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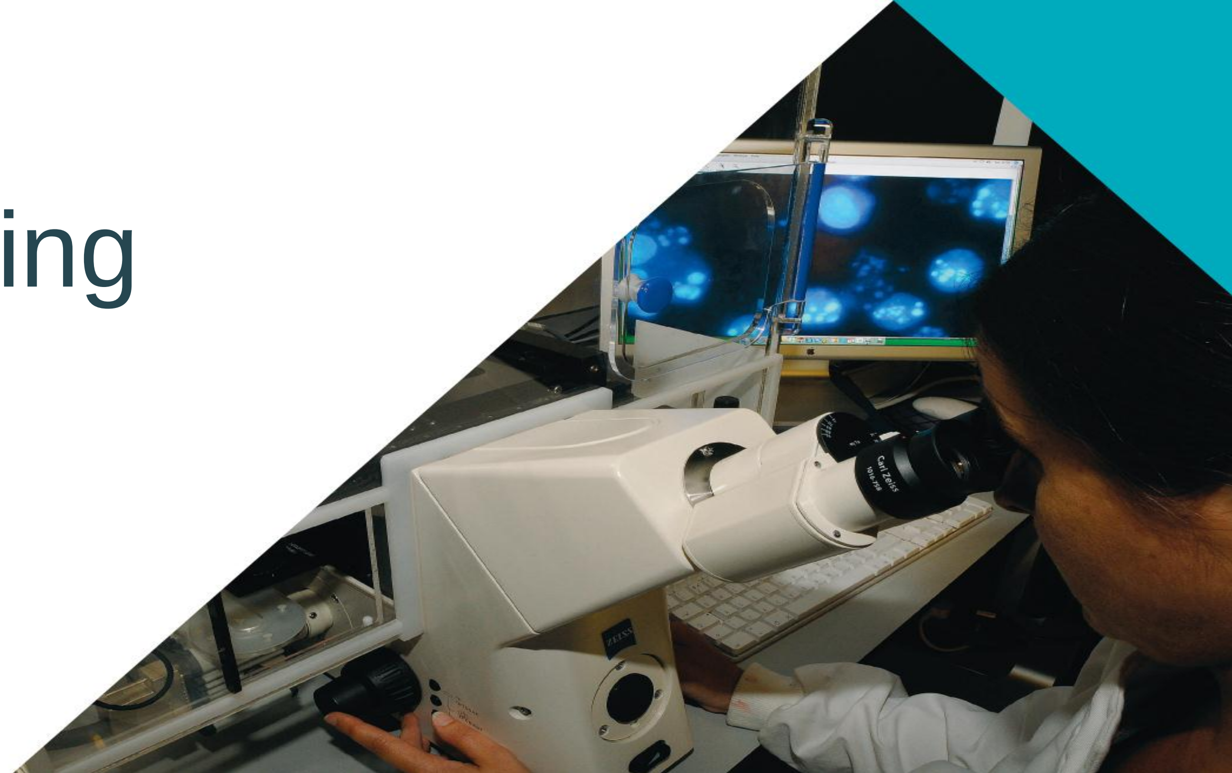
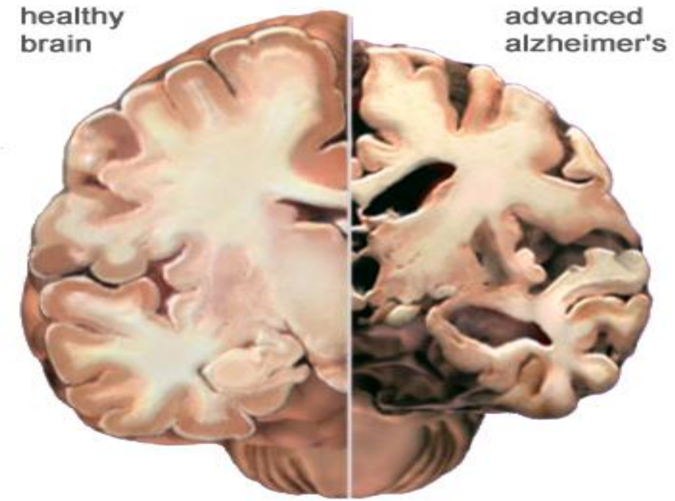
Athena SWAN Bronze Award

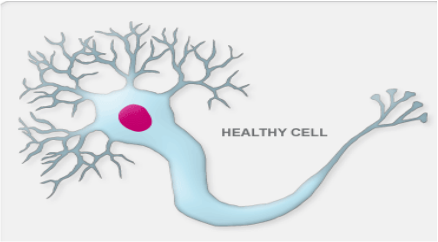
Modelling Alzheimer’s Disease Using Stem Cells

