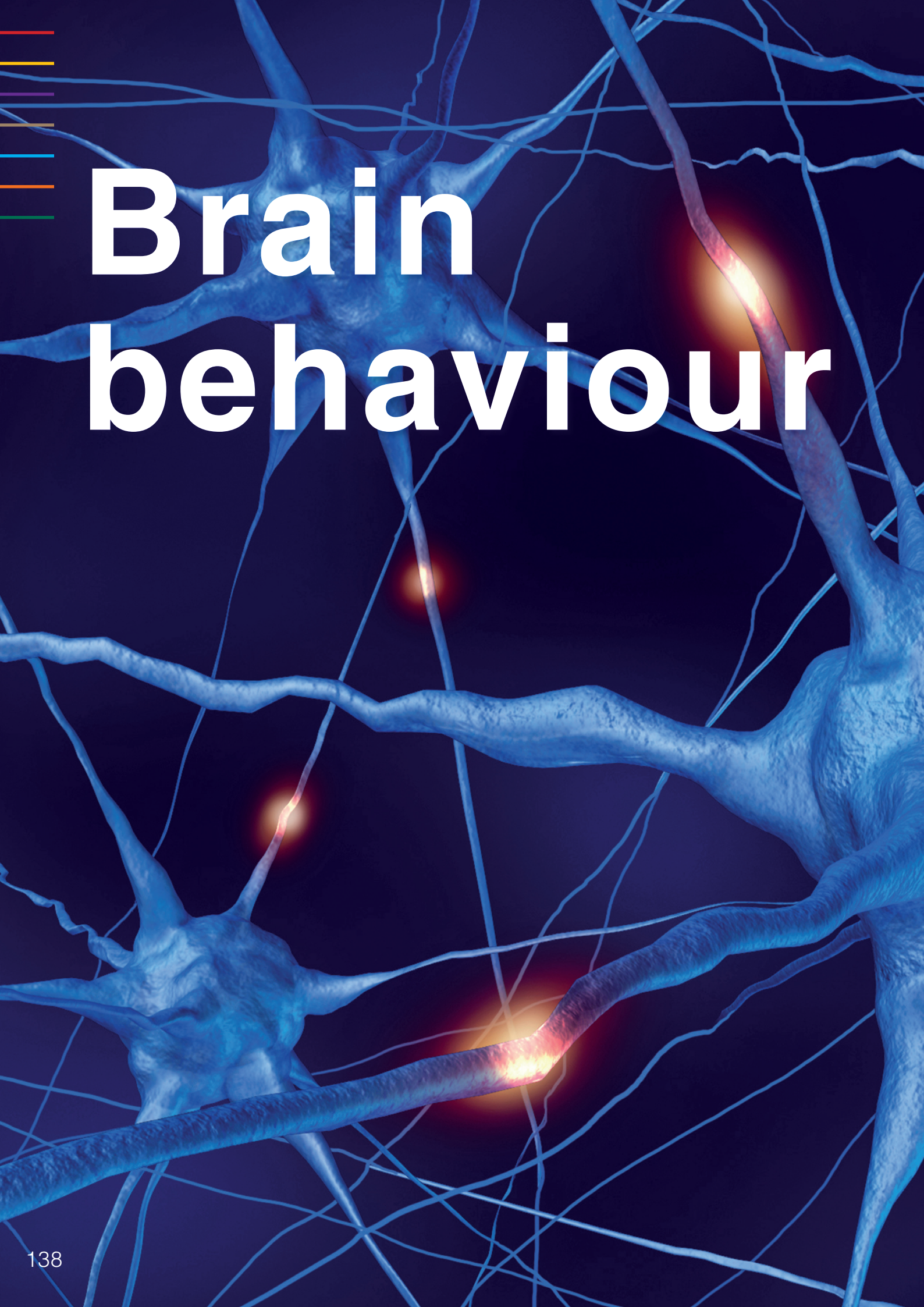
