Neurotechnology for Dementia workshop
14-16 May 2019, Royal Society's Chicheley Hall, UK

HIGHLIGHTS

Introduction

Worldwide, more than 50 million people live with dementia. This number is expected to keep increasing dramatically, with nearly 10 million new diagnoses every year. Dementia is a major cause of disability in the elderly, leading to high costs to society. Moreover, since 70% of the patients live at home, the disease also has a severe impact on the lives of their caregivers.

In 2012, the WHO has made dementia a public health priority, and in 2017 the organization released a 'Global action plan on the public health response to dementia'. The plan describes seven action areas from dementia awareness to risk reduction, diagnosis, treatment and care, support for caregivers and information systems. The last action area is research and innovation, with a strong urge to increase investments in dementia research, collaborate across nations and promote technological innovation.

Innovative technologies have the potential to not only transform dementia research by increasing our chances to find effective treatments, but also to make a huge difference in the patients' and caregivers' quality of life. They can help us to more accurately diagnose and monitor the disease, and evaluate personalized precision therapies. Ultimately, novel technologies towards neuromodulation may actively intervene to halt or even prevent the disease process.

In recent years, several large, collaborative dementia research initiatives with a strong focus on the development of innovative technologies have been launched. In 2015, the UK Dementia Research Institute (UK DRI) was founded, forming a partnership between six of the UK's top universities. In Belgium, 2018 saw the take-off of Mission Lucidity, a large collaboration between nanotechnology-hub imec, KU Leuven and its university hospital UZ Leuven, and the Flanders Institute for Biotechnology (VIB), aimed to 'decode dementia' together.

To stimulate collaborative research actions towards technologies for improved dementia research and care, the UK DRI, the EPSRC Centre for Doctoral Training in Neurotechnology at Imperial College London and Mission Lucidity jointly organized a first Neurotechnology for Dementia workshop in May. The event brought together top scientists, clinicians and engineers, all driven by a shared ambition to stop dementia.

Opening Keynote Lecture

Prof. David Sharp (Imperial College London) opened the workshop by highlighting the challenges in dementia care. "Less than 5% of dementia research focuses on care, while 85% of patients would prefer to live at home for as long as possible, where they may not receive optimal care", he said. Prof. Sharp further spoke of a 'broken care system', because an estimated 1 in 4 UK hospital beds are occupied by a person with dementia, while many of those hospital admissions could have been prevented. The multiple unmet priorities in dementia care offer opportunities for research, as new technologies could strongly improve the current situation. Prof. Sharp highlighted four **focus areas**: sensors, data integration, artificial intelligence (AI) to aid prediction and personalization, and novel assistive technologies. Ideally, it would be possible to measure behaviour passively – without the need for any wearable device. The home environment can also be adapted to make it more suited for a person with dementia. Prof. Sharp: "Using social robotics, for instance, we can use AI algorithms to predict agitation, and reduce it by adapting the lightning or music to a person's emotional state." He concluded that novel technologies offer enormous potential, and emphasized that we need a **patient-centered** exploration of their design and ethics.

Day 1: Dynamic, physiological monitoring in vivo

The first day of the workshop focused on the physiological monitoring of brain function in vivo, in animal disease models or patients.

On the side of preclinical animal models, dr. **Alan Urban** (NeuroElectronics Research Flanders) illustrated the functional ultrasound imaging (fUSi) method his group developed, that allows highly sensitive, brain-wide imaging of intact networks in freely-moving rodents. Dr. Urban: "fUSi is based on cerebral blood volume dynamics and **neurovascular coupling**, which are relevant because the brain has as many capillaries as neurons." The technique is not yet available in the clinic, but the first trials hereto are ongoing. Dr. Urban envisions future innovations towards '4D fUSi' which would allow longitudinal measurements from multiple channels.

Prof. **Simon Schultz** (Imperial College London) showed the incredible innovations in live imaging and recording in mice: **two-photon targeted automated in vivo patching** (intracellular electrophysiologial recording), imaging circuits during active behaviour, and whole brain ex vivo two photon imaging. All of those techniques can be combined. "Two-photon targeted patching is harder than blind patching in vivo, because there are fewer targets, but it can be successfully automated", said prof. Schultz. Finally, he illustrated an application of the method: hippocampal imaging during a memory task in the 5xFAD model for Alzheimer's amyloid pathology, followed by the generation of a high-resolution image of the amyloid plaque load.