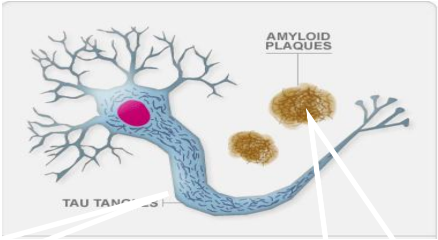
Dr Eric Hill

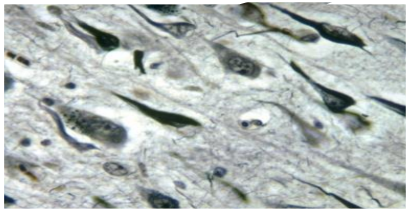


Alzheimer's disease

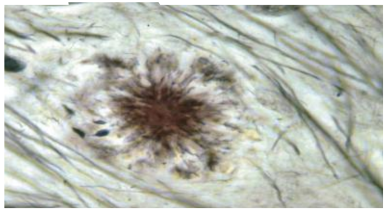








tau

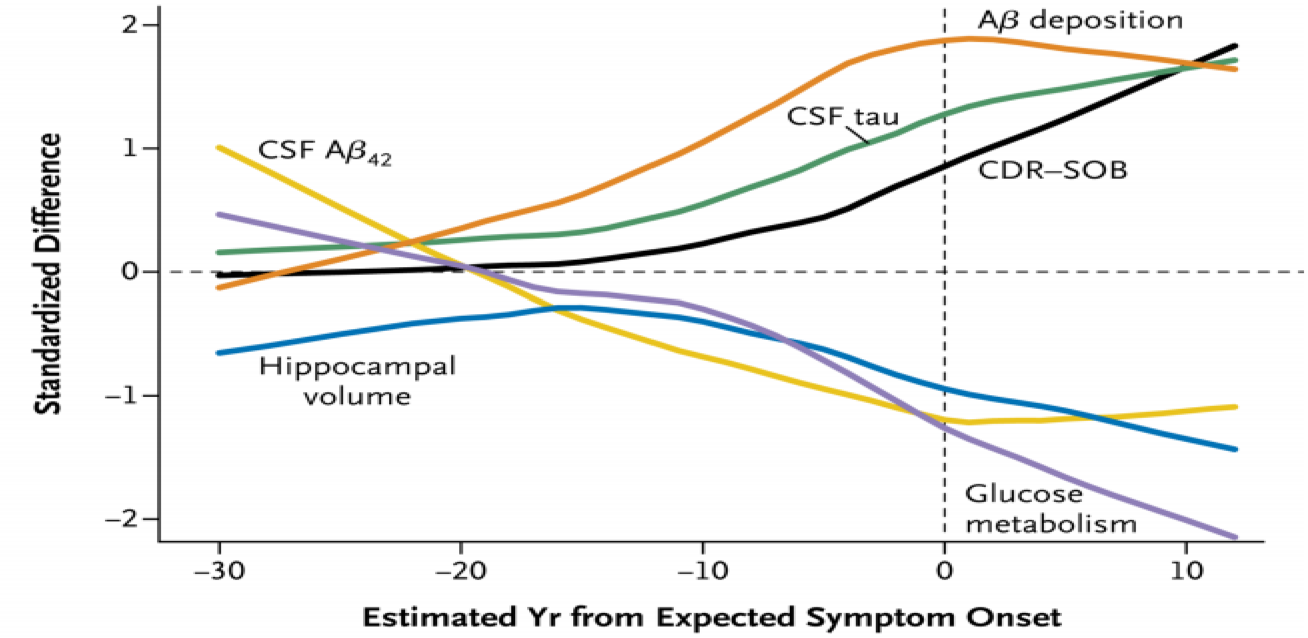


amyloid

Drug development

Agent	Target/mechanism	Outcome
Simvastatin	HMG CoA reductase inhibitor	Negative
NSAIDs	Inflammation	Negative
Rosiglitazone	Insulin	Negative
Latrepiridine	Mitochondrial function	Negative
AN1792	Amyloid immunoRX	Negative
Tramiprosate	Amyloid aggregation	Negative
Tarenflurbil	Gamma secretase	Negative
Avagacestat	Gamma secretase	Negative
Bapineuzumab	Amyloid immunoRX	Negative
Solanezumab	Amyloid immunoRX	Negative (+/-)
IVIG	Nonselective immunoRX	Negative
LY2886721	Beta secretase	Negative

Changes in the brain of an AD patient



N Engl J Med. 2012 August 30; 367(9): 795–804. doi:10.1056/NEJMoa1202753.

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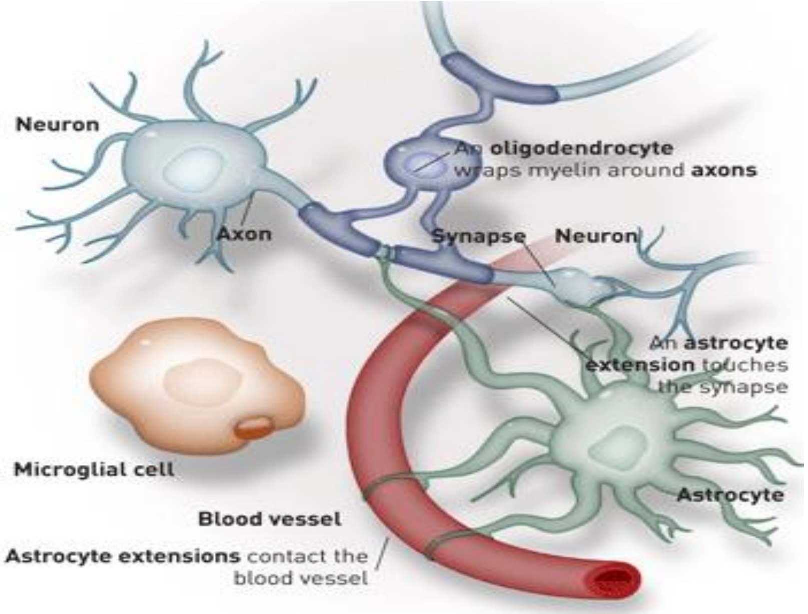
Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease

Stem cell research in my laboratory



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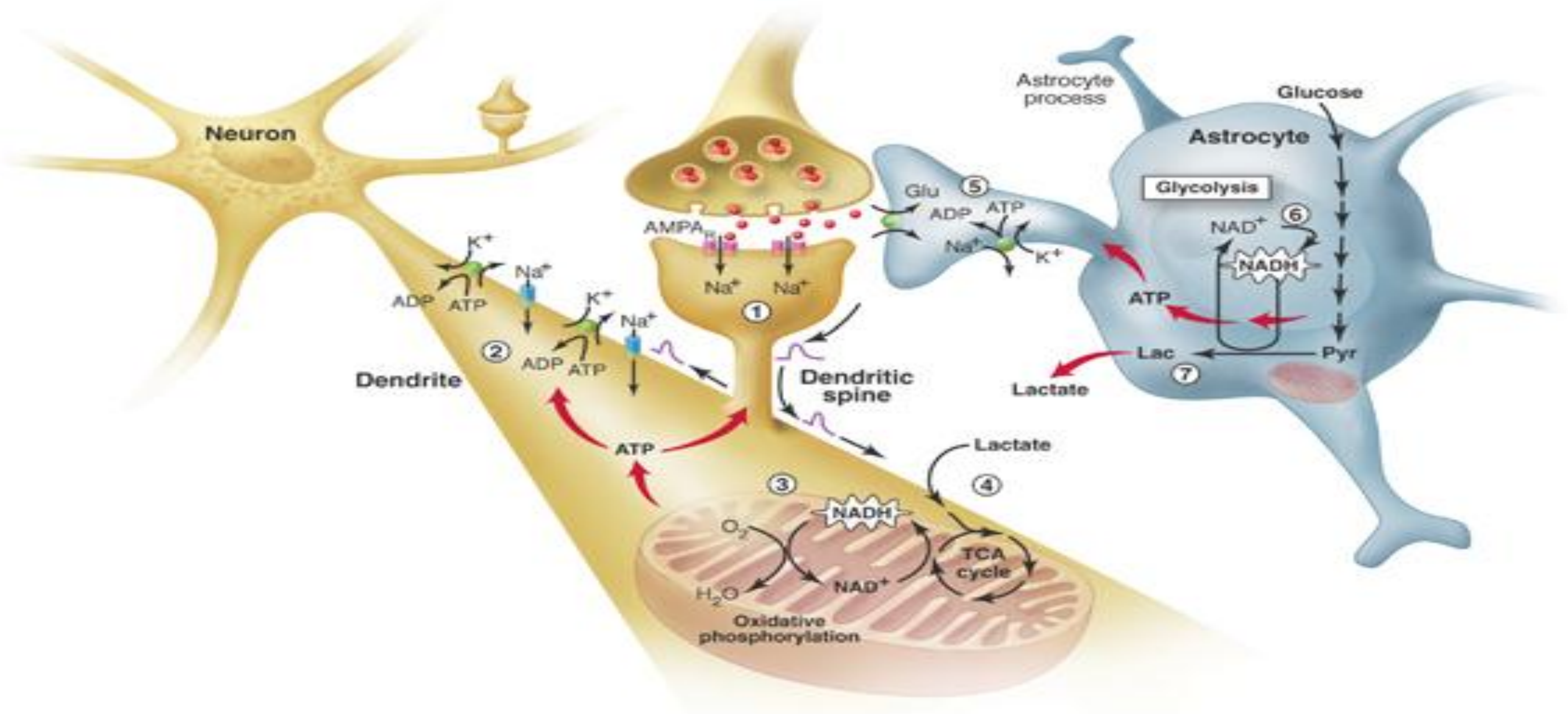
NEURAL STEM CELLS
ALZHEIMER'S DISEASE
Hill GROUP

The tripartite synapse



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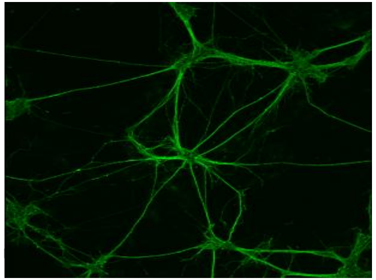
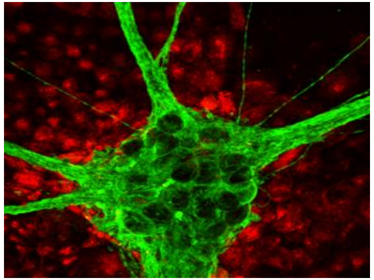
Pellerin and Magistretti 2005

