

BRAINTRAIN NEWSLETTER 6

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), Tel-Aviv (2015) and Coimbra (2016) 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.

Each team has now been working on its work packages for over three years now. 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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BRAINTRAIN EXTENDED FOR ONE YEAR, WITH A NEW PARTNER ON BOARD

On June 13th, 2017 the European Commission officially approved of a 12-month extension of the project, thus postponing its conclusion to October 31st, 2018.

This additional year will allow for the clinical studies/trials carried out under WP4 to meet their recruitment and analysis targets. Indeed, a number of studies faced a slow initiation due delays in regulatory approvals as well as the need to expand the patient recruitment routes when the originally established clinical collaborations did not yield the expected recruitment figures.

The operational modifications (updated timeline and reorganization of resources)

consequent to the extension have been discussed and agreed by all partners at the 2016 Annual General Meeting (AGM) in Coimbra. The extension and strategies for completing the trials have been supported as well by the Independent Advisory Board (IAB).

This amendment to the grant agreement also (and finally) validates officially the accession of the Max Planck Institute for Human Cognitive and Brain Sciences (MPG) to the BRAINTRAIN consortium, effective May 8th, 2016. Following Nikolaus Weiskopf's move from London to Leipzig, MPG has taken over UCL's tasks in the project, mainly under WP2 (Methods development). Welcome (again) to Nik and his team!



BRAINTRAIN team members (Oct.2016).

WSMD2017 - WORKSHOP ON SCHIZOPHRENIA AND OTHER MENTAL DISORDERS (JUNE 15TH-16TH, 2017 – UNIVERSITY OF PISA)

David Linden, Coordinator of BRAINTRAIN, attended an international workshop at Pisa University that brought together several EU-funded consortia around the topics of neuroimaging and transfer technologies for mental health. The workshop was organised by the physicist Alberto Del Guerra (University of Pisa), psychiatrists Paolo Brambilla (Milan) and Silvana Galderisi (Naples) and Lara Passante and Elisabetta Vaudano of the European Commission. A common theme was the quest to utilise the considerable methodological advances made over the last 25 years in

imaging technology – including high-field magnetic resonance imaging (MRI), combined MRI and Positron Emission Tomography (PET), combined MRI and electroencephalography (EEG), and real time functional MRI – to advance mechanistic understanding and ultimately treatment of mental and neurodegenerative disorders. There are currently major challenges in the area of drug development in psychiatry, including gaps in knowledge about disease mechanisms – and consequentially difficulty in target identification – and the often long observation/

follow-up times, which make trials very lengthy and costly. Neuroimaging has the potential to contribute both diagnostic markers for patient stratification and surrogate biomarkers that could be used as outcomes, which could greatly increase the efficiency of clinical trials. However, it was recognised that much still needed to be done in order to obtain such validated biomarkers for use in psychiatry. Through the funding mechanism of the Innovative Medicines Initiative (IMI), a public-private partnership, the NEWMEDS project (<https://www.imi.europa.eu/content/newmeds>) had the aim of developing tools that enable early decision making in clinical trials, for example through PET. Another IMI project, whose scope is very relevant to BRAINTRAIN, is the EU-AIMS consortium (<https://www.eu-aims.eu/>), a large autism research initiative, which has developed a specific fMRI test battery probing the reward, social cognition, inhibitory control and emotion systems (monetary and social incentive delay task, theory of mind task, flanker task, face processing task).

Two recently funded IMI consortia in mental health and clinical neuroscience were represented at the workshop. The RADAR project aims to tackle the problem that patients' self-reports of symptoms and events (for example seizures) can be unreliable by developing more objective monitoring protocols and technologies, based on smartphones and wearable devices, for epilepsy, depression and multiple sclerosis (<https://www.radar-cns.org>). The PRISM consortium starts from the recognition that social withdrawal is a clinically and functionally relevant factor in several mental and neurodegenerative disorder and investigates this symptom complex in psychosis and Alzheimer's disease with a combination of psychometric and neuroimaging approaches (<https://www.imi.europa.eu/content/prism>).

