Assessment of the Aging Brain Using Computing Technology

Jeffrey Kaye

Layton Professor of Neurology & Biomedical Engineering

ORCATECH - Oregon Center for Aging & Technology

NIA - Layton Aging & Alzheimer's Disease Research Center

DISCLOSURES

Research support to Oregon Health & Science University from: NIH (U2C AG054397, P30 AG008017, P30 AG024978, R01 AG051628, R01 AG051628, U01 AG010483, U24 AG057437), National Science Foundation, the Department of Veterans Affairs, Merck, AbbVie, Novartis, Kyowa, and Eisai

Compensated (in the last 24 months) for serving on Data Safety Monitoring Committees for Eli Lilly and Suven

Compensated for serving on the Scientific Advisory Board for Sage Bionetworks

Receive reimbursement through Medicare or commercial insurance plans for providing clinical assessment and care for patients

Serve on the editorial advisory board and as Associate Editor of Alzheimer's & Dementia and as Associate Editor for the Journal of Translational Engineering in Health and Medicine

The fundamental challenge...
Detecting (assessing) meaningful change

- Current Outcome Measures - cognitive tests, functional scales - *are poorly sensitive to change*
- Current Assessment Paradigms (brief, sparsely spaced queries, exams, self-report methods) - *do not optimally identify meaningful, ecologically valid change.*

ORCATECH
SENSING LIFE KINETICS

OREGON HEALTH & SCIENCE UNIVERSITY

Change the Paradigm⇢ Improve the Signal

- **Brief**
- **Episodic**
- **Clinic-based**
- **Inconvenient**
- **Obtrusive**
- **Proxy Measures of Function**
- **Cognitive Tests Artificial**
- **Inter-rater/test Variability**
- **Intra-person Variability**

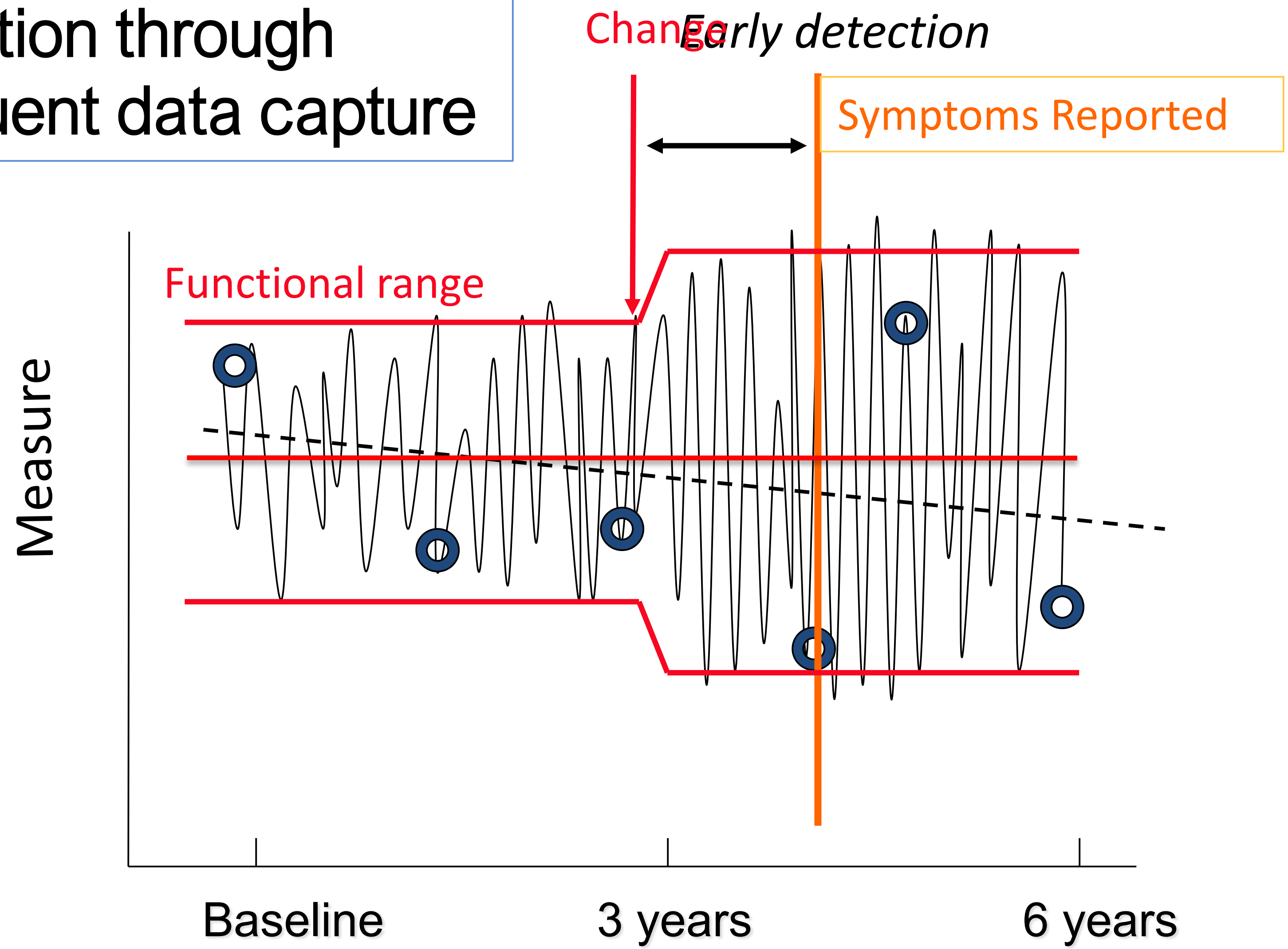
Araujo, et al. **How Much Time Do You Spend Online? Understanding and Improving the Accuracy of Self-Reported Measures of Internet Use.** Communication

Error Estimated Minutes of Internet Use > 90 minutes/day

	Self-Reports		Tracking Data	
N = 690	Yesterday	Average day	Yesterday	Average day
Self-Reports				
Yesterday	1	.797**	.294**	.311**
Average Day		1	229**	.291**
Tracking Data				
Yesterday			1	.702**
Average Day				1

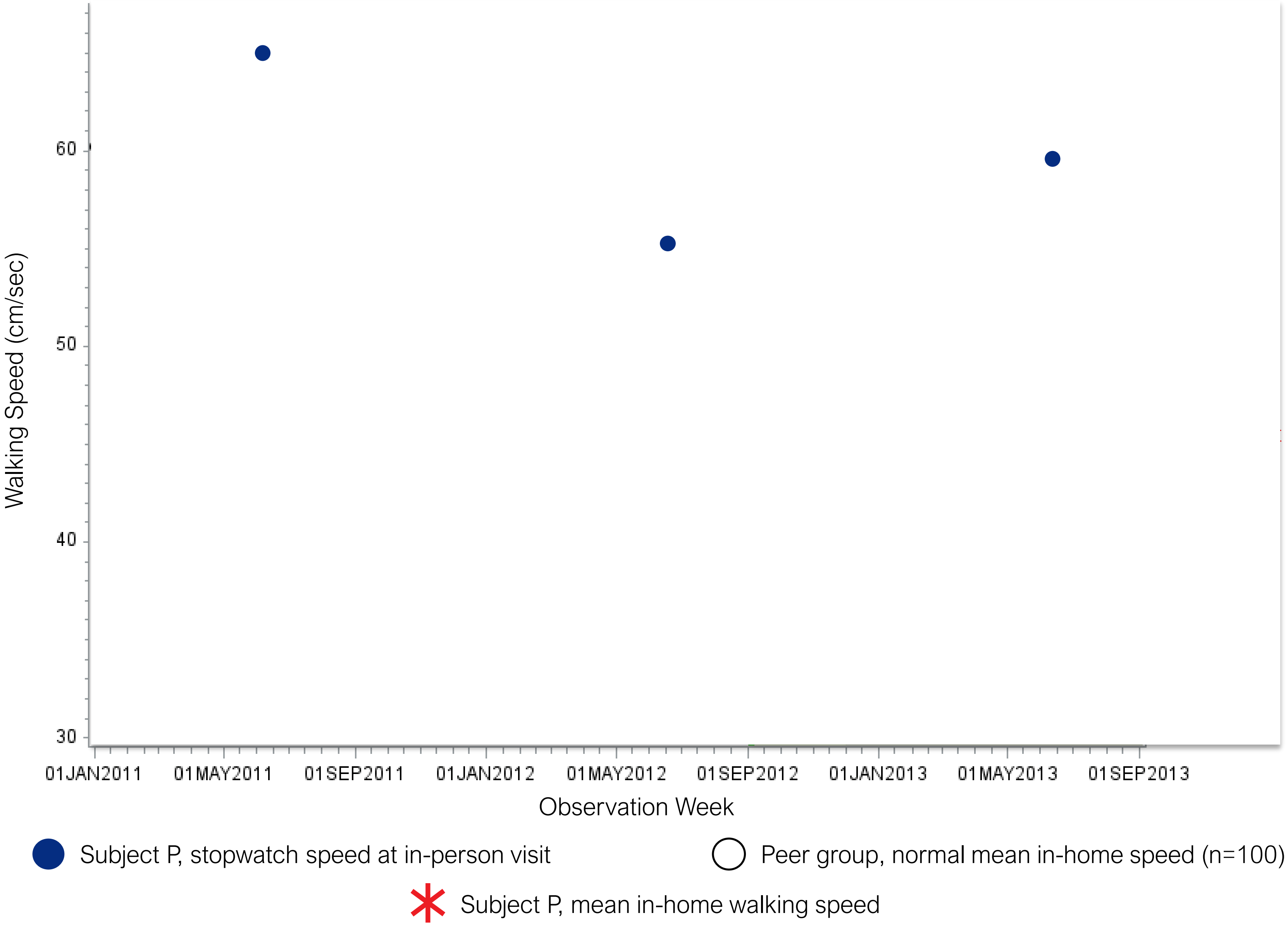
How changing the approach may improve the ability to detect *meaningful* change

Improved signal detection through high dimensional frequent data capture



Example: The Power of High Dimensional Frequent Data Capture

Changes prior to diagnosis and remotely identified response to therapy



The Value of High Dimensional Frequent Data Capture

Example: Increase the *efficiency and value* of clinical trials


Hiroko Dodge


Chao-Yi Wu

MCI Prevention Trial - Sample Size Estimates

	Current Method	Continuous Measures	
	LM Delayed Recall*	Computer Use**	Walking Speed**
SAMPLE SIZE TO SHOW 50% EFFE	688	10	94
SAMPLE S SHOW 30 EFFECT			
SAMPLE S SHOW 20 EFFECT			

- Reduces required sample size and/or time to identify *meaningful* change.
- Reduces exposure to harm (fewer needed/ fewer exposed)
- More precise estimates of the

Model	Outcome	Empirically Derived Slope Differences			Treatment effect size			
		Group effect on slope	Standard error	p-value	20%	30%	40%	50%
Generalized Linear Mixed Effects Model	Likelihood of 30th percentile low	0.03454	0.01407	**0.01**	**22**	**14**	**10**	**10**
	Likelihood of 40th percentile low	0.02660	0.01335	**0.04**	**50**	**28**	**20**	**16**

