



UNIVERSITY OF TORONTO
FACULTY OF MEDICINE

Preventing Dementia: The Depression-Diabetes Nexus

Roger S McIntyre

Assoc. Professor of Psychiatry and Pharmacology, University of Toronto
Head, Mood Disorders Psychopharmacology Unit,
University Health Network

Toronto Dementia Research Alliance

University of Toronto Psychiatry

- 14 Academic divisions/programs across 7 fully affiliated hospitals
- 17 endowed chairs and 2 endowed professorships
- 682 Active Faculty members, 183 full-time and 499 part-time
- 79 members hold appointments in the Institute of Medical Science.
- 155 Residents
- 60 Fellows



Mood Disorder Psychopharmacology Unit (MDPU)/ UHN

- **Lead Centre:** International Mood Disorders Collaborative Project. UHN- Cleveland Clinic (University of Texas, SA)
 - n=1 250 patients
- **Lead Centre:** International Centre of Excellence in Mood Disorder Research UHN-Gulf Region (Kuwait and Saudi Arabia)





MDPU Capabilities

- Biomarkers (neuroimaging, biofluids, genetics)
- Endophenotypes
- Predictors (i.e. illness, treatment)
- Transdisciplinary intervention



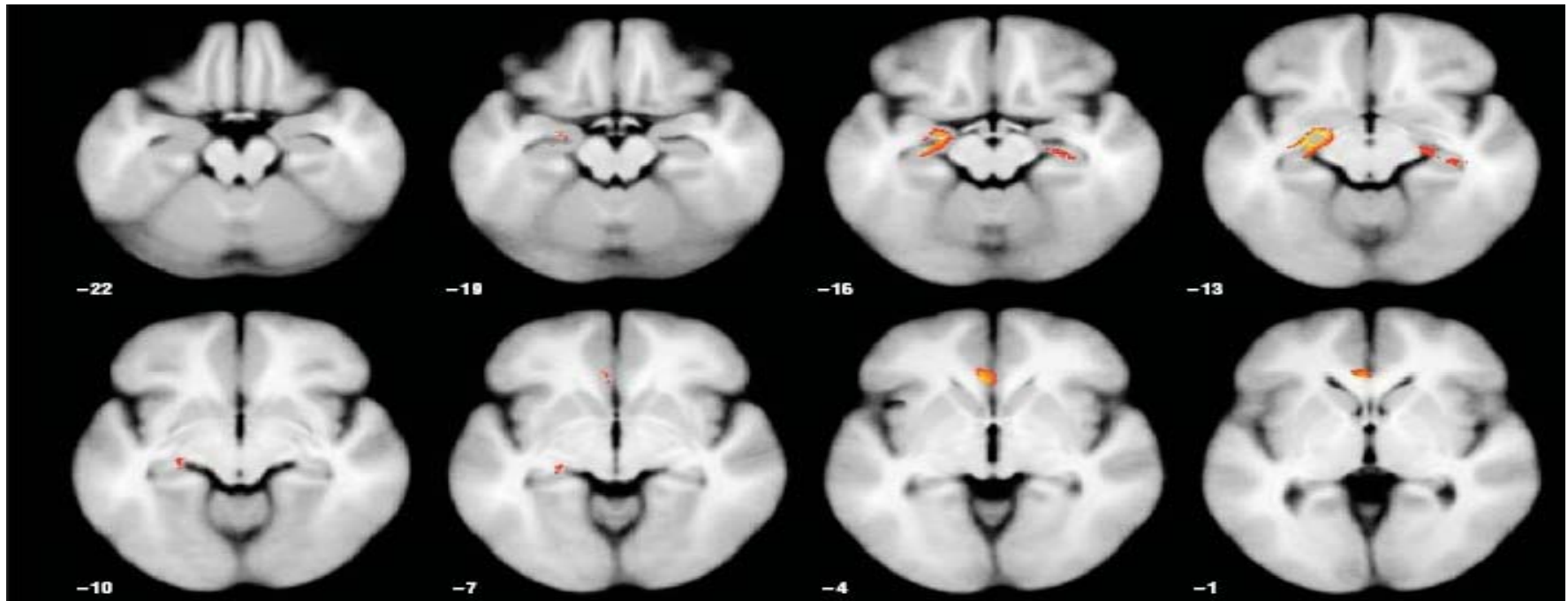
MDPU-Research Mission Statement and Synergism with TDRA

- To identify avenues that cause, prevent and modify disease course in mood disorders

- To identify ultra-high risk individuals for dementing disorders and initiate primary and secondary prevention

