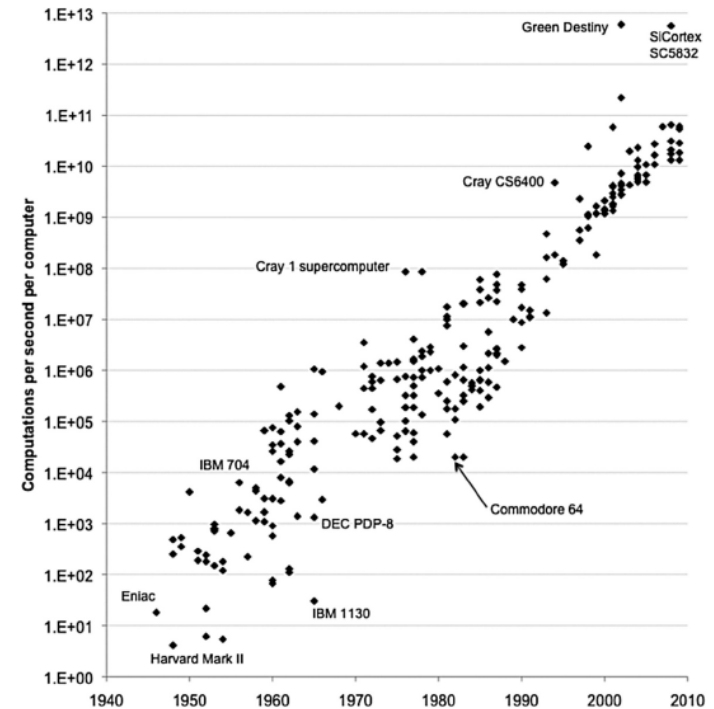
In the course of your deliberations, I encourage you to reach out to a wide range of constituencies, including scientists, ethicists, legal scholars, and members of the public, to ensure that your findings and the neuroscience enterprise faithfully reflect and strengthen our values as a Nation.

Sincerely,

Why now? –

Because of good pre-conditions for substantial advances in the field of neuroscience

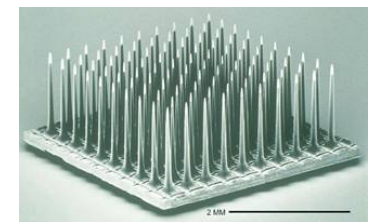
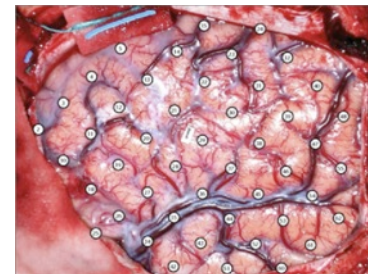
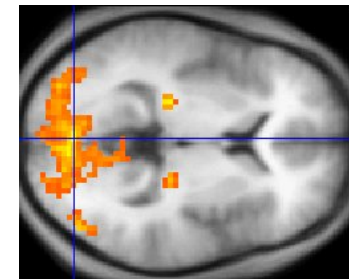
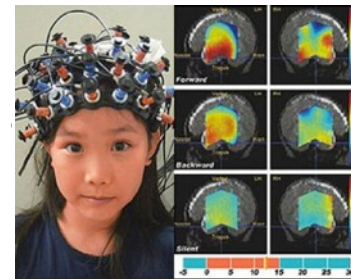
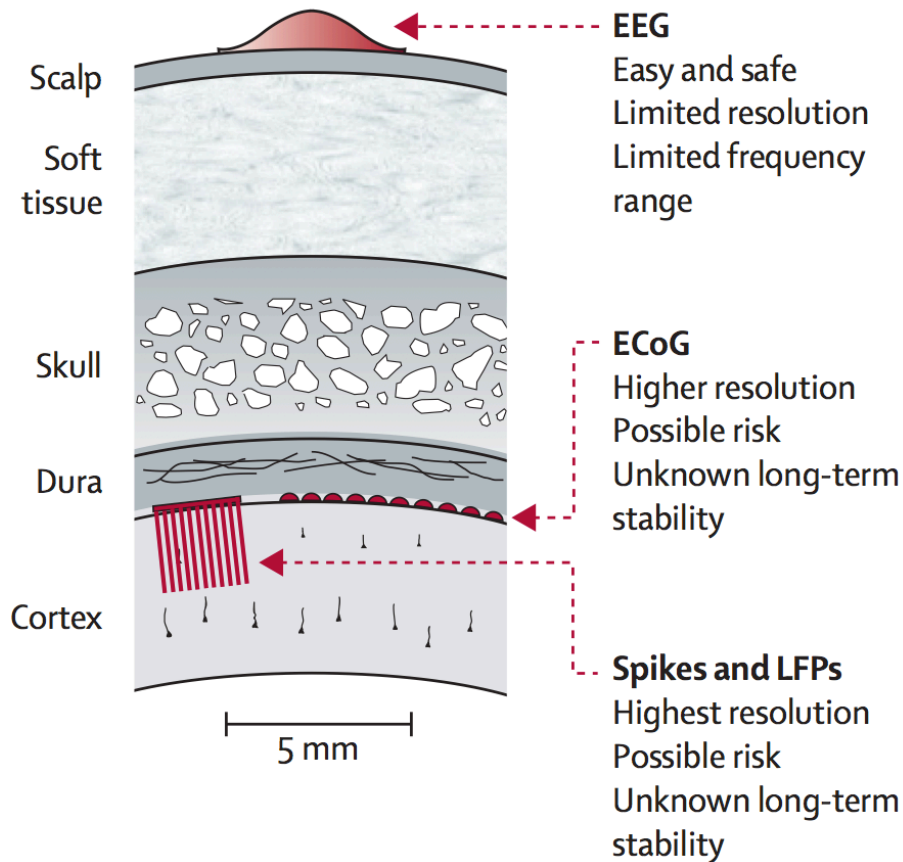
- Exponential development of available computational capacities
- Application of cybernetics/artificial intelligence
- Progress in the sensor and material science (biocompatibility, nanotechnology)



