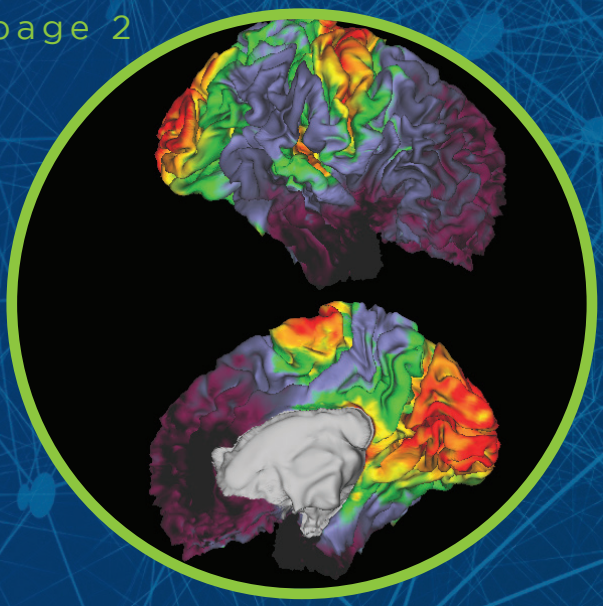
UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

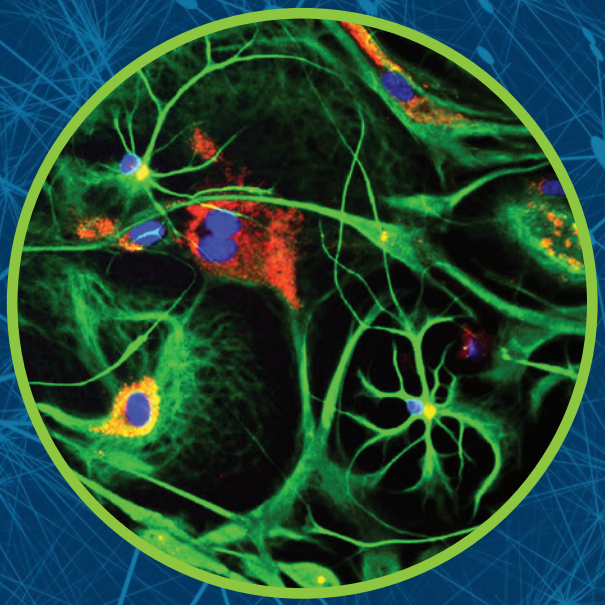
Neuroscience Institute

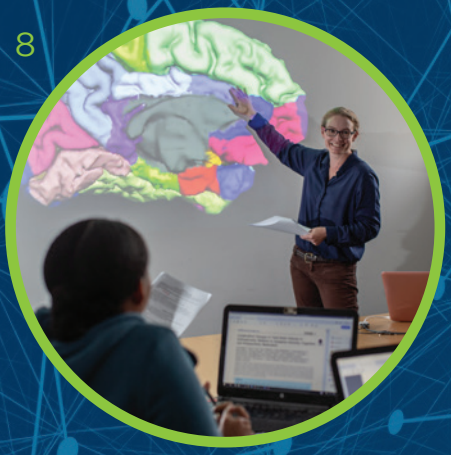
Research Strategy

2022 – 2026

CONTENTS

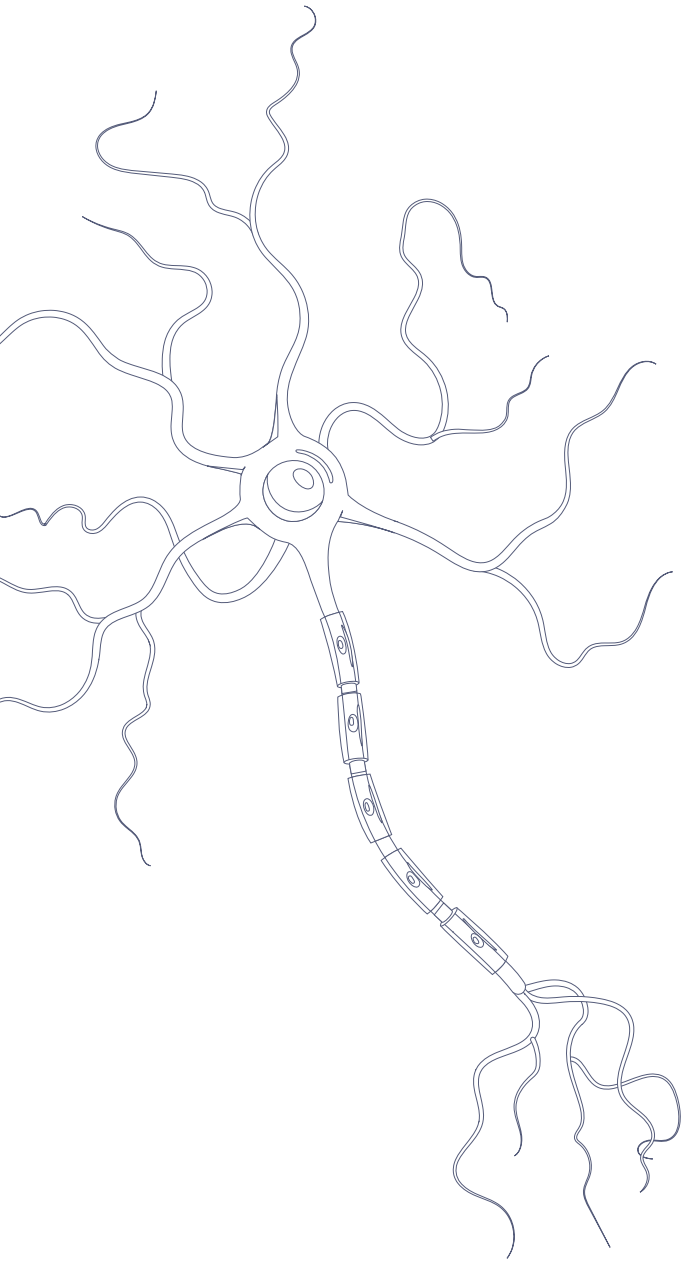






Vision and Mission

Our vision is an Africa where people achieve their full potential through brain health. Our mission is to advance research, training, and advocacy through an interdisciplinary network of scientists and clinicians, sharing skills and expertise to improve lives and advance our understanding of the human brain.