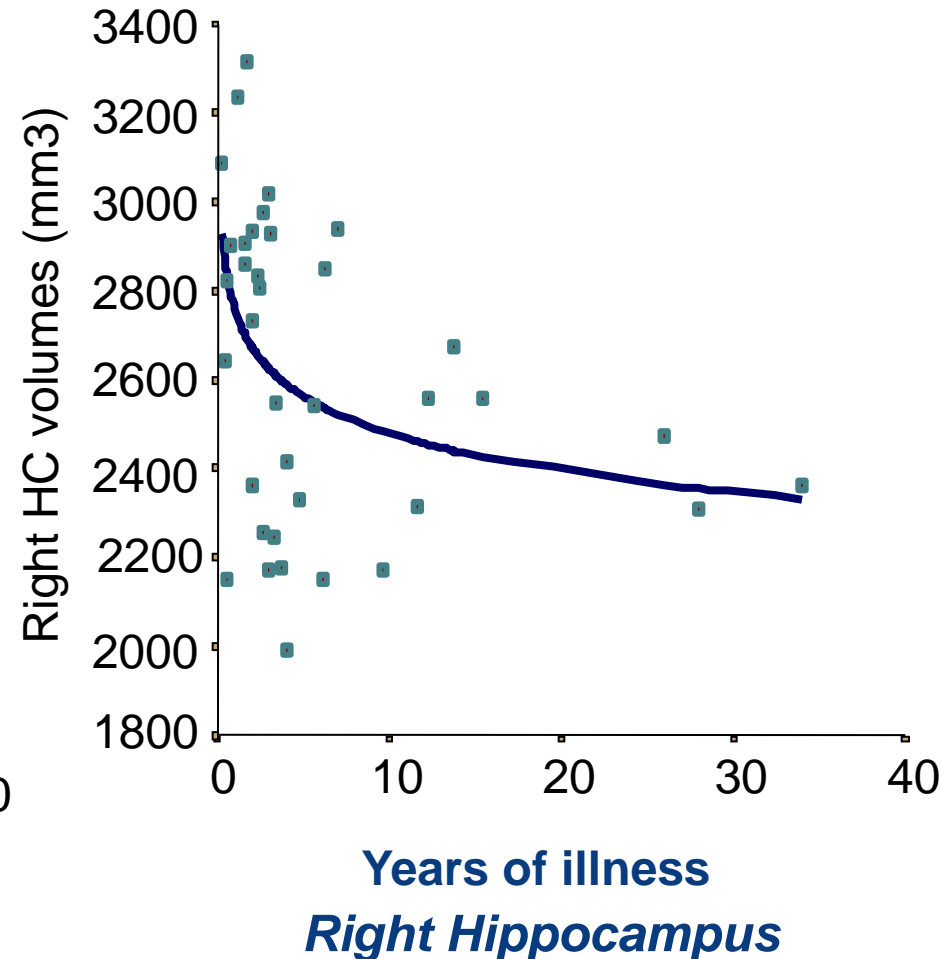
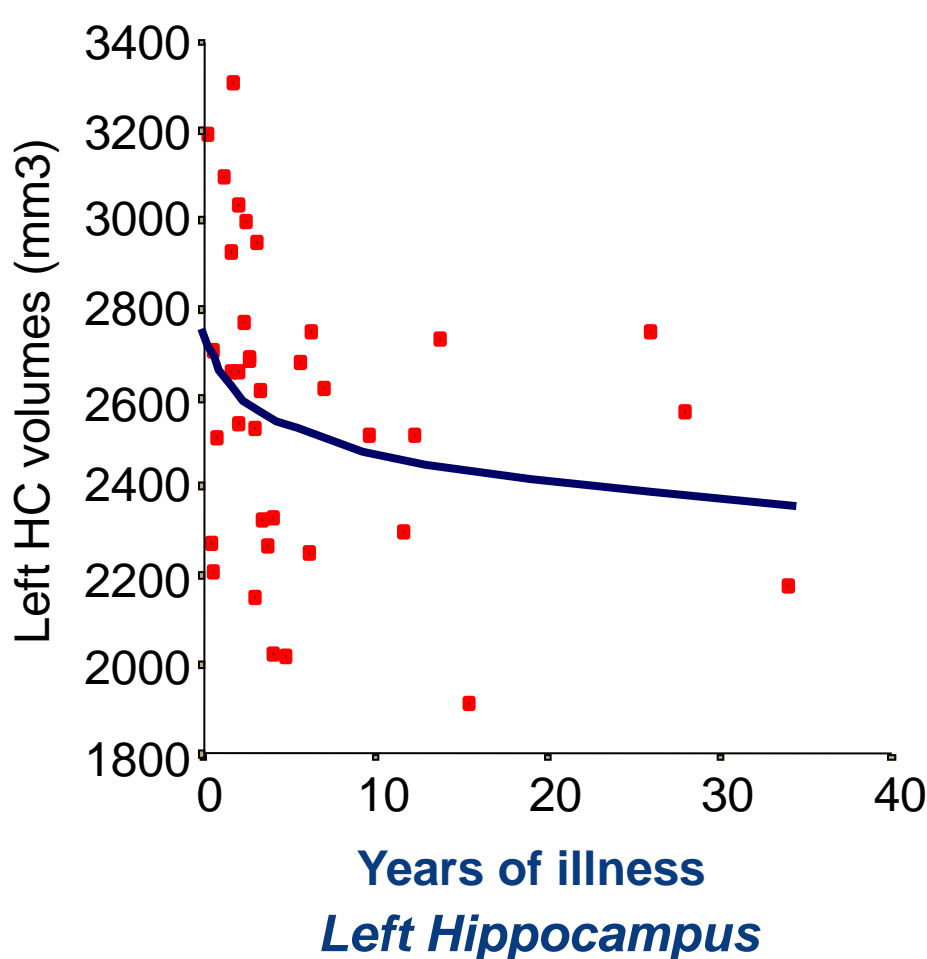


