Scientia

REVOLUTIONARY DEVELOPMENTS IN PSYCHOLOGY & NEUROSCIENCE

EXCLUSIVE:

- MQ: Transforming Mental Health

HIGHLIGHTS:

- The Neurobiology of the Human Language System
- Linking Blood Vessel Development to Psychiatric Disorders
- BeMoBIL: Imaging Human Brain Activity in Motion
- Denying Dementia with Earlier Diagnosis

Issue: #122

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WELCOME...

This special issue of *Scientia* celebrates research exploring the inner workings of the human nervous system, with a particular focus on the brain. We meet many dedicated researchers in the fields of psychology, neuroscience and neurorehabilitation, who are progressing our understanding of neuronal and psychological functioning, as well as developing interventions for practical and clinical benefit.

Our first section in the issue delves deep into the fascinating world of human psychology. Here, we begin by investigating how the human brain processes and acquires language at different stages of development. In this section, we also explore the various genetic and environmental factors that put young people at risk for addiction later in life. We then conclude this section with an exclusive interview with MQ: Mental Health, in which we can read about the significant challenges facing mental health research worldwide.

Our middle section focuses on the latest developments in neuroscience research, where we meet researchers who are delving deeper into the biological mechanisms that take place within the brain. Importantly, we can read how improving our understanding of molecular and cellular processes in the brain – even at the early stages of foetal development – can help us develop treatments for devastating neurological and psychological conditions.

Finally, we move into the specialist field of neurorehabilitation. In this section, we present the work of scientists who show us how understanding the brain from psychological and neuroscientific perspectives can inform much-needed treatment innovations in the field of neurorehabilitation. We also meet researchers who combine the latest technologies with an improved understanding of the nervous system to benefit those affected by brain and spinal injury.

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Meet The Team...

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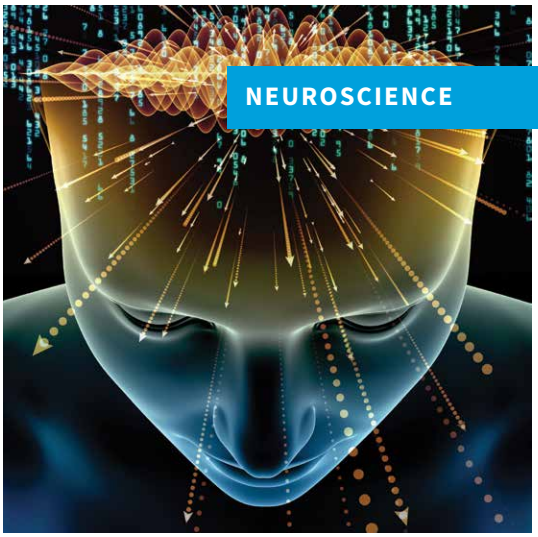

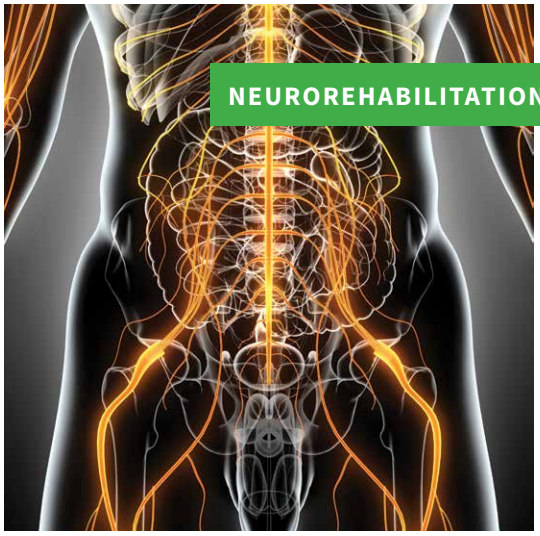

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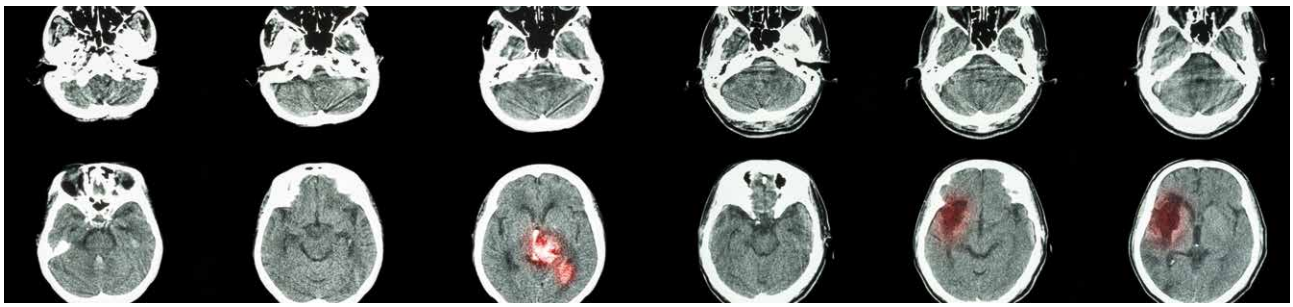

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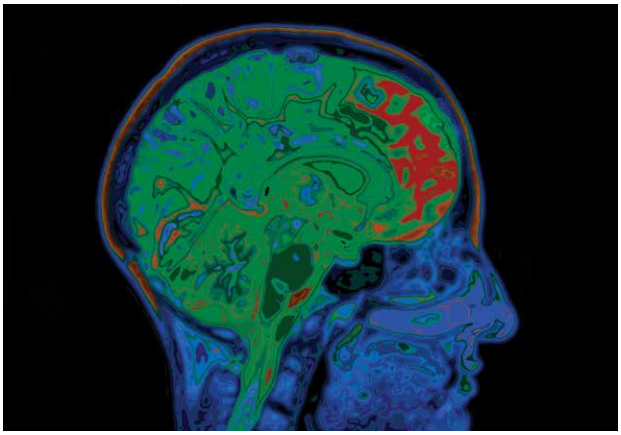


PSYCHOLOGY

UNDERSTANDING THE INNER WORKINGS OF OUR MINDS

Psychology, broadly speaking, is the scientific study of the mind, but within this there are numerous different branches, focuses and applications. In this section, we showcase the work of researchers working across the range of disciplines within this fascinating field. We read about theory-driven research into components of cognitive development, such as language and decision-making, before moving into the arena of atypical psychology, including understanding addiction.

First, we showcase the work of Professor Angela D. Friederici at the Max Planck Institute for Human Cognitive and Brain Sciences, in Leipzig, Germany. With a background in both linguistics and neuroscience, Professor Friederici's work demonstrates the power of adopting interdisciplinary approaches to tackle complex phenomena. We show how her work combining theoretical concepts in linguistics with knowledge and techniques from neuroscience has provided evidence that particular aspects of human language result from processes in specific brain areas. We also consider how such advances in our understanding of the functional specificity underpinning human language capabilities may advance our insights into the evolution of language.

We then turn to the work of Dr Tilmann Betsch who is based at the University of Erfurt in Germany. Here, we read how Dr Betsch is informing our understanding of how children make decisions. More specifically, we can read how decision-making is influenced by various factors, such as probability and experience, across the developmental trajectory. In an exciting step forward, Dr Betsch and his team are now looking at how situations can be optimally structured for children in such a way that promotes their capacity for decision-making.

Moving on to pathological psychological conditions in young adulthood and beyond, we present the work of Dr William Lovallo (University of Oklahoma Health Sciences Centre, USA) and Dr Ashley Acheson (University of Arkansas for Medical Sciences, USA). We read here how these researchers are striving to understand the factors that may predispose individuals to addiction. The majority of existing research focuses on individuals who are already addicted, for example, to alcohol or drugs. Dr Lovallo and Dr Acheson take an alternative approach by exploring the interactions between the genetic and environmental factors that put young people at risk for addiction later in life. Crucially, by understanding the contributing factors to the development of addiction at a relatively young age, we can seek to improve much-needed clinical interventions in this field.

We conclude this section with an exclusive interview with Lindsey Bennister, Chief Executive Officer of MQ: Mental Health – the UK's first charity set up to specifically to fund mental health research. MQ: Mental Health focus their work on improving treatments and, ultimately, preventing the onset of mental illnesses across the lifespan. We can read about the challenges facing mental health research, and the importance of taking a global perspective in understanding the causes of mental illness.

THE NEUROBIOLOGY OF THE HUMAN LANGUAGE SYSTEM

For centuries, scientists have been investigating the origins and development of the human language system, yet many questions remain unanswered. **Professor Angela Friederici**, Founding Director of the Max Planck Institute for Human Cognitive and Brain Sciences, in Leipzig, Germany, has carried out extensive research exploring how the human brain processes and acquires language at different stages of development by merging linguistic theory with brain-imaging studies.

The Origins of Language

Language is a fundamental part of the human experience and one of the most complex human cognitive functions, allowing people to communicate and share knowledge with one another from an early age. Scientists have been discussing the origins of language for centuries, but a widespread consensus on these theories has yet to be attained.

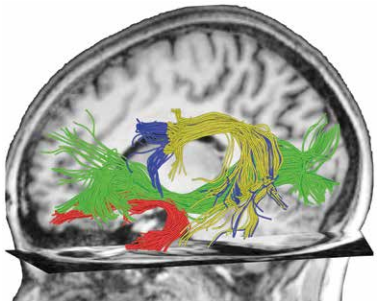
Achieving a better understanding of the mechanisms of language in the human brain and comparing these to those of other animals could help scientists to determine how this important cognitive function has evolved over time. According to linguistic theories, human languages are rooted in the ability to combine words into higher-order structures, establishing grammatical dependencies between words and arranging these in particular sequences in a sentence.

Past studies comparing the language production capabilities of a normal hearing child, a deaf child, and a chimpanzee, found that while the children were able to produce sequences of more than two words by the ages of three and three and a half years respectively, the chimpanzee almost never uttered more than one consecutive word. However, recent research has found that several species of monkeys, such as the chimpanzee, Campbell's, putty nosed monkey, and Diana monkeys, were able to combine specific alarm calls into context-specific call types, for instance, when surrounded by predators or neighbouring groups.

Professor Angela Friederici, Founding Director and Scientific Member of the Max Planck Institute for Human Cognitive and Brain Sciences, in Leipzig, Germany, has a background in both linguistics and neuroscience. Professor Angela Friederici has carried out extensive research exploring how the human brain processes language, while also comparing the observed neurobiological mechanisms for language in humans with those in non-human primates.

Linguistics Meets Neuroscience

Over the course of her career, Professor Friederici has conducted a large body of research exploring the neural basis of language. This work could ultimately help to broaden the current understanding of how this important cognitive function evolved over time. She proposes that if the neurobiological mechanisms of language are still a matter of debate it is partly because the term 'language' itself often lacks a tangible definition.



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Early scientific studies often primarily focused on regions of the brain called the frontal and temporal cortex that are involved in vocal production and speech perception rather than on language as a cognitive knowledge system. In other words, many researchers defined language as 'acoustic communication', without taking into consideration the complexity of the human language system. Professor Friederici suggests that this definition of language is too simplistic and limited, proposing an alternative one that considers both linguistics theory and neurobiological evidence.

'Rather than equating language with "speech" or "communication", we propose that language is best described as a biologically determined computational cognitive mechanism that yields an unbounded array of hierarchically structured expressions.'

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A paper outlining some of her research findings explains: 'Rather than equating language with "speech" or "communication", we propose that language is best described as a biologically determined computational cognitive mechanism that yields an unbounded array of hierarchically structured expressions.'

The Neurobiology of Language

The work of Professor Friederici and her colleagues at the Max Planck Institute for Human Cognitive and Brain Sciences focuses on trying to identify the functional architecture and neuroanatomical basis of language in the brain, at different stages of development. To do this, they use different established methods of analysing brain activity and anatomical structure, including electroencephalography (EEG), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), and structural imaging such as diffusor tensor imaging (DTI).

Their work has provided evidence that supports the definition of the human language system as a unique and autonomous cognitive mechanism, yielding a huge variety of structured phrases and sentences. Professor Friederici's brain-imaging studies on children and young adults suggest that the human language system is grounded in several brain networks, with the syntactic hierarchy building ability to create sentences localised in a particular part of the brain called 'Broca's area' that works together with other areas of the cortex to achieve language comprehension. She argues that this functional relationship is also supported by white matter fibres which form fast and reliable connections between the language-related areas across the brain. These have been found to be more prominent in the human brain than in the brain of other primates.

Professor Friederici and her team have also linked particular regions of the brain with a theoretical linguistics principle, known as 'merge'. Merge is defined as the basic computational process that allows humans to bind words together hierarchically to form larger syntactic structures and sentences. This human-specific binding process was found to have a neural basis in a very specific area of the brain, called Brodmann Area (BA 44). This area of the brain is increasingly activated when processing syntactic phrases of words.

In the research paper outlining these findings the team states that: 'The localisation of the activity and its consistency point toward the fundamental neurobiological nature of the operation of "merge" itself, thereby providing a novel view on the relation between linguistic theory and neurobiology.'

Language Learning at an Early Age

Human infants acquire language skills quickly, regardless of the environment in which they are born. Similar to other cognitive abilities, the development of language involves three main interacting factors, genetics, external input or experience, and other independent principles specific to language. In terms of predetermined genetics, one proposed language-specific component is known as universal grammar.

Universal grammar defines the characteristics that a language should have for the human brain to successfully acquire it. 'Languages' or

word sequences that do not conform to universal grammar principles, also known as 'impossible languages', should be, as the term suggests, impossible for infants to learn. All real languages, however, are acquired easily, probably because universal grammar is part of human nature. External experience input, on the other hand, is what determines what language a child will learn, due to exposure to it in their surrounding environment.

Past studies suggest that universal grammar without any language input, as in deprived children, is not enough for a child to successfully acquire language. But even with impoverished experience infants can build linguistic structures that they have never heard from adults in their environment.

In her research, Professor Friederici found a correlation between the increasing accuracy in processing complex sentences throughout human stages of development and the activation of two key language processing regions in two areas of the brain called Broca's area and the superior temporal gyrus.

Moreover, accuracy and speed of processing were found to correlate with the maturation of the white matter fibres connecting these two brain regions. These findings are compelling evidence that brain function and white matter structure are the best predictors of development of cognitive performance.

Recently, Professor Friederici and her colleagues investigated brain structures of people who had acquired different native languages, comparing the brains of Mandarin Chinese, English, and German speakers. The researchers used machine learning to classify the speaker's respective mother tongues based on their brain connectivity profiles. The results revealed a largely shared neural network that was shaped differently according to the specific processing demands of each language.

Speakers of Chinese showed stronger connectivity between the two hemispheres of the brain. This could be linked to processing pitch and the tonal characteristics of the language. German speakers, on the other hand, showed greater connectivity between the regions of the brain that are involved in grammar processing. Finally, English speakers showed higher connectivity between brain regions that reflect the key role of meaning associations in the English language.

This is the first study offering substantial evidence that the life-long use of a particular language creates a unique fingerprint in the brain of its speakers.

Evolutionary Implications

If compared with brain-activity and behaviours observed in other animals, the evidence collected by Professor Friederici and her team could shed light on the evolution of language.

The team's work has highlighted the functional specificity of a particular portion of Broca's area and its fibre connections to the cortex that appears to form the neural basis behind humans' ability to process hierarchical language structures.

This language processing ability is absent in non-human primates, who show similar patterns in electrical brain activity to those of human pre-linguistic infants, but not to those of human adults. As the brain of human infants is not fully developed, the similarities observed with non-human primates might indicate that, for different reasons, they both lack access to the neural circuits enabling the processing of hierarchical language structures.

If this is the case, these neural circuits might be a key evolutionary advancement playing a crucial part in enabling the unique human faculty of language.

Paving the Way for Future Research

The human language system is a complex and fascinating cognitive ability that distinguishes our species from others inhabiting planet Earth. When it comes to the evolution of language and its development throughout the human lifespan, however, much is yet to be understood.

Professor Friederici and her team have made important contributions by collecting evidence that has helped to unveil the neurobiological basis of human language processing. Her studies have found a connection between theoretical concepts in linguistics and neuroscience, suggesting that particular aspects of human language are processed in specific areas of the brain.

In the future, Professor Friederici's findings could pave the way towards a broader understanding of how the brain processes language, prompting more studies that focus on the brain regions she has identified.

Professor Friederici has also carried out several other studies exploring the cognitive development of infants. For instance, she and her team also found evidence pointing to a systematic relationship between brain structure and the development of the human ability to recognise that others can have different beliefs about the world. A concept known as the Theory of Mind. She describes how her team hope to, 'investigate to what extent specifically human cognitive abilities such as Theory of Mind, music and mathematics are dependent on brain structures that compared to non-human primates are more developed in humans.' Further comparisons between the patterns of brain activity her team has observed in humans and those of non-human primates might ultimately lead to many fascinating new discoveries about language and other important aspects of human cognition.

Meet the researcher

Professor Dr. Dr. h.c. Angela D. Friederici

Founding Director and Scientific Member

Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

Vice President, Max Planck Society

Professor Angela D. Friederici is the Founding Director of the Max Planck Institute of Cognitive Neuroscience (since 2004, the Max Planck Institute for Human Cognitive and Brain Sciences) in Leipzig, as well as the former Director of the Centre of Cognitive Science at the University of Leipzig and an honorary professor at the University of Leipzig, the University of Potsdam, and the Charité University Medicine in Berlin. As part of her academic journey, she completed a Psychology program at the University of Bonn and Linguistics programs at the Universities of Bonn and Lausanne. She holds a Diploma in Psychology and a PhD in Linguistics from the University of Bonn. Professor Friederici is an internationally recognised expert in both neuropsychology and linguistics. Her research focuses primarily on how the human brain processes and acquires language throughout the lifespan. Over the course of her career, Professor Friederici has written and published over 400 academic articles and book chapters, as well as editing a number of books about linguistics, psychology and neuroscience. Her recent book 'Language in Our Brain' covers the major findings of the field. She has served on the advisory boards of several journals and is currently a member of countless scientific organisations, including Academia Europaea, the Academy of Sciences Leopoldina and the Berlin-Brandernburg Academy of Sciences. Professor Friederici has received numerous awards and honours, including the Alfried Krupp Prize for Young Scientists, the Gottfried Wilhelm Leibniz Price awarded by the German Research Foundation 1997 and more recently the Carl-Friedrich Gauß Medal in 2011.

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FURTHER READING

AD Friederici, Language in our brain. The origins of a uniquely human capacity, Cambridge, MA: MIT Press, 2017.

AD Friederici, N Chomsky, RC Berwick, A Moro and JJ Bolhuis, Language, mind and brain, Nature Human Behaviour, 2017, 1, 713–722.

AD Friederici, Evolution of the neural language network, Psychonomic Bulletin and Review, 2017, 24, 41–47.

MA Skeide, AD Friederici, The ontogeny of the cortical language network, Nature Reviews Neuroscience, 2016, 17, 323–332.

E Zaccarella, AD Friederici, The neurobiological nature of syntactic hierarchies, Neuroscience & Biobehavioral Reviews, 2017, 81, 205–212.

WHAT CHILDREN CAN AND CANNOT DO IN DECISION MAKING

Human beings are asked to make a wide variety of choices throughout the course of their life, in both childhood and adulthood. **Dr Tilmann Betsch**, Professor of Social, Organisational and Economic Psychology at the University of Erfurt in Germany, has carried out extensive research investigating children's decision making processes, focusing on their development and the potential deficits present in childhood.

Decision Making in Childhood

Due to its uncertain and ever-changing nature, the world we live in compels us to make many challenging choices every day. Making these choices generally involves processing available information, consulting others, browsing the internet, or accessing other sources of information.

Similar to adults, children face situations that require them to make more or less important decisions. Their decision making capabilities, however, might not yet be fully developed. Adults have been found to be quite efficient and adaptive at making decisions. They are able to apply various decision strategies contingent upon contextual demands and are sensitive to variations in the probability of decision outcomes.

Probability plays a key role in decision making and past research has often explored the use of stated probabilities in both adult and child decision making. Alternatively, other studies have focused on experience-based decision making, where children learn the frequencies of decision outcomes from feedback and use the information they have acquired to make choices.

Studies that integrate these two paradigms, exploring both probability and experience in children's decision making, however, are still limited. To fill this gap, Professor Tilmann Betsch has carried out numerous studies with children, investigating the role of both probability and experience in their decision making processes and comparing these with strategies used by adults.

Investigating Children's Decision Making Strategies

The research carried out by Professor Betsch and his colleagues focuses on the development of decision making processes in childhood, particularly on the use of different cognitive strategies at different developmental stages. 'Everyday, children face many choices,' says Professor Betsch. 'Today's parents and educators make a lot of effort to include children in decision making, and nevertheless, we are not yet sure what kind of choices children can make on their own. Our research addresses this question. We investigate when and under what circumstances children can make successful decisions.'

Childhood is a critical period for the development of decision making strategies, during which children

gradually become more equipped to deal with risky or uncertain situations. In his research, Professor Betsch has investigated these processes in children from different age groups, while also comparing them with those observed in adults.

'Decision making is complex and requires us to perform multiple cognitive processes, such as information search, information integration, rule use, and others,' explains Professor Betsch. 'While children master some of these processes quite early, they spectacularly fail at others until the age of 12. Our aim is to investigate the development of these capabilities and deficits during childhood.'

‘We investigate when and under what circumstances children can make successful decisions.’

Probabilities in Children’s Decision Making

In decision making, behavioural outcomes are governed by the rules of probability that summarise the probabilistic relationships between choices and their outcomes. Most decision consequences are not certain, but more or less probable. For example, when choosing a restaurant for dinner, a high-quality restaurant will probably serve a tasty meal, but one can never be sure about that.

Past research suggests that, in complex environments or situations, children fail to use probabilities up until a late school age. In their research, Professor Betsch and his colleagues looked closely at how children use probability in decisions and at whether this varies across different age groups. In a series of experiments, the researchers tested six-year-olds, nine-year-olds, and adults in decision making tasks in which probabilities must be considered.

According to psychological theories, in these situations, decision makers must be sensitive to differences in outcome probabilities and should be able to weigh these carefully during their choice. Professor Betsch found that six-year-olds mostly neglect probabilities while nine-year-olds partly rely on them.

Feedback in Decision Making

Information about probabilistic relationships can be conveyed in the form of stated probabilities, for instance by stating the probability of winning in gambling scenarios. This information can also be acquired gradually during the choice-making process while receiving feedback from the surrounding environment. In his work, Professor Betsch investigated whether children of different age groups prefer feedback-based strategies over probabilistic information.

He found that while children did not systematically use feedback to direct their choices, six-year-olds were over-responsive to negative choice outcomes and this prompted them to make biased decisions based on recent feedback. Irrespective of whether they received feedback from the environment, six-year-old and nine-year-old children showed a tendency to neglect probabilistic information in their decision making – the former age group entirely and the latter only partly.

Moreover, when the six-year-olds chose systematically, they were found to rely on invalid information, which led to poorer outcomes overall. Nine-year-olds also applied invalid choice rules, but they also used some choice rules based on probability.

These findings suggest that children tend to neglect probabilities in complex decision making, regardless of whether feedback is provided, and that probability-based strategies start to develop gradually at elementary school age.

The Pre-decision Search for Information

Past research in this field has found that when making decisions, children at preschool and elementary school age search for information without a systematic plan. This finding is somewhat surprising, as other psychological studies suggest that in other cognitive domains, for instance when solving mathematical problems, children in these age groups tend to use different identifiable strategies.

However, using a different research approach that allows for greater strategy variability, such as sonification (the use of sounds for pattern detection) and visualisations of patterns, Professor Betsch and his colleagues explored pre-decision information searching in children, identifying combinations of search patterns that the children used systematically.

In contrast to adults, children displayed no dominating information search strategy, but rather used a limited number of strategies and alternated between them, even when presented with different examples of the same type of task.

In another study, Professor Betsch found that while elementary school children systematically used probabilities as weights in their decisions, they were unable to apply probabilities before the actual decision making when searching for decision-relevant information.

The Development of Weighted-additive Strategies in Deterministic Environments

Not all decisions require us to consider probabilities. For example, when choosing a specific product to purchase, such as a candy bar. In this case, the adult in question would weight each of the available choices' attributes (such as price, flavour or calories) that could have different values according to the individual making the choice. Accordingly, the challenge in a deterministic decision environment is not to consider probability, but to consider all the relevant information in a systematic fashion.

Adult decision makers often apply the so-called weighted-additive strategy: Individuals determine the expected value of each of the possible choice alternatives, by weighing each of the aspects or attributes of the alternatives in terms of their respective relevance. They then choose the alternative that provides the best total package of attributes, that is, that yields the highest expected value.

So far, very little is known about the development of this complex information integration strategy in childhood. To uncover more about the age at which it consolidates, Professor Betsch and his colleagues carried out a series of studies that compared children's choices in deterministic environments with those of adults.

Overall, they found that all age groups, even six to seven-year-olds, applied a complex weighted-additive strategy, but that children did so unintentionally. This suggests that the ability to make quick and good decisions by holistically integrating a variety of different information is already present in young children, at least in deterministic decision environments.

Future Horizons in Children's Decision Making Research

Understanding and becoming responsive to the probabilistic relationship between real-life decisions and their outcomes is an important developmental step that usually leads to decision competence, ultimately helping individuals to better deal with the situations presented to them.

Professor Betsch has greatly contributed to the study of decision making strategies, shedding light on the developmental stages at which humans acquire these important capabilities. His findings suggest that children develop an understanding of probabilistic decision making strategies at elementary school age, but that they are not yet equipped to use these for pre-decision information searching. On the other hand, children make much better decisions in deterministic environments when consideration of probabilities is not required.

In light of recent attempts by organisations such as UNICEF that are aimed at actively involving children in decision making processes, Professor Betsch and his colleagues are now carrying out further studies, exploring ways in which children could be helped to develop and better apply their decision making abilities.

'So far, our research has focused on children's abilities and deficits in decision making,' explains Professor Betsch. 'Now, we want to concentrate on environmental factors. What should a decision look like so that children can handle it successfully? In the future, we hope to be able to advise parents and teachers on how to structure decision situations for children.'

Meet the researcher

Professor Tilmann Betsch
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Professor Tilmann Betsch is the Chair of the Department of Social, Organisational and Economic Psychology at the University of Erfurt, in Germany. He holds a Diploma in Sociology and Psychology from the University of Mannheim, as well as a PhD in Psychology from the University of Heidelberg. Prior to his post at the University of Erfurt, Professor Betsch worked as a research associate and associate professor to Professor Klaus Fiedler at the University of Heidelberg. Over the course of his career, he has carried out numerous studies relevant to various areas of psychology, particularly attitude formation, judgment, decision making, routines, and intuition. His current research focuses on the development of decision making capabilities in childhood, investigating how children process information and how they act when in risky situations.

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REFERENCES

T Betsch, A Lang, Utilization of probabilistic cues in the presence of irrelevant information: A comparison of risky choice in children and adults, Journal of Experimental Child Psychology, 2013, 115, 108–125.

T Betsch, A Lang, A Lehmann, JM Axmann, Utilizing probabilities as decision weights in closed and open information boards: A comparison of children and adults, Acta Psychologica, 2014, 153, 74–86.

T Betsch, A Lehmann, S Lindow, A Lang, M Schoemann, Lost in search: (Mal-) Adaptation to probabilistic decision environments in children and adults, Developmental Psychology, 2016, 52, 311–325.

