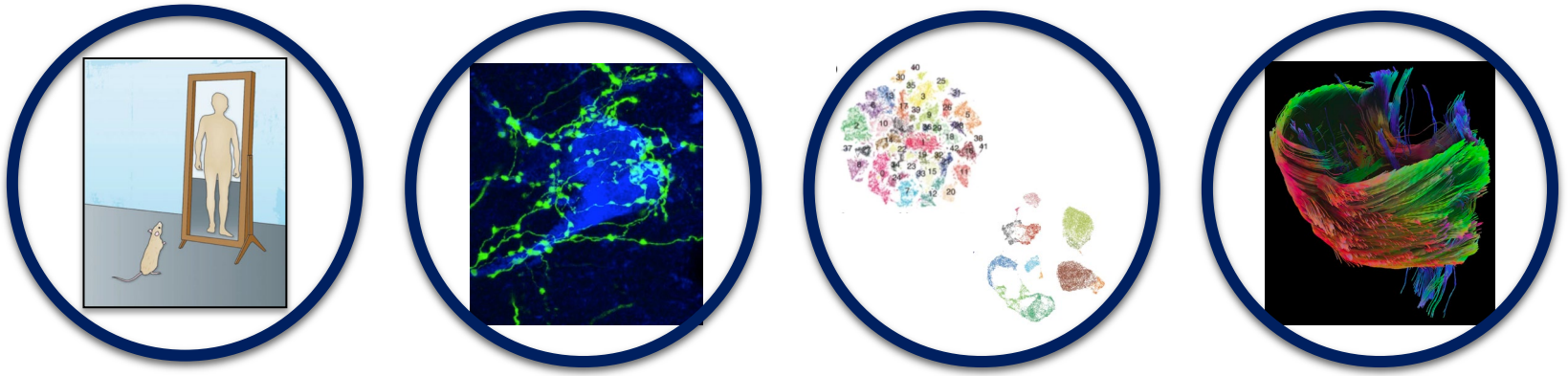
Combining human and pre-clinical studies

Why is this important and how can it be done?



Veronique VanderHorst MD PhD

Associate Professor of Neurology

Beth Israel Deaconess Medical Center/Harvard Medical School

RCCN Workshop: Multidisciplinary Research in Aging and Team Science

May 20-21, 2026, Bethesda



Combining human and pre-clinical studies Introduction

Introduction

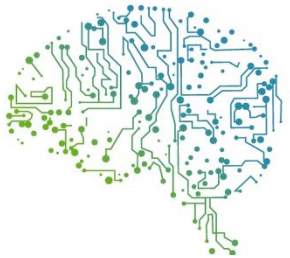
- Context: my journey
- Circuits and the brainstem



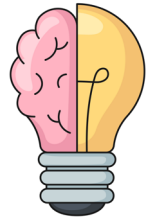
Cristina Gattardi

Studying circuit dysfunction in the context of ADRD: 4 pieces of a puzzle

- Location: Where to look, where are the pathologies?
- Connectivity: How can we study connectivity?
- Neuron subtypes: New opportunities
- Function: The importance of matching outcome measures between models to assess function/symptoms



Challenges and Opportunities: Summary



Juicy fish


Cristina Gattardi

Introduction: My journey

Brainstem and spinal anatomy, plasticity, sex differences

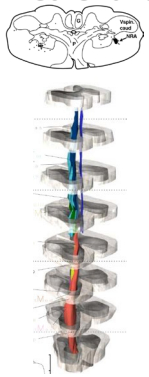
Groningen, Netherlands

Karolinska Institutet, Sweden

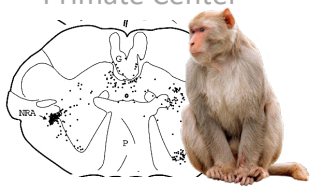


PhD

MD



UCSF/Wisconsin Primate Center



Neurology & Movement Disorders BIDMC

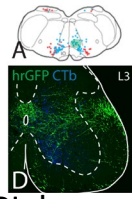
Gait (walking) disorders





Innovative wearable technologies





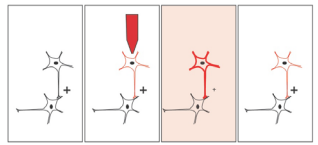
NIA R01 AG047976 (subcontract PI; human)
NINDS R01 NS079623 (PI; mouse)

Brainstem circuit function & pathology

Translation of potential interventional tools



(Philantropy)