Our home and heritage

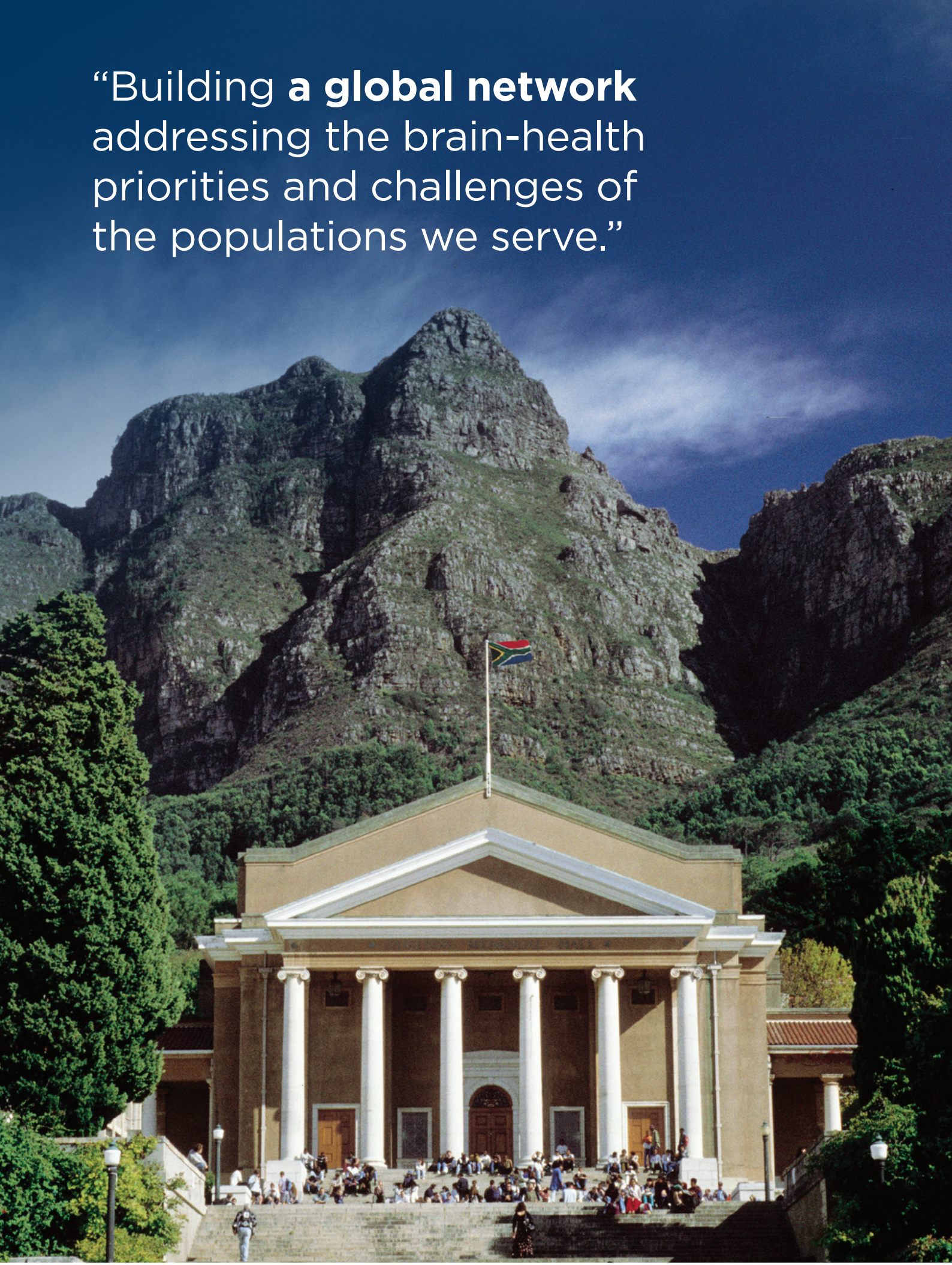
The Neuroscience Institute (NI) was accredited as an interdisciplinary research institute by the University of Cape Town in 2015, building on a legacy of high-impact research programmes in the Faculty of Health Sciences. Jointly funded by the university, the provincial government, and philanthropic donors, the NI is situated on the Groote Schuur Hospital campus and is integrated with the hospital's first-rate clinical platform. This includes the leading children's hospital in Sub-Saharan Africa, the Red Cross War Memorial Children's Hospital.

