Scientia

CHARTING NEW FRONTIERS IN PSYCHOLOGICAL AND BRAIN SCIENCES

EXCLUSIVES:

- Alzheimer's Research UK
- Meningitis Research Foundation

HIGHLIGHTS:

- Trauma in Childhood: How Adversity Affects Brain Development
- Searching for the Genetic Roots of Psychiatric Disorders
- Neurotechnology for Cognitive Brain Mapping and Digital Therapeutics

Issue: #137

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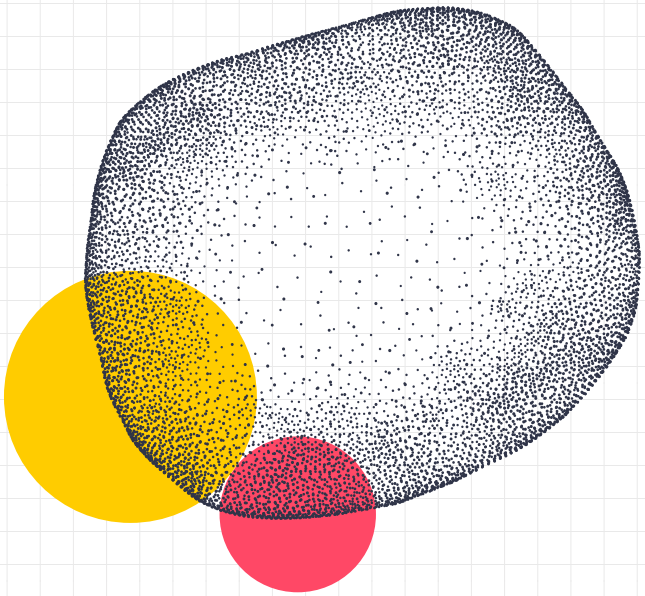

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WELCOME...

This riveting and thought-provoking issue of Scientia showcases the work of scientists charting new frontiers in psychological and brain sciences. The brain is, by far, the most complex organ in the human body. It is responsible for our thoughts, what we do and what we don't do, our external experience of the world and our internal sense of self. As such, it is often said that 'we *are* our brains'. It should not, then, be unexpected that conditions affecting the brain can have deleteriously severe impacts on people's lives. And at the same time, conditions affecting the brain are notoriously difficult to treat.

In our first section, we meet the researchers working to ameliorate the negative impacts of adversity and trauma on mental health. From advances in understanding how childhood trauma impacts brain development to recognition of the complex and interacting factors associated with alcohol use disorders, this section highlights critical advancements being made in building brighter futures through scientific endeavour.

Our second section showcases the work of researchers unravelling the complex and multifaceted causes of disease. Focussing on neurodevelopmental disorders (such as those on the autism spectrum) and psychiatric diseases (such as schizophrenia), this section illustrates the critical role that genes play in susceptibility for a wide range of disorders and diseases, and how this knowledge can be used to improve diagnosis and treatment.

Our final section celebrates recent advances in understanding and treating clinical disorders. From improving the diagnosis and treatment of neurological diseases including Alzheimer's disease and epilepsy to exploring the effects of music on patients with disorders of consciousness, this section highlights how scientific and technological advances are driving cutting-edge insights and informing treatment innovation. We also meet Ian Wilson, Deputy Chief Executive of Alzheimer's Research UK and Vinny Smith, Chief Executive of the Meningitis Research Foundation, to hear about their vital work.

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Meet The Team...

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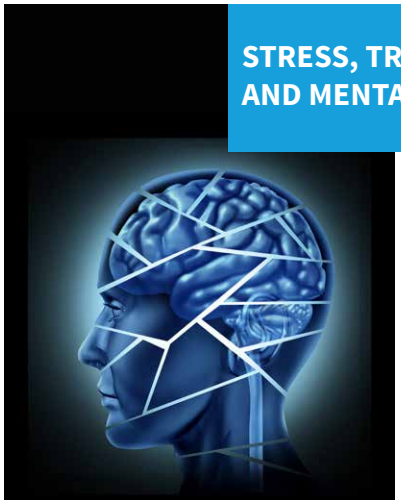
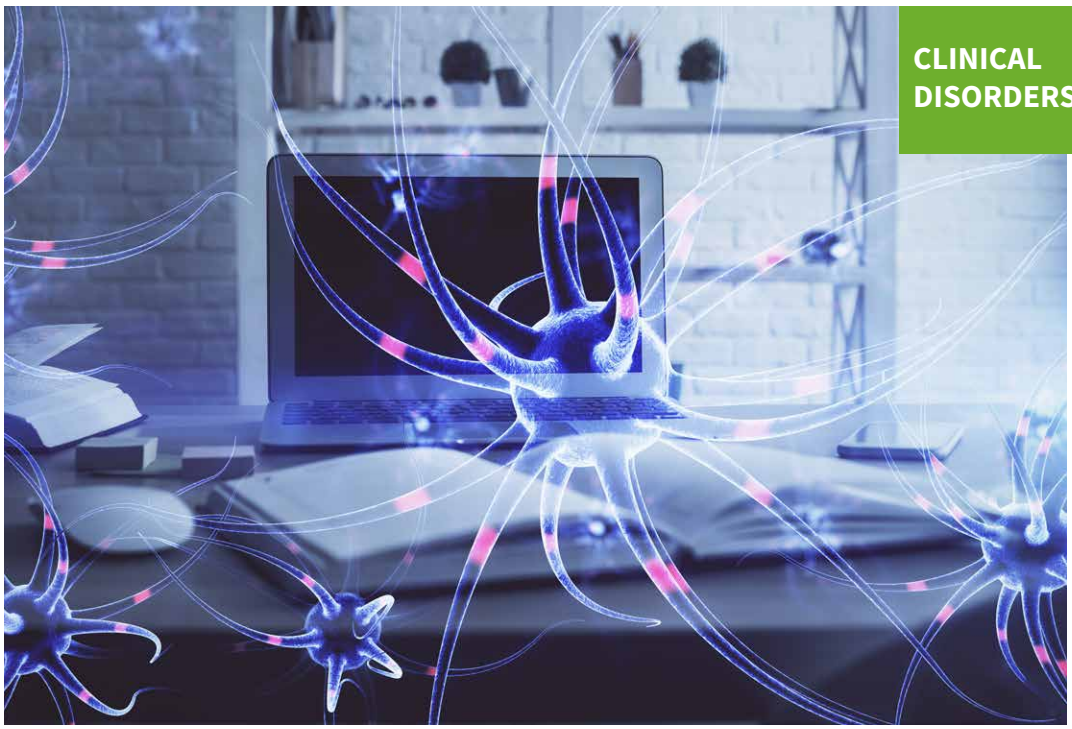


STRESS, TRAUMA AND MENTAL HEALTH

GENETICS AND DISEASE



CLINICAL DISORDERS

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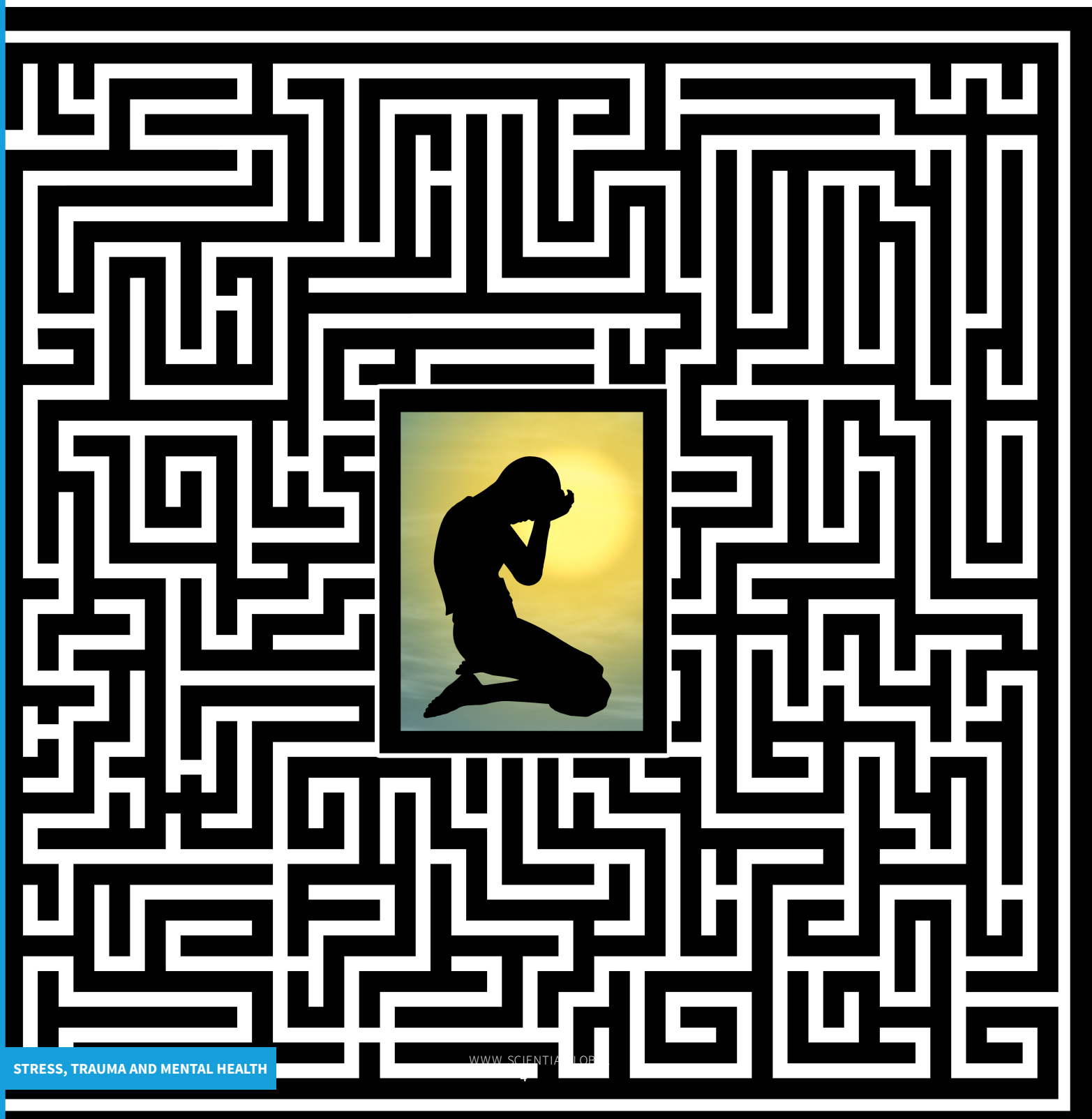


OVERCOMING ADVERSITY AND TRAUMA

The first section in this issue is dedicated to the researchers working to help ameliorate the negative impacts of adversity and trauma on mental health. Traumatic events such as interpersonal assault and car accidents are relatively commonplace, and the likelihood of being involved in or witness to a traumatic event at some stage in our lives is unfortunately high. As a result, posttraumatic stress disorder (PTSD) is a prevalent psychiatric condition, detrimentally affecting the lives of millions of people globally. A clearer understanding of the complex factors contributing to the development of trauma and stress responses including PTSD, anxiety and alcohol use disorders is an urgent necessity.

We open this section by meeting Dr Tanja Jovanovic from Wayne State University, who is exploring how childhood trauma impacts brain development, increasing the risk of developing mental health issues in adulthood. We read how her work may help identify the children at risk of later developing anxiety or PTSD. Critically, this could allow the use of prophylactic interventions to overcome the negative impacts of adverse experience.

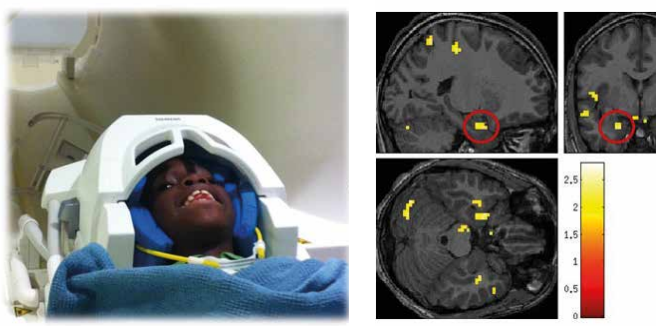
Dr Israel Liberzon and his colleagues at the Texas A&M Health Sciences Center are working to uncover the dysfunctional neural networks in the brain that contribute to PTSD symptoms. We read how his newly developed, comprehensive model of PTSD provides a more precise neurobiological understanding of the disorder, with the potential to improve success in translating research into clinical interventions.

Professor Tara Perrot at Dalhousie University is also working to better understand how our early developmental experiences influence our stress reactions and resilience later in life. Professor Perrot further proposes that even the experiences of our parents before we are born influence our own well-being. We read how her research holds important implications for understanding human stress reactivity in the current day.

We conclude this section by meeting Dr Sara Blaine from Auburn University. The current prevalence of alcohol use disorders is a serious concern given the negative impacts on individuals, their families, and society more widely. A better understanding of the complex and interacting factors associated with alcohol use disorders is required if we are to develop more effective treatments. We read how Dr Blaine is elucidating the critical role of stress and in doing so, driving the development of personalised treatments in this field.

TRAUMA IN CHILDHOOD: HOW ADVERSITY AFFECTS BRAIN DEVELOPMENT

Exposure to childhood trauma increases the risk of developing mental health issues in adulthood. However, the processes through which this occurs are currently unknown. Using magnetic resonance imaging, laboratory-based measurements of fear, and the assessment of clinical symptomatology, **Dr Tanja Jovanovic** from Wayne State University is investigating the effect that trauma has on brain development. She hopes her findings will help identify those children at risk of anxiety or post-traumatic stress disorder so that preventative measures can be put in place to ensure brighter futures for children in their adulthood years.



Testing brain responses to fear in the laboratory. Credit Tanja Jovanovic.

Post-traumatic Stress Disorder

Around one in four adults will face mental health issues during their lifetime. Depression, anxiety and post-traumatic stress disorder (PTSD) are all prevalent, with about 8% of the population experiencing the latter. PTSD can develop after traumatic events, ranging from experiencing violence to witnessing a car accident. The resultant symptoms in adults can be numerous, such as vivid and distressing re-experiencing of the trauma, struggling to fall and stay asleep, strong physical reactions to reminders or triggers, panic attacks and irritability. For some, these symptoms last for a few weeks, for others, it can be much longer. PTSD is also associated with high levels of comorbidity with other forms of psychopathology such as depression, anxiety and alcohol/drug abuse.

Children with PTSD similarly present with symptoms of sleep problems and aggression. However, they can also exhibit developmentally related behaviours, such as reproducing their trauma through play or drawings, forgetting previously mastered skills such as toilet training, and demonstrating separation anxiety.

Critically, adversity at a young age can alter how a child's brain develops and this may lead to mental health issues such as PTSD, anxiety and depression later in life. But how this happens is not yet known.

Dr Tanja Jovanovic is a Professor in the Department of Psychiatry and Behavioural Neurosciences at Wayne State University in Detroit. She and her team are working on unravelling the science behind how trauma exposure can lead to PTSD, so that they can predict who may be most at risk to later psychopathology. Importantly, if approaches aiming to prevent the development of psychopathology can be implemented with children who have been deemed high-risk thanks to Dr Jovanovic's research, they may be spared from future psychological distress.

Influences on the Response to Trauma in Childhood

Throughout the years, Dr Jovanovic has published many studies on psychopathology in children. With colleagues, she has established that girls and boys react differently to trauma, with girls more likely to blame themselves and fear a repeat of the ordeal. Such differences in how individuals react to trauma lead to

differential risks for the development of subsequent mental health problems.

Age differences also occur in relation to the experience of trauma. A study published by Dr Jovanovic and colleagues in 2016 showed that the availability of a mother during a fear conditioning experiment (involving the learning of fear in response to a given stimulus) in younger children, but not adolescents, allowed them to better discriminate between dangerous and safe signals. This effect is known as 'maternal buffering' and is consistent with the perspective that a child's parenting environment is significant for their learning of danger and safety signals. However, the quality of the mother-child relationship, at least as rated by the mother, did not influence the maternal buffering effect. In another study, they found that children of mothers who had experienced a lot of trauma and had many PTSD symptoms also had problems learning safety signals, independent of their age and own traumatic experiences.

Another way a mother can impact their child's mental health is through their level of emotionality. If a mother is less able to manage her emotions (known as emotion dysregulation) and finds parenting to be very stressful and overwhelming, she is more likely to pass on anxiety to her children, which puts them at higher risk for additional mental health issues.

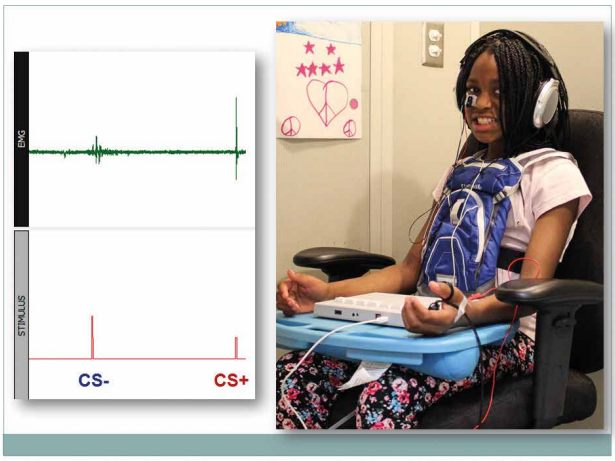
Testing the Impact of Trauma on Brain Development in the Laboratory

Dr Jovanovic and her team are currently conducting a longitudinal study to investigate the effect of trauma on brain development and how this might lead to PTSD. Longitudinal studies are used to observe the same variables (or outcomes) over a period of time. In this case, the critical variable is how trauma affects a child's brain development. During this ongoing study, children in Detroit aged 9 years, along with their primary caregivers, are being recruited to participate for over 3 years. When they first start the study, they are asked if they have experienced any traumatic events in their lives, complete some laboratory tests, and undergo a magnetic resonance imaging (MRI) brain scan.

An MRI forms detailed images using radio waves and a magnetic field. Because this technique allows clinicians to see irregularities in tissues and organs, it is often used to identify tumours, strokes and other disorders. Dr Jovanovic is using MRI to see how different parts of children's brains are physically altered as a result of trauma.

Functional magnetic resonance imaging (fMRI) is slightly different from MRI because it is used to show brain activity.

‘As part of our research, we have uncovered several biological factors that can make some children more vulnerable to PTSD and anxiety.’



Measuring electromyography in response to presented stimuli in the laboratory. Credit Tanja Jovanovic.

When a part of the brain is active, it requires more oxygen to function, so oxygenated blood flow increases to that area. An fMRI detects these changes and, for Dr Jovanovic, allows her to see which parts of the brain are being used in children with varying levels of fear.

The laboratory tests the team perform to measure fear are known as fear conditioning paradigms, such as the fear-potentiated startle (FPS) test. This involves measuring the reflexive (involuntary) physiological reaction to a neutral stimulus such as a loud sound or bright light, for example. The neutral stimulus is repeatedly paired with an aversive air blast until it starts to signal danger, while a different, unpaired, stimulus signals safety. The individual’s responses to these stimuli are recorded physiologically, such as through the eyeblink contraction and heart rate. Reacting more strongly than normal to the danger or safety stimulus may reveal an anxiety or trauma-related disorder, or a higher ongoing level of fear.

Every 6 months, the participants return to the laboratory and are asked if they have experienced any new trauma, and each year they undergo another fMRI brain scan.

Trauma’s Mark on the Brain

Although data collection is still in the early stages, a number of interesting findings have already emerged. Despite the observation that the children recruited have experienced significant violence within their neighbourhood, they are resilient, with little evidence of PTSD symptomatology. This seems to be due to higher activation in their regulatory and protective brain areas such as the hippocampus and prefrontal cortex when the fear areas, like the amygdala, are also activated. Regulatory and protective areas in the brain are in charge of controlling functions like emotion, reasoning and judgement. Dr Jovanovic says that this, ‘may suggest that children with high trauma have higher levels of fear, but also that other areas are working harder to control the fear.’ She also notes that ‘As we continue to follow these children as they grow it will be important to see which children continue to be resilient and which start to show symptoms so that we can learn how to help them.’

Not only were the activation levels of parts of the participants’ brains altered but so were the sizes. More specifically, exposure to urban violence resulted in a smaller hippocampus and larger amygdala. While these structural changes may have the potential to lead to future psychopathology, they could also provide a survival mechanism to allow the brain to adapt to the threats in the environment and overcome the trauma.

Previous studies have shown that having a specific version of a gene called ADCYAP1R1 is associated with increased FPS and PTSD in adult women. However, Dr Jovanovic wanted to examine how this genotype (the version of the gene) and trauma affects development in children as well. Her work indicated that there is a link between higher fear in children with greater exposure to violence and this variation of ADCYAP1R1. They found that this fear worsens with age, so they think children with this genotype may be at higher risk of PTSD as they get older. Gender was also an important factor, as girls with this variation of the gene showed more fear than boys. In addition, they found that girls who have experienced trauma show accelerated pubertal development, which leads to higher fear responses.

Next Steps

Dr Jovanovic is planning further studies into psychopathology in relation to genetics and neurobiology. Hormonal changes, sex differences and the environment will also be explored to discover how they affect brain development and fear. She hopes that her research will be used to identify those who are most likely to develop future mental health issues as a result of experiencing trauma.

In her own words, Dr Jovanovic explains, ‘our research has indicated several areas that interventions can target for vulnerable children to prevent future psychological distress.’ PTSD can have a long-lasting effect, not just on the sufferer, but also their loves ones. Marital problems are more common with people who have PTSD and their children are more likely to have anxiety, depression and behavioural problems. But, if at-risk children are identified, they can be helped through interventions such as counselling, exercise, mindfulness and many other methods, to allow them to lead happier lives with brighter futures.

Meet the researcher

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Dr Tanja Jovanovic received her PhD in Neuroscience and Animal Behaviour from Emory University in Atlanta, Georgia. Afterwards, she served as Assistant Professor in the Department of Psychiatry and Behavioral Sciences at the Emory University School of Medicine. She is now a Professor in the Department of Psychiatry and Behavioural Neurosciences and the David and Patricia Barron Chair for PTSD Neurobiology at Wayne State University. Dr Jovanovic directs the Detroit Trauma Project which investigates how urban trauma exposure impacts the brain. In addition, she is the lead investigator on several federally funded grants from the National Institutes of Health. Her many achievements include over 170 published papers, serving on national and international grant review panels and an Independent Investigator Award from the Brain and Behavior Research Foundation.

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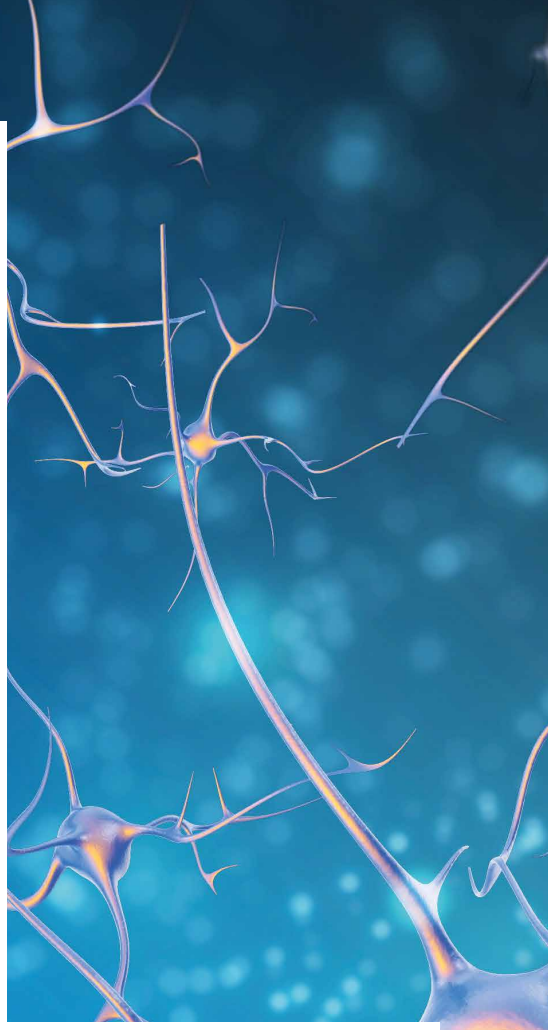
Detroit Trauma Project

UNRAVELLING THE NEURAL NETWORKS UNDERPINNING POSTTRAUMATIC STRESS DISORDER

Posttraumatic stress disorder (PTSD) is a prevalent psychiatric condition, significantly impacting the lives of millions of people globally. Sadly, symptoms often persist despite treatment. A better understanding of the brain abnormalities involved in PTSD is crucial to improving therapy development. **Dr Israel Liberzon** and his colleagues at the Texas A&M Health Sciences Centre have been working to uncover the dysfunctional neural networks that contribute to PTSD symptoms to inform the development of more effective interventions.



The Impact of Trauma

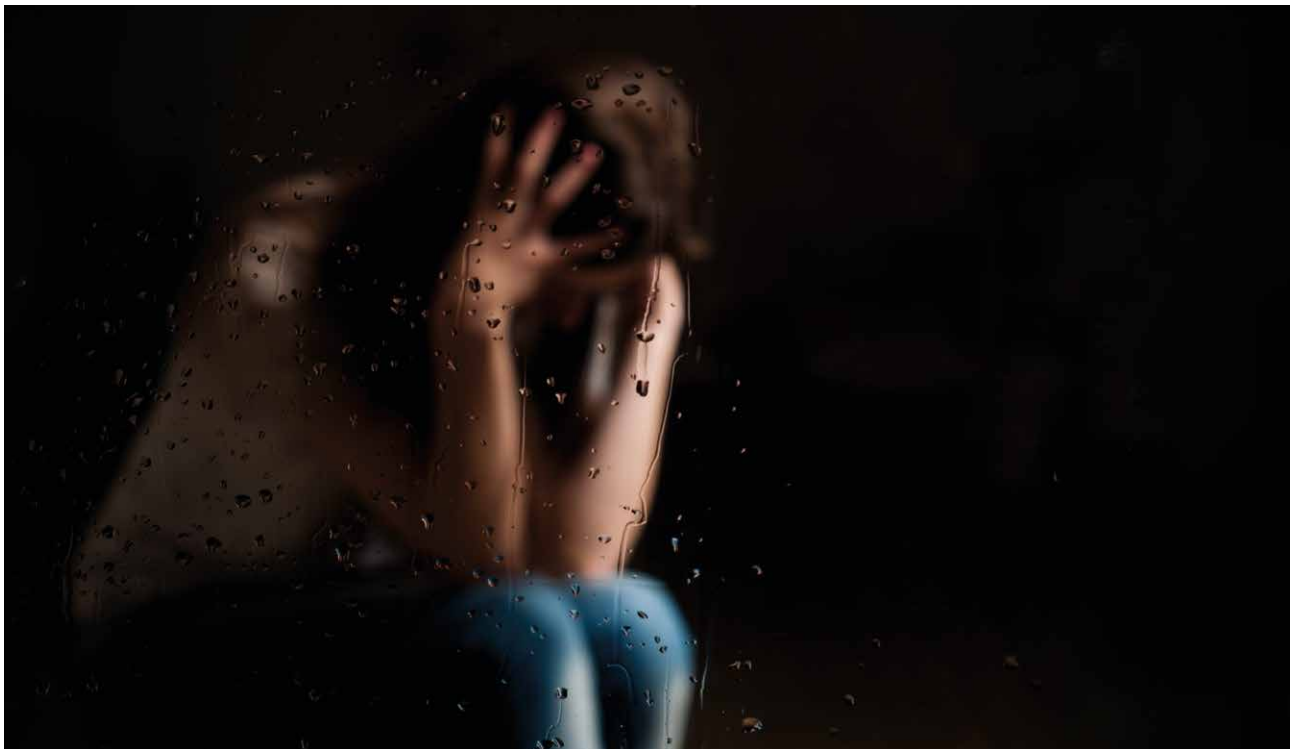
Being involved in or witness to a traumatic event at some stage in our lives is more than likely. Traumatic experiences – from military combat to road traffic accidents to violent assaults to natural disasters – are commonplace across the world and often result in debilitating consequences. One such consequence for individuals can be the development of posttraumatic stress disorder (PTSD).

