Scientia

BUILDING BRIGHTER FUTURES THROUGH INNOVATION IN PSYCHOLOGY AND NEUROSCIENCE

EXCLUSIVES:

- Malaysian Psychological Association
- Children and Young People's Mental Health Coalition

HIGHLIGHTS:

- The Coordination of Neuronal Communication
- The DOZE App: A Unique Approach to Overcoming Sleep Problems in Young Adults
- Investigating the Links between General Anaesthetics and Alzheimer's Disease
- Leveraging New Technologies to Treat Brain Injury

Issue: #131

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WELCOME...

This important and timely issue of Scientia showcases the scientists striving to build brighter futures for humankind through their pioneering endeavours across disciplines in psychology and neuroscience. At the current time, our generation is facing unprecedented challenges and uncertainty worldwide as the COVID-19 pandemic unfolds. The pandemic – and the responses to the pandemic – have placed mental health as a priority onto the global agenda. Meanwhile, the emerging needs of our ever ageing population remain an urgent societal issue. These two topical themes feature prominently in this critical issue where we meet the dedicated scientists who are driving innovation to promote optimal mental and social well-being across the globe.

The first section in this edition is devoted to cognitive neuroscience, the study of the relationships between brain and behaviour. Here, we meet the researchers who are shedding light on the fascinating complexities of the brain. From explaining how we create the perception of a unified word to how we can communicate social information without even using words, this section provides an enthralling account of key and contemporary issues in cognitive neuroscience.

Our second section is dedicated to mental health. We open with an exclusive interview with Dr Rozainee Khairudin, President of the Malaysian Psychological Association, to gain a unique insight into current issues across the globe in psychology and mental health. We then meet the researchers who are striving to better understand potentially devastating psychological difficulties and those who are developing ground-breaking interventions to alleviate causes of psychological distress. We conclude this section with an exclusive interview with Oliver Glick, Policy Officer at the Children and Young People's Mental Health Coalition, where we consider their vital work in promoting the psychological well-being of children in the UK, and the impact of the current pandemic on this very vulnerable sector of society.

Our third and final section celebrates recent advances related to the study of neurodegeneration and rehabilitation that have the potential to bring clinically significant improvements to the lives of many. Here, we meet the researchers who are directly confronting the challenges of ageing, disease and injury. From identifying novel compounds to treat currently incurable diseases to advancements in the newly emerging fields of neural engineering and neurophilic design, this section provides an exciting insight into the dramatic and revolutionary advances in healthcare we may see in the very near future.

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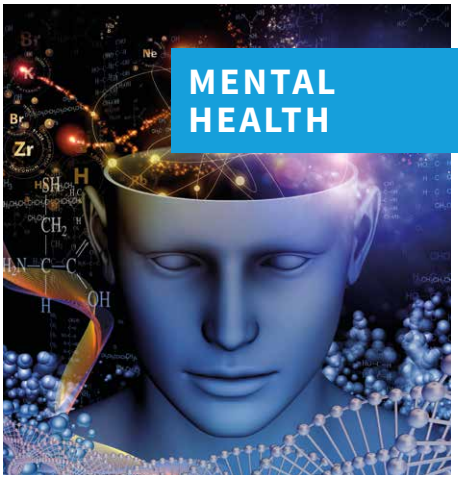

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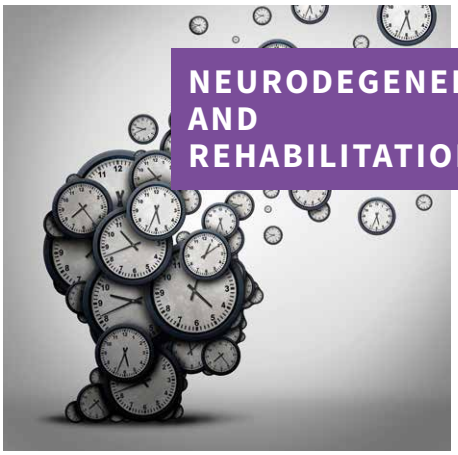

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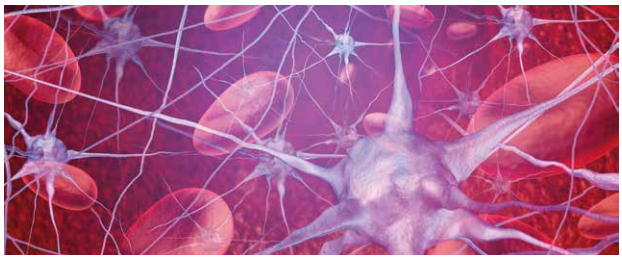

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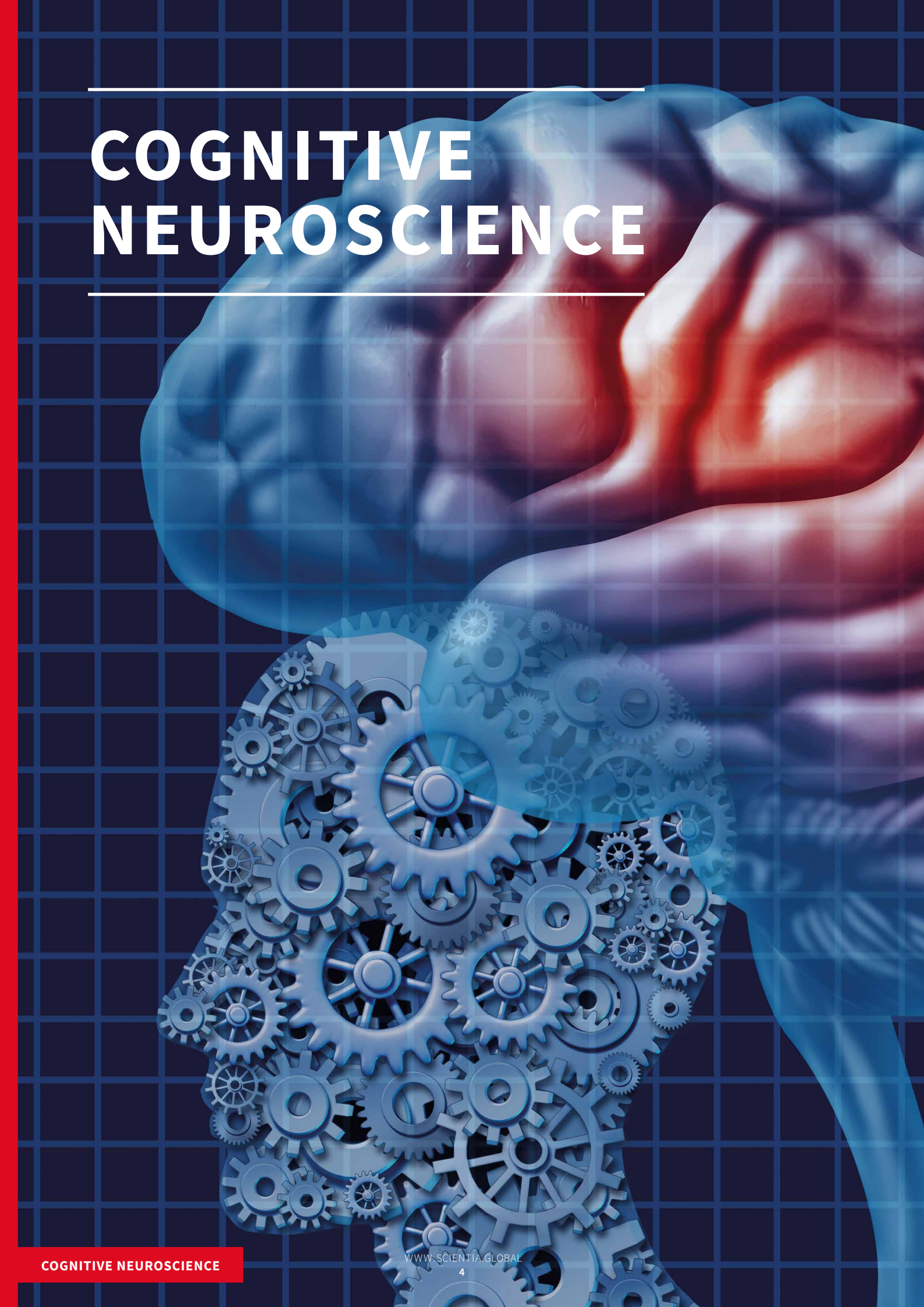


SHEDDING LIGHT ON THE COMPLEXITIES OF THE BRAIN

We begin with Professor Wolf Singer at the Max Planck Institute for Brain Research in Frankfurt, who has devoted decades of research to understanding the neuroscientific basis of our mental lives. We read how our brains create the perception of a unified world and the implications of Professor Singer's recent research for understanding psychiatric disorders such as autism and schizophrenia.

Professor Mark D'Esposito of the University of California, Berkeley, studies how different parts of the brain work together to create working memory, the cognitive system that temporarily and actively holds information in mind. We read how Professor D'Esposito integrates novel experimental approaches with classic behavioural and cognitive studies to build a comprehensive understanding of how working memory functions in the brain by building networks between neurons.

We then turn to Professor Jeansok Kim from the University of Washington who explores the underlying brain mechanisms of fear in animals and humans. We read of his novel and highly realistic approaches to study fear that mimic risky conditions in the wild, and how his findings are challenging existing paradigms as well as driving forward our understanding of fear. Remaining on the topic of emotion, we then consider the work of Dr Bettina Pause at Heinrich-Heine-Universität Düsseldorf. Dr Pause has conducted extensive research into human communication and sensory perception. Her work has shown that we can quickly and effectively convey emotional states such as anxiety and aggression to others through social chemosensory signals that are processed in the brain, often without the explicit awareness of either the sender or the recipient.

Finally, we meet the researchers working on the cognitive neuroscience of sport and exercise. Professor Kirk Erickson at the University of Pittsburgh is a key driving force behind the emerging field of 'health neuroscience'. We read how he is providing powerful evidence that exercise has beneficial effects on both the brain and cognition across the lifespan and for different clinical groups. We conclude this section by meeting Professor Matthias Weigelt from the University of Paderborn, Germany. Professor Weigelt takes a cognitive neuroscience approach to understand deceptive actions in sports and we read of the important ethical considerations raised by his research.

THE COORDINATION OF NEURONAL COMMUNICATION

More than a century of research in neuroscience has demonstrated that neurons and specific areas of the cerebral cortex are specialised in their function. For example, separate aspects of a visual stimulus (such as its colour, shape, and motion) are processed by specialised neurons distributed across several cortical areas. A critical question is how information from these separate neurons is combined in the brain to create a coherent visual perception. **Professor Wolf Singer**, at the Max Planck Institute for Brain Research in Frankfurt, has devoted decades of research to understanding the neurophysiological basis of our mental lives, including how it is that we create our perception of a unified world.

Neural Communication in the Brain

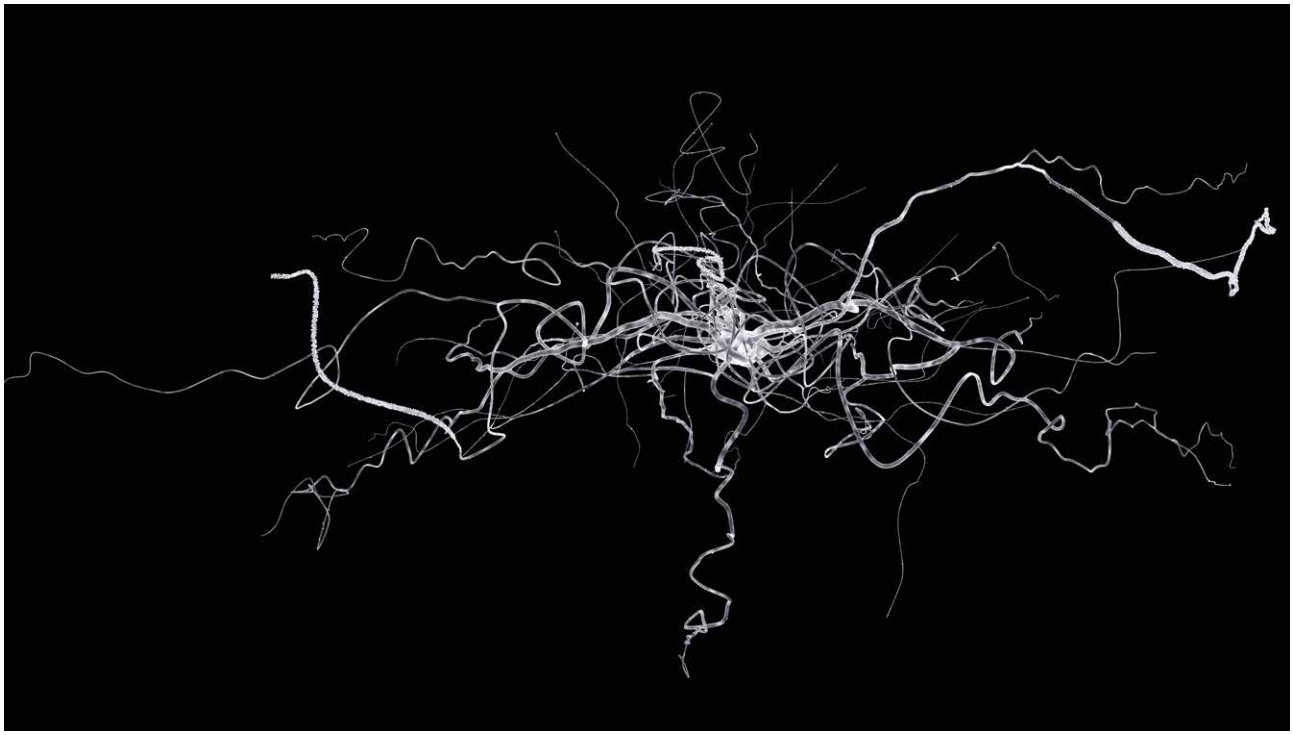
The central nervous system in humans is comprised of billions of neurons that communicate with one another to share information. This results in a hugely complex system of trillions of connections between neurons. Neurons communicate using electrical events (known as action potentials) and chemical neurotransmitters, creating unfathomable complex patterns of activity.

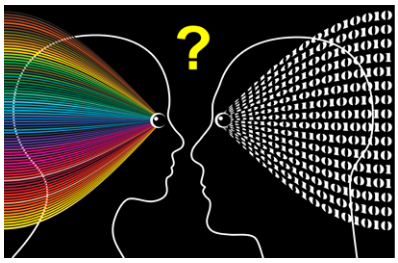
Higher cognitive processes, such as perception, attention, memory, and language, all arise from the activities of neurons and the communication between them. These activities are often rhythmic and sometimes even synchronous – they are then referred to as neural oscillations. These oscillations can be characterised by their frequency, amplitude, and phase just as the oscillations of a pendulum. Oscillations can become synchronised within specific groups of neurons and this is known as 'local synchronisation'. However, the oscillatory activity of neurons or groups of neurons that are physically spaced further apart can also synchronise, and this is known as 'global synchronisation'.

The activities of neurons can be observed using a variety of neurophysiological techniques, and these are utilised depending upon the requirements of the research question. The gold standard is to study the activity of individual neurons – that is, single cell recordings – with micro-electrodes and optical methods. These techniques are invasive and therefore cannot be used for research in human studies. It is also possible to assess the collective activity of large populations of neurons distributed across the brain with electroencephalography, magneto-encephalography or magnetic resonance tomography. These technologies have a number of severe shortcomings related to their poor spatial or temporal resolution, but they are non-invasive and can be applied in obtaining measurements from human research participants.

To date, neural oscillations and synchronisation have been linked to many different types of cognitive function, including visual perception. But critical questions still remain – including that of the specific functions of observable patterns of oscillation. The question how the responses of neurons that are distributed both within and across different areas of the brain are bound together to give rise to coherent perceptions has been a particular interest for Professor Wolf Singer, of the Max Planck Institute for Brain Research in Frankfurt, for many years.

‘I took a Polaroid screen shot, wrote on it “the visual sniff,” and taped it on the rack, where it remained for several months.’





Setting the Scene: Developmental Studies in Visual Neuronal Plasticity

Professor Singer’s early research, conducted in the 1980s, focused on neuronal plasticity and the specific question of how experience shapes the development of the visual system. These experiments were conducted primarily in young and adult cats. By plasticity, we mean the extent to which neurons can change and adapt as a result of experience and learning.

It was already known from the seminal studies of Hubel and Wiesel that during the so-called critical period for visual development, neurons in the visual system remain malleable and adapt in response to visual exposure. This experience-dependent plasticity is an essential prerequisite for the maturation of normal visual functions.

Using convergent neurophysiological, neuropharmacological, and behavioural approaches, Professor Singer provided evidence that the mechanisms mediating developmental plasticity closely resemble those underlying learning in the adult and, like the latter, are supervised by modulatory systems that control arousal and attention.

The most notable finding from this work, however, was Professor Singer’s replicable observation that specific visual stimuli result in synchronous oscillatory activity in groups of spatially segregated neurons. To put it more simply, he saw that groups of neurons, which could even be located in separate areas of the brain, were firing at the same time within intervals of a few milliseconds when participating in the processing of features belonging to the same object.

The ‘Visual Sniff’

Professor Singer was aware that similar oscillations had been observed almost a decade before in the olfactory bulb – a neural centre in the brain associated with the sense of smell – of rabbits while they were sniffing. In an autobiographical work, Professor Singer recounted his sense of the importance of this observation which led to a new and exciting research trajectory: ‘I took a Polaroid screen shot, wrote on it “the visual sniff,” and taped it on the rack, where it remained for several months.’

From a methodological perspective, the techniques utilised in Professor Singer’s laboratory reflected a significant step forward, allowing simultaneous long-term assessment of the activity of larger groups of spatially segregated neurons in awake animals. These techniques were later adopted widely in the research field. In collaboration with other scientists, Professor Singer proceeded to explore further the observations of synchronous oscillatory activity – with intriguing theoretical implications.

Exploring Neural Synchrony and Oscillations

Later work by Professor Singer and colleagues investigated the synchronisation of neural activity in response to consciously perceived stimuli compared to stimuli presented outside of conscious awareness in human participants. Adopting established unconscious priming paradigms from experimental psychology, the researchers looked at both local and global neural activity in response to consciously perceived and unconsciously processed stimuli.

Clear and distinct patterns were observed. Both conscious perception and unconscious processing were found to result in local synchronisation of responses in areas involved in the analysis of the visual stimuli, suggesting that both unconscious and conscious processing engage similar local circuits. However, global oscillations reflecting synchronisation of neurons distributed across the brain were observed only when stimuli were consciously perceived. Critically, Professor Singer and colleagues proposed that this global synchronisation is one of the mechanisms through which stimuli become available to conscious awareness.

By the turn of the millennium, research into synchronised oscillatory activity began to look at how specific disturbances may account for the features of psychiatric disorders. Disturbances in the oscillatory activity of neural responses of schizophrenic patients had been proposed by this time, but little evidence was available to show how such disturbances might reflect, or be associated with, cognitive performance, of which certain elements are known to be impaired in schizophrenia.

Work by Professor Singer and colleagues extended previous work to investigate how such disturbances in neural synchrony in schizophrenia would be manifested in a behavioural task. More specifically, the researchers assessed the responses of patients on a Gestalt visual perception task.

In Gestalt perception tasks, separate parts of the image have to be bound together. For example, if you look at a cat, the signals from the fluffy fur, long tail, bright eyes, pointed ears, and so on have to be integrated in order to generate what you are consciously aware of, the overall image of a cat. It is known that schizophrenic patients, and to some extent also patients suffering from autism spectrum disorders, are impaired in perception tasks requiring integration of details into a coherent whole. As this integrative function is thought to depend on the large-scale synchronisation of local oscillatory processes it was hypothesised that patients might have deficits in the temporal coordination of neuronal activity.

Using an advanced analysis of electroencephalography data, Professor Singer and colleagues did indeed observe impaired large-scale synchrony of neurons distributed across the brain of schizophrenic and autistic patients. Most importantly, the impairment of temporal coordination was correlated with the severity of the clinical symptoms. The researchers proposed that this disturbance of synchronisation is a likely cause for at least some of the cognitive impairments commonly observed in schizophrenia and autism.

Looking to the Future

Current work in Professor Singer's laboratory is exploring further the functional significance of the complex dynamics emerging from the dense and reciprocal interactions between large numbers of neurons taking advantage of a new and enhanced technique for recording neural activity. In consideration of findings to date, Professor Singer has proposed that the brain adopts a computational strategy that capitalises on the complex dynamics generated by networks of reciprocally coupled neurons.

To test this theory, Professor Singer is in the process of conducting a series of studies designed to further investigate the links between neuronal dynamics and perception. Critically, in addition to obtaining correlational evidence – the dominant approach in the field to date – Professor Singer aims to obtain causal evidence. In other words, he aims to manipulate the system using learning paradigms in order to investigate the consequences on network dynamics and perception. However, in view of the mind-boggling complexity of the system, Professor Singer feels that he and his colleagues are still far away from understanding the neuronal algorithms underlying even simple cognitive and executive functions. However, with the advent of techniques that allow simultaneous recording of activity from up to a thousand neurons and the availability of nearly unlimited computer power for the analysis of these data, there is now some hope to at least test some of the advanced theories.

Given the increasing recognition of disturbances in neural dynamics and the relevance to understanding psychiatric disorders such as schizophrenia and autism, Professor Singer further elaborates that 'the results are likely to be relevant for clinical investigations and diagnostics by providing interpretable markers of dynamic processes.' This would be a revolutionary achievement in terms of clinical psychiatry, where diagnosis (and thus treatment) is vulnerable to criticism due to being inherently subjective.

Thus, over more than three decades, work conducted by Professor Singer has made a unique and substantial contribution to our understanding of the neurophysiological underpinnings of complex cognitive function. Findings already have significant implications for our understanding of how we create coherent visual scenes, and how information becomes available in our conscious awareness. Ongoing work promises to shed even more light on how it is that the neural substrates in the brain support our perception and understanding of the world around us.

Meet the researcher

Professor Wolf Singer
Director Emeritus
Max Planck Institute for Brain Research
Frankfurt
Germany

Professor Wolf Singer studied Medicine in Munich and Paris, obtaining his MD from the Ludwig Maximilian University in Munich in 1968. He then completed his PhD at the Technical University in Munich in 1975. He is the Director emeritus at the Max Planck Institute for Brain Research in Frankfurt, Founding Director both of the Frankfurt Institute for Advanced Studies and of the Ernst Strüngmann Institute for Neuroscience, and Scientific Director of the Ernst Strüngmann Forum. His research is focused on the neuronal substrate of higher cognitive functions. Professor Singer is the recipient of an outstanding number of honours and awards, commiserate with his lifelong contribution to neuroscience and society.

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EVERYDAY MIRACLES: UNRAVELLING THE MYSTERIES OF WORKING MEMORY

To accomplish even a simple goal, our brain must coordinate thousands of pieces of information, remember which parts are relevant, and ignore anything that is extraneous. **Professor Mark D'Esposito** of the University of California, Berkeley, studies how different parts of the brain work together to create working memory, the cognitive system that temporarily and actively holds information in mind allowing us to complete complex tasks.

Whether you realise it or not, by this point in your day you have accomplished many seemingly minor tasks. Though it probably felt effortless to you while you were going about your routine, your brain has had to coordinate vast amounts of information to get you to where you are now, reading this article.

All these activities required paying attention to the right details, coordinating a series of complex actions, and filtering out an incredible amount of irrelevant information from your environment. Professor Mark D'Esposito and his team at the University of California, Berkeley, want to understand how the brain manages these everyday feats and what is happening between the cells of the brain to make it all come together.

Where Working Memory Works

Working memory refers to information we have readily available to us, because it was either recently experienced or recently retrieved from long-term memory, even though the cue for this information is no longer present. For example, being told a new telephone number and then holding it actively in mind while you then hunt for a pen and paper to scribble it down.

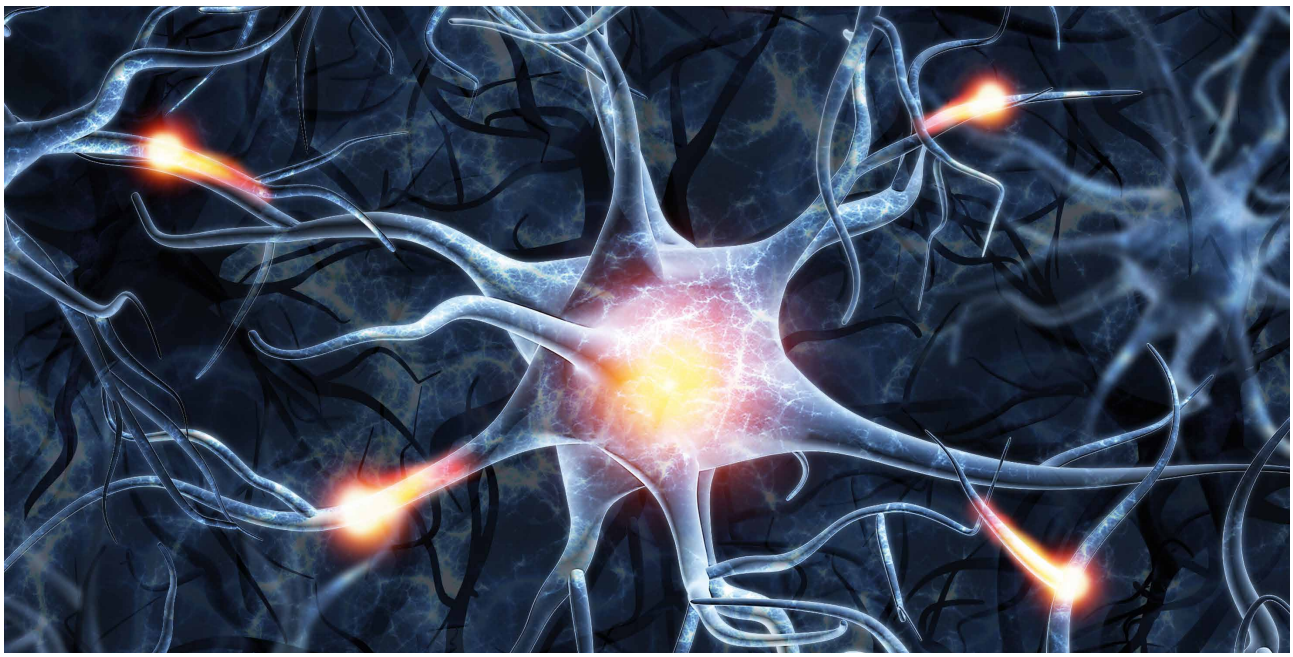
The information stored in working memory tends to be replaced by more recent events after a period of time if it is not being used. You can probably easily recall your own telephone number, because most of us have that safely stored in our long-term memory. However, on being told a new telephone number, we have to actively maintain this in our working memory by repeating it our head, otherwise it will quickly fade from recall. Working memory helps us to accomplish tasks efficiently by allowing us to keep using recently acquired relevant information.

The most prominent model of working memory is the state-based model. In this model it is proposed that working memory relies on the allocation of attention to existing mental representations, effectively focusing attention to activate information already stored internal representations, whether semantic knowledge (e.g., letters, digits, words), sensory, or

motoric. By paying attention to these mental representations, the brain brings them into working memory to help complete a task.

Professor D'Esposito and his team at the University of California, Berkeley, want to understand how the neural cells of the brain function to create working memory. Unlike processes such as vision and hearing, working memory is not relegated to specific areas of the brain. Rather, it appears to be an emergent property of several systems working together.

‘Neurologists like myself, are convinced that the secret to solving the mystery of how the brain works can be answered by understanding how neurons communicate.’



One of the earliest experiments demonstrating the neural basis of working memory was performed with monkeys in the early 1970s. Researchers measured the activity of single neurons while the monkey performed a task that required them to retain information for a brief period of time. They found that the neurons started firing when the information was acquired and continued to fire at regular intervals until the information was no longer needed.

Professor D’Esposito has progressed these early studies taking advantage of functional magnetic resonance imaging (fMRI) that can be used to measure activity in the brain. Professor D’Esposito and his team found that when people are completing a working memory task requiring information to be kept in mind during a short delay period, the brain continued to show sustained activity after the initial memorisation phase – even though the to-be-remembered information was no longer present. Critically, rather than being buffered in a particular or specific part of the brain, this process of working memory appeared to involve many brain areas acting in unison.

Finding the Brain’s Control Centre

Neurons in the brain are organised into regions or modules that handle specific types of information. The prefrontal cortex, the foremost and most evolved part of the brain compared to other species, is the region of the brain that gives us conscious control over our actions and allows us to process complex thoughts. Other regions of the brain are dedicated to different sensory or motor functions, such as the visual cortex and motor cortex.

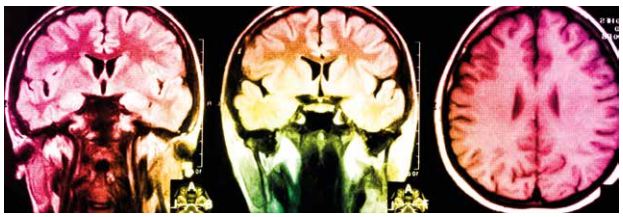
Professor D’Esposito has found that when a region of the brain is involved in the initial sensing of information, it is also active while that information remains in working memory, along with the prefrontal cortex. His team is interested in the roles the prefrontal cortex plays in both working memory and cognitive control and understanding the functions of smaller modules of neurons within this critical brain region.

Using fMRI to study brain activity, Professor D’Esposito’s team asked participants to perform matching tasks where the information was ranged from concrete (such as matching squares by colour), to mildly abstract (matching a red square to a hexagon, or a blue square to a star), to very abstract (matching a shape if the object is blue, or orientation if the object is red).

They found that abstract tasks engaged the prefrontal cortex depending on the complexity and level of abstraction. The prefrontal cortex appears to maintain more conceptual representations of information needed in working memory to complete a task – it maintains the rules that must be followed while the sensory regions maintain the relevant concrete information.

Professor D’Esposito and his team have also demonstrated that specific smaller regions within the prefrontal cortex appear to be separated into functional modules that manage increasing levels of abstraction. In his fMRI studies, as tasks required keeping more conceptual information in working memory, clusters of neurons were active towards the front of the brain in this region.

These findings suggest that conceptual, more abstract rules are stored in the anterior portion of the prefrontal cortex.



Such rules are those allow us to generalise from one situation to the next – for example, figuring out an unusual mechanism by which a door is opened, such as having to pull a cord rather than turn a knob, even if we have no prior experience of using that mechanism to open a door. In contrast, concrete rules are those which specific responses are tied to specific behaviours, such as when driving a car – mirror, signal, manoeuvre. These types of rules are stored in the posterior regions of the prefrontal cortex.

Importantly, the prefrontal cortex is proposed to be the part of the brain that imbues our ability to orchestrate thought and action based on our goals and intentions, rather than being driven automatically by the world around us. In other words, it allows us to control the focus of the rest of the brain to accomplish goals. Professor D'Esposito believes that the prefrontal cortex exerts executive control over the rest of the brain through top-down processing.

This means that when the prefrontal cortex identifies a goal, such as finding a friend in a crowded venue, it directs how information managed by other areas of the brain should be processed and attended to, in this example, tuning out irrelevant details and focusing on key facial features.

In his studies, Professor D'Esposito has found that this occurs through two primary processes – regulating selective attention to specific signals by enhancing relevant signals while suppressing irrelevant ones. His team has confirmed this functionality by studying the fMRI activity of healthy people during different tasks and comparing them to the fMRI activity and task performance of patients with brain injuries that specifically affect the prefrontal cortex.

Networking for Success

Recognising that the prefrontal cortex and other regions of the brain all chip in to create working memory is one thing, understanding how they communicate is another. Professor D'Esposito elaborates that, 'neurologists like myself, are convinced that the secret to solving the mystery of how the brain works can be answered by understanding how neurons communicate.'

Professor D'Esposito and his team's present work focuses on how neurons form networks within the brain that make working memory and executive control by the prefrontal cortex possible. Each neuron in the brain can only perform a single function, so he hypothesises that complex representations of situations are formed by how the modules in a network interact with one another. He proposes that working memory emerges from the way the prefrontal cortex interacts with all the other areas of the brain related to an experience or task.

He explains: 'Just like Facebook connects people, this enormous network in our heads connects neurons, and they, it turns out, communicate with each other in much the same way we do with our friends and family members.' We reach out to different members of our social network to fulfill different needs, just as our neurons interact with different parts of the brain to accomplish what is necessary for a task.

Bringing it All Together

The effects of widespread neurotransmitters, like dopamine, that act as modulators of overall brain activity have often been overlooked in models of working memory and cognition. The importance of dopamine in regulating brain activity and function is highlighted by the key role it plays in Parkinson's disease, when the brain cells that produce dopamine become damaged and no longer release this transmitter, resulting in disrupted cognitive ability and movement.

In his quest to understand the biological mechanisms that create memory and thought, Professor D'Esposito has focused in on the role these modulating transmitters may play. He has found that dopamine levels in different areas of the brain play a critical role in modulating working memory. There is an optimal level of this important neurotransmitter needed to perform working memory tasks. Too much dopamine or too little disrupts normal function.

The team propose that when dopamine is elevated in the prefrontal cortex, we focus on the information already active in our working memory, when it is higher in a region of the brain called the striatum, our brain begins switching over the items held in working memory. Changes to dopamine levels in the prefrontal cortex or the striatum could have different consequences for cognitive stability and flexibility. For instance, high levels of dopamine in the prefrontal cortex could promote stability but reduce flexibility. This mechanism helps to coordinate large areas of the brain and maintains the balance between focus and flexibility that makes human thought so adaptable.

The Full Picture

By integrating novel approaches to brain imaging and neurotransmitter measurements with classic behavioural and cognitive studies, Professor D'Esposito is building a comprehensive understanding of how the brain leverages different mechanisms to make working memory work. Illuminating how these everyday mental processes occur offers powerful insights into how the brain functions and shines light on the mysteries of the human mind.

Meet the researcher

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Professor Mark D'Esposito earned his medical degree at the SUNY Health Science Center at Syracuse and completed clinical training in Neurology at Boston University Medical Center. After prestigious appointments at the Memory Disorders Research Center at Boston University and Braintree Rehabilitation Hospital and the University of Pennsylvania School of Medicine, he was recruited to the Helen Wills Neuroscience Institute at the University of California, Berkeley to become Professor of Neuroscience, and the Director of the newly created Henry H Wheeler, Jr Brain Imaging Center. He is also practicing neurologist at the Northern California VA Health Care System. His research investigates how the brain supports high-level cognitive processing, how the brain recovers from injury, and potential treatments for the injured brain. Over the course of his career, Professor D'Esposito has published over 375 academic articles as well editing books about cognitive neuroscience and neurology. He is currently Editor-In-Chief of the Journal of Cognitive Neuroscience, and past President of the Society for Behavioral and Cognitive Neurology and Chair of the Organization for Human Brain Mapping. Professor D'Esposito has received numerous awards and honors including the Norman Geschwind Prize in Behavioral Neurology from the American Academy of Neurology and election to the American Association for the Advancement of Science.

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UNDERSTANDING FEAR IN ANIMALS

Research into animal fear typically utilises laboratory techniques based on Pavlovian fear conditioning, but these approaches are limited. **Professor Jeansok Kim**, from the Department of Psychology, University of Washington (USA) has developed a much more realistic way to study fear that closely mimics risky conditions in the wild. New discoveries by Professor Kim and his team are challenging existing paradigms and providing exciting insights into the underlying brain mechanisms of fear in both animals and humans.

Time for a New Approach

All animals have to search for resources, including food, water, and shelter. Ironically, while searching is absolutely essential for their survival, it may also bring about their demise if they encounter a predator. To confront this dilemma, animals have developed the ability to feel afraid. In human terms, fear may not be seen as beneficial, but, for animals in the wild, recognising potentially dangerous situations – as a result of genetics and experience – may be what keeps them alive.

This ability to instinctively recognise and respond appropriately to certain dangers (even threats never encountered before) varies for each species, depending on their environment. For example, the main fear response for the woodland deer mouse is to freeze and this confuses its predator's sensitivity to movement. However, the desert deer mouse opts to leap as high as possible to avoid the snake's strike.

For a long time now, research into fear has relied on Pavlovian fear conditioning, where an innocuous stimulus (like a tone, for example) is associated with an aversive stimulus (such as an electric shock) which, in turn, activates a fear response. In this case, animals learn quickly that a tone is followed by an electric shock and start demonstrating conditioned fear responses as soon as they see the tone.

While the Pavlovian fear conditioning paradigm has allowed many major developments, Professor Jeansok Kim, based at the Department of Psychology, University of Washington (USA), believes it is now time for a new approach. According to Professor Kim, the fear conditioning approach does not allow us to explore the much more dynamic range of fear responses that animals need to survive in the wild.

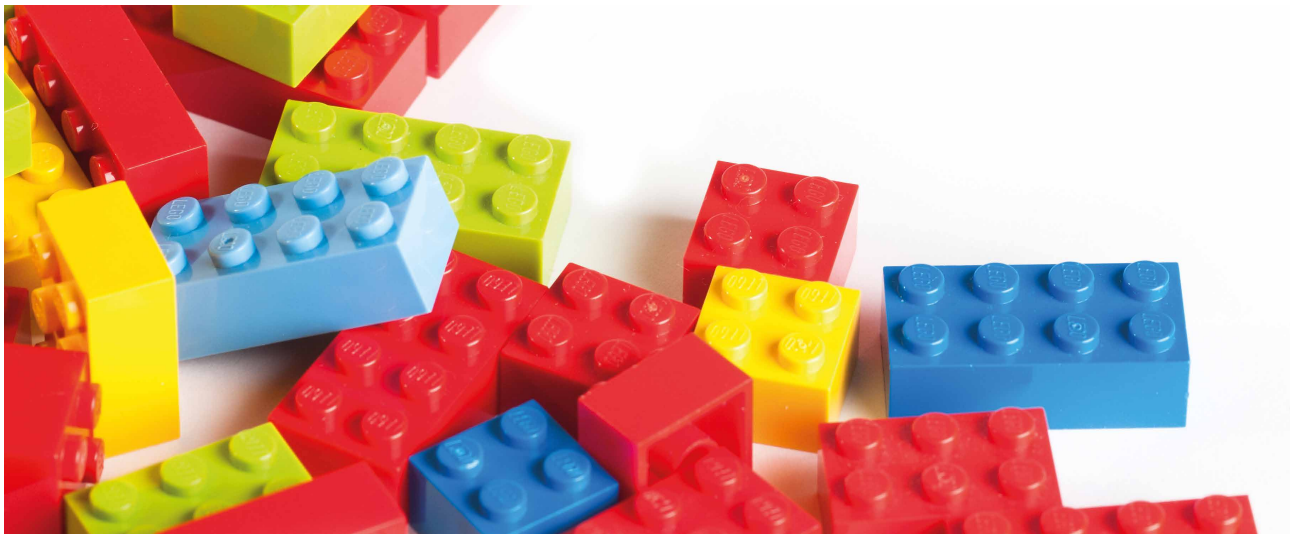
To observe a wider variety of responses, Professor Kim and his team developed a much more naturalistic environment to study rats, where the animals' fear responses are not confined in small cages but instead expressed freely in a large enclosure, with a safe nest and a risky foraging area. In this enclosure, just as in the real-world, food does not come easy: the rats need to leave the safety of their nest, and face a LEGO robot

called Robogator that is programmed to surge toward the animal as it emerges from the nesting area in search of food. With moving eyes, jaw, and tail, the Robogator simulates an unpredictable attack by a predator, allowing Professor Kim and his team to obtain data that is not possible with real predators.