Brain-Machine Interfaces (BMI)

- In BMI, electric, magnetic or metabolic brain activity becomes recorded, classified and translated online into control signals of machines allowing real-time communication between a human brain and a machine.
- Two forms of BCI can be distinguished:
 - invasive (recordings are made from within the skull)
 - non-invasive (recordings are made from outside the skull)

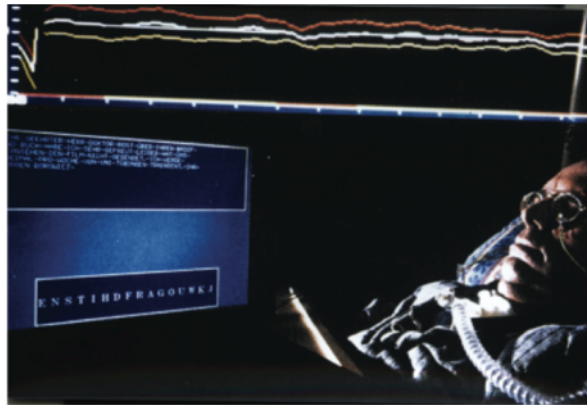
Invasive and non-Invasive BMI



Non-invasive BMI

- 1929 Hans Berger discovers the EEG

- 1952 Sources of distinct EEG activity described (Gesundheit)

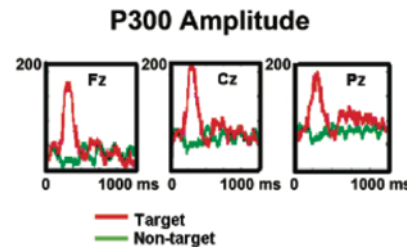


- 2005 SMR-based MEI established at NIH

LIEBER-HERR-BIRBAUMER-

HOFFENTLICH-KOMMEN-SIE-MICH-BESUCHEN,-WENN-DIESER-BRIEF-SIE-ERREICHT-HAT.-ICH-DANKE-IHNEN-UND-IHREM-TEAM-UND-BESONDERS-FRAU-KÜBLER-SEHR-HERZLICH,-DENN-SIE-ALLE-HABEN-MICH-ZUM-ABC-SCHÜTZEN-GEMACHT,-DER-OFT-DIE-RICHTIGEN-BUCHSTABEN-TRIFFT.FRAU-KÜBLER-IST-EINE-MOTIVATIONSKÜNSTLERIN.OHNE-SIE-WÄRE-DIESER-BRIEF-NICHT-ZUSTANDE-GEKOMMEN.-ER-MUSS-GEFEIERT-WERDEN.-DAZU-MÖCHTE-ICH-SIE-UND-IHR-TEAM-HERZLICH-EINLADEN.-EINE-GELEGENHEIT-FINDET-SICH-HOFFENTLICH-BALD.

MIT-BESTEN-GRÜSSEN-
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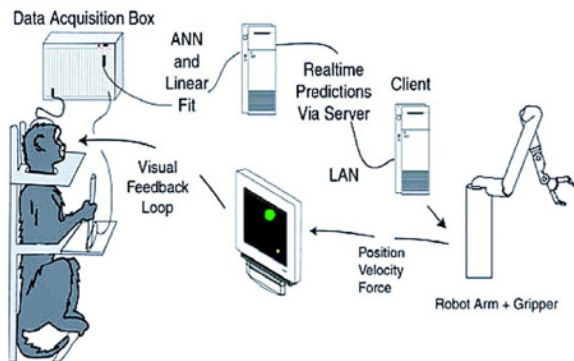
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potentials (SCP)

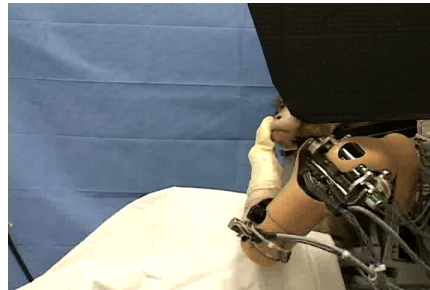
hythms (SMR)

Invasive BCI

- 1969 Eberhard Fetz: “Operant Conditioning of Cortical Unit Activity” (*Science*): *monkey uses electrode to deflect robotic arm*
- 1989 Georgopoulos: reconstruction of movement direction from single neurons (M1)
- 1990ies: Schwartz, Nicolelis, Donoghue