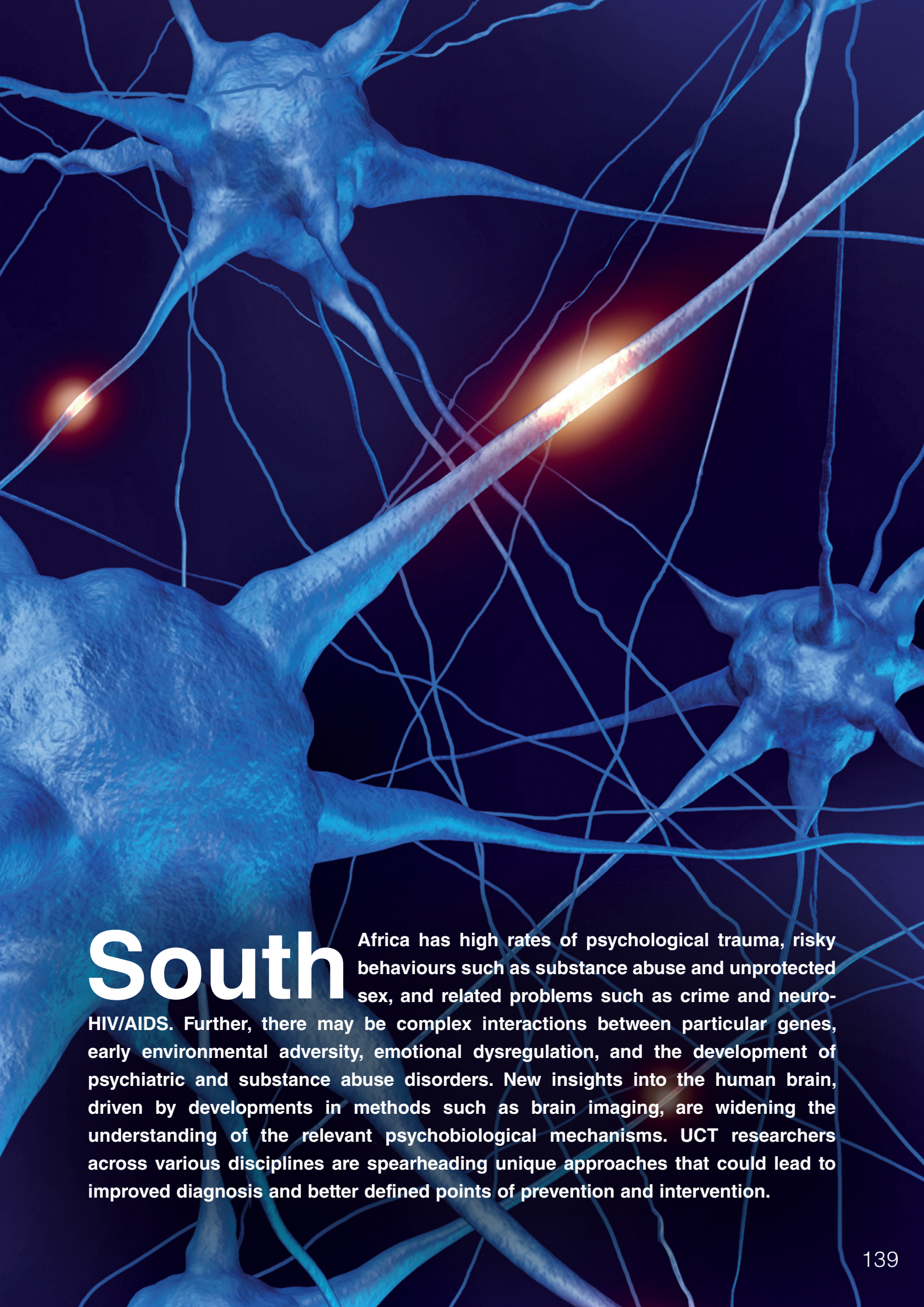


