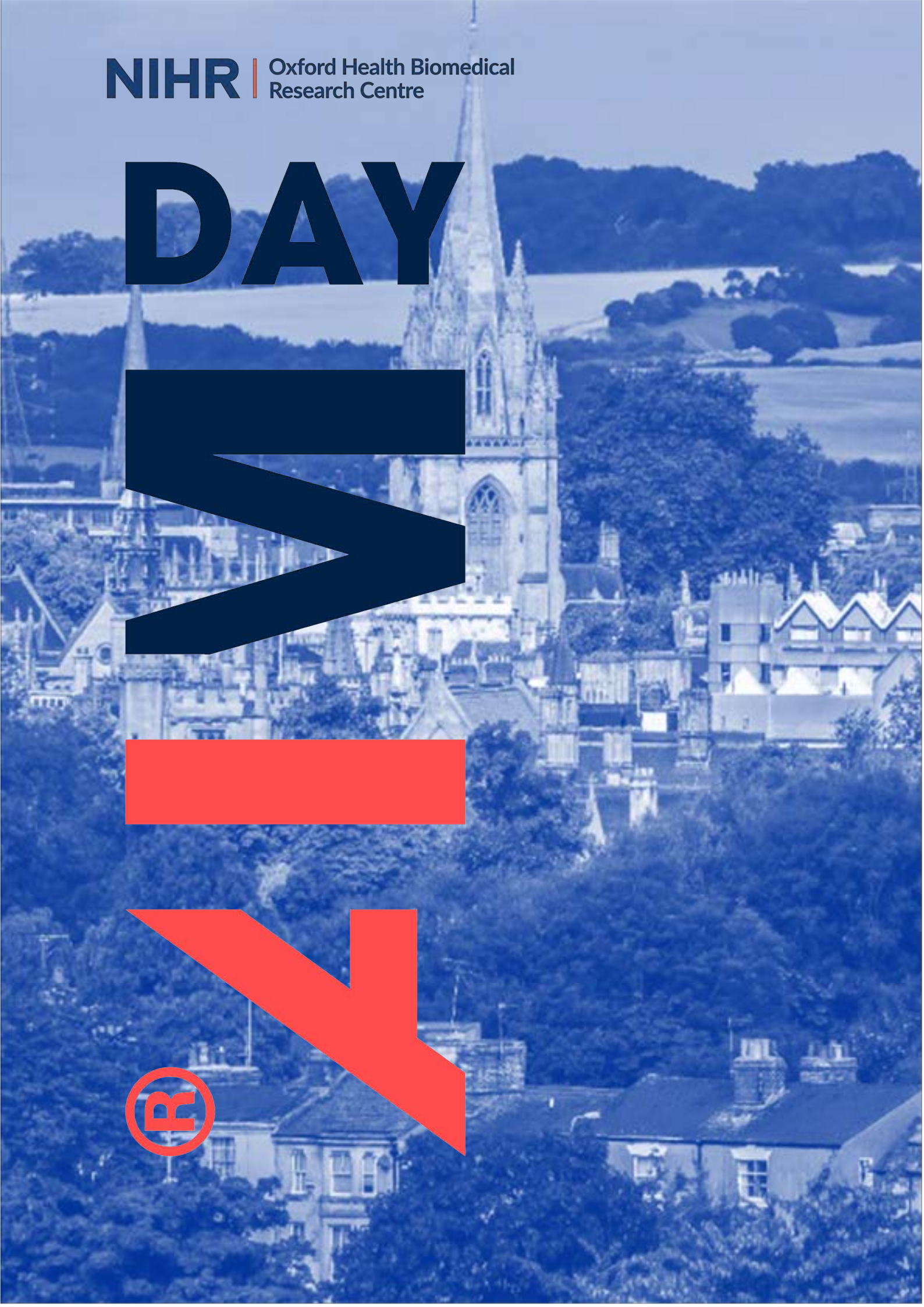
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Oxford Health BRC AIMday

Introduction

by Susannah Murphy

Developing treatments for psychiatric disorders is notoriously difficult, not least because animal models are often not a good proxy of the human condition. Within this context, integrating human models of core processes into drug development pipelines can be a powerful way to screen novel compounds and establish their relevance for the treatment of psychiatric disorder.

Researchers in Oxford have made significant progress in understanding the cognitive neuroscience of core processes relevant to psychiatric disorder, including emotional processing, cognition, stress, reward, inflammation and the affective components of pain. Through our collaborations with Industry, we have a track record of integrating human neurocognitive models of these processes into treatment development pipelines to facilitate the successful translation of evidence from preclinical animal models to early clinical trials.

On Wednesday 7 July 2021, we hosted an Academic Industry Meeting Day (AIMday) in Experimental Medicine in Psychiatry. This provided us with an opportunity to bring together Oxford academics with external companies for a day of networking, discussion and ideas exchange. We invited external companies to submit questions in advance on topics that they thought would benefit from discussion with academics. On the day, these questions formed the basis of a series of nineteen roundtable discussions with groups of academics and clinicians from Oxford.

It was a fantastic day; we had 86 researchers, 53 industry representatives and 15 companies in attendance and the workshops were lively and interactive. A broad range of topics was covered, including neuroimaging, EEG, sleep, neurostimulation, big data, AI and digital therapeutics. In order to capture some of the discussions that we had on the day, we asked some Early Career Researchers to write a blog on one of the sessions that they attended, which we have pulled together in this collection. We hope these will give a flavour of the questions, ideas, insights, challenges and opportunities identified through this networking event.

