TRINITY COLLEGE

INSTITUTE OF NEUROSCIENCE

FROM MOLECULES TO MIND

SKILLS AND TECHNIQUES

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MODELS OF DISEASE

Researchers in TCIN have developed a range of animal models offering the ability to study the following:

Alzheimer's disease and cognitive impairment

- Transgenic models of Alzheimer's disease
- Aβ infusion models
- Aged animal model
- Basal forebrain cholinergic lesion model
- Dementia-associated delirium

Depression

- Interferon-α-induced depression
- Olfactory bulbectomy
- Chronic mild stress
- Restraint stress

Multiple Sclerosis

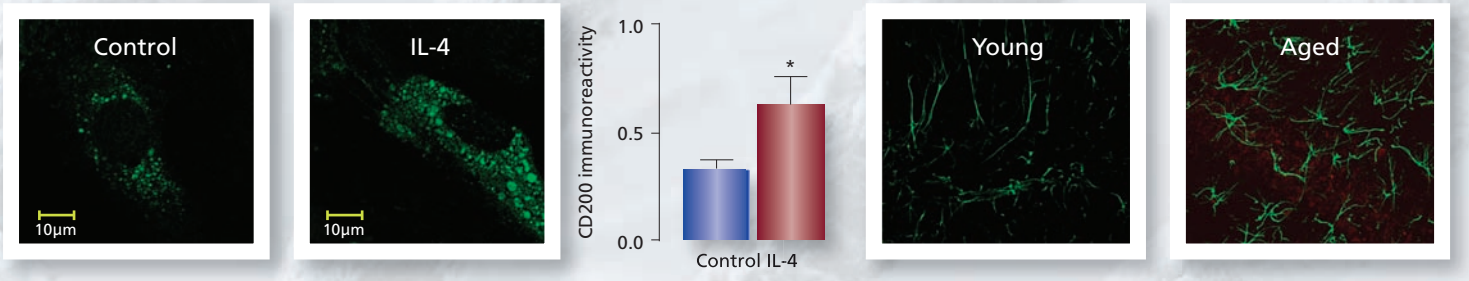
- EAE (including relapsing/remitting); mice and rats

Stroke and Ischemia and Cell Stress

- Middle cerebral artery occlusion (MCAO) model
- Traumatic brain injury
- Oxygen-glucose deprivation
- Hypoxia/re-oxygenation
- Excitotoxicity (glutamate, NMDA, kainate)
- Oxidative stress
- Inflammatory stress

Other disease models:

- Prion disease: ME7 mouse model
- Motor neurone disease
- Macular degeneration and retinitis pigmentosa



IL-4 increases neuronal CD200 expression

Astrocytosis is evident in hippocampus of aged rats as shown by GFAP staining (green)

THERAPEUTIC INTERVENTIONS

Researchers in TCIN use both pharmacological and non-pharmacological interventions to ameliorate pathology in a variety of disease models.

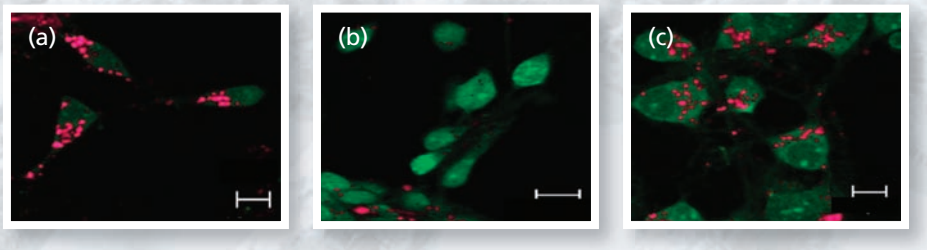
Methodologies for CNS delivery of therapeutics

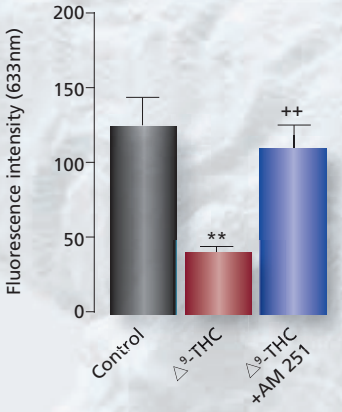
- Intrahippocampal and other deep sites
- Intracerebroventricular injection
- Osmotic minipump chronic infusion

Non-pharmacological interventions

- Electroconvulsive stimulation
- Deep brain stimulation
- Exercise protocols
- Dietary manipulation

CELLULAR AND MOLECULAR METHODOLOGIES





Exposure of neurons to the cannabinoid △9-THC destabilises lysosomes as shown by the loss of acridine orange staining (b); compared with control (a). The cannabinoid receptor antagonist, AM 251 attenuates the effect of △9-THC (c). Scale bar = 10µm

Researchers use a range of cellular and molecular approaches to investigate functioning of the nervous system. These include:

