

The mind-body interface

Summary report of the 2017 FORUM Annual
Lecture

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Contents

Executive summary	4
FORUM Annual Lecture - molecular mechanisms in bioelectronic medicine	7
Panel discussion - the mind-body interface.....	11
Translating evidence to the clinic	12
Integrating mental and physical care in the NHS	15
Annex I - Delegates.....	20
Annex II - Programme	24

Executive summary

The traditional separation of the mind and body – described by Cartesian dualism – has led to a false dichotomy between treating mental and physical health. The separation of the delivery of these two aspects of healthcare fails to address the high levels of co-morbidity between long-term physical and mental illness. Recent mechanistic insights further highlight the importance of greater integration. Historically, the immune system was seen as distinct from the central nervous system, both outside of its control and influence and spatially separated from the brain by the blood-brain barrier. However, new research has unveiled a more detailed understanding of the direct interactions between the brain and body, underpinning a paradigm shift in healthcare delivery towards better integration of mental and physical care pathways.

"Some people are called 'dualists' – they believe that matter is one thing and the mind is something completely different." (Francis Crick, 1994)¹

Recent research has demonstrated direct interaction between the central nervous system and the immune system via the vagus nerve. This is further supported by studies suggesting that immune system disorders can profoundly affect the central nervous system and brain, with a potential role in a number of mental health disorders and neurodegenerative diseases. In addition, there is a growing understanding of the different aspects that may influence mental health including genetic, inflammatory, social and environmental factors, and the broader interplay between mental and physical health.

¹ Francis Crick (1994). *The Astonishing Hypothesis: The Scientific Search for the Soul*.

Therefore, the Academy's 15th FORUM Annual Lecture, held on 6 September 2017, brought together a range of experts to discuss the implications of advances in understanding the mind-body interface. Professor Kevin Tracey, President and CEO, Feinstein Institute for Medical Research first explored the mechanisms by which the brain attenuates the immune system and how disruption of this '*inflammatory reflex*' can lead to symptoms common to many autoimmune diseases such as rheumatoid arthritis. He described the exciting potential to target this interaction through a new type of therapy – bioelectronics – which uses electrical stimulation of the vagus nerve to control the immune system and symptoms. To embed this approach, he underlined the need for basic, cross-disciplinary research to elucidate new neural pathways and interactions between the mind and body that could be targeted for treatment of a range of diseases.

Following Professor Tracey's talk was a panel discussion, which explored the research advances that are driving new ways of thinking about the link between the 'mind' and the body, opportunities of these advances for healthcare delivery and how the healthcare system needs to evolve to embrace these new approaches. Key points of discussion included:

- The need to address the dearth of investment in mental health research when compared with funding for other therapy areas, and the importance of attracting interest in this field as new evidence and treatment opportunities emerge.
- The growing evidence base for the links between mental and physical health, including the role of inflammation.
- Opportunities to use this knowledge to identify novel biomarkers to drive development of new therapies and facilitate patient stratification, as well as targeted use of anti-inflammatory interventions to treat mental health disorders.
- The high, unmet need in treating mental and physical co-morbidities alongside one another which reduces treatment effectiveness, negatively impacts patient experiences and creates unnecessary cost burden for the UK healthcare system.
- Opportunities available in both the short- and long-term to better integrate mental and physical healthcare services through establishing new models of care, building an integrated workforce and overcoming stigmatisation.

This meeting was convened as part of the Academy's FORUM programme, which was established in 2003 to recognise the role of industry in medical research and to catalyse connections across industry, academia and the NHS. We are grateful for the support provided by the members of this programme and are keen to encourage more organisations to take part. If you would like information on becoming a member, please contact FORUM@acmedsci.ac.uk.

2017 FORUM Annual Lecture

The keynote lecture from Professor Kevin Tracey was followed by a panel discussion chaired by Professor Sir Robert Lechler PMedSci. Professor Tracey was joined by four guests who further explored the academic, industry, NHS and patient perspectives of the mind-body interface:

- Professor Ed Bullmore FMedSci, Vice-President Immunopsychiatry, GlaxoSmithKline, and Head of the Department of Psychiatry, University of Cambridge
- Professor Matthew Hotopf FMedSci, Professor of General Hospital Psychiatry, King's College London
- Professor Brenda Penninx, Professor of Psychiatric Epidemiology, EMGO Institute for Health and Care Research, VU University Medical Center Amsterdam, Netherlands
- Melissa Smith, Ophthalmology nurse and service user, East Sussex Healthcare NHS Trust

The key points of discussion from both the lecture and subsequent debate are summarised in this meeting report. A recording of this event is also available and the full agenda and participants list can be found in Annexes 1 and 2.

FORUM Annual Lecture - Molecular mechanisms in bioelectronic medicine

In his keynote, Professor Kevin Tracey, President and Chief Executive Officer at The Feinstein Institute for Medical Research, gave an overview of the key discoveries that have led to our understanding of the '*inflammatory reflex*' – that is, the way in which the immune system is controlled by the brain. He described how this finding can be used to design treatments for a range of diseases using bioelectronic medicines, which employ electrical stimulation to directly control the immune system.

Inflammation and disease

Professor Kevin Tracey opened by describing his early experience with a patient, Janice, who was admitted with severe burns. Despite seeming to make good progress with her recovery, she suddenly passed away from septic shock. The unexplained circumstances of Janice's death led to a drive to better understand the role of the immune system in septic shock, which in turn uncovered the broader interface between neuroscience and immunology.

Through initial research, he discovered that tumour necrosis factor (TNF) – an inflammatory cytokine – was involved in the immune response to shock, supported by research showing

that anti-TNF antibodies protected baboons against septic shock induced by bacteria.² This was the first therapeutic description of anti-TNF therapy, which has progressed into a highly successful class of treatments for autoimmune diseases caused by chronic inflammation.

Research into cytokines thus gave rise to the cytokine theory of disease.³ This asserts that in some cases, cytokines can cause the symptoms of major diseases such as fever, pain and tissue injury. However, cytokines can also play an important role in biological processes when properly regulated such as having anti-microbial activity, acting as growth factors and directing cell recruitment. Balanced regulation of cytokines is key to retaining their protective properties and vital internal activities without driving their damaging effects.

