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October 30, 2017

OECD

The State of Mind in Economics

Brain imaging- fMRI and beyond

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Who We Are

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> 70%
of critical clinical decisions are influenced by the type of technology we provide[1]

12,500
granted patents globally

46,000
employees

Access for
1.08 bn people
in developing countries[2]

€13 bn
revenue

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75
countries with direct presence

World market leader
in most businesses

Biggest supplier
of medtech infrastructure

> €1 bn
R&D spent

>209,000
patients every hour[2]

1 AdvaMedDX, "A Policy Primer on Diagnostics", June 2011, page 3
2 Siemens AG, "Sustainable healthcare strategy - Indicators in fiscal 2014", page 3-4

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Our innovations – 120 years track record

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1901
Nobel prize winners (Physics + Medicine)

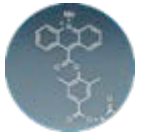
1896
Industrially manufactured X-ray appliance for medical diagnostics

1956
CLINISTIX – dry chemistry testing for glucose in urine

1957
Fully automated discrete chemistry analyzer for whole blood or serum

1967
First real-time ultrasound scanner

1975
First Siemens CT scanner



1982
First acridinium ester based chemilumin-escence immuno-assays

1983
First Siemens MRI scanner

1998
First Siemens track-based laboratory automation system

syngo

1999
First intuitive medical IT platform from Siemens

2001
First PET/CT system from Siemens

2005
First Dual Source CT scanner

2006
Diagnostic analyzer integrating four technologies in one system

2008
Robotic-assisted angiography system

2009
Multi-modality 3D imaging network

2008
Digital radiography, wireless flat panel detector

2011
First integrated, simultaneous whole-body MRI and PET

2014
"Free breathing"CT scanning with dual X-ray sources & detectors

2012
Wireless transducers for ultrasound

2014
Cloud-based network: teamplay

2015
Wide-angle image acquisition breast tomosynthesis

2016
Liquid biopsy

2015
First Twin Robotic X-ray scanner for enhanced patient care and productivity

2017
Lab diagnostics solution for immunoassay and clinical chemistry: Atellica™ Solution[1]

Future

Enterprise Services

Advanced Therapies

Molecular Diagnostics

Digital Health Services

Outcomes

Costs

1) Product availability may vary from country to country and is subject to varying regulatory requirements.

Engineering success –
With broadest and deepest portfolio

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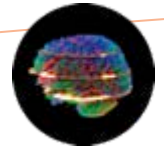
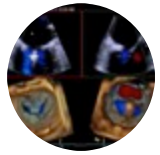


Diagnostic Imaging
Computed Tomography, Magnetic Resonance Imaging, Molecular Imaging, Radiography & Fluoroscopy, Imaging IT

Undisputed market leader in diagnostic imaging

Advanced Therapies
Cardiology, Interventional Radiology, Radiation Oncology, Surgery

Empowering innovative therapy concepts



Ultrasound
Cardiology, Radiology

Versatility and functionality across clinical questions

Laboratory Diagnostics
Immunoassay, Chemistry, Hematology, Hemostasis, Specialty Testing, Automation, IT and Services, Molecular Diagnostics[1]

Delivering clinical and workflow excellence

Point of Care
Blood Gas, Diabetes Urinalysis, Coagulation, Cardiology

Lab-accurate, actionable, timely results at the point of care

Services
System Services, Education, Enterprise Services, Digital Services

Transformative services to maximize opportunities and minimize risks

1) Incubated within Business Function Strategy & Innovation
2) Image courtesy Diagnostic Imaging: CMRR, Minneapolis, MGH, Boston
Image courtesy Advanced Therapies: IHU Strasbourg, France

