BRAINTRAIN NEWSLETTER 4

BRAINTRAIN started in November 2013 and is coordinated by Cardiff University (Professor David Linden, Wales, UK). Our consortium brings together 13 complementary partners, including 10 academic research institutions, one small medium sized enterprise, a larger industrial partner and a technology transfer/management company.

To achieve our objectives, BRAINTRAIN program comprises 6 complementary workpackages. WP1: Coordination and management of the consortium, **has strong links *to all other WPs as its objective is to ensure good management and timely implementation of the BRAINTRAIN workprogramme, communication between the different WPs via regular meetings and reports. So far, we have met thrice: in Cardiff for the Kick-off meeting (2013) and in Maastricht (2014) and Tel-Aviv (2015) for the annual meetings. In between, we have had regular ExCom meetings, where WP leaders meet and discuss the strategic points of the project. You can find in the Braintrain secure intranet the main information related the contractual aspects and the meetings. We look forward to the next annual meeting to be held in Coimbra in October 2016.***

Each team has now been working on its work packages for about three years. The next pages provide an overview of what we have been doing so far and a focus on some important developments.

BRAINTRAIN will focus on 4 objectives

Objective 1

Develop new or optimize existing imaging technologies

Objective 2

Validate their application to mental disorders by integrating imaging data with complementary knowledge resulting from bioinformatics and clinical data.

Objective 3

Allow the diagnosis of mental disorders at the pre-symptomatic stage or early during development.

Objective 4

Better measure disease progression.

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OPENING OF THE NEW CARDIFF UNIVERSITY BRAIN RESEARCH IMAGING CENTRE (CUBRIC), MAINDY ROAD, CARDIFF

On June 7th, Queen Elizabeth II officially opened Cardiff University's new neuroimaging centre and heard about the ongoing research in neurofeedback. The Queen and the Duke of Edinburgh were given a tour of Cardiff University's new £44m Brain Research Imaging Centre, which is the biggest of its kind in Europe and one of the best equipped in the world.

There are four magnetic resonance imaging (MRI) systems in the new building: a 3 Tesla scanner for clinical studies, a 3 Tesla for experimental/ cognitive neuroscience studies, an Ultra-high field 7 Tesla scanner, and the National Microstructure Imaging Facility (3 Tesla "Connectome" scanner). There are also multiple brain stimulation and cognitive testing laboratories, clinical suites, and magnetoencephalography (MEG) and electroencephalography (EEG) facilities.

Queen Elizabeth II observes a real-time fMRI experiment at the Cardiff University Brain research Imaging Centre

STANDARDIZATION WORKSHOP

On September 27th, Nikolaus Weiskopf, Steffen Volz and Rainer Goebel held a workshop on standardization, on the premises of the Max-Planck-Institute for Human Cognitive and Brain Sciences in Leipzig, Germany.

Currently, real-time fMRI neurofeedback cannot be performed on standard clinical scanners, but requires in depth technical knowledge of the operators. A general issue is the lack of reliable, fast, easy-to-use and standardized access to the acquired data. So far, most research groups have developed their own or modified approaches to data access. The workshop aimed at making this step easier in the future, in the belief that a standardized interface and open image reconstruction systems available across all platforms could make the method more widely available and pave the way for clinical trials.

To discuss the needs of neurofeedback and the consequent technical requirements of such an

interface, the workshop brought together developers of real-time analysis software, experts in real-time image reconstruction and representatives of scanner manufacturers, such as Michael Hansen, from the National Heart, Lung and Blood Institute (National Institutes of Health (NIH), USA); Martin Uecker, from the Institute for Diagnostic and Interventional Radiology (University Medical Center Göttingen, Germany); Robert W. Cox, from the Scientific and Statistical Computing Core at the National Institute of Mental Health (NIH, USA); Scott Hinks, from GE Healthcare; Rolf Lamerichs, from Philips Medical Systems; and Heiko Meyer, from Siemens Healthineers.

The participants – a small group of about 20 presenters and attendees – actively interacted and addressed the following topics (among others):

- Export of image data via TCP/IP in the NifTI format (http://nifti.nimh.nih.gov/);
- Export of raw data in the ISMRMRD format (http://ismrmrd.github.io/);
- Import of externally reconstructed images back into the scanner's image database;
- Bi-directional communication between external hardware and MRI scanner;
- Real-time control and mechanisms to ensure real-time operation (e.g. time stamping).