Major Depression Associated with Decreased Brain Volume

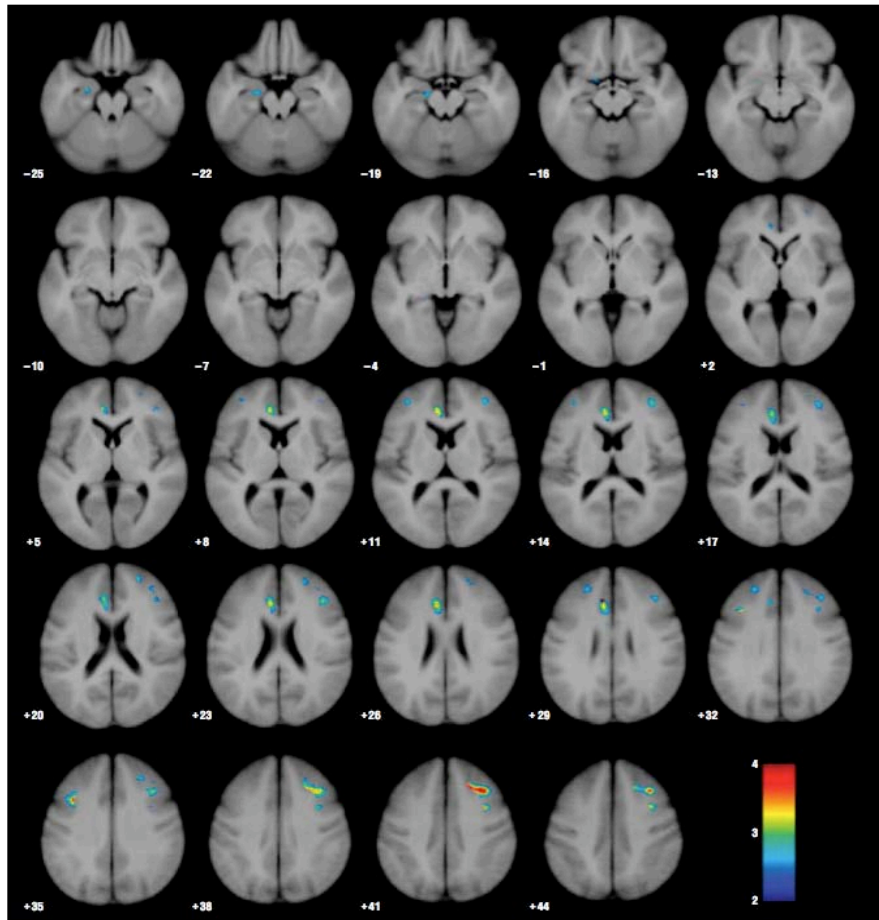


- 3-year **prospective** study comparing 38 patients with 30 healthy controls
- Significant decline in gray matter density was noted in hippocampus, amygdala, anterior cingulate cortex, and dorsomedial prefrontal cortex
- Threshold was set at $P < .001$

Multiple Episodes/Longer Illness Duration Associated with Greater Hippocampal Volume Loss

