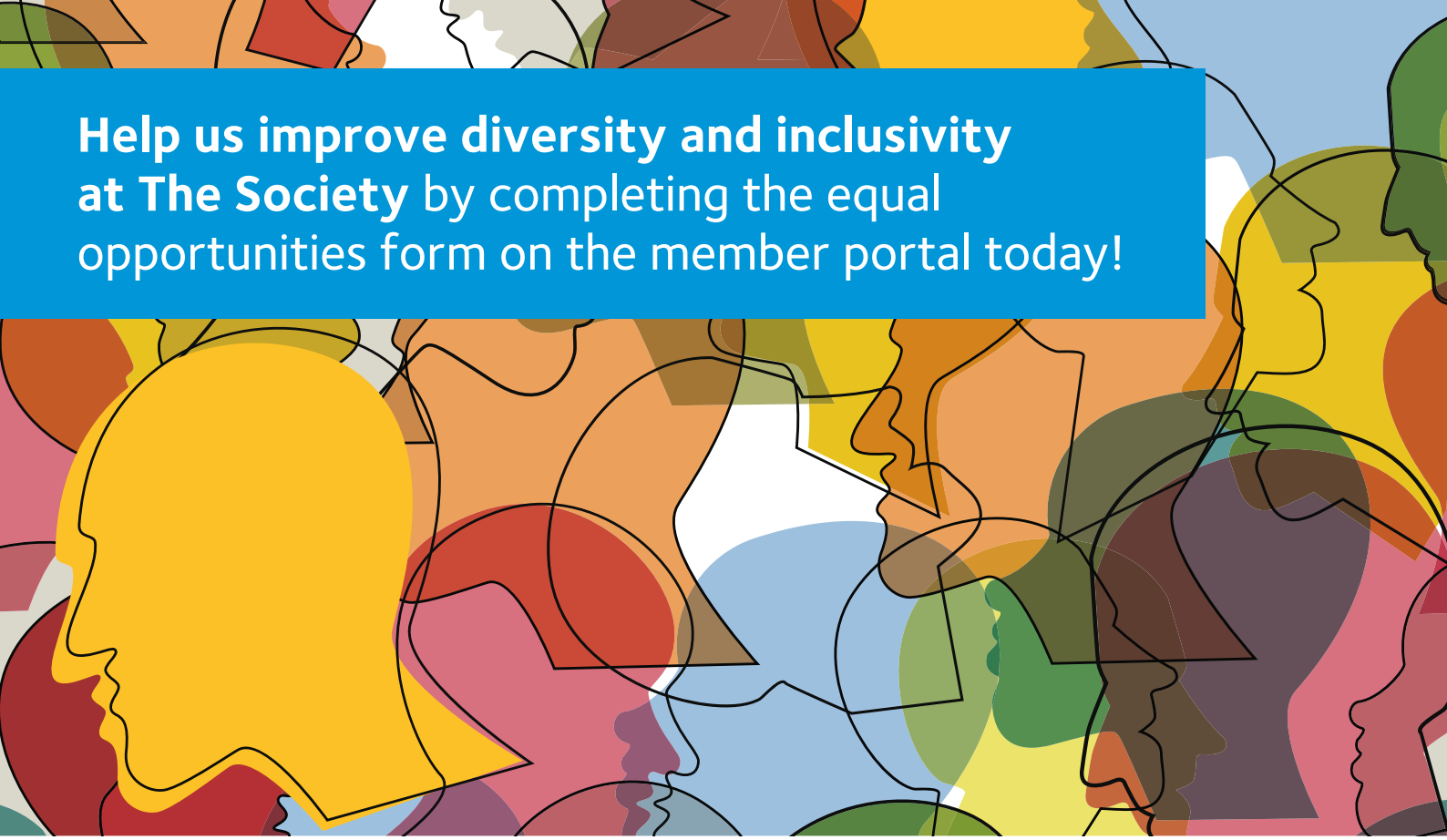
PN
Physiology News

Issue 111 / Summer 2018

Attitude at altitude

The logistical, personal and scientific challenges of high-altitude research

The Physiological Society



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The Physiological Society

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Physiology News

We welcome feedback on our membership magazine, or letters and suggestions for articles for publication, including book reviews, from our Members.
Please email Julia Turan at **magazine@physoc.org**

Physiology News is one of the benefits of membership, along with reduced registration rates for our high-profile events, free online access to our leading journals, *The Journal of Physiology*, *Experimental Physiology* and *Physiological Reports*, and travel grants to attend scientific meetings. Membership offers you access to the largest network of physiologists in Europe.

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Welcome to the Summer 2018 edition of *Physiology News*

Introduction

News & views

Policy Focus

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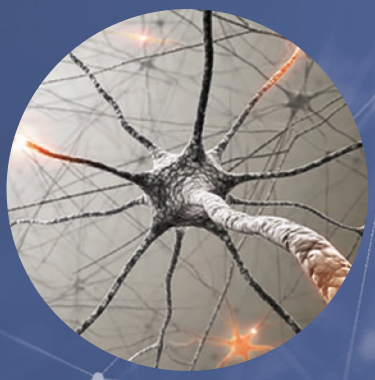
Features

Membership

Cover image: Photo of the late Chris Willie, a postdoctoral fellow at the University of British Columbia, just after completing a maximal exercise test at the top of the Ev-K2-CNR pyramid laboratory.

Love to sleep? Come and find out about the mechanisms that regulate your sleep and body clock, and what happens when they go wrong.



Join us to solve the many exciting, unanswered questions in sleep science.

Sleep, synaptic homeostasis, and neuronal firing rates
Chiara Cirelli, Wisconsin Institute for Sleep and Consciousness, USA

Genes and neurons that regulate sleep in zebrafish
Jason Rihel, University College London, UK

Neural networks and sleep
Vladyslav Vyazovskiy, University of Oxford, UK

Submit your oral communication or poster from 1-30 September.
Find out more and register at: **www.physoc.org/sleep_circadian**

The Physiological Society

Sleep and Circadian Rhythms from Mechanisms to Function
5-6 December 2018
Barbican, London, UK

Introduction to your Editors

Under the new framework for *PN*, primary responsibility for the content of *PN* is divided between the Scientific Editor, who curates the academic and physiologically focused pieces, and Managing Editor, who highlights the activities of Society members/staff and oversees overall production of *PN*. Both work together with the support of the editorial board to produce an exciting issue of *PN* each quarter.

Keith Siew *Scientific Editor*

Keith's first taste of The Society was as a physiology/pharmacology undergrad attending the 2009 Dublin meeting where he sat and read through his first copy of *PN*. Little did he know that he would eventually become a Council Affiliate Representative, serve on numerous committees, get on the *PN* Editorial Board and eventually become its youngest Scientific Editor. This all happened whilst attempting to finish an MSc in imaging, and PhD in medicine and start an international postdoctoral fellowship pursuing his passion for renal physiology and technological innovation. It is his hope to strengthen and modernise *PN* and give back to a Society which has given him so much.

Julia Turan *Managing Editor*

Julia triturated, pipetted, imaged, and analyzed, during her undergrad years studying neurobiology. Since then, she has shifted into the world of science communications, hoping to promote a language of science legible to all. She completed her MSc in Science Communication and Public Engagement at the University of Edinburgh.

In Spring of 1992, The Physiological Society Newsletter began an experiment. The scope of the Newsletter was to be expanded to include a broad range of articles on physiology, the activities of our members and political commentary of the academic scene. The result of this experiment was the eventual transmutation of a Newsletter into a Magazine and establishment of the rechristened *Physiology News* (*PN*) as a cornerstone of our community.

Physiology News is your magazine: it should reflect your diversity, satisfy your broad interests, celebrate your achievements and commemorate those no longer with us. Having thrived through several redesigns, relaunches and now 'under new management', the magazine at its heart has, and always will be, for the membership by the membership! However, as The Society continues to grow and the way we consume information changes, *PN* must also evolve to keep pace with a modern world.

The development of the new Society website, presents us with an opportunity to revamp *PN*, offering both old and new articles in dual format (webpage and hardcopy/PDF), improving shareability and searchability of content, as well as opening up the potential for supplementing the traditional hardcopy with embedded multimedia content (i.e. short videos and audio clips of authors and their work).

It is more important now than ever to not just simply be aware of, but to actually deliver on our environmental and social responsibilities. Going forward, The Society must lead by example, be that on position statements of best practice for data in research and publication (pg 16), or by printing on FSC-certified paper and shipping printed materials in potato starch-based plastic alternative packaging, like this and subsequent issues of *PN*.

Another key issue of our time is representation; simply put it matters! Our Society and discipline is diverse, and it was important for us to appoint a *PN* Editorial Board that not only reflected this diversity in terms of background knowledge but also gender, geography, career type and stage (pg 8-9).

Similarly, this issue of *PN* is no less diverse, with an article exploring the neuromuscular consequences of ageing that we all must face (pg 32-35), reminders of the lessons that can be learned from comparative physiology (pg 29-31) or those giving us rare insight into the real stories behind the research papers (pg 24-28). *PN* also serves as a place for us to challenge the status quo, with an article from our former Editor Bill Winlow on the propagation of the action potential (pg 38-42), and to make calls to arms, like our education and teaching theme leads identifying the salient issues in higher education (pg 36-37), innovations in education technology with 3D and virtual reality (pg 43) or the importance of starting healthy lifestyle education young (pg 46-47).

Another important function of *PN* is to provide an outlet for our members to express themselves. Thanks in large part to the previous editor, Roger Thomas, Letters to the Editor have seen a resurgence. We believe they are a healthy forum for discourse and provide a rare uncensored platform for one to pose questions or draw attention to that not often given the spotlight (Letter from Lamarck; pg 6-7). It is our hope that this tradition continues to live on during under our tenure, and we welcome your ideas and stories, so get in touch with pitches, as well as feedback about the magazine, at **magazine@physoc.org**

Finally, we'd like to thank Austin Elliott, who steps down at this year's AGM, for his service on the board since 2015.

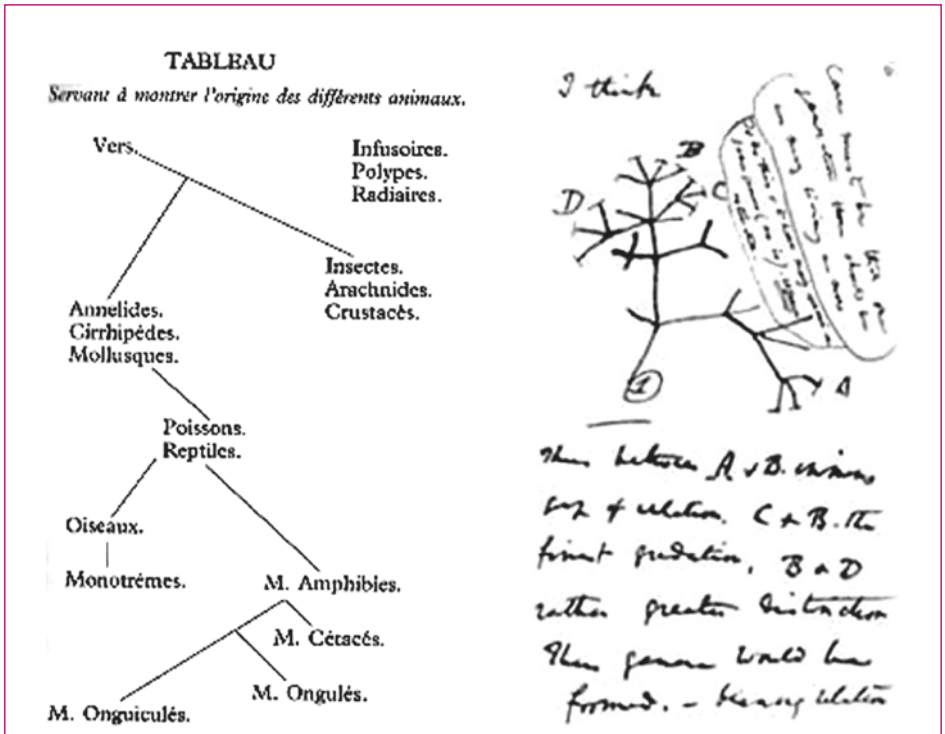
Lost in translation

Denis Noble
University of Oxford, UK

Eight years ago[1] *Denis Noble dreamt that he was the Editor of PN and had received a letter from Lamarck, which he imagined he had translated into English for readers of PN. Much has happened since then so it is not surprising that Jean-Baptiste Lamarck has appeared again in Denis' dreams over the New Year 2018.*

Jardin des Plantes, Paris, le 1 janvier 2018.

Monsieur le Rédacteur,
Puis-je profiter de votre Société la plus distinguée encore une fois...



Left: Lamarck's tree of life from the addition to *Philosophie Zoologique*, 1809. Right: Darwin's first sketch of a tree of life from his first notebook on transmutation of species (1837). Lamarck draws his tree from the root downwards. Darwin does so from the root upwards. But they clearly had the same idea.

May I use your most highly distinguished Society, and its eminent *Physiology News* magazine, once again to present my reflections on what has transpired since I last wrote a letter to you?

First I welcome the special issue of your *Journal of Physiology* devoted to *the integration of evolutionary biology with physiological science*.[2] I did not call myself a physiologist. After all, I had only just coined the word biology. But if your Society had existed in 1809 I would have loved to be a member, as was your great Charles Darwin at your foundation in 1876. We didn't call evolution 'evolution' in my day. 'Evolution' was the development of the embryo, itself a physiological (functional) process. Evolution in your modern sense was called transformationism. Charles Darwin praised me for championing the transformation of species against creationists like Cuvier.[3]

You rightly used the subtitle *physiology returns to centre stage* in the special issue. You physiologists understand the nature of function in biology. It is what distinguishes biology from physics. That is why I regarded biology as a separate discipline and introduced its name, *biologie* in my language, to emphasise that point. I also said that living organisms have innate tendencies, what I called 'le pouvoir de la vie'. Sadly, that phrase earned me the misunderstanding that I was a kind of vitalist. That is far from true. I vigorously opposed the vitalism of Bichat and other vitalist physiologists of my day.[4]

I note with pleasant surprise that your Society's bold initiative was followed two years later by your national academy, The Royal Society, which, in collaboration with The British Academy, organised a meeting on *New Trends in Evolutionary Biology*, now also published in a special journal issue.[5] Pleasant for me because after the withering attack on me at my funeral by Georges Cuvier[6] I imagined that my reputation could never recover.

Those two magnificent volumes of British journals have done much to reassure me that not all is lost. So, why am I writing this letter to you? There are still two other matters on which I would like to correct the historical record. These are the inheritance of acquired characteristics and the famous 'tree of life'.

When I am referred to at all in your evolutionary biology textbooks, I am usually a figure of ridicule. It is not widely understood that Charles Darwin agreed with the inheritance of acquired characteristics and

[1] Notes by Denis Noble (2010). *Physiology News* **78**, 31.

[2] The integration of evolutionary biology with physiological science(2014). *Journal of Physiology* **592**, 2237–2438.

[3] Preface to the fourth edition of *The Origin of Species* (1866).

[4] This is very clearly explained in André Pichot's introduction to a reprint of *Philosophie Zoologique*. Flammarion, Paris, 1994. 'Philosophy' was synonymous with 'science' in Lamarck's time. Hence the journal title 'Philosophical Transactions of the Royal Society'.

[5] New trends in evolutionary biology: biological, philosophical and social science perspectives (2017). *Interface Focus* **7**(5).

[6] http://www.victorianweb.org/science/science_texts/cuvier/cuvier_on_lamarck.htm

[7] This theory is formulated in Darwin's later book: *The Variation of Animals and Plants under Domestication* (1868).

[8] Spadafora (2017), Sperm-mediated transgenerational inheritance. *Frontiers in Microbiology* **8**, 2401. DOI: 10.3389/fmicb.2017.02401. eCollection 2017. Spadafora concludes: 'On the whole, this phenomenon is compatible with a Lamarckian-type view and closely resembles Darwinian pangenesis.'

[9] It is true that the bulk of *Philosophie Zoologique* fits the view he is expressing, but he made a late addition at the very end of the book that already contains the essence of the tree viewpoint. In the Flammarion reprint of *Philosophie Zoologique* there is a diagram on page 649 that must rank, as Gould says, as the first construction of an evolutionary tree. Lamarck even writes 'In its production of the different animals, nature has not fashioned a single and simple series.' (Gould's translation). See Fig. 1, left. Darwin's first tree sketch is shown on the right. I doubt whether Darwin knew of Lamarck's conversion to branching trees.

[10] 'In its production of the different animals, nature has not fashioned a single and simple series' (Gould's translation)

[11] Lamarck JB (1820). *Système analytique des connaissances positives de l'homme*. pp. 134–148.

he even formulated a theory for how it could work. He called the objects of transmission from the soma to the germline 'gemmules'.[7] I had a similar idea. I called them 'subtle fluids'. The modern discovery of transmission of RNAs through the germline could surely achieve what he and I postulated.[8]

This is beginning to be understood. But there is something else highly important on which Darwin and I agreed. This is his famous 'tree of life': the branching network of development of new species from previous ones. By contrast, I am represented as believing that evolution was a single 'ladder of life', from simple to more complex, following my idea of le pouvoir de la vie.

It is true that this was my view when I wrote *Philosophie Zoologique* in 1809.[9] But as I further studied worms (remember that I was Professor of worms and insects at the Jardin des Plantes) I came to the clear conclusion that a single ladder could not be true. To use my terminology, the 'internal' worms (such as tapeworms) and 'external' worms (such as earthworms) could not possibly be fitted into a single ladder of life. In my 1815 *Histoire naturelle des animaux sans vertèbres*,[10] and again in my last book, *Système analytique des connaissances positives de l'homme*, published in 1820, I corrected this mistake.[11] Your great, and sadly lamented, evolutionary biologist Stephen J Gould clearly outlined the history of my ideas. After doing so, he concluded:

'how can we view his [Lamarck's] slow acknowledgement of logical error, and his willingness to construct an entirely new and contrary explanation, as anything other than a heroic act, worthy of our greatest admiration and identifying Lamarck as one of the finest intellects in the history of biology?'[12]

Veuillez accepter, cher Monsieur le rédacteur, l'expression de mes sentiments les plus distingués,

Jean-Baptiste Pierre Antoine de Monet, Chevalier de la Marck

Lamarck repeatedly uses the word 'branch': 'The polyps ... seem to divide into three branches'; '... the crustaceans come from another branch separate from the arachnids'; '... the reptiles ... another branch seems to lead to the lizards, towards the mammals' (my translations).

[12] Gould, SJ (2000). A tree grows in Paris: Lamarck's division of worms and revision of nature. In *The lying stones of Marrakech*. Harmony Books, Chapter 6. I am very grateful to Jonathan Bard, (author of *The Principles of Evolution, Systems, Species and the History of Life*, Garland Science, 2016) for drawing my attention to Gould's scholarly and insightful essay. In a review of Bard's valuable book I wrote 'The book I needed as a student and young researcher.' I still think that.

International relations

David Eisner

President, The Physiological Society

I am sure that all readers would agree that science is an international activity and should not be constrained by national borders. This point has been thrown into strong relief by worries over the consequences of Brexit for European funding as well as restrictions on overseas scientists coming to work in the UK. Members of The Society's Policy and Communications Committee and staff have joined with the rest of the scientific community to try to influence decisions in this area.

The Physiological Society has also been thinking about its own international relations. The Society is, of course, truly international. Our journals have international Editorial Boards and readerships. Indeed, of the three journals, only *Experimental Physiology* currently has an Editor-in-Chief residing in the UK or Ireland. Meetings have always been international; typically, more than a third of those attending our annual main meetings come from overseas. As regards our membership, 30% live overseas. Readers will not be surprised to learn that the country with the greatest number of members, after the UK, is the USA. What may be less expected is that Nigeria is the third most represented country with 51 members, more than Ireland (47).

The Society has long participated in joint meetings with overseas societies. For many years, up to about 2007, there were typically one or two such joint meetings every year. The number of such meetings has declined in recent years, perhaps an unintended consequence of the move to having one main meeting a year. For many years, members of The Society have participated in the meetings of the International Union of Physiological Sciences (IUPS), which meets every four years. The Society is also a member of the Federation of European Physiological Societies (FEPS). This September in London, will be the first in a series of Europhysiology meetings organised together with the German and Scandinavian Physiological Societies, and FEPS. The next meetings in this series will be held in Berlin (2020) and Copenhagen (2022). The Europhysiology meetings in Berlin and Copenhagen will constitute the annual meetings of The Society in those years.

In 1935, The Society established the post of Foreign Secretary, occupied until 1945 by AV Hill, who at the time was concerned about the plight of scientists at the hands of the Nazis (see *Physiology News* 106). Hill was succeeded as Foreign Secretary by ED Adrian, GL Brown and AL Hodgkin. In 2001, the post was renamed as the more politically correct 'International Secretary'. I was actually the last International Secretary as the post was abolished in 2007 with the idea that all of the activities of The Society had an international dimension and there was therefore no need to have a single role.

Concern has been raised recently at Council that current arrangements do not make it easy for us to coordinate our international activities. Simple questions include: how do we decide which countries and societies to interact with? How do we coordinate the international activities covered by journals, meetings, policy, education and membership?

A major aim of The Society's new strategy is to enthuse the public, in particular 16- to 25-year-olds, with physiology. Much of what we do occurs in the UK and Ireland. I have, however, been very impressed by activities carried out by our members in areas as far flung as Pakistan, South Africa and Canada. Should The Society be helping its members more with their engagement internationally? If so, are there countries we should prioritise in order to make best use of finite funds?

The Society is often approached for financial help with meetings organised by other societies, particularly those in developing countries. What criteria should be used to decide which of these to prioritise? To what extent should The Society make use of IUPS and FEPS for international activities as opposed to setting up its own bilateral links?

To address these, and other, questions, we have set up the International Working Group chaired by Stefan Trapp with the remit of making recommendations as to the way forward. I would like to encourage readers to send their thoughts to either Stefan (**s.trapp@ucl.ac.uk**) or myself (**eisner@manchester.ac.uk**).

An introduction to the Editorial Board

We're excited to introduce the new members of the Editorial Board, and welcome back long-serving ones. Members join us from around the world, bringing expertise across physiology, including research, education, clinical and industry backgrounds.

Peter Aldiss
University of Nottingham

I am a British Heart Foundation funded PhD student at the University of Nottingham. Having completed my undergraduate degree in Exercise, Nutrition and Health at Nottingham Trent University, my research is now focused on the role of diet, exercise and the environment in regulating brown adipose tissue metabolism. I am a member of The Physiological Society's Affiliate Working Group and the European Young Endocrine Scientists (EYES) committee where I hope to help advance opportunities for early career scientists. It is in this capacity that I joined the *Physiology News* Editorial Board where I represent early career researchers to ensure our voice is heard and our thoughts are expressed going forward.