T Betsch, K Wünsche, A Grosskopf, K Schröder, R Stenmans, Sonification and visualization of pre-decisional information search: Identifying toolboxes in children, Developmental Psychology, 2017, 54, 474–481.

A Lang, T Betsch, Children's neglect of probabilities in decision making with and without feedback, Frontiers in Psychology, 2018, 9, 191.

S Lindow, A Lang, T Betsch, Holistic information integration in child decision making, Journal of Behavioral Decision Making, 2017, 20, 1131–1146.

UNIVERSITY OF ERFURT

THE INTERACTION BETWEEN GENETICS AND ENVIRONMENT IN ALCOHOL AND SUBSTANCE USE DISORDERS

The longstanding collaboration between **Dr William Lovallo**, of the University of Oklahoma Health Sciences Centre, and **Dr Ashley Acheson** of the University of Arkansas for Medical Sciences, is shedding important light on how individuals differentially react to stress and regulate their emotions, particularly young adults with a family history of alcoholism.

Alcohol Use Disorders

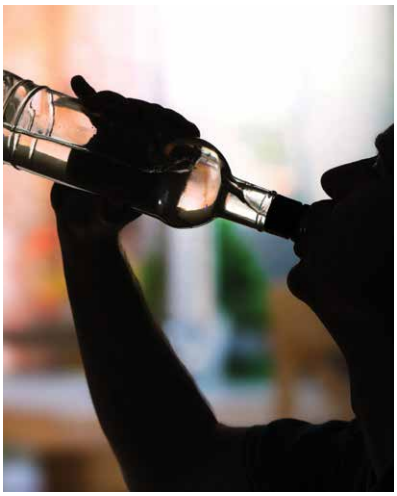
Humans respond to environmental stress cues, such as extremes of temperature, but also to psychological stressors, which can result in the development of fears about present and future threats to self-esteem. These psychological stressors impact upon mental health – and are likely to affect physical health too. One of the biggest questions in this research field is why, as individuals, do we vary so extensively in our responses to these cues?

The stress axis consists of the autonomic (unconscious) and endocrine (hormone) systems and is vital for maintaining physical health when faced with environmental challenges. Normal physiological balance should occur somewhere in the middle of the stress reactivity scale. Deviations above or below this point may demonstrate changes in the stress axis causing, or caused by, disease. Abnormalities in reactivity may also present a specific risk factor for disease.

The work of Dr William Lovallo and Dr Ashley Acheson, respectively from the University of Oklahoma Health Sciences Centre and the University of Arkansas for Medical Sciences, is concerned with the physiological response to psychological stress and individual differences in stress reactivity. Of particular interest to these researchers is how young adults with a family history of alcoholism respond to stress and how they regulate emotion.

Alcohol use disorders are the most common of all the addictive disorders. Children born into families with a history of drug and alcohol problems are predisposed to developing the same disorders. Dr Lovallo and Dr Acheson propose that young adults from families with such disorders may have distinct differences in stress reactivity, cognition, and emotion compared to those from families without a history of such disorders.

This topic that has been neglected in favour of studies on persons who are already addicted. However, Dr Lovallo and collaborators have started



examining family history differences in personality and temperament traits, alongside cognitive function, behavioural impulsivity, stress physiology, and brain function. The group has also begun to examine specific gene mutations and how these may impact on such characteristics. As individuals with a family history of alcoholism often grow up in disturbed family environments, Dr Lovallo and Dr Acheson have also asked whether there is an interaction between genetic and environmental factors that may predispose individuals to alcoholism.

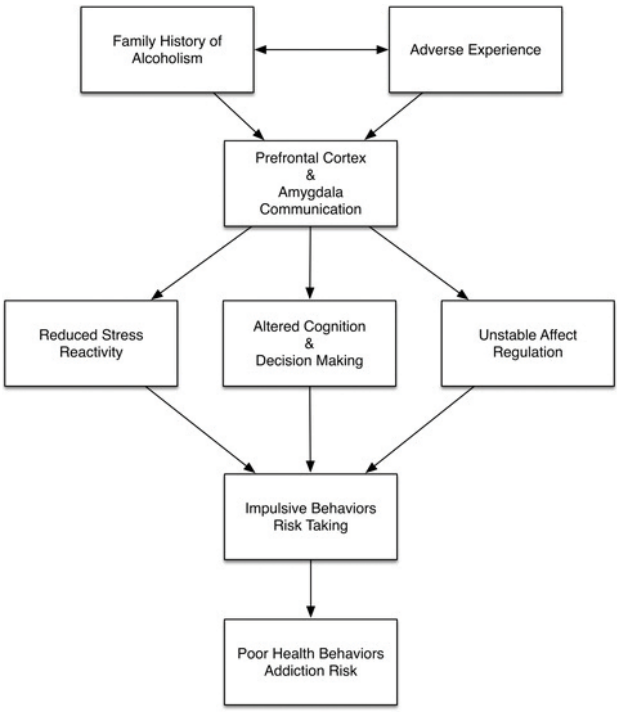
‘These Gene x Environment analyses promise to yield insights into the personal characteristics that put persons at the greatest risk for alcoholism.’

Findings from the Oklahoma Family Health Patterns Project

Dr Lovallo and Dr Acheson played a major role in implementing the Oklahoma Family Health Patterns Project, which set out to study young healthy adults (i.e., those with no psychological or physical health disorders), with and without a family history of alcoholism. The large number of participants (over 1,000) and consistent protocol used over many years (since 2001) mean that this dataset provides a critical resource for assessing variations in stress reactivity between healthy young adults. Investigating the children of such families removes some of the confounding factors that may be seen in the parents. For example, it is difficult to distinguish whether reduced cortisol response in recovering alcohol-dependent participants is a consequence of prolonged alcohol exposure or a pre-existing condition. The researchers also asked whether there were long-term consequences of a stressful life experience, such as robbery or rape, on response to stress later in life. They used a protocol involving the simulation of stressful psychological situations, including a public speaking task and repeated work on mental arithmetic problems, to compare the responses of individuals who had experienced a stressful event during their life, and those that hadn’t. They found, as predicted, that a previous stressful life experience had a long-lasting impact on the reactivity of the stress axis. This finding was independent of family history of alcoholism.

More recently, with an increased cohort size of 1031 participants, Dr Acheson and Dr Lovallo were able to identify three components which distinguished between individuals with a family history of alcohol and drug use disorders and those without this family history. Component 1 was associated with internalising traits, such as depressive and anxiety traits. Component 2 was associated with externalising traits, such as impulse control and antisocial behaviour. Finally, component 3 was associated with estimated intelligence. Taken together, it was possible to use these components to distinguish between individuals with and without a family history of alcohol or substance abuse disorders, with component 2 being most robustly associated with family history.

Dr Lovallo is now conducting further work in this area and explains ‘we are extending this by starting a Gene x Environment analysis on our cohort to examine genetic vulnerabilities to early life adversity.’



Factors Influencing the Development of Alcohol and Substance Use Disorders. Credit: William Lovallo

Alcoholism and Response to Stress

One of the main findings to emerge from the collaborative work between Dr Lovallo and Dr Acheson is that individuals at risk of developing alcohol use problems later in life have a blunted stress hormone and cardiovascular response to psychological stress. Normally, being placed in a stressful situation results in classic symptoms, including a racing heart and other responses caused by the release of stress hormones, but this was not seen in either patients being treated for alcoholism or in healthy young adults from families with a history of alcohol abuse (in other words, those at risk of developing alcoholism later in life).

The second major determinant of this blunting response was found to be the amount of adversity an individual had experienced as a child and adolescent – such as physical or sexual abuse, or separation from parents before the age of 15. Whilst these data suggest that there is a certainly a link between early life adversity and risk of developing alcoholism, there is still more work to be done unpicking the precise mechanisms of cause and effect.

Changes in the Brain

It is important to consider what changes in the brain are linked to the differences observed in stress reactivity. The same region of the brain that is used to evaluate the surrounding environment is also responsible for choosing future courses of action and forming physiological responses to the stressor. These brain regions are also affected by previous learnt responses. Therefore, brain imaging work by Dr Lovallo and his colleagues has focused on these areas of the brain, namely, the prefrontal cortex and the limbic system.

These systems work together to perceive a stressor, decide on a behavioural response and consequently, to create the physiological response to that stressor. Previous work by Dr Lovallo and Dr Acheson demonstrates a decrease in the function of neurons in the prefrontal cortex of individuals with a family history of alcohol abuse.

Using a specialised imaging technique called diffusion tensor imaging, the group identified differences in the white matter bundles in the brain. These bundles are used to connect distant brain regions, including connecting those regions used for hearing and vision to the limbic system. More specifically, differences in white matter integrity were found in two studies investigating two different age groups and were more pronounced in individuals with a greater number of relatives with alcoholism, compared to those without a family history of alcoholism. More work is needed to explain whether these changes are associated with genetic changes and whether they increase vulnerability to the effects of early life stress.

Although it has been well-established that there is a genetic predisposition for alcohol and drug use problems, Dr Lovallo and Dr Acheson have further explored this association by looking for single genetic mutations that can be linked to particular pathways and processes in the body. Their research has focussed on four main sets of mutations in particular genes; those linked to the breakdown of a particular neurotransmitter (COMT gene), those linked to regulation of the stress hormone, cortisol (FKBP5 gene), those linked to the serotonin transporter molecule (5-HTTLPR gene) and those linked to the receptor for an opioid molecule (OPRM1 gene).

A particular variation of the FKBP5 gene appears to be associated with early life adversity, as individuals with a rare version of the gene, known as the A-allele, have a blunted decreased working memory function, according to a study published in 2016 led by Dr Lovallo. In related work, the researchers concluded that cortisol levels are especially sensitive to early life adversity if individuals have a particular variant of the COMT gene, which in turn affects regulation of stress. Finally, work arising from the Oklahoma Family Health Patterns Project demonstrated that a particular version of the 5-HTTLPR gene is associated with negative mood in individuals with a family history of alcohol abuse.

Implications for Health

Understanding the role that personal experience has in the development of alcohol and drug use disorders is vital to the formulation of care plans for those affected. Although it may not be possible to undo damage that has already been sustained, increased knowledge is crucial to elucidate how and why some young adults are more likely to suffer from these disorders than others, and to help identify those most at risk later in life.

Meet the researchers

Dr William Lovallo
VA Medical Centre
Oklahoma City, OK
USA

Dr Ashley Acheson
University of Arkanas for
Medical Sciences
Little Rock, AR
USA

Professor William Lovallo obtained his PhD in Biological Psychology from the University of Oklahoma in 1978. Professor Lovallo is currently Professor of Psychiatry and Behavioural Sciences at the University of Oklahoma Health Sciences Centre and is also a Senior Research Career Scientist and Director of the Behavioural Sciences Laboratories at the VA Medical School in Oklahoma City. His research focuses on the impact of stress on health and he maintains an active collaboration with Dr Ashley Acheson. Professor Lovallo's ongoing contribution to research has included a number of research and advisory roles, including positions on the editorial boards of several prestigious journals.

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Dr Ashley Acheson holds the position of Associate Professor of Psychiatry and Behavioural Sciences at the University of Arkansas for Medical Sciences. He completed his PhD in Behavioural Neuroscience at the University of Buffalo in 2005 and then completed a postdoctoral fellowship in substance abuse and psychopharmacology at the University of Chicago and a fellowship in neuroimaging at the University of Texas Health Science Center at San Antonio. Dr Acheson's research focuses on identifying behavioural and biological processes which contribute to the risk of developing alcohol and substance use disorders. He has collaborated with Dr Lovallo on the Family Health Patterns Project for over a decade.

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UNIVERSITY OF ARKANSAS

The UNIVERSITY of OKLAHOMA

MQ: TRANSFORMING MENTAL HEALTH

Our mental health is important at every stage of our lives, from childhood to adolescence and throughout adulthood. MQ: Transforming Mental Health is an international charity dedicated to researching the causes of mental health conditions and the development of effective treatments across the lifespan. Based in the UK, MQ takes a global perspective in the mission to improve our understanding of mental illness.

In this exclusive interview, we speak with Lindsey Bennister, MQ's Chief Executive (May – November 2018) to find out more about the exciting work of MQ and their vision for transforming the future of mental health worldwide.

To start with, please can you tell us a bit about the background of MQ – one of the newest research charities, set up to specifically fund research in mental health. Can you tell us how MQ came to fruition?

MQ exists to fill a major gap in the mental health sector – bringing, for the first time, a major charity voice to champion and fund mental health research.

A start up grant from Wellcome enabled MQ to get off the ground. And since 2013, we've begun funding innovative research (with over £10 million awarded to date), growing networks of academics, charities and people living with mental illness, and, crucially, starting to build long-term public support for research.

You became the Chief Executive of MQ in May 2018, bringing a wealth of leadership experience from the charity research sector. What are your aims for MQ?

The chance to join and lead MQ was an unmissable opportunity and something that doesn't come up very often. MQ has a unique and absolutely vital role to play in transforming mental health. It provides, through research, real hope for better understanding, treatment and support for millions of people affected by mental illness.

Over the past five years, the organisation has set out a transformative research agenda and begun to put mental health research in the public eye like never before. This presents an exciting platform for growth.

Working with the excellent and dedicated team at MQ, I am going to build on these developments to create a movement for mental health research that can truly transform lives.

We know that one in four of us will experience a mental health problem each year – yet the MQ Landscape Analysis in 2015 reports that only 5.8% of the UK's research budget is spent on mental health. Why do you think there is such a disparity between research spending and the scale and impact of mental health difficulties in the UK? What can MQ do to change this?

The disparity in funding for mental health research is stark – and, frankly, lets down generations of people living with a mental illness.

Almost 15 million people in the UK will be affected by a mental illness each year. Every family is likely to be touched in some way by its devastating impact. But not enough is being done to improve our understanding, develop better treatments and give hope for prevention.

For every person affected by mental illness, just £8 is spent on research per year. For cancer the figure is £178. This difference is unacceptable.

There is a fundamental issue underlying these figures — the lack of charitable funding for mental health research. And this is why MQ was set up. In the UK, for every £1 spent by the government on mental health research, the general public donates just 0.3p, less than half a penny. Compare that with the equivalent charitable donation for cancer: £2.75.

‘For every person affected by mental illness, just £8 is spent on research per year. For cancer the figure is £178. This difference is unacceptable.’

CREDIT: MQ: Transforming Mental Health

But the transformative role of a charity runs much deeper than just raising funds. In fact, what has been missing – and what MQ is working to build – is unprecedented public support for research, pressing Government and industry to invest more, shaping research agendas, and demanding vital progress.

History has shown us – with conditions like cancer and HIV - that when researchers, Government, industry and the public come together, huge advances are possible. To do this we need to inspire, to show potential, but also to demonstrate the impact of research.

The good news is that the timing could not be better. The UK is a world leader in mental health research and the NHS is a world leading institution. Awareness of mental illness is growing rapidly and stigma is being tackled, thanks to campaigning from leading charities and members of the Royal Family.

We’re reaching a tipping point – and now is the time for mental health research.

The Brighter Futures programme aims to tackle mental health problems in young people. What are the most significant mental health problems experienced by young people and how can MQ address these? Do you think mental health difficulties are preventable?

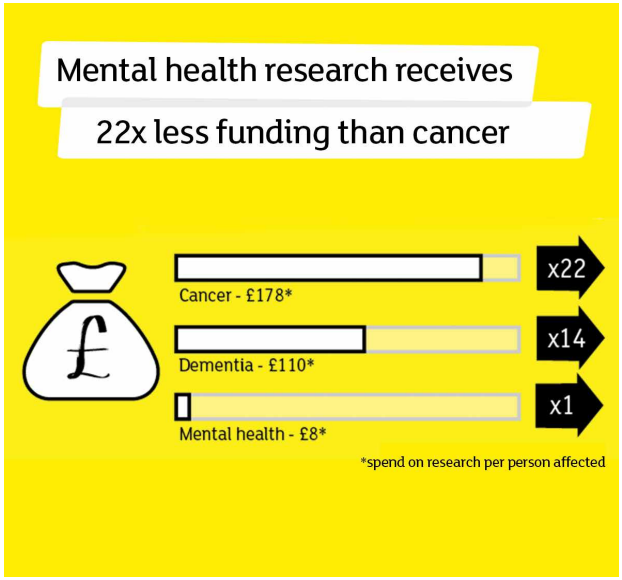
One in 10 young people aged 5–16 has a diagnosed mental health condition – that’s the equivalent of three children in every classroom. The most common conditions, depression and anxiety, have severe life-long impacts if left unaddressed. Critically, suicide is now the highest cause of death for young people.

Despite the scale of the challenge, the truth is that not enough is being done to take it on. Our methods of identifying mental health conditions remain imprecise, meaning many young people are forced to wait up to a decade for an accurate understanding of their condition. Treatments and interventions, which in some cases have barely changed for 30 years, are too often ineffective.

We know that prioritising mental health research can help us to bridge the major gaps in our knowledge, gain greater understanding and insights into mental health, and transform outcomes in the future.

Through our Brighter Futures research programme, we’re funding two groups of international scientists who are building evidence-based models to universally predict and identify young people at risk of developing depression or suicidal thoughts and behaviours. We’re harnessing the power of data through our Adolescent Data platform to transform research. And we’re working with partners in the sector to coordinate and drive research in the field.

Taken together, our programmes provide real hope for getting young people the help they need sooner – reducing the devastating, life-long impacts of mental illness and, ultimately, saving lives.



CREDIT: MQ: Transforming Mental Health

The MQ Adolescent Data Platform for Mental Health Research NHS data is described as 'an unprecedented resource for researchers and policy makers'. But where does this data come from and how will it be used?

We know that harnessing the power of data is crucial if we want to truly understand mental illness and take on the biggest challenges. And with 75% of mental illness beginning by the age of 18, the more we can understand at the earliest opportunity, the greatest long-term impact we can have.

Huge amounts of data currently exist – from within the NHS, schools and current research. But at the moment, it's time-consuming and difficult for scientists and policy-makers to access the data or the results they need.

Our Adolescent Data Platform aims to improve the speed and effectiveness of research into young people's mental health. Billions of pieces of data will be accessible from this platform, ranging from administrative health, social and education data, to psychological and clinical data, as well as information from research studies. This will all be held within the privacy-protecting SAIL Databank at Swansea University Medical School. The Adolescent Data Platform will anonymously bring all this data together under one roof, preparing it so it's easy to work with and therefore speeding up research itself.

This is the biggest platform of its kind, addressing a significant gap in young people's mental health research. It also offers the opportunity to get scientists from different fields working together, breaking down silos and building a truly bio-psycho-social model to understand mental illness. Ultimately, it will make it easier for researchers and policy-makers worldwide to use and learn from data, reducing the costs and time involved in mental health research and facilitating new insights.

One thing that seems to set MQ apart from other research charities is the large social media presence, along with substantial celebrity and politician support, as seen in the current We Swear campaign. Why you think this has been so successful?

Our We Swear campaign has been an invitation to the public to say enough is enough – that our understanding and treatment of mental illness must improve, and that research has to be at the centre of real change.

Mental illness doesn't discriminate and can affect anyone from any walk of life. Our wide-ranging support reflects this. The celebrities, politicians, researchers, and members of the public backing us all bring their own unique stories – and a steadfast desire to champion improvements.

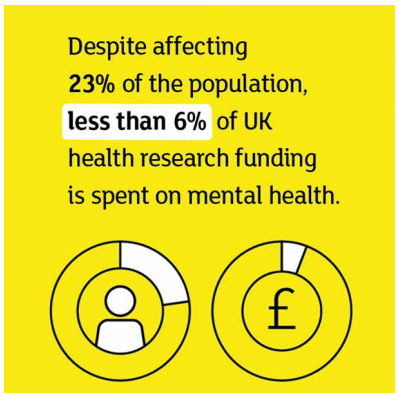
What's striking is how much the idea of research has been key. While awareness is rising and stigma is being tackled, we hear from our supporters every day about the challenges they face in getting a correct diagnosis or the right treatment. Too often people are left with huge questions about their condition and what can be done to help.

Research offers hope for answers – and that's what drives our supporters, and all of us, in what we do.

Finally, what do you see as the biggest challenges facing mental health research over the next decade and how do you think the MQ can address these?

Clearly increasing the amount of research funding available is a major challenge ahead. And this relies on building unprecedented public support.

‘We’re reaching a tipping point – and now is the time for mental health research.’



CREDIT: MQ: Transforming Mental Health

To do this, we need to work with colleagues in the sector and our supporters to demonstrate the potential impact of research and – in the next decade –begin to show improvements made as a result of the work we do.

In tackling mental illness, a major challenge we face is that there is no single cause. There are many risk factors that have been identified that increase risk of mental illness, including trauma, poverty, and biological factors such as genes. Progress will come from understanding how these risk factors interact with, and impact on, each other. At MQ, we are funding several projects that aim to do just that – the goal being that, one day, we may be able to identify someone who is at high risk of becoming unwell early on, so that we can intervene early to prevent mental illness from impacting their life.

Addressing challenges within the sector are key too. To make advances, we need to break down siloes – both within the mental health community and within research. At MQ we fund research across scientific disciplines – and champion projects that look to combine areas of expertise. We also hold one of the largest international mental health science meetings annually, bringing together experts to share knowledge and foster collaborations.

Finally, it is critical to make sure that the views of people affected by mental illness inform and drive the development of research into the future., Without the involvement of those with lived-experience, we cannot hope to address the most pressing challenges and deliver the ground-breaking progress we desperately need. This is precisely why raising awareness of the issues surrounding mental health and engaging with the public at large are so important to MQ.

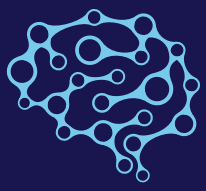
www.mqmentalhealth.org/

MQ Transforming mental health through research

Mental Health in the UK

Mental health problems are one of the **main causes of the overall disease burden**, in the UK and worldwide

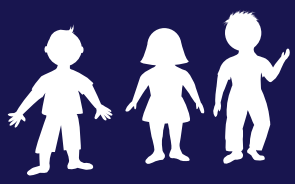
1 in 4
of us experience mental health illness every year



Mixed **Anxiety & Depression** is the most common mental health disorder in the UK

£35 bn
Annual cost of mental illness to UK employers due to lost productivity

5,821
suicides were recorded in the UK in 2017 (75% of which were male)



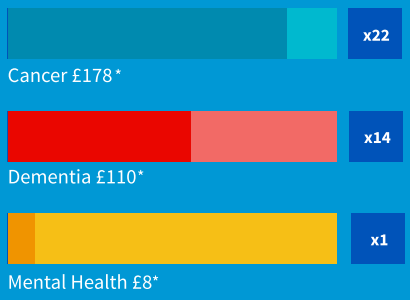
Approximately **3** children in every school class have a diagnosable mental health condition

However...

Mental health research receives just

5.8%

of total UK health research funding

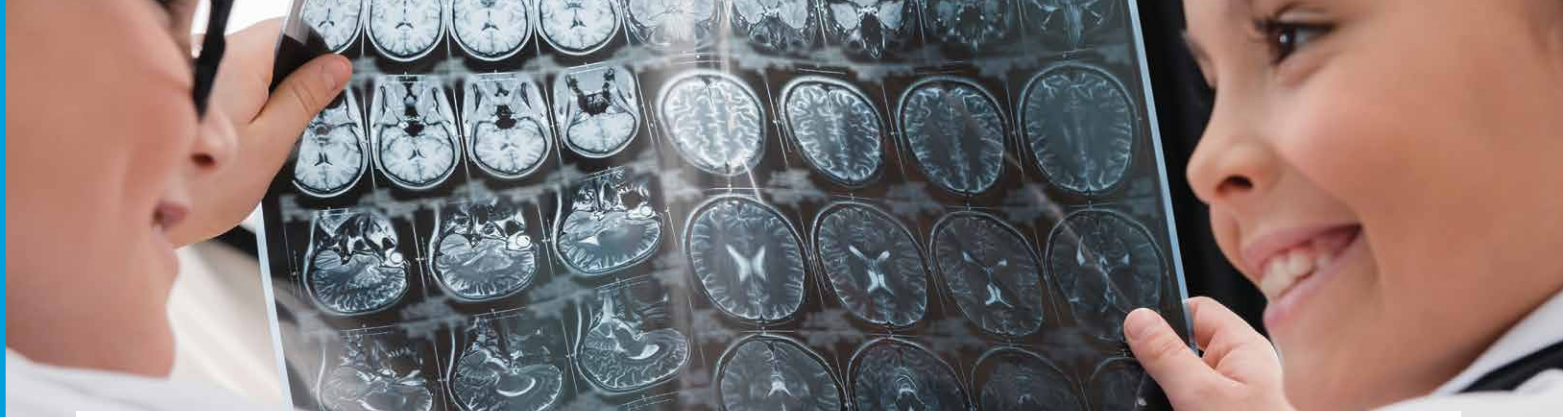


Mental health research receives **22x less** funding than caner

*spend on research per person affected

Sources: WHO, MQ: Mental Health, Centre for Mental Health

NEUROSCIENCE



SHEDDING LIGHT ON BRAIN BIOLOGY

From the senses that provide us with information about the outside world to the thought processes that allow us to make sense of it, scientists strive to unlock the biological mechanisms within the brain that make us who we are. In this way, new avenues are also being opened up for the treatment of life-changing neurological and mental health conditions. In this section of the edition, we explore these fast-growing areas of research.

To open this section, we introduce the research of Dr David Furness and his team at Keele University, who work to understand the first stages of the hearing process by investigating the cells that convert sound to electrical signals to be deciphered by the brain. Their research has revealed the cellular and molecular machinery involved in intricate detail through high-resolution imaging, which may allow us to better understand hearing loss.

The adult brain is staggeringly complex, and the development of this intricate structure and the mechanisms controlling its behaviour are still only partially understood. Revealing such processes at play during the brain's development is key to understanding and treating a range of neurological and mental health conditions such as autism, epilepsy, schizophrenia and depression. Dr Anju Vasudevan of Harvard Medical School and McLean Hospital is using innovative techniques to understand how the neurotransmitter GABA regulates the development of blood vessels in the brain with a view to discovering new treatments for these disorders.

