Neuroscience has a “frontier” feel to it. The most complex organ in the body, the brain represents the ultimate challenge to many researchers and its study requires particular sophistication. Through a transdisciplinary approach that connects cutting-edge technology with a wide range of different scientific disciplines, basic and clinical neuroscientists at UCT are tapping into local opportunities and advancing research that has benefits for communities both in Africa and internationally.
A NEW VIEW OF THE BRAIN: RELYING ON TRANSDISCIPLINARITY

The vast majority of brain and behavioural research worldwide has been done in WEIRD populations: that is, in regions of the world that are westernised, educated, industrialised, rich and democratic. Only a minority of such work has happened in African populations, despite the rich diversity of the continent’s genes and cultures.

In addition, there is a major research gap when it comes to the mental health of African populations. More than 95% of research publications in the area of psychiatry emerge from high-income countries, even though the majority of those suffering from common mental disorders live in low- and middle-income countries.

There is therefore enormous scope for basic and clinical neuroscientists in South Africa, not only to verify and corroborate existing data, but to add new information and take the field in novel directions. For example, there is a key opportunity for UCT researchers to study neuro-HIV, substance disorders, trauma- and stressor-related disorders, psychotic disorders and neurodevelopmental disorders. Given that the demographics of Africa are slanted towards the youth, and given the early age of onset of these disorders, there is a particular need to examine them early in life.

At the same time, the brain is enormously complex. To find answers to the most pressing questions within these areas, UCT scientists are embracing an inter- and transdisciplinary approach to research. Interdisciplinarity is an increasingly powerful approach to research that crosses disciplinary boundaries to create an holistic approach to data collection. It applies to research efforts focused on problems that cross the boundaries of two or more disciplines. Transdisciplinarity is an emerging idea in research that can suggest an even tighter synthesis creating a new intellectual framework, but is also applied to activities that reach outside the academic research environment to act in partnership with non-academic collaborators.

Brought together by developments in cutting-edge technology, such as brain imaging, experts from a number of different disciplines are able to frame problems collectively, acquire and interpret data, and generate significant findings that are reliant on and relevant to the local context.

THANKS TO A SINGLE INSTRUMENT, WE HAVE BEEN ABLE TO BRING TOGETHER A TEAM THAT HAS SPARKED COLLABORATION AND RESEARCH THAT WOULDN’T OTHERWISE HAVE HAPPENED.

A CROSS-FACULTY COLLABORATIVE APPROACH

Leading some of UCT’s most meaningful work in basic and clinical neuroscience is the Brain and Behaviour Initiative (BBI). One of the university’s six Signature Themes, the BBI has three main arms of research: psychological trauma, substance use disorders and neuro-HIV.

Committed to a cross-faculty, collaborative approach to research in the cognitive and affective neurosciences, the BBI is not only generating new research data, but also creating a new framework within which scientists can achieve results. Many students in the BBI have supervisors from different departments and disciplines. In the last year, this interdisciplinary approach led to 27 peer-reviewed journal articles and one patent.

With technology such as the Siemens 3 Tesla Magneton Allegra, housed at the Cape Universities Brain Imaging Centre (CUBIC) (see p125), BBI scientists integrate brain-imaging data, genetic testing and neuropsychological assessment in the hope of gaining new insights into key basic and clinical questions of relevance to South Africa and the continent.

“Brain-imaging technology has been essential for the success of the BBI project, as well as for the research productivity of a very diverse multidisciplinary team of basic and clinical scientists,” says BBI director Professor Dan Stein.

“Thanks to a single instrument, we have been able to bring together a team that has sparked collaboration and research that wouldn’t otherwise have happened. In that way, we are facilitating conversations between different experts in different departments,” says Professor Ernesta Meintjes, who holds the DST/NRF SARChI Chair in Brain Imaging, located in the Medical Research Council (MRC) Medical Imaging Research Unit in the Department of Human Biology.

In neuroscience, understanding the structural and functional aspects of the brain and its development increasingly relies on the integration of multiple methodologies. Similarly, brain-imaging studies may require a successful conversation between imaging scientists, neuropsychologists and clinicians.

A co-ordinated research effort is required from start to finish, with psychiatrists generating patient samples, psychologists developing the paradigm that is measured during imaging, geneticists gathering DNA data on subjects being examined,
The Siemens 3 Tesla Magnetom Allegra is a compact, dedicated brain MRI scanner. The Siemens 3 Tesla Magnetom Allegra is a compact, dedicated brain MRI scanner.
The findings are consistent with international studies that also showed no association between ART-regimen CPE and cognitive outcomes. Locally, the study gives reassurance to clinicians, as South Africa’s current low CPE-scoring first-line regimen performed as well as higher CPE-scoring regimens.