Control of the immune system by the brain

The vagus nerve comprises over 100,000 nerve fibres, of which 80% are sensory and connect the brain to almost every organ in the body. Professor Tracey explained that if the vagus nerve is involved in normal physiology and homeostasis of most organs, it could also interact with the immune system; termed as the '*inflammatory reflex*' – the regulation of the immune system by the vagus nerve.⁴

Research has shown how the immune system can be regulated by the brain via the vagus nerve. Professor Tracey discovered that administering an anti-TNF drug, semapimod, to the brain of animals with an induced stroke, triggered a decrease in TNF levels in the rest of the body even though the drug was not present there.⁵ This led to the theory that the general decrease in TNF was due to nerve impulses to the rest of the body from the brain, demonstrated by cutting the vagus nerve which restored production of TNF in the body.⁶ Therefore, nerve impulses were somehow '*turning off*' TNF production in the body. The final, definitive experiment showed that electrical stimulation of the vagus nerve decreased TNF production in the body, even in animals with a severed vagus nerve.⁷ This suggested that an electrical implant could potentially treat symptoms of diseases caused by TNF.

This has also led researchers to consider the mechanism of the placebo effect and the potential role of the vagus nerve. It is known that inflammatory markers such as c-reactive protein (CRP) are reduced in placebo groups in clinical trials for inflammatory diseases such as rheumatoid arthritis, and it is possible that this placebo effect is modulated through the vagus nerve. It was suggested that the connections in the brain trigger such a reaction through the placebo effect, and so other forms of mental stimulation such as meditation, exercise and cognitive behavioural therapy, could be of value.

² Tracey KJ, et al. (1987). *Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia*. Nature **330**, 662-664.

³ Tracey KJ (2007). *Physiology and immunology of the cholinergic anti-inflammatory pathway*. J Clin Invest **117(2)**, 289-296.

⁴ Qin S et al. (2006). *Role of HMGB1 in apoptosis-mediated sepsis lethality*. J Exp Med **203(7)**, 1637-1642

⁵ Meistrell ME, et al. (1997). *Tumor necrosis factor is a brain damaging cytokine in cerebral ischemia*. Shock **8(5)**, 314-318.

⁶ Rosas-Ballina M, et al. (2008). *Splenic nerve is required for cholinergic antiinflammatory pathway control of TNF in endotoxemia*. Proc Natl Acad Sci USA **105(31)**, 11008-11013.

⁷ Borovikova LV et al. (2000). *Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin*. Nature **405(6785)**, 458-462.

Manipulating the inflammatory reflex

Using this information, Professor Tracey and other researchers worked to understand how the brain controls TNF production. Most TNF is produced in the spleen which is directly connected to the vagus nerve. By imaging the macrophage cells in the spleen, responsible for TNF production, it was shown that electrical stimulation of the vagus nerve stopped TNF production. Further research found that nerve impulses converged on a subset of cells that produce the neurotransmitter acetylcholine, which turns off the production of TNF in the macrophages.^{8,9,10} These are a unique type of immune cell named CD4 TChAT cells, thought to be anti-inflammatory by inhibiting cytokine production. Their role in normal tissue homeostasis is not known, although they are found in many tissues such as the thymus, gastrointestinal tract and lymph nodes. In addition, the macrophages responsible for TNF production have been shown to be stimulated by CD4 TChAT cells.¹¹ Disabling the macrophage receptor that interacts with the CD4 TChAT signal results in cells overproducing TNF as they can no longer respond to the electrical signals. Stimulation of these receptors not only decreases TNF but also reduces other inflammatory cytokines such as IL-6, IL-8 and HMGB1, whilst IL-10, an anti-inflammatory cytokine, actually increases. This builds a comprehensive picture of the biological pathway underlying the inflammatory reflex.

Professor Tracey described how uncovering the role of acetylcholine in this pathway has provided new potential targets for the treatment of autoimmune diseases. These include stimulating the macrophage acetylcholine receptors, which has been shown to protect mice from arthritis.¹² It has also been suggested that acetylcholinesterase inhibitors (AChEI), which prevent the breakdown of acetylcholine, could be used to activate this pathway in situations where the vagus nerve is compromised. The AChEI galantamine has been shown to increase vagus signals when applied to the brain, and a recent clinical trial found improvements in some biomarkers of patients with metabolic syndrome when treated with AChEI.^{13,14}

Towards bioelectronic medicine

Following elucidation of the mechanistic pathways, Professor Tracey and colleagues carried out trials of an electrical implant to see if it could be used to treat diseases caused by overproduction of cytokines. This is an exemplar in the burgeoning field of bioelectronics. One trial was conducted in rheumatoid arthritis patients for whom other therapies, such as methotrexate and biologics had failed.¹⁵ A small electrical stimulator (similar to a pacemaker)

⁸ Rosas-Ballina M, et al. (2011). *Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit*. Science **334(6052)**, 98-101.

⁹ Wang H, et al. (2003). *Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation*. Nature **421(6921)**, 384-388.

¹⁰ Olofsson PS, et al. (2016). *Blood pressure regulation by CD4+ lymphocytes expressing choline acetyltransferase*. Nature Biotechnology **34**, 1066-1071.

¹¹ Olofsson PS, et al. (2012). *$\alpha 7$ Nicotinic Acetylcholine Receptor ($\alpha 7nAChR$) Expression in Bone Marrow-Derived Non-T Cells Is Required for the Inflammatory Reflex*. Mol Med. **18(1)**, 539-543.

¹² van Maanen MA et al. (2009). *Stimulation of nicotinic acetylcholine receptors attenuates collagen-induced arthritis in mice*. Arthritis Rheum **60(1)**, 114-122.

¹³ Pavlov VA, et al. (2009). *Brain acetylcholinesterase activity controls systemic cytokine levels through the cholinergic anti-inflammatory pathway*. Brain Behav Immun **23(1)**, 41-45.

¹⁴ Consolim-Colombo FM, et al. (2017). *Galantamine alleviates inflammation and insulin resistance in patients with metabolic syndrome in a randomized trial*. JCI Insight **2(14)**, 93340.