Replicated on independent data set, 2019

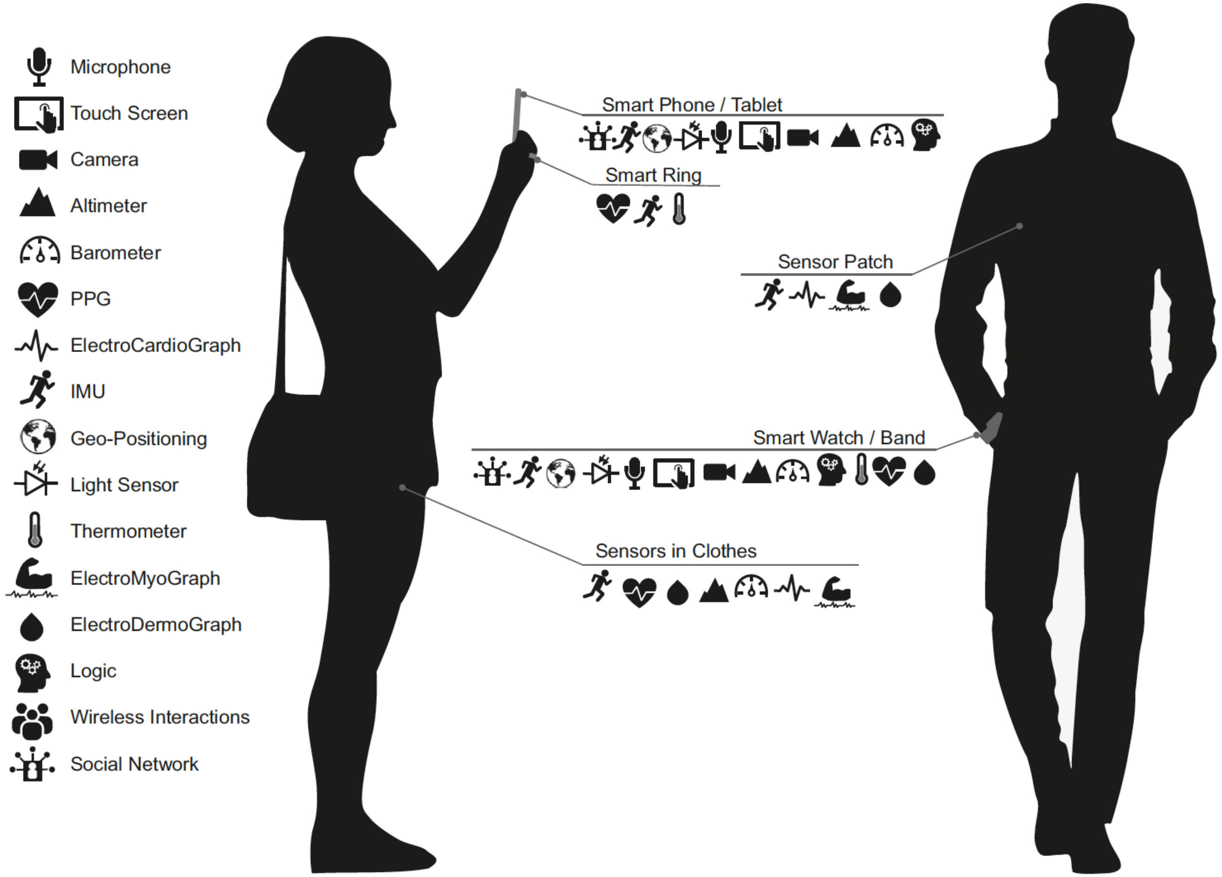
Similar results with sleep data: Wu, 2019

ORCATECH
SENSING LIFE KINETICS

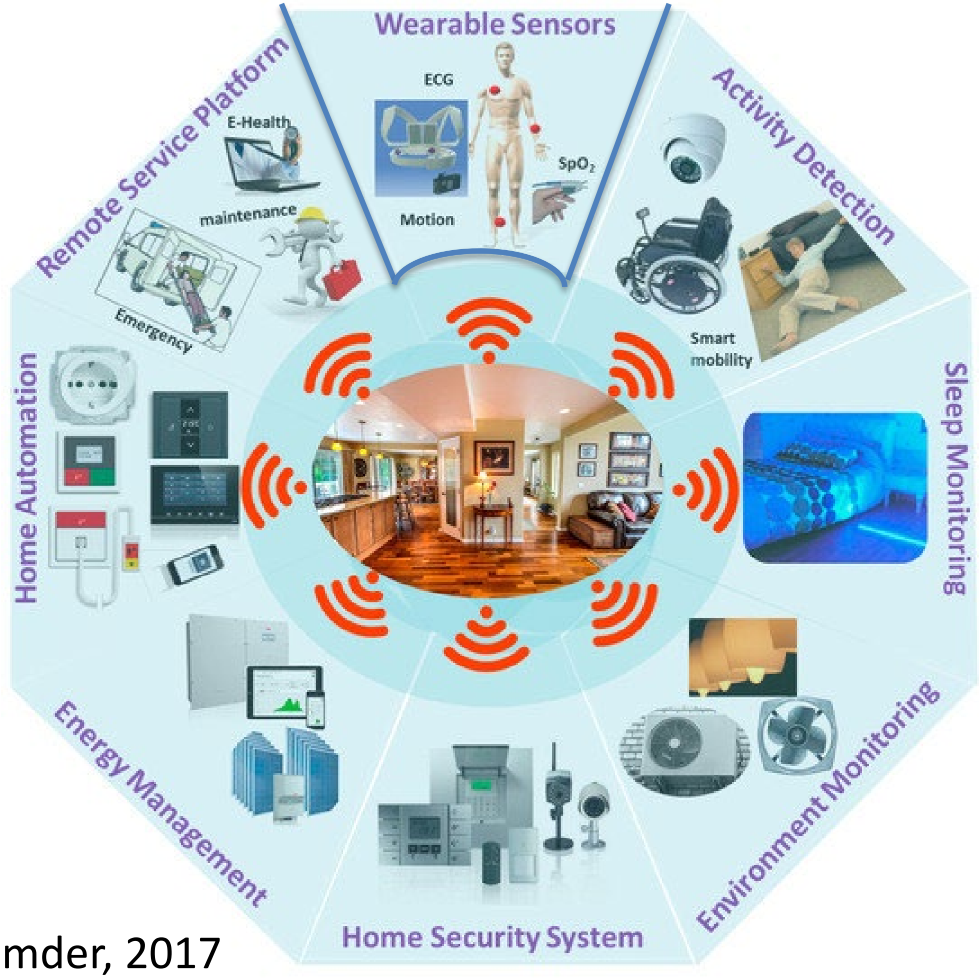
Dodge, et al., PLoS One, 2015, Wu et al. CTAD, 2019

OREGON HEALTH & SCIENCE UNIVERSITY

Many ways to capture this data…*Is it working?*



Kourtis, 2019



Majumder, 2017

Evidence for What Works... (systematic reviews, examples)

Vegesna A, Tran M, Angelassio M, Arcona S. Remote Patient Monitoring via Non-Invasive Digital Technologies: A Systematic Review. Telemed J E Health. 2017 Jan;23(1):3-17

Ienca M, Fabrice J, Elger B, Caon M, Pappagallo AS, Kressig RW, Wangmo T. Intelligent Assistive Technology for Alzheimer's Disease and Other Dementias: A Systematic Review. Journal of Alzheimer's Disease. 2017 Jan 1;56(4):1301-40.

Van der Roest HG, Wenborn J, Pastink C, Dröes RM, Orrell M. Assistive technology for memory support in dementia. Cochrane Database of Systematic Reviews 2017, Issue 6. Art. No.: CD009627.DOI: 10.1002/14651858.CD009627.pub2.

Lussier M, Lavoie M, Giroux S, Consel C, Guay M, Macoir J, Hudon C, Lorrain D, Talbot L, Langlois F, Pigot H. Early Detection of Mild Cognitive Impairment With In-Home Monitoring Sensor Technologies Using Functional Measures: A Systematic Review. IEEE journal of biomedical and health informatics. 2018 May 7;23(2):838-47.

Byambasuren O, Sanders S, Beller E, Glasziou P. Prescribable mHealth apps identified from an overview of systematic reviews. npj Digital Medicine. 2018 May 9;1(1):12.

Granja C, Janssen W, Johansen MA. Factors Determining the Success and Failure of eHealth Interventions: Systematic Review of the Literature. J Med Internet Res 2018;20(5):e10235

Bakker JP, et al. A systematic review of feasibility studies promoting the use of mobile technologies in clinical research. npi: Digital Medicine. 2019 Jun 6;2(1):47.

Mancioppi G, Fiorini L, Timpano Sportiello M, Cavallo F. Novel Technological Solutions for Assessment, Treatment, and Assistance in Mild Cognitive Impairment. Front Neuroinform. 2019 Aug 13;13:58. doi: 10.3389/fninf.2019.00058.

Piau A, Wild K, Mattek N, Kaye J. Current State of Digital Biomarker Technologies for Real-Life, Home-Based Monitoring of Cognitive Function for Mild Cognitive Impairment to Mild Alzheimer Disease and Implications for Clinical Care: Systematic Review. J Med Internet Res 2019;21(8):e12785

Summary of Evidence & Gaps

- Overall, few studies relative to other research areas: a small field
- Benefits may be reported but mainly based on low-quality studies (small samples, short study periods, non-diverse populations, not replicated)
- Technologies used are wide-ranging (passive sensors, wearables, apps, integrated multi-domain systems...) and used in many settings/combinations of assessments and interventions
- Standardization gaps: variability in the devices or technologies used (hardware/software), and limits in specification of the systems deployed and the analytic algorithms applied
- Usability and adoption
- Deployment barriers are prevalent (ease of use, research expertise, costs, *lack of evidence of efficacy or effectiveness*)

National Institutes of Health

To Address Gaps - Build Evidence

CART - *Collaborative Aging Research Using Technology*

Department of Veterans Affairs

- *Initiative established to address needed research capability for evidence building (facilitated by technology) in aging research.*
- Goal: Design and implement a scalable, disseminated technology system ('platform') for more effective aging research, ultimately deployable to 10,000+ homes
- *Focus on diversity, use case flexibility, technology agnosticism, "future-proofing", facilitating secure data sharing.*
- Interagency U2C (U2CAG054397) with NIH (NIA, NIBIB, NCI, NINDS, NINR, NCATS, OBSSR,) *and* VA
- Research Team: ORCATECH/Oregon Health & Science University, NIA, and U. Miami, Cornell, Rush, OSU, U. Penn, Intel, VA VISN 20

