Following changes in brain structure and function with multimodal MRI in a year-long prospective study on the development of Type 2 diabetes

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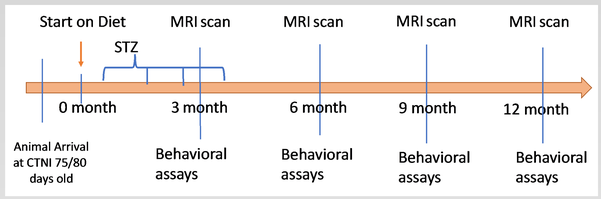
Introduction

The development of Type-2 diabetes (T2DB) is a devastating disease affecting over 462 million people worldwide. To our knowledge there has never been a prospective MRI study following disease progression from a normal brain to fulminating diabetes in the same subject. T2DM can be modeled in rats by giving them a high fat high fructose diet and exposing them to a drug streptozotocin that harms the pancreatic β cells that reduce insulin secretion to regulate glucose utilization. These rats will develop T2DM as they age. We used non-invasive multimodal MRI to follow changes in brain microstructure and function for one year.

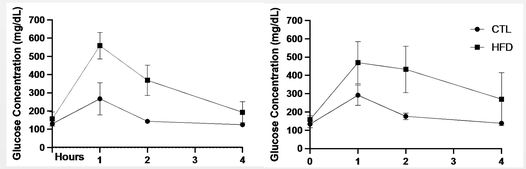
Methods

- Animal Model: SD female rats (n = 20) were given either HF/HF diet or chow-fed (n=10 per group) starting from 90 days old. HF/HF rats were given low dose of streptozotocin (25mg/kg) four times in the first four months, while normal diet-fed control rats were given vehicle. Weight (Fig. 2) were monitored every week and glucose tolerance (Fig. 1) were detected in the progression.
- Behavioral Assays: Open Field (Fig. 3) and Novel Object Recognition (Fig. 3) were tested every 3 months. Hot Plate (Fig. 3), Rotarod and Barnes Maze were test at 12 months.
- Multimodal MRI and data analysis: In each scanning session, anatomy with measure of voxel-based morphometry (Fig. 4) was utilized to detect the change of volume in 174 brain areas, while diffusion weighted imaging (DWI) with measure of apparent diffusion coefficient (Fig. 5) and fractional anisotropy was used to evaluate gray matter microarchitecture as a suggestion of neuroinflammation and edema.



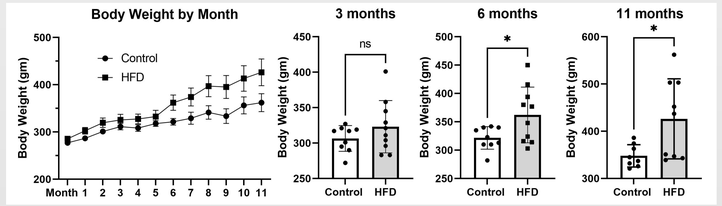
Shown above is a time-line of experimental procedures

Fig 1. Glucose Tolerance



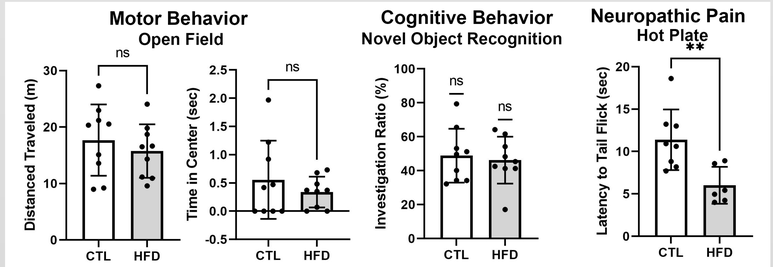
Shown are blood glucose concentration response to glucose challenge in HF/HF/Stz and control groups at 3 months (left) and 9 months (right). Data are expressed as mean ± SD.