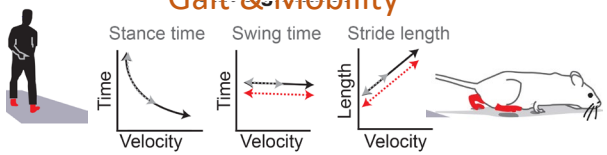


Resilience proteins

NIA R01AG075728 (human; team science; subcontract PI)

Translatable outcome measures

Gait & Mobility



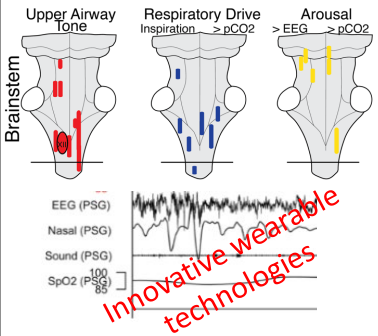
Spin-off from Gait studies

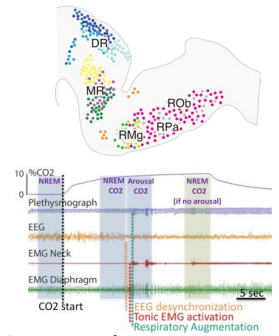
Sleep Disordered Breathing







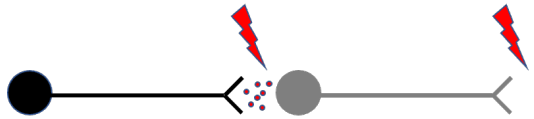




NIA R01AG075728 (Multi-PI; human)
P01 HL149630 (PPG; Proj. 4 PI; mouse)

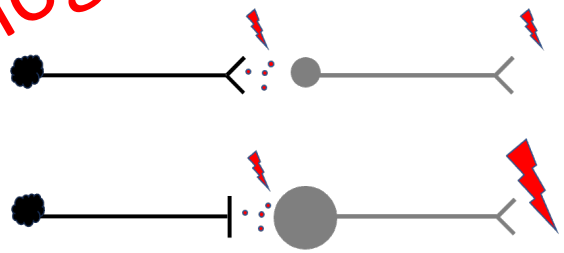
Combining human and pre-clinical studies
Introduction: Neural circuits and function