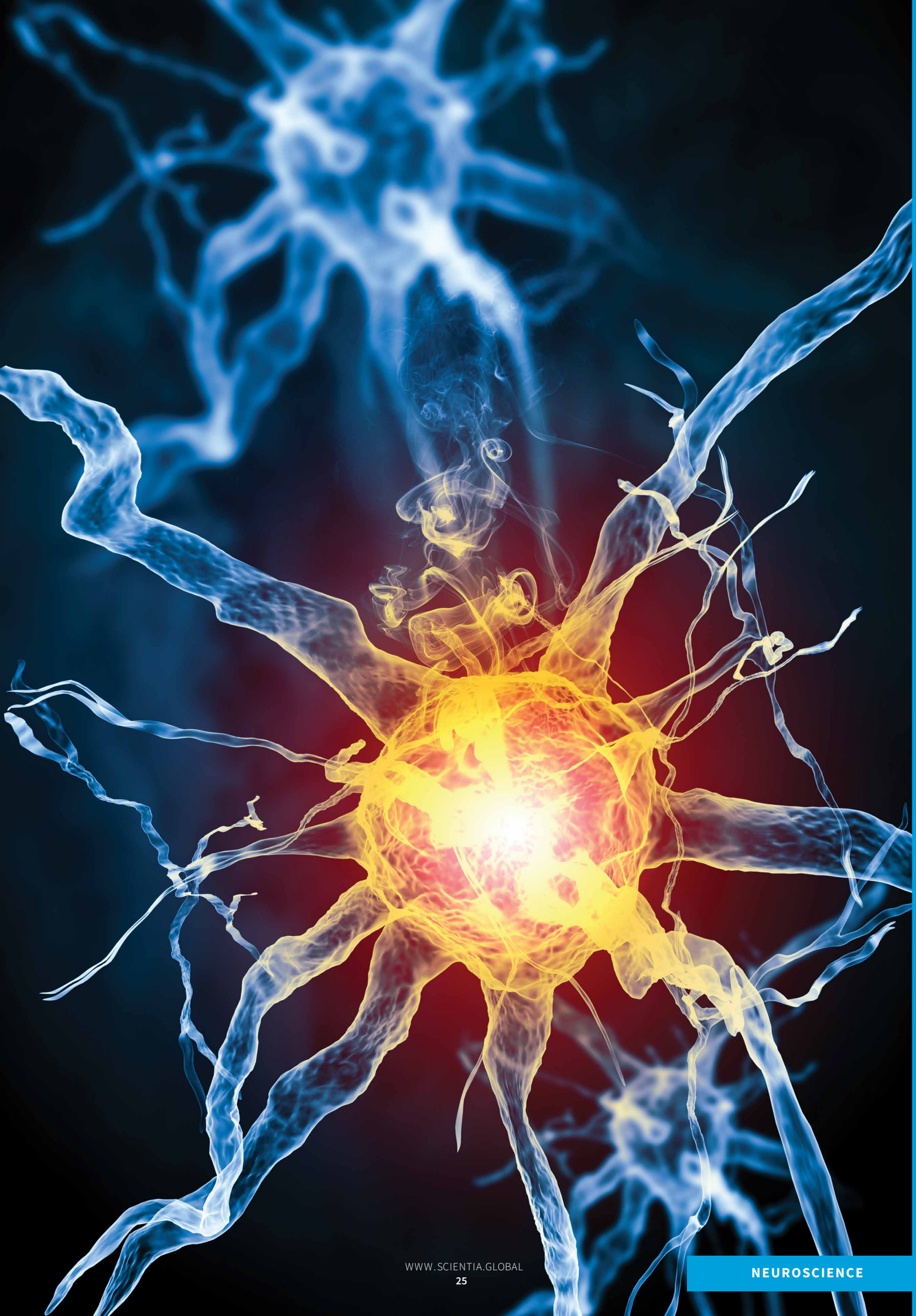
Professors Gerhard Rammes at the Technische Universität München and Rainer Rupprecht at the University of Regensburg are also studying this enigmatic neurotransmitter through the use of novel compounds. In our next article in this section, we show how they use their approach to identify areas of damage and inflammation in the brain. Through their research, the team is discovering potential therapeutic strategies to treat diverse conditions related to inflammation and GABA signalling, such as anxiety disorders and Alzheimer's Disease.

At the University Medical Center Hamburg-Eppendorf (UKE), Dr Roland Bender is focusing his research efforts on increasing our understanding of anxiety disorders in men and women. Here, we introduce his team's work in exploring how sex hormones and their actions on the brain could explain some of the differences in mental health conditions observed between the sexes.

Next, we introduce a striking hypothesis presented by Dr George Brewer of Michigan University Medical School, who after many years studying the actions of zinc and copper on the brain has come to an interesting conclusion. He presents the case that a toxic form of copper found in water supplies and in many vitamin supplements could play a significant role in the development of Alzheimer's Disease.

Finally, we explore the work of Professor Klaus Gramman and his team at the Berlin Technical University, who are developing new techniques for measuring people's brain activity when they are in motion. These researchers aim to better understand our thinking processes when we are actively exploring our environment. By developing this technology, which previously required participants to remain totally still, the team is revealing how we interact with the world around us. Further technological developments of this kind could be used to allow faster interactions between humans and machines.

By devoting their efforts to unravelling the neurological processes that control fundamental aspects of human behaviour, the researchers in this exciting section are working to better understand the human brain and the processes underlying many devastating neurological and psychological conditions.



UNDERSTANDING HEARING AT THE CELLULAR LEVEL

How do we hear and process sound? **Professor David Furness** at Keele University, UK, is endeavouring to answer this question. By utilising modern microscopical techniques, his team is visualising and identifying the proteins that enable us to convert sound into electrical signals in the hearing pathway.

Every day we are greeted by sound, whether it is the sound of cars passing by on the street, the sound of the birds chirping as we wake up, or the sound of our alarm clock. For some individuals such as musicians, sound is integral to their livelihood. For others, such as people with deafness, the loss of sound significantly impacts on their lives.

Our ability to perceive sound by detecting vibration changes in the ear, or hearing, is one of the traditional five senses. Auditory science is a research field in neuroscience dedicated to identifying the precise mechanisms by which we hear. It is currently understood that specialised cells called hair cells, named after the tiny hair-like structures that sprout from them, are the site through which sounds are converted into electrical responses. This process is known as mechanoelectrical transduction (MET). These electrical responses are then amplified to increase sensitivity and tuning before being carried to the lower areas of the brain, through the auditory nerve, for processing.

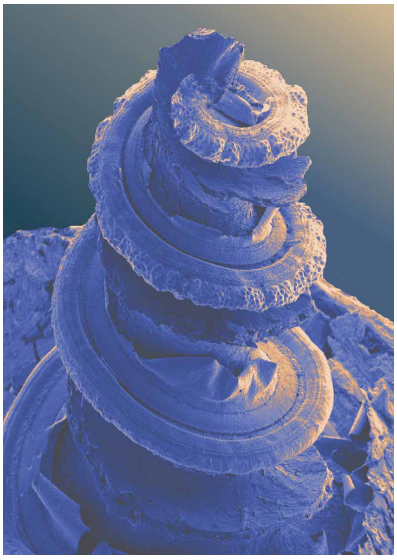
What remains to be identified is the precise cellular pathways that underpin such phenomena. Where exactly are they and how do they develop? Endeavouring to answer this research question is Professor David Furness and his team at the University of Keele.

Professor Furness describes how, 'sound stimuli enter the inner ear through the outer ear, pass through the middle ear, and set up vibrations in the inner ear. These reach the hair cells and cause the tiny hairs to be pushed backwards and forwards. It is this movement of the hairs that pulls on very tiny filaments (called the tip links) that trigger the opening of special ion channels in the membrane of the cell, causing the hair cell to respond and send signals to the brain. Our work focuses on localising the proteins involved in this process and determining how they develop.' To achieve this, Professor Furness and his team utilise sophisticated imaging techniques and the latest technology in microscopy.

Getting to Grips with Tip Links

To appreciate the complexity of Professor Furness's work at the cellular level, it is imperative to understand the structure of the fine hairs on the hair cell. These hairs, or 'stereocilia', form rows in a staircase like arrangement, increasing in height from shortest to tallest.

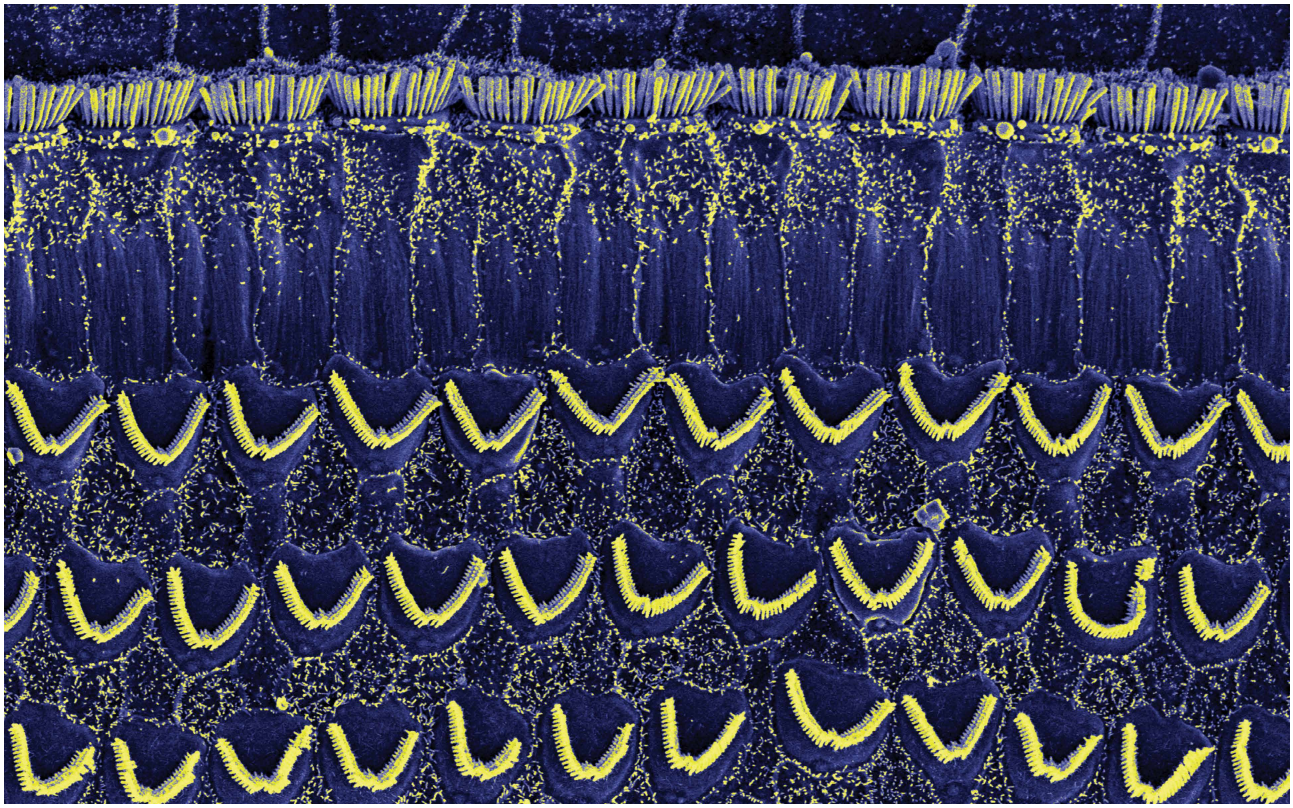
Between each stereocilia is a tip link that forms a bridge between the shortest and the tallest filament. At the site of the shortest stereocilium, there exists a protein complex that is responsible for opening the ion



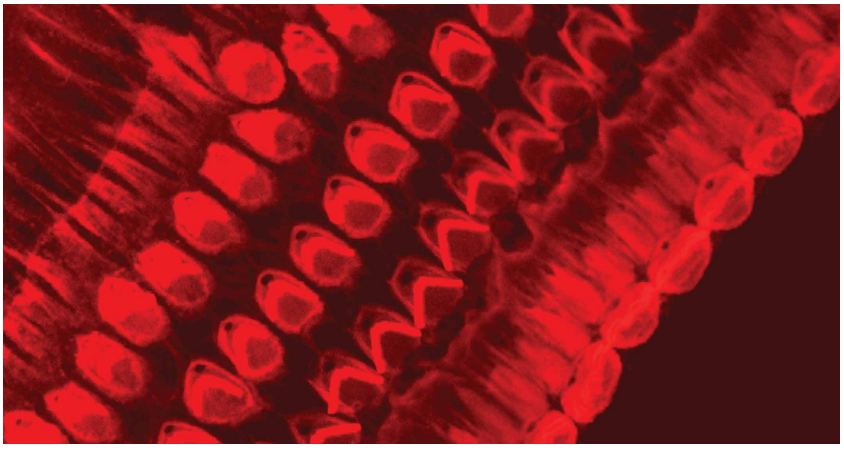
channels involved in creating the electrical signal that is sent to the brain. Deflection of the hair bundle in which the stereocilia stand causes tension on the tip link filament, causing the ion channels to be opened by this protein complex.

If deflection occurs in the opposite direction, the tension is withdrawn, and the tip link relaxes resulting in the channel closing. Professor Furness describes how his team, 'has shown using precise electron microscopic studies that two of the proteins important for hearing (LHFPL5 and TMC1) are located at the tips of some of the hairs, showing them to be in an ideal location for interaction with the tip link and detection of sound stimuli.'

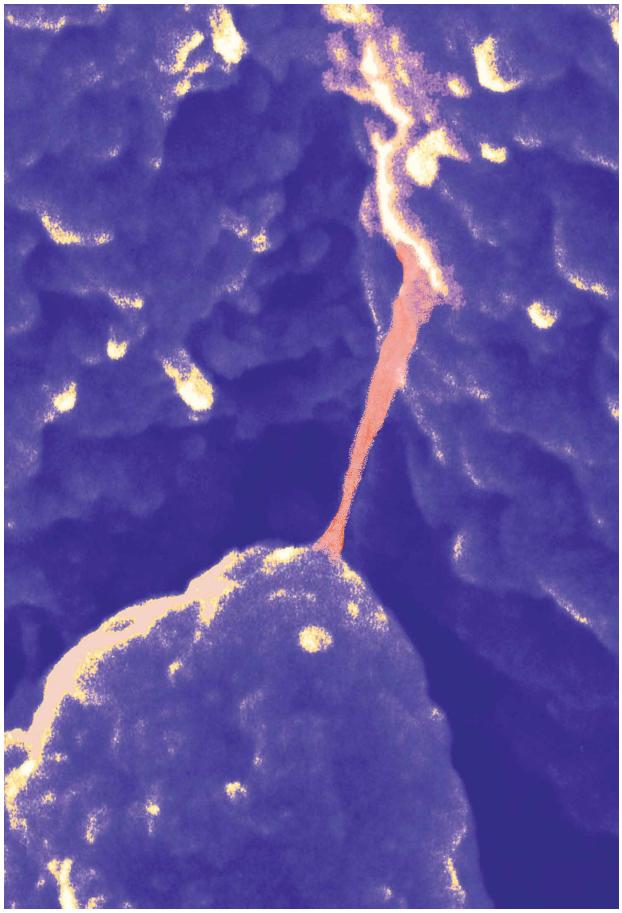
‘Sound stimuli enter the inner ear through the outer ear, pass through the middle ear, and set up vibrations in the inner ear. These reach the hair cells and cause the tiny hairs to be pushed backwards and forwards. It is this movement of the hairs that pulls on very tiny filaments (called the tip links) that trigger the opening of special ion channels in the membrane, causing the hair cell to respond and send signals to the brain. Our work focuses on localising the proteins involved in this process and determining how they develop.’



In order to demonstrate the importance of a protein in a process, scientists often use animal models in which these proteins are eliminated so that they can no longer serve the function that they are believed to. Previous research has demonstrated that mice lacking the protein protocadherin 15 (PCDH15) have a reduced number of tip links and their hair bundle structure is malformed. A consequence of this structural alteration is the production of currents that flow in the opposite direction to normal and the disruption of mechanoelectrical transduction.



Interestingly, this abnormal current is also independent of two other proteins involved in producing an electrical current, the channel proteins TMC1 or TMC2, as this current occurs in mice that have had these proteins removed through manipulating their DNA. A third protein, lipoma HMGIC fusion partner-like 5 (LHFPL5), has been found to interact with PCDH15 and TMC1 and is required for the targeting of both of these proteins to the stereocilia tip links. In mice lacking PCDH15, LHFPL5 is also absent. It is therefore thought that LHPL5 may act as the link between PCDH15 and the ion channels that create the electrical signal during mechanoelectrical transduction.



Investigating the Role of LHFPL5

Professor Furness and his team conducted a complex study to test the idea that LHFPL5 is associated with the development of electrical transduction of sound and the maturation of the mechanoelectrical transduction apparatus in young animals.

To achieve this, the team adopted 'immunofluorescent' and 'immunogold' labelling techniques to evaluate the changes in the distribution of LHFPL5 in mice during development. These techniques involve using fluorescent molecules or gold particles to label specific proteins so that they can be seen using a microscope, creating beautiful scientific works of art. The addition of gold particles allowed the team to use a very sensitive technique called transmission electron microscopy (TEM), which allowed them to identify the precise locations of LHFP5 molecules. This technique offers a much higher resolution compared to traditional microscopy methods.

The team has demonstrated that the LHFPL5 protein first appears in the hair bundles at the first day of birth and continues to increase in expression until the mice are three days old, before then declining. The team's immunogold labelling experiments illustrate that whilst LHFPL5 is initially localised throughout the hair bundle, by 12 days old the location of the protein is refined to the link-tips of the shortest stereocilia.

Professor Furness and his team concluded that this refinement of the location of LHFPL5 coincides with the maturation of the hair bundle and the production of an electrical current. Further, LHFPL5 becomes refined to its adult location by 12 days of age – the time at which mice start to hear. A crucial finding of the team's research is that they could detect LHFPL5 up to the age of 21 days, suggesting that this protein is a permanent component of the mechanoelectrical transduction complex along with the tip links.

Labelling the shortest stereocilia also illustrates that LHFPL5 is located at the lower end of the tips and appears to follow the tenting of the tip. Tenting is a process in which there is a change in the shape of the membrane at the very top of the stereocilia, and it is thought to result from an increase in the membrane tension that is required for producing an electrical response. The team has determined that the location of LHFPL5 is consistent with this protein's role in mechanoelectrical transduction as a potential linker between the PCDH15 protein at the lower end of the tip link and TMC1. They also suggest that it interacts with both of these proteins.

Professor Furness's work has greatly contributed to our understanding of the cellular interactions responsible for the process of auditory transduction and hearing, and also presents avenues for further research. Professor Furness says that, 'other researchers interested in the topic of hair-cell function will benefit from these research outcomes because this project helps to confirm whether TMC proteins form the transduction channel of hair cells. Thus, researchers will be able to develop new strategies to explore further into the mechanisms of transduction.'

What's Next?

Now that the location of the protein LHFPL5 has been determined, Professor Furness and the team wish to explore further its role in hearing. Professor Furness describes how, 'we hope to continue to localise other proteins involved in this process in hair cells, and then see how they all fit together to allow sound to be detected.'

In the future, the team aims to use a sophisticated machine that produces neutron beams to probe hair cells further. Utilising neutrons, the team will be able to achieve even higher resolution images to study the complex at the lower end of the tip links and how the proteins there interact. They hope to build a model of the protein complex in the laboratory and image it in a special type of electron microscope to work out where the proteins are in the complex and how they bind together.

The research team also wish to explore their findings in the context of hearing loss and damage. Professor Furness says, 'we will then look at how mutations in these proteins affect the assembly of this complex and thereby understand better their role in hearing and hearing loss.'

Meet the researcher

Professor David Furness
Keele University
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David Furness is a Professor of Cellular Neuroscience at Keele University where he conducts extensive research into the cellular mechanisms of hearing. Professor Furness completed an undergraduate zoology degree at the University of Manchester after being fascinated by microscopy as a child. After winning the Zoology prize for his third-year project as an undergraduate, he was offered a PhD position to continue his work into animal stomachs and the ultrastructure of rumen protozoa. Professor Furness then undertook a post-doctoral position at Keele University and was introduced to hearing research and the auditory system. In 1995 he was made Director of the Electron Microscope Unit (EMU) and contributed to the development of a new neuroscience course at Keele University for which he was course director until his promotion to reader in 2001. Professor Furness has most recently been promoted to a personal Chair in Cellular Neuroscience and is research lead for the School of Life Sciences at Keele.

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FURTHER READING

S Mahendrasingam, R Fettiplace, KN Alagramam, E Cross and DN Furness, Spatiotemporal changes in the distribution of LHFPL5 in mice cochlear hair bundles during development and in the absence of PCDH15, PLoS ONE, 2017, 12, e0185285.

Keele UNIVERSITY

LINKING BLOOD VESSEL DEVELOPMENT TO PSYCHIATRIC DISORDERS

The research of **Dr Anju Vasudevan**, from the Department of Psychiatry at Harvard Medical School and McLean Hospital, focusses on the early development of blood vessels in the brain and how defects in this process may be associated with a diagnosis of neuropsychiatric disorders, such as autism, epilepsy, schizophrenia, and depression after birth. Her work paves the way for innovative new therapies targeting blood vessel development in the field of psychiatry.

One in four people in the USA and internationally suffers from some form of neuropsychiatric illness during their life. Similar statistics are reported in the UK. Whilst drugs and other therapies exist to treat some of the symptoms, there are no cures for the underlying causes of neuropsychiatric illnesses.

Understanding the responsible mechanisms, and therefore the opportunities for novel therapeutic strategies, underpins the research of Dr Anju Vasudevan and her group at Harvard Medical School and McLean Hospital. In particular, they investigate the novel roles of blood vessels in the brain and how defective development of brain vascular networks can contribute to neuropsychiatric disorders. Whilst blood vessel abnormalities typically come to mind in relation to blood pressure, cancer or stroke, mental health disorders are rarely considered in this context.

////Subheading: The Role of Vascular Gamma-aminobutyric Acid in Neuropsychiatric Disorders

Gamma-aminobutyric acid, more commonly known as GABA, is a well-known factor in the development of the brain and nervous system. It serves as an excitatory neurotransmitter before birth and as an inhibitory neurotransmitter after birth. GABA is released by a particular group of neurons, the GABAergic interneurons that are found in the cerebral cortex of the brain. The cerebral cortex is the largest region of the brain and is associated with cognitive function (e.g., memory and attention) and consciousness.

Abnormalities in GABAergic interneurons have been linked to the development of autism, epilepsy, anxiety, depression, and schizophrenia. It has been previously shown that abnormal brain development in the early embryonic phase is also linked to these disorders and therefore, GABA-mediated signalling during development has been extensively studied over decades. In addition, an age-related decline in the amount of GABA in the brain is associated with neurodegenerative diseases and a decrease in cognitive function.

Dr Vasudevan's work emphasises that brain development is not just determined by neuronal signalling, but that development of the associated

Images from Dr Vasudevan's laboratory show the close interaction of GABAergic neurons with the periventricular vascular network (Images 1–2) and expression of GABA and its receptor signaling components in these endothelial cells (Images 3–5)

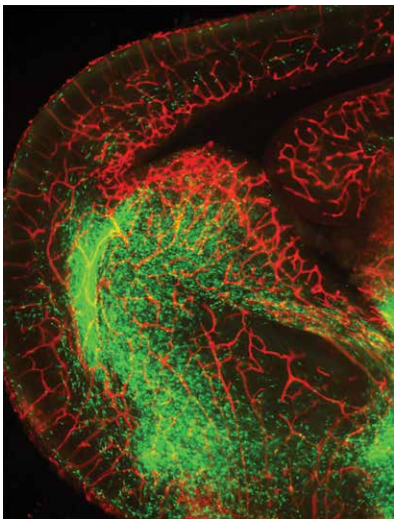

Image 1: Migrating GABAergic neurons (shown in green) are closely associated with the periventricular vascular network (shown in red) in the embryonic forebrain. Credit Anju Vasudevan

‘As a research topic, our work has produced a really new way to think about the origin and mechanisms of psychiatric illness.’

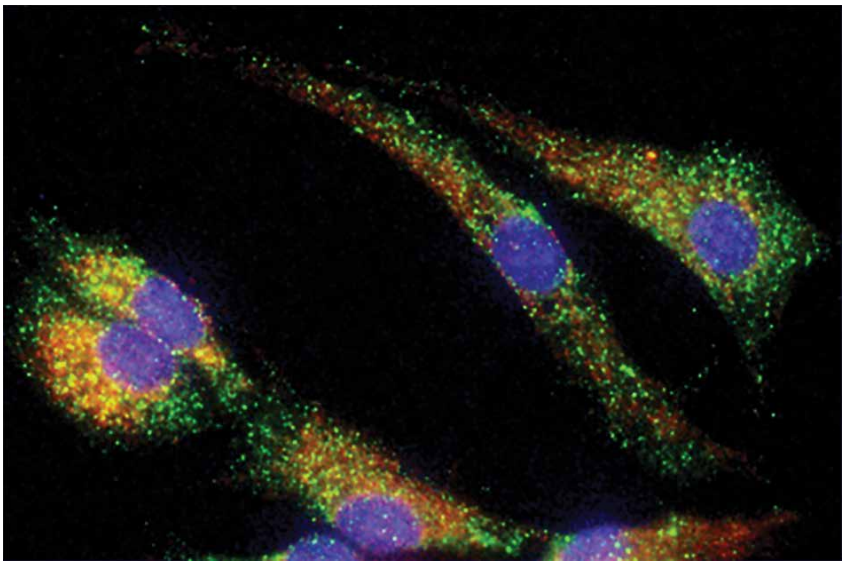

Image 2 : Periventricular endothelial cells express $GABA_A$ receptors. Credit Anju Vasudevan

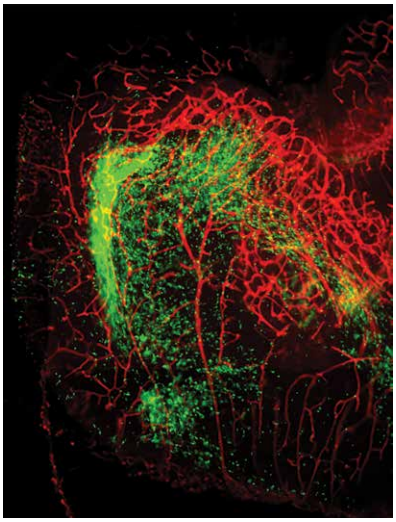

Image 3: The rhombic vascular patterns of the periventricular network (shown in red) ensheath migrating GABAergic neurons (shown in green) during their journey to the developing neocortex. Credit Anju Vasudevan

blood vessels is critical. It focusses on the process of angiogenesis, the development of new blood vessels. Dr Vasudevan has identified different populations of blood vessels in the brain: pial and periventricular. These differ in their origin, gene expression profile, and developmental mechanisms. The periventricular vascular network is of specific interest here as it emerges ahead of neurons and provides vital guidance to processes that follow during brain development, for instance, neurogenesis – the generation of new neurons and neuronal migration.

Dr Vasudevan has shown that immature neurons rely on guidance from periventricular vessels to migrate from the region of their birth to the place in the mature brain where they carry out their functions. Indeed, genes believed to be involved in neurogenesis and neuronal migration are also found in periventricular endothelial cells (the cells that line the interior surface of blood vessels and are the ‘building blocks’ of blood vessels). Interestingly, several genes previously believed to be confined to only GABAergic interneurons are prominent in forebrain endothelial cells compared to other regions of the brain. This key evidence has opened new doors for studying the role of vascular GABA signalling with respect to psychiatric disorders.

Predominantly, this indicates that multiple pathways in both neuronal and endothelial cells may co-exist in patients with psychiatric illnesses, making it crucial to understand the interactions between the different cell types and independent pathways in each cell type. Delineating this process in careful detail underpins the research focus of Dr Vasudevan.

Recent studies in Dr Vasudevan’s laboratory reveals how interfering with GABA release by endothelial cells in an animal model, results in dysfunctional behaviour similar to that seen in psychiatric diseases, including impaired social interactions, depression, anxiety, and reduced communication. It highlights how important vascular GABA is for shaping angiogenesis, neurogenesis, and neuronal migration during prenatal brain development. This has huge implications for the way that neuropsychiatric illness is approached, suggesting that instead of adopting only a neuronal perspective, understanding the defects within cerebral endothelial cells is of critical importance.