More details on the workshop's contents can be found on BRAINTRAIN website.

TRAINING COURSE AT ANNUAL MEETING OF ORGANIZATION FOR HUMAN BRAIN MAPPING

The Organization for Human Brain Mapping is the largest grouping of scientists dedicated to the non-invasive study of the human brain. Over the last two decades its annual meetings have been a focus point for methodological development in data acquisition and analysis, but also a forum for the applications of neuroimaging and neurophysiology in cognitive and clinical neuroscience. At this year's conference in Geneva, BRAINTRAIN PI Rainer Goebel, together with Professor Stephen LaConte of Virginia Tech, Roanoke, VA, USA, convened at training course on "Real-time fMRI: Fundamental Principles for Clinical Applications". BRAINTRAIN PIs Nikolaus Weiskopf and David Linden were also amongst the speakers. Nik Weiskopf spoke about "Technical Aspects of Real-time fMRI" and covered sequence development and optimisation and online motion correction techniques. Rainer Goebel presented new developments in algorithms and software for "Real-time processing and analysis of fMRI data". Steve LaConte gave an overview of real-time multivariate analyses of fMRI data, a field in which he has been particularly influential. Youry Koush of EPFL, Lausanne, Switzerland spoke about his development of connectivity-based neurofeedback.

In the section on clinical applications, Cassandra Sampaio-Baptista of the Oxford Centre for Functional MRI of the Brain, Oxford, UK, presented her group's work on fMRI-based neurofeedback in stroke. David Linden presented a roadmap in six steps towards the implementation and evaluation of clinical neurofeedback protocols. These six steps or questions are:

1) What is your clinical question and patient group?
2) What is your mechanistic model for the intervention?
3) What are your target areas/ networks and how do you target them?
4) What procedures can you use to maintain effects?

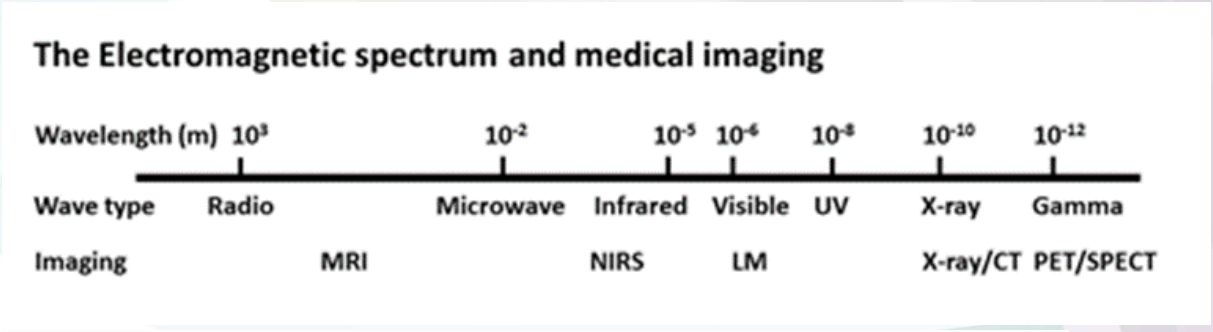
5) What are the best outcome measures?
6) What is the best study design?

They had an interesting discussion with colleagues interested in methods development but also with clinical researchers in psychiatry and neurology about the scope of setting up clinical studies in different disease areas. The last point, about study/ trials design and control groups/ conditions, proved particularly challenging. David Linden argued that there is no "one size fits all" solution for control conditions for clinical neurofeedback trials. He looks forward to further discussions about implementation and evaluation of neurofeedback at the BRAINTRAIN stakeholder workshop in Coimbra on October 24th, 2016.