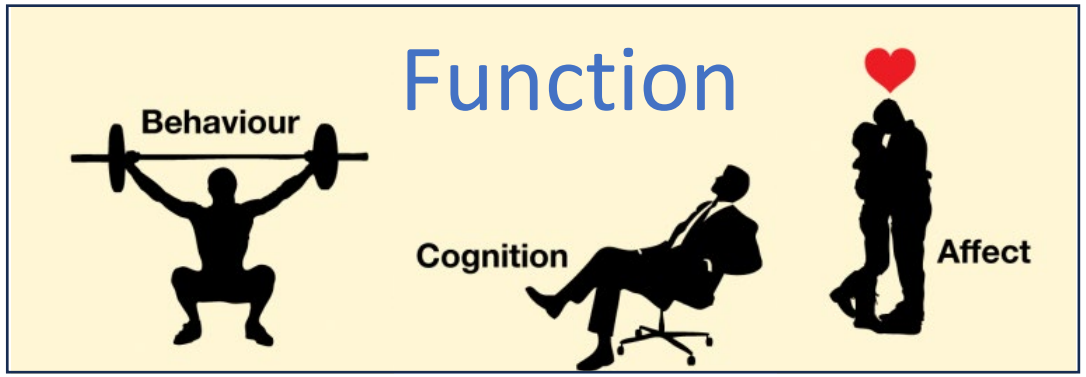
Circuits

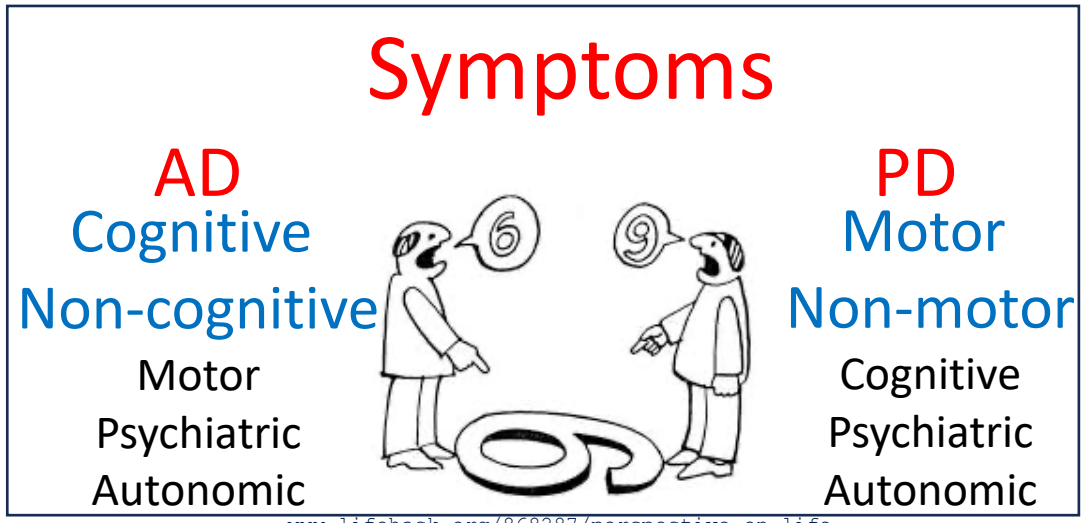


Circuit Dysfunction

Pathologies



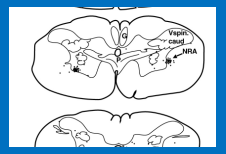




www.lifehack.org/868287/perspective-on-life

Symptoms are the result of circuit dysfunction:

- dependent on location of pathology rather than pathology type alone



Combining human and pre-clinical studies
Introduction: Brainstem circuits and function

Well conserved structure and function

Normal





Breathing
Walking
Balance
Muscle tone
Arousal

- How does this impact symptoms/(dys)function?
- Disease propagation?

Early site for common neuropathologies

Disease

PD (asyn)



AD (tau)



ALS (TDP-43)



Jucker and Walker, Nature 2013

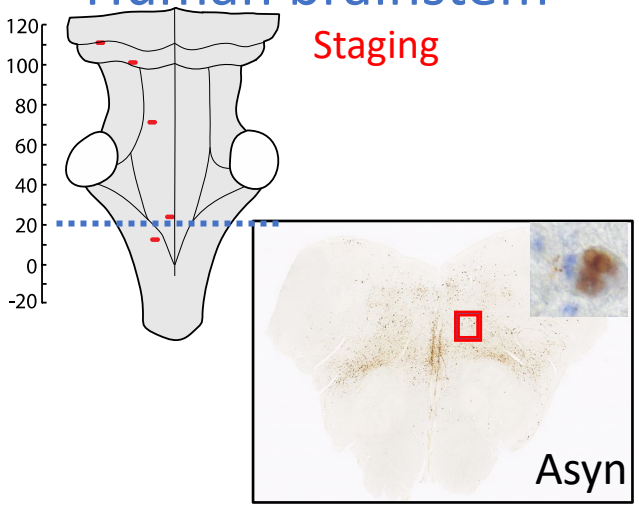


Combining human and pre-clinical studies

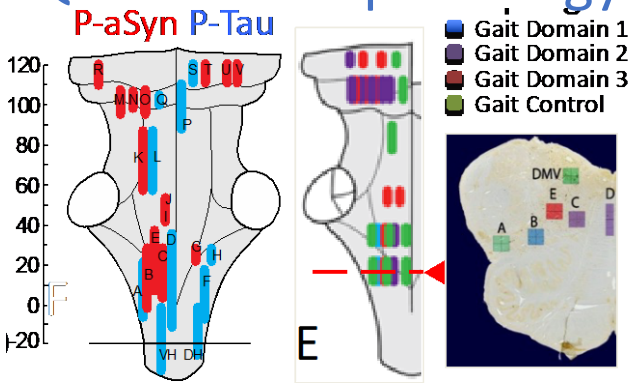
Location: Where to look?