This inspirational setting attracts researchers and clinicians from across the region, building a global network addressing the brain-health priorities and challenges of the populations we serve. In aligning with UCT's Vision 2030, and the United Nation's Sustainable Development Goals (SDGs), we strive to be a world-class research institute, contributing to a better future for Africa's people.

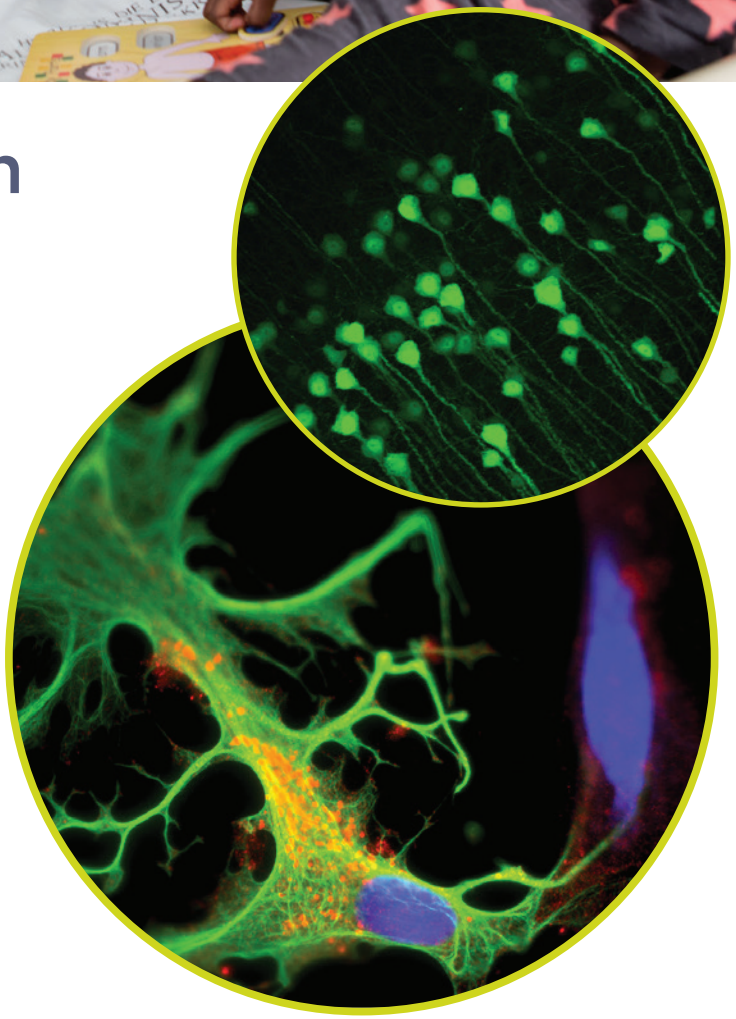
A space designed to serve and connect people and disciplines

Investigators and their students have access to exceptional clinical resources and state-of-the-art neuroscience methodologies through the NI, with a focus on innovation and mentorship. This is a vibrant interdisciplinary environment housing all relevant clinical disciplines, with shared facilities such as clinics, meeting venues, postgraduate student workspaces, as well as a dedicated research neuroimaging suite that includes both 3T MRI and PETCT. We have an established platform for specialised training programmes in the clinical neurodisciplines. In addition, we have expanding capacity for molecular diagnoses and genomics, a newly established brain bank (with an adjacent biorepository), and two new laboratories for neuroscience research and innovation.

"Building **a global network** addressing the brain-health priorities and challenges of the populations we serve."