Susannah Murphy is a Senior Research Fellow in the Department of Psychiatry and Deputy Theme Lead of the Oxford Health BRC Experimental Medicine Theme.

Her research uses a translational experimental medicine approach to provide an early characterisation of the effects of novel psychiatric treatments in humans. She has active programs of work characterising the neuropsychological effects of novel antidepressant targets, including ketamine and the 5-HT_4 receptor.

She works with a number of pharmaceutical companies (e.g. UCB Pharma; J&J; Zogenix) who recognise the value of deploying an experimental medicine approach in the drug development process.

Sleep and Circadian Rhythms: biology to new therapeutics

by Pilar Artiach Hortelano

Circadian Therapeutics workshop

Sleeping and talking about how important sleep is are two of my favourite things to do. The first has always been the case for me, but the second has been growing as I learn more and more about this fascinating topic. With these interests in mind, joining the session led by Professor Vladyslav Vyazovskiy and the team of Circadian Therapeutics on sleep and its treatments was a great opportunity to discuss the current state of research within the field. Many exciting topics were touched upon in the course of an hour, highlighting the importance of sleep for our overall physical and mental health, and ultimately calling for the integration of this domain in the clinical practice. Let me tell you more about it.

Starting with the basics, we were introduced to how the sleep/wake cycle depends on two systems, the circadian system, with the suprachiasmatic nucleus as a "master clock" directly influenced by light; and the homeostatic drive to sleep, which increases throughout the day getting us ready for sleep by the end of the day. During our sleep, many beneficial processes take place: our energy reserves are topped up, toxic and harmful waste is removed, and growth and repairing processes occur, making sleep crucial for a balanced and healthy wake period – no wonder it is one of my favourite things. For this reason, sleep in relation to health and disease has received more and more attention in the past years. In particular, an impaired sleep/wake cycle is known to have detrimental emotional, cognitive, and physical consequences in the general population, and is especially present in several psychiatric and neurodegenerative disorders. Interestingly, the relationship between sleep and health in the latter not only flows in one direction: many of these disorders, such as schizophrenia, depression, or bipolar disorder, present underlying sleep disturbances, which worsen the mental illness.

With this bidirectional relationship existing in many mental illnesses, Circadian Therapeutics presented us with four drug classes aiming at improving objective measures of sleep, such as sleep duration or sleep robustness, and mainly focusing on clinical population. Their approach aims to be a short-term treatment that can stabilise sleep disturbances in those patients whose cognitive-behavioural therapy, or other psychosocial interventions have previously been ineffective. Importantly, patient's well-being, potential side-effects, and any other subjective experience while taking the treatment are also well considered. Beyond the potential clinical application of these treatments, there is also the potential that these interventions might be of more general use, for example to minimise/prevent jet-lag.

Taken together, Circadian Therapeutics emphasizes the important role that the sleep/wake cycle plays in mental health and works towards the integration of this domain in the clinical practice surrounding a wide range of neuropsychiatric disorders.

Pilar Artiach is a Research Assistant working in the Psychopharmacology and Emotion Research Lab (PERL) based at the Department of Psychiatry, University of Oxford. She works on the Reward Emotion Learning and Ketamine Study (RELAKS) that aims to understand the effect of ketamine on reward and punishment processing. Previously she was an intern in PERL analysing a functional magnetic resonance imaging data set looking at the effects of lithium on emotional regulation in healthy individuals as part of her master's in Cognitive and Clinical Neuroscience from Maastricht University, The Netherlands.

How can we advance treatment discovery and development in psychiatry targeting cognition?

by Michael Colwell
Braxia Scientific Corp workshop

Throughout the workshop with Braxia Scientific CEO Dr. Roger McIntyre, many important questions about the future development of psychiatric medicine were laid bare. We began with a 20-minute run-through of Braxia's mission and future goals concentrating on cognition and reward as a means to target psychiatric problems in a transdiagnostic approach. Cognition, as Dr. McIntyre succinctly put it, is a "principal determinant of a person's general function" – indeed, the impairment of cognition is estimated to account for two-thirds of disability in depression. In spite of the clear problem of cognitive impairment in psychiatric illness, there remains only one U.S. FDA-recognized drug for enhancing cognitive function: vortioxetine. Accordingly, one of Braxia's goals is to address this unmet need through exploration of novel therapeutics, including ketamine.

There was a clear theme of caution punctuated throughout the workshop – within treatment discovery and development in psychiatry, common methodological pitfalls must be avoided to ensure treatment is robust enough to cross the threshold from research trial to clinic. Principally, we must ensure patients enrolled in trials are appropriately selected to the treatment. In failing to do so, we run the risk of increasing placebo efficacy and reducing treatment efficacy – a crucial matter of internal validity that could compromise the ability of clinical trials to accurately estimate a drug's efficacy. Certainly, the wisdom within these tales of caution are something that many early career researchers such as myself would do well to pay close attention to.

One further line of inquiry throughout the workshop discussion centred on the promise of ketamine as a rapid-acting antidepressant in treatment-resistant depression. In particular, it was considered whether ketamine might have pro-cognitive effects; following a single small (subanesthetic) dose of ketamine, treatment-resistant patients report sharp reductions in suicidal ideation, which Dr. McIntyre proposed might be explained by ketamine promoting greater cognitive ability to inhibit impulsive behaviour. While these pro-cognitive effects of ketamine are still a matter of debate, the workshop chair, Dr. Susannah Murphy, highlighted the importance of exploring these effects in translational healthy volunteer studies. The exciting future potential for ketamine in treating cognitive impairment in depression is one to certainly keep an eye on.