Differentiation of NT2.D embryocarcinoma cell line

RA
28 days
↓
Re-plating
↓
Second re-plating

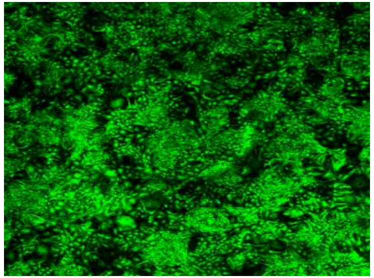
High mitotic inhibitors	**Low mitotic inhibitors**
3 weeks	**4 weeks**
↓	↓
Neurons	**Neurons and astrocytes**



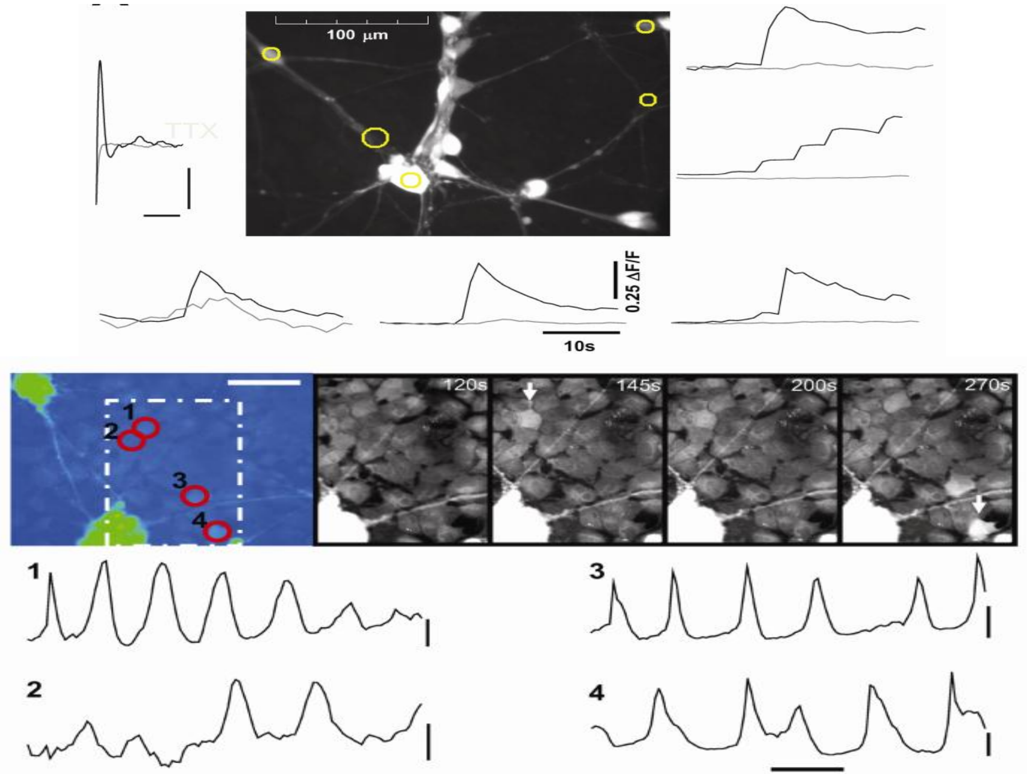


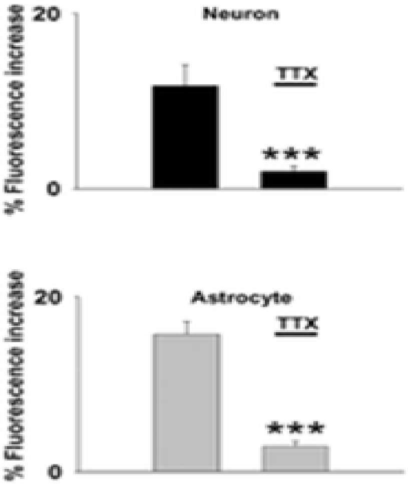
→ **re-plating**

Astrocytes



Do cells display spontaneous and evoked network activity?





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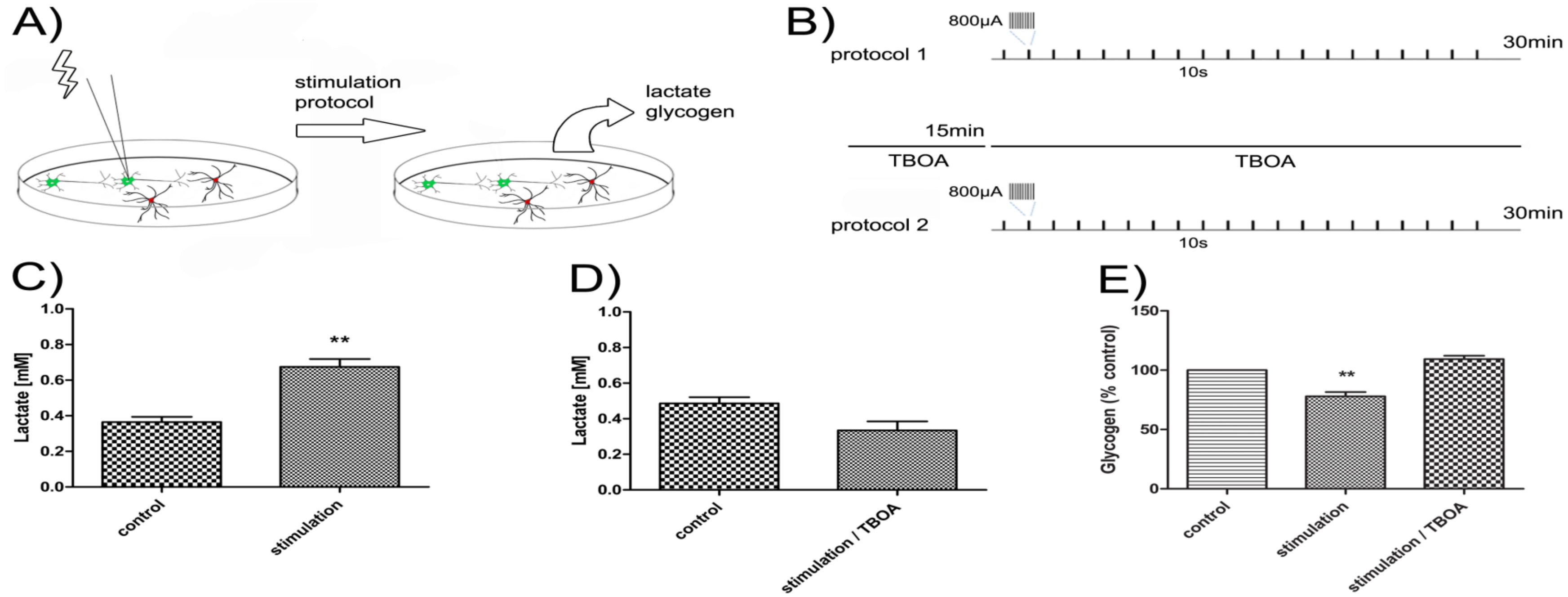
Do stem cell derived astrocytes respond to neuronal activity?