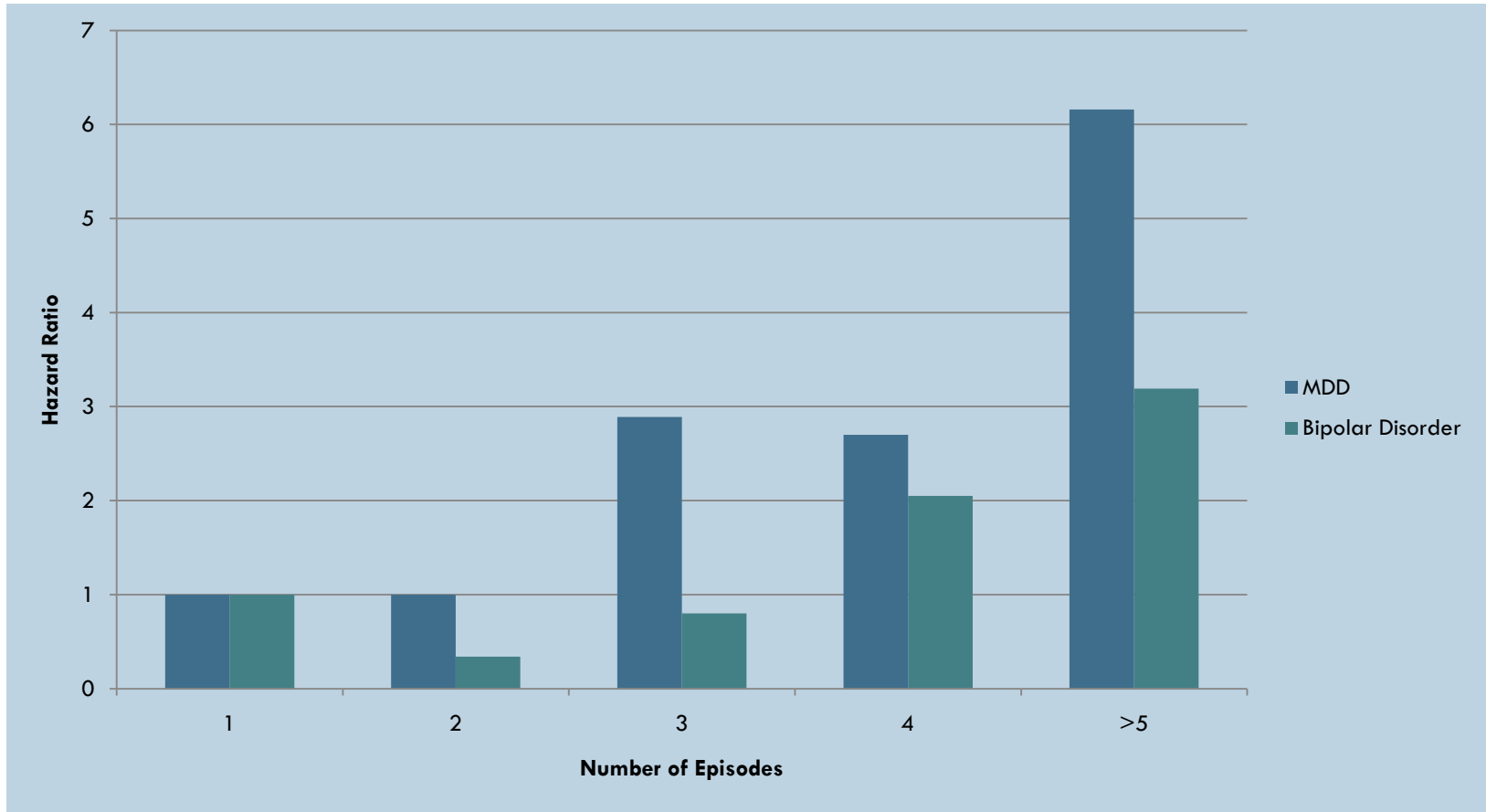


Greater Decline in Gray Matter Volume in Unremitted Compared with Remitted MDD Patients



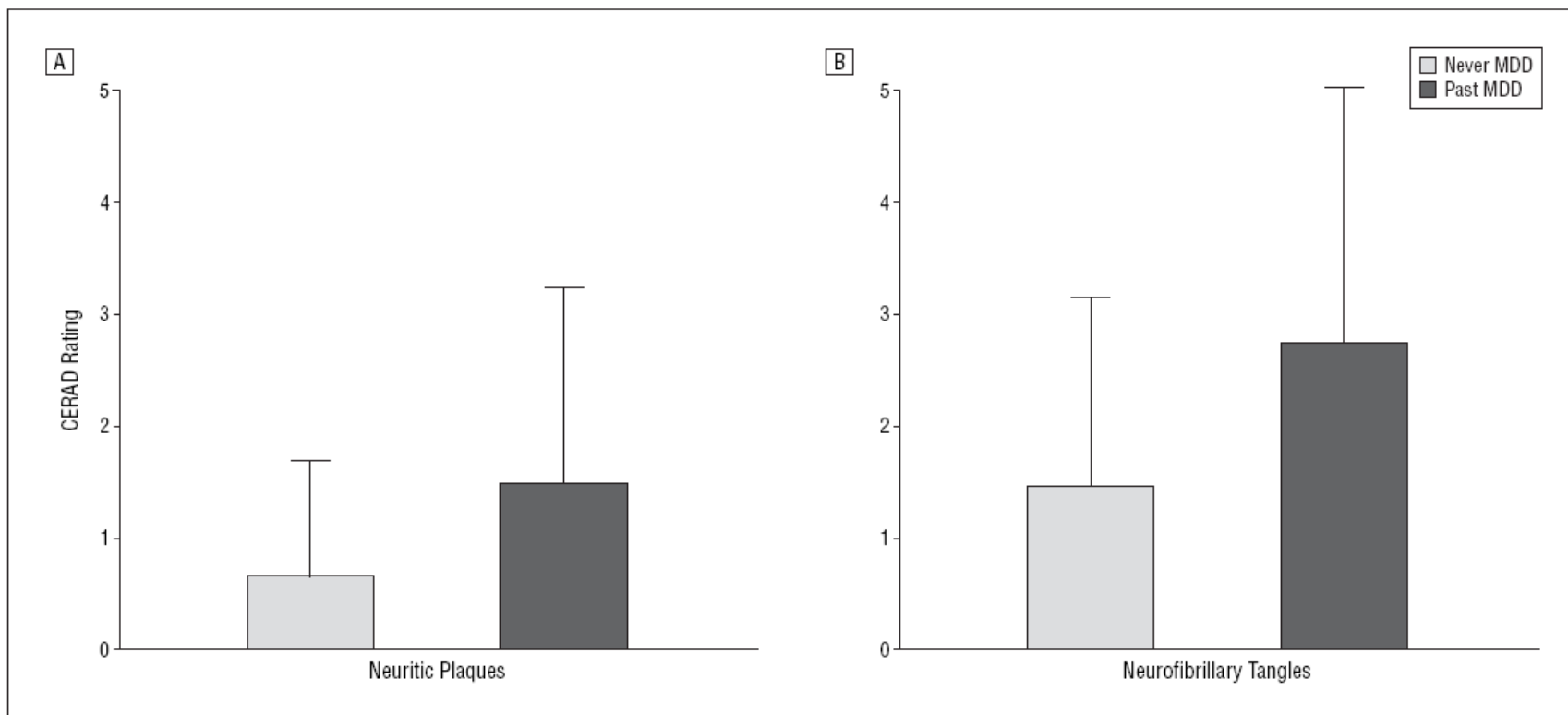
- 3-year prospective study comparing 38 patients with 30 healthy controls
- Significantly greater decline in gray matter density was noted in non-remitted versus remitted major depressive disorder patients in:
 - Hippocampus
 - Anterior cingulate cortex
 - Dorsomedial prefrontal cortex
 - Dorsolateral prefrontal cortex
- Threshold was set at $P < 0.01$