Brain – most challenging organ

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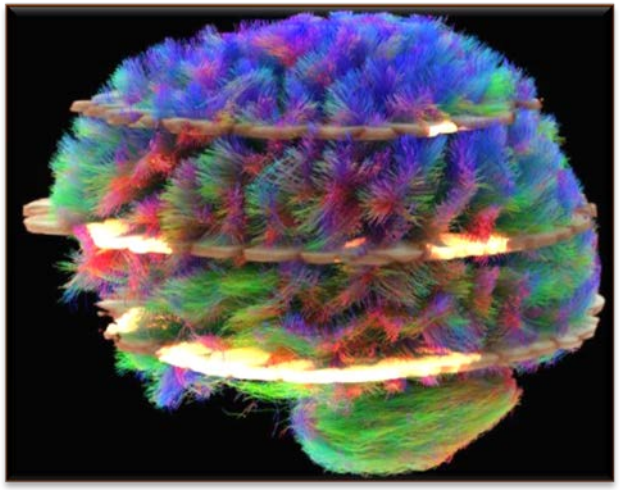
Memory capacity 100-1,000 terabytes

100 trillions synapses



1 neuron connected to up to 10,000 other neurons

Hundreds of neuronal subtypes

100 billion neurons

HC SI MR SI

Stevens CF Curr Biol 8: R708-R710; Image courtesy of Massachusetts General Hospital and Athinoula A. Martinos Center for Biomedical Imaging

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Brain Imaging applications and health economics

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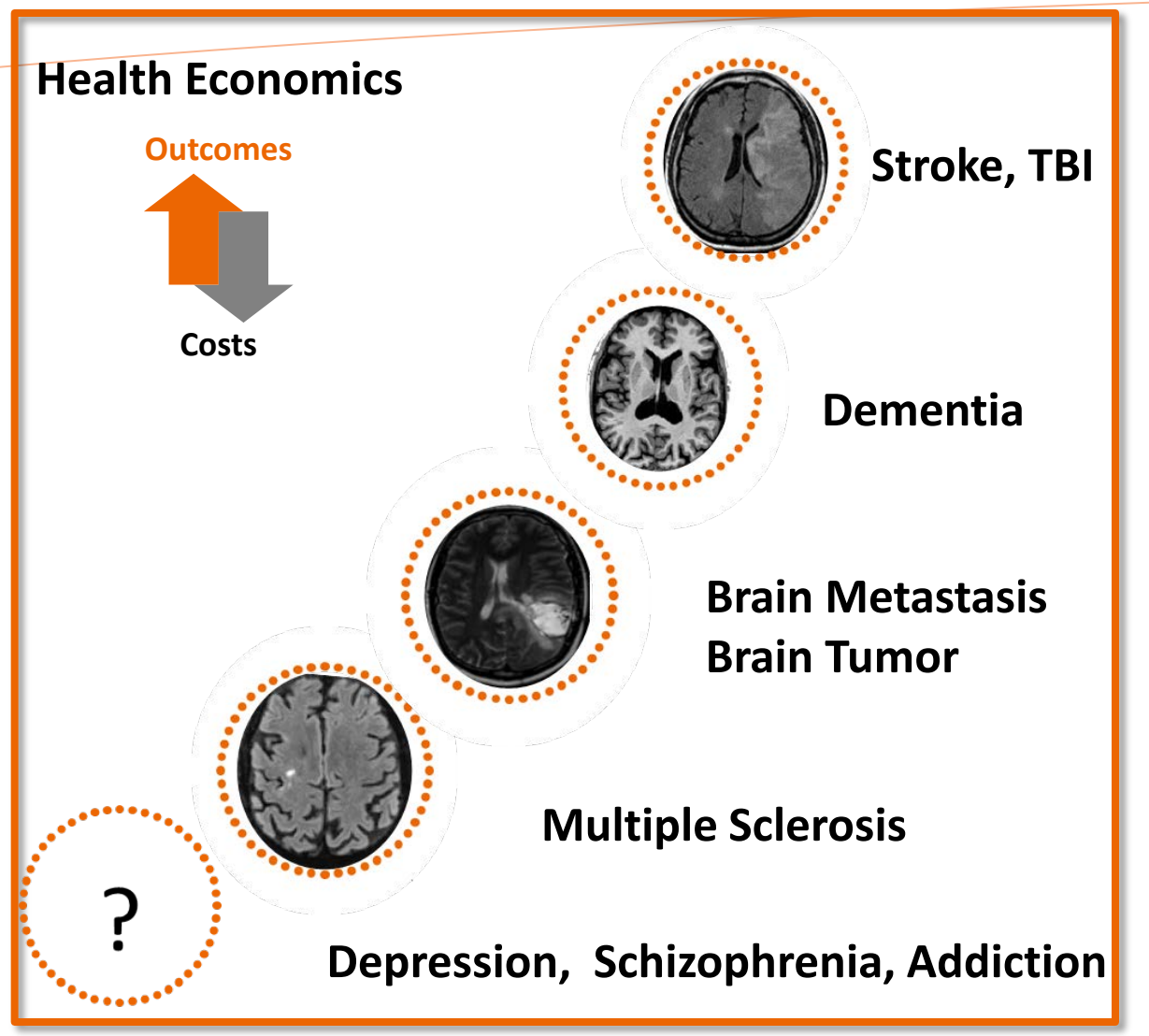