Taken together, the workshop was a thoroughly engaging and enlightening one, and has personally left me with a lot to consider. I would like to thank both Dr. McIntyre and Dr. Murphy for facilitating such a brilliant session, and I look forward to hearing about future developments from Braxia Scientific Corp.

Michael Colwell is a DPhil student working in the Department Of Psychiatry (University of Oxford), currently supervised by Prof Catherine Harmer and Dr Susannah Murphy.

He is highly interested in novel approaches to targeting the cognitive impairment that co-occurs with mental illness, particularly making use of pharmacological and psychological approaches

Linking behavioural phenotypes with clinical outcomes in drug development

by Angharad de Cates
Lundbeck workshop

Until recently, as a psychiatrist, it felt that we were behind other specialities in producing new drugs with clinical success. There have been some recent successes with ketamine and brexanolone, but I was interested to find out more from a drug company themselves what might be holding them up. So, I joined my boss, Catherine Harmer, Professor of Cognitive Neuroscience at the University of Oxford, who chaired this AIMday session linking Lundbeck and Oxford researchers. The goal was to discuss and brainstorm solutions for the issues around linking behavioural phenotypes with clinical outcomes in drug development.

Pradeep Nathan, VP and head of Experimental Medicine at Lundbeck, kicked off the session by outlining the main problem from their point of view. The current hit rate for success of a new drug at the phase II/III stage is 40%. 30% of those failures are due to poor efficacy of the drug (i.e. it doesn't work according to the pre-defined measures). The problem is likely to be how we measure potential efficacy of a drug earlier on in the development pathway (i.e. at phase Ib – initial tests of can a drug work after preliminary safety testing). In other words, these initial measures are not identifying those agents with the best chance at long term success. So, how can we produce phase Ib biomarkers and / or measures that better match clinical endpoints, and thereby reduce the phase II/III failure rate in drug development?

Lundbeck have already performed some initial analyses suggesting some likely phenotypes to probe at phase Ib, including apathy, anhedonia, emotional bias, attention and sleep. They were looking for opinions and thoughts on these.

This sparked a sequence of questions and comments between researchers and Lundbeck to clarify the limits of the discussion and allow inspiration to flow. It was clarified that:

- Although imperfect (as typically designed to measure disease progression), the use of the certain validated questionnaires for clinical efficacy cannot be changed for regulatory reasons (e.g. MADRS to assess whether a drug is an antidepressant).
- Subjective or objective phase Ib measures are both potentially important to Lundbeck, although sometimes these may not necessarily correlate. For that reason, we may need to think outside the box (i.e. sleep disturbance assessed via the MADRS at phase III may not directly relate to subjective sleep report as a phase Ib phenotype).
- It may not be appropriate to focus on a single symptom biomarker for a single disorder – it may be better to focus instead more globally on function and quality of life transdiagnostically.
- All measures need to be fully characterised with confidence intervals, accepting that there will be some variance in any measure.
- We need to think about the test-retest reliability of measures, and perhaps focus on those where this is greatest. For example, fMRI can be a problem here!
- We need to consider the potential feasibility and participant / patient burden of any measures.

At the end of the session, the general agreement

was that incorporating functioning into a model with behavioural and imaging biomarkers, and using this to explore the biological mechanisms underlying the phentotypes, may be most helpful going forwards. The bigger the data the better to improve reliability, but we need to be cautious not to blindly use large multi-site studies as significant time and resources are required to ensure equivalence across the sites (without which the data can be meaningless). Large data banks and machine learning may be helpful, but again this should be done carefully to ensure valid results.

For me as a clinician and researcher, a major take home point was to remember not to lose sight of the eventual goal with mental health research. There was a suggestion that, perhaps to maximise scientific accuracy in our research, we may look for increasingly complex interactions of various biomarkers of illness and drug response. Even if these may be valid scientifically, to be of practical use they need to be able to translate into outcomes that can be used to measure clinical improvement reliably.

Angharad de Cates is a Wellcome Trust-funded clinical PhD student in PERL based at the Department of Psychiatry, University of Oxford.

For her PhD, she is investigating specific serotonin receptor agonists and whether these agents have antidepressant and pro-cognitive effects in humans, using both neuroimaging and neurocognitive tasks. She is also a Specialist Registrar in Adult Psychiatry at Oxford Health NHS Foundation Trust.

How can academia and industry work together to meet the challenges of developing reliable digital strategies and decentralised clinical trials and minimise the effect of 'noisy' data.

by Amy Gillespie
P1Vital workshop

Led by Gerry Dawson, the co-founder of P1Vital, this session was framed around the company's work in digital therapeutics; they described an exciting app allowing patients in primary care to monitor their mental health symptoms, get immediate feedback, and have clinical concerns automatically flagged to their GP (including lack of response to treatment or deterioration in symptoms). The acknowledgement of how often patients with mental health problems get lost in the system - prescribed treatments and then left with minimal follow-up - and the drive to make a real impact on improving this situation, struck a chord with me. I've met many people in this situation, both when recruiting research participants for studies about depression, and in my personal life. Hearing this talk left me feeling optimistic that there may be simple effective ways to progress.

An ongoing discussion throughout the session focused on how patients perceive these digital interventions, and how to balance the benefits of AI-driven interactions with the human desire for a sense of connection. One solution is to incorporate both (e.g. telephone calls triggered by digital monitoring) and then the question becomes a matter of proportion. P1Vital also mentioned that getting feedback was hugely important to patients;

receiving an immediate summary and response to their questionnaire responses, and being able to track their symptoms and spot patterns was considered a big bonus of the app. The effort put in to ensure the interface is both appealing and intuitive also becomes really relevant, and is an area where academia should definitely be learning from industry!

