UCDAVIS MMPC Mouse Metabolic Phenotyping Center

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Assessment of Cognitive Function in Mouse Models of Metabolic Dysfunction

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Associations with T1DM & T2DM

- All cause cardiovascular mortality
- Coronary artery disease
- Peripheral artery disease
- Stroke
- Retinopathy
- Renal failure
- Diabetic foot syndrome
- Erectile dysfunction
- **Dementia**
- Heart failure

Norman et al, 2011

T1DM & dementia

Key references	Summary	Conclusions
Brismar, 2002	Decrease in fast activity in temporo-occipital regions	**T1DM associated with increased cognitive decline. Unclear if T1DM predisposes to dementia or if cognitive decline is associated with hypoglycemia.**
Brands, 2005	T1DM pts have slowed mental speed & flexibility; not associated with hypoglycemia	
Brands, 2006	Older T1DM pts have reduced but non signficant reduction in cognitive function	
Musen, 2006 & 2008	Lower density gray matter; hypoglycemia not associated with cognitive decline	
Jacobsen, 2007	Decline in cog fn, motor speed & psychomotor efficiency; not associated with hypoglycemia	
DCCT/EDIC, 2007	Decreased cognitive function & decline of motor speed & psychomotor efficiency	
Northam, 2009	Youth with T1DM have lower IQ performance	
Asvold, 2010	Early exposure of children to severe hypoglycemia has reduces cognitive function	

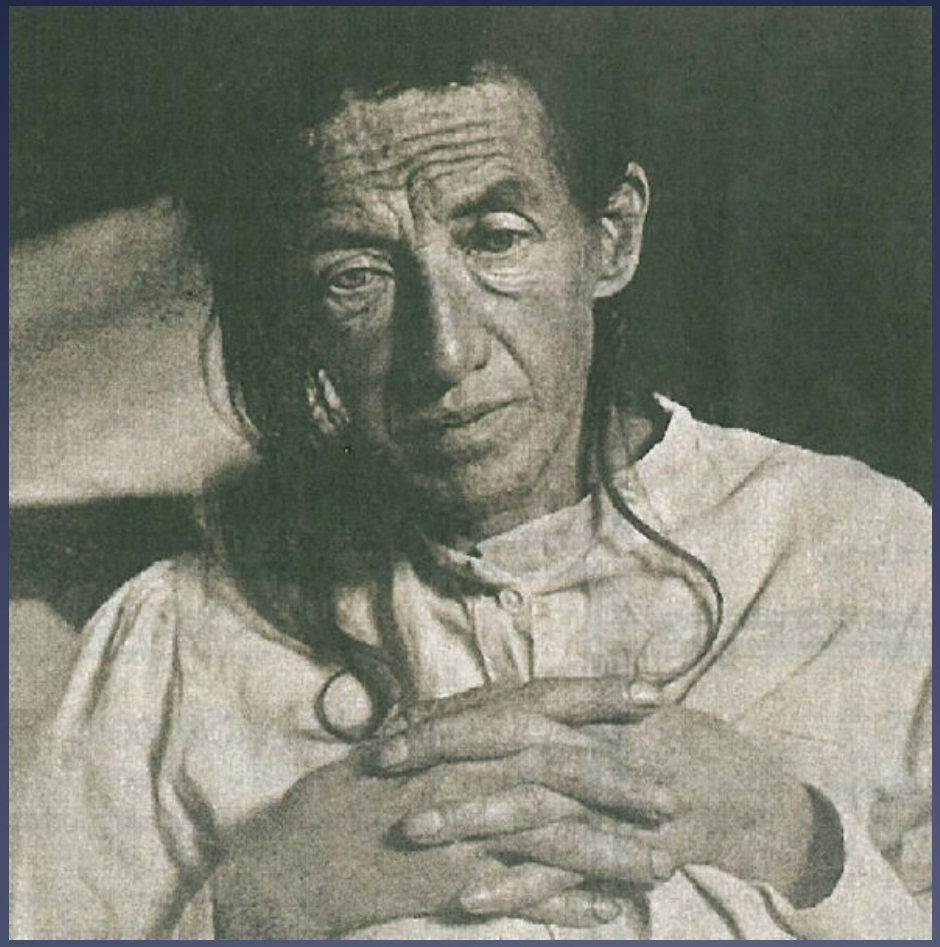
Norman et al, 2011

T2DM & dementia

Key references	Summary	Conclusions
Ott, 1999	T2DM increased risk of dementia & AD	**T2DM strongly associated with minimal cognitive impairment, dementia, vascular dementia, & Alzheimer's disease**
Vermeer, 2001	T2DM associated with increased risk of brain infarcts, but not silent infarcts	
Peila, 2002	Associated with dementia, AD, & vascular dementia. ApoE4 enhanced the association between T2DM & dementia	
Xu, 2004	Increases risk of dementia, vascular dementia, & AD	
Luchsinger, 2005	DM & smoking are strongest risk factors for AD	
Luchsinger, 2007	T2DM is a stronger risk factor MCI within minority pop.	
Gouw, 2008	T2DM associated with WMH progression & lead to cognitive decline	
Toro, 2009	Associated with MCI	
Whitmer, 2009	Hypoglycemia associated with increased risk of dementia	

Norman et al, 2011

Dementia is the progressive decline in cognitive function due to damage or disease of the brain greater than what might be expected with normal aging.