Several of the presented projects bring together European imaging cohorts, aiming for harmonization of data acquisition, input and analysis. For example, Klaus Ebmeier (Oxford University) presented the H2020-funded "LIFEBRAIN" programme: "Healthy minds from 0-100 years: Optimising the use of European brain imaging cohorts" (<http://www.lifebrain.uio.no/about/>). Another priority for imaging cohort work is to test biomarkers across cohorts, which is one of the aims of several groups working on predictive imaging markers of psychosis risk, in order to pave the way to clinical translation (<https://www.pronia.eu/>).

These kinds of initiatives tackle one of the challenges of the next wave of European neuroimaging consortia, how to integrate data (and equally importantly: metadata) across cohorts and how to future-proof them for exploitation beyond the lifetime of individual projects, for example through embedding them in ongoing clinical research cohort work or links with routinely acquired clinical data, which is also one of the aims of BRAINTRAIN. Another part of our exploitation strategy, presented at the workshop, is to liaise with the clinical neuroimaging community to develop principled recommendations for protocol and trial design, which fits well with the current very promising climate of knowledge sharing, harmonization and collaboration across sites and institutions.



BRAINTRAIN DISSEMINATION WORKSHOP AT CARDIFF UNIVERSITY BRAIN RESEARCH IMAGING CENTRE (CUBRIC)

The Cardiff arm of BRAINTRAIN assesses the effects of fMRI neurofeedback training (NFT) on recovery from alcohol dependence. The purpose of the Cardiff BRAINTRAIN Dissemination Workshop was (a) to inform attendees about the research project and (b) to solicit their ideas about how results obtained from the research might be integrated into clinical practice. The workshop also included (a) presentations on related interventions for alcohol dependence and (b) the health-economic and feasibility implications for using NFT in clinical practice.

Approximately 25 clinicians and other practitioners working in the area of alcohol misuse and dependence attended the workshop held on June 22nd, 2017 and organized by Miles Cox, David Linden, and Raman Sakhuja. They came from a wide geographical area across North and South Wales and from London. The workshop was supported by BRAINTRAIN and by Health and Care Research Wales – and its smooth running was secured by the administration teams of the Division of Psychological Medicine and Clinical Neurosciences at Cardiff University’s School of Medicine and of CUBRIC.

The morning session included three presentations:

- Professor David Linden (CUBRIC): Overview of BRAINTRAIN;
- Professor Miles Cox (Bangor University & Cardiff University): Attentional and Motivational Training for Reducing Excessive Drinking;
- Professor Chris Chambers (CUBRIC): Web- and Smartphone-Based Interventions for Investigating Behaviour Change in Eating.

Following these presentations, Professor Linden conducted a tour of the facilities at CUBRIC. Workshop participants were shown (a) a brain-imaging scanner, like the one in

which participants in BRAINTRAIN are being tested and (b) additional facilities at CUBRIC, such as the laboratory for studying sleep disorders.



CUBRIC – Reception area



CUBRIC – MR Simulator

After the lunch hour, the following additional presentations were delivered:

- Professor Deborah Fitzsimmons-Warm (Swansea Centre for Health Economics): General Aspects of Health Economics in Relation to New Interventions for Addictions;
- Dr Lee Hogan (Betsi Cadwaladr University Health Board & Bangor University): Use of Mental Strategies in Individual Counselling to Help Addicted Patients Devalue Alcohol and Set Healthy, Alternative Goals;

- Dr Raman Sakhuja (Cwm Taf University Health Board): Neurofeedback & Transfer Technologies;
- Dr Rachel McNamara (South East Wales Trials Unit, Cardiff University): Evaluation of New Technologies into Practice

Focus Group

The workshop concluded with a focus-group discussion in which participants gave their reactions to the day's presentations and considered the feasibility of using fMRI NFT as a treatment for alcohol misuse and dependence. Several salient themes emerged from the discussion:

- The financial cost of delivering fMRI NFT as a treatment for alcohol misuse and dependence is an important consideration; nevertheless, a cost-benefit analysis might well show that financial gains derived from the intervention outweigh the cost of delivering it. However, a more important consideration than the cost is the availability of the technology for delivering the intervention. Admittedly, the availability of fMRI installations and trained operators is limited, particularly in rural areas of Wales. This, then, makes it particularly important for transfer technologies to be developed.
- The results of the BRAINTRAIN project might well reveal that not all excessive drinkers benefit equally from the high-tech intervention. Thus, it is important to identify the characteristics of drinkers who are most and least likely to benefit. In turn, stratification of patients to receive the intervention and with the optimal intensity is paramount.
- In future, a hub-and-spoke model might be developed in which (a) high-tech hubs would deliver fMRI NFT, (b) spokes in NHS

outpatient clinics would use cognitive/motivational training strategies based on principles derived from the fMRI NFT, and (c) outreach teams would support BRAINTRAIN techniques through the use of mobile (e.g., smartphone-based) interventions.

- Especially for future applications, it is important to identify the underlying mechanisms (i.e., "active ingredients") of fMRI NFT. These might include (a) exposure to the salient stimuli used in fMRI NFT, (b) the rewarding experience of being able to control one's own brain reactions, (c) physiological self-regulation, and (d) the cognitive strategies that patients use to control their brain reactions.

- The on-going research project is being conducted with alcohol-dependent patients. It is, however, also important to evaluate the effectiveness of fMRI NFT with early-stage problem drinkers, who constitute a much wider spectrum of the population of drinkers. fMRI NFT might also be used in the context of primary prevention. Admittedly, however, this might not be cost-effective inasmuch as brief, less expensive, guided self-help interventions have already been shown to be effective for the earlier stages of problem drinking.

In summary, we are encouraged by clinicians' enthusiastic responses to the fMRI NFT that is being used in the Cardiff arm of BRAINTRAIN and their excellent suggestions for taking BRAINTRIN forward in the future.

Professor Miles Cox, Cardiff University & Bangor University, Wales, U.K.

For the World Health Organization's Global status report on alcohol and health see: http://www.who.int/substance_abuse/publications/global_alcohol_report/en/

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:

✚ Oxford's team has been very active over the last few months.

K. Cohen-Kadosh, C. Zich, M. Luehrs, S. Haller, S. Lisk, and J. Lau presented a poster titled *Dynamic fMRI-based neurofeedback under the microscope – evidence from the developing brain* Oxford Neuroscience Symposium, on March 22nd, 2017.

Additionally, on May 19th, 2017 K. Cohen-Kadosh gave a talk on *fMRI-based neurofeedback under the microscope* at the annual meeting of the Society for Biological Psychiatry in San Diego.

Oxford's team also took part in the following Public engagements with Science:

- On January 9th, 2017: teacher training session on *The developing social brain in childhood and adolescence: challenges and opportunities* at St Catherine's School, Bramley.

- On January 31st, 2017: Public lecture titled *Is youth wasted on the young?* At Bradfield College's Cafe Scientifique, Bradfield.

- On May 26th, 2017: Teacher training session on *Development in childhood and adolescence- from brain to behaviour and back* at Haberdashers Aske's School for Boys and Girls, Elstree.

✚ T. Hendler (Tel-Aviv University) also took part in the annual meeting of the Society for Biological Psychiatry in San Diego, and on May 19th, 2017 gave a talk titled *Amygdala-Neurofeedback Reduces Traumatic Stress Vulnerability during the symposium on Training Limbic Activity Modulation with Neurofeedback* (link to abstract: [http://www.biologicalpsychiatryjournal.com/article/S0006-3223\(17\)30523-1/abstract](http://www.biologicalpsychiatryjournal.com/article/S0006-3223(17)30523-1/abstract)).

Publications:

Todd N, Josephs O, Zeidman P, Flandin G, Moeller S and Weiskopf N. (2017) **Functional Sensitivity of 2D Simultaneous Multi-Slice Echo-Planar Imaging: Effects of Acceleration on g-factor and Physiological Noise.** *Front. Neurosci.* 11:158. doi: 10.3389/fnins.2017.00158

Sousa T, Direito B, Lima J, Ferreira C, Nunes U, Castelo-Branco M (2016) **Control of Brain Activity in hMT+/V5 at Three Response Levels Using fMRI-Based Neurofeedback/BCI.** *PLoS ONE* 11(5): e0155961. doi: 10.1371/journal.pone.0155961

✓ *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 Leipzig, Germany on October 16th-18th, 2017*