While I was listening to people discuss the hesitation with digital interventions, I couldn't help but be reminded of a podcast I'd heard last year about the idea of artificial intelligence replacing psychiatrists. One point that has stuck with me is that when we approach these conversations, we always seem to compare AI to "gold standard" interactions with clinicians that meet all of a patients' needs, and not to the messier reality of frequently rushed interactions that can leave patients feeling quite unsatisfied (and unfortunately, sometimes more distressed). Does a face-to-face appointment with a clinician always involve detailed feedback and lead to regular monitoring? Does it always meet a patients need to feel heard and seen...?

Another theme from the workshop was the challenge of convincing different stakeholders of the benefits of these primary care-based mental health interventions. Part of the problem is that improving the identification of patients who need follow-up will - in the short-term - inevitably create more work for GPs. This is simultaneously a success and something quite difficult to sell to already struggling healthcare workers (though GPs sold on the importance of mental health seemed to welcome these initiatives). The much bigger problem is the fragmented nature of the NHS and their budgets, and government departments in general - these kinds of interventions may increase workloads and cost initially, but down the line they will almost certainly reduce costs with less demand for secondary care and social care services, and a happier, healthier population. But recognising this takes a big picture view, a sense of scale, a real commitment to investing in mental health - and I think everyone on the call could relate to the frustration in achieving that.

To finish on a rallying cry, perhaps one of many positive outcomes of collaborations between industry, academia and healthcare can be to have a much stronger voice and much broader vision in the fight for mental health care.

Amy Gillespie is working as a postdoctoral researcher with the Psychopharmacology and Emotion Research Lab (PERL), led by Professor Catherine Harmer. She is broadly interested in research which helps us understand the mechanisms of psychiatric problems and their treatments, with specific interests in developing and utilising (online) cognitive tasks for experimental medicine studies.

What are the biomarkers for psychiatric illness and specifically for post-traumatic stress disorder (PTSD) and what is the role of these biomarkers in predicting real-world impact?

by Alice Quinton
Jazz Pharmaceuticals workshop

On the morning of the AIMday, researchers and representatives from the Oxford and Dublin-based Jazz Pharmaceuticals gathered on Zoom with the goal of discussing the use of biomarkers of PTSD to

predict real-world impact.

The resulting conversation explored the many challenges and considerations of making clinical trials, research and development in PTSD generalisable to the patient population. One such challenge discussed was the high levels of co-morbidity in PTSD. Producing an accurate biomarker would help to disentangle the disorder from other co-occurring disorders, allowing us to establish clinical efficacy in PTSD symptoms specifically. However, by ignoring the complexities of comorbidities one risks overlooking a very real part of a patient's experience of their disorder and subsequently the impact of a treatment in a real-world setting.

Researchers tend to focus on what makes PTSD unique: the intrusive reexperiencing of the trauma. This relies heavily on self-report measures, such as diaries, which come with variable degrees of reliability. There is the added complexity of many patients involved in clinical trials have often developed PTSD as a result of childhood or multiple traumas.

In order to produce a clean experimental model that isn't the product of decades of life experience, PTSD can be modelled in healthy volunteers by using a paradigm in which people *without* PTSD are shown a traumatic video. The trauma is therefore more tightly defined, rather than relying on self-report, allowing researchers to identify biological or cognitive markers. This may not provide the direct patient impact that industry looks for but, in the opinion of the scientists on the Zoom call, the yield of mechanistic information from seeing if a drug then produces a signal in these healthy volunteers is invaluable for demonstrating how specific the drug's effects are to trauma itself.

Symptom scales, such as the commonly used and adapted child and adolescent trauma scale (CATS), delivered by self-report or interview were also placed under scrutiny by those in the workshop. Although these scales offer a great overview of PTSD symptoms in the clinic, Dr Susannah Murphy proposed that future work needs to look at integrating these scales with experimental models earlier on in drug development; "we must look at complementing rating scales with other measures that tap into the psychological processes that are relevant to the disorder".

Once good cognitive biomarkers have been established, neuroimaging may be a useful tool to garner information about treatment response. "It sounds so binary; who responds and who doesn't. But of course, it's a continuum", explained Dr Jacinta O'Shea, "if a drug fails at the expense of an endpoint of a clinical trial, that's a massive failure of resources. But, if you have a well-defined cognitive and MRI biomarker, you get additional information that tells us if we are on the right track".

There is clearly much to consider. Excitingly, Jazz Pharmaceuticals has a history of pursuing innovative drug development in disease areas with limited treatment options; exemplified by their recent acquisition of GW Pharmaceuticals pipeline of drugs targeting the endocannabinoid system. With several industry sponsored trials in the neuroscience space, Jazz is keen to improve the translational potential of pre-clinical studies. Melinda Setanoians (Associate Director Medical Affairs, Jazz Pharmaceuticals), is enthusiastic about collaboration with healthcare and academia in order to support patient communities; "We have an obligation to invest in the development of thinking in this field - as continuing to invest in the field will ultimately benefit the patient".

Alice Quinton is a research assistant in the Clinical Psychopharmacology group. Her current work focuses on exploring the role of inflammation in emotional processing and depression.
This year, she will be starting the MRC-DTP at King's College London with a PhD exploring trauma and post -traumatic stress symptoms in autistic children.
She has a keen interest in developmental neuroscience and is fascinated by how the course, maintenance and treatment of mental illness is impacted by co-occurring diagnoses and adverse life events.

