



Le Malattie Degenerative Cerebrali: dai Meccanismi Patogenetici alla Diagnosi

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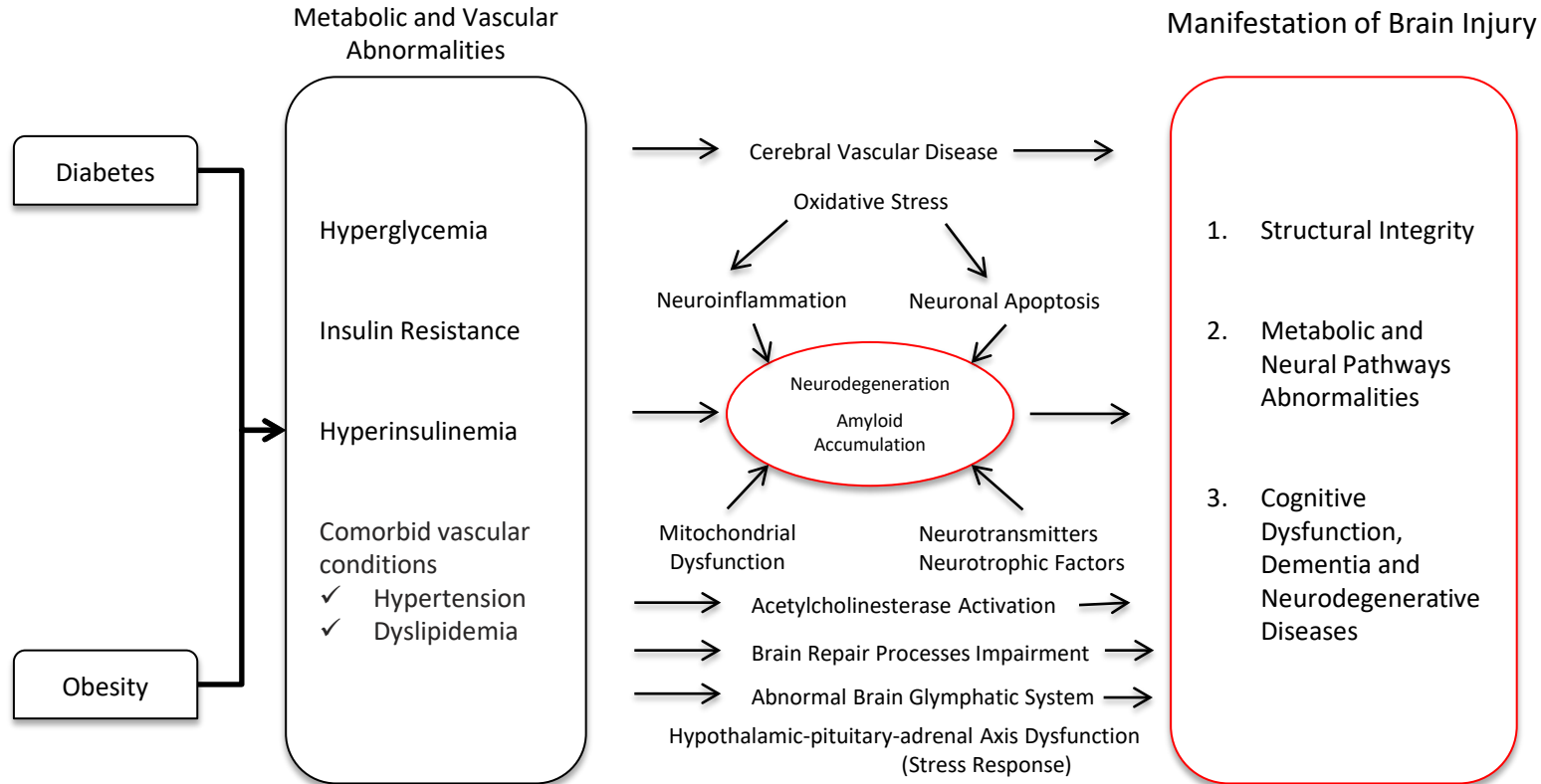
Disclosures

Il Dr. Giuseppe Daniele dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

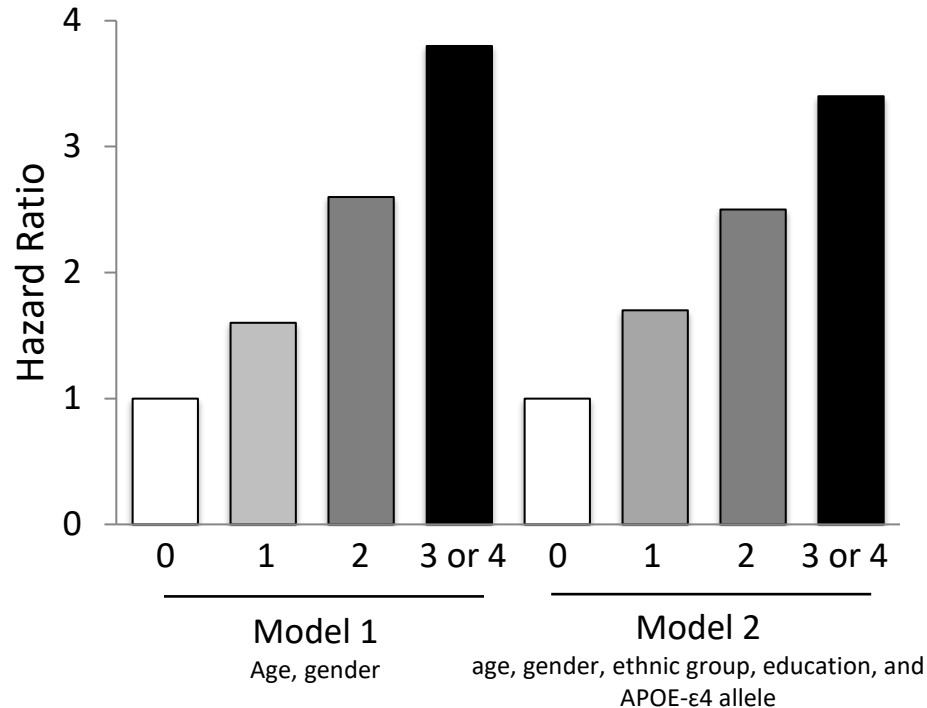
- Eli Lilly
- Astrazeneca

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Impact of Obesity and Diabetes on Human Brain