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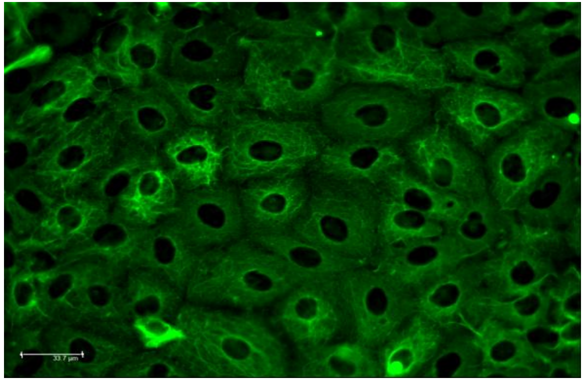
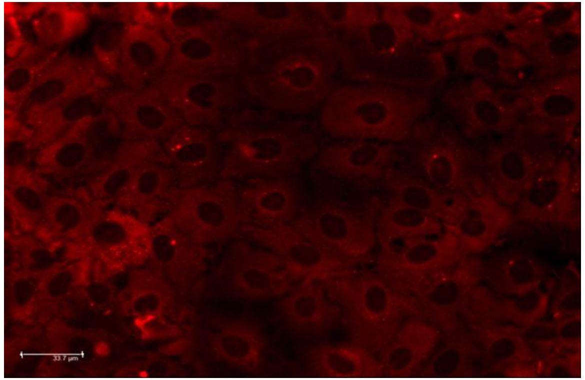
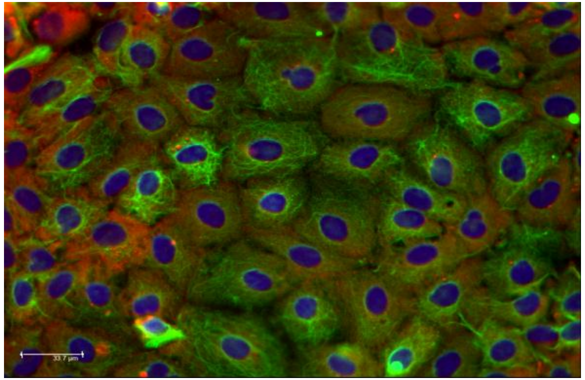
Stem cell derived astrocytes contain glycogen



GFAP



Glycogen



Merge

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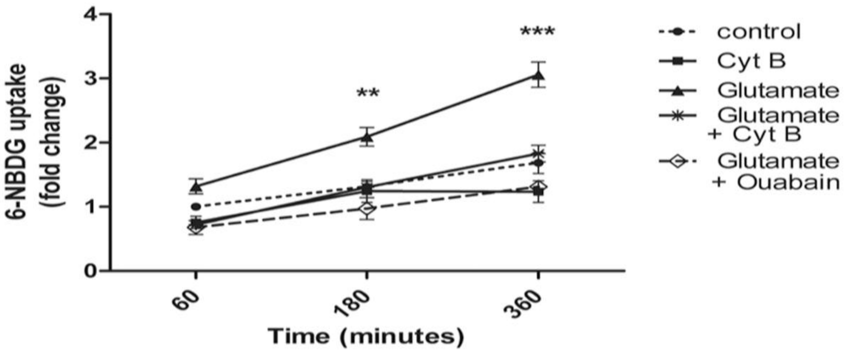
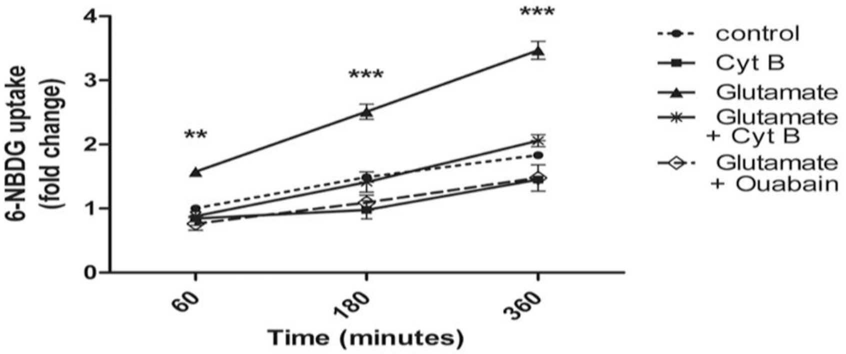
Glutamate induces glucose uptake in stem cell derived astrocytes

Neurons and astrocytes



Astrocytes



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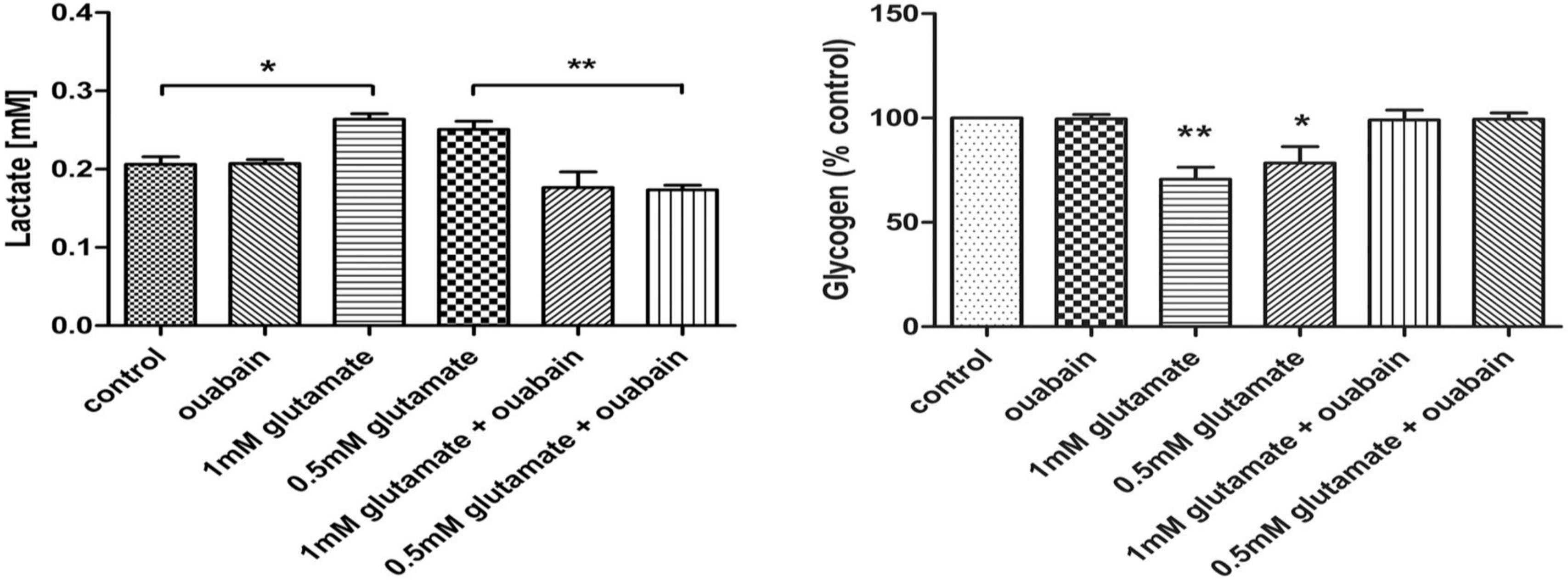
Glutamate induces glycolysis and glycogenolysis in stem cell derived cultures



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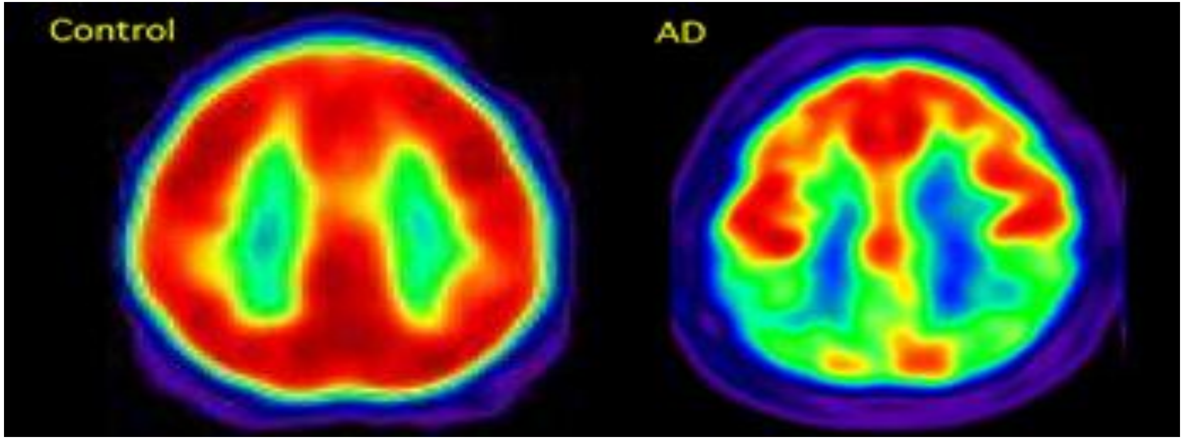
Summary

- NT2 derived cultures are electrophysiologically competent.
- Show evidence of a functional Astrocyte to Neuron lactate shuttle.
- Stem cell derived astrocyte produce glycogen.