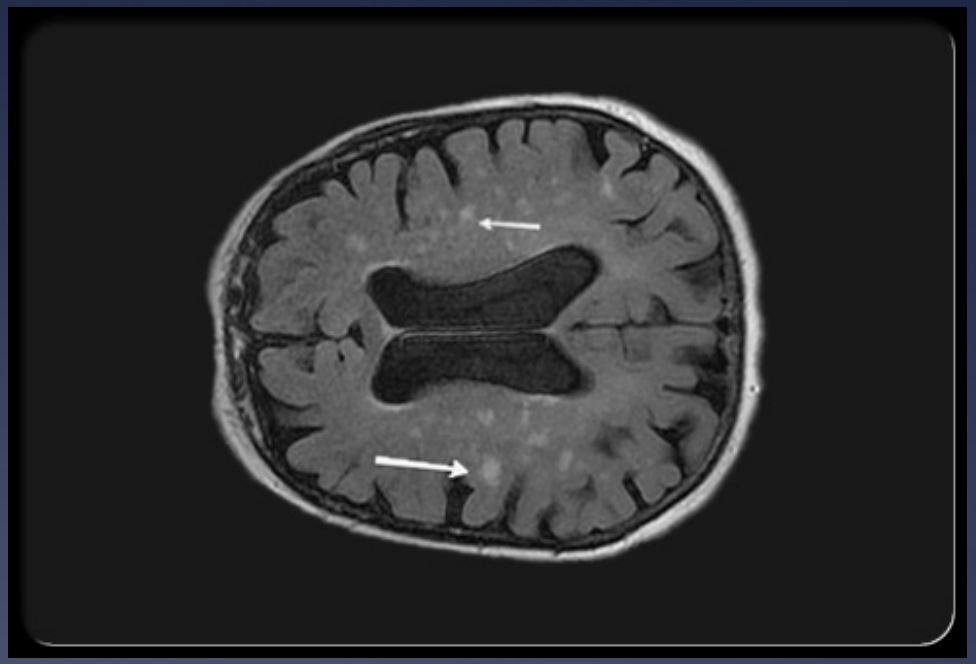
Mrs. Auguste D

Types of dementia

- Alzheimer's Disease
- Vascular dementia
- Other

Causes of cognitive impairment

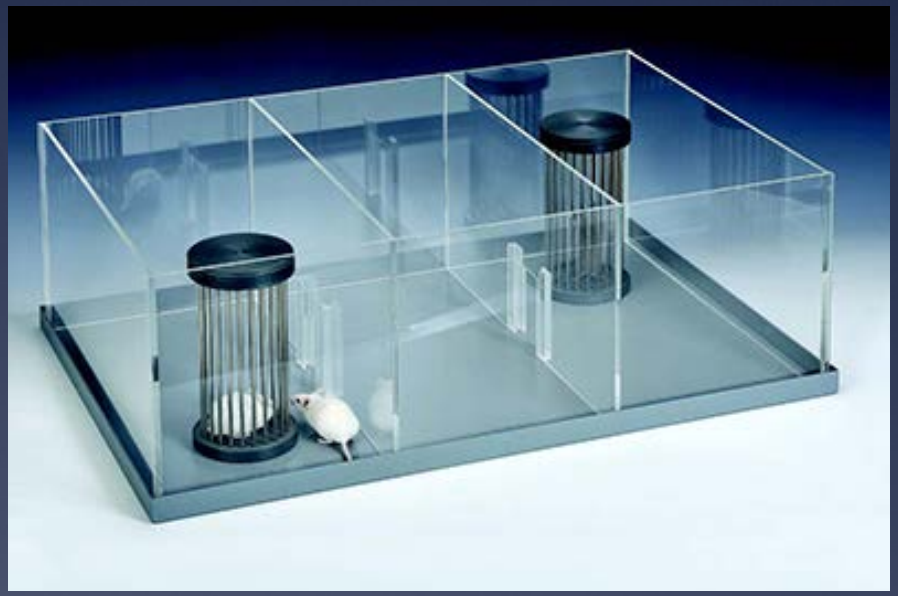
- Macrovascular disease, e.g. stroke
- Microvascular disease, e.g. T1DM or T2DM
- Direct metabolic effect on the brain, e.g. diabetes



Vascular/multi-infarct dementia; www.rxlist.com

ASSESSMENT OF COGNITIVE DECLINE IN MOUSE METABOLIC MODELS

* Overall plan: To assess and develop mouse models of cognitive decline that mimic the human condition and to investigate specific genes that regulate cognitive function.



Three tiered platform

- **Tier 1**: An investigator can submit a mouse and changes in cognitive function will be assessed over time without intervention.
- **Tier 2**: An investigator can submit a mouse that will be challenged, for example with a Western (high-fat) diet, and cognitive function compared to unchallenged mice.
- **Tier 3**: An investigator can submit a mouse and we will cross this mouse with currently available mouse models of cognitive impairment, such as the LDLr-/- mouse. Tier 3 studies will enable us to test specific genetic effects on a model of cognitive decline.

COGNITIVE ASSESSMENT

Normal cognitive function → Metabolism → Dementia, e.g. Alzheimer's, vascular dementia

ASSAYS

- Morris water maze
- T-wave alternation test
- BBB permeability
- Lipid droplet assays
- Brain MRI
- Brain PET
- Brain metabolism (Case Western)
- Brain histology

“Of all the things I miss, the thing I miss most is my mind.”

Unknown

“As you get older, your interest in dementia grows exponentially.”

J.C. Rutledge

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