Imaging signs	Burden of disease
➢ Bleeding, Ischemia CT, MRI	Very high
➢ Atrophy, ➢ Exclusion of vascular disease MRI, CT, PET	Very high
➢ Tumor lesion MRI	High
➢ Lesion detection, Atrophy MRI	High
➢ Imaging not established in clinical routine	Very high

Images courtesy of Massachusetts General Hospital and Athinoula A. Martinos Center for Biomedical Imaging

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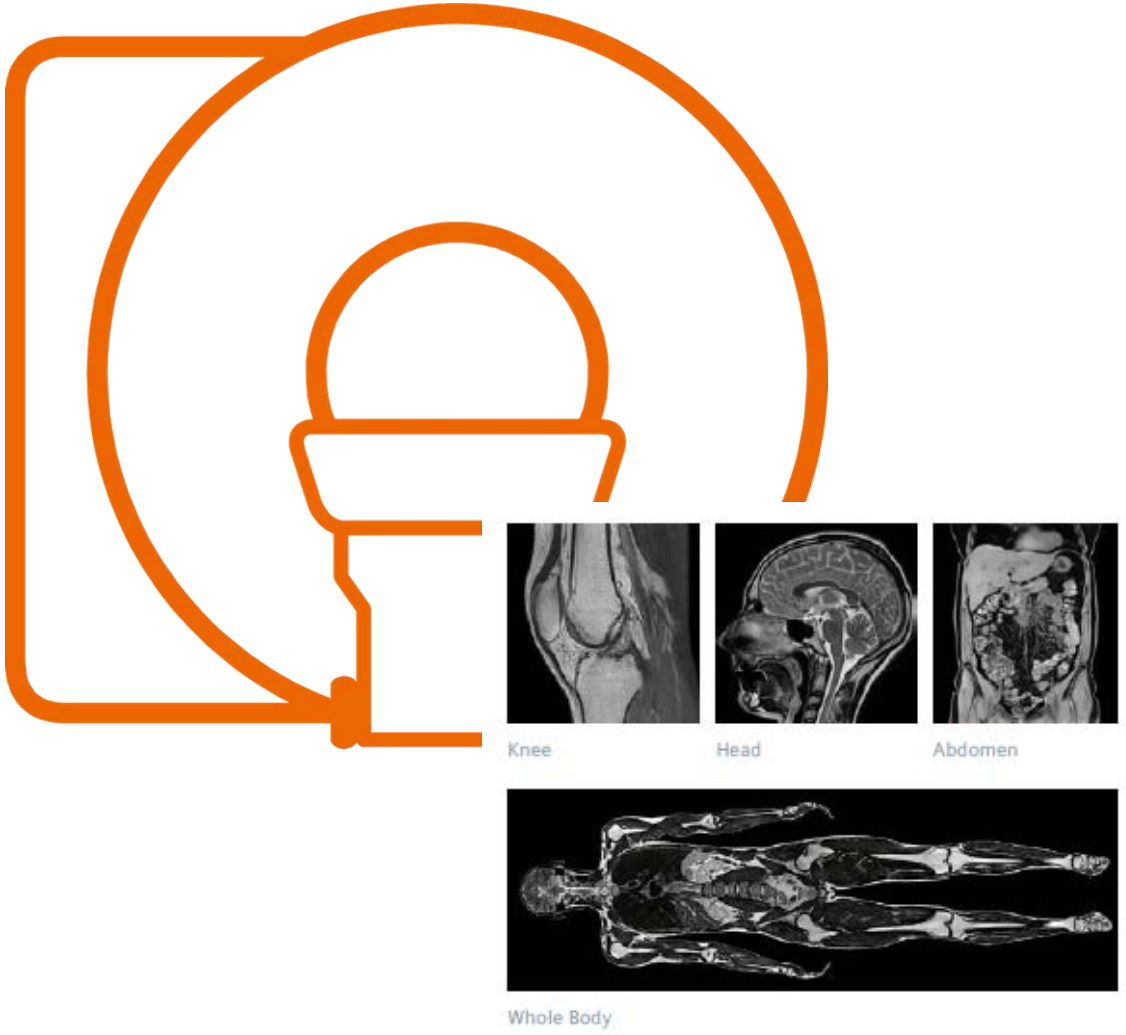
Magnetic Resonance Imaging (MRI)