Ronan Berg
University Hospital Rigshospitalet

I am an MD (2009) with a PhD in medicine (2014) and have been a member of The Physiological Society since I was a student. I currently serve as a clinical fellow in nuclear medicine at University Hospital Rigshospitalet in Copenhagen, Denmark, and I furthermore hold a five-year Visiting Professorship at the University of South Wales. My research focuses on the mechanisms of organ failure in critical illness, notably the effects of hypoxia and acute systemic inflammation on cerebral and pulmonary function, using both human experimental and clinical models. I am a dedicated medical teacher engaged in the development of innovative teaching strategies in cardiovascular and respiratory physiology, as well as medical ethics.

Mark Dallas
University of Reading

I have been a member of The Physiological Society since I started my PhD studies at the University of Leeds. After completing a successful Alzheimer's Research UK fellowship, I moved, in 2013, to take up a lectureship in neuroscience at the University of Reading. I have benefited throughout my career from membership of The Society through travel grants and also my first research grant. My research is looking at the ability of gasotransmitters to regulate ionic homeostasis within the brain. More recently, we are specifically interested in glial cells and their role in neurodegeneration. As well as being part of the *Physiology News* Editorial Board, I also serve as The Physiological Society's Neuroscience Theme Lead.

Karen Doyle
NUI Galway

I am a Senior Lecturer in Physiology and Principal Investigator. My research involves studying neurovascular stress and investigating novel strategies to protect brain tissue from damage. Within this, my focus is on understanding the pathophysiology of occlusive stroke and reperfusion injury. My research group investigate the characteristics of human blood clots that cause ischaemic strokes and the effect of reperfusion on the survival of brain tissue. I was leader of Galway Neuroscience Centre (2004–2009) and a former Vice President of Neuroscience Ireland (2007–2009). I also received the President's Award for Teaching Excellence in NUI Galway (2015) and the National Teaching Experts Award (2015), National Forum for the Enhancement of Teaching and Learning in Higher Education (in Ireland). I have been a member of The Physiological Society since 2002 and have enjoyed making a contribution to The Society by serving on the Editorial Board of *Physiology News* since 2015.

Fiona Hatch
Cello Health Communications iScience, Medical writer

I completed my undergraduate degree in Biological Sciences at the University of Bristol and I went on to do a PhD in cardiology in the field of calcium signalling and ageing at the University of Hull. Since completing my PhD in 2013, I worked as a postdoctoral researcher at the University of Surrey focusing on intracellular signalling, atrial fibrillation and left ventricular hypertrophy. At this point, I decided to move away from academia and journeyed into the world of medical communications. I now work for Cello Health Communications, an agency that provides medical writing and management assistance to pharmaceutical companies. During my PhD and postdoctoral positions, I was an active Physiological Society member and sat on the Education and Outreach Committee and the Policy Committee. I recently joined the *Physiology News* Editorial Board in 2017 and I hope to provide an industry-based perspective to the magazine going forward.

Philip Lewis
University Hospital of Cologne

I hold a BSc in physiology from University College Dublin, a PhD in physiology from University College Cork, and have been employed as a postdoc at the University Hospital of Cologne (Germany) for about a year and a half. I first joined The Society as an undergraduate, and it has given so much to me since: opportunities to present work at Society meetings, visit other laboratories to learn techniques, and meet countless Society members who bring fascinating research and enthusiasm to our field. It is a privilege to be part of the new *Physiology News* editorial board and to give something back. My research interests are broad – as a PhD trainee I worked on skeletal muscle functional and molecular adaptation to hypoxia in animal models. I now research chronobiology and sleep contributions to health and disease in humans.

Dervla O'Malley
University College Cork

I am a Lecturer and Principal Investigator in the Department of Physiology and the APC Microbiome Institute, University College Cork, Ireland. My research is focussed on investigating the role of enteroendocrine L-cells in cross-barrier translation of microbial signals to the host nervous system. I have also received funding from the Irish Health Research Board to investigate cognitive dysfunction in neuromuscular disorders. I joined the *Physiology News* Editorial Board in order to become more involved with The Physiological Society, which has supported my career since I was a postgraduate student. I believe *Physiology News* has an important role in keeping members up to date with society activities and the latest physiological research. Also, as a scientist in the Republic of Ireland, I hope to offer a diverse viewpoint, to enrich the publication and broaden its appeal.

Katherine Rogers
Queen's University Belfast

I am a Senior Lecturer in the School of Nursing and Midwifery at Queen's University Belfast, Northern Ireland. I teach on a wide range of bioscience modules in undergraduate and postgraduate courses. My doctoral thesis was in cell signalling and pharmacotherapeutics in molecular oncology. While I still maintain an interest in this field, my current research focuses on bioscience education and, in particular, innovative pedagogical methods to make science more accessible and engaging for students on health-related degree programmes in higher education. The Physiological Society has been very supportive to me in my academic career, so I joined the *Physiology News* Editorial Board to become more involved with The Society and to help make physiology more engaging to a wider audience. I hope that my involvement with the Editorial Board will help to further publicise *Physiology News* and to increase the readership to a wider audience, particularly among higher education students and postgraduates.

Lalarukh Haris Shaikh
Palantir Technologies

I became a member of The Physiological Society during my PhD in Medicine from the University of Cambridge, which was funded by the British Heart Foundation. As an Affiliate Member of The Society, I really enjoyed learning about physiology sub-disciplines that were different from mine and were featured throughout *Physiology News*. I felt this made my own research more innovative. After a postdoc investigating drug targets for primary hyperaldosteronism due to secondary hypertension, I decided to move towards industry where I am now leading pharmaceutical, healthcare and finance initiatives using data to power decisions such as the top few drug targets that are most likely to make phase I of a clinical trial.

Alongside my current role, I also co-founded and currently sit on the executive board of a mental health charity that aids in reintegrating patients who suffer from mental illness back into mainstream society.

Christopher Torrens
University of Southampton

I am an Associate Professor in Physiology at the University of Southampton. I am a vascular physiologist by training and started off my career between the Placental & Perinatal and the Microvascular & Endothelial areas of physiology. As my career has progressed I have become more involved in teaching and so I am now most likely to be found in the Vascular & Smooth Muscle as well as the Education & Teaching Themes. I joined The Society in 2001 during my PhD. Since then, I have been a Society Representative, served on the Education & Outreach Committee and became a Fellow Member in 2017. Throughout my time as a member, I have always read *Physiology News* and its diverse output of news, research and members' views. Now, as a member of the Editorial Board I want to ensure it continues to promote physiology, The Society and the great work done by our members.

Want to contribute to *Physiology News*?

We welcome pitches including cutting edge science, historical pieces, personal stories about careers in physiology, book reviews, and policy or education-related topics. Get in touch at **magazine@physoc.org** with a preliminary title, a sentence or two summarising the focus of the article and a brief list of a bullet points summarising the various sections, like a short outline.

Reports of The Society's recent Committee meetings

The purpose of these short updates is to keep you informed about the work of our Committees. The following summaries detail the meetings of the past few months.

Council

The main points of business at the March Council meeting included a presentation from the Head of Technology and Infrastructure on the *General Data Protection Regulation*. All organisations are required to be compliant with the incoming legislation by 25 May 2018, otherwise large fines could be faced. It was noted an external auditor had been engaged and had met with key members of staff to review The Society's data asset registers and understand key data handling processes. Recommendations would be reviewed and implemented to ensure The Society was compliant and Trustees would receive a full update in May.

The Chief Executive highlighted that The Society had submitted evidence to the Brexit Science and Innovation Summit which had been published on the Science and Technology Committee (Commons) website. The Society had then been invited to take part in the Science and Technology Committee's Brexit Science and Innovation Summit on 22 February.

Trustees approved the Strategy 2018–2022 – a copy of which has been sent to members. It was agreed that the next steps are for the Chief Executive and the senior management team to develop a road map that will set out what steps are needed to achieve the goals and objectives. Going forward, this will inform staff objectives including key deliverables and would be reported to Council on a regular basis so that progress against the strategy could be assessed over time.

Another important point of business included an update on the Governance Review. The purpose of the Governance Review is to provide an independent assessment of The Society's current governance arrangements, taking into account best practice and The Society's Strategy 2018–2022, and to make recommendations for improvements. Lucy Carter, Director of Wellspring Consulting has been engaged to carry out the review.

Council also approved the appointment of Matt Taylor as The Society's first External Trustee. Matt will take up his role of Trustee at The Society's AGM. Matt has a background as a business strategist and has experience in income diversification and sustainability. His undergraduate degree was in Human Sciences, first class, and he went on to undertake an MSc in Medical Anthropology, which demonstrates his personal engagement with physiology.

Finally, Council formally prescribed the 2018 Annual General Meeting to be held on Sunday 16 September, 12:45, at QEII Centre in London.

Education & Outreach Committee

The Society's new Strategy for 2018–2022 formed much of the focus of discussions at the Education and Outreach Committee meeting in April. It was agreed that most of the Committee's existing initiatives remain relevant in the context of the new strategy, but that a few aspects may need to be refocused. In particular, The Society's Public Engagement work will be redefined by targeting funding more specifically. Further details about these new grants will be released in 2019.

With a growing strategic focus on careers, the Committee agreed that a research project into how students decide to study physiology at University and the career pathways open to them after graduation will help to inform future activity. While this project is being scoped out, it was agreed that the existing 'Understanding Life' booklet should be refreshed so that The Society has an up-to-date careers resource ready for dissemination by Physiology Friday!

There was much discussion surrounding higher education policy, including a potential collaboration with the Institute of Physics, Royal Society of Chemistry and the Royal Society of Biology, on a STEM-wide questionnaire for academics across all career pathways; this work would support The Society's previous efforts on the reward and recognition of teaching in higher education.

The Committee also received a report on the Physiology MOOC that was held in 2017 and was pleased to note that over 8,000 participants enrolled on the course; it was reported that a second run took place in late spring 2018.

Finance Committee

At their April 2018 meeting, the Finance Committee received the Audit report from Audit Partners Haysmacintyre and approved the draft Trustee Annual Report for recommendation to Council. The Committee agreed some amendments to the Investment Policy Statement which would allow Cazenove Capital Management some further flexibility to maximise returns. The Committee received an update on the financial agreements for Europhysiology 2018 and 2020 and discussed the risk exposure to The Society. The Committee also received an update on the identified key risks facing The Society and the associated mitigation processes and recommended actions; this will be reported to Council.

History & Archives Committee

The History & Archives Committee met on 23 April. It discussed plans to host a public symposium this year on the impact of the First World War on physiology and biomedicine. Appropriate venues, dates and speakers are now being researched. The Committee welcomes anyone with a keen interest in this area to make themselves known to The Society's staff. It also discussed how best to maintain accurate records for The Society's archives and, in particular, how to note Honorary Members. As a result, the Committee revisited the important need for a Grey Book. To this end, it received an update regarding the plans for a new Society website. The Committee remains especially keen that the site should provide an accessible platform for The Society's impressive archives and historical resources.

Meetings Committee

The Meetings Committee agreed on its immediate priorities for 2018–2019 following the publication of The Society's five-year strategy. Key components include providing a range of scientific meetings that support knowledge exchange and networking and meet the needs of today's researcher, both members and the wider community, with an appropriate geographical spread. We will ensure excellence in all of the programmes and content we offer by setting rigorous processes for selection.

The recipients of the 2019 Prize Lectures were agreed for Annual Review, GL Brown, Hodgkin-Huxley-Katz, R Jean Banister and Joan Mott. The call for Sharpey-Schafer will reopen as in 2019 this lecture should be given by an established physiologist.

To build on the initiatives already in place to support early career researchers, the committee agreed to hold 'Future Physiology' annually from 2020 and also reinstate poster competitions at the annual conference.

Finally it was agreed that satellite meetings be held around Physiology 2019, not only to increase the scope of physiology being presented at the annual conference but also to give members the opportunity to host a one-day meeting. The call for this will open on 1 July 2018.

Membership & Grants Committee

The Membership & Grants Committee met for the first time this year in April. The agenda included a review of the uptake of membership and travel grants (including lab visits), Society Representatives' activities and the Member Insight Project.

Focusing on The Society's new strategy, the committee discussed how to optimise membership engagement with The Society and the best approaches for strengthening the future pipeline of physiologists. The new website presents existing opportunities to showcase physiologists and their research as well as develop our community.

Membership numbers and diversity were, as always, a focus, and it was keenly noted that there continues to be an increase in the number of members across all categories.

Following the success of last year, preparation is under way for the second Society Representatives 'Best Practice' meeting, and we discussed how we can ensure our Representatives are supported to bring enhanced value to the role.

Policy & Communications Committee

The Policy and Communications Committee met in early May. The Committee received updates on regular work areas, including recent consultations on animal research. Keith Siew was elected to be the Committee's representative on the International Working Group. Discussions took place on how policy work fits into the wider Society strategy and how it may be possible to influence curricula in training for the medical professions.

Publications Committee

The Publications Committee met in late April 2018. The meeting was chaired by Debbie Baines, who was voted into this position formally at the last Council Meeting. The Editors-in-Chief of *The Journal of Physiology*, *Experimental Physiology* and *Physiological Reports* presented their Editorial Reports, with all journals reported as being in good health following a successful year. *Experimental Physiology* reported especially strong growth, particularly in submission rates, total cites and social media reach.

The Committee outlined our journals' commitment to increasing transparency and openness. As a result, we hope to implement an updated statistics policy over the coming months. The Committee also agreed that we should step-up our efforts in targeting submissions from under-represented physiological subjects and geographical areas with advice on best practice for publication in our journals. Furthermore, it was discussed that the journals should keep an eye out for interesting multidisciplinary work involving physiology, to ensure that we continue to publish the most pioneering physiology research. Finally, the Committee confirmed the Publications Strategy 2018–2022.

Bringing you snippets of the latest intriguing research

Children are as fit as endurance athletes

Researchers have discovered how young children run around seemingly all day without getting tired: their muscles resist fatigue and recover in the same way as elite endurance athletes. This study could help develop athletic potential in children and improve our knowledge of how disease risk, such as of diabetes, increases as our bodies change from childhood to adulthood.

DOI: 10.3389/fphys.2018.00387

Scientists say they've transplanted a memory from one snail to another

Researchers have transferred memories between sea snails by injecting RNA from a trained sea snail into one that hasn't been trained, and observing the trained response in the second snail. This could aid in both restoring lost memories, and easing the trauma of painful ones.

DOI: 10.1523/ENEURO.0038-18.2018

Grey hair may sprout when the immune system is activated by infection

Hair pigmentation over the course of a lifetime depends on melanocyte stem cells that reside in the hair follicle. The loss of these stem cells leads to the growth of non-pigmented, or grey, hairs. This study highlights the impact of innate immune activation on melanocyte stem cell physiology and suggests a connection between viral infection and hair greying.

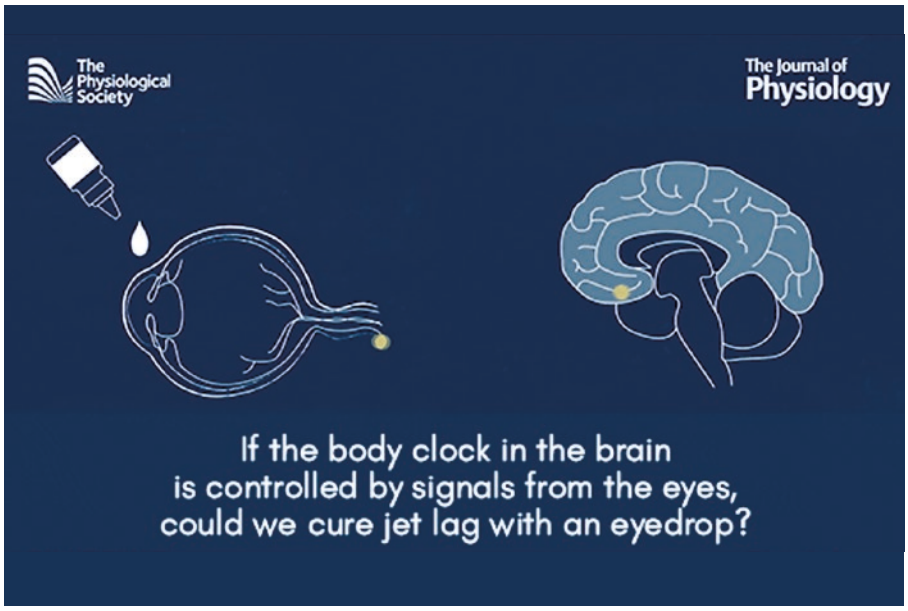
DOI: 10.1371/journal.pbio.2003648

Scientists have confirmed a new DNA structure inside human cells

Scientists have identified a new DNA structure never before seen in living cells. The so-called i-motif had previously been identified *in vitro*, but not *in vivo*. This study visualizes the structures and sets the challenge for scientists to figure out what these structures are doing inside our bodies.

DOI: 10.1038/s41557-018-0046-3

Physiology Feed continues on page 13



Can we cure jet lag with eye drops? The latest video in our series about the research in our journals

Our body clock has effects throughout our bodies, causing daily fluctuations in our mood, hormone levels, body temperature, metabolism and more. Learn more in our video about research from *The Journal of Physiology* suggesting that vasopressin cells in the suprachiasmatic nucleus, the master clock, are regulated by cells in the eye called retinal ganglion cells. This may mean that eye drops could be developed to cure jet lag, and help combat certain sleep disorders. Watch here: **youtube.com/watch?v=9z6fYJgDZDM**

Congratulations to our newest Fellow Members

- Stuart Egginton, University of Leeds
- Sarah Hall, Cardiff University
- A Mark Evans, University of Edinburgh
- Anton Wagenmakers, Liverpool John Moores University
- Richard Naftalin, King's College London
- Elaine Del Bel, University of Sao Paulo
- D George Stephenson, La Trobe University
- Richard Ferguson, Loughborough University
- Michael Collis
- Gareth Leng, University of Edinburgh
- Giovanni E Mann, King's College London
- Anthony Angel, University of Sheffield
- Jonathan Cole, University of Southampton
- KW Ranatunga, University of Bristol
- Dianne Ford, Newcastle University
- Jacob Sweiry, University College London
- Gladys Pearson, Manchester Metropolitan University
- Lee Romer, Brunel University
- Peter Cahusac, Alfraisal University

Voice of the Future

Chrysia-Maria Pegasiou
University of Sussex,
Brighton, UK

Asking key political figures science policy questions is not something every early career scientist has the opportunity to do. In the midst of Brexit and University strike action, Voice of the Future seemed like the perfect chance to address issues that affect us all.

This year's event was held on 13 March. The discussion was kicked off by Sam Gyimah MP, Minister of State for Universities, Science, Research and Innovation. As a recently appointed Minister, he seemed eager to answer all our questions. The discussion revolved around funding and job security for EU members in the post-Brexit era. We were assured that Government would do everything in their power to secure the status of EU scientists in the UK, and to ensure that funding would still be available for researchers across Britain. As an EU citizen myself, I could not help but wonder why EU scientist and citizen status in general had not been secured in the first place.

Next up, was Chi Onwurah MP, Shadow Minister for Business, Energy and Industrial Strategy. She seemed like an extremely passionate advocate for science and research, being an engineer herself. A lot was said about empowering women in science and giving equal opportunities to students from lower socioeconomic backgrounds, as well as the north/south divide. The Labour manifesto was brought up on numerous occasions, especially in the context of security following Brexit.

The panel then changed. Stephen Metcalfe MP and the Science & Technology Select Committee took the stand. The discussion felt a bit less rehearsed. It was quite encouraging to see how passionate MPs are about science and how engaged they can be with developing technologies and the hot topic of internet security.

After what seemed like a long morning, it was finally my turn to sit on the 'horseshoe'. Dr Rupert Lewis, Director of the Government Office for Science, had agreed to answer our questions. My question revolved around the recent news regarding the EMA (European Medicines Agency) move to Amsterdam. I was assured that Britain would continue to receive industrial funding following the move. Was I completely convinced? Maybe not.

All in all, I think the Royal Society of Biology did well in bringing scientists and politicians together. It's true questions were rehearsed, so we were not able to challenge the politicians as much as we may have wanted. However, as change does take time, I am hopeful that young scientists will have opportunities to voice their concerns and change science policy in the coming years.

Member Spotlight: The Ultra Cycle Diaries

We have rolled out a series of blogs (**bit.ly/CycleBlogs**) and videos (**bit.ly/CycleRace**) following one of our Members, Dan Brayson, on a 4000 km ultra-endurance cycling race across Europe and discussing the consequences of such a race on the human body. He collected data about his performance to explore the physical and psychological challenges created by heat, fatigue and altered patterns of nutrition. As well as following the ups and downs of his adventure, his blog and vlog series stresses what happens in our body when we exercise, including the importance of the brain and mindset in challenging ourselves.

We're on a mission to showcase the work of our Members. If you're interested in featuring your work in writing or in videos, get in touch at **magazine@physoc.org** with a 500-word public-friendly piece about your research.

Editorial Board Fellowship winners

Congratulations to our inaugural Editorial Board Fellows who will be joining *The Journal of Physiology*'s Editorial Board from 1 July 2018. Successful candidates have been assigned a mentor from our Senior Editorial Team, who will teach them the fundamentals of our peer review process.

- Pawel Ferdek, Jagiellonian University, Krakow
- Melanie Gareau, University of California, Davis
- Javier Gonzalez, University of Bath
- David M Maclean, University of Rochester Medical Center
- Vincenzo Marra, University of Leicester
- Christopher West, The University of British Columbia
- Calum Wilson, University of Strathclyde
- Alicia D'Souza, University of Manchester

This new molecule could become a cure for the common cold

Scientists have developed a new molecule that prevents viruses from replicating by inhibiting human N-myristoyltransferases. Preventing host-cell N-myristoylation rapidly and completely prevented viral replication without inducing cytotoxicity. This opens the door to a new a therapeutic strategy in tackling viral infections.

DOI: 10.1038/s41557-018-0039-2

Women feature only rarely as first or last authors in leading journals

A longitudinal study carried out by the University of Washington looking at 15 major science and neuroscience journals revealed that female first authors outnumbered men in only one journal. Women represented about 15% of senior or last-author spots in *Nature* and *Science* and fewer than 40% in *Neuropsychology Review*. The study also found that journals with higher impact factors had a lower proportion of women as both first and last authors.