Mood Disorder Episode Frequency Increases Risk for Dementia



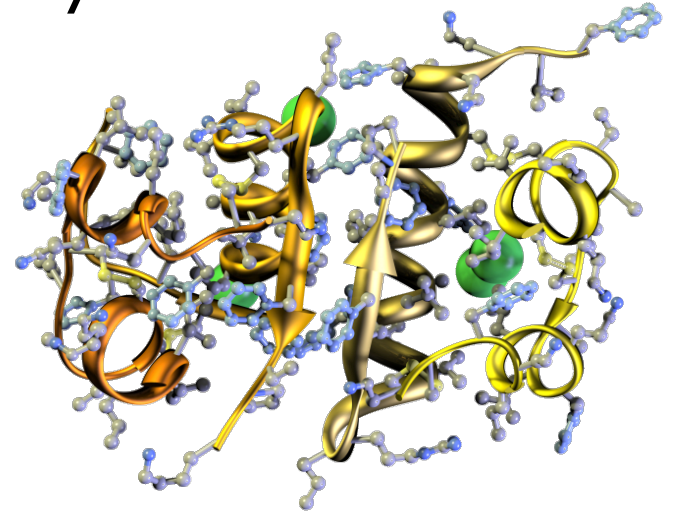
Major Depression Increases AD Neuropathology in the Hippocampus

ARCHIVES OF
GENERAL PSYCHIATRY

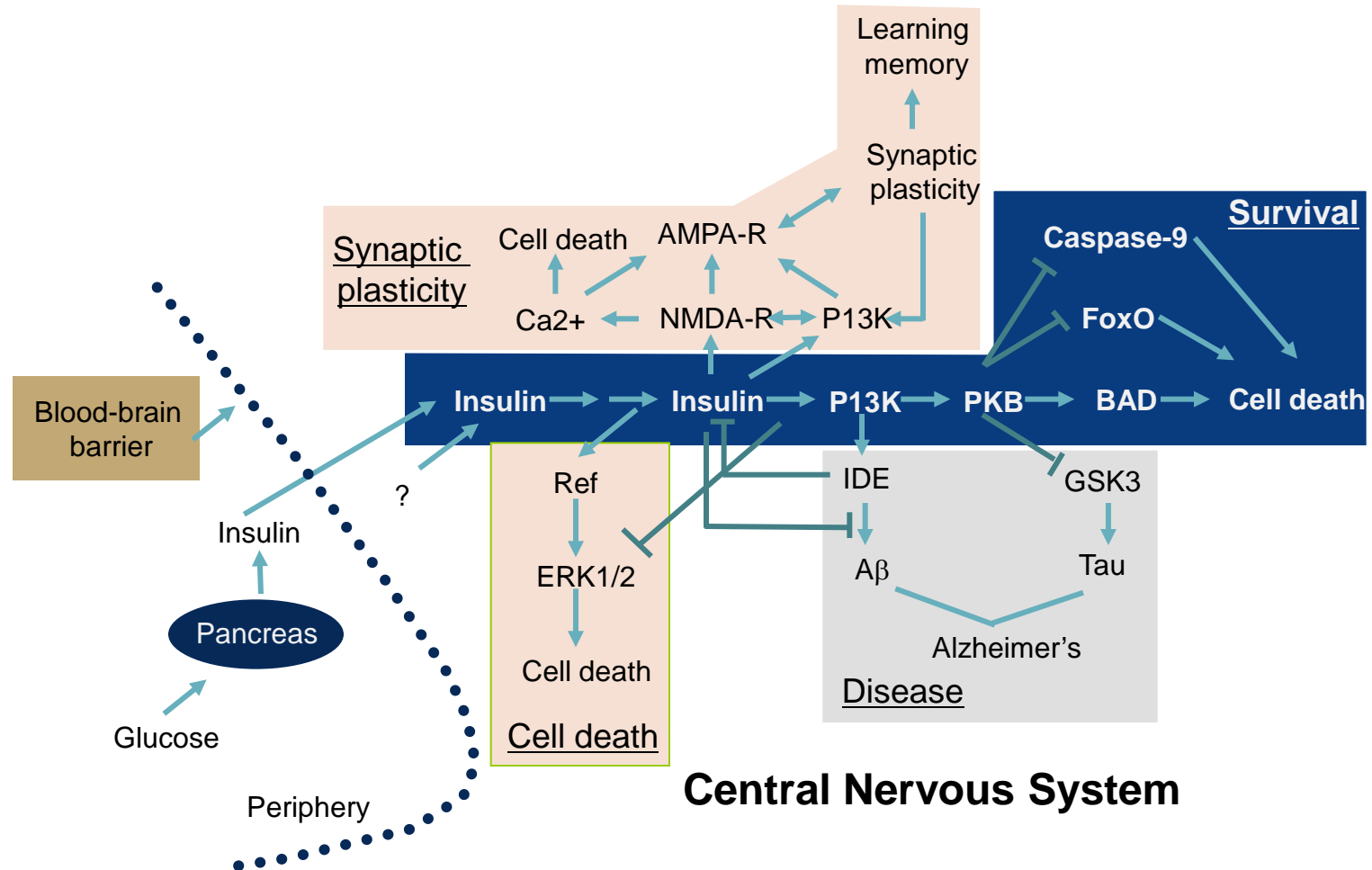


Insulin: Critical for Normal CNS Function

- Neurotrophic
- Synaptic plasticity (i.e. memory formation)
- Neurodevelopment
- Neuroprotection
- Neuromodulation (e.g. acetylcholine)
- Feeding and behavior