Electrophysiology

- *In vivo* and *in vitro* analysis of synaptic plasticity (LTP, LTD, PPF)
- Single cell recording
- Patch clamp
- Neuronal ensemble recording with multielectrode arrays in the freely-moving animal
- Transcranial direct current stimulation

Genetic manipulation

- Transgenic and knockout mice
- Drosophila-based models
- siRNA and viral gene therapy

Cell culture systems

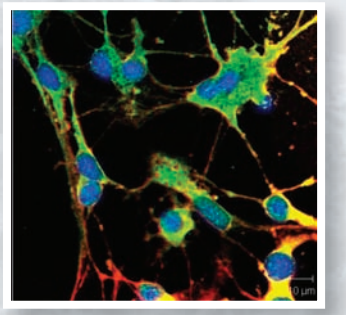
- Primary cultures of neurons and glia
- Primary T cell cultures
- Endothelial cell cultures
- Stem cell cultures

Analyses include:

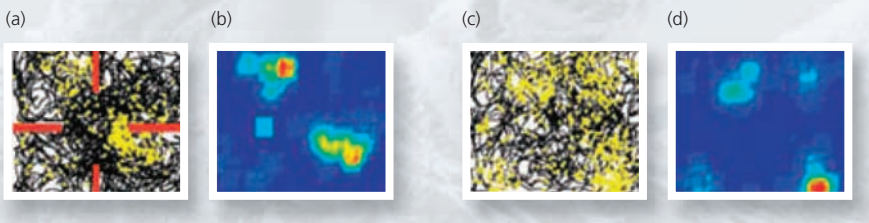
- Cell death and viability assays
- Cytokine, neurotrophin and neurotransmitter release
- Cell signalling
- Reactive oxygen and nitrogen species production
- Lysosomal stability
- Mitochondrial function

Techniques include:

- ELISA
- HPLC
- Real time PCR
- Flow cytometry and Immunohistochemistry
- Immunoprecipitation and Western Immunoblotting
- Proteomics



Confocal image of cultured neurons



Low frequency recording at 3.43 Hz

Higher frequency recording at 13.36 Hz

Location-based electrophysiological recordings of subiculum place cells. Figures (a) and (c) show positional and directly recorded spiking data and figures (b) and (d) are contour plots of the same recordings.

BEHAVIOURAL ANALYSIS

Researchers use a range of techniques to assess animal behaviour and cognition. These include:

Cognitive testing

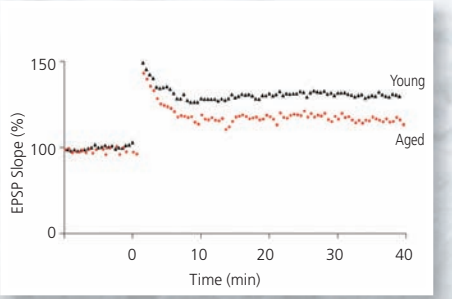
- Morris water maze
- Water plus maze
- Radial arm maze
- Temporal order memory task
- Episodic-like memory tasks
- Object displacement and object recognition tasks
- Operant conditioning tasks (e.g. delay tasks, alternation tasks, response tasks)

Stress and anxiety tests

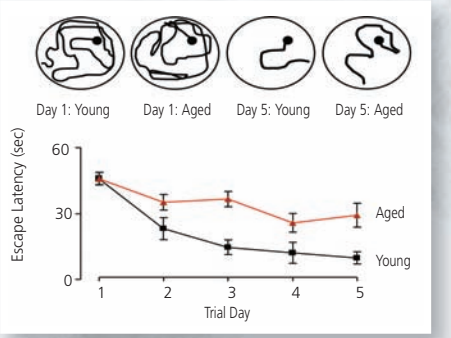
- Forced swimming test
- Novelty-suppressed feeding
- Saccharin preference testing
- Elevated plus maze
- Open field testing
- Stress-induced hyperthermia

Additional methodologies

- Rotarod
- Automated home cage monitoring for full behavioural phenotyping
- Bioradiotelemetry (body temperature, heart rate and locomotor activity)



LTP in dentate gyrus is decreased in aged rats



The time required to find the hidden platform in the Morris water maze is greater in aged rats. Sample path trajectories for Days 1 and 5 are shown.

IMAGING

1. Magnetic Resonance Imaging

TCIN houses two Magnetic Resonance Imaging (MRI) machines. A 3 Tesla MRI is used for human analysis and a small bore 7 Tesla MRI is available for animal imaging.