Human brainstem

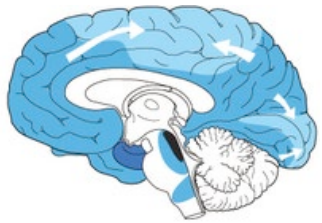
Staging

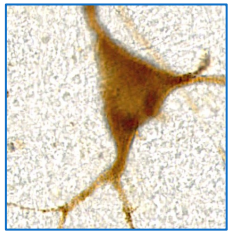


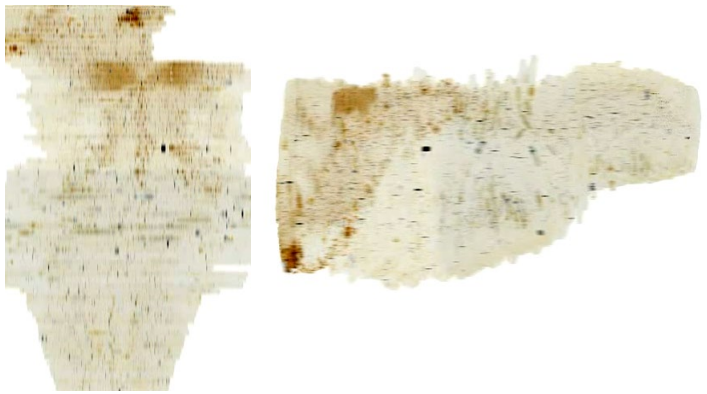
Quantitative pathology



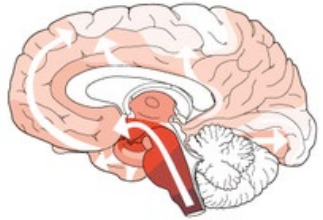
Phosphorylated Tau

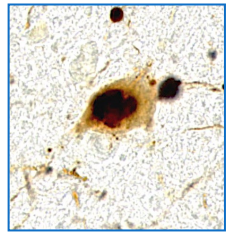






Phosphorylated α-synuclein







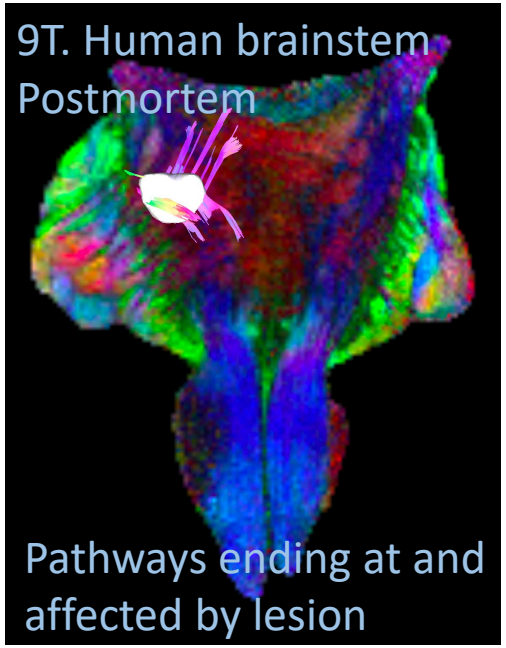
- ✓ Help focus pre-clinical studies on regions that matter
- ✓ Engineer pre-clinical models to re-capitulate parts

Combining human and pre-clinical studies
Connectivity: How can we study this?

MRI

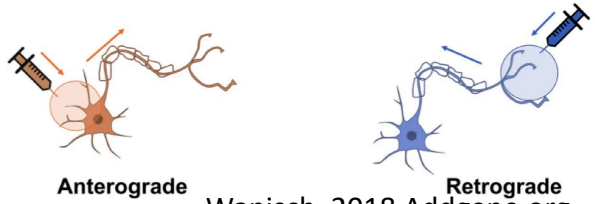
Tractography

Functional

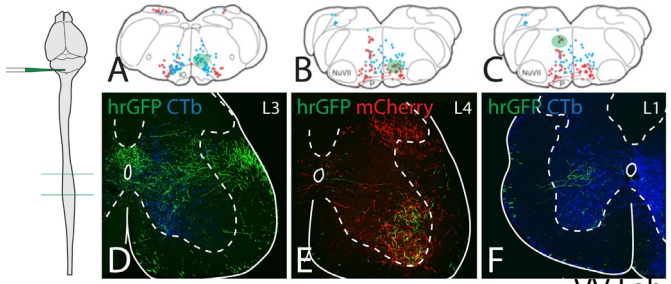


Gopal Varma, VanderHorst, Buchman, unpublished

Neuronal tract tracing?