This study forms part of a collaborative research programme into HIV-associated neurocognitive disorders by the departments of Psychiatry, Psychology, Neurology and Geriatric Medicine. According to study partner Professor Marc Combrinck from the Division of Geriatric Medicine, the value of this body of information extends to a broader understanding of cognitive impairment.

“Investigating the role of inflammation of the brain resulting from infections in the body, such as HIV, contributes to how we understand neurodegeneration that occurs both in HAND and in the degenerative disorders of older persons such as Alzheimer’s disease,” says Professor Combrinck.

“Although they work in different ways, the theme seems to be the same in both groups. If we can somehow limit the inflammation, we could potentially retard or slow the progression of neurodegenerative diseases.”

While studies have been done internationally to support the link between inflammation and Alzheimer’s disease, the application of that thinking is a first for South Africa. “We are certainly the first people to look at this question on the continent and particularly in South Africa, where we have a high rate of HIV infection and systemic infections in general,” says Professor Combrinck.

DRUGS AND THE DEVELOPING BRAIN

HIV infection is just one influence on neurodevelopment being investigated by UCT scientists. The effects of substance abuse are also a significant focus, with a particular interest in the impact on prenatal children and young adolescents.

Animal studies have shown that methamphetamine (MA) crosses the placenta of MA-exposed pregnant rodents, affecting the developing foetus and, in particular, the central nervous system (CNS). Furthermore, human studies have shown that MA crosses the human placenta, as well as the blood-brain barrier, to exert effects on the foetal brain.

“The CNS development and maturation require a carefully patterned sequence of events and processes, more complex and extending over a longer period than any other organ system. Thus, the CNS is particularly vulnerable to prenatal environmental influences,” says Dr Kirsten Donald from the Division of Developmental Paediatrics in the Department of Paediatrics and Child Health.

With very few studies having looked at the longitudinal effects of substance exposure on the developing brain, Dr Donald has published work in the journal Metabolic Brain Disease in January 2014 using brain-imaging technology to identify potential changes in brain volumes and cortical thickness of six-year-old children from the Western Cape with prenatal MA-exposure.

COMBINING THE EXPERTISE OF A RANGE OF DISCIPLINES ALLOWS AN INTEGRATED AND FAR MORE SOPHISTICATED APPROACH TO THESE ISSUES.

“Measuring functional brain development is difficult, both because the brain is a complex, hierarchical system and because few non-invasive methods are optimised for infants and young children,” says Dr Fleur Howells, a lecturer in neuroscience in the Department of Psychiatry and Mental Health, who is interested in the translation between basic and clinical neuroscience, and who has collaborated with Dr Donald.

The research done by a team of cognitive and neuroimaging neuroscientists, paediatric neurologists, developmental paediatricians and psychiatrists reveals that in-utero exposure to MA results in structural changes, mainly of striatal, parietal and temporal areas, with measurable differences between genders. In light of a global increase of MA use, this study is an example of the strategic placement of UCT to counteract a global dearth of research. This is not only because MA use is prevalent in South African communities, but also because the university has access to expertise and technology that makes investigating complex brain systems possible.

“Transdisciplinary collaboration is a huge advantage in this field, where an understanding of structural and functional aspects of brain development cannot be addressed using a single-dimension approach,” says Dr Marcin Jankiewicz, director of CUBIC.

“Combining the expertise of a range of disciplines allows an integrated and far more sophisticated approach to these issues, both in terms of the methodology used to investigate neurological and functional effects of environmental exposure on early brain development, and by providing a broad context for interpretation of these findings and their potential significance,” concurs Professor Colleen Adnams, head of the Division of Intellectual Disability in the Department of Psychiatry and Mental Health, who, like Professor Meintjes, has made major contributions to understanding the effects of alcohol on the developing brain.

A DIFFERENT KIND OF GENE POOL

Genetics plays a part in this collective approach to brain development research. Shareefa Dalvie, a PhD student in the Division of Human Genetics, supervised by its head, Professor Raj Ramesar, examines how genes interact with environmental measures to impact on brain volumes in adolescents with alcohol-use disorders (AUDs).

“Previous studies have indicated that early-life adversity, genetic factors and alcohol dependence (AD) are associated with reduced brain volume in adolescents,” says Dalvie. “However, data on the interactive effects of early-life adversity, genetic factors and AD on brain structure in adolescents are limited.”

To decode this, Dalvie is examining whether specific polymorphisms in particular candidate genes interact with childhood trauma to predict alterations in brain volume in adolescents with AUD. Combining genetics with neuroimaging and psychology, researchers assess participants for trauma using the Childhood Trauma Questionnaire in conjunction with brain-imaging results.

Although this investigation is currently in progress, the work adds to research Dalvie has already done in understanding AUD in the South African population. Alcohol use is prevalent in the Western Cape, and so she has published on genetic polymorphisms that may increase risk in this population.