It's All in the Brain

Studies have identified a particular area in the brain – known as the amygdala – as the crucial structure regulating fear in animals, including humans. However, it has been very difficult to determine its exact functions due to technical difficulties in quantifying these responses in natural fear responses with real and unpredictable predators.

‘Looking beyond the amygdala and toward a circuit-level understanding of fear behaviour will provide more power to the treatment of fear-related disorders, but it is imperative that future studies use diverse and representative experimental designs to best converge upon the functions of fear circuitry.’



Using the Robogator, Professor Kim observed that rats would initially venture out of the nest, only to run back and freeze inside the nest at the first sight of the robot. Eventually, hunger would start to win over their fear, and the animals would start stretching and popping their heads out of the nest to scan the area. When they attempted to venture out of the nest, the Robogator was used to trigger their fear response once again. This meant that the animals could not retrieve food that was far away from the nest, and were only able to obtain food that was more closely placed to safety. Professor Kim proposed that ‘the farther the food is from the nest, the more strongly the fear motivation for self-preservation inhibits the hunger motivation for foraging. Nonetheless, the fact that rats do not simply avoid foraging altogether in the presence of the Robogator but instead make repeated efforts to procure the food indicates the utilisation of risk assessment on the part of the animal.’

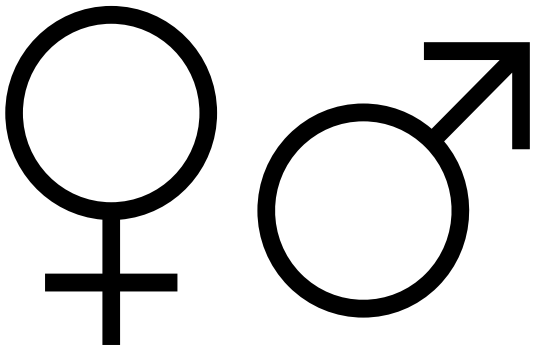
Repeating the same experiment with animals with either an inactive or an overactive amygdala confirmed its involvement in these demonstrations of fear responses: rats with low amygdala activity did not show any fear towards the Robogator – at most, they paused temporarily but did not flee to the nest. In contrast, animals with heightened amygdala activity took longer to leave the nest and covered a shorter distance to collect food.

Looking further at how the amygdala dynamically interacts with the prelimbic cortex (a structure implicated in decision making) during naturalistic problems of foraging, Professor Kim identified a dual response to dangerous situations: a short and fast period of activity in the amygdala in anticipation of an imminent predatory threat as the animal moves towards food, and a slow and longer period of activity in the prelimbic cortex as the animal exits the nest, as if preparing for an upcoming danger. Professor Kim suggested that this short burst would enable a quick escape while there is still time to do so, followed by a prolonged period of re-assessing the situation, maintained by the longer periods of brain activity.

Professor Kim’s hope is that ‘this ethological approach may be useful in revealing how the amygdala and its associated circuitry are involved in risk-taking and thrill-seeking behaviours in humans, and in addressing the neuronal basis of the basic approach–avoid conflicts that may contribute to human psychopathologies. Aberrant activity and wrong spike synchrony may underlie complex fear-related conditions, such as anxiety, panic, and PTSD.’

Not Just the Amygdala

Having demonstrated how the amygdala regulates fear responses even in naturalistic settings, Professor Kim was keen to analyse what other parts of the brain may also be involved. He was particularly keen to explore an area called the periaqueductal gray, which, although already implicated in fear responses, remains a mystery in terms of underlying mechanisms. Some previous studies have suggested that independent activity is undertaken by the amygdala and periaqueductal gray, whereas others seem to suggest that they function in an intertwined manner, with both contributing to fear responses.



Using his newly-developed approach as well as traditional fear conditioning, Professor Kim assessed the involvement of the periaqueductal gray, by itself and also in combination with the amygdala.

In the fear conditioning approach, while an inactive amygdala meant that the animals never showed any signs of fear, an inactive periaqueductal gray area did not stop frightened behaviours, mainly jumping and running. In contrast, in the large foraging chamber, the animals opted to run towards the safety of the nest instead. The different responses 'further highlight the importance of the context in which brain stimulation occurs in the expression of fear responses,' says Professor Kim. 'In other words, the environmental setting can significantly influence the behavioural readout.'

These results are important for a second reason. The model tentatively proposed so far places the periaqueductal gray area as acting after the amygdala in promoting a fear response. Professor Kim is now leaning towards the reverse scenario, suggesting that the amygdala is receiving instructions instead. More studies are still needed to confirm these underlying mechanisms in the brain.

When it comes to humans, it is possible that aberrant activity in the periaqueductal gray area contributes to fear-related psychopathologies such as anxiety, phobic, panic, and posttraumatic disorders. 'Looking beyond the amygdala and toward a circuit-level understanding of fear behaviour will provide more power to the treatment of fear-related disorders, but it is imperative that future studies use diverse and representative experimental designs to best converge upon the functions of fear circuitry,' states Professor Kim.

Females vs Males

There are fear mechanisms that seem to be shared by all species: the decision to go out and search for food needs to take into account the risk associated with meeting predators. One big question is whether there any differences between men and women. Anxiety and other mental health disorders tend to afflict more women than men – might this stem from fundamentally different fear mechanisms between the sexes?

Male and female rats do react differently to dangerous situations. Both demonstrate fear in response to danger but in contrasting ways. Males opt to increase the amount of food collected in each trip to cover their needs whereas females sacrifice their body weight rather than chance an encounter with a predator. This is not surprising, as females usually attribute higher importance to caring for their offspring while males put more effort into reproducing. Risk-taking males are more likely to achieve social dominance and win female attention.

Human fear vs Animal fear

Predation has been a major driving force in the evolution of fear in all animals, including humans. Observing and monitoring activity in conditions similar to those in the real world will continue to advance our understanding of the underlying fear mechanisms in the brain. This includes revisiting the results obtained from traditional fear conditioning studies so that we can better understand how fear shapes behaviour when animals are making real-world choices.

Future research also needs to evaluate whether human fear and animal fear involve the same mechanisms. This approach 'may provide a deeper insight into human disorders that are abnormal amalgamations of innate/learnt fear, risk-assessment, and decision-making processes,' concludes Professor Kim.

Meet the researcher

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Professor Jeansok Kim obtained his doctorate in behavioural neuroscience at the University of California, Los Angeles, USA, in 1991. He then took up a postdoctoral position followed by a research assistant professorship, both positions being held at the University of Southern California (also in Los Angeles). From 1996 to 2002, Professor Kim held positions first as an assistant professor and then as an associate professor at Yale University, New Haven, USA. In 2003, Professor Kim took up his current professorial appointment in the Department of Psychology at the University of Washington, Seattle, USA. Professor Kim is a distinguished academic, having received multiple awards throughout his career. In addition to being a popular invited speaker at conferences across the world, Professor Kim has amassed considerable funding, contributed to more than 100 publications, and serves as an editor and reviewer for a number of high impact journals reflecting his ongoing scientific contribution to his research field.

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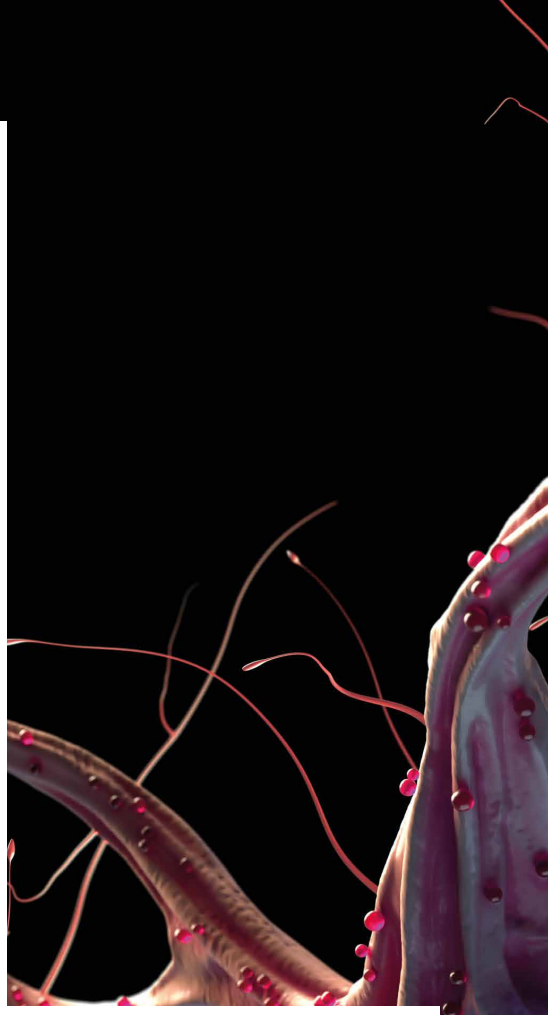
K M L B

MORE THAN JUST WORDS: THE CHEMICAL COMMUNICATION OF SOCIAL INFORMATION

As humans, we communicate our emotions to others in several different ways, including touch, motion, facial expression, and of course, speech. We can also communicate social information through chemosensory signals. **Dr Bettina Pause**, a professor at Heinrich-Heine-Universität Düsseldorf, has carried out extensive research exploring human communication and sensory perception, and in particular, how we quickly and effectively convey emotional states such as anxiety and aggression to others without even using words.



How Humans Communicate Emotion

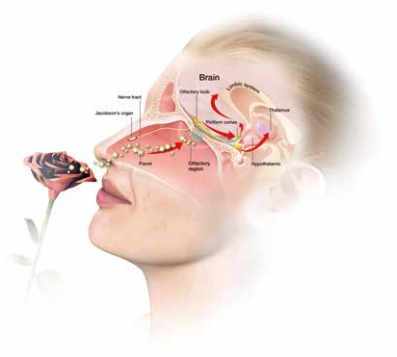
Social communication is a vital human need, essential for survival and reproduction. Furthermore, the experience of isolation and loneliness can have serious repercussions on both our psychological and physical health. Strikingly, the negative impact of social exclusion on our wellbeing is comparable to that of high blood pressure, obesity, and smoking – three factors that are known to increase the risk of serious disease and even mortality.

In recent years, neuroscientists have found that one way in which we communicate social information to others is through chemosensory signals. These are chemical and sensory signals given off by humans, as well as other animals, in specific situations that can be detected by others through sensory perception, and in particular, the sense of smell. Although chemosensory communication is somewhat poorly understood at the current time, it does seem clear that it offers several evolutionary advantages.

So far, most research has investigated the neuronal underpinnings of social chemosensory signals primarily within the context of kin recognition, partner selection, reproductive state, and the phenomenon known as emotional contagion, which is our tendency to feel and express emotions that are similar to those around us.

Importantly, these signals do not appear to be processed within olfactory areas of the brain, but rather, in the regions responsible for processing social information, providing a very strong clue to their underlying function. The processing of social chemosensory signals appears to be very similar to the processing of other social signals although chemosensory signals are typically communicated in the absence of explicit awareness on the part of either the sender or the recipient.

Dr Bettina Pause, a professor of biological psychology at Heinrich-Heine-Universität Düsseldorf, has been investigating chemosensory communication among humans for several years. She leads one of the most

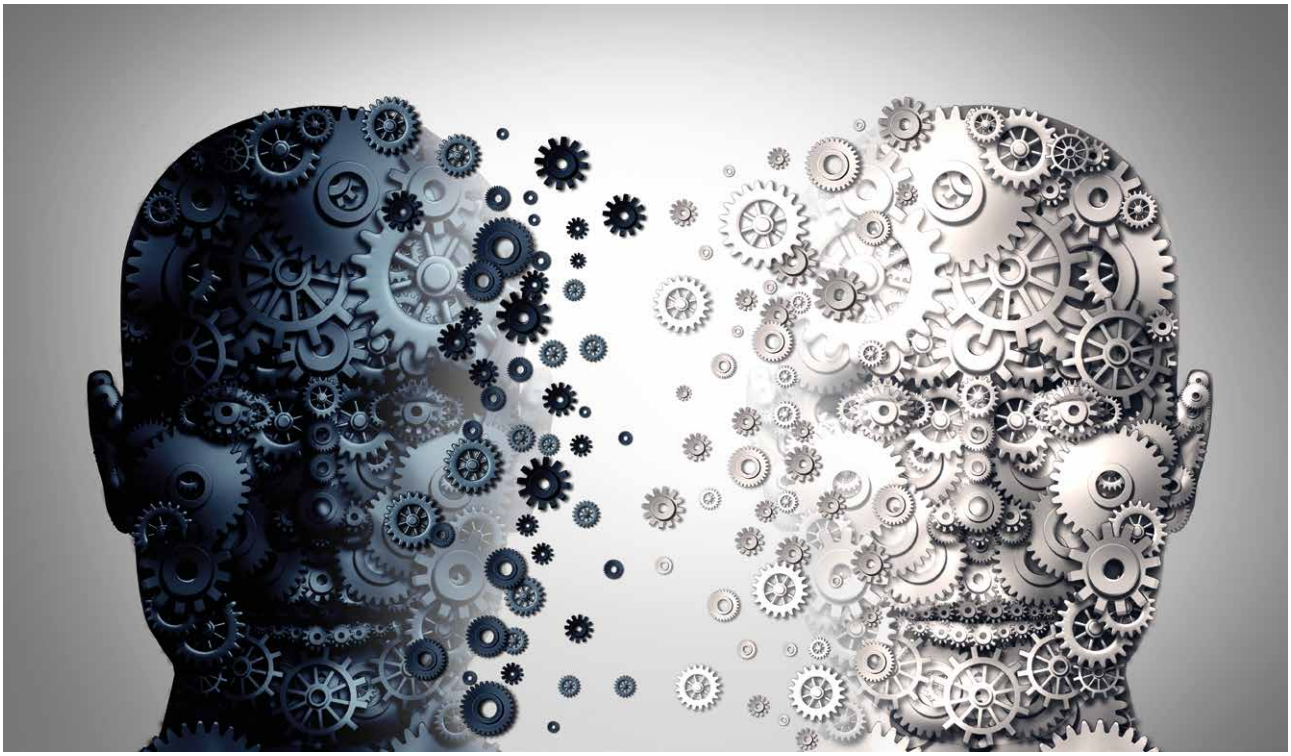


Olfaction in the Human Brain

prominent laboratories in the field and is responsible for significantly driving forward this exciting field of research. As Dr Pause notes, 'The investigation of chemical communication offers a unique way to understand human social relationships.'

So far, Dr Pause and her colleagues have primarily investigated the chemosensory communication of stress, anxiety, and aggression. To measure chemosensory signals, they use axillary (armpit) sweat, urine, and blood samples. 'Due to the high signal specificity, the long signal duration and the honest nature of the

‘The investigation of chemical communication offers a unique way to understand human social relationships.’



signal, chemical communication is phylogenetical ubiquitous and highly efficient,’ Dr Pause explains. ‘Multimodal studies show that in humans, chemical social signals are processed preferentially, but without cognitive interference.’

Communicating Anxiety

From an evolutionary perspective, it is likely to be advantageous to communicate stress related to a potential threat to others around us – and chemosensory signals are a particularly effective way of doing this.

‘Chemosensory communication of stress between members of a given species is ubiquitous among the animal kingdom, as it promotes individual and group survival,’ says Dr Pause. Dr Pause has observed that stress can be transmitted from person to person on a subconscious level through chemosensory signals. ‘I have shown that humans are capable of effectively processing the chemosensory anxiety signals of other humans,’ Dr Pause explains. ‘These signals prime perceptual, neuronal, and motor systems in the perceiver, thereby stress-adaptive behaviour is triggered.’

Dr Pause’s findings suggest that the chemical communication of stress and anxiety between individuals could be contagious, with stress-related emotions being transmitted subconsciously from the stressed/anxious individual to others. Interestingly, however, both the person transmitting the stress and those perceiving it are unaware that this transmission is taking place. ‘The processing of chemosensory anxiety signals does not require attentional mediation,’ says Dr Pause. ‘On the contrary, the anxiety sweat samples we collected most often do not convey an olfactory impression.’ In other words, we are generally unaware of the information that we are either sending or perceiving through chemical communication.

Dr Pause has shown that the chemosensory signals associated with anxiety are primarily processed in empathy-related brain regions, rather than in those associated with olfaction. Moreover, she found that very anxious people tend to be more sensitive to stress-related chemosensory signals. ‘Chemosensory anxiety signals are preferentially processed in highly anxious individuals, demonstrating their high sensitivity to social cues of harm and danger,’ Dr Pause explains.

Perceptions of Anxiety during Pregnancy

Dr Pause has also investigated the processing of anxiety-related chemosensory signals in pregnant women. She collected samples of axillary sweat from a group of men who were about to take an exam and presented them to non-pregnant women and women at different stages in their pregnancy. She then analysed the neuronal reactions in the brain to these samples of sweat to determine whether pregnant women differed in their sensitivity to the odour compared with non-pregnant women.

Interestingly, she found that pregnant women processed stress-related

Dr Pause and her Working Group in Düsseldorf

chemical signals significantly less than non-pregnant women, which suggests that pregnancy reduces the perception of anxiety. This reduced perception of anxiety could have an evolutionary explanation, as it ultimately prevents stress from affecting the baby's development. 'In pregnant females, the chemical contagion of anxiety seems to be absent,' says Dr Pause. 'As stress in the pregnant female can have fatal consequences for the health of new-borns, the reduction of stress perception in pregnant women protects the physiological and psychological health of offspring.'

Communicating Aggression

Dr Pause has also explored the human chemosensory communication of aggression. To do this, she collected sweat from a group of men and women who were taking part in either a very competitive computer game that was meant to raise their aggression levels or a non-competitive construction game. These sweat samples were then presented to other men and women and their neurobiological responses were analysed. Dr Pause and her colleagues found that the chemosensory signals of aggression given off by males elicited peak activity in the brains of both men and women, with women responding more strongly.

In other words, detecting male aggression signals appears to be of greater importance for women than for men. Typically, males are physically stronger than females and thus aggression could pose a greater threat, so it is advantageous for females to be more responsive. 'Our recent studies show that not only stress and anxiety, but also aggression can be transmitted between humans via chemosensory signals' confirms Dr Pause.

Olfactory Perception and Depression

Past studies have suggested that the emotional system of mammals has partly evolved from their olfactory system. For instance, studies on rats have shown that regions associated with olfaction form a close relationship with the cortical amygdala, which is associated with emotion, survival instinct, and memory.

Dr Pause explored whether maladaptive emotional states, such as depression, are associated with different olfactory processing. She found that depressed patients have a reduced sensitivity to odours; a finding that was later replicated by other laboratories worldwide. While this reduced sensitivity to odours was primarily observed in individuals suffering from major depressive disorder, it was also sometimes present in healthy individuals experiencing temporary depressive states.

Dr Pause's explanation for the decreased sensitivity to odours she observed in people suffering from depression is that their olfactory bulb, the primary brain region involved in processing smells, may be dysfunctional. 'A dysfunctional olfactory bulb could result in an over-activation of brain areas related to negative emotional states, such as the amygdala,' says Dr Pause. 'Later studies confirmed that I was right, as they found the olfactory bulb in depressive patients to be reduced in size.'

Paving the Way for Fascinating New Discoveries

In very recent work, Dr Pause has been investigating the mechanisms of episodic memory, that is, the ability of humans to remember and mentally 're-experience' particular episodes from their past, as well as its relationship to emotional and odour processing. In addition, she has been exploring social communication in homosexual individuals. So far, her findings suggest that homosexual individuals dampen interpersonal conflicts by showing reduced aggressive and increased empathic social skills. However, most of her present work is still dedicated to the definition of conditions which compose a chemical signal from a mixture of socially derived volatile molecules

The research already carried out by Dr Pause and her colleagues offers valuable insight into how the human brain responds to chemosensory signals, particularly those associated with stress, anxiety, and aggression. Dr Pause's observations undoubtedly pave the way for further discoveries about chemosensory communication of emotions among humans, as well as the relationship between olfactory processing and mental health.

Meet the researcher

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Dr Bettina Pause has been a professor of biological psychology at Heinrich-Heine-Universität for over ten years. She obtained her PhD in psychology from the University of Kiel, where she also worked as a scientific assistant for several years. In addition to her academic studies at the University of Kiel, Dr Pause has completed several short specialisation courses and participated in a variety of research projects at different universities worldwide. In 1997, for instance, she conducted research at the Washington and Lee University in Virginia (USA), funded by a scholarship from the Gustav-Lienert Foundation. Over the course of her career, Dr Pause has published a vast number of papers in renowned scientific journals investigating topics including the functionality of olfactory information processing in humans and implicit social communication via chemical signals. In 2009, Dr Pause received the Reinhard-Heynen and Emmi-Heynen-Preis prize for outstanding scientific achievements from Heinrich-Heine-Universität. In March 2020, Dr Pause's book introducing human chemical communication to a broad audience, titled 'Alles Geruchssache' and published by Piper Verlag, will become available on the German market.

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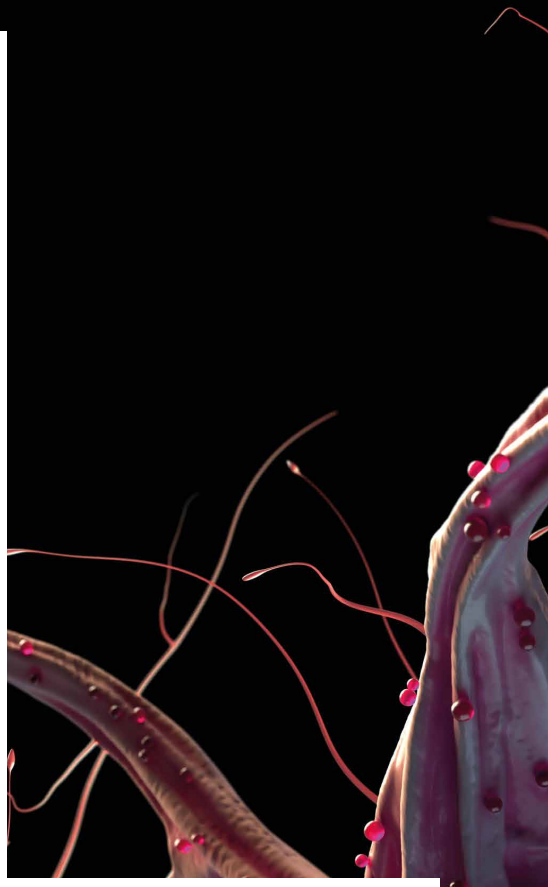
hhu Heinrich Heine University Düsseldorf

HEALTH NEUROSCIENCE: HOW AND WHY EXERCISE IMPROVES COGNITIVE HEALTH



We all know exercise is good for us. In addition to the renowned physical benefits, **Professor Kirk Erickson** in the Department of Psychology at the University of Pittsburgh is providing powerful evidence that exercise may improve cognitive faculties throughout the lifespan. Read on to discover the wide range of ways in which exercise can help us to live our lives to the fullest across the years, and how the emerging field of health neuroscience may inform public health policy for our better good.

Sedentary Lifestyles in the Digital Era

Exercise is crucially important for our physical health yet, despite this, many of us do not achieve the recommended levels of physical activity. A major cause of this is the impact of the digital era in encouraging us to lead increasingly sedentary lifestyles. From sitting behind our computers for work to driving or taking public transport from A to B, for many of us, there is little physical exertion in our day to day lives compared to that of our prior generations.

This is of particular concern due to the long-established link between lack of exercise and the development of chronic diseases, including obesity, type 2 diabetes, and cardiovascular disease, all of which are on the rise at a global level at an alarming rate.

In addition to the detrimental impact of lack of exercise on our physical health, increasing evidence obtained over the last 20 years suggests that our brain and cognitive faculties (such as memory and attention) are also negatively affected. However, when we do exercise, the benefits can be significant. Professor Kirk Erickson in the Department of Psychology at the University of Pittsburgh, USA, is a pioneer in elucidating the beneficial impacts of exercise on brain structure, function, and cognition in the emerging field of health neuroscience.

Neuroprotective Effect of Exercise in Old Age

The hippocampus is a small neural structure in the brain, implicated in both learning and memory. As we age, physical deterioration to the hippocampus in the form of shrinkage is both a precursor to and cause of impairments to memory. In older adulthood, increasing difficulties with memory are often considered part of the normal aging process, as well as a hallmark symptom of neurological disease (such as Alzheimer's disease and other forms of dementia) when the impairments are substantially more severe.

Professor Erickson and colleagues noted in a paper published in 2011 that existing research indirectly suggested

that exercise may increase the size of the hippocampus in the brain in older adults but that this suggestion had not yet been confirmed or quantified. To address this, they conducted a randomised controlled trial in which they recruited 120 older adults without dementia, and allocated participants to one of two groups: an aerobic exercise group or a control group who completed only stretching exercises.

‘The results from this trial could transform scientific-based policy and health care recommendations for approaches to improve cognitive function in cognitively normal older adults.’

The findings were astonishing – aerobic exercise training increased hippocampal volume by 2%, which the researchers explained effectively reversed age-related loss in hippocampal volume by 1 to 2 years compared to the control group. Furthermore, this was associated with demonstrable benefits to spatial memory, a specific type of memory related to information about our environment and location (how to find our way to the local shops, for example). These findings provided the first direct evidence that aerobic exercise has a neuroprotective effect on critical cognitive functions in aging. In other words, undertaking such exercise can reduce or, to an extent, ameliorate ‘normal’ age-related cognitive decline.

Exercise as an Effective Intervention Post-stroke

Professor Erickson and his team then turned their attention to the effects of exercise in either preserving or potentially even improving cognition following stroke. For survivors of stroke, cognitive impairment presents significant challenges through being associated with further deterioration in health, lowering of quality of life, and decreased independence in daily life skills and self-care.

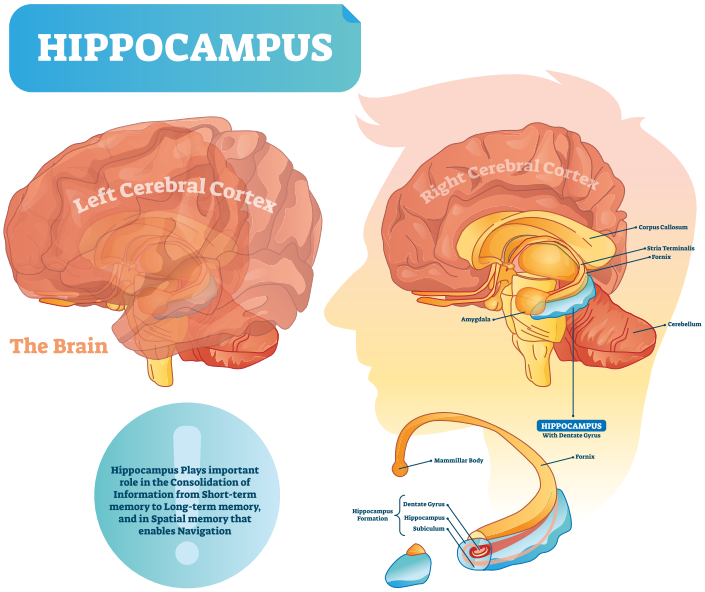
Using a statistical technique known as a meta-analysis, Professor Erickson and colleagues evaluated the combined findings from 14 separate randomised controlled trials (constituting a total of 736 participants) that had tested the effects of exercise on various measures of cognitive function. Conducting a meta-analysis allows a more powerful and reliable estimation of the effects of a given intervention than can be derived from a single study alone.

Professor Erickson found that benefits to cognition were most pronounced for combined aerobic and strength training programs (as compared to either activity being completed in isolation). Benefits were found even in the chronic post-stroke phase (which in this study was on average around 2.5 years), suggesting that exercise as an intervention can be effectively utilised even some time after the stroke itself.

Benefits of Exercise in Children

To date, the majority of research has focused on the benefits of exercise in older adulthood. However, there is converging evidence that childhood is a key stage of development in which physical activity may also provide tangible benefits. In a review paper published in 2017, Professor Erickson and colleagues synthesised the available literature on the effects of exercise in childhood.

Here, the researchers noted that greater integrity of grey matter in the brain, a critical structure associated with a wide range of functions including muscle control, sensory perception, and higher-level functions (such as memory), is associated with greater levels of physical fitness in children and adults alike. The researchers also noted that levels of physical activity can be directly linked to measures of academic success in school children. Such findings are, of course, of keen interest to educationalists, parents, as well as society more broadly, given the profound implications of being able to increase academic attainment in our younger generations.



Taking a reasoned approach, Professor Erickson and colleagues pointed to limitations in the existing research and highlighted avenues for future research. First, they argued for the need for causal rather than merely correlational evidence to elucidate the underlying mechanisms of benefit for exercise in children. Second, they suggested that the circumstances that confer the greatest benefits for exercise on cognition, such as the age of child, duration, frequency, and intensity of exercise, should be identified as a priority.

The Emergence of Health Neuroscience: From Theory to Public Health

The approach adopted by Professor Erickson and colleagues in understanding how the brain affects and is affected by health behaviours such as exercise is known as health neuroscience. This is a new and interdisciplinary field of work, offering both great potential but also, as with any new approach in science, challenges to be overcome in maximising its potential application.

Professor Erickson and colleagues argue that it is not sufficient to merely describe the relationships between our physical health, brain function, and cognition, but rather, that the overarching aim of health neuroscience should be to use empirical findings and the associated theoretical perspectives for the better good, in this case, to improve public health.

As part of work for the USA Physical Activity Guidelines Advisory Committee in 2018, Professor Erickson and colleagues summarised the evidence suggesting that exercise has beneficial effects on both the brain and cognition, and concluded that this is likely to be the case across the lifespan and for different clinical groups. Although they acknowledged that important gaps in the evidence remain, the consistency and magnitude of evidence supporting the beneficial effects were deemed as 'truly remarkable' with the potential to inform the development of public health policies aiming to improve cognitive health across the lifespan.

Striding Forward: *Investigating Gains in Neurocognition in an Intervention Trial of Exercise* (IGNITE)

Professor Erickson is committed to progressing this important field of health neuroscience. To this end, he is currently working on the large-scale *Investigating Gains in Neurocognition in an Intervention Trial of Exercise* (called IGNITE), which is planned to run until the end of 2022. Almost 700 cognitively healthy adults aged between 65–80 years of age are being assigned to one of the following exercise conditions each lasting one year in duration: moderate-intensity aerobic exercise condition (150 minutes per week), moderate-intensity aerobic exercise condition (225 minutes per week), or light-intensity stretching and toning control condition (150 minutes per week).

Participants are undertaking an extensive battery of assessments as outcome measures, including measures of cognition, blood biomarkers, and psychosocial questionnaires at several timepoints. In addition, brain magnetic resonance imaging, physiological biomarkers, cardiorespiratory fitness, physical function, and positron emission tomography are also being utilised as assessments, representing an ambitious yet methodologically robust and comprehensive clinical trial.

On completion, this landmark study will allow the researchers to address key questions about exercise and cognition; most notably, whether the current USA guidelines of 150 minutes of exercise per week are sufficient to elicit benefits to cognition in older adults. Findings will also begin to address the issue of the potential dose-response relationship between exercise and brain and cognitive outcomes. To put it more simply, findings will help determine whether more exercise equates to better cognitive function. As Professor Erickson notes, 'The results from this trial could transform scientific-based policy and health care recommendations for approaches to improve cognitive function in cognitively normal older adults.'

By using exercise as a model within the new field of health neuroscience, Professor Erickson is aptly demonstrating how rigorous experimental and theoretical approaches can help address the monumental need to improve human health and cognition across the lifespan in our current age.

Meet the researcher

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Professor Kirk Erickson completed his PhD at the University of Illinois at Urbana-Champaign in 2005 and then undertook a three-year postdoctoral position at the same institution. In 2008, he moved to the University of Pittsburgh to take up an assistant professorship and rapidly rose through the ranks to be promoted to his current position of professor in 2017. Professor Erickson is widely acclaimed as a scientist, having most recently been appointed as a Distinguished Scientist at Murdoch University (2019–2020) and as a Fellow at the Academy of Behavioral Medicine Research from 2016. From 2016–2018, Professor Erickson was appointed to the Physical Activity Guidelines Advisory Committee by the United States Secretary of Health and Human Services, reflecting his significant contribution to healthcare policy and societal issues. Professor Erickson is an active editor and reviewer for a number of prestigious journals, and has published a total of more than 200 journal articles and book chapters. An impressive track record of funding continues to support Professor Erickson's research into brain changes in late adulthood and the factors that promote successful aging.

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CURRENT FUNDING

National Institutes of Health
UPMC Enterprises
Canadian Institutes of Health Research
Australian Research Council

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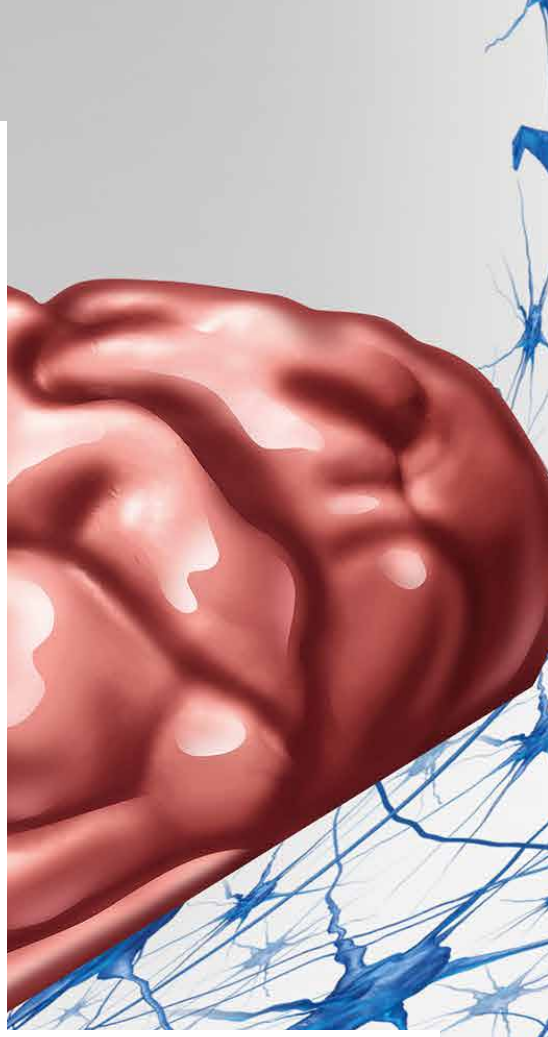
IGNITE

THE PSYCHOLOGY AND ETHICS OF MAXIMISING PERFORMANCE IN COMPETITIVE SPORTS

In sporting performance, developing a competitive edge over opponents is essential. **Professor Matthias Weigelt** at the University of Paderborn, Germany, specialises in the application of psychological theory and methods to the understanding and enhancement of athletic performance. Read on to discover how by taking a cognitive neuroscientific approach to understanding deceptive actions in sports, Professor Weigelt is unravelling the processes underlying expertise in responding to head fakes in basketball with critical ethical implications.



Don't Believe Everything That You See

In many sports, athletes use disguised or deceptive actions to increase their competitive edge against their opponents. When disguising an action, the athletes attempt to mask all indicators of their planned move, such as a volleyball player hiding for as long as possible whether he/she plays a smash or a lob. The head fake in basketball is a deceptive (or misleading) action, and occurs, for example, when a player passes to the right side, while simultaneously looking to the left side in a bid to hoodwink the other players as to their intended move. Similar manoeuvres can be found by competitors in a range of sports, including football, cricket, rugby, and martial arts.

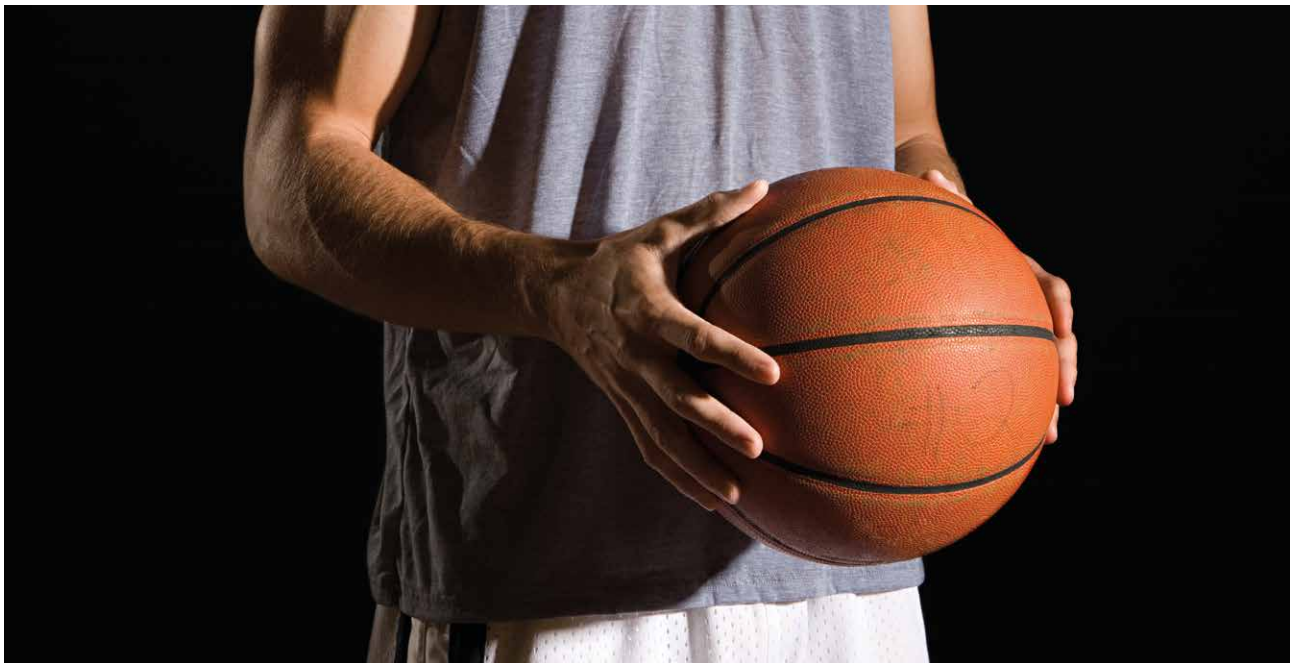
Research in this field has found that both skilled and unskilled participants can be fooled by deceptive actions. However, novices are more vulnerable to the effects than skilled athletes and suffer greater impairments to performance. For example, expert football players are better able to anticipate the direction of penalty kicks, and expert basketball players are better able to determine whether another player will pass the ball or fakes a pass to a teammate. It has been argued that the greater visual and motor expertise of skilled athletes contribute to their increased anticipation skills and ability to react accordingly.