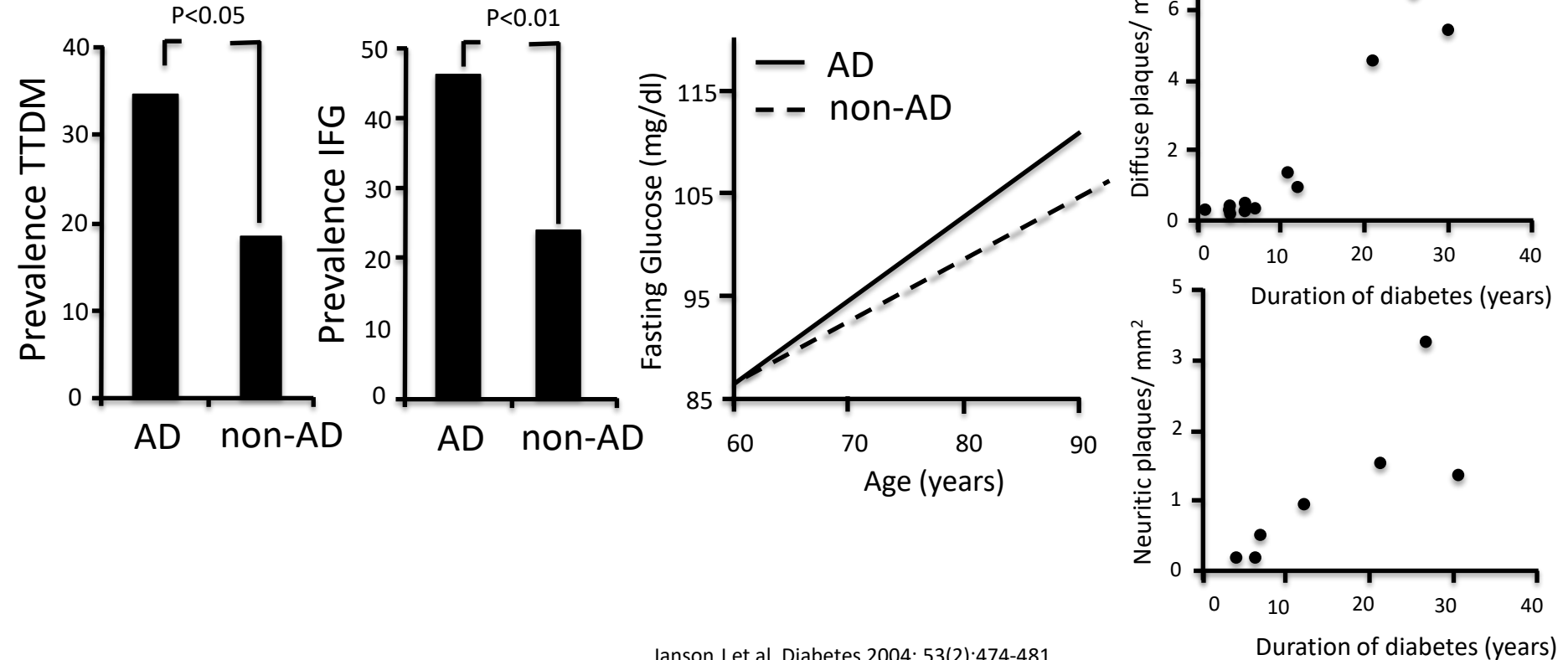


Two-way connection between Metabolic and Neurodegenerative Diseases

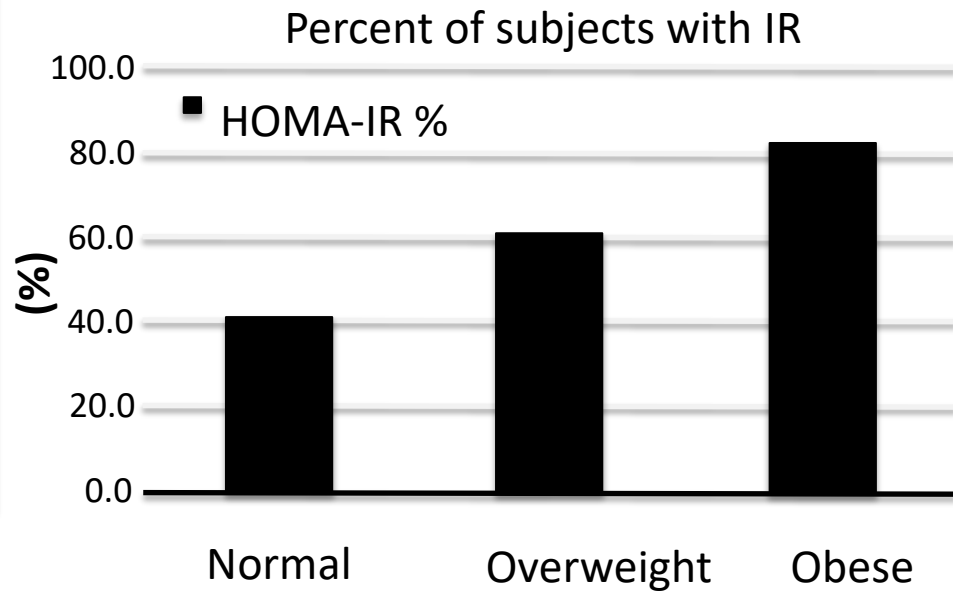
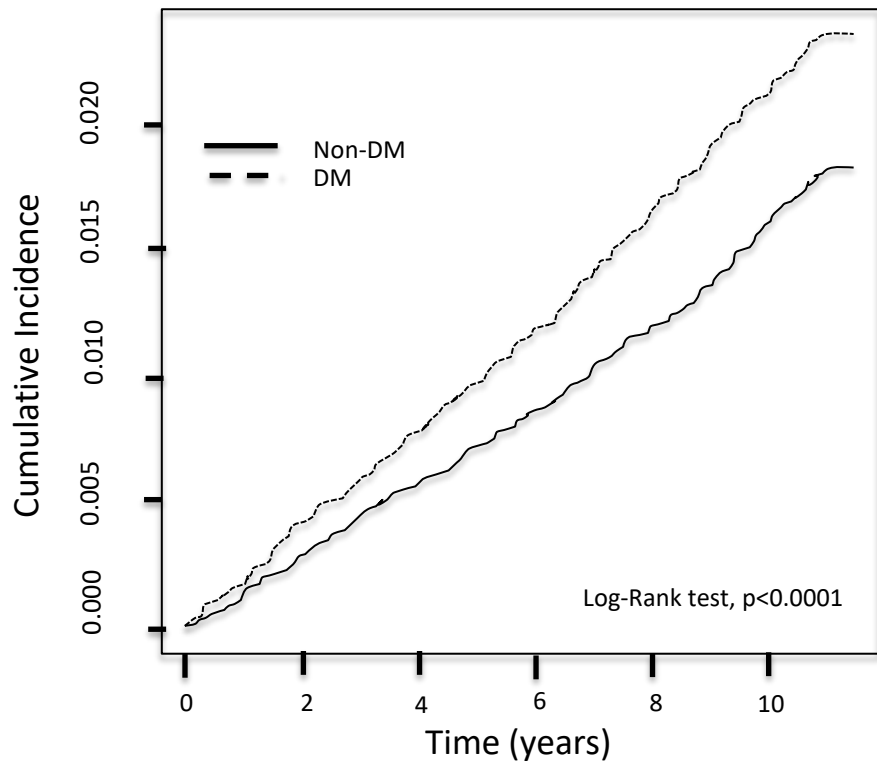


Risk Profile	Model 1	Model 2
No risk factors	1.0	1.0
DM only	3.6 (1.8,7.1)	3.8 (1.8, 8.2)
HTN only	1.4 (0.9,2.1)	1.5 (0.9,2.4)
HEART only	1.7 (0.8, 3.3)	1.0 (0.4,2.6)
SMOKE only	2.2 (1.1,4.7)	2.2 (1.0,4.9)
DM + HTN	3.3 (1.9,5.4)	3.3 (1.9,5.9)
DM + HEART	3.5 (1.4,9.0)	3.7 (1.2,11.1)
DM + SMOKE	13.7 (1.8,101.7)	7.4 (0.5,108.9)
HTN + HEART	2.3 (1.5,3.5)	2.3 (1.4,3.7)
HTN + SMOKE	2.2 (1.0, 4.7)	2.7 (1.2,6.1)
HEART + SMOKE	3.1 (0.4,22.5)	5.9 (0.7, 46.9.)
3 or 4 risk factors	3.8 (2.4,5.9)	3.4 (2.1,5.7)

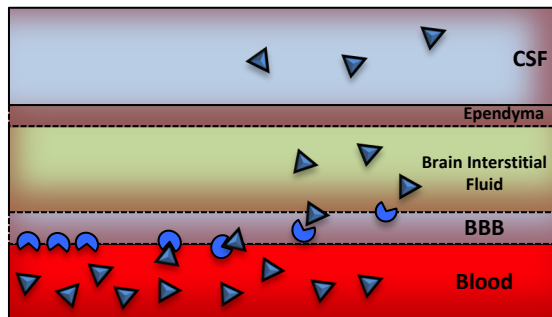
Two-way connection between Metabolic and Neurodegenerative Diseases



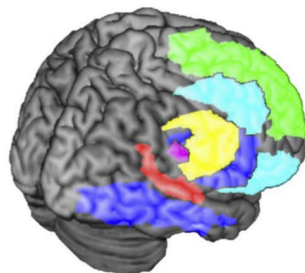
Two-way connection between Metabolic and Neurodegenerative Diseases



Brain Insulin Action and Brain Insulin Resistance



Saturable, receptor-mediated process



Insulin sensitive brain regions

Neuronal Metabolism
Neuronal Development
Synaptic Efficacy
Neuronal Firing
Neuronal Survival