CLINICAL TRAINING

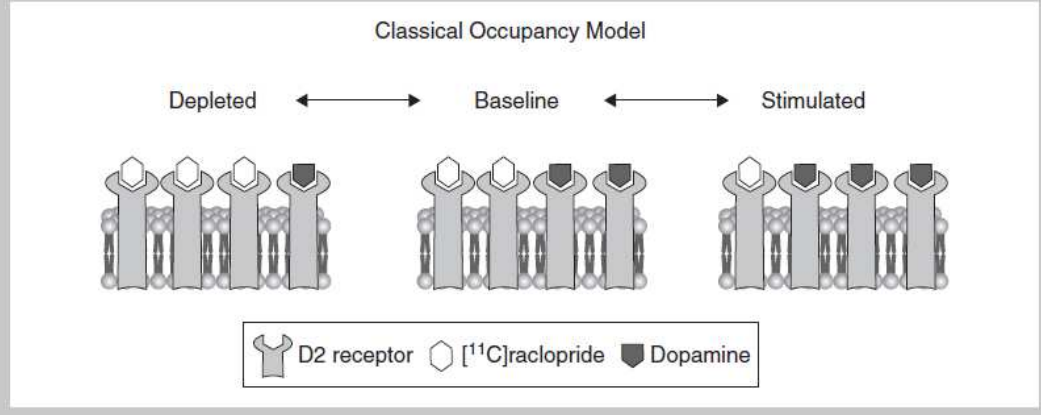
Members of the BRAINTRAIN consortium are actively involved in research and clinical training. One current example is the training course we did at the Annual Meeting of the Organization for Human Brain Mapping (see this newsletter, *Dissemination*). Another is the training module "Neuroimaging and Neurophysiology in Psychiatry" developed by David Linden for the psychiatric trainees on the Welsh rotation attending the preparation course for the Membership exam for the Royal College of Psychiatrists. This module helps trainees to understand the background, scope and clinical applications of the different neuroimaging (and neurophysiology) techniques and provides them with knowledge about current clinical guidelines and algorithms for the selection of the right neuroimaging investigation.

The training session generally starts with a group exercise on the question "When did I last order a brain scan and what did it tell me?" The examples tend to come from the areas of acute confusion in elderly patients or unusual first presentations of psychosis. We discuss how neuroimaging can help us determine underlying organic causes and how it can inform management. The lecture part starts with the basics of the biology and physics underlying the signals that are captured by the key neuroimaging/ neurophysiology techniques used in psychiatry, magnetic resonance imaging (and sometimes computer-assisted tomography), radioligand techniques (positron emission tomography, PET, and single photon emission computed tomography, SPECT) and electroencephalography (EEG).



Source: D. Linden, Neuroimaging and Neurophysiology in Psychiatry, Oxford University Press, 2016.

In order to demonstrate the specific relevance to psychiatry we discuss the occupancy model used in many PET studies, which can be used to demonstrate target engagement of new drugs with a specific neurotransmitter receptor.



The classical occupancy model of PET radioligand studies.
The occupancy model is the basis for the estimation of synaptic dopamine concentrations from the binding of radioligands to dopamine receptors. In the depleted state (lack of dopamine), more ligand (raclopride) can bind to D2 receptors, whereas less ligand will bind in the stimulated state, when more D2 receptors are occupied by dopamine. Emission of signal from the labelled raclopride thus allows inferences on local dopamine concentrations.

Source: D. Linden, The Biology of Psychological Disorders, Palgrave Macmillan 2012.

We then move on to clinical guidelines (with a focus on practice in the United Kingdom) for the use of neuroimaging (MRI or CT) in the diagnostic workup of psychiatric syndromes. In the United Kingdom, the National Institute for Health and Care Excellence, which advises the National Health Services on the use of clinical resources, does not recommend routine neuroimaging in patients with a first episode of psychosis, but we also discuss scenarios in which neuroimaging would be recommended. Examples of cases where changes in mental state were the first manifestations of a detectable brain disease, for example limbic encephalitis or a brain tumour, are always instructive in this respect. We have similar discussions about the current recommendations for the use of neuroimaging in the workup of dementia and learning disabilities.

One topic which always brings up interesting discussions is the use of EEG in psychiatry, especially in relation to the understanding of the brain processes underlying altered mental states. Most trainees are aware that EEG can be indicated to exclude underlying epileptic activity (for example to rule out a non-convulsive status epilepticus). What is appreciated less, however, is that EEG can be helpful in the workup of suspected functional neurological disorders, for example in the differential diagnosis between epileptic and non-epileptic attack disorders or in the investigation of functional blindness, where visual evoked potentials can be helpful in demonstrating intact retino-cortical signal transmission.