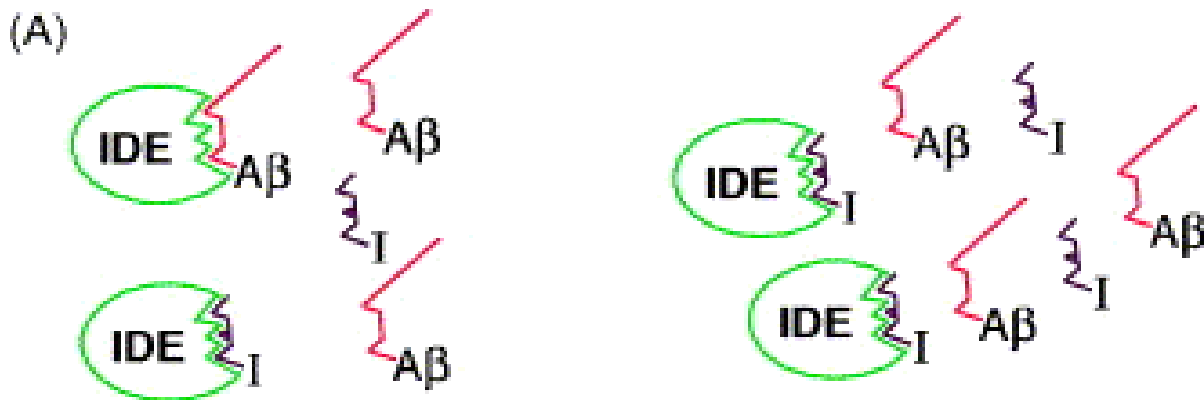


Insulin: A Mediator of AD Neuropathology?



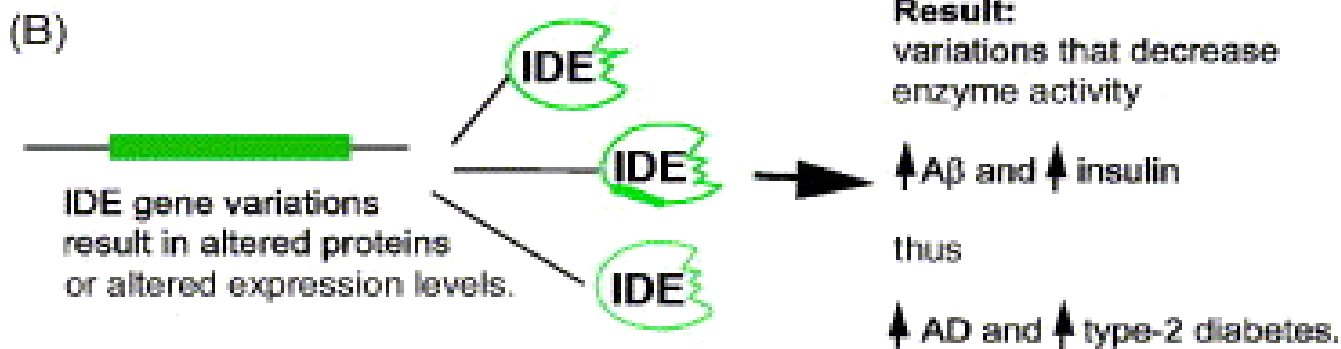
NMDA-R=N-methyl-D-aspartate receptor.

Insulin-Degrading Enzyme and Alzheimer's Disease

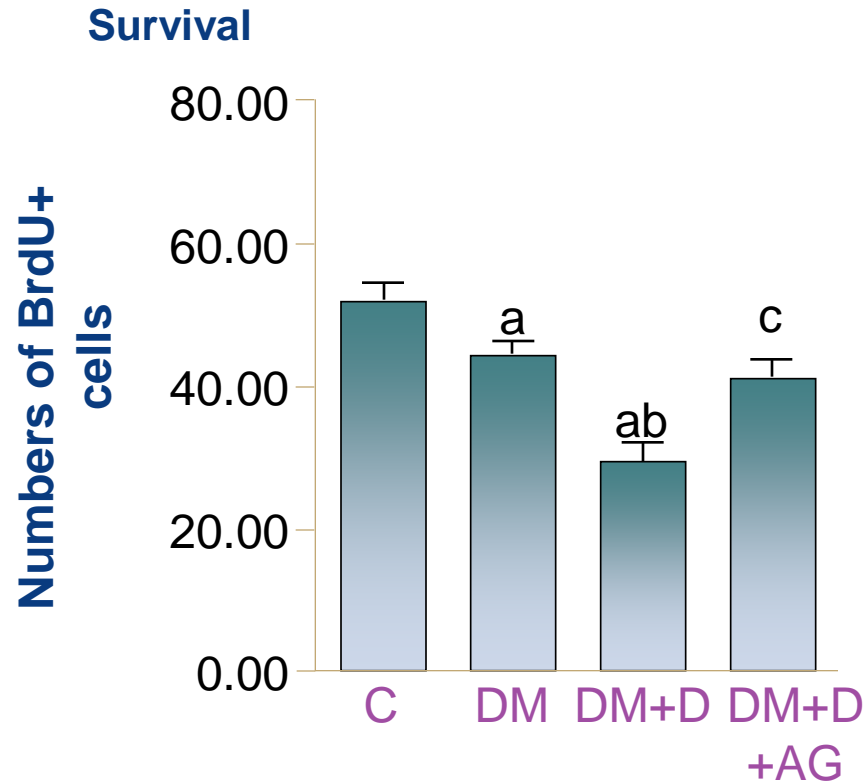


IDE has higher affinity for insulin, illustrated by binding "fit".