How can experimental medicine methods assist in the development of digital therapeutics?

by Andreea Raslescu
P1vital Ltd./P1vital Products Ltd workshop

Just after lunch break, we gathered for a thought-provoking session hosted by Dr Gerry Dawson, Chief Scientific Officer and director of P1vital Ltd. P1vital and its sister company P1vital Products are pioneering work in the area of digital therapeutics, with three healthcare focused technologies developed in the last 5 years (PReDicT, ispero and Distractor).

The first problem raised by the session isn't a new one: in the UK, people suffering from depression can spend as long as 12-14 weeks on the waitlist for evidence-based psychological therapies, during which their mental health continues to decline. But what if patients had something to help them manage their low mood while they wait for formal sessions with a therapist? Since the beginning of the pandemic in March 2020, P1vital Products have been working on enriching their patient monitoring technology, ispero, for this exact purpose; the newest ispero module, iActivate, delivers digital behavioural activation (BA) therapy on any device with an internet connection. If patients were offered iActivate at their initial assessment at the GP clinic and then still got to see a therapist several weeks later, they might even find that the number of therapy sessions they need is reduced.

The excitement from those of us on the call who use BA in our research was immediately palpable. This is a treatment that has gained popularity in recent years with patients and providers alike, due to being both conceptually simple and effective. But for iActivate to be adopted for use in the NHS, evidence would be needed to show better outcomes in participants receiving point of care digital therapy compared to participants on the therapy wait list. Whilst this is usually provided by means of an RCT, RCTs are long and expensive, and if the COVID pandemic has taught us anything it's that treatment development could be moving a lot more quickly in areas of unmet need.

A potential compromise would be to demonstrate potential efficacy through the means of behavioural and fMRI biomarkers currently used in drug discovery. However, the selection of adequate biomarkers is not an easy feat, as raised by multiple session attendees. Methods of objectively quantifying activation provided by mobile phones, such as pedometry and GPS tracking, fall short in care settings because mobile phones are not certified medical devices. Moreover, there are still considerable gaps in our knowledge of how psychological treatments affect brain and behaviour, and it could transpire that the brain process or behaviour measured is a consequence rather than a predictor of treatment efficacy. Behavioural

therapeutics also require significantly more effort than medication from participants, and so individual effects may vary widely – but this is also where an objective rather than subjective measure of mood could prove crucial.

It's not all doom and gloom, though. A practical first step for P1vital would be to show that iActivate is not inferior to in-person behavioural activation therapy, in a randomised control vs. therapist vs. app design. Shorter, fast-fail type trials with 10-30 subjects should also be considered, provided that a suitable biomarker, and adequate funding, is available.

We all left the session in agreement that there need to be quicker ways for new technologies to get from conception to patient. For ispero, there is no limit to the types of AI-guided therapy programs it can host. We could go one step further and even dream of algorithms that decide how ispero is used together with therapist-led sessions and antidepressant medication. For me, one thing is certain: with so many of us committed to progress in the mental health space, progress is but guaranteed.

Andreea Raslescu is a 1st year DPhil student in the Department of Psychiatry, University of Oxford.

Her current research examines how antidepressants impact affective learning under different environmental conditions.

Prior to her DPhil, Andreea completed a BA in Experimental Psychology also at the University of Oxford, and worked in clinical research management as a graduate for four years.

Should different treatment modalities be considered within the same framework, allowing for joined up approaches between psychological and pharmacological treatments?

by Tereza Ruzickova
Psious workshop

As an early career researcher, I was very grateful to get to be a part of the Oxford AIMday. The whole day was packed with stimulating, nuanced conversations on interesting ideas and the best ways to tackle them through academia-industry collaboration.

I particularly enjoyed the session with the Spanish company Psious - with Xavier Palomer Ripoll, CEO, and Iris-Valerie Stracke, Head of the Medical Department. Psious specialises in building a complex Virtual Reality platform, currently including over 100 VR environments, that can be used for various forms of psychotherapy. Apart from the standard exposure paradigms that are usually translated into VR, such as treatment of various types of phobias and anxiety disorders, they have also explored this technology in the context of eating disorders, trauma treatment, mindfulness, pain management and even bullying. In addition to these environments, they also provide the rest of the VR kit, including a headset and electrodermal sensors, as well as their own training on how to use the technology in clinical practice.

The question we were discussing at our session concerned combining different types of treatments within the same explanatory model, particularly when it comes to combining psychotherapy and

pharmacotherapy. I have been fascinated by this question for a while, since these two treatment types are sometimes presented as opposing camps. At Oxford I have learnt about many intriguing ways in which these treatments can be explored at the same level of explanation, through cognitive models, and I believe this has great potential for improving our treatment understanding and its efficacy.

The session was chaired by the research clinical psychologist Dr Andrea Reinecke, who has extensive experience in combining psychological interventions and drug treatments with a mechanistic model in mind. One interesting approach she has described concerns combining exposure training for anxiety with a drug that acts as a cognitive enhancer. The idea is that an important process of re-learning needs to take place during exposure treatment - the client likely expects to have a terrible time when facing the stimuli they most fear, whether in real life or in VR, but with the right coping strategies they can learn that it's not as bad as predicted. This prediction error is thought to be a crucial learning signal for the brain, allowing it to update its understanding of the stimuli and to reduce phobic responses in the future.