Once trainees understand the background of EEG and MRI techniques we can move on to discuss research applications of these techniques. Within the context of BRAINTRAIN, neurofeedback (using functional MRI and/or EEG) provides a very suitable example of the translatability of clinical neuroimaging techniques. We can use it to explain how we can map out disease-relevant circuits with fMRI

(as we do in BRAINTRAIN for alcohol dependence, PTSD, eating disorders, autism and anxiety) and then aim to train patients to modify them through self-regulation training. Beyond the didactic aim of explaining the versatile clinical and research uses of neuroimaging and neurophysiology in psychiatry this example also serves to induce trainees to think of the brain as a dynamic and plastic, rather than fixed and immutable, organ.

Any colleagues who are interested in running such training modules for their psychiatric trainees are welcome to contact David Linden.

DISSEMINATION

The objective of WP6 is to insure an effective dissemination using different tools. A brochure was distributed to the partners, a logo for BRAINTRAIN was created and we have a public website which is updated regularly. In parallel, partners are very active presenting neurofeedback research at national and international conferences and invited seminar talks. We can list the following:

- **Since our last newsletter, BRAINTRAIN partners Rainer Goebel, Nikolaus Weiskopf and David Linden contributed to an Educational course on "Real-time fMRI: Fundamental Principles for Clinical Applications" at the 2016 Human Brain Mapping conference, on June 26th (see above, *Training Course at Annual Meeting of Organization for Human Brain Mapping*).**

  The Organization for Human Brain Mapping (OHBM) is the primary international organization dedicated to using neuroimaging to discover the organization of the human brain. Its 2016 Conference took place from June 26th to 30th in Geneva, Switzerland.

- **On September 20th, David Linden gave a talk on BRAINTRAIN at the Central Institute for Mental Health in Mannheim, Germany.**

- **Nikolaus Weiskopf, Steffen Volz and Rainer Goebel presented BRAINTRAIN to the speakers and attendees of the workshop on standardization held in Leipzig, Germany on September 27th (see above *Standardization workshop*).**

- **On October 24th, Miguel Castelo Branco will host a workshop on "Medical devices in brain research: from design to clinical application" in Coimbra, Portugal.**

  The event will address different aspects of medical devices for neuroscience, representing an opportunity to gather national and international experts in medicine, research, design and commercialization of medical devices, regulation and entrepreneurship.

  A detailed agenda and additional information can be found on BRAINTRAIN website.

Publications:

W. Miles Cox, Leena Subramanian, David E.J. Linden, Michael Lührs, Rachel McNamara, Rebecca Payle, Kerenza Hood, Gareth Watson, Joseph R. Whittaker, Raman Sakhuja and Niklas Ihssen. Neurofeedback training for alcohol dependence versus treatment as usual: study protocol for a randomized controlled trial. Trials, 2016 Oct 3. Doi: 10.1186/s13063-016-1607-7

Gal Raz, Alexandra Touroutoglou, Gadi Gilam, Christine Wilson-Mendenhall, Tamar Lin, Tal Gonen1, Yael Jacob, Shir Atzil, Roee Admon, Adi Maron-Katz, Talma Hendler*, Lisa Feldman Barrett*. Functional connectivity dynamics during film viewing reveal common networks for different emotional experiences. Cognitive, Affective, & Behavioral Neuroscience (2016): 1-15.

Cohen, Avihay, Nimrod J. Keynan, Gilan Jackont, Nilli Green, Iris Rashap, Ofir Shany, Fred Charles, Marc Cavazza, Talma Hendler, Gal Raz. Multimodal Virtual Scenario Enhances Neurofeedback Learning. Frontiers in Robotics and AI (2016).

- ✓ ***The BRAINTRAIN website is available at the address: www.braintrainproject.eu***
- ✓ ***The extranet where you can find all the important documents regarding the agreement, the meetings and the dissemination is available at this address: https://extranet-braintrain.atreal.fr/***
- ✓ ***The Next Annual meeting will be held in Coimbra, Portugal on October 25th-26th, 2016***