DOI: 10.1038/d41586-018-03804-2

Sexual-minority students more likely to abandon science majors

Findings published in *Science Advances* found the first direct evidence of LGBQ students leaving degrees in scientific disciplines compared to their heterosexual peers. The study looked at 4000 first year university students across 78 institutions and compared responses using a survey when the students had reached their final year.

DOI: 10.1038/d41586-018-03178-5

Researchers are keeping pig brains alive outside the body

Scientists have managed to keep pig brains alive for as long as 36 hours after they had been decapitated. 100-200 pig brains obtained from a slaughterhouse were used during the study led by Yale University neuroscientist Nenad Sestan. The scientists were able to restore circulation to the brains using a system of pumps, heaters, and bags of artificial blood warmed to body temperature.

bit.ly/2IFg0qd

A unified voice for the life sciences

The passion for understanding the processes of life unites us all in the biosciences. The Royal Society of Biology (RSB) represents the full breadth of the life sciences and aims to speak with a unified voice on bioscience issues. Working in partnership with organisations like The Physiological Society is essential to achieve that breadth of representation.

The Physiological Society engages with the work of RSB through your Council, Committees and staff, to ensure that the priorities and concerns of your members are heard in the wider discussions in which we all participate.

Through our policy work, we aim to ensure those making decisions that impact the future of life sciences hear our messages. As we approach leaving the EU, being part of the development and delivery of policies that affect fields such as physiology is a key priority.

Through our engagement with the High Level Working Group on Brexit and Science, co-chaired by senior Government ministers, there are opportunities to communicate concerns and priorities highlighted by The Physiological Society's members in areas such as collaboration, funding, innovation and the environment for science.

We are also focusing on the future innovation landscape of the UK, as outlined by the Government's Industrial Strategy. In our response to the Green Paper and the House of Lords' consultation on the Life Sciences Industrial Strategy, and in oral evidence to the House of Commons' Science and Technology Committee, we emphasised the importance of considering the full breadth of the life sciences, and we are pleased to note that their report reflected these recommendations.

Many policy areas require specific disciplinary input. The Physiological Society continues to play a key role in developing RSB's *in vivo* policy positions and communication as well as channelling expert detail into discussions with the Home Office.

Running parallel to our science policy work, the RSB also informs and influences education policy and STEM education provision; a high-quality science education is the vital foundation of our biosciences community.

This year we are developing our own framework for the biology curriculum for ages 5–19, and we continue to work alongside the Institute of Physics, Royal Society of Chemistry, Association for Science Education and Royal Society to support the development of the best STEM education possible.

We have answered calls for advice from the Department for Education, the Devolved Administrations and elsewhere, with co-ordinated responses on current policy topics, including accessibility, and we continue to be active on issues relating to the Teaching Excellence Framework.

Our varied outreach and engagement calendar of activities; competition participation of over 50,000 school pupils awards to highlight excellence and commitment in teachers, technicians and communicators, have been a dynamic way to encourage and reward achievement, and Degree Accreditation schemes have recognised institutions that offer educational programmes equipping students with the right skills for employment and the next chapter in their lives.

Alongside our CPD and training opportunities, registration and Chartership, we will continue to ensure that beyond formal education, bioscientists have support and development opportunities at every stage of their career.

Hearing from our members and member organisations remains central to all of our work. The articulation of concerns and aspirations to us by The Physiological Society is vital to developing our communications, and a key relationship. Recently, Lord Willetts, Minister for Science at the time of our formation in 2009, emphasised how important it remains that we speak with one voice on key bioscience issues, encouraging us all to continue this with enthusiasm. He was speaking to welcome Dame Julia Goodfellow as our third President, and we look forward to working with her, our committees and volunteers, and with The Physiological Society to develop and deliver the best future for UK bioscience.

Our latest Public Engagement Grant Winners

Getting to Know Your Brain
Andrew Young & Jaime McCutcheon, University of Leicester

During Brain Awareness Week (run by the Dana Foundation), almost 200 sixth form students from widening participation schools attended talks and demonstrations by neuroscientists from the University of Leicester. In the evening, a similar event was held for members of the public.

Delivering the Placenta
Michelle Desforges, University of Manchester

The University of Manchester's Maternal and Fetal Health Research Centre created games that explain the placenta's role in the body of a pregnant woman. Our grant will develop these games further. Scientists and artists will collaborate to use the games in sessions for members of the public who have experienced pregnancy complications or loss, as well as for various engagement events held by the University of Manchester.

I'm a Scientist, Get Me Out of Here
Shane McCracken

As part of the 'Sleep Zone' this November, hundreds of students will log on to challenge physiologists, including our members, in live, text-based chats to answer questions about what happens in the human body when we sleep, and about their own research. The students will then vote for their favourite researcher who will win a £500 prize to spend on further physiology engagement. Members can now apply to take part at **http://imascientist.org.uk/scientists**

Naked Body: How a Human Works
Chris Smith

The group at The Naked Scientist podcast will create a top-to-bottom audio-visual tour of human physiology. In 50 instalments broadcast on the radio and disseminated as podcasts, they will explore the major organs, systems and tissues, explaining how each 'works' and how things can go wrong. Alongside this, they will create relevant drawings and animations. Physiologists will be invited to help write, fact-check and narrate the videos.

Maria Karabova (third from the right), winner of The Physiological Society Gold Prize for Biological and Biomedical Sciences, along with other awardees at STEM for Britain.

Sitting is the new smoking: research of The Physiological Society Gold Prize for Biological and Biomedical Sciences winner

Maria Karabova

Kings College London,
London, UK

Ten years ago, I walked by St. Thomas Abbey every Monday morning on my way to biology lectures, feeling privileged to study in the town where Gregor Mendel built the foundations of modern biology. This made winning The Physiological Society Gold Prize for Biological and Biomedical Sciences, at STEM for Britain 2018, especially meaningful for me.

STEM for Britain 2018 is an event founded by the late Eric Wharton, fostering greater dialogue and engagement between early career researchers and parliamentarians, held annually at the Houses of Parliament.

The findings I presented demonstrate the powerful impact of regular early-life exercise on brain health as we age. These results are particularly important in light of the expansion of the elderly population. While medical advancements enable us to live longer, this increase in life expectancy sadly seems to go hand in hand with the rising prevalence of incurable age-related brain diseases.

One such disease is Alzheimer's disease (AD) – a neurodegenerative disorder that manifests on a molecular level as an accumulation of amyloid-beta plaques and neurofibrillary tangles in the brain. Clinical symptoms include a progressive deterioration of memory and other cognitive capacities, ultimately robbing people of their memories, daily independence and dignity. While we are still searching for an effective cure, it makes sense to focus on prevention, mitigating the risk factors that play a role in AD development.

A recent review of the influences contributing to the onset of memory loss and Alzheimer's disease revealed that 'sitting is the new smoking'; in other words, a sedentary lifestyle represents the third greatest risk factor worldwide. For centuries, we have intuitively known that physical activity is beneficial for our wellbeing. Hippocrates said, 'If we could give every individual the right amount of nourishment and exercise we would have found the safest way to health.'

Surprisingly, the effect of regular physical activity early in life, such as in childhood, on longitudinal maintenance of brain health has previously never been explored – even though the evidence suggests that boosting physical activity could potentially represent a new frontier for preventing memory loss and AD symptoms in the elderly.

In the second year of my undergraduate studies, I had the opportunity to spend a year abroad at the University of California in Irvine. This is where I came across Carl W Cotman, a world-leading expert on exercise and brain health. I decided to interrupt my studies and undergo a year-long work placement under his supervision. He kindly trusted me to join his project aiming to systematically map the effect of early-life exercise on brain ageing.

As such a study is difficult to conduct in humans, we turned to mice. We provided young mice (2 months old) with access to running wheels for two days, two weeks or four weeks and tested their spatial memory with behavioral tests in adulthood (6 months and 9 months) as well as in old age (18 months). The results were nothing short of remarkable.

In adulthood and old age, activity and mobility was significantly improved in mice that exercised for two or four weeks in young age compared with those that only exercised for two days or remained sedentary.

In addition, mice that were regularly active for two or four weeks in young age performed significantly better in memory tests in adulthood as well as in old age. We hypothesised that regular early-life exercise creates a type of cognitive reserve, which protects the ageing brain and renders it resilient to cognitive decline. While the molecular changes underlying this protective effect are not clear, our results indicated that an increase in structural synaptic plasticity as well as brain-derived neurotrophic factor availability may be a good starting point to look at.

I hope that the work I presented will contribute to STEM for Britain's goal of building a bridge between the scientific community and the parliamentarian, and that our results will serve as a catalyst for implementing more youth movement programmes to battle the alarming rise in age-related memory loss and Alzheimer's disease.

Best practice for data in research and publication – Society recommendations

Henry Lovett

Policy and Public Affairs Officer,
The Physiological Society

Research revolves around the acquisition and interpretation of data. New developments are continually enhancing capabilities in both of these activities, and the complexity of data that can be presented in scientific investigation is increasing massively. The onus is on the researcher to ensure that their data is up to scratch in terms of accuracy, completeness and accessibility in order to demonstrate their conclusion is reliable and make their research reproducible.

The Physiological Society has recently released a policy position statement suggesting how its Members can follow best practice to ensure good data. It also covers how its peer organisations can ensure the best standards in publishing, and how future audiences can use data effectively as evidence in policymaking.

Robust and reliable data gathering starts in experimental design. Studies should be large enough to ensure conclusions are valid, with statistical methods determining sample sizes. This avoids the waste of time and effort and, in *in vivo* experiments, follows the principle of reduction in animal use to the minimum number necessary to generate a statistically valid conclusion. Accuracy can also be dependent on the equipment and techniques used; these concerns should be addressed in any publication using the data.

Subsequent analysis of experimental data should be transparent, using appropriate statistical protocols set out in the initial discussion of the hypothesis. If experimental data is being used to derive a predictive test or scale, care must be taken to understand the range of 'normal' values across the potential diversity of subjects the test may be applied to in future.

Awareness is growing throughout science and the public concerning the issues of reproducibility affecting published research. The necessity of accurate and detailed description of experimental techniques and conditions is well stated by former President of The American Physiological Society Peter Wagner, who writes:

'It is not a problem per se for two purportedly identical studies to disagree, because if both are adequately described, the reason(s) for discrepancies can usually be found, and this alone may considerably advance the field. It is when the outcomes are in doubt because of poor descriptions or statistical errors that we waste our time, resources, and dollars and put future research (and even clinical care) at risk.'

As ensuring reproducibility is such a critical aspect of research, The Society recommends training for early career researchers in how to design reproducibility into their experimental techniques and demonstrate it with transparency in their write-ups.

When publishing, it is becoming more common for funders and/or journals to require that experimental data is made available to readers. Some go further and mandate particular techniques when using and reporting statistics. We recommend that other journals replicate the model of The Society's journals by appointing a Statistics Editor, who is involved in the review process of submitted manuscripts to ensure statistical accuracy and appropriateness. This means both that the accuracy of data analysis can be checked by an expert, and that the reviewers can concentrate on the design of the study and the conclusions.

These and other recommendations are explored in more detail in the position statement, which can be found in the Policy section of the Society website.

2018 *Forthcoming events*

7 September

From Lab to Clinic: Pathways to Translational Brain Machine Interfaces for Rehabilitation
University of Reading,
Reading, UK

www.physoc.org/labtoclinic/

13 September

Early Career Physiologists' Symposium (ECPS 2018)
QEII Centre,
London, UK

www.europhysiology2018.org/ECPS2016

14-16 Sept.

Europhysiology 2018 – Main Meeting
The QEII Centre,
London, UK

www.europhysiology2018.org

5-6 December

Sleep and Circadian Rhythms from Mechanisms to Function
Barbican,
London, UK

www.physoc.org/sleep_circadian/sleep-and-circadian-rhythms-mechanisms-function

Meeting Preview

Researchers' Futures programme workshop

22 October 2018,
Charles Darwin House
London, UK

physoc.org/supporting-our-researchers-futures

Chrissy Stokes

Head of Professional Development and Engagement,
The Physiological Society

Whilst postdoc positions can help to develop scientific skills and knowledge, they can cast emerging scientists in the shadow of their Principal Investigator. With fewer permanent posts and greater competition for grant funding, the transition to scientific independence and that first permanent post can be difficult.

An article published in *Nature* in 2016 suggested 'young scientists today face a harsher, more competitive, stricter, more dispiriting workplace than their bosses and senior colleagues did at the same stages of their own careers.' And the situation has not improved since then.

As the guardians of their disciplines, learned societies have a role in smoothing this transition, to allow the best scientific minds and future leaders to flourish, by providing support in an open and inclusive way.

As part of this support, The British Ecological Society and The Physiological Society are building a year-long support programme for 30 members looking to take the next step.

The programme will begin with a one-day workshop in London on 22 October 2018 covering areas such as applying for funding, preparing your CV and creating your profile. Throughout the year, participants will be encouraged to liaise as part of a facilitated peer-support network. They will also receive further support from the sponsoring Societies, such as bespoke online training.

Apply by 9 September to join this network and ease your transition to scientific independence.

Are you a young scientist seeking scientific independence, or your first permanent post? Join this workshop and peer-support network to help progress your career.

Virtual reality and a robotic device are used to elicit physiological responses to fear.

Meeting Preview

Focussed Symposium: From Lab to Clinic – Pathways to Translational Brain Machine Interfaces for Rehabilitation

7 September 2018,
University of Reading,
Reading, UK

physoc.org/labtoclinic/

Ioannis D Zoulias & Orla Fannon

University of Reading,
Berkshire, UK

The development of brain-machine interfaces (BMIs) has been accelerating over the last decade due to the exciting possibilities these technologies present. Recent breakthroughs in BMIs, complemented by technologies such as virtual reality, robotics and functional electrical stimulation, have provided very promising results for rehabilitation, and the recovery of function and motor control after accident or illness.

Despite these promising results, the use of BMI technologies is primarily confined to the laboratory environment, with limited clinical use. Some of the reasons for this are the variation in physiological differences from person to person, the divergent needs of people with disabilities, poor accessibility and usability of BMI techniques for clinicians, and the difficulty in forging new collaborations between BMI researchers and clinicians.

This symposium aims to streamline the translation of BMIs, developed by researchers, into clinical interventions. Joined by clinical experts and academics who have successfully translated their BMIs to the clinic, participants will discuss pathways available for researchers to advance their BMI research to a clinical setting.

Emphasis will be placed on encouraging early career researchers' progression in this field; building new collaborations and bridging the gap in knowledge to facilitate the clinical transfer of research are especially important early in a research career.
Early career researchers will also have an opportunity to present their work (through oral communications or a poster presentation) and, crucially, glean relevant advice from experts on how to transfer their specific research to the clinical environment.

A panel discussion comprising researchers, clinicians and members of funding bodies will address questions directly from the audience. To encourage audience participation, the panel will address pre-submitted questions from delegates, as well as questions posed in the session, either directly or through Twitter. At the end of the symposium, further networking opportunities will be available during a wine reception with all speakers and delegates.

The symposium will cover a variety of topics in BMI research, with applications to the rehabilitation of motion (e.g. stroke or spinal cord injury), prosthetics, BMIs for affecting psychological conditions and BMIs for enabling communication (e.g. BMI spellers).

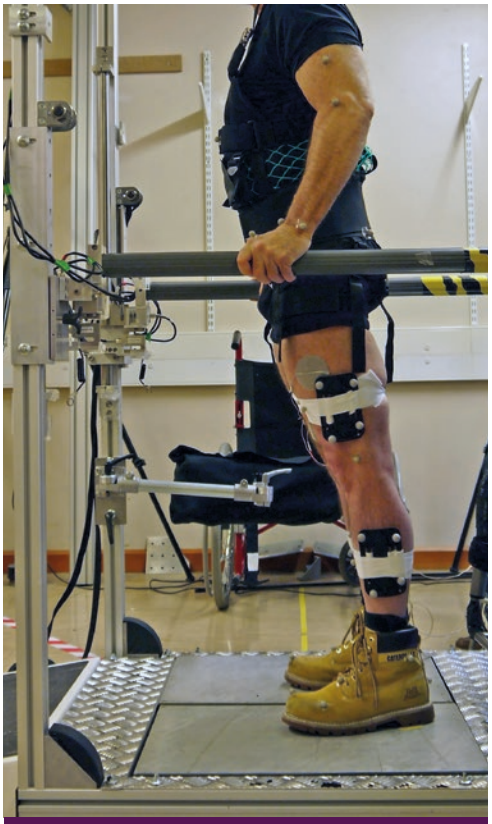
The keynote talks will focus on high impact international BMI clinical research, obtaining novel physiological insights through clinical BMI investigation, and understanding the clinical and patient perspective when designing novel BMI ideas and forging clinical collaborations.

Miguel Nicolelis (Duke University, USA) a pioneer in the field of BMI, will discuss his experience in numerous clinical BMI studies. Of particular interest are his laboratory's recent breakthrough findings on restoring function in people with complete spinal cord injuries through a BMI complemented by virtual reality and a robotic exoskeleton. Using this novel hybrid system in patients with paraplegia resulted in an unprecedented recovery of motion.

Dario Farina (Imperial College, UK) will present his ground-breaking research in applications of BMIs using robotic prosthetics and will outline the opportunity for obtaining insights into brain physiology through clinical research using BMI and neuromodulation.

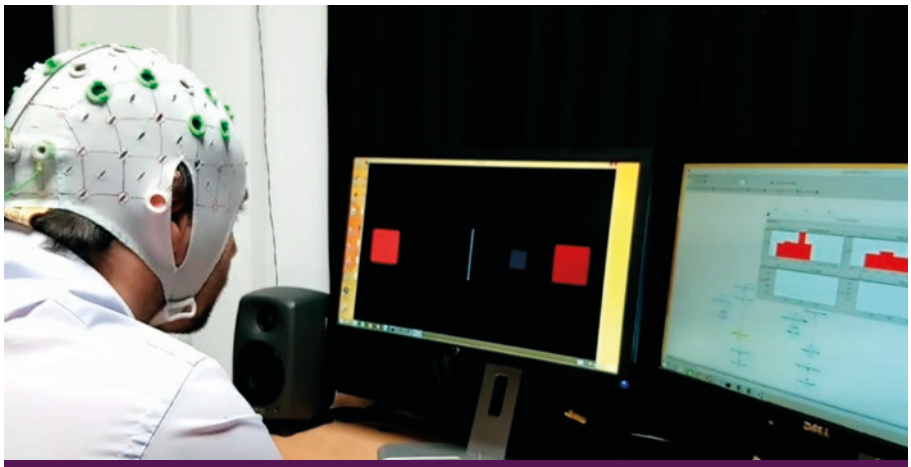
The clinical viewpoint will be presented by Claire Guy (Rookwood Hospital, UK). Claire will be giving her views from decades of experience in physiotherapy and neurorehabilitation (spinal cord injuries, MS, stroke and others) and her own involvement in research projects.

This meeting aims to foster new collaborations between clinicians and researchers at the early stages of BMI development. We expect the formation of long-lasting collaborations and a subsequent increase in clinical trials and adoption of BMIs in clinics. This topic is highly relevant in today's physiological research landscape, as a critical mass of research on BMIs for rehabilitation is likely to revolutionise the outcome of currently debilitating conditions and to provide unique insights into the physiology of neural mechanisms.



Functional electrical stimulation can be used to stimulate paretic limbs and assist people with complete paraplegia to stand on their own. BMIs which use motion intention for directly controlling muscle stimulation may result in significant recoveries of lost motion and function.

This BMI detects intention to move the user's arm. A soft robotic actuator strapped on the arm assists with the physical motion. The motion is mirrored within a virtual environment to give the user the illusion of moving their own arm, unassisted.



A BMI game. The red boxes on the screen flash at different frequencies; the neural signature from the visual cortex (steady state visual evoked potential) can reveal which box is being attended to, and move the blue box towards the corresponding box.

'Recent breakthroughs in BMIs, complemented by technologies such as virtual reality, robotics and functional electrical stimulation, have provided very promising results for rehabilitation, and the recovery of function and motor control after accident or illness'

Meeting Preview

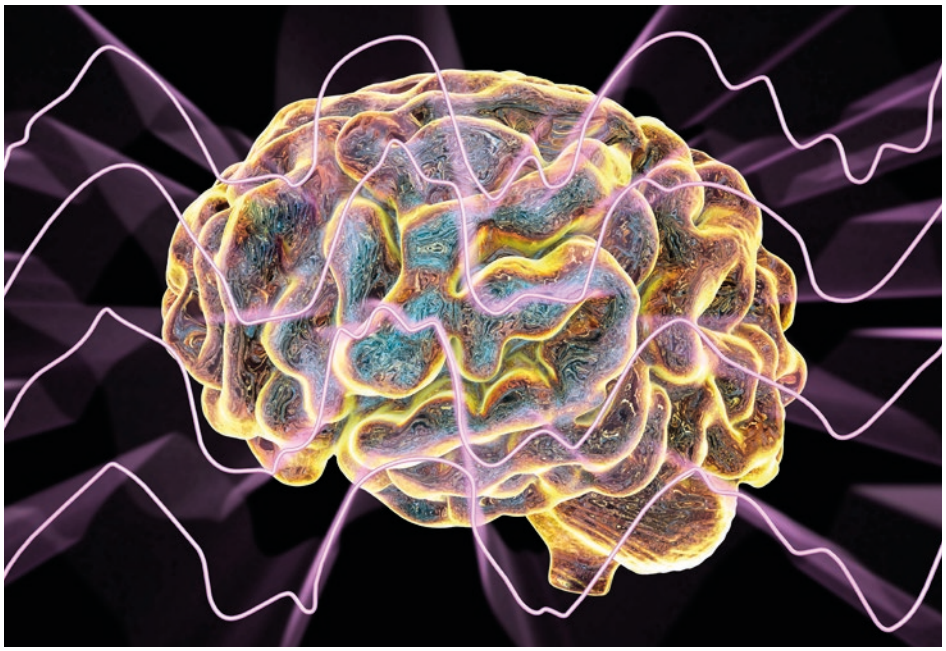
Sleep and Circadian Rhythms from Mechanisms to Function: Why should I attend?

5–6 December 2018,
Barbican, London, UK

physoc.org/sleep_circadian/programme-25

Connor S Qiu

Imperial College London,
London, UK



Sleep and circadian rhythms are essential elements of physiology that govern life in ways we are only beginning to uncover. These topics are gaining increasing recognition as key research avenues amongst the array of physiological processes that occur in our bodies. The field received a deserved boost in recognition when the 2017 Nobel Prize in Physiology or Medicine was awarded to Jeffrey C Hall, Michael Rosbash and Michael W Young for pioneering work on the molecular mechanisms that control circadian rhythms. The increasing relevance of translating the importance of sleep and circadian rhythms to the public realm has inspired the founding of movements such as SleepImperial (**sleepimperial.com**).