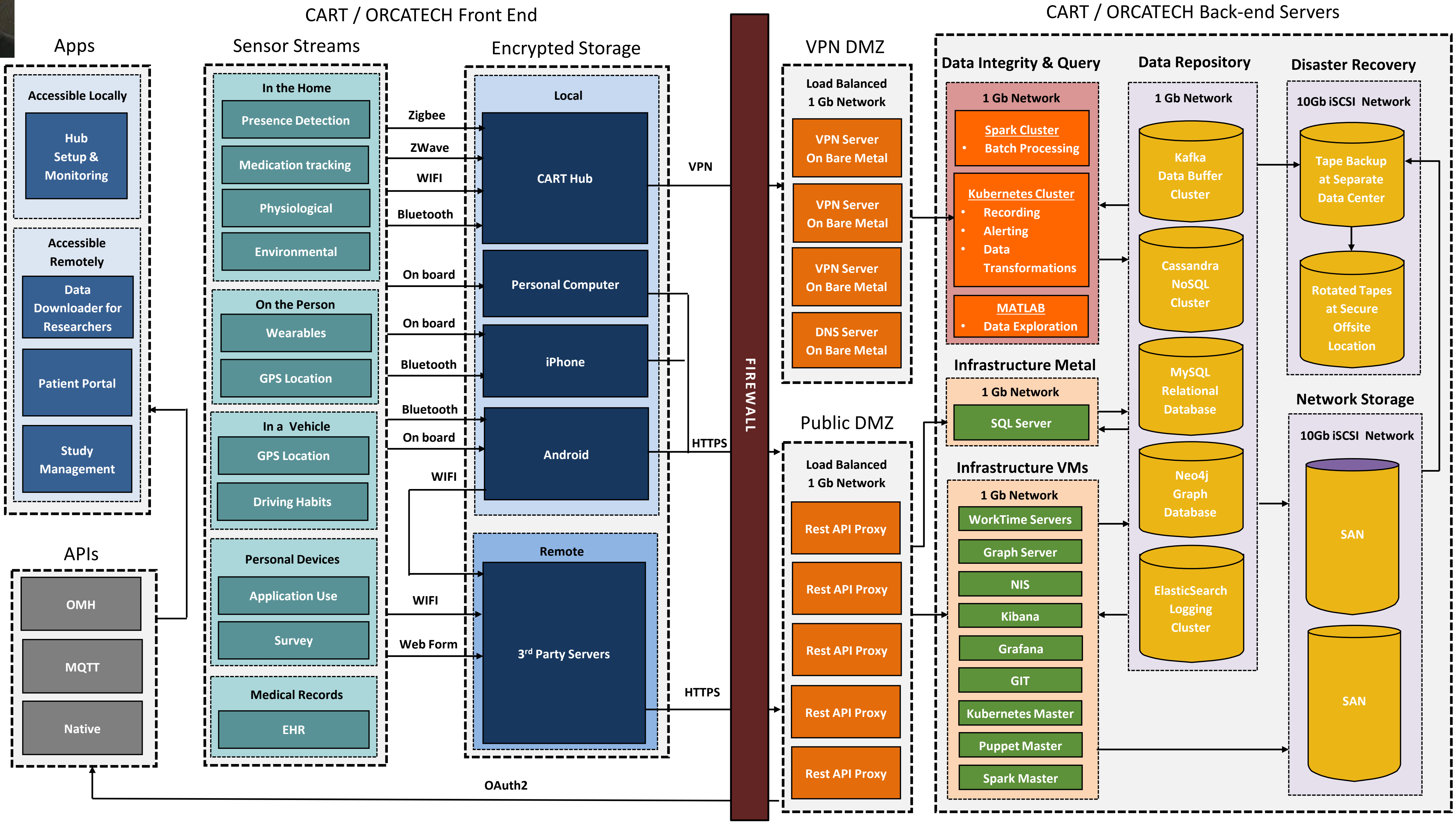
The CART Initiative

Technology Agnostic, Use-case Flexible, Sharable Research Platform

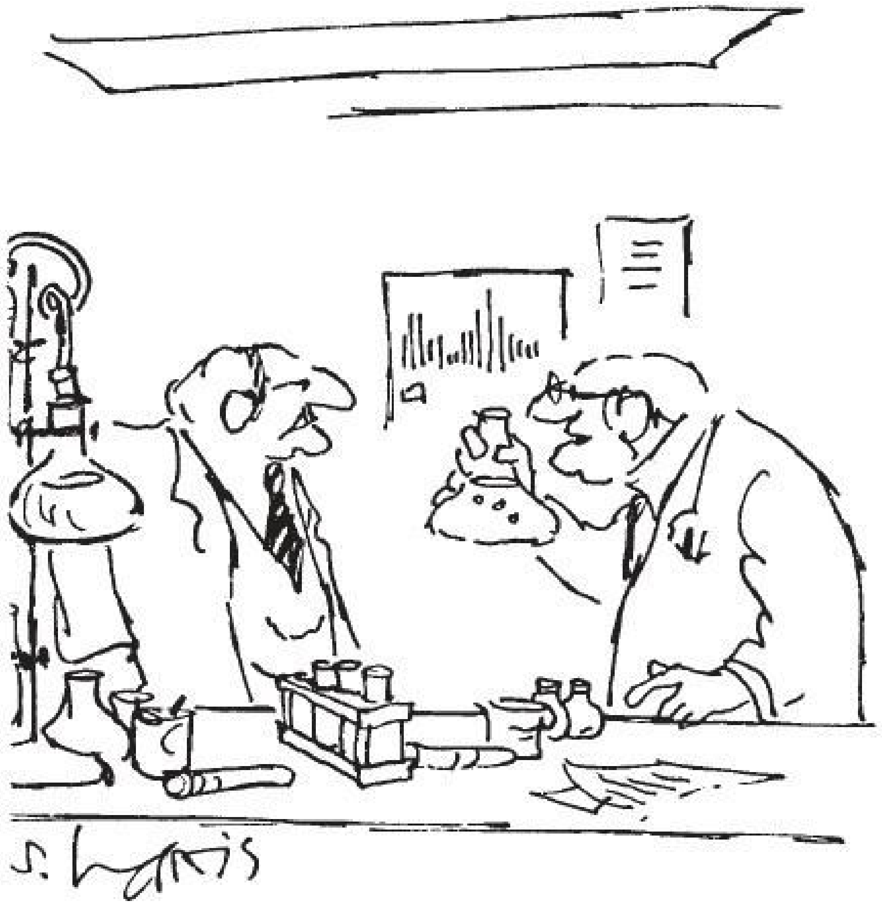
Kaye et al., 2018; Lyons et al., 2015

End-to-End System

Thomas Riley



Considerations for Research Assessments

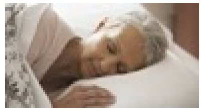


"IT MAY VERY WELL BRING ABOUT IMMORTALITY, BUT IT WILL TAKE FOREVER TO TEST IT."

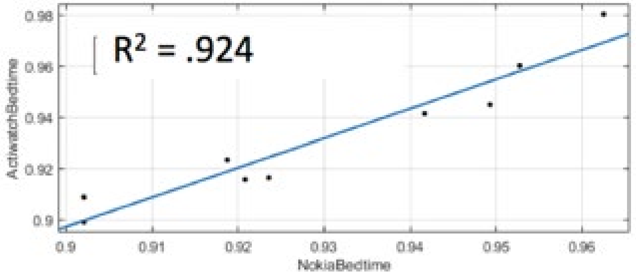
Validation

Kaye et al. CTAD, 2019

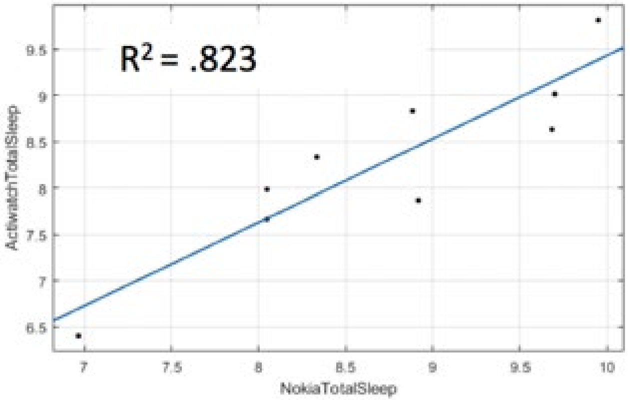




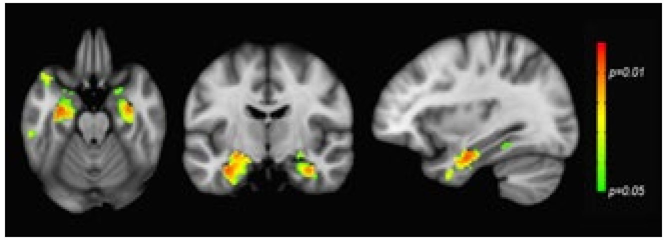
Bedtime: Withings Watch vs. Actiwatch

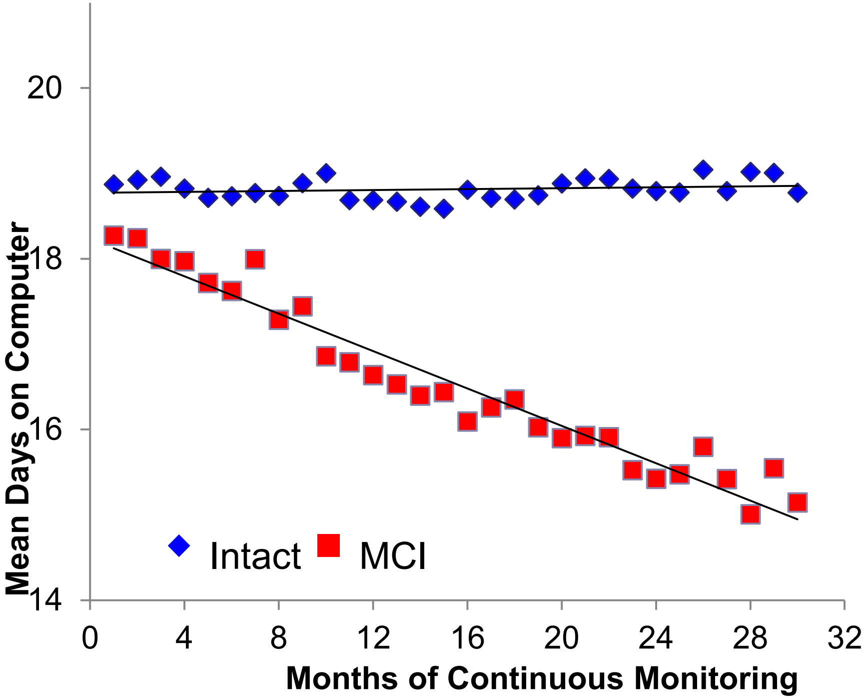


Sleep Duration: Withings Watch vs. Actiwatch

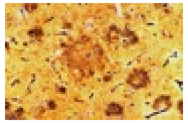


Kaye, et al. AAIC 2019

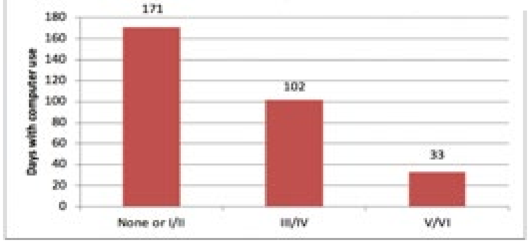




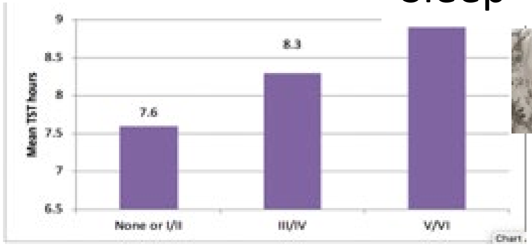
Kaye, et al. Alzheimers Dement. 2014;
Silbert et al., Alzheimers Dement, 2015