Hypometabolism in AD



A Composite Picture of Glucose Metabolism Using PET and the Tracer FDG

The AD patient on the right shows reduced glucose metabolism in temporoparietal cortex, a hallmark of the disease

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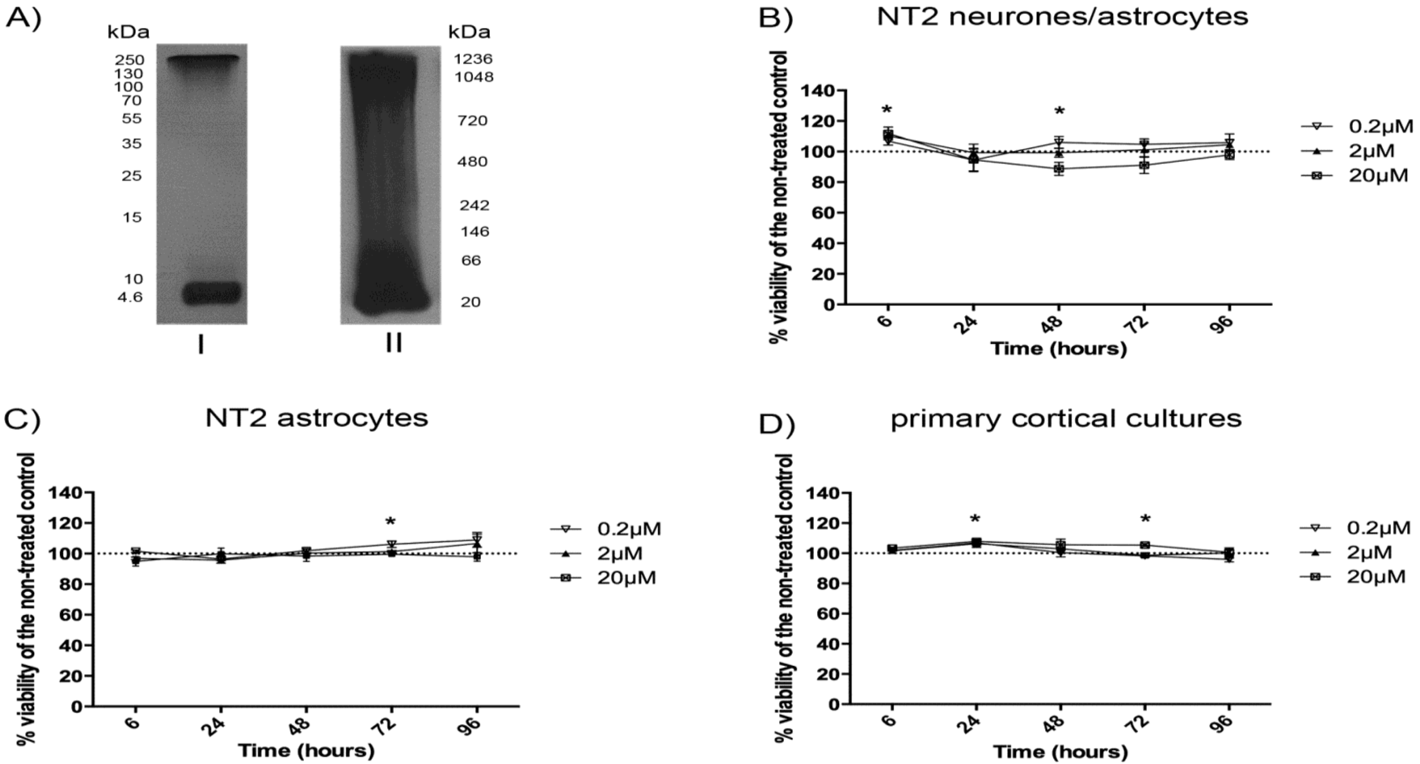
Viability of cultures following treatment with Aβ1-42



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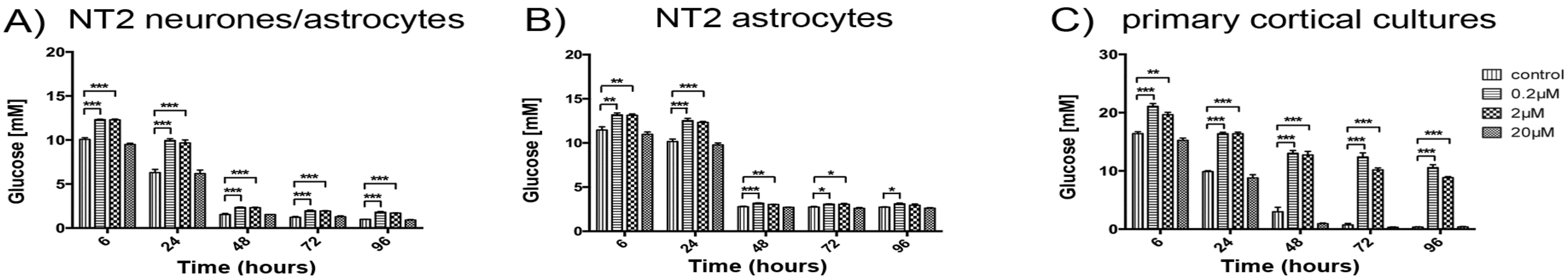
Effects of amyloid on glucose uptake



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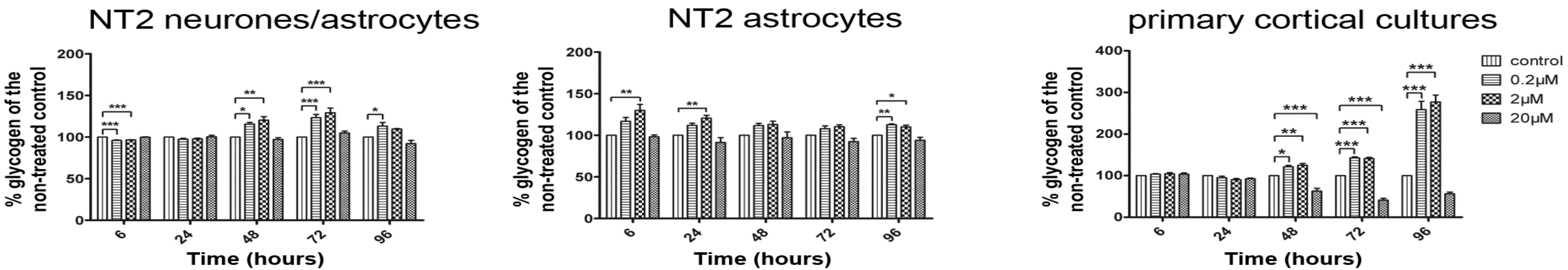
Effect of Amyloid on glycogen metabolism