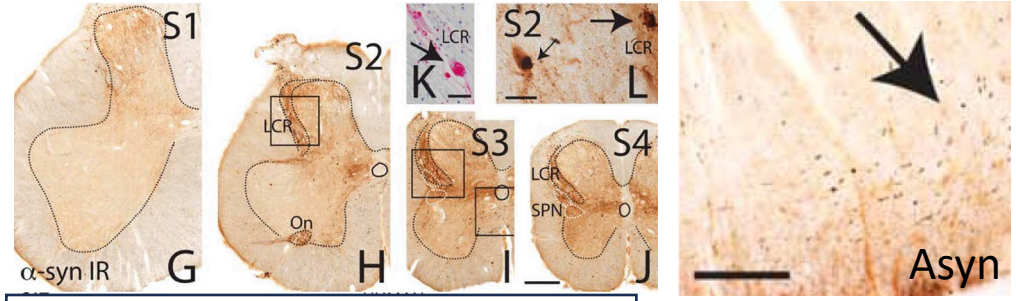
Wanisch, 2018 Addgene.org



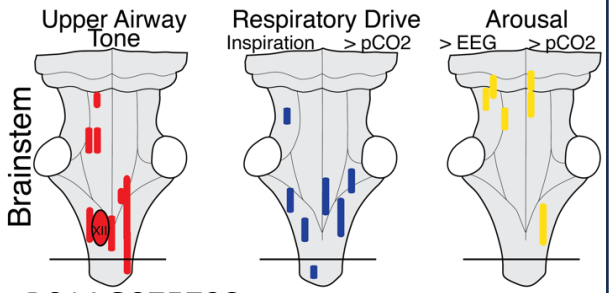
VV Lab

- ✓ Widely used in pre-clinical models
- ✓ Develop detailed connectivity maps using genetically engineered models and tools
- ➢ Invasive & Tissue harvest
- Dependent on pre-clinical models

Some pathologies behave as tracers!



Sleep Disordered Breathing and ADRD pathologies



R01AG075728

Buchman, Lim, VanderHorst;

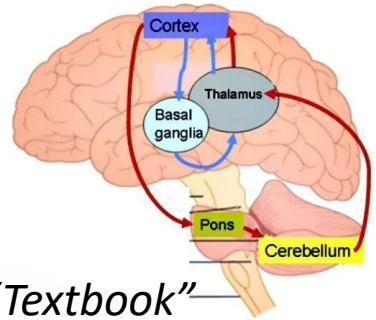
RADC Rush Univ Med Ctr, MAP

VanderHorst et al., Annals of Neurology 2015

- ✓ Identify homologous regions
- ✓ Compare patterns between models
- ✓ Hypothesis generation/testing

Combining human and pre-clinical studies
Neuron subtypes: New opportunities

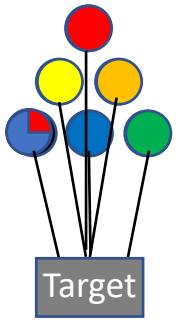
Wiring diagram



"Textbook"

A general function

Intermixed neuron subtypes



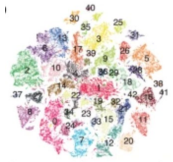
RNAseq tools

Human dorsal striatum (forebrain)



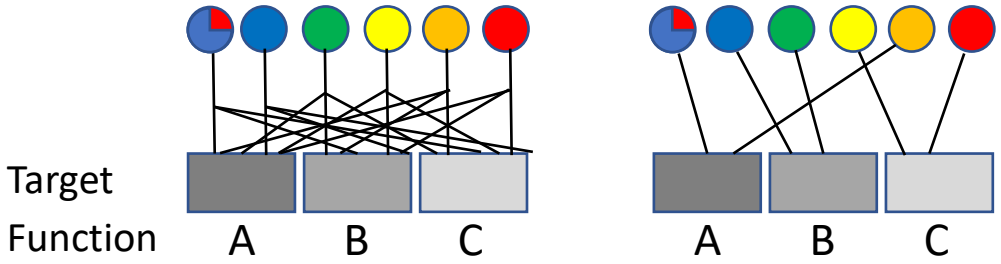
Garma et al., 2024
Nature Communications 15, 6164

Mouse dorsal pons (brainstem)

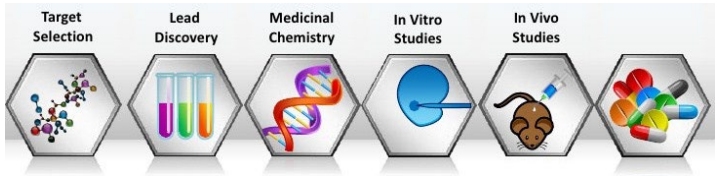


Nardone et al., 2024
Nature Communications, 15, 1966

Impact on wiring diagrams?



- ✓ Which neuron subtypes are affected by pathologies?
- ✓ Are there differences in selective vulnerability, propagation or resilience between regions and/or neuron sub types Examples LCr vs LCc, SN vs VTA

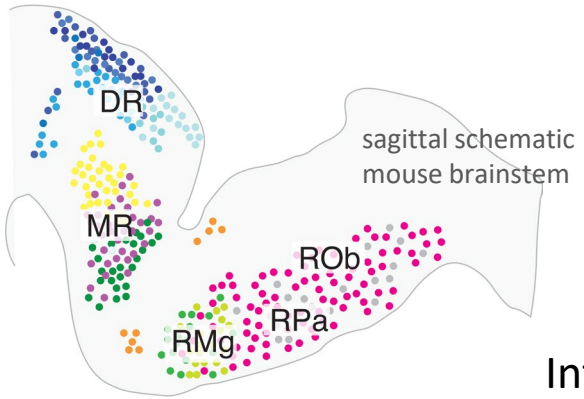


- ➢ Composition of each structure differs: lots of work
- ➢ Requires postmortem tissues (CNS): resources
- ➢ Connectivity still dependent on pre-clinical models