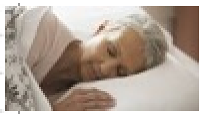


Cognition

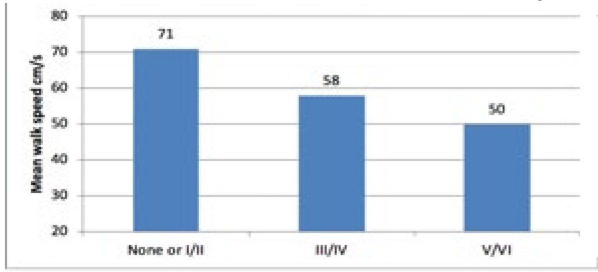


Sleep

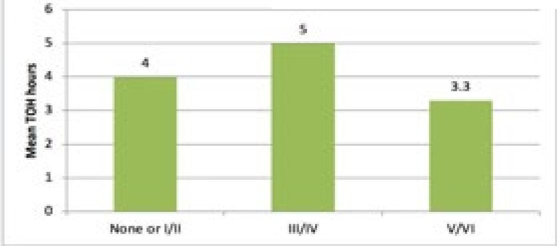




Mobility



Socialization



ORCATECH
SENSING LIFE KINETICS

Diversity Matters: CART Enrollment

Characteristic mean (SD) or %	Low-Income	Veterans	Latino	MARS
n	73	117	29	68
Age (years)	71.4 (6.5)	70.8 (6.3)	73.1 (7.1)	76.8 (6.0)
Female (%)	73	44	79	79
Live alone (%)	92	15	69	76
Drives a car (%)	40	89	91	89
Uses a smart phone (%)	77	73	100	85
Has an iPhone (%)	28	39	58	43
Follow-up time, months	14.5 (4.4)	13.4 (3.8)	9.5 (5.0)	8.5 (4.5)
MoCA or MMSE*	24.9 (2.9)	23.3 (3.4)	25.1 (3.3)	28.7 (1.2)
IADL	0.2 (0.5)	0.3 (0.9)	0.2 (0.4)	N/A
MCI (%)	18	38	21	7

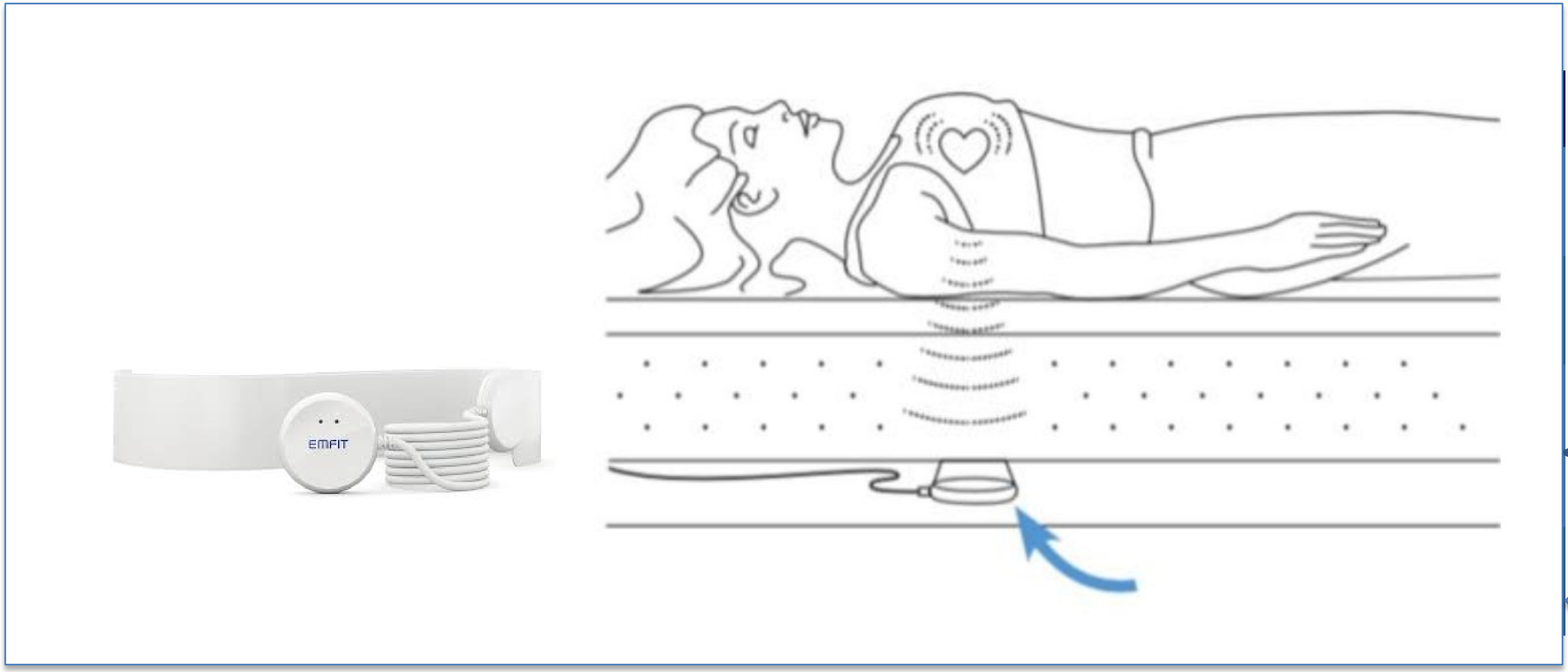
94% remain actively enrolled after a mean of 12 months of follow-up

* RUSH data is for MMSE

The CART Initiative

Compliance matters: CART Participant Experience

Measured compliance with non-passive monitoring

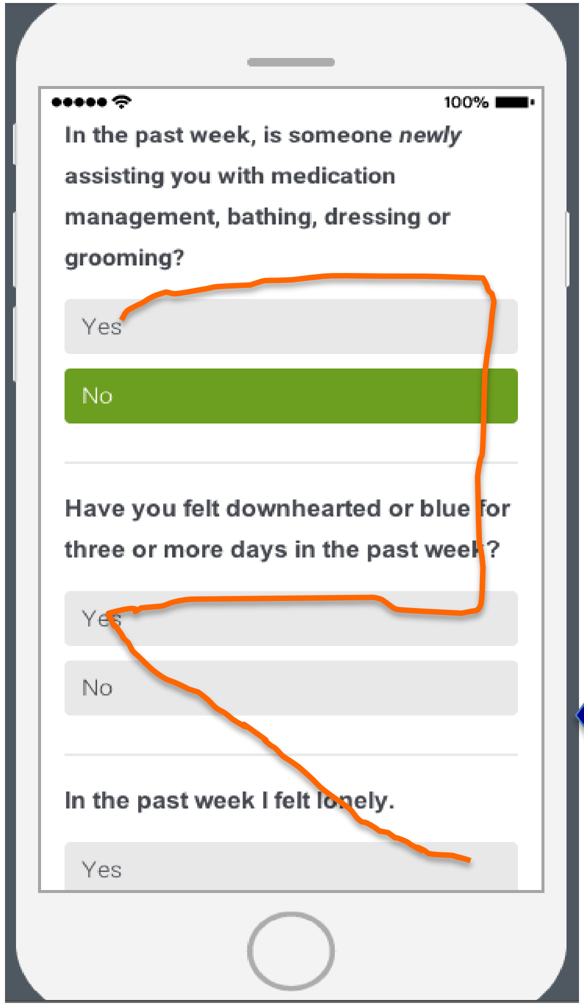


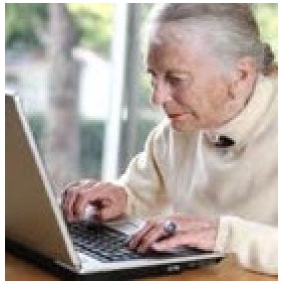
High total wear compliance

But 30-37% did not wear the watch at night!

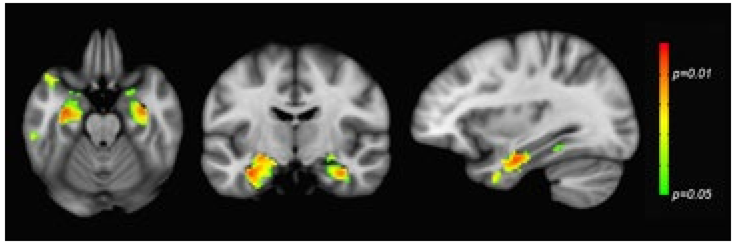
AAIC, 2019

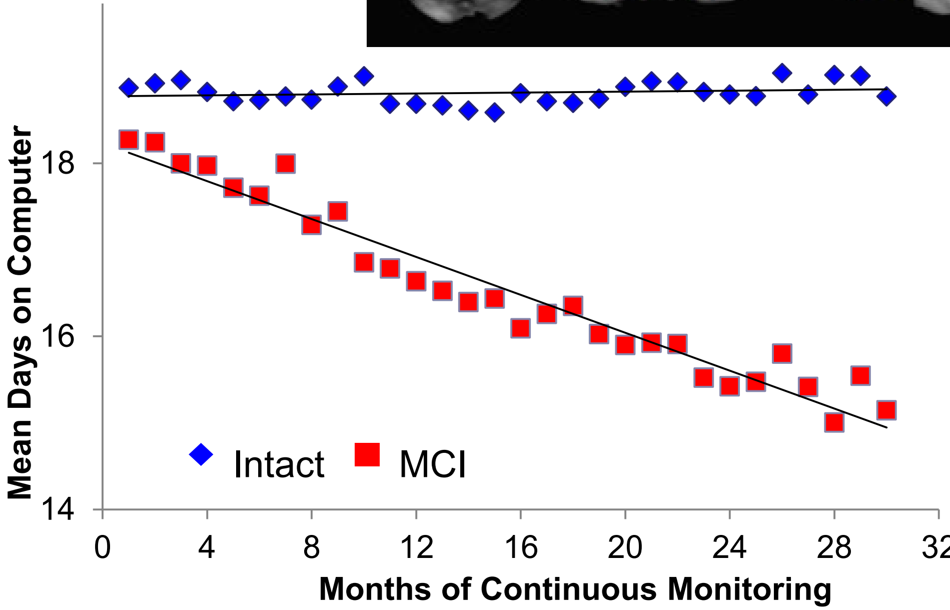
Assessing Cognition, Behavior, Motor Function:
Computer Use