¹⁵ Koopman FA, et al. (2016). *Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis* PNAS **113(29)**, 8284-8289.

was inserted under the collar bone and connected to the vagus nerve. The device was commercially available to treat epilepsy and was reprogrammed to give a suitable parameter of electrical stimulation to the vagus nerve without other side effects. When the device was turned on, symptoms improved and biomarkers associated with inflammation decreased. Upon turning off the device, symptoms and biomarkers returned. There was a strong correlation between the clinical biomarkers such as TNF and the patient-reported score of symptoms. Current five-year follow-up studies have shown many of the patients are still benefitting from use of the device. Professor Tracey noted the importance of understanding underlying mechanisms to connect basic research to therapeutic development and trials, and felt that such an approach could uncover new networks between the brain and body, leading to new treatments in other disease areas.

Whilst it has been known for some time that vagus nerve activity is decreased in many inflammatory diseases, it was thought that this nerve damage was caused by the immune overreaction. Now, research shows that nerve damage may be present before inflammation, implicating disruption of the vagus nerve as a possible cause of inflammation. For example, research has shown that patients with reduced vagus nerve activity are more likely to have 'pre-arthritic symptoms' such as increased heart rate, and are more likely to develop rheumatoid arthritis.¹⁶

Professor Tracey concluded by emphasising that bioelectronics medicine is bringing together the fields of neuroscience, molecular biology and engineering to create new devices for tackling diseases which remain poorly treated. There is now major investment in this area, both focused on the basic science and its translation, with notable opportunities for SMEs and start-ups. The first clinical trials are now underway in rheumatoid arthritis and Crohn's disease using bespoke bioelectronics devices that can be adjusted wirelessly by a physician. These bioelectronics could potentially offer a safer, cheaper and more effective alternative to medications.

¹⁶ Koopman FA, et al. (2016). *Autonomic Dysfunction Precedes Development of Rheumatoid Arthritis: A Prospective Cohort Study*. *EBioMedicine* **6**, 231-237.

Panel discussion - the mind-body interface

The panel discussed the current research landscape for understanding the mind-body interface, including the growing clinical and genetic evidence for an intimate link between the brain and the body. This has implications for the way in which we approach the treatment and management of both mental and physical health. The opportunities offered by new research for translating evidence into clinical practice were also explored, such as using novel biomarkers, repurposing medicines and developing new imaging techniques. These tools can support the personalisation and integration of mental and physical healthcare to improve patient experience and health outcomes. Finally, the panel considered some of the challenges for the health system that might emerge from a shift towards such an integrated, holistic model of care, including issues around stigma, cross-disciplinary training and patient engagement, and possible ways to tackle these challenges.

Introduction

Professor Tracey was joined by experts from across the life sciences sector to explore the mind-body interface in a panel discussion chaired by Professor Sir Robert Lechler PMedSci, President of the Academy of Medical Sciences. These were:

- Professor Ed Bullmore FMedSci, Vice-President Immunopsychiatry, GlaxoSmithKline, and Head of the Department of Psychiatry, University of Cambridge
- Professor Matthew Hotopf FMedSci, Professor of General Hospital Psychiatry, King's College London
- Professor Brenda Penninx, Professor of Psychiatric Epidemiology, EMGO Institute for Health and Care Research, VU University Medical Center Amsterdam
- Melissa Smith, Ophthalmology nurse and service user, East Sussex Healthcare NHS Trust

Mechanisms underpinning the mind-body interface

The growing evidence base for the mind-body interface

Professor Bullmore emphasised that vagus nerve stimulation has been used to treat depression since 2001, but the mechanism of action is not well understood. It was previously assumed that the electrical stimulation travelled up the vagus nerve to the brain where it acted to reduce symptoms of depression. However, new research suggests that the treatment may in fact work via the peripheral nervous system, where stimulation reduces inflammation in both the body and brain, thereby modulating the symptoms of depression.

These new insights have led researchers to carefully consider the causal link between inflammation and depression. Professor Bullmore highlighted that some drugs and toxins that cause inflammation have been shown to trigger depressive symptoms. This includes studies showing that endotoxins – molecules found on certain bacteria – can trigger depressive symptoms when administered to animals and humans.¹⁷ Similarly, use of interferon-alpha (IFN- α) to treat hepatitis c (by activating the immune system) was found to trigger major depressive disorder (MDD) in a subset of patients receiving this treatment.¹⁸ Subsequent research found that patients at risk of developing MDD after treatment share a range of risk factors including environmental and genetic.¹⁹ These risk factors can help predict those individuals who may be at risk of developing MDD if treated with IFN- α .

Professor Bullmore concluded that this indicates that inflammation can be sufficient to cause depression. It was agreed that these sources of evidence suggest a strong link between the brain and immune system, highlighting the roles of the brain and body in influencing both mental health disorders and inflammation. However, he cautioned against believing that depression is '*all in the body*'. While inflammation may be sufficient to induce depression, he stressed that it is not necessary, nor the only factor affecting risk of depression; many other

¹⁷ DellaGioia N & Hannestad J. (2014). *A critical review of human endotoxin administration as an experimental paradigm of depression*. *Neurosci Biobehav Rev.* **34(1)**, 130-143.

¹⁸ Lotrich FE (2009). *Major depression during interferon-alpha treatment: vulnerability and prevention*. *Dialogues Clin Neurosci.* **11(4)**, 417-425.

¹⁹ Smith KJ, *et al.* (2011). *Risk factors for the development of depression in patients with hepatitis C taking interferon-a*. *Neuropsychiatr Disc Treat.* **7**, 275-292.

factors influence the risk of developing depression beyond that of the immune system, such as genetic and environmental factors.

Finally, as well as the negative implications of immune disorders on mood, the panel also discussed the potential role of the immune system in positive moods such as happiness. Whilst there is some evidence to suggest that low inflammatory gene expression is linked to happier feelings, the panel felt that such research was still in the early stages and a greater understanding of the underlying mechanisms was needed.²⁰

The genetics behind the mind-body interface

Professor Bullmore spoke about the growing evidence suggesting that genetics play a role in risk of depression; recent research has revealed 165 genes that might underlie susceptibility for depression.²¹ Many of the genes identified in this, and other studies, were also associated with immune response, providing further indication of the link between the immune system and depression.²² Professor Bullmore suggested that this consistency provides confidence that the immune system is intimately involved in depression.