Although clinical diagnostic criteria have changed over the decades (and will no doubt continue to evolve), PTSD is diagnosed according to core clusters of symptoms: intrusive and avoidant symptoms, negative cognitions, and hyperarousal. Despite the intensive research into PTSD to date, an understanding of the fundamental neurobiological abnormalities that are associated with PTSD and its symptoms has remained elusive. Without this understanding, current clinical treatments and interventions are often untimely and lacking in specificity. Improved knowledge of the underlying mechanisms of PTSD, however, would allow a move towards personalised treatment plans and even the prevention of PTSD.

Researching Posttraumatic Stress Disorder

Until recently, the understanding of the underlying mechanisms in PTSD was limited to the effects of the condition on physiological markers that could be readily measured, such as heart rate changes and the concentrations of stress hormones in blood and saliva. Genetic studies have identified genes that appear to be linked to PTSD, but these observations require confirmation as so far, they appear to be more preliminary and non-specific. Improvements in neuroimaging methods have enabled recent research efforts to focus on the effects of PTSD within specific neural circuits, which are the electro-chemical communication networks within the brain. Furthermore, how abnormalities in these circuits can influence the presentation of symptoms can be studied.

Powerful PTSD models have been developed from such research, including the abnormal fear learning model, exaggerated threat detection model and the diminished emotional regulation/executive function model, which are each linked to specific neural circuits and correspond to underlying molecular and cellular mechanisms. However, these experimental models leave several aspects of PTSD unexplained, including complex symptoms and substantiated neurobiological findings.



The Altered Contextualisation Hypothesis

Dr Israel Liberzon and his colleagues have identified the need for a PTSD model that would encompass and explain multiple aspects and presentations of the disorder. 'Ultimate cure or recovery is possible only if the underlying mechanism of the disease is fully uncovered,' notes Dr Liberzon. The team proposed a new altered contextual processing (CP) model, focussing on the deficits in the neural circuits that are responsible for processing contextual information and regulating emotional responses. This comprehensive CP model will provide a more precise neurobiological understanding, ultimately contributing to improved success in translating research into clinical interventions.

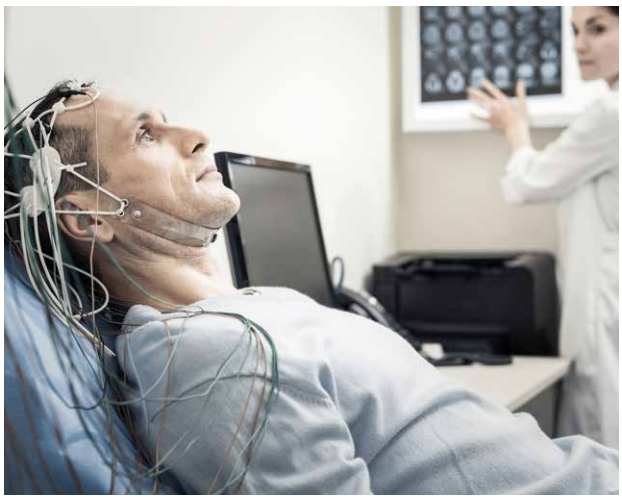
Contextual processing involves perception and cognitive interpretation of general, emotional and other signals in a situation, to determine its overall meaning, for example 'safe' or 'dangerous' environment. Various signals from a given situation or environment are assembled and stored as contextual representations, which can be later utilised to produce an appropriate response according to the needs of a future situation. A lack of precision and flexibility in these representations, necessary for correctly inferred circumstances and appropriate behavioural responses, is likely responsible for a broad range of symptoms in PTSD.

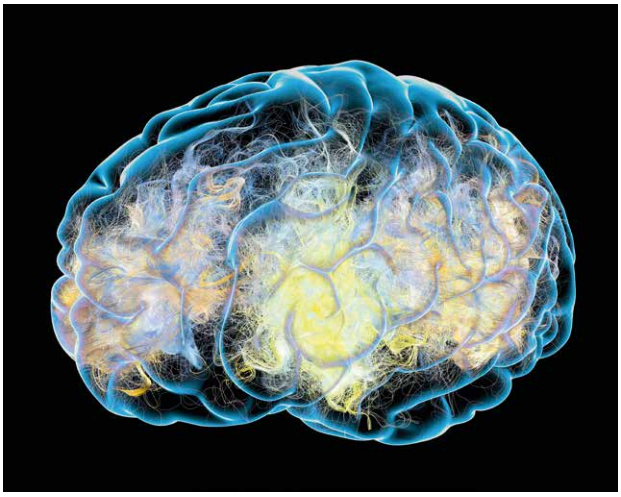
Investigating the Neural Networks Involved

There is much research to suggest that dysfunction in the context processing circuitry plays a central role in the mechanisms underlying PTSD, and several specific brain regions have been identified as potential contributors.

The hippocampus, responsible for establishing new memories, appears to contribute to increased vigilance and arousal in PTSD sufferers by excessively recalling traumatic experiences even in incorrect contexts. The prefrontal cortex, interconnected with the hippocampus, seems to accumulate the features of similar contexts to connect different experiences over time. Dysfunction in this hippocampal-pre-frontal-thalamic network could induce misinterpretation and fear learning of innocuous cues as traumatic signals, causing disproportionate fear behaviours and emotional overreaction in PTSD. Dr Liberzon and his colleagues investigated the possible role of this hippocampal-pre-frontal-thalamic network in relation to their CP model; they found a diminished ability to learn appropriate fear/safety behaviours and reactions, alongside reduced activity in these brain regions of individuals with PTSD. The team proposed that such a dysfunctional network could lead to the inappropriate linking of erroneous emotions to different contexts.

In his published work, Dr Liberzon speculates 'if a context is identified as "unsafe," attention is focussed on potential threat cues, leading to hypervigilance; but if contextual information that should alert one to danger is missed, this might lead to recklessness and re-traumatisation,' linking the neurobiological abnormalities to previously unexplained aspects of PTSD. In this way, the CP model provides a robust framework for integrating underlying mechanisms with multitude of clinical presentations in PTSD. Genetic and animal model studies have corroborated Dr Liberzon's findings and hypotheses, with new research consistently implicating the





hippocampal-pre-frontal-thalamic circuitry in the genetic and developmental defects linked to PTSD.

Results emerging from electrophysiological studies, where the electrical inputs and signals between cells and anatomical structures are measured, have indicated that disrupted hippocampal-pre-frontal-thalamic network communication contributes to abnormalities in the stress hormone systems through sleep disturbance, leading to interrupted memory formation and consolidation in PTSD. Dr Liberzon's CP model of PTSD is therefore proving to be a general, parsimoneous explanation for the genetic, hormonal, and psychophysiological mechanisms of the disorder.

Tackling the Spectrum of Symptoms in Treatment

Using the concept of intermediate phenotypes (IPs) – clinical presentations that are linked to an underlying dysfunctional neurological mechanism – Dr Liberzon suggests that disorders like PTSD should be considered more like syndromes, that combine specific neurobiological IPs that produce a unique version of the condition in affected individuals. He states that 'identifying distinct IPs will facilitate the development of more valid animal models needed to further dissect the mechanistic neurobiology of all "types" of PTSD,' while emphasising that 'further elucidation of the cellular and/or molecular mechanisms is critical.'

Working on the basis of previous research, Dr Liberzon and his colleagues have most recently conducted a study assessing volume abnormalities in different brain regions implicated in PTSD. Coming together with scientists and clinicians across the globe, Dr Liberzon and the team have been able to perform one of the most comprehensive analyses to date, assessing the effects of PTSD in the brain regions of nearly 1400 affected individuals. They found PTSD to be associated with smaller volumes in brain regions involved in emotion, sensory information and memory processing, with greater volume reduction in these areas corresponding to increasing severity of the PTSD symptoms.

'Our findings support current thinking on deficits in emotion neuro-circuits in PTSD and shed new light on the involvement of sensory brain circuits' notes Dr Liberzon. Such findings will be crucial in identifying individualised presentations of the disorder, or dominant symptoms and dysfunctional mechanisms in a given patient, leading towards the potential for a more specifically targeted treatment and a more personalised medicine approach.

As both a physician and a scientist, Dr Liberzon is dedicated to easing the suffering of individuals with mental health difficulties, particularly those with PTSD. 'We cannot wait for the ultimate solution, and best available care must be developed and administered,' he explains.

Future Paths for Research

Now a Professor and Department Head of Psychiatry at the Texas A & M Health Sciences Centre in the USA, Dr Liberzon plans to continue his research with 'rigour and intensity', having identified the hippocampal-pre-frontal-thalamic circuitry as a key neural circuit affected in PTSD patients.

Dr Liberzon already has substantial backing to explore this promising avenue of research, and intends to continue working towards better treatment strategies and intervention approaches in PTSD, in combination with personalised medicine approaches. 'This was a challenging but immensely gratifying path,' notes Dr Liberzon. He indicates that future research will also investigate links with PTSD to other diseases, such as heart disease and the involvement of inflammation, to improve the understanding of the impact of co-existing diseases on the severity and presentation of PTSD, since the effects of these disorders add further to the detriment of the overall health of an individual.

Dr Liberzon hopes that continuing a career in translational science, engaging in research and clinical practice simultaneously, will prove effective in easing the suffering associated with PTSD more efficiently.

Meet the researcher

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Dr Israel Liberzon received his MD in Israel at Tel Aviv University after studying Biology. His postdoctoral training began in Israel, before moving to the University of Michigan in the USA, where he was appointed Professor of Psychiatry and Psychology. Dr Liberzon's defining interests stem from his career as a physician-scientist, devoting his work to easing the suffering of individuals with PTSD by researching the risk and resilience factors important in the disorder. Having developed the most widely used animal model of PTSD, he continues to develop new hypotheses on the underlying dysfunctional mechanisms to improve treatment strategies. As an expert in his field and co-leader of the development of an international PTSD group, Dr Liberzon has been invited to lecture around the world, training the next generation of successful researchers. Now, as Professor of Psychiatry at the Texas A&M Health Sciences Center, Dr Liberzon intends to continue studying the neurobiology of individual presentations of PTSD taking into account the impact of other health conditions on the severity of the disorder.

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HOW THE EARLY ENVIRONMENT INFLUENCES STRESS RESPONSES IN ADULTHOOD

Professor Tara Perrot and her team at Dalhousie University, Canada, are working to better understand how early development – including the experiences of parents before their offspring are even born – may influence the stress reactions and resilience of their offspring later in life. This research involves not only looking at the brain and hormones but also the gut, and holds important implications for understanding human stress reactivity in the current day.

What Makes Some People Resilient?

High levels of stress for a prolonged duration can have severe and devastating effects on individuals' mental and physical health. In the developed world, we are seeing increasing rates of anxiety and depression, and need to better understand what may influence levels of resilience if we are to better help those affected.

Stress is an inevitable part of life, yet some people seem able to better cope with it – they seem to have better resilience. Professor Tara Perrot and her team at Dalhousie University in Halifax, Nova Scotia, are working to explain why this is the case. In outlining the overarching purpose of her work, Professor Perrot explains, 'Our goal is to understand the sources of variability in how individuals respond to stress – why do some suffer from stress-related illnesses while others are resilient?' More specifically, Professor Perrot and her team are investigating how it is that early-life events influence later-life responses to stress. Critically, uncovering the sorts of environments that lead to better resilience later in life could help us to build the right environments to set up our offspring for lives with a lesser impact from stress.

Professor Perrot and her team work primarily with rats to model various behaviours, environments, and stressors to better understand the role that these different influences may play in the development of better – or worse – responses to stress in offspring when they have reached adulthood. Professor Perrot's team use this approach to explore their keys areas of interest – various hormones and responses in the brain and, more recently, gut bacteria and diet and its influence on these factors – which are similar to those found in humans. From an experimental perspective, it is relatively easy to adjust the environment that rats live in to test how such changes can influence stress in mothers both at the time, and in their offspring later on in life.

Early Life Influences

The researchers have gone right back to the start of the life cycle in their bid to better understand the factors that influence our reactions to stress. One stressful event that can be measured and tested in the laboratory in animal models is exposure to predators (this may even be just the scent of a predator). Exposure to predators may indicate an ongoing threat and so increases the stressfulness of the environment. Professor Perrot and her team have shown that exposure to this stressor can change the way that mother rats behave when their offspring are young. Interestingly, this was the case whether it was the mother that experienced the exposure to the predator, or the father.

‘Our goal is to understand the sources of variability in how individuals respond to stress - why do some suffer from stress-related illnesses while others are resilient?’

One recent study by Professor Perrot’s research team found that the father being exposed to this type of stress, even before mating, had an effect on the behaviour of the mother rat. The female rats somehow had a way of detecting this previous experience of stress in the males, and adjusted their behaviour toward the males’ young. Specifically, they continued to treat the environment as a potentially high-stress environment with possible predators afterwards, which affected their maternal behaviours towards their offspring.

There are two types of behaviour in mother rats that occur within the first week after giving birth that have been shown to affect the way that a particular hormone system within the brain responds to stress in the pups later on in adulthood, as well as how anxiety-prone these adult offspring are, and whether their thinking and memory are affected by stress. These are all relevant responses to stress in humans, too. These are the behaviours that the researchers were interested in measuring to identify any changes in behaviour on the part of the mother.

This work has important implications. As Professor Perrot explains, ‘The quality of a mother’s care has profound effects on the development of the stress response system in the offspring… anything that alters her care can alter her offspring’s future stress responding.’

As well as monitoring maternal behaviour following predator stress for either of the parents (including exposure of a pregnant mother to the scent of a predator in a separate experiment), the researchers also investigated the role of the environment the rats were housed in, to see if this could be a further source of stress and could tell us more about how the animals responded to this.

The mothers’ behaviour was influenced by both types of stress – predator presence (in the lives of either parent) and the quality of the housing they were in. Better housing partially offset the increase in stress-responses of the offspring, either through the improved environment at an early age or better quality maternal behaviour towards the pups when they were young.

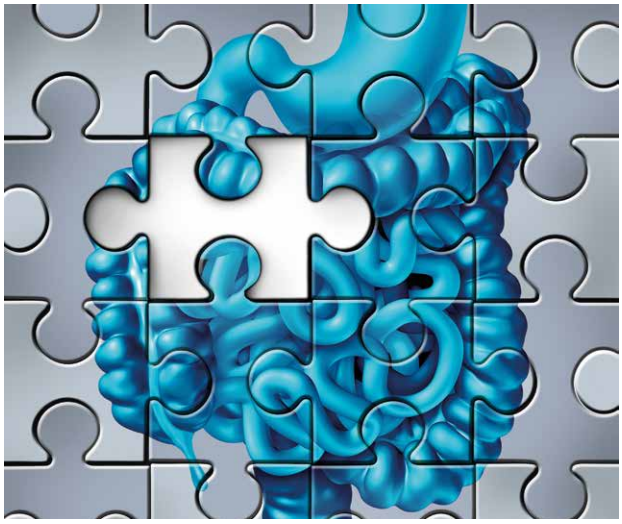
Beyond the Brain

More recently, Professor Perrot and her team have expanded their investigations to look beyond the brain – that is, investigating the hormonal responses produced within the brain, and anxiety and depressive behaviours as the result of input from a wider system. They have begun to look at the effects that could occur through changes in other areas of the body, primarily the gut, and the effects that poor diet may have.

For humans, obesity and poor diet are increasing problems in the developed world, and Professor Perrot’s team are investigating the role that diet may play on stress resilience – this includes the diet of both parents before and, in the case of the mother, during pregnancy.

Recent work by Professor Perrot’s team has found that, similar to the stress of a predator as described earlier, exposure of the father rat to a high-fat diet affected the female’s preference for a mate, and had subsequent effects on her behaviour to their offspring and the stress responses of those offspring. The

‘The quality of a mother’s care has profound effects on the development of the stress response system in the offspring…anything that alters her care can alter her offspring’s future stress responding.’



high-fat diet seemed to act as a stress in the father’s life and resulted in similar problems to the more apparently obvious stressful environmental factor of the presence of a predator.

Research has also shown how high-fat diets and obesity in human mothers may act as a source of stress and detrimentally affect the development of their foetuses, leading to neurodevelopmental problems – including anxiety and depressive disorders. In collaboration with their industrial partner, Rosell Institute for Microbiome and Probiotics by Lallemand, Professor Perrot’s team is actively exploring the interaction of diet and stress, including the potentially beneficial effects of probiotics.

Implications for Coping with Stress

All of these findings provide important clues about our environment, both external and internal, and how these may interact to impact on our later ability to cope with stress. Critically, our ability to cope with stress, and our resilience to the effects of stressful life events, seem to stem from very early experiences and influences.

These findings are of importance because they demonstrate some of the ways through which the stresses experienced by parents may be exhibited or passed along to their offspring, and the subsequent impacts that these behaviours have. If we can identify equivalent behaviours in people, we may be able to prevent the development of such environments or stop them from having such a significant and damaging effect. Paying attention to living environments and their impact on producing or relieving stress is also important, and one that has important implications for public health.

Another important finding arising from Professor Perrot’s work is the increasing evidence for sex-related differences in the levels of stress-related hormones, and anxiety- and depressive-related behaviours seen in the rats raised during these types of experiments. These findings suggest that there is some further role that sex hormones may play in the development of susceptibility to stress or resilience, and that warrants further investigation.

Professor Perrot and her team always include male and female pups in their experiments so that they can identify any differences and test whether different factors affect each sex differently. Given the differences in the numbers of men and women who display low levels of resilience and anxiety- and depressive-related behaviours, as well as the types of behaviours shown in response to stress, research such as Professor Perrot’s that routinely investigates these differences is essential.

This is not to say that we cannot overcome the influence of our early environment with respect to coping with stress as adults. One of Dr Perrot’s passions outside of the lab is researching and sharing information about activities that individuals can undertake to reduce the unhealthy effects of stress on the brain and body. These activities include consuming a healthy diet, taking regular exercise, and engaging in mindfulness-based activities such as yoga and meditation. Over the next few years, Dr Perrot plans to increase the number of presentations and workshops she gives in her effort to provide the general public with tools to effectively deal with daily stress.

The research of Professor Perrot and her team has important implications for public health bodies, the guidance given to prospective and new parents, and for the development of strategies to overcome these differences and help individuals with lower levels of resilience.

Meet the researcher

Professor Tara Perrot
Dalhousie University Life Sciences Centre
Halifax, Nova Scotia
Canada

Professor Tara Perrot received her PhD in neuroscience in 1998 from Western University, Canada. Following her progression through a range of academic positions, Professor Perrot is now Professor at the Department of Psychology and Neuroscience at Dalhousie University, Canada. Her research focuses on the factors that affect the development of resilience to stress, and in particular, understanding the responses to stress from a variety of perspectives, including behavioural, hormonal, and neural in both animal models and humans. Professor Perrot has published more than 50 peer-reviewed journal articles and several book chapters in her field of expertise, with many of these including undergraduate and graduate trainees she has supervised over the years. She has given numerous invited presentations, and is an active reviewer of grants, manuscripts, and other scholarly activity. Finally, Professor Perrot has a demonstrable commitment to scientific outreach, including participating in an interview for a Telefilm Canada-funded documentary in 2015 and public lectures on keeping your brain healthy. Aligned with these professional interests, Dr Perrot has a registered company called Fit Brain, the goal of which is to provide individuals with tools to combat stress and maintain brain and body health. The company is in its infancy, but to date, Dr Perrot has provided stress management workshops to management professionals and graduate students in the Halifax area and most recently, nature retreats to the general public that focus on stress-reduction. She is a 200h certified yoga practitioner and an active yogi. She is currently working toward her Atlantic Master Gardener certificate, which will enable her to include horticultural activities in future offerings. She invites you to visit her recently launched website for more information and to contact her with questions or to enquire about a workshop or retreat.

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W: https://fbmahonebay.com
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DALHOUSIE UNIVERSITY

EEAR LAB
Early Environment and Adult Resiliency

THE INFLUENCE OF STRESS ON THE DEVELOPMENT AND RECOVERY OF ALCOHOL USE DISORDERS

The prevalence of Alcohol Use Disorders represents a serious concern given the deleterious impacts observed on individuals, their families, and society more widely. A better understanding of the factors associated with the development and recovery of Alcohol Use Disorders is essential to the development of more effective treatments. This is the focus of research by **Dr Sara Blaine** from Auburn University, USA.

Alcohol Use Disorders

Alcohol Use Disorders are relatively common conditions that can lead to an array of physical and psychological problems. Alcohol Use Disorders are characterised by the loss of control over alcohol consumption despite detrimental social, occupational or health consequences.

Worryingly, 18% of Americans suffer from an Alcohol Use Disorder at some point during their lifetime and up to 8% of Americans develop severe Alcohol Use Disorders. The socioeconomic consequences of Alcohol Use Disorders are experienced nationally, with the USA losing more than $235 billion per year in health-related costs, productivity losses, premature death, and legal costs.

Dr Sara Blaine from Auburn University investigates how a person's genetic background interacts with their experiences of stress to influence drinking behaviour and change brain function.

Drinking Initially Relieves Stress

Dopamine and Serotonin are neurotransmitters (chemical messengers between neurons) released by the brain's reward circuits that play a role in how we feel pleasure. They are released during pleasurable situations, such as eating chocolate or exercising, and stimulate us to seek further enjoyment. This activity in the brain's reward system motivates us to seek out the cause of enjoyment again and again.

Alcohol consumption activates our brain's reward circuits at a very high level. Dopamine and serotonin increase feelings of relaxation and reduce anxiety. As individuals progress into Alcohol Use Disorders, alcohol consumption is driven more by the anxiety reduction than the increased feelings of relaxation. This means that individuals learn to consume alcohol as a coping mechanism when they are anxious or sad as a remedy or relief. Those with Alcohol Use Disorders will consume greater quantities of alcohol to cope, and over time will develop a tolerance, thereby requiring more alcohol to bring back those initial

feelings of anxiety reduction. As a result, individuals may become binge drinkers without recognising how much they depend on alcohol for relief.

The National Institute on Alcohol Abuse and Alcoholism defines binge drinking as consuming four or more drinks per drinking episode for women, and five or more for men. Consuming more than eight drinks per week for women or more than 15 drinks for men is also considered binge drinking.

22oz BEER -
~5% ABV

2 DRINKS

22oz MALT LIQUOR -
~7% ABV

2.5 DRINKS

750ml BOTTLE OF WINE
~12% ABV

5 DRINKS

1.5oz SINGLE SPIRIT
& MIXER - 40% ABV

1 DRINK

16oz SPIRIT
- 40% ABV

11 DRINKS

25oz SPIRIT
- 40% ABV

17 DRINKS

Standard drink equivalents of popular alcoholic beverages.

For some, such as those with greater genetic risk, high stress levels, or a history of trauma, alcohol consumption can produce a heightened relaxation and anti-anxiety response compared to individuals without these factors. The reliance on alcohol to provide relief from negative feelings or stressful situations can therefore be more intense.

Repeatedly Drinking to Relieve Stress Leads to More Stress

In recent research, Dr Blaine found that many of the genetic risk factors that shape an individual's response to alcohol also influence their response to stress. These genetic risk factors relate to how the brain and body respond to cortisol, a hormone that affects almost every organ and tissue in our bodies. Our daily cortisol rhythm helps us wake up in the morning and affects our energy throughout the day. Critically, it is also known as the 'stress hormone'.

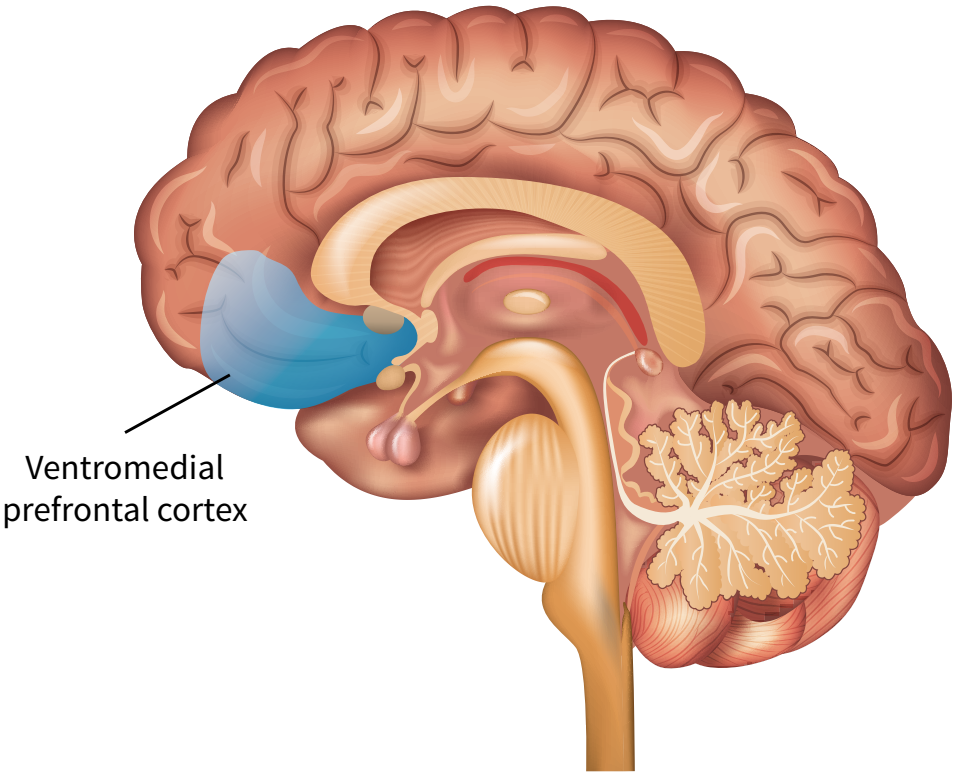
The hypothalamic pituitary adrenal (HPA) axis regulates the body's response to stress: during stressful situations, the HPA axis is activated which stimulates the release of cortisol. Cortisol helps initiate and maintain our 'fight or flight' response to stress. ***However, this same process of cortisol release is also observed with alcohol consumption, contributing to alcohol's initial stimulating and energy increasing effects.***

As people learn to respond to stress with alcohol intake, the HPA axis begins to release cortisol in response to any cues that remind the person of drinking, such as the sight of people they drink with, the bars they frequent, or a commercial for their favourite beer. Therefore, cortisol release is linked to craving as it reminds the individual how good alcohol has made them feel previously and will stimulate anticipatory dopamine release. This is how HPA axis activation by stress can stimulate an individual's desire to seek out the feel-good effects alcohol can bring, but in doing so, more cortisol is released, exacerbating feelings of stress and resulting in a self-destructive cycle.

