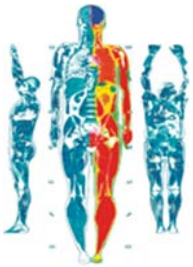


MRC Neuroscience of Obesity Workshop: Gut – Brain Communication

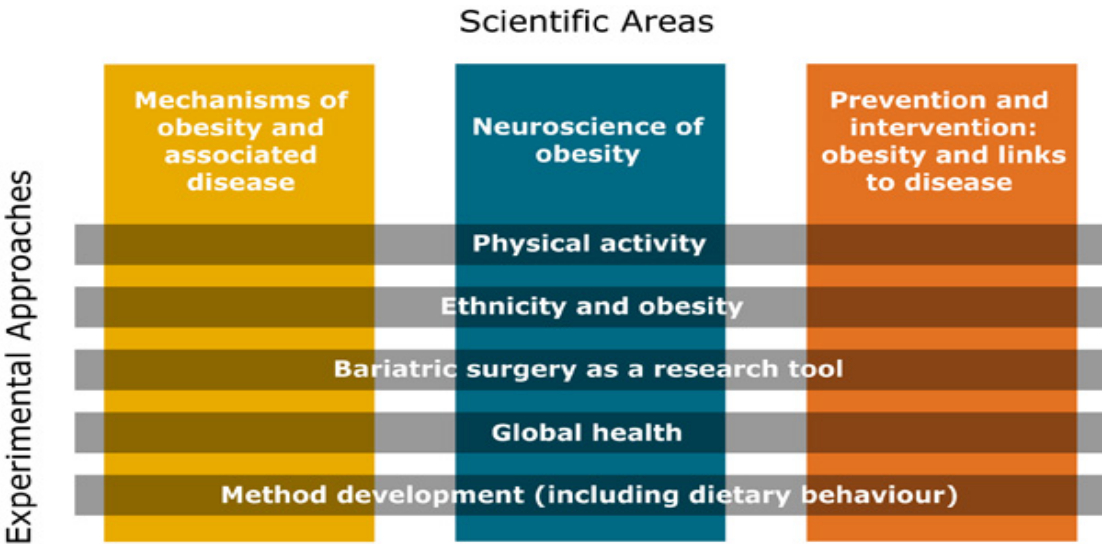
REPORT OF THE WORKSHOP HELD ON 9 & 10 OCTOBER 2014

Background and meeting objectives

The meeting was hosted by the MRC Metabolic Diseases Unit (MDU) and held under the aegis of two MRC Research Boards - the Population and Systems Medicine Board (PSMB) and the Neuroscience and Metal Health Board (NMHB).

Obesity and its related diseases place a significant burden on healthcare systems and tackling obesity is a government-wide priority in the UK. Within the MRC's broad remit, a significant amount of research relevant to obesity and obesity-related disease is funded. In 2013/14, the MRC spent over £23 million on research relevant to obesity through research grants and to its units, centres and fellowships. Further information on the MRC's activities in relation to obesity and the microbiome can be found via the links provided.

In 2010 the MRC held a meeting of leading obesity researchers to produce a coherent set of priorities for MRC obesity research, taking into account current activities, opportunities, tractability and clinical relevance. Eight priorities for MRC obesity research were identified and divided into two categories: scientific areas and experimental and conceptual approaches. Some research priorities were considered to be areas of strength for UK research where significant progress was being made, whereas others were viewed as under-developed and in need of stimulation.



Aims of the Workshop

The aim was to hold a small and highly interactive workshop focused on the neuroscience of obesity, and gut-brain communication in particular. Both PSMB and NMHB had previously identified this as an important area where the MRC portfolio should be strengthened.

Four planned sessions covered:

i) Gut/brain communication, including how bariatric surgery exerts its physiological effects
ii) Neuronal mechanisms of energy homeostasis - hypothalamus/brainstem
iii) Hedonic, behaviour, addiction and higher cognitive function, including brain imaging
iv) Novel therapies and drug targets

The agenda and list of participants for the workshop can be found at Annexes 1 & 2.

The workshop drew together experts from across the spectrum of research with the aim of considering how the field had evolved since the MRC developed its obesity priorities in 2010, and identifying priority topics through which the MRC could make an impact.

The overall aim was to shape the future strategy for the MRC in this field by:

- Highlighting the UK's strengths
- Discussing barriers to progression
- Identifying and prioritising key interdisciplinary research challenges and translation opportunities relevant to this field
- Bringing together a broad spectrum of scientists and clinicians with relevant expertise
- Facilitating collaborative and interdisciplinary interactions and encouraging high quality, multidisciplinary grant applications from the scientific community

Format of the meeting

The workshop took the form of a short retreat to encourage wide-ranging discussion and creative thinking around the area. The workshop began early evening on the 9th October with short briefing presentations from Professor Hugh Perry and Professor Sir Stephen O'Rahilly, followed by dinner. On the following day each of the four sessions were led by two key experts with the aim of stimulating whole group discussions on each topic. Short biographies of the speakers and session leads can be found at Annex 3.

The following key questions were used to guide each discussion session:

- Where is the field now? (UK strengths and weaknesses with respect to research/ infrastructure/technology)
- Where should the field be heading?
- What are the priority research gaps?
- What questions should be addressed to improve our understanding of the field?
- What are the key barriers to collaboration/joint working across disciplines on these questions. How can these be overcome?
- What are the potential translational gains/opportunities and what is needed to achieve them?

Discussions were centred around:

1. The here and now –e.g. what 'quick wins' might be addressed.
2. Short/medium term challenges – e.g. progress with any therapies currently being tested, hot topics in translational research and what might be 'in the pipeline' for improvement.

3. Long term prospects – e.g. outcomes resulting from an increased understanding of the biology and how this might shape future scientific and clinical direction in the field.

Pre-Workshop Survey

Prior to attending the workshop, participants were asked to complete a short survey to identify:

i) Two priority research gaps which, if addressed, would improve our understanding of this field
ii) Two key issues/areas which, if addressed, would enable progression in the field

The participant responses were included in the workshop papers and collated without attribution (Annex 4). These responses were used to inform the direction of the discussions in the four sessions on day 2.