Ultrasound imaging and optical imaging can also be combined, as in the new modality coined '**photoacoustic imaging**' by prof. **Paul Beard** (University College London). The technique works by "encoding the optical contrast onto acoustic waves", but is still preclinical and remains to be further optimized in rodents. So far, it is possible to obtain whole-body information in small rodent-sized scanners, allowing non-invasive imaging of the vasculature in brain and body, including the presence of amyloid plaques in an Alzheimer's mouse model.

On the applied human side, prof. **Mark Woolrich** (University of Oxford) illustrated new computational methods applied to fMRI/EEG/MEG data to measure brain network dynamics. These can reveal a person's transient brain states, changes of which can be indicative of underlying dementia.

Prof. **Zoltan Takats** (Imperial College London) is a pioneer in mass spectrometry and has developed mass spectrometric imaging for **metabolomics**. This provides crucial information on the concentration and chemical composition of brain metabolites. The resolution is impressive: "It's like doing 1000 immunostainings in a single experiment", says prof. Takats. Furthermore, "virtual stains" can predict immunohistochemical results, without having to do the actual stains. The method allows **metabolic network**-based diagnostics and prognostics, as illustrated by prof. Takats in samples from Alzheimer's patients and a rat model for Parkinson's disease.

Prof. **Matthew Brookes** (University of Nottingham) introduced his work towards a 'wearable quantum brain scanner' based on **magnetoencephalo-graphy** (MEG), that has a much better spatial resolution and is a lot more sensitive than electroencephalography (EEG). Prof. Brookes: "There remain a few drawbacks before we can use it at a large scale in people, for instance that the current helmet has one size that may not fit all, but the signal-to-noise ratio is very good and keeps improving." He further highlighted the possibility to measure brain activity during visual stimulation by **virtual reality** (VR), which will revolutionize the types of experiments we can run.

Finally, prof. **George Malliaras** (University of Cambridge) presented new organic or 'bio'electronic devices that bridge the dynamics and complexity of soft biological tissue on the one hand, with the typically static, hard electronics on the other hand. Some of these have already been tested in the clinic, for instance to record from the brain surface in epilepsy patients while they are undergoing surgery. The devices offer great potential for future neuromodulation approaches.

Brain Lecture

The first day was closed with the Brain Lecture by dr. **Walter Koroshetz** (director of the NIH National Institute of Neurological Disorders and Stroke). Dr. Koroshetz started his lecture with encouraging words: "Neuroscience today is where the field of physics was in the early 1900s", having new tools available to allow a **technology-driven revolution**. He summarized the open questions and key challenges in neurodegeneration research, touching the complex science of neurodeg-eneration that involves changes in the cardiovascular system, metabolism, immune function… Dr. Koroshetz further highlighted the goal of the NIH **BRAIN Initiative**: "to provide funding for the development of neurotechnologies that allow us to see healthy and diseased brain circuits in action". Hereto, we need **maps**, **tools** and **knowledge**, as acknowledged in the **seven high priority research areas** of the Initiative *(i.e. brain cell types, circuit diagrams, monitoring neural activity, interventional tools, theory & data analysis tools, human neuroscience and integrated approaches)*. Dr. Koroshetz concluded with some of the most recent scientific advancements, including single-cell transcriptomics, the first successful adaptive deep brain stimulation in Parkinson's disease patients, and the promising first results from antisense oligonucleotide therapy against Huntington's disease.

Day 2: Functional coupling and modulation of large-scale neuronal activity

On the second day of the workshop, we moved from monitoring of brain function to active intervention, by diving deeper into functional coupling and the modulation of neuronal activity at a large scale.

Barun Dutta (imec) opened the day by presenting the grand challenge of his team's **Neuropixels** project: mapping the activity of the whole brain. Neuropixels are digital CMOS neural probes designed for high-resolution *in vivo* recording of brain activity. They allow multimodal applications (such as the integration of optics), have active electrodes at an increasingly higher density, and are reliable and uniformly manufactured. While they are currently only available for the rodent brain, Dutta revealed that imec aims to have a first prototype for non-human primates ready by mid 2020. Neuropixel probes are currently in high demand – Dutta hopes to see 250 labs worldwide using them by the end of the year.

An interesting application of neural interfaces was provided by prof. Andrew Jackson (Newcastle University), who investigates neuroplasticity and oscillations during sleep in animals. He showed that the oscillatory activity can be modulated using closed-loop optogenetic implants. Since sleep plays a role in cognition and is commonly affected in dementia patients, these experimental tools can contribute to new biomarkers and therapies, such as targeting the modulation of memory consolidation during sleep.

