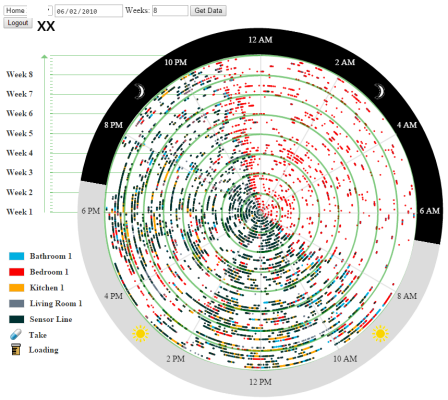

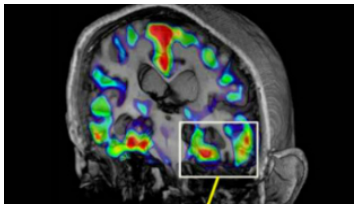

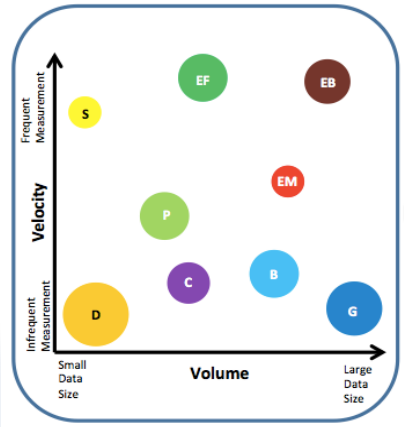

Advancing the Clinical Science of Dementia:

Not Just Your Grandfather's Assessment

Jeffrey Kaye, MD
Layton Professor of Neurology & Biomedical Engineering
Oregon Center for Aging & Technology
NIA - Layton Aging & Alzheimer's Disease Center
kaye@ohsu.edu

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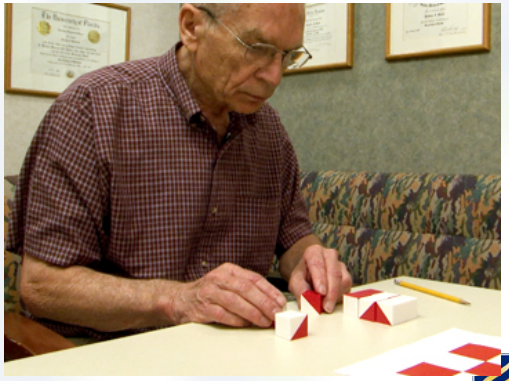
April 16, 2016 Four Seasons Hotel, Vancouver, B.C.

OREGON HEALTH & SCIENCE UNIVERSITY OHSU

The fundamental limitation of current research... The ability to detect meaningful change.

Cardinal features of change - *slow decline punctuated with acute, unpredictable events* - are challenging to assess with legacy tools and methods.



