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Secondary neurodegeneration after stroke: Neuropathological changes and potential therapeutic targets

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Health and Biomedical Innovation Seminar Series
University of South Australia

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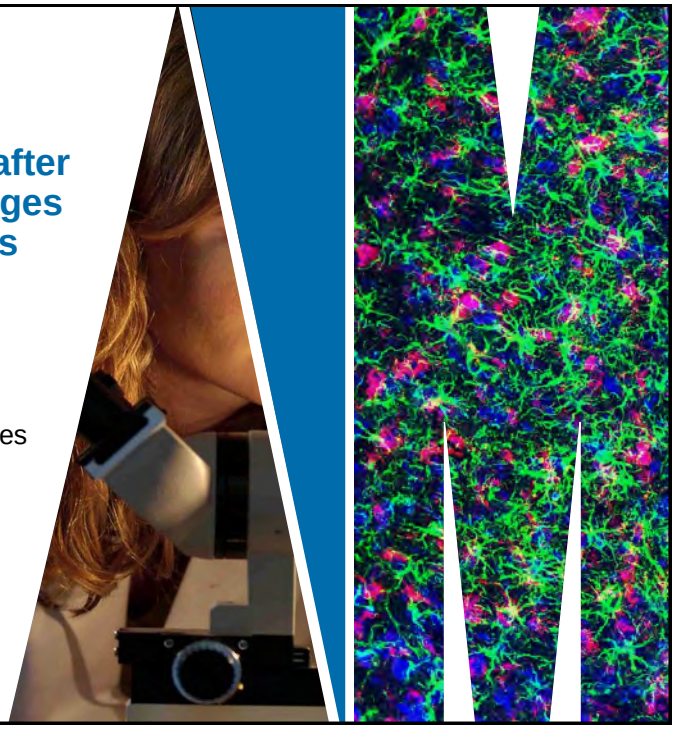
THE UNIVERSITY OF NEWCASTLE AUSTRALIA

HMRI Hunter Medical Research Institute

NHMRC CENTRE OF RESEARCH EXCELLENCE
Stroke Rehabilitation and Brain Recovery



Tyrosine hydroxylase lab 2010

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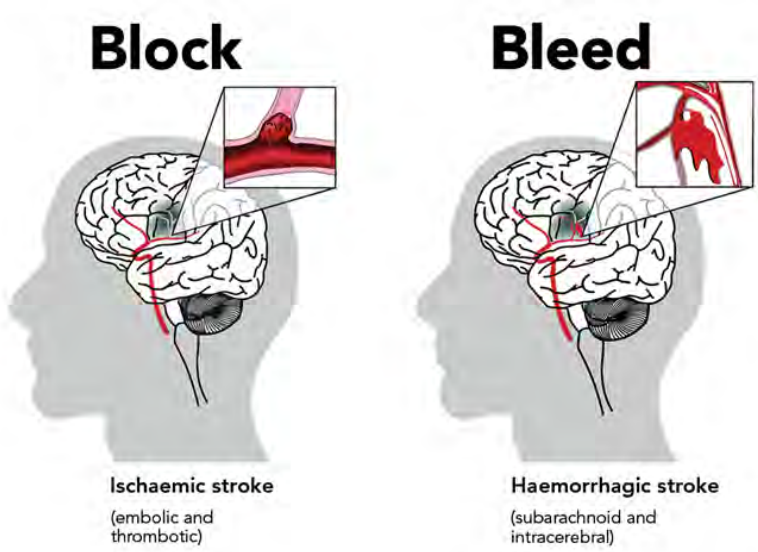
Translational NeuroRecovery Lab 2019 - current

Stroke



1 in 4 of us will have a stroke

>13.7 million new strokes each year, and still increasing…

>80 million people living with stroke, and ~40% working age (under 60 years old)

~2/3 of stroke survivors will have some form of post-stroke complications, including **cognitive impairment**

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Cognitive impairment is common after stroke

Brain at risk → Cognitive impairment → Dementia

- Up to 80%
- Memory, learning and executive function

~30% develop vascular dementia

Levine et al. (2015) JAMA
Weinstein et al (2014) Int J Stroke
Pendlebury and Rothwell (2009) Lancet Neurol

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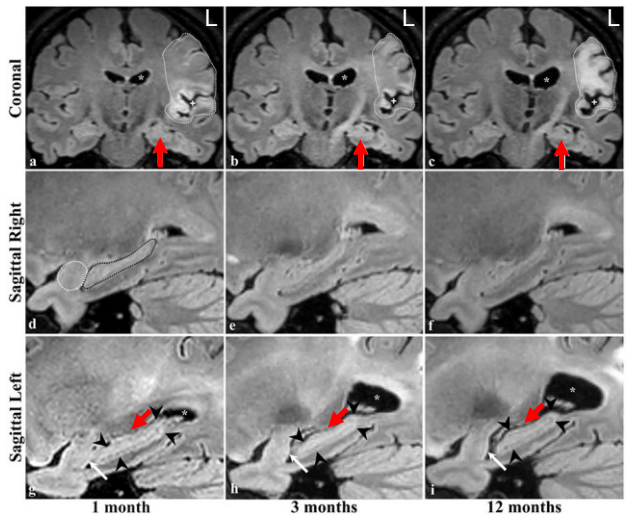
Stroke-induced regional brain atrophy (hippocampus)



Haque et al. (2019) Front. Neurol.