Workshop Report

Session 1: Gut/brain communication, including how bariatric surgery works

Session Leads: Fiona Gribble & Carel Le Roux

A brief introduction by the session leads highlighted the importance of this particular area of obesity research. GLP-1-based medicines are already a multi-billion pound industry for Type 2 Diabetes and gut peptides are also currently under development for the treatment of obesity. Furthermore, bariatric surgery is highly effective and results in dramatic and sustainable weight loss. Based on the pre-workshop survey responses, four key areas for discussion were identified:

- Gut microbiota
- Enteric nervous system and signalling between gut and brain
- Bariatric surgery
- Gut hormones

Gut microbiota
A number of workshop attendees felt that this was an important area of research, where there are currently gaps. A good deal of effort in this area was from outside the UK. The key points raised during the discussion were:

- Despite experimental evidence that the microbiome can play a causal role under experimental conditions in rodent models, its role in the development of obesity in humans is still unclear and causality remains to be addressed. Whilst large-scale studies may provide evidence of correlations between microbiome composition and human obesity, the demonstration of causality in humans requires interventions that both perturb the gut microbiota and modulate obesity.

- It may not be necessary, and it may in fact impede progress, to take a reductionist approach and study individual populations of gut bacteria. Gut microbiota exhibit regional heterogeneity - stool samples are not useful because they do not reflect populations higher up the gastrointestinal tract. Efforts should be focused on understanding the overall function(s) of the gut microbiota as a community and how functions vary across different human populations. Current understanding in this area is very limited.

- The main research gap, for which there was considerable support and which could become a UK strength, is the “black box” of communication between gut microbiota and brain. This was highlighted as an important area where basic scientific efforts are

needed. Work is required to identify and characterise the plethora of signals, going beyond short chain fatty acids, and the signalling routes underlying gut bacteria – host communication.

- There is also a gap in understanding of the local effects of the gut microbiota on barrier function and inflammation.

- The large intestine was very important in harvesting energy from ancestral diets. It was argued that it would be interesting to recreate these dietary conditions and determine effects on energy balance in humans.

- Studying the metabolism and energy balance of colectomy patients, with significant alterations in their gut microbiota, could be a critical experiment.

- There was support for the utility of both human studies and mouse models in this area. The impact of the microbiome on obesity and on insulin sensitivity should be separated out.

Enteric nervous system and signalling between gut and brain

The key points raised during the discussion were:

- The enteric nervous system (ENS) has been shown to express receptors for gut hormones. However, how the ENS interacts with the gut-brain axis and the importance of the ENS in appetite regulation are largely unknown. The development of tools, such as transgenic mice, to address these gaps would be valuable.

- There are tools available which would allow progress in this field, such as viral gene delivery techniques enabling the targeting of subsets of neurons. However, it was felt that the UK has been left behind in this area.

- Little is known regarding the ENS in obese humans and this is an important gap. Do ENS disorders affect metabolism/physiology and are effects direct or indirect? Work is currently dominated by rodent studies. However, it was argued that human pathology is complex and therefore, animal models remain important.

- The metabolic role of the autonomic nervous system is ill-defined. Work should focus on the link between metabolic diseases and autonomic neuropathy. The autonomic nervous system may play a role in the development of obesity-associated co-morbidities.

Bariatric surgery

Bariatric surgery has profound effects on body weight and metabolism, and changes individuals' attitude to food entirely. It is a very important tool which can provide valuable insight, however, we are a long way from understanding how it works. The UK has a strong track-record and is recognised internationally as a pioneer in this field of research, particularly with regard to rodent models of bariatric surgery. This reputation has also attracted principal investigators from abroad. The key points raised during the discussion were:

- The mechanisms underlying the dramatic beneficial effects of bariatric surgery remain incompletely understood. This was identified by the MRC workshop attendees as a key priority for obesity research. The relative contributions and interactions of different systems such as the enteroendocrine system, the nervous system and the gut microbiome following bariatric surgery require further investigation. The ultimate goal would be to mimic the effects of bariatric surgery pharmacologically.

- It is important to distinguish between the effects of bariatric surgery *per se* versus the effects of body weight loss and severe caloric restriction alone.

- Transplantation of gut microbiota from different parts of the post-surgery gut into germ-free mice may be an interesting experiment.

- A question raised was how many bariatric procedures should be studied in rodent models? It was argued that depth was better than breadth and that the focus should be on the main procedures carried out in humans, namely sleeve gastrectomy and Roux-en-Y gastric bypass (these account for 60% of total procedures).

- Bariatric surgery research would greatly benefit from workshops and training centres/programmes on animal models/procedures. This was identified as an important gap and received considerable support from the MRC workshop attendees.

- It is important for human studies to be conducted alongside rodent studies. Rodent models of bariatric surgery closely mimic effects in humans.

- Could we learn from non-responders? They are a heterogeneous group of patients and a big cohort would be required to distinguish them. However, information gleaned from such studies could be interesting.

- Understanding the effects of bariatric surgery in humans would be facilitated by a cross-disciplinary approach, combining the efforts of human feeding behaviour scientists, peptide biologists and clinicians.

- Functional imaging in humans is a powerful tool and should be coupled with bariatric surgery.

- Medical devices have thus far not been very effective. Efforts in this area are mainly from the US. This area could profit from engagement with industry.

Gut hormones

The importance of gut hormones, both physiologically and as drug targets, is well-recognised. Furthermore, this is an area of research where the UK has world-leading expertise. The main points raised during the discussion were:

- Gut hormones can act via multiple mechanisms and there is a tendency to investigate pharmacological doses/effects. Physiologically, the effects of individual gut hormones are likely to be modest but amplified when in combination. However, it is difficult to design experiments to unpick this complexity and determine optimal gut hormone levels/profiles. It is important to prove their physiological relevance and elucidate the pathways responsible for their effects.

- Clarification is required regarding the role of gut hormones locally in the gastrointestinal tract versus centrally to modulate appetite. It was proposed that we should capitalise on new techniques to discriminate between the action of peptides in the gut and the brain. The hedonic role of gut hormones, beyond hunger and fullness, is also incompletely understood.

- Food/nutrients have potential for the prevention of obesity. Work should focus on functional foods which increase gut hormone secretion more effectively and have enhanced satiety properties. This was deemed to be an important strategic gap.

- Improved understanding of the differences along the gastrointestinal tract and which regions underlie plasma gut hormone profiles would help to identify which pool of enteroendocrine cells should be targeted.

Session 2: Neuronal mechanisms of energy homeostasis - hypothalamus/ brainstem

Session Leads: Giles Yeo & Julian Mercer

Genetic approaches have almost exclusively directed obesity research to the brain, and in particular the hypothalamus. Moreover, many obesity pharmacotherapies target the brain to promote negative energy balance. The neuronal mechanisms of energy homeostasis therefore represent a critical focus for basic and translational research in the field of obesity research. Based on the pre-workshop survey responses, four key areas for discussion were identified:

- Hypothalamus
- Hindbrain
- Signal in and integration of cues from the periphery
- Onward signalling and crosstalk

The session began by considering the question: *What are our strengths as a neuroscience community in the UK, and what are the opportunities and potential barriers?* The key points raised during the discussion were:

- UK strengths include classical neurophysiology and the identification of function.