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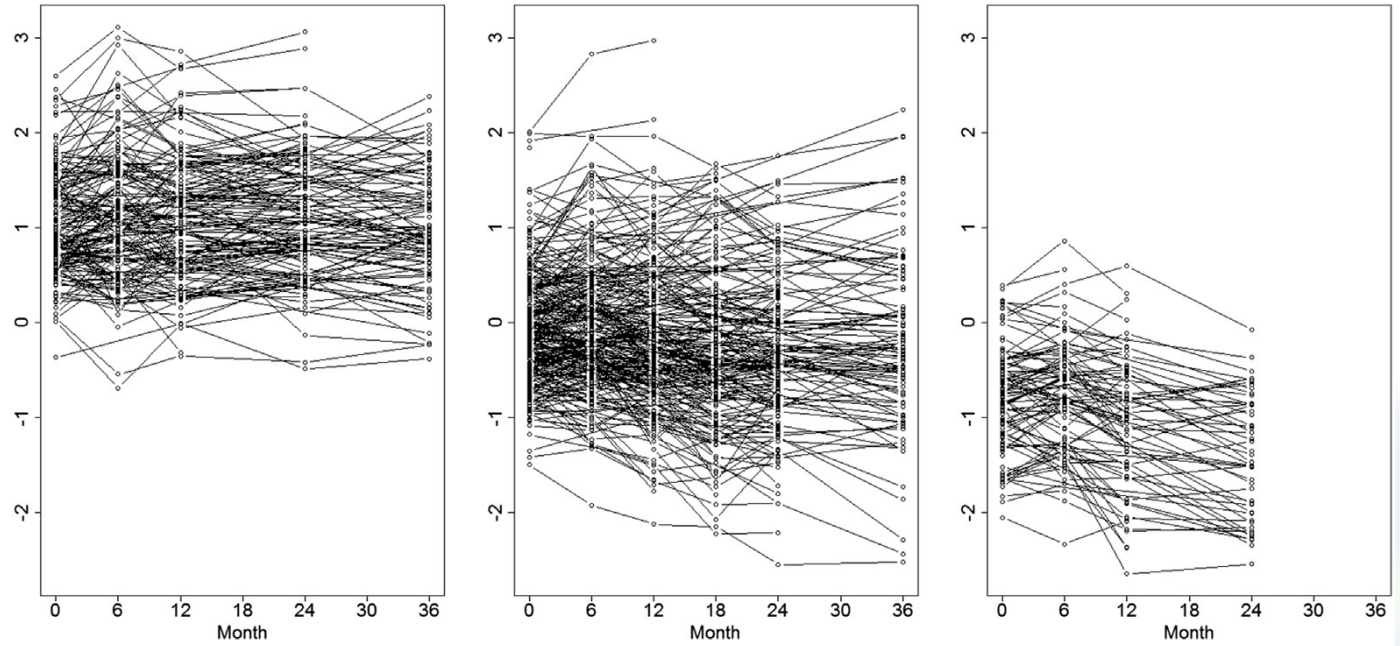
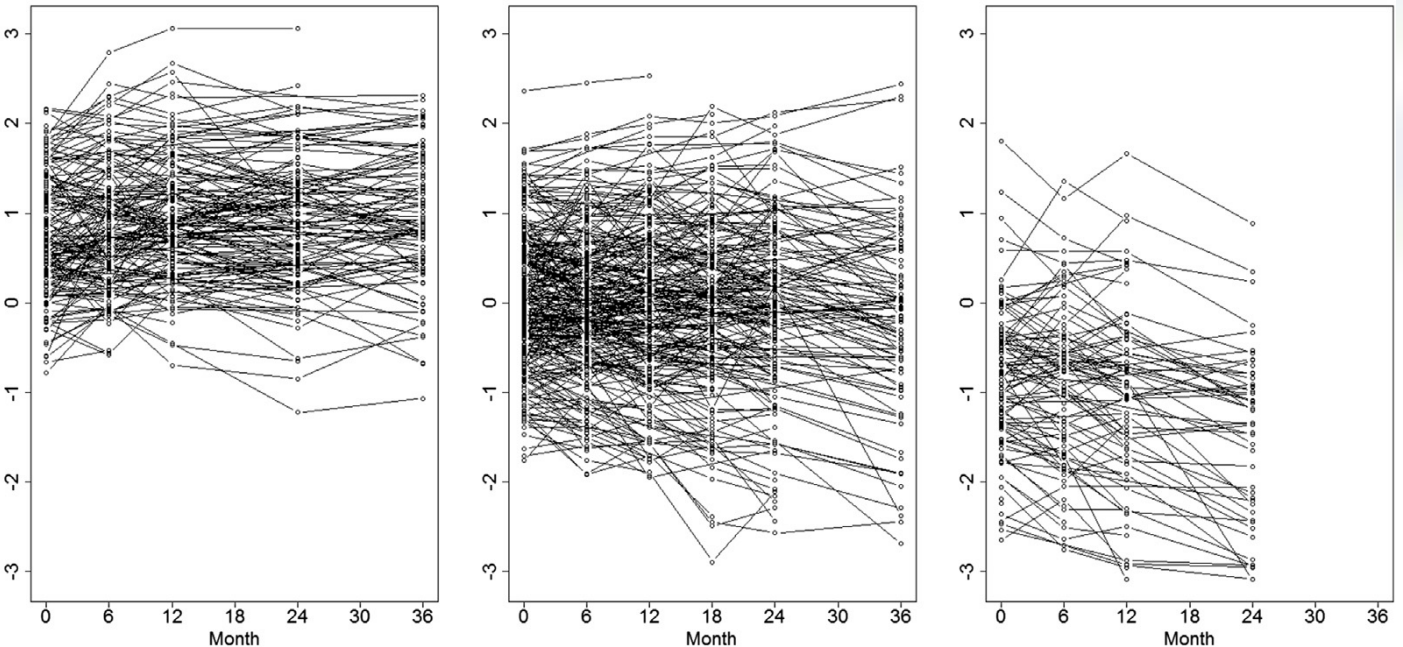
Example of challenge of detecting change with current data: Variability in baseline and progression of cognitive tests (ADNI data from Dodge et. al., 2014)

Memory (ADNI-Mem Z-score).



Executive function (ADNI-Exe Z-score)



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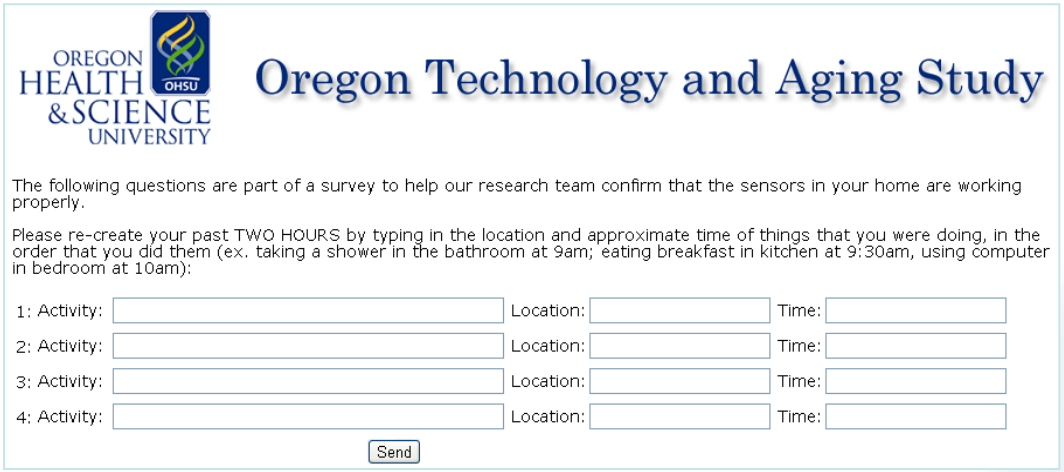
Challenge of Detecting Change: Self Report Inaccuracy

Are you sure?: Lapses in Self-Reported Activities Among Healthy Older Adults Reporting Online. Wild et al., 2015

"What were you doing during the past 2 hours?" n=95; Mean age 84 yrs



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Oregon Technology and Aging Study

The following questions are part of a survey to help our research team confirm that the sensors in your home are working properly.