- Non-invasive imaging technology
- Magnetic moment of proton of hydrogen atoms
- Scanner consists of **a strong magnet** (**1,5 T; 3 T; 7 T**) with radio transmitter and receiver
- Uses magnetism and radio waves to produce body images
- Produces series of slices of-tissue **contrast images based** on signal intensities („T1, T2 contrast“)

Magnetic Resonance Imaging Basics

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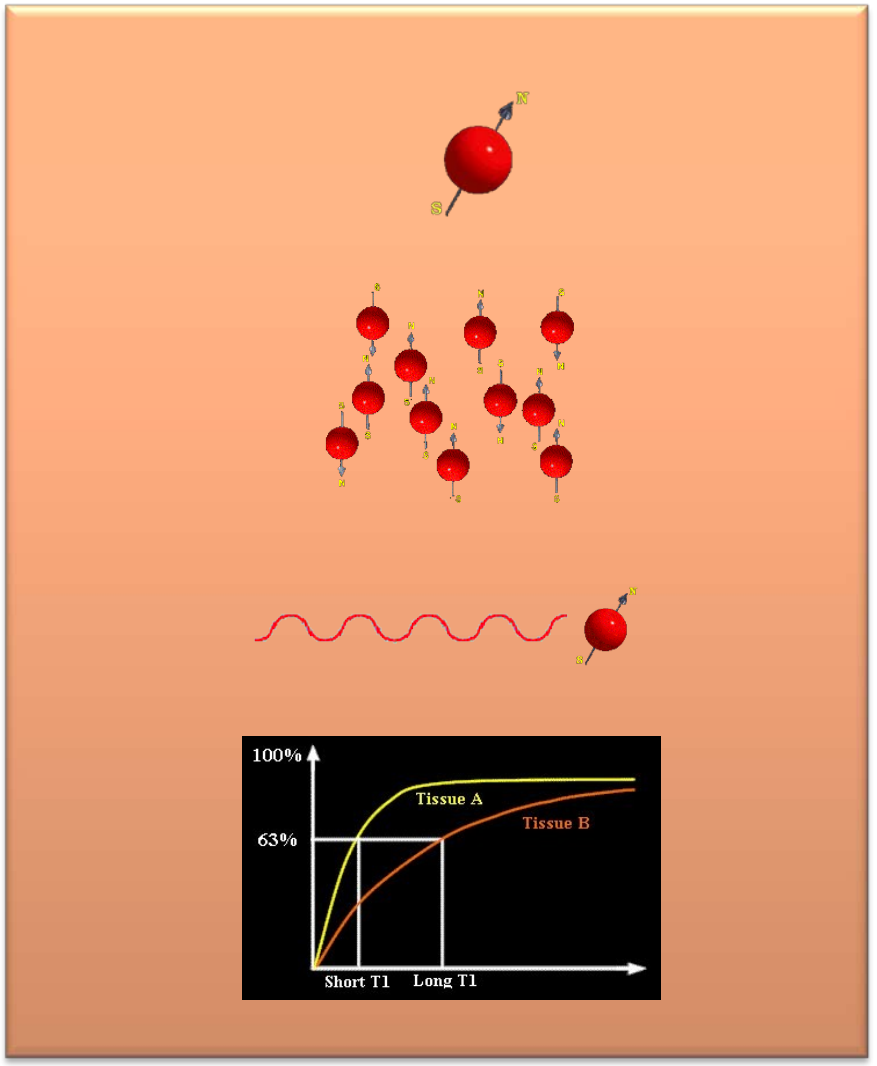
- **Protons** of hydrogn atoms ´behave like small magnets:´ **have a magnetic moment.**
- When placed into a strong magnetic field, they tend to get the same orientation.
- Sending an **radio frequency (RF) pulse** we can deflect them from this common orientation.
- After the pulse is switched off, they return to the original orientation emitting an electromagnetic signal.
- This relaxation takes different time for different tissues.