The embodied cognition literature proposes that observing actions leads to activation of the so-called mirror neuron system in the brain. This simulates the observed actions in the absence of completing that action oneself. Mirroring an observed action in this way is important for understanding the actions of others, predicting the actions of others, and also for inferring the action intentions of others.

The role of expertise in the recognition of deceptive actions and the underlying cognitive processes remain a key focus in both the sports psychology literature and for our understanding of human cognition more generally.

The Importance of Context

Professor Matthias Weigelt at the University of Paderborn, Germany, takes a cognitive neuroscientific perspective in researching deceptive actions in sports. Noting the differences between experts compared to non-expert athletes in their responses to deceptive actions and the experimental evidence suggesting that neither perceptual nor motor expertise can fully explain why experts are better at discriminating deceptive actions than non-experts, Professor Weigelt has sought to understand the role of context, using the head fake in basketball as a paradigmatic example.



Contextual, or situational information, plays an important role in our processing of complex actions. The probability of an opponent conducting a specific action depends on a number of factors, including the current tactic of the team, the game score, and so on. At higher levels of competition, participants will likely know about the preferences and tendencies of their opponents in specific situations and this is also likely to influence their expectations about action outcomes.

Professor Weigelt and colleagues recruited healthy male and female volunteers without specific basketball expertise. They were presented video sequences of trials of basketball players passing the ball to the left or the right side, either with or without performing a head fake, in three experimental head fake frequency groups (20% fake-frequency, 50% fake-frequency, and 80% fake frequency). They were instructed to respond to the player's pass direction as quickly and as accurately as possible, while ignoring the gaze direction of the player. It was of interest under which frequency schedule participants' reactions to head fakes were slower, signifying a larger head-fake effect.

The head-fake effect was found for all three fake frequency schedules – that is, participants typically fell for the manipulation of head orientation regardless of the frequency of this. However, the head-fake effect was larger in the 20% fake-frequency group than in the 50% and in the 80% fake-frequency group. This overall pattern indicates that global context played a more important role than local context, which was assessed by analysing participants' responses in relation to the previous trial they had been presented. When incongruency between trials (i.e., frequency of head fakes) was lower, reactions times were faster and vice versa. In other words, participants' overall expectations about the frequency of head fakes changed their processing strategy, and not simply what they had viewed in the immediately preceding experimental trial.

Such modulations of the head-fake effect by context may be based on conflict monitoring processes, which happen in the dorsal anterior cingulate cortex (ACC), a brain area which detects conflict in information processing and triggers adjustments in cognitive control by projecting the information to different brain areas, such as the prefrontal cortex, where the conflict will be resolved.

In a neuroscientific investigation, Professor Weigelt and colleagues used electroencephalography (EEG) to examine the neural processes underlying participants' performance under the different frequency schedules. The EEG signal showed a modulation of the N2 component (a neural signature of conflict detection in the ACC), depending on the frequency schedule. Specifically, the N2-component was strongly pronounced for head fakes during the low frequency schedule (20% fake-frequency), which shows the neural signature of conflict detection in the ACC when the head fake came rather unexpectedly, whereas the N2-component was absent when the head fake was normally expected during the high frequency schedule (80% fake-frequency).

Professor Weigelt and colleagues also found that the head-fake effect is still present after larger amounts of practice and that it occurs independent from explicit instructions to ignore the gaze direction, but they acknowledge that these findings require exploration, and also that replication of these findings in professional athletes would be an important next step.

A Different Story for Experts?

In a later study, Professor Weigelt and colleagues extended this work by comparing the head-fake effect in expert basketball players, football players, and non-athletes. Two potential accounts of the superior performance of expert athletes in overcoming head-fake effects informed this work.

The first account proposed that the accumulation of sustained practice and experience may mean that experienced athletes may be better able to discriminate relevant from irrelevant stimulus features. In other words, experienced athletes have developed the ability to generally suppress conflicting information and are therefore less distracted by the head fake relative to the other information available, such as other bodily movements by their opponent and their knowledge of their opponent's typical game tactics.

The second account proposed that experienced athletes may have developed greater control over their processing of irrelevant information (such as head orientation in the head fake). By demonstrating greater cognitive flexibility in terms of their focus (or weighting) on various factors and their relevance based on past experience (i.e., their experience of that opponent's previous behaviour), it may be that expert athletes are less susceptible to head fakes.

As before, participants were presented images of basketball players, who were looking to the left or right, while passing the ball in the same or the opposite direction, and their task was to indicate the pass direction as quickly and as accurately as possible, while ignoring the player's gaze direction.

Professor Weigelt and colleagues found, once again, seemingly robust evidence for the head-fake effect, and that this was independent of expertise (that is, being an expert basketball player, expert football player, or non-athlete). However, closer inspection of the data indicated some important facets. The head-fake effect disappeared for the basketball experts – but not in football players or non-athletes – when the immediately preceding trial had been a head fake. This suggests that the basketball experts were either able to ignore the irrelevant information from gaze when it had found to be futile in the previous trial, or bolster attention towards more task-relevant information following the presentation of conflicting evidence in the previous trial.

In terms of the two theoretical accounts originally proposed, data from this study could not confirm which one is correct. Furthermore, as Professor Weigelt and colleagues suggest, the two accounts are not mutually exclusive and further research is required to untangle the cognitive processes underlying the effects of expertise on responding to head fakes. However, from a practical perspective, findings provide further evidence for the effectiveness of head fakes as a strategy in basketball, albeit one to be used with caution given that experienced basketball players develop the ability to overcome the effects of head fakes when these are repeated.

The Inside Story

To better understand the cognitive processes underlying responding to head fakes, Professor Weigelt and colleagues conducted a novel neuroscientific investigation. Non-invasive brain stimulation techniques, such as transcranial direct current stimulation (tDCS), temporarily alter neural activity in specific brain regions and in this way, modulate cognitive performance.

An established literature in cognitive neuroscience indicates that interference processing and conflict resolution (such as proposed to be required in responding to head fakes) is specifically associated with left dorsolateral prefrontal cortex activity in the brain.

Professor Weigelt and colleagues recruited healthy, novice basketball players, who underwent a head fake task, based on those used in their earlier studies, but adapted for use with the tDCS method. Anodal tDCS or cathodal tDCS was applied to either activate or deactivate the left dorsolateral prefrontal cortex, respectively. The key finding was that in comparison to cathodal tDCS, anodal tDCS decreased the reaction times to head fake trials.

Theoretically, this finding suggests a key role for the left dorsolateral prefrontal cortex in influencing performance in response to head fakes, consistent with the literature in cognitive neuroscience in which anodal tDCS stimulation has been found to improve performance on several cognitive tasks.

'Brain Doping'?

This experimental work highlights the possibility of using neuroenhancement techniques, such as tDCS, to increase athletic performance in competitive sports. There are already some examples of the application of this in the sporting arena, including the use of a tDCS intervention to improve the performance of Olympic skiers in the USA.

Professor Weigelt and colleagues argue that the effects of tDCS can be inconsistent and unreliable on an individual basis, which presents a methodological concern in utilising this approach. But more importantly, we are faced with an ethical question – is increasing the performance of athletes using neuroenhancement something we wish to endorse? In addition to advancing our understanding of the cognitive processes underlying sporting expertise, Professor Weigelt and colleagues emphasise the need for critical debate surrounding the ethics of modifying the performance of competitive athletes.

Meet the researcher

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Professor Matthias Weigelt studied sport science, social sciences, and psychology at the universities in Jena (Germany), Charlottesville (USA), and Reading (UK). He completed his doctoral program in psychology, neuropsychology, and sport science at the Ludwig-Maximilians-Universität Munich and completed his PhD at the Max Planck Institute for Human Cognitive and Neurosciences in 2004. After completing postdoc positions at the City Hospital in Munich-Bogenhausen and at the University of Bielefeld, he was called to the Saarland University and became a Professor of Sport Psychology in 2010. One year later, Professor Weigelt moved to the University of Paderborn, where he is now the head of the Psychology and Movement Science Group. His well-funded research focuses on both basic and applied topics of human performance in daily activities, clinical settings, and sports. Currently, Professor Weigelt is the Vice President for Research and International Affairs of the German Society of Sport Psychology and one of the editors of the German Journal of Exercise and Sport Research.

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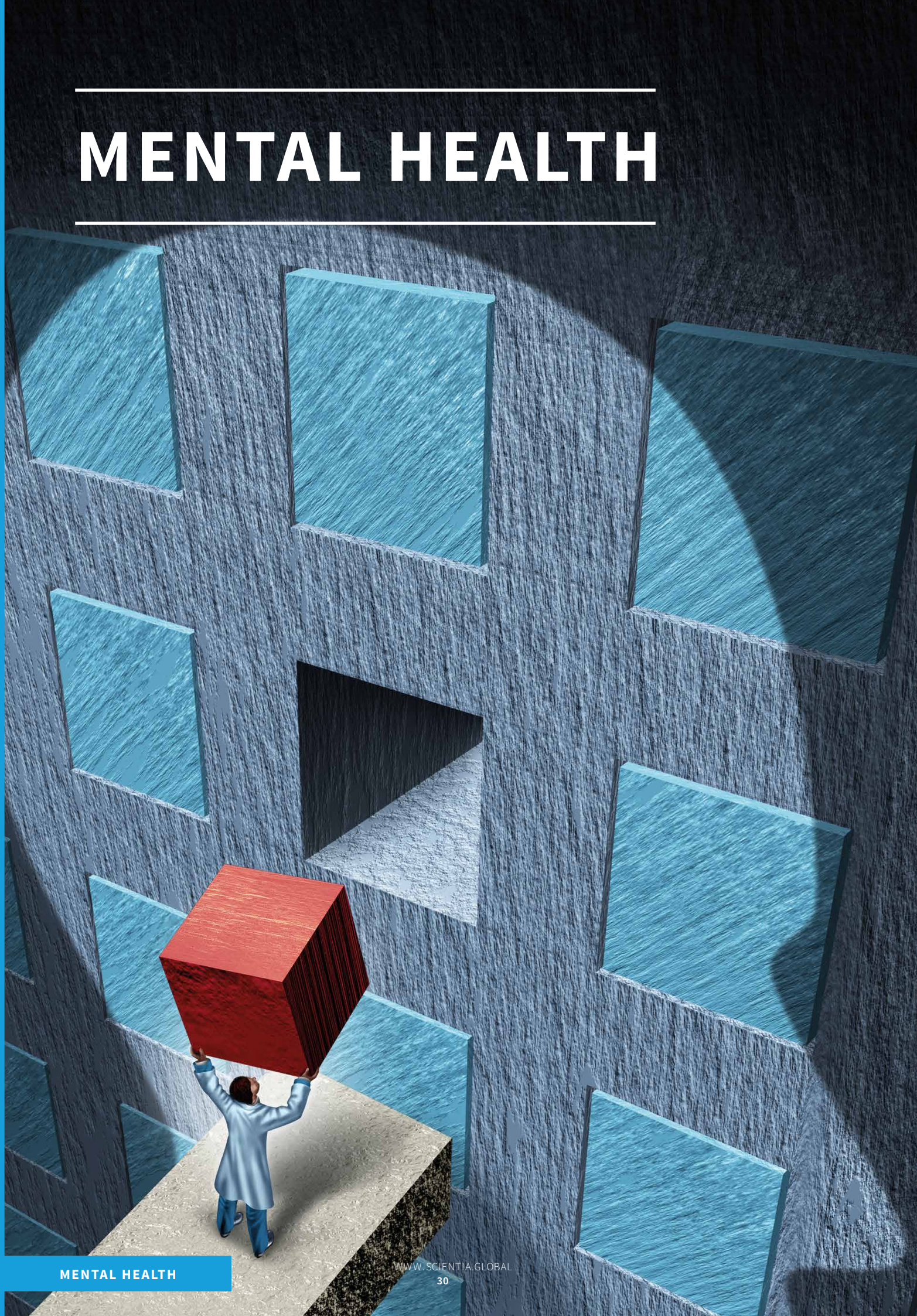
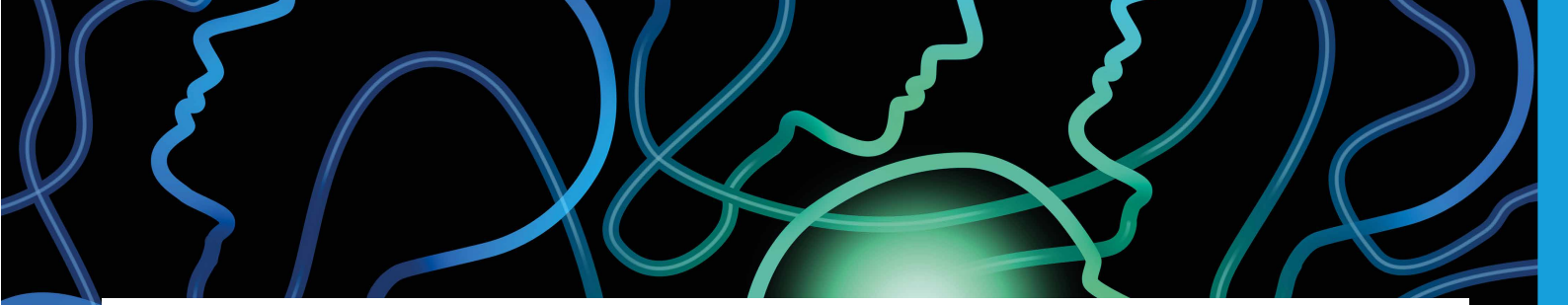
PADERBORN UNIVERSITY

MENTAL HEALTH





KEY ADVANCES IN IMPROVING MENTAL HEALTH ACROSS THE GLOBE

The second section of this critical issue of Scientia showcases the important work of researchers in the field of mental health. Positive mental health is critical to our wellbeing, yet difficulties are sadly commonplace, which can place tremendous burdens on individuals, their families, the economy and society more broadly. In the UK, it is estimated that one in four individuals will face mental health difficulties in any given year. These range from PTSD and common problems such as anxiety and depression, to more severe conditions such as bipolar disorder and schizophrenia. In the current context of the global COVID-19 pandemic, mental health difficulties are increasing and better understanding and ultimately improving mental health is more important than ever.

We open this section with an exclusive interview with Dr Rozainee Khairudin, President of the Malaysian Psychological Association (PSIMA). We read of PSIMA's vital work in establishing psychology as a profession in Malaysia and, in particular, their important work addressing the impact of the pandemic on the psychological well-being of the people of Malaysia. We are reminded of the truly global scale of COVID-19 and the power of the global response to challenge and uncertainty.

Common mental health conditions such as anxiety disorders are the focus of Professor Christine Larson at the University of Wisconsin-Milwaukee. By improving our understanding of the relationship between brain function, cognitive processing and emotion, Professor Larson is identifying new and more effective treatment targets. We also read of her most recent work looking to better understand posttraumatic stress disorder (PTSD), a condition that is prevalent yet often severely debilitating. Dr Raymond C. Rosen, Dr Brian P. Marx and Professor Terence M. Keane at the National Center for PTSD at the Department of Veterans Affairs in Boston, Boston University and Healthcore – New England Research Institutes also work in the field of PTSD. We read of their long-term observational research investigating PTSD symptom trajectories among veterans who have served in Iraq and Afghanistan, and how this may benefit treatment, identification of risk factors and diagnosis of PTSD in the future.

We then turn to the important work of Dr Colleen Carney at Ryerson University, Canada. Poor sleep is a common difficulty issue for teenagers and young adults. Unfortunately, the impact of poor sleep is substantial and is associated with the development of mental health difficulties. We read how Dr Carney has developed an innovative app to alleviate sleep problems in teenagers and young adults which has already provided promising results.

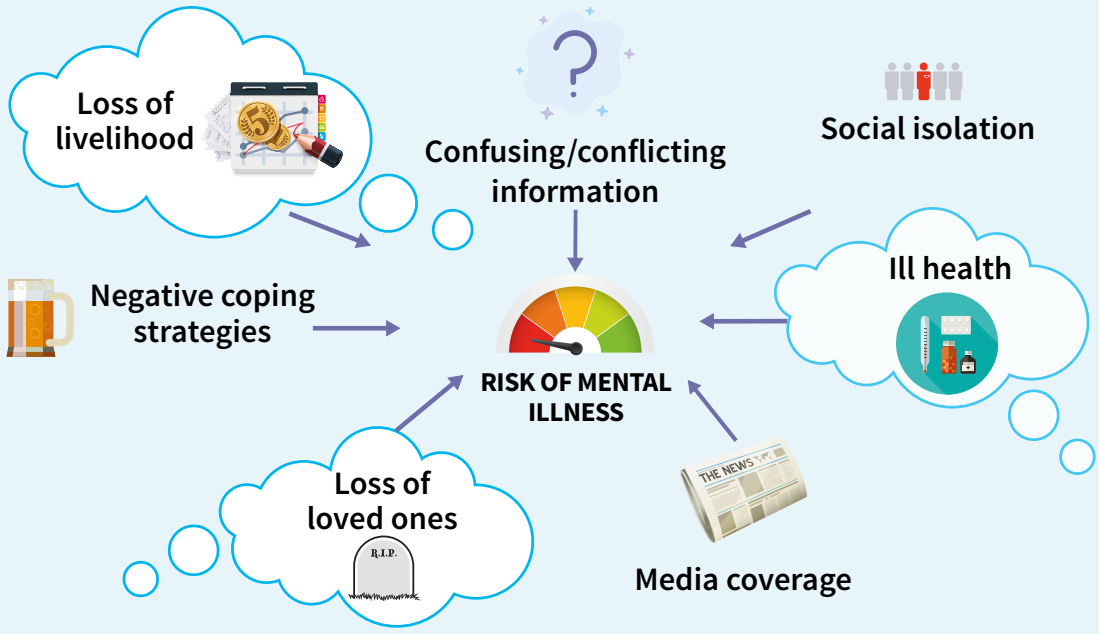
More effective treatments for severe mental health conditions such as schizophrenia are needed as a matter of priority. Dr Samuel Clark at Terran Biosciences Inc and his colleagues at Stony Brook University, New York, are working to achieve exactly that. We read how they are investigating the potential of blocking the kappa receptor in the brain to reduce the symptoms of the disease and their plans to extend this work to other psychiatric diseases.

Consistent with the focus on breaking new ground in psychiatry, Professor Susan Voglmaier of the University of California, San Francisco, combines research and training in psychiatry and neuroscience through running an active laboratory. We read how Professor Voglmaier believes that by building a better understanding of the brain biochemistry and molecular mechanisms of neuropsychiatric disease, the development of specialised treatments will also be driven forward.

We conclude this section on Mental Health with an exclusive interview with Oliver Glick, Policy Officer at the Children and Young People's Mental Health Coalition. This UK-based organisation brings together more than 200 leading charities with the aim of bringing together the sector's voice, experience and campaigns. We read of their impressive achievements over the past decade as well their future plans, and take time to consider how children and young people in the UK have been affected by COVID-19.

IMPACT OF THE COVID-19 PANDEMIC ON MENTAL HEALTH

Triggers for Anxiety and Common Fears About COVID-19



People Already Living with Mental Illness

80% said that COVID-19 and the measures to contain it have made their mental health worse

47% said that their mental health had become worse because they are now receiving less support from mental health services

36% said they had not booked or attended medical appointments which they felt they should have due to worries about catching the virus, burdening the NHS or because appointments were unavailable

(~800 people surveyed by Rethink Mental Illness in the UK)

Individuals May Develop a Mental Illness for the First Time

Specific at-risk groups:

People with pre-existing medical conditions

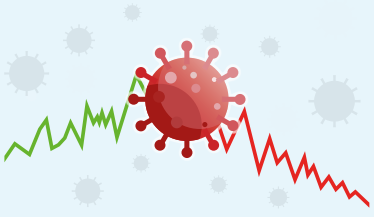
Children and young people

Older adults

Pregnant and new mothers

Healthcare workers

Healthcare Workers During COVID-19 Pandemic
Canada: 47% reported the need for psychological support
China: High rates of reported depression (50%), anxiety (45%) and insomnia (34%)
Pakistan: Moderate (42%) to severe (26%) psychological distress reported
(UN Policy Brief)



The Future for the UK?
The economic impact of COVID-19 is predicted to:
- Result in an additional **500,000** people experiencing mental illness
- **Exacerbate inequality** between demographic and ethnic groups
- Increase rates of **suicide**

Sources: United Nations Policy Brief: COVID-19 and the Need for Action on Mental Health; Rethink Mental Illness; British Medical Association; Centre for Mental Health (UK); NIHR Maudsley Biomedical Research Centre

MALAYSIAN PSYCHOLOGICAL ASSOCIATION

The Malaysian Psychological Association was established in 1988 to promote the field of psychology in the country. In this exclusive interview, we speak with Associate Professor **Dr Rozainee Khairudin**, President of the Malaysian Psychological Association, to hear about their critical work in developing psychology, which during the global COVID-19 pandemic, is more important than ever.

To begin, can you tell us how the Malaysian Psychological Association was established?

The Malaysian Psychological Association (PSIMA) is registered with the Registrar of Societies Malaysia (Jabatan Pendaftaran Pertubuhan Malaysia; PPM-002-10-24031988). The establishment of PSIMA was initiated by several psychologists. It all started in 1980 with a discussion between several psychologists who were attending a seminar at the National University of Malaysia (UKM; Universiti Kebangsaan Malaysia). Later, in 1983, the Department of Psychology at UKM organised an international conference on Cross-cultural Psychology. Here, some of the local psychologists continued discussing the potential for setting up the association. Finally, in 1988, the association was officially launched, and this event was attended by 24 psychologists. Several members, especially the counselling psychologists and educational psychologists, were also involved in the drafting of the Counsellors Act 1998, the result of which counsellors and counselling psychologists can register as counsellors.

PSIMA was established to provide a platform for its members to meet and interact while encouraging them to practice psychology in accordance with ethical guidelines and a professional code of conduct. Currently, one of PSIMA's main priorities is to work with the Malaysian government to institute registration for professional psychologists to safeguard the profession of psychology and ensure a high level of service and ethical practice.

PSIMA approached the Malaysian Qualification Agency (MQA) in 2010 to set up Program Standards for Psychology. It was approved by the MQA Council and since 2013, all institutions of higher learning in Malaysia are required to follow set standards when designing psychology programs. Beginning in 2011, several psychologists from PSIMA were involved in drafting the Allied Professions Act (Akta Kesihatan Bersekutu) through which Clinical Psychologists can be registered as an Allied Health Professional, and this was approved by the Malaysian Parliament in 2016. In addition, PSIMA was established to encourage greater cooperation, coordination and partnership among the Malaysian universities' psychology departments to raise the standards of academic programs and encourage more research collaborations in Malaysian psychology.

To fulfil the purpose of establishing PSIMA as a professional non-governmental organisation, various conventions, seminars and conference

Figure 1.
Poster on Awareness and Psychological Health Care During the COVID-19 Pandemic Published by PSIMA.

have been organised over the past years to gather professionals and students in the psychology professions from local areas and overseas. To date, PSIMA has more than 1,000 members from across the country as well as international members.

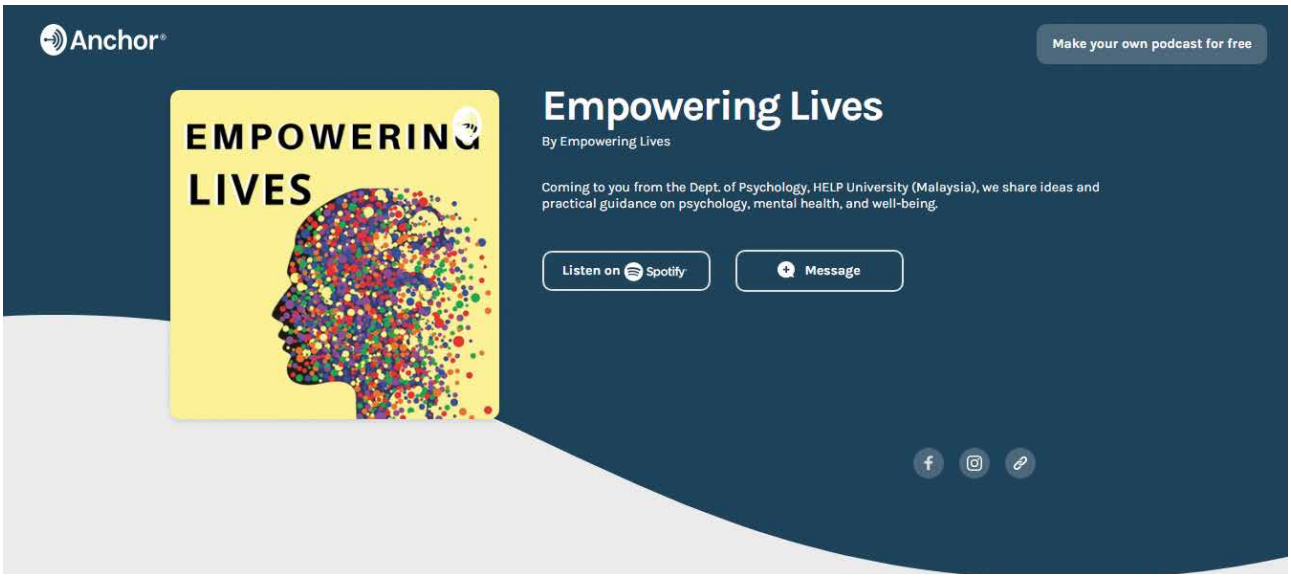


Figure 2.

Figure 3.

What is the overarching vision at the Malaysian Psychological Association? As President, what are your aims for the future of psychology in Malaysia?

The overarching vision of PSIMA is to provide a platform for its members to meet and interact while encouraging them to practice psychology in accordance with our established ethical guidelines and professional code of conduct.

As President, my aim for the future of psychology in Malaysia is that the field can serve the people not only in providing education in the field of psychology but also as a professional service in maintaining the psychological well-being of the community. Malaysia is a country that consists of very diverse ethnicity and culture. Psychology is about the minds and behaviours of people. With diverse backgrounds and cultures come different views and perspectives, partly attributable to differences in upbringing. Psychology can be the bridging platform to harmonise people from different backgrounds. Particularly, in times of crisis such as the COVID-19 pandemic, psychologists have to play the utmost important role in ensuring the mental health as well as the physical well-being of the people.

Psychology is a wide-ranging and varied field. How do you promote the education and training of psychologists given this diversity?

PSIMA has established an Academic Council Board. The president is the head of the board. This board consists of relevant PSIMA council members and all heads of department from all universities throughout Malaysia that offer psychology programs. The board meets at least three times each year. All matters relating to academic programs, including quality control, teaching and learning, and training, are discussed at this Board. In this way, PSIMA can successfully promote academic matters with regard to the diversity of psychology as a discipline in Malaysia.

Across the globe, the COVID-19 pandemic has highlighted the impact of challenging times on psychological as well as on physical health. What particular issues have you faced in Malaysia as a result of COVID-19? How has the Malaysian Psychological Association sought to address these?

Malaysians have not been spared by the pandemic. Some of the particular psychological issues that people in Malaysia are facing in these challenging times are cognitive distress and anxiety. The government enforced a Movement Order Control (MCO) from 18th March 2020 to contain the spread of the virus which was then extended to 28th April 2020. The uncertainty about the pandemic, coupled with the new routines that people have had to adapt to during the MCO imposed worry, anxiety and emotional instability. The enforcement also brought socio-economic sacrifices. The limitation of usual business resulting from the MCO imposed financial hardship on many people, leading to psychological distress.

What lessons do you think we might learn from the COVID-19 pandemic about sustaining our psychological health more generally?

What we might learn from the COVID-19 pandemic is that it is critical to sustain

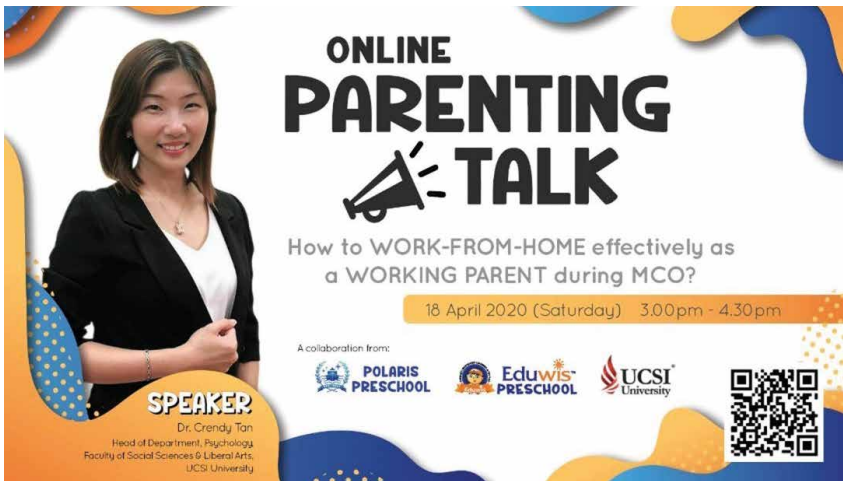


Figure 4.

not only our physical but also our psychological health. The COVID-19 pandemic has led to a global crisis. For most people, this has been a new and previously unexperienced type of life event. It is very easy for negative thoughts to crop up in our minds, but we need to fight those thoughts and try to be positive. Positive thinking can help in coping with such a crisis. We know that the uncertainty of things can make our mental health worse and that expectations can increase anxiety. Therefore, it is important that we stay resilient. Social support is also important for our psychological health and we should talk with others – one's spouse, siblings, parents, and children, for example.

Finally, how best might psychologists engage the general public in understanding the importance of psychology in our day to day lives?

One of the most important roles of psychologists is to convey the awareness of how prudent it is to have well-balanced psychological health. Psychologists are commonly known to cure those with troubled psychological well-being. However, psychologists can also promote psychological health to allow one to become an even better person. Psychologists should be the leaders in promoting well-being.

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Addressing Mental Health Needs in a Global Pandemic

The PSIMA has sought to address the impact of the COVID-19 pandemic in several ways. These approaches have included spreading awareness about the importance of psychological health to Malaysians, offering help for those who are facing psychological issues during the COVID-19 pandemic, using social media to promote psychological health and well-being, and undertaking research to investigate the impact of the COVID-19 pandemic on psychological well-being among Malaysians. These findings are contributing to the development of interventions and programs for Malaysians suffering from psychological impact during and after the COVID-19 pandemic.

The PSIMA has collaborated with Briged Bakti Negeri Selangor in conducting tele-psychotherapy for those affected by the COVID-19 pandemic crisis. The service is offered through the BBMSel-PSIMA Tele-PsychoTherapy Centre, using videoconferencing, WhatsApp video calls, telegram video calls, messenger video calls, and other video call applications. Cases are handled by professionals in clinical psychology and counselling.

A number of studies have and are still being conducted by PSIMA academic members to investigate the psychological impact of COVID-19 pandemic. The study titled 'The Perception, Stress and Psychological Distress of the Coronavirus Disease 2019 (Covid-19) among Malaysians after the Outbreak' has identified that greater worry about the COVID-19 pandemic is associated with greater levels of stress, anxiety, and depression. Further research studies are examining the relationships between mindset, personality and coping in combating anxiety during the COVID-19 pandemic.

To help address this impact on mental health, the psychology department at HELP University in Malaysia started a series of podcasts on psychological issues relating to COVID-19 (Figure 2) and other members of PSIMA appeared on radio and social media such as FBLive and other online apps to promote the importance of mental health (Figure 3). Advice has also been offered on how to work from home more effectively during these challenging times (Figure 4).

UNDERSTANDING BRAIN FUNCTION, COGNITION, AND EMOTION IN PSYCHOPATHOLOGY

Mental health conditions such as anxiety disorders significantly impact on the quality of life of sufferers, their physical health and psycho-social functioning. Given the high prevalence and extent of impairment inflicted on affected individuals, the economic cost to public health is substantial. **Professor Christine Larson** at the University of Wisconsin-Milwaukee, USA, seeks to identify new and more effective targets for intervention by better understanding the relationship between brain function, cognitive processing, and emotion.

From Survival to Pathology

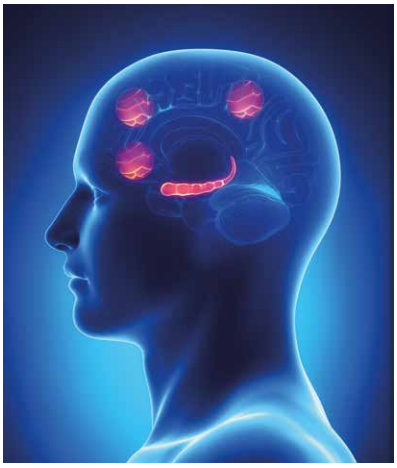
From an evolutionary perspective, our survival depends on the rapid identification of threats in the environment. Known as the fear response, this detection of threat occurs quickly and automatically without the need for detailed processing of the immediate situation. In a life or death situation, such as being faced by a predator, it is critical to react quickly and decisively to maximise the potential for successful 'flight or fight'.

In modern-day life, however, this mechanism may malfunction leading to psychopathological states, such as anxiety disorders. While some psychological unease and discomfort is an inherent experience at some periods through our lives, in more severe and extreme forms it becomes a pathological reaction, significantly impacting on the quality of life of sufferers, their physical health and also their psycho-social functioning. Symptoms of clinical anxiety, such as generalised anxiety disorder, include recurrent, intense worries and fears in relation to everyday situations accompanied by physiological responses such as shaking, sweating and difficulty in breathing.

Understanding the links between brain function, cognition, and emotion is fundamental to better understanding and treating common clinical disorders.

Fear and the Amygdala: Links to Anxiety

A large and established body of research implicates the amygdala, a small almond-shaped mass of cells in the brain, as being critical to fear responses. Laboratory research in animals has shown that lesions to the amygdala inhibit their usual fear responses to threat stimuli. In humans, neuroimaging studies of the brain have shown increased activation in the amygdala when participants are viewing negative stimuli, such as fearful faces.



Professor Christine Larson and her team at the University of Wisconsin-Milwaukee, USA, extended this work by using functional magnetic resonance imaging (fMRI) to explore the underlying relationship between dispositional anxiety and amygdala activity, and the links with performance on an emotional working memory task. Working memory is the mental process through which we hold information in mind for immediate use (such as when we rehearse a telephone number). Working memory

‘Our long-term goal is to characterise the neurobiology of cognitive-affective factors that confer risk for long-term distress in the aftermath of a trauma, ultimately with the goal of identifying individuals in most need of early intervention.’

has only limited capacity, and as such, there is only so much information we can hold in our immediate mind at any one time).

In the emotional working memory task used by Professor Larson and her team, threatening faces were used to assess the ability of participants to remove their working memory bias away from fearful stimuli in order to effectively hold neutral stimuli in working memory. The team found that heightened amygdala activity as assessed using fMRI was associated with poorer performance on the emotional working memory task, and that this effect was greater in those participants with higher dispositional anxiety, which was assessed using a self-report measure. These findings are important because dispositional anxiety is associated with increased risk for later developing clinical anxiety, and this seems to be driven by increased amygdala activity in response to threat.

Brain Networks Underlying Anxiety

Much work in laboratory animals has focussed on identifying the brain networks between different parts of the brain associated the learning of fear responses, and the unlearning of these –also known as fear extinction. As you might expect, the amygdala plays an important role, as do the parts of the brain associated with learning and memory, such as the hippocampus. Research in animals has shown that successful fear extinction depends on plastic changes in connectivity between these regions that happened during extinction learning. Much less work, however, has been conducted in humans so such changes in connectivity are not so well understood.

Professor Larson and her team conducted a study to address this by examining the underlying mechanisms of fear extinction in human participants. Participants underwent fMRI scanning to detect changes in connectivity between key brain regions of interest, including the amygdala and hippocampus, while completing established paradigms for the learning and extinction of fear responses. Unexpectedly, they found that participants with higher levels of dispositional anxiety did not demonstrate weaker fear inhibition connectivity pathways in the brain, but rather, a strengthening of the fear expression pathways during extinction training. In other words, for individuals with dispositional anxiety, a maladaptive strengthening of fear responding meant that attempts to reduce or extinguish this were unsuccessful.

Phobias, Fear, and the Amygdala

In a separate line of research, Professor Larson and her team explored whether phobic reactions may also depend on amygdala activity. A phobia is a specific type of anxiety disorder in which individuals have an intense and irrational fear of objects, places, or situations. Common examples of these include heights, spiders, and snakes. In

the UK for example, spiders are rarely venomous to the extent that they could harm a human, but spider phobia is extremely common. Although an individual with a specific phobia may know that their fear is irrational, they are unable to inhibit their excessive fear reactions associated with it, with a debilitating effect on their daily lives.

Using fMRI to assess amygdala activity, Professor Larson and her team compared the reactions of female participants who were either spider-phobic or non-phobic to pictures that contained either spider stimuli, negative stimuli, or neutral stimuli. By closely examining the time-course of amygdala activity in response to the pictures, they identified that the amygdala of spider-phobic individuals responded much more quickly to pictures of spiders than to the other types of pictures and also when compared to the non-phobic individuals. The researchers suggest that individuals with phobias are 'over tuned' to respond to information related to the target of their specific phobia.

The Underlying Brain Networks of a Personality Trait

Harm avoidance is a personality trait in which individuals tend to avoid specific situations that they perceive as being dangerous (rather than those that are objectively considered dangerous). An example might that of being overly concerned and worried about being in an unfamiliar situation that others feel comfortable about.

Personality traits, such as harm avoidance, reflect relatively stable characteristics associated with an individual over the course of their lifetime and for this reason, are likely to have established brain connectivity networks. However, much less is known about such brain connectivity networks than for diagnosable disorders such as anxiety and depression, which are likely to fluctuate in presence and severity over time.

Professor Larson and her team used fMRI to explore the connectivity between brain networks in a sample of young and healthy participants who had completed questionnaire measures of anxiety and harm avoidance and who were simply resting in the scanner (rather than completing any form of specific task as in their earlier studies). Previous researchers had identified disruption to several brain connectivity networks in depression and anxiety. To their surprise, Professor Larson and her team did not replicate these findings in terms of participants' dispositional anxiety, and there was no apparent relationship between anxiety and harm avoidance, suggesting that these are separate psychological constructs. However, they demonstrated that harm avoidance is associated with disrupted functional connections in key networks which the researchers suggest reflect difficulties in the ability of individuals to distract their attention from feared objects or situations.

Building on Progress

The work already conducted by Professor Larson and her team has shone new light on how anxiety disorders and specific personality traits are underpinned by specific brain activity and connectivity between regions. Understanding these underlying processes and how they relate to cognitive processing and emotion is critical to the development of novel and much-needed interventions for mental health difficulties.

Professor Larson and her team are taking all this work forward. They now plan to further unravel the individual differences in both anxiety and vulnerability to anxiety. They also plan to identify the genetics associated with the brain function correlates of key cognitive processes such as learning and extinction of fear responses in anxiety that they so elegantly demonstrated in their previous research.