Please re-create your past TWO HOURS by typing in the location and approximate time of things that you were doing, in the order that you did them (ex. taking a shower in the bathroom at 9am; eating breakfast in kitchen at 9:30am, using computer in bedroom at 10am):

1: Activity:		Location:		Time:	
2: Activity:		Location:		Time:	
3: Activity:		Location:		Time:	
4: Activity:		Location:		Time:	

Send

- 26% *No Match Between Sensors & Report*
- 49% Partial Agreement
- 25% Full Match

Area	Firings	Time
Kitchen 1	1	0:00:00
Bedroom 1	14	0:01:52
Kitchen 1	1	0:00:00
Living Room 1	3	0:00:22
Living Room 1	1	0:00:00
Bathroom 2	1	0:00:00
Living Room 1	1	0:00:00
Kitchen 1	1	0:00:00
Bedroom 1	4	0:01:12
Kitchen 1	5	0:00:33
Living Room 1	1	0:00:00
Kitchen 1	1	0:00:00
Living Room 1	1	0:00:00
Kitchen 1	1	0:00:00
Bedroom 1	1	0:00:00
Kitchen 1	1	0:00:00
Bedroom 1	1	0:00:00
Kitchen 1	10	0:01:03
Living Room 1	1	0:00:00
Kitchen 1	1	0:00:00
Living Room 1	1	0:00:00
Computer Room	3	0:00:14

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The Changing Clinical Research Paradigm

- Brief
- Episodic
- Clinic-based
- Subjective
- Obtrusive
- Inconvenient

- Pervasive Computing
- Wireless Technologies
- "Big Data Analytics"

- Real-time
- Continuous
- Home-based
- Objective
- Unobtrusive
- Ambient

EVIDENCE

- New Observations & Discovery
- Maximally Effective Clinical Research
- Useful & Trusted Products & Services
- Better Outcomes for Patients & Families

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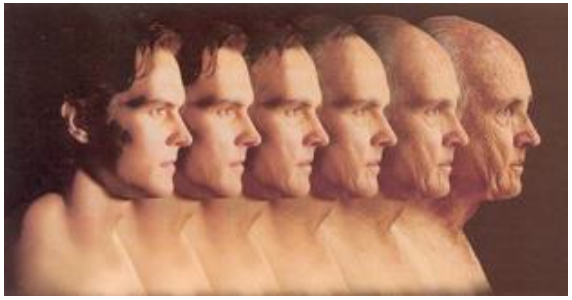
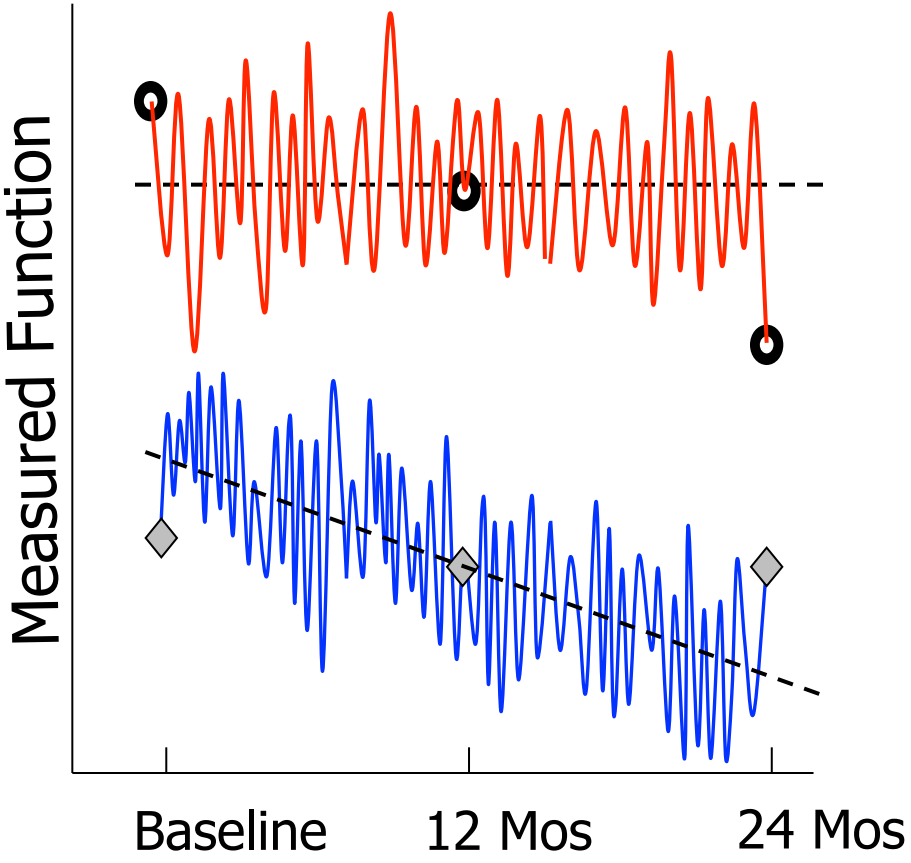
Improving detection of change: The case for continuous, objective, measures



- More data points ➔
- More accurate estimates of trajectories (slopes over time)
- Earlier detection of change



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Many ways to approach/collect data using pervasive computing and "digital biomarkers"

- **Domain** (genetic, environmental, clinical); **frequency** (episodic, continuous); **certainty** (supervised, unsupervised); **method of capture** (device, procedure); **locus of capture** (home, work, hospital)

"Resist the law of the hammer"

- In a growing diverse IoT, connected world, less focus on devices to be used; more on when, where, and how to practically and reliably capture longitudinal data.