Nicolelis et al. Nat Neurosc. 2003

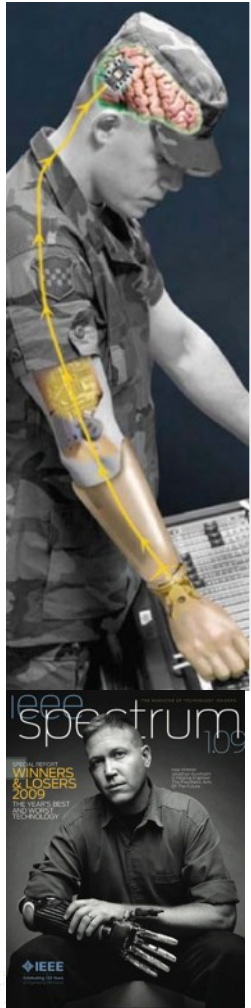


Velliste et al. Nature 2009



Donoghue et al. Neuron 2008

DARPA (Defense Advanced Research Projects Agency): Revolutionizing Prosthetics



- Vision (2006): „The Revolutionizing Prosthetics program will create, within this decade, a fully functional (motor and sensory) upper limb that responds to direct neural control. By 2010, DSO will deliver a prosthetic for clinical trials that has function almost identical to a natural limb in terms of motor control and dexterity, sensory feedback (including proprioception), weight, and environmental resilience (22 degrees of freedom)“.
- The four-year device will be directly controlled by neural signals. The results of this program will allow upper limb amputees to have as normal a life as possible despite their severe injuries.
- Funds spent by 2013: 120.2 Mio. USD
- Bottleneck: cortical control of the orthosis



Two major properties of BCI/BMI

1. assistive / biomimetic BCI/BMI



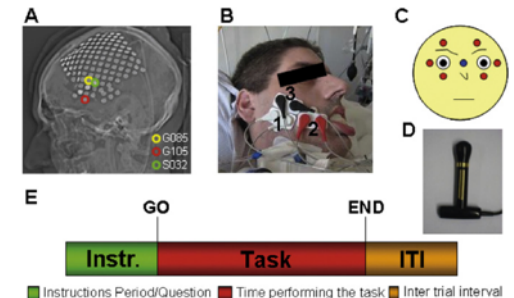

 Wearable interfaces
 for hand function recovery
 FP7-ICT-298551

Patient with full arm/hand paralysis after brachial plexus
 injury controlling the exoskeleton
 Tübingen - November, 2012







Soekadar, Birbaumer & Cohen, 2011



Two major properties of BCI/BMI

1. brain activity that is associated with certain behavior (e.g. hand movements) can be identified and used to reconstruct that specific behavior: assistive / biomimetic BCI
 - Problem: high resolution required (invasive); encoding not fully understood; recording cortical activity is just the tip of the iceberg; self-paced mode; daily-life robustness
2. A BCI can induce use-dependent neuroplasticity:
e.g. facilitation of motor recovery: restorative / biofeedback BCI





Stroke

- After stroke, co-ordinated activity of the motor system (motor planning, sensory feedback and integration e.g.) can become severely disturbed.
 - Extensive neuroplastic changes on synaptic, neuronal and circuit level:
 - new synapses strengthening and rewiring (Chklovskii et al. 2004) following LTP/LTD
 - dendritic sprouting
 - peri-infarct reorganization (vicarious reorganization, Jaillard et al. 2005)
 - change of activity in remote cortical regions (Frost et al. 2003)
 - The ability to desynchronize the affected hemisphere in the SMR-range correlates with clinical motor outcome after stroke (Platz et al. 2002; Tecchio et al. 2007)
- 



Rational of a restorative/biofeedback BCI in stroke

- Using a restorative BCI follows two hypotheses:
 - by inducing CNS plasticity that produces more normal activation, normal brain function will be restored
 - contingent sensory input (reward) induces CNS plasticity (rewiring) that facilitates restoration of normal motor control

Can a stroke patient with a complete paralysis control a SMR-based BCI?