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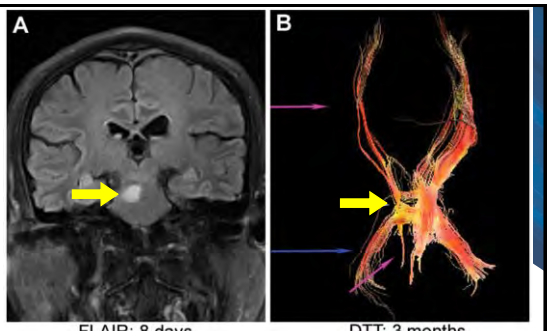
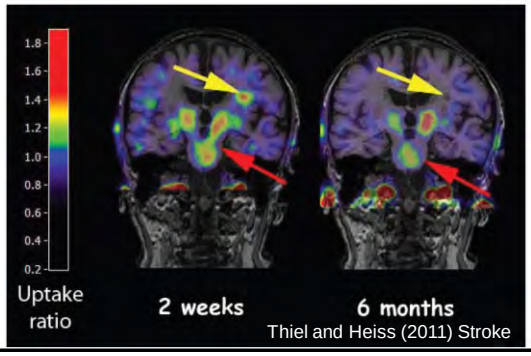
Stroke-induced regional brain atrophy

- **Wallerian degeneration**
- **Neuroinflammation**



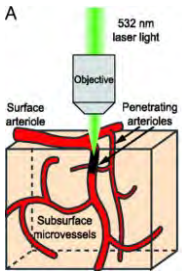
Zhang et al. (2012) Stroke

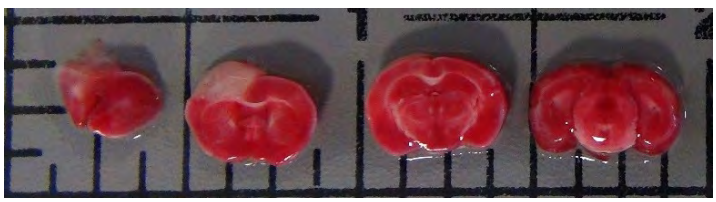


Thiel and Heiss (2011) Stroke

Photothrombotic stroke model

Motor and sensory regions of the cerebral cortex





Ong et al (2017) JCBFM
Ong et al (2018) Stroke
Bezanilla, Ong et al (2019) Exp Neurol

Aims:

To investigate the long-term functional consequences of cortical stroke

To explore the neuropathological changes (hippocampus)

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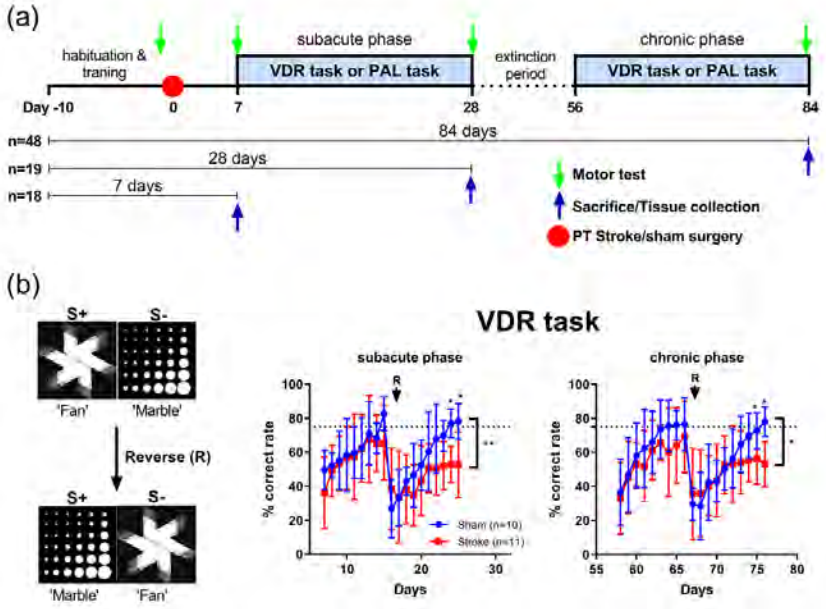
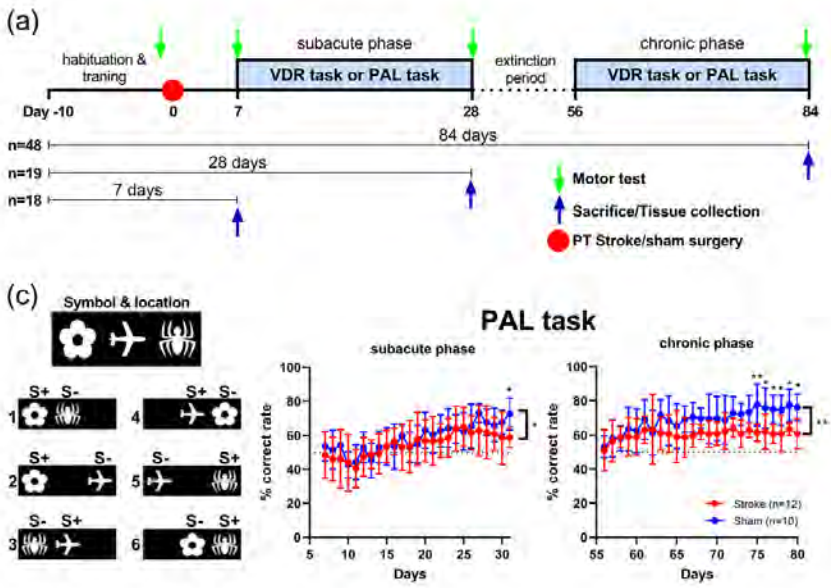
Cortical stroke impairs cognitive flexibility