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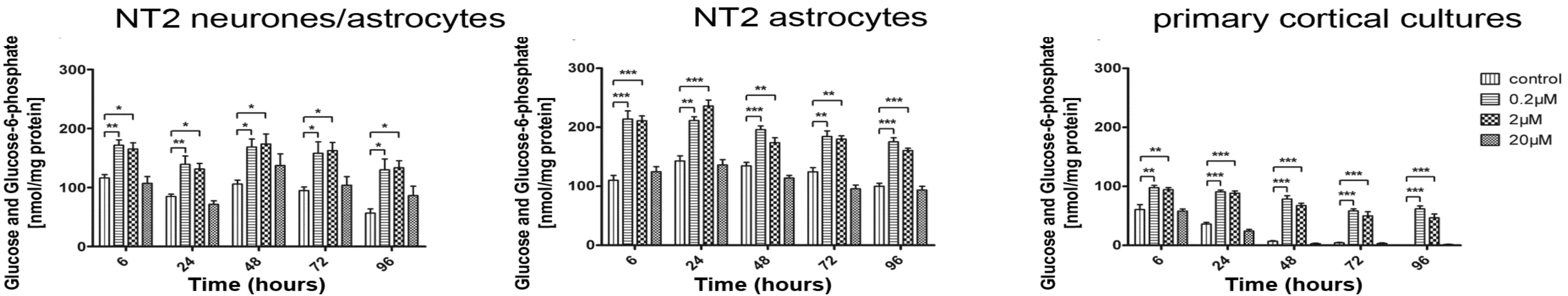
Effect of Amyloid on intracellular glucose levels



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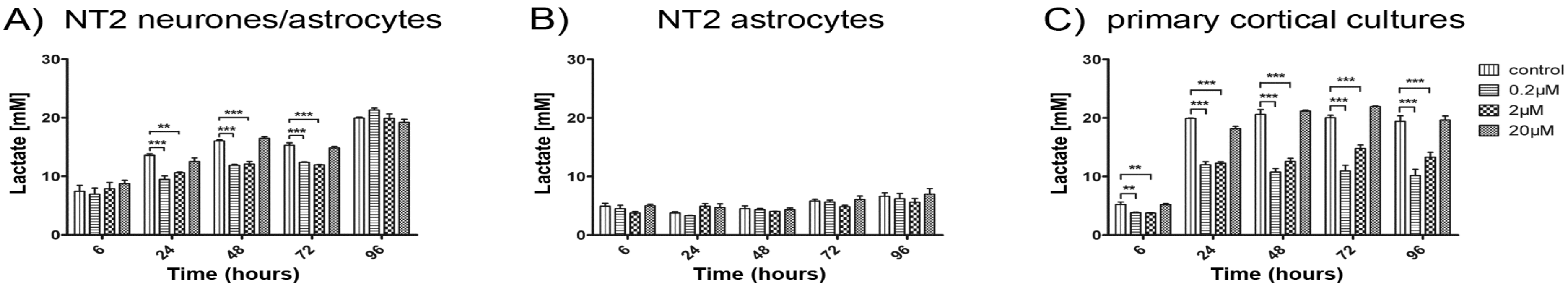
Effect of Amyloid on lactate metabolism



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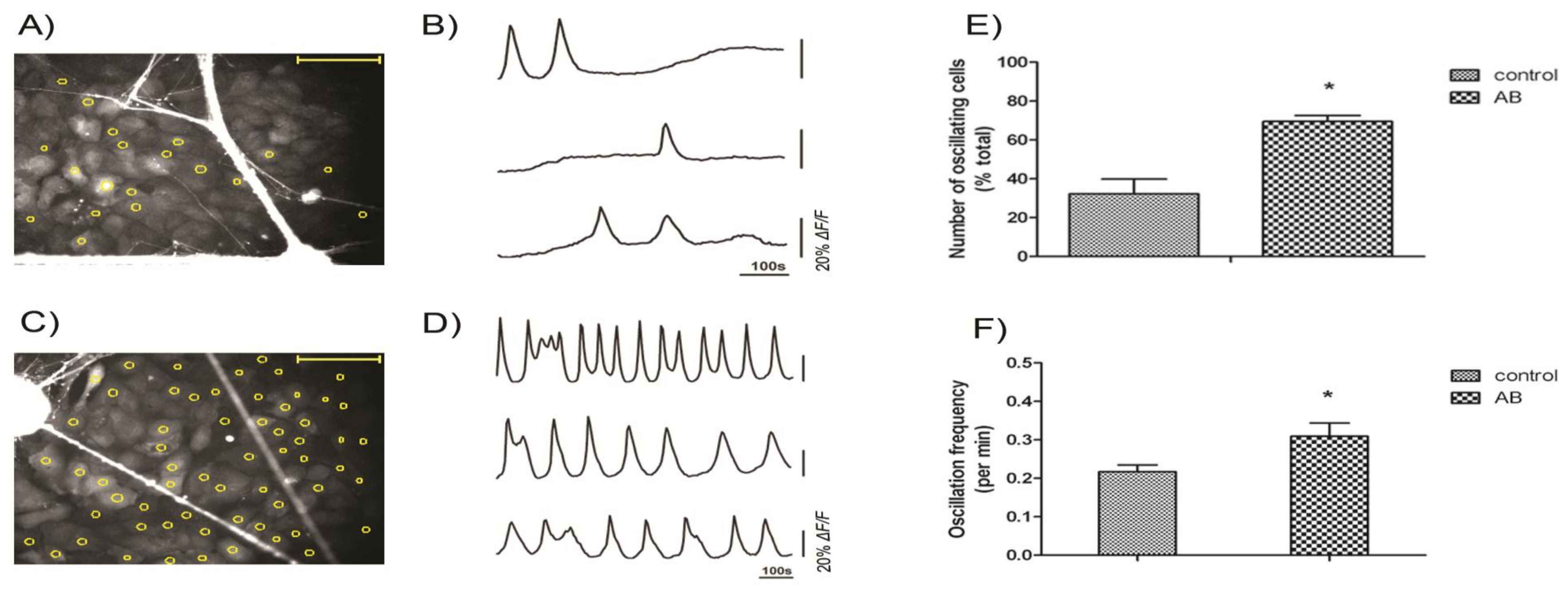
Effects of amyloid on spontaneous calcium activity in astrocytes



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Conclusion

- Aβ induces hypometabolism in both rat and human stem cell derived neurons and astrocytes.
- Disruption of the energy/redox balance within cells
- Altered calcium signalling

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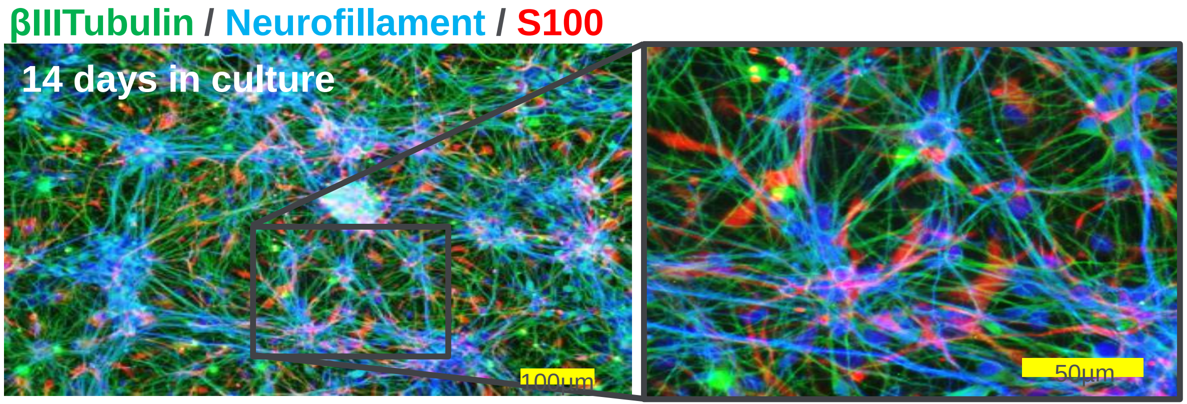
What are the long term implications of chronic energy imbalance in the brain?