- Buch et al. 2008

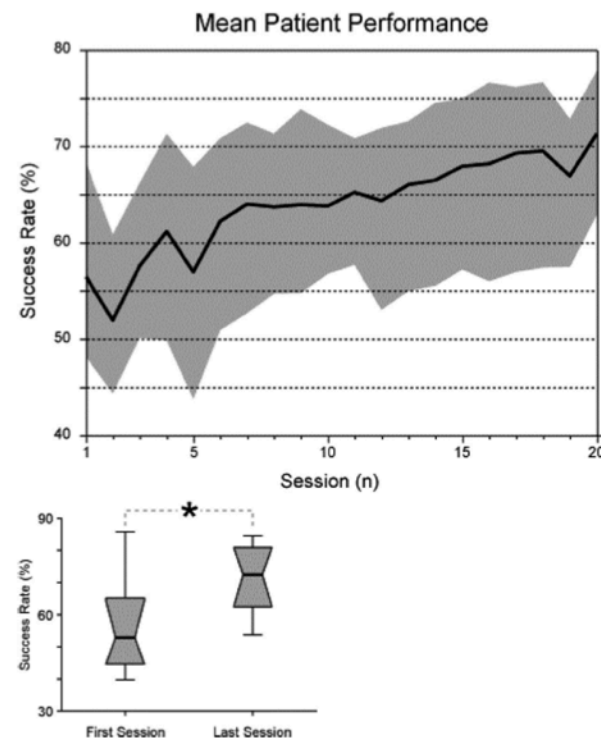
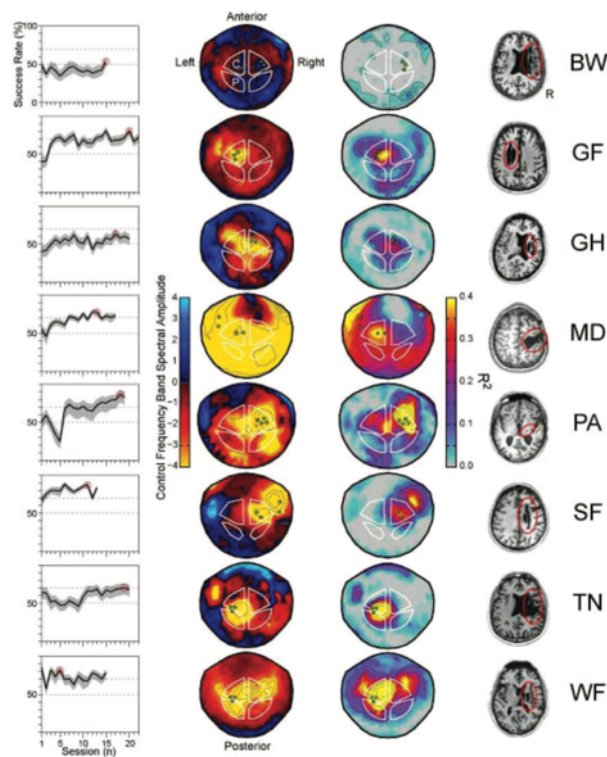
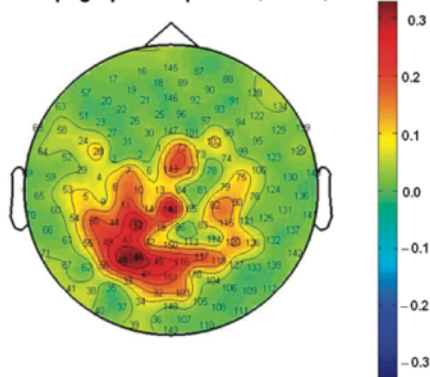
Think to Move: a Neuromagnetic Brain-Computer Interface (BCI) System for Chronic Stroke

Ethan Buch,* MA; Cornelia Weber,* MA; Leonardo G. Cohen, MD; Christoph Braun, PhD;
Michael A. Dimyan, MD; Tyler Ard, BS; Jurgen Mellinger, BS; Andrea Caria, MS;
Surjo Soekadar, MD; Alissa Fourkas, PhD; Niels Birbaumer, PhD

(*Stroke*. 2008;39:910-917.)



Topographic map of R^2 ($f = 9$ Hz)





Preliminary: Clinical Outcome

Neurorehabilitation and
Neural Repair
24(7) 674–679

Combination of Brain–Computer Interface Training and Goal-Directed Physical Therapy in Chronic Stroke: A Case Report

**Doris Broetz¹, Christoph Braun, PhD^{1,2}, Cornelia Weber³,
Surjo R. Soekadar, MD¹, Andrea Caria, PhD¹,
and Niels Birbaumer, PhD^{1,4}**

- A 67-year-old hemiplegic patient, 14 months after stroke
 - No active finger extension; depended on assistance for personal hygiene and dressing.
 - Could not drive a car, walked slowly with a cane and with a stabilizing orthosis on his left ankle joint
 - The patient never walked over uneven ground such as grass.
 - Used a wheelchair for all distances greater than 1000 m.
 - During walking, spasticity brought his arm in flexion in front of the trunk.
 - Could not extend his fingers and was unable to use his hand or arm for any relevant activity of daily living. Moreover, the paralyzed arm prevented him from standing up and walking.
- 

Broetz et al. 2010

Table 1. Test Parameters of Motor Function

Functional Test	FMA Passive and	Measurement	rest	movement	imagery	worth ^a	10-m Walk ^a	GAS
Baseline						8	18:18 s	-4
After 1 year						4	13:00 s	+10

Abbreviations: FMA, Fugl-Meyer Assessment; GAS, Global Assessment Scale.