Our conference this December intends to promote and highlight the current trends and major research directions occurring globally in the sleep field. To give a snapshot of what to expect at this conference, we put the spotlight on three outstanding researchers that are speaking, and provide a whirlwind tour of their life's work.

Think about the continuum between sleep and wakefulness for a moment. An interesting and useful question to consider is what controls their relative levels in humans. Chiara Cirelli at the University of Wisconsin-Madison has done exactly this in her research about why we sleep. In her recent *Science* paper (de Vivo *et al.,* 2017) she has assessed synaptic strengthening and weakening during learning by measuring nearly 7000 synapses in mouse motor and sensory cortices using three-dimensional electron microscopy. This amazingly detailed work supports the idea that synapses are recalibrated during sleep to enable synaptic strengthening and brain plasticity during wakefulness. This notion was first proposed with her long-time collaborator, Giulio Tononi, and together they pioneered the 'synaptic homeostasis hypotheses', which Chiara will discuss during her talk.

Sleep and wakefulness operates under approximately a 24-hour cycle, our body clock, which has adapted in our bodies over time with evolution. The light that enables us to see has profound effects on this body clock. Russell Foster leads a research group that discovered the photoreceptors in the retina that relay this information to our body clock. Russell, based at the University of Oxford, is known to The Physiological Society for his public lectures in 2011 and 2013. He's also given a TED talk, 'Why we sleep' (which can be found at **ted.com**). By receiving this information, our body is able to acclimatise to changing environments by changing the settings of our default body clock. These synchronisations have far-reaching consequences on our performance, productivity and health. He now runs the Sleep and Circadian Neuroscience Institute (SCNi) group at Oxford University, and we are delighted he will be joining us to discuss his latest research.

In addition to studying 'normal' sleep, there is a vast field of research looking at disordered sleep. Narcolepsy, for example, is a medical condition that causes individuals to fall asleep suddenly and without warning throughout the day, and currently has no cure. This condition can have profound effects on emotional wellbeing and quality of life. Emmanuel Mignot of Stanford University is credited with discovering the cause of narcolepsy. The neuronal signalling molecule hypocretin (or orexin), which has wide-ranging effects on wakefulness, arousal and appetite, is found to be lacking in the brains of individuals diagnosed with narcolepsy. Emmanuel and colleagues were able to isolate mutations in the hypocretin receptor 2 that cause canine narcolepsy (Lin *et al.,* 1999). Parallel work on the east coast also showed that hypocretin deficient mice also have narcolepsy (Chemelli *et al.,* 1999). This ground-breaking work has led to many developments in the genetics of sleep disorders, and we are delighted that Emmanuel will be joining us to discuss these at the meeting.

> 'Our conference this December intends to promote and highlight the current trends and major research directions occurring globally in the sleep field'

The conference has an outstanding programme of speakers and seminars aimed at elucidating the exciting science and wider societal implications of sleep and circadian rhythms. It will satisfy your intellectual appetite and help further your research. We hope you are as excited as we are about the programme, which you can view online at the link at the top of this article.

We look forward to warmly welcoming you to 'Sleep and Circadian Rhythms from Mechanisms to Function' at the world-class arts and learning centre, the Barbican in London from 5 to 6 December 2018.

Meeting Notes

How to Expect the Unexpected: Prediction and Prevention of Preterm Birth – GL Brown Prize Lecture

10 May 2018,
University of Southampton,
Southampton, UK

Jane Cleal

University of Southampton,
Southampton, UK

Preterm birth, defined as birth before 37 weeks of gestation, is a global problem, responsible for over a million deaths each year. While progress has been made over the last 20 years to reduce the number of preterm births, this has been limited by poor understanding of the physiology of human childbirth and a lack of investment into potential therapeutics.

In her GL Brown Prize Lecture, Rachel Tribe discussed spontaneous preterm birth. Preterm birth is described as a syndrome as it is caused by multiple pathologic processes: multiple pregnancy, infection, placental abruption and stress. However, there is still no established early pregnancy screening test or effective treatment for preventing or inhibiting preterm labour.

Rachel is using a multidisciplinary approach to help unravel the complexity of spontaneous preterm syndrome. She described an impressive range of research that spanned the pipeline – from molecules to clinical impact.

This includes basic science in both animal and human tissue to identify novel uterine smooth muscle targets for the development of tocolytic therapies (for the treatment of preterm labour). Rachel and her team have identified K_V7 channels as a key regulator of uterine contractility in term and preterm myometrium (a layer of uterine muscle). Specifically, channels comprising the $K_V7.4$ isoform seem to be the most important in the uterus, and there is potential to repurpose existing drugs for use in preterm labour.

A major focus of Rachel's work is also exploring the early pregnancy events that lead to preterm labour. The working hypothesis is that an early maternal inflammatory response is associated with differences in the resident vaginal microbiome that leads to cervical shortening and preterm birth. She has identified key ethnic differences in the vaginal environment and host response which has led her team to pursue a precision medicine approach to early pregnancy prediction of preterm birth that considers maternal ethnicity as well as pregnancy history and other socio-economic factors.

Rachel Tribe meeting with early career researchers after her lecture (chaired by Jane Cleal, one of the Society Representatives at Southampton University).

Rachel explained how, by working closely with a clinical team led by Andrew Shennan and co-supervising clinical and midwifery PhD students, their research data has informed the development of a mobile phone app. This 'QUiPP' app quantifies the risk of preterm birth by combining knowledge of obstetric history with quantitative fetal fibronectin (fFN) (a protein that acts as a biological 'glue' at the chorio-decidua interface) and transvaginal ultrasound measurements of cervical length. The QUiPP app is currently being used on an *ad hoc* basis by clinicians in the UK, Europe, USA and Australia to inform management in high-risk preterm birth clinics, and recently the team have launched an implementation study (EQUIPPT) across 13 UK centres.

The lecture was extremely well received, attracting around 100 attendees from all career stages and therefore playing an important role in promoting the physiological sciences and The Physiological Society. As Rachel has been an active member of The Physiological Society since 1996 and a Trustee since 2013, Early Career Researchers (ECRs) were particularly interested in meeting with her after the lecture to discuss her work and the role of The Physiological Society in supporting her career. The Society's support includes the opportunity to meet and network with physiologists, training workshops and support to attend conferences, all of which are vital for the ECRs in developing their career.

In 1975, The Physiological Society established the GL Brown Prize Lecture in memory of the physiologist Sir George Lindor Brown. This is an annual series of lectures aimed at a younger audience in order to stimulate an interest in physiology.

Rachel Tribe, the 2016–2017 awardee, is a Fellow Member, and Reader of Women's Health at King's College London. She trained as a physiologist at the University of Sheffield and gained her PhD at UMDS, London. She leads an active research team of scientists and clinicians, with her work focusing on translational research aimed at tackling the complications of preterm birth and pregnancy-associated conditions.

At the University of Southampton, we were privileged to be one of the selected Institutions to host the lecture, as Rachel's work is of great interest to many researchers in our institution. This was the last of the six lectures Rachel presented across the UK (Cambridge, Cardiff, Dublin, Manchester, Edinburgh, Southampton), travelling 2085 miles to do so!

Congratulations to the 2018 winner of the GL Brown Prize, Andrew Parker, University of Oxford, UK. His talk will be entitled 'Seeing in depth with the brain: the physiology of the third dimension'.

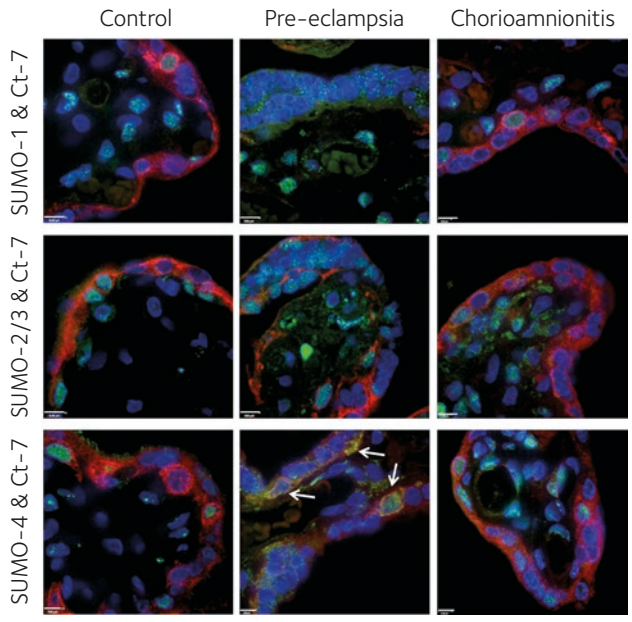
The Journal of Physiology

Spatiotemporal distribution of small ubiquitin-like modifiers during human placental development and in response to oxidative and inflammatory stress

Dora Baczyk, Melanie C. Audette, Etienne Coyaud, Brian Raught, John C Kingdom. 596(9), 1587–1600 (1 May 2018)

Small ubiquitin-like modifier (SUMO) peptides are post-translational modifications of proteins that are linked to various cellular processes. This SUMOylation can occur in response to stresses such as hypoxia and inflammation, both of which are implicated in diseases of abnormal placentation, such as pre-eclampsia. This study shows that SUMO isoforms are present in placentas throughout gestation, however, their expression profiles differ by both location and gestational age. Using placental extracts, the researchers show that hypoxia, oxidative stress and inflammation change the localisation of SUMO isoforms, altering their interaction with cytoskeleton proteins. Finally, expression of these SUMO isoforms are also different in placentas from pregnancies complicated by pre-eclampsia.

DOI: 10.1113/JP275288



SUMO (green) and cytokeratin-7 (Ct-7; red) immunostaining in placentas from severe pre-eclampsia and severe chorioamnionitis.

Keratin proteins are reduced in pre-eclamptic placentas compared to control and those with chorioamnionitis. SUMO-1 is predominantly cytoplasmic in pre-eclamptic placentas (29 weeks' gestation) and exhibited mild cytotrophoblastic perinuclear expression in chorioamnionitis (32 weeks' gestation). SUMO-2/3 cytoplasmic expression was increased in placentas with chorioamnionitis. SUMO-4 expression was increased in the cytoplasm of pre-eclamptic placentas and demonstrated co-localization with Ct7 (arrows). Representative images shown compared to age-matched control placentas (31 weeks); n = 4. Scale bar: 7 μm.

Predictive neuromechanical simulations indicate why walking performance declines with ageing

Seungmoon Song & Hartmut Geyer. 596(7), 1199–1210, (1 April 2018)

Walking performance declines with age. Not only does walking speed slow, but walking is also less energy efficient. Such changes have a negative impact on the quality of life for the elderly population. Using a computational model, these researchers have investigated the changes that occur during ageing that underlie this decline in energy efficiency. The model looks at a range of factors including body mass, neural conduction speeds, muscle mass and strength as well as range of movement. Of all parameters, the changes in muscle strength and contraction speed appear to be the ones that underlie the changes in walking speeds and energy efficiency in the elderly the most.

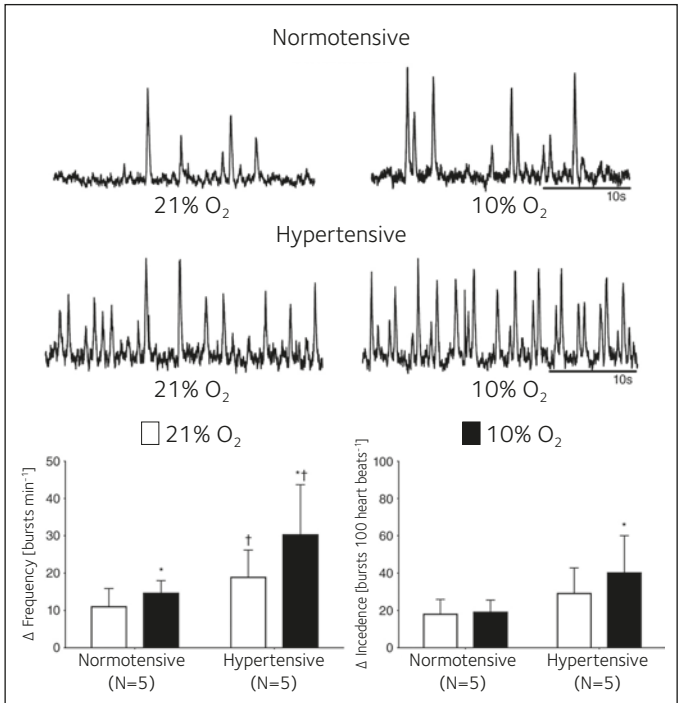
DOI: 10.1113/JP275166

Reduced arterial vasodilatation in response to hypoxia impairs cerebral and peripheral oxygen delivery in hypertensive men

Igor A Fernandes, Marcos P Rocha, Monique O Campos, João D Mattos, Daniel E Mansur, Helena NM Rocha, Paulo AC Terra, Vinícius P Garcia, Natália G Rocha, Niels H Secher, Antonio CL Nóbrega. 596(7), 1167–1179 (1 April 2018)

In response to hypoxaemia, there are a number of local adaptations that maintain perfusion and oxygen delivery to the tissues. The researchers show here how these adaptations are blunted in people with hypertension, using a model of isocapnic hypoxia to remove any influence of low $PaCO_2$. In both normotensive and hypertensive subjects, periods of hypoxia produce changes in ventilation and heart rate. However, dilatation of both the femoral and vertebral arteries is blunted, as is the change in blood flow. This is associated with an increased frequency of sympathetic activity following hypoxia in the hypertensive subjects.

DOI: 10.1113/JP275545



Original recordings for muscle sympathetic nerve activity (MSNA) parameters during normoxia and isocapnic hypoxia.

Experimental Physiology

UBC-Nepal expedition: The use of oral antioxidants does not alter cerebrovascular function at sea level or high altitude

Alexander B Hansen, Ryan L Hoiland, Nia CS Lewis, Michael M Tymko, Joshua C Tremblay, Michael Stembridge, Daniela Nowak-Flück, Howard H Carter, Damian M Bailey, Philip N Ainslie. 103 (4), 523–534 (1 April 2018)

Hypoxia increases oxidative stress, both within the brain and systemically, which is thought to affect the regulatory mechanisms that maintain cerebral blood flow. In this randomised, placebo-controlled and double-blinded crossover study, the effect of an orally ingested cocktail of antioxidants (consisting of vitamins C and E and α-lipoic acid) on cerebrovascular regulation in native healthy low-landers was tested at sea-level (344 m) and high altitude (5050 m). High-resolution duplex ultrasonography of the internal carotid artery and transcranial Doppler ultrasound of the middle cerebral artery in 12 healthy volunteers at sea-level showed no evidence of changes in cerebral blood flow in response to antioxidant ingestion *per se*, and the cerebral vasodilatory responses to hypercapnia and hypoxia were likewise found to be unaffected. Similarly, high-resolution duplex ultrasonography of the internal carotid and vertebral arteries did not reveal any signs of change to cerebral blood flow in response to antioxidant ingestion in nine volunteers ~12 days after ascent to high altitude. Even though oxidative stress is likely involved in the alternations in cerebrovascular function that occur in response to both acute and chronic hypoxia, an oral antioxidant cocktail known to attenuate systemic oxidative stress does not appear to affect cerebrovascular function or cerebral blood flow, neither at sea level nor during acclimatisation to high altitude.

DOI: 10.1113/EP086887

The haemodynamic response to incremental increases in negative intrathoracic pressure in healthy humans

William S Cheyne, Jinelle C Gelinas, Neil D Eves. 103(4), 581–589 (1 April 2018)

Negative intrathoracic pressure generated during spontaneous inspiration transiently decreases right atrial pressure, increasing the gradient for venous return to the heart, and subsequently increasing both right and left ventricular stroke volume. While changes in intrathoracic pressure are thought to result in adverse cardiopulmonary interactions in various lung diseases, the cardiovascular effects of incremental increases in negative intrathoracic pressure during spontaneous healthy breathing remain unclear. In the present study, 23 healthy volunteers breathed spontaneously in the supine position while intrathoracic pressure, estimated by the pressure in the lower part of the oesophagus, was rendered progressively negative (at five levels ranging from $^{-}5$ to $^{-}25$ cmH_2O) by increasing inspiratory resistance. Meanwhile, transthoracic echocardiography was performed to evaluate the associated changes in cardiac volumes and function. Even though the interventricular septum was pushed leftwards from an intrathoracic pressure of $^{-}10$ cmH_2O, left ventricular function was not affected until intrathoracic pressure passed $^{-}20$ mmH_2O, where left ventricular end-diastolic volume and stroke volume were reduced. Hence, increases in negative intrathoracic pressure to $\geq$ $^{-}20$ cmH_2O are required before left ventricular function is adversely affected, causing a reduction in stroke volume in the healthy state. The reduction in stroke volume probably involves reduced left ventricular filling due to a combination of a left-shift of the interventricular septum and increased left ventricular afterload.

DOI: 10.1113/EP086654

Physiological Reports

Role of afferent and efferent renal nerves in the development of AngII-salt hypertension in rats

Jason D Foss, Jessica Fiege, Yoji Shimizu, John P Collister, Tim Mayerhofer, Laurel Wood, John W Osborn. 6(3), e13602, (6 February 2018)

New evidence suggests that catheter-based renal denervation is a potential treatment for resistant hypertension, but the mechanisms remain unclear. In recent work, amelioration of deoxycorticosterone acetate-induced salt-sensitive hypertension was shown to be dependent on the ablation of different renal nerves and was associated with decreased renal inflammation. This study used a rat model to investigate the effects of complete catheter-based renal denervation, selective ablation of afferent renal nerves or sham denervation on the mean arterial pressure after two weeks of angiotensin II-induced salt-sensitive hypertension. Although angiotensin-II resulted in an increase in mean arterial pressure of approximately 50 mmHg, there were no between-group differences nor were the kidney T-cell counts affected by the denervation procedures. These results suggest that neither afferent nor efferent renal nerves contribute to this model.

DOI: 10.14814/phy2.13602

Beneficial effects of thyroid hormone on adipose inflammation and insulin sensitivity of obese Wistar rats

Ana C Panveloski-Costa, Caroline Serrano-Nascimento, Paula Bargi-Souza, Leonice L Poyares, Gabriela de S Viana, Maria T Nunes. 6(3), e13550, (1 February 2018)

Obesity is the pandemic of the century with associated illnesses such as type-2 diabetes affecting increasing numbers of patients. Thyroid hormones play an important role in glucose metabolism, and there is evidence of an increased prevalence of thyroid dysfunction in obese and diabetic patients. This study investigated the effects of triiodothyronine (T3) on glycaemic control, insulin sensitivity and subclinical inflammation in the diet-induced obesity of rats. As expected, obese rats exhibited impairment of glycaemia control, increased inflammatory cytokines in white adipose tissue, decreased serum thyrotropin concentration, and increased sodium/iodide symporter and thyrotropin receptor content in the thyroid gland. Results showed that T3 treatment improved insulin sensitivity, glucose tolerance, and reduced inflammatory cytokine content in white adipose tissue. Within the thyroid gland, sodium/iodide symporter and thyrotropin receptor protein were reduced. This evidence reinforces the beneficial effects of T3 treatment on obese rats.

DOI: 10.14814/phy2.13550

Maintaining your attitude at altitude

The logistical, personal and scientific challenges of high-altitude research

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Humans are the only mammals to have colonised all of Earth's most extreme environments, and the mechanism(s) of human adaptation in the different domains have naturally attracted the attention of physiologists for centuries. Permanent settlements and sojourners at high altitude are subject to potent environment stressors, specifically low levels of oxygen, colder temperatures and increased ultraviolet radiation. Therefore they undergo various physiological adaptations and acclimatisation. Hence, populations that have thrived at high altitude for millennia have evolved distinct physiological phenotypes, and the study of these unique traits continues to draw scientists to uncomfortable environments, notably to advance our understanding of the physiological adaptation to acute and long-term hypoxia exposure.

Our research team is one of few that conducts large-scale high-altitude research expeditions globally. These expeditions are an exceptional challenge as they require the organisation of 30–50 people, ~1–3 tonnes of equipment, the structure to perform ~20 cutting-edge research studies and the necessary funding for these projects. Most importantly, these expeditions require a large, cohesive team that can perform at the highest level, all while suffering from high-altitude related illness. Herein, we discuss phenotypic differences between high-altitude natives and the importance of high-altitude research, and provide some behind-the-scenes insight on previous and forthcoming expeditions.

Phenotypic differences between high-altitude natives

The indigenous populations of the Tibetan, Andean and Ethiopian plateaux have developed three separate physiological adaptive strategies to thrive in their respective harsh hypoxic environments. Although there is considerable debate regarding specific durations, the general consensus is that the Old World plateaux (Ethiopian and Tibetan) have been settled for longer than the Altiplano in the New World (Andeans). These plateaux have spawned magnificent empires including the Ethiopian, Tibetan, Tiwanaku and Inka. The different steps of oxygen transport and utilisation yield impressive function at high-altitude in these populations compared to low-landers. When native low-landers are transplanted to altitudes above 2500 m, hyperventilation and increased red blood cell formation in the bone marrow (erythropoiesis) compensate for the reduced oxygen levels in the blood. Andeans (Quechua and Aymara populations) present what can be considered an exaggerated form of typical low-lander high-altitude adaptation with increased haemoglobin levels and haematocrit and high oxygen saturation, together increasing the oxygen content in arterial blood so that it actually exceeds that of low-landers at sea level.

Population	O_2 saturation (%)	Haemoglobin (g/dl)	Haematocrit (%)	Arterial O_2 content (ml/dl)
Low-landers at sea level (Wolfel *et al.*, 1991; Lundby *et al.*, 2017)	98	14	45	22
Low-landers at altitude (Wolfel *et al.*, 1991; Lundby *et al.*, 2017)	90	16	50	20
Ethiopians (Beall *et al.*, 2002; Claydon *et al.*, 2008; Hoit *et al.*, 2011; Cheong *et al.*, 2017)	92–96	15–16	48	20–21
Tibetans (Beall, 2006, 2007)	88–92	14–16	48	16–20
Andeans (Winslow *et al.*, 1989; Jansen & Basnyat, 2011)	92–94	18–20	54	20–26
Andeans with chronic mountain sickness (Maignan *et al.*, 2009; Villafuerte *et al.*, 2014)	84	23	68	26

Table 1. Estimates for haematological parameters in high-altitude natives and low-landers at ~4000 m.