- Mouse genetics is a UK strength which offers a number of opportunities. The UK possesses the expertise and infrastructure to make mouse models on a considerable scale. In addition, participants emphasised that there are many more GWAS hits to investigate.

- Whilst UK scientists were quick to apply new technology (not just genetic engineering) to metabolic disease, the UK was lagging behind other countries in relation to the development of new methods. There is a need to invest substantial funding into progressing technology and to ensure that UK neuroscience centres of excellence place an emphasis on developing technology, with engineers and computer scientists working alongside neuroscientists.

- There is a need to ensure the UK was at the forefront in understanding how brain circuits process information to create neural representations that guide behaviour. It was recognised that this would require multidisciplinary approaches linking cutting-edge genetic tools and other new technologies to enable classical neurophysiology to be applied in a smarter, more targeted way.

- It was noted that the UK Brain Banks Network provides high quality brain tissue to scientists and clinicians to carry out cutting edge neurosciences research. The members of the Network will also explore the scope for greater specialisation of some brain banks to address particular research needs. Participants discussed the possibility of capitalising on the collection by linking samples to appropriate clinical data (e.g. Body Mass Index - BMI).

- As a weakness of UK neuroscience research, the legislative framework from the Home Office is a short-term barrier that needs to be addressed. It was suggested that it would be impossible to recreate John O'Keefe's Nobel-prize winning research with same speed and ease today. Closer working between the Home Office and scientists to explore new approaches could be implemented. Submitting reports on new experimental approaches with small numbers of animals, in the first instance, would ensure confidence in the cost-benefit relationship.

In light of the unexplored GWAS hits, the session then turned to addressing the question: *Should we concentrate on what we know or invest in finding new neural contributors to the neuroscience of obesity?* The key points raised during the discussion were:

- There was a need to study existing mouse models in much more detail – this was particularly important when looking for potential drug targets.
- Even though pro-opiomelanocortin (POMC) and the melanocortin 4 receptor (MC4R) are well studied, not enough is known about important components upstream of these key mediators e.g. nutrition, movement/physical activity, fat cell products.
- There are areas where overseas groups have a strong lead - for example the work of Scott Sternson and Brad Lowell in relation to Agouti-related peptide (AgRP) – and it may be better for UK researchers to focus on areas where they can develop novel insights.
- Participants agreed that key leads may be missed by focusing on one system - there was a need to take a more holistic view of the problem and examine both established and new players regulating appetite and their possible interactions.
- Much research had focused on the homoeostatic regulatory system in the hypothalamus and dysregulation leading to obesity. It was agreed that it would be productive to look for higher level changes e.g. in relation to seasonality and synaptic plasticity. Digression from an ideal bodyweight would simply represent physiological flexibility/adaptation to particular circumstances.

The following key points emerged from a discussion on the role of imaging:

- The ability of brain imaging to spatially and temporally locate brain areas involved in processing metabolic cues was emphasised.
- One limitation is the language of interpretation around brain imaging. Can we better develop a cogent neuroscientific vocabulary for interpreting brain imaging and relating it to physiology and mechanisms? How do we best link changes at the single cell level, to fMRI scans and physiology, through to behavioural change?
- It was suggested that the UK community needs to better utilise small animal brain scanning and also to capitalise fully on the recent significant investment in human imaging (including 7T) that had been made through the Clinical Research Infrastructure Initiative. The challenges of accommodating obese patients in scanners were highlighted.

The focus of the session then moved to the hindbrain and the following points were made:

- Much of our research in the neuroscience of obesity is focused on the hypothalamus but brain sites sensing metabolic cues may be distributed throughout the brain. In fact, many key conduits located in the hypothalamus are also expressed in the brainstem. A key question that was highlighted was to understand whether these distributed sites may be redundant circuits.
- Hindbrain systems are known to control both energy balance and cardiovascular disease. In this regard, the treatment of obesity via increased energy expenditure may be held back by side-effects on the cardiovascular system. It was suggested that the hindbrain may play a role in this via autonomic output.

Finally, participants discussed the importance of the 'connectome':

- It was important to recognise that the system under study is a neurocircuit and it is likely that neural sites interact - one site cannot be studied in isolation.

- The Allen Mouse and Human Brain Atlases were invaluable resources for neuroscientists. The Allen Mouse Brain Connectivity map provided brain-wide, cellular level mesoscale connectome information. The Human Connectome Project will map connections between brain regions whilst the human Brain Initiative will look at connectivity between small clusters of neurons.

- There is a need for an integrated framework for metabolic function and food intake, linking brain connectivity with functionality – a 'functional connectome' which shows the generation and processing of key signals, how they are routed, combined and co-ordinated, leading to behavioural and physiological outcomes. In addition, it is important to understand the flexibility/adaptability of the system in relation to external influences (e.g. quantity and type of food available). For this reason experts in metabolic function and obesity should work with neuroscientists to produce a common neural map which researchers could update as they publish.

Session 3: Hedonic, behaviour, addiction and higher cognitive function, including brain imaging

Session Leads: Paul Fletcher & Sadaf Farooqi

The session discussion acknowledged the complexity of eating behaviour and challenges inherent in studying and understanding it. Eating behaviour is driven and modified by multiple factors: hunger, metabolic requirement (basal and energy expenditure), early life programming, the environment (physical and social) and beliefs (cultural and individual). Given these multiple interacting factors it is difficult to determine what drives food related decisions and food consumption on a day-to-day basis. BMI serves as a cumulative record of these decisions but in itself only tells us that there has been excess energy intake surplus to requirements, not how or why. The issue is rendered more complex by the fact that most of our food related decisions are habitual and driven by environmental factors, rather than deliberated or goal directed. For example, the clock that tells you it is 1:00pm is an extremely important environmental signal that motivates eating lunch.