Professor Penninx described how risk factors for depression are more than just the genes that are involved, but also includes how these genes are expressed, known as 'epigenetics'. Epigenetics can reveal signs about a person's biological age, which may differ from chronological age. Two measures of biological age, telomere length and methylated DNA have been found to be affected by a range of environmental and genetic factors, including depression.^{23,24} Studies have shown that in individuals with depression, measures of telomere length and methylated DNA suggested that their cells were physiologically 'older' than would be expected based on their chronological age. This suggests an intimate link between molecular biology and physiology, and what is taking place in the brain.

Professor Penninx stressed that whilst the immune system may act as a trigger and genetics may determine susceptibility for some patients with depression, again, these factors must be considered within the broader range of risk factors, triggers and potential areas for stratification. She called for more research into the precise mechanisms of depression and cautioned that stratification and treatment personalisation may only apply to subsets of patients.

Addressing the funding gap

Professor Bullmore emphasised that mental health disorders are a major cause of poor health, affecting 27% of people in the UK and causing 15% of all disease burden. Despite this, mental health research is chronically underfunded, amounting to just over 5% of disease specific research funding.²⁵ This has resulted in a poor understanding of the biology of mental health relative to other fields, leading to a shortage of new biomarkers and treatments for

²⁰ Fredrickson BL, et al. (2013). *A functional genomic perspective on human well-being*. PNAS **110(33)**, 13684-13689.

²¹ Leday GR, et al. (2018). *Replicable and Coupled Changes in Innate and Adaptive Immune Gene Expression in Two Case-Control Studies of Blood Microarrays in Major Depressive Disorder*. Biol Psychiatry. **83(1)**, 70-80

²² Jansen R, et al. (2016). *Gene expression in major depressive disorder*. Mol Psychiatry **21(3)**, 339-347.

²³ Verhoeven JE, et al. (2014) *Major depressive disorder and accelerated cellular aging: results from a large psychiatric cohort study*. Mol Psychiatry **19(8)**, 895-901.

²⁴ Research unpublished but in press.

²⁵ Mental Health Foundation (2010). *Economic burden of mental illness cannot be tackled without research investment - so why is there a rumour that the EU will exclude it from the next 7th Framework Programme call?* BMJ **341**, c6083.

common mental health problems such as depression. He stressed that research is now beginning to uncover new mechanistic insights that reveal an intimate link between mental and physical health and it is important to ensure sufficient funding for such research. As part of this, he advocated for researchers and clinicians to think differently about molecular targets in psychiatry by taking a multidisciplinary approach that overcomes the traditional divide between mental and physical health.

Professor Bullmore described how some of this new way of thinking is being realised in applying immunotherapy to psychiatry. He gave an overview of the MRC Immunopsychiatry Consortium between universities and industry which is conducting a range of preclinical and clinical research to uncover opportunities for the use of existing immunotherapies for mental health problems. The collaboration between industry and academia was highlighted as vital for accessing expertise and capabilities across the discovery pathways.

New imaging technologies to drive translation

A need for new imaging technologies that enable the biological mechanisms underlying the mind-body interface to be determined, in turn driving the development of new treatments, was also highlighted. These technologies often rely on target or cell-specific probes that allow high resolution and specific imaging of targets of interest. The panel described how technologies such as positron emission tomography (PET) could image cells of interest in the brain, such as microglial cells, using targeted probes that bind to molecules on the cells. However, they felt that at present there was a lack of such known molecules and a need for more research into new molecules for PET imaging.²⁶ Full-body PET imaging that simultaneously captures both the central and peripheral nervous system could be a powerful tool for elucidating the role of immune responses in the periphery affecting the brain.

Translating evidence to the clinic

Treatment stratification of patients with mental health disorders

Anti-inflammatory interventions for depression

The panel discussed the potential for using biomarkers to predict the onset of mental health problems before symptoms emerge. Possible biomarkers include those linked to inflammation, such as c-reactive protein (CRP), which appears to be an indicator of response to anti-depressants.²⁷ This suggests that generalised inflammation may not be responsible for depression, but in fact it is a subset of inflammation driven by CRP that plays a role in depression. Following this, Janssen are now carrying out a trial using sirukumab, which targets the inflammatory marker IL-6, in depressed patients with elevated CRP levels – the first anti-inflammatory trial for depression. In addition, longitudinal studies have shown that children with higher levels of inflammatory markers such as CRP and IL-6 at the age of eight were at greater risk of depression in adulthood.²⁸ These studies suggest that patients with depression could be stratified based on biomarkers such as these to help tailor treatments.

²⁶ Tronel C, et al. (2017). *Molecular Targets for PET Imaging of Activated Microglia: The Current Situation and Future Expectations*. *Int J Mol Sci.* **18(4)**, 802

²⁷ Raison CL, et al. (2013). *A Randomized Controlled Trial of the Tumor Necrosis Factor-alpha Antagonist Infliximab in Treatment Resistant Depression: Role of Baseline Inflammatory Biomarkers*. *JAMA Psychiatry* **70(1)**, 31-41.

²⁸ Valkanova V, et al. (2013). *CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies*. *J Affect Disord* **150(3)**, 736-744.

Other biomarkers for depression

As outlined above, depression has been increasingly linked to physical disorders. The Netherlands Study of Depression and Anxiety examined a range of biomarkers and genes in ~2000 depressed and ~650 control patients, and found that those with depression have increased levels of the 'stress' hormone cortisol, higher heart rates and increased inflammatory biomarkers.²⁹ In addition, a range of metabolites that are associated with disease correlate with depression. These include biomarkers of metabolic syndrome such as cholesterol and oxidative stress molecules. These metabolites are observed over the course of the depression and prevalence of metabolic syndrome also increases risk of staying in a depressed mood.

Opportunities for repurposing existing medicines

Several panel members touched on the fact that there are a large number of trials of anti-inflammatories in other disease areas. Many of these studies included measures of mental health, including depressive symptoms, as part of the study, and a 'mega-analysis' of these found a positive treatment effect of anti-inflammatories on depressive symptoms.³⁰ This effect was statistically significant even when other factors were accounted for such as improvement of physical symptoms, and was higher for drugs targeting inflammatory cytokines such as IL-6. However, these studies only included patients that were not clinically diagnosed with depression, so whether such results would be seen in clinical depression is not yet clear.