Finally, Professor Larson and her team are also turning their attention to posttraumatic stress disorder (PTSD), a psychiatric disorder that for some individuals, develops in the aftermath of trauma. PTSD is associated with significant distress and impairment, high rates of co-morbidity with other disorders such as anxiety and depression, as well as risk of suicidality. Exposure to trauma is extremely common and not everyone exposed to trauma develops PTSD. What is critical is that we don't know what factors in the immediate post-trauma period predict the development of later PTSD for an individual.

Professor Larson and her team now plan to utilise their extensive knowledge base and experimental methodologies to better understand which individuals are at risk of developing PTSD after trauma. In a concluding note, Professor Larson explains, 'Our long-term goal is to characterise the neurobiology of cognitive-affective factors that confer risk for long-term distress in the aftermath of a trauma, ultimately with the goal of identifying individuals in most need of early intervention.'

Meet the researcher

Professor Christine Larson
Department of Psychology
University of Wisconsin-Milwaukee
Milwaukee, WI
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Professor Christine Larson completed her PhD in clinical psychology at the University of Wisconsin-Madison in 2003. Following a position at Michigan State University, Professor Larson returned to Wisconsin at the University of Wisconsin-Milwaukee in 2007 in the role of Assistant Professor. Here, she rapidly rose through the academic ranks and is now Professor of Psychology as well as Director of Clinical Training. With her research group, she explores the cognitive-affective processes associated with psychopathology using multimodal neuroimaging, electrophysiological, behavioural, and molecular genetic techniques. Professor Larson has attracted substantial funding to support her work and has published more than 60 peer-reviewed papers and three invited book chapters to date. She has received numerous honours and awards, and in 2016 was elected Secretary of the Society for Psychophysiological Research.

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CURRENT FUNDING

National Institute of Mental Health
National Institute of Health
Medical College of Wisconsin
Marquette University Innovation Fund

FURTHER READING

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PROJECT VALOR – EXPLORING PTSD RISK FACTORS AND OUTCOMES IN COMBAT-EXPOSED VETERANS

Posttraumatic stress disorder (PTSD) is a prevalent and often debilitating condition that follows exposure to a traumatic experience and can result in depression and increased suicide risk in vulnerable individuals. Researchers at the National Center for PTSD at the Department of Veterans Affairs in Boston, Boston University and Healthcore – New England Research Institutes are conducting a long-term observational study investigating PTSD symptom trajectories among male and female veterans who served in Iraq and Afghanistan.

PTSD Among Combat-exposed Veterans

PTSD is an often-debilitating mental disorder that usually develops as a response to one or more traumatic events. Men and women serving in combat situations are at particular risk for trauma exposure – either themselves or among their fellow combatants.

The recent revision of the Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-5) divides PTSD symptoms into four clusters: intrusive thoughts, avoidance, negative alterations in cognitions and mood, and changes in arousal and reactivity. Individuals who develop the disorder tend to re-live their traumatic experiences in the form of intrusive thoughts, nightmares, and/or flashbacks. They can also display feelings of isolation, anxiety, irritability, and guilt.

PTSD is particularly common among war veterans, as their job often involves exposure to crude acts of violence and brutality, as well as death. The condition is most often chronic, although the determinants of remission or relapse are not well understood.

Research investigating trends in PTSD among combat-exposed army veterans is of crucial importance, as it can help to gain a better understanding of how the disorder develops and manifests itself in different individuals over time. Given the growing number of women who join the military, studies have also started exploring the nature and extent of gender differences in PTSD-associated symptoms.

PTSD has sometimes been described as 'a signature injury' for men and women returning from serving in Iraq and Afghanistan, with researchers estimating its prevalence to be around 10–18%. Yet studies exploring PTSD symptom trajectories and gender differences among veterans who served in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) are still somewhat limited.

To address these unexplored areas of research, an interdisciplinary research team from the National Center for PTSD, United States Department of Veteran Affairs Boston (VA Boston), Boston University School of Medicine, and HealthCore – New England Research Institutes have designed and are conducting a unique long-term study of the natural history and outcomes of PTSD among combat-exposed veterans who served in Iraq and Afghanistan.

Project VALOR

Project VALOR (Veterans' After-discharge Longitudinal Registry) is a long-term observational study developed in response to the need for more in-depth data and a better understanding of the risk factors and resilience predictors among veterans with PTSD. This study is fielded by a highly trained and dedicated research team led by three co-principal investigators, two of whom represent the National Center for PTSD, VA Boston, and Boston University (Drs Terry Keane and Brian Marx) and a third, Co-Principal Investigator, Dr Raymond Rosen, former Professor of Psychiatry and Psychology at Rutgers University, and Principal Scientist at HealthCore – New England Research Institutes.

'The project represents a uniquely successful collaboration between researchers at the National Center for PTSD at the VA Boston Healthcare System and HealthCore – New England Research Institutes, a private, non-governmental research organisation,' they explain. 'This highly productive

public and private collaboration has resulted in two dozen peer-review publications and more than 70 scientific presentations at professional conferences and meetings.'

The project was designed following the Agency for Healthcare Quality and Research's recommendations for longitudinal disease registries. The high level of involvement of participants and effective retention over a long follow up period, in addition to the comprehensive, interview, self-report and medical record data analyses, are unique features of the study. The very broad and in-depth type of data collected by the researchers as part of the primary goal of the VALOR registry allowed them to test multiple hypotheses and research questions related to long-term trajectories or outcomes of PTSD in combat-exposed veterans.

Unique Design and Methodological Features

- First comprehensive, gender-balanced longitudinal study of PTSD outcomes in combat-exposed veterans returning from Iraq and Afghanistan.
- Most comprehensive assessment to date of medical records, interview data and self-report questionnaires from more than 1500 combat exposed veterans.
- Longitudinal data collected at four separate time intervals between 2008 and 2016.
- Multivariate trajectory analyses to assess outcome pathways and predictors.
- Inclusion of a large comparison group (400) of male and female veterans without PTSD.

Gender Similarities and Differences in PTSD Trajectories

The primary aims of Project VALOR were to examine trajectories of PTSD symptomatology and diagnosis – the nature and the extent of military sexual trauma and associations of PTSD with mild traumatic brain injury, major depressive disorder, and suicidal ideation among combat-exposed women and men. After analysing the data collected from participating veterans, the researchers found risk factors and outcomes of PTSD to be remarkably similar across different genders, for all but one assessed factor.

They explain that: 'Female veterans have many of the same psychological reactions to PTSD and share many of the same risk factors as men, with one notable exception – female veterans report substantially higher rates of military sexual trauma than their male counterparts.' Health-related quality of life, a term that describes the quality of psychosocial functioning within and across domains (such as work, relationships and education), was generally similar in participating veterans with PTSD, regardless of their gender.

PTSD was associated with reports of lower mental and physical health-related quality of life for both male and female combat-exposed veterans. The researchers also found that, 'suicide potential is significantly greater in both male and female veterans with more intense combat experiences, and among those with a history of mild traumatic brain injury, and depression, in addition to symptoms of PTSD.'

Both male and female veterans with PTSD also reported long-term physical changes, termed 'premature ageing', which included features of a metabolic syndrome, such as weight gain, blood pressure and cholesterol increase, and greater risk of type two diabetes.

Assessing the Validity of Diagnoses

In additional studies, the researchers used the data from the VALOR registry to investigate whether diagnoses recorded in the participants' electronic medical databases matched those gathered using diagnostic interviews and self-report questionnaires. 'Although most veterans were confirmed with a diagnosis of PTSD, according to interviews by trained research staff, a notable minority (~15%) do not have a PTSD diagnosis in their medical records,' explain the researchers. 'Conversely, some veterans with PTSD diagnoses in their medical records do not meet criteria for the diagnosis when interviewed by research staff.'

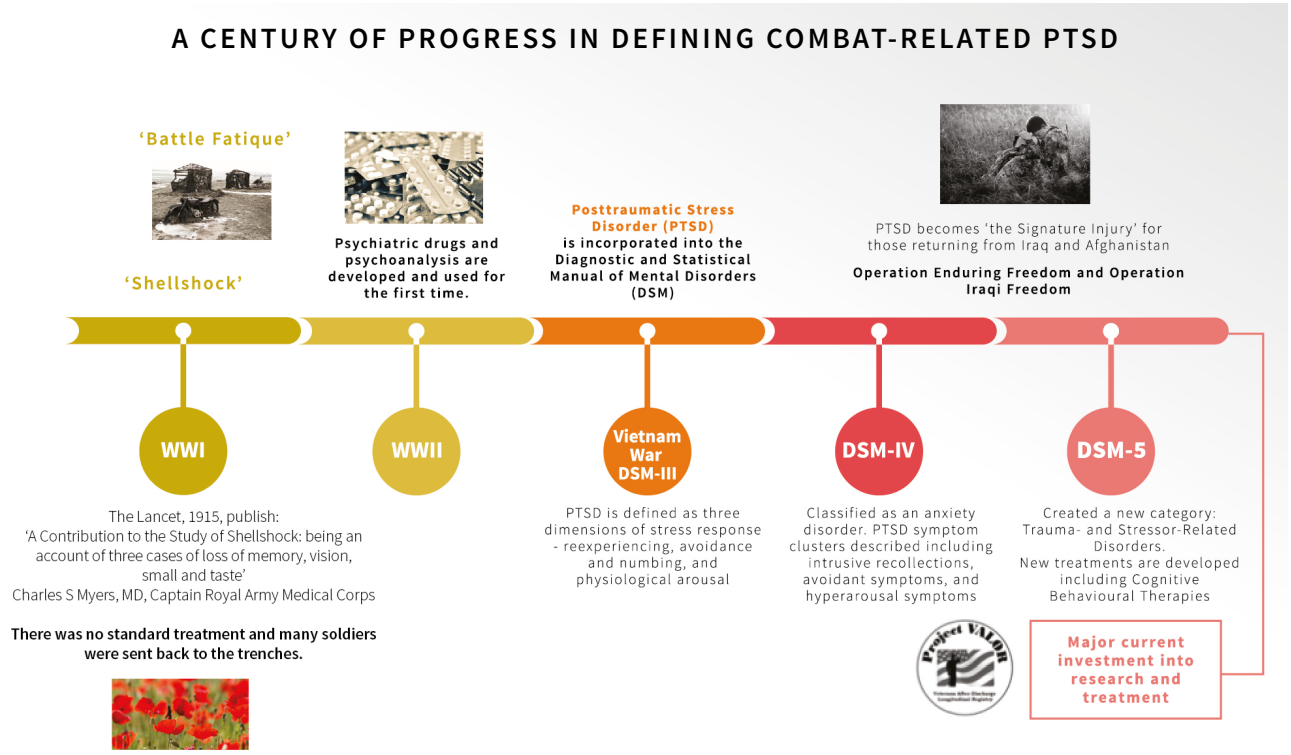
Study participants who had false-negative PTSD diagnoses, meaning they were initially not diagnosed but were found to have PTSD using the researchers' diagnostic measures, were more likely to report lower levels of combat exposure, panic, and PTSD avoidance symptoms. Candidates with false-positives, whose PTSD diagnoses were not confirmed by the interviews and questionnaires, were more likely to have sought treatment for emotional problems and reported less functional impairment.

On the other hand, the majority of veterans with concordant diagnoses (i.e., true positives) reported severe symptoms and other co-existing conditions, such as depression or substance abuse. Overall, individuals who presented the most and least severe symptoms in the diagnostic interview were more likely to have matching past and present diagnoses.

A Valuable Data Registry for PTSD-related Research

Project VALOR is a carefully designed and timely registry study that collected data to help better evaluate the clinical course and health outcomes of PTSD in combat-exposed veterans returning from Iraq and Afghanistan.

A CENTURY OF PROGRESS IN DEFINING COMBAT-RELATED PTSD



The data registry compiled by Dr Rosen, Dr Marx and Dr Keane is a uniquely useful resource, designed to assist researchers, military leaders, and treatment providers who are looking to better understand PTSD and related problems among combat-exposed veterans.

Studies carried out by Drs Keane, Marx, and Rosen revealed important information about diagnostic accuracy and the determinants of discordance between research and clinical diagnoses, as well as gender differences (relatively few) and the long-term associations and consequences of PTSD (relatively many). Those with more severe symptoms were less likely to be misdiagnosed, in addition to veterans with other medical or psychiatric conditions.

Signs of traumatic brain injury (TBI) were evident in three of four (74.8%) male veterans with PTSD, and almost half (48.0%) of female veterans with PTSD had also showed signs of TBI. Among the women, approximately one-quarter of female veterans (28.8%) had personal experience of military sexual assault. Among male veterans, evidence of traumatic brain injury was predictive, along with PTSD symptoms and signs of depression, of a significant increase in suicidal thoughts and urges.

Future plans for the registry include, 'determining the long-term impact of medical and psychological treatments for VALOR participants with PTSD and examining other biological and psychological sequelae to long-term PTSD exposure,' says the team of researchers. The VALOR registry has already contributed important new data on the association of metabolic syndrome and premature ageing in both male and female veterans with PTSD.

Highlights of Study Findings

- Female veterans have similar sequelae and PTSD outcome trajectories to male veterans, despite a higher reported prevalence of military sexual trauma than their male counterparts. Signs of premature ageing were observed in both male and female veterans with PTSD.
- Veterans with PTSD had markedly elevated rates of depressed mood, sleep difficulties and interpersonal problems compared to the non-PTSD group. Veterans with PTSD also had higher rates of minimal brain injury (mTBI) compared to those without PTSD.
- The team observed a mismatch rate of about 30% between the medical records and interview-based diagnoses of PTSD. Approximately half of the mismatched diagnoses were in the direction of false positives, and half were in the false negative direction (i.e., diagnosis on interview, but not in the medical record).
- Suicide risk was significantly greater in both male and female veterans with more intense combat experiences, and among those with a history of mild traumatic brain injury with or without depression.

The investigators plan to continue their analysis of long-term outcomes or trajectories of care among veterans with or without disability benefits, and among those engaged in medical or psychological treatments. Researchers are likely to continue using the data to identify long-term trends in PTSD symptoms and sequelae among male and female returning veterans. Eventually, this could lead to better-tailored treatments, more reliable diagnoses, and to the identification of specific PTSD risk factors.

Meet the researchers

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Former Professor of Psychiatry and Medicine
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Dr Raymond C. Rosen is a Principal Research Scientist at HealthCore/ New England Research Institutes and former Professor of Psychiatry and Psychology at Rutgers University, New Jersey. He had undergraduate training at the University of Witwatersrand, Johannesburg, South Africa and received his PhD in Clinical Psychology from State University of New York at Stony Brook in 1972. He served as Chief Psychologist and Associate Dean at Rutgers Medical School from 1995–2005, prior to joining New England Research Institutes in 2006. His major areas of research include mental health disorders and treatments, with a special focus on Post-Traumatic Stress Disorder (PTSD), insomnia and other sleep disorders, patient outcomes and quality of life, and men's and women's sexual health. Dr Rosen has designed and directed several large, longitudinal registry studies of health outcomes, including Project VALOR.

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Brian P. Marx, PhD, is a professor at Boston University. He holds a BS in Psychology from Boston University and a PhD in Clinical Psychology from the University of Mississippi. Dr Marx has worked as a professor at several universities, including Oklahoma State University, the University of Oklahoma, Temple University, and Boston University. For over a decade, he has also been working as a staff psychologist at the National Center for PTSD at the Department of Veterans Affairs (VA) Boston. Over the course of his career, Dr Marx has received multiple awards, honours and grants and has a large number of publications in his name, exploring his primary research interest, Post-Traumatic Stress Disorder (PTSD).

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Terence M. Keane, PhD, is a Professor and the Assistant Dean for Research at Boston University. He has attained a BS in Psychology from the University of Rochester, as well as an MA and PhD in Clinical Psychology from Binghamton University. Dr Keane has worked as a Professor of Psychiatry at the University of Mississippi Medical Centre, Tufts University School of Medicine and Boston University. He has also covered positions in Veteran Affairs medical centres and is currently the Director of the Behavioral Sciences Division at the National Center for PTSD and the Associate Chief of Staff for Research & Development at the VA Boston Healthcare System.

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PROJECT WEBSITE

http://www.projectvalor.net/

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THE DOZE APP: A UNIQUE APPROACH TO OVERCOMING SLEEP PROBLEMS IN YOUNG ADULTS

Poor sleep is a common difficulty issue for teenagers and young adults worldwide. Unfortunately, the impact of poor sleep is substantial with clear links to mental health difficulties. **Dr Colleen Carney**, an Associate Professor and the Director of the Sleep and Depression Laboratory at Ryerson University, Canada, is committed to helping people sleep better. Dr Carney has recently turned her expertise to the development of an innovative app to alleviate sleep problems in teenagers and young adults.

Sleep Issues in Early Adulthood

Sleep problems are a significant issue in early adulthood, with around two-thirds of young adults reporting some sort of sleep issue. Typical issues include difficulty either falling or staying asleep, falling asleep at unhelpful times such as during the day, and feeling the need to sleep for extended periods when possible, such as weekends.

Teenagers are particularly susceptible to sleep problems due to their natural shift towards later sleep times and the requirement to maintain early rise times to attend school. This delayed circadian rhythm related to a teenager's sleep pattern is confounded by increased sensitivity to evening light and peers reinforcing activities that take place later in the day. As a result, teenagers can suffer from pathological levels of sleepiness and insomnia.

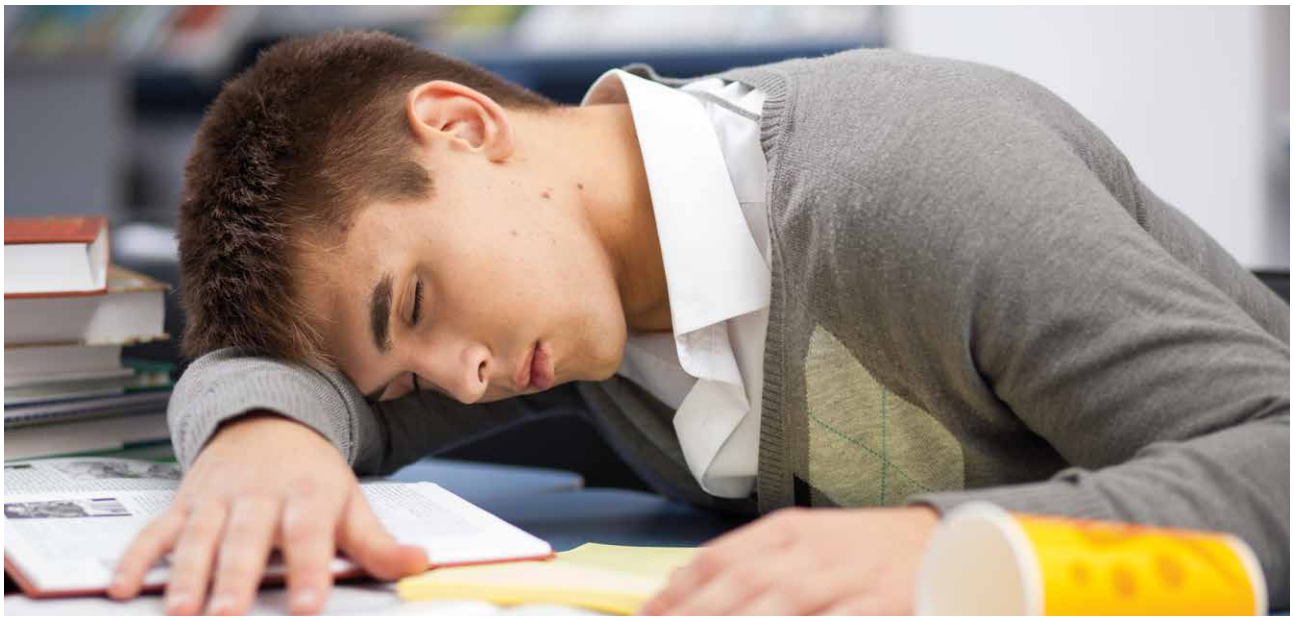
Insomnia is defined clinically as a difficulty falling asleep or staying asleep on a regular basis, and is associated with an increased risk for poor mental functioning, depression, substance abuse, and even suicide. Indeed, over half of young adults who suffer from insomnia also have a mental health disorder. Studies have shown that treating insomnia directly can help manage or even prevent the onset of depression and other mental illnesses. It is therefore critical for the well-being of teenagers to find a way to improve their sleep and to encourage long-term good sleep habits.

Cognitive Behavioural Therapy for Sleep

Dr Colleen Carney, an Associate Professor at Ryerson University and the Director of the Sleep and Depression Laboratory at the same institution, has developed with her team a free, evidence-based sleep app called 'DOZE' to help improve sleep in young adults.

Although we know that improving sleep benefits mood and alertness across the board, finding the most appropriate intervention for young adults is particularly challenging. Current interventions targeted at adults are inappropriate as they do not address the pubertal shift towards later bedtimes, and treatments for children focus on parental control

‘Despite lots of fatigue, insomnia and struggles with mental health, very few were seeking professional help – this was the impetus for the app and self-management.’



over bedtimes, which for teenagers, are overly prescriptive. The DOZE app addresses these gaps in the provision of sleep interventions for young adults by utilising self-management and principles of cognitive behavioural therapy (CBT), already known to be effective in improving sleep.

CBT is an evidence-based psychological intervention that assumes that changing thoughts, attitudes, and behaviour can have an impact on physiology, and the way people feel. Through identifying thinking that can be unhelpful and behaviours that have a negative impact on the problem, and teaching individuals the skills required to cope with health-related problems, CBT can be used to successfully treat a wide range of conditions including anxiety, depression, and insomnia.

However, there are multiple barriers for individuals when it comes to accessing CBT in its traditional face-to-face format. These include the lack of available professionals to administer sleep-specific CBT. In recent years, there has been increasing interest in the use of technology to remotely deliver psychological therapies on a large and readily accessible scale, including CBT.

Dr Carney and her colleagues saw that the development of a bespoke app that could be easily utilised on mobile devices such as smartphones, presented a unique opportunity to address the needs of teenagers and young adults in relation to improving their quality of sleep and subsequent well-being. In discussing this approach, Dr Carney explains that ‘we decided that we would use the technology they are drawn to and their natural inclination towards self-management.’

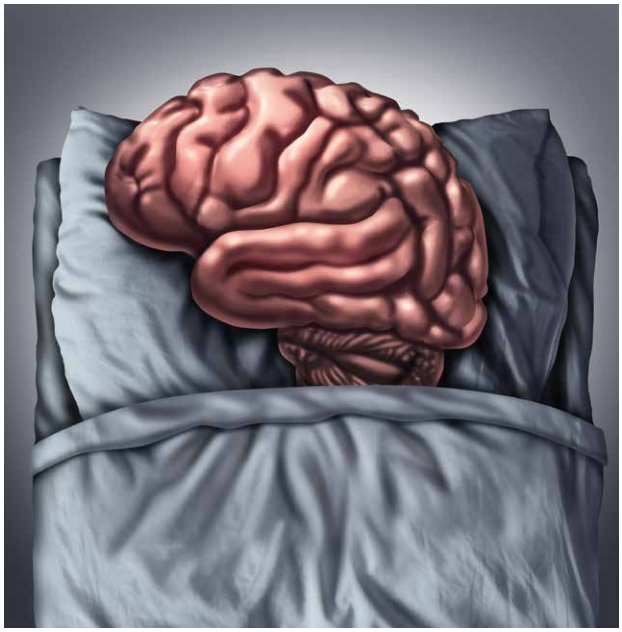
Using Technology to Treat Sleep Problems

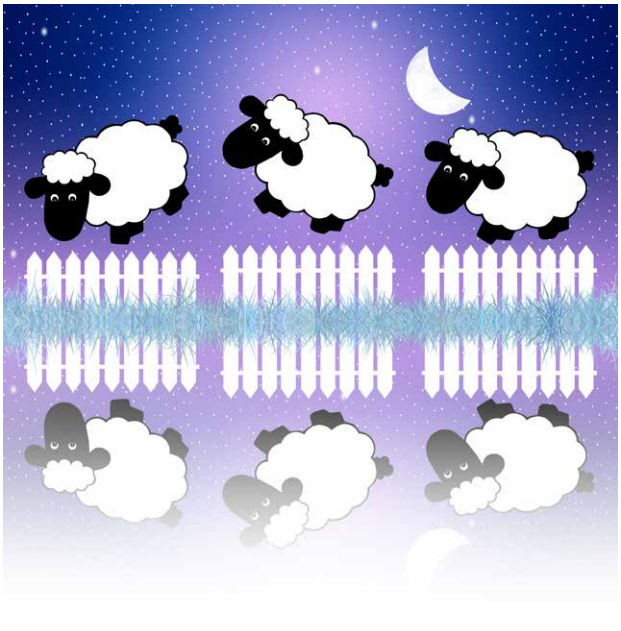
Dr Carney’s app was originally developed in connection with Ryerson’s Chang School to track sleep in undergraduates. Initial feedback highlighted the importance of an app that is user friendly, and that also provides tips and tricks on how to improve sleep, in addition to functioning as a sleep diary.

This work was useful for the subsequent development of DOZE. DOZE (**D**elivering **O**nline ‘**Z**ZZ’ with **E**mpirical support) utilises a web self-management system that allows young adults to access information and interactively learn about strategies to promote sleep. The principle behind the app was to utilise evidence-based sleep treatments that young adults would want to use and that healthcare providers would be able to refer their patients to. To ensure ready access and engagement, DOZE combines web-based delivery to provide information about sleep and supplemental resources with a smartphone app that provides instant assessment and feedback on monitored sleep behaviours.

The DOZE app builds on elements from the initial app that assessed sleep habits and patterns, including time spent in bed, variability in sleep schedule, amount of sleep at night, amount of sleep in a 24-hour period, sleepiness, waking mood, daytime stress, and daytime fatigue rating. Additional features include the dose and timing of sleep-interfering substances, timing of devices with screens, and self-reported worry about sleep. The accompanying web-based interface provides access to information on evidence-based sleep-promoting treatments based on principles of stimulus control, sleep hygiene, counter arousal strategies, and calculating the optimal time-in-bed.

‘By learning about your sleep system, there are some changes you can make in your habits that can get better results from your sleep system.’





Studies confirm that it is most effective to provide young adults with immediate access to treatment resources, and an app is the most efficient way to provide this support. As such, the DOZE app ‘places evidence-based techniques into the hands of those who need it most’ notes Dr Carney. The main goal of CBT approaches to treat insomnia is to increase the young adult’s sleep self-efficacy. The DOZE app aims to help young adults identify patterns in their sleep patterns and devise sleep schedules that are consistent with their current sleep regulatory system.

Feasibility testing

Dr Carney and colleagues have put DOZE through rigorous feasibility testing. In one trial, 51 young adults aged between 15 and 24 were enrolled. Although 77% of these participants did not meet the clinical cut-off for insomnia, 93% were not currently seeking professional help for their sleep problems. ‘Despite lots of fatigue, insomnia and struggles with mental health, very few were seeking professional help – this was the impetus for the app and self-management’ explains Dr Carney.

For four weeks, the participants used the app for sleep monitoring, goal setting, and as an information resource regarding sleep. Dr Carney and her team found that the most common goal set by participants was to reduce the variability of getting into and out of bed, followed by altering the time-in-bed based on feedback. The third was to reduce lingering in bed after the alarm. It was also found that young people used a variety of tips to help them achieve their goals. The most commonly accessed tips were on getting help winding down, how to live in an early bird’s world when you’re a night owl, help with fatigue management and getting up in the morning.

Although assessing efficacy was not the aim of this feasibility trial, it was found that the app did have a meaningful impact on sleep. By characterising participants as ‘good sleepers’ or ‘poor sleepers’ (above or below the insomnia cut-off threshold, respectively), Dr Carney and her team found that both groups saw improvements in sleep. In just two weeks of using the app, poor sleepers became good sleepers.

There were also improvements in daytime sleepiness, energy levels, and overall quality of life. This shows that by simply giving young people feedback on sleep and providing them with resources to learn how to improve sleep, then allowing them to make choices as to what they want to change can have a positive impact. Dr Carney believes that ‘By learning about your sleep system, there are some changes you can make in your habits that can get better results from your sleep system.’

Meeting the Sleep Needs of Young People

Dr Carney is currently working with industry partner Ian Chalmers from Pivot Design to redesign and develop the app technology to make it more user friendly. Dr Carney’s ultimate goal is to make the app freely available to young people struggling with sleep. Dr Carney concludes by emphasising the autonomy that the app provides young adults, explaining ‘I think what is most important is that, they like it, they use it, and they set goals they can achieve, and it helps them sleep better.’

Meet the researcher

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Dr Colleen Carney is an Associate Professor at Ryerson University and the Director of the Sleep and Depression Laboratory. Dr Carney is also the President of the Association for Behavioural and Cognitive Therapies (ABCT) Insomnia Special Interest Group. She is a leading expert on sleep with over 15 years' experience in behavioural sleep medicine and cognitive behavioural therapy (CBT) for the treatment of insomnia and its comorbid illnesses. Dr Carney has over 100 publications, including nine books on CBT for insomnia. Dr Carney is currently working on her 10th book titled *Goodnight Mind for Teens: Skills to Help You Quiet Noisy Thoughts and Get the Sleep You Need*, which is due to be released later this year. She is a recognised thought leader in this important field and her work is featured in many news outlets, including the New York Times. Dr Carney was recently featured on the Netflix series A User's Guide to Cheating Death. Dr Carney trains students and professionals in CBT and is a passionate advocate for improving the access to evidence-based treatments for insomnia.

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KAPPA OPIOID RECEPTORS: A NEW TREATMENT TARGET FOR SCHIZOPHRENIA

Schizophrenia is a serious psychiatric disorder that affects around 1% of the global population, producing debilitating symptoms that significantly impact upon the quality of life of sufferers. Even with treatment, prognosis is often poor with a high risk of relapse. **Dr Samuel Clark** of Terran Biosciences Inc and colleagues at Stony Brook University, New York, are investigating the potential of blocking one type of opioid receptor in the brain – the kappa receptor – to reduce the symptoms of the disease.

Schizophrenia and the Need for Novel Interventions

Schizophrenia is a complex and often lifetime disorder, associated with a wide range of symptoms across different domains. The positive symptoms include hallucinations and delusions, often associated with psychosis, whereas the negative symptoms include social withdrawal and reduced expression of emotion. Another cluster of symptoms has been described as cognitive, referring to the deficits to attention and memory.

Despite decades of investigation into the causes and underlying neurobiological features of schizophrenia within the brain, the treatments that are currently available are far from perfect – or even effective for all patients. Existing treatments often only ameliorate the positive symptoms leaving other symptoms untreated. Furthermore, existing treatments frequently come with unpleasant side-effects that, understandably, diminish the motivation of patients to adhere to their prescribed medication regime.

Opioid Receptors in the Brain

Dr Samuel Clark and colleagues at Terran Biosciences Inc and Stony Brook University, New York, are investigating the specific role of the kappa opioid receptor in schizophrenia. Kappa is one of the three different types of opioid receptor in the brain – the others are known as mu and delta. Common painkilling opioids, such as morphine, attach to the mu opioid receptors. However, other drugs can activate the other receptors, or even all of them, at the same time.

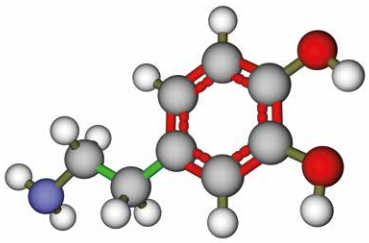
Opioid drugs are commonly known for their medical application in providing analgesia but also for recreational abuse and addiction. In simple terms, opioids work by attaching to specific proteins, the opioid receptors. When this happens, the drugs and the receptors fit together like a key in a lock. When opioids attach to opioid receptors, they cause the release of chemical messages creating specific patterns of activation in the brain, primarily associated with the relief of physical and psychological pain.

There are also drugs that block the opioid receptors, stopping them from becoming active and thus exerting their effects. Returning to the key analogy of activation by a drug on a receptor, a receptor blocker is the equivalent of a blank key being put into that lock. It fits but doesn't work, and critically, stops another key from being used at the same time.

The Kappa Opioid Receptor

In an attempt to develop drugs with the same effects as existing opioids but without the potential for abuse and addiction, researchers turned their investigations to the kappa opioid receptor. As early as in the 1970s it had been discovered that activation of the kappa receptor was as effective as that of the mu receptor in terms of providing

‘Opioid antagonists are potentially very effective treatments for schizophrenia.’



pain relief. Thus, several drugs were developed to specifically and selectively activate only the kappa receptor but these were found to have very different effects to the existing opioid drugs. Healthy participants in clinical trials reported severe hallucinations and delusional thinking – very similar to psychosis experienced by people with schizophrenia. On this basis, clinical trials exploring the analgesic properties of drugs activating the kappa receptor were terminated.

Shortly afterwards, other researchers started investigating whether blocking all three types of opioid receptor would have the opposite effect in patients who already had schizophrenia. Lars M Gunne and colleagues conducted a small pilot study exploring the effects of intravenous naloxone, a synthetic drug that blocks the kappa, mu, and delta opioid receptors. Dr Clark describes these findings as ‘miraculous…the patients with schizophrenia had immediate loss of hallucinations on top of what was achieved with standard antipsychotic therapy.’

Further studies ensued with the aim of replicating these promising initial findings. Although the majority reported that patients experienced significant improvement in their schizophrenic symptoms, a number of studies reported a lack of efficacy. This meant that research exploring the potential of kappa opioid receptor blockers as a novel treatment target in schizophrenia was pushed aside – until very recently.

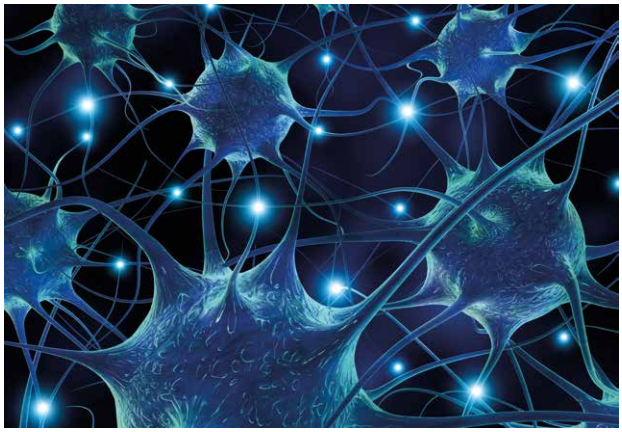
Dr Clark and colleagues recently conducted a review of all of the clinical trials that have examined the impact of kappa antagonists in schizophrenia. In consideration of this, Dr Clark explains, ‘many of the studies that failed to find an effect used older less reliable diagnostic criteria and nearly all studies were underpowered,’ before concluding that ‘opioid antagonists are potentially very effective treatments for schizophrenia.’

Having now also published the first comprehensive review of the literature in this field, Dr Clark and his colleagues can point to a wealth of research that supports the idea that blocking the kappa opioid receptor should act as a highly effective treatment for the range of symptoms associated with schizophrenia. These key papers have brought this line of investigation back to the fore, many years after the potential significance of the kappa opioid receptor in schizophrenia had been identified.

Determining the Underlying Mechanisms

Original thought was that the neurotransmitter dopamine, released as a chemical messenger to allow certain brain cells to communicate, was of particular importance in schizophrenia. Dopamine plays a key role in a host of different activities and experiences, including sleep, mood, learning, and the

'Amazingly, these drugs provide a large benefit above and beyond whichever antipsychotic therapy the patients are currently taking. Perhaps most importantly, is the fact that they may treat the negative symptoms as well as the positive symptoms. There are currently no FDA approved drugs for the negative symptoms of schizophrenia.'



feeling of pleasure. A stable amount of dopamine is essential to the healthy functioning of our brains, and disruptions to its supply have been implicated in a variety of conditions, in addition to schizophrenia.

As such, treatments for schizophrenia have typically targeted dopamine receptors and this represents the dominant approach in current pharmacological therapies. However, these approaches do not satisfactorily alleviate all symptoms. On the basis of their extensive research, Dr Clark and his team propose that kappa opioid receptors are the underlying culprit underpinning the unstable dopamine levels traditionally associated with schizophrenia, and that these receptors should be targeted together with dopamine receptors themselves.

Importantly, kappa opioid receptors play a role in regulating the amount of dopamine that is released in our brains. If the kappa opioid receptors are not functioning properly – as Dr Clark and his team hypothesise is the case in people with schizophrenia – then they are not performing their anticipated role in maintaining the production of a stable amount of dopamine.

Kappa Opioid Blockers as Treatments

The researchers argue that the kappa opioid receptors may be over-activated in people with schizophrenia, leading to changes in dopamine levels that cause too little activation in some parts of the brain but oversensitivity in others. These complex effects are proposed to underlie the range of different types of symptoms (i.e., the positive, negative, and cognitive symptoms). Dr Clark and colleagues suggest that by preventing this over-activation of the kappa opioid receptors, it is possible to treat more of the symptoms of schizophrenia than has been possible with existing pharmacological interventions.

Bringing together their work to date, Dr Clark and his colleagues have identified four different drugs that they believe will provide effective treatment: naloxone, naltrexone, nalmefene, and buprenorphine. As these drugs have already approved by the Food and Drug Administration (FDA) and the European Medicine Agency for use in other conditions, they have already been tested for safety, and naltrexone is currently widely available on prescription.

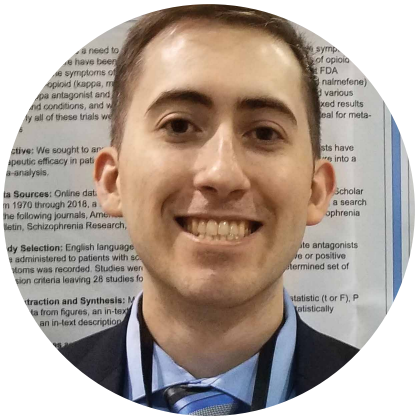
Dr Clark notes, 'Amazingly, these drugs provide a large benefit above and beyond whichever antipsychotic therapy the patients are currently taking. Perhaps most importantly, is the fact that they may treat the negative symptoms as well as the positive symptoms. There are currently no FDA approved drugs for the negative symptoms of schizophrenia.'

Dr Clark and his colleagues are working to develop even better treatments for schizophrenia based on this research, with drugs in development that block just the kappa opioid receptors, in the hope that these can ameliorate the symptoms but without the side effects that occur when blocking the other two types of receptor.

Benefits Beyond Schizophrenia

Dr Clark established Terran Biosciences Inc with the aim of optimising existing and developing new treatments for psychiatric illnesses by developing a worldwide collaboration of researchers and by applying a precision medicine approach to the development of new therapeutics. The approach of Terran Biosciences is different to the usual method of developing drugs in individual siloes of work as adopted typically by pharmaceutical companies. Instead, the focus is to use advanced diagnostic imaging and technologies such as patient specific organoid 'minibrains' to more specifically target the development of therapeutic drugs tailored to the patient's unique symptoms. By taking a more targeted approach to developing drugs, the need for large financial returns is reduced and focus is placed instead on the need that a potential treatment could fulfil.