In some instances (~10%), this adaptive response is perturbed with an excessive production of red blood cells, and thus elevated haematocrit, and reduced oxygen saturation. The resultant exceptionally thick blood combined with hypoxaemia leads to so-called chronic mountain sickness, which involves cardiovascular and neurogenic sequelae. Andeans appear to be especially susceptible to this maladaptation, and large increases in haemoglobin and blood viscosity may not represent the ideal adaptive strategy. Indeed, Old World high-altitude natives, such as Tibetans and Ethiopians, exhibit alternative adaptive strategies and, perhaps as a result, display a negligible incidence of chronic mountain sickness. Hence, Tibetans (and Sherpa) present lower haemoglobin concentration and oxygen saturation at similar altitudes compared to Andeans, resembling an unacclimatized low-lander at high-altitude. Tibetans, whose genetic composition may have been influenced by Denisovan ancestors, seem to rely on enhanced blood flow to sustain oxygen delivery and cellular metabolic adaptations to more efficiently utilise oxygen. Less is known about Ethiopian highlanders (Amhara) of the Simien Plateau, but they do appear to have low haemoglobin concentration and higher than expected oxygen saturation due to an increased affinity of haemoglobin for oxygen. Conceivably, these three phenotypes thus represent distinct evolutionarily driven strategies which permit survival and performance at high-altitude (see Table 1).

The Importance of high-altitude research

Why does this all matter? This is likely the most common question a scientist encounters. Large-scale research expeditions, often requiring transplanting sophisticated laboratories to high-altitude, take great effort and thus necessitate justification. The reasons for undertaking these expeditions are multifaceted, with implications for military deployment to high-altitude (i.e. Afghanistan), the growing number of low-landers vacationing to increasingly accessible high-altitude destinations, and commercial flight personnel who are exposed to mild hypoxia during flight; and importantly, these data furthermore have translational implications for patients in critical care and other clinical incidences of hypoxia. Fundamentally, high-altitude physiology research affords incredible insight into biological adaptation to hypoxia that can be gleaned through physiological-phenotyping of high-altitude natives. The timing of this research is urgent, as migration and modernisation are rapidly changing traditional ways of life and high-altitude exposure in high-altitude natives (Beall, 2013). Lastly, from personal standpoints as graduate students that have had the opportunity to contribute to multiple high-altitude expeditions, the learning opportunity from these expeditions is unparalleled. The immensely rewarding aspects of high-altitude research expeditions is only possible following the seemingly insurmountable task of organisation. Our research group is currently amid a ~5-year-long, multiple population, single-stress study design. We will provide a brief overview of the projects, experiences and logistical hurdles faced with our 2016 Nepal expedition, our current 2018 Peru expedition and lastly, the potential for an Ethiopia expedition in 2020.

High-altitude research expedition – Nepal 2016

In the fall of 2016, ~40 researchers spanning 10 universities and six countries gathered in Kelowna, British Columbia, Canada, to undertake one month of intensive baseline, 'sea-level' testing (344 m altitude). This included studies of cerebrovascular, pulmonary vascular, peripheral vascular, cardiac and autonomic function. After the whirlwind of baseline collection, the entire Cerebrovascular Physiology Laboratory from the University of British Columbia (Okanagan campus) was torn down and packaged into Pelican cases for travel to Nepal. For those that have experienced the hectic Tribhuvan International Airport in Kathmandu, you would understand that there was a possibility that the cases would never emerge from the baggage carousel. Incredibly, all of our equipment (amounting to ~2 million dollars) arrived unscathed. The team reconvened at the Kathmandu Guest House located in Thamel for a week of intensive data collection on each other and a subset of Sherpa who had agreed to descend from the Khumbu Valley a couple of weeks prior. Testing proceeded relatively smoothly, save a comical number of electrical fires and unavoidable gastrointestinal problems amongst the team.

Figure 1. (Left) One of the several 'laboratories' our research team constructed in the Kathmandu Guest House hotel to conduct our studies in partially de-acclimatised Sherpa. (Right) This is an example of the infamous electrical grid in Kathmandu. Unsurprisingly, this resulted in several electrical issues during data collection in Kathmandu.

'The timing of this research is urgent, as migration and modernisation are rapidly changing traditional ways of life and high-altitude exposure in high-altitude natives'

Figure 2. The entire high-altitude research team together one last time at the pyramid laboratory prior to descent back to Kathmandu.

Figure 3. The majestic Ev-K2-cnr pyramid laboratory located near Mt. Everest at 5050 m.

Notably, the recurring blackouts and severe electrical noise were a particular nuisance for studies attempting to acquire direct nerve recordings for assessment of autonomic function (Fig. 1).

Upon completion of the round of data collection in Kathmandu, all of our equipment was repacked and bound for Lukla, Nepal, where it would be carried by one of three ways: 1) on our backs, 2) by local Nepalese porters, and 3) by yaks and dzos (a yak–cow hybrid). Physiological function was measured at several locations during ascent in both us low-landers and the impressive local Sherpa en route to the penultimate destination, the beautiful Ev-K2-CNR Pyramid laboratory (Figs. 2 and 3). There, six semi-permanent labs were set up and were the foundation of over 10 distinct studies, which would consume our lives for the next ~four weeks.

It was the late Chris Willie, at the time a postdoctoral fellow from UBC Okanagan and one of the key expedition leaders, who had mentored several of us graduate students and encouraged us to become integral members of the expedition team. Our skill development over the course of the expedition improved exponentially, in large part due to Chris' commitment to mentorship, while still coordinating parts of the expedition and leading his own study which focused on the influence of iron levels on the pulmonary vasculature. This was a classic example of the experiential learning that emerges in field studies when there is a cohesive team. At the end of the expedition, we had successfully performed comprehensive, state-of-the-art physiological research on a cohort of low-landers and Sherpa. On the last nights at the Pyramid, over some sharp-tasting Nepalese whisky, discussion began on what's next – and the plan to follow-up by testing Andeans on the Altiplano in Peru was conceived before we had even begun our descent. Come to think of it, most of our ambitious research projects have been planned while under the influence of either whisky or strong IPAs.

High-altitude research expedition – Peru 2018

Thanks to some fortuitous networking connections to researchers at the Universidad Peruana Cayetano Heredia, who have an established reputation for hosting international physiology research collaboration, our research group is in the midst of final preparations for an expedition to Cerro de Pasco, Peru, scheduled for the summer of 2018. Like Nepal, this will consist of an international contingent and a large team (~40) of co-investigators. Research questions will similarly focus on cardiovascular, cerebrovascular, cardiac and pulmonary function, with the goal to study both well-adapted healthy Andeans and maladapted Andeans with chronic mountain sickness. Unlike Nepal, where a major logistical hurdle is hauling the equipment up the mountain as part of a ~8-day trek, Cerro de Pasco can be reached from Lima, Peru, in ~six hours by vehicle. However, research in Peru is not without its own unique difficulties, such as customs requiring product manuals for all equipment and consumable items in Spanish, an extraordinarily difficult feat given we will be bringing ~300 different pieces of equipment and consumable items. Additionally, organising a schedule for each research project which involves the recruitment of both low-landers and high-altitude natives is an overwhelming undertaking to ensure that all studies are completed within a timely fashion, while avoiding carry-over effects from other studies. Prior to leaving for Peru in June, many team members will be travelling to Kelowna (BC, Canada) for Chris Willie's funeral. Although no longer with us, Chris is again serving as an inspiration and catalyst to bring our group together.

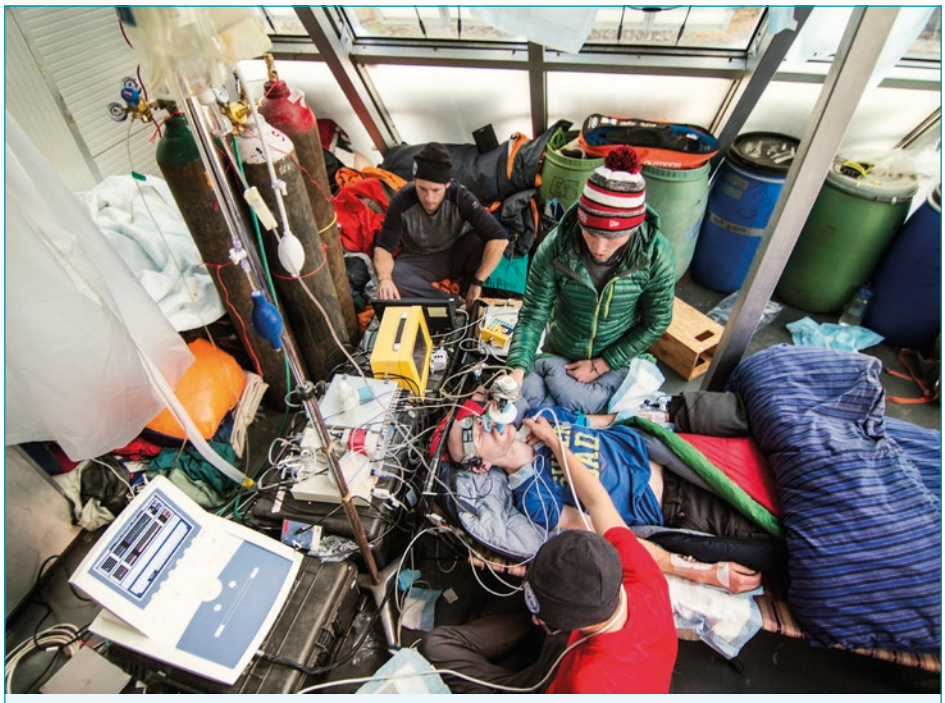

Figure 4. A group of PhD students collecting data for one of several high-altitude-related research projects.

Projected high-altitude research expedition – Ethiopia 2020

Ethiopia will be the final installment in our trilogy of high-altitude adaptation studies. However, the government of Ethiopia recently declared a state of emergency, and the political stability in the country will certainly influence the feasibility of such a project. However, at a recent conference, we were instructed by a well-respected senior researcher to 'be bold', 'push boundaries' and continue to pursue what seems to be the impossible. Ideally, research of Ethiopian highlanders should include studying the Amhara in the Simien mountains, and the Oromo in the Bale mountains. Despite being closely related ethnic groups that live at similar altitudes, the former have resided at high-altitude for millennia, the latter for ~500 years. The least studied population of high-altitude natives tempts the physiologist, and time will tell how long it takes us to clear the logistical hurdles necessary to complete our investigation.

Significance of high-altitude field work

Successful expeditions require the construction of an effective research team, with perhaps the most integral components being resiliency, tranquility and a compatible sense of humour (Fig. 4). In our experience, individuals have spanned the career spectrum – from undergraduate student to senior principal investigator. This has piqued interest in students, who have gone on to pursue graduate degrees and remain active and successful researchers in the field today. The development of such researchers follows the patience and mentorship of study leaders – like Chris Willie, who managed to strike a balance between conducting high-quality field research and dedicating one-on-one time to training. Chris was a product of this system, learning under the tutelage of Phil Ainslie, and while in Nepal coming full circle and assuming a mentorship role himself. Chris achieved the highest honour for doctoral research in Canada (i.e. Vanier scholarship) and produced over 50 publications (many with >100 citations), including seminal papers on the regulation of regional brain blood flow during alterations in arterial blood gases. Most impressively, Chris did all of these things by the young age of 32, while simultaneously leading several ambitious alpine climbing expeditions all around the world. The many people that came across Chris in his lifetime were inspired by him and his incredible ability to balance a scientific output at the highest level while living a minimalist life focusing on his true love: the mountains and rock climbing. Both of us had the pleasure of knowing Chris for many years and we were at times frustrated with him. We would wonder why he didn't fully commit himself to research? Without exaggerating, Chris would have likely surmounted ~100 research publications by the end of his PhD if he worked the hours of a regular PhD students. However, after Chris's passing he left us with the final lesson that life is far too short to take too seriously, and to always make time for your personal life and related passions (see front cover).

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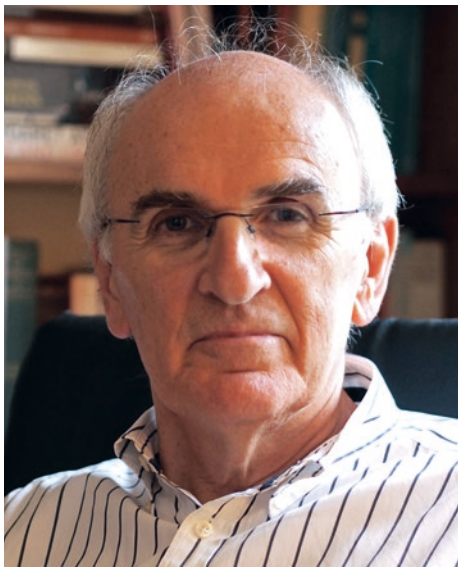
On the blood pressure... 'of Mice and Men'

Why do most mammals – large and small – have much the same blood pressure?



David Miller

University of Glasgow and the History & Archives Committee, The Physiological Society

It is a fascinating fact that the blood pressure, the mean arterial pressure, of mice and men (or women) is much the same. An obvious corollary is that it can thus have little to do with the *absolute* scale of total peripheral resistance or gravitational effects on the cardiovascular system, given how different we are from mice in both respects. It is the shared requirements of the mammalian ultrafiltration kidney that are predominant in setting the mean arterial pressure ... 'of mice and men'.

A simple thought is rarely noted by the textbooks: why does blood pressure – mean arterial pressure (MAP) – stand at the *absolute* level that it does? Considerable physiological 'effort' is expended by the body in sustaining the regulation of MAP, but why specifically at around 100 mmHg in most mammals, large or small?

Over the years that I was charged with lecturing on the cardiovascular system (CVS) to Glasgow's medics, dentists and science students, the core concept of blood pressure and its regulation obviously figured large. In any basic course, we devote considerable time to explaining the physiology whereby arterial blood pressure is monitored and, through the interplay of various autonomic, hormonal and 'local' mechanisms, regulated. The particulars associated with posture and movement in humans merit attention: the potential for lower limb 'pooling' of blood when standing, the consequences of starting – and then sustaining – vigorous physical activity, be it running or static load-lifting. The matter has clear clinical relevance: the consequences of failures in regulation are all too obvious.

Directly asking students – or even colleagues – 'why is MAP about 100 mmHg?' commonly generates a vague response along the lines of 'overcoming the resistance of the vascular tree' and various aspects of 'overcoming the effects of gravity'. But MAP is very much the same in cats or horses, as well as in mice or men. Indeed, with some notable and informative exceptions mentioned later, the great majority of mammals have broadly similar MAPs (see Fig. 1 and e.g. Dawson, 2014, Poulsen *et al.*, 2017) with an average around 100 mmHg. The graph shows MAP values for over 40 mammalian species (not individually specified in the source paper) plotted against the body masses on a log scale. Although there is clear variation amongst species of similar body mass, there is no strong correlation with body mass per se, even across four orders of magnitude. (Note that I am not dealing here with the often considerable, entirely normal MAP variability within species understood to be diurnal, circadian, ambient-temperature or seasonally dependent features, or the effects of hibernation, estivation, etc.) Thus, whatever has determined the *absolute* value of MAP through evolutionary time, given the huge range of mammalian body sizes and shapes with broadly similar MAPs, it can have had little to do with the *absolute* peripheral resistance, nor indeed with gravity.

‘The length and sheer quantity of ‘pipes’ per se is clearly not the ‘challenge’ that sets mean arterial pressure, despite how enticing the idea seems to many’

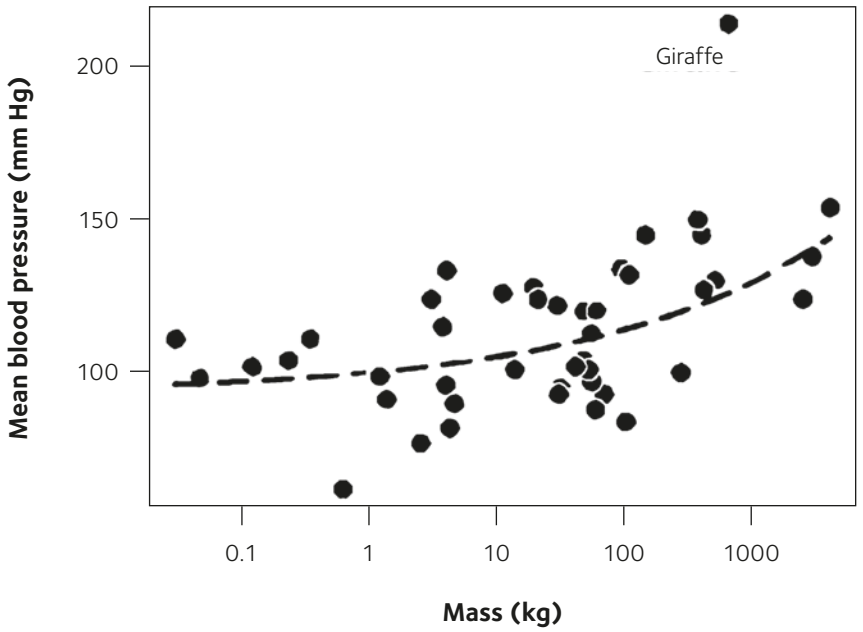


Figure 1. Mean arterial pressures for over 40 mammalian species vs body mass. Species range from mice (extreme left) to elephants (extreme right). The fitted line excludes the giraffe. (Slightly revised after White & Seymour, 2013: their Fig. 1B. See that paper for further details)

In brief, the physiological system that ‘requires’ the *absolute* value of MAP we observe is the mammalian ultrafiltration kidney (the inverted commas round ‘requires’ – and elsewhere – are to excuse my short-circuiting millions of years of mammalian evolution in this account. I’ve also neglected birds and other vertebrate classes here. And I am all too aware that asking teleological ‘why?’ questions will offer potential pitfalls). For normal function, the kidney’s glomerular capillary blood pressure (GCP) must be about 60 mmHg, not much higher, or lower. That pressure is in turn defined, for a given species, by largely invariant aspects of blood chemistry, plasma oncotic pressure, capsular hydrostatic pressure and the like that collectively determine how ultrafiltration can proceed. Beyond that, there is an adaptive requirement for mammals to be able to sustain this absolute pressure in the capillaries of Bowman’s capsule despite the range of normal physiological ‘challenges’ to MAP posed by the rest of the system. These challenges include major flow redistributions during exercise, at rest, during digestion-absorption, etc. As junior-level lectures routinely expound, GCP is sustained in the face of these challenges via the autoregulation of glomerular arteriolar tone, neuro- and hormonal regulation and other processes both local to, and remote from, the kidneys. Giving scope for this adaptive requirement is what determines that blood pressure at the proximal end of the glomerular afferent arteriole must be appreciably higher than GCP. Furthermore, there is unavoidably some pressure drop along the renal arterial tree that leads to the afferent arterioles proper. It is these factors defining a rather precise absolute pressure that can explain the ‘set point’ for MAP and the consequent tightness of its homeostatic regulation. In hypothetical terms, the mere perfusion of all other organ systems could readily be achieved at much lower arterial pressures, provided the resistance of those organs and tissues were lower. The pulmonary circulation is an obvious example, albeit one with its own qualifications defining pulmonary flow and blood pressure. The length and sheer quantity of ‘pipes’ per se is clearly not the ‘challenge’ that sets MAP, despite how enticing the idea seems to many: consider once again the mouse-man comparison.

The key point in understanding MAP regulation is that, in general, it is the various regulatory controls that keep total peripheral resistance (TPR) high – much higher than the mere ‘plumbing’ necessitates. The consequence is that, for most organs and tissues most of the time, a considerable pre-capillary drop in pressure is necessarily assured by the resistance of the local arteriolar system. Thus, we could reasonably ask a new question: why is so much force wastefully dissipated across the resistance arterioles most of the time? The advantageous result of high TPR is that a high MAP can be sustained in the face of highly variable, function-dependent flows through the various organs and tissues

that are 'plumbed' in parallel from the major arteries. It is also an obvious evolutionarily advantage for all mammals to keep their blood volume as low as possible, so a system capable of the 'demand-dependent' flow-redistribution of a minimised total blood volume, in tandem with a variable cardiac output, is the evolutionary corollary. The result is that, apart from the situation in the glomerulus of Bowman's capsule, capillary perfusion pressures are very much lower than MAP (typically at 10-20 mmHg). The consequence of raised capillary perfusion pressures in all these other tissues is oedema – excessive ultrafiltration. Thus, the dissipation of pressure, whilst wasteful on the face of it, ensures that the CVS meets all of these considerations. Overall, the dissipation of pressure in the arterioles of most tissues most of the time has proved evolutionarily advantageous, even if not energy-efficient when seen in isolation.