This can be understood in our conceptualisation of the brain as a predictive organ, one that aims to constantly model our environment (both internal and external), predicts changes in the environment and efficiently implements appropriate responses to it. In this conceptualisation, the brain strives to make predictions and optimise behaviours such that they can be implemented as efficiently as possible (habitually), minimising the need for energetically expensive deliberation. A striking illustration of this predictive model is shown by the anticipatory rise in ghrelin levels when people believe they are about to have an indulgent creamy milkshake compared to a healthy one, even though both drinks are identical apart from their labels. However there are two important consequences of this striving for efficiency. The first is that actions/behaviours become dissociated from the value of their outcome. Habitual behaviours remain unaffected by changes in the value of the outcomes they result in and continue to be activated by environmental cues, even though their outcomes are no longer valued or now potentially harmful (e.g. continued consumption despite obesity). The second consequence is that the outcome, or the reward, also becomes dissociated from its value, as it results from a habitual behaviour that does not factor in its value, or how it may have changed since the last time it was encountered. Computational neuroscience approaches can help us study and understand eating behaviour and help us examine critical questions such as: Is the brain aware of existing adiposity stores when it makes food related decisions?

In addition to the above, participants discussed the following specific areas:

- *The need for more precise measurement tools for characterising obesity relevant phenotypes:*

    - *Quantification of eating behaviour phenotypes:*
      This is a major challenge, as accurately measuring food intake remains a significant hurdle in this area. Most present tools rely on self-report or some form of active subject participation in the measurement. Recent advances have included using body mounted cameras to capture images of foods eaten, chewing rate and purchasing behaviour, and developing the sophistication to extract precise data on the eating behaviour from these outputs alone, e.g. determining portion size and calorie content from a photo of a meal. Critical to these tools is the ability to accurately measure behaviour without the process of measurement significantly modifying the behaviour itself. It was agreed that this is an important area of future research.

    - *Quantification of energy expenditure and physical activity:*
      In this area there has been significant progress in the development of sensewear technology that can accurately and unobtrusively measure activity. It is important to integrate this with the eating behaviour phenotype given the coupling of energy intake and expenditure and the role that energy expenditure plays in both determining intake as well as its effects on appetite control.

- *The effect of our present day environment on eating behaviour and body weight:*
  There have been significant changes in our food environment (particularly over the last few decades) compared to the environment we evolved in, and these have had an effect on food intake and body weight. Changing the food environment is an important part of any anti-obesity strategy. However, this altered environment also poses some important questions such as: How do individuals maintain a healthy body weight in this environment? What factors drive thinness?

- *The challenges of selectively targeting food reward to treat overeating and obesity:*
  Food reward has been an important therapeutic target in recent years, with cannabinoid and opioid agents that have aimed at reducing food reward and therefore intake and weight. However, a challenge with these drugs has been that their effects have not been limited to food rewards and achieving this degree of specificity remains an important gap.

- *The potential value of examining other conditions in which eating behaviour and weight are affected:*
  Studying these conditions can help improve our understanding of the drivers of intake. These include: anorexia nervosa, cancer cachexia, post-operative cachexia, inflammation, drug induced obesity (antipsychotics, antiepileptics), frontotemporal dementia, Huntington's disease and hypoxia related changes in appetite.

- *The food addiction model:*
  This has gained a lot of currency particularly in the USA, where it has strong proponents, and on the Internet. While there is compelling animal evidence to suggest that addiction type behaviours can be induced in animal models, there is no evidence thus far to suggest that any foods act like drugs. More recently the idea of an eating addiction, rather than a food addiction has been raised, suggesting that it is the behaviour that is the issue and that a potential substance is not involved. It is very unlikely that addictive processes underlie most of obesity but they may be relevant to specific phenotypes and this requires further research.

Session 4: Novel therapies and drug targets

Session Leads: Stephen Bloom & Lora Heisler

There is a critical need for better treatment of obesity: current pharmacological anti-obesity treatment is only moderately effective (leading to 5% of weight reduction at the most) at the expense of many off-target side-effects. In addition, although bariatric surgery is effective in many, it has some significant down-sides: some patients do not respond with weight loss, it bears the usual complications associated with major surgery, and finally not many are keen to have a major operation.

Professors Bloom and Heisler presented a short introduction to the session covering past and present drugs that have been used to treat obesity and the potential targets for effective drug treatment of obesity (e.g. central and peripheral regulation of food intake, energy expenditure, physical activity, fat absorption and metabolism). Two important advances in the field had occurred: the drug companies are now much more open to peptide drugs largely delivered by injections, and insurance companies are now reimbursing treatment with anti-obesity drugs.

The UK has the potential to be a global leader in the development of drugs by virtue of the clinical infrastructure provided by the NHS (including data linkage) and available funding schemes to support drug discovery research.

Participants discussed the potential quick wins in drug development, the short and medium term developments (which drugs are in the pipeline?) and the future for anti-obesity therapy. The following key points were made:

- Low dose combinations of existing drugs (e.g. 5-HT_{2C} receptor agonist with gut peptides) offer a quick win as they are available and could enter trials of efficacy in a relatively short period of time. Also, combination of various gut peptides have been proven to induce weight loss in rodents and an MRC-funded phase I trial in humans is imminent.

- Targeting of drugs to specific relevant tissues through manipulation such as ligation offered an additional approach of improving efficacy and limiting off-target effects.

- Another potential avenue to increase the efficacy of existing drugs is to study their mechanisms of action at the behavioural level e.g. lorcaserin: Does it increase satiety response or decrease reward of food or both? This knowledge can then be used for behavioural therapy to potentially enhance the effects.

- The following were discussed in relation to medium and longer-term goals:

  Understanding the effects of bariatric surgery – specifically to pharmacologically mimic the beneficial effects of surgery through understanding the postoperative gut hormone dynamics and the effects on appetite.

  Nutraceuticals - manipulating food to increase the hormonal gut satiety response. Proof of concept studies would need to take place first to establish whether it was possible to deliver sufficient functional nutrients to the right place in the gut and whether the gut hormone response would be powerful enough to control food intake in a sustained way.

- Areas that were explored as potential targets for obesity treatment were drug interventions aimed at increasing energy expenditure, browning of fat, inducing physical activity, or inducing malabsorption; none of which seemed attractive as primary targets of anti-obesity treatment as they have the potential to result in compensatory effects on food intake.

- Exploring the properties of the microbiome in relation to obesity treatment was discussed. However, as noted above, a lack of robust evidence linking the microbiome to causality of obesity was identified as a barrier to this approach.

- Another potential avenue to be explored was the manipulation of food to make it non-absorbable, or increasing gastric/gut transit time to allow more release of anorexigenic gut hormones.

Future strategies

The future for anti-obesity treatment was discussed: drugs, lifestyle or surgery? In general it was agreed that a combined approach would be the way forward.

Agreement was also reached that pharmocogenomics and other approaches should be used to stratify responders vs. non-responders to specific pharmacological manipulation, and to identify those who are more or less likely to experience side-effects.

Increased partnership with industry who, often by virtue of regulation, have collected large datasets, was recommended as a way forward to data mine and collectively identify better and cleaner drug targets for anti-obesity treatment.