The abnormal network function in dementia is also apparent in the form of an initial hyperexcitability, as observed by dr. Marc Aurel Busche (University College London) in Alzheimer's mouse models using two-photon imaging and pharmacology. He found hyperexcitable networks in an amyloid model, whereas tau mice displayed reduced neural activity. This led him to formulate a new pathophysiological model where initially, amyloid pathology causes hyperexcitability, followed by tau-induced neuronal silencing and neurodegeneration. Since epilepsy is a common comorbidity in Alzheimer's patients, dr. Busche's preclinical research suggests that sensors that monitor epileptic events may offer valuable insights in the disease development and progression.

Prof. Shelley Fried (Harvard University) presented his work on implantable coils for magnetic stimulation, currently under development for retinal prosthetics to restore vision in the blind. Compared to electrical stimulation, magnetic stimulation has less limitations: it is for instance more focal and stable. The coils also have the potential to allow neuromodulation of other brain regions.

Besides magnetic stimulation, also ultrasound stimulation holds promise for deep brain modulation, said dr. Ben Cox (University College London). He illustrated this with several successful examples in animals and humans. Nevertheless, he warns that the exact underlying mechanism remains unclear, and that we potential safety issues should be carefully considered, despite the low intensities used.

Dr. Nir Grossman (Imperial College London) introduced a new modality to complement the current ones, termed 'temporal interference'. This method uses parallel transcranial stimulations at slightly different frequencies to precisely target the desired area, thereby bypassing the usual trade-off between on the one hand focal, deep but invasive stimulation, and on the other hand non-invasive but superficial, dispersed stimulation. Temporal interference can be used concurrently with fMRI in humans, and is under further development for clinical applications.

Dynamic assessment of signaling in vitro and in vivo

Prof. Ian Gilmore (National Physical Laboratory) uses mass spectrometry for highly spatial chemical data, allowing single-cell metabolic profiling. He talked about the tough drug development pipeline for neurodegenerative diseases, and the new preference in pharma for drugs to 'fail fast' (i.e. in early phases, before a lot of time and money have been invested). He also emphasized the need for a strong biobank and human-based models, since nearly all failures were due to a lack of efficacy and inability to translate preclinical results from animal models.

Dr. Róisin Owens (University of Cambridge) works on the exciting emerging field linking brain disorders to our gut and microbiome. She is developing a new type of organic interfaces (a sort of organ-on-chip models) that allow monitoring longitudinal interactions of the gut-brain-microbiome axis by assessing multiple parameters using integrated fluidics and electronics.

Prof. Martyn Boutelle (Imperial College London) further eluded on how neurovascular coupling can be exploited to aid imaging. Using approved microdialysis probes, a neurochemical signature of the human brain can be obtained. The combination of microelectrodes and **on-line microdialysis** can provide novel information on brain metabolism in health and disease.

In the final talk of this session, prof. **Patrick Dupont** (KU Leuven) reviewed the use of a mathematical **graph theoretical analysis** of human brain imaging data from different recording modalities. This method is part of recent developments towards improved post-imaging analysis, and can strongly increase the usefulness of imaging as a disease biomarker.

Keynote Lecture

Prof. **Tim Denison** (University of Oxford) illustrated how economic concepts can be relevant in dementia research. Firstly, **modulatory** approaches allow cost-efficiency by leveraging the existing infrastructure. Secondly, he highlighted **platform economics**: the need to construct a '**discovery ecosystem**' that bridges team science and data analysis. Prof. Denison also called for caution, especially regarding platform dynamics and competition (something we should think about as a community), risk management, neuroethics and informed consent, and the need for a long-term follow up of subjects, even after a study is completed. His talk led to an interesting discussion with the audience on the importance of ethics and open science.

Day 3: Neural interfaces for monitoring and targeted treatment

The last day continued on the theme of targeted intervention using neural interfaces.

In the first talk, dr. **Dries Braeken** (imec) elaborated his plan to build a programmable human brain circuit on a chip, based on cells from Parkinson patients, to create a better, human experimental model of the disease. This model will allow to extract crucial information on neural networks in a diseased state – including an electrophysiological 'fingerprint' that can help to stratify patient subtypes. The project forms a cornerstone in Mission Lucidity's roadmap towards personalized medicine. In the long term, the tool will also be useful to investigate other conditions or diseases.

Dr. **Christopher Grigsby** (Karolinska Institutet) also works on improved models for Parkinson's disease, especially regarding a closer reproduction of the physical and electrical microenvironment of neuronal cells in vitro. His lab uses 'melt electrospinning' to print 3D-engineered scaffolds for brain organoids that are reprogrammed from patient-derived fibroblasts.