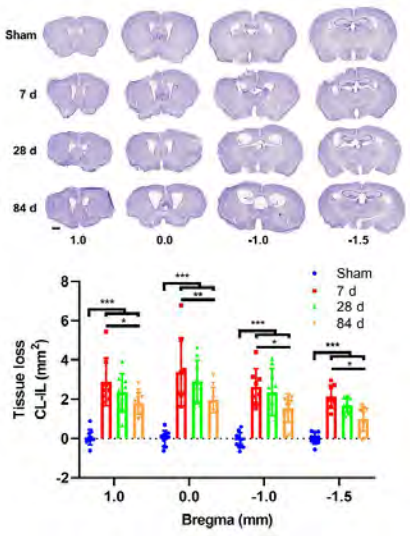
Bezanilla, Ong et al (2021) JCBFM

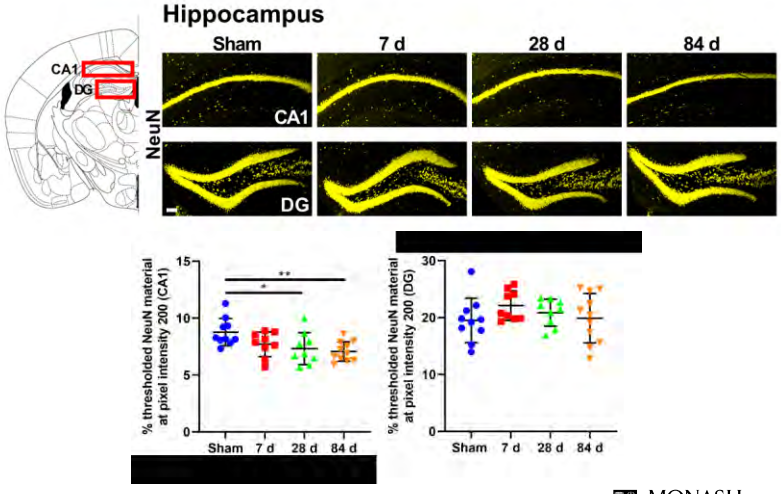
Cortical stroke impairs associative memory



Bezanilla, Ong et al (2021) JCBFM

Cortical stroke induces persistent brain tissue and CA1 hippocampal neuronal loss