Combining human and pre-clinical studies

Neuron subtype and connectivity dictate function

Serotonergic subtypes

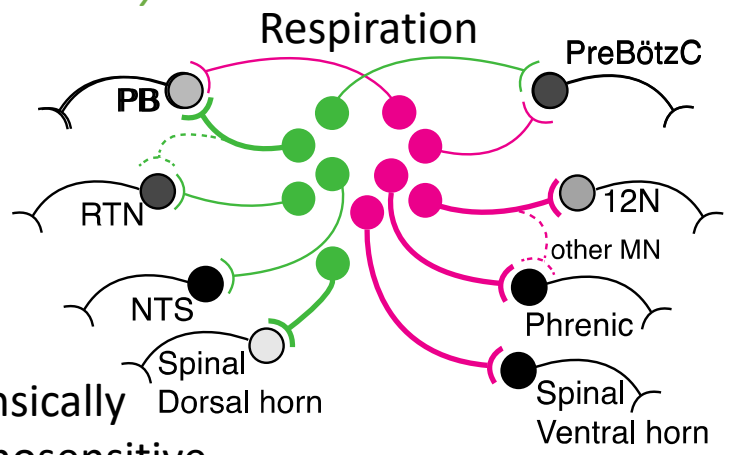


Egr2-Pet1

"sensory" centers

Tac1-Pet1

"motor" centers



Intrinsically chemosensitive

Brust, Dymecki, and colleagues, 2014
Cell Reports

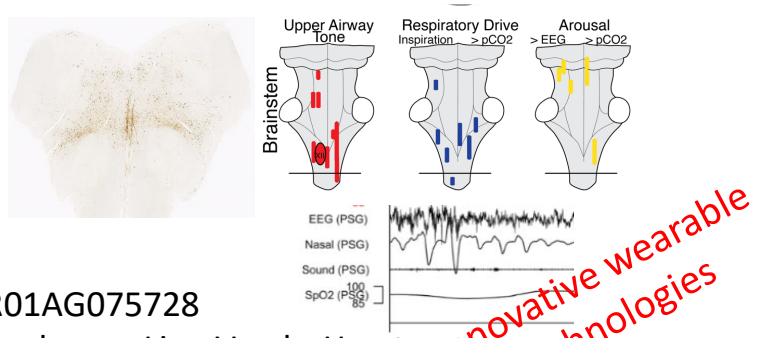
Hennessy, Dymecki, and colleagues, 2017
J. Neurosci

Decrease latency to arousal from NREM sleep

Increase upper airway tone and breathing during NREM sleep

Role in breathing, arousal and upper airway tone during sleep as relevant for sleep apnea

Are ADRD pathologies associated with Sleep Disordered Breathing phenotypes in older adults



R01AG075728
Buchman, Lim, VanderHorst;
RADC Rush Univ Med Ctr, MAP

Innovative wearable technologies

Dymecki – VanderHorst Labs HL149630

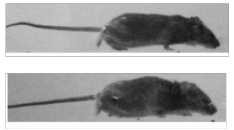
Combining human and pre-clinical studies
Function: Alignment of outcome measures is critical