The benefits of this approach are readily apparent when considering the example of investigation into the kappa opioid receptor as a treatment target in schizophrenia. However, the aim of Terran Biosciences is to extend their work across the spectrum of psychiatric diseases. Dr Clark and his world class team conclude, 'We intend to use this model to not only finish the development of therapeutics which have been proven safe and effective, but also to setup a distributed collaboration network for the continued development of a steady stream of new therapeutics. Mental illness may be one of the greatest unmet medical needs facing us today and we hope to change this with our new model.'



Meet the researcher

Dr Samuel Clark
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Dr Samuel Clark completed his BS at the Massachusetts Institute of Technology, and MD and PhD at Columbia University, where his research focused on developing new methods for imaging the living brain. He pioneered the technique of using fluorescent false neurotransmitters (FFNs) in vivo as well as a new surgical technique (PHASOR) for multiphoton imaging of the living brain. With a focus in viral gene therapies, his research utilized a variety of viral vectors for gene therapy in the living mammalian brain. He has studied the kappa opioid receptor and explored its role in schizophrenia for over 11 years. Dr Clark is the founder and CEO of Terran Biosciences, a clinical stage biotech company which aims to transform the lives of patients with mental illness by applying precision medicine through patient specific organoid 'minibrains' to the development of novel neuropsychiatric therapeutics and medical devices.

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DRIVING FORWARD TRAINING AND RESEARCH IN PSYCHIATRY

In recent years, dramatic advances have been made in brain science and molecular genetics. However, there is currently a shortage of psychiatrists with the scientific training necessary to take this knowledge and apply it in the clinic. Psychiatrist and neuroscience researcher, **Dr Susan Voglmaier** of the University of California, San Francisco, runs a research training program that supports the next generation of research scientists in the field of psychiatry. Dr Voglmaier believes that by training doctors in scientific techniques and methods, we may come to better understand mental illness and provide more effective treatments for psychiatric diseases in the future.

Training the Next Generation of Psychiatrists

The Psychiatry Research Resident Training Program at the University of California, San Francisco (UCSF) is a specialised program that aims to increase the number of qualified research psychiatrists. The program also focuses on fostering the integration of biology and psychology in advancing the treatment of neuropsychiatric disease. Dr Susan Voglmaier directs the program, where she oversees the research and clinical training of psychiatrists. Participants of the program are MDs, many of whom already have PhDs, who undertake a comprehensive training program that provides them with neuroscience or clinical research training and career mentorship in classroom, laboratory, and clinical settings. Partially funded by the National Institute of Mental Health, the program includes neuroscience workshops, leadership experiences, and individualised training to allow psychiatrist-scientists to establish and maintain the running of scientific research projects alongside their clinical training.

Neurotransmitters: Deciphering Their Role in Mental Illness

In addition to leading the Research Resident Training program, Dr Voglmaier runs an active research lab that focuses on the study of specialised proteins that are found inside of nerve cells (neurons) in the brain, called vesicular neurotransmitter transporters. Neurotransmitters are chemical signals that are transmitted rapidly (on the order of milliseconds) from one neuron to another, coordinating learning, memory, and action. Glutamate, an amino acid, is the most abundant neurotransmitter in the human brain and mediates neuronal excitation. Inside the cell, vesicular glutamate transporters (VGLUTs) package glutamate into specialised sacs or compartments called synaptic vesicles. When neurons receive electrical signals from other neurons, synaptic vesicles

fuse with the cell membrane and release glutamate from the cell. When glutamate is detected by the receptors on a neighbouring neuron, this

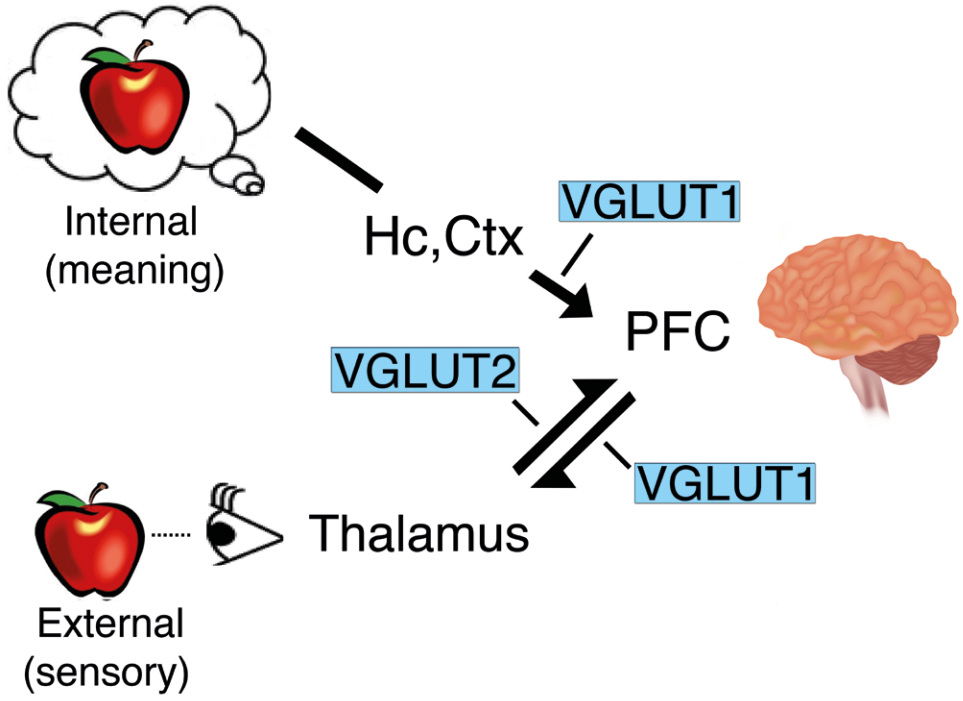

Figure 1. The VGLUT1 and VGLUT2 pathways. Credit Susan Voglmaier.

results in signal transmission. After neurotransmitter release, synaptic vesicles are broken down, reformed, and refilled with neurotransmitter for a new round of release.

There are three types of vesicular glutamate transporter, known as VGLUT 1, 2 and 3, with VGLUT1 and VGLUT2 being the most abundant. These two glutamate transporters are expressed in different areas of the brain as well as at different levels and times during the life of an organism. During development, VGLUT2 levels are highest in the womb, while VGLUT1 levels increase during brain maturation and are higher in adults compared to younger individuals. In general, VGLUT2 is expressed in glutamatergic pathways that transmit sensory information from the outside world, while VGLUT1 pathways transmit information from memory about meaning.

A precise balance of VGLUT1 and VGLUT2 containing synaptic terminals is needed to integrate information and coordinate output behaviour. For example, when a person sees a round, red object this information is transmitted via VGLUT2 pathways and is compared to information in the brain carried by VGLUT1 pathways, to identify whether the object is a ball or an apple, and whether s/he should throw it or eat it (Figure 1).

The formation of new synaptic vesicles and their loading with glutamate need to keep up with the rapid signaling demands of the cell. If this doesn't happen, insufficient glutamate will be available for signal propagation. In the central nervous system, imbalance of glutamate signaling at the synapse is suspected to be involved in schizophrenia, major depressive disorder, and bipolar disorder. VGLUT1 and VGLUT2 each have sophisticated signals in their structure that control the take-up, transport, and release of glutamate from the synaptic vesicle as well as their sorting to reforming synaptic vesicles after they have fused with the cell membrane.

At UCSF, Dr Voglmaier's research team have unravelled a number of the molecular mechanisms that allow glutamatergic synaptic vesicle proteins to recycle from the cell membrane at the synapse and allow glutamate to refill vesicles.

In recent studies, her team found that although the basic process of glutamate transport across the synaptic vesicle membrane by both forms of glutamate transporters is identical, the recycling of the synaptic vesicle from the cell membrane at the synapse of the neuron proceeds in very distinct ways depending on whether VGLUT1 or VGLUT2 is involved. The researchers showed that the speed of take-up and recycling of the transporters differs between VGLUT1 and VGLUT2 even in the same cell type, demonstrating that the proteins themselves control the rate of their recycling. This is an important and new finding, as previous studies had assumed that all synaptic vesicle proteins recycled equivalently. However, the scientists found that VGLUT1 exhibits faster rates of recycling than VGLUT2.

These differences in the speed of vesicle recycling likely shape the rate, amount, and pattern of how much glutamate is released at the synapse and that will subsequently be available for cell signaling. Synapses that contain VGLUT1 exhibit a lower initial probability of release of glutamate while synapses with higher levels of VGLUT2 exhibit a higher probability of release.

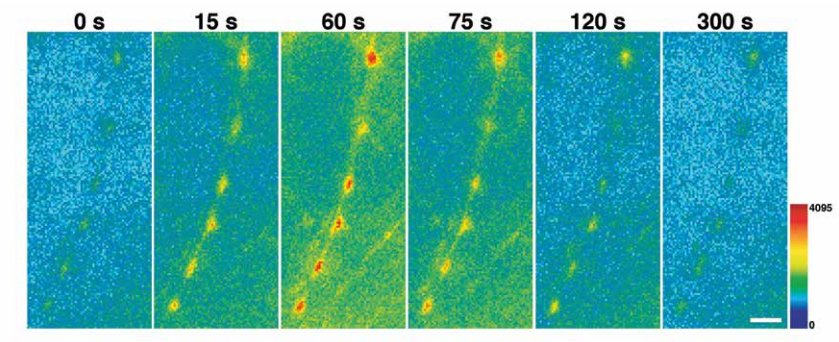

Figure 2. VGLUT-pHluorin exposed to the extracellular space. Credit Susan Volgmaier.

By exploiting the acidic environment inside the synaptic vesicle and using fluorescent genetically-encoded tools to track VGLUTs under the microscope, Dr Voglmaier's team were able to determine the makeup and function of the sorting signals and discovered additional proteins that interact with the two types of VGLUTs and mediate the differences between them.

VGLUTS and the Synaptic Vesicle Cycle

Structurally, VGLUT1 and VGLUT2 are identical with the exception of a few molecular differences at the head and tail ends of the proteins. The tail end of VGLUT1 is slightly different from that of VGLUT2, containing protein interaction domains not present in VGLUT2, and that appear to contribute to the faster recycling of VGLUT1. However, little is known about the mechanisms underlying VGLUT2 recycling. This motivated Dr Voglmaier and her team to examine how VGLUT2 recycles across synaptic membranes using the protein pHluorin.

The protein pHluorin, a pH-sensitive form of green fluorescent protein, is used in neuroscience to study neurotransmitter release. Dr Voglmaier and her team designed specialised forms of pHluorin for their studies. These consist of pHluorin fused to the side of the VGLUT facing the inside of the synaptic vesicle. The pH inside transmitter vesicles is acidic, and the VGLUT-pHluorin is non-fluorescent under these conditions. When vesicles are released, VGLUT-pHluorin is exposed to the extracellular space, which has a neutral pH, and the presynaptic terminal becomes brightly fluorescent. Following the re-internalization and reformation of the synaptic vesicles, the vesicles become re-acidified and the cycle can start again (Figure 2). The fusion of a green fluorescent molecule to VGLUT1 and VGLUT2 allowed the researchers to track their activities during neuronal signal transmission and determine how they influence the interactions of synaptic vesicle proteins, the reformation of synaptic vesicles, and the release of glutamate.

Findings from these studies confirmed that VGLUT2 recycles differently than VGLUT1. These results indicated that it is protein identity, not synaptic vesicle membrane or neuronal cell type, that controls sorting the rate and method of VGLUT uptake and release, and that VGLUT2 relies on distinct recycling mechanisms from VGLUT1. In addition, the team was able to identify interactions with other proteins that were crucial for VGLUT1 trafficking at the synaptic membrane.

Synthesised Medicine

When the biochemical mechanisms of a particular disease are elucidated, specialised drugs can be designed to target the condition at a microscopic level. These synthesised drugs can be made in the lab via a series of chemical reactions using molecular building blocks to create larger molecules with the desired makeup and confirmation. Examples include molecules with the potential to block a particular molecular mechanism from occurring by binding to a target, at the site of the reaction or elsewhere. These drugs can be tailored to be delivered at specific potencies to the tissue where they are needed, leaving surrounding cells unaffected.

The rate of modern drug synthesis and development methods continue to gain momentum, along with novel delivery and targeting systems, such as nanotechnology. The first step in drug creation and development is the study and understanding of the process of disease. Dr Voglmaier hopes that her work will lead to a sufficient understanding of the molecular pathways that could be exploited to invent new drugs to increase or decrease the recycling of glutamate and other important neurotransmitters at the synapse level.

The Future of Medicine and Mental Health

The research in Dr Voglmaier's lab continues to provide excellent training for scientists in the field of neurobiology. In addition, through the UCSF Department of Psychiatry's Research Resident Training Program she provides training and support to a new generation of psychiatric clinician-scientists, who work at all levels of analysis, from molecular and cellular biology, to human participant research, to health systems. Dr Voglmaier thus contributes to the development of mental health specialists with the ability to understand and integrate their psychiatric clinical practice with laboratory, clinical, and health services research. We can hope that other institutions will follow the UCSF blueprint created by Dr Voglmaier. As scientists work towards a better understanding of the brain biochemistry and molecular mechanisms of neuropsychiatric disease, it is hoped that the ability to synthesise specialised medicines for major mental illnesses, which have so far evaded effective treatment, will become the norm.

Meet the researcher

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Professor Susan Voglmaier completed her MD and PhD in Neuroscience at the John Hopkins School of Medicine in 1997. She then completed her medical residency in psychiatry at the University of California, San Francisco (UCSF), where she also worked as a clinical and research fellow in both Psychiatry and Neurology. Dr Voglmaier is currently an attending psychiatrist in the Adult Psychiatric Clinics at UCSF where she specialises in psychotic, anxiety, and mood disorders and performs resident supervision and medical student teaching. In addition, she is an Associate Professor in the Department of Psychiatry at UCSF, where she studies the regulation of synaptic vesicle recycling and neurotransmitter release, methods to image these processes, and animal and cellular disease models. She has also been a Faculty Member in the Neuroscience Program at UCSF since 2007 and is the Co-Director of the Psychiatry Research Resident Training Program.

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March of Dimes
UCSF Program for Breakthrough Biomedical Research
Whitehall Foundation

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UNIVERSITY OF CALIFORNIA

CHILDREN AND YOUNG PEOPLE'S MENTAL HEALTH COALITION

The Children and Young People's Mental Health Coalition (CYPMHC) brings together more than 200 leading charities in the UK with the shared goal of improving the mental health and well-being of children and young people. In this exclusive interview, we speak with **Oliver Glick**, Policy Officer at CYPMHC, to hear about their achievements over the past decade and future plans.

To begin, please tell us how CYPMHC was established and what is your overarching aim as a coalition?

The Children and Young People's Mental Health Coalition was formed in 2010 with 28 member organisations. The goal then was to bring the sector's voice, experience and campaigns together. That goal is the same today but now we have over 200 members! It was set up thanks to the generosity of the Zurich Community Trust and was hosted by the Mental Health Foundation between 2010 and 2018. The coalition is now hosted by the Centre for Mental Health.

Our vision is for all infants, children and young people to grow up in a society that prioritises, invests, listens and attends to their mental health and wellbeing. As a coalition, we only exist because our members do – we champion and aid their work. We have three strategic aims – prevention and promotion, early intervention, and skills and confidence.

CYPMHC celebrates its 10th birthday this year. What have been CYPMHC's most significant achievements to date?

We are proud of our work Informing the Future in Mind policy initiative. Future in Mind is a government initiative designed to change how Child and Adolescent Mental Health Services (CAMHS) are delivered – a crucial national service. CYPMHC was a member of the Children and Young People's Mental Health Taskforce. The work of this taskforce led to a £1.25 billion commitment and the initiation of the transformation programme.

Our lobbying also prompted the government to commission the children and young people's mental health prevalence study in 2015 which was published in 2018. These data are important for decision-makers and society to get a clear picture of the levels of need of our children and young people, and making sure that investment and government attention match that need.

We have been very active in the COVID-19 response, something I'm pleased about as this is such a crucial time for children's mental health. We have championed our member research and policy, which is developing all the time, and work to ensure that important findings get to decision-makers when it matters.

"Lockdown may have been traumatic for many children, so when they return to normality it needs to be 'back to better', not back to normal, in terms of support and their mental health."

Looking to the future, what aims do you have for the next ten years? What specific challenges for children and young people do you intend to address?

Overall, we exist to try and reach a society where all children and young people have good mental health. How we get there is another question. We have three leading priorities that our members have agreed on. They are prevention and promotion, early intervention, and skills and confidence. I'll explain each in turn and why we feel they are so crucial!

Prevention and promotion mean simply stopping mental health problems before they've begun and promoting good mental health. This work is so wide-ranging, as we know that many societal factors affect our mental health – from housing to poverty, from childhood trauma to sleep. That means, to stop mental health problems arising, decision-makers need to embed prevention across their policy. Prevention can be an abstract area. For example, ensuring everyone has a safe and secure home may, directly and indirectly, reduce mental health problems years later. However, if you've stopped something happening, decision-makers could come back and say, 'how do we know those problems would have arisen if we hadn't implemented that policy?'. This is an area with huge potential for change but one that requires good policy and research to implement.

Early intervention is about getting help to people as soon as their problems emerge. On average, children and young people receive help many years after symptoms arise. This is way, way too late, not only because of the suffering people endure in that time, but also because many problems are easier to treat the earlier help can begin. Services are so underfunded and stretched that they struggle to go beyond reacting to late-onset, acute issues but if we had more public health and community measures that are properly funded, we could act early.

Skills and confidence are about children: young people and everyone around them having the skills and confidence needed to take care of mental health. That includes parents and carers, as well as the workforce. Sometimes decision-makers think these are so-called 'soft skills', but they are so important. Giving people the space and language to get help, and help each other, is crucial. For example, peer support for young people is becoming more and more embedded, as we realise that young people turn to each other and rely on their networks so much anyway, that we should harness that and make sure it is impactful.

I should add that we have to adapt to the landscape of society changing all the time. We have produced a lot of policy on COVID-19 and lockdown, which of course, in January would

have been non-existent. While we have our priorities, we also have to adapt to the national situation.

How does research on children and young people inform your policy campaigns?

Research, alongside the views of children, young people and their carers, forms the backbone of our policies. We are lucky to have an amazing membership, who are collectively producing important research. Our response to the pandemic is a great example of this. Our policy has arisen from findings from frontline providers and charities, who have identified crucial issues, such as vulnerable children being even more vulnerable, and the need for remote support of parents. We can build our recommendations to decision-makers from the ground up, from the research that matters. It is important for us to not pick things we like and retrofit research. We only exist because of our members, so are led by their work.

Thinking now from a different perspective, how does the work of CYPMHC influence research?

That's where our part in the coordination and support of the sector comes in. We can look at the gaps in policy and discourse from the conversations we are in, and talk to our members about looking into research.

Recently, we held a series of member workshops on Zoom and heard from a lot of members with meaningful insight on a range of topics. Not only were we able to bring policy out of the workshops to take forward, but members who may not have conversed have gone away to join up their work. It is such a large sector that people can get a lot from joining up – they may not have done so before simply because they're doing their own work but didn't know another group could complement theirs.

Our members work hard to improve children and young people's mental health, and sometimes simply sharing key messages can improve everyone's campaigns. If decision-makers hear the same well-informed recommendation across the board, it has more chance of success.

Finally, the COVID-19 pandemic has resulted in a considerable negative impact on the mental health of many across the world. How have children and young people in the UK been affected and what can be done to help alleviate their distress?

The instinctive answer is 'badly'. But we are careful to be nuanced – this is unprecedented in the modern world, so its full effects will be unknown for a while, making the need for long term monitoring and study crucial. There will even have been positives for some children and young people. For example, some have preferred the move to online counselling and therapy, and new innovative support from charities has been really impactful.

Fundamentally, most children have not been at school, and this is a huge disruption. Schools are a source of community, play, and a place where the volunteer and charity sector can engage with children. Parents and carers have been asked to balance jobs and their own mental health in a pandemic with so much academic and pastoral care of their children. Who knows how this will affect children in the long term.

For young people, transitions to further and higher education, or into the working world, are difficult at the best of times. Young people can fall through the cracks of services at this point. Lockdown and COVID-19 have been very challenging for them. At least with most school children, we can try and get schools reopening in a way that prioritises wellbeing. But with no institutions, 16 to 18 year olds are harder to support with the current systems.

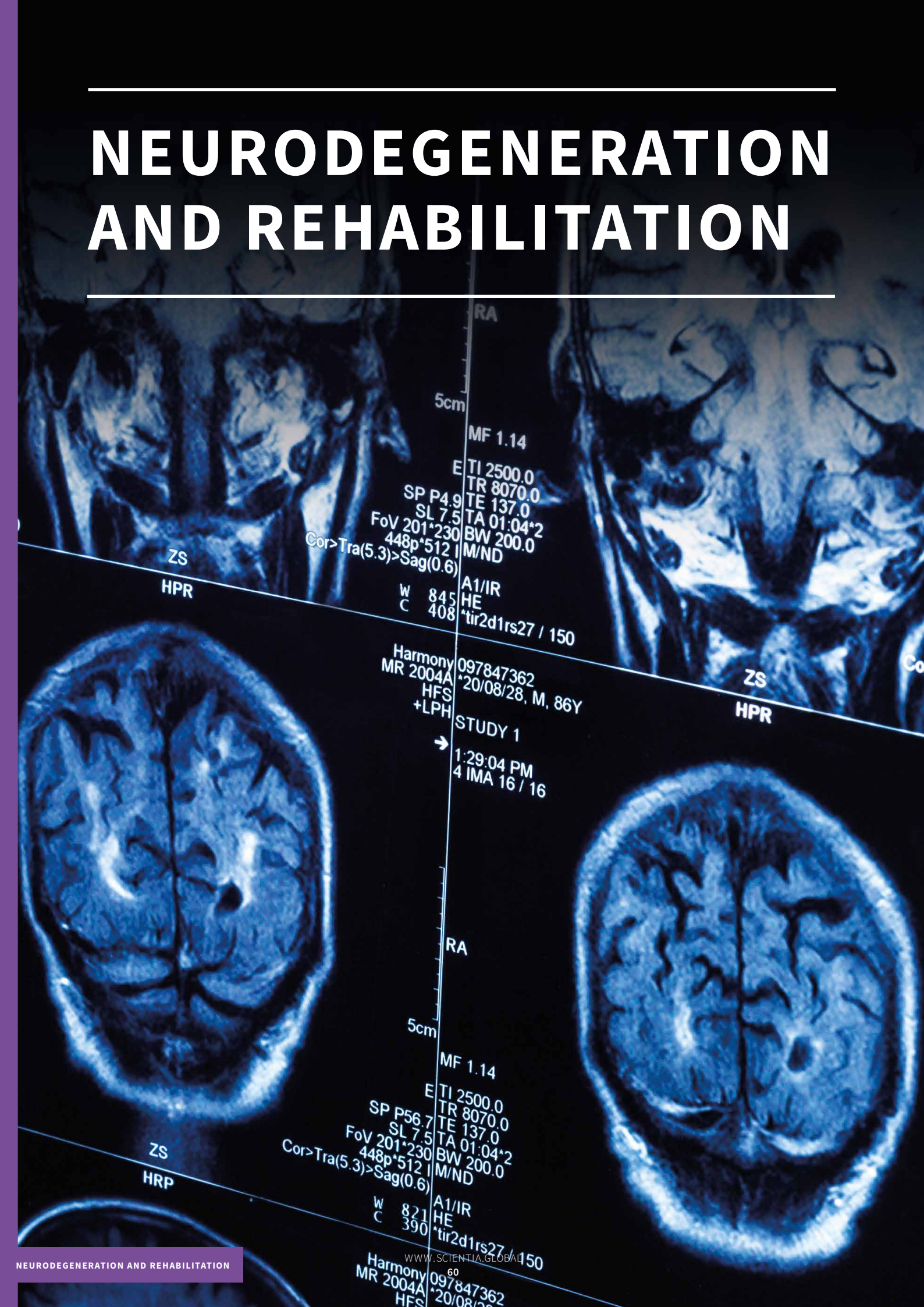
We are worried about vulnerable groups, such as children in households with domestic abuse, or young carers, for example. Groups that need support and help usually have seen that greatly disrupted. Further, those in alternative provision or not at school aren't going back, COVID-19 has highlighted what we been working on previously – that there are huge inequalities in access to support. The response needs to change things for the long term, helping to address those inequalities.

To help, we have been calling for a 'trauma-informed' approach to services and places, like schools. That means making sure schools are taking a person-centred approach to children, looking at their environment and experiences, not just how they are behaving. Lockdown may have been traumatic for many children, so when they return to normality it needs to be 'back to better', not back to normal, in terms of support and their mental health.

www.cypmhc.org.uk

Children & Young People's Mental Health Coalition

NEURODEGENERATION AND REHABILITATION



CONFRONTING THE CHALLENGES OF AGEING, INJURY AND DISEASE

Life expectancy around the world has increased steadily for nearly 200 years. The final section of this issue of Scientia showcases the work of researchers who are striving to overcome the challenges we face as a result of increases in longevity, including the risk of neurodegenerative disease and disability.

Ageing is the primary risk factor for neurodegenerative disease, the umbrella term for a range of devasting and ultimately fatal conditions, such as Alzheimer's disease and Parkinson's disease. Neurodegeneration refers to the progressive loss of structure or function of neurons in the brain, which over time, leads to impairment in cognitive abilities such as memory, ability to focus attention and decision-making. This eventually has a profound effect on the sufferer's day to day life, affecting their relationships, ability to work and ability to self-care. Neurodegenerative diseases are currently without cure and there is an urgent need to develop effective interventions.

We open this section by meeting Dr Mary Logan and Dr Sean Speese at the Oregon Health and Science University, USA, who are working to understanding how glial cells in the brain sense and respond to neuronal stress and damage arising from neurodegeneration or trauma. We read how the researchers use fruit flies as a model to study the brain and the exciting possibility of boosting innate glial immune activity to enhance neuroprotection and thus reduce or even prevent neurodegeneration. We then turn to Professor Etienne Sibille (at the Centre for Addiction and Mental Health and University of Toronto) and Professor James Cook (University of Wisconsin–Milwaukee) who use a mouse model to study cognitive impairment that arises through neurodegeneration as well as other conditions such as depression. Their cutting-edge research has shown that newly synthesised compounds targeting GABA receptors improve specific types of memory in mice, representing another potential approach in the development of effective new pharmacological options for humans.

In addition to developing effective interventions for neurodegenerative disorders, scientists are also optimising the most effective and efficient ways to safely deliver treatments into patients. One particular difficulty in the treatment of neurodegenerative disease is that drugs are unable to cross the highly selective blood-brain barrier due to its role in preventing toxins from doing just that. However, Dr Shikha Nangia at Syracuse University, USA, is determined to overcome this challenge. We read how by unravelling the secrets of blood-brain barrier permeability using advanced computational techniques, Dr Nangia is opening new horizons in the development of innovative treatment strategies.

Although ageing represents a specific risk factor for neurodegenerative disorders such as Alzheimer's disease, other factors undoubtedly play a significant role, and these remain relatively underexplored. Professor Gerhard Rammes at the Technische Universität München (Germany) and Dr Martina Bürge at St Bartholomew's Hospital (London) are working to

address this by elucidating the role that general anaesthesia may play in the development of Alzheimer's disease. We read how one particular anaesthetic, xenon, may help avoid this deleterious consequence of surgery, and may even offer neuroprotective effects, which has important implications for personalised medicine in patients with dementia.

Sustaining injury, through accidental falls, for example, can happen at any stage of life but is particularly prevalent in older individuals. This risk increases for those with neurological disorders or frailty. Dr Fay B. Horak at Oregon Health & Science University and APDM Wearable Technologies, USA, are investigating the use of APDM's novel wearable technology to monitor mobility in the daily lives of individuals to help prevent falls and identify prefrail elderly individuals. We read how this novel approach may help clinicians estimate a patient's risk of falling and propose suitable interventions that might reduce this risk and keep people active and safe in their home environments.

Injuries to the spinal cord are a particular concern for all age groups given that they can cause permanent paralysis and even lead to death. Currently, patients are faced with little hope of regaining lost functions once the trauma has occurred. We read how Dr Jerry Silver and his team at Case Western Reserve University Medical School, USA, are working to understand why nerves that are damaged through spinal injury fail to regenerate and their work identifying non-invasive, easy to administer strategies that can promote robust functional recovery.

Professor Mark D'Esposito at the University of California, Berkeley seeks to improve recovery and rehabilitation for people with brain injuries by better understanding the healthy brain. Professor D'Esposito has demonstrated that attention training programs improve cognition following brain injury, which translates into improved skills in completing day to day tasks. Furthermore, he has shown that these training sessions create lasting changes in the brain structure of patients that bring longer-term benefits.

We then turn to the field of neural engineering as applied to neuroprosthetics such as neural controlled artificial limbs for amputees. New advances have led to devices that can be operated using the nerves of the user, but the effectiveness and safety of these devices over long periods of use is a key concern. We read how Professor Dominique Durand at Case Western Reserve University is improving neuroprosthetics through developing new methods of interfacing with the nervous system, and the second line of work in which he seeks to control disorders of the central nervous system such as epilepsy through electrical stimulation of the brain.

We conclude this final section of Scientia by meeting Professor Heidi Zeeman at Griffith University, Australia, who conducts research in the innovative field of neurotrauma and the built environment. Neurodiversity relates to the broad spectrum of different brain sensitivities that individuals may have, including neurological disabilities. As part of her work, Professor Zeeman has invested heavily in determining the optimal neurorehabilitation inpatient environment following a brain or spinal cord injury. We read how her exciting research informs next generation therapeutic environments, workplace and residential design, and the design of public spaces to improve the lives of neurodiverse individuals.

PROTECTING THE BRAIN

Our nervous system has such an important function in our body that neurons have their own bodyguards. Known as glial cells, they protect brain cells against injury and prevent damage. **Dr Mary Logan** and **Dr Sean Speese**, both based at the Jungers Center for Neuroscience Research, School of Medicine, Oregon Health and Science University, USA, want to understand how these glial cells sense and respond to neuronal stress and damage in the adult brain. The Jungers Center was established because of a generous gift from Frank and Julie Jungers, and has the goal of uniting basic science and the clinic in developing treatments for debilitating neurodegenerative diseases.

The Mystery of Glial Cells

When we think of brain cells, we probably think of neurons. But there is another type of cell in the brain that outnumbers neurons by about 10 to 1. These are called glial cells, and despite their abundance, researchers understand very little about what these cells can do.

For many years they were ignored and considered simply as something to keep neurons in place – hence the name glia, from the Greek word meaning glue. However, some surprising functions are starting to come to light. It turns out these cells work as guardians for neuronal cells and can detect cellular damage. Glia cells respond quickly to trauma, caused by accident or neurodegenerative disorders, by finding affected areas and cleaning up damaged or dying neurons.

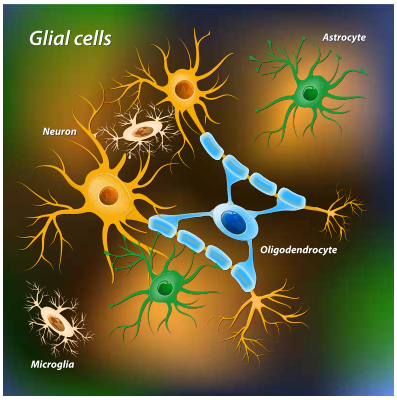
Researchers are aware of only a few players in this mechanism, with the Draper receptor being an exciting new receptor implicated in glial immune responses. In 2012, Dr Mary Logan described the key activating and inhibitory features of Draper required for glial cells to clear degenerating neurons in the adult brain, although precisely how Draper contributes to glial recognition and destruction of damaged cells is still unclear.

With a collaboration going back to 2010, Dr Logan and Dr Sean Speese at the Jungers Center for Neuroscience Research, School of Medicine, Oregon Health and Science University, USA, want to solve this mystery and have a long list of exciting questions. How do glial cells know which cells are dying and which ones are healthy? What are the cellular pathways that control the activity of glial cells? What regulates changes in glial cells in response to damage?

It's Not Easy Getting Old

Getting old is not easy. In addition to stiff joints and deep wrinkles, old age is the greatest risk for neurodegenerative disorders. Drs Logan and Speese believe this high risk is partly caused by a decrease in the ability of glial cells to protect neurons in the aged brain.

Using fruit flies as a model to study the brain, the team demonstrated that glial clean-up of damaged neurons is slower in old animals, due to a drop in the critical component Draper. In older cells, this receptor often fell below the minimum threshold needed to activate the response, significantly delaying any scrubbing operation. The researchers also showed that increasing the levels of Draper after neuron damage was enough to revert this effect in older animals, leading to speculations about



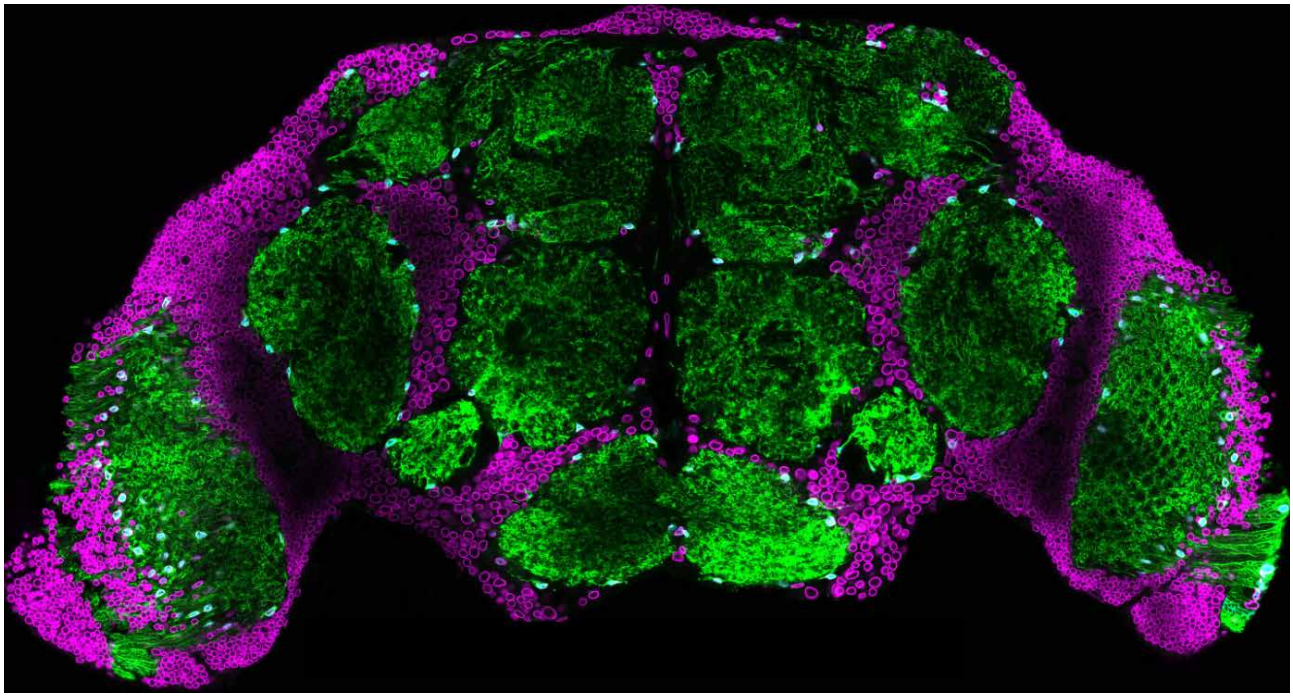
new therapeutic targets for conditions associated with dysfunctional glial responses.

'Although many proteins are undoubtedly affected by age-dependent decline in translation/stability, we propose that loss of the Draper receptor specifically impairs the activity of aged glia,' explained Drs Logan and Speese.

A New Signal

Draper seems to be a crucial player in neuronal protection. However, there is still a great deal to learn about how this receptor can help glial cells detect damage in nerve cells, and Drs Logan and Speese are keen to fill in these blanks.

‘Understanding precisely how glia recognise and degrade amyloid-like peptides will provide additional molecular and genetic targets to pursue for disease treatment.’



Drosophila *brain. Credit Sean Speese.*

As a way to impose damage in neurons, the team used a well-established method to cut the olfactory nerves in fruit flies. With this approach, they discovered a second type of receptor that is also involved in this process. This new receptor is called the insulin-like receptor and its activation within just a few hours of the injury is essential to stimulate the production of Draper and clear away debris. Not surprisingly, inhibition of this receptor prevents upregulation of Draper and proper glial immune responses after brain injury.

‘Our work now points to insulin-like signalling as a novel local communication relay between neurons and glia that initiates critical glial immune cascades,’ said Drs Logan and Speese. This receptor is known for its involvement in cell growth and energy metabolism among others, but this is the first-time insulin-signalling has been implicated in glial responses to neuronal damage.

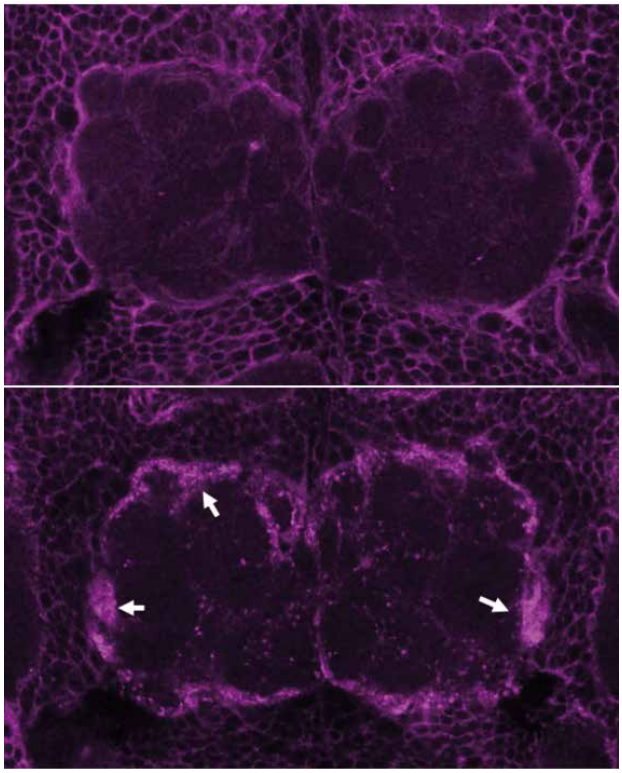
There are still many questions to answer, but the good news is that these results will encourage research groups to re-think the role of insulin-like receptors in the brain. Findings to date may even open the door for future therapies to control this signalling mechanism in a variety of conditions.