Some Self-Report Data is Necessary





Lisa Silbert

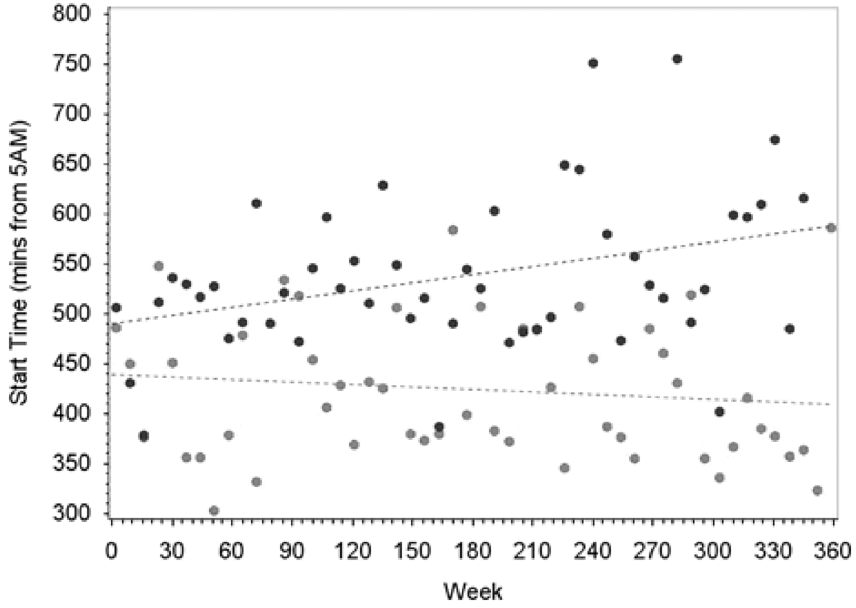
Table 4
Associations between cognitive status and mouse movement variability derived from one week of data

	Outcome, movement curvature (IQR_K)		Outcome, time spent idling (IQR_Idle)	
Covariate	Coefficient	*P* value	Coefficient	*P* value
MCI (reference: cognitively intact group)	0.013	.008**	386.8	.04*
Age (y)	−0.001	.03*	−15.0	.31
Education (y)	0.002	.05	−12.4	.70

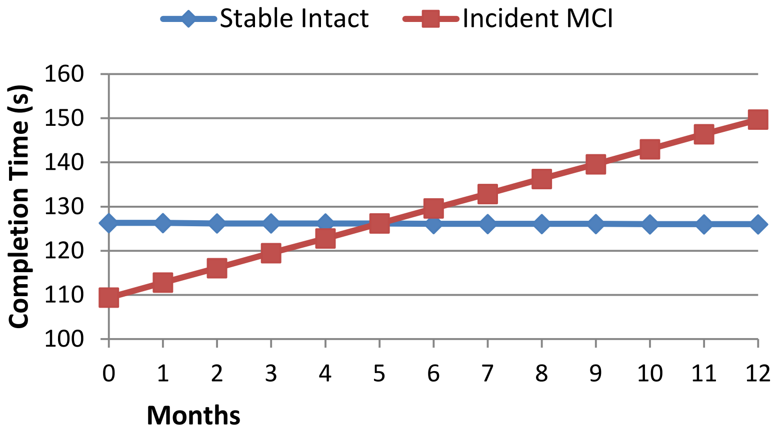
Abbreviations: IQR, interquartile range; MCI, mild cognitive impairment.
NOTE. $*P < .05$, $**P < .01$.

Kaye, et al. Alzheimers Dement. 2014; Silbert et al., Alzheimers Dement, 2015; Seelye et al. Alzheimers Dement.: Diagnosis, Assessment & Disease Monitoring, 2015; Seelye et al. Alzheimer’s Disease & Assoc. Disorders, 2015; Seelye et al., Alzheimer & Dementia, 2018

Cognition: *Computer Use, online questionnaire completion*



Longitudinal change in survey completion time by group



Adri Seelye

Time of Day Completed: Longitudinal scatter plot of differences in median questionnaire start time of day (minutes from 5 AM) by week for MCI (Black) and cognitively intact (gray) participants.

Seelye et al. Alzheimer's Dis. & Assoc. Disorders, 2015

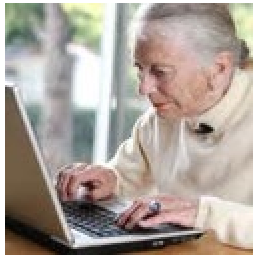
Time to Complete: Longitudinal Change in Survey Completion Time (in seconds) by Group in the 12 month period *before* MCI diagnosis (calculated regression lines from the mixed effect model)

Seelye et al., Alzheimer & Dementia, 2018

ORCATECH
SENSING LIFE KINETICS

OREGON HEALTH & SCIENCE UNIVERSITY

Experience Sampling: *Online Weekly Activity & Health Questionnaire*

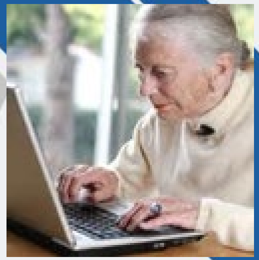


Q4.2 You / indicated that you had medication changes in the last / week. Please answer / the following quest...

1	AWAY	In the past week, have you been away from home / overnight?
2	VISITORS	In the past week, have you had visitors who stayed with you in / your home for a night or more?
3	MEDICATIONS	In the past week, have you had a change to any of your medications / OR started a new one?
4	FALLS	In the past week, have you had a fall, including a slip or trip, in / which you lost your balance a...
5	ACCIDENTS/INJURIES	In the past week, have you had any other injuries or / accidents?
6	HOSPITALIZATION/ER	In the past week, have you had any hospitalizations or emergency / room visits (not including routi...
7	HEALTH CHANGE/ILLNESS	In the past week, has your physical health limited you more than / usual? For instance, did illness...
8	LIFE SPACE	In the past week, have you had any changes in your home-space or living situation? For example, r...
9	ASSISTANCE	In the past week, is someone newly assisting you with medication management, bathing, dressing or...
10	MOOD - BLUE	Have you felt downhearted or blue for three or more days in the / past week?
11	MOOD - LONELY	In the past week I felt lonely.
12	PAIN LEVEL	Please rate your pain by indicating the number that best describes / your pain on average in the la...- No Pain:Worst Imaginable
13	PAIN INTERFERENCE	During the past week, how much did pain interfere with your normal / activities or work (including...- Pain interfered with my normal activities...

Q4.11 Did you have any other medication / changes in the past week?

Online tools for assessment: *Usability, Tests, Engagement*



Weekly Questionnaire

Usability Surveys

Retention Materials

Online Tests: Trails Test

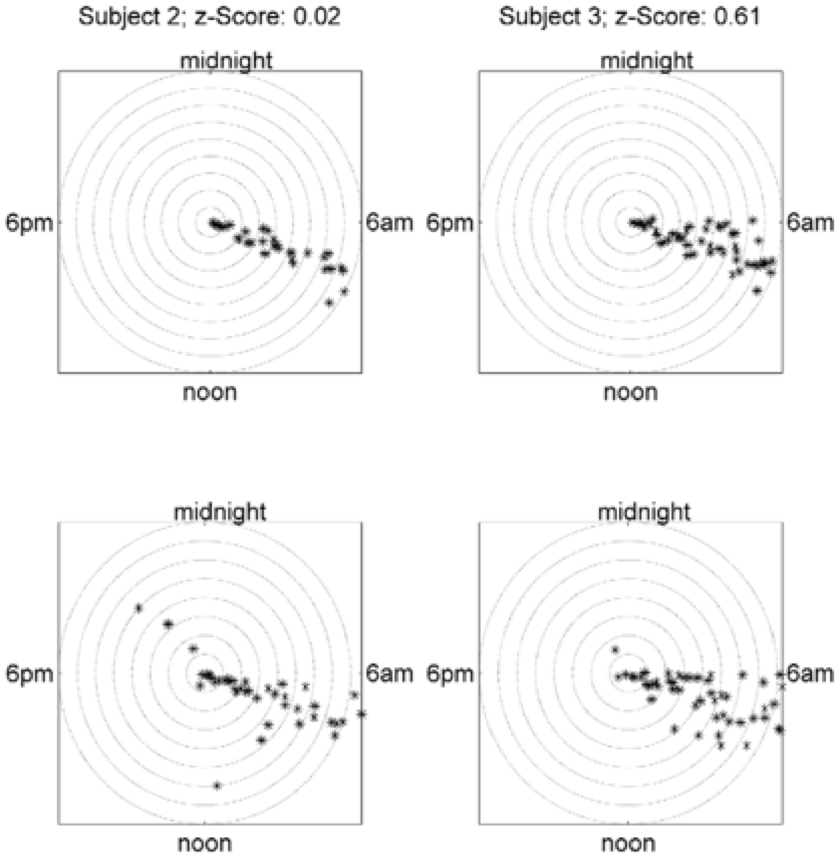
Medication Adherence (Function & Cognition):
'IADL' Task & Test of Prospective Memory

Johanna Austin

June-Aug
2015

6 Months

Feb-April
2015



Continuous monitoring of medication adherence timing may identify patients experiencing cognitive decline

- Individuals with lower cognitive function have more 'spread' in the timing of taking their medications ($p < .014$)
- Increase over time in the spread of timing of taking their medications ($P < .012$)

ORCATECH
SENSING LIFE KINETICS

Austin, et al. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 2017

Physical Activity and Mobility Behaviors

Room activity distributions & gait speed differentiating MCI vs not MCI

Room	Bedroom	Bathroom	Kitchen	Living Room	Combined
$F_{0.5}$ Score*	0.842	0.829	0.813	0.826	0.856

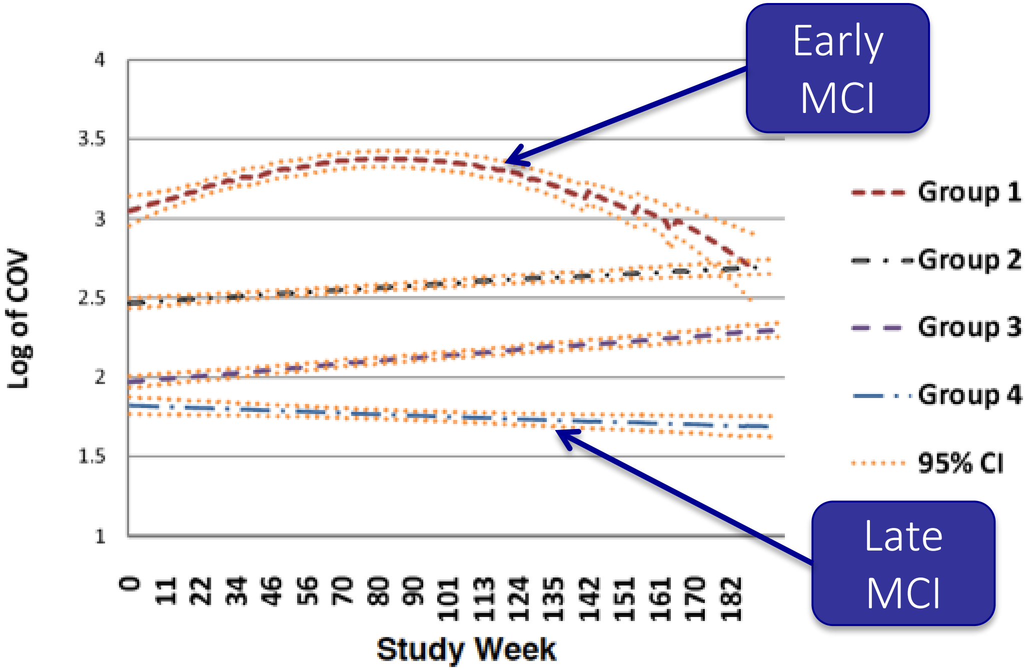
*$F_{0.5}$ Scores window size ω = 20 weeks; slide size = 4 weeks (with leave-one-subject-out cross validation)