Anatomical and structural MRI

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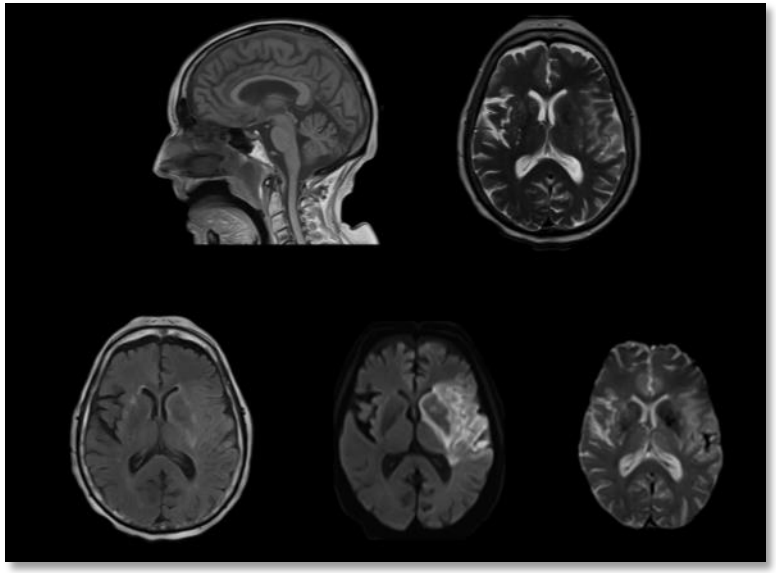
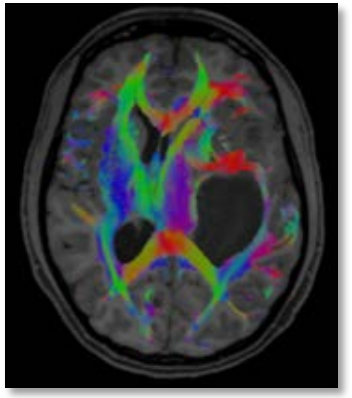
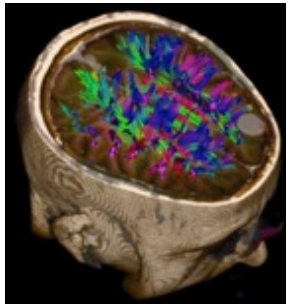
Structural MRI

- **3D T1W imaging**
  - Gray Matter (GM), White Matter (WM) and Cerebrospinal Fluid Analysis (CSF)
  - Volumetric Analysis
- **Diffusion Tensor Imaging (DTI)**
  - Measures the anisotropic diffusion properties of water molecules in the biological tissues for the generation of diffusion **aniosotropy maps**, e.g.
  - **Whole-brain tractography**







Images courtesy of Massachusetts General Hospital and Athinoula A. Martinos Center for Biomedical Imaging