Human

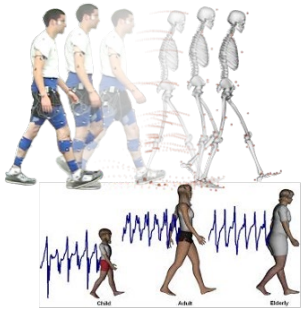
Mouse

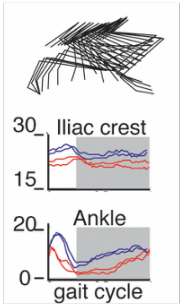
Pattern recognition



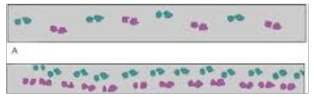


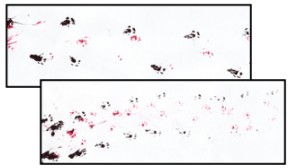
Kinematics/
Kinetics





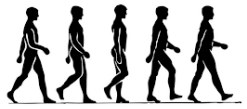
Temporal spatial
gait analysis



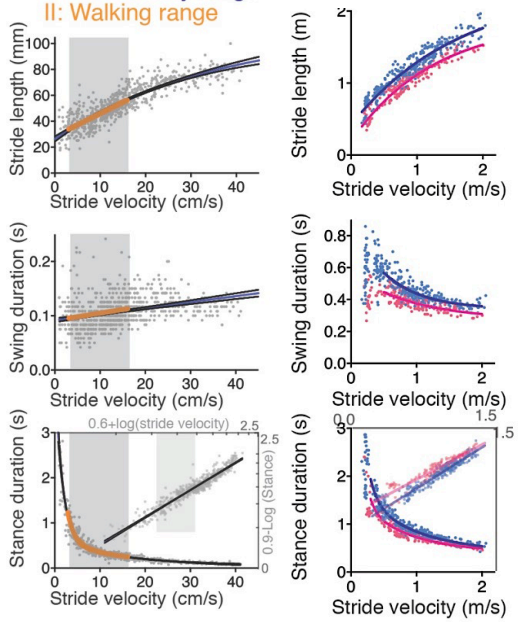


Gait signatures





I: Full velocity range
II: Walking range

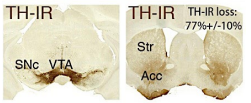


Shifts in gait signatures capture qualitative changes

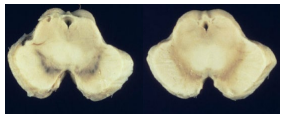
Aging
(19 vs 120 wks

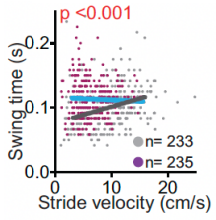


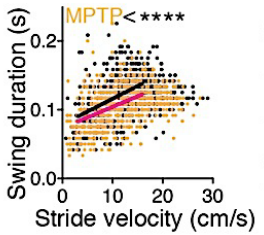
PD models

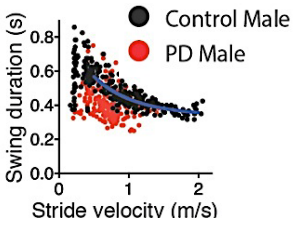


PD







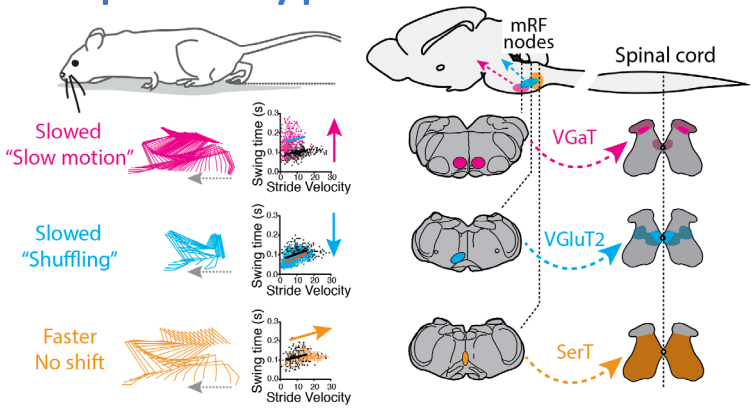


Broom et al., Scientific Reports, 2017, 2019
Broom et al., Frontiers in Aging Neuroscience, 2021

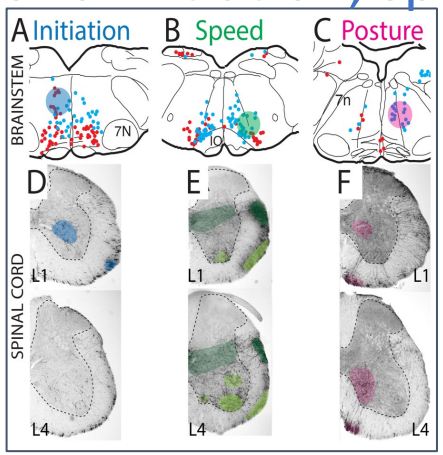
Combining human and pre-clinical studies

Integration of pre-clinical and human studies

Map cell types and sites: walking quality



and initiation, speed and postural control



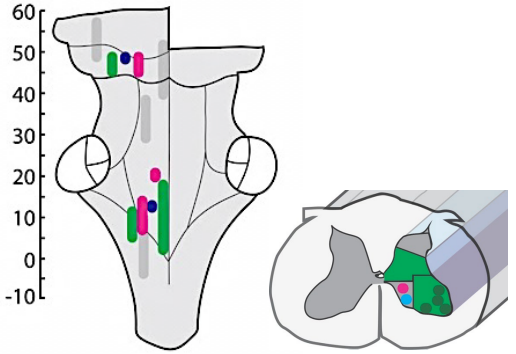
Genetic tools, cell type specific modulation, circuit mapping, functional assays (activation/loss of function)