Brain behaviour



South Africa has high rates of psychological trauma, risky behaviours such as substance abuse and unprotected sex, and related problems such as crime and neuro-HIV/AIDS. Further, there may be complex interactions between particular genes, early environmental adversity, emotional dysregulation, and the development of psychiatric and substance abuse disorders. New insights into the human brain, driven by developments in methods such as brain imaging, are widening the understanding of the relevant psychobiological mechanisms. UCT researchers across various disciplines are spearheading unique approaches that could lead to improved diagnosis and better defined points of prevention and intervention.

The science of substance abuse and other social ills

The recently published United Nations World Drug Report named South Africa one of the world's drug capitals. Drug consumption in the country is twice the world norm, with 15 percent of the population having a drug problem, according to the Central Drug Authority (CDA). Substance abuse costs the country R20 billion a year, with one out of every four rand being spent on alcohol, dagga, and methamphetamine (tik).

Alcohol is the most abused substance in the country, affecting roughly 17,5 million South Africans. According to the CDA, these drinkers each consume the equivalent of 20,1 litres of pure alcohol every year. Perhaps not surprisingly then, South Africa also has the highest rate of foetal alcohol syndrome in the world, estimated to be between 122 and 148 instances for every 1 000 live births.

UCT researchers have documented high rates of exposure to psychological trauma in South Africans, as well as high rates of risky behaviour other than substance abuse, including unprotected sex and criminal behaviour. Furthermore, there are complex interactions between these phenomena; particular genes and early adversity may interact to create vulnerability for risky behaviour. Risky sexual behaviour may ultimately lead to the development of neuro-HIV, which in turn, may impact negatively on cognitive function and decision-making.

This range of problems is profound and complex, and has far-reaching social and economic implications. Recognising that most of these issues revolve around behaviour and that behaviour emerges in the brain, new thinking at UCT may provide some solutions to these entrenched social issues. At the core of this thinking is the belief that an integrated approach to understanding behaviour, that both draws on basic neuroscience and informs public health, is needed.

"These are complex problems that involve a range of molecular, neuroanatomical, psychological, and sociological mechanisms. In addition, the methods that we use to explore them are complex and so require a range of different expertise, from physics through to psychology."

The Brain and Behaviour Initiative (BBI) is a cross-faculty, multi-disciplinary, collaborative framework at UCT that promotes research in the cognitive and affective neurosciences. Under the directorship of Professor Dan Stein, Head of the Department of Psychiatry and Mental Health at UCT, the BBI is exploring new experimental techniques, combined with new theoretical insights, to make advances in diagnostic tools and treatments for people with mind-brain function disorders.

One of UCT's six signature themes, the BBI has three main thrusts of research: psychological trauma, substance abuse disorders, and neuro-HIV.

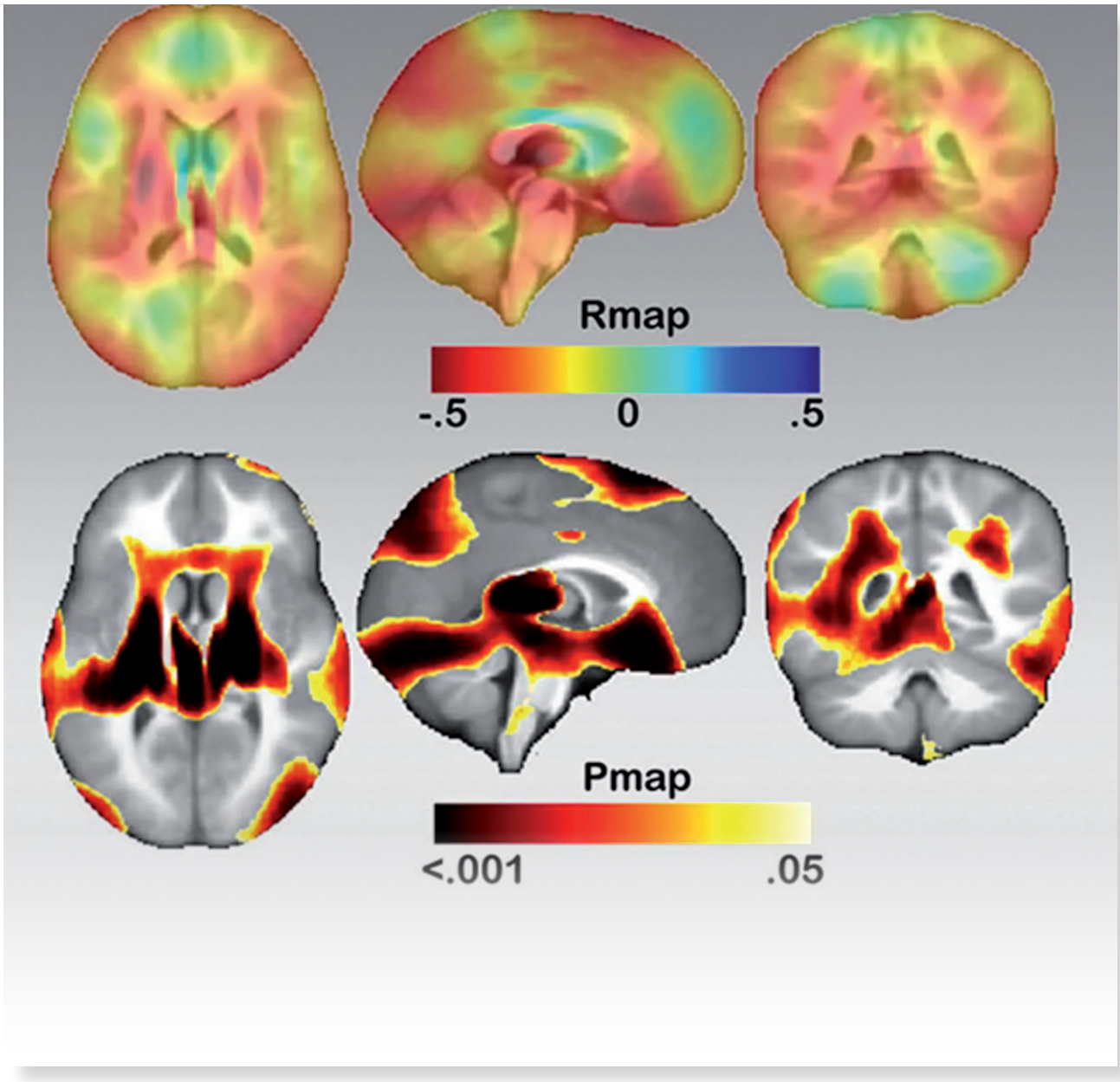
Making use of the latest in brain imaging technology, the BBI relies on cutting-edge techniques, such as cognotyping and genotyping, to demystify the inner workings of the brain. Major strides are being made in the field and opportunities are emerging in the battle against some of the country's most pressing social issues.