In line with prof. Malliaras' talk from day one, prof. **Stéphanie Lacour** (École Polytechnique Fédérale de Lausanne) spoke about the current mismatch between the brain – being very dynamic and the softest tissue in the body – and the mostly very rigid electronic interfaces. To approach this, her team develops soft, flexible, skin-like bioelectronic interfaces. She illustrated the soft implants in a nerve-on-chip model of explanted rat spinal cord, using multimodal (electrical and optogenetic) selective in vivo stimulation.

Prof. **James Fawcett** (University of Cambridge) studies the potential of plasticity as tool for recovery of brain damage. He discovered that the perineuronal nets that surround parvalbumin interneurons are involved in setting the network's excitability level and plasticity. By interfering with perineuronal net synthesis or altering the sulphation pattern of their sugar chains, the critical period of enhanced plasticity could be restored in animal models. This also improved memory, and is thus worthwhile to explore as potential treatment against dementia.

The final series of talks was focused on novel tools to monitor and assist patients in their home environments. Like prof. Sharp in his opening keynote lecture, prof. **Payam Barnaghi** (Imperial College London) also raised the case of preventable hospitalizations as core argument to stimulate at home monitoring and care. His team works on a universal **technology-integrated health management** (TIHM) system, that collects many different types of data from a range of devices, including physiological, environmental and technical sensors. Next, the system performs an integrated analysis (guided by AI) and makes the information available to a 'clinical monitoring team'. "The idea is not to replace human interactions, but to allow clinicians to make more informed decisions regarding the most optimal treatment and care for their patients", explains prof. Barnaghi. The ultimate goal of TIHM is to facilitate home diagnostics and thereby reduce the number of preventable hospital admissions.

Dr. **Aldo Faisal** (Imperial College London) also investigates the use of wearable digital biomarkers 'in-the-wild', as measurements in daily life can lead to very different results than in laboratory settings. He aims to link the human genome and ethome (our behaviour) in a Human Ethome Database. The collection of a range of digital biomarkers, allows to establish a 'digital twin'. Dr. Faisal highlighted the role multiple roles of machine learning and AI in this "AI-fication of biomedical research": to aid diagnostics by analyzing digital biomarkers, to guide intervention and to provide multi-dimensional advice, suited to every individual.

Dr. **Nick Van Helleputte** (imec) highlighted imec's ongoing developments regarding smart and digital health, consisting of patches, head-mounted devices and wristbands. He emphasized that new technologies and 'digital phenotyping' can have a role across different disease stages, and the need for long-term monitoring in a representative environment.

His colleague dr. **Ellie D'Hondt** (imec) works on high-performance computing for dementia research. She provided several examples to show that high-performance computing can bring life science data to a next level. For instance, her team assisted in image processing using deep learning in a project together with Janssen Pharmaceuticals, and contributed to the EPAD (European Prevention of AD) consortium that aims for advanced risk stratification to find successful ways to prevent AD. Her encouraging take-home message was: "do not let computational challenges stop you"!

Keynote Lecture

The workshop was closed by a final keynote lecture by dr. **David Borton** (Brown University), who emphasized the general message of the workshop: to embrace tool-driven discovery. He also provided several examples of first-in-human neuromodulation (so far only available for investigational use), especially regarding **mental illnesses**. Mood and anxiety disorders are a major socio-economic burden, and depression is the #1 cause of disability. A major problem is that there is no objective way to measure a person's 'mental state'. He showed his recent impressive results that neuromodulation of the nucleus accumbens can improve severe obsessive compulsive disorder. Dr. Borton also referred to depression as a network dysfunction, implying that neuromodulation can be a solution. In conclusion, modulatory approaches offer a big opportunity for research and care of mental illnesses, from the clinic to the home environment.

Networking and interaction

The workshop featured an impressive set of speakers; all top scientists who provided an excellent overview of the current state of the art regarding neurotechnologies for dementia.

Yet more important than the lectures, were the **interactive** aspects of the meeting. The group discussions at the dinner table, where clinicians were matched with engineers and basic scientists, led to several very interesting ideas. People from different disciplines and countries found common ground, that will undoubtedly lead to some very fruitful collaborations. Mission Lucidity delegates were very happy to introduce their mission to the UK community, and are already setting up plans to welcome them for a next meeting in Leuven.

In summary, we take home that we should fully, and together, embrace tool-driven revolutionary discoveries. Like dr. Koroshetz did in his Brain Lecture, it is very tempting to end by quoting theoretical physicist Freeman Dyson:

> *"New directions in science are launched by new tools much more often than by new concepts. The effect of a **concept-driven** revolution is to explain old things in new ways. The effect of a **tool-driven** revolution is to discover new things that have to be explained."*