A cognitive enhancer, a drug that supports learning and memory processes, could therefore be a powerful tool to strengthen this relearning process and could be used to complement VR therapy as well. On other hand, an anti-anxiety drug like a benzodiazepine could impede it - by acutely reducing anxiety during the exposure, the client would no longer have such a negative expectation and wouldn't experience as significant a prediction error. We had an interesting discussion on how other kinds of medication could be combined with VR exposure therapy in research, such as standard SSRI antidepressants, and the kinds of results we could expect from that. We also discussed practical ways in which Psious could collaborate with researchers on such a combination treatment study in the near future.

Several aspects of methodology need to be carefully considered for these kinds of research projects. For example, Dr Reinecke stressed the precaution that should be taken in research on adolescents, considering that their neurocognitive profile is still in development and may respond differently to combined treatments. Moreover, Professor Mike Browning suggested that VR may be helpful for researchers in that it allows precise control over the stimuli that participants are exposed to, thus making the intervention more homogeneous across the sample and reducing confounding effects.

At the same time, I personally would be very interested in the individual variation between how people respond to VR and the kinds of research methods we could use to understand each individual's unique treatment progress, such as network modelling. My colleague Andreea also inquired about the flexibility with which VR can be adapted in treatment itself to adjust the experience based on the client's severity or specific clinical profile. Psious explained that providing options for tailoring the environment, such as changing the size of the spider that they see in phobia exposure, is an integral part of their product and something that could be very helpful for answering different research questions.

VR clearly has exciting potential for mechanistic research on psychiatric treatment, whether through closely controlling the environmental experience that is interacting with a drug, or by generating a rich dataset that allows exploration of individual variability. Overall, it was truly inspiring to get to be a part of these conversations and to expand my own thinking beyond the standard tools I know from academia. Industry collaboration can clearly bring unique opportunities for exploring these big

questions and I hope to see (and be part of!) more of such conversations in the future.

Tereza Ruzickova is a DPhil student at the University of Oxford, where she researches behavioural treatments for depression, namely their effects on mood and emotional cognition.

She has particularly focused on using online behavioural activation as a treatment for mental health problems in the context of the COVID-19 pandemic. She is interested in mechanistic combinations of psychotherapy and pharmacotherapy in depression, as well as in predictors of clinical response.

What is the role of individual variabilities when thinking about designing experiments with neurostimulation?

by Jessica Scaife
BrainPatch workshop

This session was kicked off by the CEO of BrainPatch, Nickolai Vysokov, who introduced the company as a team of scientists developing brain-computer interfaces using AI and neurostimulation to help people deal with stress, focus better, improve sleep and even potentially treat neurological disorders. He said that BrainPatch believes in the "power of non-invasive stimulation for altering brain states".

Nickolai showcased a wearable device which had been developed to stimulate the mastoid using electrical pads. It looks like over-ear headphones and is controlled remotely from the cloud, so that wearers can live their normal lives relatively uninterrupted. He then introduced a second product (resembling an in-ear headphone) which stimulates the Vagus nerve, and collects ECG feedback. This product was developed to reduce stress, and again is wireless and can be controlled remotely. The idea for its design came out of the COVID-19 pandemic, when the world's population have been subjected to unusual levels of sustained stress and the project was funded by Innovate UK.

Anna Tarasenko, BrainPatch's Chief Neuroscientist described the design of a study in which participants had experienced induced stress under stimulation and no stimulation conditions. They were interested in finding out which cardiac biomarkers were predictive of vagal nerve stimulation treatment success. The biomarkers they used were HR variability, ECG trace, and HRV-derived parameters. In this study, they also used AI to monitor individual's transitions between different stress levels: baseline to stress and back to relaxation. However, there is individual variability it seems, in the time course of recovery of the sympathetic / parasympathetic ratio: for some it is immediately after stress, for others it is delayed. Despite these individual variabilities they were able to use convolutional neural networks trained on snippets of HRV traces and showed that the algorithms could fairly accurately predict whether the subjects were stimulated or not. Anna explained that among other things they were trying to test whether the stimulation may affect the recovery from stress.

Jacinta O'Shea chaired the workshop and focused the discussion on the key question – what are the sources of individual variability that need to be considered when designing experiments with neurostimulation? Discussing her own extensive experience in TMS and TDCS, she emphasised it was important to distinguish between sources of variation that are intrinsic to individuals (e.g. how an individual responds to stimulation, to stress, and the interaction between the two) versus those that are extrinsic and amenable to experimental control. Miriam Klein-Flugge expanded on this by emphasizing that some individual differences may be variables of interest while others are essentially nuisance variables. These two very different sources of variance call for different experimental and statistical treatment strategies.

Both agreed that cognitive state is one key factor under experimental control that can help both to control nuisance variables and increase sensitivity to detect intrinsic variance of interest. Cognitive state has a significant effect on the efficacy of stimulation – controlling participants' cognitive state by giving them a task to do is a highly effective way to reduce unwanted variance (for example, lapses in attention and fatigue).

There are also a range of parameters such as age, gender, genetic background, medications and whether someone is currently depressed that can lead to variance response to stimulation; NIMH now require collection of this information in clinical trials to account for potential unanticipated sources of variation in response to drug or medical device treatment.

Another interesting aspect to consider is the best way to experimentally induce stress in order to test the effects of stimulation. Initially, BrainPatch had used negative pictures to induce stress but this did not have a large effect on ECG, so they switched to using negative video clips. It is worth considering here that there are many different ways to induce stress experimentally, but such experimental manipulations all induce short-term acute stress. However it is usually chronic stress which is considered to be detrimental to health outcomes and ultimately it is longer term, chronic stress that might be the best target of intervention. I was also left wondering which neural circuits received cardiac feedback, which reduced the subjective experience of stress. This was not touched on by BrainPatch nor discussed in the workshop, but it is a fascinating bottom-up approach to stimulation.