A major limitation until now for studying the vascular GABA pathway was unavailability of proper mouse models. Only complete or region-specific knockouts of $GABA_A$ receptors and GABA signalling components were available and these were not specific to different cell types. Dr Vasudevan and her colleagues have created two new mouse models to overcome this problem. The first mouse model specifically blocks GABA release from endothelial cells and the second contains dysfunctional GABA receptors in endothelial cells. With the use of these models, it will be possible to study how the vascular GABA pathway controls angiogenesis, neurovascular interactions, vessel function, and complex psychiatric behaviours.

Vascular Endothelial Growth Factor

In addition to their work on GABA, Dr Vasudevan and her colleagues have studied another molecule that plays an important role on brain development. Vascular endothelial growth factor (VEGF) is a protein that is indispensable for angiogenesis. Hitherto, it was generally believed that

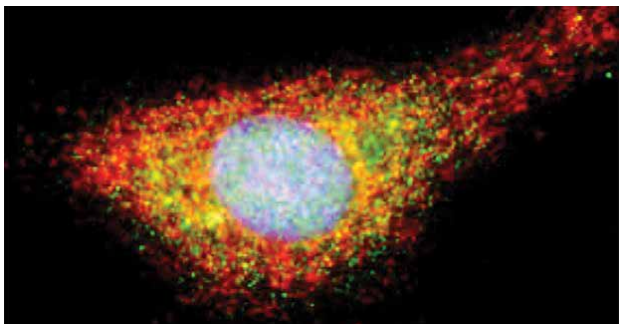

Image 4: Periventricular endothelial cells express GABA. Credit Anju Vasudevan

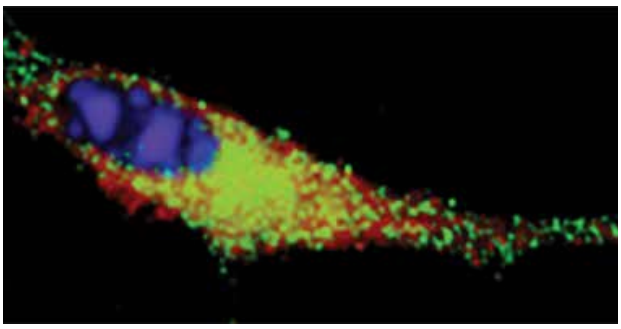

Image 5: Periventricular endothelial cells express vesicular GABA transporter. Credit Anju Vasudevan

neurons, and the cells that go on to develop into neurons, are the principal source of VEGF that binds to receptors expressed on endothelial cells in order to drive angiogenesis.

But deletion of vascular endothelial growth factor exclusively from endothelial cells resulted in an abnormal increase in proliferation of neurons and altered neuronal migration during brain development illustrating the importance of vascular VEGF. Whilst it is not yet clear how this protein may be linked to psychiatric disorders, recent studies in Dr Vasudevan's laboratory show that the endothelial VEGF signalling pathway may be either under direct control or actively interacting with the endothelial GABA signalling pathway. Further work is expected to elucidate an alternative therapeutic target.

Dr Vasudevan beautifully sums up her findings so far with, 'Our data illustrate the intimate and symbiotic [of benefit to both parties] relationship between endothelial cells and neurons of the developing brain that respond meticulously and independently to VEGF signals depending on the cell type that secretes it.'

Searching for a Cure

The ultimate aim of Dr Vasudevan's work is to open new avenues for treatment, based on a thorough understanding of the origin and mechanisms of psychiatric disease. Her work has already demonstrated that variation in endothelial GABA levels during embryonic brain development can explain some of the diversity seen in psychiatric disease symptoms.

There are two sides to her approach; the first explores the prenatal brain and the second considers the adult brain. In terms of the brain before birth, Dr Vasudevan is currently investigating whether pro-angiogenic compounds can be used to save neurovascular interactions during a critical window in prenatal brain development and whether in doing so, it may be possible to ameliorate postnatal behavioural symptoms. In the adult brain, cell transplantation may offer the possibility to introduce a novel source of vascular GABA to rescue the neural circuits in the diseased brain.

In order for this transplantation process to work, Dr Vasudevan stipulates that the cells must be able to disperse efficiently from the site of administration to the site of activity. They must be able to fully differentiate into mature neurons, and they must be able to integrate into the existing neural machinery. So far, studies have shown that transplanted cells can take several long months to disperse through affected areas. This is where the discovery by Dr Vasudevan and her group is so important. Using the pre-formed vascular networks in adults would allow the natural transport of GABAergic neurons in the diseased brain along with stabilised GABA release.

The group at McLean Hospital have successfully generated endothelial cells derived from human stem cells and are using these to co-transplant human GABAergic neurons into a mouse model. If this approach does decrease the time it takes for the transplanted neuronal cells to disperse in the brain, this is a major step forwards in the advancement of endothelial-neuron based therapy to a clinical setting.

What Next?

The research of Dr Vasudevan and her group will continue to isolate and study new components of the vascular GABA signalling pathway in the embryonic, postnatal, and adult brain. They plan to use innovative approaches to harness the potential of blood vessels to heal the diseased brain. As more pieces of the puzzle are solved, the chances of developing effective treatments for neuropsychiatric disorders improve study by study.

GABA has been referred to as a 'phoenix' that appears amidst renewed enthusiasm, only to fade away and be reignited after a time. Hopefully the work of Dr Vasudevan will prevent this elusive molecule from fading into the ashes and will go on to improve the outcome for those patients who suffer from psychiatric disorders.

Meet the researcher

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Dr Anju Vasudevan obtained her PhD in neuroscience at the University of Cologne in 2004. She then held post-doctoral and junior faculty positions at Massachusetts General Hospital/ Harvard Medical School before setting up and becoming the Director of the Angiogenesis and Brain Development Laboratory at McLean Hospital in 2011. She is currently an Assistant Professor of Psychiatry at Harvard Medical School and Associate Neuroscientist at McLean Hospital. Dr Vasudevan's research centres on mechanisms that define the formation of new blood vessels in the central nervous system, and how these influence key events involved with brain development and behaviour. Defects related to the formation of blood vessels at the earliest stages of development may play a role in the emergence of neuropsychiatric disorders in childhood and later in life; therefore, this work has major implications for understanding disorders such as autism, epilepsy, schizophrenia, and depression. Dr Vasudevan is an established neuroscientist with an impressive publication and funding record.

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FURTHER READING

S Li, KT Peeyush, S Joshee, T Kirschstein, S Subburaju, JS Khalili, J Kloepper, C Du, A Elkhal, G Szabó, RK Jain, R Köhling, A Vasudevan, Endothelial cell-derived GABA signalling modulates neuronal migration and postnatal behaviour, Cell Research-Nature, 2018, 28(2), 221–248.

S Li, K Haigh, JJ Haigh, A Vasudevan, Endothelial VEGF sculpts cortical cytoarchitecture, The Journal of Neuroscience, 2013, 33(37), 14809–15.

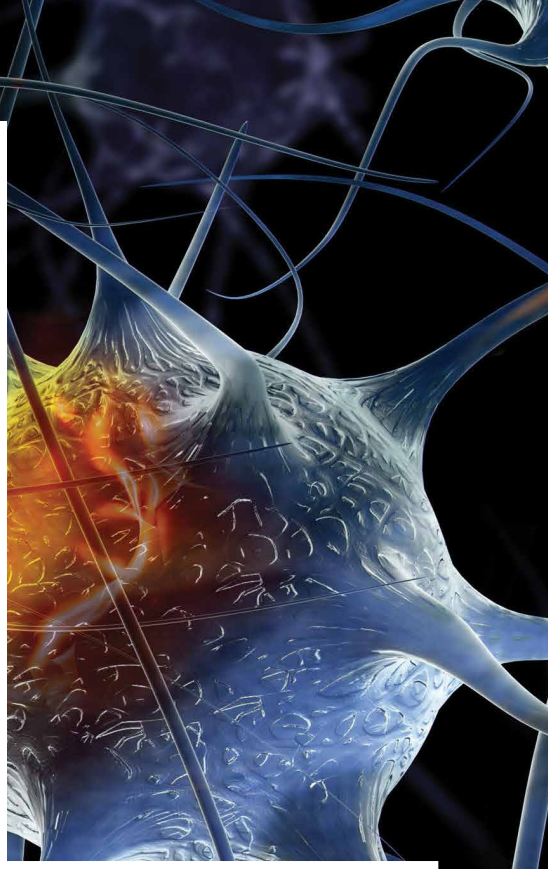
C Won, Z Lin, KT Peeyush, S Li, L Ding, A Elkhal, G Szabo, A Vasudevan, Autonomous vascular networks synchronise GABA neuron migration in the embryonic forebrain, Nature Communications, 2013, 4, 2149.

A Vasudevan, JE Long, JE Crandall, JLR Rubenstein, PG Bhide, Compartment-specific transcription factors orchestrate angiogenesis gradients in the embryonic brain, Nature Neuroscience, 2008, 11(4), 429–39.

VE RI TAS
HARVARD MEDICAL SCHOOL

THE TRANSLOCATOR PROTEIN: FROM IMAGING FACILITY TO PHARMACY

The diagnosis of brain conditions relies heavily on non-invasive imaging techniques to identify the affected areas. A protein known as the 'translocator protein' is increased in areas of brain inflammation and can be used as an imaging marker to diagnose various conditions. **Professors Gerhard Rammes** and **Rainer Rupprecht** go beyond the use of the translocator protein (TSPO) in imaging, to investigate whether molecules that bind to this protein could be used to treat various conditions in the nervous system.



A Window into the Brain

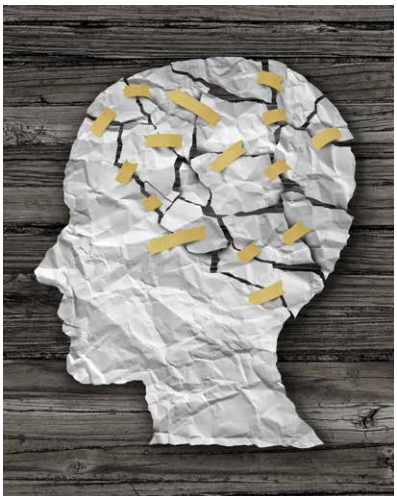
Brain conditions are particularly challenging for doctors to diagnose and treat. Unlike many other organs, it is not usually possible to take a sample of brain tissue to analyse under the microscope. So, clinicians rely on various imaging techniques to identify areas of inflammation within the intact brain, and the hunt is always on for more accurate and more specific imaging options.

One method is to use radioactivity to send a signal from within the brain that can be picked up outside the body. Radioactive molecules have been developed that can be administered to a patient, which attach themselves to specific disease-relevant marker protein molecules wherever they are found in the brain. Such molecules that can selectively attach themselves to specific proteins are known as ligands. Once attached to disease-relevant protein molecules, the radioactivity from these ligands can then be measured by a detector and an image built up of where they are in the brain. This is a form of a technique called 'positron emission tomography', or PET for short.

One target under investigation for this use is the translocator protein (TSPO). This protein is present in the brain at low levels, but is increased locally in areas of inflammation, such as that caused by injury or neurodegenerative diseases. This is because it is present in high levels in cells that are involved in the inflammatory response to injury. One major function of TSPO is in the production of steroids – signalling molecules that can influence many different brain processes.

Various studies have tested the use of PET to image TSPO in different conditions including stroke, Alzheimer's disease, multiple sclerosis, Huntington's disease, Parkinson's disease, depression and Amyotrophic lateral sclerosis (ALS). However, there are still many potential applications of this technique that have not yet been investigated.

The increased presence of TSPO molecules in damaged brain regions suggests that it may also be playing a role in the processes that lead to brain disease. Therefore, Professor Rainer Rupprecht of the University of Regensburg, and Professor Gerhard Rammes of the Technische Universität München not only investigate TSPO as an imaging marker for various conditions, but also explore it as a potential target for treatment. So far, they have been focussing on anxiety disorders, depression and Alzheimer's disease.

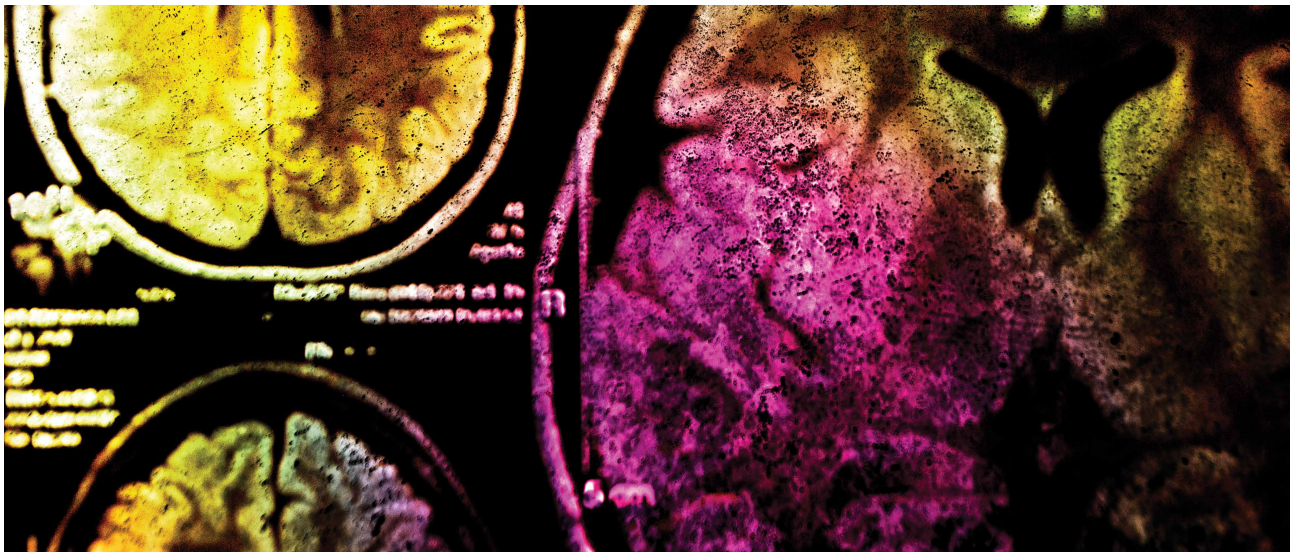


Professor Rupprecht explains that working together is an important part of their strategy: 'Currently we are about establishing a collaborative research group to approach this goal in an interdisciplinary manner from biophysics over neuroimaging to psychiatry.'

New Ligands, More Applications

Research is still ongoing to find improved TSPO ligands, and to apply the technique to more diseases. Recently, in collaboration with Professor Bartenstein from the Ludwig-Maximilan-University, Munich, Professor Rupprecht's research team tested the efficacy of a new TSPO ligand, called

‘Currently we are about establishing a collaborative research group to approach this goal in an interdisciplinary manner.’



18F-GE-180, for imaging in multiple sclerosis and brain cancer patients.

Multiple sclerosis is a disease that, amongst other things, involves chronic inflammation in the brain. Currently, the diagnosis of multiple sclerosis relies heavily on magnetic resonance imaging, in which the secondary effects of inflammation are visible. However, TSPO is present in activated inflammatory cells, so it could provide a more directly relevant imaging marker. Similarly, the diagnosis of brain tumours using magnetic resonance imaging does not determine the true extent of the tumour spread, so improved methods are required. The TSPO protein has been found to be increased in cancer cells and in brain tumours and could therefore provide an alternative target for diagnosis for these kinds of cancers. In order to test the suitability of TSPO imaging for multiple sclerosis and brain cancer, the researchers administered their new ligand to patients and performed a PET scan. They also performed a magnetic resonance imaging scan, which provided information on the location of different brain regions in each patient. They used this reference map to measure the strength of the radioactive signal produced by the ligand in different brain regions.

Using this method, the research team found that the disease-affected areas in multiple sclerosis patients, and the tumours in cancer patients, showed higher levels of TSPO ligand molecules than the healthy parts of the brain. The team also made suggestions as to the best ways to use this information for diagnosis.

These findings are important, as they demonstrate the utility of this new ligand, which was previously untested in this context, and provide information for the development of improved diagnostic methods.

Making the Leap: From Marker to Therapy

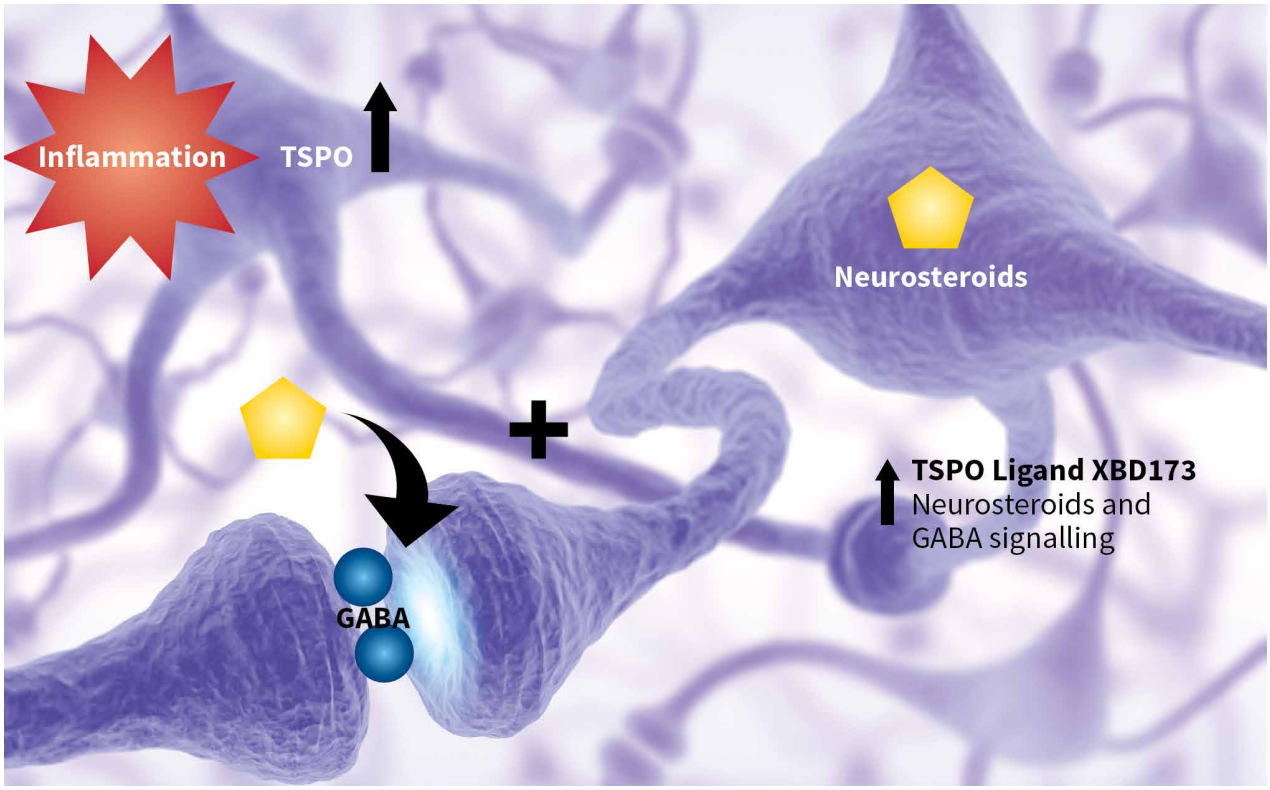
In addition to being a marker of inflammation in the brain, TSPO has been found to play a role in the progression of many conditions. Indeed, TSPO ligands have previously been tested as therapeutic options for nerve pain and traumatic brain injury.

Professors Rammes and Rupprecht have been taking this further and investigating the possibility of using TSPO ligands to treat anxiety disorders. Anxiety disorders are characterised by feelings of worry and fear, accompanied by physical symptoms such as shakiness or a fast heart rate. Some estimates suggest that up to 30% of people will be affected by this disorder at some point in their life.

During anxiety attacks, certain neurosteroid levels in the brain are reduced, and administering such steroids has been found to reduce such attacks in rodents. As TSPO is involved in steroid production in the brain, this opens up the possibility of targeting the translocator protein with a ligand, as a treatment for anxiety.

Professors Rammes and Rupprecht have investigated this possibility using a TSPO ligand called XBD173, which has already been found to be safe for use in humans. They found that XBD173 was able to counteract anxiety attacks in rodents and induced anti-anxiety activity in humans. They also compared the effects of XBD173 with those of an existing anti-anxiety medication called alprazolam. It was found that the TSPO ligand did not cause the sedative side effects or withdrawal or tolerance effects observed with alprazolam.

The team also looked into the mechanisms that could be responsible for the anti-anxiety effects of XBD173. They found evidence to suggest that XBD173 was increasing neurosteroid



levels in the brain, and therefore enhancing the effects of a signalling molecule called GABA. Existing anti-anxiety drugs also increase GABA signalling.

These important findings suggest that altering GABA signalling through the XBD173 TSPO ligand, instead of the route taken by existing anti-anxiety medications, can provide the desirable anxiety-reducing effects without the undesirable sedative side effects, withdrawal or tolerance effects. It is also exciting evidence for the use of TSPO ligands to treat psychiatric disorders, whereas previous research has focused mainly on brain injury.

Future Directions: Collaborating on Alzheimer's Disease

Following on from the successful use of XBD173 to reduce anxiety measures, Professors Rammes and Rupprecht are now beginning to test the role of TSPO in Alzheimer's disease. Globally, there are approximately 50 million people living with Alzheimer's disease, the main symptoms of which are memory impairment and progressive cognitive decline. It has a severe impact on quality of life and costs health services huge amounts of money every year.

Alzheimer's disease brains are characterised by an accumulation of a protein called amyloid-beta, and the death of brain cells. Currently, there isn't an effective treatment for Alzheimer's disease and researchers all over the world are on the hunt for drugs that will reduce the effects of amyloid-beta accumulation.

An increase in TSPO levels has been identified in Alzheimer's disease patients, and these patients also have decreased steroid levels in the brain. This suggests that increasing steroid production with a TSPO ligand may be beneficial. In fact, other TSPO ligands have been tested in rodent models of Alzheimer's disease and were found to reduce memory impairment and signs of degeneration within the brain. The great advantage of investigating XBD173 is that it has already been proven to be safe in humans, making its route from the lab to the clinic much simpler.

In order to establish whether TSPO ligands are a possible treatment for early Alzheimer's disease, Professors Rammes and Rupprecht will ask whether it can reduce the detrimental effects of amyloid-beta on the function of brain cells. To do this, they will apply XBD173 to living slices of rodent brains with amyloid-beta accumulations and measure the way the cells communicate with each other. They will also test whether treatment with XBD173 can improve memory impairment in rodents with Alzheimer's disease.

Professor Rammes summarises the project well: 'The question is, if the TSPO [translocator protein] ligand XBD173 is able to reverse the toxic effects of amyloid-beta on learning and memory-related processes.' If the answer to that question is yes, Professor Rammes and Professor Rupprecht have suggested a new option for the treatment of Alzheimer's Disease and, as XBD173 has already been tested for safety in humans, one that is already ready for clinical trials.

Meet the researchers

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Professor Gerhard Rammes achieved his PhD from the University of Birmingham, UK, in 1996. Since then, has since held positions at the University of Erlangen and the Max-Planck Institute for Psychiatry in Munich, Germany. He is currently a Professor in the Department of Anesthesiology at the Technical University of Munich, where his team uses multiple techniques investigate the effect of centrally acting drugs, including anaesthetics, on the function of the brain. He has a particular interest in processes relevant to learning and memory, and has been investigating the impact of anaesthetics, benzodiazepines and centrally acting neurosteroids on the pathology of Alzheimer's Disease.

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Professor Rainer Rupprecht studied medicine at the University of Erlangen from 1980 to 1986. Since 2011, he has been the Chair of the Department of Psychiatry and Psychotherapy at the University of Regensburg, Germany. He has been contributing high impact research in the area of translocator protein imaging and therapeutics for almost 10 years. Professor Rupprecht is Assistant Editor-in-Chief of the *World Journal of Biological Psychiatry* and is coordinator of the Federal Ministry of Education and Research (BMBF) programme entitled 'Optimised treatment of depression'. He also received the Anna Monika Prize for depression research in 2012.

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Universität Regensburg

SEX ON THE BRAIN – THE NEUROBIOLOGY OF SEX HORMONES

The prevalence of anxiety and mood disorders is on the rise worldwide. Men and women experience different types of anxiety disorders at different rates – this may be partially due to sex specific differences in the brain. To understand this difference **Professor Roland Bender**, in the lab of Professor Gaby Rune, at the University Medical Center Hamburg-Eppendorf (UKE), Germany, studies how the male and female brain respond differently to sex hormones.

Steroid sex hormones, such as testosterone and oestrogen, are a critical part of healthy human development, serving essential functions in growth and reproductive maturity. Both males and females have naturally occurring levels of the full suite of sex hormones, oestrogen plays a role in normal male biology, just as testosterone plays a role in female health.

However, the overall concentrations of these hormones circulating in the bloodstream are different between the sexes and lifetime exposure patterns vary significantly. In addition to their expected roles, sex hormones carry out functions in the brain that are not necessarily related to gender or reproduction.

Sex hormones have been shown to affect areas of the brain associated with memory, emotional processing, and numerous psychiatric disorders. In light of this, researchers are working to understand how the brain accounts for variation in hormone levels between the sexes. The research team at the Institute of Neuroanatomy, headed by Professor Gaby Rune, University Medical Center Hamburg-Eppendorf (UKE) in Germany, is interested in illuminating the different ways that male and female brains utilise and respond to sex hormones.

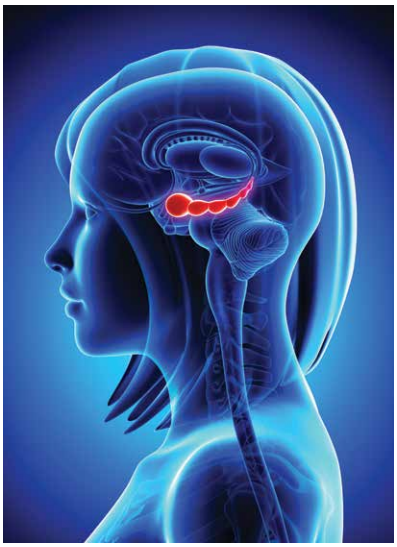
The human brain is composed of networks of millions of brain cells, called neurons, whose firing patterns are the underlying basis of every thought we have and sensation we experience. Neurons communicate with one another through tiny branches called dendritic spines that touch neighbouring cells at contact points known as synapses.

When a neuron is stimulated enough to fire, its synapses release neurotransmitters, the brain's messenger molecules, that either stimulate or dampen a response in its neighbour. Professor Bender's team is specifically interested in synaptic plasticity, the ability of neurons to form new connections with one another by forming new synapses in the amygdala, an area which is particularly related to fear. He says that, 'we want to identify molecular mechanisms of neuronal plasticity in the amygdala that work in males and females differently.'

Professor Bender explains that, 'there is undoubtedly a difference between males and females with respect to exposure to sexual hormones throughout life, which can be expected to result in differing molecular mechanisms within the brain to cope with this, because all the predominant sexual hormones also influence neuronal function.'