Further work is exploring which biomarkers are most predictive of treatment response to selective serotonin reuptake inhibitors (SSRIs), a common treatment for depression. One such trial, biomarkers for depression (BIODEP), led by Professor Bullmore, has stratified patients by response to SSRIs to determine which biomarkers are most predictive of treatment response, and whether anti-inflammatories potentially offer a better treatment response for those who do not respond well to SSRIs.³¹

Integrating mental and physical care

The interaction between mental and physical comorbidities

Professor Hotopf outlined one of the problems of modern healthcare – as we become better at preventing death and extending life spans, more people develop comorbidities. He explained how the number of chronic physical health conditions increases with age, and comorbidities are higher in people with a lower socioeconomic status. Mental and physical health problems are often comorbid with each other and negatively impact the other, and people with major mental health disorders have a life expectancy of 10-17 years fewer than those without a disorder.³²

In addition to exacerbating symptoms of comorbidities, mental health problems also affect health outcomes for physical disorders. For example, studies show that people with severe mental health problems and ongoing cardiovascular disease are more likely to suffer from

²⁹ Jansen R, *et al.* (2016). *Gene expression in major depressive disorder*. *Mol Psychiatry* **21(3)**, 339-347.

³⁰ Research unpublished but in press.

³¹ www.hra.nhs.uk/news/research-summaries/biomarkers-in-depression-biodep/

³² Chang CK, *et al.* (2011). *Life Expectancy at Birth for People with Serious Mental Illness and Other Major Disorders from a Secondary Mental Health Care Case Register in London*. *PLoS ONE* **6(5)**, e19590.

heart failure than those without a mental health disorder. In addition, research shows that people with depression who have a heart attack are more likely to die within six months than those without depression, and rheumatoid arthritis treatment response is poorer in patients with comorbid depression. Such findings are mirrored across many areas of physical health.³³ Further, it was noted that in general, quality of care for physical health problems is lower in those with mental health disorders such as psychosis.

Professor Penninx described how stress, ubiquitous in the busy, modern world, can have dramatic effects on both physical and mental health. She described one study, comparing monkeys raised in isolation to those raised in a social group, which found that the isolated monkeys not only experienced depression, but also physical differences such as a higher heart rate. Stress induced by watching sports can also increase cardiovascular disease mortality in men.^{34,35} These studies demonstrate the notable impact of both chronic and acute stress on health, offering insight into the opportunities to improve integration of mental and physical healthcare. Professor Penninx also described how MDD is a stress-related disorder that has both physical symptoms and those relating to poor mental health. MDD affects 6% of the population making it one of the most prevalent mental health disorders. Several studies have shown that MDD increases risk for many other physical conditions, suggesting that it is a driver for physical health disorders. However, the mechanisms for how stress and depression affect physical health are not well understood. There are a multitude of physical systems affected by stress which are interconnected to the brain, and evidence increasingly suggests a bi-directional relationship.

Making the case for integrated care

With the scale of mental and physical comorbidities, and the emergence of new evidence on the biological links between these, panellists felt that there was now a compelling case for better integration of mental and physical care pathways in the NHS. Professor Hotopf described how collaborative care for patients with both mental and physical illnesses has been shown to benefit both aspects of health and improve satisfaction with quality of care. In one study, patients with poorly controlled diabetes or coronary heart disease alongside depressive symptoms were cared for by staff with training in both mental and physical health. As well as driving an improvement in mental health, physical parameters such as blood pressure, cholesterol and HbA1c also improved.³⁶

Professor Hotopf described a new programme being undertaken at King's College London to improve integrated care. The Integrating Mental & Physical Healthcare: Research, Training & Services (IMPARTS) programme is an initiative that aims to assist physical health staff to better integrate physical and mental healthcare pathways, and address challenges related to delivering more integrated secondary care.³⁷ The core principles to IMPARTS are: building informatics infrastructure to enable routine collection of patient reported outcomes; development of mental healthcare pathways for patients identified through screening; training

³³ Frasure-Smith N, et al. (1993). *Depression following myocardial infarction. Impact on 6-month survival.* JAMA **270(15)**, 1819-1825.

³⁴ Witte DR, et al. (2000). *Cardiovascular mortality in Dutch men during 1996 European football championship: longitudinal population study.* BMJ **321**, 1522.

³⁵ Wilbert-Lampen U, et al. (2008). *Cardiovascular Events during World Cup Soccer.* N Engl J Med **358**, 475-483.

³⁶ Katon WJ, et al. (2010). *Collaborative Care for Patients with Depression and Chronic Illnesses.* N Engl J Med **363**, 2611-2620.

³⁷ Rayner L, et al. (2013). *Embedding integrated mental health assessment and management in general hospital settings: feasibility, acceptability and the prevalence of common mental disorder.* General Hospital Psychiatry **36(3)**, 318-324.

staff in mental health management skills; supporting self-help materials tailored to specific long-term conditions; and facilitating the development of new, low cost psychological treatments. The IMPARTS programme is now being trialled in 40 different clinical settings at King's College London and Guy's and St Thomas' hospitals, and aims to institutionalise mental health in physical healthcare pathways. This includes mental health questionnaires and quality of life measures as a standard part of physical healthcare. The programme also aims to train physical health staff in mental health skills and identify gaps in resources.

New approaches to care pathways

The panellists also described the opportunity to bring significant benefits to patients by making relatively small changes to care pathways. For example, Professor Hotopf reiterated that depression is a very good marker for poor health outcomes, and can be measured simply through patient questionnaires. However, it is not routinely recorded as part of physical care clinics which presents a missed opportunity. The panel felt that there is a significant value proposition for treating people with chronic low mood and depression. Integrated care and the tools that it uses could offer great opportunities to address comorbidities of mental and physical health. For example, the use of anti-inflammatories for improving depressive symptoms is being investigated. Personalisation of care based on the nature of patient's condition will not be possible for everyone, but for select groups it could prove vital.

One potential way to address co-morbidities is by promoting lifestyle and behavioural changes that allow patients to becoming more involved with self-care. Whilst medications are important, it was noted that patients often prefer a holistic approach to care that may also alleviate the need for certain medications. One participant noted that studies have shown that CRP is higher in children who have suffered abuse and questioned whether such markers could be used to identify children who are at risk of mental health problems later in life for early intervention.³⁸ There is a wealth of emerging evidence that inflammatory markers such as CRP are linked with depression, as well as neurodegenerative diseases such as Alzheimer's disease. Professor Penninx suggested that there is some evidence that lifestyle interventions, such as frequent exercise, decrease inflammatory marker levels, which could have implications for later mental health. However, more evidence is needed to show that lifestyle interventions can have a positive impact on mental health through biological mechanisms linked to the immune system. Other interventions such as exercise and nutrition programmes have been shown to improve mood as well as physical health, but are rarely offered in clinics. Professor Hotopf also remarked that patients with psychosis are more likely to suffer from cardiovascular disease due to higher rates of smoking, and that cessation treatment could be offered alongside standard psychosis care pathways to help treat this common co-morbidity.