^aFor these items, a low score indicates a better outcome.

pretreatment assessment (1st MEG measurement)

1

2

3

125

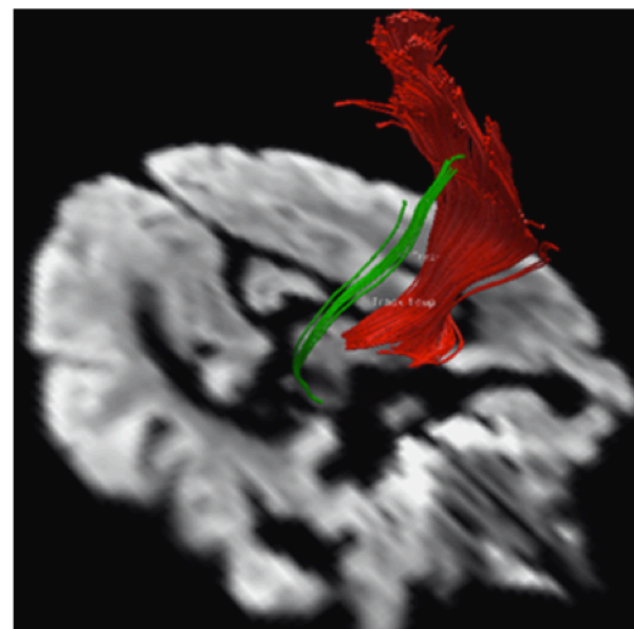
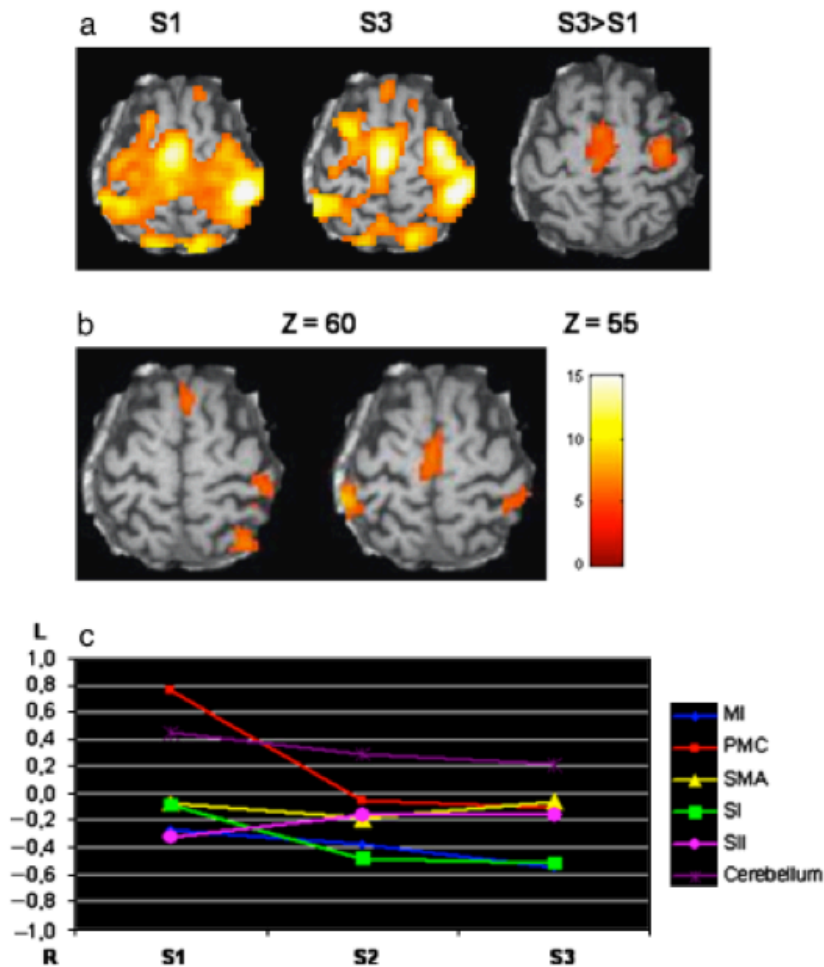
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$\mu T / Hz^{1/2}$

ment (follow up)
ent (behavioral data)

