What can the transcriptome tell us about regional vulnerability to age and cognitive impairment

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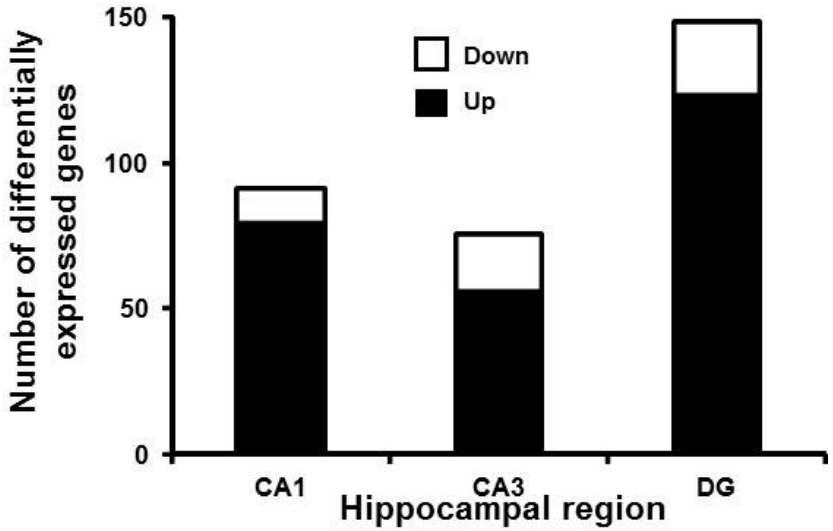
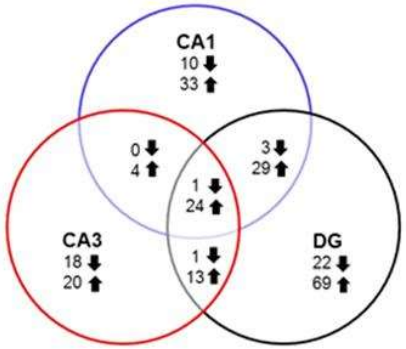
McKnight Inter-Institute Collaboration on Epigenetics

Most genes increase expression and DG is most responsive to age



Overlap of up regulated genes



Gene symbol	Gene Name
C3	complement component 3
Card11	caspase recruitment domain family,
**Cd4*	Cd4 molecule
**Cd74*	Cd74 molecule, major histocompatibility complex, class II invariant chain
Cdh1	cadherin 1
Csf1r	colony stimulating factor 1 receptor
Ctss	cathepsin S
Ctsz	cathepsin Z
Cx3cr1	chemokine (C-X3-C motif) receptor 1
Fcgr2b	Fc fragment of IgG, low affinity IIb, receptor (CD32);
**Gfap*	glial fibrillary acidic protein
Gpr183	G protein-coupled receptor 183
Gpr84	G protein-coupled receptor 84
Itgb2	integrin beta 2
Ncf1	neutrophil cytosolic factor 1
Nckap1l	NCK associated protein 1 like
**Trem2*	triggering receptor expressed on myeloid cells