Hiroko Dodge

Ahmed Akl

Akl et al. Journal of Ambient Intelligence and Smart Environments, 2015

Trajectories of gait speed over time



Dodge, et al. Neurology, 2012

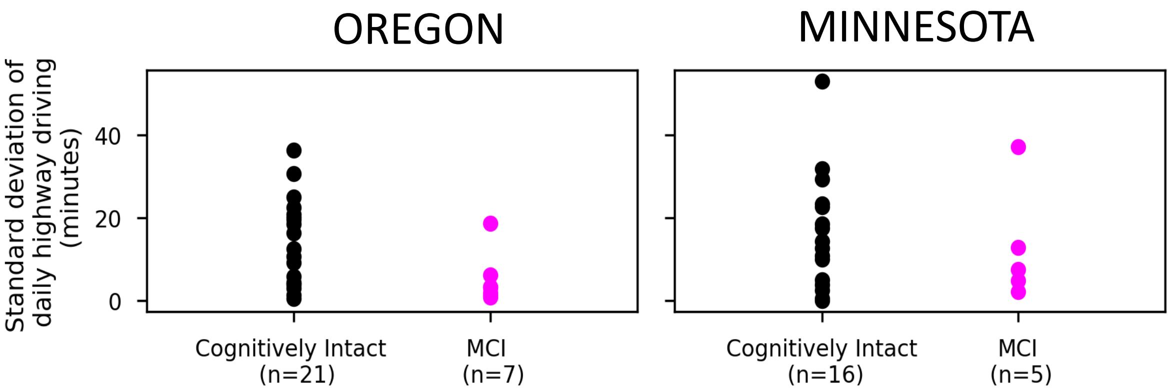
ORCATECH SENSING LIFE KINETICS

Physical Activity & Mobility: *Out of home assessment - Driving (and Cognition)*

Table 2. Summary Driving Characteristics; (Per day; six month observation period)

Variable	Total	Intact	MCI	p-value
N	28	21	7	
Mean # of (one-way) trips per day	4.2 (1.0)	4.1 (0.9)	4.7 (1.4)	0.19
Day-to-day variability in # of trips	2.1 (0.6)	2.1 (0.5)	2.3 (0.8)	0.49
Mean distance driven per day (miles)	20 (13)	22 (13)	14 (11)	0.06
Day-to-day variability in distance driven	26 (17)	31 (17)	13 (12)	0.01*
Mean time driven per day (hours)	0.9 (0.4)	0.9 (0.4)	0.8 (0.4)	0.26
Day-to-day variability in time driven	0.7 (0.3)	0.8 (0.3)	0.5 (0.2)	<0.01**
Mean first clock starttime of driving per day	11.1 (1.2)	11.3 (1.2)	10.6 (1.4)	0.43
Day-to-day variability in first starttime (hrs)	2.8 (0.8)	2.8 (0.6)	2.7 (1.1)	0.78
Mean last clock starttime of driving per day	15.4 (1.6)	15.2 (1.4)	15.9 (1.9)	0.33
Day-to-day variability in last starttime (hrs)	3.2 (0.6)	3.2 (0.6)	3.2 (0.8)	0.79
Mean # of days monitored	206 (36)	208 (38)	201 (33)	0.70
% of days at least one trip was taken out of all days monitored	52%	49%	60%	0.21
% of driving days with >=20 miles driven	26%	27%	21%	0.51
Mean time of highway driving per day (seconds)	450 (506)	543 (533)	172 (288)	0.01*

Highway diving



Seelye et al. Journal of Alzheimer's Disease, 2017

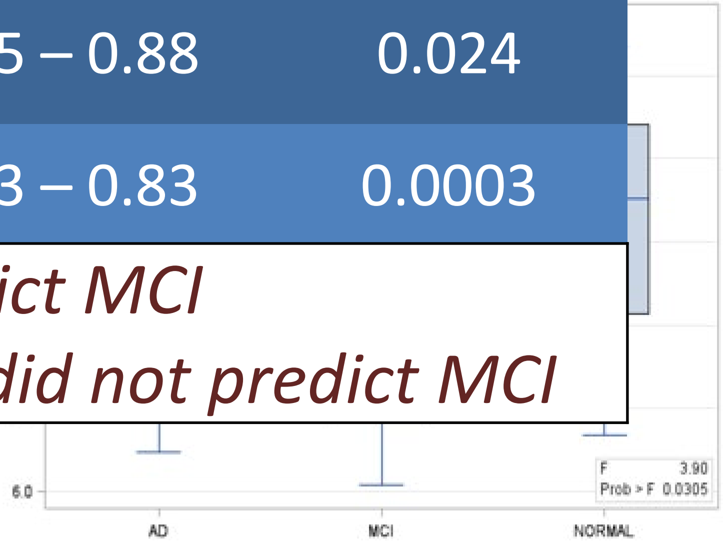
Chronobiological Behavior

No Differences Between Groups in Self-Report Measures

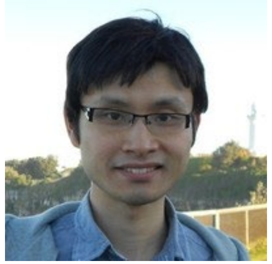
Self-Report	Intact	aMCI	naMCI	P value
				.69
				.21
				.34
				.77

CART: Association between sleep duration and MCI status (Multivariate logistic regression model)			
	Odds Ratio	95% CI	P value
Mean total sleep time (hrs)	0.74	0.56 – 0.98	0.038
Age	1.10	1.02 – 1.18	0.015
Gender (Female vs. Male)	0.36	0.15 – 0.88	0.024
Education	0.66	0.53 – 0.83	0.0003

- *Two weeks of sleep-activity did not predict MCI*
- *Self-reported night-time sleep duration did not predict MCI*



Tamara Hayes



Michael Au-Yeung

Zach Beattie

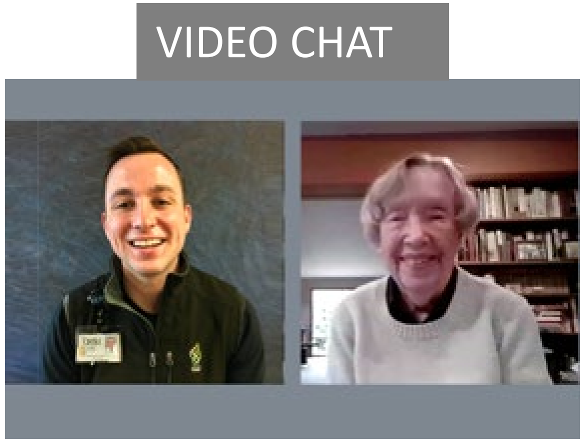
Hayes et al. Alzheimer Dis Assoc Disord. 2014
Hayes et al. IEEE Eng Med Biol Soc, 2010
Kaye et al AAIC, 2019

Assessments for Interventions

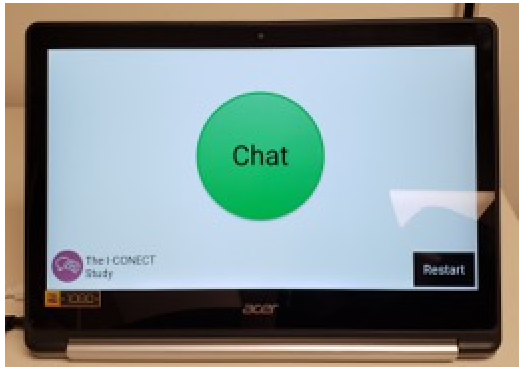
"I'm going to ask you a series of scary questions. When I'm done, let's see if you can guess why I'm asking them."

I-CONECT: *Internet-based Conversational Engagement Clinical Trials*

(PI: H. Dodge, NIA R01AG051628; NIA R01AG056102)



- Isolated 80+ yrs
- 50% African American

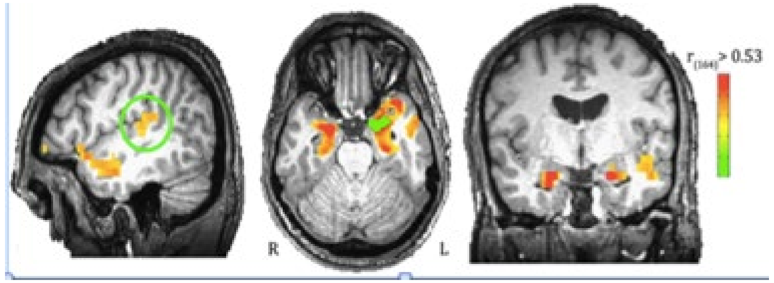


MCI
n=180

- TX n=90
- Control n=90

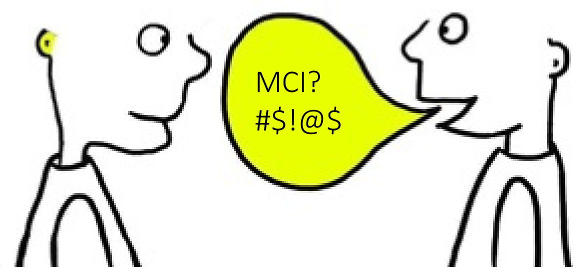
Healthy
n=180

- TX n=90
- Control n=90



TX: Video Chat, 4 times/week: 6 months, 2 times/ week: 6 months
Control: 1/wk phone check. Novel Outcome Measures: MedTracker memory, Conversational Speech & Language Quantification; vMRI, DTI, fMRI

I-CONECT Pilot/Preliminary Results



- 89% of all possible sessions completed; Exceptional adherence – *no drop-out*
- *MCI participants generate a greater proportion of words* (mean = 2985 vs. 2423 words) out of total number of words during conversation sessions (p=0.03).
- Logistic regression models: ROC AUC identifying MCI (vs. NIs) = 0.71 (95% CI: 0.54 - 0.89)

LIWC cat.	Communication	Swear	Anger	Fillers	Family
Avg. num. in MCI	46.4	7.14	37	101.5	31.14
Avg. num. in intact	38.7	4.8	49.8	141.6	41.8
p-value	0.002	0.005	0.054	0.067	0.08