Bezanilla, Ong et al (2021) JCBFM

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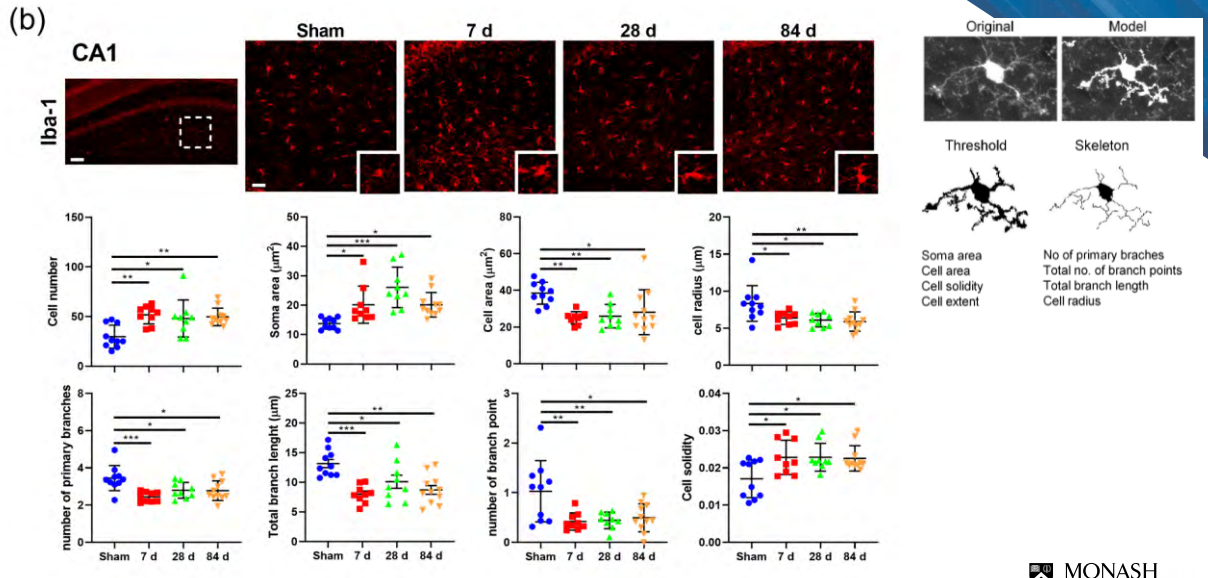
Persistent microglia activation in the hippocampus



Bezanilla, Ong et al (2021) JCBFM

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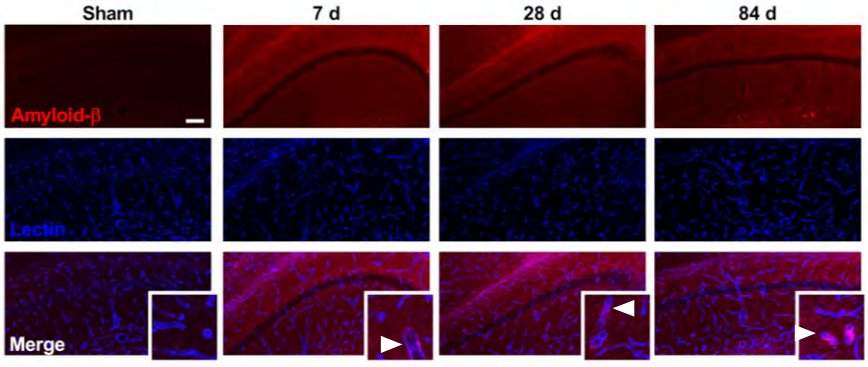
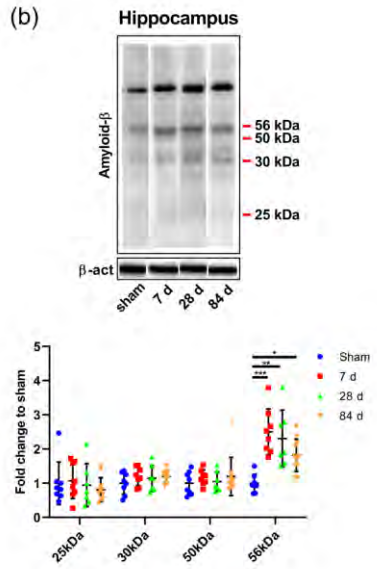
Accumulation and oligomerisation of amyloid-β in the hippocampus

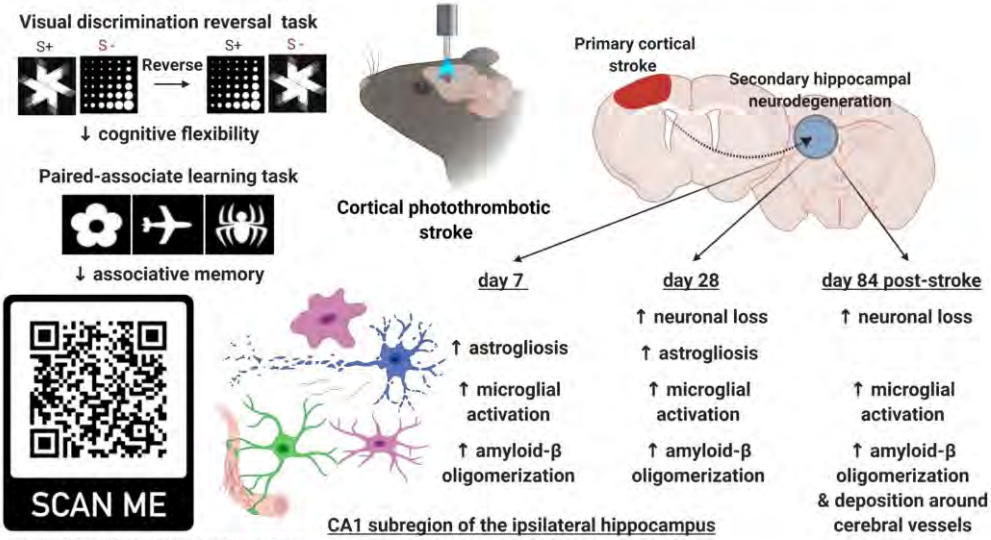




Bezanilla, Ong et al (2021) JCBFM

More than motor impairment: A spatiotemporal analysis of cognitive impairment and associated neuropathological changes following cortical photothrombotic stroke