Fig 2. Change in Body weight with Type 2 Diabetes



Weight gain (left) in the HF/HF/Stz and control groups. The scatter plots with the mean ± SD (right) show the weight of HF/HF/Stz and control groups, measured at 3-, 6-, 11-month time. *<0.05

Fig 3. Behavioral Assays for T2DB at 12 Months



From left to right, shown are open field results (total distance travelled and percentage time in the center), novel object recognition result (investigation ratio of novel object), and hot plate result (latency to tail flick) at 12 months. ** <0.01

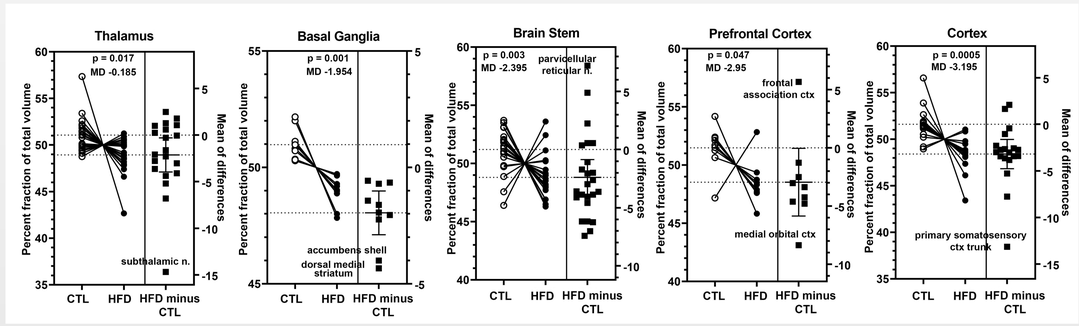
Limitations

- **These studies were only performed on female rats and do not address issues around sex differences.**
- **The experimental time is one year, further neuropathological change in elderly SD female rats which loss protection from estrogen is unknown.**

Unanswered Questions

- **Is there a sex difference in this diabetes model?**
- **How does this model affect blood brain barrier permeability and cerebral blood volume?**
- **What functional connectivity will this model influence?**
- **How does this model affect vascular reactivity with a CO2 challenge?**

Fig 4. Percent Fraction of Total Volume Composite at 12 Months



Scatter plots of volume of brain areas for the brain regions which are shown significant decrease in HF/HF/Stz group when compared with control group. The difference of brain areas between HF/HF/Stz and control groups are plotted as percent change in total volume. Each dot is a different brain area in that region. Note how in almost all case there is a decrease in volume MD = mean difference

Fig 5. Diffusion Weighted Imaging for Changes in Gray Matter Microarchitecture at 12 Months