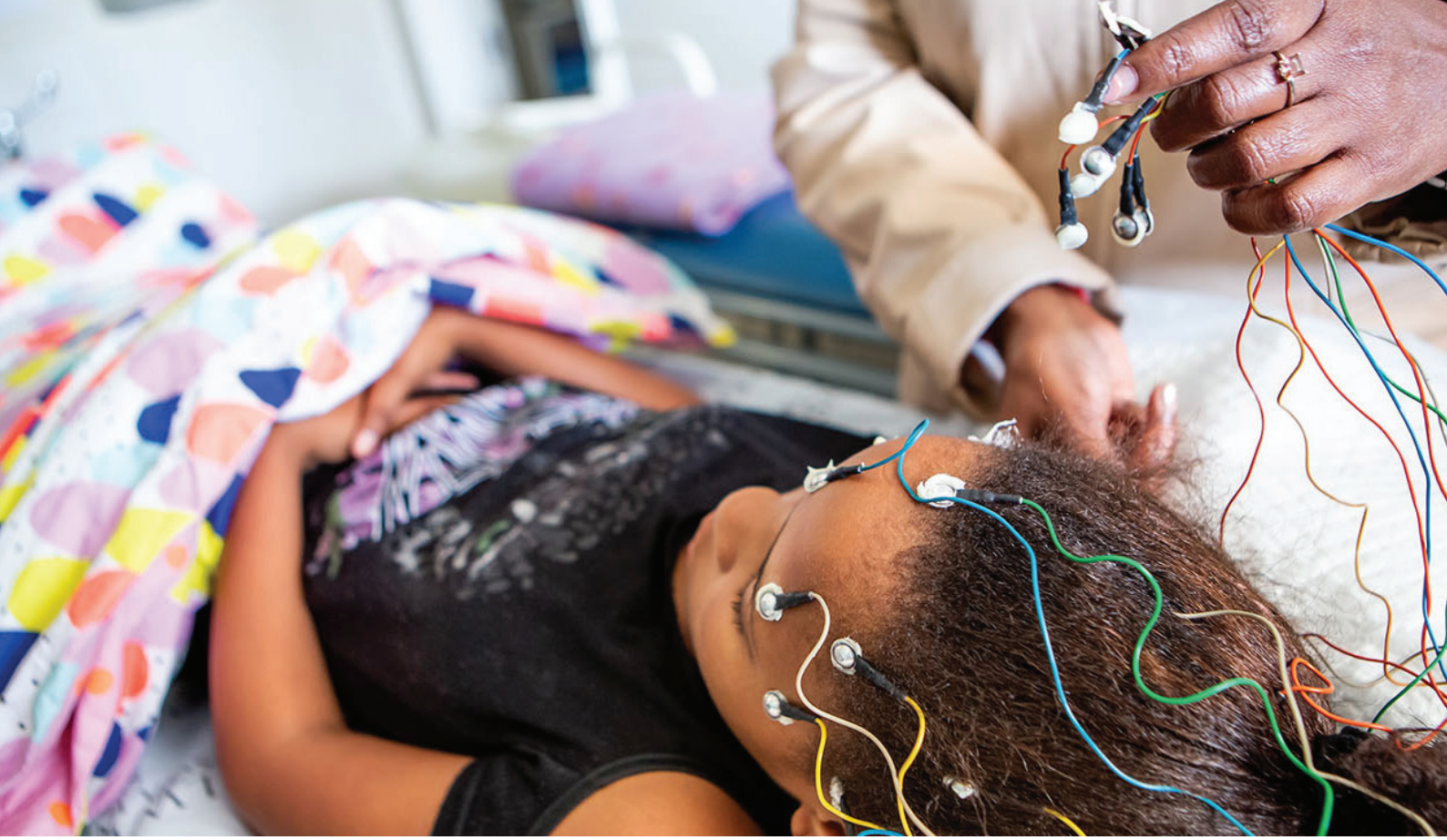


Why brain research in Africa?



Understanding the brain, and finding better treatments for conditions that affect the human brain, are important challenges for the 21st century. Early development of the brain, so critical in enabling people to achieve their full potential, is determined by a range of genetic and environmental factors. In the context of Sub-Saharan Africa, this includes an extraordinary range of risk factors, such as a higher incidence of infections, higher exposure to toxins and poor nutrition, greater exposure to trauma and violence, together with a much wider genetic diversity.

This unique context requires us to develop interventions to promote brain health and wellbeing on our continent, and also creates opportunities to make break-through discoveries of relevance to global neuroscience.



A unique and dynamic demography

Sub-Saharan Africa continues to experience accelerating population growth and, as home to 500 million children and adolescents, has a younger population than any other region of the world.

Over the last 30 years, child mortality in Africa has steadily dropped with children increasingly surviving the high-risk early years. However, these gains have also resulted in greater numbers of children living with chronic conditions, including developmental delays.

The early years play a transformative role on future growth and potential, as demonstrated by their prioritisation on development agendas, such as the United Nation's SDGs and the World Health Organisation's Nurturing Care Framework.

Burden of disease

The burden of brain insults and injuries for children and young adults in Sub-Saharan Africa may result in a spectrum of cognitive impairment and neurological disability across the lifespan.

This region has the highest global rates of traumatic brain injury that occur through road traffic accidents, falls, and assaults. It is our mission to find relief for this critical public health concern.

Sub-Saharan Africa also remains the epicentre of the infectious diseases, HIV and TB (in particular TB meningitis). As with these diseases, emerging global infections, including the novel SARS-CoV-2 virus, frequently behave differently in environments where socio-economic disadvantage and other infectious diseases are prevalent.