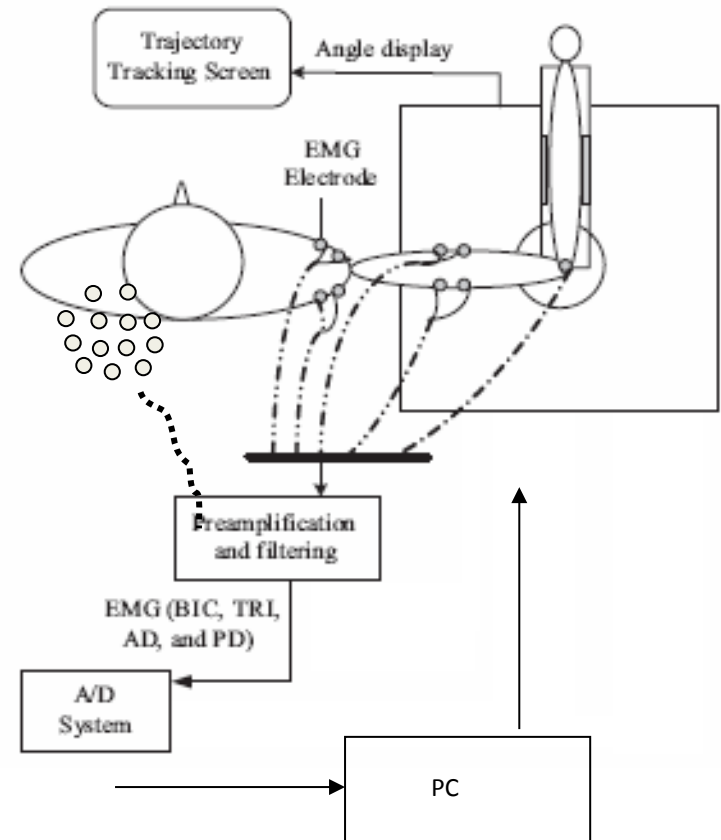
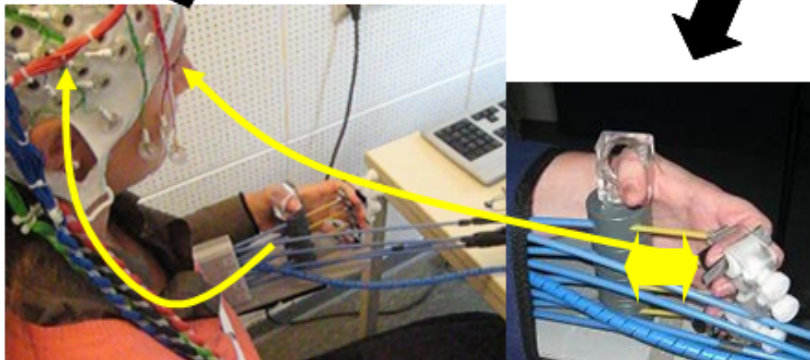
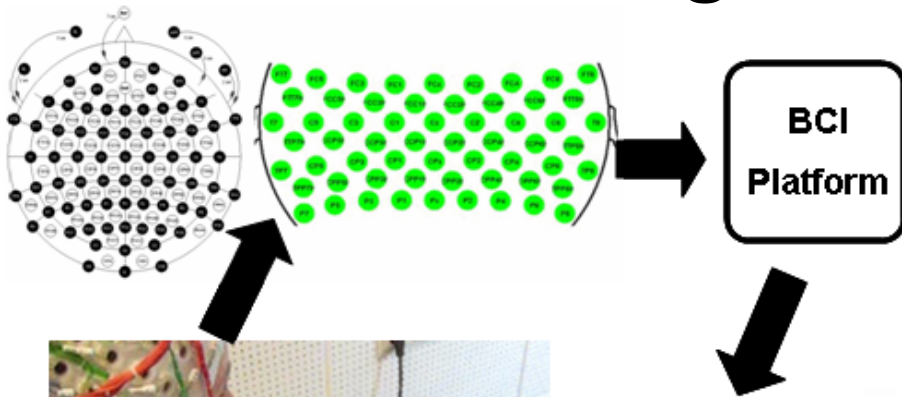
- He no longer depended on assistance for personal hygiene and wearing clothing.
- In addition to these motor task improvements, concentration and participation also increased, demonstrated by his ability to drive a car again.

Caria et al. 2010

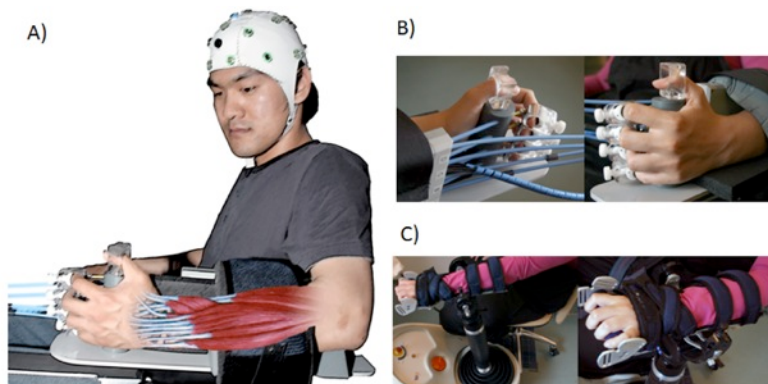


Caria A et al. Chronic stroke recovery after combined BCI training and physiotherapy. Psychophysiology 2010

Tübingen clinical trial on ipsilesional BCI training in chronic stroke

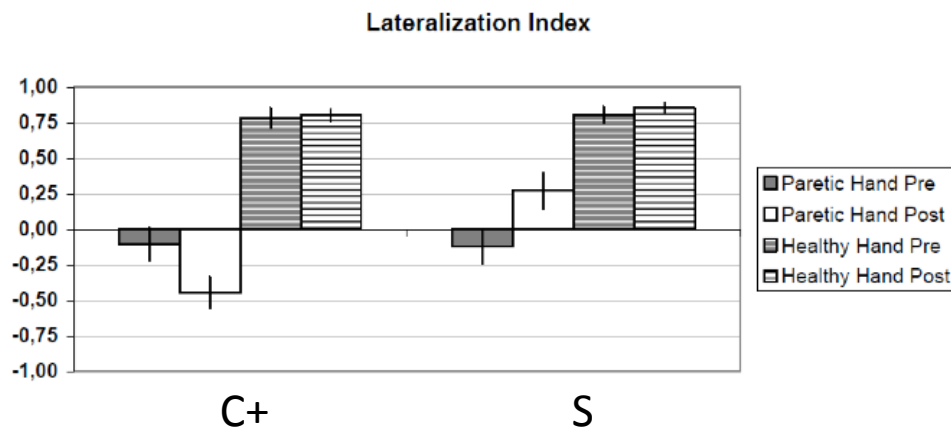


Efficacy of combined brain-computer interface (BCI) and goal-directed physiotherapy in chronic stroke: a controlled double-blind study