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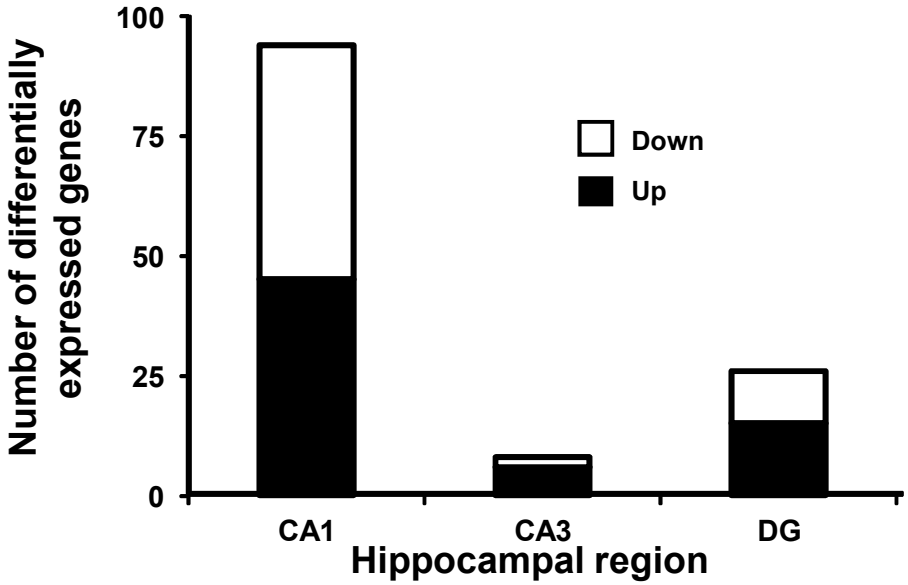
Cognition-related genes

CA1 is most responsive to differences in behavior



Aged animals tested on the episodic version of the water maze and genes were separated for impaired and unimpaired

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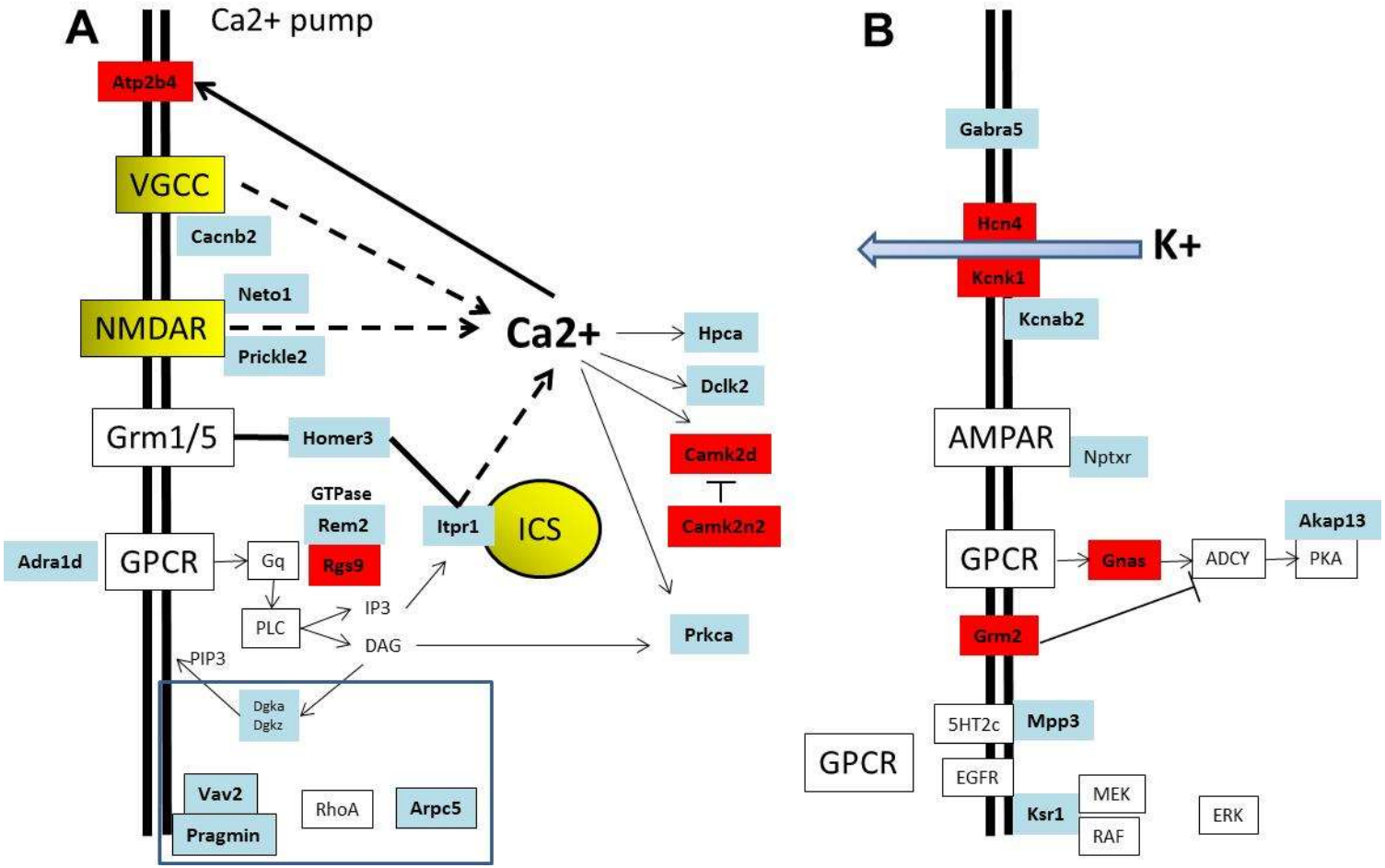
Impaired spatial episodic memory is associated with altered transcription of CA1 genes linked to Ca^{2+} regulation and neural activity