➔Be Technology Agnostic➔

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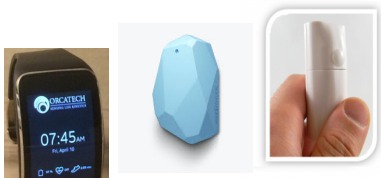
Technology 'Agnostic' Pervasive Computing Platform:

The Life Laboratory



Activity, Sleep, Mobility
Time & Location

Body Composition, Pulse,
Temperature, CO_2

MedTracker

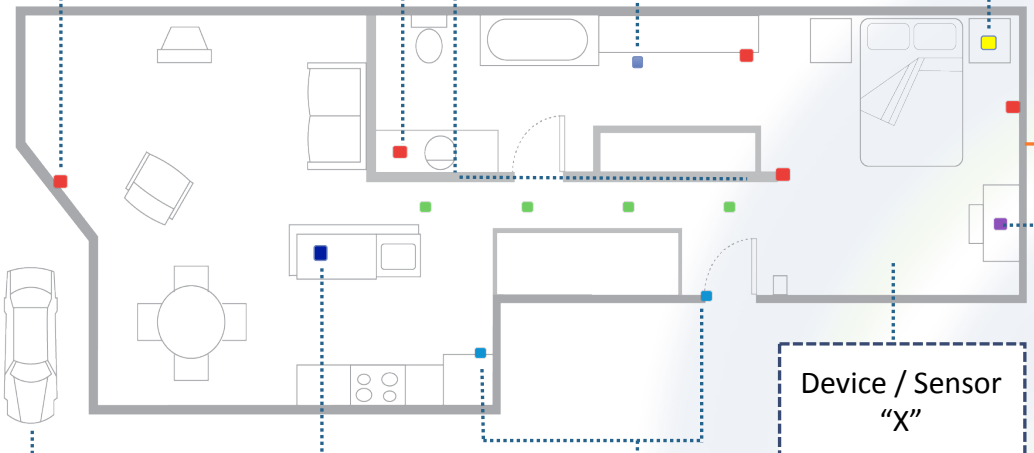
Central Secure
Data Backend

LIFE LABORATORY

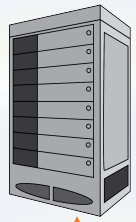
AIMS STUDY

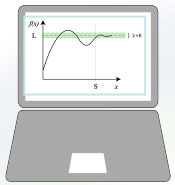
LIFE LAB BC

STUDY/SITE X



Secure
Internet





Device / Sensor
"X"

Driving

Phone Activity

Doors Open / Close

Computer Activity

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Kaye et al. Journals of Gerontology: Psychological Sciences, 2011

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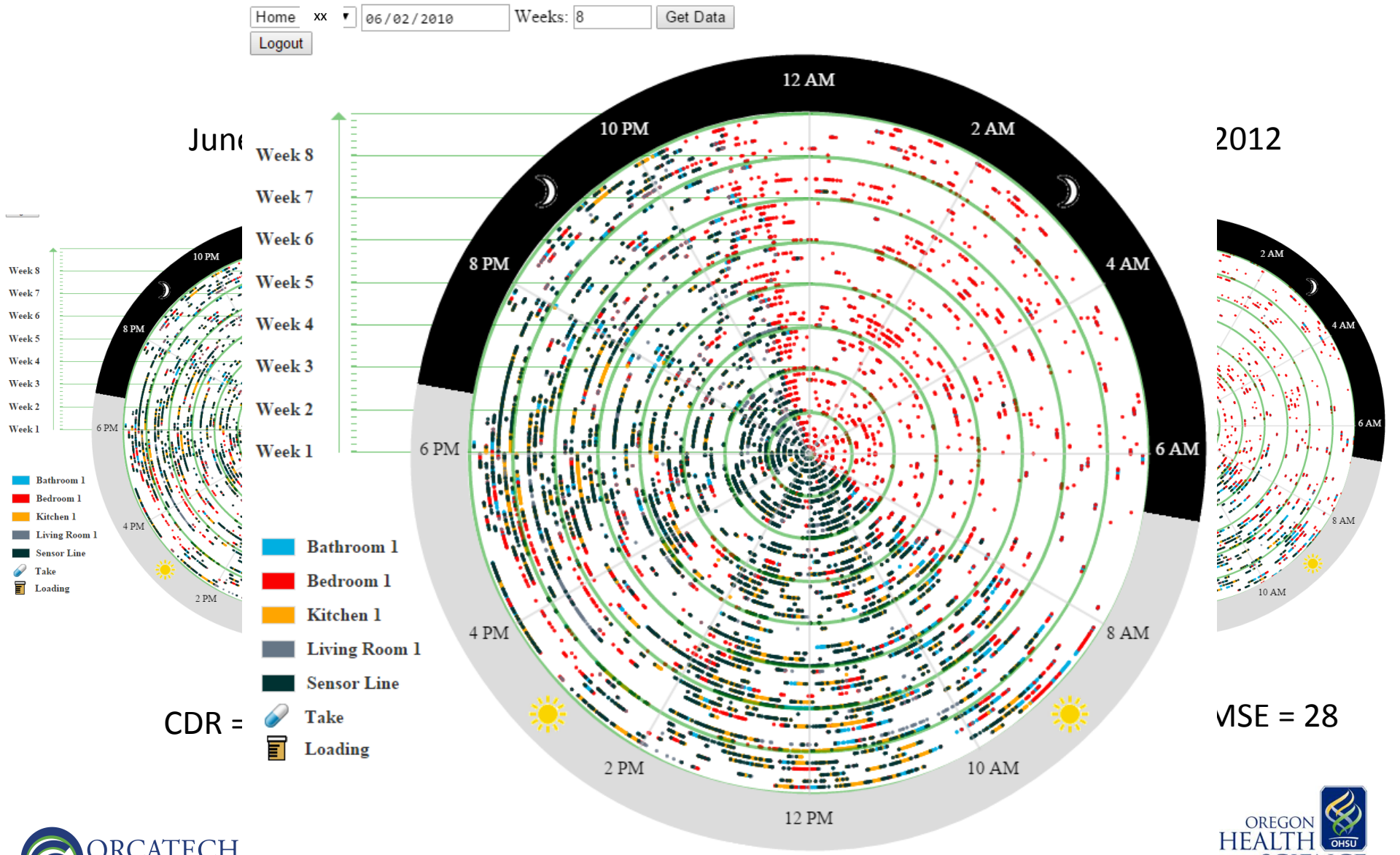
Identifying prodromal MCI