"These are complex problems that involve a range of molecular, neuroanatomical, psychological, and sociological mechanisms," says Professor Stein. "In addition, the methods that we use to explore them are complex and so require a range of different expertise, from physics through to psychology.

"Brain imaging has been a key method that has helped bring a range of different disciplines together, in order to explore research questions collaboratively," says Professor Stein. "Another focus has been on gene-environment interactions that allow us to look at issues of nature versus nurture."

Another discipline contributing to the study of the brain is economics, through the 10-year-old discipline known as neuroeconomics. Neuroeconomists model the circuit in the brain that computes comparative values of possible reward as a consumer, using economic theory. Its core method is experimentation in which people make economic choices while their brains are scanned using functional magnetic resonance imaging (fMRI).

This is one of the main activities of UCT's new Research Unit in Behavioural Economics and Neuroeconomics (RUBEN), located in the Faculty of Commerce and led by Associate Professor Justine Burns and Professor Don



This image shows regions where brain tissue volume in 10-year-old children is significantly reduced with increasing alcohol exposure. (Meintjes et al., Proc OHBM 2012, #6807.)

Ross. The RUBEN researchers are currently scanning the brains of another group of addicts – pathological gamblers – while these subjects try to control their emotional responses to monetary prizes.

Last year, researchers in the BBI, in collaboration with other institutions including Stellenbosch University and the University of Cambridge, published 14 brain and behaviour articles in peer-reviewed journals and a book, *Substance Use and Abuse in South Africa: Perspectives from Brain Behaviour and Other Disciplines*, is forthcoming through UCT Press in 2012.

With a commitment to keeping research current and relevant, and driven by the need to develop local understanding and local solutions to social issues, the BBI has a number of projects under way, the data of which should go a long way to inform prevention and intervention regarding substance abuse and related social ills in the country.

Psychology and digging for predictors

In order to define the points of intervention and prevention, the complex network of interrelated causes and effects of substance abuse and addiction needs to be fully understood.

Dr Kevin Thomas, of the UCT Department of Psychology, says strong theoretical frameworks and unique tests designed for accurate psychological measurements form the department's most important contributions to the BBI.

Signature theme associated with this theme

Brain and Behaviour Initiative (BBI)

The Brain and Behaviour Initiative (BBI) enables cross-faculty, multi-disciplinary, collaborative research in the cognitive and affective neurosciences, and brings together expertise on phenotyping, genotyping, cognotyping, brain imaging, and molecular signatures to address brain-behaviour issues. New experimental techniques include brain imaging, genetic testing, and neuropsychological assessment.

This, combined with new theoretical insights, has opened up significant potential for the advancement of novel diagnostic tools and treatments for people with mental disorders. The initial focus on trauma and resilience has extended to work in substance use and Neuro-HIV.
Director: Professor D. Stein *E-mail*: Dan.Stein@uct.ac.za *Web*: http://www.health.uct.ac.za/research/groupings/bbi/overview/

"In order to define the points of intervention and prevention, the complex network of interrelated causes and effects of substance abuse and addiction needs to be fully understood."