Jessica Scaife is a postdoctoral researcher in the Department of Psychiatry.

Her current research uses neuroimaging and cognitive biomarkers to characterise novel treatments depression and anorexia nervosa, including pharmacological and neurostimulation approaches.

Back to the future: the use of psychedelics in mood disorders

by Lorika Shkreli

Beckley workshop

Psychedelic drugs in mental health research? For some this might sound surprising or even bizarre, but there is increasing evidence that psychedelics might be used to treat mood disorders. In fact, plant-based psychedelics have been one of the very first healing agents of indigenous communities and have been used for centuries. Today, we know that they act through the same system as some types of

antidepressants, the serotonin system. Therefore, I was very excited to learn more about how this kind of treatment could work in modern times.
Our session was proposed by Beckley Psytech, which is investigating a new psychedelic drug to treat mood disorders and addiction, and chaired by Prof Guy Goodwin from the Department of Psychiatry. In this session the key question was, what might be potential biological markers for treatment response and relapse prediction in psychedelic research.

To find out more about biological markers, it is important to understand through what mechanism these drugs exert their effect on mood and behaviour. Is it that the psychedelic experience unveils the core, yet concealed, problem to the patient so that this problem can be tackled in psychotherapy? Or do the chemical components of psychedelics influence mood and behaviour through a brain cell mechanism, while the psychedelic experience itself is rather a 'side-effect'?

So far, research in rodents has shown that psychedelic drugs act through neuroplasticity, which refers to the ability of brain cells to change the way they communicate to each other. In human research, however, it is not possible to investigate the behaviour of single brain cells. Therefore, we need to focus on more general processes that are involved in neuroplasticity. For example, it was suggested to work on memory reconsolidation. This refers to the process of actively retrieving a certain memory, so that this memory is sensitive to changes in the way it is stored our brain. Thus, it might be a relevant line of research to follow.

This leads to the next question, whether psychedelics can work as a treatment on their own, like antidepressants, or if they should be used as an add-on to psychotherapy. This is particularly important, given that we know patients develop a tolerance after they have taken a drug regularly, meaning they need higher doses to achieve the same effects. Similarly, people might relapse after they stop using the drugs. One way to overcome this would be to use psychedelics as an add-on to psychotherapy, which might make the therapy effects not only stronger, but also more long lasting and reduce the chances of relapse.

In general, the discussion was enriched by practical insights from studies on ketamine, for example that the drug might be administered trough intravenous drips once a month, so that patients stay in touch with their therapists. This reduces the chance of overdose or incorrect administration, which in turn also increases safety. Further, a digital platform can be used to measure the patients' symptoms and mood, so that early signs of relapse can be detected.
It is very important to stress that not all patients will benefit from psychedelic treatment and there are certainly risks. Nevertheless, modern research techniques allow us, in a safe and effective manner, to make use of their ancient appreciation about improving mood disorders, and trying to identify which patients will benefit the most. So at this point, we are back in the future and I think this was an extremely insightful, yet almost mind-expanding, session.

Lorika Shkreli is a DPhil student at the Department of Psychiatry. She graduated from Ruhr-Universität Bochum, Germany, with a MSc in Psychology and Cognitive Neurosciences and worked afterwards as a research assistant at the department of Psychiatry, University of Cambridge. Her main interest lies in identifying biological vulnerability markers for mental illness and using this knowledge to improve current treatments by combining psychological, pharmacological, and neuroscientific approaches.

How can we identify and use EEG biomarkers for cognition, autism, sleep, depression?

by Lilian Weber
Zogenix workshop

When we treat patients, our main goal is to make them feel better afterwards. This seemingly trivial insight poses considerable challenges for clinical research: How do we define "feel better"? How much better is good enough? And how long do we have to wait to know whether our treatment has helped?
In this session of the AIMday 2021, 15 researchers from the University of Oxford meet with the Translational Research team from Zogenix to discuss the potential of EEG based biomarkers to help with defining more objective treatment outcomes in psychiatry. Zogenix are a global biopharmaceutical company specialised in developing and commercialising novel treatments for rare diseases (mainly epilepsies). Why would they think about EEG for evaluating treatment success?

Clinical endpoints – the variables we measure at the end of a clinical trial to evaluate the success of a new treatment – represent an individual's health and wellbeing *from this individual's perspective*. This makes them inherently difficult to measure and standardise, particularly in the field of mental health. But even those endpoints that we *can* measure objectively and reliably – e.g., survival, recurrence of a seizure, relapse into depression, etc. – are not always *practical* for clinical research. They often occur too infrequently, or with a huge delay. We need very large sample sizes and study durations to be able to evaluate treatment success. This slows down research, and it prevents us from studying more high-risk novel treatment options.

One example of this is clinical trials in epilepsy, which typically only enrol patients with at least 5 seizures a month, severely limiting the types of epilepsy (and patients) that can be studied. Instead of seizure count, could we use simple EEG measurements (in the absence of seizures) to say something about whether an individual has epilepsy, and is likely to have another seizure?

Maybe we can: Zogenix have recently developed an algorithm that automatically extracts features from an EEG measurement and uses these features to classify subjects into epileptic and healthy (seizure-free). In animal models of epilepsy, this algorithm achieved perfect classification accuracy – even when actual seizures were explicitly removed from the recording.