Frequent Stress and Binge Drinking Damage the Brain

After moderate alcohol consumption, the body can return to a stable state of pre-intoxication levels of cortisol. However, as a person binge drinks, greater alcohol consumption leads to more cortisol release overall. High levels of cortisol and prolonged HPA axis 'fight or flight' activation lead to toxic cellular conditions and dysfunction in the body and brain. Dr Blaine explains that this damage occurs part of the brain called the ventromedial portion of the prefrontal cortex (PFC). The PFC is important for 1) switching off the body's cortisol response when it is no longer required and 2) for **decision making and long-term goal-oriented behaviour.**

Binge drinking can therefore decrease the PFC's ability to control cortisol levels and thus drinkers will have high levels of cortisol in their blood even when not stressed. The greater levels of cortisol may increase feelings of anxiety in binge drinkers, who then turn to more drinking to re-regulate their psychological



and physical state. At the same time, PFC damage worsens a person's ability to make good decisions based on their long-term goals (instead of immediate feelings of stress), thereby decreasing control over alcohol intake.

The Risk of Relapse: Each Day of Abstinence Matters

Once the body is accustomed to regular, large amounts of alcohol, the absence of alcohol induces withdrawal, which is associated with even greater levels of cortisol in the blood and high levels of emotional stress. This enhanced stress state seen in withdrawal can lead to relapse when a person is in the beginning stages of recovery from an Alcohol Use Disorder.

Dr Blaine's work explains how damage to the PFC contributes to the difficulties associated with the first two weeks of treatment, when the drop-out risk is greatest. Specifically, Dr Blaine provided evidence that people with the fewest days of abstinence before and during treatment have the greatest damage to the PFC, in addition to brain areas central to the reward system. Additionally, Dr Blaine's research has shown that altered cortisol levels and PFC damage in the brain are highly predictive of shortened time to relapse.

In research published in 2020, Dr Blaine used functional MRI (fMRI) to measure brain activity in participants with an Alcohol Use Disorder at the start of their treatment. The fMRI does this by detecting changes in blood flow; when an area of the brain is in use, blood flow to that region increases. People with fewer days of abstinence at the time of the brain scan showed lower PFC response to stressful images, indicating decreased ability to respond to stress. At the same time, those with an Alcohol Use Disorder showed greater levels of craving after being exposed to stressful images, especially if they had been abstinent for fewer days. This is one way that fewer days of abstinence is associated with a greater likelihood of relapse during early treatment, when susceptibility to cravings and alcohol reminders will all be at their highest.

The good news was that for each additional day of abstinence during treatment, the risk of relapse in the first two weeks decreased by 14%. Each day of sobriety allows the brain to heal and to recover PFC function, which can support better decision making and development of new coping strategies. One extra day may not seem like a giant step towards Alcohol Use Disorder recovery, but each day of abstinence allows the brain to recover more fully from functional changes that have thus far supported continued drinking. Each day remaining abstinent in the early days of treatment will positively contribute to a successful physical and psychological recovery with a diminished risk of relapse.

Looking to the Future

Dr Blaine's research has confirmed that alcohol, stress, our genetics, and our neurobiology are all interacting factors in the development and maintenance of Alcohol Use Disorders. Further explorations of these interactions will help guide the development of personalised treatment for individuals suffering from an Alcohol Use Disorder.

Meet the researcher

Dr Sara Blaine
Department of Psychological Sciences
Auburn University
Alabama
USA

Dr Sara Blaine received her PhDs in behavioural neuroscience and psychology from the University of Colorado Boulder in 2014. After completing postdoctoral work at Yale University, she made the move to Auburn University's Department of Psychological Sciences in 2019, where she now serves as an Assistant Professor. Dr Blaine's research is focused on how genes, neural networks and stress influence the development of alcohol use disorders, specifically in the context of binge drinking. She actively participates in professional societies such as the Research Society on Alcoholism (RSA) and the International Society for Biomedical Research on Alcoholism (ISBRA). Among a multitude of other national and international awards, she received the K99/R00 Pathway to Independence Award from the National Institutes of Health.

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FUNDING

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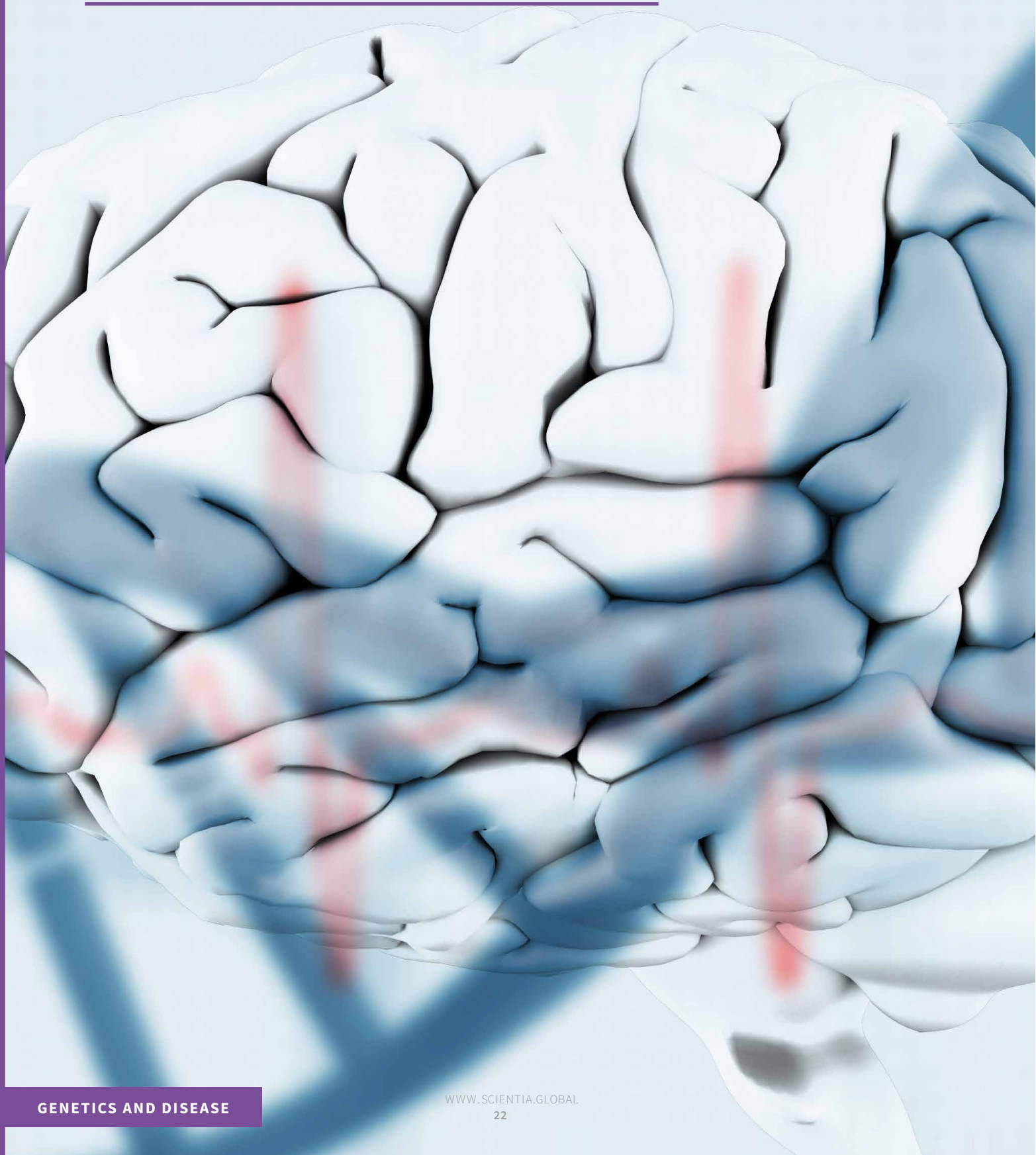
GENETICS AND DISEASE



UNRAVELLING THE COMPLEX CAUSES OF DISEASE

The second section of this issue of Scientia showcases the work of researchers elucidating the role of genetics in developmental, neurological and psychiatric disease. Although there are many possible causes of different diseases, family history is often one of the strongest risk factors, indicating a genetic basis. While we inherit a set of genes from each parent, we typically also share socioeconomic and cultural experiences with our families. As such, the interactions between genes and environmental factors, and the resultant impacts on health are extremely complex but critical to innovation in identifying those at risk as well as prevention, diagnosis and treatment.

We open this section by meeting Dr Kristen Kroll at Washington University, who specialises in the causes of neurodevelopmental disorders such as those on the relatively common autism spectrum. These diseases emerge during brain development but often impact individuals throughout their lives. We read how Dr Kroll is using different modelling approaches to progress understanding of how disruption to neural development may lead to the development of disease.

Dr Shigeki Iwase from the University of Michigan also works in the field of neurodevelopmental disorders, more specifically, those arising from histone methylation malfunctions. Histones are the proteins that our DNA wraps around, and are critical to healthy brain development. We read how Dr Iwase's work has led to important discoveries, including new and important therapeutics.

We then turn to Dr Chunyu Liu from SUNY Upstate Medical University who proposes that a more systemic approach to understanding the genetic basis of psychiatric disease may help us improve both diagnosis and treatment. We read how Professor Liu is using big data to identify the genetic and molecular changes in the brain that occur with different psychiatric disorders and develop new treatment approaches.

We conclude this section by meeting Dr Charles Vite at the University of Pennsylvania. Noting that although many inherited neurological diseases are rare but can have severe outcomes – including mortality – Dr Vite explores naturally occurring diseases in dogs and cats to inform treatment innovation. We read how Dr Vite is already delivering promising results that are supporting the development of new treatment options.

NEW MODELS TO UNDERSTAND THE INTRICACIES OF NEURODEVELOPMENTAL DISORDERS

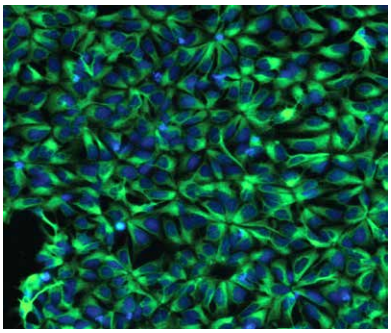
Neurodevelopmental disorders (NDDs) are a complex group of diseases that profoundly impact the human population, emerging during brain development but often affecting individuals throughout their lives. Human models of NDDs are needed, as many aspects of both the human genome sequence and brain development are human-specific and not recapitulated in animal models. **Dr Kristen Kroll**, in the Department of Developmental Biology at Washington University School of Medicine, has spent her career modelling neural development and identifying how its disruption can contribute to NDDs.

Neurodevelopmental Disorders

Autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder, and intellectual disability are examples of neurodevelopmental disorders (NDDs). According to the Centers for Disease Control and Prevention, approximately 1 in 54 children in the USA were identified as having ASD in 2016. Critically, data suggest that the prevalence of NDDs is increasing globally, while NDDs are diagnosed in individuals encompassing all countries, ethnicities, and socioeconomic backgrounds, and thus have an increasingly concerning impact on global health (World Health Organization).

Despite the widespread prevalence of NDDs, the causation of these disorders is complex and poorly understood, often involving disruption of multiple aspects of brain development. Thus, the main focus of Dr Kristen Kroll's research at Washington University School of Medicine is studying embryonic development, with a particular focus on understanding how development of the human brain is regulated and on determining how dysregulation of this process gives rise to NDDs.

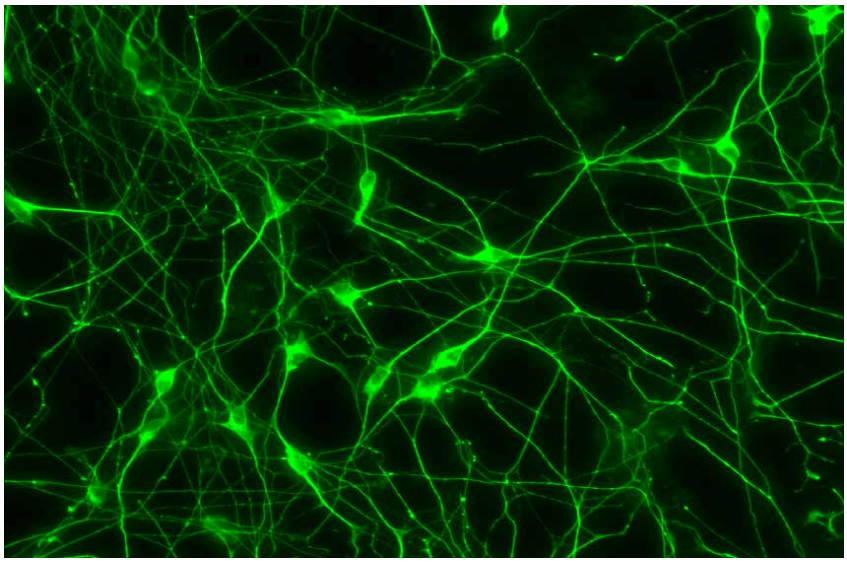
In the human brain, the cerebral cortex is a layered structure comprised of neurons responsible for mental functions including attention, awareness, perception, thought, memory, language, and reasoning. This structure begins forming during embryonic development through a complex process that must be precisely regulated. Brain development begins as some cells of the early embryo are directed to form the neural plate, with one end of this structure developing into the forebrain, from which the cortex is derived. Research in Dr Kroll's laboratory focuses on understanding how this process is controlled and identifying the regulatory networks involved. Understanding these aspects of normal brain development is essential for determining how they are disrupted to cause human NDDs.



Human stem cell-derived neural progenitor cells. Credit Kristen Kroll.

Leaps and Bounds in the Study of Embryogenesis

In her early career, as a graduate student in the laboratory of Dr John Gerhart at the University of California in Berkeley, Dr Kroll developed a new method of transgenesis for the frog *Xenopus laevis*, a vertebrate animal model of embryonic development. Transgenesis involves introducing a gene into the genome of all cells of an organism.



Human stem cell-derived interneurons. Credit Kristen Kroll.

The approach that Dr Kroll developed, in collaboration with Dr Enrique Amaya, has since been used by other researchers for many purposes, including analysing roles of particular genes in embryonic development and organ function. Transgenic lines of *Xenopus* generated by using this approach are in widespread use in the research community. Dr Kroll subsequently conducted postdoctoral work in the laboratory of Dr Marc Kirschner at Harvard Medical School, during which she identified a novel nuclear protein Geminin (Gmnn) and demonstrated roles for Gmnn in regulating *Xenopus* early embryonic development.

Following her graduate and postdoctoral training, Dr Kroll began a faculty position at Washington University School of Medicine. Work in her laboratory focused on studying how transcriptional and epigenetic regulation control embryonic development. Epigenetic regulation modulates gene expression without altering the underlying DNA sequence of the genome: DNA is compactly packed into a structure called chromatin, and modifying chromatin alters the accessibility or inaccessibility of parts of the genome, affecting the binding of transcription factors that regulate gene expression.

In early work in her laboratory, Dr Kroll and her colleagues demonstrated that Gmnn is a chromatin modifying protein essential for such epigenetic regulation to control multiple aspects of embryonic development. Her team demonstrated that embryonic cells require Gmnn to acquire a neural fate, as Gmnn promotes the expression of other genes that control aspects of later neural development, while Gmnn also antagonises acquisition of non-neural fates. This work defined several roles for Gmnn in normal embryonic development.

Uncovering the Mechanisms of Neuron Development

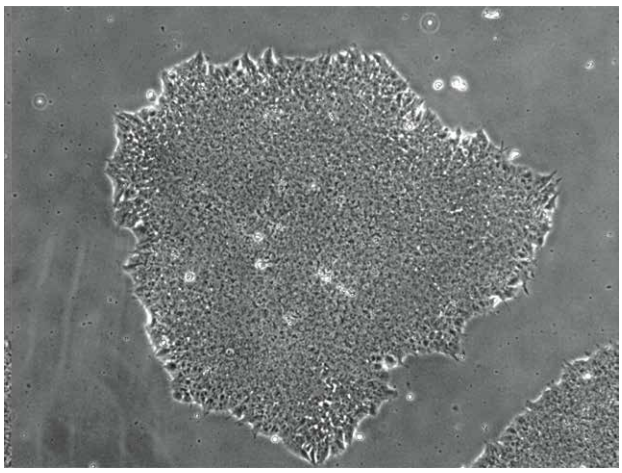
As both the human genome sequence and many aspects of brain development are unique to humans, Dr Kroll and her team currently utilise stem cell-based approaches to model human neurodevelopment. They use directed differentiation of human pluripotent stem cell models (hPSCs) to identify regulatory networks that drive the development of particular neuronal cell types that are often disrupted to contribute to NDDs. Cortical interneurons (cINs) are one such cell type: these inhibitory neurons modulate the activity of excitatory neurons in the cerebral cortex. As excitatory and inhibitory activities in the cortex must remain balanced for normal cortical function, NDDs often stem from disruption of cIN development or function.

The majority of cINs are generated in a transient foetal brain structure located below the cortex called the medial ganglionic eminence (MGE). cINs generated in the MGE migrate into the cortex and establish connections with excitatory neurons to establish normal cortical neuron connectivity and function. To study cIN development, Dr Kroll's team modified extant methods to enable the production of large numbers of MGE-like neural progenitors and MGE-derived cINs from hPSCs. This approach provides an experimentally accessible model for identifying mechanisms that control human cIN development. Subsequently, Dr Kroll's team has focused on defining how gene expression is regulated by transcription factors and chromatin modifiers during this process.

One key regulator that they focused on was NKX2-1, a transcription factor required for cIN development. Their experiments revealed that one direct target of NKX2-1 is CHD2, a protein that remodels chromatin. Mutations in the *CHD2* gene cause neurodevelopmental disorders including epilepsy, ASD, and intellectual disability. Research in the Kroll lab demonstrated that CHD2 deficiency disrupted cIN differentiation and altered cIN function. CHD2 and NKX2-1 co-bound genomic regulatory regions to co-regulate the expression of other genes required for cIN development. These studies helped identify important networks and key features of both normal and disrupted cIN development.

Building New Models of Autism Spectrum Disorder

Dr Kroll's team has also derived and characterised a number of new cellular models of ASD. The majority of ASD cases are polygenic (involving multiple genetic risk factors) and heritable, while most prior ASD cellular modelling efforts



Human stem cell colony. Credit Kristen Kroll.

have focused instead on *de novo* (new rather than inherited) cases involving rare single-gene mutations. Therefore, Dr Kroll's team attempted, for the first time, to model multiplex autism, the most common form of ASD involving inherited, polygenic risk, in patient-derived induced pluripotent stem cells (iPSCs). iPSC models were derived from three first-degree relatives with different degrees of inherited ASD (intermediate, severe, and clinically unaffected), and these were also compared with models from an unrelated, unaffected individual. iPSCs were differentiated into cINs and cortical excitatory neurons (cExNs), the major cell type that modulates cortical excitatory neuronal activity.

Cellular phenotyping showed that neural progenitor cells derived from ASD-affected family members exhibited increased cell death, by comparison with both models derived from unaffected relatives and an unrelated control. Both cExNs and cINs derived from individuals with ASD had distinct molecular signatures associated with the misregulated expression of genes associated with ASD, and those involved in neural development, function, behaviour, and cognition.

This novel study demonstrated that, even for ASD with complex aetiology, it is possible to detect affectation-linked cellular and molecular abnormalities, which can highlight pathways related to differing ASD affectation. Moreover, this work highlighted a need for the development of more cellular models that represent varied pathways to ASD, to define shared networks and pathways that are involved.

Determining Contributors to Clinical Phenotypes in Neuropsychiatric Disorders

Many neuropsychiatric disorders arise with variable penetrance (e.g., the extent to which carriers of a risk-related genetic variant express an associated phenotypic trait). One such example is copy number variants (CNVs) which micro-duplicate genomic intervals at chromosome 15q13.3, where the *CHRNA7* channel gene is located. CNVs involving this gene cause severe clinical phenotypes in some individuals but not in others. This led Dr Kroll's team to study iPSC models from a family carrying the same CNV, including duplication of only the *CHRNA7* gene, but with different clinical phenotypes.

The team compared cExNs and cINs derived from two family members carrying the same *CHRNA7* duplication, one of whom had an ASD diagnosis, while the other was clinically unaffected, as well as models from unrelated individuals without duplication. Studying neurodevelopment and function in these models revealed that, while both affected and unaffected family members with *CHRNA7* duplication had elevated *CHRNA7* gene expression, models derived from the ASD affected individual had many neurodevelopmental phenotypes not observed in the other models. These included increased neuronal progenitor cell proliferation but defective neuronal differentiation, maturation, and migration, as well as increased endoplasmic reticulum stress involving failure to properly regulate cellular calcium trafficking.

Congruent with these findings, models from the ASD affected individual with *CHRNA7* duplication exhibited reduced expression of genes involved in many neurodevelopmental processes. By contrast, the unaffected *CHRNA7* duplication carrier instead exhibited upregulated expression of many genes in these same pathways, by comparison with controls lacking *CHRNA7* duplication. These findings suggest that molecular compensation may have allowed normal neurodevelopment and an absence of clinical phenotypes in this unaffected individual, despite the presence of the same CNV at 15q13.3. Finally, as opposed to the neurodevelopmental phenotypes seen only in models from the affected individual, both models with *CHRNA7* duplication exhibited altered neuronal function consistent with elevated channel activity.

This work indicates factors that may contribute to the typically variable phenotypic penetrance caused by CNVs involving genomic micro-duplication. Furthermore, the elevated endoplasmic reticulum stress and impaired neuronal migration seen in the model from the affected individual could be reversed by using pharmacological agents identified in this research. Therefore, these models may be useful for developing interventions to remedy diagnosis-associated anomalies, both for individuals with *CHRNA7* duplication and for those with other copy number variants that cause similar phenotypes.

Current work in the Kroll laboratory focuses on using the types of modelling approaches described above to study a range of other neurodevelopmental disorders, in both subject-derived iPSC models and also in mouse models with the same mutation, particularly in cases involving the mutation of genes encoding transcription factors or chromatin modifiers.

Meet the researcher

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Dr Kristen Kroll is currently an Associate Professor of Developmental Biology at Washington University School of Medicine in St. Louis. Dr Kroll obtained her PhD from the University of California at Berkeley in 1994 and subsequently went on to complete a postdoctoral fellowship at Harvard Medical School in Boston. Dr Kroll's research team focuses on the use of human pluripotent stem cell models to study gene regulatory networks that control neuronal development and to determine how disruption of these networks contributes to neurodevelopmental disorders. Dr Kroll has received multiple awards including the Damon Runyon-Walter Winchell Foundation Fellowship, March of Dimes Basil O'Connor Award, and American Cancer Society Hope Award, and has more than 50 publications in the field of developmental biology.

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NEURODEVELOPMENTAL DISORDERS ARISING FROM HISTONE METHYLATION MALFUNCTIONS

Neurodevelopmental disorders range from those on the relatively common autism spectrum to much rarer disorders such as KDM5C-disorder and Weidemann-Steiner Syndrome. Exciting advancements in human genetics have shown that histones – the proteins our DNA wraps around – play a vital role in healthy brain development. **Dr Shigeki Iwase** from the University of Michigan studies how mutations in the enzymes that regulate histone structure and function can cause cognitive disorders. His work has led to important new discoveries, including how counterpart enzymes can be utilised for therapies.

Histones Condense the Genome

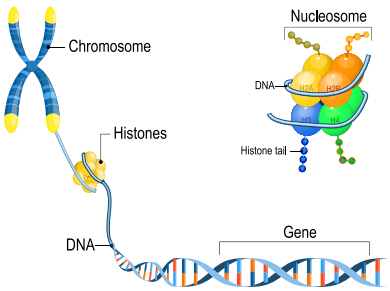
If you stretched out all the DNA contained in just one of your cells, it would create a thread around two metres long. However, safely within the nucleus of your cells, your DNA is coiled up tightly into the recognisable X shape of the chromosomes. To keep genetic material condensed and stable, it wraps around proteins called histones approximately 1.7 times. These proteins are found in groups of eight; when DNA has wrapped round one of these groups, it is known as a nucleosome. Many nucleosomes in repeating subunits create chromatin. As a result of all this wrapping and condensing, your genetic material in one cell, in the form of chromatin, is only around nine centimetres long.

The group of eight histones has a specific configuration and is made up of five variations of the protein – H1, H2A, H2B, H3 and H4. Because each histone protein is positively charged, they each bind strongly to DNA strands, which are negatively charged, thanks to the phosphate group in their backbone.

Modifying Histones for Cell Regulation

Histones also have an important role in regulating gene expression, which means controlling when and which parts of the genome are permitted to be transformed into proteins. When necessary, the proteins go through a process called covalent post-translational modification which alters the structure of chromatin, therefore impacting gene expression. Examples of post-translational modifications include phosphorylation, acetylation, ubiquitylation and methylation, all of which involve attaching a new molecule, compound or protein to the histone tail.

During methylation, enzymes called histone methylases attach one, two or three methyl groups to amino acids on the H3 and H4 proteins. It is therefore called mono-, di- or trimethylation, accordingly. These methyl groups are added to a lysine amino acid, which is abbreviated to 'K' or an arginine amino acid, abbreviated to 'R'. Depending on how many methyl groups are attached and to which amino acid, the resulting nucleosome structure can be weakened. If the attractions between the DNA strand and the histone are diminished, the DNA will start to uncoil from the nucleosome which makes it much easier for RNA polymerases (transcription enzymes) to join on and begin the process of transcription. In this way, histone methylation can turn genes 'on'. On the other hand, methylation of a lysine at the 9th position on H3 is a transcriptional silencing signal, and that gene will be turned 'off' for the time being.



Histones

The important enzymes which add on histone methylation are known as writer enzymes and their counterparts are eraser enzymes, which remove them. As with any other enzyme in our bodies, enzymes are proteins coded for by our genetics and are, therefore, subject to mutations that can alter our physiology. Studying this phenomenon, and how it may lead to intellectual disabilities and autism spectrum disorders, is Dr Shigeki Iwase from the University of Michigan in Ann Arbor. His research into how histone methylases and demethylases are vital for cognitive function has uncovered fascinating new information in his field.

Discovering a Gene Connected to X-linked Diseases

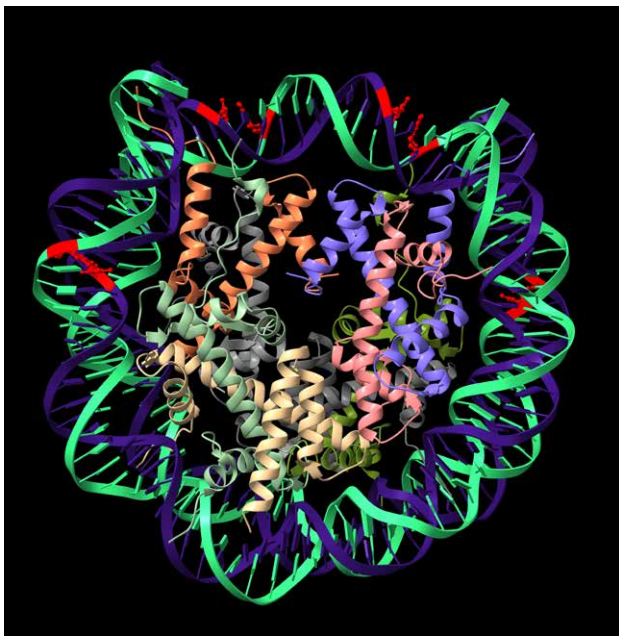
As the world of genetics research broadens and the knowledge of our inner workings deepens, scientists have realised that the histones within our nuclei can play an important role in brain development. A well-known modification to histones is the methylation of lysine 4 on H3 (H3K4me), which promotes transcription.