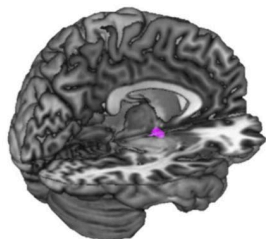
Local Insulin Sources

- Local Energy on demand
- Local Suppression of Excitation

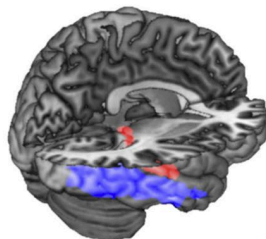
BBB

Pancreatic Insulin

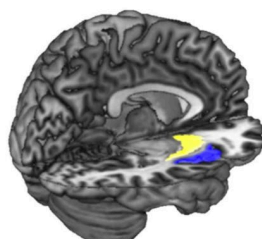
- ✓ Amyloid- β oligomers affect insulin signal
- ✓ Insulin signal impairment in dopaminergic neurons (sub. nigra)
- ✓ Inflammation
- ✓ Chronic peripheral hyperinsulinemia downregulates BBB transporters
- ✓ CNS insulin deficiency associated to impaired synaptic plasticity, memory and neurodegenerative diseases



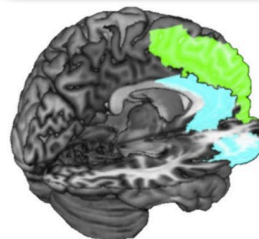
Homeostasis
Hypothalamus



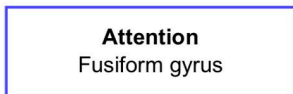
Memory
Hippocampus



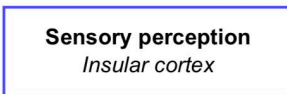
Reward
Striatum



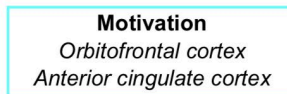
Inhibition
Lateral prefrontal cortex



Attention
Fusiform gyrus

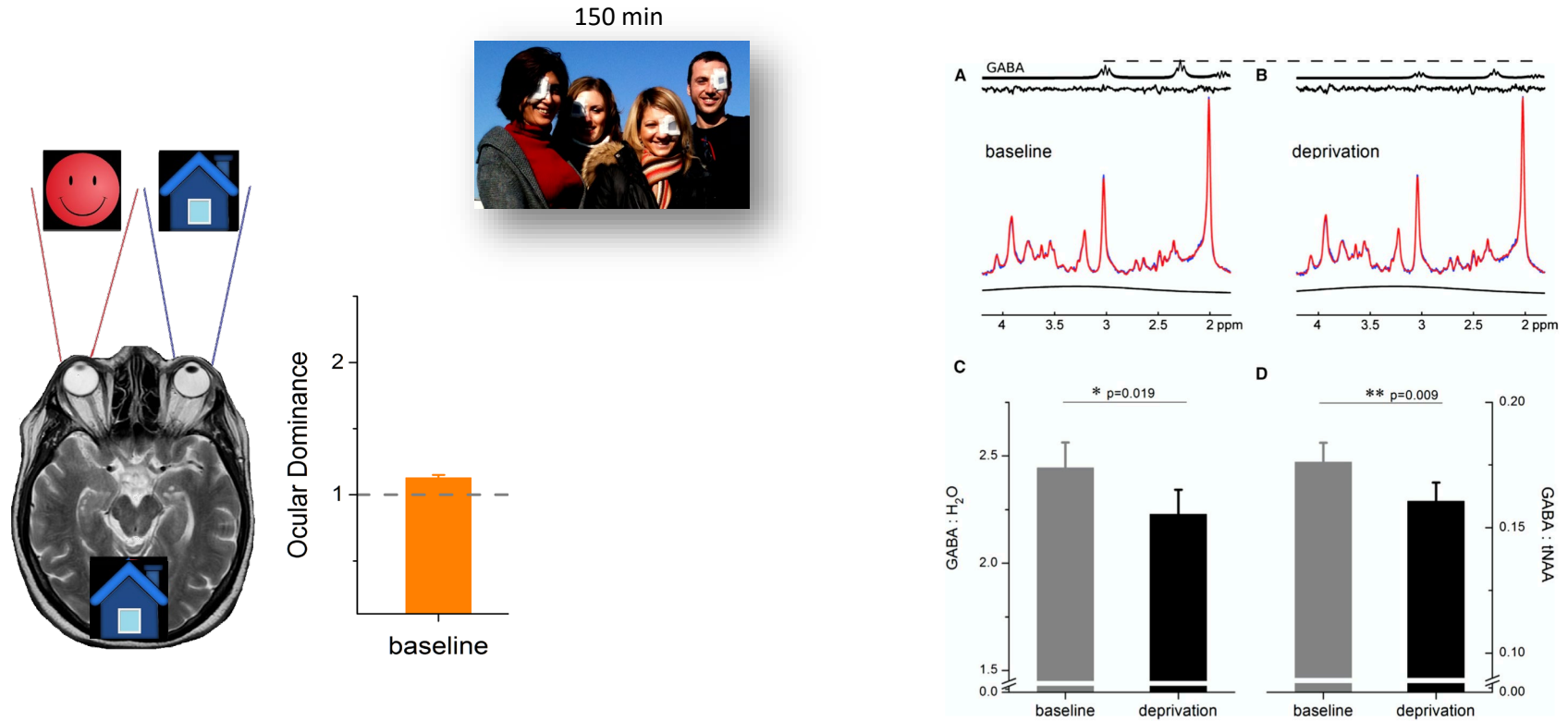


Sensory perception
Insular cortex

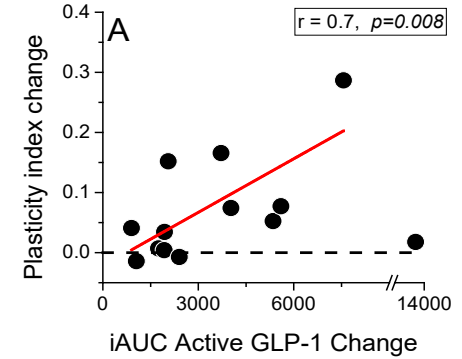
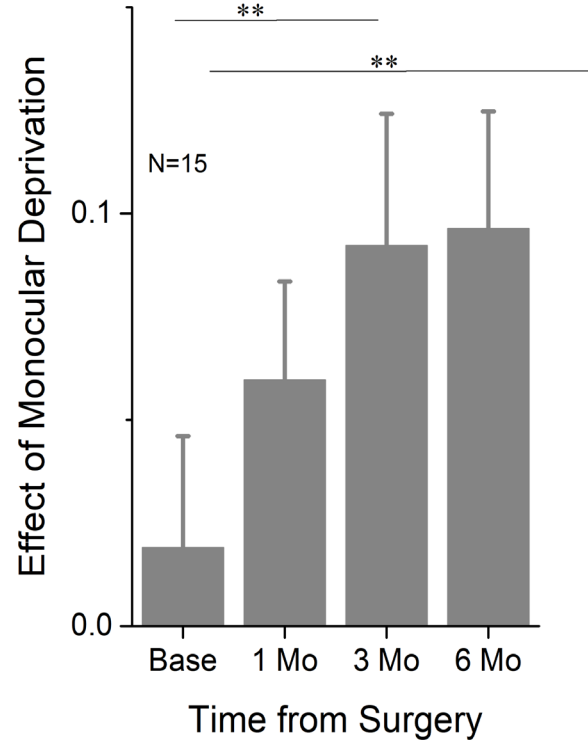
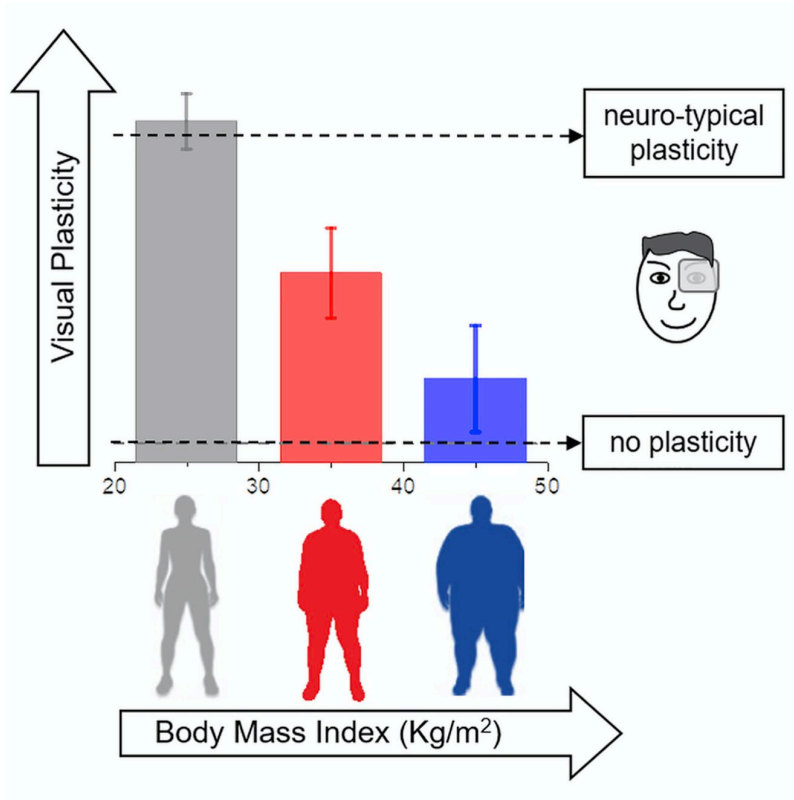