Gro up	Gender	Age	Months since stroke	lesion side	Total FMS	Δ GAS	Training Duration, days
C+	11M/5F	49.3 $\pm$ 12.5 years	69 $\pm$ 43	6 R / 4 L/ 6 bilateral?/	16.1 $\pm$ 8.45	0.88 $\pm$ 0.67	275 $\pm$ 25
S	11M/5F	50.3 $\pm$ 12.2 years	64 $\pm$ 68	6 R / 4 L /??	15.9 $\pm$ 9.45	0.63 $\pm$ 0.51	291 $\pm$ 17

fMRI BOLD
pre-post



Clinical Scores

	FMS Total	FMS Arm	FMS Hand	Ashworth	Gas Hand	GAS Walk	MAL
C+	t= -5.4	t= -4.782	z= -2.399	z= -1.426	z= -3.336	z= -3.402	z= -1.958
	p= 0.000	p= 0.000	p= 0.016	p= 0.154	p= 0.001	p= 0.001	p= 0.05
S	t= -0.365	t= 0.043	z= -0.529	z= -0.237	z= -3.223	z= -3.106	z= -2.599
	p= 0.721	p= 0.966	p= 0.597	p= 0.813	p= 0.001	p= 0.002	p= 0.009

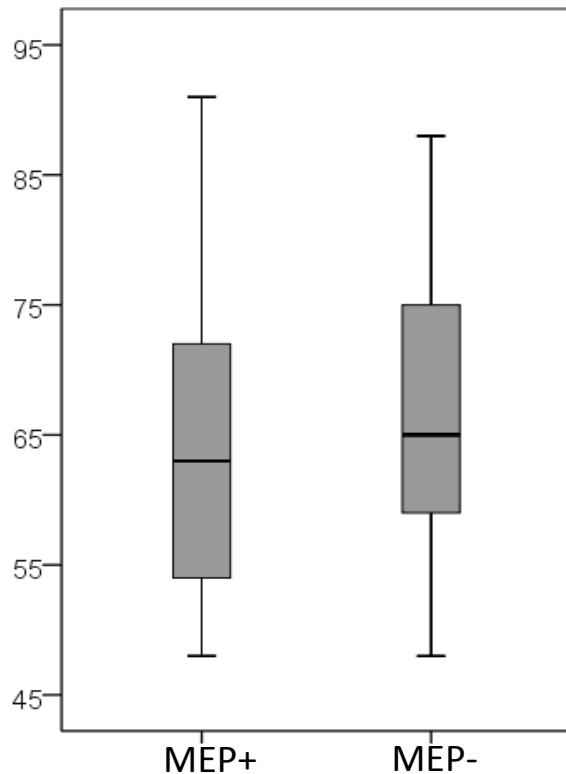
(BCI in chronic stroke, unpublished data)

Ipsilesional brain training related motor improvements and integrity of the cortico-spinal system