Finally, it was widely agreed that the drugs that are currently used are associated with too simplistic an understanding of the neuro- and gut-circuitry of body weight control. Basic scientific studies and genetic studies need to be encouraged to refine treatment targets. For this we need adequate capacity in obesity research in the UK.

Report written co-ordinated by Karen Finney with contributions from:
Arianna Psichas (session 1), Luke Burke (session 2), Hisham Ziauddeen (session 3), Agatha van der Klaauw (session 4).

MRC Neuroscience of Obesity Workshop: Gut-brain communication

9 -10 October 2014

The Wellcome Trust Conference Centre, Hinxton (http://www.wtconference.org.uk/)

AGENDA

Thursday 9 October 2014 Pre-Meeting Briefing

16:00 – 17:30 Registration and Refreshments

17:30 –17:40	**Welcome and Introduction** – Steve O'Rahilly and Hugh Perry
17:40 –18:00	**Background and Aims of the Workshop:** MRC's Obesity Research – Hugh Perry
18:00 – 18:20	**Setting the Scene** - Steve O'Rahilly
18:20 – 18:30	**Format for the meeting** – Fiona Gribble, Giles Yeo, Karen Finney
	Initial thoughts – open discussion session (All)
18:45	Close of briefing session

19:00 Pre-dinner networking

19:30 Dinner

Friday 10 October 2014	**Workshop**
8:00 – 9.00	**Breakfast**
9:00 – 9:10	**Recap: Goals of the workshop and format for the day** – Steve O'Rahilly and Hugh Perry
9:10 –10:20	**Session 1: Gut/brain communication, including how bariatric surgery works** **Session Leads: Fiona Gribble & Carel Le Roux**
10:20 – 10:40	**Tea & coffee break**
10:40 –11:50	**Session 2: Neuronal mechanisms of energy homeostasis, hypothalamus/brainstem** **Session Leads: Giles Yeo & Julian Mercer**
11:50 –13:00	**Session 3: Hedonic, behaviour, addiction and higher cognitive function, including brain imaging** **Session Leads: Paul Fletcher & Sadaf Farooqi**
13:00 – 14:00	**LUNCH**
14:00 –15:10	**Session 4: Novel therapies and drug targets** **Session Leads: Stephen Bloom & Lora Heisler**
15:10 – 15:40	**Discussion session**: Review of key priorities **Session Leads: Fiona Gribble & Giles Yeo**
15:40 – 16:00	**Further consideration of key priorities and tea break**
16:00 – 16:30	**Review and next steps – Steve O'Rahilly and Hugh Perry**
16:30	**CLOSE OF MEETING**

MRC Neuroscience of Obesity Workshop
Thursday 9 & Friday 10 October 2014, Wellcome Trust Conference Centre, Hinxton

Workshop participants

Name	Organisation
Dr Maria Adams	MRC Metabolic Diseases Unit, Cambridge
Professor Mike Ashford	University of Dundee
Dr Rachel Batterham	University College London
Professor Sir Stephen Bloom	Imperial College London
Dr Clemence Blouet	MRC Metabolic Diseases Unit, Cambridge
Professor John Blundell	University of Leeds
Professor Denis Burdakov	King's College London
Mr Luke Burke	WT/MRC Institute of Metabolic Science , Cambridge
Professor Simon Carding	UEA Norwich Medical School & The Institute of Food Research
Professor Pete Clifton	University of Sussex
Dr Tony Coll	MRC Metabolic Diseases Unit, Cambridge
Professor Roger Cox	MRC Harwell
Professor John F. Cryan	University College Cork
Professor Suzanne Dickson	The Sahlgrenska Academy at the University of Gothenburg, Sweden
Professor Fran Ebling	University of Nottingham
Professor Sadaf Farooqi	WT/MRC Institute of Metabolic Science, Cambridge
Dr Karen Finney	MRC Head Office London
Professor Paul Fletcher	University of Cambridge
Professor Gary Frost	Imperial College London
Dr Emily Gale	MRC Head Office London
Professor Fiona Gribble	MRC Metabolic Diseases Unit, Cambridge
Professor Lora Heisler	Rowett Institute of Nutrition and Health, Aberdeen
Professor Carel le Roux	University College Dublin
Professor Gareth Leng	University of Edinburgh
Professor Simon Luckman	University of Manchester
Dr Julian Marchesi	Cardiff University/Imperial College London
Professor John McLaughlin	University of Manchester
Dr Joe McNamara	MRC Head Office London
Professor Julian Mercer	Rowett Institute of Nutrition and Health, Aberdeen
Ms Kim Mugford	MRC Head Office Swindon
Dr Kevin Murphy	Imperial College London
Professor Sir Stephen O'Rahilly	MRC Metabolic Diseases Unit, Cambridge
Professor Susan Ozanne	MRC Metabolic Diseases Unit, Cambridge
Professor Hugh Perry	University of Southampton *Chair MRC Neurosciences & Mental Health Board*
Arianna Psichas	WT/MRC Institute of Metabolic Science, University of Cambridge
Dr Frank Reimann	MRC Metabolic Diseases Unit, Cambridge
Professor Wim Saris	Maastricht University
Dr Stefan Trapp	University College London
Dr Mark Ungless	MRC Clinical Sciences Centre, London
Dr Agatha van der Klaauw	University of Cambridge – Metabolic Research Laboratories
Professor Dominic Withers	MRC CSC Imperial College
Dr Giles Yeo	MRC Metabolic Diseases Unit, Cambridge
Dr Hisham Ziauddeen	WT/MRC Institute of Metabolic Science, University of Cambridge

MRC Workshop—Neuroscience of Obesity

Session leads

Professor V Hugh Perry

Hugh Perry was appointed Professor of Experimental Neuropathology at the University of Southampton in 1998. His research interests are in the field of interactions between the immune system and nervous system, and in particular how systemic infection and inflammation play a role in driving the progression of neurodegenerative disease.

He has published more than 300 peer-reviewed papers. He has sat on research advisory and funding panels for a number of different groups and chaired the Cellular and Molecular Neuroscience panel of the Wellcome Trust 2004-2007. He has acted as a consultant for biotechnology and pharmaceutical companies in the area of neuroinflammation and neurodegenerative disease.

He was elected a Fellow of the Academy of Medical Sciences (2005), was a member of the Nuffield Council on Bioethics (2006-2012) and recipient of a Royal Society Wolfson Research Merit Award (2011). He is currently Chair of the MRC Neurosciences and Mental Health Board.