Table of Significantly Higher ADC Values

Apparent Diffusion Coefficient 12 Month Diabetes	Control		HFD			
Brain Area	Ave	SD	Ave	SD	P val	Ω SQ
root of trigeminal nerve	2.62	0.19	< 2.93	0.11	0.001	0.698
sub coeruleus n.	2.23	0.22	< 2.71	0.21	0.002	0.577
pontine reticular n. caudal	2.26	0.22	< 2.76	0.20	0.002	0.576
raphe magnus	2.36	0.21	< 2.97	0.32	0.002	0.575
pontine reticular n. oral	2.15	0.19	< 2.59	0.20	0.003	0.554
median raphe n.	2.28	0.20	< 2.70	0.17	0.003	0.531
prerubral field	2.08	0.20	< 2.47	0.23	0.003	0.531
parabrachial n.	2.30	0.21	< 2.74	0.28	0.003	0.530
pedunculopontine tegmental area	2.15	0.20	< 2.57	0.21	0.003	0.530
reticulotegmental n.	2.28	0.21	< 2.72	0.19	0.003	0.530
trapezoid body	2.39	0.18	< 2.85	0.27	0.003	0.530
central medial thalamic n.	2.04	0.20	< 2.38	0.26	0.005	0.488
ventromedial thalamic n.	2.03	0.18	< 2.37	0.19	0.005	0.488
motor trigeminal n.	2.22	0.19	< 2.69	0.28	0.005	0.487
parvicellular reticular n.	2.41	0.17	< 2.76	0.20	0.005	0.467
ventrolateral thalamic n.	2.02	0.20	< 2.33	0.24	0.006	0.447
anterior thalamic nuclei	2.05	0.19	< 2.35	0.24	0.006	0.445
red n.	2.22	0.22	< 2.60	0.21	0.006	0.445
parafascicular thalamic n.	2.03	0.23	< 2.41	0.27	0.007	0.427
medial dorsal thalamic n.	2.07	0.24	< 2.45	0.26	0.007	0.426
substantia nigra compacta	2.18	0.25	< 2.61	0.25	0.007	0.426
reticular n. midbrain	2.14	0.22	< 2.51	0.21	0.009	0.407
ventral anterior thalamic n.	2.00	0.20	< 2.32	0.24	0.009	0.405
pontine nuclei	2.41	0.27	< 2.76	0.22	0.010	0.387
posterior thalamic n.	2.01	0.24	< 2.33	0.23	0.010	0.387
gigantocellular reticular n. pons	2.44	0.21	< 2.87	0.28	0.010	0.387
zona incerta	2.09	0.20	< 2.41	0.15	0.012	0.368
anterior pretectal n.	2.08	0.31	< 2.45	0.26	0.012	0.367
principal sensory n. trigeminal	2.29	0.19	< 2.72	0.27	0.014	0.349
raphe obscurus n.	2.47	0.25	< 2.88	0.29	0.015	0.334
subthalamic n.	2.15	0.25	< 2.50	0.21	0.016	0.332
reuniens n.	2.08	0.19	< 2.38	0.25	0.016	0.331
reticular n.	2.07	0.19	< 2.30	0.20	0.018	0.314
superior colliculus	2.30	0.31	< 2.74	0.29	0.021	0.297
medial pretectal area	2.44	0.58	< 3.04	0.32	0.021	0.296
ventral posteriolmedial thalamic n.	2.02	0.22	< 2.30	0.21	0.021	0.296
periaqueductal gray thalamus	2.50	0.21	< 2.86	0.28	0.024	0.281
dorsomedial tegmental area	2.29	0.31	< 2.65	0.26	0.027	0.263
inferior colliculus	2.45	0.26	< 2.80	0.31	0.027	0.263
medial geniculate	2.14	0.24	< 2.45	0.20	0.027	0.263
lateral dorsal thalamic n.	2.08	0.24	< 2.35	0.26	0.031	0.248
raphe linear	2.40	0.25	< 2.74	0.23	0.031	0.248
solitary tract n.	2.32	0.23	< 2.70	0.34	0.034	0.237
ventral posteriolateral thalamic n.	2.01	0.20	< 2.25	0.21	0.036	0.232
dorsal raphe	2.76	0.53	< 3.23	0.41	0.046	0.202