Sonia Sanchez-Bezanilla, Rebecca J Hood, Lyndsey E Collins-Praino, Renee J Turner, Frederick R Walker, Michael Nilsson and Lin Kooi Ong



SCAN ME

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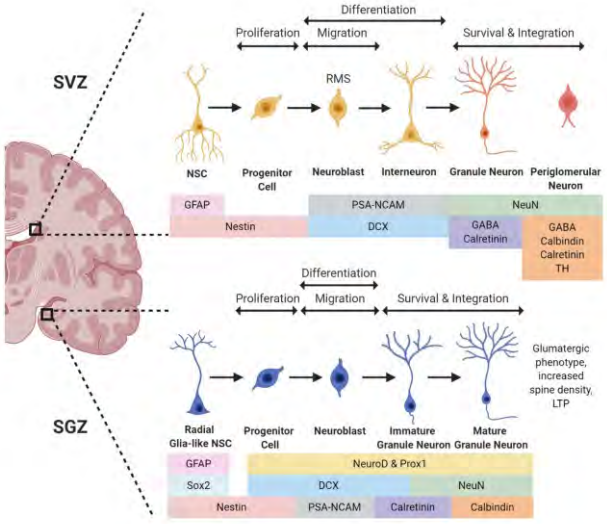
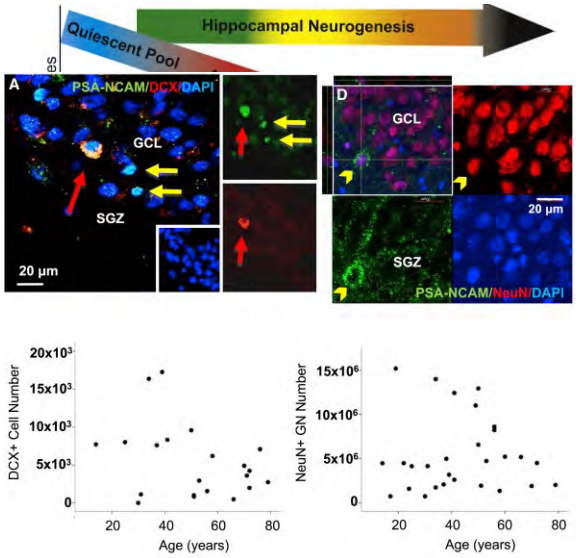
https://doi.org/10.1177/0271678X211005877
Visual abstract by @DrLinOng

Enhancing the brain's way of healing after stroke





Ong et al (2021) Regenerative Therapies in Ischemic Stroke Recovery

Boldrini et al. (2018) Cell Stem Cell

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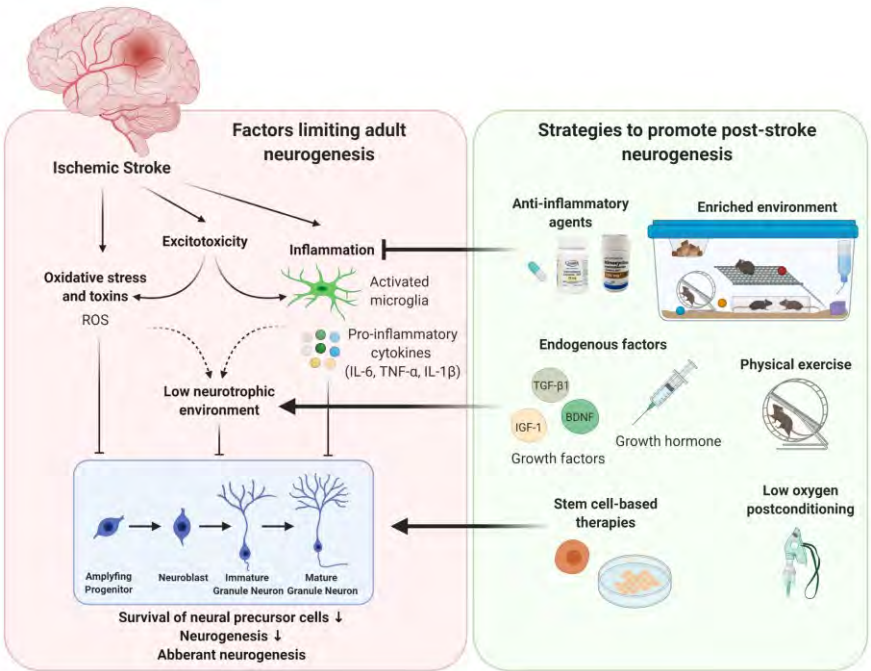