To Get to All Nooks and Crannies

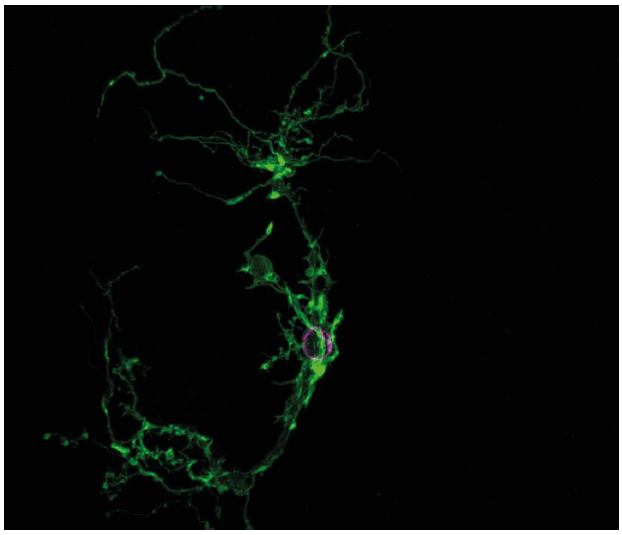
In order to complete their mission to remove cell debris from the brain, glial cells have the ability to change cell shape and size. This striking ability ensures that these cells can reach even the hard to get places to remove dead cells. However, our understanding of how these dynamic responses operate and exactly what components are involved in this process is very limited.

To answer these questions, the researchers decided to conduct an in-depth analysis of all the genes involved in this process. In this case, they cut nerves in the legs and wings of adult flies and then performed a genomics screen on the ventral nerve cord tissue, aka the ‘spinal cord’ of the fly. ‘We have developed a novel in vivo injury model in the adult Drosophila and defined a comprehensive dataset of conserved genes that are acutely up- and downregulated in response to nerve injury,’ said Drs Logan and Speese. ‘This strategy is revealing exciting new factors that are required for glia to sense and/or respond to degenerating neurons […] and provides a foundation for experiments that will rapidly advance our understanding of innate glial immunity mechanisms.’

In addition to the expected increase in the receptor Draper which the team already knew was involved, they found many other changes. One of the most relevant increases involved a protein called matrix metalloproteinase-1 (MMP-1). Crucially, they showed that this protein relies on Draper to function and, when both are present, glial cells will properly clear degenerating cellular debris. Loss of MMP-1 inhibits glial activity and delays clearance of degenerating neurons.



Top Panel: Draper protein staining in glial cells before nerve injury. Bottom Panel: Draper protein staining one day after injuring olfactory neurons. Credit Sean Speese.



Glial cell in the adult brain in which the membrane is shown in green and the cell nucleus is shown in magenta. Credit Maria Purice.

Going back to glia's morphological changes, the researchers suggest a model in which MMP-1 improves the ability of glial cells to infiltrate into all the 'nooks and crannies' where dead or damaged neurons may hide. 'In addition to providing a wealth of new data for future research,' commented Dr Logan, 'this project has identified MMP-1 as the first target transcriptional downstream of the Draper receptor and also revealed an interesting new role for MMP-1 in remodelling required for glia to infiltrate dense regions.'

Alzheimer's Disease

Continuing their quest to unveil the mechanisms behind glia's protective function, Drs Logan and Speese decided to turn their attention to when things start to go wrong in the brain. As the primary immune responders in the brain, it's easy to see how glial cells can be implicated in the onset and progression of neurodegenerative disorders. Alzheimer's disease is just one example.

One important feature of Alzheimer's disease is the formation of protein deposits outside the cells. This is known as plaque accumulation, composed of short peptides called amyloid beta. The researchers showed that increasing these damaging peptides induces Draper activity in glial cells, which in turn, is known to trigger expression of the metalloproteinase MMP1 and stimulate glial activity in the presence of neural injury. 'Understanding precisely how glia recognise and degrade amyloid-like peptides will provide additional molecular and genetic targets to pursue for disease treatment,' noted Drs Logan and Speese.

To confirm Draper's involvement, blocking this receptor in an Alzheimer's disease fly model exacerbates the problem, resulting in increased plaque formation, further locomotor dysfunction and reduced longevity in flies; whereas its increase rescued most cases, at least partially. Based on these findings, Drs Logan and Speese suggest a mechanism by which glial cells use Draper to activate a signalling cascade involving MMP1 and other components to possibly find and destroy plaques developing in the brain. 'We have discovered the Draper pathway provides neuroprotection in a model of Alzheimer's disease. Our work suggests that glial cells use the Draper receptor to find [amyloid beta] peptides and destroy them,' said Dr Logan.

From Flies to Humans

Drs Logan and Speese use fruit flies in all their experiments because they offer a powerful in vivo model to rapidly explore glial activity, but ultimately, the goal is to understand what happens in humans. The researchers believe there is no reason to assume that these results cannot be translated to mammals, and humans in particular. Just as in flies, Draper is also required for the glial activity elicited in response to degenerating or dying neurons in mammals.

The researchers propose that it is possible to use this knowledge to develop potential new therapeutic approaches to treat neurodegenerative disorders, such as Alzheimer's disease and others. 'This body of work highlights the Draper pathway as an exciting new therapeutic candidate to boost innate glial immune activity, including phagocytosis, to enhance neuroprotection with advanced age,' concluded Drs Logan and Speese.

Meet the researchers

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After four years at NPS Pharmaceuticals as a research associate followed by a PhD in neuroscience from the University of Utah and a postdoctoral fellowship at UMASS Medical School, Dr Mary Logan joined Oregon Health and Science University in 2010. During her career, Dr Logan has won multiple awards, including the Ken and Ginger Harrison Scholar Award in Neuroscience Research in 2016 and the Ken and Ginger Harrison Term Professor Award in Neuroscience Research in 2017. In addition, Dr Logan is a regular reviewer for many journals, including Cell and Nature, as well providing research supervision for a number of students and postdoctoral fellows. For the past few years, Dr Logan's team has been investigating how glial cells inform brain function and health. Currently, their focus is to understand how glial cells detect and respond to neuronal stress and damage in the brain.

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Dr Sean Speese earned a doctorate from the University of Utah in 2005 then completed a post-doctoral position at the University of Massachusetts Medical School. He then joined Oregon Health and Science University in 2010 to work with Professor Logan in the Department of Neurology. Honours and awards include the Oregon Scientist Development Award from the Oregon Health and Science University Medical Research Foundation in 2013, the National Institutes of Health Ruth L. Kirschstein NRSA post-doctoral fellowship in 2008, and the Jungers Center for Neuroscience Research – Fred Fields Scholar in 2015. Currently, the main aim of his research group is to understand the molecular underpinnings and function of a novel nuclear RNA export pathway termed Nuclear Envelope Budding.

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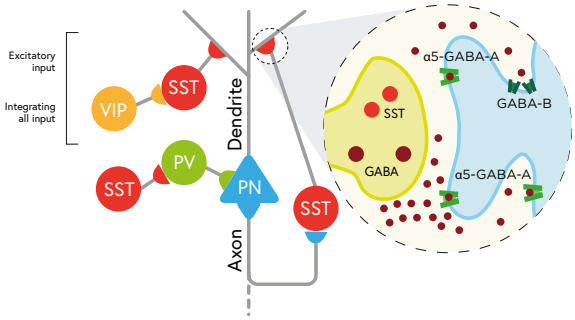
LIFTING BRAIN FOG

Effective treatments for cognitive dysfunction, such as declines in memory and other mental faculties often associated with depression or old age, may be within reach, according to **Professor Etienne Sibille** at the Centre for Addiction and Mental Health (CAMH) and the University of Toronto, Canada. Professor Sibille has shown for the first time that newly synthesised compounds targeting GABA receptors improve specific types of memory in mice, opening the door to the development of effective new pharmacological options.



Brain microcircuits: Targeting α5-GABAA-Rs for antidepressant, anxiolytic and pro-cognitive therapeutic efficacies. Glutamatergic pyramidal neuron (PN) excitatory information is controlled by various interneurons, including somatostatin- (SST), parvalbumin- (PV), and vasopressin- (VIP) expressing cells. Reproduced with permission from ACS Chemical Neuroscience

Cognitive dysfunction occurs alongside many psychiatric disorders, and as we advance in years a large proportion of us will experience some degree of age-associated cognitive impairment. Symptoms such as confusion, inability to focus attention, memory lapses, or even poor judgement, can make day to day living far more challenging than it needs to be. For many, the experience creates additional stress while decreasing quality of life.

Even if we haven't been touched by the effects of cognitive dysfunction directly, it is likely that each of us knows someone who has struggled at some point in their life with these kinds of symptoms. For instance, while the focus is mostly on mood, the majority of people with depression also suffer from cognitive dysfunction even when they are in remission. The number of people suffering from cognitive impairment of some form is estimated to be over 600 million worldwide, but effective treatment has been elusive. The impact of cognitive dysfunction isn't just a personal one, it can be wide-reaching, affecting relationships, ability to work, or even effectively manage self-care.

Despite this wide-reaching impact, scientists have yet to uncover a truly effective, well-tolerated treatment. The stated goals of Professor Sibille and his team at CAMH and the University of Toronto, Canada, are undoubtedly ambitious. As a collective, they aim to conduct cutting edge research into the neurobiology of aging and depression, and harness their discoveries to create truly effective treatments. In order to reach these goals, they employ large-scale genome, molecular, and bioinformatic approaches, as well as several animal models to test their hypotheses.

In recent years, this arsenal of methods has been turned to investigations of cognitive dysfunction across disorders and aging, to internationally recognised success. They've recently made promising steps towards an effective, well-tolerated pharmacological treatment for cognitive dysfunction, using a new approach which targets specific receptors in the brain of the neurotransmitter gamma-aminobutyric acid, also known as GABA.

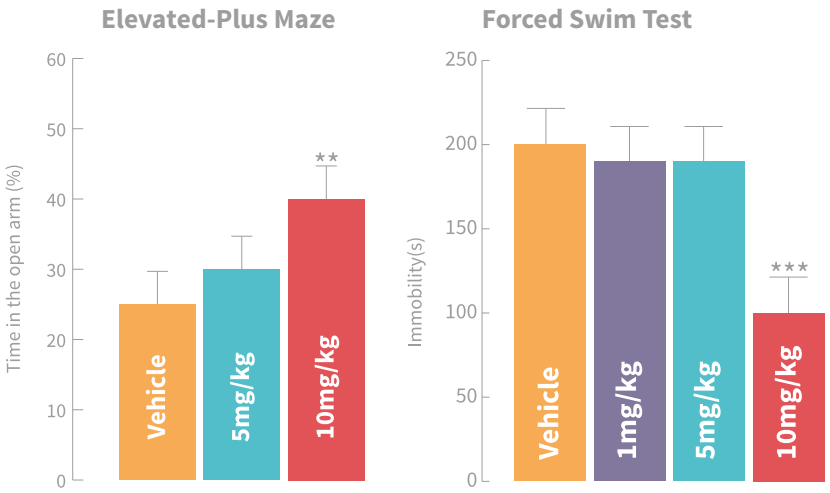
Target Practice

In the adult brain, GABA is typically associated with neuronal inhibition. More specifically, its action decreases the likelihood that a neuron will fire, and can, therefore, decrease the amount of activity in a given area. Inhibition is a vital process in the brain, offering a balance to neuronal excitation, and keeping everything in working order.

When inhibitive processes function atypically, our brain starts to run into problems. In neuropsychiatric and aging research, a reduced inhibitory activity is often identified as playing a significant role in cognitive dysfunction.

As Professor Sibille explains in a recent paper, at a cellular level, this inhibitive action is created by different types of GABA-ergic interneurons – cells responsible for GABA-release and communications between neurons. These influence the activity of other neurons, such as excitatory pyramidal neurons, which are central to coding information in the brain and to overall cognitive processing.

Not only that, but GABA-ergic interneurons come in different types, express different proteins, and are involved in various activities, each of which with differing therapeutic potential. Professor Sibille's group has now identified one of these neuron subtypes as a weak link in the brain, showing they are specifically vulnerable in brain disorders and aging, and that these neurons are involved in cognitive processing.



Acute treatment of GL-II-73 induces anxiolytic effect in the elevated plus maze (left panel), and antidepressant effects in the forced swim test (right panel) in mice and show significant differences compared to Vehicle group.
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Current therapeutics that aim to improve inhibitory processes leave a lot to be desired. Benzodiazepines interact with many types of GABA-ergic neurons and GABA receptors in a non-specific manner, meaning that the drugs have wide-ranging anxiolytic, sedative, anticonvulsant, and amnesic properties. While some of these effects are desirable, the side effects created by this kind of non-specific binding have limited their therapeutic ability. Many find the drowsiness created by treatment with benzodiazepines to be too intrusive to justify continuing these types of medication.

However, Professor Sibille and medicinal chemist colleague, Professor James Cook, from the University of Wisconsin in Milwaukee, USA, assert that by narrowing the action of a drug to specific types of GABA receptors, they can target the function that is specifically affected by the weak cells and also minimise the side effects. To this end, they have now identified which type of GABA receptor can be targeted to directly treat cognitive dysfunction, and have demonstrated the effectiveness of this approach.

Of Mice and Mazes

Professor Sibille and Dr Thomas Prevot, a behavioural pharmacologist working in his group, hypothesised that by activating α5-GABA receptors, they could rescue the identified weak interneuron link by normalising their inhibiting activity, and alleviate the associated cognitive dysfunction using their rodent models.

In order to test this, they designed and created three new ligands – small molecules that attach to receptors and facilitate their function – that would target these receptors. These took the form of imidazobenzodiazepines based on a hybridisation of two pre-existing drugs: diazepam and flumazenil. Both of these drugs are recognised for their clinical safety and effectiveness, and are known to target GABA receptors, making them ideal candidates for this kind of work. Professor Sibille's and Professor Cook's teams then worked on refining these molecules so that they target more specifically the α5 subtype.

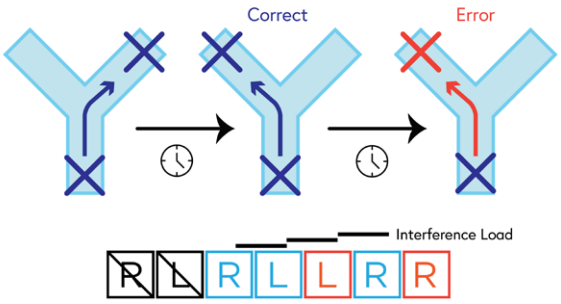
The team administered the newly synthesised ligands to mice that had been exposed to chronic stress conditions, as well as older mice, for one or 10 consecutive days. Both kinds of mice are regularly used as models for human mood disorders and cognitive dysfunction in this type of research. Any evidence that markers of cognitive functioning, such as working memory (information currently held in mind for immediate use), had been positively affected by these new ligands would provide solid reasoning to pursue further research into therapeutics produced in this manner.

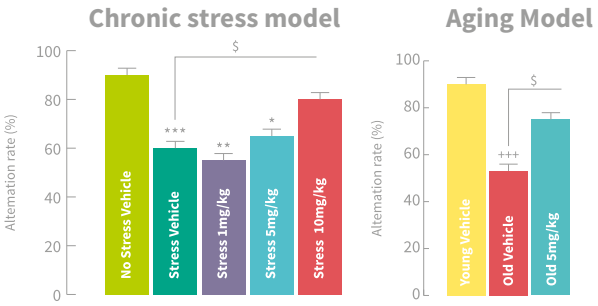
To begin with, the mice were tested against controls who had been injected with either a placebo solution or diazepam for evidence of anxiolytic and anti-depressant effects. The researchers employed two tasks: the Elevated Plus Maze and the Forced Swim Test.

The Elevated Plus Maze consists of two intersecting planks which create a 'plus' shape. Two of the arms of this plus are illuminated with bright lighting, and two arms are surrounded by an opaque wall that keeps the level of light low, and allows rodents to feel more secure. In animals that are anxious, more time will be spent in the less lit, covered areas, whereas those feeling comfortable will venture into brightly lit spaces for longer periods of time. Following ligand administration, rodents in this test spent significantly more time in the bright areas, suggesting lower levels of anxiety, and therefore, anxiolytic effects of the newly created ligands.

Similar positive effects were found in the Forced Swim test, where high amounts of time spent still in the water are interpreted as depression-like behaviours. The rodents that had been given the novel ligands spent significantly less time stationary, demonstrating the potential anti-depressant effects of the new ligands.

While these findings alone are promising, the results of tests probing cognition were even more dramatic. When testing cognitive dysfunction in the mice, researchers employed a classic Y-maze task. As the name suggests, mice are placed alone in a 'Y' shaped maze comprising three arms, each placed at 120 degrees to the others. This task is used to test spatial





Top panel. Dr Prevot demonstrates the use of the Y-Maze apparatus.

Middle panel. The Y Maze assesses spatial working memory. The mouse is placed in the start box and is free to choose between the left or right arm of the Y Maze. When an arm is chosen, the mouse stays in that arm for 30 sec and is then returned to the start box. After a delay, another trial starts in which the animal is supposed to alternate. Alternation is considered a correct choice, visiting the same arm as before is considered an error. With an increase in the number of trials, interference occurs making it difficult to remember the last trial because of the multiple trials previously performed. Lack of alternation is considered a marker for cognitive deficits. Credit Thomas Prevot.

Bottom panel. Stress (left panel) or aging (right panel) alter the cognitive performances in a working memory task, but such impairment is reversed by the use of the appropriate dose of GL-II-73 and show significant difference compared to Vehicle groups (no stress or young); $ show significant difference compared to Stress-Vehicle or Old-Vehicle group.

working memory, that is, memory about one's environment. As the maze is very simple, rodents with typically functioning working memory easily alternate between arms on successive explorations. However, rodents with impaired working memory are more prone to forgetting where they've already explored. This results in a marked increase in random wandering between arms, indicating the extent to which working memory may be impaired. This is what is observed in old mice or in mice exposed to chronic stress.

In their study, both the stressed and aged rodents dosed with two of the novel ligands had a significantly higher alternation rate than stressed and aged rodents that had received control non-active substances. Dr Prevot notes that in these tests, old mice treated with the novel ligands were performing near the level of younger, non-impaired mice. This seeming lack of disorientation indicates improvements in the way they were able to store and process information about the maze. By employing ligands that specifically targeted α5-GABA receptors, the researchers were able to significantly improve upon cognition in their rodent models of cognitive dysfunction.

Further inspection of the mouse tissues revealed that pyramidal neurons supporting information processing in the brain and that are associated with cognitive function, responded to the ligand treatment with new growth, effectively reversing the shrinking of brain cells that occurs during normal aging, and improving the connections and possibly the function of these cells on a physical level. This is particularly promising, as it suggests that the compound may be suitable for adaptation into a medication that could be taken long-term to ensure efficacy over time.

Into the Future

Professor Sibille and his colleagues believe that these findings present a strong argument for the development of novel therapeutics which target α5-GABAA receptors as a potential treatment for cognitive dysfunction across brain disorders and during aging. With this information in hand, his studies are likely to have a far-reaching effect on how we approach the treatment of cognitive dysfunction. Given the novelty of their approach, the findings of the lab may represent a coming paradigm shift in psychiatry.

Cognitive dysfunctions are associated with depression, suicidality and other neuropsychiatric conditions and are prevalent during aging and age-related brain disorders. These continue to rise, already playing a negative role in the lives of many. With this research, Professor Sibille and colleagues aim to actively pursue the creation of α5-GABAA receptor targeting drugs to tackle cognitive impairment. They hope to create more palpable medications with reduced side-effects, and in doing so, improve the lives of millions of people with various memory and other cognitive problems.

Meet the researchers

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Professor Etienne Sibille received his PhD in Pharmacology in 1999 from Cornell University Medical College, New York, then proceeded to rise rapidly through the academic ranks at the University of Pittsburgh, Pennsylvania. In 2014, he accepted the appointment of Professor at the University of Toronto and that of Senior Scientist at the Centre for Addiction and Mental Health, Toronto. From 2017, Professor Sibille has also been the Deputy Director of the Campbell Family Mental Health Research Institute, Toronto. Professor Sibille investigates the neural mechanisms of depression and aging, and develops novel treatments for associated cognitive dysfunction. He is a highly esteemed neuroscience researcher, having published more than 100 peer-reviewed papers across a range of high-impact journals, and is the recipient of many prestigious grants and awards, commensurate with his ongoing contribution to science.

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Centre for Addiction and Mental Health
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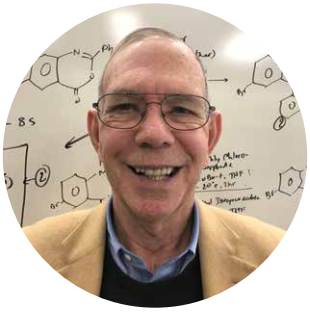

Professor James Cook
University Distinguished Professor
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USA

Professor James Cook received his PhD in organic chemistry in 1971 from the University of Michigan, USA. After completing a postdoctoral fellowship at the University of British Columbia, Vancouver, he took up a position at University of Wisconsin–Milwaukee, USA, and remains there to this day, currently in the role of University Distinguished Professor. Thus, Professor Cook has directed a university research laboratory for more than 30 years, focusing his research on synthetic organic and medicinal chemistry, and confirming his specific interest in compounds that modulate central nervous system neurotransmission. Over his illustrious career, he has published more than 500 peer-review journal articles and has filed over 60 patents, many of which have been issued. He has maintained an active collaboration with Professor Sibille since 2012.

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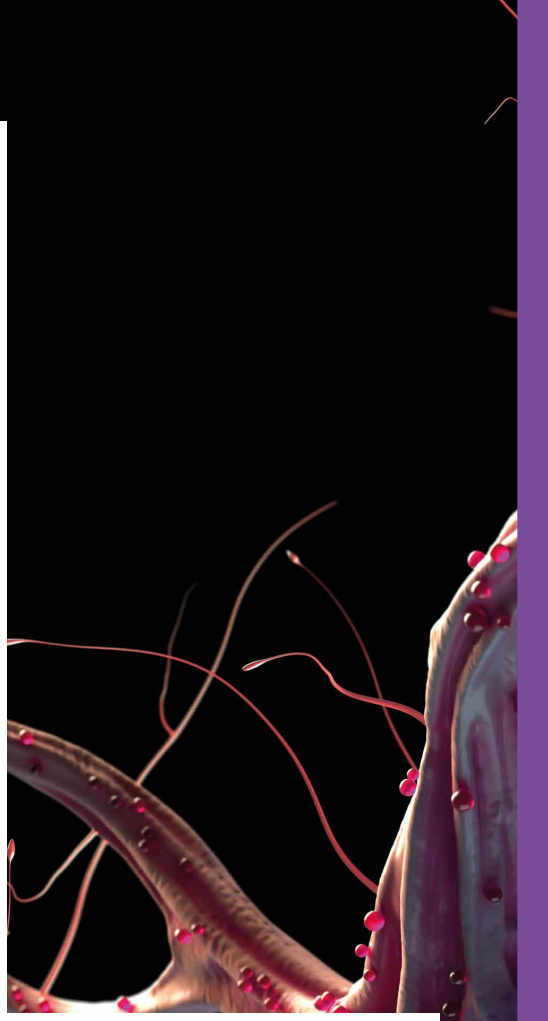
UNIVERSITY OF TORONTO

THE BLOOD-BRAIN BARRIER: MORE THAN JUST A BARRIER

Neurodegenerative disorders present a major cause of death and disability worldwide. Treatments are typically expensive, non-efficient, and invasive. Although scientists are committed to finding better treatment strategies, the challenge of penetrating the blood-brain barrier remains. This highly selective envelope protects our brain from harmful substances but also prevents drugs from reaching the brain when needed. **Dr Shikha Nangia** at Syracuse University, USA, focuses on understanding the molecular structure of this complex interface to ultimately facilitate the transport of drugs across the blood-brain barrier.



The Blood-Brain Barrier: A Blessing and a Curse

The blood-brain barrier is a highly selective barrier that allows only vital nutrients (such as glucose and water) to enter the brain and filters toxic substances present in the bloodstream. Its integrity is crucial to our survival but in some pathological contexts, it may become leaky.

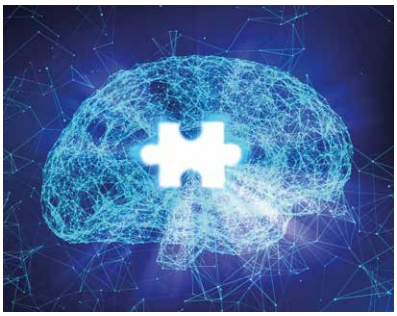
Neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease are characterised by the progressive degeneration of neurons in various brain regions. Currently available drugs are not able to effectively penetrate the blood-brain barrier. Overcoming this difficulty would open a new and unchartered horizon for the development of treatment strategies that could benefit a range of neurogenerative diseases.

Dr Shikha Nangia at Syracuse University, USA, is determined to overcome this challenge. Together with her team, Dr Nangia is progressively unravelling the secrets of blood-brain barrier permeability using advanced computational techniques.

Gatekeepers of the Blood-Brain Barrier

Dr Nangia often uses the analogy of the hook-and-loop fastener known as 'Velcro' to explain how the blood-brain barrier functions. Between the brain and the blood, there is a single layer of cells that are strongly attached to each other. This layer is principally composed of blood vessel cells (called endothelial cells), stitched together by tight junctions acting as gatekeepers. These tight junctions are formed between membranes of two adjacent cells and are primarily made of proteins named 'claudins'. Claudins were identified for the first time in 1998 by Japanese researchers and were named after the Latin verb claudere 'to close', already suggesting the barrier role of these proteins in the brain.

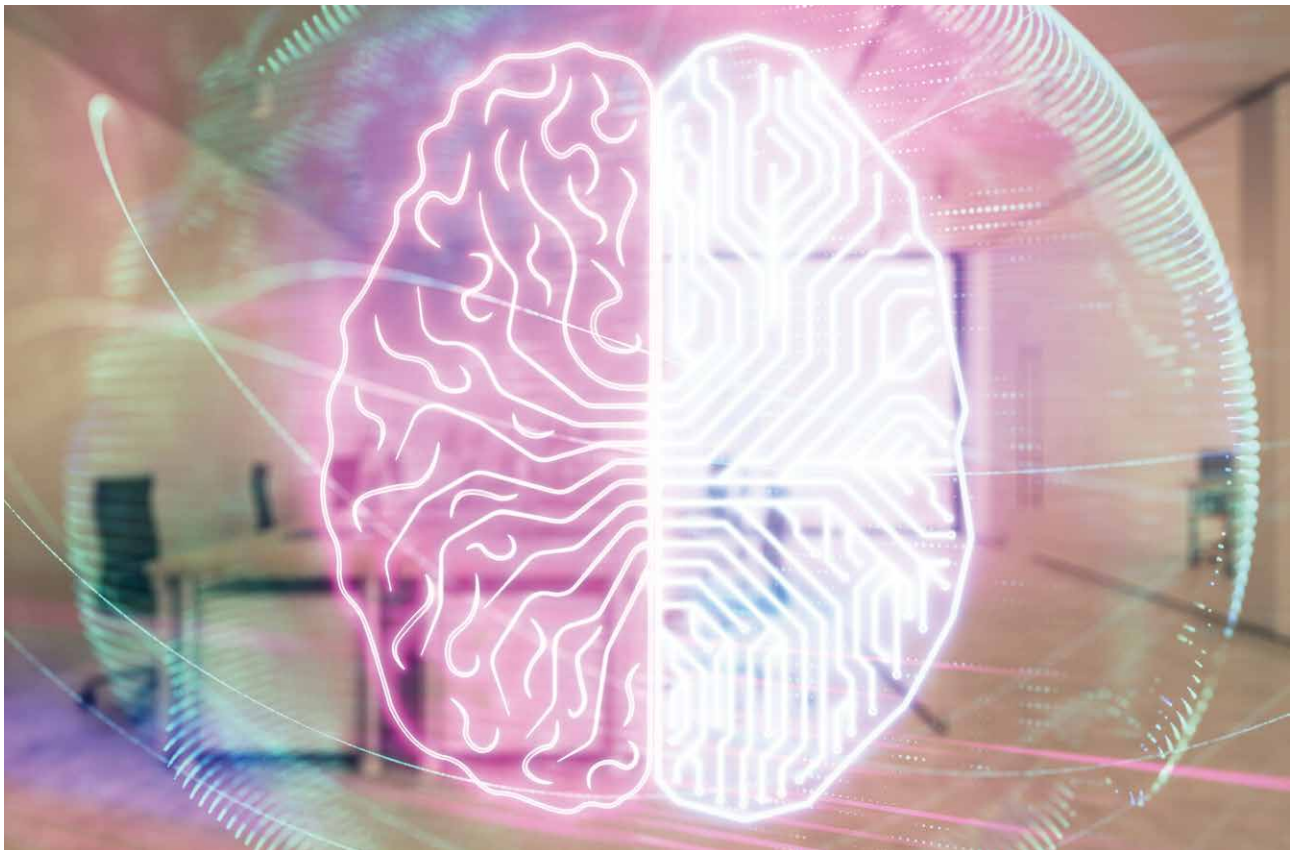
The claudins represent one of the main research areas for Dr Nangia as they have a crucial role in the permeability of the blood-brain barrier. More



specifically, they are able to form a physical fence between cells that is responsible for filtering the influx of nutrients into the brain.

The difficulties in isolating the intact tight junction strands using experimental techniques had made research progress difficult. Therefore, Dr Nangia and her colleagues developed a computational approach to get around this technical challenge. They are simulating the blood-brain barrier interface *in silico* (performed on a computer), from the basic claudin structure to tight junction aggregates.

This approach allowed Dr Nangia and her team to publish in 2015 their observation that two claudins can



spontaneously interact to form a dimer (a process known as dimerisation). Dr Nangia's team showed that among all possible dimers, there were four dimers that were observed frequently. The predicted dimers matched with the experimental results. Dr Nangia noted that out of the four dimers, two dimers could form pores to allow the passage of small molecules in and out, contributing to the tight junction permeability. Intrigued, Dr Nangia and her team measured the stability of each dimer by calculating the force needed to separate the two claudins, and found that each dimer had different stability.

They then went a step further and proposed that the lipid composition of the cell membrane might also play a role in the dimer interaction. The results showed that interactions between two claudins are driven by the lipid environment of the cell membrane. This discovery has far-reaching consequences because it provides important insight into the transport properties of the tight junctions and into the physiological complexity of the blood-brain barrier itself. Furthermore, the relevance of these findings extends beyond the blood-brain barrier as claudins are a large family of proteins that establish tight junctions in numerous other interfaces throughout the body.

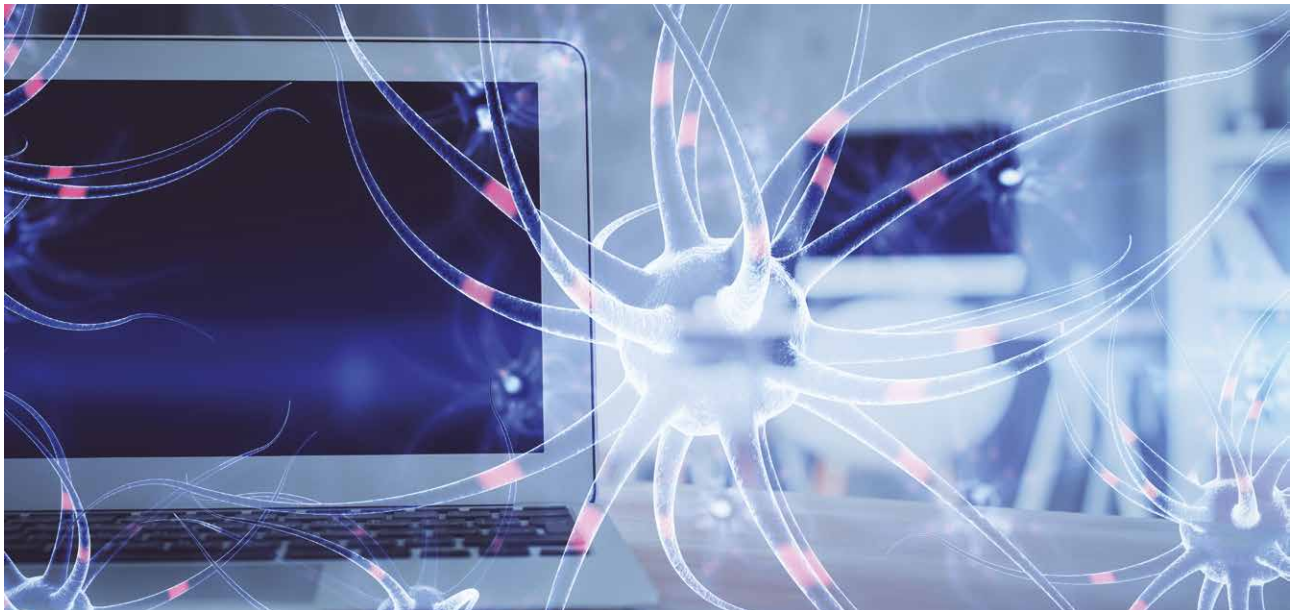
An Additional Signal to Influence Claudin Interactions

It has been well established that after they are expressed in a cell, proteins undergo a series of transformations known as 'post-translational modifications'. These modifications slightly change the protein to influence either their function or their dynamic. For example, they can act as signals to guide the final protein to its designated location.

Previous studies have demonstrated that various post-translational modifications of claudin can directly influence tight junction architecture, notably through the addition of a single palmitic acid molecule (the basic component of palm oil) – already known to play a role in tissue permeability regulation. This process is referred to scientifically as palmitoylation, with the precise function being dependent upon the proteins involved.

In this context, Dr Nangia and her colleagues reported in 2019 that claudin palmitoylation can influence the capacity of claudins to form a dimer and as well as the dimer stability. This completed another important piece of the puzzle, as they came to believe on the basis of these findings that palmitoylation has a significant impact on the permeability of tight junctions.

This finding is again applicable to many other interfaces, as explained by Dr Nangia, 'overall, this study contributes to the growing body of research focused on understanding the significance of post-translational lipid modification of



proteins in cellular and subcellular membranes and its impact on critical cellular functions.'

A Novel Approach to Study Protein-Protein Interactions

Computational approaches are often associated with having several limitations, including being highly time-consuming and expensive. In 2019, Dr Nangia and her team published details of their recently developed accessible, robust, and affordable approach to study protein interactions: PANEL, which stands for Protein AssociatioN Energy Landscape.

PANEL is based on calculating the non-bonded interaction energies between two proteins, which depend on the position and the orientation of the two proteins relative to each other in the cell membrane. The PANEL approach computes this energy for all the possible protein-protein orientations and ranks their stability. Dr Nangia further explains that the PANEL method can generate a comprehensive dataset for any interacting membrane protein – which is at least 100 times faster than other available methods. Indeed, Dr Nangia and her colleagues have used the PANEL plot to generate a comprehensive sampling of dimer conformations and provide a clear visualisation of the entire energy landscape demonstrating the dimer interaction energies.

Progressively, Dr Nangia and her colleagues are diving deeper into the tight junctions of the blood-brain barrier and they now have a clear idea of the claudin interactions necessary for maximal permeability. It is important, however, to remember that tight junctions provide dynamic interfaces that undergo continual change, and that many other physiological factors contribute to the final architecture.

Limitations and Perspectives

Using computational tools, Dr Nangia and her team have explored the depth of the blood-brain barrier, bringing fundamental findings to the scientific community. To put these findings in perspective, approximately 40 other families of proteins are known to be involved in the tight junction architecture. Though they do not directly contribute to the selectivity of the tight junctions, their structural function suggests that they also interact with claudins to strengthen the backbone of the blood-brain barrier.

Furthermore, several other studies have reported claudin aggregation into groups known as trimers, tetramers, and even hexamers, according to the number and arrangement of the protein subunits. This highlights the high level of complexity of the tight junctions in their regulation of the permeability of the blood-brain barrier.

Although many questions are yet to be answered, Dr Nangia's approach and the PANEL method will enable future research to focus on developing strategies to facilitate drug delivery into the brain. The next critical step forward is now to identify small molecules that could be used to modulate tight junctions, allowing treatments to target the brain but in a safely controlled and temporary manner. As one might imagine, the pores cannot stay indefinitely opened, as this would leave the brain vulnerable to damage through exposure to innumerable toxins.

Ultimately, modulating the blood-brain barrier and controlling its permeability will allow drugs to reach the brain via the bloodstream. This is an unchartered territory that will give rise to new challenges such as drug safety for the brain and side effects, but one that offers enormous potential for progressing treatment for neurodegenerative diseases. Dr Nangia and her team are making giant strides forward towards making such much-needed treatments a real possibility in the coming years.

Meet the researcher

Dr Shikha Nangia
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Dr Shikha Nangia received her PhD in Chemistry from the University of Minnesota, Twin Cities, in 2006. After completing postdoctoral training at Pennsylvania State University, Dr Nangia settled in 2009 at the prestigious Syracuse University, USA, where she is now an Associate Professor in the Department of Biomedical and Chemical Engineering. Dr Nangia's research focuses on using computational approaches to overcome biological barriers and to enhance drug delivery. Her research projects include exploring treatments for Alzheimer's and Parkinson's diseases, cancer, and diabetes. Her recent focus has been to examine the architecture of the blood-brain barrier with the aim to identify novel strategies to facilitate the transport of drug molecules into the brain. Using innovative computational approaches, Dr Nangia's research has received substantial funding to date. Dr Nangia has also received numerous honours and awards for her research and teaching throughout her career, and she was most recently awarded for her outstanding contribution to student experience and university initiatives at Syracuse University.

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Syracuse University

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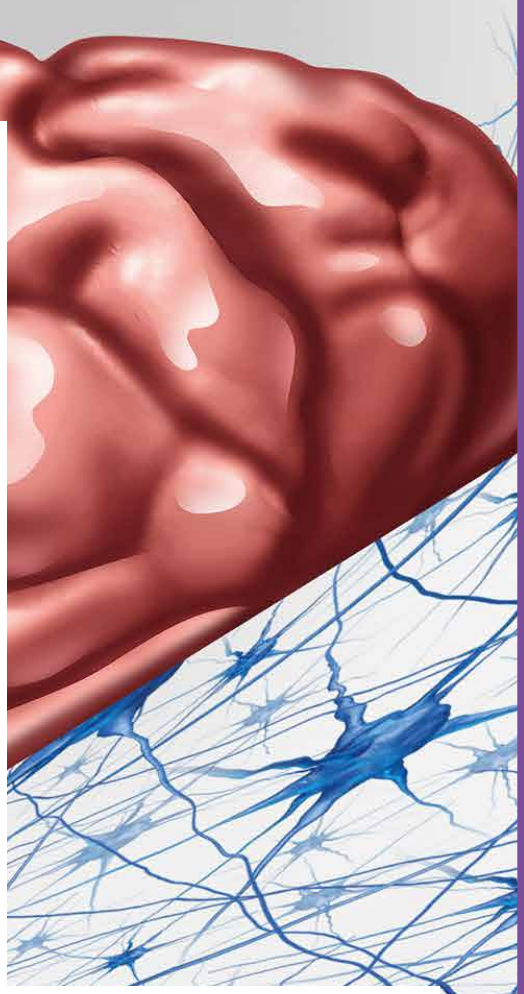
Syracuse University

INVESTIGATING THE LINKS BETWEEN GENERAL ANAESTHETICS AND ALZHEIMER'S DISEASE



General anaesthesia may increase the build-up of amyloid beta, a protein implicated in the development of Alzheimer's disease. **Professor Gerhard Rammes** and his team at the Technische Universität München, Munich, Germany, along with **Dr Martina Bürge** at St Bartholomew's Hospital, London, are researching the potential benefits of one specific anaesthetic, xenon, which in addition to having lower neurotoxicity than many other anaesthetics may also offer neuroprotective effects. These findings may have critical implications for personalised medicine in patients with dementia.