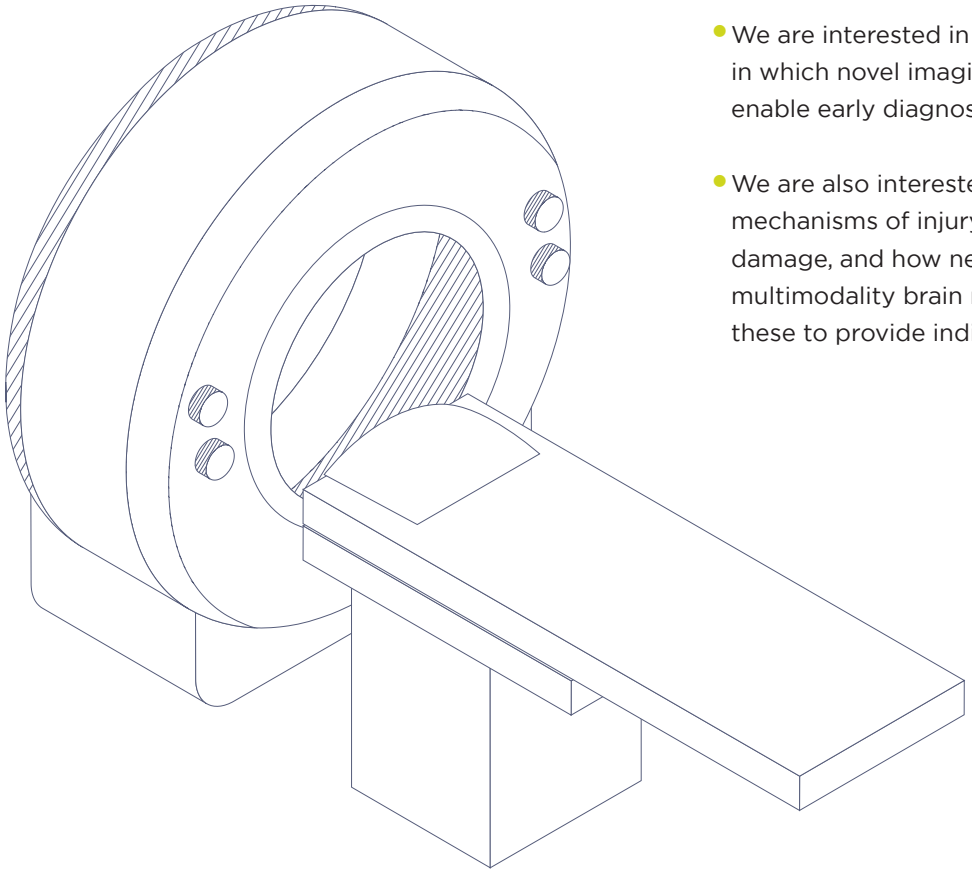
Our research

Two conceptual domains

We frame our **research ecosystem** (Figure 1) within two conceptual domains, using a range of research tools to address key questions in six priority areas.

Brain development across the lifespan

Our work on brain development spans the human lifecycle from foetal development, through childhood, adolescence and into adult life. We strive to understand the factors influencing brain health and development across this spectrum, and the mechanisms through which biological, pathological and environmental factors impact the brain. Through our research we can make earlier and more accurate diagnoses, develop more effective prevention strategies, and inform interventions to improve brain and mental health outcomes.



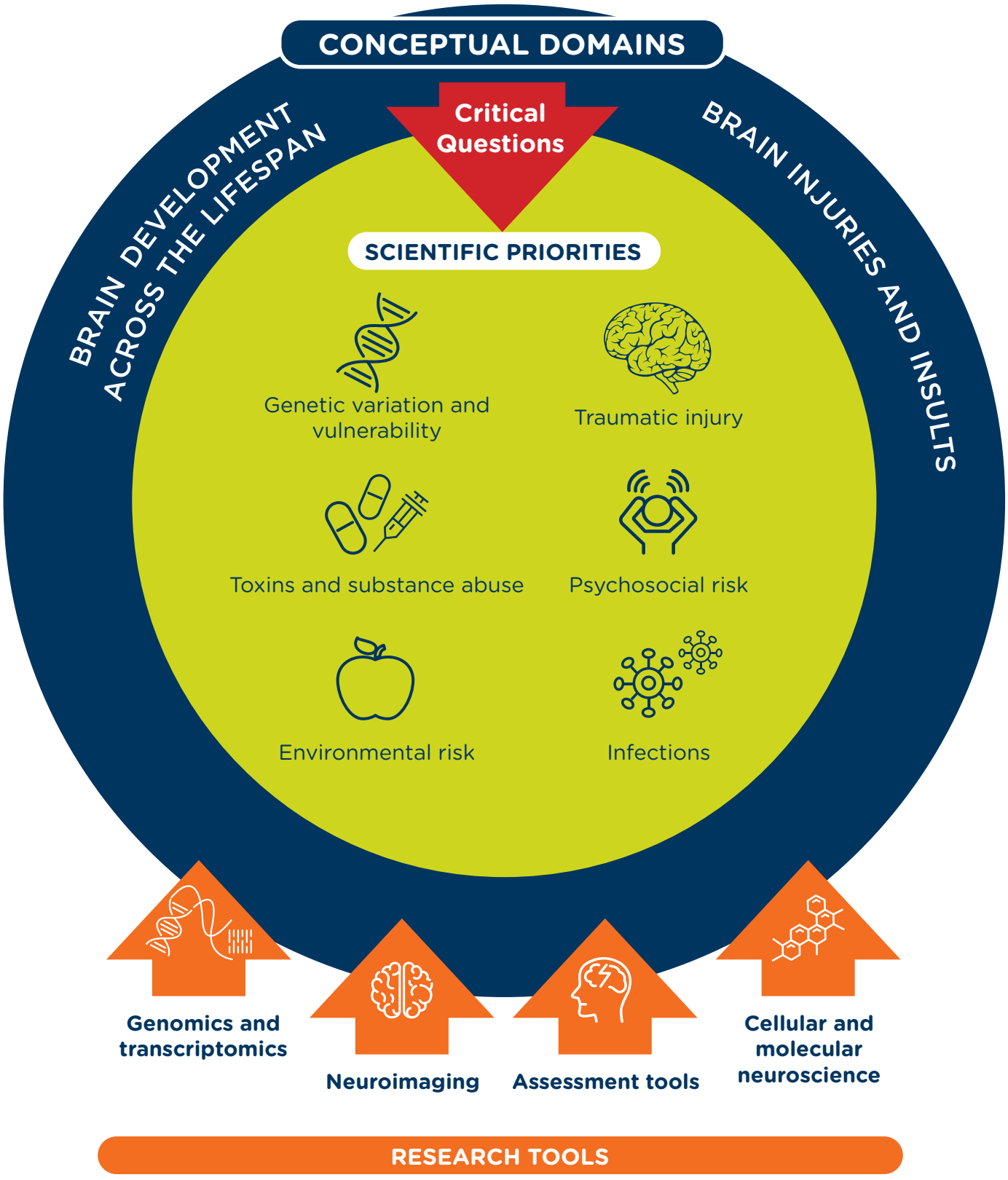
Brain injuries and insults

We focus on multiple dimensions of brain injuries and insults, specifically: disease pathogenesis, pathophysiology, neuro-immunology, drug development, neuroimaging, and biomarkers.