Building an integrated workforce

To enable full integration, there is a need to identify and implement new and existing tools to support the clinical workforce. These tools, such as systematic measurements, online resources and new integrated treatments, would allow better integration of care without requiring clinicians to become specialists. Staff training is also a vital component of an integrated healthcare system. In relation to this, Melissa Smith spoke about her experiences as both an intensive care and ophthalmology nurse. She described how many of her patients were admitted for acute medical reasons but almost invariable had complex comorbidities and polypharmacy. Amongst the difficulties of treating such complex cases, she described how

³⁸ Baldwin JR, et al. (2018) *Childhood victimization and inflammation in young adulthood: A genetically sensitive cohort study*. *Brain Behav Immun*. **67**, 211-217

consideration of the mental health of the patient was rarely a priority. She felt that in many cases, NHS staff may not understand patients' mental health needs or recognise the symptoms of mental health disorders, which may be mistaken for a 'bad mood'. Staff may also not fully understand the impact of chronic health conditions on mental health such as breathlessness, chronic pain and reduced independence, and the effects of traumatic or stressful treatments such as that for age-related macular degeneration which involves monthly injections into the eye. Ms Smith felt it to be vital that mental and physical care are managed in parallel, and that such a system of integrated care would not only improve the health of patients but also provide a more fulfilling patient experience.

In addition, Ms Smith described how NHS staff, despite being over-worked, still have enough face-to-face time with patients to pick up on aspects such as low mood or depressive feelings. However, staff do not have the time or training to intervene in these situations despite being able to act as both a listener and conversationalist for patients. She highlighted this as a notable missed opportunity for medical staff to address physical and mental health in a holistic way, and that further training and reduced workload to overcome this could lead to a better patient experience. She emphasised the need for the medical and research community to work together to promote and enable such integrated care.

Instigating culture change around mental health

Stigmatisation of mental health disorders was also proposed as a significant challenge, both preventing patients from seeking treatment as well as acting as a barrier to receiving the most effective care. It was suggested that patients may not wish to disclose their condition or seek treatment for fear of discrimination, or that clinicians may have unconscious bias that affects their proposed treatment. The integration of mental health management across all disease areas was upheld as a potential tool for reducing stigma, as well as increasing personalisation which enables a more targeted approach. This would 'normalise' mental health management both for patients and clinicians. However, the panel noted that the implementation of such a personalised, holistic system was only possible if there was evidence to support it, and more research was vital to improving this evidence base.

Conclusion

The panellists and chair summarised by emphasising that emerging evidence for the mind-body interface has provided new opportunities for better health outcomes and an improved patient experience. Professor Sir Robert Lechler emphasised that the mind-body interface is a fertile and important field of medical research, but that practical steps are required to ensure that there is a compelling value proposition, understanding of mechanistic need and appropriate funding for personalising and integrating physical and mental healthcare.

In particular, it was noted that the comparative lack of investment in mental health research stifles opportunities for understanding the biological mechanisms underlying mental health disorders. However, despite this, cutting edge research is uncovering opportunities for better understanding, predicting and treating mind and body co-morbidities - an area of significant unmet need. These new discoveries, when complemented by an integrated and holistic approach to mental and physical healthcare, will open up new frontiers for the way that mental health disorders can be managed in a joined-up, integrated healthcare system.

Annex I - Delegates

Chair

Professor Sir Robert Lechler PMedSci, Vice-Principal (Health), King's College London; Executive Director King's Health Partners Academic Health Sciences Centre, King's Health Partners

Keynote

Professor Kevin Tracey, President and Chief Executive Officer, Feinstein Institute for Medical Research, New York

Panellists

Professor Ed Bullmore FMedSci, Vice-President Immunopsychiatry and Head of the Department of Psychiatry, GlaxoSmithKline and University of Cambridge

Professor Matthew Hotopf FMedSci, Professor of General Hospital Psychiatry, King's College London

Professor Brenda Penninx, Professor of Psychiatric Epidemiology, EMGO Institute for Health and Care Research, VU University Medical Center Amsterdam

Ms Melissa Smith, Patient Representative, East Sussex Healthcare NHS Trust

Delegates

Professor Kathryn Abel, Professor of Psychiatry, Centre for Women's Mental Health, University of Manchester

Dr Esha Abrol, Foundation doctor, North East London Foundation Trust

Professor David Adams FMedSci, Pro-Vice Chancellor and Head of College of Medical and Dental Sciences and Professor of Hepatology, University of Birmingham

Dr Basma Alharthy, King's College London

Mr Matthew Balmforth, Policy Intern, Academy of Medical Sciences

Dr Rebecca Bendayan, Research Associate, University College London

Dr Elizabeth Benedikz, Programme Officer, Academy of Medical Sciences

Mr Max Berrill, Medical Student

Professor Tim Bliss OBE FMedSci, Visiting Researcher, The Francis Crick Institute

Dr Peter Bloomfield, Postdoctoral Research Associate, University College London

Professor Philip Bond, Visiting Fellow, University of Oxford

Ms Silvia Bottaro, Forum Policy Officer, Federation of the European Academies of Medicine

Dr Rachel Brown, International Policy Officer, Academy of Medical Sciences

Ms Aisling Burnand MBE, Chief Executive, Association of Medical Research Charities

Dr Martha Carruthers, Director EMEA Solutions, Johnson & Johnson

Dr Marisa Casanova Dias, Clinical Academic Mentorship Scheme Fellow, University of Cardiff