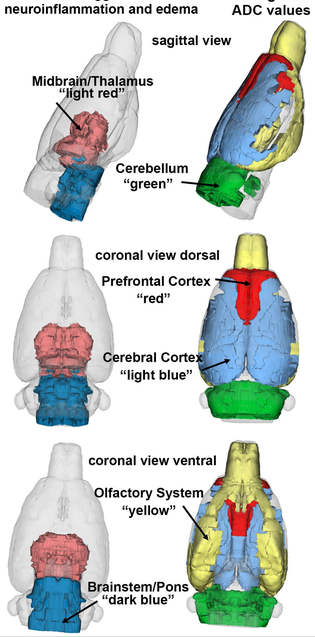


Table of Nonsignficant ADC Values

Apparent Diffusion Coefficient 12 Month Diabetes	Control		HFD			
Brain Area	Ave	SD	Ave	SD	P val	Ω SQ
entorhinal ctx	2.38	0.23	< 2.58	0.17	0.052	0.189
temporal ctx	2.09	0.23	< 2.31	0.23	0.052	0.189
simple lobule cerebellum	2.25	0.31	< 2.53	0.25	0.059	0.175
ventral orbital ctx	1.92	0.16	< 2.15	0.21	0.065	0.162
perirhinal ctx	2.19	0.17	< 2.38	0.19	0.074	0.149
flocculus cerebellum	2.33	0.20	< 2.60	0.30	0.074	0.148
1st cerebellar lobule	2.57	0.50	< 2.82	0.32	0.083	0.136
crus 1 of ansiform lobule cerebellum	2.07	0.29	< 2.35	0.25	0.092	0.124
interposed n. cerebellum	2.76	0.46	< 3.11	0.37	0.093	0.123
primary somatosensory ctx barrel field	2.13	0.19	< 2.33	0.26	0.093	0.123
5th cerebellar lobule	2.43	0.30	< 2.70	0.24	0.093	0.123
copula of the pyramis cerebellum	2.55	0.40	< 2.91	0.27	0.093	0.123
caudal piriform ctx olfaction	1.93	0.16	< 2.10	0.16	0.093	0.123
visual 2 ctx	2.10	0.25	< 2.32	0.23	0.103	0.112
anterior olfactory n.	2.00	0.18	< 2.18	0.21	0.115	0.100
paramedian lobule cerebellum	2.14	0.29	< 2.44	0.34	0.141	0.078
tenia tecta ctx olfaction	2.52	0.19	< 2.72	0.30	0.156	0.068
primary somatosensory ctx upper lip	2.01	0.13	< 2.19	0.21	0.205	0.041
granular cell layer olfaction	1.99	0.16	< 2.12	0.27	0.207	0.040
retrosplenial rostral ctx	2.34	0.37	< 2.54	0.31	0.207	0.040
7th cerebellar lobule	2.16	0.38	< 2.40	0.32	0.208	0.039
frontal association ctx	2.16	0.29	< 2.36	0.33	0.226	0.031
crus 2 of ansiform lobule cerebellum	2.01	0.30	< 2.23	0.30	0.248	0.022
retrosplenial caudal ctx	2.49	0.31	< 2.68	0.26	0.248	0.022
visual 1 ctx	2.16	0.25	< 2.30	0.19	0.248	0.022
primary somatosensory ctx forelimb	2.06	0.21	< 2.20	0.27	0.269	0.015
prelimbic ctx	1.97	0.22	< 2.14	0.25	0.293	0.007
10th cerebellar lobule	2.41	0.30	< 2.66	0.40	0.294	0.007
ectorhinal ctx	1.98	0.31	< 2.08	0.26	0.318	0.000
anterior cingulate ctx	2.21	0.25	< 2.36	0.25	0.318	0.000
secondary motor ctx	2.20	0.30	< 2.27	0.23	0.371	0.013
primary somatosensory ctx shoulder	2.21	0.33	< 2.40	0.44	0.372	0.014
external plexiform layer olfaction	2.05	0.15	< 2.16	0.26	0.400	0.020
glomerular layer olfaction	2.19	0.17	< 2.28	0.24	0.400	0.020
parietal ctx	2.24	0.34	< 2.41	0.33	0.401	0.020
primary motor ctx	2.10	0.27	< 2.19	0.26	0.431	0.025
primary somatosensory ctx hindlimb	2.25	0.31	< 2.34	0.39	0.462	0.031
olfactory tubercles	2.37	0.20	< 2.45	0.21	0.563	0.044
6th cerebellar lobule	2.33	0.44	< 2.44	0.26	0.600	0.048
primary somatosensory ctx trunk	2.27	0.38	< 2.39	0.43	0.674	0.055

Brain areas that show specific changes in gray matter microarchitecture with Type 2 diabetes at 12 months. Tables are brain areas that show significant difference (left) and non-significant difference (right) in apparent diffusion coefficient (ADC) in the HFD group as compared to control group. The 3D images (middle) are a summary of these brain areas. Control n=9, HFD n=9.

Summary

These studies provide evidence that multimodal imaging can be used to follow disease progression in the development of T2D. The expected decrease in brain volume was realized with indications of neuroinflammation in brainstem and pons with histology ongoing for gliosis in these areas.