Initial work by Dr Iwase and his team led to the discovery of a new gene labelled KDM5C. This gene codes for a H3K4me2/3 demethylase, which is an enzyme that removes methyl groups from H3K4 when it is already di- or tri-methylated. Removing the methyl groups that would promote transcription means that this enzyme is a transcriptional repressor – it prevents transcription. The team found that when KDM5C is mutated in humans, it leads to a disorder called mental retardation, X-linked, syndromic, Claes-Jensen type. This condition is characterised by significantly diminished intellectual functioning, seizures, aggression and reduced height, all presenting during brain development.

Now called X-linked intellectual disabilities (instead of X-linked mental retardation), this family of disorders is inherited recessively through the female X chromosome. Because females have two X chromosomes, they can either inherit two mutated alleles (versions of the gene) and therefore express the disorder, or inherit one mutated allele and become just carriers of the disease. If only one of their X chromosomes carries the mutation, the 'healthy' one usually nullifies the diseased one. However, males hold only one X chromosome inherited from their mother and if they receive a mutated gene from her, will present with the X-linked disease. As a result, X-linked recessive diseases are more commonly found in males.

Mice and Humans with the Same Genetic Mutation Show the Same Symptoms

Building on this research, Dr Iwase investigated how mutations in KDM5C would affect mice and whether the consequences were comparable to humans with KDM5C mutations. The team knocked out certain sections within this gene (exons 11 and 12) to make it ineffective. Subsequently, the mice exhibited a smaller body size and diminished body weight. Interestingly, in humans, around 60% of individuals who are known to have a KDM5C mutation have a shorter than average stature.



Mice containing the mutation were significantly more aggressive than their littermates without it, were much less social and showed some memory impairment. All of these traits are found in many individuals with autism who hold KDM5C mutations and in those with X-linked intellectual disabilities.

Dr Iwase also found various neuropathway abnormalities in KDM5C knockout mice. Dendritic arborisation, or dendritic branching, is an essential part of brain development whereby neurons branch out to form new synapses. This was shown to be distorted in the mice, as they exhibited shorter and thinner dendrites in their basolateral amygdala – a centre in the brain for perceiving and regulating emotion, fear and aggression.

Overall, this study demonstrated how important KDM5C is for regulating pathways that lead to the normal development and function of neuronal circuitries. All of the data gathered from this experiment strongly suggest that mutations to KDM5C cause X-linked intellectual diseases because the loss of its function leads to gene expression that presents as clinical disease. The team believes that this is not just the case in mice but humans as well, as the cognitive deficits and behaviour patterns are so alike.

'The Yin-yang Action of Writer-eraser Enzymes'

More recently, Dr Iwase examined whether a faulty histone enzyme could be modulated by using a different, functioning one.

The methylation processes of H3K4 are regulated by thirteen different enzymes but their functions in the brain are largely unknown. Genetic mutations in nine enzymes have strong associations with neurodevelopmental disorders, which are also known as brain H3K4 methylopathies in this context. Clinical genetics studies have told us that these enzymes are important in brain development.

Theoretically, as methylation modifications carried out by these enzymes are reversible, it could be possible to correct any errors by modulating the writer and eraser enzymes associated with them. Dr Iwase again used the eraser KDM5C enzyme which removes methylation, as well as including the writer enzyme KMT2A, which adds it. If a person is 'haploinsufficient' for the KMT2A gene, it means that they do not produce enough of the protein for proper function. Weidemann-Steiner Syndrome presents as a result, which causes intellectual disability and speech delay, short stature, characteristic facial features and hypotonia (decreased muscle tone).

Both of these enzymes should be found at high levels across the brain during development so that they can interact to regulate methylation. In a series of experiments on mice, the team found some fascinating results. In KDM5C-deficient mice, inhibiting KMT2A ameliorated many of the usual cognitive defects. So, the mice who could not properly remove methylation from histones when necessary, were prevented from increasing methylation which would otherwise result in disease. Likewise, cognitive issues arising from KMT2A mutation were alleviated by KDM5C deletion. It appears that controlling one of these partner enzymes amends the dysfunctions of the other, leading Dr Iwase to conclude, '…the yin-yang action of writer-eraser enzymes can be targeted to ameliorate neurodevelopmental disorders.'

Dr Iwase has helped the scientific community deepen its understanding of how methylation of histones – and dysfunctions in the process –can impact cognitive health and function. Importantly, his findings have exciting implications for the use of writer-eraser enzymes as potential remedies for neurodevelopmental disorders in the future.

Meet the researcher

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Dr Shigeki Iwase completed his Bachelor of Science at the University of Tsukuba in Japan, before achieving his PhD from the same university in 2006. He then completed his postdoctoral training at Harvard Medical School in Boston in 2012. Since then, he has received multiple awards and published numerous papers on his studies. Dr Iwase now serves as an Associate Professor in Human Genetics at the University of Michigan in Ann Arbor, where he also carries out his research. His work focusses on chromatin in our genetic material and its involvement in health and disease in the brain.

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SEARCHING FOR THE GENETIC ROOTS OF PSYCHIATRIC DISORDERS

Decades of research indicate that mental health conditions and psychiatric disorders have a strong genetic basis. Expanding our understanding of mental health by encompassing a more systemic approach may help us improve both diagnosis and treatment. **Dr. Chunyu Liu** and his team from SUNY Upstate Medical University are using big data to discover the genetic and molecular changes in the brain that occur with different psychiatric disorders. His studies are helping us understand the diversity of human behaviour and develop new methods to treat mental health conditions.

Approaching the Complicated Mind with a Vision of Systems

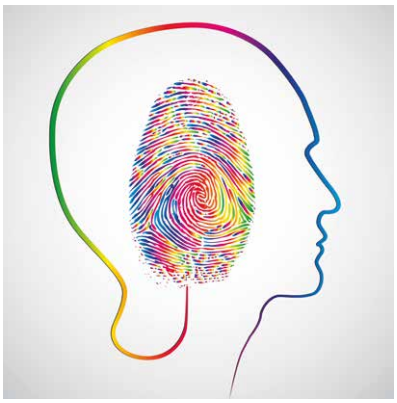
Psychiatric disorders are as elusive to characterise as they are difficult to treat. As we should expect from conditions arising in the brain – the most complex organ of the body – the aetiology of mental health disorders remains poorly understood despite significant attempts to identify the root causes. The consensus is that a combination of environmental and genetic factors increases the likelihood of mental illness, but pinpointing universal causative mechanisms has remained difficult due to the unique combination of factors pertaining to each and every individual.

Research into molecular genetics has advanced significantly in the last ten years and the rapid evolution of available technologies has been a major driving force behind this. Such technologies include genome-wide association studies (GWAS), whole-genome and whole-exome sequencing techniques, and all forms of -omics which aim to associate a specific gene (or gene variant) with a given condition.

Dr. Chunyu Liu and his team from Upstate Medical University are using these tools to explore the genetic underpinnings of human behaviour and how gene variants can be linked to mental illnesses including schizophrenia, bipolar disorder, autism spectrum disorder, attention deficit hyperactivity disorder, and others.

'I am interested in learning what determines human behaviour, including that of abnormality and so-called "mental illness" with the goal to develop effective methods for prognosis, diagnosis and treatment to reduce the associated suffering' explains Dr. Liu. His work is revolutionising what we know about the genetic architecture of major psychiatric disorders.

Dr. Liu wants to make it clear that brain research should focus on biological networks and systems, rather than single genes or factors. Known as systems biology, this approach takes into account all the components which coexist in our bodies and interact with each other. Taking a more holistic view can help link together the environmental and genetic factors and



their interactions that may increase the risk of psychiatric problems.

Searching for the Genetic Codes of Psychiatric Disorders

Searching for genes associated with a condition was once a time-consuming and expensive process. But now, whole genomes can be characterised and uploaded into a database available for researchers all over the world to access and explore.

As noted earlier, GWAS can identify specific variations of a gene which might be associated with a certain condition. These variants, known as single-

nucleotide polymorphisms (SNPs), are a version of a gene which may still perform its function but has a single nucleotide difference. This tiny change can alter gene function or expression levels, and subsequently, an individual's predisposition to a condition. Analysing SNPs in the human population, comparing people with different characteristics, can help us understand why some people are more at risk of certain conditions than others.

To perform a GWAS, researchers take DNA samples from participants with and without a condition – schizophrenia, for example – and use genotyping technology to identify SNPs. The groups of people with contrasting conditions are then compared to see if any of the SNPs are more frequently observed with a condition and thus, could potentially be used as a diagnostic tool or a target for treatment.

Dr. Liu emphasises that SNPs account for only a small percentage of the genetic risk for these highly complex disorders, representing only the very tip of the iceberg. Indeed, GWAS can identify thousands of potential genes involved in a single psychiatric condition. These genes connect to the other thousands of genes with even weaker effects that are more difficult to detect. Unravelling the different roles of 'core' genes from the 'peripheral' genes, and the connections among them, is essential to piece together the puzzle and identify key genes and biological pathways involved.

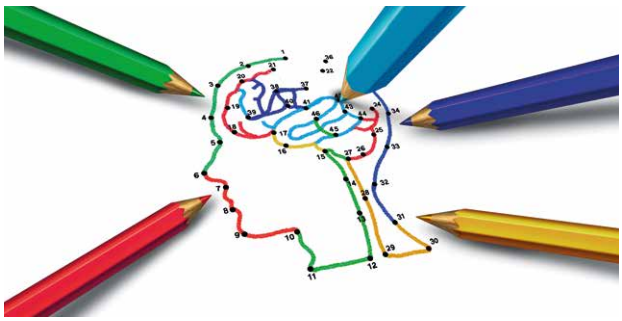
GWAS research has borne many discoveries in the field of psychiatry, but improvements to data analysis methods and reproducibility, and integration with other types of data are necessary to fully legitimise the field. Solutions may come from multi-omics integration, combined big data, and deploying machine learning data analysis.

Reading the Scripts Beyond Genetic Codes

When studying the genetic associations of a condition, it is important to remember that only 1% of the human genome is expressed into proteins. The transcriptome, on the other hand, encompasses all the genes which are transcribed from DNA to RNA. A subset of RNA, and more specifically, messenger RNA (mRNA), is the intermediary between DNA and protein. mRNA can be used as a quantitative measure to find out where certain genes are expressed. For example, if a gene's RNA is expressed highly in the brain but not elsewhere, or if the gene expressed highly in specific developmental or ageing stages, we can deduce that this gene and its protein plays a role in brain function. Moreover, this quantitative measurement of gene expression can be used to study how gene expression is regulated.

To complicate things, one gene can have many different splicing isoforms, by utilising alternative pieces of its components (so-called exons). Different isoforms can have different functions. This introduces another level of diversity into the genome. The number of different proteins produced by the genome is much larger than the number of protein-coding genes. Recent studies suggest that changes in splicing isoforms might contribute to disease risk while the overall expression level of a gene may remain unchanged. Studying this type of variation alongside other genetic differences like SNPs can reveal more and more about the changes that occur at a molecular level in psychiatric disorders.

Genes and their encoded proteins do not represent the entirety of genetic influence. A level up from this is that of epigenetic factors which alter the way genes can be expressed. These include DNA methylation, histone modifications, and non-coding RNA. Epigenetic changes are heritable and can alter the location, intensity, and timing of a gene's expression. To date, epigenetic factors have been important sources of biomarkers of disease diagnosis and treatment.



Using genetic and epigenetic technologies, Dr. Liu demonstrated that genetic differences can affect individual differences in DNA methylation. He pioneered efforts mapping genetic regulators of gene expression in the human brain, and in interpreting the results of genetic studies. Through collaboration with other researchers, concerted molecular changes in patients' brains have been uncovered.

Critically, the researchers found that different disorders have shared disordered changes. These changes are concentrated in specific brain cell types (neurons, microglia, and astrocytes), biological pathways like synaptic functions, mitochondria, and the immune response. Some of these changes are genetically determined, like those related to the neuronal functions of oligodendrocytes and astrocytes. The others might be affected by environmental factors like the immune response, mitochondria, and the blood-brain barrier.

Forging New Paths

Dr. Liu is endlessly bringing new tools, datasets, and theoretical frameworks to his research to deepen the mechanistic understanding of disease risk, and to ensure the reliability of research results. Examples include the study of cellular models of risk genes, sex and racial background of diseases. These are not only important for understanding disease mechanisms but also critical for addressing social (in)justice related to health.

Dr. Liu and his team are joining with other research laboratories using cellular models to study the functions of hundreds of risk genes identified by large genetic studies They have now confirmed that some risk genes can regulate expression of other genes, influence cell proliferation and differentiation in the brain and the electrophysiology of neurons. This type of research will be critical for revealing the underlying mechanism of psychiatric disorders.

Recent work by Dr. Liu and his team has revealed the complicated nature of sex-biased risk in psychiatric disorders, such as an up to three-fold increase in the likelihood for females to develop major depression compared to males. His research points to the role of epigenetic DNA methylation and the regulatory networks which control this, where sex differences exist in the pattern of DNA methylation and perhaps alter the subsequent gene transcription and function. This was found to be particularly prominent in genes associated with psychiatric disorders and neuronal signalling pathways, and may pave the way for studies that may lead us to refined treatment for patients of different sexes.

To date, the majority of current studies have been conducted on European descents. Dr. Liu is interested in addressing this diversity issue while serving as the first chair of the Global Diversity Committee of the International Society of Psychiatric Genetics for four years. Currently, his team is actively studying the gene expression regulation in brains of diverse population backgrounds. This is a critical gap that needs to be filled to make genetic research beneficial to all human beings without disparity.

We can clearly see how interesting new lines of research are bringing together concepts from multiple fields of study. As techniques and technologies improve, we can expect to see even further advancements in our understanding of genetics in relation to psychiatry, and compelling leads from GWAS have even suggested links between predisposition to psychiatric disorders and physical traits. Such research is providing a transformative understanding of the pathology of psychiatric disorders.

In this regard, Dr. Liu believes in big data. He believes that big data integrating factors including biology, psychology and the social environment will offer a solution to understanding highly challenging psychiatric disorders. Despite the well-accepted dominant biopsychosocial model in clinical practice, there is still a lot to be done in basic research to integrate psychological and social factors with molecular genetics. Such molecular changes and genetic factors relating to psychological stress and treatment responses are examples of topics Dr. Liu's team is now exploring.

Reproducibility of findings is the most important problem to be addressed in the research field but it may be achieved with big data and replication. Dr. Liu strongly emphasises the importance of integration and reproducibility. He explains, 'We are getting closer and closer to the truth, to the heart of the problem. We are zooming in at unprecedented speed with the big data produced by us, by the collaborative research community through the world.'

By improving our understanding of how genes control molecular pathways disrupted in disease, we can better understand the underpinnings of human behaviour in health. Dr. Liu believes that as we gather more detailed information, we will be able to reshape the psychiatric diagnostic system and develop new treatments options to fit the individuality of each person. This will bring psychiatry into the world of precision medicine, where every patient can be treated with the optimal methods specific to that individual. 'We do not have a simple, crystal clear, answer yet' Dr. Liu explains, 'But we are getting there.'

Meet the researcher

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Dr. Chunyu Liu graduated from Hunan Medical University, China, in 1998 with a PhD in Medical Genetics, before joining the faculty of the University of Chicago where he worked until 2011. In 2017, Dr. Liu began working at Upstate Medical University, Syracuse, New York, where he currently holds the posts of Professor of Psychiatry and Behavioural Sciences and Professor of Neuroscience and Psychology. Dr. Liu's research focuses on identifying molecular mechanisms of psychiatric disorders using genetic and genomic approaches to characterise the changes that occur in mental health conditions. He is a member of the American College of Neuropsychopharmacology, the American Society of Human Genetics, and the International Society of Psychiatric Genetics.

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NATURALLY OCCURRING DISEASES IN DOGS AND CATS HELP TO DEVELOP TREATMENTS FOR INHERITED NEUROLOGICAL DISORDERS

Many inherited neurological diseases are rare but can have severe outcomes, frequently resulting in disability and even death for children. New treatment options are essential to prevent suffering and decrease mortality, but to find such treatments, these diseases need to be more closely studied. **Dr Charles Vite** and his team at the School of Veterinary Medicine, University of Pennsylvania, are committed to achieving these goals. By utilising animal models and unique markers for inherited neurological disease, they have already delivered promising results supporting the development of new treatment options.

Barriers and Potential for Treating Inherited Neurological Disease

Inherited neurological diseases can present with a wide range of symptoms including hearing loss, incoordination and seizures. Despite the severity and impact of these diseases on affected individuals, effective treatment options remain lacking. This is because significant barriers have prevented the development of therapies and limited the efficacy of the therapies that have been developed.

Novel therapies are hard to come by. Their development requires a good understanding of the disease, and have to be shown to be safe as well as effective. These factors are largely dependent on establishing good models of the disease, which allow characterisation of the disease and experimental treatments. It is also important to be able to effectively evaluate the efficacy of new treatments.

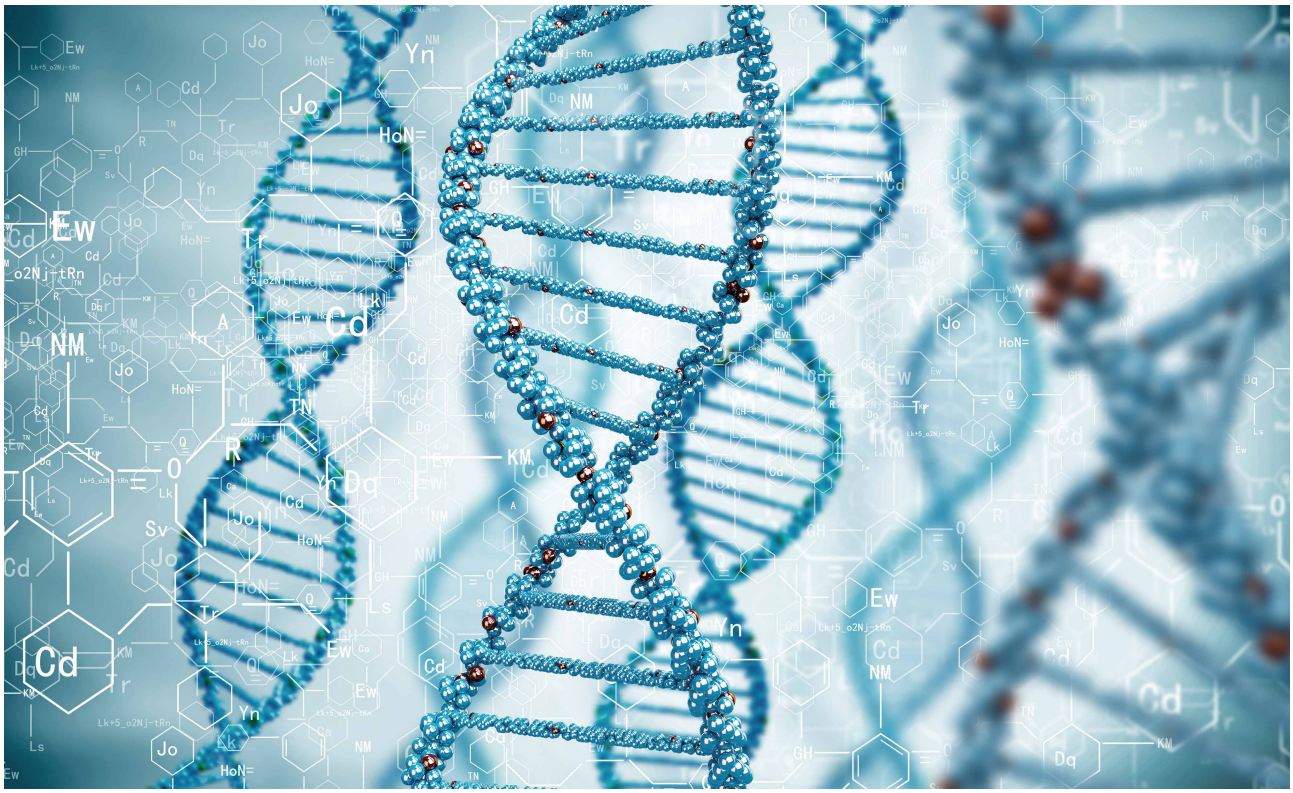
Dr Charles Vite and his team in the School of Veterinary Medicine based at the University of Pennsylvania, have performed groundbreaking research to discover new therapies for inherited neurological diseases. The team uses models of human disease in animals to look for unique markers of disease to test whether new treatments are effective. These novel therapies include gene and cell therapy which involve the addition of normally functioning genes and cells to compensate for 'faulty' genes or cells, respectively, as well as pharmaceutical drugs to treat diseases.

So far, Dr Vite's research has focussed on a class of inherited neurological diseases known as lysosomal storage diseases. Highlights of their research include the development of prospective therapies for Niemann-Pick disease type C and Krabbe disease, both of which can result in death during childhood.

This emphasises the importance of their translational research.

Cats and Dogs: Important Models of Neurological Disease

Regrettably, inherited neurological diseases such as Niemann-Pick disease type C and Krabbe disease are still poorly understood and there are few treatments available. A huge barrier to the development of treatments is that the disease must be successfully treated in an animal to show that is safe and effective before it is tested in humans. Yet, for inherited neurological diseases



this is difficult because the animal models must be able to develop the disease in a similar way to humans. In an ideal world, we would most probably use our closest relatives, non-human primates. Common non-primate animal models include sheep and pigs. However, it is difficult to model inherited neurological diseases in these animals because they rarely are affected with the same diseases that affect human patients.

The team directed by Dr Vite at the Referral Center for Animal Models of Human Genetic Disease has highlighted the advantages of using canine and feline models for inherited neurological diseases. This is because diseases including Niemann-Pick disease type C and Krabbe disease naturally occur in cats and dogs. This has revolutionised the characterisation of these diseases and helped researchers on their quest to find potential treatments. It is Dr Vite's belief that these new therapies will be used to treat both human and veterinary patients.

In a 2017 paper, Dr Vite and colleagues summarised that studying diseases in dogs and cats 'has allowed for the discovery of disease mechanisms, generation of non-invasive biomarkers for clinical evaluation during therapeutic trials, development of drug delivery and intervention protocols, safety, efficacy, and dosing studies of novel and off-label therapies, and the eventual approval of clinical therapies for many rare and devastating diseases.'

Methods for Evaluating Treatment Outcomes

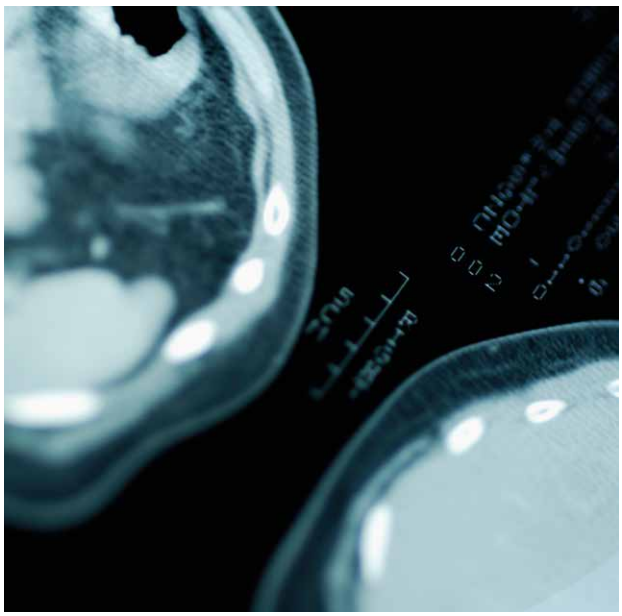
A key focus for Dr Vite and his colleagues is the identification of biochemical and magnetic resonance markers that can provide information about disease severity. Biochemical markers may include enzymes or other molecules such as lipids. In contrast, magnetic resonance markers are obtained through magnetic resonance imaging (MRI) scans that provide detailed images of the brain. Magnetic resonance markers may include changes to specific structures in the brain that may occur due to the disease.

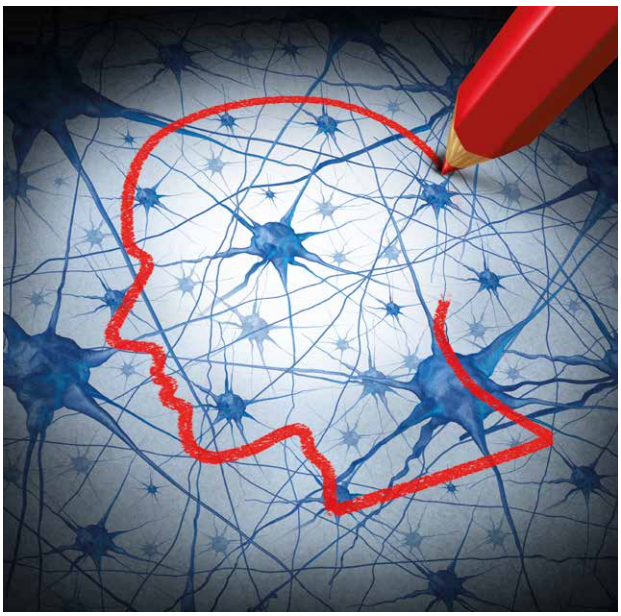
Both biochemical and magnetic resonance markers are useful for evaluating gene therapy, cell therapy and pharmaceutical drugs as treatment interventions. Dr Vite's team have used these markers to conduct translational research that improves the outcome for inherited neurological diseases, including Niemann-Pick disease type C and Krabbe disease.

Drug Improves the Outcome of Niemann-Pick Disease Type C

Niemann-Pick disease type C is a rare lysosomal storage disease that primarily affects the liver and brain and is estimated to affect as many as 1 per every 150,000 individuals. It is caused by inheriting a mutation in the NPC1 or NPC2 genes. These genes are responsible for encoding proteins that help to transport lipids, including cholesterol and sphingolipids. Lipids are found in the membranes of every cell in the body. This is the outer layer of the cell that borders the cell, protecting it from the outside environment.

Niemann-Pick disease arises when there is a build-up of these lipids, resulting in cell death. Ultimately, this can lead to organ damage. Niemann-Pick disease type C causes learning disabilities and difficulty with coordination, balance and speech. Symptoms





get progressively worse with age and lead to death during adolescence. Unfortunately, there are currently no therapies that are approved by the USA Food and Drug Administration for Niemann-Pick disease type C. Consequently, more research is required to further understand the disease and how to treat it.

In 2015, Dr Vite and colleagues discovered potential treatment options. The team treated cats that share the NPC1 mutation with a drug known as 2-hydroxypropyl-beta-cyclodextrin. They injected the cats either beneath the skin or directly into a specific region of the brain known as the cisterna magna. They showed that injection under the skin could prevent symptoms from developing in the liver. However, high doses of the drugs were required and this led to dangerous side effects within the lungs. In contrast, direct administration of the drug into the brain had promising results.

Furthermore, the researchers investigated biochemical markers of the disease and showed that the concentrations of harmful lipids and the death of specialised nerve cells were reduced. Additionally, the team utilised MRI scanning to show that there was less damage to the brain when cats were treated with the drug. Overall, this led to slower disease progression and prolonged survival time. This has provided hope for new treatment options for Niemann-Pick disease type C.

Gene Therapy: A Potential Treatment for Krabbe Disease

Krabbe disease (globoid cell leukodystrophy) is a lysosomal storage disease that can also result in neurological defects. This disease is caused by inheriting a mutation in the GALC gene which encodes a specific enzyme, a type of protein that is responsible for breaking down lipids.

In nerve cells, lipids are important components of the myelin sheath. This is a protective layer that surrounds the axons of the nerve cells that help to conduct signals in the nerves.