Memory and Age

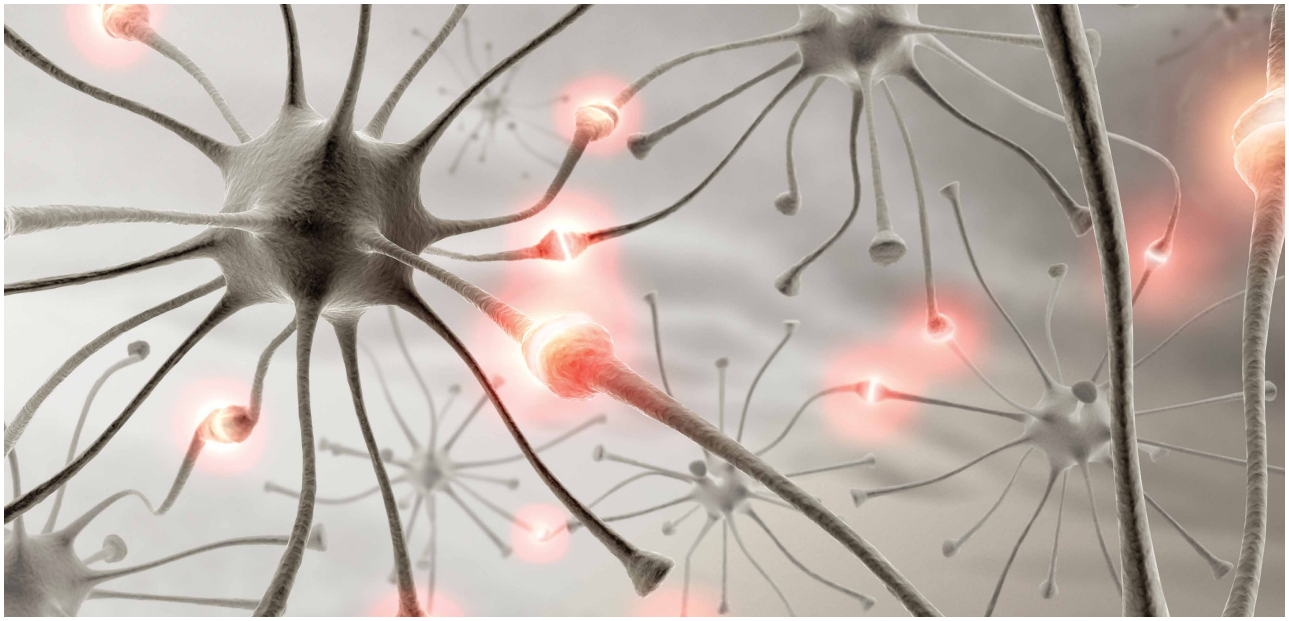
Pioneering studies supporting this assumption have been performed in the hippocampus. The hippocampus is a region of the brain that is required for converting short term memories into long term memories and storing spatial memories that aid in navigation. Within the hippocampus,



higher numbers of synaptic connections, as counted by the number of dendritic spines, is associated with better memory.

Over the past few decades, it has been hypothesised that dendritic spine number is regulated by the sex hormones produced in the gonads. In mice, both males and females lose a significant number of synaptic connections and perform poorly on memory tasks following gonad removal – these connections and cognitive performance can be restored by regular oestrogen injections for females, or testosterone injections for males.

‘We want to identify molecular mechanisms of neuronal plasticity in the nervous system that work in males and females differently.’



Further, treating animals with the hormone of the opposite sex does not necessarily restore synaptic connections – the neurons preferentially respond to the hormones associated with that animal’s sex – suggesting that the hippocampus responds to these hormones in a sex specific manner.

In post-menopausal women and elderly men, a reduction in the levels of these hormones are associated with the cognitive decline of aging. Understanding how the hippocampus utilises these hormones to maintain robust synaptic connections could help doctors better prevent and treat memory decline with age.

Professor Rune’s institute was the first to demonstrate that the hippocampus is also capable of producing its own oestrogen hormone independent of the gonads, achieving oestrogen levels within the structure that are much higher than those circulating in blood. In the female brain, this localised oestrogen works to maintain synapses and a process known as long-term potentiation, the strengthening of the connections between two neurons.

Long-term potentiation is widely held to be a key component of memory formation in the brain and is essential for learning. In mice, inhibiting the ability to produce oestrogen impairs long-term potentiation and leads to synapse loss in the female brain, but has no effect on males. These findings are consistent with observations of cognitive decline in women following menopause, when oestrogen levels drop significantly. Professor Rune’s team hypothesises that sex specific responses to sex hormones in the brain are cemented early in development during sexual differentiation.

In these situations, rather than performing as standard hormones, the behaviour of the hormone molecules is more closely aligned with neurotransmitters. Professor Rune explains how, ‘these hormones can be produced within the brain by the neurons themselves, and may thus act as neurosteroids, rather than as sex hormones coming from the periphery.’ Neurosteroids are locally produced steroids that can also influence neuronal activity and act to relieve anxiety.

In women hippocampal hormone levels cycle with blood levels of oestrogen during the menstrual cycle, suggesting that while the hippocampus is producing its own sex hormones, production is related to factors that influence hormone levels elsewhere in the body. Though the male hippocampus also produces its own oestrogen, levels of the hormone in the male brain are much lower, supporting the idea that sex hormones are utilised differently between males and females.

Professor Rune’s lab has found that in both sexes, GnRH (gonadotrophin releasing hormone) appears to start the cascade of hormonal responses that lead to increased synapse formation through stimulation of oestrogen production in females and testosterone production in males, though some steps in the male pathway are less clear. Many questions remain about how GnRH gets to the hippocampus in the first place and the implications this carries for mental health and cognitive performance.

Fear and the Female Brain

The amygdala is an area of the brain central to the processing of emotions and emotionally charged memories. As a major player in the brain’s fight or flight response to danger, it is one of the primary areas responsible for regulating fear and aggression. Damage to the amygdala can impair the ability to manage stressful situations and feelings of fear, and this region is highly implicated in anxiety disorders.

Like the hippocampus, the amygdala shows sex-specific differences that may differentially impact how men and women process fear and anxiety. Women develop anxiety disorders at nearly double the rate of men, suggesting that the biological underpinnings of anxiety regulation may operate differently between the sexes. By illuminating how sex hormones interact with the amygdala,

Professor Bender's team in the Institute of Neuroanatomy hopes to provide the foundation for interventions that could improve treatment options for anxiety sufferers.

Professor Bender elaborates: 'By identifying mechanisms of neuronal plasticity within the amygdala that are responsive to sex hormones/ sex neurosteroids we hope to get a clue how these influence amygdala functions such as the fear response, and whether differences between the sexes could help to explain the higher prevalence of women to develop certain anxiety disorders.'

In a recent study, Professor Bender's team compared the activity of oestrogen in the amygdala of male and female mice and the effects of a drug, letrozole, that inhibits oestrogen synthesis. They were specifically interested in the behaviour of the enzyme aromatase, that converts excess testosterone to oestrogen – letrozole blocks this conversion.

The team focused on the basolateral section of the amygdala, a key component of the fear circuit in the brain and found that male and female brains produce aromatase at similar levels and have a similar number of receptors for oestrogen. However, when the animals were treated with letrozole, females lost a large number of dendritic spines and long-term potentiation came to a halt, while the structure of the male amygdala was largely unaffected.

Similar to the hippocampus, synaptic plasticity in the amygdala is regulated by sex hormones in a sex specific manner. These results are the first steps in promising research into differential treatment approaches to anxiety disorders in males and females. Further, aromatase inhibiting drugs like letrozole are commonly used in breast cancer therapy – these results carry important weight for consideration during treatment selection in women with breast cancer.

The Future of Hormonal Research

Professor Roland Bender and his research group have made important strides in understanding sex specific differences in the neurological responses to sex hormones. Moving forward, the team hopes to illuminate how these differences develop early in life and learn more about the hormones and pathways that impact synaptic plasticity in the male and female brain.

Their work lays a foundation for a better understanding of how men and women may develop mood and cognitive disorders in different ways. It also sheds light on why men and women respond differently to treatments and how future interventions can better factor a patient's sex into treatments for age related cognitive decline and mood disorders.

Meet the researcher

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Professor Roland Bender completed his undergraduate education in biology and earned his doctorate in anatomy at the University of Freiburg, in Breisgau, Germany. After completing postdoctoral work at the University of Freiburg and the University of California, Irvine, he joined the faculty at the University Medical Center Hamburg-Eppendorf (UKE), Germany, where he currently serves as a Professor and the Deputy Director of the Institute of Neuroanatomy. Professor Bender is fascinated by the molecular mechanisms of neuronal plasticity that behave differently in males and females. He has won multiple teaching awards such as 'Teacher of the Year' in 2013, 2017 and 2018 at the UKE and has published numerous peer-reviewed articles on neural plasticity in the brain.

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KEY COLLABORATORS

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FURTHER READING

RA Bender, L Zhou, R Vierk, N Brandt, A Keller, CE Gee, MK Schäfer and GM Rune, Sex-Dependent Regulation of Aromatase-Mediated Synaptic Plasticity in the Basolateral Amygdala, Journal of Neuroscience, 2017, 37, 1532–1545.

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HOW TO AVOID ALZHEIMER'S DISEASE

Could copper be the cause of the current major epidemic of Alzheimer's disease? **Professor George Brewer** at the University of Michigan Medical School presents a compelling case for the role of copper in causing this debilitating disease at a time when answers are needed the most.

Alzheimer's disease (AD) is a debilitating progressive disease associated with ageing that causes cell death and tissue loss in the brain and essentially destroys quality of life. The consequence of this cell death in the brain is that people lose the capacity to think for themselves, their cognitive abilities and the recall of memories – ultimately robbing them of who they are as individuals.

It is a sad reality that many families will be exposed to the devastating effects of AD at some point in time. As our life-spans increase, AD has become a global epidemic. In fact, more than 50 million people currently suffer from the disease across the world, according to the Alzheimer's Association (https://www.alz.org/global/). This presents a major challenge to healthcare services. Pharmaceutical companies are investing huge amounts of money into scientific research that endeavours to find a cure for a disease for which no definitive cause has been identified – with constant failure resulting in frustration and a lack of hope.

However, Professor George Brewer of the University of Michigan has identified what he believes to be a preventable cause of AD – increased ingestion of a specific form of copper known as divalent copper.

Professor Brewer says that, 'when I educated myself about the history and current status of AD, two facts made a huge impression on me. These facts were that while we had an epidemic of AD in developed countries, this epidemic wasn't occurring in undeveloped countries. Second, the epidemic was new, starting during the 1900s. These facts gave me what I like to call my first epiphany about AD – namely, some environmental cause of the disease had occurred in developed countries during the 1900s.'

A New Epidemic

What does Professor Brewer mean by a new epidemic? The disease was first documented and named in 1907 after Alois Alzheimer. What is interesting is that in the later years of the 19th century, many practising clinicians studying neurology did not describe any disease with symptoms similar to AD. Even experts of the mind, such as Freud or Gower, did not mention symptoms of this disease and Boyd's Textbook of Pathology didn't include any descriptions of the characteristic changes seen in the Alzheimer's brain.

Many scientists believe that as AD is a condition that affects us during ageing, that there were simply not enough elderly individuals at that time for clinicians to be alerted to the existence of the disease. However, Professor Brewer notes that this is not the case, as census information shows us that in 1911 in France, there were 250,000 people aged 65 to 75 and 115,000 people aged 75 to 85. In the US, approximately three million people were aged 60 or over, therefore indicating that there were plenty of potential AD patients to be discovered, if they had occurred at today's rates. It is as if the disease appeared suddenly and simply out of nowhere.

Developed and Undeveloped Countries

Professor Brewer has published a number of articles, including a recent book, outlining his theory, which highlights some extremely thought-provoking statistics. He describes how only a small proportion of the elderly population has AD in undeveloped countries in comparison to developed countries.

'When I educated myself about the history and current status of AD, two facts made a huge impression on me. These facts gave me what I like to call my first epiphany – namely, some environmental cause of the disease had occurred in developed countries during the 1900s.'

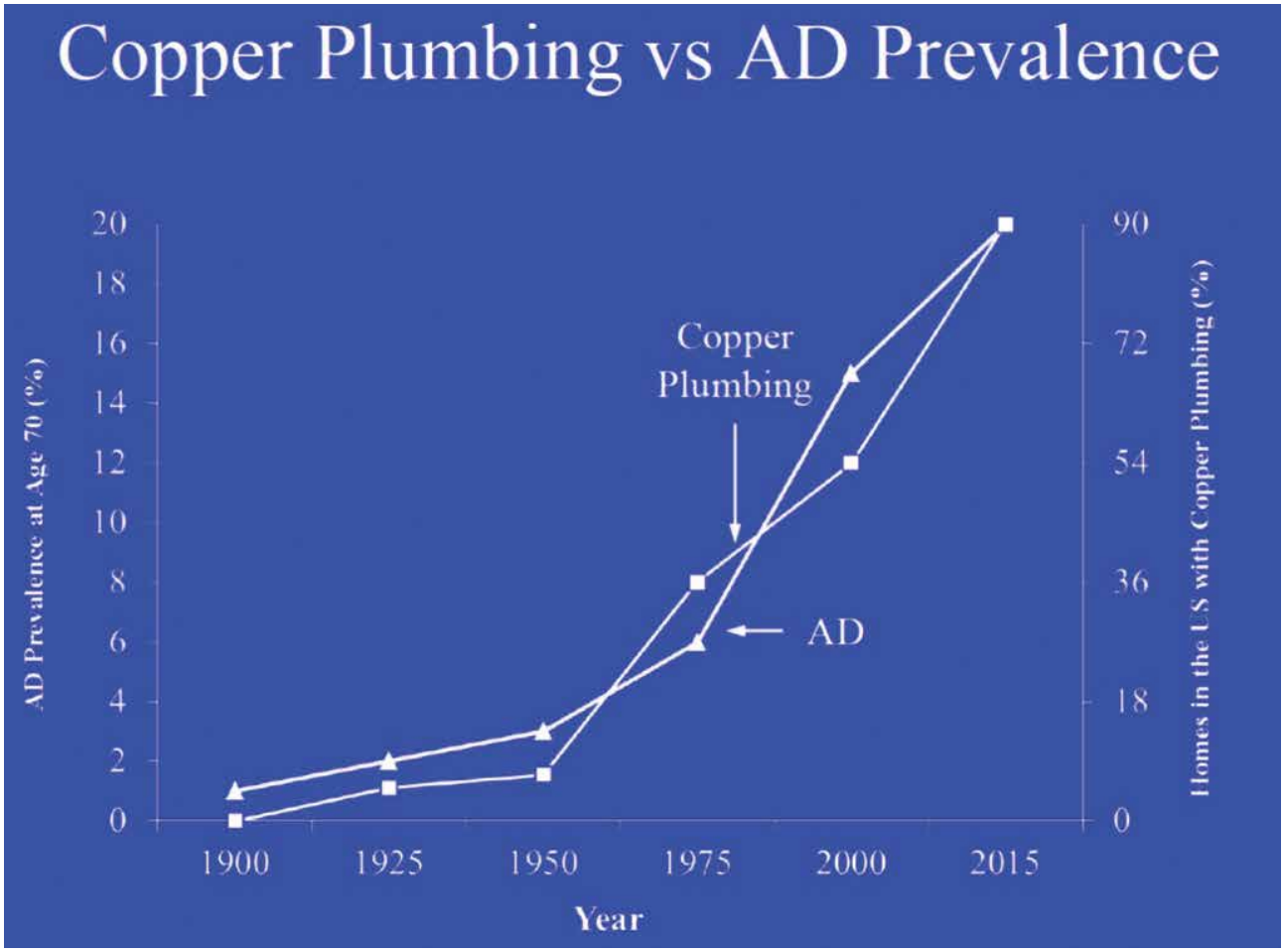

Figure One

In India for example, only 1.07% of people over the age of 65 have AD, and in Nigeria, only 0.52% of people aged 65 to 74 present with the disease. What becomes apparent when considering the facts Professor Brewer brings to the table, is that AD, in the absence of any other credible explanation, results from a change that has taken place in developed, but not in undeveloped countries, beginning in the 20th century.

There is debate as to whether the increased prevalence of AD in developed countries is due to people eating more beef with AD being a prion disease transmitted by infected beef. However, other diseases that are transmitted in this way, such as Creutzfeldt-Jakob disease (CJD, or mad cow disease) behave differently in the human body compared to AD.

A genetic aspect of the disease has also been shown. Alleles are different forms of a gene that can occur in different people, and the presence of certain alleles in an individual can determine whether they are more or less likely to develop a certain medical condition. The E-4 allele of the apolipoprotein gene has been shown to significantly increase a person's chances of developing AD.

However, Professor Brewer notes that the different versions of such genes in the population would not be expected to have changed that much from the 19th to the 20th centuries, in the time AD suddenly exploded into an epidemic. Therefore, the only credible explanation for the new AD epidemic is an environmental change. Professor Brewer presents evidence that the change that brought about the increased occurrence of AD was increased ingestion of a specific type of copper – divalent copper.

A Second Epiphany

What led Professor Brewer to the conclusion that divalent copper ingestion was causing the epidemic of AD? He says two studies were the key. The first comes from research investigating forms of AD found in animals. Research illustrates that if tiny amounts of divalent copper (0.12 parts per million) are added to the drinking water of animals with AD, they present with enhanced AD symptoms in addition to a greater number of toxic plaques in the brain.

In the US, the Environmental Protection Agency allows copper of up to 1.3 parts per million in human drinking water – 10 times more than the amount that proved toxic to animals. The second study is a human study in which it was shown that ingestion of copper-containing supplement pills, in the presence of a high-fat diet, caused cognition loss at several times the normal rate.

Professor Brewer says these two studies led to his second epiphany about AD, because what did they have in common? In both cases, the ingested copper was divalent copper. Knowing that food copper is almost all monovalent copper, he realised then how different and potentially toxic divalent copper is.

Copper – An Element with Two Sides

Before exploring the copper hypothesis, it is essential to note that copper can take the form of monovalent copper, (copper-1 or Cu+), the essential ion that is found in food, and divalent copper, (copper-2 or Cu++) which is a toxic ion. While all copper can be toxic in large quantities, it is also necessary for the healthy functioning of the body.

Since humans evolved ingesting primarily copper-1, the cells in our intestines possess a protein called copper-transporter-1 (Ctr1), which transports copper-1 to the liver where it can be safely processed. Copper-2 cannot bind to these transporters, and therefore cannot be safely processed.

This is alarming when considering that the use of modern copper piping systems as plumbing in developed countries leads to traces of copper-2 in human drinking water and that all copper supplement pills are copper-2 containing. Thus, Professor Brewer proposes the culprit for the sudden appearance of AD and its increased prevalence in developed countries is the increased ingestion of copper-2.

The Pieces of the Copper Jigsaw

So, how does the ingestion of copper-2 cause an increased risk of developing AD? The amyloid-cascade hypothesis is the most popular theory of AD development. In the brain of an AD patient, it is thought that the protein beta-amyloid accumulates and essentially clumps together to form plaques. This process occurs in the healthy brain – however, in AD this process is accelerated, and the increased presence of plaques is toxic and disrupts the normal function and survival of neurons in the brain.

Copper-2 is known to cause enhanced aggregation of beta-amyloid into plaques. It also binds to these plaques and triggers the release of damaging oxygen free radicals that are believed to kill neurons. Professor Brewer suggests that it is highly possible that copper-2 is the major trigger that causes the beta-amyloid in the brain to aggregate and become toxic.

Professor Brewer points out that the timing of the AD epidemic closely mirrors the timing of the use of copper plumbing in developed countries. This is illustrated for the US in Figure one. He also points out that the theory really comes together when you consider that currently, 90% of US homes have copper plumbing, whereas in Japan, a country that refused to use copper plumbing due to fear of copper toxicity, AD incidence is considerably lower. Interestingly, when Japanese individuals emigrate to Hawaii, where copper plumbing is used, the number of individuals with AD increases to match that of developed countries.

Furthermore, at least a third of the US population take multi-vitamin supplement pills that contain copper-2. Professor Brewer points out, as shown in the study mentioned, that when humans ingest excess amounts of such pills, their cognitive abilities decline at an alarming rate.

Summary of Data Supporting the 'Brewer Hypothesis for Copper-2 Causation of the Alzheimer's Disease (AD) Epidemic.'

- Addition of 0.12 parts per million copper-2 to the drinking water of AD animal models greatly enhanced AD. The US allowance for copper in drinking water is 1.3 parts per million, 10 times as high.
- From 1/3rd to 2/3rds of North American drinking water samples contain unsafe levels of copper-2 according to the animal model studies.
- The development of the AD epidemic closely parallels in time the increasing use of copper plumbing.
- Japan has shunned the use of copper plumbing and is a developed country with a low prevalence of AD. But when Japanese people migrate to Hawaii, where copper plumbing is used, their AD prevalence matches other developed countries.
- Ingestion of copper-2 in the form of copper-containing supplement pills has been shown to decrease cognition at six times the normal rate.
- Copper-1 is the prevalent form of copper in food and we evolved a safe mechanism for absorbing and handling copper-1, but not copper-2.
- Unlike copper-1, some copper-2 is absorbed directly into the blood and slowly damages cognition.

Figure Two

The final piece of the puzzle comes from the fact that humans were not exposed to copper-2 until the 1900s, when developed countries adopted copper plumbing and the use of supplement pills became increasingly common. See Figure two for a summary of the data supporting the copper-2 hypothesis for the causation of the AD epidemic. For more information, all the details of the case for copper-2 as a cause of AD can be found under 'Further Reading', including Dr Brewer's recently published book.

Professor Brewer's Preventive Measures

Is this all a coincidence? Professor Brewer thinks not. He agrees, the copper hypothesis has not yet been finally proven. However, the supporting evidence presented so far is very compelling. Thus, he advises everyone to take two simple preventive measures. One is to avoid taking copper-containing supplement pills. The second is to test your drinking water. If it is over 0.01 parts per million, install an inexpensive reverse osmosis device on the drinking water tap to remove excess copper. See Figure three for the best steps for prevention.

Of his next steps, Professor Brewer says: 'Stopping the ingestion of copper-2 in drinking water and copper-containing supplement pills will hopefully prevent 95% of new cases of AD.' However, this would probably not help those who already have AD. Endeavouring to help these patients, he says he and his company *Cypris LLC* are, 'working on a drug therapy which in preliminary trials halted the progression of AD over a six-month period. The next steps are to arrange a longer, larger, study of this drug in patients, with a view to bringing it to the market for the benefit of all patients.'

Personal Steps to Reduce Copper-2 Ingestion to Avoid AD

- Stop taking copper supplement pills.
- Test the copper levels in your drinking water.
- If it is 0.01 parts per million (10mg/L) or lower it is safe (about 1/3 of samples).
- If it is higher than 0.01 parts per million, put a reverse osmosis device on the tap (about 2/3 of samples).

Figure Three

Meet the researcher

Professor George J. Brewer, MD
Department of Human Genetics
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Professor George Brewer is the Sellner Emeritus Professor of Human Genetics and Emeritus Professor of Internal Medicine at the University of Michigan Medical School. Professor Brewer completed his BS degree at Purdue University, before obtaining an MD degree at the University of Chicago in 1956. Professor Brewer is an internationally recognised expert on copper and zinc and on Wilson's disease, that results from copper accumulation and toxicity. In 1997, he developed a novel Food and Drug Administration approved treatment for the condition based on his discovery that zinc caused copper deficiency. In 2000, he was named the first Morton S. and Henrietta K. Sellner Professor of Human Genetics. Professor Brewer directed the University's National Institutes of Health Training Grant Program in Genetics for 22 years and was president of the International Society for Trace Element Research in Humans, receiving the highly esteemed Raulin Award in 1998. He is a longstanding Fellow of the American College of Nutrition (the ACN), serving as President of the ACN and currently as a member of the Board of Directors. He was given the prestigious award of Master of the ACN in 1999. His work is widely published in international journals and he continues to win prestigious awards for his contributions to the medical research field. Currently, Professor Brewer is investigating the contribution of copper to the development of Alzheimer's disease and with his company, *Cypris LLC*, exploring the development of new drugs for Wilson's disease and Alzheimer's disease.

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KEY COLLABORATORS

Ramon Royal, Co-director of *Cypris LLC.*

FURTHER READING

G Brewer, Copper-2 Hypothesis for Causation of the Current Alzheimer's Disease Epidemic Together with Dietary Changes That Enhance the Epidemic, Chemical Research in Toxicology, 2017, 30, 763–768.

G Brewer, Divalent Copper as a Major Triggering Agent in Alzheimer's Disease, Journal of Alzheimer's Disease, 2015, 46, 593–604.

G Brewer, Issues Raised Involving the Copper Hypotheses in the Causation of Alzheimer's Disease, International Journal of Alzheimer's Disease, 2011, doi: 10.4061/2011/537528.

G Brewer, Environmental Causes and Prevention Measures for Alzheimer's Disease, Academic Press (Elsevier Science), Cambridge MA, 2017.

MEDICAL SCHOOL
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BEMOBIL: IMAGING HUMAN BRAIN ACTIVITY IN MOTION

As humans we are constantly on the move, but how does our brain enable us to keep up with our dynamic and changing world? **Professor Klaus Gramann** leads a team of researchers at Berlin Technical University driving forward a method of Mobile Brain/Body Imaging he originally developed with colleagues at the Swartz Center for Computational Neuroscience. Excitingly, this method allows the assessment of the neural and behavioural processes underlying our ability to understand our world and respond to it.

Brain Imaging: Windows into the Mind

Cognition refers to the mental processes involved in acquiring knowledge and understanding, encompassing our thoughts, experiences, and senses. However, the events taking place in our brains that facilitate these complex cognitive processes are yet to be fully elucidated.

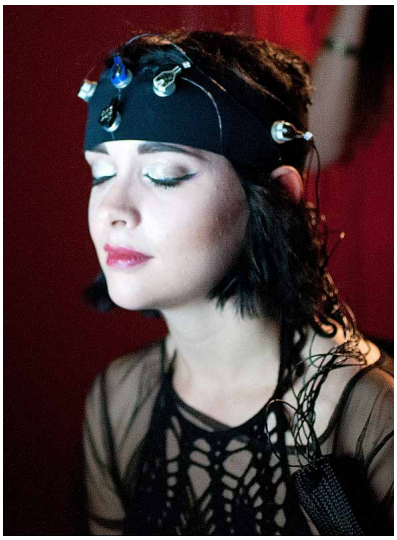
Modern imaging techniques, such as functional magnetic resonance imaging (fMRI) which measures brain activity in awake human participants, have substantially contributed to our understanding of which areas of the brain are active during different kinds of behaviours and cognitive tasks. fMRI measures blood flow, which increases in brain areas where activity is taking place.

However, one key limitation of this (and many other functional imaging techniques), is the requirement for the participant to stay still during the collection of imaging data. For example, during an fMRI scan, the person undergoing imaging must lie still in a narrow tube which runs through the middle of the machine. They are presented cognitive tasks on a 2D screen and the brain regions activated during different tasks are identified.

Although such techniques have advanced our understanding of the brain, in our day-to-day activities we don't view the world on a 2D screen, and we don't live our lives lying still. The key reason that we developed the ability to reason and think was to enable us to improve the outcome of our behavioural responses to an unpredictable 3D world to reach our cognitive goals.