"We're working at the cutting edges of theoretical frameworks," says Dr Thomas. "What we are looking for is a range of predictors – the biological and psychological reasons for addiction and substance abuse – to create models to understand who is likely to be an addict and who is not."

A major component of this is having accurate, relevant data or measurements.

"To find out why people behave the way they do, or how early childhood trauma and neglect affects them as adults, or what the connection is between decision-making capabilities and substance abuse, we need measurements," says Dr Thomas. "We need to design complex tests that accurately capture even the subtlest of cognitive functions and emotions."

These types of tests produce valuable data that are combined with theoretical insights to create what is called cognotypes – patterns of weaknesses and strengths in cognitive processes. Different disorders have particular strengths and weaknesses in decision-making, reasoning, judgement, language, attention, and memory. Substance abusers, for example, have impaired decision-making capabilities, not while on the drug necessarily, according to Dr Thomas, but people with these inefficiencies are more likely to become addicts – hence the vulnerability of adolescents whose decision-making tools are not yet fully developed.

Cognotyping is used to form the basis for diagnosis of psychological and psychiatric disorders. A person's cognitive strengths and weaknesses form a pattern and this pattern correlates to different disorders.

"What is so interesting now in neuroscience is that we have the tools to see what's happening in the brain; we can measure heart rate, skin conductance systems, eye movements. At this point, we can see into the entire body and watch how it responds to its environment. That was not possible 20 years ago," says Dr Thomas.

Imaging the brain: snapshots of cognition

The ability to see into the human brain is made possible by magnetic resonance imaging (MRI) and Associate Professor Ernesta Meintjes, of the Department of Human Biology, is using the technology to study brain development in children with foetal alcohol spectrum disorders.

"We look at different brain circuits to try to understand what is going wrong and where the damage is," says Associate Professor Meintjes, holder of the DST/NRF SARChI Chair in Brain Imaging, based at the UCT medical campus.

The longitudinal study is based on findings from a cohort of children and their mothers from Hanover Park, who were recruited when the mothers were pregnant almost eleven years ago. Researchers, professors

"At this point, we can see into the entire body and watch how it responds to its environment. That was not possible 20 years ago."

Research groupings associated with this theme

Albertina and Walter Sisulu Institute of Ageing in Africa

The Albertina and Walter Sisulu Institute of Ageing in Africa is a cross-disciplinary group within the Department of Medicine in the Faculty of Health Sciences and incorporates the divisions of Geriatric Medicine, Geriatric Neuropsychology, Geriatric Neurosciences, Geriatric Psychiatry, and a Gerontology programme. The institute strives to be an academic and research centre of excellence that addresses critical issues of ageing in Africa, and serves as a catalyst for local, national, and regional expertise and a focal point for the development of research services and training. Its mission is achieved through inter-disciplinary and cross-national partnerships and research collaboration, human resource development, and policy information in the national context and on the African continent. Areas in which research projects are currently conducted at the institute include physical, cognitive and social functioning, and quality of life; vascular risk factors and stroke; falls in older persons and quality of care; and dementia and risk factors for cognitive disorders.
Director: Dr S. Kalula
E-mail: Sebastiana.Kalula@uct.ac.za
Web: http://www.instituteofageing.uct.ac.za

MRC/UCT Human Genetics Research Unit

The group's current focus is on the genetics of colorectal cancer, inherited forms of blindness, and neuropsychiatric diseases. Recent breakthroughs include identifying the genetic basis of retinitis pigmentosa and developing therapeutics to stem loss of vision in individuals shown to carry the disease-causing mutation. A greater effort is being put into engaging with high throughput technologies and the mapping of genes for common chronic disorders.
Director: Professor R. Ramesar
E-mail: Raj.Ramesar@uct.ac.za
Web: http://www.health.uct.ac.za/research/groupings/hgru/