We have built sophisticated infrastructure to support our researchers working in the local environment. As a result, NI researchers have gained world-leading clinical experience and an exciting range of programmes:

- We seek to understand the molecular mechanisms of brain injury and the acute and chronic inflammatory responses of the brain to insult.
- We are interested in point-of-care diagnostics in which novel imaging or biomarker methods enable early diagnosis.
- We are also interested in how secondary mechanisms of injury cause progressive brain damage, and how neuro-critical care and multimodality brain monitoring can mitigate these to provide individualised patient care.

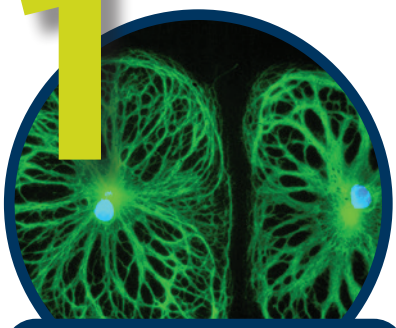
Figure 1: The Neuroscience Ecosystem



Four critical questions

Our unique setting, with a young, genetically diverse population facing exceptionally high exposure to brain insults and trauma, and world-class clinical and research facilities, allows us to address four over-arching challenges which have global relevance to the field of neuroscience.

1



Brain mechanisms

What are the neurobiological pathways underpinning healthy brain development and brain injury in our context?

Large studies of mechanisms underpinning brain growth and developmental or psychiatric disorders have been overwhelmingly based in Europe, North America and Asia. To date, very little is known about the clinical variation, and risk architecture, of intellectual and developmental disabilities and related developmental or mental health outcomes in Africa.

2

Brain and behavioural measurement

How can we accurately measure variation in brain function and behaviour in our populations?

Many tools used in high-income settings are considered the ‘gold standard’ for screening and diagnosing neurodevelopmental or mental health disorders. These tools often don’t translate well to a resource-limited setting on account of bias (construct, measurement or item bias), financial barriers (for training, translation, and proprietary materials), researcher experience and training, and the time available to conduct research in busy clinical settings. By working in and learning from colleagues across Africa, we aim to develop better tools to measure behaviours and brain function in such settings.

3

Interventions and system change

How can we improve the effectiveness and scalability of our interventions in an African context?

For our interventions to be effective and scalable, our research into brain and mental health has to be relevant to an African context, where people suffer nutritional deficiency, a wide range of medical conditions and challenging psychosocial factors.

4

Ethics of neuroscience

What constitutes ethical research and practice in relation to brain health?

Cutting-edge research in the neurosciences raises a broad range of ethical challenges. These include the appropriateness of different consent models, ethical challenges relating to data sharing practices, the ways in which genomic research can impact on stigma relating to disease, and ultimately how our interventions, including brain modulation through surgically implanted devices, affect who we are. The current (and growing) body of work requires further consultation, deliberation and documentation to establish protocols that will guide the future practice of neuroscience. We seek to include and protect vulnerable populations while making breakthrough scientific advances.

Scientific priorities

Genetic variation:
Africa has by far the greatest genetic diversity of all continents, and consequently wide variation in people's responses and vulnerability to injuries and insults to the brain. This ranges from timing of onset through to severity of phenotype and finding the genetic drivers of these developmental, psychiatric and cognitive trajectories in Africa may provide answers that can be applied worldwide.

Infections:
HIV is a highly neurotropic virus and TB, in particular TB meningitis, causes significant neurological disability. With Sub-Saharan Africa being the global epicentre of these infectious diseases, our long-term goal is prevention which requires us to understand their mechanisms, develop screening approaches and devise interventions to reduce their impact.

Traumatic brain injury:
Trauma, due to road traffic accidents, falls, and assaults, is the leading cause of death and neurological disability in Sub-Saharan Africa, with rates higher than any other region of the world. Understanding the cascade of neurological mechanisms that follow traumatic injury may allow us to prevent further damage (secondary prevention) and improve outcomes.

Toxins and substance abuse:
Sub-Saharan Africa has high foetal exposure to environmental toxins including substances such as alcohol, methamphetamine and nicotine. Understanding how these exposures affect brain development may direct prevention strategies and inform better policies to reduce substance abuse.

Environmental risks:
Understanding the effects of malnutrition and micronutrient deficiencies on brain development across the lifespan is critical in guiding effective intervention strategies. This work is particularly pertinent at present given how the already-high levels of these risks have been exacerbated by COVID-19 lockdowns across Sub-Saharan Africa.

Psychosocial risks:
Poverty and unemployment, intensified by the COVID-19 pandemic, have heightened exposure to violence and increased the prevalence of associated psychosocial risks, such as depression, anxiety, injury and post-traumatic stress disorder (PTSD). It is vital to explore safe and effective medications and behaviour strategies, as well as to find a balance between the imperative to intervene and the need to develop a trusting relationship that will enable affected individuals to share sensitive information about their lives.

“Understanding the cascade of neurological mechanisms that follow traumatic injury **may allow us to prevent further damage**”

Exploring critical questions

We are particularly interested in directing researchers within the NI network to explore critical questions that reflect our focus on the needs of African populations, through our pathway to research impact, mindful of our fundamental concern with conducting ethical research. Below we provide examples of how we can address the challenges outlined above through a range of relevant questions.