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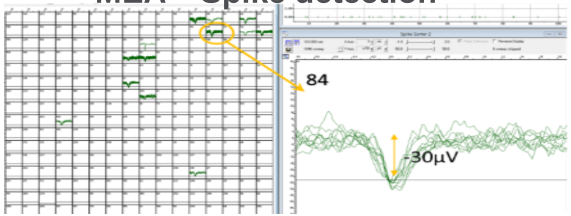
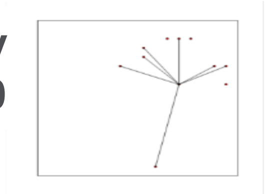
Electrophysiological characterisation of spontaneous and induced activity

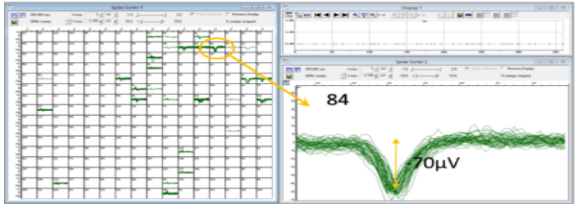
Inferred networks | **MEA – Spike detection**

Day 30

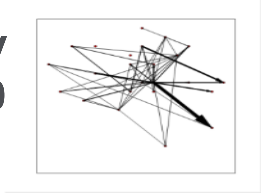


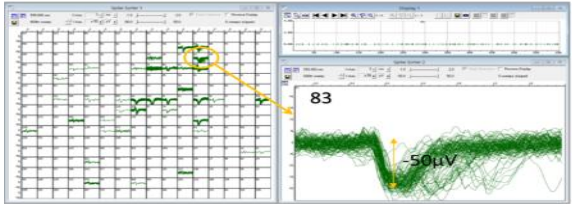
Day 50



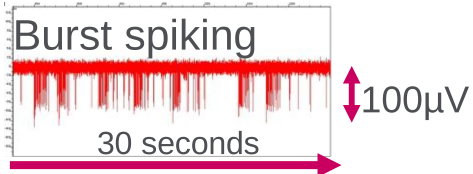


Day 100

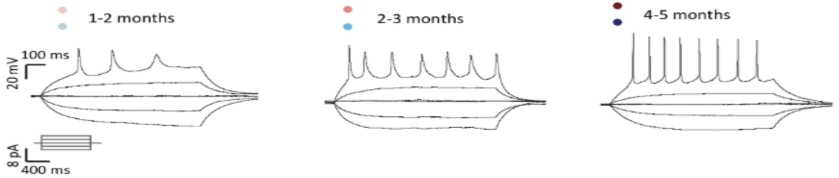


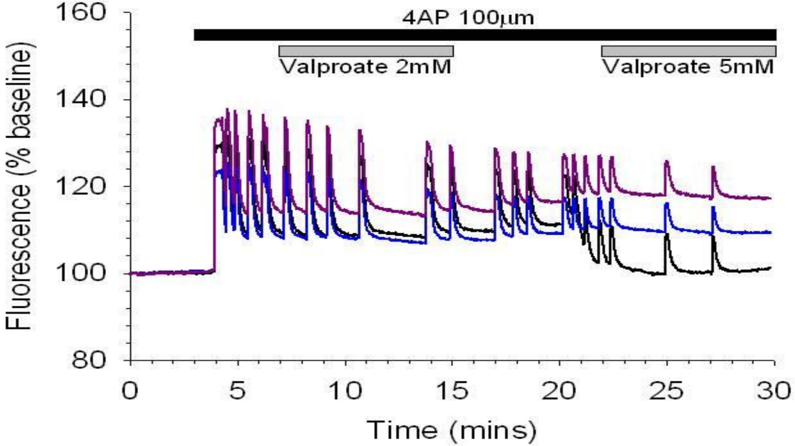


Day 110



Patch clamp





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Challenges with disease modelling

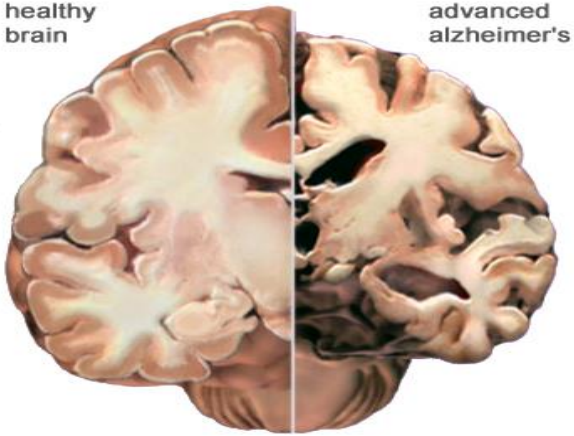
Developmental regulation of tau splicing is disrupted in stem cell-derived neurons from frontotemporal dementia patients with the 10 + 16 splice-site mutation in MAPT

Teresa Sposito[1], Elisavet Preza[1], Colin J. Mahoney[2], Núria Setó-Salvia[1], Natalie S. Ryan[2], Huw R. Morris[3], Charles Arber[1], Michael J. Devine[1,4], Henry Houlden[1], Thomas T. Warner[1], Trevor J. Bushell[5], Michele Zagnoni[6], Tilo Kunath[7], Frederick J. Livesey[8], Nick C. Fox[2], Martin N. Rossor[2], John Hardy[1] and Selina Wray[1,*]

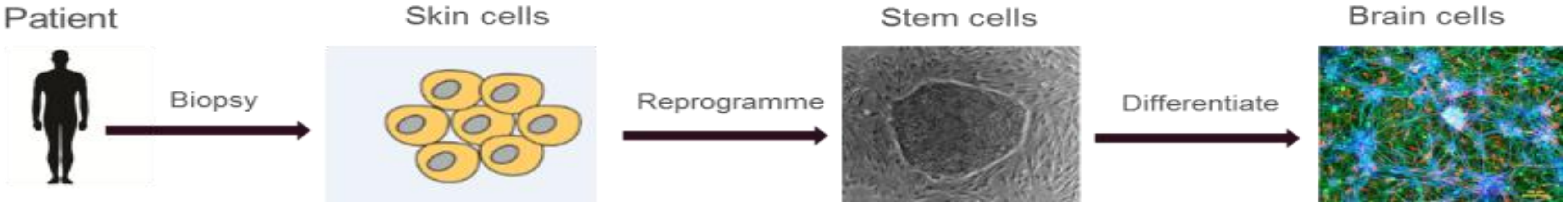
- Control neurons only express the fetal tau isoform (0N3R), even at extended time points of 100 days *in vitro*.