When lipids build up, the myelin sheath has defected growth and it becomes damaged. This impairs the ability of nerve cells to conduct signals that control motor skills. When this occurs in developing infants, it can cause blindness, deafness and paralysis, culminating in death often by the age of two. This is known as infantile Krabbe disease.

The only treatment for infantile Krabbe disease is to transplant stem cells from a healthy donor into the patient. Stem cells are cells that can transform into other cells and can produce the missing enzyme. Therefore, the stem cells prevent the onset of disease. However, stem cell transplants carry a large amount of risk and the treatment is often not effective in the long-term.

More recently, Dr Vite and his team have shown that Krabbe disease that naturally occurs in dogs can be treated using gene therapy. A 'healthy' GALC gene can be delivered by a virus that can directly infect the cisterna magna in the brain. The idea behind this is that the gene will be delivered by the virus and will encode the 'missing' enzyme. The team looked for biochemical markers such as enzyme activity and the concentration of lipids to show that the therapy had worked. Additionally, they used an MRI scan to show that loss of myelin of the nervous system had reduced. Importantly, the therapy prevented neurological defects in dogs and allowed them to live 7 times longer than dogs that had not received the therapy. This is an especially promising treatment as hopefully, it will provide a suitable treatment option for those who cannot have stem cell transplants.

Future Prospects and Research

Dr Vite and his colleagues have helped to characterise inherited neurological diseases and have presented new therapeutic options. They will continue their important work to improve our understanding of the detrimental diseases and provide new methods to evaluate new treatments and their outcomes.

Meet the researcher

Dr Charles H. Vite
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Dr Charles Vite is a veterinary neurologist. For his PhD at the University of Pennsylvania, Dr Vite used gene therapy of the central nervous system to treat alpha-mannosidosis in a feline model. After completing his PhD in 2003, Dr Vite remained at the University of Pennsylvania and has served as a Professor of Neurology and Neurosurgery at the School of Veterinary Medicine since 2018. At present, Dr Vite also serves as Director of the National Referral Center for Animal Models of Human Genetic Disease (RCAM), a Center funded by the Office of the Director of the National Institutes of Health. The RCAM houses breeding colonies for over 40 canine and feline models of human genetic diseases. Ultimately, the goal of his laboratory is to improve the understanding and treatment of neurodegenerative diseases by studying naturally occurring animal models of human diseases. Dr Vite participates in multiple societies and serves as member and chair for multiple national committees. Additionally, he is an editor and member of editorial review boards for multiple journals.

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Galyatech

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CLINICAL DISORDERS

ADVANCES IN UNDERSTANDING AND TREATING CLINICAL DISORDERS

To this day, the cure of neurodegenerative disorders such as Alzheimer's disease remains a holy grail in medical science. In this final section of Scientia, we meet the researchers charting new frontiers in understanding and treating clinical disorders affecting the brain.

We open this section with an exclusive interview with Ian Wilson, Deputy Chief Executive of Alzheimer's Research UK. Alzheimer's disease and the other forms of dementia are all progressively worsening neurodegenerative diseases, characterised by declines in cognitive functioning including memory. We read of the charity's dedication to better understanding the causes, diagnosis and prevention of these devastatingly fatal diseases – and, ultimately, finding a cure.

Dr Arun Swaminathan at the University of Nebraska Medical Center is working to improve the diagnosis and treatment of neurological diseases, including Alzheimer's disease and epilepsy. We read how novel treatment approaches including cannabidiol (CBD oil) and nutritional interventions such as a ketogenic diet may provide effective treatments in neurological diseases where conventional approaches have failed.

Difficulty in focussing attention occurs in neurodegenerative diseases, disorders such as attention deficit hyperactivity disorder, and also as part of normal ageing. Dr Adam Gazzaley from the University of California, San Francisco, is exploring how customised technology can strengthen attention capabilities in individuals across the lifespan. We read how this work has driven Dr Gazzaley to develop innovative technology companies and software as well as educate us on the benefits of experimental medicine.

Dr Jyoti Mishra, at the University of California, San Diego, is also harnessing technology in her quest to understand the processes by which mental health disorders arise. We read how she is advancing an approach known as cognitive brain mapping to investigate brain functions as well as novel digital therapeutics that are personalised to individual needs.

Mapping brain networks to understand epilepsy is the focus of research by Dr Victoria Lee Morgan at Vanderbilt University Medical Center. We read how she is using functional connectivity mapping to work out why some patients respond to treatment, and investigate what alternative interventions might work for the sizeable number of patients who do not respond to conventional treatment.

Dr Jack Jallo at Thomas Jefferson University is working to improve treatment outcomes following severe traumatic brain injury, which is associated with high rates of disability and mortality. By understanding the complex factors that influence recovery, we read how Dr Jack is progressing the design of better care management protocols to optimise patient recovery.

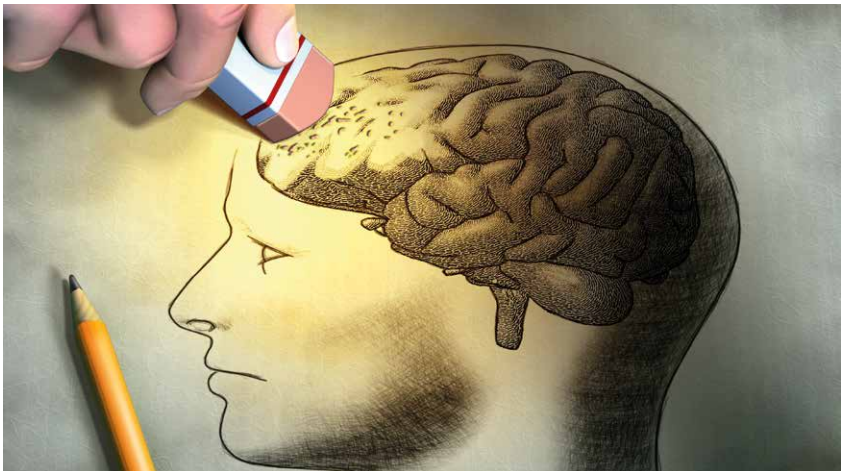
Dr Jessica Galgano, of New York University Grossman School of Medicine, takes a scientist-practitioner approach to understand the underpinnings of speech and the clinical efficacy of existing treatments for voice, speech, and language disorders. We read how her work is improving treatment options and rehabilitation techniques, leading to improved quality of life, health-related quality of life, and life participation and satisfaction for patients.

Disorders of consciousness can arise from a wide range of incidents, diseases and conditions, including traumatic brain injury, infection and tumours. Ms Teresa Grimm at Carl von Ossietzky University is exploring the effects of music on patients with disorders of consciousness by utilising a range of research methodologies. We read how her novel findings represent an important stride forward in the complex, challenging arena of improving care for patients with disorders of consciousness.

We close this final section with an exclusive interview with Vinny Smith, Chief Executive of the Meningitis Research Foundation. Meningitis and septicaemia are serious, life-threatening illnesses and the Meningitis Research Foundation is the leading UK, Irish and international charity dedicated to overcoming the challenges they pose. We read of their vital efforts in bringing together people and expertise in their mission to finally defeat these diseases.

ALZHEIMER'S RESEARCH UK

Founded in 1992, Alzheimer's Research UK is the UK's leading dementia research charity. Their work is dedicated to furthering our understanding of the causes, diagnosis, prevention, treatment and cure of diseases such as Alzheimer's. Characterised by declines in memory and other cognitive functions such as thinking and reasoning, these progressively worsening neurodegenerative and ultimately fatal diseases sadly remain without a cure. In this exclusive interview, we speak with **Ian Wilson**, Deputy Chief Executive, to hear about the vital work conducted by Alzheimer's Research UK.



To begin, please tell us how Alzheimer's Research UK came to fruition.

Alzheimer's Research UK was founded in 1992 as the Alzheimer's Research Trust, with the mission to defeat dementia through research. Cambridge-based Dr Sarah-Jane Richards and Barbara Langlois, along with Joe Pollock and Dr Martin Weale spearheaded early work in establishing the charity and bringing in our original trustees and scientists.

Shocked by the lack of investment in dementia research, this small team of pioneers originally set out to fund the building of a dedicated research centre in Cambridge, a city known as a centre of research excellence. However, their focus soon shifted to funding scientists in universities instead to ensure that as much money as possible went directly into research.

What are the main aims and objectives of Alzheimer's Research UK?

Our vision is a world where people are free from the fear, harm and heartbreak of dementia. Without effective treatments, one in three children born today will die with dementia. Today, there are no dementia survivors but our wholehearted belief is that research can and will change this.

Backed by our passionate scientists and supporters, we're challenging the way people think about dementia, uniting the big thinkers in the field and funding the innovative science that will deliver a cure.

How does Alzheimer's Research UK support research? What types of research do you focus on?

Dementia is caused by physical diseases that attack the brain and we fund a broad range of research projects to understand dementia and drive us towards better diagnosis, preventions and treatments.

We work with academics to fund the very best ideas; we also sit at the intersection between academic brilliance and the pharmaceutical industry, to ensure that potential new treatments are taken forward as quickly and as safely as possible, and of course, we are working to ensure we can detect and diagnose the diseases that cause dementia as early as possible.

Alzheimer's Research UK has invested in just under 1,000 projects across all forms of dementia since 1998. Our supporters have allowed us to fund thousands of dementia researchers based in 75 organisations across the UK and 31 international institutions.

From people to pipettes and from Aberdeen to Exeter, our funding is making a huge difference.

What are Alzheimer's Research UK's most significant achievements to date?

Our research investment is increasing rapidly and we have invested more than £136 million in groundbreaking research since 1998. Our research has identified new avenues of biology that urgently need exploring.

One of the key hallmarks of Alzheimer's disease is the build-up of amyloid in the brain. Scientists think that these abnormal protein clumps start a damaging chain reaction that gets in the way of how our brain cells work. Removing amyloid from the brain is a key target for drug development. Our scientists took the time to learn from the first trial of a treatment designed to clear amyloid protein from the brain. They saw the potential for it to guide future clinical trials. Their findings are helping researchers make smarter decisions about how new treatments are being developed today.

Of course, our charitable remit goes further, and we also hold governments to account to ensure as much funding as possible is made available for dementia research. Through our campaigning work and thanks to our amazing supporters who backed our campaign, the government recently pledged to double dementia research funding to £1.6bn over the next 10 years, which now needs to be delivered.

How is the general public involved in your work?

Dementia is one of the world's greatest challenges. It shatters lives and leaves millions heartbroken. In all, we've funded £136 million of research projects. This is only possible because of the generosity of our supporters.

Thousands of people across the country, and even more across the world, are helping us in so many ways by raising money and awareness, giving up their time to volunteer and sharing their personal stories with the media. We are always looking for new supporters to help us in our work!

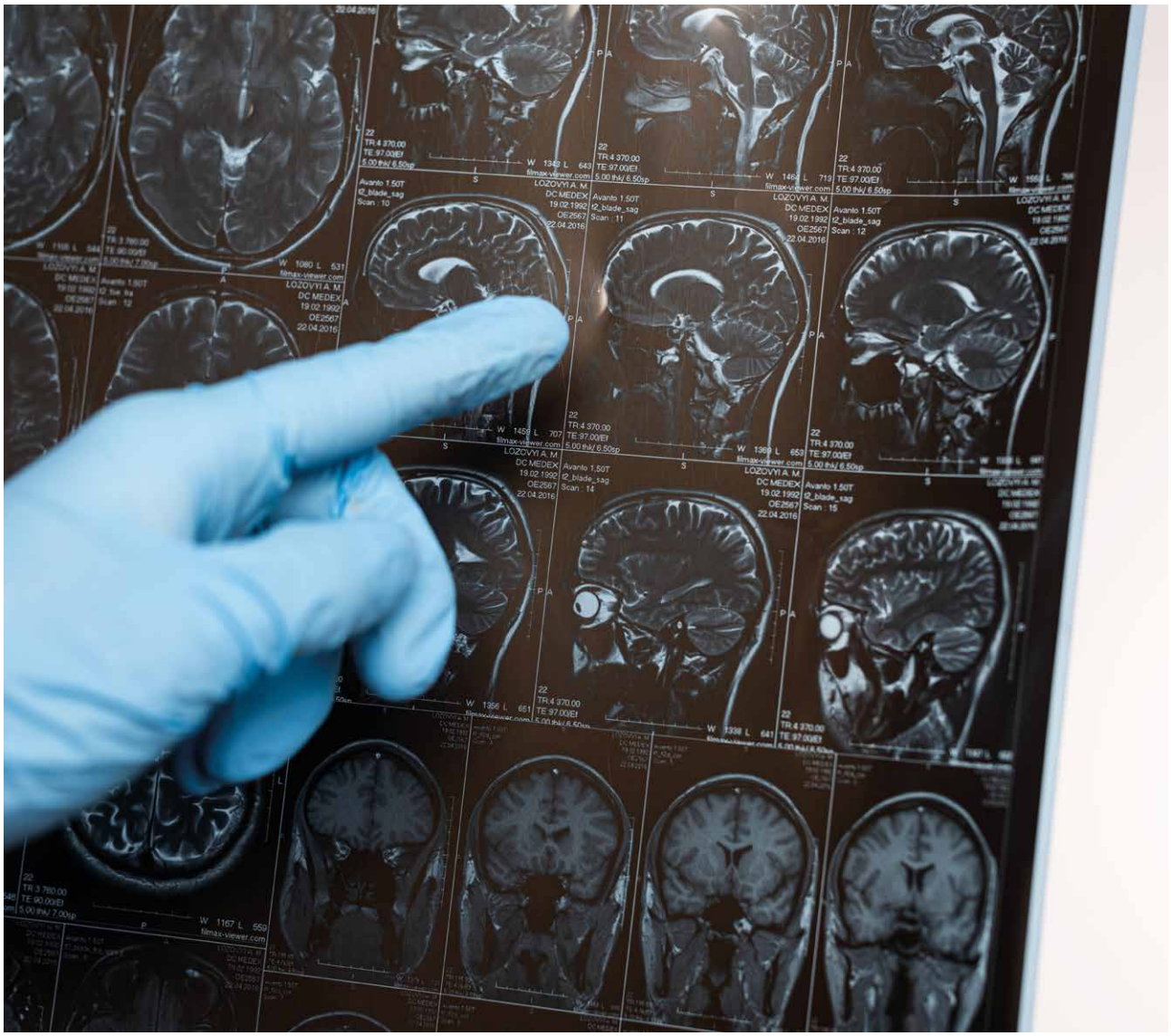
2020 was, of course, a challenging year for everyone. What specific difficulties has the COVID-19 pandemic created for Alzheimer's Research UK and how are these being overcome?

The need for investment in dementia research has never been more urgent. COVID-19 is threatening dementia research efforts, with many projects delayed and some studies cut completely, and a lack of future funding opportunities forcing many scientists to consider leaving dementia research. Losing these scientists would mean not only a loss of resource to continue vital studies, but a loss of valuable expertise that has taken years to build up.

The pandemic is also having a catastrophic impact on people with dementia. Figures show that a quarter of people who have died in the first wave with COVID-19 in England, Wales, and Scotland, also had dementia. For the sake of people with dementia and their families, we must protect progress in research.

Alzheimer's Research UK is obviously facing a predicted drop in income as a result of COVID-19, affecting our ability to fund new research this year. Yet dementia research has been making huge strides, and life-changing treatments are in our sights. Alzheimer's Research UK and our scientists have pivoted to delivering events online and conducting research in a socially distanced manner as far as possible.

The charity has also had strong financial processes in place and we are delighted to see income still continue to arrive into the charity. Even in the darkest times, it has been wonderful to see,



where possible, our fundraising activity and income continue, and it really highlights to me what incredibly loyal supporters we have.

During this period one of our Board wrote to me and said 'Crises are a test of the values and deep characteristics of an organisation, and also of the quality and characteristics of its people. It is no surprise that Alzheimer's Research UK is scoring so highly on both!'. I think this sums things up nicely.

Finally, looking now to the future, what are the long-term goals for Alzheimer's Research UK?

One of the challenges we face is that the diseases cause dementia start decades before the symptoms show. Therefore, to have the best chance of halting them, we need to intervene decades earlier, when these diseases first start to take hold. To do this we will utilise new technologies and breakthroughs in data science and machine learning to produce a revolutionary way of detecting and ultimately diagnosing the diseases that cause dementia.

The aim is to collect huge amounts of digital data generously donated by research study volunteers using smartphone apps and wearable devices, like watches and headbands. By linking data to clinical tests, such as brain scans, we'll identify digital data patterns, or 'fingerprints', which allow us to detect the earliest signs of diseases like Alzheimer's.

If we do this, we have the best chance of stopping these diseases before the symptoms of dementia start to get in the way of life, keeping people connected to their world, their families and themselves for longer.

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Alzheimer's Research UK
Make breakthroughs possible

IMPROVING THE DIAGNOSIS AND TREATMENT OF NEUROLOGICAL DISEASES

Medical conditions that affect the brain can have severe impacts on people's lives. Many of these conditions can be difficult to treat, including epilepsy which affects the brain to cause seizures and the common form of dementia known as Alzheimer's disease. **Dr Arun Swaminathan** at the University of Nebraska Medical Center specialises in the treatment of epilepsy. He also collaborates with fellow researchers to explore treatment options for Alzheimer's disease.

Finding the Best Treatments for Epilepsy

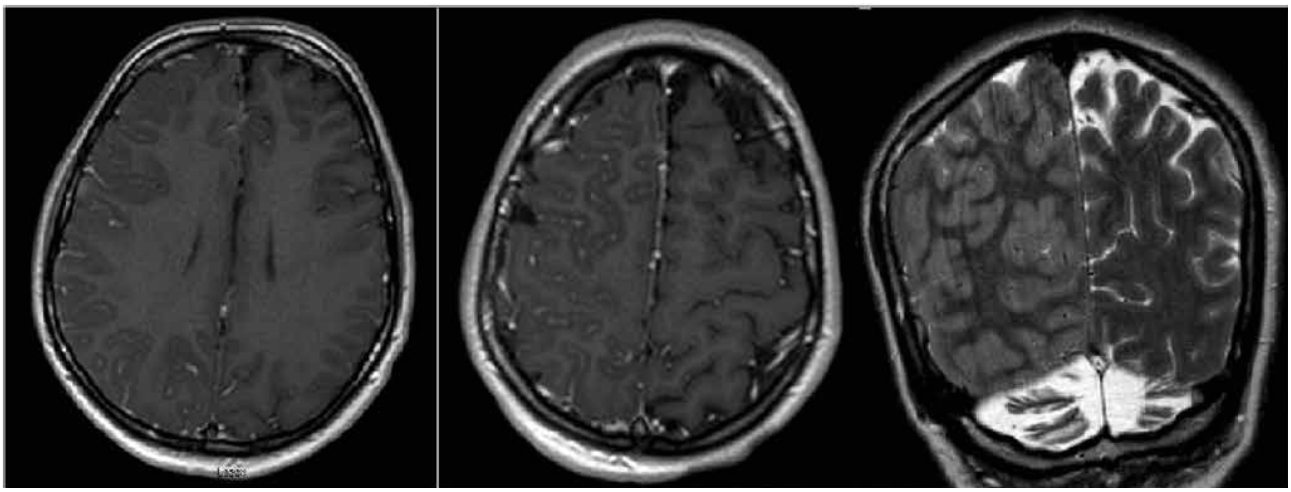
Across the globe, approximately 50 million people suffer from epilepsy. The majority of people who are diagnosed are prescribed anti-seizure medication to prevent seizures from occurring. However, a large number (about 25–30% of patients) are unresponsive to the treatment and require surgery. The surgery involves removing small parts of the brain that are thought to influence the seizures. Surgery has variable outcomes and success is dependent on many factors. These include the affected area of the brain and its baseline function as well as the surgical technique used.

Dr Arun Swaminathan at the University of Nebraska Medical Center and his colleagues sought to evaluate the treatment outcomes of epilepsy patients up to 20 years post-surgery. The researchers used past patient data to compare patients who had received a scalp electroencephalogram (EEG) or intracranial EEG. An EEG is a test that records the electrical wave patterns of the brain and can indicate if the brain activity is abnormal. This can be performed by either placing metal disks on the scalp, known as scalp EEG, or by placing electrodes into the brain (intracranial). Once this has taken place, surgery is performed and the outcome can be assessed using the Engel Epilepsy Surgery Outcome Scale. This ranges from the classification of an individual as being free of disabling features, to having rare seizures, demonstrating some improvement or finally, no worthwhile improvement or worsening.

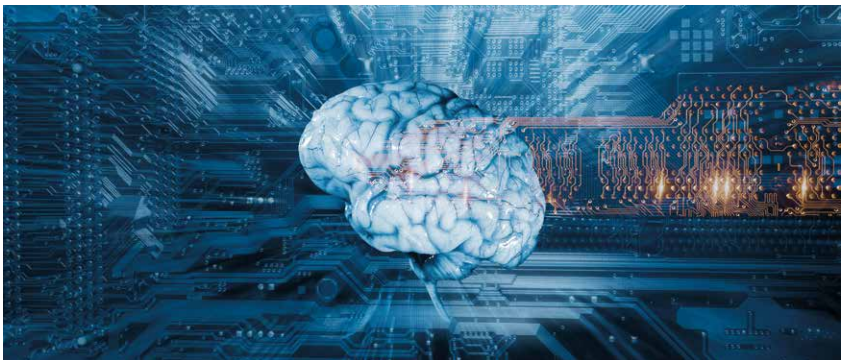
Dr Swaminathan and his team observed that epilepsy surgery has good long-term outcomes in most patients. Those who had a temporal region of the brain removed, which is involved in hearing and speech, had the best outcome with scalp EEG alone, provided they had concomitant testing supporting pure temporal epilepsy only. Additionally, they found that some patients could suffer from cognitive problems such as memory loss, as well as depression or psychosis if they had surgery on the frontal region of the brain that is involved with cognitive skills, albeit these were mild in most patients that had them. The researchers also observed that using intracranial EEG

had similar efficacy in finding the seizure onset zones as taking scans or images of the brain prior to the surgery in many patients.

Importantly, epileptic episodes do not always present as convulsive seizures. Some seizures can go unnoticed without any obvious clinical signs. This is dangerous as it can lead to delayed treatment response and result in the death of a patient. Dr Swaminathan and his team evaluated the use of EEG to detect nonconvulsive seizures using past patient data to see if experts could diagnose patients correctly given their EEG results. They also evaluated the best way to arrange the electrodes or metal plates onto the head for accurate diagnosis, otherwise referred to as a montage. They showed that the EEG could differentiate between normal and



Magnetic resonance imaging scans in spinocerebellar ataxia type 8. Reproduced from A Swaminathan, Epilepsy in spinocerebellar ataxia type 8: a case report, Journal of Medical Case Reports, 2019, 13, 333.



seizure-like wave patterns effectively and that a limited montage could provide sufficient efficacy in certain situations, especially if there were time constraints.

Learning from Experience to Improve Patient Care

Most medical conditions can be diagnosed using standard testing and tell-tale symptoms. Yet not every individual will present the usual symptoms that are associated with signs of a disease. Clinicians can take note of this and publish case reports to spread awareness of uncommon symptoms of a disease that have been observed in individual patients.

Dr Swaminathan observed that a patient with a genetic condition known as spinocerebellar ataxia type 8 was having seizures. This inherited condition leads to problems with movement, balance and coordination. Dr Swaminathan's patient was also suffering from weakness over one side of the body and brain malfunction. Although seizures are rare for somebody suffering from this condition, Dr Swaminathan concluded that it was causing nonconvulsive seizures which could be treated using anti-epileptic therapy. This treatment resulted in an improvement for the patient. Dr Swaminathan thus suggests that even if seizures are a rare occurrence in somebody with a condition that affects the brain, patients should still see an epilepsy expert to speed up diagnosis and treatment for seizures.

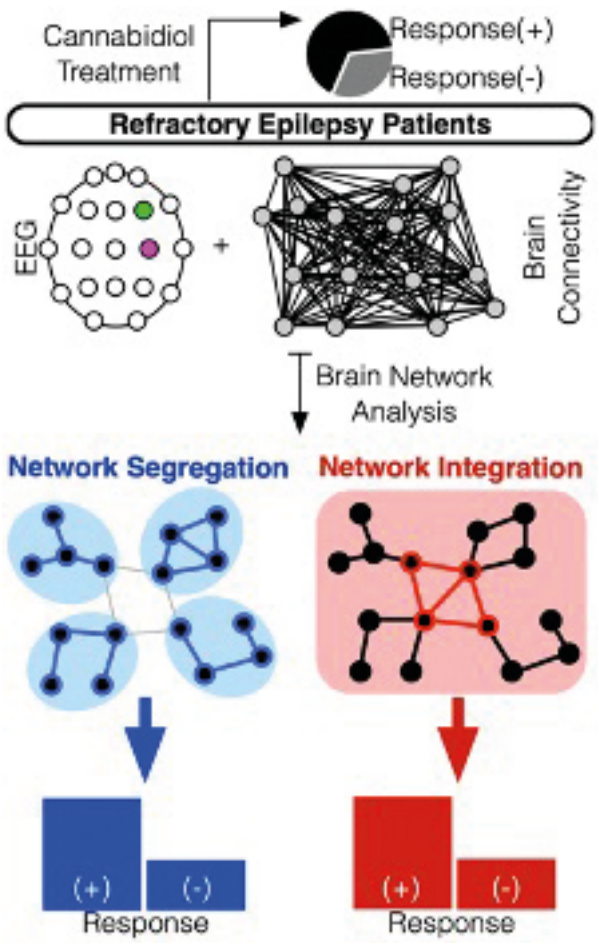
Dr Swaminathan has also drawn from his experience observing patients to propose a novel way to diagnose cancer of the larynx or 'voice box'. He identified that a 59-year-old patient was suffering from autoimmune encephalitis. This condition occurs when the body's immune system, responsible for fighting infections and unhealthy cells, attacks healthy brain cells instead.

The patient was treated with anti-epileptic drugs and steroids to prevent seizures and reduce the activity of the immune system. Although the patient recovered, they returned to hospital a year later and was found to have a cancerous tumour on the larynx. The only indicator of this was high levels of striational antibodies which attack the proteins that make up muscle. Dr Swaminathan suggested that the cancer had caused the autoimmune condition and that although rare, the presence of striational antibodies could be used to diagnose this condition in other patients with similar presentations as well.

A Novel Treatment for Epilepsy?

In many countries, cannabis is an illegal drug. However, in recent years it has been legalised to treat medical conditions including refractory epilepsy. Refractory epilepsy is a severe form of epilepsy that does not respond to recommended treatments. Cannabidiol (or CBD oil) is a chemical that is extracted from the cannabis plant and has been approved by the US Food and Drug Administration to treat epilepsy and prevent seizures in patients with refractory epilepsy syndromes like Lennox Gastaut Syndrome or Dravet's Syndrome.

Dr Swaminathan and his colleagues used EEG and graphs to measure changes in brain network dynamics



Reproduced from DE Anderson, D Madhavan, A Swaminathan, Global brain network dynamics predict therapeutic responsiveness to cannabidiol treatment for refractory epilepsy, Brain Communications, 2020, fcaa140.

when patients with previously untreatable epilepsy are administered CBD. Brain network dynamics describe how parts of the brain connect and interact with one another and how this leads to changes in brain activity. Dr Swaminathan and his fellow researchers showed that treatment with CBD led to changes in brain network dynamics that could reduce seizures and that some of these brain network signals could predict which patients would be more likely to respond to CBD treatment. This opens up a new avenue to promote exploration of CBD as a treatment option for epilepsy in patients who have been previously difficult to treat.