	What are the neurobiological pathways underpinning healthy brain development and brain injury in our context?	How can we accurately measure variation in brain function and behaviour in our populations?
Genetic variation and vulnerability	What is the genetic variation underpinning important neurological conditions such as epilepsy, stroke and autism spectrum disorders in African populations? How does age and sex impact response to brain injury? In targeting brain tumours, how does regional genetic variation intersect with epigenetic modelling, and does this allow us to map and intervene with optimal treatment at strategic points in their origin and behaviour?	How do we increase representation of African population genetics in local and global reference databases?
Infections	What are the causes of stroke in resource-constrained environments and in the context of HIV and TB infections? What are the underlying mechanisms for cognitive impairment and brain injury due to HIV exposure? What are the cellular mechanisms of neuronal injury, in the context of infection, such as neurocysticercosis and TB meningitis?	Which are the safest and most effective (for mother and child) medications for treating pregnant women with HIV? What valid tools can be used to measure functional outcomes, or to screen for mental health problems in adolescents and adults with HIV? What are the safest and most effective medications for treating psychiatric disorders in HIV infected populations? How can we improve the treatment of brain infections in a way that addresses both the infection and the organ of injury?
Traumatic brain injury	What are the molecular mechanisms and biomarkers of brain injury? How do strengths and vulnerabilities across the lifespan impact the response to brain injury?	What acute and long-term interventions are effective for improving outcomes from traumatic brain injury, using site of disease samples? What biomarkers can be used for the early identification of patients at greatest risk of severe injury?
Toxins and substance use	What are the neurobiological pathways that lead to poor outcomes in toxic substance exposure during pregnancy? What are the vulnerabilities to substance use disorders in multi-risk populations?	Are there scalable biological or behavioural interventions which are effective in mitigating the impact of prenatal substance exposure on the brain?
Environmental risks	Are there specific windows of vulnerability to nutritional deficiencies in young brains?	What are the best windows of intervention for reducing poor brain outcomes in children due to nutrient deficiencies, such as iron and folic acid?
Psychosocial risk	How does exposure to violence impact mental health and brain development?	What scalable strategies are effective for reducing depression, anxiety and PTSD in at-risk populations? What are the safest and most effective mediations and behaviour strategies for treating people suffering from depression, anxiety, and PTSD?

	How can we improve the effectiveness and scalability of our interventions in an African context?	Given the ethical challenges raised by neuroscientific research, how do we include vulnerable and under-represented populations without exploiting them?
Genetic variation and vulnerability	How do we best integrate an understanding of biological mechanisms and social determinants?	Does identifying a genetic cause lead to stigma in neurological, developmental or psychiatric disorders? How can we appropriately manage feedback of genetic findings in a way that is consistent with participant preference, and ensures understanding of these conditions in African communities? How can we responsibly share genetic data through globally-accessible platforms?
Infections	Governments should mandate antiretroviral regimens that maximise brain and mental health outcomes – which regimens achieve this? How can we contribute to developing systems that facilitate preventative therapy and limit spread of infection?	What are the best strategies for supporting people with stigmatising infections, such as HIV and TB?
Traumatic brain injury	What are the societal interventions that will limit the risk of traumatic brain injury, specifically those relating to road traffic accidents? What scalable management protocols are most effective for reducing the burden of secondary brain injury? How can we build neurocritical care and advanced brain monitoring as systems to optimize care?	How should one manage consent in the context of acute illness?
Toxins and substance use	What are the most effective public health initiatives for addressing drivers of substance use in high-risk populations? How can we integrate medical and social opportunities for addressing substance use disorders?	How should one engage with users and their families about the effects of substance abuse, in a manner which limits shame and maximises behaviour change?
Environmental risks	How do we include a scalable measure of neurodevelopment in current population-based metrics of human skills, knowledge and experience?	How do you equitably target interventions for populations that face persistent food insecurity and high nutritional risk?
Psychosocial risk	What models of step-down care are most acceptable in an African context? Question 4: What constitutes ethical research and practice in relation to brain health?	How can we balance the imperative to intervene and the need to develop the kind of trusting relationships that enable affected individuals to share sensitive information about their lives?


“We use the **latest next-generation sequencing technologies** to interrogate DNA and gene expression profiles from cell culture models to clinical biospecimens.”

Research Tools

Assessment tools

Our researchers address fundamental questions by longitudinally mapping brain development and cognitive growth across the lifespan. Mental health, cognitive impairment and psychosocial risk assessment requires screening tools to be designed for resource-poor clinical settings. Our investigators validate and implement traditional neuropsychological and neurocognitive assessments to determine whether existing measures of development and cognition are valid across African settings, and how they can be better adapted. This includes developing low-cost, open-access technology for measuring brain development.

Molecular and cellular neuroscience

Our neuroscience projects are run in laboratories affiliated with the NI. With access to a host of clinical specimens that are rarely available elsewhere, these laboratories facilitate key areas of research including biomarker discovery, molecular biology and cell culture work, and drug research and discovery.