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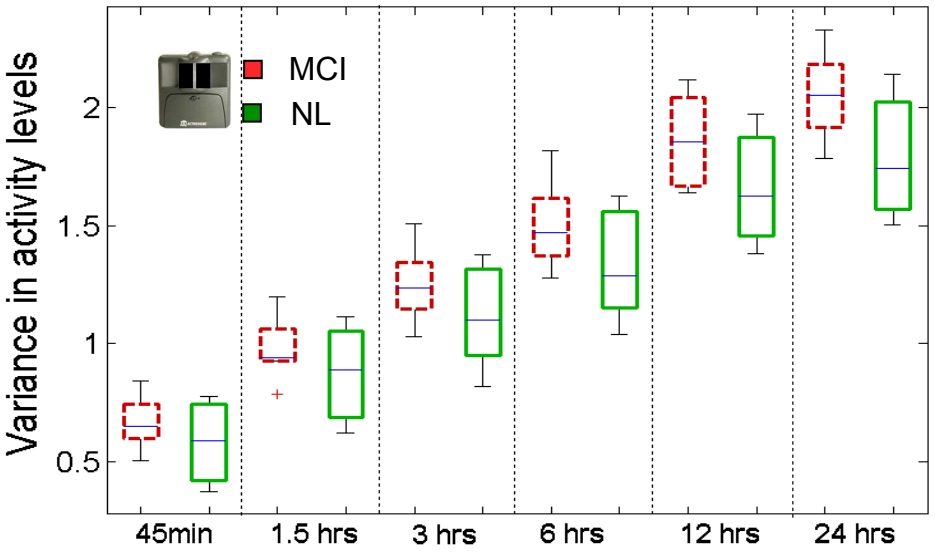
Differentiation of early MCI: Total Activity & Walking