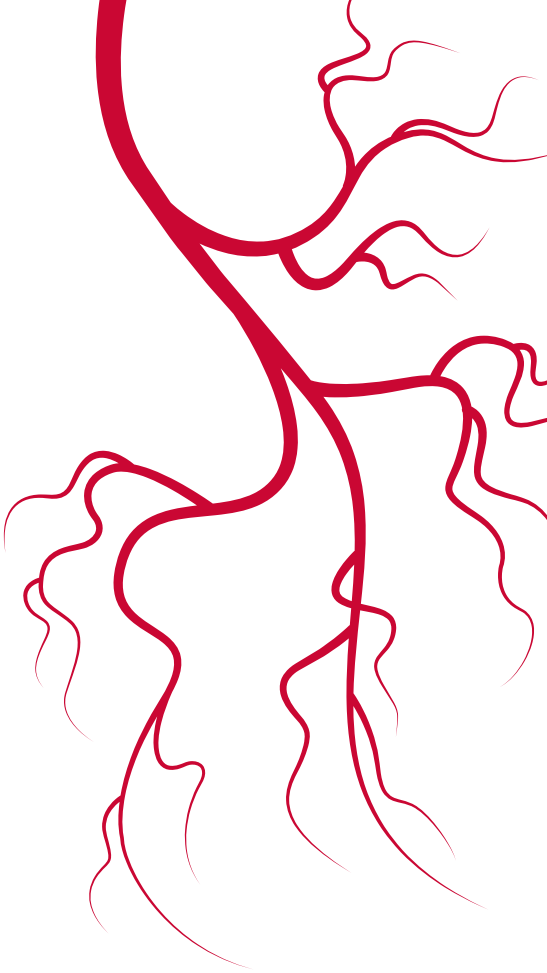
But 'what about gravity?' Isn't the high MAP 'needed' to perfuse the brain? Doesn't gravity pose a problem, at least for large mammals such as adult humans, when standing? We can put this another way round: if the evolution of an ultrafiltration kidney has delivered an average MAP of about 100 mmHg for most mammals, how far above their hearts could their brains be and yet still be blood-perfused? Decapitation scenes in horror movies are not useful to learning 'how high' blood can be pumped. In round figures, 100 mmHg equate to about 13% of one standard atmosphere pressure (760 mmHg). As hobby divers know, 1 Atm is the equivalent of about 10 m depth of water, so 13% means a 'pressure head' equivalent to about 1.3 m of water pumped against gravity (and barely less for blood: density 1.06 g/cm^3). Thus, even for the tallest humans, the top of the head can be perfused against gravity, provided only that the resistance of the arterial pathway to the head is low enough to minimise *that* pressure drop and still leave sufficient arteriolar pressure to perfuse the brain thereafter. Clearly, even the tallest mouse or cat has no such gravitational problems, nevertheless their MAP is still much the same as ours. The exceptions that prove the rule here are elephants and especially the giraffe (see Fig.1). The head of a large adult giraffe can rise over two metres above its heart. On my crude calculation, one can anticipate that adult giraffe MAP (at heart level) would need to be nearer 30% of 1 Atm – about 230 mmHg. The measured values are indeed close to that. (There is a fascinating literature exploring, for example, the extent to which a 'siphon' effect might be significant in the 'above the heart' plumbing of larger mammals, such as humans and the giraffe. Readers are directed there to learn more on the topic, e.g. Hill & Barnard, 1897, Gisolf *et al.*, 2004, Mitchell *et al.*, 2006, White & Seymour, 2013). We can conclude that an evolutionary consequence of MAP averaging around 100 mmHg for most mammals is that it has 'allowed' their heads to be up to about a metre or so above their hearts without extensive 'anti-gravity' adaptations. However, comparative physiological study of the adaptations seen in the *below*-the-heart plumbing of larger (taller) mammals also provides useful generic insight into the CVS. (Consider how the low-compliance 'pressure stocking' fascia of giraffe limbs 'combats' blood pooling near their feet, for example, or that they have very low interstitial colloid osmotic pressure, or how their *rete mirabili* regulates their brain blood pressures and flows, especially when they lower their heads well below their hearts: see, e.g. Hargens *et al.*, 1987). As perhaps the most extreme 'gravity-relevant' insight, recent work on people in Earth orbit (and thus weightless) shows that, despite the significant circulatory changes that do occur, MAP is only marginally affected (typically, but not always, reduced by *c*10 mmHg).

This topic is one where teleological 'explanations' are rife. It is seductive to assert that the body 'needs' this or that property or function 'in order to' achieve whatever physiological phenomenon is of current interest. Whilst this is often an 'in-the-trade' shorthand, we should recognise that non-specialists can too easily be left with an entirely misleading perspective on physiological mechanisms. This essay has in one sense risked a 'why' approach, but I trust the evolutionary context for this specific aspect of systems physiology is comprehensible.

If my case is compelling, it reinforces the value of comparative physiology and thereby fully recognising ourselves as the evolved animals we are in order to understand our own physiology better. The evolutionary pressures (no pun intended) and opportunities that have delivered the MAP of extant mammals are well worth studying. I hope I have convinced you that neither 'overcoming peripheral resistance' nor 'gravity' are factors in the front line for any valid account for the magnitude of the mean arterial pressure of most mammals.

Acknowledgements

I am grateful for stimulating comments on an early draft by Charles Michel (Imperial College London), Roger Seymour (University of Adelaide), Otto Hutter and Richard Burton (University of Glasgow).



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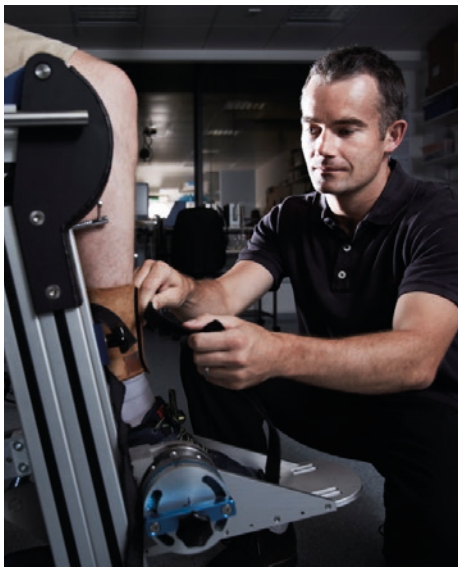
Hold your nerve

Is the nervous system to blame for muscle loss in old age?



Jamie McPhee

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Decreased skeletal muscle mass and reduced physical function in older age, commonly known as sarcopenia, is a serious condition affecting 10–20% of people aged over 65 years and is projected to affect 20–30 million Europeans by 2045. In recent years, our aim has been to develop a better understanding of the neuromuscular changes that contribute to sarcopenia. So, what have we learned?

General physical function

Let's begin by stating the obvious – on average, older people move around more slowly than younger people and the older a person becomes, the slower they move. This slowness is observed in many types of everyday activities such as sit-to-stand transitions and ascending or descending stairs, but is best represented by walking speed. A typical young adult with a walking speed of 1.85 ms^{-1} (measured during a six-minute walking test) would complete a mile in just under 15 minutes, which is 3 minutes faster than a typical 75-year-old walking at 1.49 ms^{-1}. Not so much difference between young and old, you may think, but there is considerable inter-individual variability between people of the same age. Slowness is a feature of physical frailty affecting about half of people aged over 80 years (typically walking 0.8 ms^{-1}). Such slow walking speeds are associated with a higher risk of mortality. Indeed, it could be said that the Grim Reaper's preferred walking speed is 0.82 ms^{-1}; a quirky conclusion reached by Stanaway *et al.* (2011) based on the hazard ratio of all-cause mortality being highest for people walking at this speed or slower. These are, of course, just associations, and it is unlikely that walking slowly is a direct cause of death, in the same way that grey hair is associated with ageing and infirmity but not its cause.

Nevertheless, loss of mobility has a major impact on quality of life. Not only does it reduce a person's ability to look after themselves, but slow and hesitant movements also increase susceptibility to trips and falls that can have life-changing consequences.

The decline in physical function is due, at least in part, to older adults having smaller, weaker muscles than younger adults. Hand-grip strength is commonly used to demonstrate this. Perhaps unsurprisingly, low grip strength in older age (typically <30 kg for men and <20 kg for women) is associated with an increased risk of all-cause mortality. Presumably, this association has nothing to do with one's ability to wrestle off the Grim Reaper, but is instead a component of what geriatricians have termed 'robustness'.

Large epidemiological studies tend not to include leg strength measurements, and this is unfortunate because physiological studies, which are generally smaller in scale but more detailed in methods than epidemiological studies, show that muscle changes with ageing are not straightforward processes. Muscles are not all equally susceptible. Indeed, grip strength is not representative of the performance of all muscles. When measured by magnetic resonance imaging (MRI), whole-body muscle mass in 75-year-

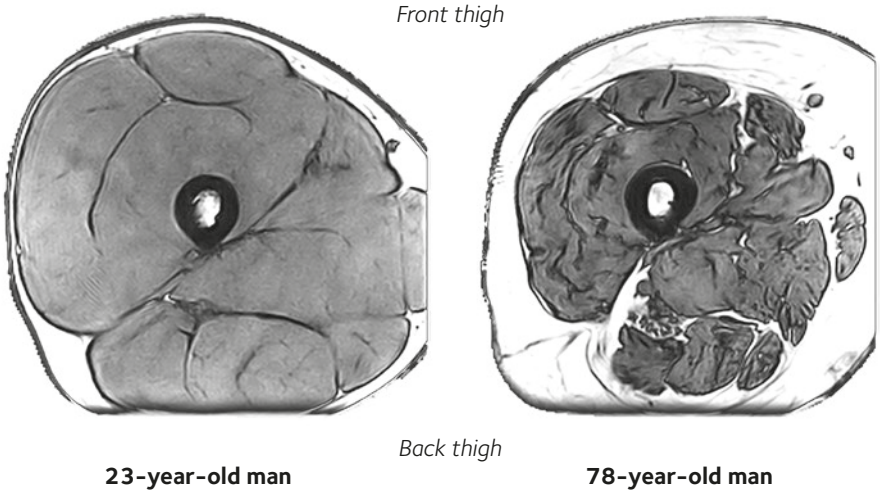

Figure 1. Mid-thigh magnetic resonance image of a young (left) and older man (right). The femur bone is in the middle creating a black ring. Muscle tissue is shaded grey, and fat tissue is white. The quadriceps muscles of the anterior thigh are typically 30-35% smaller for 75- compared with 25-year-olds.

olds was on average 15% lower when compared to 25-year-olds, but a closer look revealed upper body muscle mass was just 10% lower while leg muscle mass was almost 25% lower in older versus younger study participants (Janssen *et al.*, 2000). The large quadriceps muscles of the front thigh seem particularly susceptible to wasting and are typically about 33% smaller in 75-year-olds than 25-year-olds (McPhee *et al.*, 2018) (Fig. 1).

Measurements of maximal strength follow the same pattern of upper-limb versus lower-limb discordance observed in muscle mass. Knee extensor strength is typically around 40% lower in 75-year-olds compared to 25-year-olds, which is much greater than the 25% lower grip strength observed.

There is no question that thigh muscle weakness reduces maximal running speed and increases the effort required to negotiate stairs, but is it the cause of the decrease in walking speed and general mobility? After all, walking is not a maximal effort activity. Some studies addressing this question by pooling data from a wide range of ages and health states found that stronger people walked faster. However, within a given age group (be it younger or older) and after separating the sexes the relationship is in fact relatively weak. This is clearly demonstrated by older men having very similar strength to younger women, yet younger women walk faster and are more agile than older men. Of course, changing cardiopulmonary fitness and age-related decline of maximal heart rate, as well as orthopaedic and rheumatic conditions, a general awareness of vulnerability due to poor balance, and reduced ability to dual-task must also be taken into account.

Muscle quality and quantity

Keen readers will have noted that loss of strength is greater than the loss of muscle mass in older age. This is indeed the case.

While overall it remains true that larger muscles (determined by greater cross-sectional areas with more sarcomeres in parallel) are stronger muscles, the force produced per unit muscle mass is lower for older than it is for younger adults (McPhee *et al.*, 2018) (Fig. 2).

A great deal of effort has gone into understanding why muscle 'quality' declines in this way. It is important to remember that strength, the outward expression of muscle activity, is not only determined by the sum of forces produced from individual muscle fibres. The measured maximal strength also depends on all available motor units (the combination of alpha motor neurons and innervated muscle fibres) of the agonist muscles being fully activated and the architecture of muscle and joint structures. These features of muscle architecture and motor unit activation also change as part of the ageing process and, after accounting for these changes, it is possible to estimate the 'muscle quality' as strength per unit muscle mass (known as '*in situ* specific force'). A recent study showed that this measurement of muscle quality was reduced by 17% in older adults' quadriceps compared with younger adults (McPhee *et al.*, 2018), and this corresponds closely with a 16% lower specific tension reported for single muscle fibres (Brocca *et al.*, 2017). A five-year follow-up of the older participants revealed accelerated declines in muscle mass and strength through the eighth decade compared with estimates of changes made from age 30-70 years (McPhee *et al.*, 2018).

Although reduced muscle 'quality' and motor unit activation contribute to weakness in older age, they explain only about a third of the reduced strength. The remaining two-thirds is due to low muscle mass. Muscle mass is lost with ageing for two main reasons. First, there is a reduction of the average muscle fibre cross-sectional area, particularly affecting the larger and more powerful type 2 fibres. On average, these account for approximately 55% of total vastus lateralis (one of the four quadricep muscles) muscle fibre area in younger people and they atrophy by around 25% in older age (McPhee *et al.*, 2018). Muscle fibres of older people also show increased variability of size with some small, angular fibres and some enclosed fibres, which are hallmarks of cycles of denervation-reinnervation (Fig. 3).

The second cause of muscle loss in older age is reduction of muscle fibre numbers. However, there is surprisingly little information available about how many fibres there are in human muscles. We estimate that fibre atrophy accounts for 54% of the difference between younger and older vastus lateralis muscles, with the remaining 46% due to approximately 18% of the muscle fibres being lost (McPhee *et al.*, 2018). Type 1 and type 2 fibres are both lost during ageing.

Motor units

The loss of muscle mass in older age may be linked to declining numbers of motor units.

A motor unit comprises a single alpha motor neuron and the muscle fibres it innervates. The motor neuron cell body is located in the ventral horn of the spinal cord and projects an axon towards a target muscle where it branches to innervate muscle fibres. Large limb muscles are composed of thousands of motor units, each innervating thousands of muscle fibres. If a motor neuron dies or the axon is damaged during ageing, associated muscle fibres may lose their innervation status and become atrophied and vulnerable to apoptosis.

Direct counts of neuron cell bodies from autopsy samples in the 1970s showed declining numbers of motor neurons from age 60 years. More recent electrophysiological estimates of the quadriceps (Fig. 4) and tibialis anterior muscles suggest that 70-year-old men have on average 40% fewer motor units compared with younger men (women were not assessed). Motor unit loss appears to exceed the loss of muscle

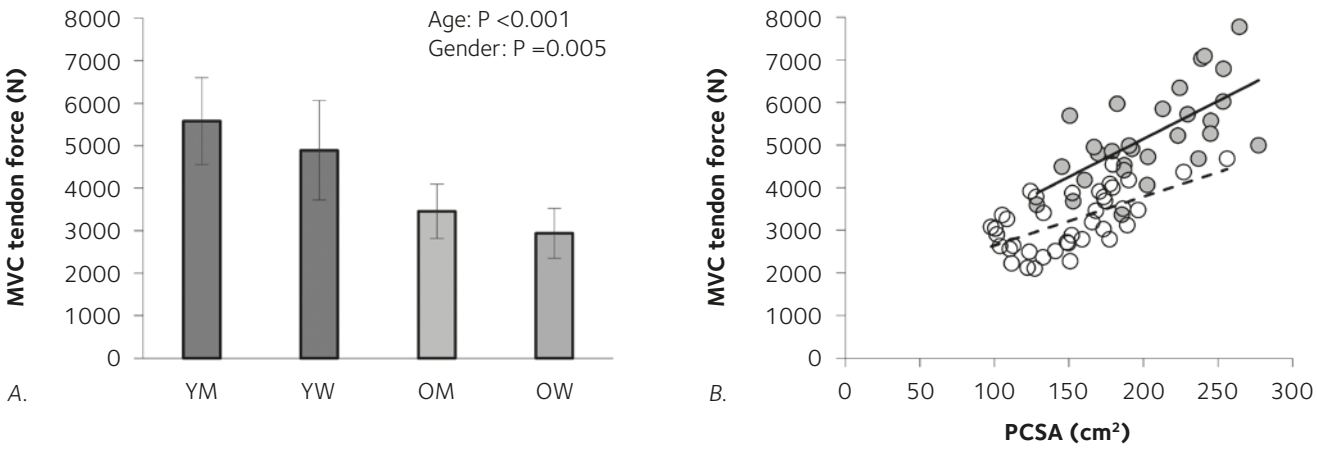

Figure 2. Patella tendon force estimated during maximal voluntary contraction (MVC), *A.* and the relationship of MVC and quadriceps physiological cross-sectional area (PCSA), *B.* YM: young men; YW: young women; OM: older men; OW: older women. Young shown with filled circles and old with open circles in *B.* Tendon force is typically 35-40% lower for 75- compared with 25-year-olds, and the loss of strength is greater than the loss of muscle mass (McPhee *et al.,* 2018).

mass and precedes sarcopenia. This is because of a compensatory mechanism whereby branching of nearby healthy motor axons can reinnervate orphaned fibres, effectively rescuing them from degradation (Piasecki *et al.*, 2018).

We do not yet know why motor neurons are lost with advancing age, nor do we know why some, but not all, orphaned muscle fibres are reinnervated. These are important areas of future research because evidence suggests that motor neurons and muscle fibres cannot be recovered once lost. It is appealing to think that motor units may be preserved in older age if they are frequently used for muscle contractions, leading to the idea that regular exercise training may protect against the full extent of motor unit loss. We have looked into this hypothesis and found no evidence that athletic older people who had been training and competing for endurance or sprint running events most of their adult lives were spared from motor unit losses. Unfortunately, we know of no way to prevent, reverse or even slow this process.

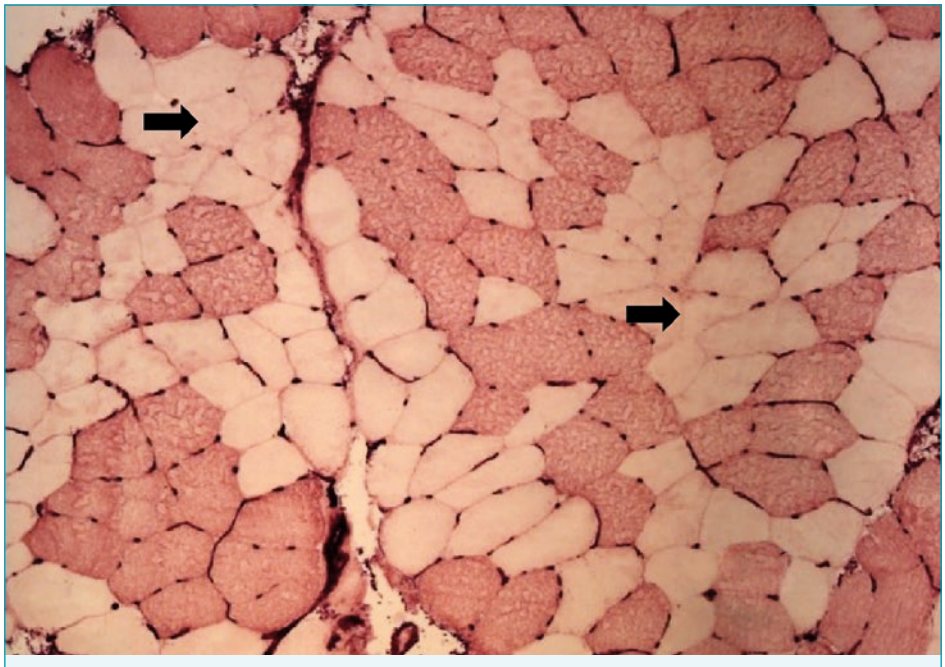

Figure 3. Muscle sample histological cross-section of an older man stained for fast myosin heavy chain. Some angular fibres are present, and arrows show enclosed fibres fully surrounded by fibres of the same type.

The benefits of regular exercise

If regular training does little to preserve motor unit numbers, what, then, are the benefits of remaining physically active into older age?

Well, the more active of you will be pleased to know that the benefits are plentiful. Anyone attending master athlete competitions will know of their dedication to training and the remarkable athletic performances of people into their 80s and, in some cases, 90s or even beyond. For instance, some 75-year-old British men run 5000 m in less than 20 minutes, which is almost 10 minutes faster than the typical time posted by a keen middle-aged park runner on a Saturday morning. Notwithstanding the achievements of exceptionally dedicated older athletes lucky enough to avoid limiting musculoskeletal complaints, there is still plenty of good news for the average older person because muscles and other body systems remain highly responsive to exercise training.

Endurance training performed at reasonably high intensity will increase cardiopulmonary fitness and muscle metabolism (McPhee *et al.*, 2016), helping to dispose of fatty acids and glucose and to utilise, rather than accumulate, fat stores. However, few older people are willing to take up running or other intense endurance activities. Instead, it is far more common for middle-aged and older people to complete relatively low-intensity activities such as walking. Lower-intensity activities are great for breaking up prolonged periods of sitting and can have many benefits for social engagement and wellbeing, but they are unlikely to improve muscle mass, strength or balance; thus, they may not prevent muscle weakness or falls risks in older age.

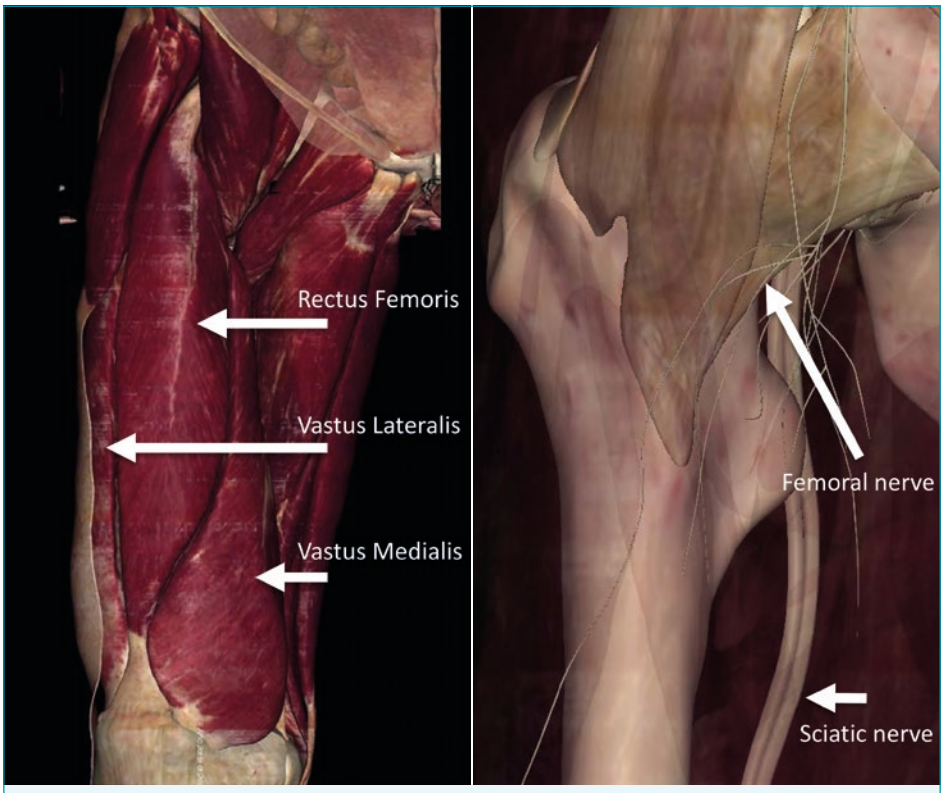

Figure 4. Anatomy of the thigh. *A.* quadriceps muscles and, *B.* nerve bundles and femur bone. Research has shown that quadriceps muscle cross-sectional area declines >30% by age 70, and numbers of motor units of the femoral nerve decline, on average, 40% by the same age.

'Motor unit loss appears to exceed the loss of muscle mass and precedes sarcopenia'

A resistance training programme can help to ameliorate type II fibre atrophy and improve muscle specific force (McPhee *et al.*, 2016). There are also adaptations within the connective tissue and tendons that make up the functional muscle tendon unit and adapted patterns of motor unit recruitment for better coordination of movements. These adaptations could increase walking speed and general physical function.