Professor Sir Stephen O'Rahilly

Stephen O'Rahilly is Professor of Clinical Biochemistry and Medicine at the University of Cambridge and Honorary Consultant Physician at Addenbrooke's Hospital. He is co-director of the Wellcome Trust-MRC Institute of Metabolic Science and Director of MRC Metabolic Diseases Unit. His research has been concerned with the elucidation of the basic causes of obesity and Type 2 diabetes at a molecular level and the translation of those discoveries into improved diagnosis and therapy for patients. His work has uncovered several previously unrecognised genetic causes of these diseases including some that are amenable to specific treatment. He remains active in clinical practice and in the teaching of medical students.

He has contributed more generally to UK science through Chairmanship of the Wellcome Trust Clinical Interest Group, the Medical Research Society and the MRC Translational Research Overview Group. He is a former member of the MRC Strategy Board, has served on the research advisory committees of several charities and companies and is President of the Society for Endocrinology.

He has won many national and international awards including the Heinrich Wieland Prize, the Inbev Baillet Latour Prize and the Zülch Prize. He was elected to the Royal Society in 2003, a Foreign Associate of the National Academy of Sciences USA in 2011 and is an Honorary Member of the German Society for Internal Medicine. He was appointed a Knight Bachelor in 2013.

Professor Sir Steve Bloom

Steve Bloom received his undergraduate medical training at Cambridge University. His house officer, senior house officer and registrar posts were largely undertaken at The Middlesex Hospital where he also received his MRC Clinical Research Fellow training. He moved to the Royal Postgraduate Medical School at Hammersmith Hospital in 1974 where his roles have included Senior Lecturer (Consultant Physician), Reader in Medicine, Chairman of the Higher Degrees Committee and Academic Board, Professor of Medicine (Honorary Consultant Physician), Director of the Endocrinology Clinical Service and Deputy Director, Department of Medicine, Director of Chemical Pathology (renamed Metabolic Medicine and later Investigative Medicine), Chief of Clinical Service Chemical Pathology and Chief of Service Endocrinology and Diabetes. Having stepped down from his 10 year tenure as Head of Division of Investigative Science in 2007, Steve now holds a dual role within Imperial College London as Head of Division of Diabetes, Endocrinology and Metabolism and Chair of the academic Section of Investigative Medicine, and also as Head of Clinical Chemistry at Imperial College Healthcare NHS Trust.

His research work over the years falls into five related categories: endocrinology clinical research, physiology and pathology of gut hormones, control of insulin release and insulin resistance, role of neuropeptides in organ control and the role of neuropeptides in CNS regulation of appetite and related hypothalamic functions. He currently leads a research group investigating hypothalamic appetite control systems and gut hormones. This group's discovery that oxyntomodulin reduces appetite offers a potential new treatment for obesity and in 2005 Steve co-founded spin out company 'Thiakis Ltd' to commercialise these findings. In 2008 Wyeth Pharmaceuticals successfully acquired Thiakis for a reported £150 million.

He has published over 1000 papers (excluding review articles). In the past Steve has been a member of the Main Scientific Board for AstraZeneca and advisory boards for Upjohn and Novartis.

In 2012 Professor Sir Steve Bloom was awarded a Knight Bachelor for Services to medical science. Steve has recently been elected a Fellow of the Royal Society of London for Improving Natural Knowledge.

Professor Sadaf Farooqi

Sadaf Farooqi qualified with Honours in Medicine from the University of Birmingham, being awarded the gold medal. After hospital posts in Birmingham and Oxford she moved to Cambridge to undertake a PhD. She identified the first single gene defect to cause human obesity in patients with a mutation in the leptin gene, published in Nature in 1997 and described their dramatic response to leptin therapy (NEJM 1999; SCIENCE 2007). As a Wellcome Trust Senior Clinical Fellow at the Institute of Metabolic Science in Cambridge, Professor Farooqi co-ordinates a programme of research into the genetic, molecular and physiological basis of human obesity. She has been invited to speak at numerous international meetings and has been the recipient of a number of awards in recognition of her contribution to Endocrinology including the Andre Mayer Award 2006 International Association for the Study of Obesity), the RD Lawrence Award 2007 (Diabetes UK), the Society for Endocrinology Medal 2012 and the European Society for Endocrinology Prize 2012.

Professor Paul Fletcher

Paul Fletcher trained in medicine and psychiatry before taking a PhD in cognitive neuroscience. He was elected to the Bernard Wolfe Professorship of Health Neuroscience, University of Cambridge, in 2008 and is also a Wellcome Trust Senior Clinical Fellowship in Clinical Science.

His research uses combinations of functional neuroimaging and psychopharmacological manipulations to explore the brain basis of disturbances in learning, inference, motivation and decision-making. Early work developing an understanding of the contributions of the frontal lobes to human learning were followed by a series of studies aimed at furthering understanding of dynamic brain responses during associative learning and characterising how alterations in these processes may underlie the suboptimal decision-making that is found in over-eating and obesity. He is especially interested in exploring how metabolic alterations may shift preferences and reward-related behaviours and how such shifts may be reflected in altered brain responses.

Professor Fiona Gribble

Fiona Gribble is Professor of Endocrine Physiology at the University of Cambridge Metabolic Research Laboratories and an Honorary Consultant in Clinical Biochemistry at Addenbrooke's Hospital. The primary interest of her research group is to understand the pathways underlying secretion of gut hormones, and their impact in diabetes and obesity. Her group specialises in the use of single cell recording techniques to dissect signalling mechanisms in enteroendocrine cells using transgenic reporter mice, and then follows the results through to assess the secretion and action of gut hormones in whole rodents and humans. Her work has been recognised by the receipt of the Lister Research Prize (2006), the Diabetes UK RD Lawrence Lecture (2008), the EASD Minkowski Prize (2010) and the Viktor Mutt Medal (2012).

Professor Lora Heisler

Lora Heisler holds a Chair in Human Nutrition at the Rowett Institute of Nutrition and Health, University of Aberdeen. Professor Heisler's laboratory investigates brain circuits regulating energy balance in an effort to identify new targets amenable to obesity pharmacotherapy. Professor Heisler was awarded her PhD from Tufts University, USA with supervisor Professor Robin Kanarek in 1997 where she investigated repurposing Selective Serotonin Reuptake Inhibitor Prozac for obesity treatment. Postdoctoral positions were held at the University of California, San Francisco USA with Professor Larry Tecott from 1997-99 and then Beth Israel Deaconess Medical Center, Harvard Medical School USA with Professor Joel Elmquist from 1999-2001. In 2001, Professor Heisler was promoted to Instructor and began her independent laboratory. Professor Heisler moved her group to the University of Cambridge, UK in 2004 to join the Department of Clinical Biochemistry with Professor Steve O'Rahilly and then obtained a tenured position in the Department of Pharmacology in 2007. In 2013, Professor Heisler's group relocated to the Rowett Institute of Nutrition and Health.