Increased insulin competes for IDE, reducing Aβ degradation.



Greater Suppression of Neurogenesis with Concurrent Diabetes Mellitus and Depression



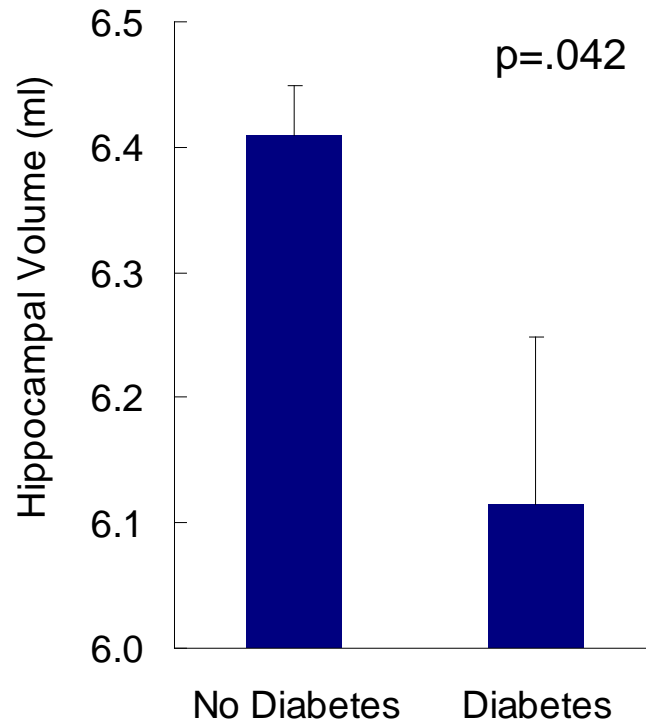
C: control rats injected with vehicle alone; DM: streptozotocin-induced diabetic rats without depressive-like behaviour; DM+D: streptozotocin-induced diabetic rats with depressive-like behaviour; DM+D+AG: aminoguanidine (AG, 10 mg/kg) administered in DM+D rats for 4 weeks

^ap<0.001 DM+N, DM+D vs CON value; ^bp<0.001 DM+N vs DM+D; ^cp<0.001 DM+D+AG vs DM+D value. Values are means ± SD.

Diabetes Mellitus and Dementia

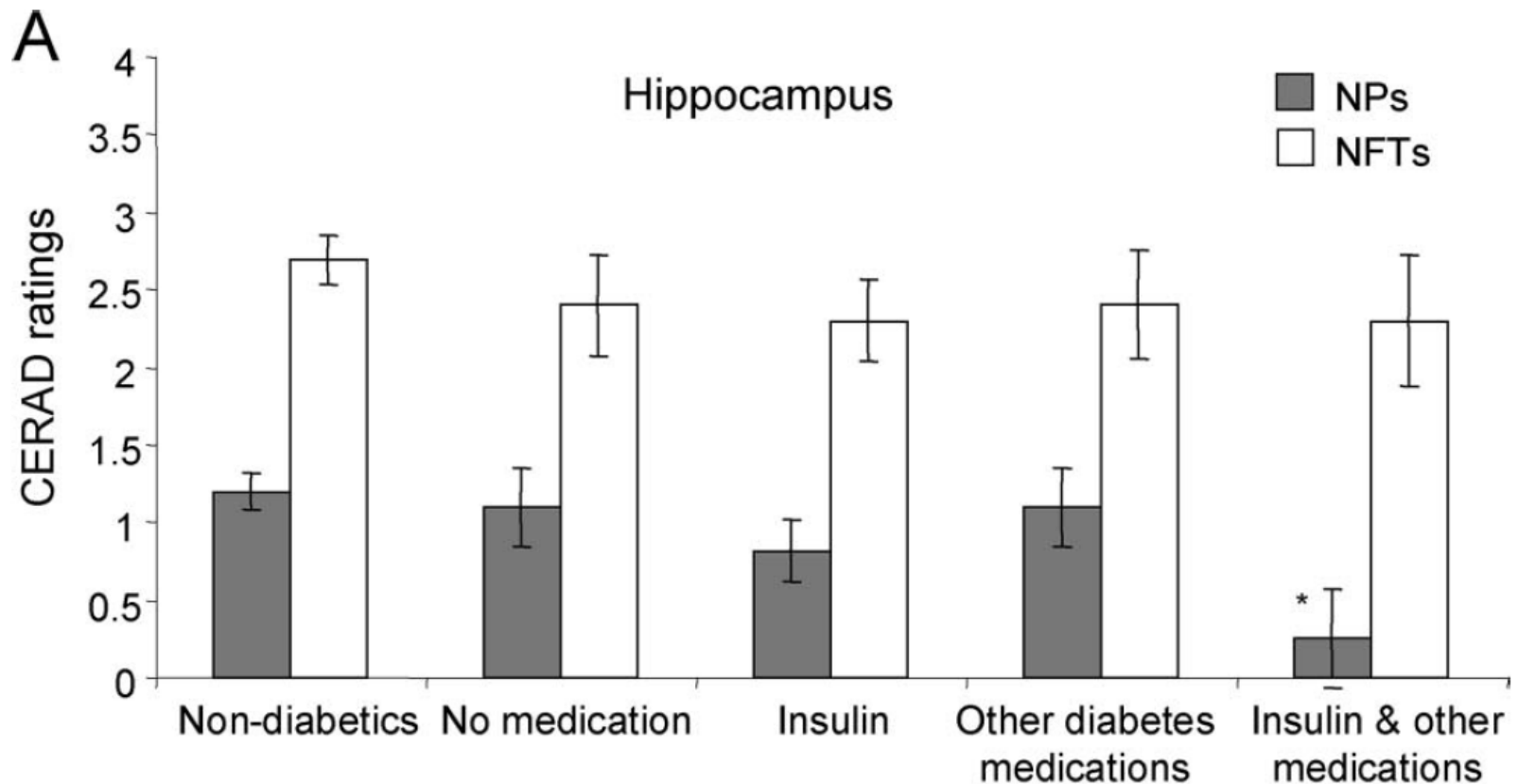
- DM increases risk of both AD and VaD, regardless of age of onset
- Type 2 DM/Abnormal FBG present in up to 80% of AD
- Altered brain metabolism noted prior to cognitive deterioration
- “Type 3 Diabetes Mellitus”