Motivation
Orbitofrontal cortex
Anterior cingulate cortex

Measuring Neuroplasticity in vivo

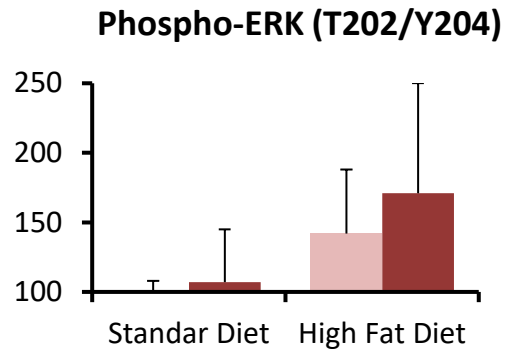
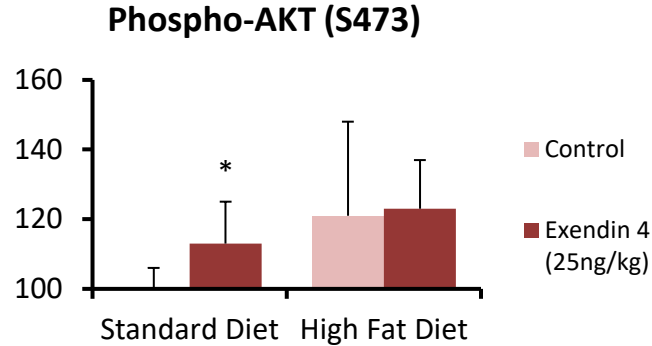


Effects of Obesity and Bariatric Surgery on Neuroplasticity

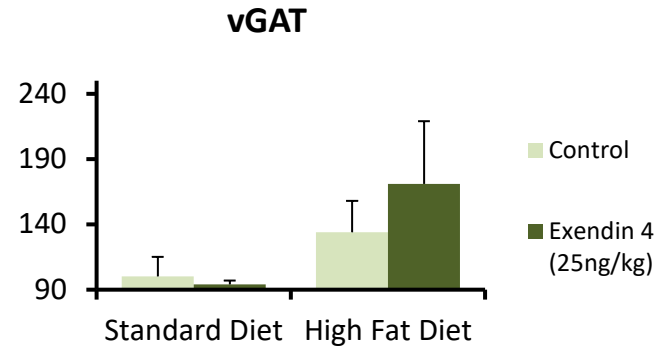
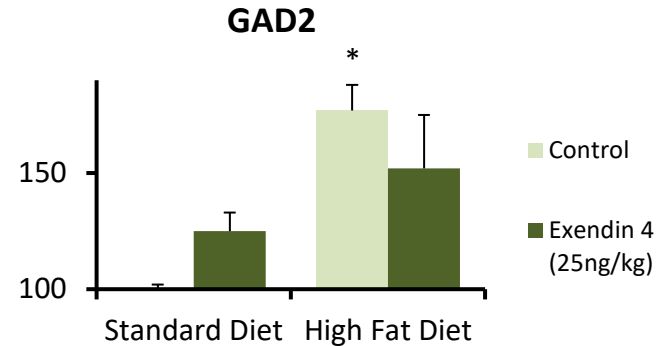


Effects of HFD and Exendin-4 on Visual Cortex Signalling

INSULIN SIGNALLING



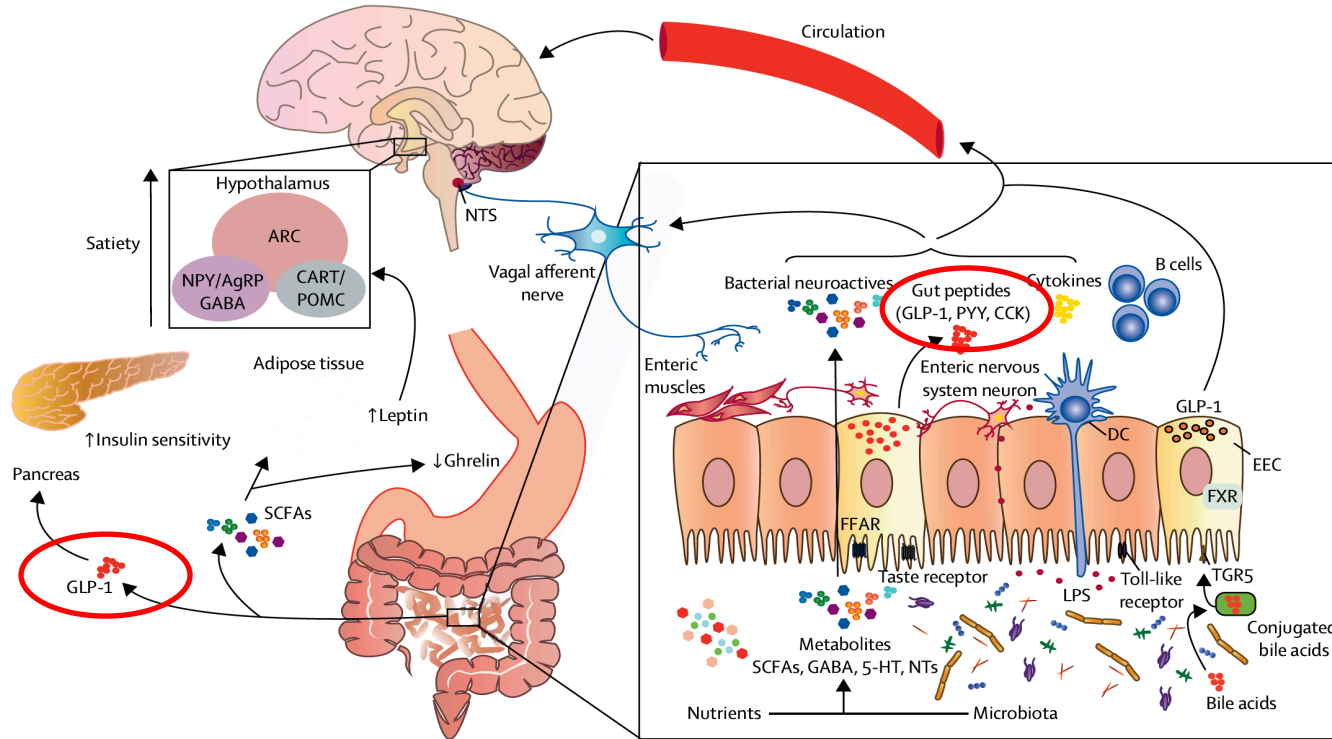
GABA SIGNALLING



Preliminary Results

*p<0.05 vs Standard Diet (control), t-Test

Gut-Brain Axis Evolution



- Autonomic Nervous System
- Neuroendocrine System
- Immune System
- Microbiota Metabolism
- Intestinal epithelium