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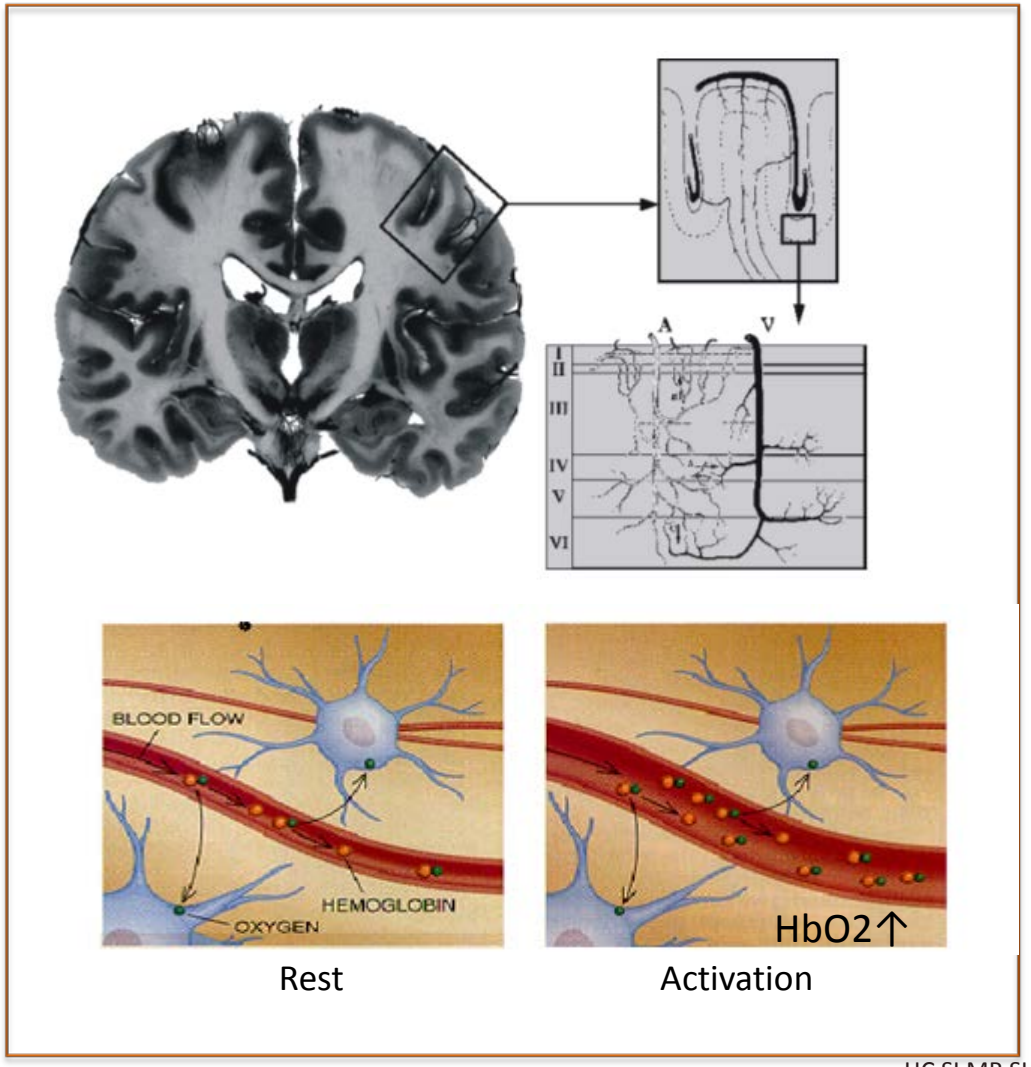
Functional MRI (fMRI)

fMRI measures cerebral hemodynamic changes during a specific task to demonstrate possible brain mechanisms of a specific neurocognitive function.