Our motor processes influence our cognition – and vice versa. Imagine, for example, navigating through a room towards a chair you want to sit on. There is constant feedback between the input you are receiving about your environment and the decisions you make based on that information. During evolution the ability to do this was critical for survival, these days it is still necessary to complete the task as well as to avoid the embarrassment of missing the chair you are trying to sit on. Therefore, it is important to have other options for brain imaging which better recapitulate how we use our cognitive abilities in real life.

Professor Klaus Gramann and the team at the Berlin Mobile Brain/Body Imaging Lab (BeMoBIL) have begun to address this by taking brain imaging out of its box and into virtual reality and the real world. They believe that the best way to

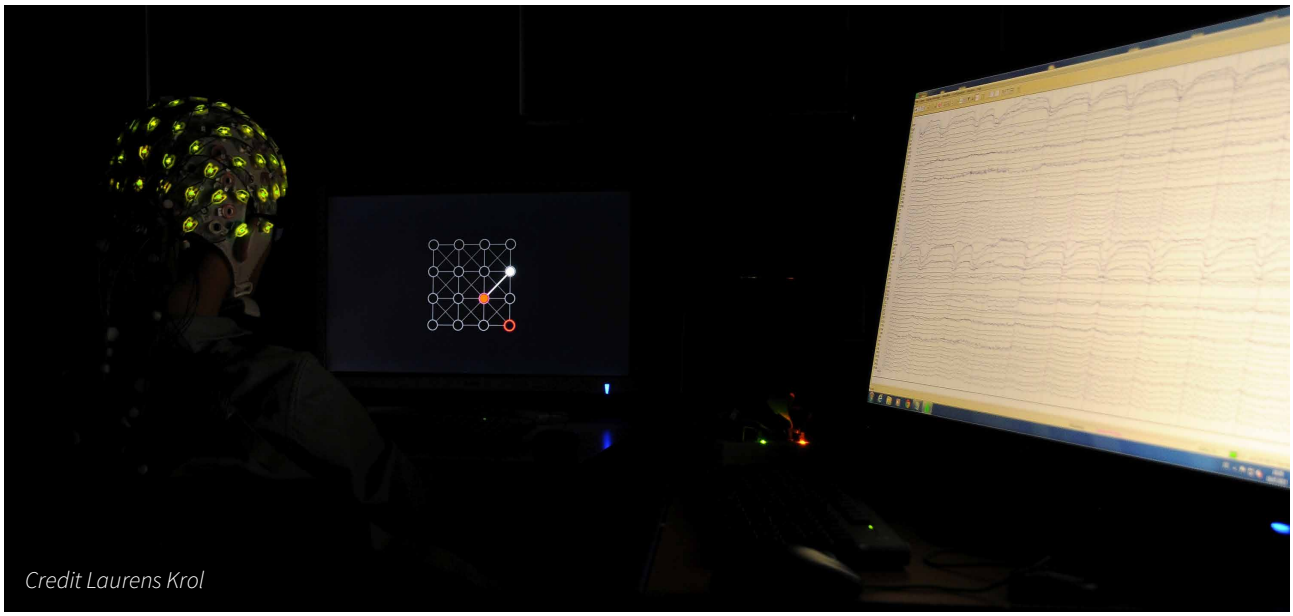


Credit Laurens Krol

really understand the neural processes underlying cognition is to study the brain as the body moves and interacts with a natural environment.

By combining mobile brain imaging methods with state-of-the-art virtual reality (VR) and motion capture technology, the team can study brain activity in participants that are free to move around and undertaking natural behaviours. In this way, the team can ask questions about the relationships between brain function and active behaviour, and can provide information for the development of human-machine interfaces.

‘This is a method that allows new insights into one of the central functions of the human brain during more natural interactions with our environment.’



Credit Laurens Krol

BeMoBIL: Letting Brain Imaging Out of Its Box

Virtual reality technology has transformed the potential for this kind of research. It is now possible to create a virtual environment with complex, unpredictable, and dynamic features representative of the world we live in, but still within a controlled laboratory setting. At BeMoBIL, virtual reality headsets are used to place participants in an environment that feels real to them but is carefully designed and controlled by experimenters.

Professor Gramann and his team have combined these VR environments with mobile electroencephalogram (EEG) recordings of brain activity. To obtain EEG recordings, small metal disks are placed on the scalp, usually contained in a cap. These sensors then pick up the electrical signals produced when brain cells communicate with each other. The electrical signals are detectable at the scalp surface and, as many sensors are placed all over the head, they can be localised to specific brain regions. In the past, EEG was considered to be too prone to noise produced by movement to be used while a participant is walking or running.

Professor Gramann and his team overcame this difficulty by developing a method for filtering out the noise in the EEG signal produced by movements. Critically, this allows the researchers to detect electrical signals at the scalp surface during locomotion. Wireless EEG technology means that there is now even more freedom for participants to move during recordings. In addition to mobile EEG equipment from Brain Products, the facility at BeMoBIL also includes advanced video motion capture technology, eyetracking equipment, and force measuring plates to enable the precise movements of participants to be recorded and synchronised with the EEG recordings.

The facility at BeMoBIL combines these three aspects to ask questions about how the brain works, and through overcoming the limitations of static brain imaging techniques such as fMRI, they are opening up many avenues for scientific discovery. As professor Gramann explains, ‘This is a method that allows new insights into one of the central functions of the human brain during more natural interactions with our environment.’

Applying MoBI Technology to Real-life Questions: Does Your House Make You Happy?

The technology available at BeMoBIL has already been used to ask scientific questions that cannot be addressed with other techniques. One interesting question is that of how architectural spaces affect our brain activity and our emotions.

The shape of buildings is an important element of architectural design, and throughout history this has been defined by artistic taste alongside practical considerations. But what is the impact of these decisions on the mental state of the human occupants of those buildings? Does a stylish building necessarily mean happy inhabitants? Professor Gramann and his team used real-life examples of the insides of people’s homes to generate generic 3D models of different room types, compatible with the virtual reality methods used at BeMOBIL.

Participants completed a short picture-based test in each virtual room, as a subjective measure of their emotional response to that environment. The researchers also recorded the electroencephalogram (EEG) of participants as they naturally moved

Credit Lukas Gehrke, http://lukasgehrke.com

around the different rooms, as an objective measure of brain activity. Video motion capture was used to track the movement of the participants around the different rooms. These room models were empty and the study focused on the impact of the shapes, proportions, and architectural features of the rooms on brain activity, rather than the contents.

The researchers identified the room forms and features which induced different emotional responses. For example, rooms containing curved forms were found to induce a more pleasurable response than those consisting of straight edges. This increased pleasure response was accompanied by increased activity in an area of the brain known as the anterior cingulate cortex (ACC). This area of the brain is thought to play a role in emotional and artistic experiences. The benefit of using mobile EEG in this kind of experiment was that the team could record very fast responses of brain activity to entry into a particular environment. They found that the architectural spaces had very rapid effects on activity in the ACC starting at around 50 milliseconds, approximately eight times faster than the blink of an eye. Before you are even aware of it your brain is responding to your surroundings and influencing your emotions.

This shows that specific architectural features have rapid but measurable effects on both the dynamics of our brain activity and our emotions. This sort of detailed information is highly valuable for the design of living and working spaces that are kind to our mental health.

Next Steps: The Marriage of Man and Machine

Our world is becoming dominated by machines – we interact with our mobile phones, computers, and tablets to carry out an enormous range of day-to-day tasks. As these machines become faster and more capable, it is increasingly the point of human-machine interaction that slows down the process. For example, as I type this article, my brain is thinking faster than I can type, my laptop is certainly capable of keeping up with the speed of my thinking, but my fingers can only move so fast. Professor Gramann and his team are interested in how we can use mobile brain imaging technology to bypass this bottleneck and allow our brains to speak straight into our machines. Understanding how the human brain encodes information related to cognition and movement is important if we are to achieve this exciting goal.

As part of the global effort towards faster human-machine interaction, Professor Gramann and a team led by Dr Zander carried out an experiment to analyse real-time brain activity in participants and use it to enable them to control a cursor on a screen.

In order to do this, the team carried out EEG recordings of brain activity while participants watched a cursor move around different segments of a grid presented on a screen. They measured the brain responses associated with each specific movement of the cursor. The patterns of brain activity associated with different directions of cursor movement were then used to build a model that would enable the computer to interpret brain activity as a specific cursor movement signal. In addition to demonstrating that EEG recordings can carry task-relevant information in a way that can be classified and understood, this experiment also provided information on the brain regions involved in such cognitive tasks. The team identified the medial prefrontal cortex (mPFC), an area believed to be involved in decision making, as the main location of these task-related brain responses.

Experiments such as these are important stepping stones towards shifting the human-machine interface to a more efficient brain-machine interface. This could have applications in almost every area of life, from enabling individuals to choose Netflix shows simply using their minds, to the development of smart living environments in rehabilitation therapy to support patients in regaining independent mobility skills for daily living.

Already Professor Gramann and his interdisciplinary team have been able to study the impact of the environment on brain dynamics, and have demonstrated a method by which brain dynamics could control elements of the environment. The potential applications of the techniques for mobile brain imaging developed at BeMoBIL are wide-ranging – and will likely answer some fundamental questions about how it is that we think.

Credit: Janosch Boerckel

Meet the researcher

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Professor Klaus Gramann gained his PhD in Psychology from the Technical University of Aachen, Germany, in 2002. He undertook postdoctoral research before being appointed as an assistant professor at the University of Munich and then spending several years at the University of California, San Diego, USA. Professor Gramann spent five months at the National Chiao Tung University in Taiwan as a visiting professor before returning to Germany, where he became Professor of Cognitive Psychology at the University of Osnabruck. He has been Professor of Biological Psychology and Neuroergonomics at the Technical University (TU) of Berlin since 2012. Professor Gramann's research interest is in mobile brain/body imaging, and he opened the Berlin Mobile Brain/Body Imaging Lab (BeMoBIL) at TU Berlin in 2014. Professor Gramann has published over 70 research papers since 2005 and has authored several books. His work has received substantial funding and he is a regular reviewer and editor for a number of prestigious journals.

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German Academic Exchange Service (DAAD)
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SPONSORSHIP

Brain Products GmbH

FURTHER READING

T Töllner, Y Wang, S Makeig, H Müller, T-P Jung, K Gramann, Two independent frontal midline theta oscillations during conflict detection and adaptation in a Simon-type manual reaching task, Journal of Neuroscience, 2017, 7, 2503–2515.

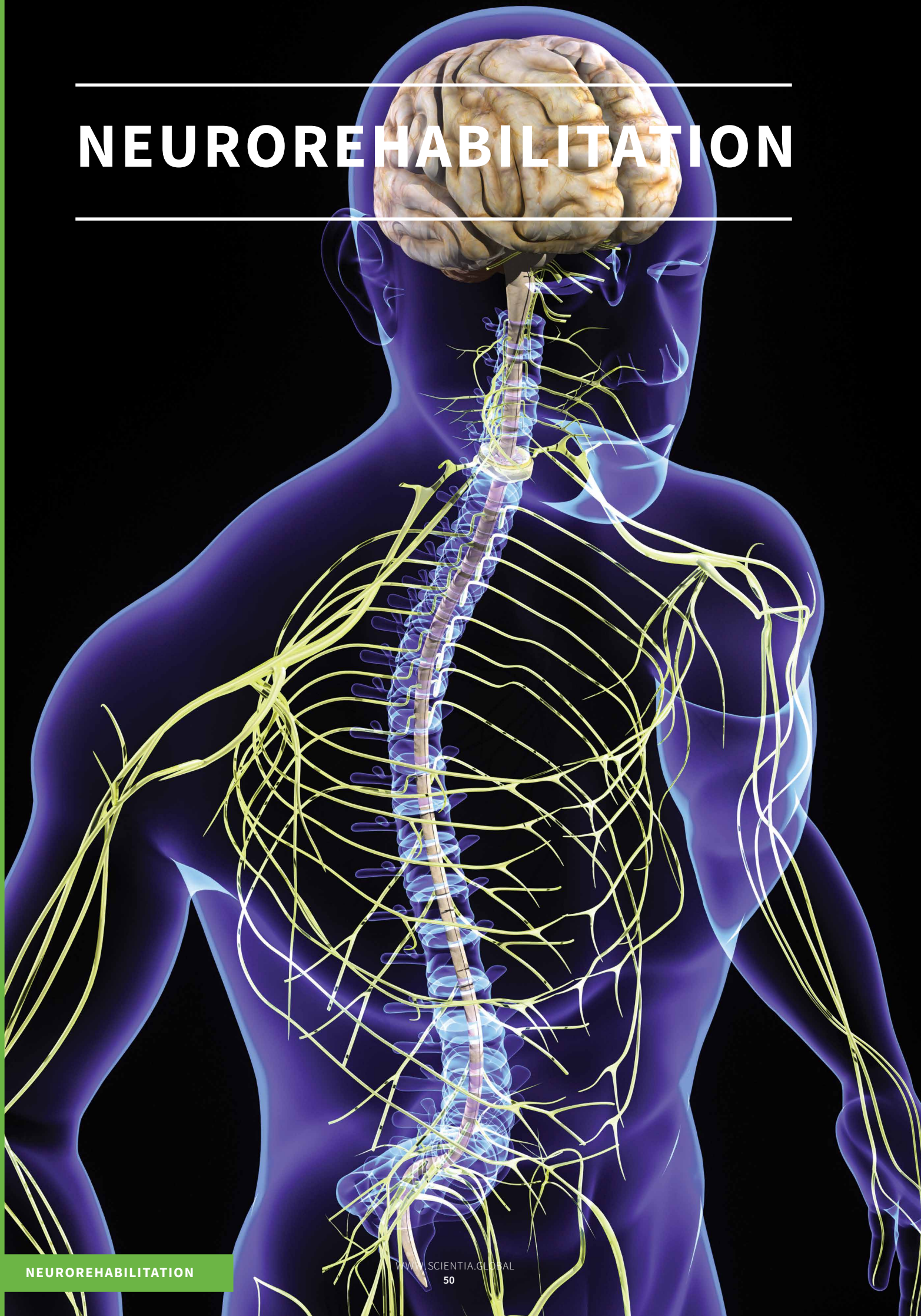
K Gramann, S Fairclough, TO Zander, H Ayaz, Trends in neuroergonomics: A comprehensive overview, Frontiers in Human Neuroscience, 2017, 11.

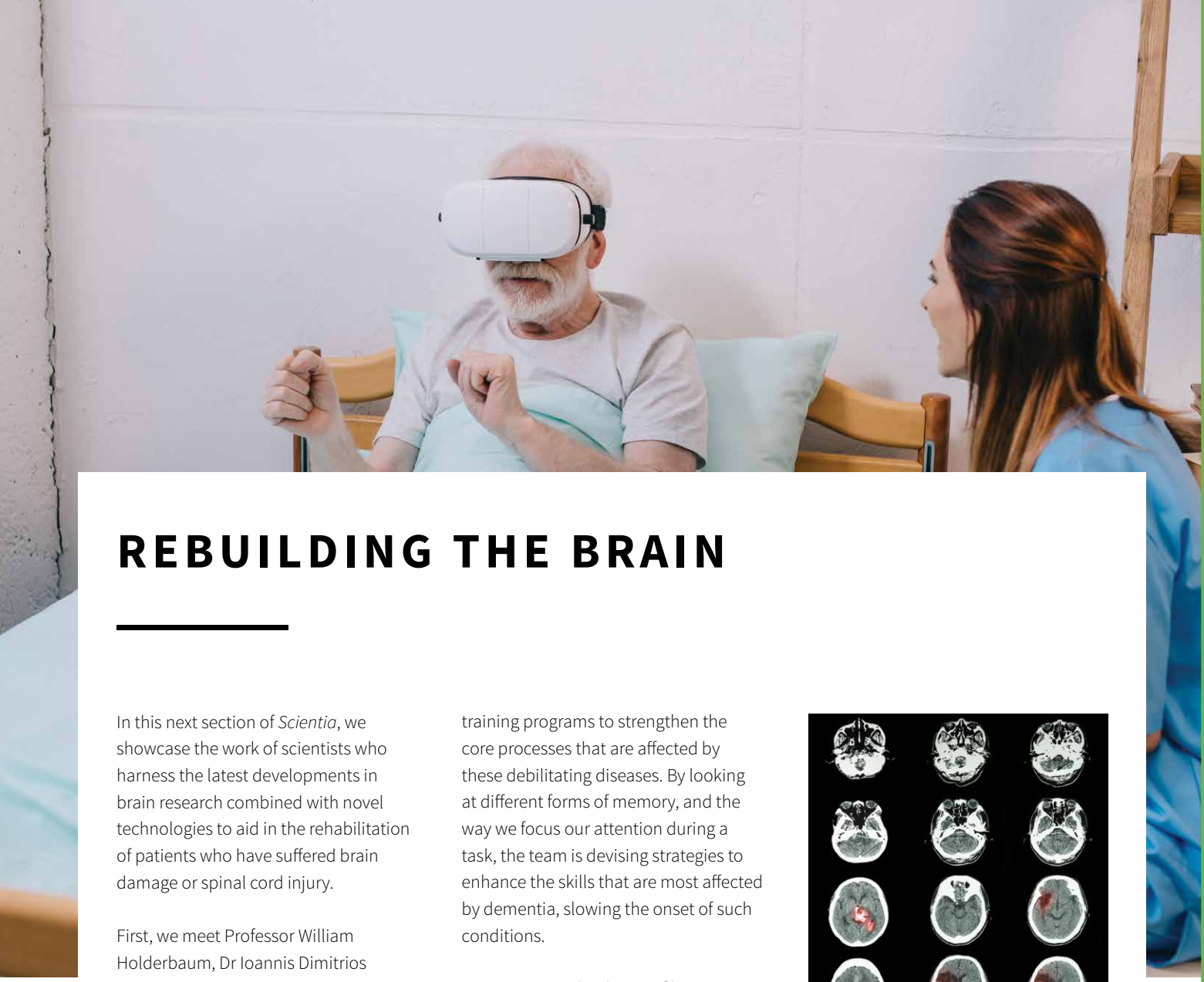
TO Zander, LR Krol, NP Birbaumer, K Gramann, Neuroadaptive technology enables implicit cursor control based on medial prefrontal cortex activity. Proceedings of the National Academy of Sciences of the USA, 2016, 113, 14898–14903.

K Gramann, DP Ferris, J Gwin, S Makeig, Imaging natural cognition in action. International Journal of Psychophysiology, 2014, 91, 22–29.

BeMoBIL Berlin Mobile Brain / Body Imaging Lab
Department of Biological Psychology and Neuroergonomics
BRAIN PRODUCTS Solutions for neurophysiological research

NEUROREHABILITATION





REBUILDING THE BRAIN

In this next section of *Scientia*, we showcase the work of scientists who harness the latest developments in brain research combined with novel technologies to aid in the rehabilitation of patients who have suffered brain damage or spinal cord injury.

First, we meet Professor William Holderbaum, Dr Ioannis Dimitrios Zoulias and Dr Monica Armengol at Reading University who are working to improve the health of people with paraplegia caused by spinal cord injuries. Without movement, the bones and muscles of unused limbs start to deteriorate and lose strength. To prevent this, the team has designed an exercise platform, where electrical stimulation is used to activate different muscle groups. This cutting-edge system, which uses motion sensors to precisely control muscle activation, is promoting better bone health by helping patients move and exercise, aiding in their rehabilitation.

Next, we meet Professor Notger Müller and his team at the German Center for Neurodegenerative Diseases (DZNE), who are working to identify key symptoms in dementia disorders, in order to aid early detection. They are also developing psychological training programs to strengthen the core processes that are affected by these debilitating diseases. By looking at different forms of memory, and the way we focus our attention during a task, the team is devising strategies to enhance the skills that are most affected by dementia, slowing the onset of such conditions.

Continuing on the theme of brain training, our next article introduces the research of Professor Sylvain Baillet and his team at the McConnell Brain Imaging Centre, who apply a technique known as neurocognitive feedback to help patients control their own brain activity. By taking advantage of the latest imaging techniques, the team is allowing patients to see how their thoughts influence their brain activity, providing them with the tools to train their own brains. This could allow patients to train damaged areas of their brain to aid faster recovery.

At the Medical University of South Carolina's Center for Biomedical Research Excellence (COBRE) in Stroke Recovery, a specialist team is developing an interdisciplinary approach to help stroke survivors. At this dedicated centre of excellence, the team combines the latest in

rehabilitation equipment with sophisticated neuroimaging technology to develop and apply novel treatments for promoting recovery after stroke.

With an increased understanding of how the brain and nervous system control key functions, coupled with the latest advances in technology, the researchers featured in this section are finding ways to enhance recovery and rehabilitation from damage that was previously difficult or impossible to treat. Such technological developments can now allow patients to train targeted areas of their brains or bodies, enhancing specific abilities that aid recovery.

WALKING AGAINST THE CURRENT

A research team at the University of Reading is helping people with paraplegia to stand, using electrical stimulation and high-tech exercise platforms to prevent long-term decline in bone and muscle.

Spinal cord injuries are far more common than you might think. Worldwide, somewhere between 250,000 and 500,000 people acquire a spinal cord injury every year. A car crash, a fall, or even an act of violence – all of these things can bring about an instant and massive change in someone's life.

Spinal cord injury affects people in more ways than just removing the ability to walk. The lack of activity causes the legs to lose strength, while both bones and muscles reduce in density. The act of standing and walking requires the legs to support the entire body weight and thus places a significant amount of pressure and loading on leg bones. Once this loading is gone, the body reacts by thinning out the unused bones – which in turn leads to a much higher chance of fractures. This effect is also seen in astronauts, where the long periods of weightlessness cause a similar lack of loading and thus bone density and muscle loss.

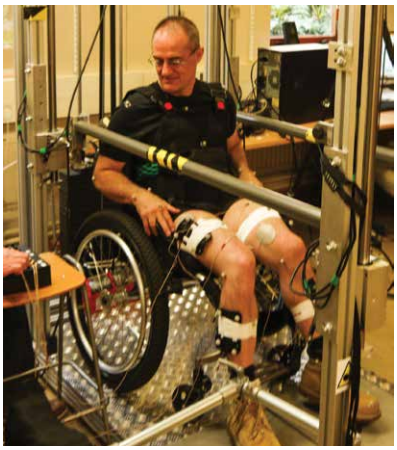
This is no surprise to those working in the field, such as Professor William Holderbaum and his research team at the University of Reading. 'People with paraplegia (those who have complete paralysis below the chest) often have weakened lower limb bones due to the total loss of leg movement,' says Professor Holderbaum. 'This leads to a reduced quality of life. The increased risk of fracture while performing daily activities such as transferring from and to the wheelchair may result in lengthy hospital stays. Additionally, such bone fractures significantly increase health risks and impact life span.'

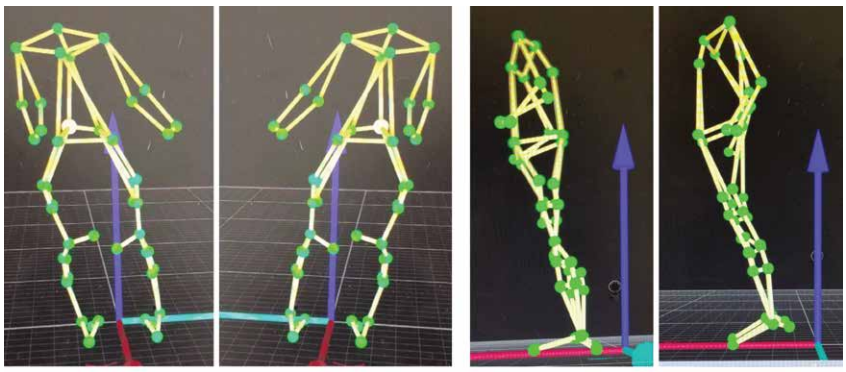
The team of researchers is developing a therapy that will minimise this bone density loss, immensely improving the quality of life for those with paraplegia. As of yet there are no widely accepted ways to prevent or reverse this loss of bone density; pharmaceutical approaches do exist but tend to have significant side-effects. However, it is possible to slow density loss by simulating the typical forces caused by walking in a healthy subject. There are several ways to provide these forces, but one of the most effective is for the individual to stand up and shift their weight around.

Standing Tall

It seems unlikely for someone with paraplegia to stand, yet technology has been available for many years to allow this. Known as 'functional electrical stimulation', or FES, the process uses electrical stimulation to induce muscle contraction.

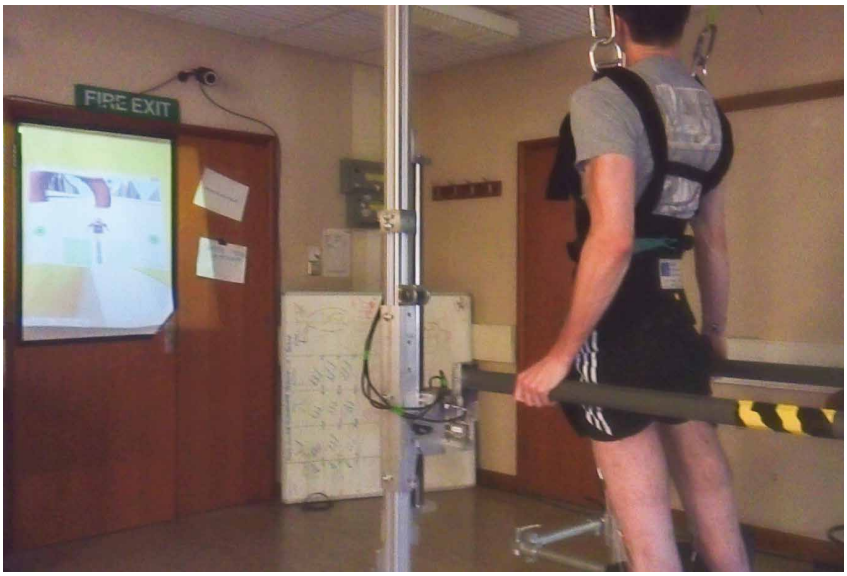
In a typical muscle, nerve signals trigger the activation of an electrical impulse within the muscle filaments – this causes contraction of the filaments and thus contraction of the entire muscle. In FES, electrode pads are placed over the muscle to be activated and transmit a low-energy electrical pulse. This pulse activates nearby nerve cells, which then transmit signals that activate the associated muscles. FES works in both healthy people and in those with spinal cord injuries – the injury does not take away the required nerve and muscle cells but merely removes the person's ability to voluntarily control them.





Lateral – Medial

Tip Anterior – Posterior



For a person with paraplegia, the FES system allows the main leg muscles to become activated, which has the effect of locking the legs in the extended position. Once this is done, the person can lean their upper body backwards to bring their centre of mass behind their back – in essentially an inverted 'C' shape. This creates a stable balanced posture that allows a person with paraplegia to stand upright, controlling their balance with upper-body movements.

There are some downsides to this technique, however. Electrified muscles do not rest and will begin to suffer fatigue, meaning that they will eventually fail to hold the locked-leg position required for standing. Many different approaches have been trialled to reduce muscle fatigue, ranging from changing the format of the electrical signals, shifting postures and activating specific muscles in different orders.

Framing the Solution

It is at this point that the Professor Holderbaum and his research team enter the picture. Their goal is to improve the currently available treatment of patients with paraplegia by more effectively slowing bone density loss. To do this, they have created one of the most advanced FES exercise platforms currently in use.