Effect of Exenatide on Brain Cortex

Characteristic (mean±SEM)	Lean (n=10)	Obese (n=10)	P-value
Age	44±6	45± 5	NS
Sex (% male)	44	50	NS
BMI	23.9±0.8	33.1±1.1	<0.0001
FPG (mg/dl)	95±2	94±2	NS
2-hour PG (mg/dl)	94±8	114±4	0.03
HbA1c (mmol/mol)	33±0.3	34±0.3	0.18
FPI (μU/ml)	3.1±1.6	14.0±7.1	<0.05

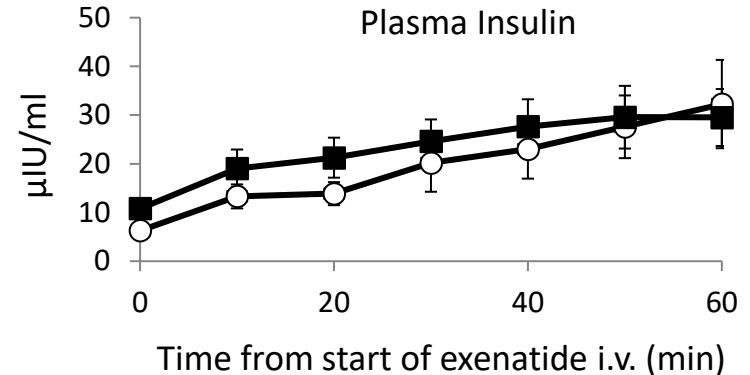
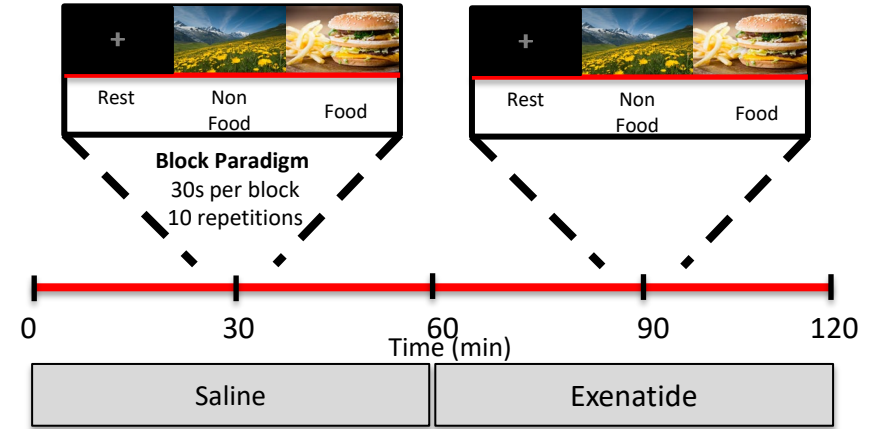
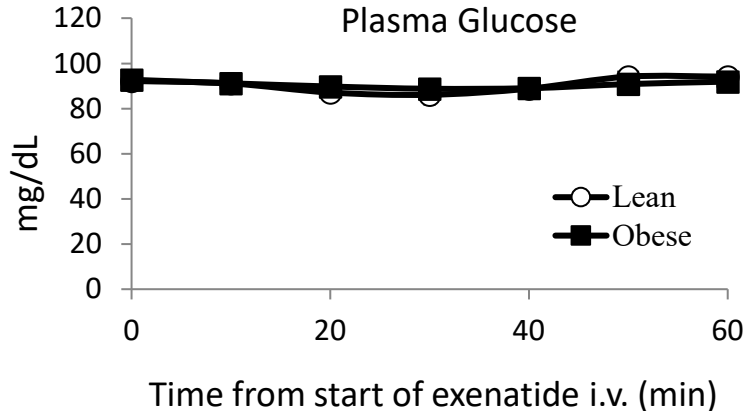
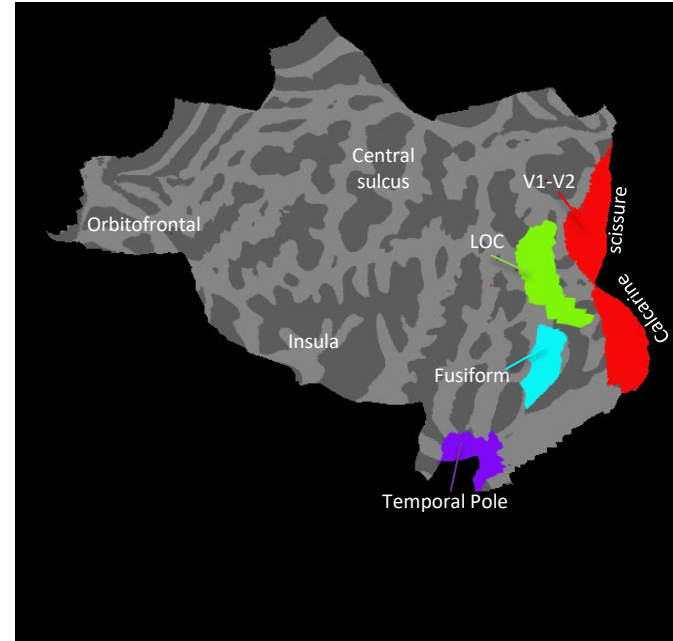
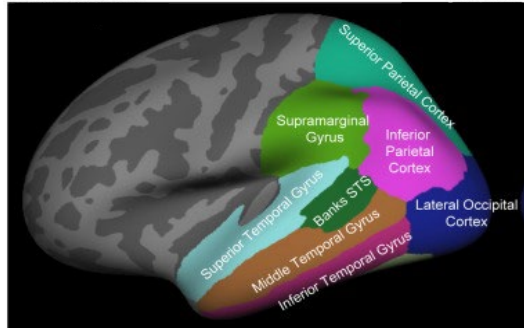
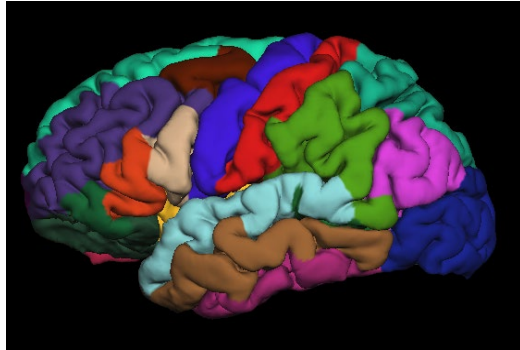


Image Data Analysis

Cortical Surfaces

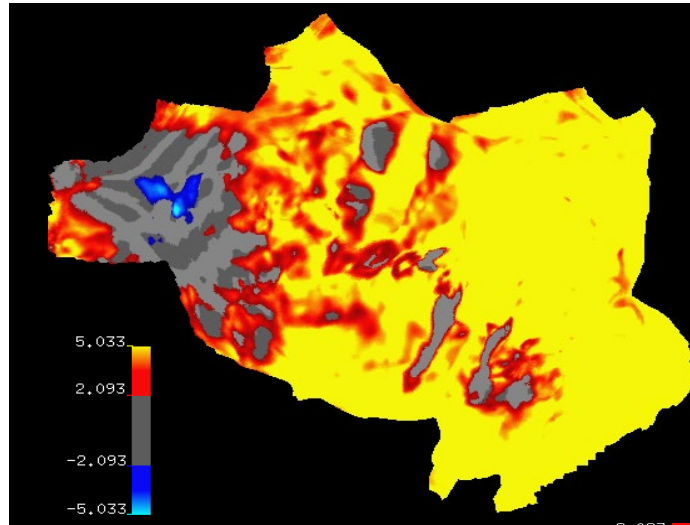


Fischl B. & Dale A.M. Proc. Natl. Acad. Sci. 2000; 11050-11055.