- Analyses of **blood-oxygen level** dependent **(BOLD)** contrast **at capillary level**
  - Measures the difference in magnetic susceptibility between oxyhemoglobin and deoxyhemoglobin as obtained **while the subject is resting and while the subject is performing a specific task**
  - By comparing MR signals, this technique can reveal hemodynamic changes related to a specific neurocognitive response.
- **Task-Related fMRI Study**
- **Resting fMRI Study**



Fox and Raichle 1986)

Task fMRI

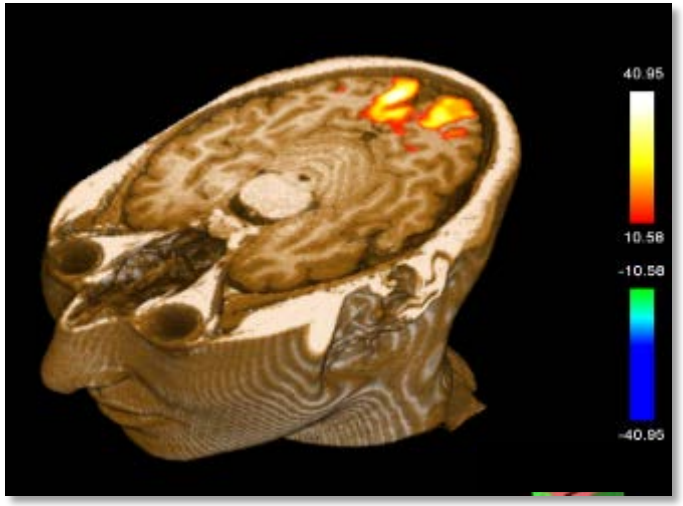
Visual, auditory, or other stimuli applied, to **provoke two or more different cognitive processes** in the subject.

- **Two conditions tested**, an experimental condition, and a control condition.
- To test the hypothesis that the signal differs between the two conditions.
  - **Block design:**

    Each block will have a duration of a certain number of fMRI scans, about 20–30 s, and within each block, only one condition (such as pictures from a computer game) is presented.
  - **Event-related designs:**

    Events are presented in a randomized sequence, and the between stimuli duration is varied.

    Design allows to better characterize the timing of the change in amplitude of the hemodynamic response in the BOLD signal.



Resting state fMRI

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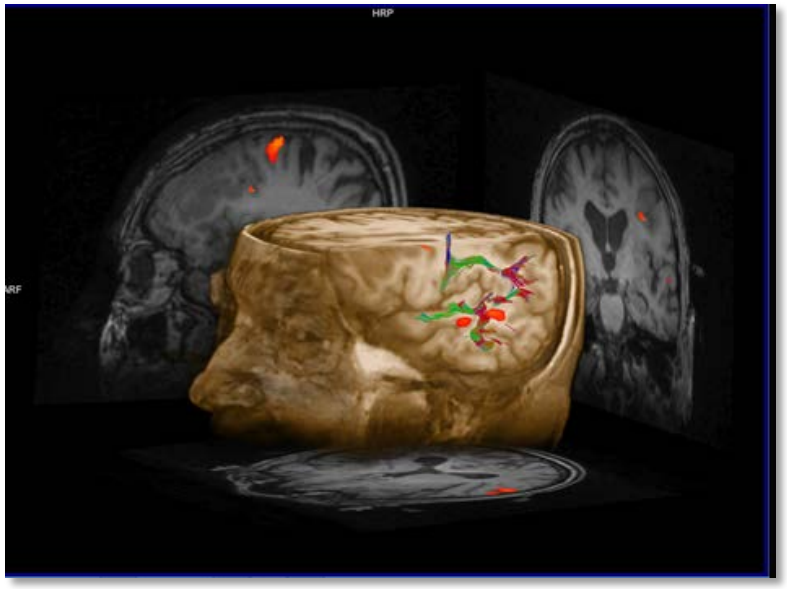
Investigation of neural circuits which exhibit **spontaneous activity at rest**.

- These slow-frequency fluctuations are temporally correlated within spatially distinct but **functionally related networks** and represent specific patterns of synchronous activity.
- Evaluation of resting-state functional connectivity provides an opportunity to characterize distributed **circuit normalities and abnormalities in neuropsychiatric illnesses**.
- However, the **interpretation** of this connectivity is **difficult**. For example, both lower connectivity and over connectivity were suggested to indicate the impaired function.



syngo.MR Neuro 3D
Images courtesy of Dr Andreas Bartsch, Radiologie Bamberg, Depts of Neuroradiology, Univesities of Heidelberg and Wuerzberg, Germany, Oxford Centre of Functional MRI of the Brain (FMRIB), University of Oxford, UK

Internet addiction

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Internet use (including smartphone use)

- Technological advancement in our society.
- Not to be criticized as addictive.
- Individuals can conduct research, perform business transactions, communicate, make vacation plans.
- Alcohol or drugs are not a necessary part of our personal and professional lives nor do these substances offer any health benefit.