Professor Carel le Roux

Carel le Roux graduated from medical school in Pretoria South Africa, completed his Senior House Officer training at St Bartholomew's Hospital, his Specialist Registrar training in metabolic medicine at the Hammersmith Hospitals and his PhD at Imperial College London. He was appointed as Senior Lecturer and later promoted to Reader at Imperial. He started his role as Chair as Head of Pathology at University College Dublin in 2012 where he now works within the Diabetes Complications Research Centre. He previously received a President of Ireland Young Researcher Award, Clinician Scientist Award from the National Institute Health Research in the UK, a Wellcome Trust Clinical Research Fellowship and an Anglo American Open Scholarship.

Professor Julian Mercer

With more than 20 years of experience in obesity-related research, Julian Mercer is currently Theme leader of Obesity and Metabolic Health research at the Rowett Institute of Nutrition and Health, University of Aberdeen, and a member of the Institute Executive Committee. He is currently a workpackage leader ('Consumer choice, diet and health') in the Scottish Government's 'Healthy, Safe diets' strategic research programme. He is also co-ordinator of the 'Full4Health' project ('Understanding food-gut-brain mechanisms across the lifespan in the regulation of hunger and satiety for health'; www.full4health.eu), and a partner in two further EU FP7-funded projects, NeuroFAST ('The integrated neurobiology of food intake, addiction and stress'; www.neurofast.eu) and SATIN ('SATiety Innovation'; www.satin-satiety.eu). He is currently Editor-in-chief of Journal of Neuroendocrinology.

Dr Giles Yeo

Giles Yeo is from San Francisco, receiving his bachelor's degree in Molecular and Cell Biology from the University of California, Berkeley. In 1994, he came to Cambridge joining the lab of Prof Sydney Brenner (Nobel Laureate 2002) for his PhD studies. In 1998 he began his post-doctoral training with Prof Sir Stephen O'Rahilly in the Department of Clinical Biochemistry, working on the genetics of severe human obesity. He was the first to report that mutations in the *melanocortin-4 receptor (MC4R)* and in the neurotrophic receptor *TRKB* resulted in severe human obesity. In 2007, Giles became Director of the core Genomics/ Transcriptomics facilities and a group leader at the University of Cambridge Metabolic Research Labs. Giles is also a graduate tutor and fellow of Wolfson College, Cambridge. His group is interested in studying the brain control of food intake and bodyweight, and how these might be dysregulated in obesity.

MRC Neuroscience of Obesity Workshop Pre-Workshop Survey Responses (List of all Priority Research Gaps submitted – no particular order)

Priority Research Gaps which, if addressed, would improve our understanding of this field
1. What other circuits and neurotransmitters are involved in regulating appetite and energy expenditure? We don't know if currently identified systems are just the tip of the iceberg or the major part.
2. What neurotransmitters are unique to appetite control and thus form a safe interventional pathway free of untoward side effects?
3. The importance of humoral and neural gut – brain communication in relation to satiety
4. Role of the microbiome in neural gut – brain activity
5. Identify the importance of the conjoint action of 'satiety' gut hormones on appetite, as opposed to their single independent actions
6. Develop an advanced methodology for human studies to characterise the relationship between 'in vivo' postprandial peptide profiles and the expression of appetite
7. Melanocortin neurons are believed to be a site of hunger signals and the MC4-R are seen to be a critical step. What are the signals of nutritional need or energy requirements that are being picked up by the MC neurons?
8. Recent findings have identified roles for fat mass (lipostatic hypothesis) and fat-free mass in the control of human appetite. What are the neural mechanisms that detect and transform information from these two components of body composition and energy metabolism?
9. Why do obese people have attenuated satiety after a meal?
10. Why does weight loss result in such a profound increase in hunger?
11. Control of gut-brain reflexes by the dorsal vagal complex
12. Interactions between brainstem and higher brain areas
13. FGF21 in periphery to brain metabolic signalling
14. Hypothalamic actions of thyroid hormone
15. How effective can 5-HT promoting drugs be in the treatment of obesity?
16. What is the role of dopamine in obesity?
17. Whether gut hormone systems can be practically exploited to treat obesity
18. Whether beneficial effects of anorectic gut hormones can be separated from their unwanted side effects
19. Mechanism of action of bariatric surgery
20. Understanding the neuroscience of the anorexia-nausea-vomiting continuum
21. Understanding the signals generated by food. What are the pathways that lead to appetite suppression post prandially?
22. The interplay between the hypothalamus and higher centres
23. While it is widely acknowledged that common obesity is a heterogeneous syndrome, is it possible to identify phenotypes or endophenotypes that could inform more targeted mechanistic research and therapeutic strategies?
24. How does the brain integrate the various central and peripheral signals to control episodes of food intake?
25. Which members of the microbiota are capable of influencing satiety and gut hormones and how they do this?
26. What is the mechanism by which the microbiome controls and communicates with the brain?
27. Understanding of mechanisms by which obesity during pregnancy influences the risk of obesity in the offspring
28. Identification of the critical time windows during which early nutrition can influence obesity risk across the life-course
29. Obesity-induced changes in microbiome-altered brain-immune function