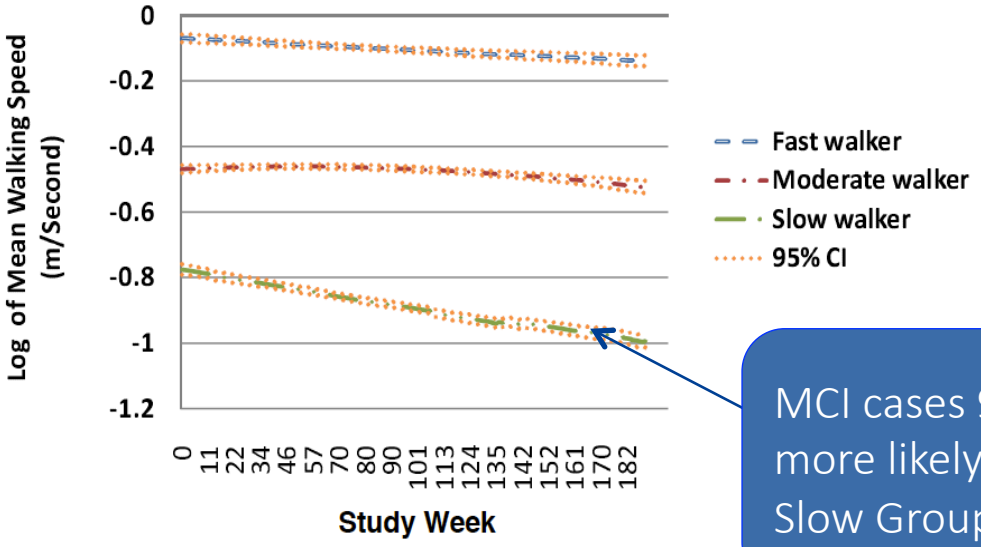


Activity patterns associated with mild cognitive impairment

Hayes et al. Alzheimers Dement, 2008

Trajectories of walking speed over time

Dodge, et al. Neurology, 2012



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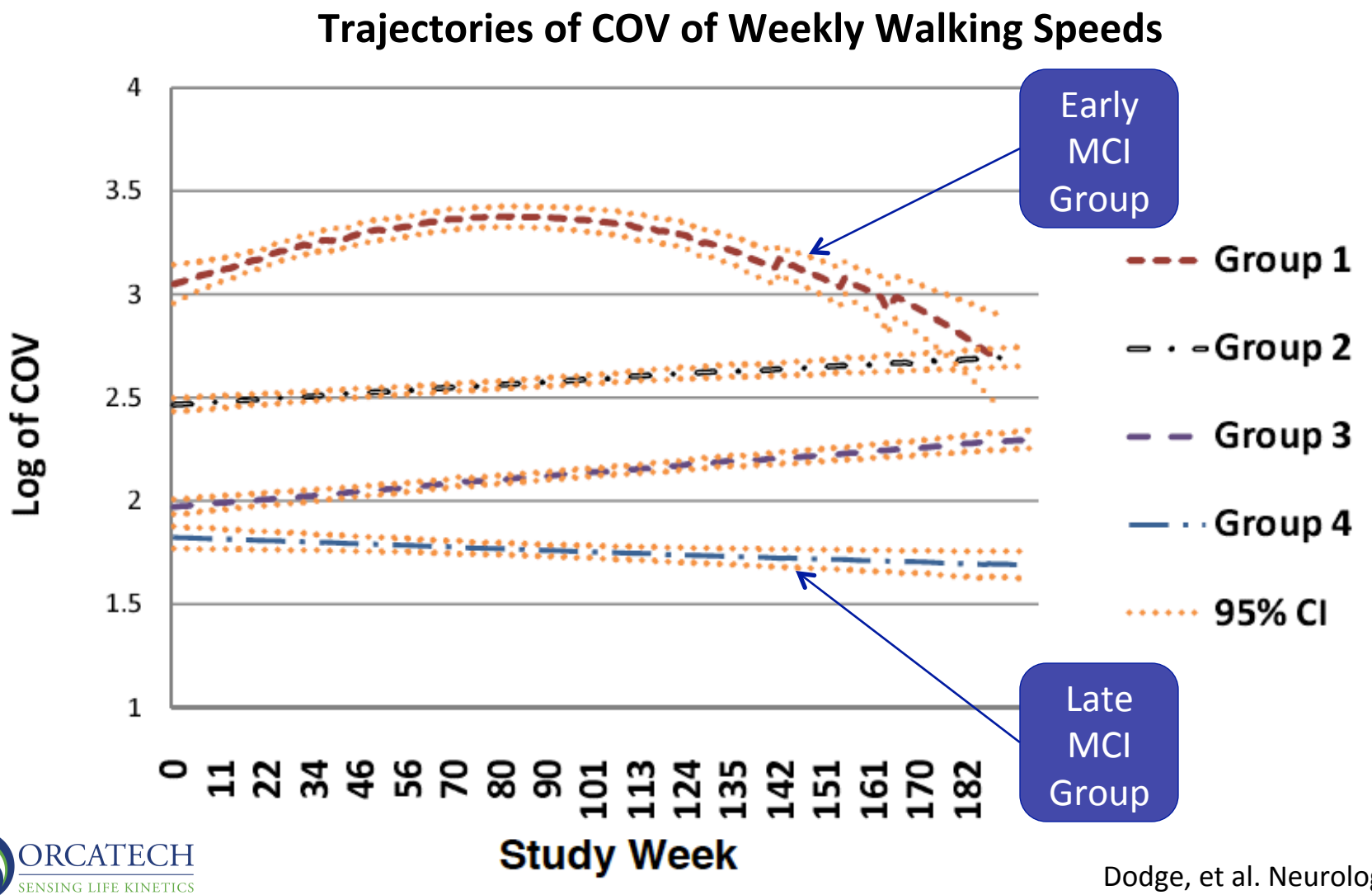
Early MCI - "high variability at baseline, then decreasing over time"

Late MCI - " low variability and declining"



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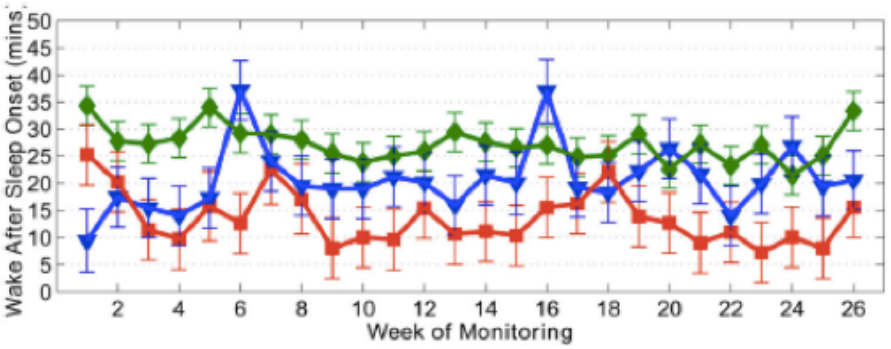
Dodge, et al. Neurology, 2012

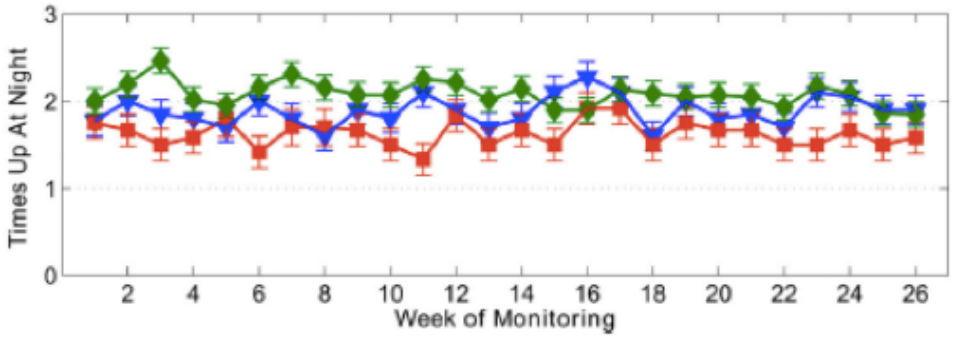
Differentiation of MCI:
Night-time Behavior & Sleep