Hippocampal Volume Changes in Diabetes Mellitus

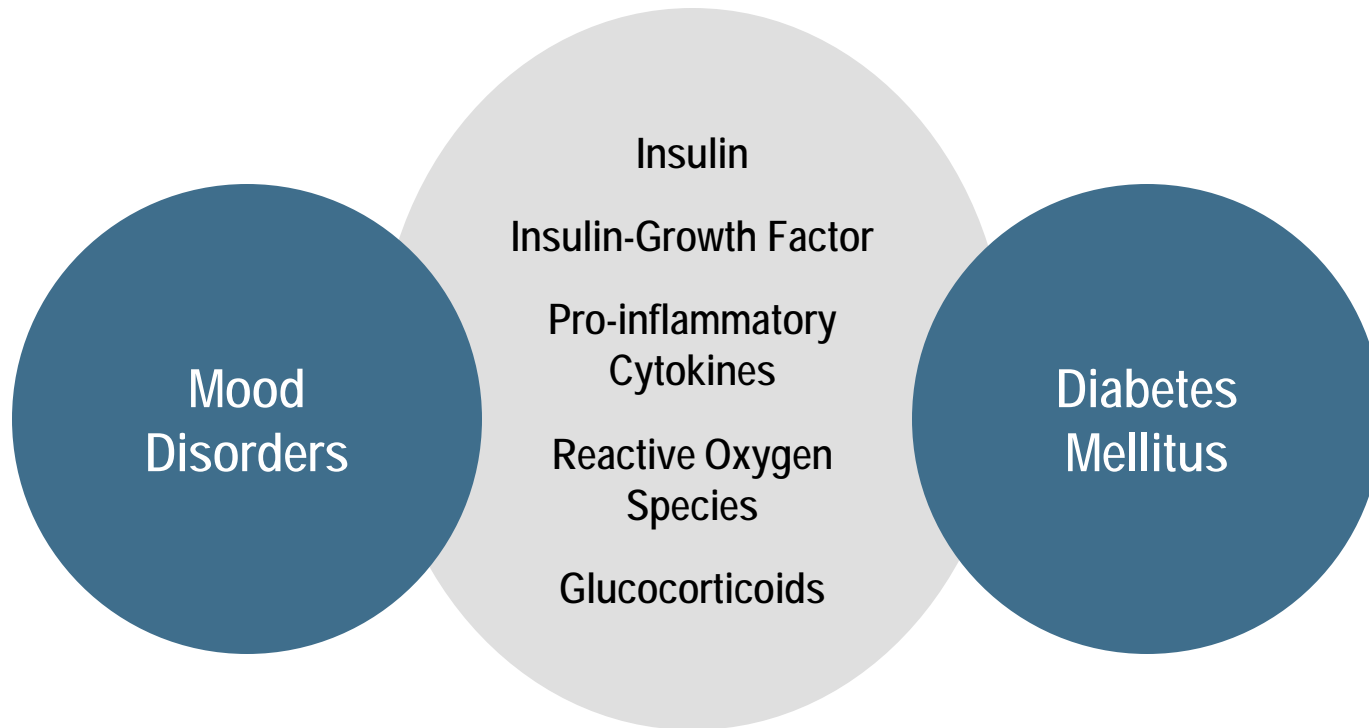


MRI=magnetic resonance imaging. Hippocampal volumes (+SE) on brain MRI in participants with diabetes (n=41) and without diabetes (n=465). Volumes are adjusted for age and sex and normalized to average head size.

Diabetes Medication is Associated with less AD Neuropathology



The Depression-Diabetes Nexus



Preventing Dementia: The Opportunity of the TDRA

- Identifying ultra-high risk individuals (latent, prodrome)
- Biomarkers
- Multi modal probabilistic modeling
- Sample size
- Specificity
- Primary/secondary prevention