PRE

**Between Groups
Comparison**

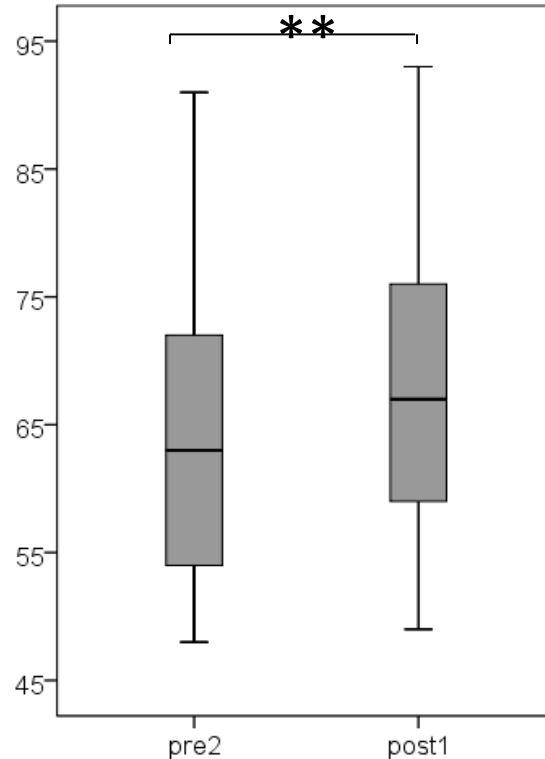
FMA



POST

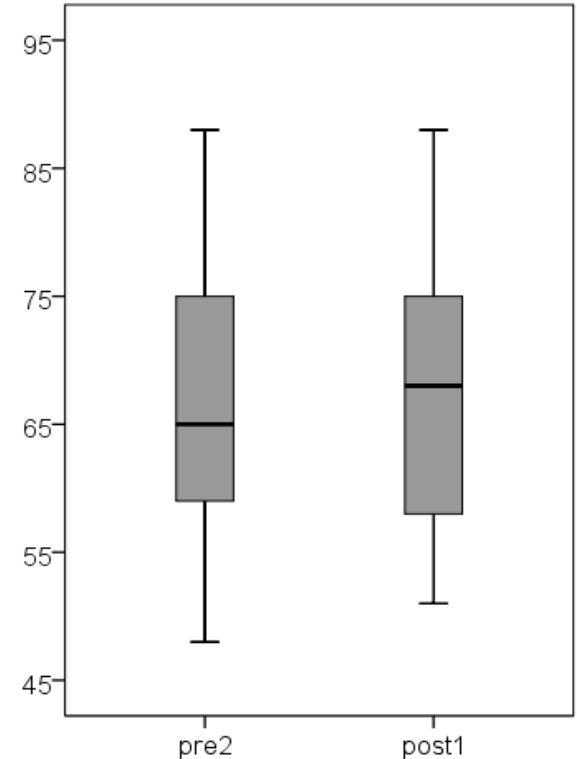
MEP+

FMA



MEP-

FMA



Further analysis

- Further analysis investigating the relatedness of MEP and motor improvements depending on different feedback types during BCI training showed that patients with no detectable upper-limb MEP receiving random feedback during BMI training did not improve.
- MEP- patients, however, showed in trend for improvement when receiving contingent BCI feedback.

Feedback	MEP	pre2	post1	paired sample t-test			
		pean	pean	t	df	p-value	
Contingent	MEPa+	66,75	71,50	5,16	7	,001	*
	MEPa-	61,50	64,38	2,16	7	,067	
Random	MEPa+	59,00	62,00	3,35	4	,028	*
	MEPa-	70,31	70,31	0,00	12	1,000	

What we learned from the Tübingen clinical trial on BCI in stroke?

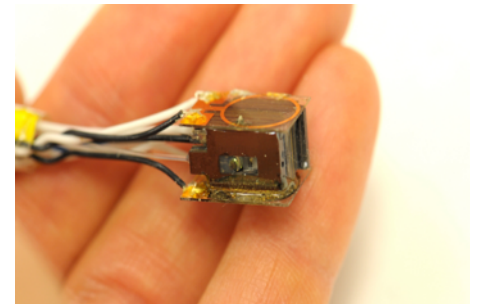
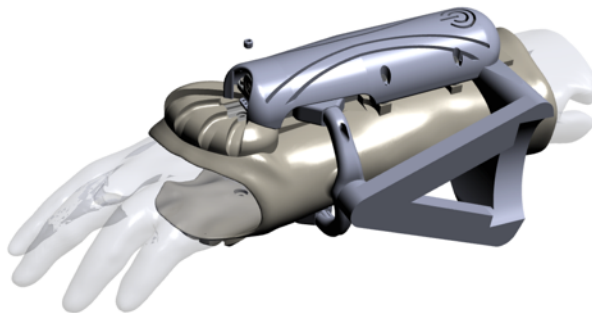
- Ipsilesional brain training can improve motor recovery in severe chronic stroke.
- There is evidence that improvements depend on cortico-spinal system's integrity.
- Brain training is associated with laterality changes.
- BMI learning was slow. Higher specificity of the BMI might further improve clinical outcomes.

Summary

- The coming two decades promise **substantial advances in neurotechnology**. Currently, technological and political frameworks are very good and become fostered by large funding initiatives in the US and Europe.
- The **development of real-time systems** that allow identification of brain activity related to specific behavior at high temporal and spatial resolution plays an important role and might become the **basis of novel diagnostic and therapeutic brain-machine interfaces (BMI)**.
- BMI technology might help to answer **very fundamental research questions** about the nature of the brain, while equally important in **clinical applications**, e.g. treatment of stroke, depression and dementia.
- The advancements in neurotechnology require a broad societal discourse and discussion about globally accepted **“neuro”-ethical standards**.

Future steps:

- Translation of clinical-based BMI training and brain stimulation to **home environments**
- **Merging assistive and rehabilitative BMI** in invasive and non-invasive BMI
- Implementation of **new techniques** to accelerate research results into clinical application (e.g. miniaturization, using available platforms, such as smartphones etc., new sensor technology, e.g. solid-gel electrodes or optic atomic magnetometers)

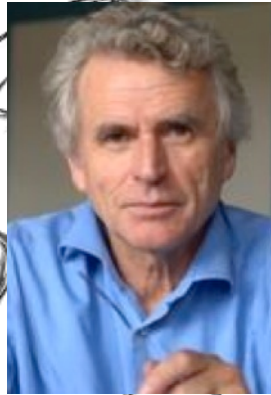


Fragen zur Überleitung in die Diskussion

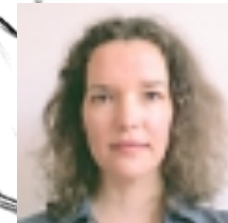
- Gibt es einen wissenschaftlichen Nachweis zentraler Reorganisation und peripherer Funktionserholung im Kontext von BMI-Gebrauch?
- Gibt es eine Methode, die es in Echtzeit erlaubt, zentrale Aktivierung durch periphere Bewegung und ggf. Stimulation nachzuweisen?

Thanks for your attention!

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