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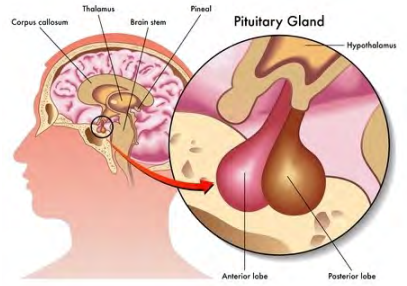
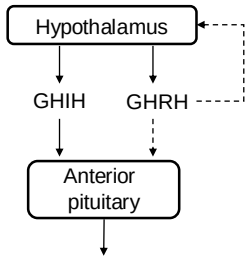
Growth hormone as “brain fertilizer” for stroke recovery





Growth hormone

Promotes neural repair after brain injury

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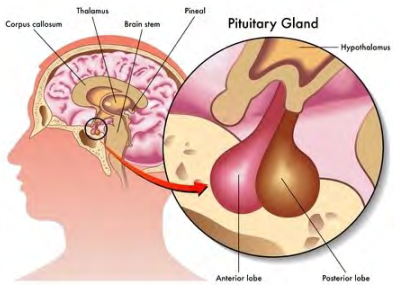
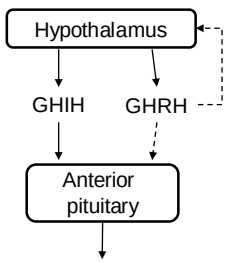
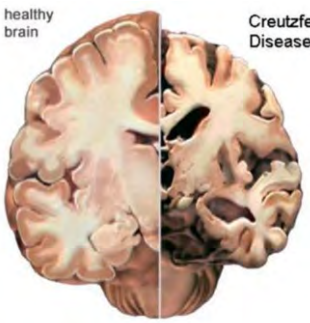
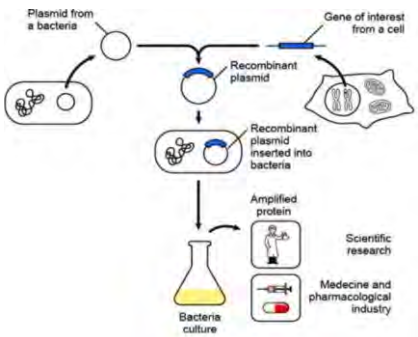




Growth hormone





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High incident of GH deficiency after stroke

Author, year	N	Characteristics	Time after stroke	GDH testing	Prevalence of GHD
Kreber et al. 2019	139	Age: 52 ± 0.91 Ischemic: 50%; Haemorrhagic 50%	≥ 3 months	Glucagon stimulation test	76/136 **(54%)**
Lillicrap, Ong et al. 2018	13	Age: 70 ± 7.61 (SD) Ischemic: 100% NIHSS: 11.08 ± 2.27 (SD)	4 – 10 days	GH releasing hormone + arginine	9/13 **(69.2%)**
Boehncke et al. 2011	46	Age: 61 ± 14.9 Ischemic: 100% NIHSS: 6 (1-15)*	66 – 274 days (128.2 ± 46)	GH releasing hormone + CRH	31/39 **(79.5%)**
Bondanelli et al. 2010	56	Age: 65 ± 1.3 Ischemic: 100% NIHSS: 10.75 ± 0.55	1 – 3 months (visit 1) and 12 – 15 months (visit 2)	GH releasing hormone + arginine	Visit 1: 17/56 **(30.4%)** Visit 2: 17/48 **(35.4%)** GHD was confirmed in 14 of 16 previous diagnosed cases, 3 newly diagnosed cases.
Bondanelli et al. 2006	42	Age: 67 ± 1.7 Ischemic: 100% NIHSS: 11.02 ± 0.87	19 – 209 days (61.7 ± 8.4)	GH releasing hormone + arginine	5/42 **(11.9%)**

See, Ong et al., under review

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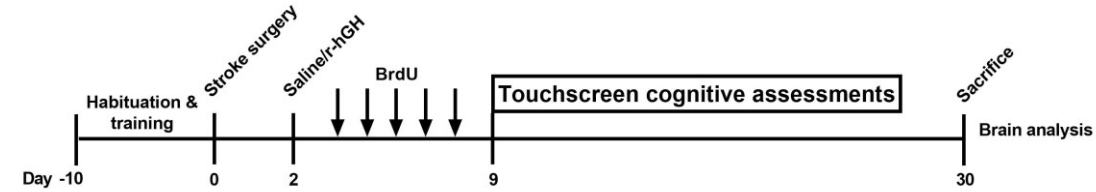

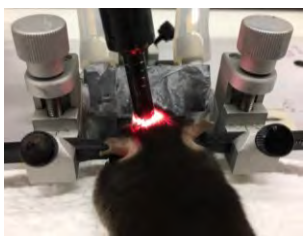

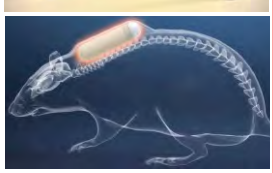

1.4 mg/kg body weight/day for 28 days

Can GH treatment improve post-stroke cognitive impairment?