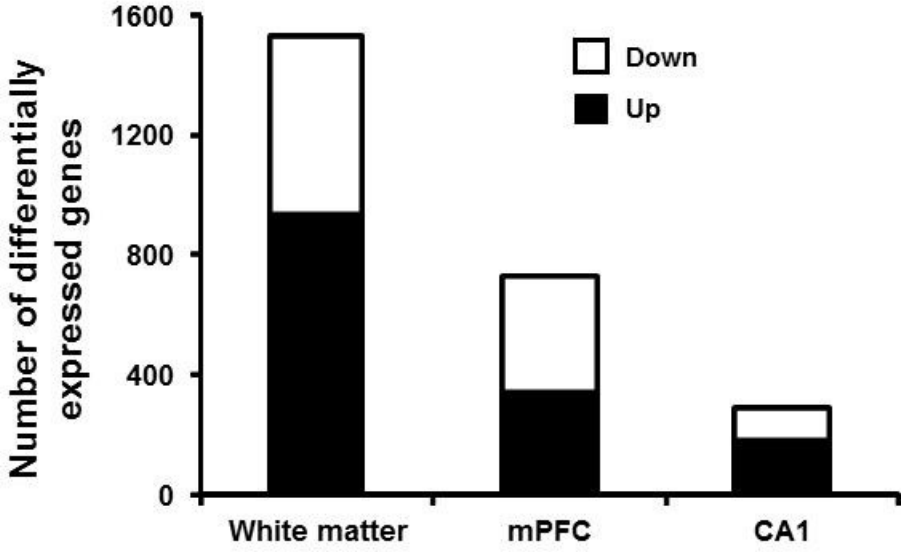


Blue = decreased expression; Red = increased expression

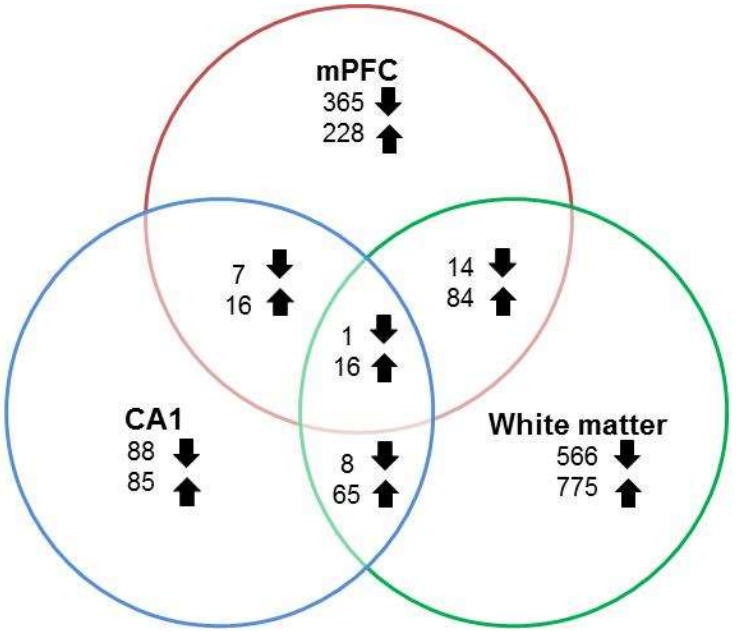
Transcription Profile of Aging and Cognition-Related Genes in the Medial Prefrontal Cortex