MRC/UCT Medical Imaging Research Unit

The mandate of the Medical Imaging Research Unit (MIRU) is to conduct world-class research in medical imaging that specifically addresses the healthcare needs of Africa. Although located in the Western Cape, the MIRU sees itself as a national facility, with the responsibility of providing an imaging platform that is available to the wider research community in the country. Its research focuses on the role of medical imaging in addressing problems such as trauma, cancer, tuberculosis, HIV/AIDS, neuromuscular disorders, cardiovascular disease, and alcohol abuse; all of which pose serious threats to public health in South Africa. In addition to using established techniques to address local healthcare needs, the MIRU is developing novel imaging methods, in areas such as magnetic resonance imaging, mammography, and microscopy, which are appropriate for our national context but that will also find application in the rest of the world. The unit has strong collaborative links with Western Cape hospitals, the local medical device industry, and international institutions.
Director: Associate Professor T. Douglas
E-mail: Tania.Douglas@uct.ac.za
Web: http://www.miru.uct.ac.za/

Sandy and Joe Jacobson, from Wayne State University (USA) and Emeritus Professor Chris Molteno from UCT, have followed the cohort closely, capturing a rich history, including how much the mothers drank at different stages during their pregnancy. For the past three years, these and other children have been scanned on numerous occasions, while doing functional tests and the findings are yielding interesting insights into foetal alcohol syndrome.

"We have found, for instance, that the parts of the brain that healthy children and normal adults would use for maths processing – a region that also handles other functions – does not work well in children with foetal alcohol syndrome. What we are seeing is that they use the whole brain instead, compensating for those parts that do not work," says Associate Professor Meintjes.

Another study is currently being undertaken to look into the protective effects of maternal choline (an essential nutrient) supplementation on foetal development. It has been shown that choline, given to pregnant rats, actually protected the foetus. As such, a new study involving infant imaging will test these protective attributes in human subjects, to establish if it has significant impact on babies born to alcoholic mothers.

DST/NRF SARChI Chairs associated with this theme

Brain Imaging

Associate Professor Ernesta Meintjes completed her undergraduate studies at the University of KwaZulu-Natal, Pietermaritzburg, and master's and PhD degrees in Physics at Oregon State University, USA. Since July 2000, she has been employed as a research officer and lecturer in the Department of Human Biology and in 2007 was awarded the DST/NRF SARChI Chair in Brain Imaging. Her current research focuses on magnetic resonance imaging methods development and application. She has significant expertise in prospective motion correction and application of these methods to study brain development in children with foetal alcohol spectrum disorders and HIV infection, and in the study of cardiac disease.