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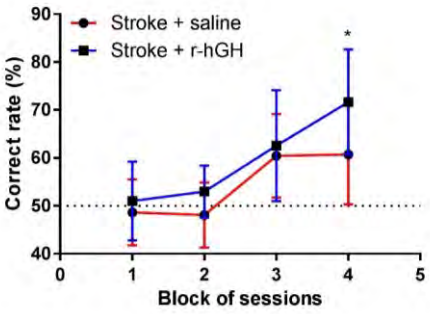
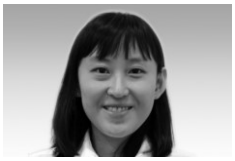
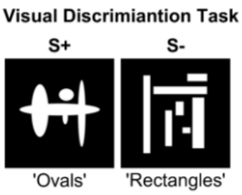
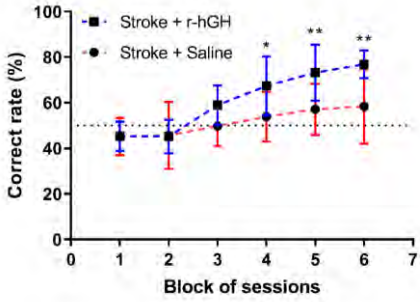
GH treatment improves cognitive function after cortical stroke

Ong et al. (2018) Stroke

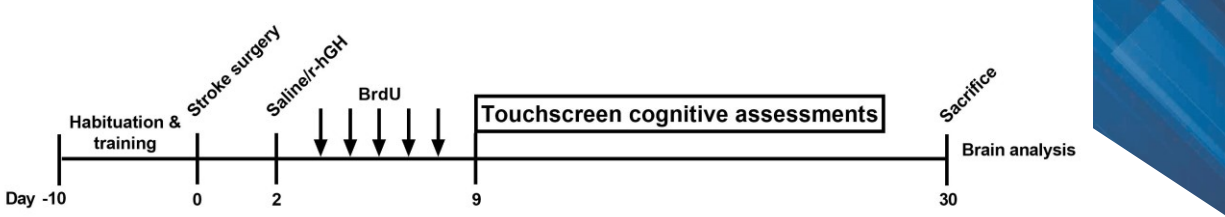


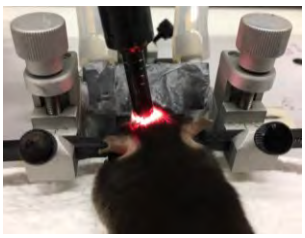


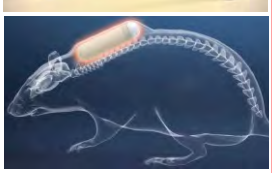




Bezanilla, Ong et al. (2020) IJMS



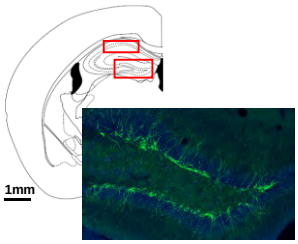




1.4 mg/kg body weight/day for 28 days

Can GH treatment improve post-stroke cognitive impairment?

Can GH treatment enhance neurorestorative processes?