General Anaesthesia and Alzheimer's Disease

Almost two hundred years ago, the discovery of general anaesthesia was considered a medical miracle, allowing millions of patients to undergo invasive, life-saving surgery without awareness or pain. Although a fundamental component of modern medicine, how precisely general anaesthetics result in the loss of consciousness remains a mystery.

One current view is that anaesthetics may bind to neuronal proteins, such as receptors in the brain, and modulate many components of cognitive function, that is, the mental processes underlying thinking and memory. Although fulfilling the immediate aim of loss of consciousness, unfortunately, this may also result in lasting effects that are linked to the development of Alzheimer's disease later in life.

Alzheimer's disease, along with other forms of dementia, is characterised by progressive memory impairment and cognitive decline to functions including language and attention. Other symptoms may include disorientation, impairments in judgement, and changes in mood and behaviour. As of 2019, nearly 44 million people are living with Alzheimer's disease worldwide and this number will, due to demographic changes, inevitably rise. Currently, there is no cure and no treatment to date can even slow its progression.

Identifying causal influences on the development of dementia is critical. Professor Gerhard Rammes and his team at the Technische Universität München, Munich, Germany, along with Dr Martina Bürge at St Bartholomew's Hospital, London, are trying to discover how general anaesthesia may lead to dementia. Professor Rammes notes the current debate in this field and explains, 'It is controversially discussed whether general anaesthesia increases the risk of Alzheimer's disease or accelerates its progression, but the discussion is still ongoing.'

Ideally, anaesthetic drugs in clinical practice should be chemically stable, inflammable, relatively non-toxic, display minimal side effects, both in the short- and longer-term, and have no

interactions with other administrated drugs. Unfortunately, not many of the drugs in the operating room tick all these boxes.

Xenon, one of the drugs that Professor Rammes and colleagues is particularly interested in, fulfils many of the desired qualities of a general anaesthetic. Once inhaled, this noble gas harmlessly permeates the body tissues until it engages with proteins, leading to a physiological shutdown that safely knocks patients unconscious.

‘It is controversially discussed whether general anaesthesia increases the risk of Alzheimer’s disease or accelerates its progression, but the discussion is still ongoing.’

Mysterious Amyloid Beta Plaques

Previous experiments on animals and cell models show that anaesthesia can increase the build-up of amyloid beta, a protein that slowly and insidiously piles up in the brains of people with Alzheimer’s disease. Yet is it not entirely clear what is going on: when abnormal pieces of amyloid beta protein, known as amyloid beta 1-42 and 1-40, attach onto each other, they form the infamous plaques associated with Alzheimer’s disease.

Currently, there are two main theories connecting anaesthesia and amyloid beta plaques to Alzheimer’s disease. Some researchers argue that all general anaesthetics may increase the build-up of amyloid beta, and thus, accelerate or deteriorate the disease the disease. However, Professor Rammes and colleagues have shown that this is unlikely to be the case – interestingly, receiving xenon does not seem to increase the likelihood of developing Alzheimer’s disease nor aggravate it. But what *do* we know about the relationship between general anaesthesia and this permanent, debilitating condition?

In order to tackle the question of whether anaesthetic drugs influence the progression of dementia, Professor Rammes’s team utilised slices taken from the brains of male mice that they could pharmacologically manipulate and study in the lab. To establish proof of concept, the researchers first examined whether amyloid beta plays a role in a process known as long-term potentiation (LTP). LTP refers to the strengthening of the connections between neurons in the brain and thus forms the cellular basis of long-term memory. In the brain slices of male mice, the researchers found that as the formation of beta-amyloid to toxic aggregates increased over time, LTP decreased. This was an expected finding and already evidenced, given that Alzheimer’s disease results in memory loss.

Anaesthetic Xenon to the Rescue?

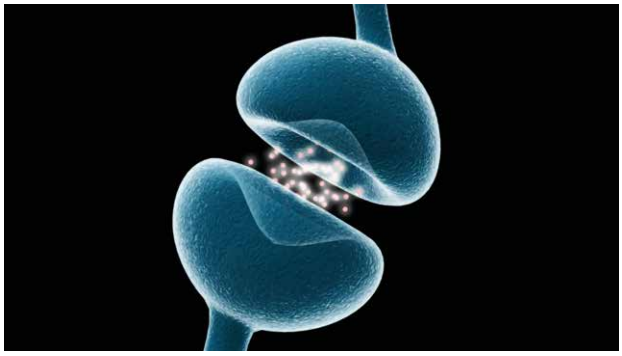
Professor Rammes did not stop his investigation at amyloid beta-induced LTP. His team extended their efforts to two anaesthetics, S-ketamine, and xenon. Both drugs are antagonists at NMDA receptors, known to be important for a number of processes in the brain. After confirming that neither of these two drugs impacts upon LTP in their own right at a specific low concentration, the researchers looked at how they may, however, affect amyloid beta-induced LTP.

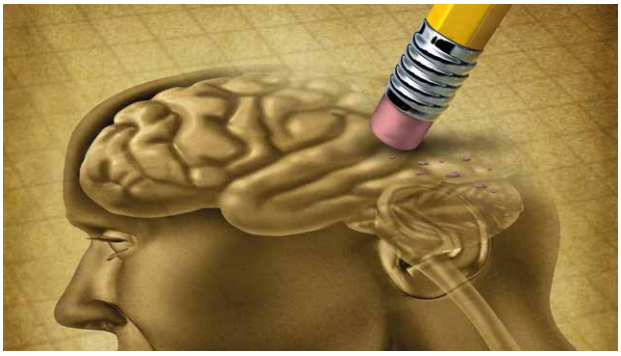
First, they found out that S-ketamine wasn’t ideal. Xenon, however, did reduce the amyloid beta-induced impairment of LTP. Yet, it did not reach the level it was at before the amyloid beta already caused harm. Xenon accomplished that at low doses, however, the treatment was not sufficient to simulate deep anaesthesia, but, rather, a sedated state. The researchers warned that once the dose was increased, xenon may show an even bigger effect.

Professor Rammes and his team have conducted these initial tests on the amyloid beta peptide 1-42 (Aß1-42), a chopped off part of the total amyloid beta protein. While Aß1-42 is believed to be the main culprit in the early pathogenesis of Alzheimer’s disease, there are also other protein parts that play a significant role. One of them is amyloid beta 1-40 (Aß1-40), a slightly smaller version of the amyloid beta protein.

When testing the effects of xenon on Aß1-40, the anaesthetic did not add to the recovery of amyloid-beta-induced LTP. In a recent paper, Professor Rammes notes, ‘None of the drugs tested were able to ameliorate the Aß1-40-induced impairment of LTP suggesting that the target receptors

‘Here we found that the gaseous aesthetic xenon protects neurons against the toxic effects of Aß1-42, the most pathogenic form of amyloid beta species and restores long-term potentiation, a cellular correlate for learning and memory, in hippocampal slices.’





mediating synaptic dysfunction may differ between the different Aß species.’

However disappointing, the researchers confirmed that xenon may accomplish its goal by acting on one amyloid beta variant (i.e., the most toxic form), but not another one. Future research now needs to consider the differences between these two amyloid beta pieces and the target at which xenon acts to eliminate beta-amyloid-induced LTP.

New Players Enter the Game

Professor Rammes’s team was aware that xenon preferentially targets the so-called NMDA receptors in the brain. These play an important role in learning and memory. Interestingly, when neurons encounter beta-amyloid molecules, NMDA receptor targets open, leading to Ca2+-influx, large-scale swelling and, ultimately, to their destruction. Only after the researchers used the drug xenon or radiprodil, a specific NMDA receptor subunit 2B blocker, were these NMDA receptors on the surface on the neurons seen to close, resulting in memory improvement at least in the presence of amyloid beta.

At the cellular level, the team has found that xenon may partly reverse LTP reduced by amyloid beta 1-42. ‘Here we found that the gaseous aesthetic xenon protects neurons against the toxic effects of Aß1-42, the most pathogenic form of amyloid beta species and restores long-term potentiation, a cellular correlate of learning and memory, in hippocampal slices,’ Professor Rammes explains.

Looking to the Future

At first glance, Professor Rammes’s findings suggest that a beneficial alternative as an anaesthetic of choice for Alzheimer’s patients may be xenon. If xenon can restore LTP and reduce the damage formed by amyloid beta, why not use xenon instead of other anaesthetics in patients suffering from this disease? Unfortunately, there are other factors to take into account.

The problem is that xenon is rare – 87 parts per billion. Another difficulty is its steep price tag. It has been proposed that capturing xenon back from the patient through some sort of a xenon recycling process may be an option. In time, this may make the gaseous anaesthetic more economically viable.

Still, we have a long way to go. The research by Professor Rammes has so far focused exclusively on male brain slices but more studies are in the pipeline. Future research will look at the effects of xenon in mice, both males, and females, and see how different doses of that same drug affect the animals. The team’s next step also involves linking autophagy, a process in which cells clear out the damaged protein, and xenon. However, in Alzheimer’s disease, the cells’ cleaning crew goes on strike. Once in place, it will be important to see whether xenon can mediate this strike.

In further work, a mouse model of Alzheimer’s disease will be used to assess cognitive performance after xenon anaesthesia to unravel the potentially beneficial effects. Finally, since Aß1-42 proteins are prone to aggregate, thus forming toxic oligomers, the team will investigate the interaction of xenon and other anaesthetics in this aggregation process. It is obvious that apart from the intrinsic processes influencing Aß generation/degradation, a potential acceleration of Aß oligomerisation by anaesthetics and thereby promotion of Aß toxicity would have critical implications for the practice of clinical anaesthesia.

Through their research, Professor Rammes and his team are forging the way ahead for understanding the link between anaesthesia and the development of dementia, and setting the necessary scene to apply these concepts in the clinic. The translation of this work from bench to bedside, will, of course, be an ongoing challenge. Nevertheless, Professor Rammes is committed to addressing the issues that are critical to Alzheimer’s patients undergoing surgery. Ultimately, he hopes his results will have critical implications on personalised medicine. By ensuring a patient’s safe and predictable postoperative response and recovery, individualised anaesthesia for Alzheimer’s patients may be more effective.

Meet the researchers

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Professor Gerhard Rammes achieved his PhD from the University of Birmingham, UK, in 1996. Since then, he 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 and Intensive Care at the Technische Universität München, Munich, where his team uses multiple techniques investigating 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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Dr Martina Bürge obtained her MD from the University of Freiburg, Germany, in 2011. During her anaesthetic training at the Department of Anesthesiology and Intensive Care at the Technische Universität München, Munich, she joined Professor Rammes's team as a postdoctoral researcher and has been involved in investigating the interactions of anaesthetic drugs and Alzheimer's disease since 2012. She currently works as a Senior Clinical Fellow in cardiac anaesthesia and intensive care medicine at St Bartholomew's Hospital in London, UK.

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WEARABLE TECHNOLOGY TO DETECT RISK OF FALLING AND FRAILTY

Accidental falls are one of the leading causes of injuries and accidental death for the elderly, and the risk of falling increases significantly in those with neurological disorders or frailty. **Dr Fay B Horak** and her colleagues at Oregon Health & Science University and APDM Wearable Technologies, USA, are investigating the use of APDM's novel wearable technology to monitor mobility in daily life of individuals at risk of falling to help prevent falls and identify prefrail elderly individuals.

Measuring Mobility

Elderly people, especially those with muscle loss and weakness, a feeling of fatigue, slow walking speed, and low levels of physical activity (known as frailty) have over a 50% chance of falling each year. Individuals affected by neurological disorders, such as Parkinson's disease (PD) and multiple sclerosis (MS), are at an even greater risk of falling and seriously injuring themselves. Falls in older people often lead to hospitalisation, nursing home admission, and even death. Accidental falls are more common in individuals with impaired mobility, in other words, those experiencing difficulty walking, poor balance, sensory loss or muscle weakness.

Past studies have confirmed an association between impaired mobility and fall-related incidents but evaluating the mobility of individuals outside of laboratory or healthcare settings is very challenging. Many clinicians believe that medical examinations do not reflect the actual functional mobility of their patients in their everyday lives. When people are observed performing a short walk they pay attention to their walking and tend to do their best. In everyday life, people need to attend to other things while they walk, meaning that their automatic walking patterns are often more affected by their impairments.

In addition, mobility can fluctuate over time due to many different factors, such as a patient's fatigue, quality of sleep the night before, the effects of medications or characteristics of their surrounding environment. To accurately and reliably measure people's mobility, therefore, walking and turning mobility needs to be monitored continuously throughout their day.

Recent technological advances are opening up new possibilities for the development of tools to monitor mobility in daily life. Wearable devices and inertial sensors, for instance, could allow clinicians to collect valuable data about movement quality and quantity throughout the day. Daily monitoring of abnormal movement patterns could, in turn, help clinicians to estimate a patient's risk of falling and propose suitable interventions that might reduce this risk and keep people active and safe in their home environments.

Dr Fay Horak and her Research Group (Summer 2019)

Smart Socks developed by APDM Wearable Technologies

‘Our research addresses the feasibility, methodological advantages and challenges of measuring digital gait characteristics during free-living activity in PD, MS, ataxia, and elderly fallers.’

Measuring the Quality of Gait

Despite the potential of such wearable technology, there is currently no commercially viable technology for daily monitoring of quality of foot movements while walking in daily life. With this in mind, Dr Fay B Horak, a Professor of Neurology at Oregon Health & Science University, USA, has been working with APDM Wearable Technologies to explore how instrumented socks may help to monitor mobility more effectively. APDM was founded with the objectives of creating novel technologies to enable the scientific community to conduct quality research in movement science, accelerate clinical trials by introducing a new generation of biomarkers and validated endpoints, and improve the quality of life of people with movement disorders through precision medicine for neurodegenerative diseases.

Monitoring Daily Mobility using Wearable Sensors

Over the past decade or so, Dr Horak and her team have conducted extensive research exploring the potential of wearable technology in healthcare settings, particularly for gathering patient data before and after medical examinations. Now they have extended this technology so patients can wear instrumented socks during daily life for weeks in their home environments. ‘Passive, unsupervised monitoring of the quality of mobility in daily life using wearable inertial sensors has great promise for improving the care of patients with neurological disorders that affect walking and balance control,’ Dr Horak explains. ‘Clinical practice would benefit from valid, sensitive, reliable measures of quality of walking in community settings that reflect disease type, disease severity and responsiveness to intervention. The quantification of gait characteristics in unsupervised environments, however, presents considerable challenges.’

According to Dr Horak, effectively and continuously recording data characterising the quality of a patient’s movements, gait (i.e., style of walking), and balance could have many advantages. First, it would allow researchers and clinicians to attain more accurate and sensitive mobility measures, helping them to better understand how neurological disorders affect gait and balance in everyday settings, that is, outside of medical examination rooms.

The collection of much more and more accurate data would enable faster and cheaper clinical trials with smaller groups of participants as well as measuring behaviour that better reflects their mobility in everyday settings. In addition, wearable sensors could help to identify patterns and variations in a patient’s mobility over time, which might indicate progression of disease, responses to medication, fatigue, or symptoms of a specific neurological disorder. This information could allow doctors to identify recovery or degenerative patterns after treatment, without the patient having to return to the doctor’s office.

The Benefits of Continuous Monitoring

The wearable devices used by the researchers in most of their studies are Opal Sensors and more recently, prototype Smart (instrumented) Socks, developed by the innovative medical device company known as APDM Wearable Technologies, based in Portland, Oregon.

Dr Horak and her colleagues carried out a study exploring the benefits of daily monitoring, in which they compared gait metrics collected in the laboratory to those gathered using wearable sensors 14 hours a day for 7 days of daily life. Interestingly, continuous monitoring allowed them to differentiate specific gait characteristics of people with PD and MS, as well as those of healthy subjects, better than short walks in the clinic. The differences between gait metrics collected in the laboratory and at home were particularly accentuated in individuals with PD. For example, they found that people with PD walk much more slowly in daily life than they do when observed by medical professionals.

Discriminating Neurological Disorders with Gait Metrics

In a different set of studies, Dr Horak and her team tried to uncover digital gait patterns or characteristics that might be particularly useful for measuring the quality of mobility. The key goal was to determine specific gait, turning, and movement-related metrics that could help to predict future fall risk in PD and MS patients. They found that quality of turning while walking was even more sensitive than quantity of turning or walking (activity or step counts) to discriminate mobility in daily life from people with PD and same age adults without PD. People with PD turned more slowly with many more steps, even when the disease was very mild and their walking speed was still normal.

'We also study how gait and turning characteristics versus activity measures during daily life can discriminate people with pathology and detect risk (i.e., prodromal neurological disease before motor signs are clinically obvious, fall risk, and so on),' Dr Horak comments. 'We have found that the quality, but not the quantity, of mobility in daily life is sensitive to PD, whereas the quantity of mobility is sensitive to MS.' For example, although turning speed is slow in PD, they turn over 100 times an hour and have long walking bouts, just like people without PD. In contrast, people with MS show shorter and fewer walking bouts than age-matched people without MS. People with MS also show abnormalities in quality of walking such as slow speed and more variability of walking.

Dr Horak and her colleagues found that some gait measures are particularly important when distinguishing walking patterns in daily life of people with different neurological disorders. For example, the angle of the foot at heel strike is lower in people with PD but the height of the foot off the floor is higher in people with Spinocerebellar Ataxia (SCA). This suggests that different mobility metrics are particularly discriminative when assessing the mobility of people with different disorders, and thus, medical interventions should be designed accordingly.

In addition, very short bouts of walking might be more helpful to differentiate mobility and motor signs associated with PD than longer bouts. In fact, the duration of continuous walking performed by people alters their gait characteristics. That is, healthy people and people with MS walk with faster steps per minute the longer the walking bout. In contrast, people with PD do not increase their steps per minute when walking longer distances.

Developing Effective Technology to Monitor Daily Mobility

Dr Horak and her colleagues are using these findings to develop a new technology to measure gait-related activity in people with mobility impairments and assess their risk of falling called Smart Socks, developed by APDM Wearable Technologies.

Smart Socks are comprised of an instrumented ankle bandage with software and cloud storage that calculates hundreds of gait-related characteristics. The instrumented socks continuously monitor not only how many steps and turns a person makes per day but also the quality of those steps and turns. Unlike many existing techniques for measuring gait with sensors, the system can also characterise gait in people that shuffle their feet by detecting the angle and height of the foot while walking, as well as coordination and asymmetries of steps which is not possible with gait sensors place on the waist or wrist. The instrumented socks are comfortable, easy to wear, and only need to be charged at night like mobile phones.

New and Efficient Tools to Assess the Risk of Frailty and Falls

The research carried out by Dr Horak and her colleagues has important implications. Their work suggests that monitoring gait-related metrics on a daily basis could help to better assess the risk of falling for people with limited mobility, allowing doctors to gain insight about their patients both inside and outside of healthcare facilities.

'Our research addresses the feasibility, methodological advantages and challenges of measuring digital gait characteristics during free-living activity in PD, MS, ataxia, and elderly fallers,' Dr Horak explains. 'We also compare gait characteristics collected during free-living walking versus laboratory walking and how they relate to patients' severity of disease and perceived quality of life.' They are now following people for a year after wearing the socks for a week to determine if they can predict risk of future falling better than from clinical or instrumented assessments.

The researchers will now evaluate this passive, unsupervised mobility monitoring system in a rigorous series of tests and trials, so that it can eventually be put on the market and aid clinicians, clinical trialists and other research teams in evaluating their patients' mobility and assessing their risk of falling.

Meet the researcher

Dr Fay B Horak
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Dr Fay B Horak is a professor and the director of the Balance Disorders Laboratory at Oregon Health & Sciences University (OHSU). At APDM Wearable Technologies, she holds the title of APDM Fellow which represents the company's pre-eminent technical and research distinction. It is the highest level of scientific/technical achievement and it is granted in recognition of outstanding foundational contributions to APDM combined with a sustained record of scholarly leadership demonstrated by research, invention, and scholarly publications at the highest levels of international excellence. Dr Horak is also is a Senior Research Fellow at the University of Bologna (Italy), as well as an adjunct professor at Simon Fraser University (Canada), the University of Waterloo (Canada), and Pacific University (USA). Dr Horak holds a BS in Physical Therapy from the University of Wisconsin, an MS in Neurophysiology from the University of Minnesota and a PhD in Physiology and Biophysics from the University of Washington. Before she started working at OHSU, she held teaching and therapeutic roles at several other institutions, including the University of Washington and the University of Minnesota. Dr Horak's research focuses on neurological disorders that affect balance and gait in the elderly including Parkinson's disease and multiple sclerosis. She has published over 300 scientific articles in prestigious journals and has received numerous honours and awards, including a Merit Award from the National Institutes of Health.

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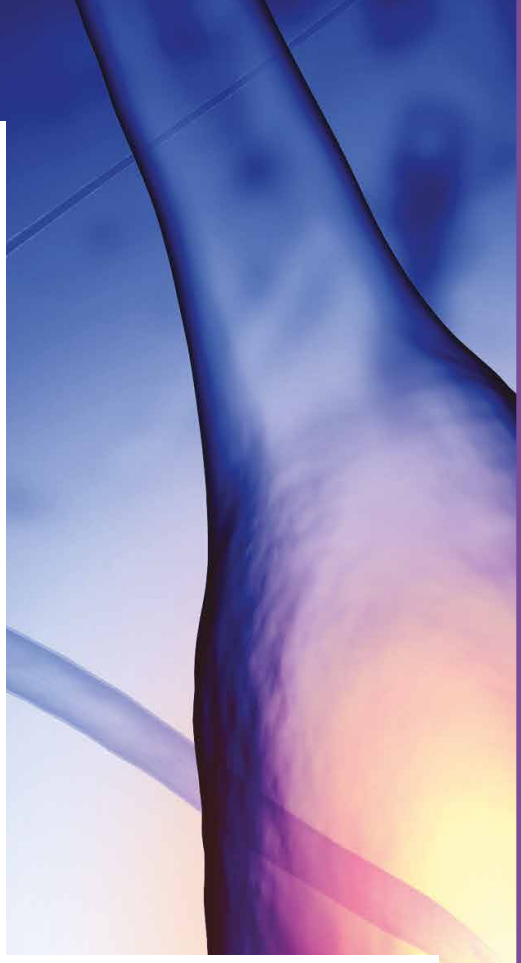
SPINAL CORD DAMAGE AND EMERGING TREATMENTS

Injuries to the spinal cord can cause permanent paralysis and even lead to death, with little to no hope of regaining lost functions once the trauma has occurred.

Dr Jerry Silver and his team at Case Western Reserve University Medical School, USA, have been working to understand why nerves that are damaged through spinal injury don't regenerate and to identify non-invasive, easy to administer strategies that can promote robust functional recovery.



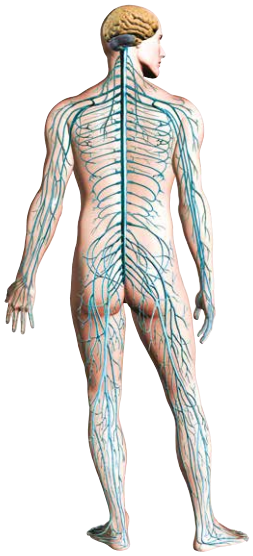
Repairing Broken Spinal Cords

The spinal cord houses an incredibly important circuitry that conveys sensory signals from the extremities upward to the brain, as well as motor commands from the brain downward to the relay nerve cells in the spinal cord that, in turn, project out to the muscles. However, the spinal cord also plays a critical role itself in the generation of patterned movements, such as walking. Thus, when the nerve pathways that travel up and down within the spinal cord are damaged, muscle paralysis as well as sensation loss occur below the level of the lesion. Although more commonly associated with the inability to move limbs, paralysis following spinal injuries also affects important basic autonomic functions – such as sweating, urinating, and breathing.

Dr Jerry Silver at Case Western Reserve University Medical School has been working to understand what happens when nerves in the brain and spinal cord (the so-called central nervous system or CNS) are damaged, and why they don't naturally repair themselves in the same way that peripheral nerves in the arms and legs can. By understanding the molecular mechanisms that lead to the formation of barriers to regeneration in the CNS, his team hopes to develop ways to overcome these obstacles and repair nerves with the aim of restoring function and, thus, bringing relief to the millions of people affected by paralysis.

Can Damaged Nerves Regrow?

Dr Silver's research started by investigating whether it was even possible for an adult nerve cell to regrow within the environment of the damaged adult spinal cord. It had long been thought that this would be impossible. Nerve cells consist of elaborate long extensions (called axons) that grow out from the main cell body – it is these axons that make the connections called synapses with other nerve cells, and it is the axons within the spinal cord that are severed when the bony spine is impelled into the cord when it is violently broken. Axons can be incredibly lengthy, some reaching almost the entire span of our bodies. One challenge for researchers working in the field of spinal injury was to determine whether damaged axons



have the intrinsic capacity (in other words, a strong enough growth motor) so that, in principle, they had at least the potential to replace the damaged ones.

Dr Silver and his team found that, indeed, this was possible, even long after the damage had occurred. To demonstrate this, they conducted a simple but elegant experiment. First, they purified in cell culture, fully adult nerve cells that were genetically pre-

‘The exciting discovery… has opened the door to the production of specific blocking peptides as well as long-acting enzymes […] When combined with additional strategies to enhance intrinsic neuronal growth potential as well as targeted rehabilitative therapy, we may be able to elicit recovery even after a near lifetime of paralysis.’

labelled with a fluorescent protein such that the cells could be easily visualised. This first step served not only to harvest the nerve cells but also to cut all the axons away from the cell bodies that, nevertheless, remain alive. Next, they collected the axon-less nerve cell bodies and very gently re-implanted them into the pre-lesioned spinal cord of an unlabelled adult host animal so as not to create any damage or scarring at the implant site. It was a huge surprise to the scientific community when they found that axons could, indeed, regrow robustly in the spinal cord and reach out quickly over long distances. However, they also found that when the new axons reached the area of severe lesion damage and scarring, they stopped growing abruptly and started to deteriorate. The researchers suspected that there was some sort of chemical produced by the scar tissue around the break itself that was hostile to axons and stops even exuberantly growing new ones from extending further.

Understanding Scar Tissue

Inflammatory damage to the spinal cord after the initial injury can continue to spread outward from the lesion epicentre into surviving tissue to cause further loss of function. The development of scar tissue encases the lesion core and plays an important role in the protection of the healthy nerve cells from further harm. However, it is now clear that once the important task of protection is complete, the same structure that provided protection soon after the injury then develops into a barrier to the regrowth of the cut axons.

Dr Silver and his team began investigating what the culprit was within the scar that was stopping axon regrowth, and what they could do to reduce or overcome the growth inhibitory effect of the scar, once it had mitigated the danger of the initial injury. As they had already shown that axons can regrow once past or through the scar, they understood that this could be the key to returning or improving function to the injured area.

The researchers found that a particular family of potently inhibitory molecules was being produced in the scar tissue, and that when newly regenerating axons encountered them, it caused the growing tips of the axons to become so tightly stuck (much like a fly on flypaper) that they could no longer move forward. These sticky molecules are known as chondroitin sulphate proteoglycans (CSPGs).

Bridging the Scar Tissue and Repairing the Nerve Damage

With the culprit that stops the growth of axons near the scar tissue identified, the next step was to find a way to selectively eliminate CSPGs. Dr Silver and his team investigated the use of a special enzyme (called chondroitinase) that consumes the CSPGs once injected into the cord, stopping them from having such detrimental effects. Using these enzymes, the researchers found success in re-growing axons and improving function in animals that had problems with their limbs and also their diaphragm (which was hampering them from breathing), and those that had problems with their bladders. As these are common and potentially fatal conditions in humans following paralysis, the improvements in these specific areas were especially promising.

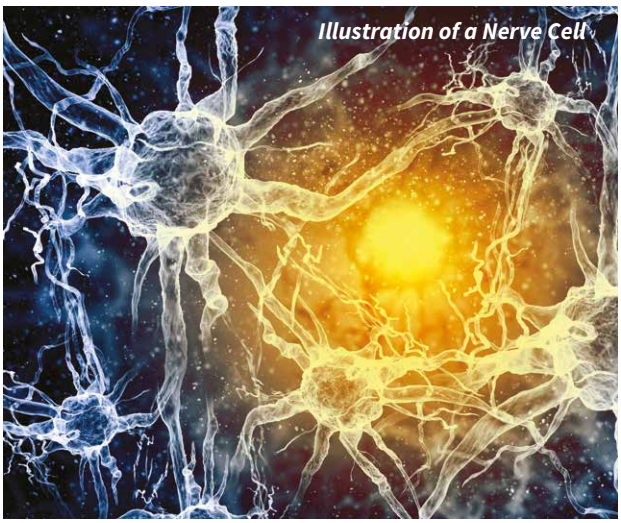


Illustration of a Nerve Cell

The use of enzymes to breakdown CSPGs has been widely investigated, with researchers attempting to optimise various factors, including the timing of administration and appropriate amount of targeted physical therapy. Benefits have been shown in many different animal models, including non-human primates and at long chronic timepoints post-injury. However, problems still exist as the enzyme is of bacterial origin, must be injected directly into the spinal cord, and acts only over a very short distance. Supplementary treatments may also be required to ensure optimal spread of the enzyme and that the regrown axons go on to make the right connections. Studies are ongoing by a variety of research teams around the world to overcome these challenges.

To overcome the need to directly inject a molecule into the spinal cord, Dr Silver and his colleagues tested a novel systemic approach to see what effect it would have on axon regrowth. They identified a receptor molecule called protein tyrosine phosphatase sigma or PTPσ on the axons that acted as a 'helper' to cause CSPGs to be overly adhesive. This newly discovered PTPσ receptor provided a way for the axons to detect CSPGs, signalling them to stop and become entrapped. Dr Silver and his team developed a molecule that negates this signal, allowing the regenerating axons to ignore and bypass CSPGs. When the molecule, known as intracellular sigma peptide (ISP), was administered noninvasively via injections under the skin, it interfered with CSPG/receptor signalling within the spinal cord, allowing for robust axon regrowth resulting in greatly improved bladder function and improved locomotion in animal models with spinal cord injury.

Beyond Spinal Cord Injuries

In working to understand what controls the regrowth of axons after spinal cord injury, Dr Silver's team has also discovered several medical conditions involving nerve injury where scarring also occurs and CSPGs impact axon regrowth.

Axons that are severed in the peripheral nerves, such as those found in the arms and legs, do have a limited capacity to regrow. However, when the lesion is severe and closer to the body, a CSPG laden scar also hinders recovery because damaged peripheral axons also upregulate the same PTPσ receptor. Dr Silver and colleagues have shown that ISP can help heal injuries to peripheral nerves by speeding up the growth of injured nerves across and beyond the scar to the muscles they control.

Multiple sclerosis (MS) is an inflammatory mediated nervous system disease that affects both the brain and spinal cord. It damages the myelin, the material that wraps and insulates your nerve cells. The loss of myelin slows down or blocks the electrical message that travels between your brain and your body, leading to MS. Again, CSPG filled scar-like plaques that form in the damaged areas play a critical role in preventing recovery by blocking migration of immature, potential myelin forming stem cells that exist in huge numbers within the CNS. In animal models of MS, Dr Silver and colleagues recently found that ISP promotes the migration of the stem cells into the lesion with return of the myelin sheath leading to functional recovery.

Dr Silver has also teamed up with investigators who study scars that form after heart attack. When a heart attack occurs, sympathetic axons that control the heart rate are damaged in the vicinity of the forming scar. Just like in the spinal cord, these cut axons die back away from the lesion core and their regenerating tips become entrapped within the outer edges of the scar, causing irregular heartbeats known as arrhythmias which can be lethal. In animal models of heart attack, systemic treatment with ISP promoted new growth of the damaged axons back into the scar, stopping the arrythmias.

Dr Silver and his colleagues have teamed up with the company NervGen Pharma, whose vision is to restore life's potential to patients by creating innovative solutions for the treatment of nerve damage. Together, they have identified an ISP analogue known as NVG-291 to treat human patients. It is their hope that this technology can improve the lives for the many people living with debilitating nerve damage.

Meet the researcher

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Dr Silver received his PhD from Case Western Reserve University in 1974 and then completed postdoctoral research at Harvard University. Dr Silver is currently Professor in the Department of Neurosciences at the Case Western Reserve University School of Medicine, and Co-inventor and Scientific Advisor at NervGen Pharma. Over the past several decades, Dr Silver's laboratory has concentrated research efforts on learning about the molecules that reactive glia produce in scars following spinal cord injury that actively block regeneration. Dr Silver is the recipient of many prestigious awards and serves on the editorial board of a number of high impact journals. He has served as lead or senior author on more than 175 publications to date.

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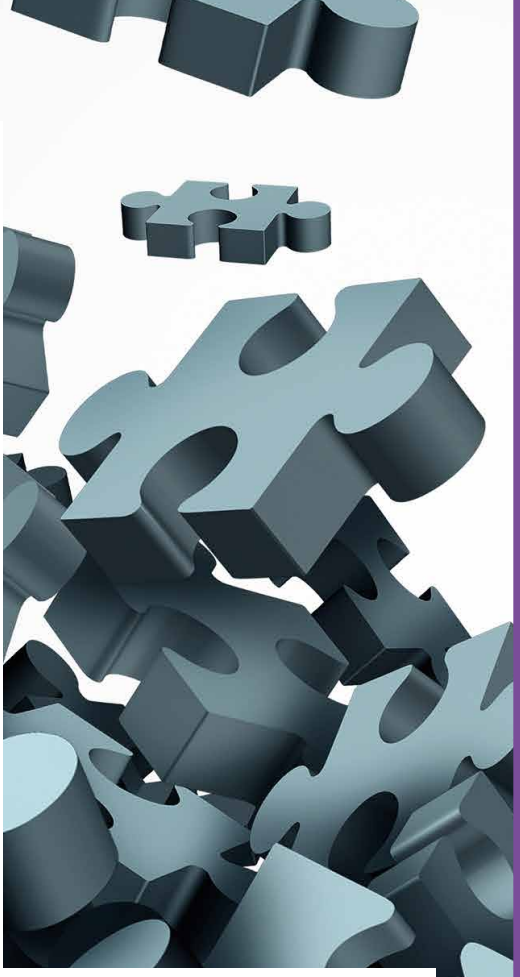
LEVERAGING NEW TECHNOLOGIES TO TREAT BRAIN INJURY



The brain is the most mysterious organ in the human body – despite decades of research, we have just begun to scratch the surface in understanding how the brain works and how we can help it to heal following an injury. **Professor Mark D'Esposito** of the University of California, Berkeley, uses advanced imaging technology to illuminate how the connections in our brain function in order to find new ways to aid brain healing after injury.

The human brain is the most advanced and complex information processing instrument on earth. Despite decades of trying, we have not been able to create a computer that performs complex operations with the speed and nuance of the brain. The brain is composed of a vast network of neurons, the number of which is greater than the connections between every electronic device on earth, and their constant communication creates what you and I experience as consciousness.

Professor Mark D'Esposito of the University of California, at Berkeley, is a neurologist seeking to understand how the networks of neurons within our brain function together, and how we can leverage this understanding to treat people with traumatic brain injuries and other neurological disorders. Using advances in functional magnetic resonance imaging (fMRI) he is mapping neuronal networks to illuminate how the brain works.

Thinking in Modules

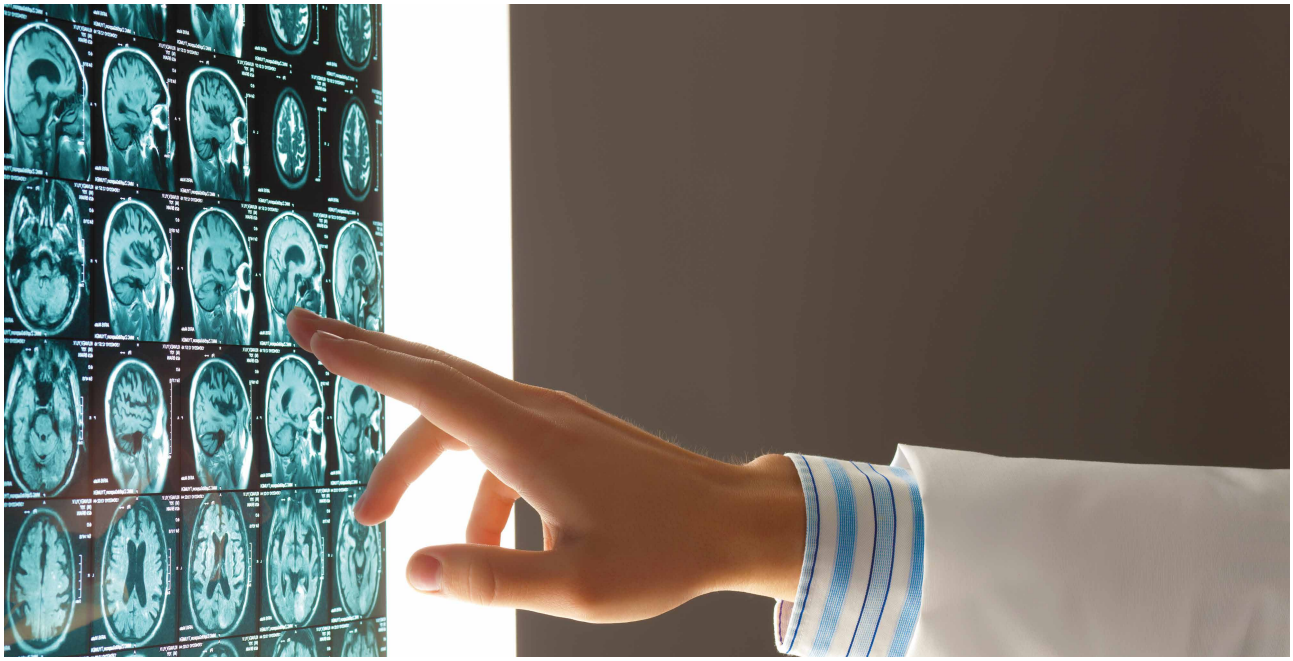
While we are still working to understand how the brain works as a whole, we have some ideas about how it works in general. We know that some areas of the brain perform specific functions, such as processing sounds. This is because the brain cells or neurons in these areas share similar purposes and must communicate rapidly to produce efficient responses. Professor D'Esposito refers to these areas as modules. He explains: 'Facebook is a helpful metaphor: think of your closest friends on the social network as being in your module, the people closest to you and with whom you are most likely to communicate.'

While these brain modules may perform fairly specific functions, they must also share information with other areas to create the full human experience – for example, processing a sound, interpreting it as speech, and then understanding the message requires the tight coordination of multiple modules, but happens so seamlessly in a healthy brain that our perception of a sound and its message seems instantaneous.