Dr Sheng-Chia Chung, Research Associate, University College London

Mr Joe Clift, Policy Manager, Academy of Medical Sciences

Mr Jonathan Cohen, Founder, Cohen Strategic

Dr Sean Cross, Clinical Director, King's College London

Dr Gareth Cuttle, Project Manager, Neuroscience, Royal College of Psychiatrists

Dr Zeine Daoudi, Psychiatry Trainee, King's College London

Professor Adrian Davis OBE, Director, AD Cave Solutions Limited

Dr Katrina Davis, Researcher, AD Cave Solutions

Kathryn Southworth, Director, AD Cave Solutions

Ms Liberty Dixon, FORUM Policy Manager, Academy of Medical Sciences

Professor Klaus Dugi, Medical Director, Boehringer-Ingelheim

Professor David Edwards FMedSci, Professor of Paediatrics and Neonatal Medicine, King's College London

Sir Christopher Edwards OBE FRSE FMedSci

Ms Melanie Etherton, Communications Officer, Academy of Medical Sciences

Dr Christopher Exeter, Director, International Strategy Group, UnitedHealth Group

Professor Elizabeth Fisher FMedSci, Professor of Neurogenetics, University College London

Professor Tamsin Ford, Professor of Child and Adolescent Psychiatry, University of Exeter

Dr Katharine Fox, Policy Officer, Academy of Medical Sciences

Dr Sandrine Geranton, Lecturer, University College London

Professor Pietro Ghezzi, Research Lead for the Department of Clinical and Experimental Medicine, Brighton & Sussex Medical School

Sir David Goldberg FMedSci, Professor Emeritus, King's College London

Dr Samantha Goldman, Head of Medical Affairs, AstraZeneca

Sir John Grimley Evans FMedSci, Professor Emeritus, Nuffield Department of Clinical Medicine, University of Oxford

Professor Ashley Grossman FMedSci, Professor of Endocrinology, Oxford Centre for Endocrinology and Diabetes, University of Oxford

Dr Emily Grossman, Science Communicator

Dr Luiz Guidi, Policy Intern, Academy of Medical Sciences

Dr Neil Harrison, Clinician Scientist Fellow, Brighton and Sussex Medical School

Dr Joseph Hayes, Clinical Fellow, Division of Psychiatry, University College London

Dr Iona Heath OBE, President, Royal College of General Practitioners

Dr Isobel Heyman, Honorary Professor, University College London

Professor Irene Higginson OBE FMedSci, Professor of Palliative Care; Director of Cicely Saunders Institute, King's College London

Ms Ayuko Higginson, Student, University College London

Ms Marjorie Hodge

Professor Allan Hoffbrand FMedSci, Emeritus Professor of Haematology, University College, London

Miss Lucie Hooper, Policy Research Manager, Cancer Research UK

Professor Stephen Hunt FMedSci, Professor of Molecular Neuroscience, Department of Cell and Developmental Biology, University College London

Ms Candace Imison, Director of Policy, Nuffield Trust

Professor William James OBE FMedSci, Professor (Honorary), London School of Hygiene and Tropical Medicine

Ms Wendy Jarrett, Chief Executive, Understanding Animal Research

Dr David Jefferys, Senior Vice President, Eisai Europe

Professor Martin Johnson OBE FMedSci, Professor of Reproductive Sciences, Anatomy School, Physiology, Development and Neuroscience, University of Cambridge

Professor Terry Jones FMedSci, Medical Physicist, The PET Research Advisory Company

Professor Peter Jones FMedSci, Professor of Psychiatry, Department of Psychiatry, University of Cambridge

Ms Cynthia Joyce, Chief Executive, MQ Mental Health

Dr Carol Kan, Research Student, King's College London

Dr Tatiana Kassessinoff, Business Consultant

Dr Susan Kay, Executive Director, The Dunhill Medical Trust

Dr Terry Kemple, President, Royal College of General Practitioners

Professor Ann Louise Kinmonth OBE FMedSci, Emeritus Professor of General Practice, University of Cambridge

Dr Jeff Kipling, Science Policy Adviser, JRK Consulting

Professor Sanjeev Krishna FMedSci, Professor of Molecular Parasitology and Medicine, Centre for Infection and Immunology, St George's University of London

Dr Belinda Lennox, Clinical Senior Lecturer, University of Oxford

Dr Gemma Lewis, Research Associate in Psychiatric Epidemiology, University College London
Dr Tom Livermore, Senior Policy Officer, Academy of Medical Sciences
Dr Rachel Macdonald, Head of Grants and Programmes, Academy of Medical Sciences
Dr Fiona Marshall FMedSci, Founder, Director and Chief Scientific Officer, Heptares Therapeutics
Dr Monica Marta, Consultant Neurologist, Queen Mary, University of London
Ms Marsha McAdam, Service User Champion, Patient Information Forum
Professor Elizabeth Miller OBE FMedSci, Consultant Epidemiologist, Public Health England
Mr Damian Mole, Clinical Senior Lecturer and Honorary Consultant Surgeon, MRC Centre for Inflammation Research
Dr Hadeil Morsi, Academic Clinical Fellow, University of Nottingham
Dr Claire Mouchot, Senior Science Officer, French Embassy in the UK
Dr Helen Munn, Executive Director, Academy of Medical Sciences
Dr Ian Newington, Senior Programme Manager, National Institute for Health Research
Dr Chiara Nosarti, Reader in Neurodevelopment and Mental Health, King's College London
Dr Peder Olofsson, Senior Researcher, Karolinska Institute
Dr James O'Malley, Policy Manager, Arthritis Research UK
Dr Andy Pain, Medical Team Lead, Boehringer-Ingelheim
Dr Rachael Panizzo, Programme Manager for Mental Health and Addiction, Medical Research Council
Dr Rashmi Patel, Academic Clinical Lecturer, Institute of Psychiatry, Psychology and Neuroscience, King's College London
Sir John Pattison FMedSci
Dr Niels Plath, Vice President, Lundbeck
Dr Rachel Quinn, Director of Policy, Academy of Medical Sciences
Professor Pamela Rabbitts FMedSci, Fellow, Leeds Institute of Cancer Studies and Pathology, University of Leeds
Professor Humphrey Rang FMedSci OBE, Emeritus Professor of Pharmacology, University College London
Ms Jo Revill, Chief Executive Officer, British Society for Immunology
Mr Marco Ricci, Staff Writer, Pharma Phorum
Ms Holly Rogers, Communications and Engagement Manager, Academy of Medical Sciences
Dr Ivana Rosenzweig, Consultant Neuropsychiatrist, Head Sleep and Brain Plasticity Centre, King's College London
Professor Polly Roy OBE FMedSci, Professor of Virology, Department of Pathogen Molecular Biology, London School of Hygiene and Tropical Medicine
Ms Kundai Rukambiro University College London
Professor Stephen Scott OBE FMedSci, Director, National Academy for Parenting Research, Institute of Psychiatry, King's College London
Mr Adam Scott
Ms Yasmin Shand, Fundraising Officer, Academy of Medical Sciences
Professor Sukhvinder Shergill, Professor of Psychiatry & Systems Neuroscience, Institute of Psychiatry, Psychology & Neuroscience, King's College London
Ms Alex Shimmings, Managing Editor, Scrip
Professor Jonathan Slack FMedSci, Professor Emeritus, University of Bath
Dr Richard Smith OBE FMedSci, Director, UnitedHealth Chronic Disease Initiative
Professor Stephen Smith FMedSci, Non-Executive Director, Great Ormond Street NHS Trust
Ms Beckie Smith, Reporter, Research Fortnight
Dr Francesca Solmi, Research Associate, University College London
Professor Peter Somogyi OBE FMedSci, Professor of Neurobiology, Department of Pharmacology, University of Oxford
Miss Roxy Squire, Senior Policy and Public Affairs Officer, Medical Research Council