Vulnerability to aging across brain regions

Transcription in the white matter and mPFC are more responsive to aging than CA1



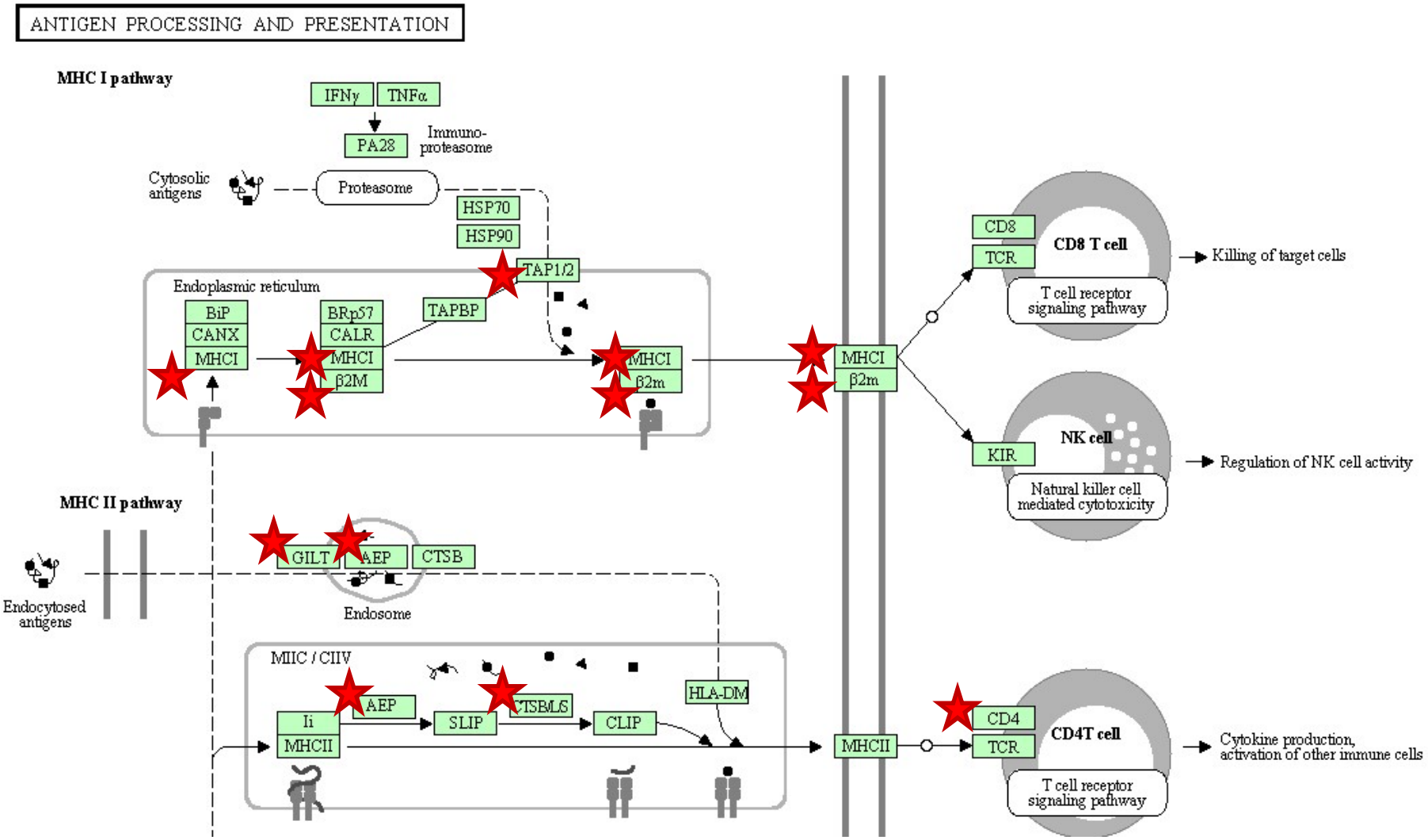
Overlap is mainly observed for up regulated genes