- Time points of 365 days *in vitro*, reveal a switch in tau splicing to include six tau isoforms as seen in the adult human CNS

Biological age



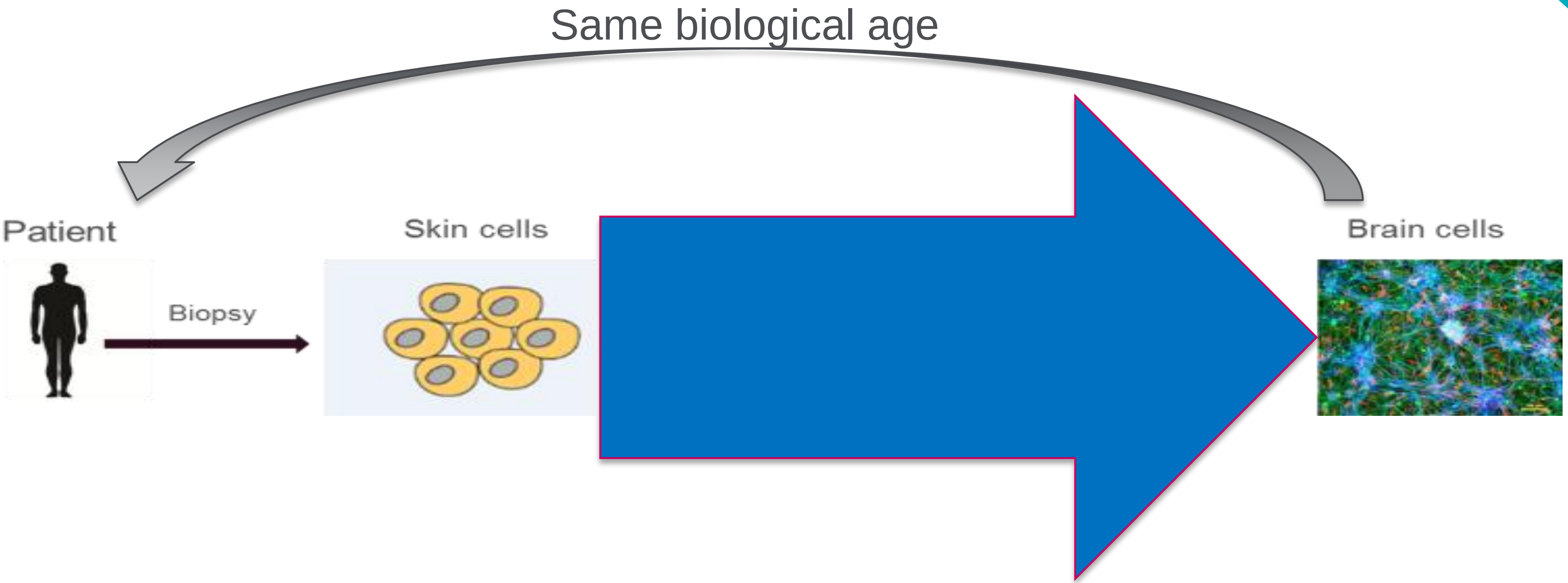
Foetal/postnatal



Human iPSC-Based Modeling of Late-Onset Disease via Progerin-Induced Aging

Justine D. Miller,[1,2,3] Yosif M. Ganat,[1,2] Sarah Kishinevsky,[1,2] Robert L. Bowman,[3,4] Becky Liu,[1,2] Edmund Y. Tu,[1,2] Pankaj K. Mandal,[6,7] Elsa Vera,[1,2] Jae-won Shim,[1,2] Sonja Kriks,[1,2] Tony Taldone,[5] Noemi Fusaki,[8,9] Mark J. Tomishima,[1,2] Dimitri Krainc,[10] Teresa A. Milner,[11,12] Derrick J. Rossi,[6,7] and Lorenz Studer[1,2,*]

Direct reprogramming



Directly Reprogrammed Human Neurons Retain Aging-Associated Transcriptomic Signatures and Reveal Age-Related Nucleocytoplasmic Defects

Jerome Mertens, Apuã C.M. Paquola, Manching Ku, Emily Hatch, Lena Böhnke, Shauheen Ladjevardi, Sean McGrath, Benjamin Campbell, Hyungjun Lee, Joseph R. Herdy, J. Tiago Gonçalves, Tomohisa Toda, Yongsung Kim, Jürgen Winkler, Jun Yao, Martin W. Hetzer, Fred H. Gage

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Acknowledgements

Prof Michael Coleman
Dr David Nagel
Dr Elizabeth Woehrling
Dr Rhein Parri
Dr Marta Tarczyluk
Dr Erin Tse

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BBSRC bioscience for the future

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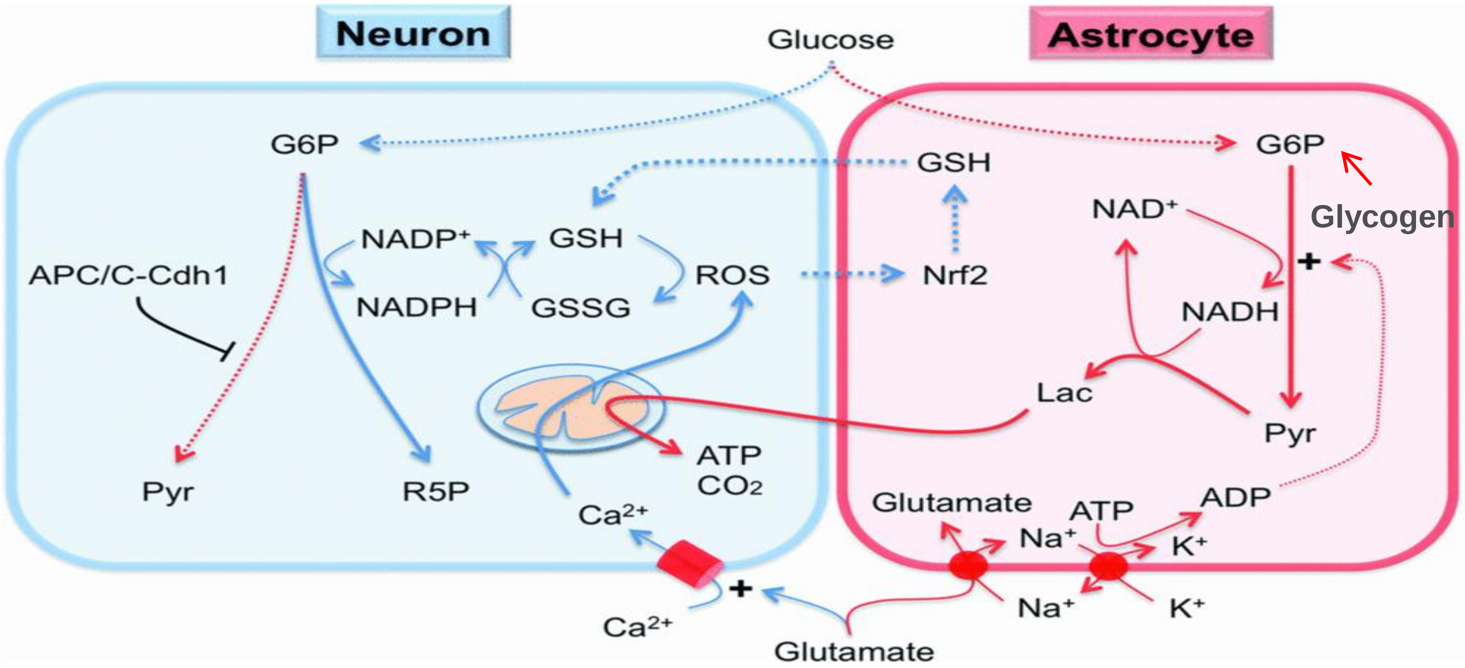
MRC Medical Research Council

Alzheimer's Research UK
The Power to Defeat Dementia

Astrocytes and neurons couple glucose metabolism to antioxidant defence



Biochemical Journal 2012 443, 3-11 - Seila Fernandez-Fernandez, Angeles Almeida and Juan P. Bolaños