Mr James Squires, Policy Officer, Academy of Medical Sciences

Professor Andrew Steptoe FMedSci, British Heart Foundation Professor of Psychology, Epidemiology and Public Health, University College London

Professor Joyce Taylor-Papadimitriou FMedSci, Senior Fellow/Visiting Professor, Guy's, King's and St Thomas' Medical School

Professor Chris Thiemermann FMedSci, Professor of Pharmacology, William Harvey Research Institute

Ms Alison Tingle, Research Liaison Officer & Research Development Lead, Department of Health

Dr Mark Toms, Executive Director, Medical Affairs, Merck Sharp & Dohme

Professor Federico Turkheimer, Professor of Neuroimaging, Institute of Psychiatry, King's College London

Dr Margriet Vervoordeldonk, Director and Therapeutic Project Leader, Treatment Discovery, Galvani Bioelectronics

Dr Michael Warwick-Sanders, Head of Pharmacovigilance UK & Ireland, Boehringer Ingelheim Ltd

Professor Christine Watson FMedSci, Professor of Cell and Cancer Biology, Department of Pathology, University of Cambridge

Dr Ursula Wells, Section Head, Health Protection Research, Department of Health

Mr Greg White, Chief Executive, Faculty of Homeopathy

Professor Roger Williams OBE FMedSci, Director, Institute of Hepatology

Dr John Williams, Managing Director, Birmingham Health Partners, University Hospitals Birmingham

Professor Steven Williams, Professor of Imaging Sciences and Head of Department of Neuroimaging, Institute of Psychiatry, King's College London

Professor William Wisden FMedSci, Chair in Molecular Neuroscience, Imperial College London

Ms Rebecca Wise, Cancer Prevention Grants Manager, Cancer Research UK

Ms Jeanne Wolstencroft, University College London

Professor Patricia Woo OBE FMedSci, Emeritus Professor of Paediatric Rheumatology, Division of Infection and Immunity, University College London

Dr Naho Yamazaki, Head of Policy, Academy of Medical Sciences

Dr Anna Zecharia, Director, Policy & Public Affairs, British Pharmacological Society

Dr Weijia Zhang, Doctor, University College London

Annex II - Programme

Wednesday 6 September 2017, 14.30-18.30

British Academy, 10-11 Carlton House Terrace, St. James's, London, SW1Y 5AH

14.30 – 15.00	Registration and refreshments
15.00 – 15.10	Welcome and introduction Professor Sir Robert Lechler PMedSci (chair), President, Academy of Medical Sciences
15.10 – 16.00	Keynote - Molecular mechanisms in bioelectronic medicine Professor Kevin Tracey, President and Chief Executive Officer, The US Feinstein Institute for Medical Research
16.00 – 17.15	Panel discussion: Integration across the mind-body interface <i>Chaired by Professor Sir Robert Lechler, President, Academy of Medical Sciences</i> <ul style="list-style-type: none"> • Professor Ed Bullmore FMedSci, Vice President of ImmunoPsychiatry, GlaxoSmithKline, and Head of Department of Psychiatry, University of Cambridge • Professor Matthew Hotopf FMedSci, Professor of General Hospital Psychiatry, King's College London • Professor Brenda Penninx, Professor of Psychiatric Epidemiology, EMGO Institute for Health and Care Research • Melissa Smith, Ophthalmology nurse and service user, East Sussex Healthcare NHS Trust • Professor Kevin Tracey, President and Chief Executive Officer, The US Feinstein Institute for Medical Research
17.15 – 17.20	Closing comments from the President Professor Sir Robert Lechler PMedSci, President, Academy of Medical Sciences
17.20 – 18.30	Drinks reception

Annex III – Glossary

AChEI – acetylcholinesterase inhibitor

An acetylcholinesterase inhibitor increases acetylcholine levels by inhibiting the breakdown of acetylcholine by the acetylcholinesterase enzyme.

CD4 TChAT – CD4 positive ChAT (choline acetyltransferase) expressing T-cells

A type of cell found in the spleen that can modulate TNF production in response to signals received from the vagus nerve.

CRP – c-reactive protein

A protein found in the blood, of which levels increase in response to inflammation.

IFN- α – interferon-alpha

A cytokine that can be used in the treatment for hepatitis c.

Inflammatory cytokine

A signalling molecule produced by immune cells that promotes inflammation.

MDD – major depressive disorder

Clinically diagnosed depression.

PET - positron emission tomography

A medical imaging technique.

SSRI – selective serotonin reuptake inhibitor

A common class of drug most often used as antidepressants as they increase serotonin levels in the brain.

TNF – tumour necrosis factor

A particular family of cytokines produced in the body that promote inflammation.

Vagus nerve

A cranial nerve that connects the brain to many major organs in the body and, amongst other functions, plays a role in the homeostasis (or normal operation) of those organs.



Academy of Medical Sciences
41 Portland Place
London, W1B 1QH
+44(0)20 3141 3200

info@acmedsci.ac.uk
www.acmedsci.ac.uk

 [@acmedsci](https://twitter.com/acmedsci)

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