Food for Thought

Further surprising treatment options have been proposed to treat epilepsy. Since the 1930s, it has been suggested that a ketogenic diet can prevent seizures in children and teenagers who suffer from refractory epilepsy. A ketogenic diet is a low carbohydrate, high fat diet which has become a trendy way to lose weight, but the exact mechanism of how this may prevent seizures is unknown.

Dr Swaminathan and his fellow researchers reviewed four different diet therapies and their effects on young patients from previous research. They concluded that there is no superior ketogenic diet that can be used to treat seizures in young patients but that some patients do respond better than others. They also pointed to the importance of maintaining a balanced diet for long-term health.

Other conditions that affect the brain may also be treated using a nutritional approach. Alzheimer's disease is a form of dementia leading to irreversible memory loss and impairments to cognition that eventually reduce the patient's quality of life and ability to self-care. Although it affects a large number of individuals, there is no known cure.

Nutritional approaches to slow, prevent or stop the progression of Alzheimer's disease have been investigated. Dr Swaminathan and colleagues reviewed several of these approaches including the use of vitamins, antioxidants, plant flavonoids and omega-3 fatty acids. Despite being a safe treatment option, unfortunately, there is no overwhelming evidence that any of these approaches can reverse the effects of the disease. More optimistically, Dr Swaminathan suggests that nutritional interventions may still be able to supplement other approaches and improve treatment outcome along with improving the probability of preventing such diseases.

Using Artificial Intelligence for Diagnostics

Not only is Alzheimer's disease difficult to treat, but it is also hard to diagnose. Numerous methods have been proposed as potential diagnostic tests, including scanning the brain and assessing performance on psychological measures. Unfortunately, these methods can be imprecise or limited, prompting Dr Swaminathan and colleagues to seek out the use of novel technology to improve diagnostic approaches.

Artificial intelligence (AI) involves teaching computers to think and work like humans and comes with numerous applications. Dr Swaminathan and his collaborators used a branch of AI known as 'deep learning' to train a computer model to be able to classify whether a patient has Alzheimer's using brain images taken by an MRI scan. They then tested the computer model with patient data and found that the model could accurately diagnose Alzheimer's disease. Critically, further investigation could lead to this being used within clinical settings and to study other kinds of dementia and neurodegenerative disease as well.

As we can see, Dr Swaminathan's clinical and research work extends beyond the field of epilepsy to improve the diagnosis, treatment, and ultimately, quality of life for patients with a broad range of neurological diseases.

Meet the researcher

Dr Arun Swaminathan
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Dr Arun Swaminathan is an Assistant Professor at the University of Nebraska Medical Center. He gained his medical degree from Lokmanya Tilak Medical College in Mumbai in 2004. He then moved to the USA to undertake a residency in neurology. Before commencing his current role, Dr Swaminathan undertook a clinical neurophysiology and epilepsy fellowship at the University of Pennsylvania. He now specialises in the treatment of epilepsy and works at a level 4 centre, which offers the highest level of epilepsy care for all patients. Dr Swaminathan is involved in aspects of epilepsy care, including diagnostics, treatment and epilepsy surgery. He is also involved in the field of research and has collaborated extensively with fellow researchers to explore treatment and diagnosis of epilepsy and Alzheimer's disease. He hopes that his research can be implemented to improve the lives of patients with these diseases.

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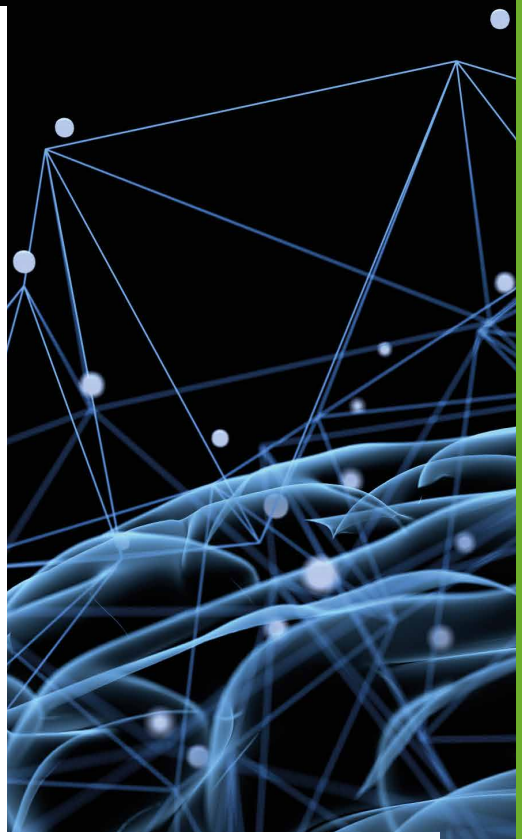
University of Nebraska Medical Center

FOCUSSING THE MIND WITH ADAPTABLE AND CUSTOMIZED TECHNOLOGY



Attention disorders range from attention deficit hyperactivity disorder to multitasking difficulties due to aging. Regardless of the cause, such difficulties can have a negative impact on peoples' lives. **Dr Adam Gazzaley** from the University of California San Francisco has carried out extensive research exploring how customized technology can be utilized to strengthen attention capabilities in individuals across the lifespan. His work has driven him to develop innovative technology companies and software as well as educate us on the benefits of experimental medicine.

Attention Disorders Across the Population

Our minds are amazingly complex and are often engaged and productive. However, in some cases, our attention can be disrupted and difficult to maintain. One situation where this occurs is in attention deficit hyperactivity disorder (ADHD). Often diagnosed between the ages of six and twelve years, ADHD usually presents in children as being inattentive, and hyperactive and impulsive. Inattentiveness can mean a child is easily distracted, forgetful, has difficulty organizing themselves and tasks and has an apparent inability to listen carefully. When a child is hyperactive and impulsive, they may be unable to sit still, constantly moving and fidgeting, excessively talking, interrupting conversations and have little sense of danger.

Although ADHD is genetic and can run in families, other factors such as being born prematurely and brain damage may also contribute to its incidence. Once it has been carefully diagnosed, ADHD may be treated with drugs to alleviate symptoms as well as various therapies to aid a patient to better understand their condition and how to deal with it. Available therapies may include cognitive behavioral therapy, social skills training, psychoeducation and behavioral therapy. Some researchers believe that diet could also play an important role in alleviating ADHD and that taking supplements of omega-3 and omega-6 may be helpful.

Within the field of attention disorders, but separate to ADHD, negative alterations to cognitive control are also common in elderly populations. As people age, many experience a decreased ability to multitask and ignore distractions, and up until recently, there has not been a neurotherapeutic treatment for this issue. Brain injury, depression, dementia, and autism can all also affect how a person's neural pathways function.

Covering many domains within attention deficit, Dr Adam Gazzaley is a neuroscientist and entrepreneur who has conducted ground-breaking work into treating these types of disorders with technology. He works on his research in the Neuroscape center

that he founded at the University of California San Francisco, as well as two other innovative technology companies that he co-founded – Akili Interactive and Sensync.

Neuroscape engages in six research areas of neuroscience, including healthy aging, video game training, non-invasive brain stimulation, cognitive neuroscience, cognitive brain-computer interface, and mobile assessments. The findings from studies in these topics are then applied to their educational division which develops and assesses tools to help cognitive development in children and their clinical division for real-life use as novel therapies for a broad range of medical conditions.

Improving Cognitive Control Through Technology

In 2013, Dr Gazzaley and his team published a paper that was featured on the cover of the prestigious science journal Nature. The paper described how they had been able to use a custom-made video game that improved the attention abilities and memory of older adults.

In this research, the team tested people aged 20–79, with around 30 people representing each decade of life. To start, they all played a diagnostic version of a specifically developed game called NeuroRacer, whereby they were given a sign task and sometimes a driving task. The sign task involved quickly responding to a new sign appearing but only when they could see a green circle on their screen This measured their perceptual discrimination ability. By including an additional 'sign and drive' task that required them to also drive a car on a winding road, they also tested the participants' concurrent visuomotor tracking. An algorithm then determined the difficulty at which participants maintained 80% accuracy in the tasks. Put simply, Dr Gazzaley measured each person's ability to multitask and he found that this ability diminished in a linear fashion as age decreased.

Each participant's score was used to customize their subsequent games so that they all played at a level of difficulty adjusted for their ability. Some of the adults between the ages of 60 and 85 were given the task of playing NeuroRacer in multitasking mode for three hours a week for four weeks. Meanwhile, others only played the game in single-task mode and some did not play at all. At the end of the month, compared to the other groups, those playing the sign and drive version significantly improved their multitasking abilities on the game as well as other cognitive control functions like working memory and sustained attention. The improvement in multitasking on the game lasted an impressive six months after the experiment and demonstrate that the prefrontal cognitive control system in the brain is flexible and can be retrained, even in older age groups.

Dr Gazzaley's interesting work reveals that adaptable and customized video games can not only assess cognitive abilities but also improve them. NeuroRacer is a research tool developed at the Neuroscape center and Dr Gazzaley's digital medicine company, Akili, licensed the software so that they could create the clinical product called EndeavorRx. Excitingly, EndeavorRx has been FDA cleared in the USA to be given as a treatment for inattention in children with ADHD.

Introducing Meditation to Young People

In a further study, Dr Gazzaley and his team investigated how another software program could benefit attention span in younger generations, this time inspired by meditation. Young people are very familiar with multitasking, thanks to the need to balance technology, education, work, and social lives, which are all demanding on their attention. However, boosting their sustained attention span is known to be a difficult task.

During a six-week intervention, Dr Gazzaley asked 59 adults aged 18–35 to use Neuroscape's meditation app called

MediTrain. This app uses traditional meditation techniques of guided attention to the breath and stillness of the mind, but it also incorporates what is known as closed-loop software. This is where the software receives immediate performance feedback and continually adjusts a user's experience to be personal to them. After each session, the participants self-reported how well they kept their mind from wandering by focusing on breathing and the app noted and adjusted their next session accordingly.

The team found that after using the app for six weeks, the young adults displayed improved sustained attention and working memory, which was linked to positive alterations in key areas of cognitive processing and task performance in the brain.

Combining a practice that is thousands of years old with brand new technology is another pioneering way in which Dr Gazzaley has shown that attention can be trained and improved.

Meditation for Teens with Mental Health Challenges

Building on his work in meditation, Dr Gazzaley investigated how the exercise could be applied to adolescents who have experienced difficulties in their upbringing. Adversity during childhood, especially neglect, has a strong link to cognitive dysfunction, frequently resulting in ADHD in adolescence. They discovered that no previous studies had tried to produce interventions that would improve neurocognitive issues in this specific group.

The team set out to test how closed-loop technology could be utilized again. They recruited 45 adolescents aged between 10 and 18 who had experienced trauma during childhood, and assigned them into one of three groups. One group completed digital activities targetting internal attention, another group had external attention activities, and the third was a control group with no intervention. Internal attention essentially means meditation – selectively processing your own thoughts to focus on the breath and removing distracting thoughts. On the other hand, external attention refers to selecting and modulating sensory information (audio, visual, and so on) whilst experiencing distractions.

Using neuroimaging, the team found that childhood neglect has a negative impact on a part of the brain called the dorsal anterior cingulate (dACC), which has an important role in brain development during adolescence. One of the key findings from this study was that closed-loop digital mediation can partially correct this issue.

Improvement to dACC functional connectivity was correlated with the improvement of behavior in the children. Notably, meditation was beneficial for the sustained attention of the children in addition to lessening hyperactive behavior, which was still in effect one year after the intervention. Another positive behavioral outcome was enhanced performance at school.

Through this novel thinking and research, Dr Gazzaley provided more evidence that introducing meditation to children can have hugely beneficial impacts on their day-to-day lives by helping them to develop their attention abilities.

Improving High-fidelity Memory in Older Adults using Virtual Reality

Early in 2021, Dr Gazzaley and his colleagues published a study on the use of a virtual reality (VR) spatial wayfinding game (Labyrinth-VR) as a cognitive intervention for high-fidelity memory declines in healthy older adults. High-fidelity memory refers to our ability to recall rich, detailed information from long term memory on demand, and this involves an awareness and selection of the most relevant information to effectively achieve that goal.

A total of 48 older adults with typical cognitive performance for their age, were assigned to 12 hours of computer gameplay over four weeks using either the Labyrinth-VR or control game (not requiring recall of detailed information or route navigation). Tests of memory were undertaken before the intervention and on completion.

After the four-week intervention, older adults in the VR group demonstrated reliable gains in high-fidelity memory compared to the participants in the control game condition. These gains reflected performance comparable to younger adults, indicating important, cognitive benefits after only four weeks of training. Critically, this landmark study is the first demonstration of benefits to high-fidelity memory in normally aging adults.

Expanding Neuroscience

Dr Gazzaley encompasses all of his work at Neuroscape and Akili with the phrase 'experiential medicine'. His imaginative and original ideas have pushed forward the field of neuroscience into developing technologies that can be adapted and personalized to an individual's needs in order to improve their cognitive function – from children to older adults. It is without a doubt that Dr Gazzaley's work will have an exciting impact on many lives in the future.

Meet the researcher

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Dr Adam Gazzaley studied for his BS in Biochemistry at Binghamton University in New York, before completing an MD and PhD in Neuroscience at Mount Sinai School of Medicine (also in New York). He then completed a neurology residency at the University of Pennsylvania, and postdoctoral training in cognitive neuroscience at the University of California, Berkeley. Dr Gazzaley has an impressive range of academic appointments, awards, and appointments in the field of neuroscience and he currently holds the position of the David Dolby Distinguished Professor of Neurology, Physiology and Psychiatry at the University of California, San Francisco (UCSF). He is the founder and executive director of Neuroscape at UCSF and co-founder of neuroscience-based companies Akili Interactive, Jazz Venture Partners, and Sensync.

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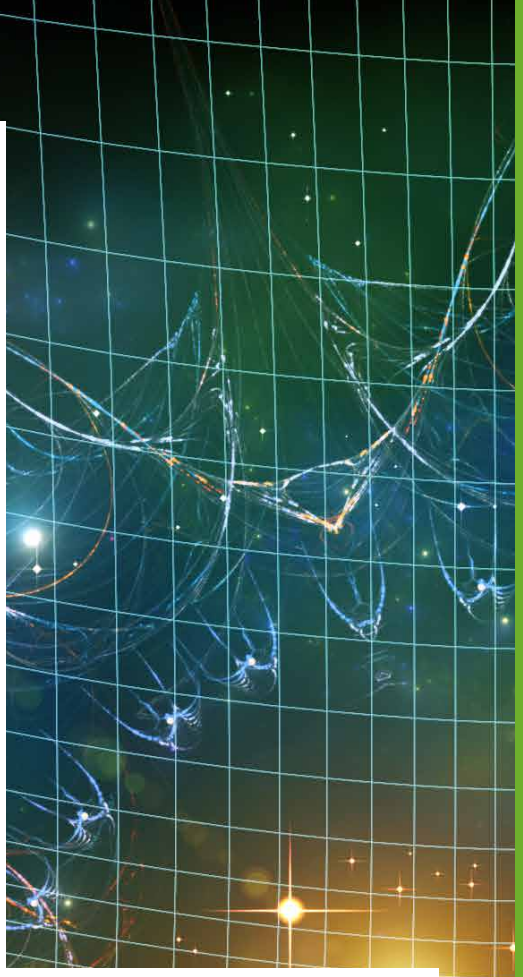
NEUROTECHNOLOGY FOR COGNITIVE BRAIN MAPPING AND DIGITAL THERAPEUTICS



Environmental factors and genetics both play a part in how our brains function, whether that be in a healthy or disordered manner. Understanding the processes by which mental health disorders arise is an important step in developing effective therapies. **Dr Jyoti Mishra** founded NEATLabs at the University of California, San Diego, to work towards this goal. Her exciting research is advancing cognitive brain mapping to investigate brain functions as well as novel digital therapeutics that are personalised to individual needs.

Brain Function and Dysfunction

Our brains are wonderfully complex organs that help us to navigate the world. Webs of neurons interact through electrical signals to provide us with sensory information, thoughts and emotions. However, when the normal processes in the brain become dysfunctional, concerns with mental health arise. Depending on a variety of factors such as which brain circuits or which area(s) of the brain are affected in specific dynamic patterns, different issues can develop. These conditions commonly manifest as depression, anxiety, post-traumatic stress disorder (PTSD) and attention deficit hyperactivity disorder in the general population.

Mental health disorders are on the rise, so uncovering the processes in the brain that cause them is essential to evolving new, effective therapeutics. Traumatic life events can play a role in brain dysfunction in many people, but the biological mechanisms behind them are still not completely understood.

Using innovative technology, Dr Jyoti Mishra is developing our knowledge surrounding this issue and pushing forward the field of neuroscience. Within the Department of Psychiatry at the University of California, San Diego, Dr Mishra founded the Neural Engineering and Translational Labs (NEATLabs). Here, she is the director of human research and works on improving neurotechnology for cognitive brain mapping (i.e., mapping of the brain dynamics underlying our cognitive abilities) as well as personalising digital mental health therapies to patients. Her research has highlighted how contextual influences and environments can alter brain development and normal function as well as how closed-loop technology is an exciting and promising opportunity to improve brain health.

The Brain Engagement Platform

At NEATLabs, Dr Mishra and her team recently developed a scalable, mobile platform called *BrainE*, which is short for Brain Engagement. This platform uses wireless electroencephalography (EEG) recordings to rapidly test how essential aspects of cognition (such as

attention, working memory, rewards, emotions) are processed in the brain. An EEG is carried out by attaching small, metal electrodes (discs) all over the scalp. When a specific region of the brain is activated, electrical signals are generated through the firing of a large population of underlying neurons (brain cells) and these are picked up by the electrodes. This information is passed to the EEG machine, which records the activity at each electrode as peaks and troughs on an electroencephalogram.

The types of cognition the team initially tested were selective attention, response inhibition (i.e., successful control of impulsive responses), working memory, and processing of object-based and emotion-based interference. Over 100 healthy young adults were given tasks that assess each of these functions separately and tested using

BrainE for cognitive brain mapping. The platform allowed the team to carefully investigate the neural processes taking place during the presentation of stimuli in these various cognitive contexts. Given its comprehensive and rapid measurement of brain function underlying different cognitive abilities, its cost-effectiveness and high scalability, Dr Mishra believes *BrainE* will be a useful tool for creating frameworks for mental health investigations. She plans to use *BrainE* for understanding the mechanisms of mental disorders in different contexts and for finding therapeutic targets.

Loneliness Versus Wisdom

Recently Dr Mishra leveraged *BrainE* to study how two health indicators – loneliness and wisdom –drive neural circuits in an emotional context. Loneliness manifests when an individual's social needs are not met, and it is known to be a psychosocial determinant of poor health. The feeling can harm mental health and may also negatively impact physical health. Acute stress disrupts the immune system and accelerates the risk of dementia as well as increases the risk of suicide, meaning loneliness is related to high morbidity and mortality.

At the other end of the spectrum, wisdom is associated with better health and well-being. It can be described in a number of ways, but one definition is using your experience, knowledge, insight and empathy to influence your thoughts and actions. Wisdom is a complex component of personality – it requires pro-social behaviours, emotional regulation and self-reflection. Research has shown that loneliness and wisdom are not frequently found together, perhaps because aspects of wisdom like compassion (including towards oneself) are sometimes reduced in lonely individuals. In addition, wisdom may act as a sort of protective factor from loneliness.

As these are two opposing yet potentially linked characteristics, Dr Mishra and her team decided to investigate their neural and cognitive processing in the context of an emotion bias task. Faces showing positive, negative, threatening and neutral emotions were shown to 147 participants who had also self-rated their sense of wisdom and loneliness. Interestingly, the team found that loneliness was associated with slower cognitive processing when angry emotional faces were presented. Loneliness also enhanced attentiveness to threatening stimuli. Conversely, wisdom was associated with faster processing speed when happy emotional stimuli were presented. Using the EEG data, they could identify which relevant brain areas were activated during these tests.

According to Dr Mishra, these results using *BrainE*, 'show that loneliness and wisdom may opposingly drive neural circuits based on emotion context'.

The Impact of Negative Childhood Experiences on Brain Development

Dr Mishra believes it is very important to understand brain function based on life experiences and environmental context. Environmental factors like trauma from neglect or abuse during the childhood years have a big impact on how the brain develops and this can have bearing on a child's behaviour into

adolescence and adulthood. However, the biological reasons for this are not entirely clear. So Dr Mishra and her colleagues decided to investigate the effect of childhood trauma on brain connections as well as executive dysfunction in a large sample of 392 adolescents. The term executive dysfunction covers a range of emotional, cognitive and behavioural difficulties. For instance, issues with problem-solving, planning and organisation among others can be indicative of executive dysfunction. The team studied which brain connections are influenced by childhood trauma and thereby, underlie executive dysfunction. Importantly, they took these findings to predict future high-risk alcohol consumption in youth.

In this study, the team leveraged data from a National Institutes of Health dataset of adolescents, who self-reported on childhood trauma and executive dysfunction. These adolescents were interviewed about their alcohol and substance use at the beginning and then every year for four years. In addition, the adolescents were given a functional magnetic resonance imagining (fMRI) scan, which shows the regions of the brain that are activated (displayed as an image of the brain rather than on a time-graph as in an EEG) just while resting.

Perhaps unsurprisingly, experiencing trauma in childhood had a strong link to executive dysfunction in the adolescent years. The fMRI scans revealed functional brain networks particularly from core regions that control cognition, for example, the dorsal anterior cingulate cortex and the anterior insula, that mediate the link between executive dysfunction and childhood trauma. Dr Mishra's team further leveraged machine learning to show that the functional brain networks impacted by trauma can help to accurately predict high-risk drinking in follow-up years. Therefore, this research is useful for developing a prognosis of alcohol use disorder in individuals who have suffered adverse childhoods.

A Climate and Mental Health Emergency

Another environmental factor that is becoming ever more concerning is climate change. With climate change comes an increase in weather-related disasters like wildfires. In 2018, the Camp Fire in California was the deadliest in the state to date. Living through such an experience was undoubtedly traumatic so Dr Mishra systematically studied how the wildfire affected the mental health of residents in the vicinity of the fire.

Six months after the disaster, Dr Mishra and her team sampled 725 people who had had varying degrees of exposure to it and measured their mental health. The incidences of PTSD, depression and anxiety disorder were assessed, and participants additionally reported their personal resilience and mindfulness.

They found that direct exposure to the fire significantly increased the risk of mental health disorders, especially PTSD and depression. Notably, high resilience and mindfulness lowered these risks whilst childhood trauma and sleep disturbance exacerbated them. This study emphasises how the climate change emergency may, 'impact the mental wellbeing of the global population, and we must find ways to foster individual resiliency'.

Mindfulness as a Digital Therapeutic Approach

As we've already seen, adverse experiences during childhood can significantly impact brain development. Dr Mishra wondered whether a mindful meditation approach that is digitally delivered can serve as an innovative therapy. The team in this study designed a closed-loop technology, which is software that, 'is adaptive to the performance capabilities of the individual and uses reinforcing feedback to drive effective learning'. This design was applied to a meditation programme for adolescents who had experienced neglect in their childhood living in a low/middle-income setting.

After completing the period of meditation via closed-loop engagement, the adolescents showed great improvement in several domains. Their academic performance was better and attention abilities were enhanced whilst hyperactive behaviour was reduced. These improvements were linked to a strengthened connection in an area of the brain called the dorsal anterior cingulate cortex which develops critically during adolescence. This study showed how new, personalised (individually adaptive) technologies can be implemented to strengthen brain function, cognition and behaviour.

An Exciting Future

The innovative and novel research that Dr Mishra has completed is guiding the field of neuroscience, particularly clinical and translational research in an exciting direction. By providing insight into the effects of environmental factors on mental health and exploring personalised, accessible and sustainable mental healthcare solutions, her work is sure to be at the forefront of a new age of digital medicine to improve human well-being.

Meet the researcher

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Dr Jyoti Mishra completed her BSc in Biochemistry at Delhi University and went on to study for an MSc in Life Sciences at the National Center for Biological Sciences in India. She achieved her PhD in Biology with specialisation in Computational Neurobiology from the University of California, San Diego (UCSD) in the USA. She is also completing her MBA from the UCSD Rady School of Management. Having fulfilled both academic and industry postdoctoral positions and receiving multiple honours, Dr Misha is now an Assistant Professor in the Department of Psychiatry at UCSD. She founded NEATLabs within this department and directs their human research into advancing neurotechnology for cognitive brain mapping and digital therapeutics for mental healthcare.

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FUNDING

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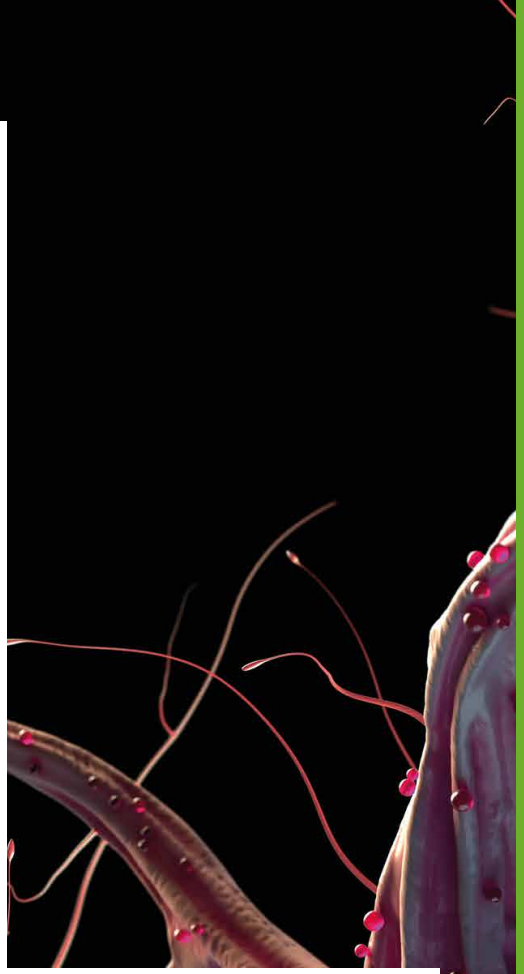
MAPPING BRAIN NETWORKS TO UNDERSTAND EPILEPSY

Epilepsy is one of the most common causes of disability worldwide, but for many patients, treatment fails to be effective. **Dr Victoria Morgan** and her team from the Department of Radiology and Radiological Sciences at Vanderbilt University Medical Center are using functional connectivity mapping to find out why some patients respond better to treatment and what alternative ways there may be to tackle this debilitating disorder.



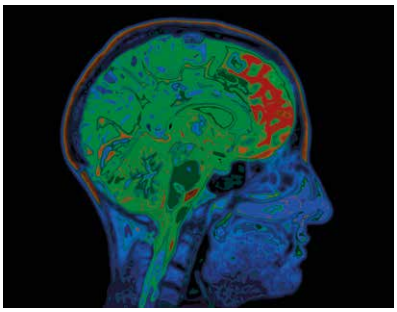
Epilepsy: A Global Problem

Epilepsy is a neurological disorder characterised by recurrent seizures which are the result of abnormal, synchronous firing of neurons in the brain. Under normal conditions, neurons aren't in sync and fire when they receive signals. In epilepsy, however, changes to the threshold allowing firing can trigger mass activation of neurons and 'bursts' of synchronised electrical activity.