Clinical Neurosciences Research

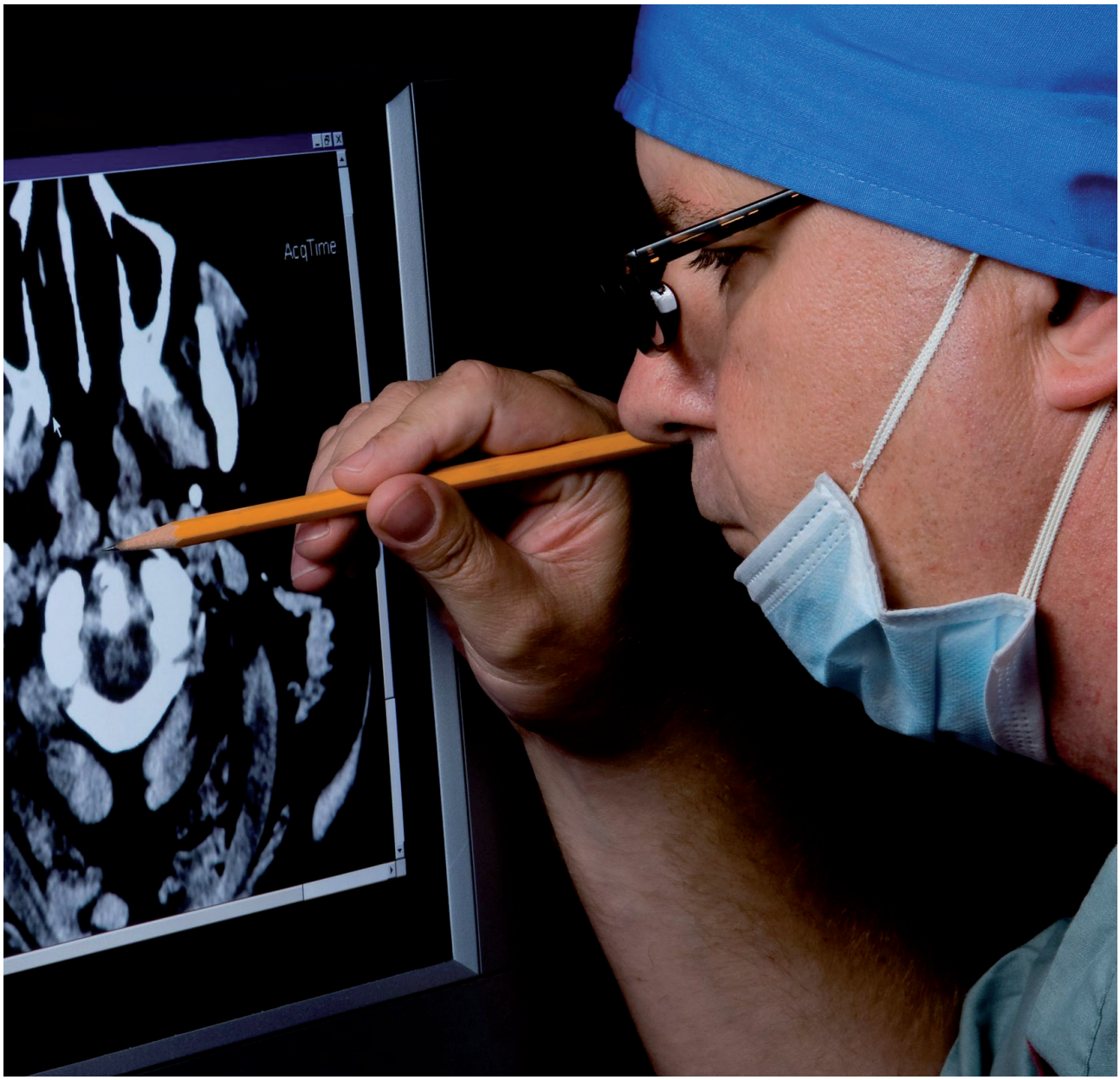
Associate Professor Marc Combrinck is a neurologist who trained in medicine and biochemistry at the University of Cape Town and Groote Schuur Hospital. He was a research fellow at the University of Oxford before returning to South Africa in 2004. His research interests lie in dementia, neuro-inflammation, and mechanisms of neuro-degeneration. He continues this work in Cape Town, using clinically based observational studies of cognitive impairment in the elderly and in HIV-associated brain disorders. In 2011, Associate Professor Combrinck was also appointed to the prestigious William Slater Chair of Geriatric Medicine, the first endowed chair in the subspeciality of geriatric medicine in South Africa.

DNA and diagnosing brain states

Across campus, in the Faculty of Science, the Department of Molecular and Cellular Biology is applying another well-established animal model to find out whether the cells in the immune system retain information of early-life stress. This research, if successful, will have major implications for diagnosis of cognitive and psychological disorders in humans.

"We already know that there is a constant interaction between the immune system and the brain. The question is, if something happened to you as a child, how does that then translate into behaviour in adulthood? There must be some imprinting of that early childhood stress," says the department's Professor Nicola Illing.

A study was done on mice to see whether this epigenetic modification – imprinting of stress in the cell – could be picked up in the circulating immune cells. Mouse pups were separated from their mothers every day for a month until they were weaned. Once adults, these stressed mice were contrasted against a group that had a 'happy upbringing' and it was found that the stressed mice were indeed stressed and behaved differently to otherwise normal mice. The immune cells from those mice were analysed for the expression of messenger RNA transcripts – essentially a read-out of what is expressed in the cells.



The ability to see into the human brain is made possible by magnetic resonance imaging (MRI). UCT is growing its expertise in this area and is home to the DST/NRF SARChI Chair in Brain Imaging.

Analysis showed that there was a difference between the two groups of mice, and that the early-life stress could be picked up in messenger RNA. To test this using a human model, blood samples from non-tik users, tik users, and tik users who are also psychotic, have been collected to investigate whether there are changes in DNA, RNA, and proteins in their immune cells.

"We're going to look at repeating what we did in the study of mice in this controlled situation and see if there's a difference between these groups in terms of what the immune cells are doing," says Professor Illing. "The possibility of using non-invasive means for diagnosing psychological states is truly ground-breaking."

As the complexity of the human brain unfolds through the work of the Brain and Behaviour Initiative at UCT, and as new methodologies allow researchers to find clear links between the brain and behaviour, solutions to a vast range of South Africa's social problems could emerge, and energies can then be used on measures of prevention and intervention.

"Given the relationships between research and development, and between research and good clinical care, it is important that solid research is conducted here at UCT that will inform our approaches to solving the complex social issues we face in South Africa," Professor Stein says.