Zogenix goes one step further to ask: Could we use such algorithms to "detect" psychiatric illness, such as autism spectrum disorder, or depression? But what determines a good biomarker in psychiatry? Can we use spontaneous EEG activity to quantify how depressed an individual currently is? This is where our discussion gets going.

While seizures occur spontaneously, psychiatric symptoms are often defined in terms of interactions with the environment. For example, correctly detecting the emotion in someone else's facial expression: it seems unlikely that impairments in this ability would show up in spontaneous (or "resting-state") EEG. But we might be able to extract the relevant signal much more *efficiently* if we measure EEG while our participants are engaged in a *task that probes the impaired function*.
So is task-based EEG the answer? And what are current obstacles to use task-based EEG as a biomarker? Our discussion touches on several important points here:

First, the data for the biomarker should be easy and quick to acquire. Hours-long spontaneous EEG sounds more feasible than hours-long task engagement. Luckily, some promising EEG tasks are simple but still interestingly linked with psychiatric symptoms. Take for example the auditory mismatch negativity: its measurement only requires participants to passively listen to a sequence of tones, and its amplitude is consistently reduced in individuals with schizophrenia.

Second, we must be able to measure the signal accurately and reproducibly. This issue has not yet received the attention it deserves, and there is work to do in optimising our tasks accordingly.

Lastly, and most importantly, if we want to use such signals as surrogate endpoints in clinical trials, we will need solid evidence that our biomarker consistently and accurately predicts the clinical outcome of interest. It seems to me that we have a long way to go, but also a lot to win, if we can design EEG biomarkers that provide us with some interim evidence about the safety and efficacy of treatments.

Lilian Weber is a postdoc working with Laurence Hunt at the Department of Psychiatry.

She has a background in Psychology and Physics and did her PhD on Translational Neuromodeling at ETH Zurich with Klaas Enno Stephan.

She uses mathematical models, pharmacology, and EEG to understand how drugs affect the way that we form and update beliefs about the external and internal (bodily) world, and how this might help us in understanding psychiatric symptoms.

Should we aim towards a coordinated effort on standard and novel analytical approaches?

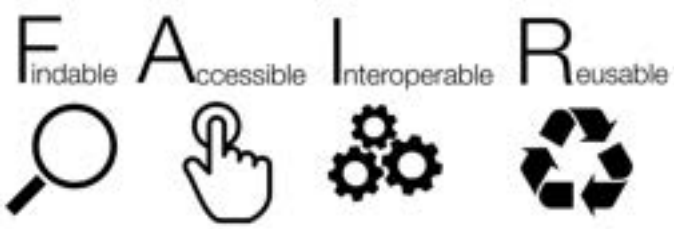
By Laura Winchester
Lundbeck workshop

The key idea for this session was how both industry and academia could work together to achieve common data management and analytical approaches, to make it easier to share resources between us. Both Lundbeck and the Oxford researchers started with imaging data analytical pipelines as an example of an approach that could be optimised. We first described our different motivations in research: Lundbeck were interested in generating reproducible, validated and rigorously tested pipelines to make (expensive) decisions about new compound progression, whereas the academic researchers were focused on novel approaches which were often individual initiatives leading to many new but often less reproducible analytical pipelines. Both these are key to innovative problem solving so the discussion followed about how to combine advantages from both strategies and what barriers might prevent progress. The key barriers discussed were the differing incentives in our respective systems, which are apparent in the broad motivations of how we work.

Other potential issues raised included whether should there be a combined effort across companies to share data and how that might be achieved. For example, making non-competitive data available or making the best use of public imaging databases to establish consistency. Suggestions from the Lundbeck participants on improvements also included streamlining contractual arrangements and improvements to reliability and predictive patterns for treatment response.

Oxford Health BRC AIMday

To develop these ideas, the first step highlighted from this process was sharing current research and data to allow mutually beneficial pipelines to be reused. The issues with data sharing are huge but a small step in the process is to make the intention to share data or pipeline a designed-in feature of the project from the start, so that when the decision is made for sharing the content is ready. The FAIR Guiding principles were explained in detail by Professor Susanna Sansone, one of the authors of the original resource, which gives a framework of principles to follow to enable effective use and re-used of research materials.



Professor Sansone also introduced examples of FAIR applied in industry and some of the current working partnerships (INCL, Pistoia Alliance, IMI Fairplus Project) which focus on the pharmaceutical companies and newer methodologies such as AI.

The next step we discussed in the process is how can we as a community can incentivise these improvements for which there were six main points:

- Funding of research to develop the guidelines (highlighting issues with continued funding to update as technology progresses)
- Funding of research to develop community data standards which incorporate the FAIR guidelines
- Making our own data available
- Normalise reporting using community data standards without hampering innovation
- Funding for research support roles which focus on embedding good data management processes ("Data Champions")
- Joint lobbying or policy engagement with industry and academic partners to promote the agenda for standardisation.

The session overall highlighted the many strengths and possibilities of coordinated efforts for analytical approaches. Few concerns were raised about a reduction in novel approaches, with more emphasis on the potential benefits of reducing the friction in re-use and waste of poorly reproducible findings, it seemed to me that by using shared approaches it would be possible to combine resources to create more efficient and robust novel approaches rather than constrain researchers.

Laura Winchester is an Alzheimer's Research UK Fellow specialising in bioinformatics in the Department of Psychiatry at Oxford University.

Working on dementia and Alzheimer's Disease she is interested in the application of large scale multi-omics data to better understand disease variants and therapeutics.