Normal -

NA-MCI -

A-MCI -





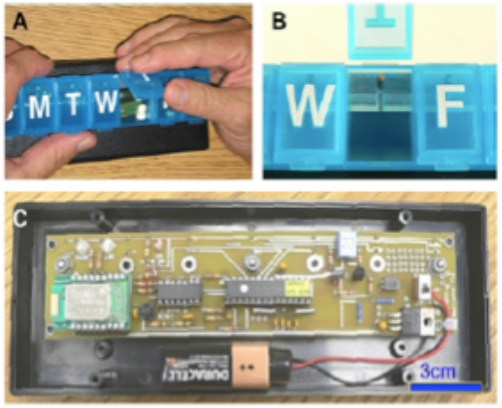
Objective Measure	Intact	aMCI	naMCI	P value
Movement in Bed (sensor firings)	9.4 ± 0.4	7.8 ± 0.9	10.9 ± 0.7	p < 0.05 (aMCI < naMCI)
Wake After Sleep Onset (mins)	27.2 ± 1.2	13.5 ± 2.6	20.6 ± 2.0	p < 0.001 (aMCI < intact, naMCI)
Settling Time (mins)	2.5 ± 0.07	2.3 ± 0.15	3.1 ± 0.11	p < 0.001 (naMCI > intact, aMCI)
Times up at night (# times)	2.1 ± 0.04	1.6 ± 0.10	1.9 ± 0.08	p < 0.001 (aMCI < intact, naMCI)
Total Sleep Time (hrs)	8.3 ± 0.04	8.5 ± 0.09	8.5 ± 0.07	NS

No Differences Between Groups in Self-Report Measures

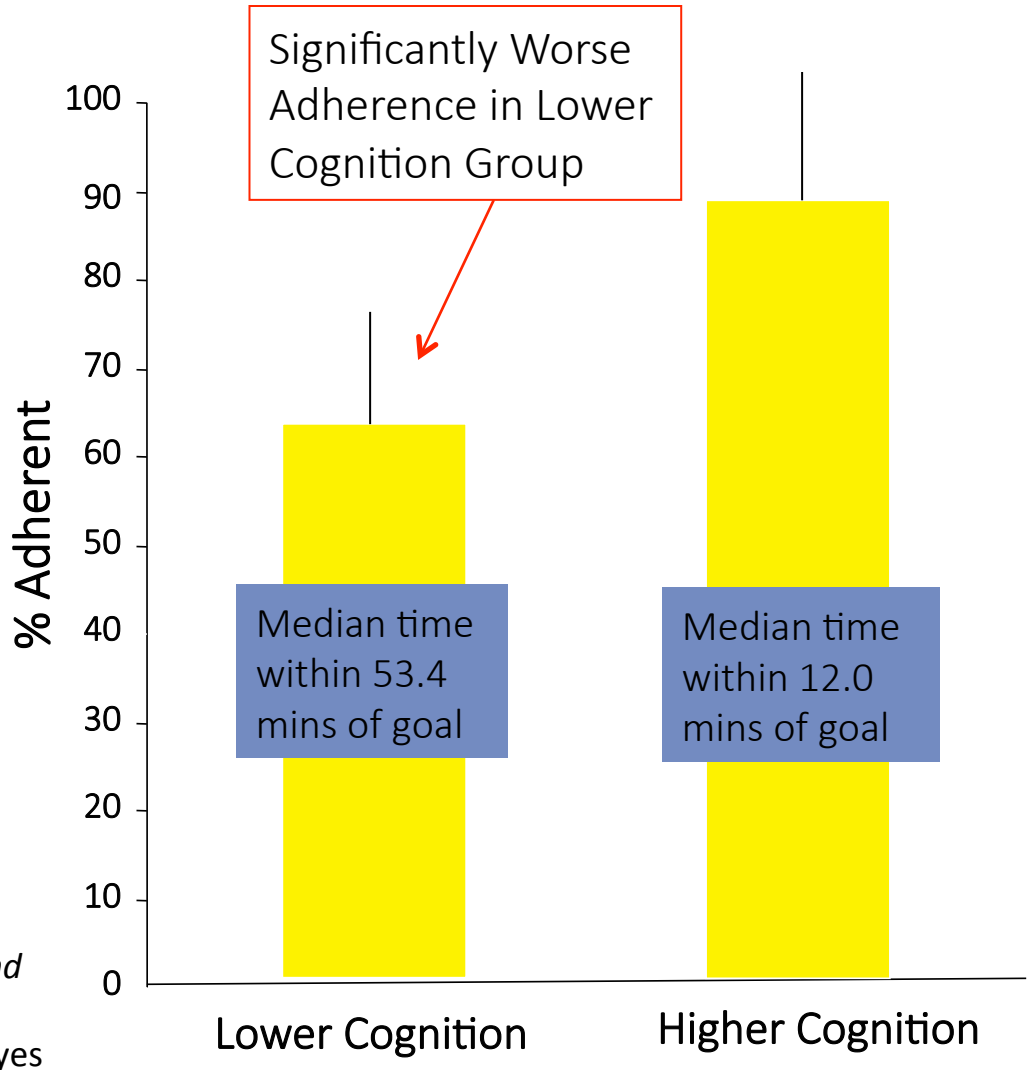
Self-Report Measure	Intact	aMCI	naMCI	P value
Subjective Daytime Sleepiness	1.8 ± 0.2	1.5 ± 0.3	2.0 ± 0.3	0.69
Subjective Insomnia	1.3 ± 0.2	0.8 ± 0.3	1.6 ± 0.3	0.21
Subjective Restlessness	1.0 ± 0.1	0.4 ± 0.3	0.7 ± 0.2	0.34
Times up at night	1.1 ± 0.1	1.0 ± 0.3	1.0 ± 0.2	0.77