Temporal lobe epilepsy (TLE) is one of the most common forms of epilepsy. This is a type of focal epilepsy, where seizures arise from one or more discrete locations called the seizure focus. In this case, the focus is within the temporal lobe. This is in contrast to generalised epilepsy where seizures can originate from much of the brain simultaneously. The initial treatment for most patients with epilepsy is anti-epileptic drugs, which aim to dampen down the electrical hyperactivity responsible for triggering seizures. In almost 40% of patients, however, drugs fail to work or have intolerable side effects.

For focal epilepsy, the next step is to try surgery, which is often preferable to long term drug treatment anyway. When patients come into the clinic with drug-resistant focal epileptic seizures, neurologists can perform tests to attempt to identify the exact location of the seizure focus, and, in TLE, this generally tends to be the hippocampus. Surgery is then performed to remove this area. While technological advancements have continually increased our ability to accurately identify the focus, the success rate of these surgeries has not improved as we would expect. Clearly, there is something else at play.

Dr Victoria Morgan at the Vanderbilt University Institute of Imaging Science at Vanderbilt University Medical Center is using her expertise in biomedical engineering and magnetic resonance imaging (MRI) to find out why focal epilepsy is so difficult to treat. 'Even in cases where the clinicians are most confident in the localisation of the seizure focus, the success rate is about 80%,' explains Dr Morgan, 'This is the mystery I am interested in solving.'



Nodes and Edges

Much effort has been put into understanding what patient variables are associated with differing surgical outcomes. In TLE affecting the hippocampus, younger age and a history of fewer tonic clonic seizures prior to surgery have been observed to correlate with success but attempts to design predictive tests have so far done little to improve results. Refining these tests would be a significant step forward for epilepsy treatment, and since brain surgery is associated with high risks it would be undesirable to perform this procedure on patients for whom it is less likely to benefit.

‘Even in cases where the clinicians are most confident in the localisation of the seizure focus, the success rate is about 80%. This is the mystery I am interested in solving.’

For years, scientists have been searching for the best way to visualise the brain in order to understand different disease states. With epilepsy, much of the attention has been given to the focus to try and identify how and why seizures arise. Dr Morgan, however, believes that looking at the brain as a network of interconnected points is much more useful in understanding epilepsy.

Network connectivity mapping allows the brain to be viewed as a collection of points, referred to as ‘nodes’, and the intercommunication between these nodes, called ‘edges’. By looking at the complex system formed by these nodes and edges we can learn more about how the brain acts during normal functions, such as memory retrieval or movement, and compare this to how it acts in abnormal situations, like seizures. Functional connectivity mapping relies on the use of functional MRI (fMRI), which measures changes in blood flow to different regions of the brain that correlate with changes in neuronal activity. Structural connectivity mapping uses diffusion-weighted MRI to look at how water moves along white matter tracts across the brain.

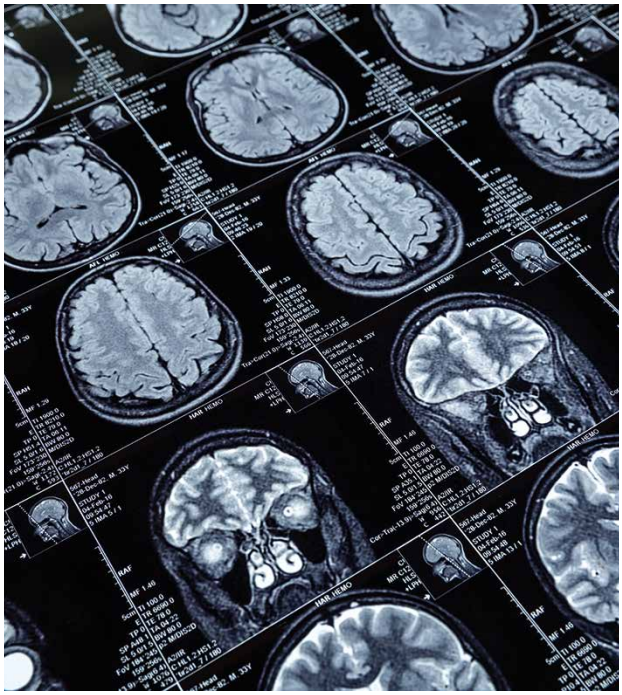
Dr Morgan’s research has suggested that while the seizure focus may be similar in groups of patients, the way that activity is propagated around this network of nodes and edges may be different. This may explain why, even when the focus is identified, surgery is ineffective.

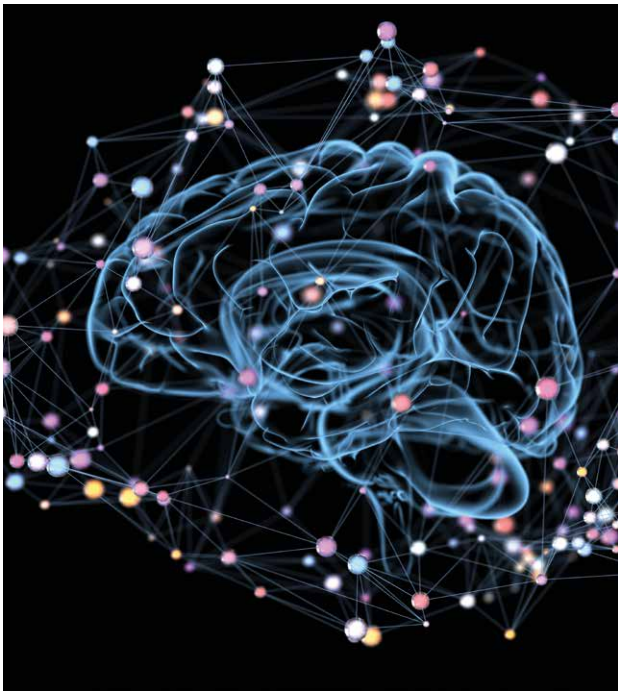
Changing Networks

‘What makes my work unique is that I am developing a general framework around the idea that epilepsy networks evolve even before the first seizure occurs and continue to evolve over years prior to and after surgery,’ notes Dr Morgan. Using MRI, Dr Morgan and her team were able to show that epileptic patients have differences in their functional and structural connectivity networks compared to healthy controls. Identifying such a difference can allow for the development of a biomarker, a characteristic of a disease which aids in diagnosis.

Dr Morgan noted that these changes also correlated with how severe their epilepsy was and how long they had been suffering from it. This kind of analysis has been studied before and has huge potential to be used clinically to assess an individual’s disease progression. But Dr Morgan states the changes seen and the techniques used need to see improvements in sensitivity, specificity, and generalisability to be wholly useful.

Other challenges that need to be overcome are how to implement such a complex measure. Analysing networks requires replicable methods and using connectivity biomarkers is computationally intensive. In addition, results can be ambiguous or difficult for clinicians to interpret. Indeed, some studies have reported conflicting changes, with some finding increases and others finding decreases in functional connectivity between certain areas. It’s clear that connectivity mapping needs to see advancements in methods before it is used in the clinic, and Dr Morgan hopes to be the one to achieve this.





Predicting Outcomes Can Help Improve Treatment

One of Dr Morgan's key findings is that patients whose seizures were reduced following surgery tended to share a particular network structure before they underwent the treatment. Patients with different networks were much less likely to respond in the same way and saw little or no improvement after surgery. Interestingly, in the successfully treated group, there were certain pathways in the network found to be associated with the length of time until a rare seizure occurred post-surgery. This kind of foresight provided by MRI and connectivity mapping is an invaluable tool when trying to treat such a complex neurological disease. Dr Morgan's models were able to successfully predict which patients would be less responsive to treatment in cases where the currently used predictive models would not.

While the most desired outcome of epilepsy treatment is total remission of seizures, Dr Morgan's model allows for a spectrum of success. Importantly, the length of time which passes before seizure recurrence may be associated with different networks and mechanisms. Earlier, severe recurrence may suggest a larger difference between their network and the success-predictive network, while later, milder recurrence may be more similar. These slight variances in networks can mean the difference between surgery which accurately targeted the epileptogenic system and focus, and that which did not.

'Long-term outcomes years after surgery are at least partially dependent on how networks evolve after surgery,' adds Dr Morgan. The main premise of her work is that the integrity of the seizure-associated network both before and after surgery is significant in predicting recurrence of epilepsy symptoms.

The network structure itself is unique to each patient, being affected by age, genetics, medication, and type of seizure, but general patterns can be found, nonetheless. Dr Morgan hopes to quantify this connectivity network in pre- and post-surgical patients to properly elucidate the relationship to seizures and their recurrence. 'My hypothesis is that conventional clinical methods will be successful in patients with a specific focus and network combination,' she elaborates. Ultimately, by identifying which networks respond to which treatments we can improve success rates and better help patients.

The Future of Epilepsy Biomarkers

Dr Morgan's work presents an innovative new landscape for epilepsy research. Developing new biomarkers is an essential step forward in improving the way we treat epilepsy, especially biomarkers that can distinguish between different treatment outcomes. Dr Morgan also hopes to study the long-term development of seizures in humans, something which has not been studied in this way before. The characterisation of post-surgery recurrence networks is an incredibly significant finding in epilepsy research and paves the way for a new era of understanding neurological disorders.

Going forward with her research, Dr Morgan has three main goals she wants to achieve. First, to understand how networks change over years of duration of TLE prior to surgery. Second, to quantify exactly how networks can evolve post-surgery and lead to a resurgence in seizure activity. And finally, to combine this information into biomarkers to predict those patients with the best chance of long term seizure freedom from surgery. When these three targets are achieved, Dr Morgan believes that MRI networking mapping will be used as an effective and accurate predictive biomarker to aid treatment and help us understand this complex disease.

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FUNDING

Current:
National Institutes of Health: 1R01NS110130. The Role of Network Connectivity in Post-Surgical Seizure Recurrence in Temporal Lobe Epilepsy
National Institutes of Health: 1R01NS108445. MRI Connectivity Biomarkers of Treatment Response in Focal Epilepsy

Past:
Epilepsy Foundation Research Grant: Localization of Epileptic Activity Using Resting Functional MRI
National Institutes of Health: 1R01 NS055822-01A2. Temporal Clustering Analysis for Detection of Irregular Transient fMRI Activation
National Institutes of Health: 1R01NS075270-01A1. MRI Structural and Functional Connectivity Changes in Temporal Lobe Epilepsy

FURTHER READING

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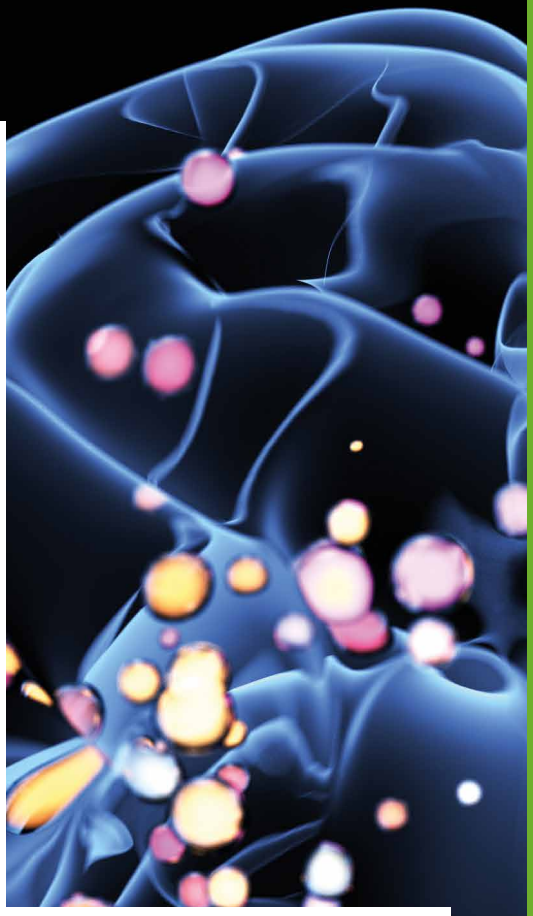
VANDERBILT UNIVERSITY
MEDICAL CENTER

IMPROVING PATIENT OUTCOMES IN TRAUMATIC BRAIN INJURY



Severe traumatic brain injury (TBI) is associated with high rates of disability and even mortality. Understanding the relationship between patient outcomes and the treatment received, as well as other physiological factors such as inflammation, can improve how we approach TBI. **Dr Jack Jallo** and his team from the Department of Neurological Surgery at Thomas Jefferson University are researching the factors that influence TBI recovery to help design better care management protocols and optimise patient recovery.

Traumatic Brain Injury: Mechanisms of Damage

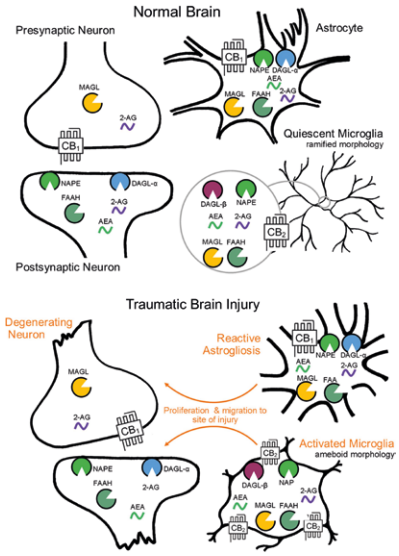
Globally, around 10 million people are affected by traumatic brain injury (TBI) each year. Treatment varies based on the severity of injury, but success is often reliant, at least in part, on managing sequelae of injury. This is because, while the immediate injury puts patients at risk of death or disability, it is often the subsequent progression of damage that is most dangerous. When the brain undergoes such trauma, it responds by triggering a cascade of inflammation in an attempt to repair the damage and provide vital nutrients and oxygen to cells. Unfortunately, this inflammation can become uncontrolled and may play a significant role in secondary injury, contributing to cell death and further dysfunction.

Inflammation can cause swelling or oedema which increases the pressure in the skull, creating what is known as intracranial pressure (ICP). The brain is extremely sensitive to this change, and ICP over 20mmHg is the most frequent cause of death in TBI patients. While inflammation is initiated by the body in an attempt to increase blood flow to the damaged tissue, uncontrolled inflammation can increase ICP and reduce cerebral blood-flow, complicating outcomes. When this occurs, treatment primarily involves neurosurgical intervention and the removal of a section of the skull to relieve the pressure, a procedure that comes with risks of its own.

Dr Jack Jallo is a neurosurgeon from Thomas Jefferson University (TJU), who is dedicated to ascertaining the factors that affect patient outcomes from TBI and establishing how treatment can be improved. To identify novel therapeutics for TBI, he has explored the effects of tissue oxygenation following injury, craniotomy and surgical intervention, as well as the role of the cannabinoid system in inflammation.

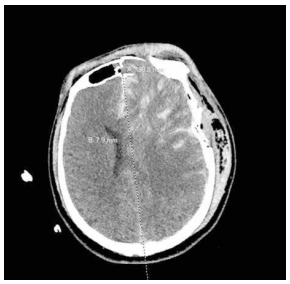
Care Related Patient Outcomes

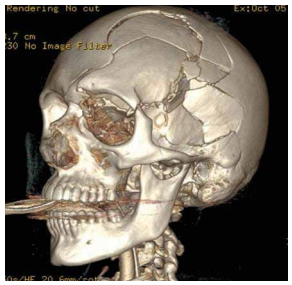
As the Director of Neurotrauma and Critical Care at TJU, Dr Jallo has years of experience working in a level one adult trauma centre. His observations of trauma care and TBI have informed his key papers detailing the different outcomes among patients depending on their level of treatment.



Reproduced from LD Schurman, AH Lichtman, Endocannabinoids: A Promising Impact for Traumatic Brain Injury, Frontiers in Pharmacology, 2017, 8, 69.

When quantifying these differences, it is essential to take into account that there may be variances in treatment between centres. Comparatively, level one trauma centres are capable of dealing with a much higher volume of patients and tend to have more specialised and interdisciplinary teams, while level two centres are slightly less specialised. Studies have shown that, on the whole,





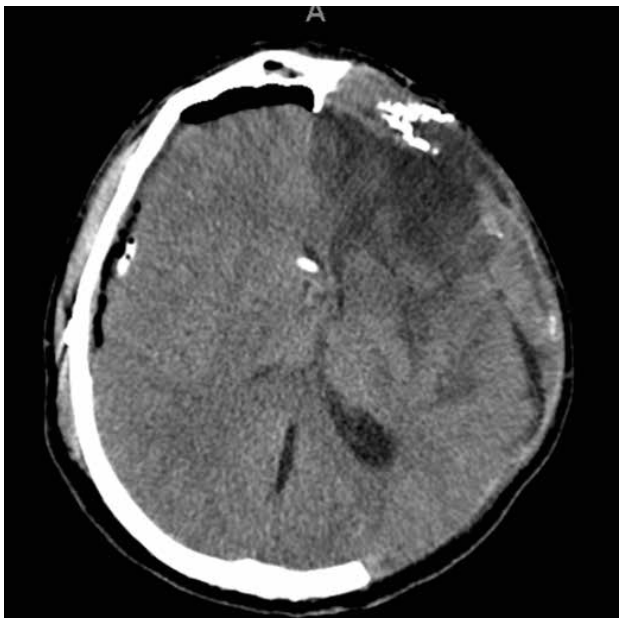
severely injured patients have an increased survival rate when treated at level one trauma centres. Dr Jallo's research also confirms that for TBI, patient outcomes are generally better when they receive specialised and directed care, such as craniotomy, in a level one centre.

When dealing with TBI, a mainstay of trauma centres since the 1960s has been the use of ICP monitoring. The idea is, that by keeping tabs on a patient's ICP using intracranial devices we can better predict which patients may need surgery. This could be useful in cases where brain swelling is delayed following injury or occurs silently, allowing doctors to perform risky neurosurgery only when necessary.

However, when publications came out questioning the benefit of ICP monitoring in severe TBI, hospitals observed a decrease in the use of this technique. In a recent paper, Dr Jallo and his colleagues are hesitant to denounce the practice, and instead, recognise significant limitations, such as small sample size, associated with the previous publications. It remains clear that, as a time-sensitive condition, TBI treatment would likely benefit from ICP monitoring that allows for more personalised care, and Dr Jallo emphasises the need for more research into its use.

In a further trial on monitoring patient progression, Dr Jallo noted that brain tissue oxygenation also associated quite well with outcomes. It was found that combining oxygen monitoring with ICP monitoring improved management of severe TBI and reduced the amount of brain tissue which was starved of oxygen. A hugely important aspect of TBI care is preventing secondary damage from occurring, being able to identify when that might happen is a significant advantage.

Dr Jallo's work has shown that it is essential to take into account the variation in care that patients receive so that we can untangle the downstream effects from physiological differences relating to the injury itself. Furthermore, the way we define and categorise TBI also has implications for patients down the line.



Defining Injury

The majority of emergency room visits for head injury are classified as mild TBI (mTBI). These cases generally have higher rates of recovery, but for some mTBI patients, chronic cognitive or neurological deficits can persist. Can these cases really be described as 'mild'? Following the universally approved definition outlined in the American Congress of Rehabilitation Medicine, mTBI is diagnosed only if the loss of consciousness is for less than half an hour, and in general, post-trauma amnesia (PTA) should resolve within 24 hours. Nevertheless, there is room for significant variation within the mTBI group.

Clinicians have noticed that a subset of mTBI patients shows significantly worse outcomes 6 months post-injury. Researchers, therefore, coined the term complicated mild TBI (cmTBI) to describe cases where patients may have more extensive damage, such as lesions in the brain, which can cause this. Categorising patients presents a problem for treatment as it may not fully appreciate the nuances of injuries between individuals, meaning that the right level of care cannot be applied.

In an observational study of cmTBI patients, Dr Jallo noticed that only 25% of the sample had PTA for less than 24 hours. In nearly half of patients, it was present up to seven days, and for a third of patients, it was reported for more than a week. The duration of PTA seems to correlate more clearly with performance on cognitive tests, and Dr Jallo believes it should be used alongside other measures when defining TBI. This may help refine outcome predictions and improve rehabilitation treatments offered, but the limitations of the study should be noted, such as the lack of a control group. Further research into the use of PTA duration as a possible diagnostic factor is essential to help advance our understanding of TBI.

Targeting the Endocannabinoid system

Developing new treatments for TBI has been a challenge for a long time. After initial surgical attempts to prevent brain swelling, it becomes difficult to accurately target and prevent secondary injury from occurring. Novel immunomodulatory therapies have been identified which target the inflammatory response, preventing it from going into overdrive and suffocating the brain as a by-product.

The cannabinoid system, which functions to communicate certain signals in the brain and body, has been shown to play a significant role in inflammation. A particular receptor known as CB2R is present on immune cells in the brain and can help to regulate inflammation and the response to injury. Using molecules called agonists which bind to and stimulate CB2R, we can increase this anti-inflammatory effect, which may be helpful in treating TBI.

Dr Jallo and colleagues used mice to show that early administration of a CB2R agonist after TBI can reduce the expression of markers associated with inflammation. This may be due to the ability of CB2R to prevent immune cells from entering the bloodstream of the brain. Developing safe and effective drugs to do this would increase the number of tools we have available to treat TBI and hopefully reduce secondary injury.

Interestingly, one of the long-term outcomes of TBI, chronic headache, may be associated with disruptions in the cannabinoid system. Alterations in the sensitivity of neurons in regions associated with headache may be due to disturbances in the balance of chemical transmitters, such as cannabinoids. Modulating this with exogenous cannabinoids, such as THC and CBD, has been shown to improve post-traumatic headache as well as other conditions like migraine. Further research into this could support the push for legalisation of cannabis, which has been shown to have a multitude of benefits for many health conditions.

The Future of TBI Research

Dr Jallo's work into the causes of and treatments for TBI is vitally important if we want to improve outcomes for patients. His position at the interface of clinical medicine and scientific research gives him a unique perspective on how the care we administer can affect clinical outcomes, as well as the physiological mechanisms associated with TBI.

Finding novel ways to treat injuries of the brain requires a deep understanding of the endogenous systems involved. It is common with brain diseases that the body's attempts to heal the damage can end up doing more harm than good. Unravelling the threads that influence this balance can help us target them for more effectively and identify new tools to treat TBI.

Meet the researcher

Dr Jack Jallo
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Dr Jack Jallo is a neurosurgeon at Thomas Jefferson University who specialises in the evaluation and treatment of cervical, thoracic, and lumbar spine injuries, as well as spinal tumours. He earned his MD from George Washington University in 1990 and completed his PhD in physiology at Temple University Hospital in 2003. He completed a neurosurgical residency at Temple University as well as a fellowship in neurotrauma and critical care. In addition to being a neurosurgeon, Dr Jallo is also currently a professor at Thomas Jefferson University and the executive director for critical care. His research explores methods to improve outcomes from traumatic brain injury. He has authored a number of articles and textbooks with the goal of educating patients and surgeons. He is on the board of both the Pennsylvania Emergency Health Services Council and the Pennsylvania Trauma Systems Foundation and since 2017 has been a member of the American College of Surgeons Committee on Trauma as well as the Joint Council on Neurotrauma and Critical Care.

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09/2014–08/2017: Central Pain Mechanisms and Novel Therapeutic Strategies in a Model of Closed Head Injury through the Department of Defense. The goal of this project is to study potential biomarkers, therapeutic interventions, and pathological mechanisms of chronic migraine headache in a model of concussion. Grant #: W81XWH-14-1-0594 (MR130514). Role: Co-Investigator.

9/01/12–8/31/2015: Investigator-Initiated Research Award Department of Defense PR 110398 to M. Elliott. U.S. Army Medical Research & Materiel Command through Thomas Jefferson Medical College: Trigeminal Sensitization in a Pre-clinical Model of TBI: Implications for Post-Traumatic Headache. Using a traumatic brain injury (TBI) animal model of controlled cortical impact (CCI), the investigators propose to elucidate mechanisms of central sensitisation underlying post-traumatic headache (PTH) disorders. They hypothesize that increased levels of two crucial molecular mediators – calcitonin gene-related peptide (CGRP) and inducible nitric oxide synthase (iNOS) – following TBI contribute to sensitisation of the trigeminovascular system. The well-defined experimental design is aimed at determining the role of endogenous and exogenous CGRP and iNOS in driving sensitisation in the acute and post-traumatic period. Amount: $1,095,000. Role: Collaborating Investigator

7/01/10-06/30/11: NIH through Emroy University University of Michigan through Temple University Neurological Emergencies Treatment Trials (NETT) – ProTECT III. The major goal of this project is to determine the efficiency of administering intravenous (IV) progesterone (initiated within 4 hours of injury and administered for 72 hours, followed by an additional 24 hours taper) versus placebo for treating victims of moderate to severe acute TBI (Glasgow Coma Scale score 12–4). Role: Principal Investigator.

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EXPLORING THE NEURAL MECHANISMS OF SPEECH AND LANGUAGE TO INFORM CLINICAL PRACTICE

The neural mechanisms behind speech and voice production are intricate but not yet fully characterised. For speech and vocal disordered populations, understanding the central mechanisms behind speech and sound production is essential to improve treatment options and rehabilitation techniques. Taking a scientist-practitioner approach, **Dr Jessica Galgano**, of New York University Grossman School of Medicine and founder of Open Lines Speech and Communication, is researching the underpinnings of speech and the clinical efficacy of current treatments for voice, speech, and language disorders.

The Voice and the Brain

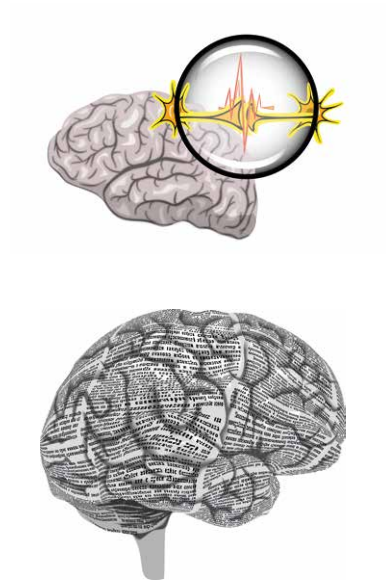
Speech and language are fundamental components of human experience. Speech allows us to express our thoughts and feelings, communicate ideas, and connect with the world around us. Despite its ubiquity, the brain mechanisms which allow speech to occur are not fully understood. Speech and voice disorders affect almost 30% of people at some point in their lives and are the main cause of communication difficulties. For these individuals, uncovering the pathways and underpinnings of how speech is produced in the brain can help us develop new and more effective treatments and rehabilitation programmes.

When considering how the brain is activated during speech, it is important to identify the different components involved. Voice refers to sound produced by speech organs, namely the larynx, while speech refers to articulation and movement of the lips, mouth, and tongue to produce specific sounds. Language, on the other hand, concerns the myriad cognitive processes involved in producing and understanding the rules of linguistics and communication.

Revealing the neural circuits and pathways associated with voice and speech in normal populations can help identify the networks involved and how these may change as we age or when damage or illness occurs. Dr Jessica Galgano has brought together a team from a number of universities and academic medical centres around the country, including Colombia University, Memorial Sloan Kettering Cancer Center, Princeton University, University of Colorado, and Yale School of Medicine. Together, they are striving to characterise these neural pathways to help people with speech or voice disorders as a result of stroke, cancer, Parkinson's disease, and other neurological conditions.

Emotionally Speaking

One of Dr Galgano's main findings during her time as a researcher relates to the role of emotional pathways in the brain during the production of speech. The impact of emotive states on voice



has been studied comprehensively in many fields, ranging from medicine to the arts, and the voice can reflect an individual's emotional state. Indeed, researchers have described the voice as the 'barometer of emotion' due to the significant influence that psychogenic stress can have on voice.