In the absence of effective or acceptable pharmacological and nutritional interventions, resistance training remains the best available intervention to combat sarcopenia. However, few older people are fond of lifting weights in the local gym. Perhaps there are cultural or confidence barriers, or perhaps it is inconceivable for healthcare providers who do not themselves lift weights in the local gym to prescribe it for older people to combat weakness and low muscle mass.

For these reasons, mixed exercise sessions involving some light resistance, moderate intensity endurance and balance exercises are recommended to maintain or improve physical function amongst older people. Yet, the largest trial of mixed exercise training for previously sedentary older adults at risk of developing weakness showed very little improvement of physical function after training three times per week for more than 24 months (results of the LIFE Study, e.g. see Santanasto *et al.*, 2017). This might indicate diminishing returns in older age, possibly due to irreversible motor unit declines that already occurred, or it could be that the resistance exercise allocation was simply not enough.

Either way, there is no easy answer to the question of what types of exercise older people should do to maintain health and physical function. For now, the pragmatic response is that everyone should complete activities they enjoy because they are more likely to maintain these activities over the months and years.

Acknowledgements

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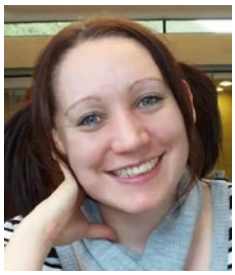
What does the future hold for the teaching of physiology in UK Higher Education Institutions?

Seeking meaning in a constantly shifting landscape



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'There is no feeling in life as rewarding as successfully imparting knowledge to others'

Quote from Nick Hillman, Director of the Higher Education Policy Institute, in the foreword to The Physiological Society's 'Recognising Teachers in the Life Sciences' 2015 publication.

A Theme Leads' report

We are experiencing a period of tremendous turbulence in the running of our degree programmes in UK Higher Education Institutions (HEIs). Some of the recent changes that we have had to urgently address are:

- **The advent of the Teaching Excellence Framework (TEF)**
  Currently this is deployed at the institutional level but will soon to be filtered down to us at course and subject level too.

- **The removal of the government cap on student numbers**
  The expansion of provision and uptake of higher education continues apace (Scott, 1995). This has a disproportionate impact on laboratory-based disciplines such as physiology, because running practical sessions is a very expensive and time-consuming business, quite apart from the time one then needs to set aside for assessing such work.

- **Students being largely responsible for funding their own education**
  This has led to profound changes in the relationship between institutions and their students. This in turn has meant that courses now put much more emphasis on the future employability prospects of our students with employability skills often being 'embedded' within our curricula. This is a particular problem for the teaching of physiology, as many students do not realise the range and variety of career paths a degree in physiology opens up to them.

- **Massive Open Online Courses (MOOCS) and e-mediated learning**
  What is the role of the traditional, didactic lecture in a large lecture hall in this brave new world? At a very practical level there is a current debate about whether or not we should video or audio record our lectures for students to download at their convenience. If our lecture halls are half empty, how do we engender learning communities within our institutions?

- **University league tables and the National Student Survey (NSS)**
  As a consequence of trying to boost league table rankings and NSS scores, there has been a shift towards performance management of academic staff. Universities thus become more like businesses with burgeoning numbers of university administrators employed to address league table, TEF and NSS metrics.

Academics in the future can present themselves as physiologists in a number of different ways reflecting their expertise, interests and the stage of their career.

Much of this activity is unrecognisable to those of us who started off our careers as laboratory-based scientists interested primarily in research. However, with the much heralded re-emphasis of the importance of learning and teaching in UK HEIs (Willetts, 2013), academics are having to think a bit more deeply about their pedagogic practice and their roles as physiology educators. In making the dispositional shift from a research focus to one involving teaching and learning, academics have been assisted by the development of the UK Professional Standards Framework by the Higher Education Academy (now part of Advance HE) and the various types of Fellowships aligned to different levels of the Framework. This professionalisation of the academic workforce alongside the increasingly prevalent requirement for university lecturers to obtain a teaching qualification makes the role of teaching and learning in UK HEIs more explicit. Indeed, our institutions must make an annual return to the Higher Education Statistics Agency (HESA) on academic staff teaching qualifications.

We, as Education Theme Leads, would argue that the current environment represents a period of unprecedented transition where careers may be more fluid, flexible and generally amenable to formal career development and progression. Academics in the future can present themselves as physiologists in a number of different ways reflecting their expertise, interests and the stage of their career. For instance, many academics seek to communicate physiology to the wider community via Outreach Activities, Citizen Science projects, production and dissemination of e-learning tools and Public Engagement roles. This broadening out of what it means to be a physiologist can act as a source of inspiration and renewal to us all as well as to our learners.

The Physiological Society via the Education Theme has played a pivotal role in disseminating and translating many of these developments to the community. In particular, in aiming to help academics reframe their careers in this multi-dimensional and fragmented world, The Physiological Society has produced materials such as 'Recognising Teachers in the Life Sciences'. This publication sought to '*Raise the status and valuation of teaching in careers in Higher Education*' (Harris, 2015).

Equally pertinent is the fact that there will be a session at the forthcoming Europhysiology Conference (14–16 September 2018 at the QEII Centre, London) devoted to *Innovations in Physiology Education* organised by Sarah Hall from Cardiff University, which is part of a move to integrate the physiology education theme more fully with the other research-orientated themes at Physiological Society conferences in the future.

'We should be proud of, and excited by, the role we are playing in moulding and enthusing the next generation of physiologists as well as informing wider society'

Consequently, it is a fascinating time to be a physiology educator. There are many avenues open to us to explore and develop our careers. The Physiological Society, alongside others, has devoted considerable time and energy to supporting academics in the pedagogic elements of their practice, funding Education Theme workshops, providing the David Jordan teaching grants which give up to £10,000 to academics to conduct a pedagogical project or develop an educational resource and promoting teaching as a way to further one's career. Working with and for students is now much more the explicit focus of the activity of many in our universities. We should be proud of, and excited by, the role we are playing in moulding and enthusing the next generation of physiologists as well as informing wider society. After all, if there is one thing that physiologists are good at it is adapting to environmental stresses and integrating new ideas, so we are all very well placed to thrive in the current, shifting HE landscape!

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Mysteries of the action potential

From 1952 to infinity and beyond?

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Electrochemical signalling allows rapid communication between neurons to coordinate sensory information and the responses of billions of cells around the body. Students are taught that these electrical nerve impulses, or action potentials, propagate through local changes in potential difference along the cell membrane caused by the opening of ion channels, which in turn trigger neighbouring voltage-sensitive ion channels to open, and so forth, like a set of dominoes. Here, we reconsider the fundamental nature of action potentials and whether their generation may also involve a pulsatile mechanical element arising from ion channel opening and subsequent transmission of kinetic energy through the lipid bilayer via a 'soliton' (a self-reinforcing solitary wave packet that maintains its shape while it propagates at a constant velocity).

The Hodgkin and Huxley (H&H) action potential model described in 1952 predicts the nature of ionic currents crossing cell membranes, which creates a potential difference that changes over time due to changes in the ionic equilibrium. It is well supported by electrophysiological measurements and observations. Recent evidence suggests that a 'force-from-lipid' model (Brohawn *et al.*, 2014) could transmit pulses into mechanosensitive ion channels in the absence of other cellular components and might also explain propagation through the membrane lipid. We envisage that it would take the form of a soliton known as an action potential pulse (APPulse) which would be the precursor of ion channel opening. Action potentials are critical to the operation of the brain, and computation and timing of the action potential is important in considering any possible computational requirements. This is particularly true when striving to model artificial intelligence (AI), where accurate coding and timing of action potentials are paramount.

Action potential models and mechanisms in AI must correlate with perceived observations and incorporate physical elements to accurately reflect the movement of ions and action potential spread across the entirety of the cell membrane. Thus, the mechanisms that define the speed of the action potential will directly affect the available methods of reliable computation available to an artificial brain neural network where changes in accuracy of action potential timing would make any form of computation unreliable. Therefore, it is important to consider the standpoint from which the action potential is viewed.

The physiological viewpoint

Measurements of the action potential are taken from both sides of the membrane and

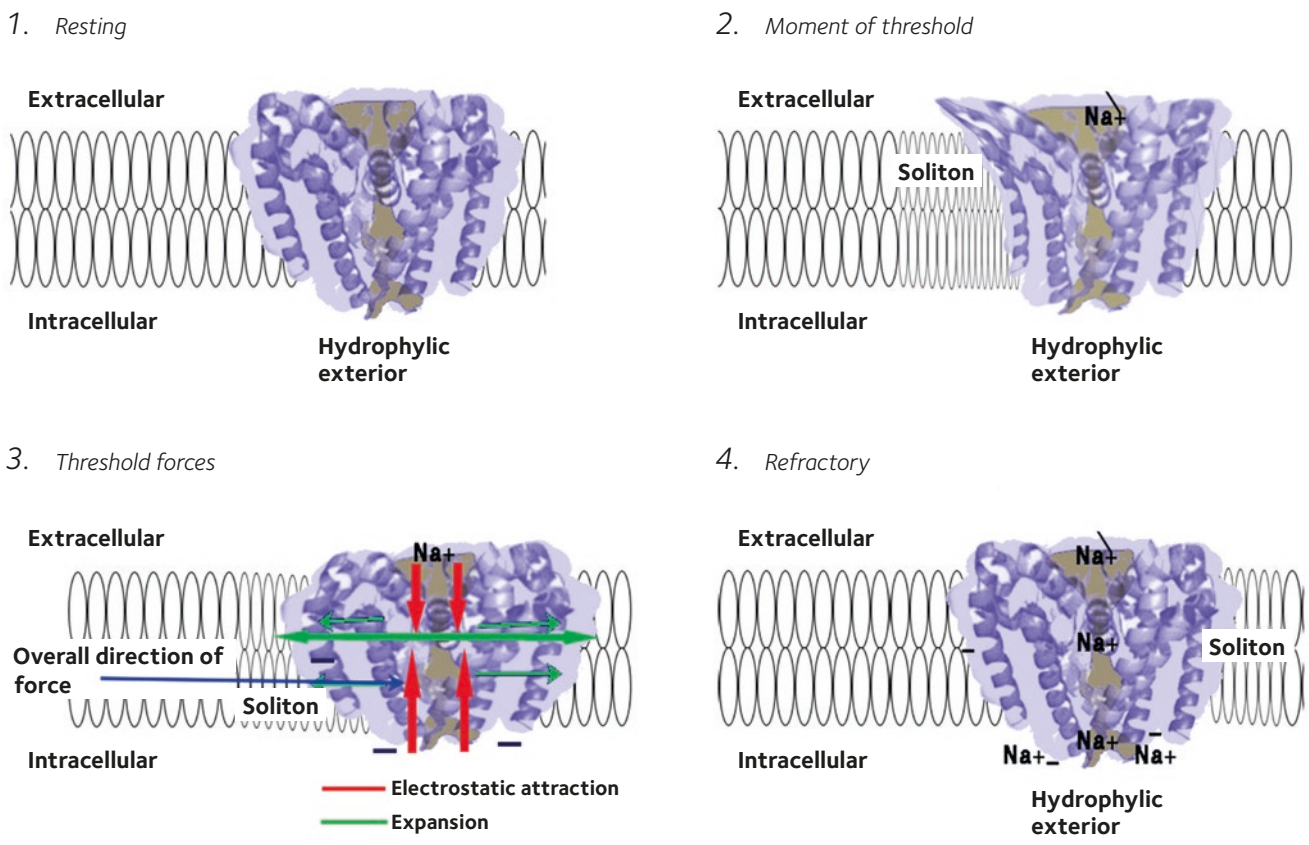

Figure 1. The APPulse. Illustration of how force-from-lipid may act on a eukaryotic voltage-gated sodium ion channel modelled from the American cockroach (adapted from McCusker *et al.*, 2012 and Shen *et al.*, 2017).

1. *Resting.* Na^+ selective ion channel embedded in a membrane at resting state. The main structure of a channel is four coiled helices. One of these helices is connected to a hydrophilic, negatively charged spiral placed intracellularly.
2. *Moment of Threshold.* As a soliton approaches, the ion channel pressure will develop on the sides of the ion channel displacing the helices and destroying the electrostatic insulation across the membrane. Positive charges are then attracted to the intracellular space but also to the hydrophilic surfaces of the pore and are drawn inwards.
3. *Threshold Forces.* Movement of the hydrophilic negatively charged spiral due to incoming Na^+ ions undoes the main spiral, which causes the pore to open mechanically in an iris movement (McCusker *et al.*, 2012). At threshold, contraction of the structure during pore opening generates forces along the surface of the membrane as the helices are pressured outwards. This action is synchronised to the arrival of the soliton, and the mechanical energy is transferred to the soliton, thereby reducing entropy.
4. *Refractory.* When sufficient positive charges have reached the interior, equalising charge adjacent to the hydrophilic spiral, the forces equalise and the pore will close. The pore and structure of the ion channel protein is now at rest. Any further soliton or disturbance to the membrane will not cause activation of the ion channel pump until the excess Na^+ ions in the vicinity of the hydrophilic regions and the activating spiral are removed by diffusion. The ion channel is refractory until this charge is cleared, thus allowing for further electrostatic attraction.

Synchronisation is achieved between the ion channel pump and the soliton, whereby electrostatic forces are converted into mechanical force and then transferred to a soliton.

measure the potential difference across a wide area – this is the macroscopic view. Electrophysiologically, 'patch clamp' studies may assess areas of membrane at the microscopic level when examining single or at least a limited number of ion channels.

An action potential may be measured with intracellular microelectrodes in continuum with the cytosol – but is a product of the ion changes at the surface of the membrane. Small diameter axons (approx. 0.2 µm) have low concentrations of widely spread ion channels (Holden and Yoda, 1981; Catterall, 2012). Patch clamp studies can measure the potential changes at the membrane but cannot measure live action potentials. As the action potential progresses, the micro-pipette measures current not from a point on the membrane, but from a temporally adjusted area including multiple ion channels, and may not reflect the mechanisms of propagation from a single point.

The Hodgkin Huxley equation and Cable Theory

The H&H equation describes ionic flow across the membrane in mathematical terms over the time period between when the membrane reaches threshold and the end of the refractory period. At any one point on the membrane, at any moment, the polarity can be thought of as being in one of three states: resting, polarised or refractory. The membrane can be considered polarised

immediately before the threshold takes effect, as after that point there is no return. After threshold, the membrane is in the refractory state as no further action potential can be created without a return to the resting state.

The action potential typically has a maximum speed of ~ 1 m/s in unmyelinated axons (Waxman and Bennett, 1972). We know therefore that there is a 'leading edge' just before depolarisation and that, in order to advance the action potential, this leading edge must have the innate property of self-propagation. In effect, the leading edge also instigates the refractory period once the depolarising wave has passed. Patch clamp recordings of single ion channels have demonstrated that threshold, the depolarisation spike, and the refractory period can all be explained by the movement of Na^+ through its channel alone (Holden and Yoda, 1981; Catterall, 2012). Thus, the physical origins of the potential changes associated with the action potential can be directly attributed to the ion channel mechanisms, with the activity of the Na^+ channels defining its progression. This implies that the only element of the action potential that is responsible for its live propagation is defined by the mechanism that causes the threshold at the leading edge. The threshold alone is the initiator of the action potential and the rate limiter to the speed of the action potential. The action potential over a given surface is temporally stable and, for example, in the small neurons of the cortex, timing differences are accurate to under a millisecond.

The timing of the spike is therefore directly related only to the threshold. The threshold may be better defined temporally so that it is not a potential difference but a change over time. The rest of the action potential is only concerned with the refractory period and stabilisation to resting potential and is irrelevant to speed of transmission, although of course the refractory period can affect the frequency of transmission. All of the above should be fairly obvious to neurophysiologists.

The physical and biophysical viewpoint

As above, the mechanism that defines the threshold can be investigated with the knowledge of the properties of just the Na^+ channels and the membrane. Cable Theory defines the potential arising from ion disparity across the membrane acting as a capacitance. Historically, Cable Theory comes from a direct analogy from capacitance theory and considers charge over the whole surface of an insulator.

The depolarisation of the membrane during the action potential is analogous to the discharge of a charged capacitor, and the mathematics of cross-current resistances appear to work correctly over a large part of the membrane in the macroscopic view experimentally. This is the basis for the H&H model. A capacitor charging under voltage clamp therefore acts as expected when the potential changes, as each measurement is independent of time.

In an electrical capacitor, the change of charge is due to electrons. The charge of an electron is not fixed to its atom, and charge at any place on the plate surface rises immediately. The same charge may be measured at any location on the surface; because it is charge that is created rather than current, there is always spread of potential from one site on a plate to the other. During charging, this occurs when electrons align and is a time-dependent process, subject to the lateral resistance of the plate. Electrons have the ability to spread their charges freely and are not fixed by location since they are freely distributed and, importantly, charge is evenly spread along the insulator.

When H&H were conducting their experiments, an accurate depiction of the membrane, ion channels and specifically inter-channel distances was not available and channels were assumed to be 'separated by an infinitesimal distance'. It was not until the 1970s to 1980s when single patch clamping became available (Hamill *et al.,* 1981) that accurate measurements of channel density became known (Hille, 1992). At the time that H&H described longitudinal flow, the assumption was that there was a mechanism by which activation of an ion channel during threshold would activate adjacent ion channels and produce a cumulative and on-going propagation – just as the charging electrons distribute evenly and almost instantaneously. However, the mechanism of propagation between channels was not identified then and has still not been identified today.

The action potential does not take place across the whole neuron or axon at once, but travels across the neuronal membrane. By the time a propagating action potential is measured by a pipette from the interior of the axon, the threshold of the action potential has already passed and the resulting measurement is a result of all the combined ionic changes over a very wide portion of membrane. The observed action potential results from the imbalance of positive ions across the membrane during voltage clam-induced steady state, and may be predicted from the H&H model.

Intra-ion channel distances have been measured accurately, although this distance is variable. Single (or low multiple) ion channel recording using a patch clamp pipette of ~1.5 µm diameter is reliant on a low density of ion channels within the isolated membrane 'patch'. As the membranes examined contain many different ion channels, we can

A 'soliton' mechanical pulse accompanies a stable action potential propagating at constant velocity (Anishkin *et al.,* 2014; Takahashi *et al.,* 2016).
Ion channel separation is too great to allow for ion channel interference from adjacent channels caused by ionic charge (Johnson, 2015).
Ion channels can be opened by mechanical stimulus (Browhan *et al.,* 2014; Takahashi *et al.,* 2016).
Deformation of the membrane occurs by activation of ion channels (Machta & El Hady, 2015).
Entropy (thermodynamic) measurements do not follow the H&H action potential but do follow the APPulse (Howarth, 1968; Tasaki & Byrne, 1992)

Table 1. Evidence supporting the Action Potential Pulse (APPulse) concept.

confidently say the Na^+ channels are spaced at least 1.5 µm apart, otherwise two channels are detected. As Hille (1992) points out, 'channels are not crowded' together and the distance a Na^+ ion has to affect another is limited by the time taken to travel through the ion-specific channel and to the next channel. The ionic radius of Na^+ is known and is about 116 picometres (Shannon, 1976), indicating that a Na^+ ion has to lie adjacent or in very close proximity to the Na^+ channel. The time required for charge to spread from one ion channel to the next can be calculated from the ionic radii and the diffusion coefficient (Goodman *et al.*, 2005). A conservative simple Speed-Time calculation suggests that the maximum speed Na^+ ions can travel between channels is less than a thousandth of what is necessary for propagation (Johnson, 2015). Cable Theory only models the ion flows of the action potential under conditions of voltage clamp, but as yet there is no known mechanism for propagation of the action potential provided by Cable Theory. This suggests that the H&H model only demonstrates the electrically measured activity surrounding the underlying mechanism of propagation from one channel to the next, not the mechanism itself.

Is there evidence for a mechanical component in action potential propagation?

For propagation to occur, positive ions (i.e. Na^+) would have to behave as electron-like particles for the diffusion kinetics to make sense. Therefore, without a mechanical component the H&H action potential cannot propagate.

As mentioned above, the 'force-from-lipid' model (Brohawn *et al.*, 2014) could also explain propagation through the membrane lipid, via a soliton mechanical lipid pulse which is coupled to forces created by the electrostatic opening of ion channels (Fig. 1). A substantial body of evidence supports the APPulse concept (Table 1).

The action potential measured by H&H is a measure of the sum of all the potential changes of all charges across the membrane over a wide area. There is a timing dissonance for the observer where the latency caused by the pipette creates the impression of a combined effect of all the ion channels over a large period of time. The result is always a combination of effects from many ion channels, some open, some closed and some inactivated and thus contributing to the refractory period of the action potential.

Positive ions do not behave as electrons and require time and the correct diffusion coefficient to move. Calculation of ion channel distribution from single channel studies demonstrates that Cable Theory can only account for the action potential in its stable states (resting or maintained by voltage clamp) (Takahashi *et al.*, 2016), but the ion channels are spread too far apart for the H&H model to work. The longitudinal resistance in the H&H arrangement is always infinite as there is no mechanism that provides surface spread depolarisation. Surface spread and thus speed of the action potential must therefore occur by another mechanism – the APPulse suggests that this is by a mechanical 'soliton' wave coupled to entropy provided by the ion exchangers described (Takahashi *et al.*, 2016).

A deconstruction of the action potential yielded evidence for a synchronised oscillating pulse structure energetically derived from the ion exchange mechanisms (Hodgkin and Huxley, 1952; Takahashi *et al.*, 2016) and a subsequent mechanical pulse. Such a pulse mechanically opens ion channels leading to further depolarisation (Takahashi *et al.*, 2016). This model can also help to explain action potential transmission in myelinated nerve. The pulse could be controlled by the ion channels, because if there are insufficient ion channels to produce enough energy for the pulse to reach the channels at the next node of Ranvier, then it will fail as in ion channel blockade.

Therefore, the action potential travels at a speed commensurate with the membrane dynamics of the axon: the transmission dynamic of any axon or part of an axon may be different depending upon the membrane components and the physical formation of the membrane. At any time, the transmission dynamic represents the exact state of the axon and everything that affects its transmission timing, speed and refractory state. Speed of axonal transmission, and therefore the time impulses take to reach their destination, is variable and depends upon the axon type and diameter.