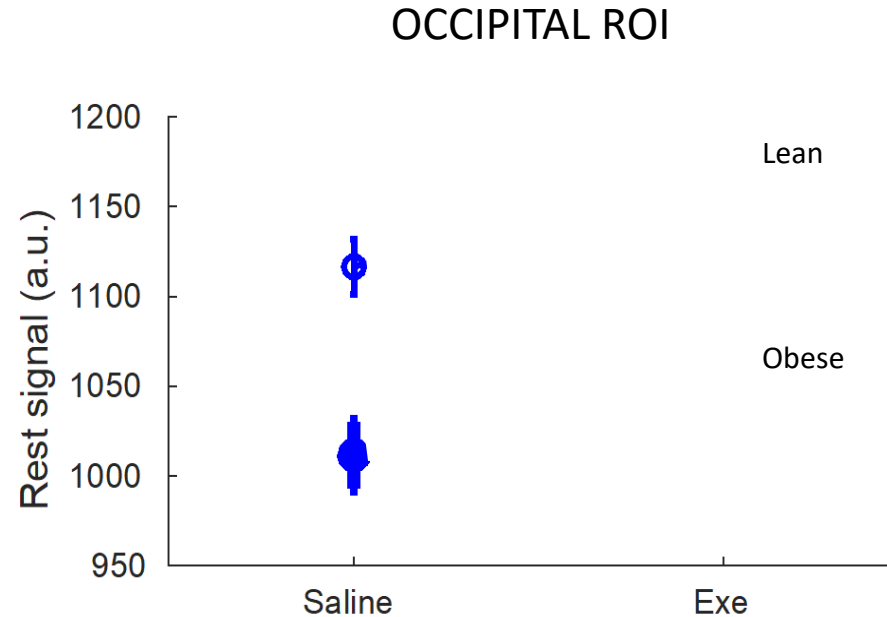
Dale A.M., Fischl B. & Sereno M.I. NeuroImage 1999; 9(2): 179-194. SEP

Salat D.H. et al. Cereb. Cortex 2004; 14(7): 721-730.

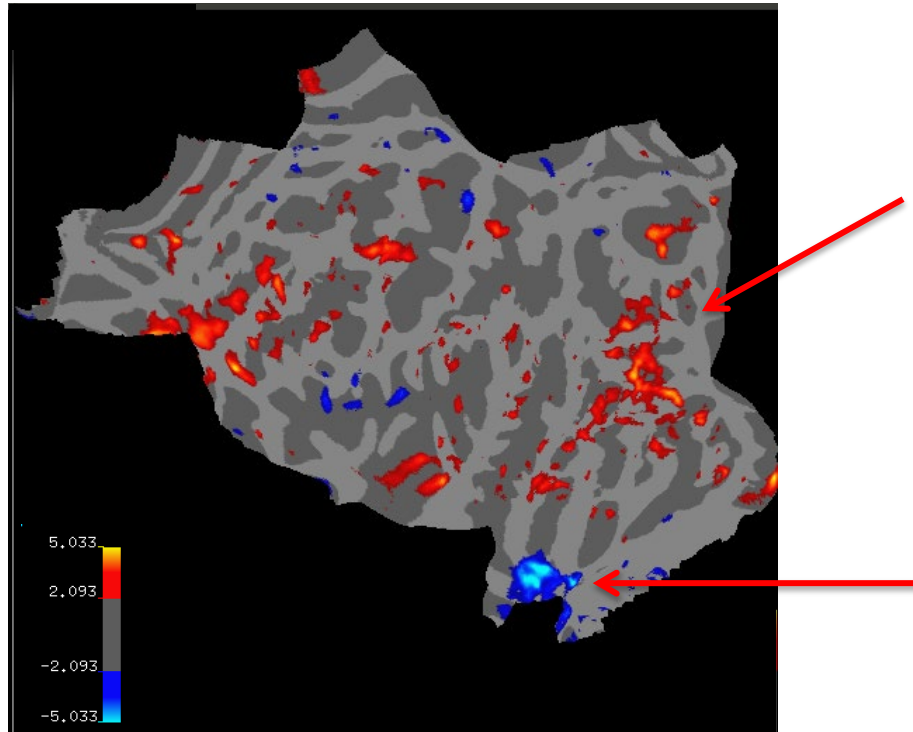
Effect of Exenatide on Raw BOLD Signal at Rest



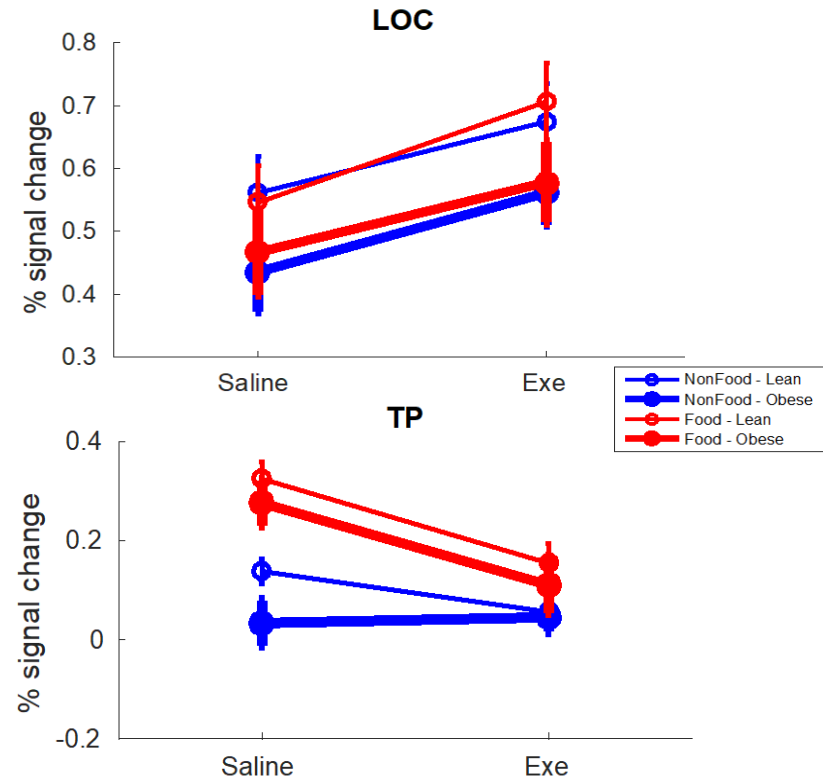
Effect of Exenatide on Raw BOLD signal at Rest



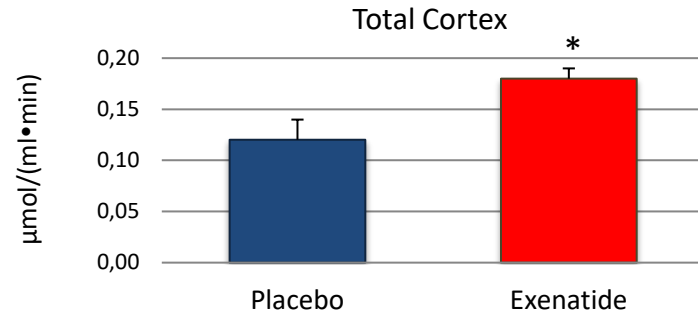
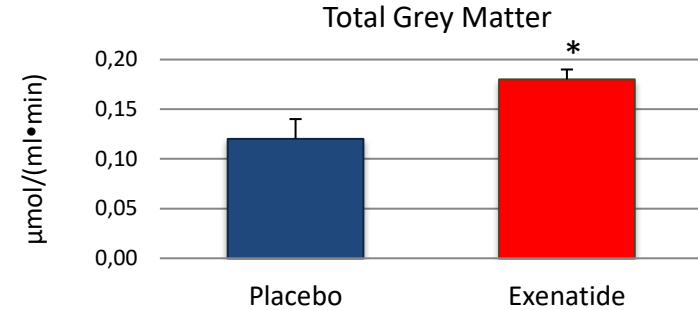
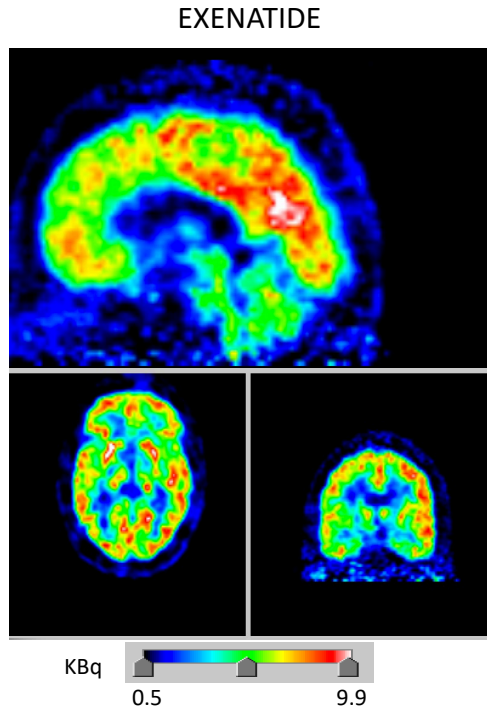
ROI* with Exenatide in Response to Food Images