The platform is equipped with a number of sensors that measure the forces applied by the user. A motion capture system, similar to those used in the film industry, can record and reconstruct the current body position of the user. Using this data, a computer calculates which muscles to activate and when – a purpose-built FES device created by the team can activate up to 16 muscles at once to help users hold their balance and perform exercises.

A skiing video game demonstrates the current body posture and exercise output. This not only keeps users of the system entertained during the program but also provides instant feedback to ensure that the correct exercise posture is achieved. By co-ordinating FES and voluntary movement, the system provides exercise and leg loading while preventing the muscles from becoming too quickly fatigued. This entire process works with people who have paraplegia – it is essentially an automated standing and exercise device.

This system certainly sounds impressive, but the real question is whether it improves patient outcomes. To determine this, the team performed a study with the help of participants who had suffered a spinal cord injury. It was divided into two phases, termed leg conditioning and intervention. The leg conditioning phase consisted of a three-month training program involving daily use of the FES system designed to build leg muscle strength. This stage is vital for long term success – muscles begin to lose mass after only six weeks following a spinal cord injury, so it is imperative that prior strength is rebuilt before performing any standing exercises.

In the following intervention phase, the participants of the study were allowed to stand within the exercise platform, where they performed a number of load-bearing exercises as part of a skiing game. To ensure that the participants were ready for the process, the researchers first tested that they could undergo FES for one hour without showing significant signs of muscle fatigue and that they were able to balance by moving their upper body.

The participants came to the laboratory twice a week for six months to perform an hour of exercise. While in the exercise frame, the system used surface electrodes to stimulate between eight and 12 muscles in the lower limbs. This spread of muscle activation was performed so as to provide a wider loading of the bone and thus a more consistent degree of bone improvement

throughout. The research team designed the exercise program to focus on side-to-side and front-to-back movements – these motions are ideal for providing compression forces along the bone while avoiding shear forces across the bone, thereby minimising the chances of causing damage.

At the same time, the team used force sensors and motion capture systems to record the movement and forces being experienced by the participants. The researchers also took x-ray scans of the participants' legs, both before and after the intervention phase. They used this information to assess bone density in the affected areas and thus the effectiveness of the treatment.

'We found that our system shows an improvement of bone in certain areas, unlike previous systems which only decelerated the rate of bone loss,' states team member Dr Monica Armegol. 'We saw a small increase in bone density, even in those participants that were in the period of rapid bone loss. Although outcomes in bone density vary depending on the time since injury, the obtained results are really positive and encouraging for the spinal cord injury community.'

The information obtained from the intervention phase measurements was then used to adjust the parameters of a biomechanical model developed to simulate the characteristics of the participants. The ultimate goal of the model is to understand the distribution of internal forces in the bones and joints (e.g., ankles, knees, and hips) of the participants, especially as they perform various movements in the exercise frame. This is important for determining which stances lead to the best results in terms of bone development – for example, shifting the main force against the ground forwards on a foot increases pressure at the ankle by up to 60%.

It is well-established that there is a relationship between the force that bones are subjected to and the corresponding development of that bone. What is not well-understood is just how those factors interact – in particular the exact amount of force, and the frequency in which this has to occur for bone formation. The research team's goal is to more fully understand these interactions. Their hope is that the combination of biomechanical models and bone imaging will better link motion and bone response and thus the overall impact on bone health.

The Pace of the Future

So, where does Professor Holderbaum and his team want to go from here? There are many different goals and much work remaining. From a research point of view, the team is interested in studying more complex movements, and obtaining additional data to help them better predict when and where bone formation will occur. At the same time, the group is also interested in expanding the availability of the system, whether it be examining the role that these exercise-games can play in rehabilitation, or developing a home-based standing frame for wider accessibility.

This is just the first step on the long road to assisted walking for people with paraplegia – but if the work of the group is anything to go by, it will one day be a road well-travelled.

Meet the researchers

Dr Ioannis Dimitrios Zoulias
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Dr Ioannis Zoulias works with signal processing and control for safe FES-assisted standing of people with paraplegia. His research focuses on the clinical applications of human machine interactions. Dr Zoulias recently received funding from the Physiological Society to organise a symposium on transferring Brain-Machine interface technology into the clinic. He is a keen promoter of science outreach, and has a great track record in taking part in science public engagement events (for example, RI - Christmas Lectures (BBC) and Big Bang Science Fair).

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Professor William Holderbaum is a Professor in Mathematics and Engineering at the University of Reading, UK. Prior to this, he was a research assistant at the University of Glasgow in Scotland, UK. He was then appointed Lecturer at the University of Reading in October 2001, senior-lecturer in 2010 and Professor in 2014. He is also currently a Professor at the Manchester Metropolitan University and a Lecturer in Mathematics at the Open University. He has received government and charity funds to support his research projects in Functional Electrical Stimulation (FES) control and Robotics, the latest of which is the development of a FES system for bone health maintenance in spinal cord injury patients, funded by EPSRC.

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Dr Monica Armengol is interested in studying the biomechanics of different pathologies such as spinal cord injury and osteoarthritis. Her research focuses on the development of diagnostic tools and the design of better rehabilitation therapies. Dr Armengol is also very interested in transferring technology out of the lab and putting it into the hands of people. She has been awarded prizes for entrepreneurship and has taken part in many outreach events to encourage young women to pursue careers in STEM.

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PROJECT WEBSITE

http://fesreading.uk/

FUNDING

ESPRC Project

University of Reading

DENYING DEMENTIA WITH EARLIER DIAGNOSIS

The development of dementia in older age has a potentially devasting impact on quality of life. Tackling dementia earlier rather than later is vital because of its nature as a progressive disease. **Professor Notger Müller** and his team at the German Center for Neurodegenerative Diseases (DZNE) Magdeburg, Germany, are striving to target the key symptoms of dementia, developing methods able to prevent their appearance later in life.

Dementia is a medical condition that has remained a challenge for science for many years. The human brain is incredibly complex, so understanding how it functions is no easy task. Our ability to make informed decisions, perform tasks and retain memories all stem from our 'super-computer' brains. Our brains give us a purpose and an ability to control what we do.

However, as with any computer, faults and issues gradually surface over time. From problems with internal wiring, to inner build-ups of harmful material, each progressive issue may not stop it from working entirely, but could seriously affect its ability to function properly, as occurs when dementia conditions develop in the brain.

Dissecting Dementia

The term 'dementia' does not represent just one condition. Instead, it is an overarching, umbrella term used to describe a multitude of cognitive brain diseases that affect the brain's ability to function. For instance, Alzheimer's disease and Parkinson's disease are two widely-known dementia conditions, but there are a number of lesser-known rarer conditions such as Creutzfeldt-Jakob disease and Dementia with Lewy bodies.

In a similar way to cancer, dementia diseases develop in different ways physiologically, so it is difficult to produce a 'one-for-all' cure for them all. There are, however, a number of overlapping characteristics and symptoms within dementia that have been a major focus of associated research over the years.

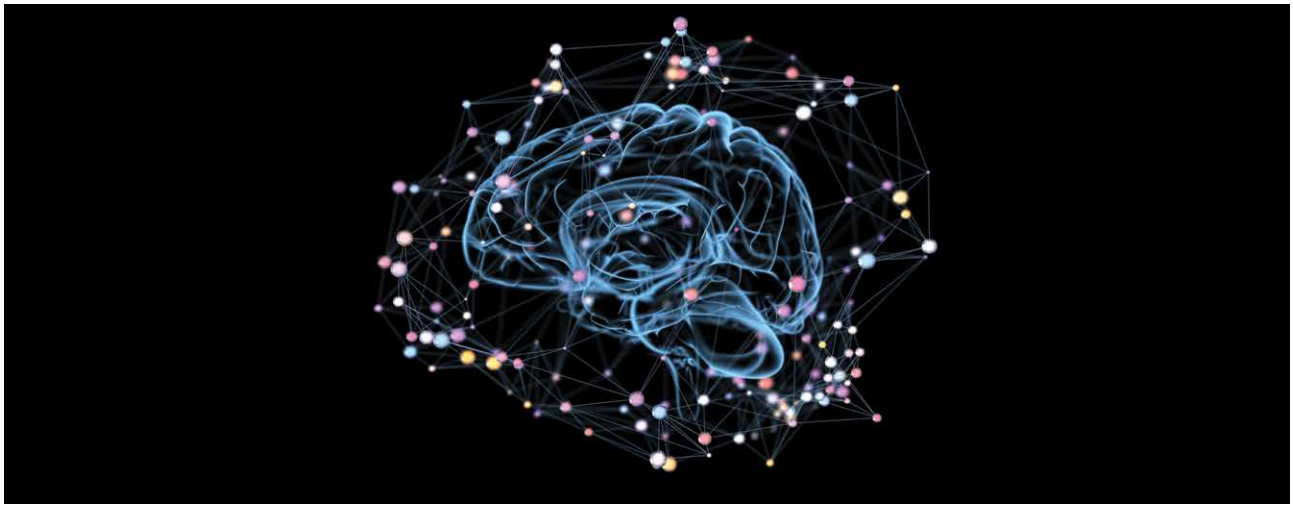
Professor Notger Müller and his team at the German Center for Neurodegenerative Diseases (DZNE) are aiming to address this by developing training programs that can prevent or postpone the symptoms of dementia and other neurodegenerative diseases by targeting these core symptoms.

Prevent or Cure?

Dementia actually describes the set of symptoms caused by the disease, rather than the disease itself. These typically include memory loss, as well as difficulties in solving problems, communicating effectively and making decisions. These symptoms often develop over time, starting off small before eventually becoming more severe later in life. Equally, as they develop due to damage in the brain, they can also affect a person's behaviour, leading to mood swings and potentially to aggressive tendencies.

Whether it is Alzheimer's disease or Parkinson's disease, symptoms can develop in different ways across dementia conditions. However, the main cause of all forms of dementia comes from the death of neurons – the brain cells that process and transmit information from our brains to the rest of our body. These often die as a result of a malfunction to the communication systems within the cell itself, although death can also be initiated by our own body's immune system.

‘We have shown that training this core function, i.e. the ability to filter out distracting information, has positive effects on other cognitive processes, such as memory and decision making and, therefore, the potential to promote mental fitness in general.’



However, unlike other cells of the body, brain cells cannot simply divide and be replaced. Once they are gone, they are gone for good, hence why most forms of dementia are classed as progressive conditions that cannot be reversed. The best course of action, therefore, is to try and tackle these symptoms earlier on, before they become a problem.

Professor Müller’s recent research has focused on developing methods that can improve our ability to filter out distracting information allowing us to remain attentive to particular tasks. ‘Instead of training very specific cognitive functions, our research focuses on the improvement of so-called core functions, especially related to selective attention,’ he says. ‘We have shown in the past that training this core function, and filtering out distracting information, has positive effects on other cognitive processes, such as memory and decision making.’

Professor Müller and his team have effectively found that mental fitness could be improved by promoting our ability to filter information. By targeting these core functions and abilities the team hopes to develop training programs that could combat the appearance of symptoms associated with dementia, such as memory loss.

They also aim to identify specific biological signs that can determine how likely it is for somebody to develop dementia, so this group of people can be targeted for early treatment and intervention. As Professor Müller puts it himself: ‘There is growing evidence that the effective treatment of dementia should start as early as possible. However, for such an early diagnosis, we still lack biomarkers that indicate the likelihood of developing dementia. Our research group focuses on identifying these biomarkers.’

Filter Training vs. Memory Training

During their recent research, Professor Müller and his team compared the neuronal and memory effects of typical memory training against an alternative attentional filter training approach. Using a group of 29 young and healthy patients, the team used a medical imaging technique known as fMRI to visualise the activity of the brain while the patients performed a certain memory task. This task was designed to test the patients’ ability to respond to certain stimuli – designed to gauge a reaction – by filtering out colour-based information and storing it in their memory.

The results of this study found that filter training prevented the storage of unnecessary memories and was a more effective method for choosing which memories to retain. Memory training, on the other hand, was found to increase retention of *all* of the available information, including the distracting material, therefore making filter training a more efficient method for brain training.

In a paper published in 2016 they describe how their findings, ‘demonstrate a tight connection between working memory and attention. This potentially could open up avenues to ameliorate memory deficits in patients with cognitive impairments.’ Based on these findings the team propose that filter training could potentially be used to promote memory retention in dementia patients.

Decisions, Decisions, Decisions

Following on from this the team continued their investigations in this area. This time, however, the team investigated the impact of filter training on decision making – another skill that becomes difficult after the onset of dementia. As stated in their research paper: ‘Decision making has a high practical relevance for daily

performance. Its relation to other cognitive abilities such as executive control and memory is not fully understood. Our research asks whether training of either attentional filtering or memory storage would influence decision making ability.'

To investigate this, the team used the Iowa Gambling Task (IGT) – a game designed to assess and simulate real-life decision making. Within this task, participants developed profitable or unfavourable decision strategies to try and gain or lose money. Participants have to pick cards from four different decks to maximise their monetary gain. Two of these decks offer the opportunity to make large gains but are associated with greater losses, whereas the other two decks result in smaller wins but also smaller losses.

The 29 young and healthy participants were trained over five days using either memory training or attentional filtering training, performing the IGT task at the end of each day. Results found that, while both memory training and filter training improved the participants' performance of the task, only the filter trained group were found to make more profitable decisions. The study, therefore, suggests that decision making is influenced more by training to filter out 'irrelevant distractors', than by training to store information in working memory. Essentially, more informed decisions were made when participants learnt to ignore distractions.

Professor Müller states that, 'we have shown that training this core function, i.e. the ability to filter out distracting information, has positive effects on other cognitive processes, such as memory and decision making and, therefore, the potential to promote mental fitness in general.'

Targeting Dementia in the Future

Professor Müller's future work now aims to test whether his team's training programs can delay the onset of dementia. His team also aims to investigate the potential effect of physical exercise on the filter training program, eventually looking to personalise training regimens to individual patients, depending on their specific needs. Professor Müller describes how, 'we want to test whether our training programs can indeed postpone the onset of dementia and can delay the course of disease. Furthermore, we want to investigate whether the training success can be boosted by including physical exercise into our attention training program.'

By diagnosing dementia earlier, and designing methods able to postpone its onset, Professor Müller and his team are tackling a highly problematic disease head-on. Their work will not only influence patients already suffering from dementia, but also millions of young, healthy individuals around the world likely to suffer from the condition later in life.

Meet the researcher

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Professor Notger Müller studied Medicine at the University of Heidelberg, Tübingen and Berlin, Germany between 1989 and 1996. During that time, he also studied for a PhD at the Free University Berlin, before he spent one year as a postdoctoral researcher at Berkeley, USA. He then became a Resident and Postdoctoral Researcher first at the University of Leipzig in 1998, thereafter at Charité University Clinic Berlin from 2000. He later went on to work as a Consultant in Neurology at Goethe-University Frankfurt between 2002 and 2006, before becoming a Senior Consultant at the Dementia Unit in Magdeburg in 2008. After leaving that role four years later in 2012, Dr Müller has since worked as the Professor and Head of the Neuroprotection research group at DZNE Magdeburg. In 2005, he received the award for Best Clinical Teacher from the University of Frankfurt and in 2012 the Theo and Friedel Schöller-Price for Ageing Research Award.

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Prof. Robert T. Knight, UC Berkeley

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BMBF (Federal Ministry of Education and Research)
Robert Bosch Foundation

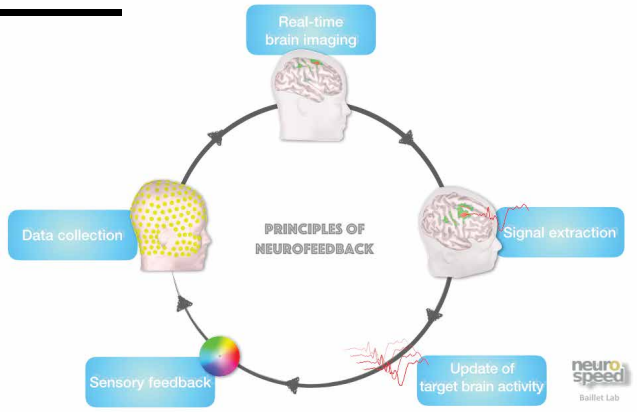
FURTHER READING

M Schmicker, M Schwefel, AK Vellage and NG Müller, Training of Attentional Filtering, but Not of Memory Storage, Enhances Working Memory Efficiency by Strengthening the Neuronal Gatekeeper Network, Journal of Cognitive Neuroscience, 2016, 28, 636–642.

M Schmicker, P Müller, M Schwefel and NG Müller, Attentional Filter Training but Not Memory Training Improves Decision-Making, Frontiers in Human Neuroscience, 2017, 11, 138, 1–7.

BRAIN TRAINING

Gaining insight into the brain and its inner workings improves our understanding of behaviour and our knowledge of the diseases and treatments of our most complex organ. **Professor Sylvain Baillet** and his research team at the McConnell Brain Imaging Centre of the Montreal Neurological Institute, are illuminating the brain and its functions using the latest real-time imaging technology.



Visualising Brain Activity

Over the past 40 years there have been remarkable advances in the technology developed to see the brain structures inside our heads in a safe and non-invasive manner. A range of sophisticated medical imaging instruments, Computed Tomography (CT or CAT scanner) and Magnetic Resonance Imaging (MRI) for instance, can reveal the diversity of tissues inside the body with impressive clarity.

These sophisticated imaging systems virtually cut body parts in a slice by slice manner. They then stack these slices together to form a complete three-dimensional (3D) picture of our anatomy. The disadvantage of a CT scanner is that it exposes the patient to potentially harmful X-rays. However, MRI produces images with considerably better resolution than CT. It uses a very strong magnetic field and radio waves to probe inside the body revealing the anatomy of soft tissues in great detail.

An MRI scan can also produce images related to brain function and activity. Functional Magnetic Resonance Imaging (fMRI) is a special technique used to measure local variations of oxygen consumption and blood flow related to how hard neurons are working across the brain. Functional brain mapping aims to understand how different parts of the brain contribute to certain functions.

Many psychologists and cognitive neuroscientists use brain imaging to describe brain activity when someone is engaged in a specific task. The fMRI images can show parts of the brain 'lighting up' or 'working together' when research participants perform a memory task, or listen to music, process their native or a second language, do mental calculations or engage their visual attention – just to name a few of the significant categories of tasks important to neuroscience research. For example, if a person is listening to music, then their primary auditory cortex, a region on both sides of the brain, will become active, followed by many others. The fMRI results are often represented as still images with brighter areas to illustrate activity overlaid on the anatomy of the brain.

The technique has proven very successful in revealing the brain regions involved in a great diversity of tasks. Yet, its main limitation is the fact that brain activity is poorly resolved in time. fMRI signal fluctuations are related to the physiology of blood flow and oxygenation, which is considerably slower (typically a hundred times slower) than that of neural activity. Other techniques that record brain activity on a faster time scale include electroencephalography (EEG) that measures and records 'brain waves'. These waves are electrical fluctuations in brain activity and are frequently used to help diagnose diseases such as epilepsy, sleep disorders and brain injury. EEG is a very valuable and inexpensive tool for doctors, however, it does not give a precise location of the brain regions activated during a task.

Indeed, the anatomical origins of brain wave patterns are tricky to interpret as the signals are distorted as they pass through the head tissues, especially the skull, before being recorded by electrodes that are placed on the skin surface.

Just imagine if we could record images of brain activity at superfast speeds and let the person watch this activity on a computer screen. Imagine if they could then control a pre-determined aspect of their own brain activity, as a cerebral workout exercise, using brain-activity information being fed back to them in real-time?

That's exactly what Professor Baillet and his team of researchers at McGill University are developing with a technique called real-time magnetoencephalography (MEG). They are using MEG imaging to expand and study the efficacy of a range of techniques that may allow people to 'train their brain', based on real-time, objective measures of

‘Our ultimate hope and aim is to enable patients to train specific regions of their own brain related to their condition and help them recover lost functions in a more personalised manner, faster.’

their own brain activity. His goal is to understand how such neurofeedback techniques work, what the actual physiological effects are, if any, and how they can be translated efficiently and rigorously to clinical interventions, and consumer electronics products for brain wellness.

MEG: How it Works

The brain is composed of tens of billions of cells called neurons – these are linked together by cable-like fibres called axons. Fast electrical impulses are passed between brain cells along these fibres, as communication signals. When these signals converge at a certain brain location, they accumulate and trigger the cellular computation of information by the brain.

The electrical currents generated by neurons are around a nanoampere (a billionth of an Ampere). The kettle in your home may use about 10 Amperes to boil water for a cup of tea. An electrical current produces a magnetic field – the strength of the magnetic field is measured in a unit called a Tesla. For instance, the Earth’s magnetic field measures 0.05 mT (milliTesla) at the equator, and a typical clinical MRI scanner has a field strength of 1.5 to 3T.

The magnetic flux generated outside the brain by these tiny electrical currents is between 10 and 100 million times smaller than the Earth’s magnetic field. Incredibly, these very small magnetic signals caused by the electrical signals deep inside the brain can be measured using sophisticated measurement technology. The vast majority of MEG instruments include Superconducting QUantum Interference Devices (SQUIDs). These sensor devices are cooled to a few degrees above absolute zero, or −269°C, using liquid helium. At this temperature, the SQUID becomes superconducting, meaning the device has no electrical resistance. Therefore, the device has the best sensitivity for detecting small magnetic fields without being compromised by thermal noise in the sensing electronic circuits.

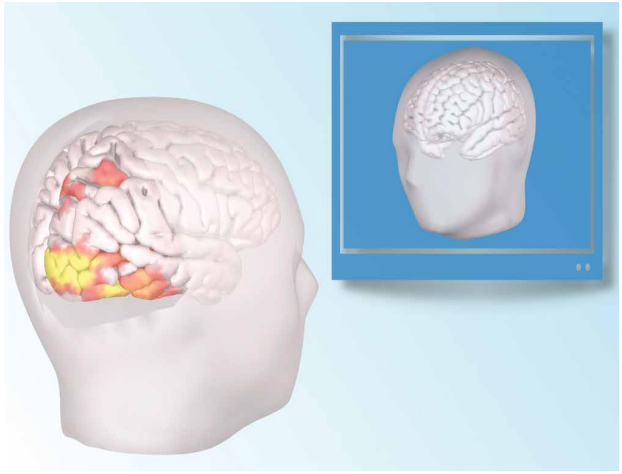
A SQUID operates continuously, and so it can measure the fastest brain activity. MEG sensing technology is currently seeing a lot of exciting innovations – new cost-effective approaches, potentially not requiring sophisticated absolute-zero cooling, are being developed and tested. They hold the promise of more accessible, more flexible and versatile, possibly wearable, MEG imaging in the near future.

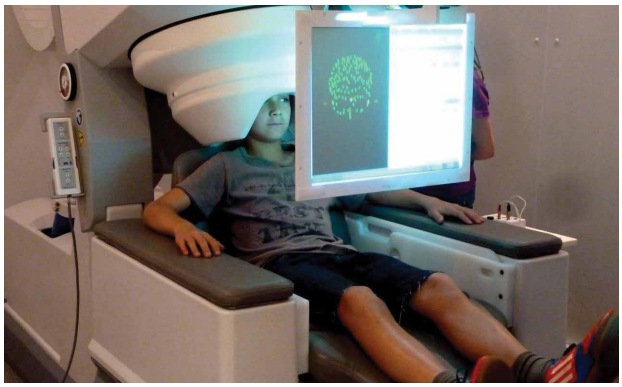
Brain Signals that Train the Brain

Training to perform a task to a high degree of skill takes a lot of practise and repetition. This applies equally to the study of mathematics or performing in sports and music. People who have developed a functional disability in speech or walking after a brain injury, such as that caused by a stroke, can re-learn or develop new skills through personalised learning strategies. Current intervention strategies often involve learning to compensate or to find ways to work around a disability or learning difficulty. ‘Our main objective is to enable people to train specific regions of their own brain, in a way that relates to a particular function, or a clinical condition. For example, we hope to see people with epilepsy able to train their brain to reduce the occurrence of seizures,’ says Professor Baillet.

Neurofeedback encompasses various methods for training specific parts of the brain relevant to learning a task or skill. Previous research using EEG has shown potential for this technique, coupled with real-time analysis of brain signals, to provide timely feedback to participants about specific aspects of their brain activity. One major issue with EEG apparatus though is that signal quality can be severely degraded by body and eye movements, or just by the fact that the contact of the EEG electrode with the skin can become loose. Poor signal quality means poor effectiveness and specificity of the procedure.

Professor Baillet’s lab has developed the





technology and expertise for MEG to provide real-time feedback to participants so that they can learn how to modulate specific aspects of their brain activity in pre-determined brain regions by receiving sensory feedback from the MEG machine. The audio or visual feedback provided can come in different flavours – from simple tones or coloured shapes, to more elaborate video games – the goal is always to encourage participants to do better towards a specific objective, using reinforcement learning strategies that reward progress to reaching the target objective.

The definition of these target signals and their anatomical origins is an active field of research – they need to be specific to the participant and the objectives of the training. For neurofeedback to become truly effective for wellness and for clinical purposes, its signal targets need to be rigorously validated, ideally using the same strict testing protocols as those for evaluating the treatment efficacy (and side effects) of new drugs beyond placebo.

To perform neurofeedback using MEG the subject sits within the machine, under a helmet that contains three hundred SQUID sensors. Signals are recorded continuously, and they are transferred to a specialised computer system for real-time processing. In one of Professor Baillet's experiments, the task involved the subject viewing a coloured disk on a computer screen and mentally changing its colour.

There is no manual for participants to change their brain activity in a predetermined manner. For neurofeedback to be successful, the person learns by trial and error, navigating different mental states and adjusting to the immediate feedback provided. Humans are particularly good at acquiring this skill via multiple training sessions, just like any new skill.

Early results from Professor Baillet's research have shown that, using real-time MEG, targeted brain regions adopt the patterns of brain activity that were aimed for after seven to twelve short training sessions. His team also reports that such modifications with training do not affect other brain regions, making the training anatomically specific. Professor Baillet says, 'the remarkable thing is that with each training session, the training program helps subjects reach their next target aim faster, with the bar being raised for each new session, in the same way you raise the bar in a high jump competition.'

These results point the way forward for future research, especially the effect of such training on actual task performance in working memory, reading or sustained attention for instance. If the method is proven effective, translation to portable EEG solutions are next, with high-quality electrodes harnessed to the computing power of smart phones or even cloud technology.

New Technologies Arising from the Research

Alongside these exciting developments in brain imaging using MEG, Professor Baillet and his team are actors at the forefront of open science. They provide other international researchers access to their custom-made software called 'Brainstorm' (http://neuroimage.usc.edu/brainstorm/). This free, open-source application is used for MEG, but also EEG and any form of multimodal electrophysiology data, for advanced analysis and visualisation.

Brainstorm has a research community of more than 17,500 registered users worldwide. More than 700 journal articles were published by Brainstorm users over the past 6 years. Professor Baillet's research group has also established the Open MEG Archives, a free and open library of MEG and other brain related data (https://www.mcgill.ca/bic/resources/omega). They started this data repository as there were very limited open resources of MEG data available to other researchers. Sharing data helps to standardise research experiments and enables the reproducibility and generalisation of scientific results for scientists and the public across the world. The archive includes related MRI and demographics data for volunteers and patients and is continuously expanding. Follow the links for more information about these open-science initiatives.