Table 4: Average number of words grouped into LIWC categories

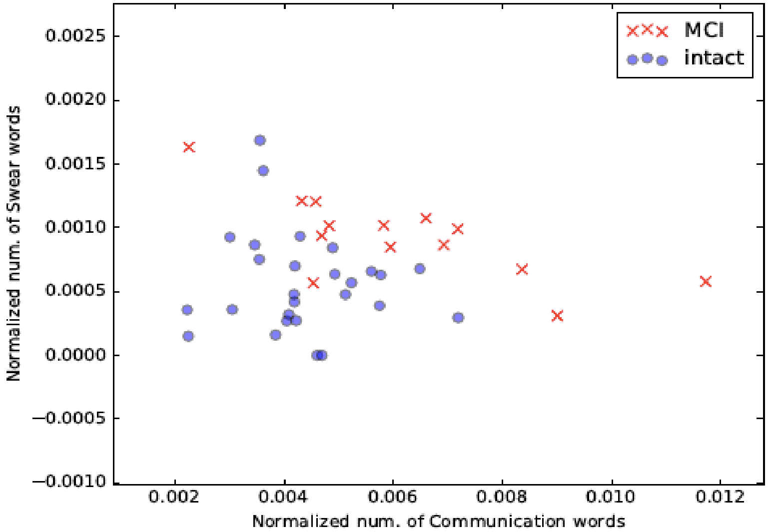
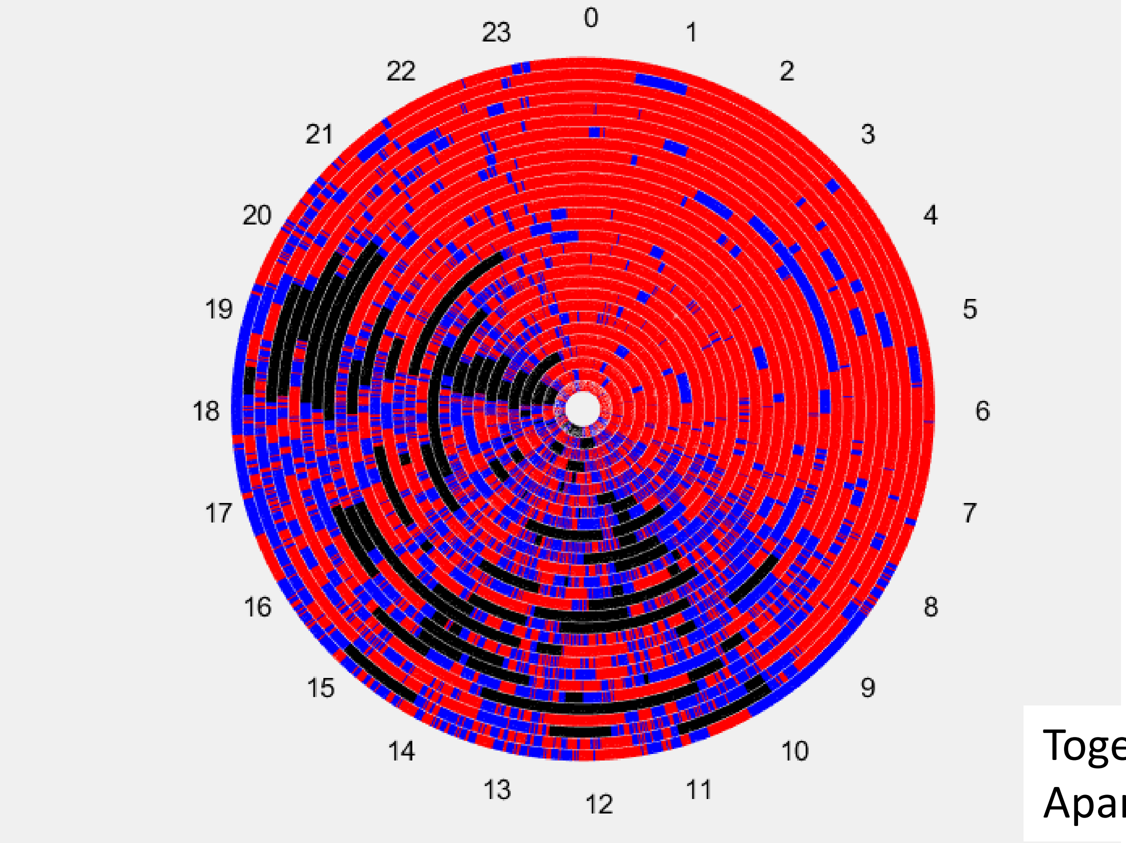


Figure 1: scatter-plot of features derived from Communication and Swear word categories

Dodge et al. Current Alzheimer Res. 2015
Dodge et al. Alzheimer's & Dementia: Translational Res. & Clinical Interventions, 2015
Asgari et al. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 2017

EVALUATE – AD: *Ecologically Valid, Ambient, Longitudinal and Unbiased Assessment of Treatment Efficacy in Alzheimer's Disease*

- Establish Digital Biomarkers sensitive to clinical change associated with conventional AD TXs
- ORCATECH / CART platform (60 subjects: 30 patients/30 care partners; 30 households)



Couples & Caregiving: Time spent together

Together

Separate

Out of Home

Together: 1285 minutes (21.4 hrs/day)
Apart: 155 minutes (2.6 hrs/day)

Neil Thomas

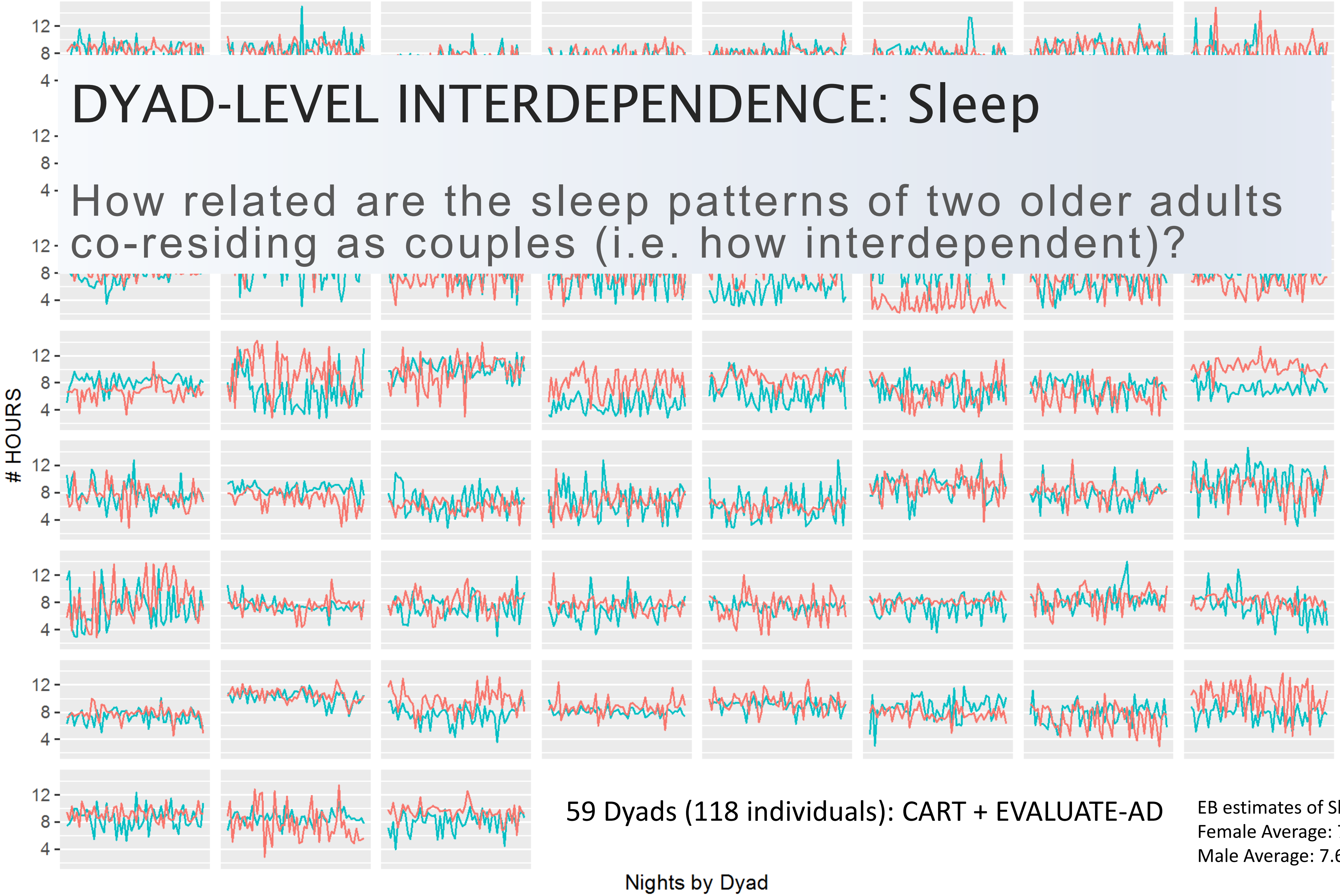
ORCATECH
SENSING LIFE KINETICS

Reynolds et al. 2017, unpublished
Thomas et al. Dement Geriatr Cogn Disord, 2019

OREGON HEALTH & SCIENCE UNIVERSITY

DYAD-LEVEL INTERDEPENDENCE: Sleep

How related are the sleep patterns of two older adults co-residing as couples (i.e. how interdependent)?



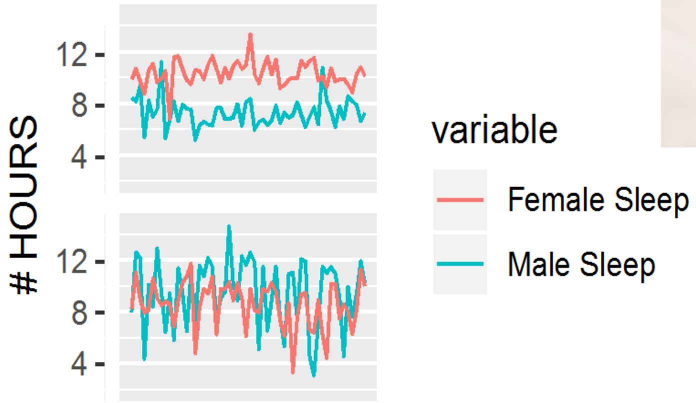
Lyndsey Miller, PhD, NIA K01

59 Dyads (118 individuals): CART + EVALUATE-AD

EB estimates of Sleep (i.e. fixed effects)
Female Average: 7.94 ± 1.9 hours
Male Average: 7.68 ± 1.5 hours

DYAD-LEVEL INTERDEPENDENCE - Sleep

How related is the ***variability*** in sleep patterns of two older adults co-residing as couples?