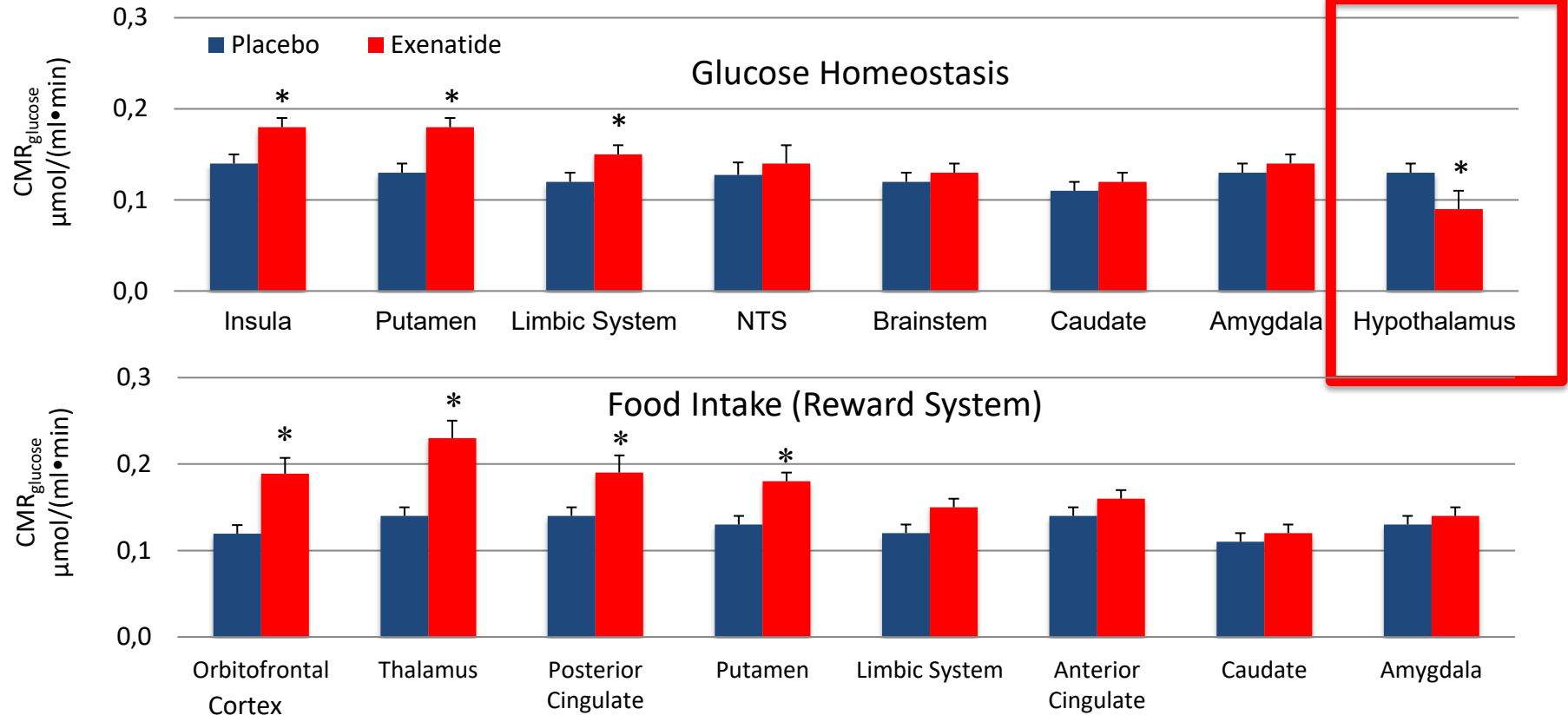
ROI*: Region Of Interest



Brain Glucose Uptake in Response to Exenatide

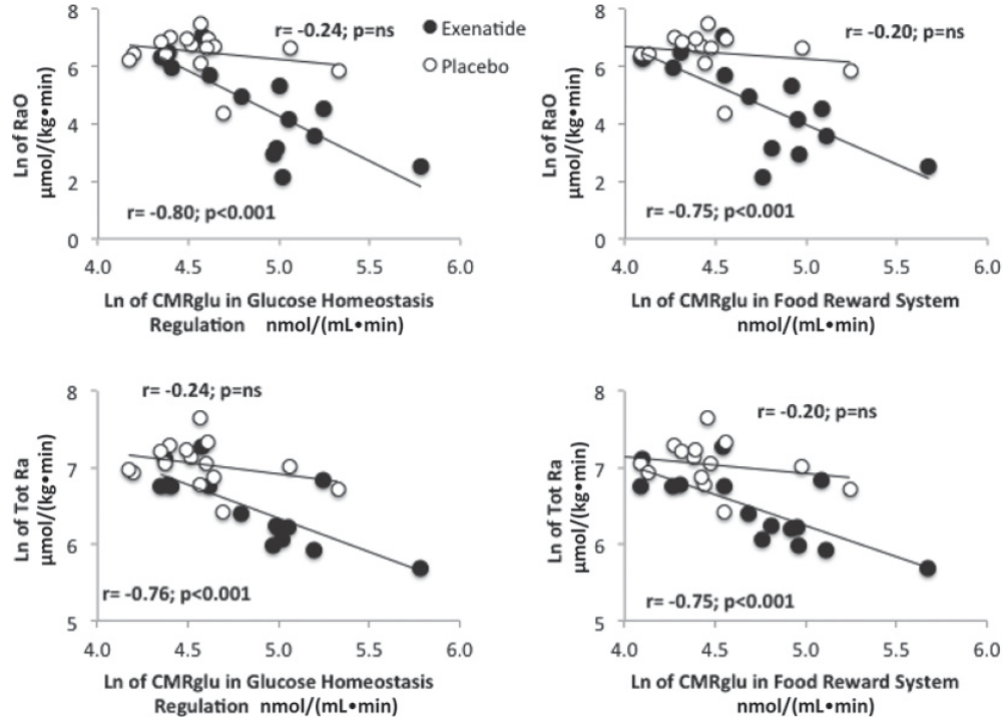


Exenatide Effect on Brain Areas Involved in Glucose Homeostasis and Food Intake

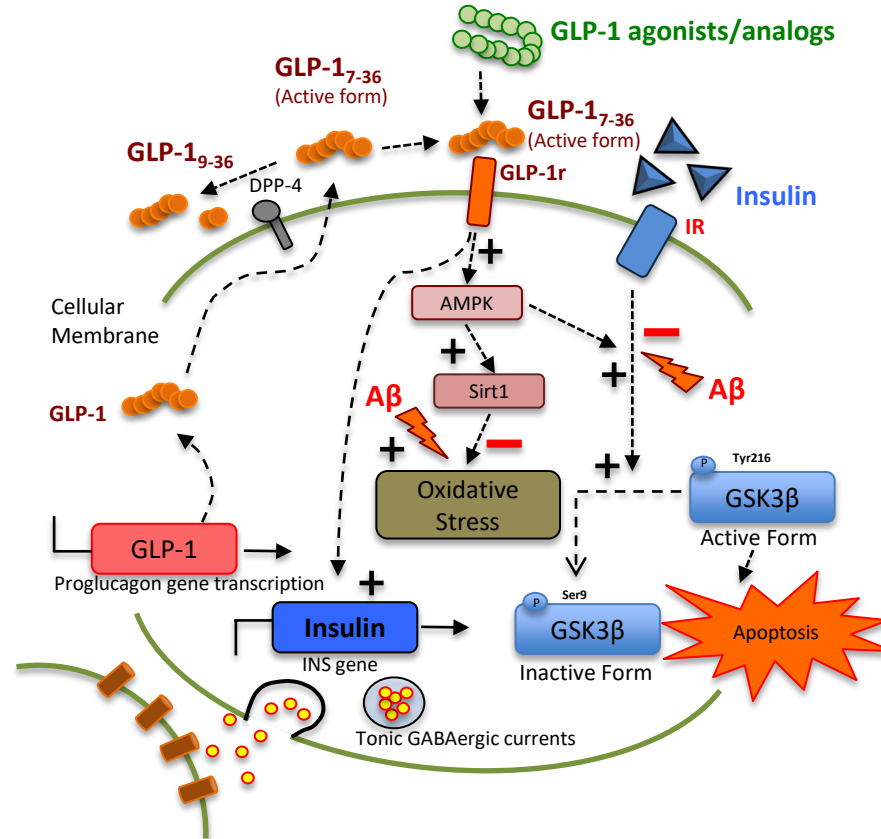
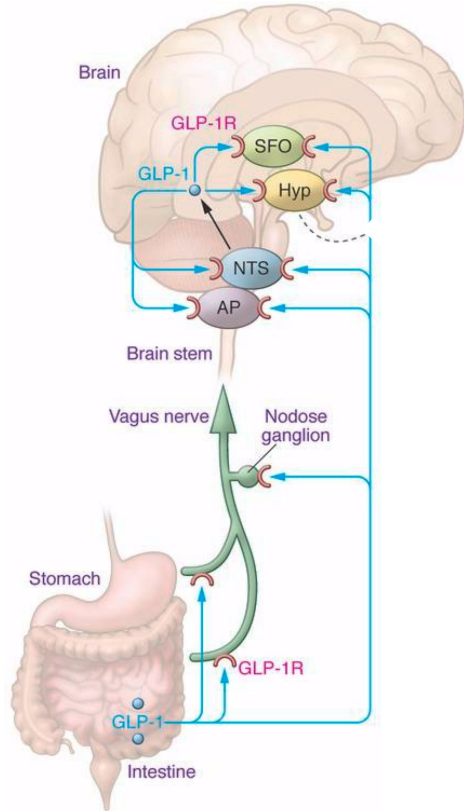


*:p<0.05

Exenatide-mediated Reduced Glucose Absorption Correlates with Reduction of Glucose Cerebral Metabolic Rate

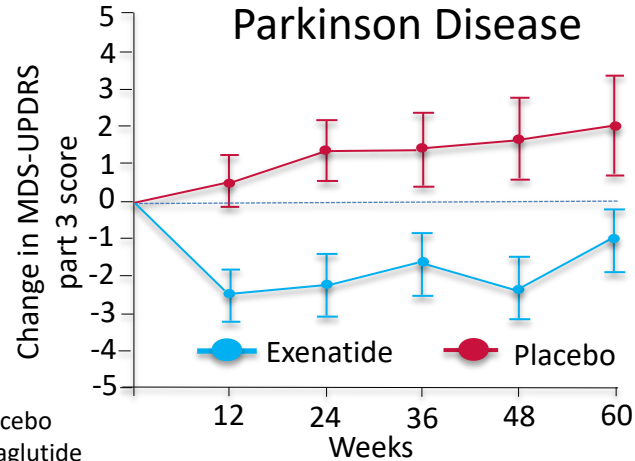
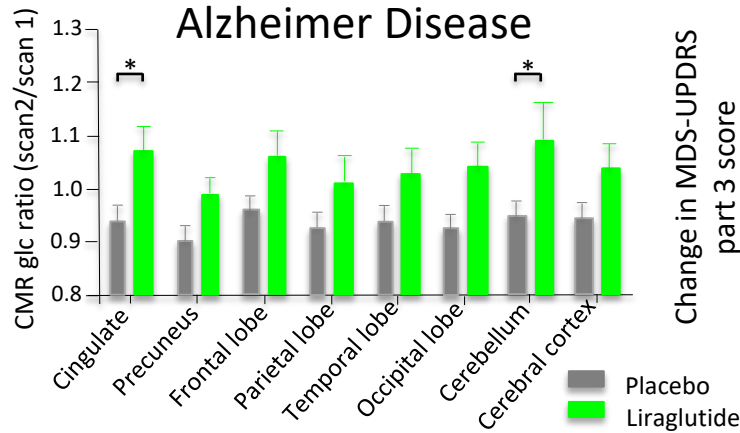


Restoring Brain Insulin Signaling through Brain GLP-1 Action

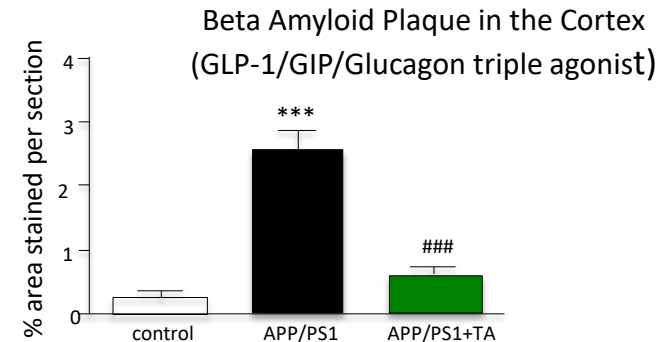
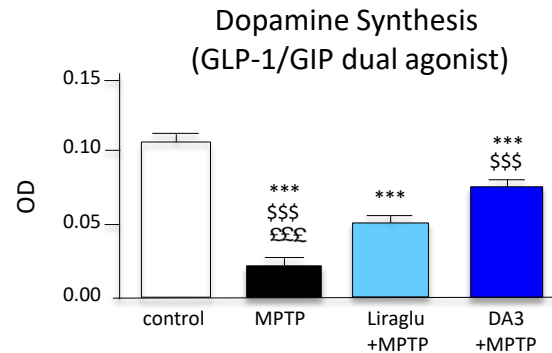
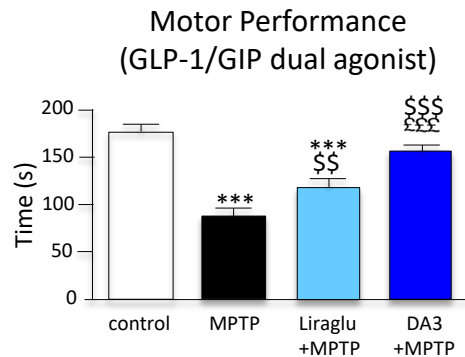


- ✓ GLP-1 is produced in PPG neurons in NTS
- ✓ GLP-1 acts as neurotransmitter or neuromodulator (neuronal projection to other areas)
- ✓ GLP-1 receptors are expressed in insulin-containing neurons of cerebral cortex
- ✓ GLP-1 enhances synaptic and tonic inhibitory GABAergic currents
- ✓ Hyperglycemia increases both GLP-1r and insulin gene expression

Gut Hormones and Neurodegenerative Diseases



Drug	Duration	ID: NCT
Exendin-4		
PD; 2 mg	12 months	03456687
AD; 5-10 µg	18 months	01255163
Lixisenatide		
PD; 10-20 µg	12 months	03439943
Semaglutide		
PD; 1 mg	48 months	03659682
NLY01		
HS; 0-25-10 mg	2 months	03672604
Liraglutide		
AD; 1.8 mg	12 months	01843075
PD; 1.2-1.8 mg	14 months	02953665



Athauda D et al Lancet. 2017 Oct 7;390(10103):1664-1675
Yuan Z et al. Eur J Pharmacol. 2017 Oct 5;812:82-90

J. Tai et al. Brain Research 1678 (2018) 64–74
Gejl M et al. Front Aging Neurosci. 2016 May 24;8:108

Conclusion

- Diabetes and neurodegenerative diseases share common mechanisms leading to peripheral and/or central insulin resistance
- Peripheral insulin resistance amelioration is associated to improved brain plasticity in morbidly obese subjects
- Dual/triple agonists treatments are associated to a promising neuroprotective effects that may be brought into clinical use in the near future