Despite the pervasive problem of AUDs, Dalvie says there has been a paucity of previous research investigating genetic variants associated with this phenotype in a
South African population. Her work therefore serves to increase the body of evidence investigating genetic variants and alcohol-use disorders in genetically admixed populations.

Various other doctoral students and postdoctoral fellows are also engaged in studies of genetics that are adding to body of work at UCT. Dr Natasha Koen, program manager of the BBI, is doing her PhD in the area of the genetics of post-traumatic stress disorder (PTSD). Her project has attracted funding from the National Institutes of Health, and indeed, the range of funding obtained by different BBI investigators attests to the novelty and significance of this work.

Professor Jack van Honk, a lecturer in the Department of Psychiatry and the Institute of Infectious Disease and Molecular Medicine, confirms the value of studying South African populations. He has studied people with Urbach-Weithe disorder, a genetic condition that is associated with amygdala damage and is more commonly found in South Africa than elsewhere. His work has led to new insights into brain plasticity, and has been published in a range of prestigious journals (see p131).

Various other doctoral students and postdoctoral fellows have helped strengthen brain imaging locally. These include Dr Samantha Brooks from the UK and Dr Paul Taylor from the USA, each of whom has unique skills. Other postdoctoral research fellows, such as Dr Joe Ramondo and Dr Jonathan Ipser, have returned to South Africa after stints abroad. A European and South African Research Network in Anxiety Disorders (EUSARNAD) grant has been particularly helpful in encouraging academic exchange such as these (see p130).

An international research exchange involving the University of Southampton, UCT and 11 other institutions, EUSARNAD aims to develop a greater understanding of anxiety disorders and develop more effective treatments for patients by using non-specialist health workers to treat mental disorders in Africa. AFFIRM’s work will contribute towards models of how to deliver low-cost mental health interventions, which will ultimately inform ministries of health across Africa. It is also building capacity in the area by funding fellowships for students from Ghana, Ethiopia, Uganda, Malawi and Zimbabwe to complete an MPhil in Public Mental Health at UCT.

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Associate Professor Crick Lund and his team at the Alan J Flisher Centre for Public Mental Health, of which he is director, are looking at ways of narrowing this gap. One such project is AFFIRM (Africa Focus for Intervention Research in Mental Health), part of a global drive to find low-cost interventions

LOCAL PROBLEMS, GLOBAL IMPACT

Much of this research involves collaborating, not only across disciplinary boundaries, but also across geographical boundaries.

It is notable that students from a number of different countries have been attracted to the BBI. Several international postdoctoral fellows have helped strengthen brain imaging locally. These include Dr Samantha Brooks from the UK and Dr Paul Taylor from the USA, each of whom has unique skills. Other postdoctoral research fellows, such as Dr Joe Ramondo and Dr Jonathan Ipser, have returned to South Africa after stints abroad. An international research exchange involving the University of Southampton, UCT and 11 other institutions, EUSARNAD aims to develop a greater understanding of anxiety disorders and develop more effective treatments for patients.

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PRIZE WINNER SEeks WAYS TO ROLL OUT LOW-COST MENTAL HEALTH CARE IN AFRICA

There is currently just one psychiatrist for every two million people on the continent, and one psychologist for every two-and-a-half million. At least 75% of people living with mental disorders in low- and middle-income countries have no evidence-based mental health care. “If you were to only use specialists to treat mental disorders in Africa, the queue would stretch halfway across the continent,” says Associate Professor Crick Lund of the Department of Psychiatry and Mental Health.

Associate Professor Lund and his team at the Alan J Flisher Centre for Public Mental Health, of which he is director, are looking at ways of narrowing this treatment gap. One such project is AFFIRM (Africa Focus for Intervention Research in Mental Health), part of a global drive to find low-cost interventions

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“Through collaboration, we can use research to inform the scaling up of mental health services in African countries, so that we can provide African ministries of health with models to deliver low-cost mental health interventions,” says Associate Professor Lund. His work, along with that of his colleagues, is also funded by the Department for International Development (DFID) in the UK and by the European Union, and has played an important role in influencing South Africa’s recently published mental-health policy.

**BETTER UNDERSTANDING OF THE BRAIN**

The value of basic and clinical neuroscience research to inform better standards of care is not limited to public mental health. Across the UCT campus, a good deal of work is being done to better understand the brain to enhance health outcomes.

Professor Anthony Figaji, head of the Paediatric Neurosurgery Unit in the Division of Neurosurgery, is doing exciting work in the area of paediatric neurosurgery. Internationally recognised for his work in the management of acute brain injury in children, he is currently also the head of Paediatric Neurosurgery at the Red Cross War Memorial Children’s Hospital.

With a focus on coupling clinical expertise with innovative technology, Professor Figaji’s work aims to improve the care of patients in acute coma and to grow the discipline of neurocritical care in South Africa. His work has initiated a comprehensive intraoperative neurophysiological monitoring programme to increase the safety of operating on tumours in high-risk areas of the brain and the spinal cord, which was previously unavailable in South Africa.