Expertise includes

- MRI sequence development
- Hardware development

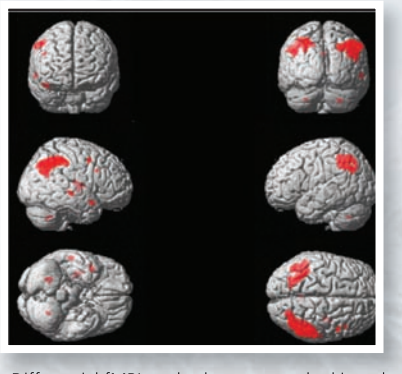
Analysis

- Diffusion analysis
- Diffusion Tensor Imaging
- Voxel Based Morphometry
- T1, T2 and T2* analysis
- fMRI
- Blood flow analysis
- Arterial Spin Labelling

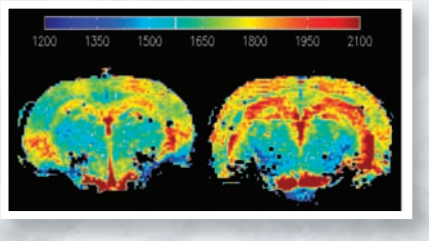
2. Two Photon & Confocal Microscopy

TCIN has extensive expertise in the use of these systems to examine:

- Neurogenesis
- Pre- and post-synaptic labelling
- Live cell imaging



Differential fMRI study, the areas marked in red show areas of brain atrophy specific to Mild Cognitive Impairment (MCI)

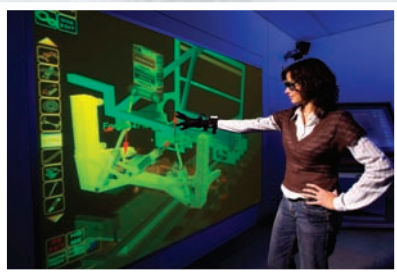


T1 relaxation time is increased in hippocampus and cortex of the aged rat

HUMAN COGNITION

TCIN has significant strength in the area of human cognition and behaviour. The following tests are conducted:

- Human behavioural testing: Attention, Memory, Executive function,
- Multisensory integration; Visual discrimination; Neuropsychological function
- Eye tracking
- Object recognition
- Object categorization
- Deductive reasoning
- Counterfactual imagination
- Virtual reality
- Transcranial magnetic stimulation
- Classical and instrumental conditioning
- Reward-related decision making
- Goal-directed and habitual learning
- Reversal learning
- Social cognition
- Mentalising
- Decision Biases
- Neuroeconomics



CLINICAL ANALYSES

Clinical studies are conducted at our University teaching hospitals. Specifically, we have a dedicated memory clinic, a falls clinic and a syncope clinic at St. James' Hospital, and a range of clinical studies are also conducted at St. Patricks Hospital and AMiNCH, Tallaght.

Particular expertise

- Autonomic function tests
- Neurally-mediated syncope test
- Cognitive function assessments
- Balance
- Neurocardiovascular instability
- EEG
- ERP
- Behavioural methods for improving brain function in clinical groups and in normal ageing

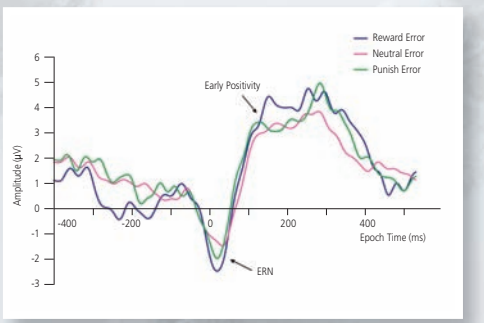
Clinical cohorts

- Child and adult ADHD
- Traumatic brain injury
- Progressive disorders from acquired brain injury
- Schizophrenia
- Mild Cognitive Impairment
- Alzheimer's Disease
- Depression

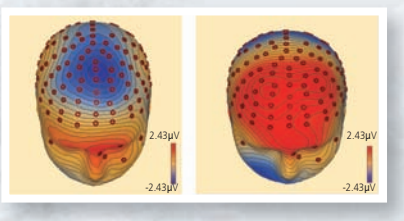
Additional Analyses:

TILDA Health centre based tests include: Anthropometric analyses, Grip strength, Visual acuity, Contrast sensitivity; Macular densitometry, Heel ultrasound, Phasic blood pressure, Heart rate variability, Pulse wave velocity, Gait & balance assessment.

St. James Hospital based tests include: Cerebral blood flow, Sampling & analysis of blood, plasma and cerebrospinal fluid, Task dependent measurements of blood pressure, Heart rate and temperature.



Graphic of ERP study of reward & punishment effects on error awareness in a Go/No-Go Task



Contour map of ERP study of reward & punishment effects on error awareness in a Go/No-Go Task

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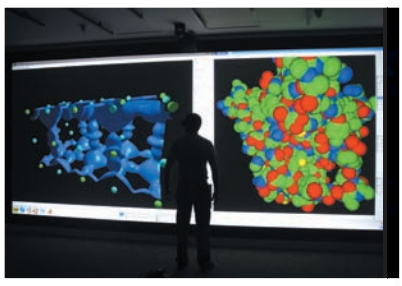

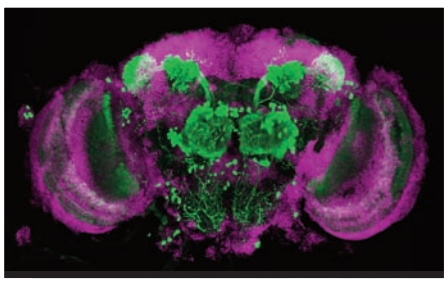

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