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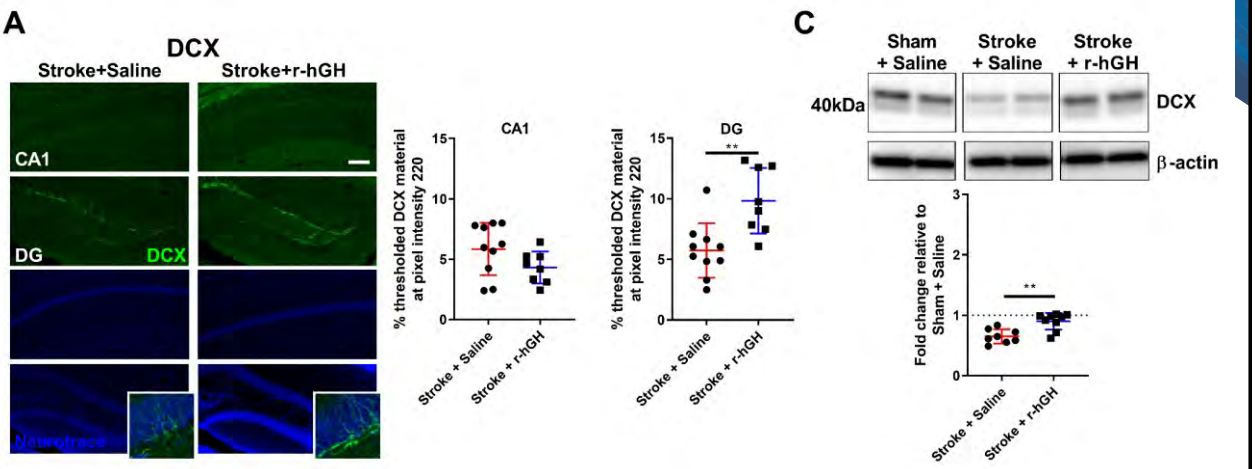
GH treatment promotes neurogenesis in the dentate gyrus of the hippocampus



Bezanilla, Ong et al. (2020) IJMS

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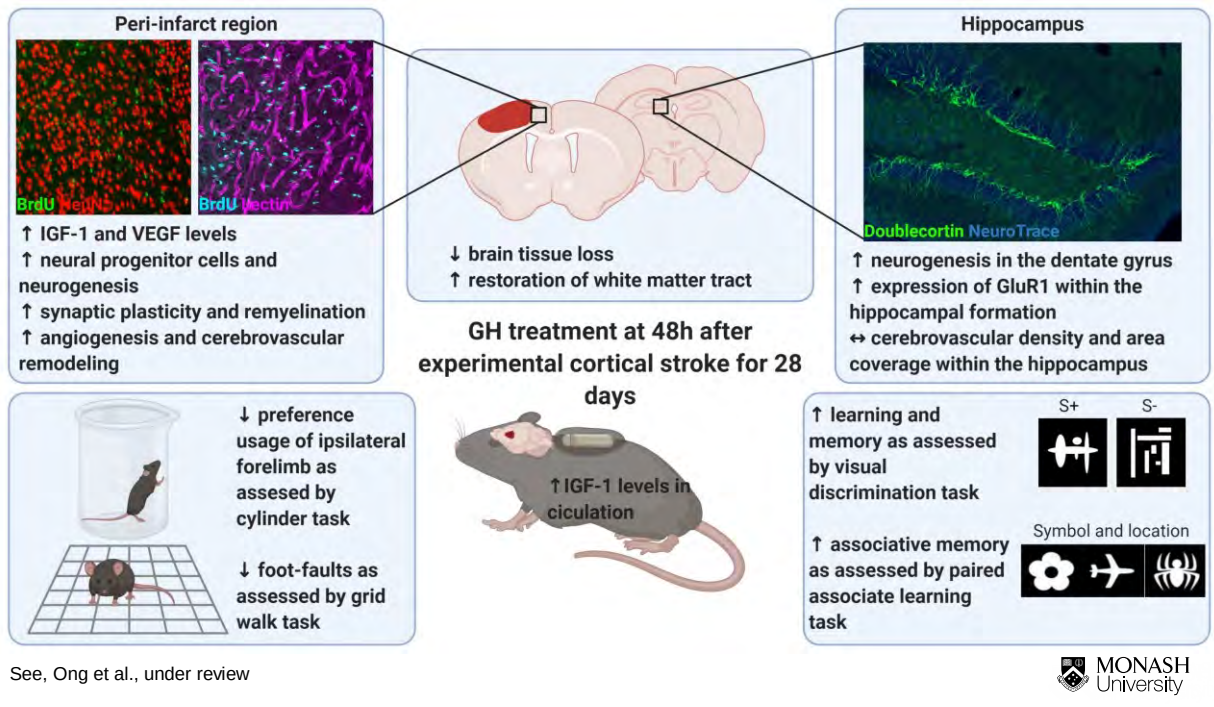

See, Ong et al., under review

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Summary

Stroke triggers a neurodegenerative condition

- Neuronal death, neuroinflammation, accumulation of neurotoxic proteins
- Post-stroke cognitive impairment

Therapeutic strategies to enhance the brain's endogenous capacity for neurorestorative processes after stroke

- Growth hormone treatment promotes neurogenesis and cognitive function

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Acknowledgments



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Monash University Malaysia
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International Society for Neurochemistry

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THE UNIVERSITY OF NEWCASTLE AUSTRALIA
HMRI Hunter Medical Research Institute
NHMRC CENTRE OF RESEARCH EXCELLENCE Stroke Rehabilitation and Brain Recovery
ISN International Society for Neurochemistry
INTERNATIONAL BRAIN IBRO RESEARCH ORGANIZATION

Thank you for listening

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