Our basic neuroscience laboratories are equipped with a wide range of state-of-the-art technologies that allow our researchers to interrogate brain slice, and dermal and neuronal cell cultures using various techniques, including:

- patch-clamp electrophysiology and local field potential recordings
- in vitro optogenetics
- fluorescence microscopy including Ca^{2+} imaging
- in vivo EEG wireless telemetry
- organotypic hippocampal slice cultures
- computational and theoretical modelling

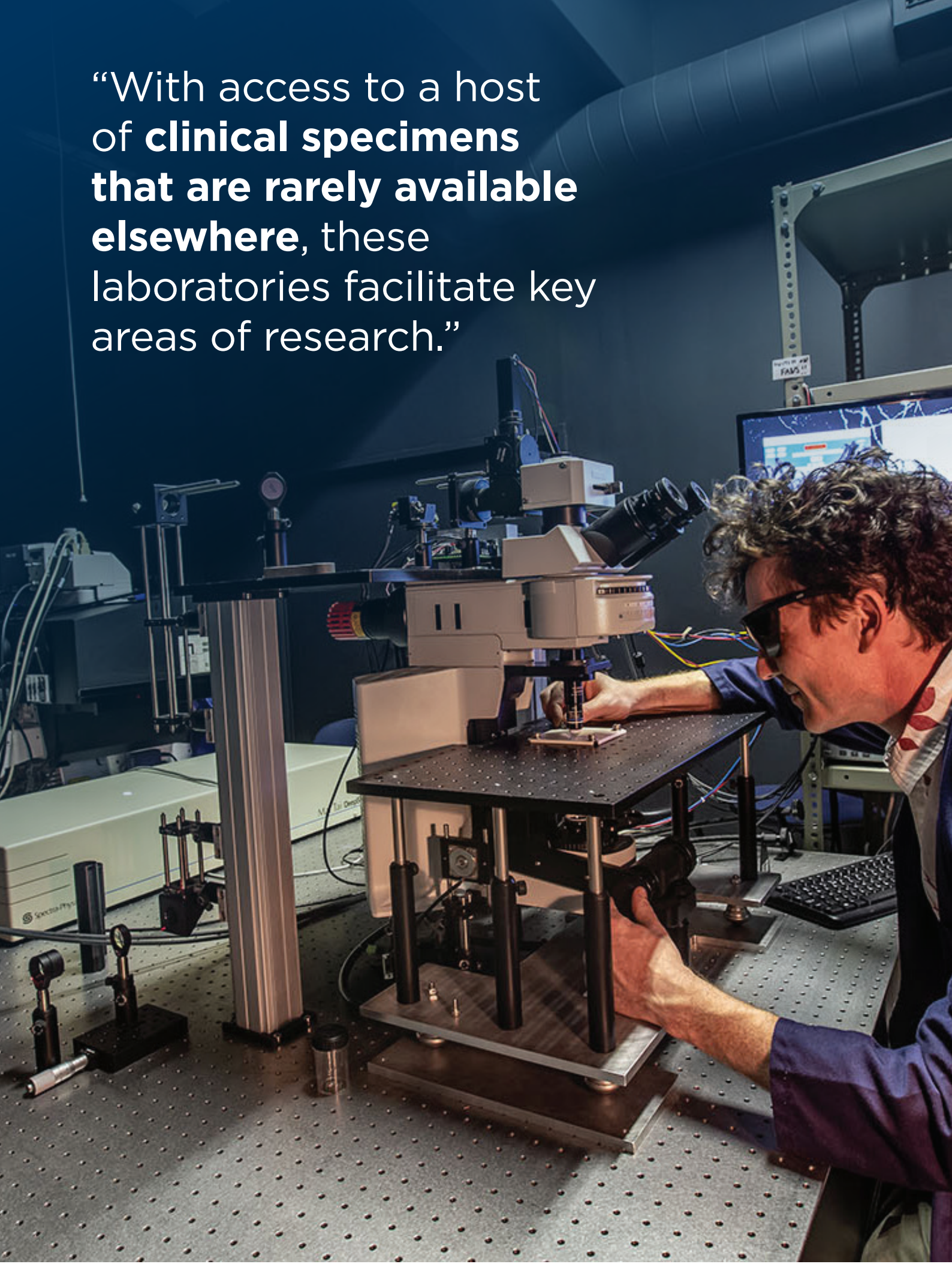
Genomics and transcriptomics

Africa has the highest genetic diversity in the world, with genetic variation affecting vulnerability to brain injury and insult. Identifying the genetic drivers of brain development in Africa may provide answers with worldwide application. We use the latest next-generation sequencing technologies to interrogate DNA and gene expression profiles from cell culture models to clinical biospecimens. These methodologies include the latest genome-wide analysis techniques, including whole genome sequencing, bulk RNA- sequencing, single cell RNA-sequencing, and ATAC-sequencing.

Neuroimaging

The Cape Universities Body Imaging Centre (CUBIC), situated adjacent to the NI, is a joint initiative between Siemens, Stellenbosch University, the University of Cape Town and the South African Medical Research Council. The core focus of CUBIC is collaborative imaging research, and technical support is provided by the Imaging Science research group based in the NI. CUBIC houses state-of-the-art, large-bore Siemens 3T Skyra MRI and Biograph mCT Flow 64 PET-CT scanners.

CUBIC has network facilities, consultation rooms and common working areas, and in the PET-CT suite are injection rooms, a cooling room and a hot lab. Three MR physicists, three MR radiographers, two nuclear medicine radiographers and a nuclear medicine physician provide technical and expert services.



"With access to a host of **clinical specimens that are rarely available elsewhere**, these laboratories facilitate key areas of research."

Integration of Research Disciplines with Research Programmes

Innovative science is grounded in foundational disciplines, with collaboration across groups and between expertise. This is reflected in the NI's organisational structure, which includes groupings from across the Health Sciences Faculty, and beyond.

Figure 2: Integration of Research Disciplines with Research Programmes

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