A condition known as adductor spasmodic dysphonia causes the vocal folds to come together abnormally when speaking, becoming especially

pronounced during anxious states and resulting in strangled or shaky speech. Strong emotions can influence anyone's speech, such as when people experience difficulty expressing grief or the loss of voice during stressful situations, like being put on the spot. Improving our understanding of how emotion and speech are interlinked can help improve therapies and treatments for patients and deepen our understanding of how cognitive and emotional processes are integrated during speech.

There is substantial evidence so far to suggest that an area called the periaqueductal gray (PAG) is strongly associated with vocalisation and respiratory control during vocalisation, even in lower mammals. The PAG forms an interface between the forebrain limbic system and medullary autonomic centres. It receives afferents from the hypothalamus and amygdala, the latter which is an integral part of the limbic system, or the emotional brain.

When animals vocalise this typically reflects a heightened level of stimulation of the PAG and conveys information about the animal's emotional state. Lesions of the PAG are known to disrupt vocalisations in humans and other mammals, be involved with emotional responses, and show greater activity in humans when a threat comes close. For these reasons, Dr Galgano considered the PAG is an important part of the network needed to coordinate respiratory and laryngeal motor patterns that play a part in voice production, especially under heightened emotional states or stress.

Visualising the Voice: Informing Clinical Practice Through Research

Functional magnetic resonance imaging (fMRI) allows scientists to visualise regions of neuronal activation by detecting changes associated with blood flow in the brain. In a key study, Dr Galgano used fMRI to look at which areas of people's brains are more or less active during different activities: sustained vocalisation of the 'uh' sound with closed lips or sustained exhalation through the nose. When studying the brain signals associated with speech it is important to be able to differentiate the signals associated with movement of the mouth from the signals associated with voice production in the larynx itself.

This means that when designing tasks for trial subjects to perform, researchers must include some sort of control, where normal movements of the mouth and respiratory system can be compared to vocalisations in order to identify the differences. Comparing the two activities provides a baseline to see which areas are more active during the production of voice specifically, rather than just activation of motor neurons in the throat.

Dr Galgano's findings were clear. During vocalisation, an area called the left ventral laryngeal motor area (LMA) was coupled with activation in the PAG. Whole brain analysis also revealed increased coupling between the PAG and the amygdala, an area heavily involved in emotion and anxiety. The functional connectivity between these regions was significantly more pronounced during voluntary production of vocalisations compared to exhalation and suggests that motor voice control is linked with parts of the limbic system.

This discovery is consistent with what we know to be the case in animals, where the PAG and amygdala have a close relationship to allow integration of anxiety behaviours in response to threat. In humans, a similar connection may mean that stressful situations or strong emotions can affect the PAG's ability to mediate motor control during voicing and speaking. Elucidating the brain areas involved in this can help us identify the processes which might be disrupted in psychogenic or neurogenic disease.

This important work underscores the importance of exploring the basic mechanisms of change underlying the neuronal networks that govern both emotion and voice and speech in clinical as well as research settings. As Dr Galgano explains, the human voice provides critical insight into an individual's anxiety as well as their ability to regulate their emotions. As such, the potential impact of emotion on symptomatology should be considered a key part of clinical evaluation and intervention.

Vocal Potential

Before she researched emotional influences on speech, Dr Galgano studied the nerve potentials which occur to initiate it. This is of particular importance for patients suffering from Parkinson's disease, where initiation of a movement or action is acutely impaired. Her work identified a novel method to analyse these potentials using high density electroencephalography which overcame shortcomings associated with earlier methods. A brain region known as the middle frontal gyri and the bilateral LMAs were localised as the source of the voice-related potential. Identifying these areas can help us find out the pathways involved in initiating speech, something which has previously been very difficult to study.

Other important aspects of voice and speech under investigation include the complex pathways which control the precise, coordinated movement required to modify pitch. This is something we do unconsciously and naturally during speaking and singing but takes a great deal of synchronisation between respiratory and articulatory systems. Neuroimaging techniques can allow researchers to more clearly delineate such networks underlying control of the voice.

Dr Galgano recognised that previous attempts to find neural correlates of the movements associated with pitch control were impacted by difficulties controlling confounding variables and separating the physical and cognitive aspects. Using fMRI, Dr Galgano and her team were hoping to properly identify the central cortical mechanisms involved in pitch variation.

Her findings were in accordance with prior research and also identified a region known as the insula as being active during modulation of pitch. This area has previously been shown to be involved in the detection of sound, which is an essential component of vocal monitoring and adjustment.

Many other areas were identified as having an involvement in voice control, and interestingly, though the inferior frontal gyrus in the right hemisphere produced greater activity than the area of the left hemisphere during high and low pitch generation, the left hemisphere of the brain showed increased activation on the whole during high pitch production vs. comfortable production and low pitch production vs. comfortable production, except for bilateral activation in the cerebellum. Dr Galgano suggests this may be due to its role in controlling the rhythm and intonation of speech (prosody) and its involvement in language production. Future studies could take a more in-depth look at why the left hemisphere plays a slightly larger role in pitch to better understand how the minutiae of speech are controlled.

The Road Ahead

The importance of speech and language for our health and emotional wellbeing should not be overlooked. Communication is a major aspect of our lives as social beings and furthering our understanding of how we produce speech in health and disease can help improve the way we treat such disorders.

Dr Galgano describes a case study of a woman suffering from vocal cord paralysis following metastatic cancer and chemotherapy. Interestingly, the physical changes to her throat and larynx following surgery seemed to bring about changes in the neural pathways in her brain involving speech production. The functional changes which occurred in the brain maps of the patient before and after surgery suggest that the central nervous system (CNS) has a significant ability to modulate neural networks and reorganise areas involved with planning, implementation, and control of systems needed for voice production.

The clinical improvements observed in this patient correlated with the changes in neural activation and lend credence to the theory that CNS changes can improve the ability to produce voice, possibly due to the ability to process new sensory information following surgery. Understanding the way in which the brain can adapt to such changes can perhaps further our knowledge of how neural changes affect physiology. Dr Galgano integrates these understandings and insights gained from cutting-edge research from diverse medical fields and applies it to the latest clinical best practices with the use of the proprietary PRESENCE Approach™, which uniquely addresses any impact emotions or psychological states may have on one's ability to think and communicate.

The work of Dr Galgano has improved the lives of thousands of individuals suffering from speech disorders and voice pathologies. Her research continues to advance the field of study to allow new rehabilitation techniques and treatments to be developed and improve our knowledge of the neural underpinnings of and the impact of emotion and stress on speech and voice.

Meet the researcher

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Dr Jessica Galgano earned her PhD (distinguished) from Columbia University in Biobehavioural Sciences in 2007, having joined Memorial Sloan Kettering Cancer Center as an assistant research scientist in 2006 and New York University Grossman School of Medicine as an associate research scientist and later as a faculty instructor in 2010. Her research has focused on the neural underpinnings of speech and voice and the effectiveness of current treatments for neurogenic speech disorders with a special interest in the direct structural and functional connections between core limbic system structures and voice/speech-motor areas. Dr Galgano's future investigations will further describe these connections, both via brain imaging studies and other types of investigations, to inform individuals about the importance of managing mental health for successful communication, ultimately leading to improved quality of life, health-related quality of life, and life participation and satisfaction.

Dr Galgano is the founder of Open Lines Speech and Communication where she uses her expertise to help adults and children suffering from cognitive, speech, voice, and swallowing disorders while also pursuing certification in anxiety management and furthering her studies with a doctorate in clinical psychology. She is a recipient of several awards and grants given by the National Institute of Health (NIH), National Institute of Deafness and Other Communication Disorders, National Institute of Mental Health of the NIH, Columbia University, and New York University. Dr Galgano also serves as Vice President and Treasurer of the Board of the Parkinson's Unity Walk and is a member of the American Speech Language and Hearing Association.

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- 2007: Recipient of the National Institute of Health, National Institute of Deafness and Other Communication Disorders Ruth L. Kirschstein National Research Service Award for Individual Predoctoral Fellows [F31]
- 2007: Recipient of the Carol N. Wilder scholarship. Columbia University, Teachers College
- 2006: Recipient of the Spencer Foundation Research Training Grant: Dissertation Grant. Columbia University, Teachers College
- 2005: The Organization of Human Brain Mapping Travel Award, partially funded by an R13 Award from the National Institute of Mental Health of the NIH (Award # 2 R13 MH062008-06, 'Conference on Functional Mapping of the Human Brain')

OPEN LINES

THE EFFECT OF MUSIC ON PATIENTS WITH DISORDERS OF CONSCIOUSNESS

Disorders of consciousness may arise from a wide range of incidents, diseases and conditions, including traumatic brain injury, infection and tumours. With her collaborators, **Ms Teresa Grimm** at the Department of Music in Carl von Ossietzky University, Germany, is exploring the existing literature and delivering novel findings on the effect of exposure to music for patients who are living with a condition which results in a loss of consciousness.

The Consciousness Controversy

The term 'disorders of consciousness' (DoC) incorporates a plethora of conditions, including minimally conscious state in which patients have partial preservation of conscious awareness, unresponsive wakefulness syndrome (formerly called 'vegetative state') and coma, where the patient exhibits neither wakefulness nor awareness.

There are various conflicting and controversial opinions about the conscious state and what treatments and provisions should be offered to patients and the families of patients who are living with a disorder of consciousness.

At its most extreme, the opinion of some clinicians and scientists of patients who are living with conditions which cause a loss of or decrease in consciousness, is that the individuals are no longer human beings. From this perspective, consciousness is what defines humanity.

Ms Teresa Grimm, at the Department of Music in Carl von Ossietzky University, Germany, takes a different stance. She argues that the treatment of patients with DoC must follow scientifically rigorous and empirical methods aiming to create a dignified environment and restoring their 'personhood'.

In support of her beliefs, Ms Grimm argues that the brains of babies are not fully developed at birth, and following the more extreme beliefs would lead to the conclusion that babies are not human until their levels of awareness and consciousness are fully developed. With a clear focus on the rights of patients to be treated in a way which may improve their quality of life, humanity and personhood, Ms Grimm and her colleagues are now investigating the role that music may play in this.

Ms Grimm further counters the consciousness confers humanity argument by defining the myriad of occasions when all humans are not fully conscious based on the definition of consciousness as being aware and wakeful. First, during some stages of sleep individuals are not conscious of their surroundings, and we have all experienced times where our mind wanders or goes blank, and these are both examples of reduced

consciousness. Furthermore, activities that we do automatically, such as driving a car or conducting some other routine action, occur without the need for full conscious thought.

Disorders of Consciousness and Music

By the nature of their condition, patients with DoC are unable to engage in verbal communication, but given the effect of music on both the cortical and subcortical regions of the brain, Ms Grimm proposes that an intervention approach based on the patient's historical music preferences may be used to effectively induce an emotional response. In the case of people with DoC, the preferred songs can be delivered by close relatives or friends.

Importantly, music that we have listened to in our younger years is

maintained in a specific section of our memory known as 'autobiographical memory'. Furthermore, music is well known to produce a reminiscence response in the majority of individuals.

Music Therapy and Quality of Life

In addition to selecting music which may stimulate autobiographical memory, music therapy can be used in which a music therapist develops a personal relationship and contact with the patient. Therapists adapt their approach and methods to align with the patient's response, which may be extremely subtle. The music therapists are highly attentive to the patient's response, and match their musical choices to the patient's physiological signs, such as breathing rate, which is used as a measure of the patient's level of stimulation.

This approach focuses on the patient's quality of life. Ms Grimm and her collaborators believe that we need to drive a shift of our focus from the argument of what makes a person human, to a more empathetic focus on asking what the person needs. Music therapy can also be used as a diagnostic instrument for consciousness. Dr Wendy Magee and her colleagues developed an assessment which is called MATADOC (Music Therapy Assessment Tool for Awareness in Disorders of Consciousness).

A Systematic Review of Musical Interventions in Disorders of Consciousness

Ms Grimm and colleagues conducted a systematic review of the existing research pertaining to the use of musical interventions for patients with DoC. A systematic review is a rigorous, structured approach used to assess the outcomes of research studies. Effectively, a systematic review collates studies, defines study biases, and ultimately attempts to draw a combined conclusion from the body of evidence.

Study Inclusion Criteria and Data

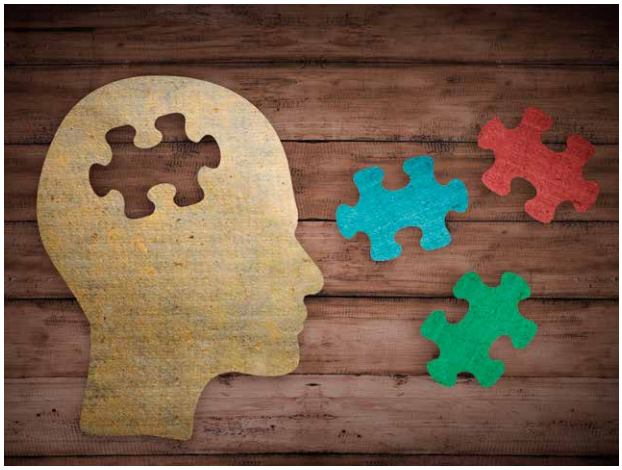
The researchers identified 22 studies published between 1900 and 2017 which reported the findings from a variety of musical interventions on a total patient cohort of 329 individuals with DoC. The ages of the patients ranged from 5 to 91 years, and the causes, where noted, covered a range of initiating conditions, such as injury and infection.

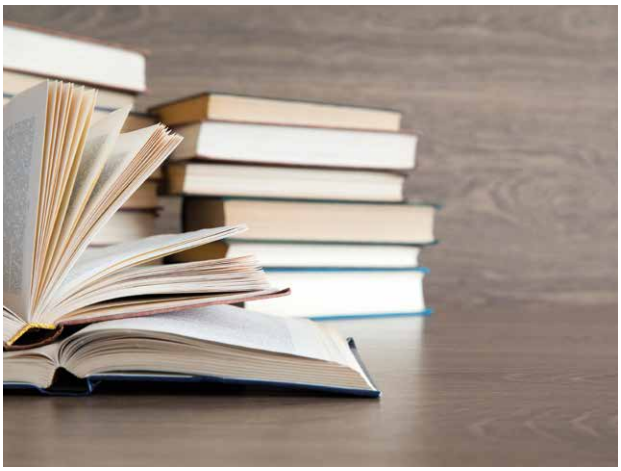
Where details of the patients' conditions were provided in the 22 studies, they broadly fell into the categories of unresponsive wakefulness syndrome (44%), coma (20%) and minimally conscious state (19%), with approximately 16% of patients remaining unclassified.

Music Interventions

In the studies reviewed, the patients were exposed to either recorded or live music, with live music largely delivered in the form of a music therapy intervention. The researchers defined the interventions as being based on music having a meaningful biographical association for the patient, music forming the basis of the relationship between the patient and the therapist, or both.

The varied nature of the 22 studies led the researchers to conclude there was no apparent commonality in terms of the structure or properties of the musical interventions delivered to patients. Given the nature of the conditions that the patients suffered from, interaction and responses were, predictably, extremely limited.





Study Quality and Rigour

The researchers assessed the potential bias of the studies by assigning scores for a number of key points about each study, including the method, design, and relevance to the review questions. The studies were then categorised into high, medium and low risk of bias groups. Of the 22 studies, only four had a low risk of bias, with the others either being medium or high risk.

The quality of the methods used was variable, with only three of the studies being randomised controlled trials in which control groups using healthy participants were included. The high level of bias observed was largely attributed to the lack of blinding in the studies. Blinding refers to the process of participants and researchers being prevented from knowing certain information that may somehow influence them and therefore, influence the results of a study. Of course, in some circumstances, blinding is next to impossible to ensure.

Results and Conclusions of the Review

Ms Grimm and her colleagues noted that the studies, while admittedly lacking in some areas, did frequently exhibit robust patient responses to the musical interventions. The patient responses occurred at both the behavioural and physiological level, with the recorded behavioural changes including body movement (directed towards the source), reduced agitation, changes in facial expression and visual fixation, changes to breathing patterns and the production of sounds. From a physiological perspective, the researchers noted that the studies report variations in heart rate, blood pressure, breathing rate and oxygen saturation, all of which appear to be observed with a high level of consistency. Furthermore, in some studies, changes to both functional and metabolic brain activity were observed.

Given the variations in music type – biographical and non-biographical – and the range of responses recorded in these studies which did show potentially positive indicators, the researchers recommended that both in-depth qualitative studies and well-controlled quantitative studies are needed to determine the longer-term effects of music intervention in patients living with DoC.

A Qualitative Study – Interviewing Music Therapists

Ms Grimm and her colleagues conducted an interview-based study in which eleven trained music therapists working with patients living with a range of DoC participated.

In evaluation of the responses, the researchers concluded that therapists use a wide range of different strategies, all largely focused on the aims of the therapy. The therapists further explained that they respond and alter therapy by changing their singing or playing in response to even slight responses by the patient, such as changes to breathing. Some of the therapists found it not appropriate to turn on the radio in a patient's room and leave the room. The patients may be overstimulated. When the patient showed visual fixation or even eye contact, the therapists evaluated this as a sign of consciousness. It was found that in cases where the noted response was capable of being repeated, would therapists report efficacy of an intervention.

A Quantitative Study and the Future

Ms Grimm and colleagues have also undertaken a quantitative intervention study, which is still to be concluded. In this study, Ms Grimm is liaising with family members to determine patients' preferred musical choices and she is working directly with patients with DoC to introduce the musical intervention.

While the outcomes of this study are yet to be published, Ms Grimm highlights the ongoing challenges of this type of research, where the patient conditions vary across the spectrum of consciousness disorders, and their individual musical likes also vary, making the process complex. Nonetheless, findings will undoubtedly represent another important stride forward in the complex, challenging arena of improving care for patients with disorders of consciousness.

Meet the researcher

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Following the completion of her degree in cognitive linguistics, Ms Teresa Grimm undertook a series of internships in hospitals, where she specialised in neurological rehabilitation. Working with patients with disorders of consciousness (DoC) stirred Ms Grimm's interest in determining if the reactions to music that she had observed in these patients was incidental or repeatable and systematic. Ms Grimm then secured a PhD placement to conduct this work within the Department of Music at Carl von Ossietzky University. Having conducted a systematic review, a qualitative interview study with music therapists, and a quantitative study of patients with DoC, Ms Grimm has finalised the work for her PhD and is currently awaiting her viva voce.

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FURTHER READING

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CARL VON OSSIETZKY
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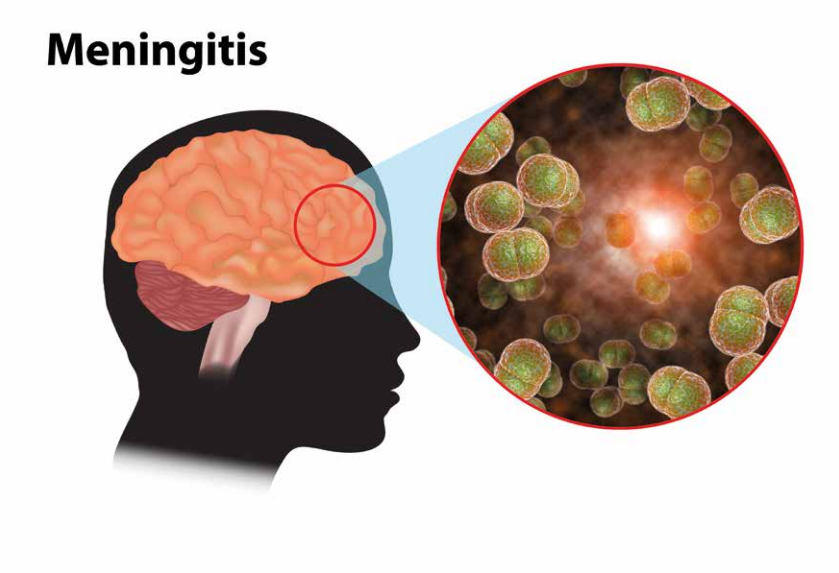
MENINGITIS RESEARCH FOUNDATION

Meningitis and septicaemia are serious, life-threatening illnesses that can kill within hours. The Meningitis Research Foundation (MRF) is the leading UK, Irish and international charity working to bring together people and expertise to defeat these diseases. In this exclusive interview, we speak with Vinny Smith, Chief Executive, to hear about their vital work, key achievements and future plans.



To begin, please tell us how the MRF came to fruition.

MRF was founded by a family who tragically lost their son to meningitis just over 30 years ago. Driven by this awful experience, they decided it was important to set up a charity that could raise awareness and increase research into the disease so that other families did not have to go through what they had.

You became the Chief Executive of the MRF in 2015, bringing with you a wealth of diverse leadership experience. What are your aims for MRF?

Our aims are driven by the families we support. They ask us to help prevent new cases, to ensure those who do get the disease are diagnosed and treated effectively by trained and resourced health workers, and to make sure people have the information, advice and support they need. We achieve this by enabling research that supports better policy and by transforming engagement in meningitis as an issue from global policy right down to individuals and the support they need. If we're successful, this will ensure MRF stays the world's leading meningitis charity.

What would you say are MRF's most important achievements to date?

When MRF was founded, outbreaks in the UK and Ireland were at far higher levels than they are today. Thanks to our work and our partners, rates in the UK and Ireland have come down significantly since then through the introduction of new and effective vaccines. This is an incredible achievement that we and our supporters played a major role in achieving. Over the past 3 years we built on this great platform and in November last year the World Health Assembly passed its first ever resolution on meningitis with a goal to defeat the disease by 2030. We led the calls for this to happen and have been instrumental in the process.

How does MRF support research? What types of research do you focus on?

We support research in four ways. By convening people and expertise through research conferences, meetings and the Global Meningitis Genome Partnership for which we are the secretariat. We directly fund research, for example, into genomics building on the success of the MRF Meningococcal Genome Library and Global Meningitis Genome Library. We partner on research into long term impact of meningitis in people's lives. And we create and share the best available data and evidence on progress being made against meningitis around the world through the Meningitis Progress Tracker.

How is the general public involved in your work?

Our supporters and public shape our whole strategy and approach. In the past three years they have been instrumental in guiding the priorities of the new global roadmap for meningitis and we have just finished consulting with them about our next 5-year strategy. They have also often been directly involved in research as participants in studies or trials. On top of that, they are the most incredible advocates for change, holding policy makers to account and demanding change.

We are, of course, in the midst of the COVID-19 pandemic. How has this affected the work of MRF?

As an organisation everything has changed. As with most other charities, our income has dramatically decreased for the time being because supporters cannot fundraise like they used to because of lockdown measures that have to be in place. This means we have had to reduce our investment in research, make some people redundant, move office, work from home, and put some work on hold as a result. But what drives us and what motivates our team and our supporters and the public hasn't changed at all. That's why, with their help, we're still here and with the news of coming vaccine programmes we continue to be optimistic about our work.

Finally, looking now to the future, MRF has the stated aim of defeating meningitis by 2030. What will this ambitious goal involve over the next ten years?

In short it requires the largest global collaborative effort for meningitis ever attempted. It will mean ending epidemics; dramatically reducing new preventable cases; and ensuring the people who do survive with after affects including disability get the support they need. This requires better use of and access to existing vaccines as well as new vaccines. It requires better diagnosis and treatment, including new rapid diagnostic tests. It requires better surveillance and data on the disease and its impact. It needs support for people living with the often lifetime impact of 'surviving'. It requires engagement, advocacy and awareness for policy makers and citizens to deliver change on the ground. And of course it will need funding – lots of it.

W: https://www.meningitis.org/
@M_R_F

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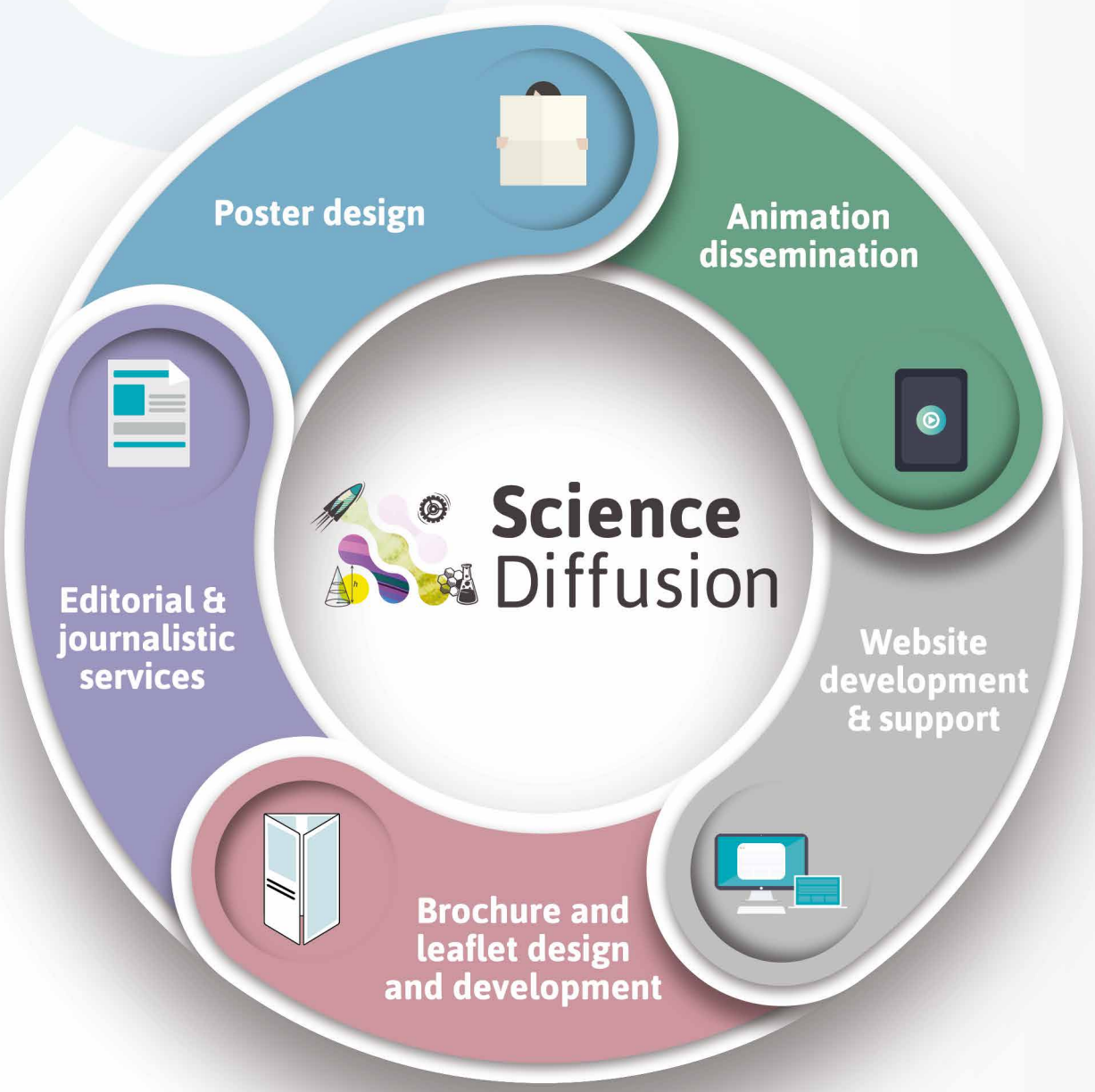

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worldwide cancer research

EVERY DAY, MILLIONS OF LIVES ARE TURNED UPSIDE DOWN BY CANCER

#LivesTurnedUpsideDown

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