Professor Mark Salms, head of the Department of Psychology in the Faculty of Humanities, has brought together psychoanalysis and neuroscience in seminal ways. One example is the work of Dr Melike Fourie, a postdoctoral fellow working with professors Salms, Stein and Pumla Gobodo-Madikizela of the University of the Free State, on mapping the brain’s empathetic response to expressions of forgiveness and remorse in post-apartheid South Africa by exposing participants to similar scenarios to those seen at the hearings of the Truth and Reconciliation Commission (TRC).

Dr Fourie and her colleagues recently published a paper on how people who suffered significant childhood maltreatment may differ in their responses to empathy-inducing stimuli from individuals who did not experience childhood hardship.

Professor Don Ross, the Dean of Commerce, is developing the area of neuroeconomics at UCT — a field that brings together ideas and methods from neuroscience and economics to address key areas of relevance to South Africa, including substance use disorders and gambling.

In collaboration with Professor Harold Kincaid, another A-rated scholar in the School of Economics, Professor Ross has revealed interesting similarities between gambling and addiction in South Africa and in the developed world. The results of their study examining gambling and addiction in the informal settlement of Khayelitsha show that the apparently high levels of pathological gambling in the community most likely reflect boredom owing to unemployment, rather than a true public health problem.

“As a very interesting sidelight of the project, quantitative estimates of risk preferences, based on experiments, found that the distribution of these preferences among Khayelitsha adults was very similar to what we observe in samples from rich countries,” says Professor Ross. “That is, the overwhelming majority of subjects were moderately risk-averse. This is contrary to widespread expectations that poverty generates a wide range of relatively extreme responses to risk, from extreme risk aversion to recklessness.”

This is just one more example of how research in an African context is helping to enrich a global understanding of the brain and human behaviour that is being translated into better treatment and better outcomes for people in a variety of contexts. Indeed, given that Africa, and particularly South Africa, has one of the most diverse human populations in the world, large-scale studies of disease and disorder should be carried out using African samples. Considering their vast expertise, access to cutting-edge technology and track record of collaborative research leadership, it stands to reason that UCT scientists are the ideally placed partners in the future of basic and clinical neuroscience discovery.

**A CO-ORDINATED RESPONSE TO ANXIETY DISORDERS**

UCT is playing a major part in improving knowledge about anxiety disorders on an international scale. Through a partnership with the European and South African Research Network in Anxiety Disorders (EUSARNAD), the university is facilitating an international research exchange that aims to develop a greater understanding of these disorders and more effective treatments for patients.

The backbone of any effective treatment is rigorous, empirically tested data and a dedicated research team, according to EUSARNAD. To support this, the project brings together researchers from UCT and 11 other institutions to produce first-rate research. By placing individual exchange researchers in institutions with novel populations and methodologies, this international collaboration allows for greater attention to important questions about anxiety. The result is a stronger body of data that can be used to inform more effective care.

The EUSARNAD initiative was first launched in 2011 by David Baldwin, professor of psychiatry at the University of Southampton and honorary professor in the Department of Psychiatry and Mental Health at UCT, as the Anxiety Disorders Research Network. The collaboration originated within the network of a number of leading research centres in Europe and with support from the European College of Neuropsychopharmacology.

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**LARGE-SCALE STUDIES OF DISEASE AND DISORDER SHOULD BE CARRIED OUT USING AFRICAN SAMPLES.**

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**NEW INSIGHT INTO THE ROLE OF THE “SOCIAL BRAIN”**

Research led by Professor Jack van Honk from the Department of Psychiatry and Mental Health and the Institute of Infectious Disease and Molecular Medicine, together with collaborators from the Netherlands and a range of other countries, has brought new insight into the role of the amygdala or “social brain” through investigating a rare genetic developmental disorder that is found in South Africa.

Urbach-Wiethe Disease (UWD) has been reported in a community in the Namakauland region, where 40% of the world’s approximately 100 reported cases of the condition are found. Studying five female patients, Professor von Honk examined lesions of the basolateral amygdala characteristic of the disease to reveal that it made the patients hypersensitive for fearful expressions.

The findings have important implications for the understanding of the basolateral amygdala’s role in an array of social behaviours, and especially its role in fear and anxiety disorders. Furthermore, they highlight the value of brain-imaging capabilities and the importance of UCT’s geographic location.

“Cultural neuroscience holds promise for South Africa, given the genuine cultural diversity of the population and the modern neuroimaging infrastructure in Cape Town,” says Professor von Honk, an NRC A-rated scholar, who published his work on UWD in *PNAS* (Proceedings of the National Academy of Sciences of the United States of America), one of the world’s most prestigious scientific journals, last year.