Priority research gaps which, if addressed, would improve our understanding of this field (cont.)
30. Central/hypothalamic neuron bioenergetic re-programming by a chronic high fat/sugar diet
31. Clarify the neural mechanisms underlying dysregulated energy and glucose homeostasis in obesity and type 2 diabetes
32. Clarify the circuitry coordinating glucose homeostasis and the consequence of prolonged positive energy balance and obesity on insulin sensitivity
33. Role of autonomic nervous system and enteric nervous system in metabolic disease
34. How does post-prandial release of satiety signals translate into neuronal activity: circulation vs. lymphatic vs. neuronal (e.g. vagal)?
35. Further investigation of extra-hypothalamic forebrain sites in the modulation of feeding behaviour – especially the ventral tegmental area and its projections, hippocampus and prefrontal cortex
36. Further investigation of brain ➧ gut communication, which is much less well understood than gut ➧ brain communication
37. Impact of the microbiota on brain function (with respect to metabolic control)
38. Altered food preference after RYGB surgery: a role for gut hormones?
39. Functional physiology of the enteric nervous system – its role in sensing and communicating inputs from the intestinal microbiota to the CNS to affect central metabolism
40. Mechanistic understanding of cross-kingdom cross-talk in the GI-tract and its significance to host metabolism
41. The mechanistic basis of food choice and food preference
42. Timing and patterning of food and energy intake
43. Discriminating the neural networks that regulate appetite from those that regulate metabolism and glucose homeostasis
44. Understanding where and how appetite regulating hormones access the brain
45. What natural neural signals initiate and terminate eating (on the time-scale of decision-making, seconds/milliseconds)?
46. How does the brain estimate/misestimate what is right/wrong to eat?
47. Pharmacological activation of neurochemically defined populations of cells to elucidate critical populations implicated in drug effects
48. The exploration of additive/synergistic effects upon dual compound therapy administration
49. Establishing the role of different gut hormones in fasting, post-prandial and post bariatric surgical metabolism and appetite/satiety
50. How multiple metabolic signals are integrated to regulate behaviour and metabolism
51. How multiple behavioural and metabolic effectors of energy balance are coordinated
52. Can food composition really be changed to affect longer term food intake by neuroendocrine mechanisms?
53. Is psychology/hedonics within the current social and abundant environment all that matters….. forget gut-brain biology??
54. What are the key factors that shift choices from immediate, short-term rewards (e.g. taste) to delayed, longer-lasting rewards (e.g. health)?

MRC Neuroscience of Obesity Workshop Pre-Workshop Survey Responses (List of all Key Issues submitted – no particular order)

Key issues/areas which, if addressed, would enable progression in the field
1. Global assessment of all changes associated with hunger/satiety and energy regulation by feeding, using a number of approaches
2. Role of diet (e.g. probiotica) in gut-brain communication
3. Experimental devices such as sleeves and pacemakers to stimulate gut – brain action to increase satiety
4. Identify and distinguish the 'satiety' functions of gut hormones from their other functions in managing the digestion and absorption of nutrients in the GI tract
5. Does a true 'satiety' function of gut hormones really exist?
6. How is it possible to reconcile findings in the field of human energy balance and appetite control with the neuroscience models and (largely) animal data sets that inform the postulated brain mechanisms?
7. The mechanisms by which bariatric surgery increases satiety and reduces hunger
8. Improving interventions that can result in weight loss maintenance
9. Funding to allow the generation of specific transgenic mouse models
10. Realistic funding to allow cutting-edge basic research
11. Are obese states FGF21 responsive? The value of rodent models
12. Plasticity of the adult hypothalamus - do peripheral hormones or diet programme structural change?
13. How far does obesity resemble 'addiction'?
14. What is the relationship between obesity and depression?
15. Effects of the manipulation of gut hormone release or chronic administration of combinations of anorectic gut hormones on body weight in the obese
16. Precise mechanisms/circuits by which peripheral gut hormones act to centrally regulate food intake
17. Mechanism underlying the co-ordination of gut hormone release
18. How gut hormones influence central appetitive pathways
19. Improvement in tools for human research
20. Improvement in metabolic imaging in humans
21. The impact of our environment (the built environment as well as other stimuli such as advertising) on food intake
22. Changing the focus of, and the regulatory standards for, anti-obesity therapeutics
23. The value of microbiome wide association studies vs. significant investment in GWAS studies which fail to make headway in major diseases
24. The need for a clear MRC strategy on how to fund microbiome research
25. Identification of loci within the genome which are susceptible to epigenetic modification in response to diet during critical periods of development
26. Determination of the metabolic parameters associated with obesity during pregnancy that lead to programming of obesity risk in the offspring
27. Understanding better the bi-directional brain/hypothalamus - immune cell functional links
28. Increased understanding of brown adipose tissue bioenergetics

MRC Neuroscience of Obesity Workshop Pre-Workshop Survey Responses (List of all Key Issues submitted – no particular order)

Key issues / areas which, if addressed, would enable progression in the field (cont.)
29. Delineation of the neurocircuitry regulating appetite and energy expenditure to identify points amenable to pharmacological intervention for obesity and type 2 diabetes treatment
30. Clarify how dysregulated energy balance is established and maintained to promote the development of obesity and type 2 diabetes
31. Tool development/core facilities: good antibodies for g-protein coupled receptors and for ion channels, viral vectors
32. A further move away from viewing obesity as the result of dysregulated homeostatic mechanisms, and instead emphasising the role of reward and decision making processes in modulating feeding behaviour
33. Clarification of the concepts of 'food addiction' versus 'feeding addiction' and their importance for obesity
34. Role of gut-brain signalling in weight loss maintenance in the post-obese state. Do gut hormones have potential as a therapy?
35. Integration of immune-neural-endocrine derived cell signalling in the intestinal epithelium in response to microbiota and food derived stimuli
36. New model systems to interrogate the complexity of GI-tract homeostasis and the network of different cellular components that influence host metabolism; better integrative models of human obesity to better define the relative contribution endogenous versus exogenous factors play in its aetiology
37. Addressing progression towards overweight and obesity rather than obesity treatment, including behaviour change
38. Are there GWAS genes or rare obesity mutations that can give novel insight into mechanism; do we have the right animal models and phenotyping/physiology tools to investigate mechanism in vivo?
39. Is the effect of bariatric surgery on T2D-mediated by the gut-brain axis, or is the rapid effect on glucose a peripheral effect (reduced fat in key organs and/or impact on islet function)?
40. How to maintain a (healthy) steady-state in an uncertain world is the key general question in obesity research. There are useful answers/insights to this question in other fields (engineering, psychology, economics). We need to address the problem of the different disciplines not "comparing notes" on this general question.
41. We need better ways to measure function of genetically-defined brain neurons at the time-scale relevant to obesity prevention – i.e. seconds for blood glucose control, hormone secretion, and food selection
42. The physiological underpinnings of weight loss following bariatric surgery
43. How to make foetal programming data relevant to pregnant mothers and their lifestyle choices
44. Establishing whether the endogenous pool of gut hormones could be exploited for the treatment of diabetes/obesity, and if so, which pool
45. Need for tools to manipulate subpopulations of brain cells (not just electrical activity but also specific signalling pathways) in a spatio-temporal controlled manner
46. A centre with capacity for brain imaging in the very obese, ideally not supine, would be a vital core facility
47. Very large prospective cohorts with detailed metadata including microbiota sequentially resampled
48. What are the key factors that shift choices from immediate, short-term rewards (e.g. taste) to delayed, longer-lasting rewards (e.g. health)? Given that these factors are likely to operate at many levels, from the molecular to the cognitive to the environmental, how can we establish an integrated scientific approach to characterising, exploring and modifying them?