Ianov et al., in press 2016

Transcription Profile of Aging and Cognition-Related Genes in the Medial Prefrontal Cortex

Age-related increase in expression of immune response genes in the mPFC

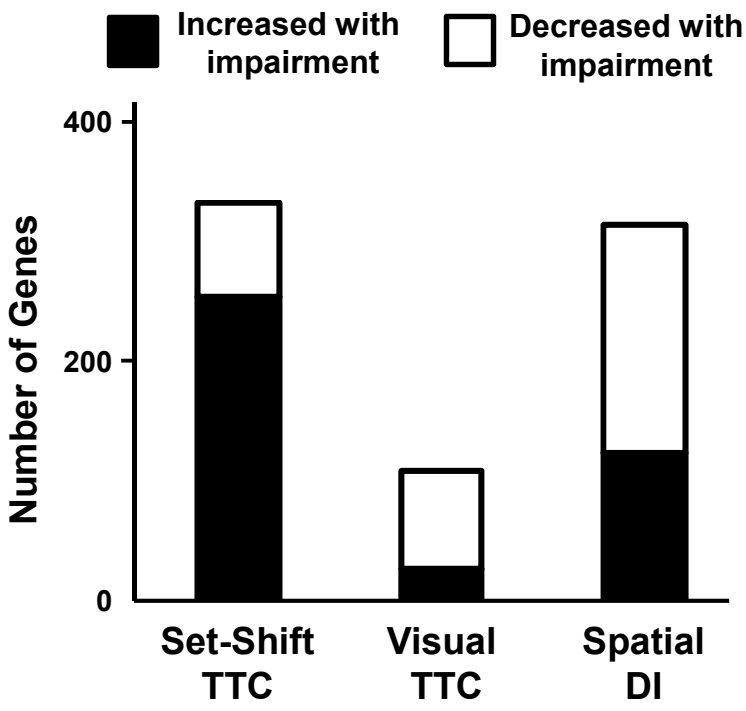


Ianov et al., in press 2016

Transcription Profile of Aging and Cognition-Related Genes in the Medial Prefrontal Cortex