Random Effects (within-dyad covariances)	Std. Estimate (r)	P-value (two-tailed)	95% CI
M-F Sleep Covariance (Level) (score x at some time point)	**0.130**	**< 0.001**	**[0.096; 0.162]**
M-F Sleep Covariance (Velocity) (speed that a score is changing: dx/dt)	**0.532**	**< 0.001**	**[0.390; 0.671]**
M-F Sleep Covariance (Acceleration) (rate that speed is changing: d^2x/dt^2)	**0.262**	**< 0.001**	**[0.191; 0.330]**

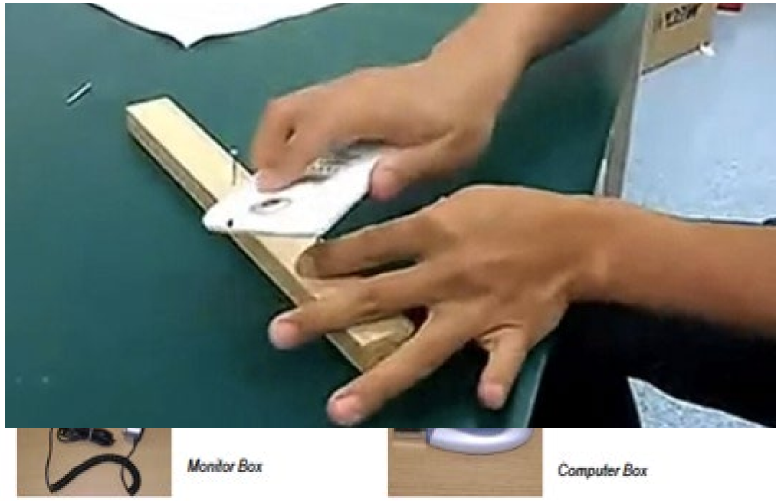
Summary

A wide range of pervasive computing solutions are available for deployment in dementia research

Many ways to use this technology to improve assessment:
The right tool for the right job

We have Come a Long Way – HBA 2005

"If you have a smartphone everything is not an app"



Much to do: Need to grow & move the field forward

Current Participants: 511
Current Homes: 432

"One finger cannot lift a pebble." **Hopi proverb**

Please Collaborate!

ORCATECH-CART 'Ecosystem'

Acknowledgements

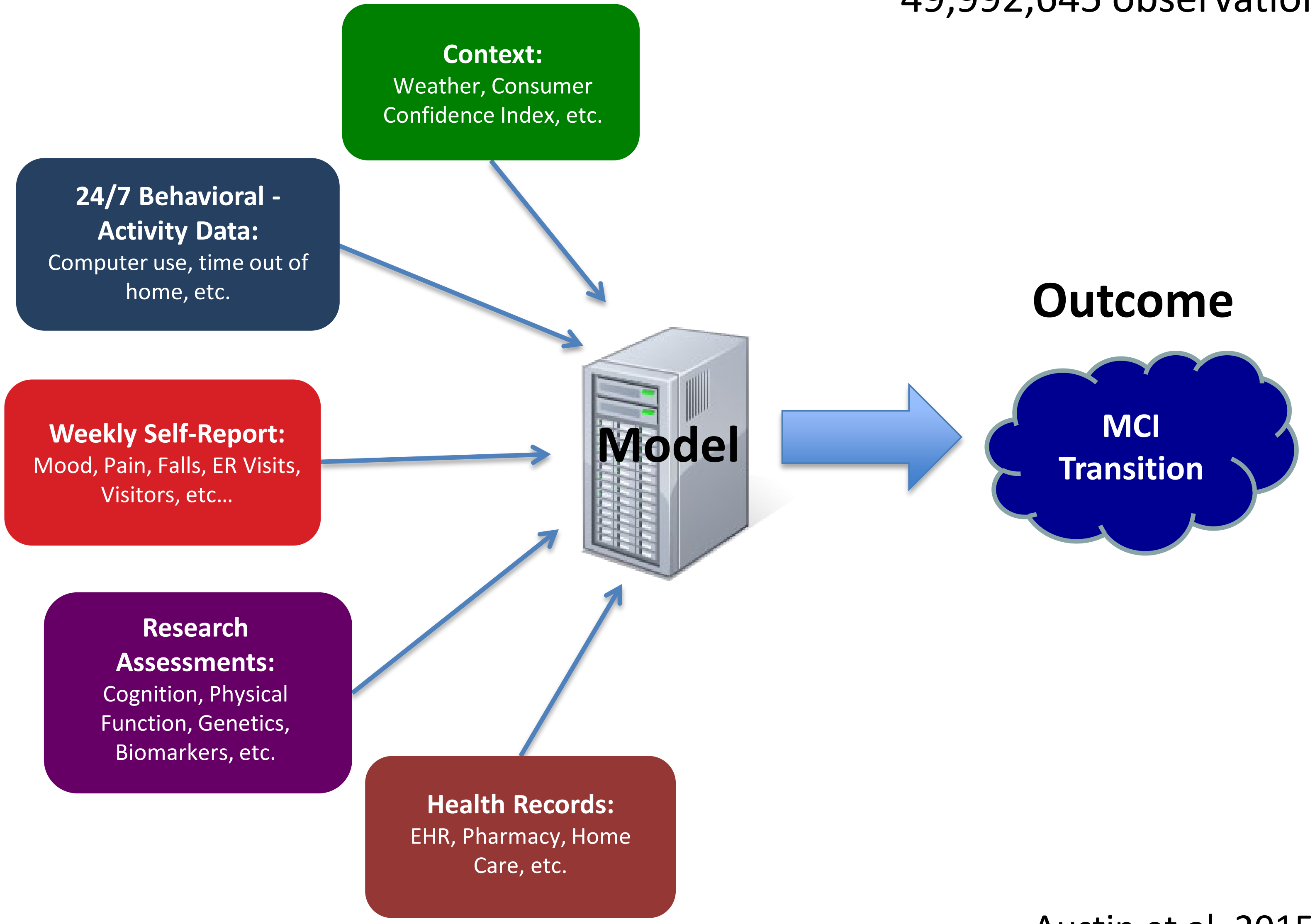
PEOPLE:

- Steve Agritelley
- Carlos Almirola
- Michael AuYeung
- Lisa Barnes
- Zach Beattie
- Hannah Bernard
- Chelsea Burchett
- Patrick Chiang
- Kevin Cosgrove
- Kathleen Crowe
- Sara Czaja
- Hiroko Dodge
- Sejal Dua
- Ames Elliott
- Nicole Fleming
- Charlene Gamboa
- Ona Golonka
- Sarah Gothard
- Farzin Guilak
- Sam Harbison
- Stephanie Irish
- Sindy Jaramillo
- Victoria Jimenez
- Jason Karlawish
- Jeff Kaye
- Judy Kornfeld
- ChinChin Lee
- Jonathan Lee
- Emily Lehman
- Miranda Lim
- Daria Loi
- Emily Lore
- David Lowenstein
- Jennifer Marcoe
- Nora Mattek
- Charlie Quinn
- Christy Reynolds
- Thomas Riley
- Nathaniel Rodrigues
- Gregory Sebastian
- Nicole Sharma
- Sarah Shull
- Lisa Silbert
- Nina Silverberg
- Mary Alice Siqueland
- Tim Truty
- Rachel Wall
- Sarah Weingast
- Kathy Wild
- Jonathan Williams
- Phelps Witter
- Chao-Yi Wu
- Alex Yeargers
- Jon Yeargers
- Tracy Zitzelberger

FUNDING: NIH U2CAG0543701 (Office Of The Director, National Institutes Of Health (OD), National Center For Advancing Translational Sciences (NCATS), National Institute Of Biomedical Imaging And Bioengineering (NIBIB), National Institute Of Nursing Research (NINR), National Institute On Aging (NIA), National Institute Of Neurological Disorders And Stroke (NINDS), National Cancer Institute (NCI) and the Veteran's Administration); VA grant IIR 17-144, Oregon Roybal Center for Translational Research on Aging (NIA P30 AG024978), MARS, R01AG22018; the Oregon Clinical Translational Research Institute CTSA award (UL1TR002369).

High dimensional data fusion model predicting MCI

49,992,645 observations



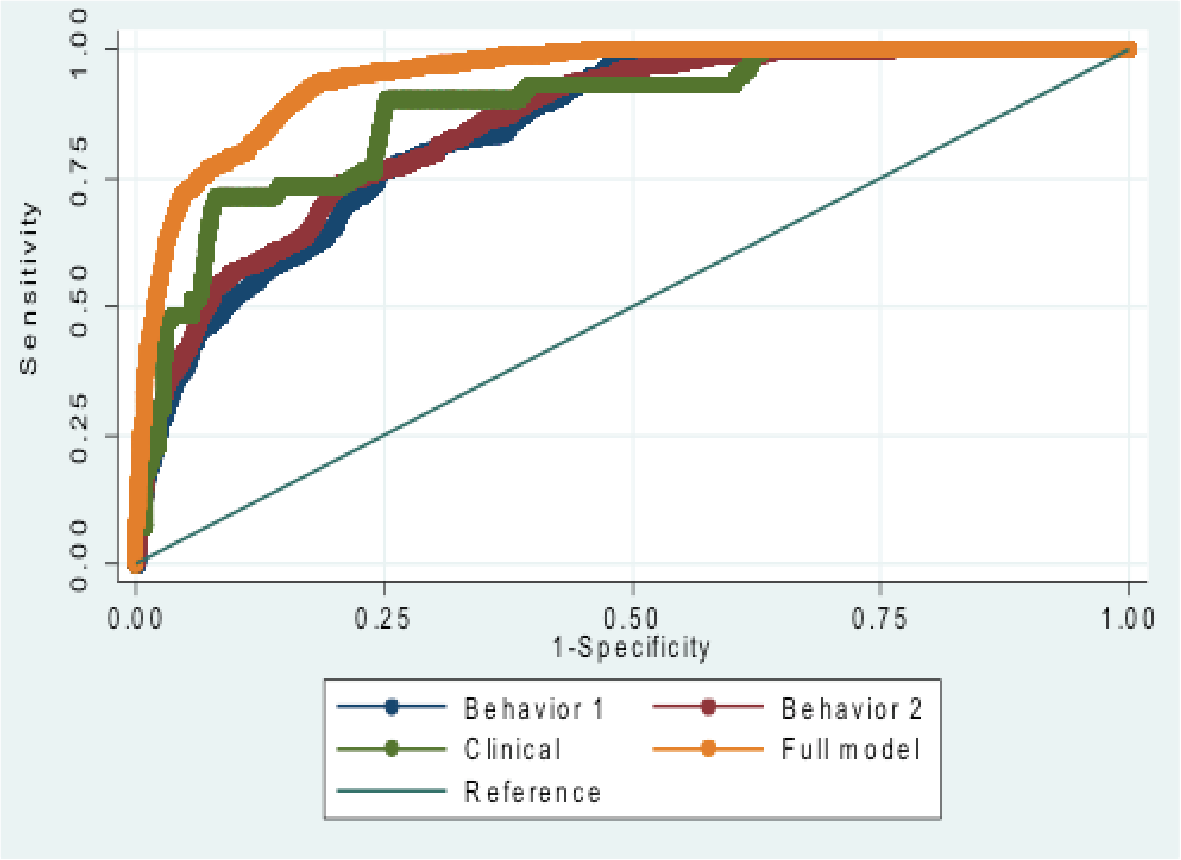
Austin et al. 2015

ORCATECH
SENSING LIFE KINETICS

OREGON HEALTH & SCIENCE UNIVERSITY

Predicting MCI Transitions: Sensitivity Analysis

- Likelihood of a MCI transition within the next 24 months – ROC AUC under curve= 0.95



Model Fit & ROC/AUC Results	
Model	AUC (SD)
Behavior 1	0.85 (0.004)
Behavior 2	0.85 (0.004)
Clinical	0.88 (0.004)
Full	0.95 (0.002)