Conclusion

The action potential as expressed by Hodgkin and Huxley (1952) is a measurement of the progression of ionic charge over the axon membrane, but it cannot represent the mechanism of propagation. This is because the physical properties of Na^+ ions cannot allow flow of charge from one ion channel to the next in the time available. There must therefore be another mechanism present, and we propose that this is provided by a 'soliton' mechanical pulse, which is the force-from-lipid mechanical force that opens the Na^+ channels. This coupled APPulse fulfils the requirement for a continuing action potential where Cable Theory fails.

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The future of education? Using 3D animation and virtual reality in teaching physiology

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After 30 years in cardiovascular research, my job abruptly became more teaching-focussed. This was quite an upheaval, and it presented me with the challenge of engaging with the scholarship of teaching and learning. After a period of mild confusion, I was alerted to the David Jordan Teaching Award. Aimed at Society members who were trying to get started in educational research, this scheme seemed ideal for me. With no real expectation, I applied for the award and was successful. Four years on from completion, do I think it made a difference? The short answer is: YES, a huge difference. The longer answer follows below.

My project was titled 'Creation of anatomically accurate 3D animations for teaching physiology'. The idea seemed simple, but the technical aspects would be challenging. Put simply, could 3D volumetric image data, collected using confocal laser scanning microscopy, be used within sophisticated animation software to create 3D animations for teaching physiology? Once we overcame the technical challenge of converting the scientific data into the animation software, we set about building an animation of vascular structure (Daly *et al.,* 2014) and neurotransmission within the vascular wall (Daly *et al.,* 2016; **bit.ly/2I8PWiY**).

The neurotransmission animation was then used in an educational-multimedia study to examine the effect of animation versus stills in teaching and learning. Overall, we observed very strong student satisfaction with the 3D approach. However, we did not detect any improvement in learning when using animation (Daly *et al.,* 2016). One of our conclusions was that extraneous cognitive loading was too high in the animated version of the presentation. This opened another avenue of research into the relevance of various multimedia learning theories (Mayer, 2014) as applied to 3D animations, and multimedia.

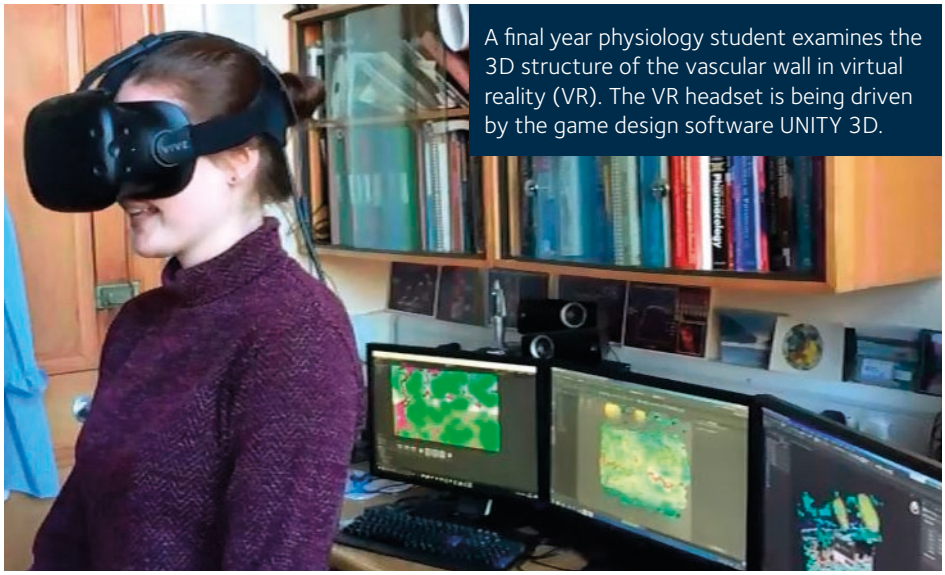
The success of the workflow we established through the David Jordan Teaching Award enabled us to create more animations which can be found on my YouTube channel (**bit.ly/2KO2Apj**). One of the animations (Development of Atherosclerosis) had 40,000 views in the last year.

More recently, the animation work has evolved to incorporate virtual reality (VR). Fully immersive VR headsets are reasonably accessible and affordable. Over the course of a few months, I worked on the data flow to take my 3D structures from animation software to computer game design and then to VR (learn more about the process in this video: **bit.ly/2I5lO8b**).

I presented the results of our recent educational research on cognitive loading of animations and VR at Pharmacology 2017 and won the prize for best oral communication. Briefly, our study found that student preference, for the design of educational 3D animations, was to have both narration and on-screen text. This contravenes one of the educational theories (the redundancy principle) which suggests that both text & narration in a multimedia presentation would reduce learning. However, this theory, and many like it, need to be re-examined for their relevance to VR, augmented reality (AR) and mixed-reality (combined VR & AR) educational designs.

Since being awarded the David Jordan Teaching Award, I have presented posters and oral communications at six education symposia. As a lifelong researcher in cardiovascular science, I would never have envisaged how much my career could be shaped by a single grant award. I now have the perfect way to combine my interest in laser scanning confocal microscopy, image analysis, 3D animations and virtual reality. I also have an avenue of educational research to investigate (i.e. the optimal design of VR learning environments and cognitive loading of 3D animations).

If you are interested in breaking into the educational research world then the David Jordan Teaching Award is ideal, and I would thoroughly recommend applying. I am extremely grateful to The Physiological Society for the award as it has provided me with a completely new avenue of research to pursue.



A final year physiology student examines the 3D structure of the vascular wall in virtual reality (VR). The VR headset is being driven by the game design software UNITY 3D.

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The three wise professors: Autonomy, Mastery and Meaning. Which one to supervise your PhD?

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Throughout the years, I have been mentored by three professors: Professor Autonomy, Professor Mastery and Professor Meaning. In order to be a professor, you must have an element of all three, but like science, all of them have a bias.

Professor Autonomy

A doctoral journey is not for the faint-hearted no matter where you start, but this is particularly true if you start it with Professor Autonomy.

Professor Autonomy invented the term 'independent researcher' (or perhaps, universities invented the term as a cover for professors who leave you up s*** creek without a paddle). In the quest for guidance you will be reminded of your status as an independent researcher. However, autonomy in relation to your educational journey does not mean autonomy in terms of your role in Professor Autonomy's research ambitions. In this context, you will wonder if Professor Autonomy was derived from Professor Autocratic.

Professor Autonomy is a big fan of mastery but only after you've proceeded with an inappropriate study design, collected questionable data and made what seem to him like utterly speculative interpretations. Cue demotivation and the need to develop resilience – fast. Professor Autonomy's meaning lies largely in the next grant he or she is trying to obtain and in demonstrating superiority to university colleagues. As you become more informed, you may find there is little meaning other than the metric.

Every autonomous professor has a silver lining. Firstly, his or her drive toward the metric provides opportunity via grant funding for students. Secondly, provided you have sufficient resilience to begin with, you will experience failure and criticism of a magnitude that will develop a level of resilience you did not know you had. Finally, you will be an independent thinker, a skill that will sustain the rest of your intellectual life. Independent thought begins to emerge from a weariness to intellectual punishment beatings. You eventually learn to fight back with intellect. If you like research but need to develop resilience, don't start here – you won't make it through.

You will spend long hours in a lab collecting data you don't fully understand but as your professor will remind you – it is of course central to the 'bigger picture' and 'your thesis' (whenever you get to write that). Maintaining your autonomous and therefore largely un-informed status means you will chart this course for longer than you should. In meetings about your PhD you will be encouraged to become part of the academic community and bring your own ideas to the table, provided they don't interfere with your time in the laboratory.

Professor Mastery

Professor Mastery is just that. Everything is flawless: your registration form, your weekly meeting appointment, your ethical application, your study design, your protocol and your data. Professor Mastery is patient and will teach you every trick of the scientific trade until you are capable of publishing systematic reviews worthy of inclusion by the Cochrane collaboration.

You will publish early and often; there will be no last-minute writing of a thesis, as is the case with Professor Autonomy. Speaking of autonomy, you will not have much, particularly in the early days. This is a system designed to perfection, and although you will be free within the system, there is not much room to get lost. Professor Mastery slowly increases the autonomy you are afforded toward the end of the process, without ever completely removing the shackles.

Professor Mastery finds meaning in your education, as well as the advancement of his own scientific career. Professor Mastery is the perfect starting point no matter what end of the spectrum you perceive your resilience or scientific capabilities to be. If you start with Professor Mastery, quickly move on to Professor Autonomy or Professor Meaning otherwise you may have a career of mastery with little meaning. In the words of Adam Grant, 'practice makes perfect but it doesn't make original'.

If you start with Professor Autonomy, then move to Professor Mastery next. You can already think for yourself; he or she will show you how to turn that thinking into tangible productivity.

Professor Meaning

There are two times when you want to encounter Professor Meaning. Really early in your doctoral journey in order to be inspired or much, much later, but not too late. To maximise the value of Professor Meaning you need to have already acquired the skills of Professor Autonomy and Professor Mastery, but not be too far gone that you no longer have the will to change the course of your career.

There is no time for any developmental skills with Professor Meaning; he or she assumes autonomy and mastery like a cup of coffee that morning. Professor Meaning does not even know where to get an ethics form (seriously). Someone else takes care of that; he or she cannot remember whom.

Professor Meaning is totally focused on making a difference. The evidence of this will be littered around the University in the form of admiring and resentful colleagues, books and public engagement. Professor Meaning is not to be confused with Professor Publicity who is not discussed here. Professor Meaning uses publicity to advance the issues he or she finds meaningful rather than advance public persona.

Professor Meaning cultivates a people-centred environment for he or she knows that this is the only way to achieve anything meaningful. The administrators, placement students, PhD candidates and lecturers are all part of one giant human wheel rolling toward meaning. Outsiders will portray Professor Meaning as a maverick and perhaps arrogant; he or she simply believes that something different is possible. Professor Meaning is still human and draws on the compassion of the human wheel during times of sticks and stones.

Experience of working with all of them at some point is better than only having met one or two in the correct order. Good luck!

Syrian hamsters, auditory hallucinations and autophagy in Alzheimer's: Greater Manchester Physiology Symposium

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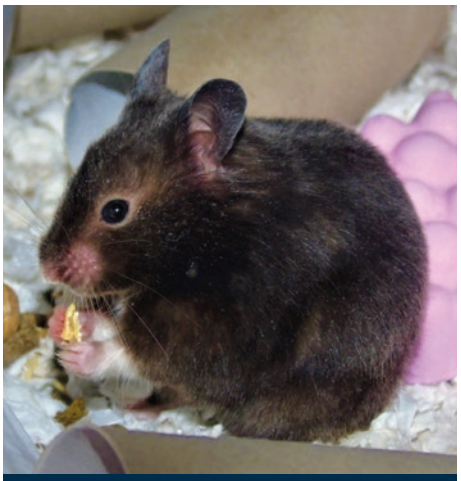
In our busy everyday lives, it is easy to lose touch with research occurring down the road at other institutions. Our one-day conference in April brought together nearly one hundred enthusiastic physiologists from across the three Universities in Greater Manchester (University of Manchester [UoM], Manchester Metropolitan University [MMU] and University of Salford [UoS]). Bringing together researchers across physiological disciplines allows us to form unexpected collaborations, and to keep physiology alive and kicking in our own cities and beyond. Rather than organising a meeting themed around a certain topic, we focused on inviting speakers at different stages of their research careers.

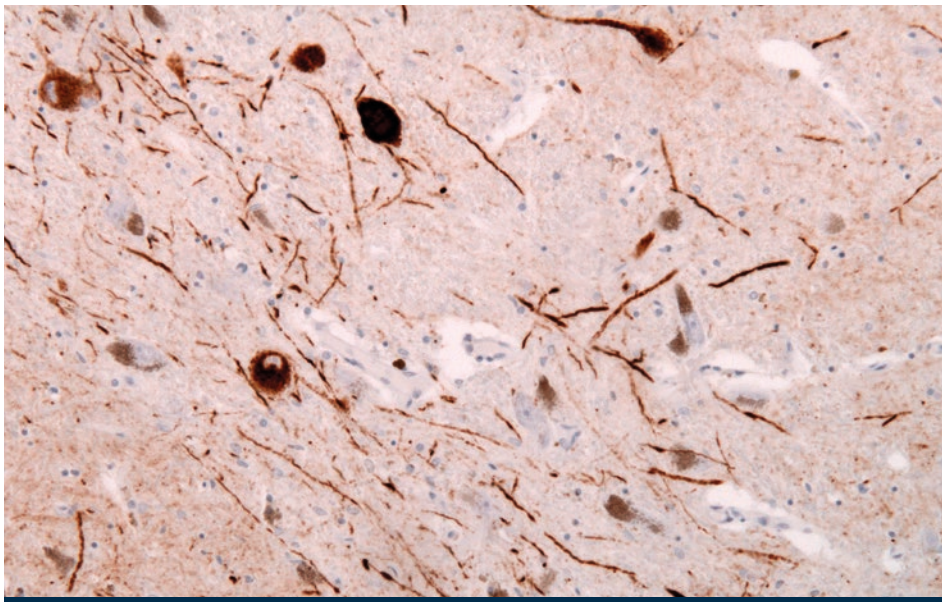
For example, Jess Caldwell (UoM) talked about her PhD, investigating possible treatments for heart failure. She focuses on the T-tubules (which deliver extracellular calcium ions to the atria); they are lost following heart failure, leading to a loss of synchronicity in atrial contraction. Although there is some regeneration of the T-tubule network after heart failure, this tends to be disorganised compared to control cells. Jess has found that transfection of neonatal cells with amphiphysin II (Amp II) can lead to the formation of T-tubules, meaning that Amp II may be involved in restoring T-tubules in patients with heart failure.

Andrew Loudon summarised his 40 years of research into body clocks. He explained that, in hibernating mammals, behaviour (such as mating) is driven by melatonin, which is secreted by the pineal gland. As this gland is light-sensitive, it responds to day length; in Syrian hamsters, gonad growth is stimulated by an increase in day length. Melatonin acts on cells in the pars tuberalis (a small part of the pituitary gland that contains cells that secrete TSH [thyroid stimulating hormone] to control the animal's metabolism and growth). Logically, thyroidectomy locks these animals into a state in which they are unable to breed, migrate and perform other essential behaviours.

Keeping on the subject of neurophysiology, Llwyd Orton (MMU) introduced the second most common form of dementia, dementia with Lewy bodies (DLB). It is often misdiagnosed, as the symptoms, including fluctuating cognitive decline, REM sleep disorder and recurrent visual hallucinations, are found in other neurodegenerative conditions. Llwyd's interest lies in auditory hallucinations. He has found that applying kainate (acid occurring naturally in some seaweed) to the auditory cortex generates gamma oscillations, which may lead to hallucinations. These oscillations were found to be faster in a mouse model of DLB than in control mice. These mice also developed epilepsy at lower doses of kainate than controls. Llwyd conducted a systematic review which demonstrated a high prevalence of auditory hallucinations in DLB patients compared to patients with Parkinson's Disease.



Andrew Loudon is an expert on body clocks and has studied physiological changes during hibernation in Syrian hamsters. Image by Ryukyu Inu.



Llwyd Orton studies auditory hallucinations in dementia with Lewy bodies. Image by Jensflorian, Immunohistochemical staining of Lewy Neurites in a case of Lewy Body Dementia (DLB).

Gemma Lace-Costain (UoS) gave an animated account of her research into Alzheimer's Disease (AD). She first provided an overview of what is known about AD – namely that an abnormal accumulation of protein leads to cognitive impairment and cell death. She then discussed her research into protein degradation in the brain and the different mechanisms of autophagy. She has measured markers of autophagy in human brain tissue from the Manchester Brain Bank and found that in some regions of the hippocampus there is a decline in these markers as tau pathology increases. This suggests that switching on autophagy may have beneficial effects in terms of slowing down the development of AD. In a very interactive talk, she asked how many audience members had a 'favourite protein' and mentioned how she reassures students that it is OK to be a geeky scientist!

The symposium ended with Rachel Tribe's GL Brown Prize lecture entitled 'How to expect the unexpected?' See p. 21 for more about her talk.

I'd like to thank the other Physiological Society Reps, Ian Kay (MMU) and David Greensmith (UoS), as well as my colleagues, Holly Shiels, Liz Sheader and David Eisner, for helping to organise the day, and of course The Physiological Society for funding it.

Better start them young: healthy lifestyle education in middle school – an event organised as part of Physiology Friday

Veronica Guadagni & Marc J Poulin

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Esther Veurink & Jean-Francois Belanger

Branton School, Calgary Board of Education, Calgary, Alberta, Canada

Every October, The Physiological Society participates in public engagement activities to celebrate Physiology Friday, a day dedicated to showcasing human and animal research for the general public. Last year, members of the Laboratory of Human Cerebrovascular Physiology (**www.ucalgary.ca/poulin**) directed by Marc Poulin at the University of Calgary embraced this opportunity. To our knowledge, we were the only Canadian site to participate.

Our Laboratory investigates the role of aerobic exercise and nutrition on sleep and cognition. We study how lifestyles can have an impact on brain health and well-being, with a special focus on healthy brain aging.

In 2010, we started the *Brain in Motion* study: a longitudinal study with nearly 300 participants, looking at the effects of a six-month aerobic exercise intervention on cerebrovascular regulation in sedentary, healthy, older adults. While the implementation of healthy lifestyles in midlife can help prevent and/or delay cardiovascular diseases and dementia in later life, education about the importance of healthy lifestyles needs to start much earlier. This was the rationale behind our Physiology Friday initiative.

We partnered with the health teacher Esther Veurink and her class of 11–12 year old boys and girls at Branton Junior High School. A few weeks before Physiology Friday, we split the class into four groups to study how these four themes relate to brain health: i) exercise, ii) sleep, iii) nutrition and iv) stress management/reduction.

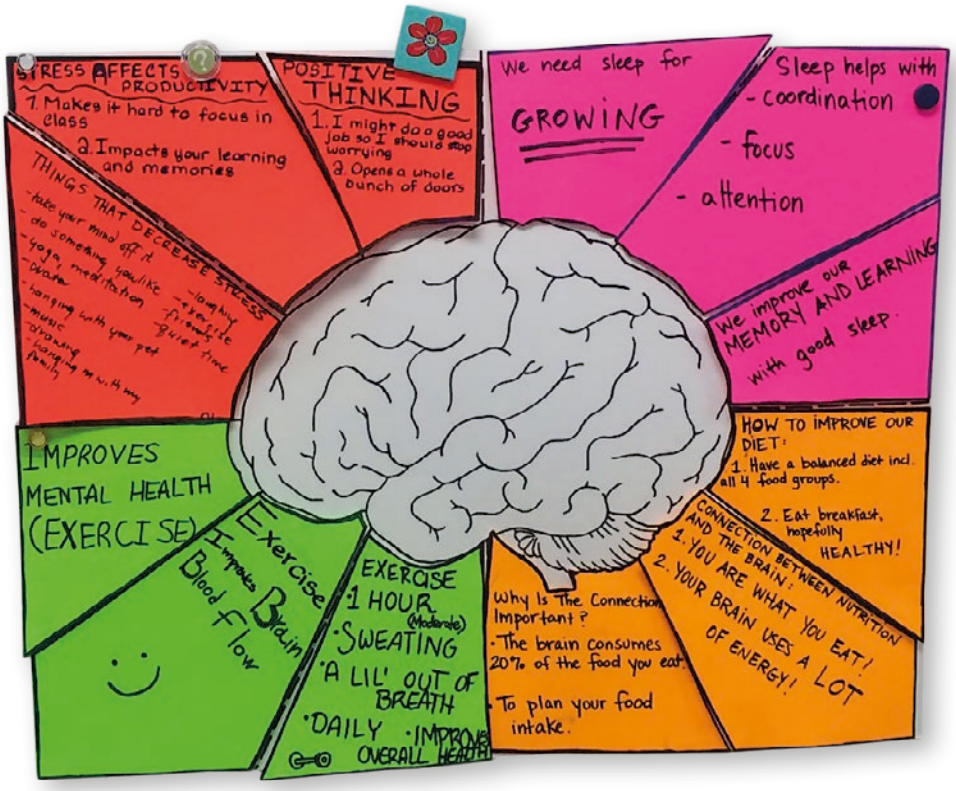
On Physiology Friday, the students gave short presentations to the class about each theme. During these presentations, the students completed a puzzle of the brain that stated important concepts related to their topic.

The four mentors/facilitators showing the delicious brain-shaped cupcakes.

In the weeks following the event, the students completed an electronic survey about their experience. Sixty-seven per cent of students indicated that they already had a basic knowledge of the topic, 70% indicated that they learned new information, and 80% indicated that they were more interested in physiology/brain health after Physiology Friday. Seventy-three per cent of children indicated that they changed something in their daily lives after Physiology Friday, and 97% said they would recommend Physiology Friday to a friend.

Overall, the event was a huge success! The students learned a lot and will hopefully reflect on the importance of adopting a healthy lifestyle starting at their young age. The experience was very useful for the mentors/facilitators as well. We really valued the opportunity to practice the ability to shift from scientific 'jargon' to a simpler language to target a different audience as part of a community engagement event. At times, we get so immersed in the technicality of our research that we forget the importance of focusing on the big picture and on how to communicate our science in a manner that makes our main findings accessible and understandable to society as a whole.

We look forward to engaging several more classes at our second rendition of the event this October.



The completed brain puzzle.

The Physiological Society's techniques workshop feedback: Introduction to Molecular Biology

Alina Luchkova

PhD Student
Department of Blood Circulation,
Bogomoletz Institute of Physiology,
Kiev, Ukraine

I am a young researcher at the Department of Blood Circulation in Bogomoletz Institute of Physiology in Kiev, Ukraine. I am writing my PhD thesis now about the influence of hydrogen sulfide on calcium homeostasis in the mitochondria of rat hearts.

In my work, I mainly use physiological and biochemical methods of investigation. I was looking for training to improve my professional skills and study new molecular biology techniques. The Physiological Society's 'Introduction to Molecular Biology' techniques workshop was just what I was looking for, and surpassed my expectations. I was familiar with some of the techniques we covered (DNA and RNA extraction, and PCR), but I had not done ligation, transformation or Western-blotting before. We used the improved versions of basic molecular biology techniques: kits and silica-based columns for DNA and RNA extraction, ready-made PAGE gels and safe dye for Western-blotting. It is important to learn the methods used in well-developed institutions all over the world.

I would like to express a special gratitude to The Physiological Society for organising the training and giving me the opportunity to see gorgeous London, which I dreamed of visiting from English classes in school.

'I was looking for training to improve my professional skills and study new techniques ... [the workshop] was just what I was looking for and surpassed my expectations'

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