Worley…VanderHorst, under revision; BioRxiv

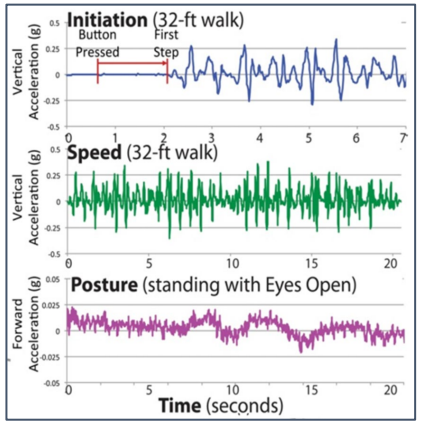
Pathology circuit location and burden is associated with gait /motor dysfunction

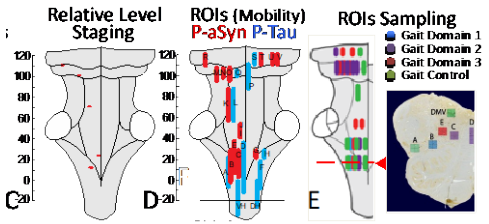
ROI selection

Posture Speed Initiation

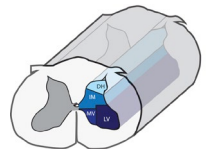


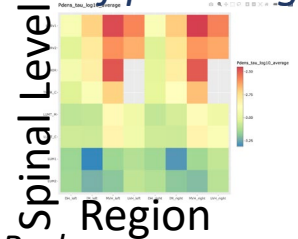
Wearable devices





Quantification of pathology





Buchman and VanderHorst, collaboration RADC at Rush University, Memory and Aging Project, AG047976



Combining human and pre-clinical studies Challenges and opportunies: Summary



Selection of circuit nodes to study (location):

→ Pathology maps from post mortem human samples help focus pre-clinical studies on regions/circuit nodes that are highly relevant

→These data can be used to engineer pre-clinical models to re-capitulate parts

Functional connectivity maps:

→Develop detailed cell type specific connectivity maps using genetically engineered models and tools, but heavy reliance of pre-clinical models as we rely on tract tracing

→Between preclinical and human models, identify homologous regions, compare patterns of circuits maps and pathology sites for hypothesis generation

→Clinical-pathological studies serve to test hypotheses generated in pre-clinical models (indirect)

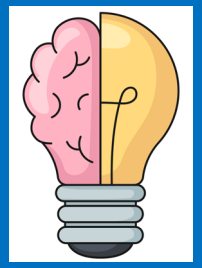
Neuron subtypes:

→Impact on wiring diagrams: Many regions and disease states to explore, requiring resources (human postmortem specimens)

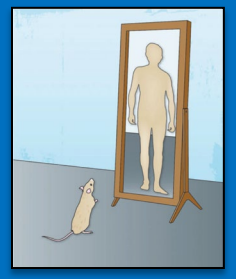
→Questions: Differences in selective vulnerability, propagation or resilience between regions and/or neuron sub types and how does this impact (dys)function?

Outcome measures: →alignment of outcome measures between pre-clinical and human models is critical for translation

→requires extra times and effort, a hurdle in pre-clinical research with abundant simpler outcome measures



Combining human and pre-clinical studies
Challenges and Opportunities



Requires a team of experts with different specializations/fields with differences in scientific language and expectations

→ Open mind to learn about other research cultures and language: flexibility and patience

→ Early training and efforts to get scientists/clinicians out of their silos/departments and change the culture: Translational Hubs

Avoid getting deterred by the differences between models as this is a pitfall

→Look for common ground to leverage knowledge from both fields

Advances in pre-clinical (faster pace) and human studies may not be in sync

→ Due to different time scales, tissue scales, tissue quality, fewer pipelines and $$ challenges

→ Resources and infrastructure needed to catch up including (CNS) tissues from *well phenotyped* human subjects

Need for integration of preclinical and human studies, to inform design and hypotheses before the studies are initiated

Support:

Gait:
R01 NS079623
R01 AG047976
P30 AG010161

Sleep disordered breathing:
R01 AG071638
P01 HL095491 (Project 4 PI)
P01 HL149630 (Project 4 PI)
Harvard/MIT Joint Research Grants Program in Basic Neuroscience

Resilience & Omics:
R01 AG075728

Dystonia and Parkinson's disease:
Bachmann Strauss Dystonia and Parkinson's Foundation
Center for Mind Brain Restoration
RJG Foundation
Grateful patients

We are grateful for the valuable donations of time and tissues by human subjects, patients and their caregivers

Thank you!

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