In order to understand how the brain works, it is critical to understand how the brain functions as a whole. Professor D'Esposito explains that, 'it is presumed that each brain module performs a discrete function, such as producing language or seeing the world around us. However, brain modules must also communicate with each other to accomplish more complex behavior – such as multitasking or solving a mathematical problem.'

A primary focus of Professor D'Esposito and his team's research has been understanding how different modules of the brain work together in a network to create goal-directed behaviour, and what those connections imply for the treatment of traumatic brain injuries and other neurological disorders. 'My take-home message is simple,' he says,

‘My take-home message is simple: a greater understanding of the function of the healthy brain will undoubtedly lead to a better understanding of the damaged brain.’



‘a greater understanding of the function of the healthy brain will undoubtedly lead to a better understanding of the damaged brain.’

Historically, it has been assumed that damage to a specific area of the brain only impacts processes that that area manages – for example, damage to the visual cortex would only affect a person’s ability to see. However, Professor D’Esposito and his colleagues have found that this is not always the case and that may actually be good news for patients with brain injuries.

The Pieces That Form the Whole

Executive control refers to a collection of mental processes that are necessary to identify, plan, and execute the behaviours needed to complete a goal. These processes, including selective attention, working memory, task switching, sequencing, and planning, are essential to navigating everyday life. A common effect of brain injury is the loss of executive control – patients struggle to pay attention, organise, and develop strategies that help them get things done.

This is particularly true of injuries to the prefrontal cortex, the area of the brain where many executive control processes are localised, that gives us the experience of conscious control and abstract thought. The prefrontal cortex is believed to be one of the most critical connector areas of the human brain, having extensive reciprocal connections to virtually all cortical and subcortical structures. This places the prefrontal cortex in a unique and privileged position to monitor and manipulate diverse cognitive processes. Thus, dysregulation of the prefrontal cortex, whether through direct injury or indirect effects of damage to other modules of the brain, leads to symptoms that strongly impact the lives of those afflicted.

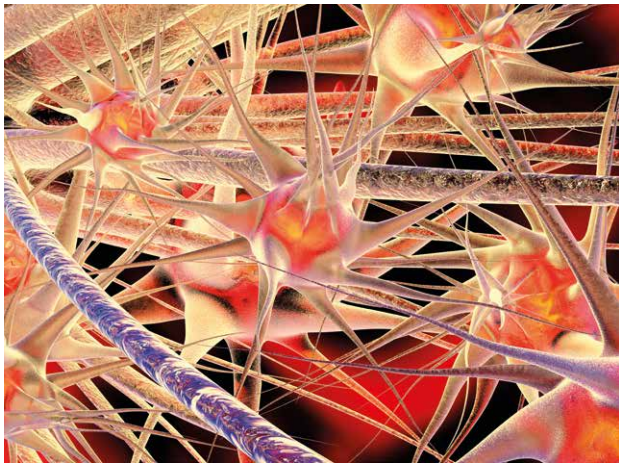
A critical finding that has shaped the work of Professor D’Esposito’s team, is the discovery that localised brain damage impacts the large-scale function of the brain as a whole, particularly when the damage impacts an area of the brain that had served as a connector for multiple modules across the brain. Using fMRI scans to observe the brain activity of a group of patients with damage to a specific area of the brain, they were able to demonstrate that undamaged regions were also dysregulated following the injury.

These findings explain many of the unpredictable symptoms experienced by patients that have suffered a brain injury that are often seemingly unrelated to the function of the area that was injured.

The more modules that are connected to a damaged area, the more widespread the dysregulation will be. While at the surface this may seem like an undesirable finding for patients with brain injuries, Professor D’Esposito sees these network connections in a different light – by understanding how the network is connected, we can look for ways to reconnect it following trauma.

Reprograming the Networks of the Brain

Professor D’Esposito and his team took note of clinical studies that were helping patients improve attention and problem-solving skills through training programs and suspected that these



strategies could be used to improve executive control functions in patients with brain injuries. Specifically, they predicted that attention would serve as a keystone process that could improve cognitive function in these individuals.

Attention training activities included mindfulness-based regulation practices and goal-management strategy making. They piloted training sessions with two groups. One group was given educational seminars and another underwent attention training over five weeks. They found that while participation in the educational seminars had no effect, the training sessions created lasting behavioural changes that not only improved the patients' performance on executive function tests, but more importantly, improved their ability to complete tasks in real life scenarios.

When Professor D'Esposito and colleagues took this experiment a step further and took fMRI scans of the brains of patients in the training study, they made an even more exciting discovery. The training sessions weren't just helping patients learn new tricks, they were actually changing the neural pathways being used during attention tasks.

In the extrastriate cortex, one of the brain modules associated with the training task, all patients showed increased neural connections. Interestingly, training had different impacts on each patient's prefrontal cortex, depending on how they had processed information prior to training. Those who had been more goal-oriented prior to training shifted towards processing more irrelevant information after training. In contrast, those who had been more focused on irrelevant information prior to training shifted to toward more goal-relevant information after training. In both cases, training improved overall executive control, regardless of the shift made. This suggests that different people with different predispositions will use different strategies to cope with forming new neural networks.

Taken together, these results indicate that not only is it possible to use training programs to improve the experience of people with brain injuries, but these training sessions create tangible and lasting change in the brain's structure that benefit the long-term health of patients that receive them. Professor D'Esposito notes that, 'understanding brain connectivity in this way helps us develop rehabilitation therapies that stimulate the brain to reconfigure itself with new functional connections that bypass damaged brain regions that serve as connector hubs.'

Understanding Individual Responses

Though cognitive training and rehabilitation benefits can benefit patients with brain injuries, the degree to which each patient sees results varies drastically. Professor D'Esposito and his colleagues wanted to understand why some patients experienced transformative results, while others were showing only minor improvements, even when their brain injuries were similar in size and location. They again turned to fMRI, comparing the baseline scans taken prior to the training interventions, and the results each patient experienced following rehabilitation.

Patients with highly modular brains, that is, more connections within modules than between modules, prior to training were most likely to see great improvements with training. Professor D'Esposito has repeated these studies with aging adults and found that older adults with more modular brains are also more responsive to both cognitive training and the neurological benefits of physical exercise. These findings suggest that the brain has an easier time rerouting the connections between modules than it does trying to recreate more broad, undefined networks.

These findings have enabled Professor D'Esposito and his team to use fMRI to predict which patients will respond best to treatment and are spurring them to identify ways to enable similar responses in patients whose brains are less optimally wired to benefit from treatment. For now, these discoveries are helping neurologists to tailor treatment plans with the highest likelihood of success.

Professor D'Esposito notes: 'We still have much to learn about optimal brain states, such as whether we can alter or optimise them or why brain states differ from one person to the next. But our findings nevertheless highlight the tremendous power of brain imaging and its potential impact on medical treatments.'

The Future of Brain Health

Through advances in imaging technology, Professor D'Esposito and other neurologists are making powerful discoveries about how the brain works that have major implications for how we approach the treatment of brain damage in the future. He concludes that, 'recent scientific advances have given us basic knowledge of the functional architecture of the human brain. We are now in an excellent position to develop effective treatments for the millions of individuals who suffer from brain disorders.'

Meet the researcher

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Professor Mark D'Esposito earned his medical degree at the SUNY Health Science Center at Syracuse and completed clinical training in Neurology at Boston University Medical Center. After prestigious appointments at the Memory Disorders Research Center at Boston University and Braintree Rehabilitation Hospital and the University of Pennsylvania School of Medicine, he was recruited to the Helen Wills Neuroscience Institute at the University of California, Berkeley to become Professor of Neuroscience, and the Director of the newly created Henry H Wheeler, Jr Brain Imaging Center. He is also practicing neurologist at the Northern California VA Health Care System. His research investigates how the structure of the brain impacts how it recovers from injury and potential treatments for the injured brain. Over the course of his career, Professor D'Esposito has published over 375 academic articles as well editing books about cognitive neuroscience and neurology. He is currently Editor-In-Chief of the Journal of Cognitive Neuroscience, and past President of the Society for Behavioral and Cognitive Neurology and Chair of the Organization for Human Brain Mapping. Professor D'Esposito has received numerous awards and honors including the Norman Geschwind Prize in Behavioral Neurology from the American Academy of Neurology and election to the American Association for the Advancement of Science.

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FUNDING

National Institutes of Health
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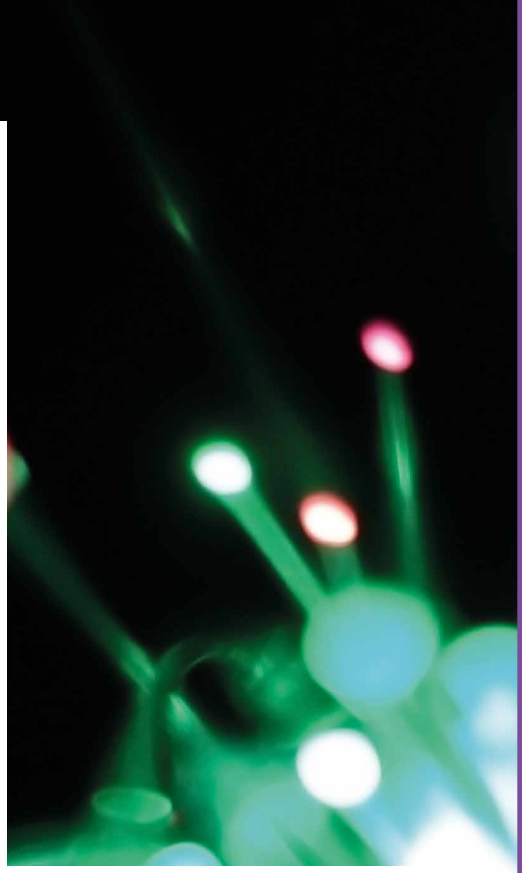
PLUGGING INTO THE NERVOUS SYSTEM

New advances in neural engineering have led to devices that can be operated using the nerves of the user, but the effectiveness and safety of these devices over long periods of use is a key concern. **Professor Dominique Durand**, Director of the Neural Engineering Center at Case Western Reserve University, leads a team of scientists looking to improve neuroprosthetics through developing new methods of interfacing with the nervous system.



New Advances for Amputees

Until recently, the concept of prosthetic limbs that can be controlled by the human nervous system was confined to the world of science fiction. Recent advances have given us prostheses that can interact directly with the nervous system, giving the user back the use of an arm or a leg, or a fully articulated hand with each finger individually controllable.

With more than 1 million limb amputations taking place globally each year, the need for safe and effective prosthetics is critical. The greatest challenges facing fully functioning, user-controlled prosthetics are reliability and safety, and ensuring that the prosthesis responds to real, measurable nerve signals and can be attached over a long period of time without causing damage to the nerves.

One of the researchers addressing these challenges in a novel way is Professor Dominique Durand, E L Lindseth Professor of Biomedical Engineering and Neurosciences and also Director of the Neural Engineering Center at Case Western Reserve University, USA.

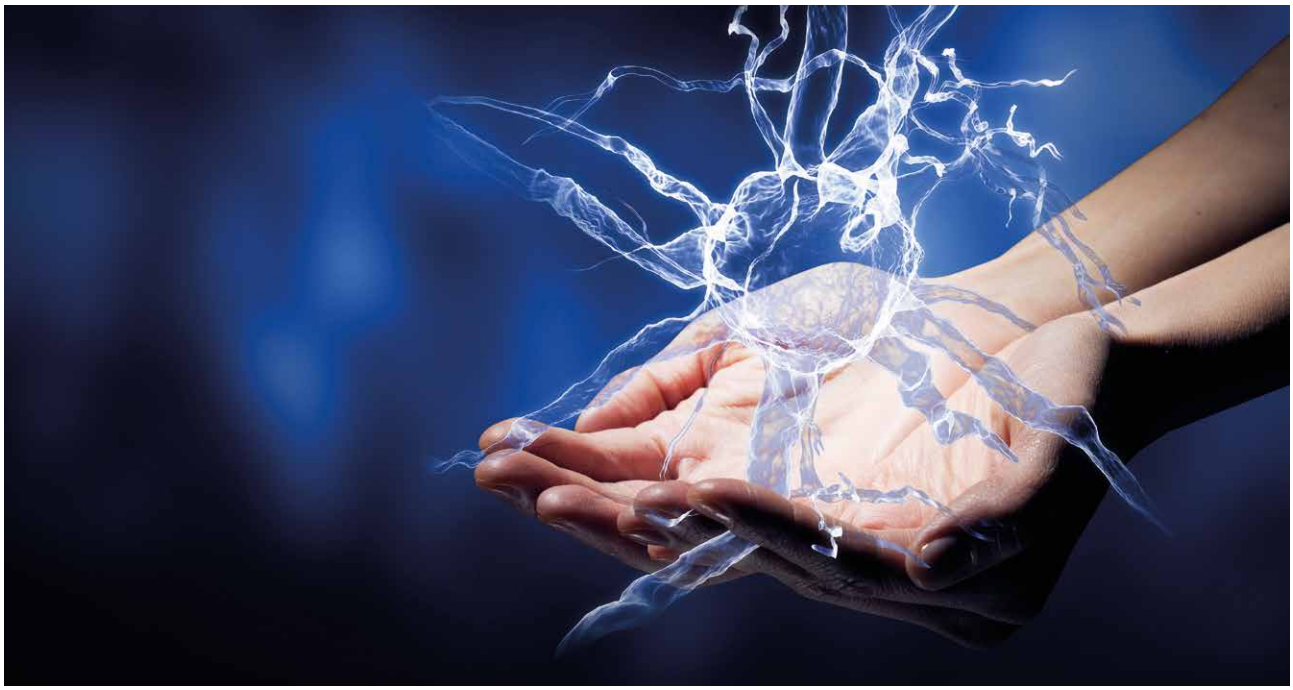
Professor Durand and his team work in the emerging field of neural engineering, a new discipline at the intersection of neuroscience, neurology, and engineering. Neural engineering is an interdisciplinary research area that involves applying engineering techniques to the study and manipulation of the nervous system, with the aim to better understand how the nervous system works and provide new treatments for neurological dysfunction. Fields within neural engineering include, but are not limited to, the development and use of neural interfaces for neuroprosthetics, such as neural controlled artificial limbs for amputees or altering neural activity by direct stimulation of the central or autonomic nervous system (neuromodulation).

Professor Durand's work aims to address two distinct neurological problems; the first is how to control disorders of the central nervous system such as epilepsy through electrical stimulation of the brain. The second is how to interface with the peripheral nervous system in order to restore function in patients with autonomic imbalance and give voluntary control of artificial limbs to amputees using neural prosthetics.

The Problems with Prosthesis

The majority of user-controlled prosthetics have utilised electromyography (EMG) pads that attach to the skin and detect the electric activity of existing muscles, generating signals that can then be sent to a prosthetic limb and direct it to move. However, patients with muscle damage to the upper-arm or with upper-arm amputations may not have muscles available to control the prostheses.

More recent prosthetic devices can chronically attach to the user by interacting directly with the nervous system. Instead of EMG electrodes, these devices use probes that are implanted into the body and wrap



around nerves, called cuff or wire hooks electrodes. These are limited by their ability to differentiate real nerve impulses against background noise which can be caused by static as the cuffs move against the nerves.

Cutting edge research in prosthetics has led to probes that can enter inside the nerve itself and detect nerve impulses directly. These are much better at determining which nerve impulses are 'real', but their safety is as-yet untested when used long-term in implants.

A breakthrough from Professor Durand and his group in 2017 led to the development of a novel method of allowing technology to interface directly with the nervous system. They hypothesised that probes have had limited previous success use due to their stiffness. Nerve fibres are very flexible, and the team identified the need for a flexible probe that would match the mechanical properties of the nerve to prevent the probe from moving and causing irritation over the lifetime of the implant.

The Carbon Connection

To make a much more flexible probe, Professor Durand's team formulated a probe composed of strings made of nanometre-wide strands called carbon nanotubes (CNTs). The original idea was to design an axon-like probe with dimensions and flexibility similar to other axons near the electrode. CNTs are a form of carbon, like graphite and diamond, where molecules of carbon are arranged into long tubular structures. The team spun the CNTs into an extremely thin multi-stranded yarn much thinner than the diameter of a nerve. The thinness of the probe meant that it could be implanted into the nerve with the aid of a microscopic metal needle called a microneedle.

Professor Durand's team tested the flexibility of the new yarn constructed from CNTs using a technique called atomic force microscopy and found that it was much more conductive and flexible than the platinum-iridium wire usually used for implants, with flexibility closely matching that of a nerve fibre. The team concluded this material would be perfect for the basis of a neural interface.

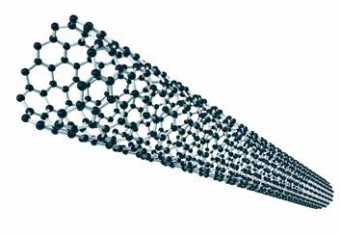
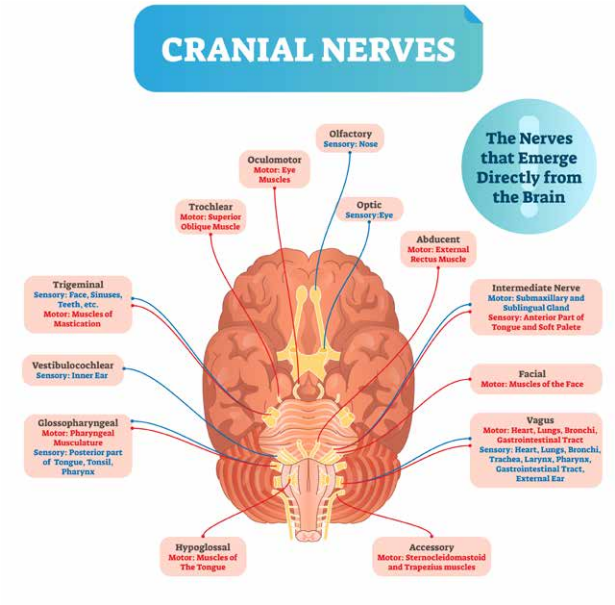
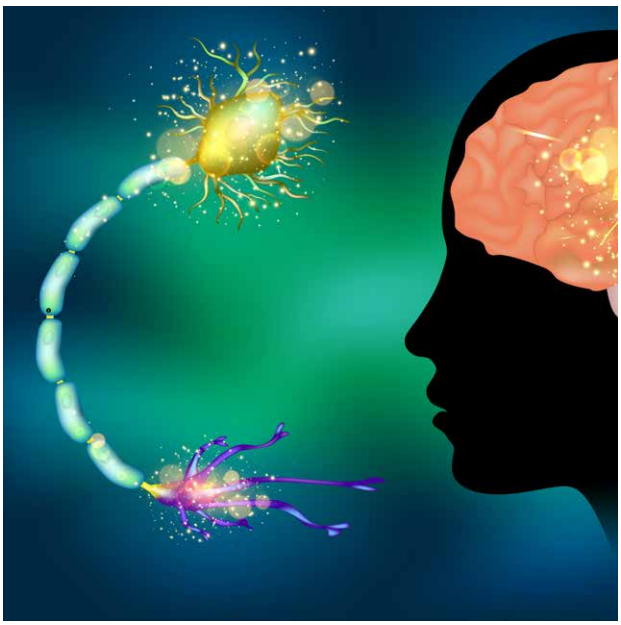


Illustration of a carbon nanotube

To test the probe, Professor Durand's team first implanted the probe into the vagus nerve of a rat. The vagus nerve is situated in the neck and is a major conduit for nervous communication between the brain and the body. It receives sensory information from the organs of the body, including the heart, lungs, and the gut. The group measured the signals generated from the vagus nerve and a large range of signals coming the various organs.

Professor Durand's team then implanted the probe in another major nerve of the neck called the glossopharyngeal nerve. This nerve transmits impulses from the carotid sinus which senses oxygen and pressure regulation. The group induced a hypoxic event in the rat, and then measured the nerve activity using the probe. They found they could detect the two types of signals produced by the carotid sinus that give information to the brain about the blood oxygen level and blood pressure.





Precision and Safety

Once the team knew the probe was effective in detecting nerve impulses, they went on to test whether the probe could detect impulses from specific parts of the nerve. Nerves are made up of bundles of tiny nerve fibres called axons that carry various signals. The carbon nanotube probe is about the size of one of these axons, which allows several probes to be implanted within very small nerves.

This approach allowed the team to measure the activity of individual bundles of axons within the nerve itself. They found when the rats were exposed to hypoxia, two different probes in the same nerve gave very different responses, indicating that each probe could selectively record different neural signals, such as baroreceptors and chemoreceptors. This shows that a greater and more accurate level of selectivity in detecting nerve impulses can be obtained using these tiny probes.

Finally, Professor Durand's group tested their hypothesis that the flexible fibres would cause less irritation after being implanted in the body over a long period of time. In other systems, long-term insertion of a probe into a nerve can cause a problem where the body's immune system responds to irritation and inflammation at the site of implantation. The foreign body response can cause a thickening of the connective tissue and scarring, which can come between the probe and the nerve leading to a significant decrease in recorded signal amplitudes. This effect can interfere with the normal function of a user-controlled prosthesis, and may even cause damage to the surrounding tissue.

The team found that chronic implantation of CNTs generated only minimal amount of inflammation around the site of implantation. The group looked at the area where the probe has been inserted and found there were few immune cells around the site of implantation, indicating a limited inflammatory reaction in response to the Carbon Nanotube probe.

New Frontiers in Neural Interfaces

Professor Durand's team's findings confirmed their hypothesis that probes made from CNTs would be more suitable for chronic implants, causing less damage, and maintaining signal for a longer period. The group hopes that these findings will pave the way for more effective carbon nanotube-based controllable prosthetics. Future work by Professor Durand and his group will also focus on the development of a new neural control system for a prosthetic arm using their novel technologies.

Critically, not only was the CNT yarn system capable of detecting nerve impulses, it was also able to stimulate nerves. Whereas detecting nerve impulses is key in designing artificial prostheses, the ability of the probe to both detect and stimulate nerves could mean it could be used to even repair nerves damaged by neurological injuries, such as strokes and spinal injury. Each year, over 100,000 people in the UK suffer strokes. It is the leading cause of disability in the UK, with two-thirds of stroke survivors suffering some sort of prolonged disability caused by damage to the nervous system.

Professor Durand's new technique opens up a host of new opportunities to combat some of the most complex and impactful problems in neurology today. Science fiction no longer, new findings from Professor Durand's lab could lead the way to new, more effective and stable prosthetics and give us new ways of treating disorders of the nervous system.

Meet the researcher

Professor Dominique Durand
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Professor Dominique Durand received his PhD in Electrical Engineering from the University of Toronto. On completion of his doctorate in 1982, Professor Durand moved to Cleveland, USA to take up an Assistant Professor position at Case Western Reserve University, Ohio where he is currently the E L Lindseth Professor of Biomedical Engineering. Professor Durand's research is focused on solving problems in the central and peripheral nervous systems through the disciplines of neural engineering, computational neuroscience, and neurophysiology. In particular, he is working on how to understand and restore neural function in both the central and peripheral nervous systems, investigating how applied currents could be used to control seizures in patients with epilepsy, and improving user-controlled prosthetics. In 2000, he was appointed Director of the Neural Engineering Center, a multidisciplinary institute dedicated to research at the interface between neuroscience and engineering. He is the founder and editor-in-chief of the Journal of Neural Engineering.

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NEUROPHILIC DESIGN: WHO WE ARE AND WHERE WE ARE

Professor Heidi Zeeman of Griffith University and her collaborators are exploring the innovative research field of neurotrauma and the built environment. They endeavour to understand the experiences of individuals with different brain sensitivities and neurological disabilities and the environments in which they live, work and recover. This work will ultimately inform next generation therapeutic environments, workplace and residential design and the design of public spaces.

In modern society, the external environment around us is constantly changing. Similarly, throughout different stages of life, our internal interpretation of and response to our environment also changes – our idea of 'home' as a child might differ significantly to the 'home' that we depict in our minds as an adult. In essence, our life experiences shape our environment, and yet our environments also shape our life experiences. Considering this, how often are we aware that our experience of the environment may be considerably different than through the eyes of another, perhaps even adversely so?

Demographics predict that an increasing proportion of the population will relocate to urban environments in the coming decades. Individuals with neurological, neurosensory, psychological or psychiatric conditions will represent a large percentage of the general population. The emerging need to recognise how individual differences and neurosensitivities contribute to a person's interaction with their environment has resulted in an ever-expanding research field, which might be termed neurophilic design, broadly relating to the human brain's unique affiliation with the built environment.

As an extension of a biophilic understanding of the world, where humans possess an inherent affiliation with the natural environment, Professor Zeeman of the Menzies Health Institute Queensland and The Hopkins Centre (https://www.hopkinscentre.edu.au/) describes neurophilic design as reliant on an evolved and complex neurocognitive system comprising reception, perception and association that determines the nature and extent of human interaction with the external environment.

The neurocognitive environment work of Professor Zeeman is centred on the foundation principles established by Kurt Lewin's Field theory in 1936 where human behaviour is a function of the person (P) and their environment (E). In a more nuanced way, the Environmental-Press model proposed by M. Powell Lawton suggests that person-related competencies and needs manifest differently in different environments, leading to dissimilar (either stressful or supportive) outcomes or levels of 'fit'. Accordingly, after neurological injury or illness, individual competencies are likely to alter, and as such, environments must also adapt to the person in order to facilitate recovery and promote optimal engagement with the environment. We are only beginning

to understand how best to modify the environment to optimise intra-individual functioning.

Over the past ten years, Professor Heidi Zeeman and her research team have conducted emergent research in this field, particularly focusing on individuals with neurotrauma such as brain injury and spinal injury. Professor Zeeman says that, 'we know that environments influence how people think, feel and behave. However, we aren't clear about the transactional nature of this important relationship. In other words, what influences what, to what degree and how? If we are able to understand the limits of brain function in relation to the environment by studying brain inflammation and extreme injury compared to normal function, then we are more likely to determine what works in terms of environmental enrichment for the general population.'

To achieve this, Professor Zeeman and her colleagues work collaboratively with experts from multiple disciplines and industry sectors. She describes how, 'our team are involved with medical professionals, engineers, virtual reality developers, environmental psychologists, nursing, allied health practitioners, architects, economists, artists, urban planners and neuroscientists to explore human sensitivity to the built environment.'

A Neurocognitive Approach (NEUROCODE©) to Placemaking

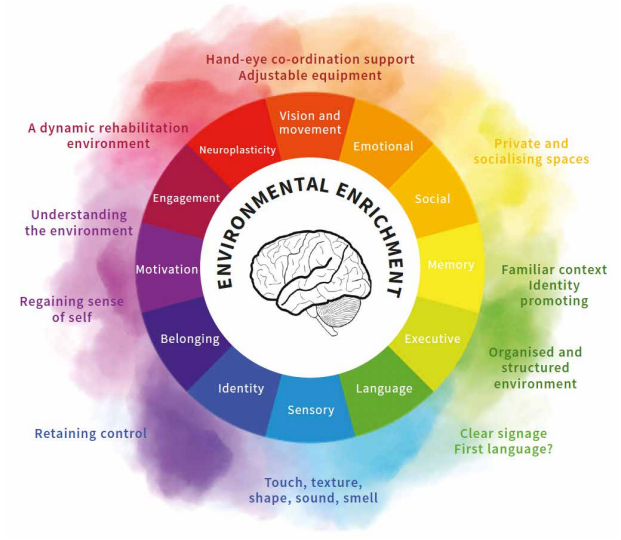
For individuals who are neurodiverse, neurosensitive, and for those who experience brain change due to ageing, injury or illness, environments can be either supportive or stressful to the human condition. Building on the neuropsychological framework of the human brain and behaviour, the neurocognitive design (NEUROCODE©) approach under development by Professor Zeeman and her team proposes a 'whole-of-brain' design system, where core aspects of brain function are mapped to specific evidence-based environment modules. Both typical and atypical brain function is addressed, allowing for a more personalised and inclusive approach to built environment design.

Intended to be used by health and design professionals, a comprehensive neurocognitive system will provide much-needed insight into how environments can optimise human performance and bring together a diverse scientific nomenclature. For instance, the approach seeks to identify evidence-based design elements that have been shown to be helpful for health settings (covering sensory features), as well as those design elements that may be unintentionally harmful for people with specific brain conditions, such as post-traumatic stress disorder, schizophrenia, dementia, autism, and traumatic brain injury.

Residential Environments for Individuals with Neurological Disability

Individuals who have a complex neurological condition, for example, a brain or spinal injury, may require high levels of health support on a daily basis, yet they are eager to regain their independence as quickly as possible. However, a lack of understanding as to how the immediate environment (such as home, transport systems and workplaces) must be specifically influenced and designed to meet the requirements of such individuals has significantly limited the residential and community-based options available to them.

As part of her PhD research, Dr Courtney Wright (supervised by Professor Zeeman) conducted a comprehensive systematic review that aimed to clarify the broader factors relating to residential needs and design solutions for this population. The review covers 26 studies in which 198 unique housing features were identified. Of the 198 features, 142 relate to the design of the house, 12 relate to the location and 54 relate to the surrounding neighbourhood (see further reading for more



information).

Dr Wright examined the question, *'what housing features reported in the literature ought to (or should not) inform housing development and design for adults with a neurological disability?'* With an industry partner, Youngcare, Dr Wright has subsequently developed an online tool from her PhD work, to assist people with disability and their family to think about the needs of their residential setting, and better identify components that would be most important.

A Cross-sectoral Approach to Inclusive Housing Development

The residential inclusion of people who require high health and support needs has traditionally been neglected in the mainstream housing market. Professor Zeeman says that people with complex disabilities 'can be at risk of either high housing mobility (cyclical patterns of temporary accommodation) or housing immobility (trapped in residential aged care homes with little option to move), and few housing solutions are just right.'

To address this problem and attract the necessary broad-based investment required to meet supply and demand, the involvement of the private housing and construction sectors is essential. However, significant commercial entities in Australia who are well-positioned to deliver cost-effective, adaptable and well-designed disability housing remain largely uncertain of the disability market, related policy frameworks, and are unclear about what end-users want and consider to be important in terms of housing design.

To ensure that housing investment is not squandered, it is critical to make timely, cross-sectoral and integrated decisions that maximise outcomes for Australians with complex disabilities. In the context of public-private partnerships, consumer preferences must be understood and mapped against the priorities of other stakeholders. Professor Zeeman and her team employed a systematic method of analytical hierarchical processing (AHP) to assess, and prioritise,

seemingly competitive choices within the multi-faceted supported housing sector to ultimately improve quality of life and housing outcomes for people with a disability.

A three-year Australian Research Council project, led by Professor Zeeman, Professor Elizabeth Kendall and Dr Ali Lakhani, and co-funded by the Motor Accident Insurance Commission (Qld), identified a set of consumer-led housing priorities, and 16 sub-areas for inclusive housing development and planning. After consulting with end-users, and professionals from the housing design, construction and health sectors, the team identified four core decision areas critical in developing inclusive housing.

End-user connectedness was prioritised above all other decision points by both consumers and professionals, followed by feasibility priorities, design priorities and build priorities. Within end-user connectedness, the subset of consumer-based priorities (in ranked order) included access to health services, community engagement, proximity to transport, safety, security and transport. Each of the remaining core decision areas was further defined by a distinct subset of priorities. The research received an Innovation Award at the 15th International Symposium on AHP in Hong Kong, July 2018, and an industry decision support resource is currently under development.

This work of Professor Zeeman and her team extends the current understanding of suitable housing for individuals with neurological impairments. Their research also provides the opportunity for future inclusive housing provisions to adopt the key features identified by the team, to create a positive environment for people with neurological conditions.

Hospital Rehabilitation Environments

Professor Zeeman and her PhD graduate, Dr Jacinta Colley, have also invested a considerable amount of time into discovering the optimal neurorehabilitation inpatient environment following a brain or spinal cord injury. Over the course of three years, Dr Colley and key stakeholders from a neurorehabilitation hospital (including patients and staff) identified that inpatient rehabilitation facilities represent a mid-point between the hospital and the home. As such, they must support two key environment-person processes – change and certainty. Importantly, Dr Colley identified that if these environments are tailored to the individual's own neurological impairment and recovery journey, there is a better chance that a more positive recovery outcome will be achieved. Specifically, when considering change, a neurorehabilitation environment should be dynamic in that it promotes individual improvement and development of independence over time. This is based on the concept that the varying levels of care that come with recovery from a brain injury require different environments at each stage, thus encouraging a natural transition into an independent environment.

With regards to certainty, neurorehabilitation also needs to place emphasis on an individual's own understanding of their environment, how it contributes to their regaining a sense of self and how it contributes to their sense of regaining control. Dr Colley and her colleagues suggest that by supporting these two key processes, the necessary pathway for promoting human engagement with the environment will be achieved.

In related work, Professor Zeeman is collaborating with project lead, Professor Julie Bernhardt of the Florey Neuroscience Institute, to develop an optimised virtual environment living lab for stroke. Evidence-based architecture is a growing field of research that will ultimately inform better rehabilitation facility design. Adopting a design science approach, this project will incorporate experiences from stroke patients, together with insights of key stakeholders representing hospital architecture and technology to model a variety of innovative designs that optimise the recovery and rehabilitation process.

Designing for the Future

Professor Zeeman says the next steps for her team are, 'to focus on experimental analysis of the brain and environment and to explore the parameters of brain plasticity to identify opportunities for precision environments, and sensory and spatial design, in order to optimise person-place interactions.' She adds that, 'we have developed, evaluated and influenced neurorehabilitation environments and services, developed conceptual models based on evidence, and we have facilitated and maintained important industry research partnerships to deliver better environments, services and support for people who are vulnerable and are in difficult times in their life.'

Nonetheless, she states, 'this is an exciting time in neuroplasticity research. Enriched environments have so much to offer people with neurosensitivity and diversity. We have the skills and tools now to better determine the impact and evidence, which have eluded us for so long. For instance, my colleague, Dr Ali Lakhani, is doing fantastic work using virtual reality to alleviate neuropathic pain after spinal cord injury, and applying geographical information systems to map disability services and environments to better inform urban planning.'

Failing to incorporate a broader understanding of inclusive design poses a threat to the long-term biological and psychosocial health and wellbeing of people with neurodiversity, young people with disability and our senior citizens. It is therefore imperative that the work of Professor Zeeman and her team continues to be applied in real-life contexts.

Meet the researcher

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Professor Heidi Zeeman is a Principal Research Fellow at the Menzies Health Institute Queensland and The Hopkins Centre, Griffith University. She completed a PhD in 2007 and began her research career at the Centre of National Research on Disability and Rehabilitation Medicine (CONROD). Professor Zeeman conducts research into human health and the built environment, in collaboration with the health, disability, urban planning, arts and construction sectors. A key focus of her work is to understand the experiences of individuals that have experienced neurotrauma within the environments in which they live, work and recover. She has completed multi-year evaluations of major public health programs and health facilities in Australia over the past decade, novel workforce training programs, predictive models of health, and guidelines for practice. Professor Zeeman is widely published in international journals and has been awarded multiple prestigious awards over her 17-year academic career, including a number of Australian Research Council grants, post-doctoral fellowships, a Fulbright Scholarship (2014) and a Churchill Scholarship (2009).

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FURTHER READING

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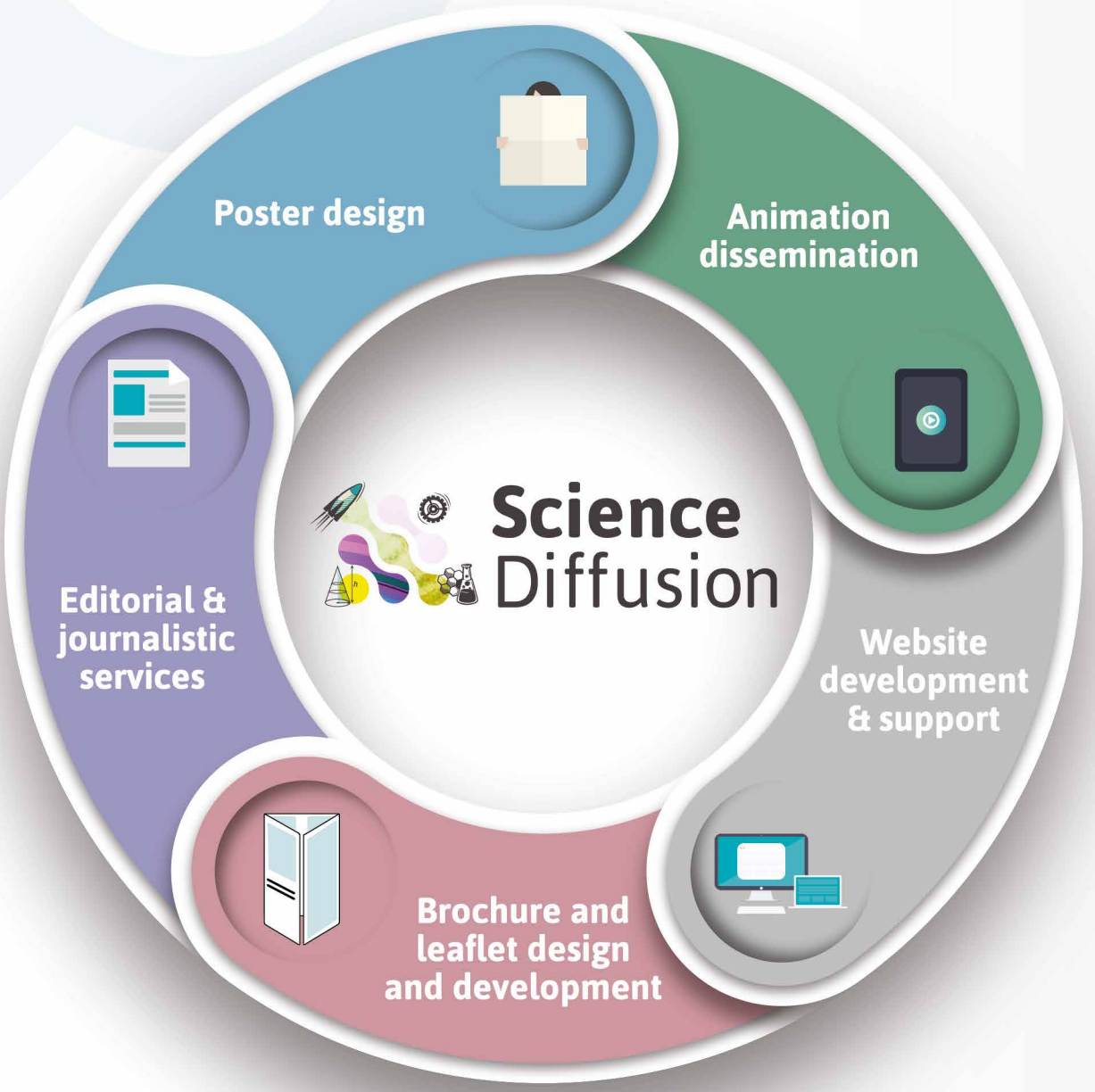

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