Future Direction

This research paves the way to use MEG both as a diagnostic tool and a novel treatment technique for patients. The team has had success with identifying the locus of seizures in severe cases of epilepsy and can see great potential for working with patients who have stroke, dementia, movement disorders or chronic depression. However, further careful research is needed to determine the actual benefits of interventions of this kind over and above the placebo effect – the positive benefits provided by simply believing that the therapy is working.

Professor Baillet's claims that, 'we need to investigate further the mechanisms and principles of neurofeedback – a process by which people can see on-going physiological information that they aren't usually aware of, in this case, their own brain activity, and use that information to train themselves to self-regulate. Our ultimate hope and aim is to enable patients to train specific regions of their own brain related to their condition and help them recover lost functions in a more personalised manner, faster. There are also considerable uncharted possibilities to improve healthy brain functions for learning, attention, the management of stress and sleep. In principle, the possibilities are endless.'

Meet the researcher

Professor Sylvain Baillet

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Professor Sylvain Baillet is professor of Neurology and Neurosurgery, Biomedical Engineering, and Computer Science at the Montreal Neurological Institute (MNI) at McGill University in Montreal. A neuroimaging physicist, he obtained his PhD in Physics from the University of Paris, in 1998. He was a Research Associate at the University of Southern California and became principal investigator with the Centre National de la Recherche Scientifique in France from 2000–2008. He then became the inaugural Scientific Director of the magnetoencephalography (MEG) program at the Medical College of Wisconsin, US. He joined McGill University in Montreal in 2011 and founded their MEG research program and core imaging platform. In 2013-2017, he was the Director of the MNI's McConnell Brain Imaging Centre. Dr Baillet has a track record in leading multidisciplinary research projects and operations in neuroimaging and neuroinformatics, in Europe, the US and Canada. Professor Baillet's research work in systems neuroscience aims to understand the dynamical mechanisms of brain activity and functions on multiple scales and to develop detection of early manifestations of disease.

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REFERENCES

S Baillet, Magnetoencephalography for Brain Electrophysiology and Imaging, Nature Neuroscience, 2017, 20, 327–339.

B Morillon and S Baillet, Motor Origin of Temporal Predictions in Auditory Attention, Proceedings of the National Academy of Sciences USA, 2017, 114, E8913–E8921.

P Albouy, A Weiss, S Baillet and RJ Zatorre, Selective Entrainment of Theta Oscillations in the Dorsal Stream Causally Enhances Auditory Working Memory Performance, Neuron, 2017, 94, 193–206.

RAISING THE BAR IN STROKE RECOVERY AND REHABILITATION

Despite the high number of stroke survivors worldwide, research to help those with chronic disabilities after stroke has long been underemphasised. The Medical University of South Carolina's Center for Biomedical Research Excellence (COBRE) in Stroke Recovery aims to address this shortfall and improve the treatment and long-term quality of life for stroke survivors.

Challenges in Stroke Research

Stroke is one of the most debilitating conditions in the United States, yet treatment options are limited. There are estimated to be seven million stroke survivors living in the country, with stroke survivors in the state of South Carolina representing one in 50 of the nation's total number of stroke cases. Each year, expenses for stroke-related hospitalisation and rehabilitation exceed $1 billion in South Carolina alone.

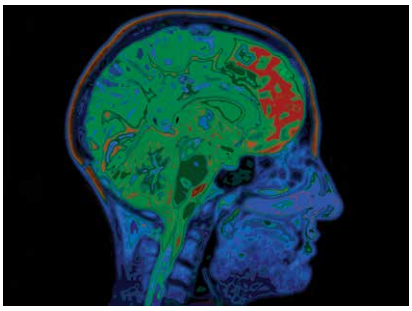
The state is situated in the 'stroke belt', a region of the US with a 50% higher stroke mortality rate than the rest of the country. Survivors in South Carolina are also younger than the national average for onset of stroke and take longer to recover. This is particularly pertinent for South Carolina's African-American population. Consequently, it is not surprising that stroke recovery is a huge public health issue within the state.

Despite major improvements in stroke prevention and acute treatment, little progress has been made in enhancing recovery. It is expected that three-quarters of stroke survivors will have some long-term disability and less than half will regain full hand or arm function, and/or the ability to walk unaided.

Researchers and clinicians at the Medical University of South Carolina (MUSC) have taken an innovative approach to tackling this devastating problem by establishing a new stroke-specific Center of Biomedical Research Excellence (COBRE) in Stroke Recovery. MUSC is funded and supported in this endeavour by the National Institute of Health's (NIH) COBRE award – an initiative supported by the NIH's Institutional Development Award (IDeA) program put in place to promote, augment and strengthen the research capabilities of institutes in IDeA states focused on biomedical research.

The COBRE in Stroke Recovery also benefits from a strong partnership with the adjacent Ralph H. Johnson VA Medical Center, as a number of investigators hold joint MUSC-VA appointments and many of the laboratories are officially recognised as shared space through a memorandum of understanding. With NIH and institutional support, the COBRE in Stroke Recovery aims to expand research infrastructure and capacity at MUSC to enable outstanding, multidisciplinary, collaborative research in stroke recovery.

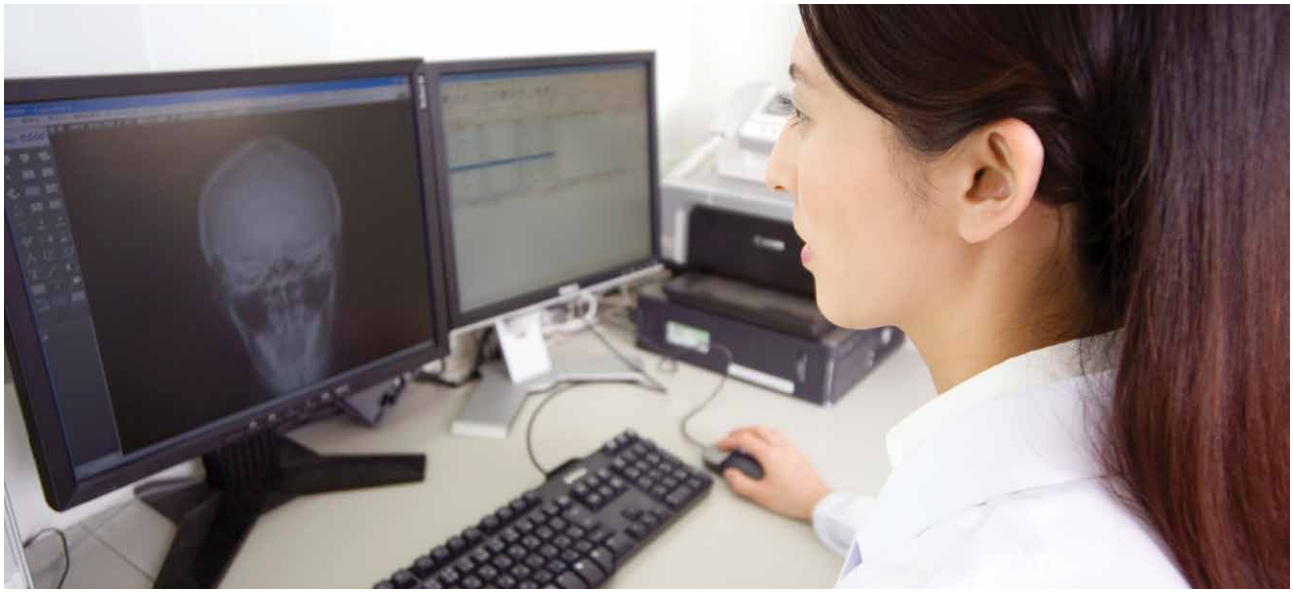
In short, the center plans to improve the treatment and long-term quality of life for stroke survivors, using cutting-edge technology and an interdisciplinary approach to understand how the brain repairs itself post-stroke and to enhance rehabilitation and patient outcomes. 'The primary focus of the COBRE in Stroke Recovery is on developing and testing interventions to rehabilitate individuals with post-stroke impairments and disabilities,' says Dr Steve Kautz, COBRE in Stroke Recovery Program Director and Principal Investigator, Chair of the Department of Health Sciences and Research in the College of Health Professions at MUSC and a Research Career Scientist at Charleston's Ralph H. Johnson VA Medical Center.



A Shared Focus on Stroke Recovery

Most stroke research focuses on the preservation of nervous system structure and function within the hours after a

‘We want to expand the measurement and intervention toolbox of clinicians treating those with post-stroke deficits to improve their outcomes. The potential for the center to assume a national leadership role in recovery from stroke is immense.’



stroke. While an eminently worthy cause that has saved lives and reduced disability, more than half of stroke survivors still have persistent disability. As such, a greater understanding of how the nervous system repairs and reorganises neural circuitry in the days, months and years following a stroke, and how the ability of neurons to change in form and function – neural plasticity – can be enhanced to maximise recovery during rehabilitation, is needed.

Under the leadership of Dr Kautz, MUSC’s COBRE in Stroke Recovery brings together an exciting team of clinicians and science researchers with expertise in an array of health disciplines. Together, they are tasked with developing core resources that will deliver an impressive number of outcomes, including the mentoring of skilled junior scientists – neurologists, physical therapists, translational scientists and basic scientists – the empowerment of senior researchers, and an opportunity to fast-track the most promising multidisciplinary research from the lab to the patient. By merging their varying experience and strengths, the team is working together to develop unprecedented recovery-based interventions for individuals with post-stroke disabilities that they hope will alter the landscape of stroke rehabilitation.

In addition to a hugely talented, multidisciplinary team, the center boasts access to a myriad of pioneering technologies and a rich assortment of equipment. While some institutions offer similarly advanced laboratories in specific disciplines, the COBRE is relatively unique in offering faculty turnkey access to a wide range of such advanced technology and expertise in multiple disciplines in an integrated manner. The center’s resources are split into four main scientific cores – each designed to support and advance stroke recovery research in animal and human studies.

The Quantitative Behavioral Assessment and Rehabilitation Core (QBAR) aims to identify the patients’ impairments and apply cutting-edge rehabilitation principles. Using high-tech, state-of-the-art equipment and expertise derived from motor and cognitive behavioural recovery measures in animal studies, the core is developing novel tools to help measure and quantify the impact of stroke on different aspects of patient behaviour and movement, such as walking and reaching. Additionally, access to rehabilitation tools and expertise is key as studies that aim to enhance the plasticity of the nervous system need to ‘teach’ the nervous system the new or refined skills enabled by the enhanced plasticity.

The Brain Stimulation Core (BSTIM) leverages skills and resources in MUSC’s Brain Stimulation Laboratory to focus primarily on brain stimulation techniques to measure brain function and to manipulate brain plasticity and or circuitry in treatments. The core provides COBRE investigators with the expertise to develop unique tools and methods to induce brain changes that can potentially treat the damage caused by a stroke.

The Neuroimaging Core (NI) takes advantage of expertise and resources within MUSC’s Center for Biomedical Imaging to explore multiple modes of structural and functional imaging

relevant to stroke recovery. This will enable the team to research specific patient deficits that arise due to specific damage that arises following a stroke and generate strategies to help stroke survivors have a better response to treatment.

The Clinical and Translational Tools and Resources Core (CTTR) provides access to the tools and resources necessary for innovative research with human subjects. By harnessing the power of biomedical informatics and biostatistics, the core is developing the Stroke Recovery Comprehensive Multidisciplinary Database, a unique research tool and information clearinghouse for demographic, behavioural, neurophysiological, imaging, and clinical data from a large, diverse pool of post-stroke individuals.

As well as being a valuable, searchable pool of stroke recovery information, the data collected from all of the center's activities in the Stroke Recovery Comprehensive Multidisciplinary Database will allow the significant advancement of individualised stroke interventions. 'We are excited by the potential for the quantitative multidisciplinary data our center collects to form a unique database that will aid the transition to a future where rehabilitation can be much more personalised to specific deficits in individual patients,' says Dr Kautz.

Developing a Sustainable, Competitive Infrastructure

The long-term plan of MUSC is the development of an independent, sustainable, multidisciplinary stroke recovery research program within the framework of the three-phase COBRE program. Currently, the center is beginning its fifth year of funding within a five-year Phase I period and the remainder of Phase I and all of Phase II will present many opportunities to move the COBRE towards the desired goal.

'The next step for our center is to continue to grow our capabilities to conduct cutting-edge stroke rehabilitation research by better understanding brain plasticity. We will continue to push to discover new ways to use the tools of neuromodulation to aid the recovery process through exploiting the brain plasticity that underlies return of function,' explains Dr Kautz.

While COBRE Phase I has been highly successful, the team believes the coming years will be even more productive as more of the Phase I investments reach the point of generating outcomes. There have been an impressive number of achievements to date. For example, all five Phase I junior investigators have now become independent researchers or Principal Investigators and the recipients of a variety of highly sought-after awards and grants.

Importantly, there has also been exceptional growth in research funding, with the number of Principal Investigators with stroke recovery funding nearly tripling since the start of the initiative. MUSC has grown annual funding for stroke recovery research from $2.1 million at the time of the COBRE award to $10.4 to date, in year five, with the possibility of additional funding before the year's end. There has also been a substantial increase in stroke recovery publications and presentations. Phase I investments have also greatly increased the diversity of disciplines represented at the center to make it extremely multidisciplinary.

The center is also involved in a growing number of clinical trials and currently supports 30 studies investigating stroke recovery processes specific to walking, balance and strength training, arm and hand function, voice and swallowing disorders, depression, visual neglect and sensation. Using an Evaluation Program, part of the administrative infrastructure of the center, it has been able to continually improve the recruitment of patients into these studies.

Notably, COBRE personnel participate in the regional coordinating center for StrokeNet, the National Institutes of Health Stroke Trials Network program at MUSC and facilitated participating in the Telerehab-trial, an NIH funded stroke study investigating the efficacy of in-person versus telerehabilitation. In another notable success, the American Heart Association is funding the WISSDOM study – a four-part study focusing on reducing stroke recovery disparities in African-Americans – led by COBRE Associate Director Dr Robert Adams.

Recognition of the uniqueness of resources gathered by the center was demonstrated by award of the National Center of Neuromodulation for Rehabilitation, one of six NIH-funded (led by NCMRR in NICHD, NIBIB and NINDS) infrastructure grants to make unique resources available to the national rehabilitation research community. The NM4R center makes the training and resources developed in the COBRE BSTIM core available nationwide and puts COBRE investigators in the forefront of the field of neuromodulation – the alteration of brain activity through targeted delivery of a stimulus, such as electrical stimulation – in stroke recovery and rehabilitation in general.

Overall, MUSC's Stroke Recovery Research Center offers world-class core resources and facilities and integrates the best work being conducted in the field. Furthermore, it has a COBRE infrastructure that makes MUSC highly competitive against other national stroke recovery research centers. The strategic goals developed and achieved in the Phase I period are crucial for Phase II planning, and Dr Kautz and his team have ambitious plans to strengthen the capabilities of the center during the five-year Phase II period. 'We want to expand the measurement and intervention toolbox of clinicians treating those with post-stroke deficits to improve their outcomes. The potential for the center to assume a national leadership role in recovery from stroke is immense if we can strengthen the center by building on our current momentum.'

Meet the Team

Dr Steven A. Kautz, PhD, is Professor and Chair in the Department of Health Sciences and Research in the College of Health Professions at the Medical University of South Carolina (MUSC), a Research Career Scientist at the Ralph H Johnson VA Medical Center and Program Director of both the Center of Biomedical Research Excellence (COBRE) in Stroke Recovery and the closely affiliated National Center of Neuromodulation for Rehabilitation.

Dr Robert J. Adams, MD, is a Distinguished Professor of Neurology and Co-Director Emeritus of the MUSC Comprehensive Stroke Center and is also the Associate Program Director of the COBRE in Stroke Recovery.

Dr DeAnna L. Adkins, PhD, is an Associate Professor in the Departments of Neuroscience and Health Sciences and Research at MUSC and a Research Health Scientist at the Ralph H Johnson VA Medical Center. She is currently investigating novel treatments to reduce stroke-induced damage and to enhance rehabilitative training.

Dr Naren Banik, PhD, is a Professor in the Department of Neurology at MUSC. He uses animal models to study neurodegenerative disorders. He serves on the COBRE Executive Committee and directs the Pilot Projects program.

Dr Leo Bonilha, MD, PhD, is an Associate Professor in MUSC's Department of Neurology and his research focuses on understanding adaptations to brain injury. He leads the EEG service of the Neuroimaging Core.

Dr Truman R. Brown, PhD, is a Professor in the Department of Radiology and Radiological Science at MUSC. He is the Director of the Neuroimaging Core and a member of the Executive Committee within the COBRE in Stroke Recovery.

Dr Mark G. Bowden, PhD, PT, is Director of the Division of Physical Therapy and an Associate Professor at MUSC's College of Health Professions and a Research Health Scientist at the Ralph H Johnson VA Medical Center. He is investigating motor learning and walking recovery after stroke.

Dr Wuwei (Wayne) Feng, MD, is an Associate Professor in MUSC's Department of Neurology and is a clinician-scientist with expertise in non-invasive brain stimulation for stroke recovery, neuroimaging and statistics.

Dr Mark S. George, MD, is a Distinguished Professor in MUSC's departments of Psychiatry, Radiology, and Neurology and serves as the Director of the COBRE in Stroke Recovery's Brain Stimulation Core and Scientific Director of the National Center of Neuromodulation for Rehabilitation.

Dr Chris M. Gregory, PhD, PT, is an Associate Professor in MUSC's Department of Health Sciences and Research and a Research Health Scientist at the Ralph H Johnson VA Medical Center and his research focuses on intervention strategies to aid walking following a stroke.

Dr Colleen A. Hanlon, PhD, is an Associate Professor in MUSC's departments of Psychiatry and Behavioral Sciences, and Neurosciences. She is currently engaged in research incorporating neuroimaging and brain stimulation techniques.

Dr Lisa M. McTeague, PhD, is an Assistant Professor in MUSC's Department of Psychiatry and Behavioral Sciences and a licensed clinical psychologist. She has expertise in neuroimaging and brain stimulation and plans to be a Junior Investigator in COBRE Phase II.

Dr Jihad Obeid, MD, is Associate Professor and Head of the Division of Biomedical Informatics in the Department of Public Health Sciences and directs the Biomedical Informatics Program for MUSC's Clinical and Translational Science Award. He oversees the biomedical informatics service of the CTTR Core.

Dr Viswanathan Ramakrishnan, PhD, is Professor of Biostatistics in the Department of Public Health Sciences at MUSC. He oversees all statistical-related programming and consulting for the COBRE as the leader of the biostatistics service of the CTTR Core.

Dr Catrina Robinson, PhD, is an Assistant Professor in the Department of Neurology at MUSC. She uses animal models to study cognitive decline post-stroke and the role of insulin in stroke recovery. She plans to be a Junior Investigator in COBRE Phase II.

Dr Nathan Rowland, MD, PhD, is an Assistant Professor in MUSC's Department of Neurosurgery and is a clinician-scientist with expertise in motor dysfunction in clinical populations and deep brain stimulation. He plans to be a Junior Investigator in COBRE Phase II.

Dr Na Jin Seo, PhD, is an Associate Professor in MUSC's Division of Occupational Therapy and her research focuses on hand rehabilitation post-stroke and rehabilitation technology development. She plans to be a Junior Investigator in COBRE Phase II.

Dr Michelle Woodbury, PhD, OTR/L, is an Associate Professor in MUSC's Department of Health Sciences and Research and Division of Occupational Therapy and her research focuses on the treatment of upper extremity function following stroke. She leads the Rehabilitation service in the QBAR Core.

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STROKE RECOVERY RESEARCH CENTER

A Center of Biomedical Research Excellence (COBRE) in Stroke Recovery at the Medical University of South Carolina

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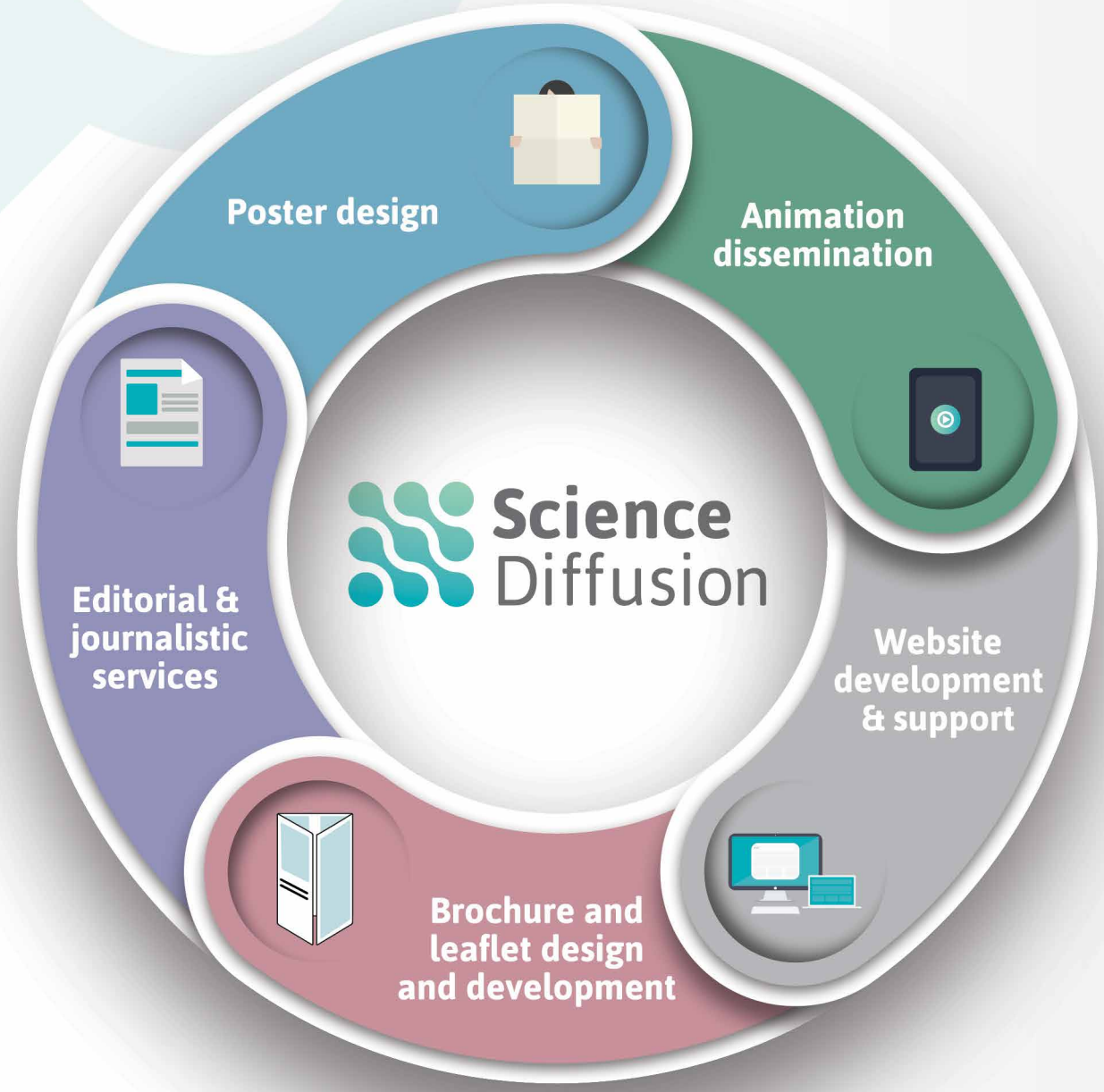

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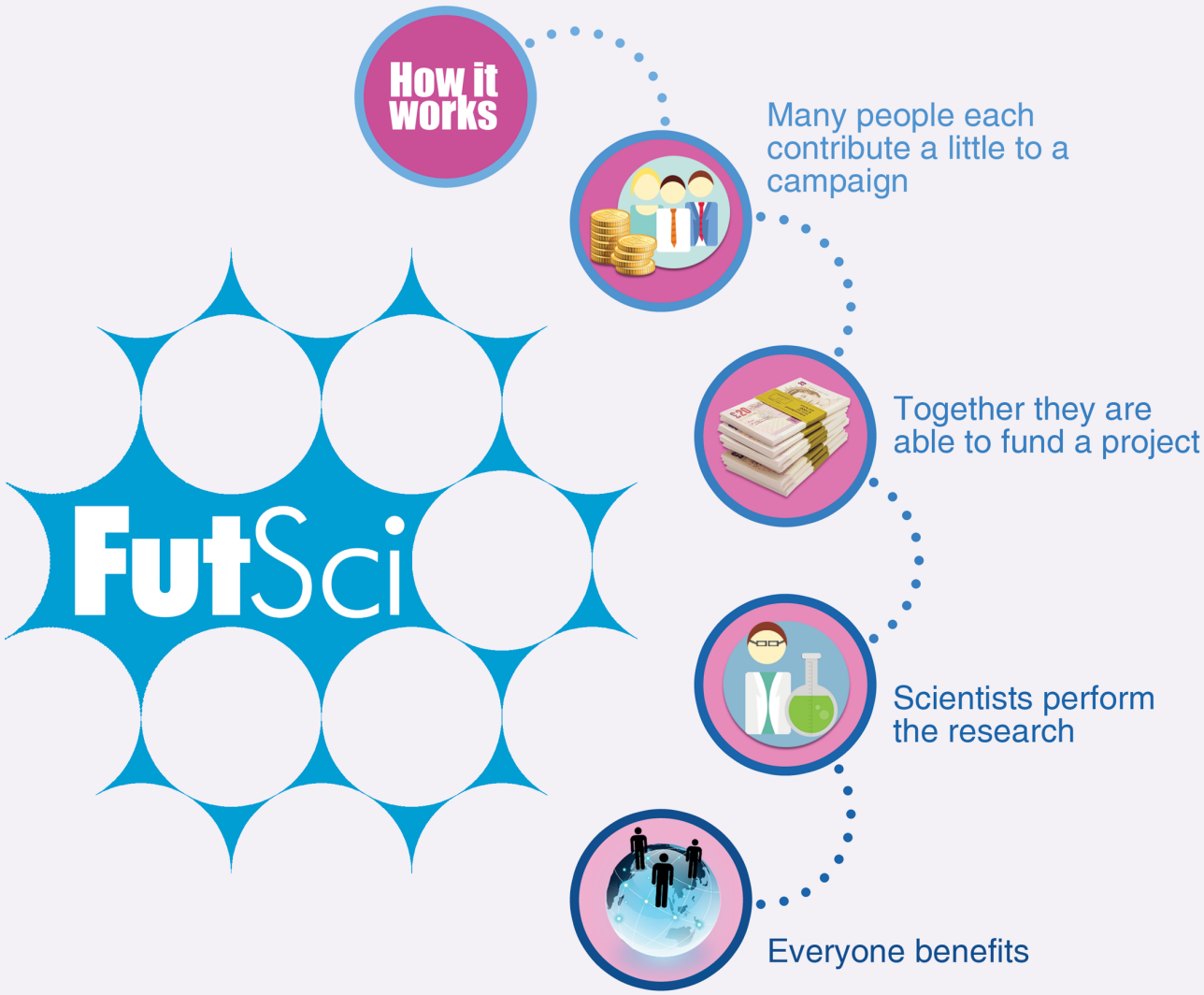

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