Many practical uses of the Internet signs of addiction can easily be masked.

Internet addiction diagnostic questionnaire (IADQ)
Internet addiction test (IAT)

1. Do you feel preoccupied with the Internet (think about previous online activity or anticipate next online session)?
2. Do you feel the need to use the Internet with increasing amounts of time in order to achieve satisfaction?
3. Have you repeatedly made unsuccessful efforts to control, cut back, or stop Internet use?
4. Do you feel restless, moody, depressed, or irritable when attempting to cut down or stop Internet use?
5. Do you stay online longer than originally intended?
6. Have you jeopardized or risked the loss of significant relationship, job, educational or career opportunity because of the Internet?
7. Have you lied to family members, therapist, or others to conceal the extent of involvement with the Internet?
8. Do you use the Internet as a way of escaping from problems or of relieving a dysphoric mood (e.g., feelings of helplessness, guilt, anxiety, depression)?

Diagnostic and Statistical Manual of Mental Disorders (DSM–5)

International Statistical Classification of Disease (ICD-10)

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Some results form fMRI studies on internet addiction

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- Brain regions involved in IA identified by fMRI, but number of subjects limited.
- Neuroanatomical changes involving prefrontal cortex, thalamus, and other brain regions.
- The pattern of IAD-related **structural differences in the brain resemble**, to some extent, those **changes observed in substance addiction.**
- Controversy exists among the scientific community regarding ***whether IAD constitutes a standalone illness.***
- **Online gaming requires good cognitive function and decision-making**, particularly under risk, **unlike substance addiction** which result in a deficit in cognitive function or risk decision.

- **To be considered:**
  - Well defined study hypothesis and study design
  - Heterogeneity of the subjects (variety in online activities, age, difference in disease stage and chronicity)
  - Structural and functional MRI data in combination with clinical data
  - Sources of physiological bias heart rate, respiration, head motion influencing fMRI
  - Many ways to analyze resting fMRI data.

HC SI MR SI

Internet Addiction, 2nd Ed, Eds C. Montag, M. Reuters, Springer

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Additional applications and technologies for brain imaging

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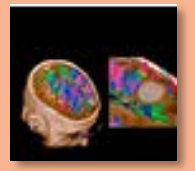
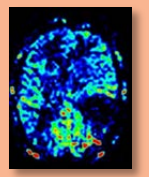
fMRI and BOLD in presurgical planning



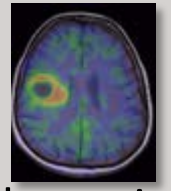
- Monitoring of **sensormotor activitiy**
- Resting state fMRI
- In **patients who are unable to cooperate**, e.g. children, sedated or paretic patients

Arterial Spin-Labeled (ASL)

- **Arterial blood water** is magnetically labeled.
- Cerebral blood flow (CBF) and **perfusion of the brain is measured.**
- **Assess resting brain function**



Positron emission tomography (PET) and MR-PET



PET: Cerebral glucose metabolism using radioisotpes (^{18}F-FDG)

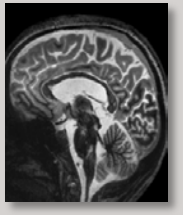
Combination of soft-tissue contrast in high spatial resolution with **metabolic information**

7T

Improved tissue contrast

High spatial resolution

Better visualization of small lesions



;Images courtesy of Massachusetts General Hospital and Athinoula A. Martinos Center for Biomedical Imaging; mMR Munich (TUM/LMU), Robarts Research Institute, London, Canada; Sir Charles Gardiner Hospital, Perth, Australia

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Now's our time to inspire the future of healthcare

Engineering success.
Pioneering healthcare.
Together.

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