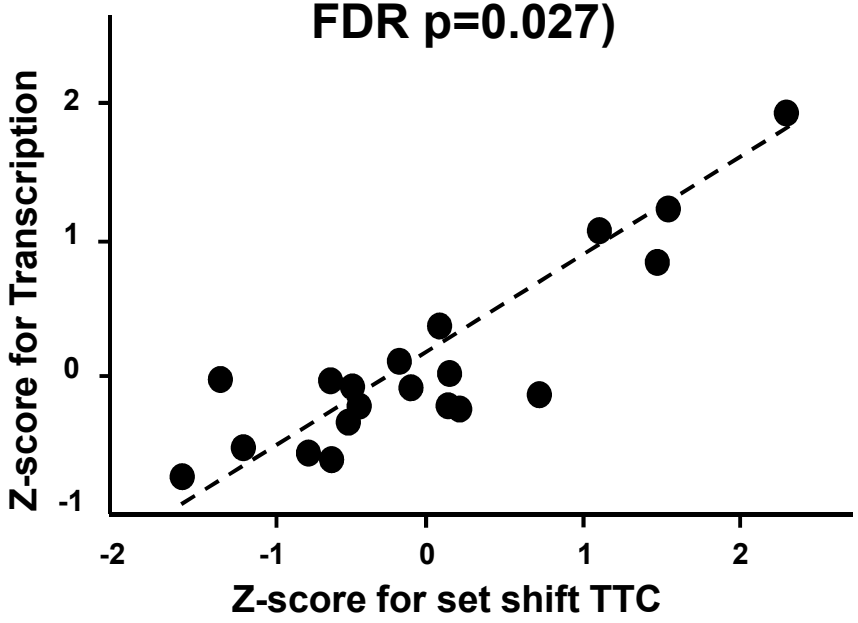
Cognition-related genes in the mPFC

Specificity of mPFC transcriptional changes



Increased gene expression in mPFC for animals impaired on attentional set-shift

Cluster enrichment indicates increase expression of genes for regulation of transcription (GO:0045449, 46 genes, FDR p=0.027)



Expression of transcription regulation genes were normalized and averaged for each animal, then plotted against normalized set shift scores.

Ianov et al., in press 2016

Transcription Profile of Aging and Cognition-Related Genes in the Medial Prefrontal Cortex

Table 6 Increased expression in the mPFC for AI vs AU

Gene symbol	Gene Name	AI vs AU Fold	Age Fold
Arc	Activity regulated cytoskeletal-associated protein	1.89	-1.19
BHLHE40	Basic helix-loop-helix domain containing, class B2	1.22	-1.08
Btg2	B-cell translocation gene 2, anti-proliferative	1.49	-1.28
Dusp1	Dual specificity phosphatase 1	1.45	-1.27
Egr1	Early growth response 1	1.57	-1.31
Egr2	Early growth response 2	2.79	-1.37
Egr4	Early growth response 4	1.53	-1.41
Hspa1a	Heat shock 70kD protein 1A	2.12	-1.26
Hspa1b	Heat shock 70kD protein 1B	1.84	-1.46
Ier5	Immediate early response 5	1.29	-1.17
Junb	Jun-B oncogene	1.50	-1.36
Klf10	Krueppel-like factor 10	1.36	-1.29
Nr4a1	Nuclear receptor subfamily 4, group A, member 1	1.60	-1.23
Nr4a3	Nuclear receptor subfamily 4, group A, member 3	1.39	-1.20
Ptgs2	Prostaglandin-endoperoxide synthase 2	1.36	-1.12
Sik1	SNF1-like kinase	1.76	-1.12

Increased expression of genes associated with neural activity and circuit remodeling in aged animals impaired on set shifting

Ianov et al., in press 2016

Plasma Exosomes as Biological Markers for Age-Related Cognitive Decline: The ACTIVE Study

Exosomes are cell-derived vesicles present in biological fluids, including blood, urine, and cell culture medium. **Exosomes** can transfer miRNA from one cell to another via membrane vesicle trafficking, thereby influencing the physiology of nearby and distant cells.

We have completed exosome sequencing on 30 elderly people, which have been cognitively tested and in some cases (n = 18) have MRI data.

~50 exosomal miRNAs are increased in elderly that are impaired on the MOCA. Some correlated with a decline in hippocampal size.

Currently we are examining ~90 more individuals in order to confirm results.

Summary

1) Vulnerability/reactivity to aging:
White matter > mPFC > DG > CA1 > CA3.

2) Cognitive decline is associated with specificity of transcription in neural circuits that underlie the behavior.
a) Hippocampal CA1 episodic memory (Ca^{2+} regulation, neural activity)
b) mPFC attentional set shift (transcription regulation, synaptic plasticity)

3) Preliminary studies suggest that exosomal miRNA may be able to identify cognitively impaired individuals.