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

Every Day Cognition: Medication adherence as a measure of cognitive function

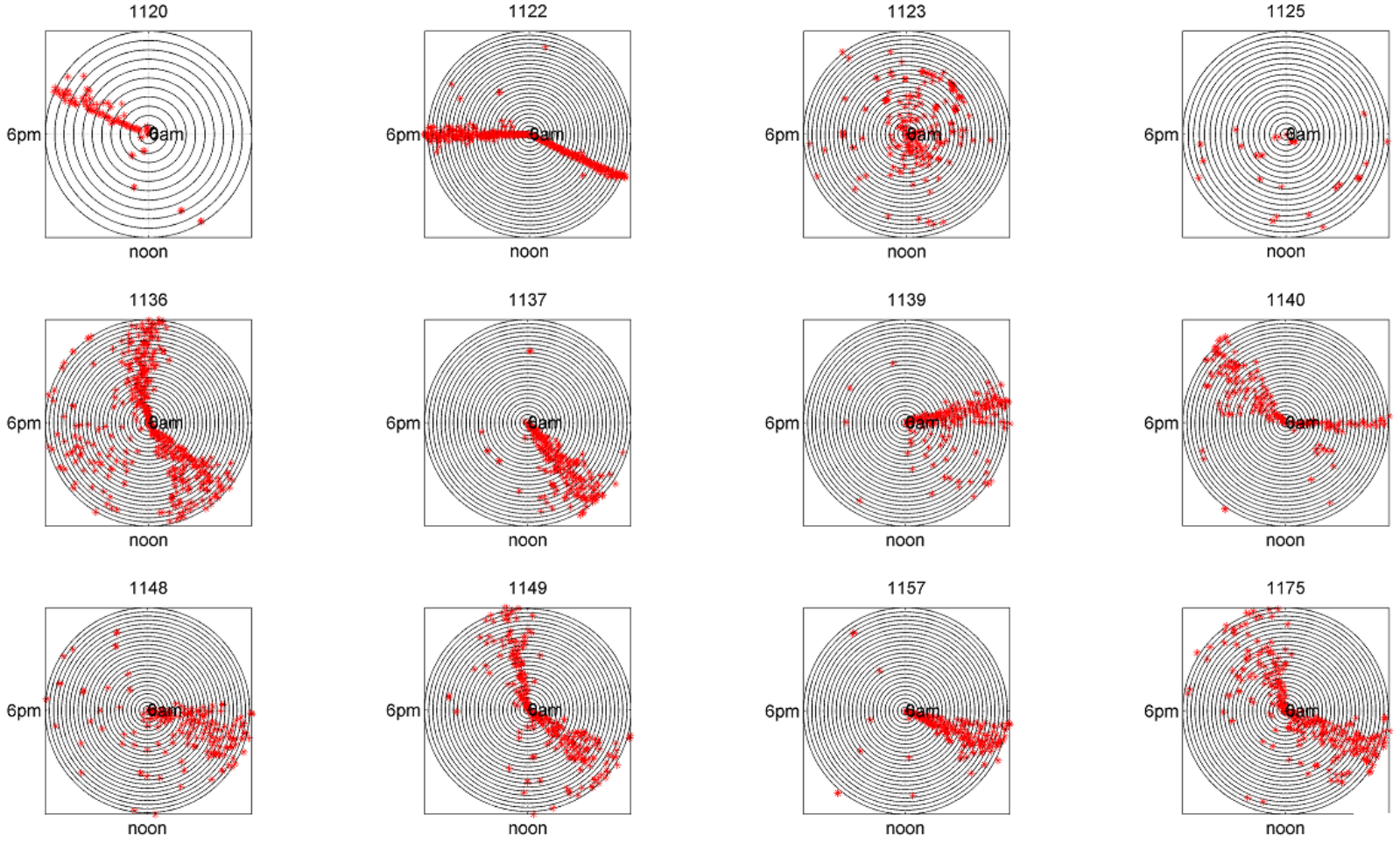


- Adherence assessed continuously x 5 wks with MedTracker taking a
- Mean Age - 83 yrs
- Based on ADAScog: Lower Cognition Group vs Higher Cognition Group



Hayes et al., *Proceedings : Engineering in Medicine and Biology Soc*, 2006; Leen, et al., *Technology and Aging,* 2007 ; Hayes et al. .*Journal of Aging Health*, 2009; Hayes et al. *Telemedicine Jounal and E-Health*, 2009

Individual patterns of medication adherence over time



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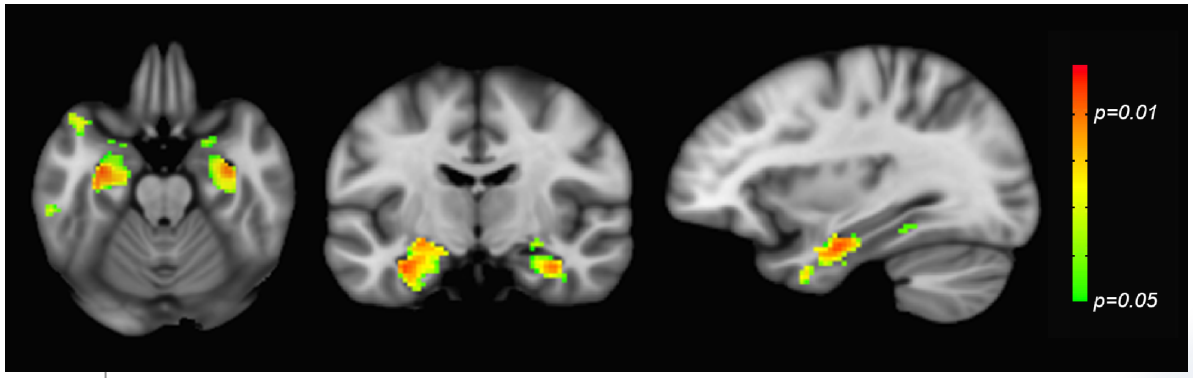
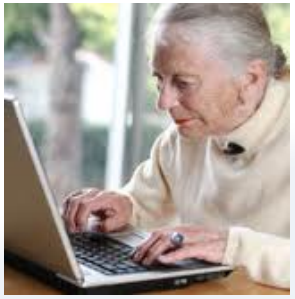
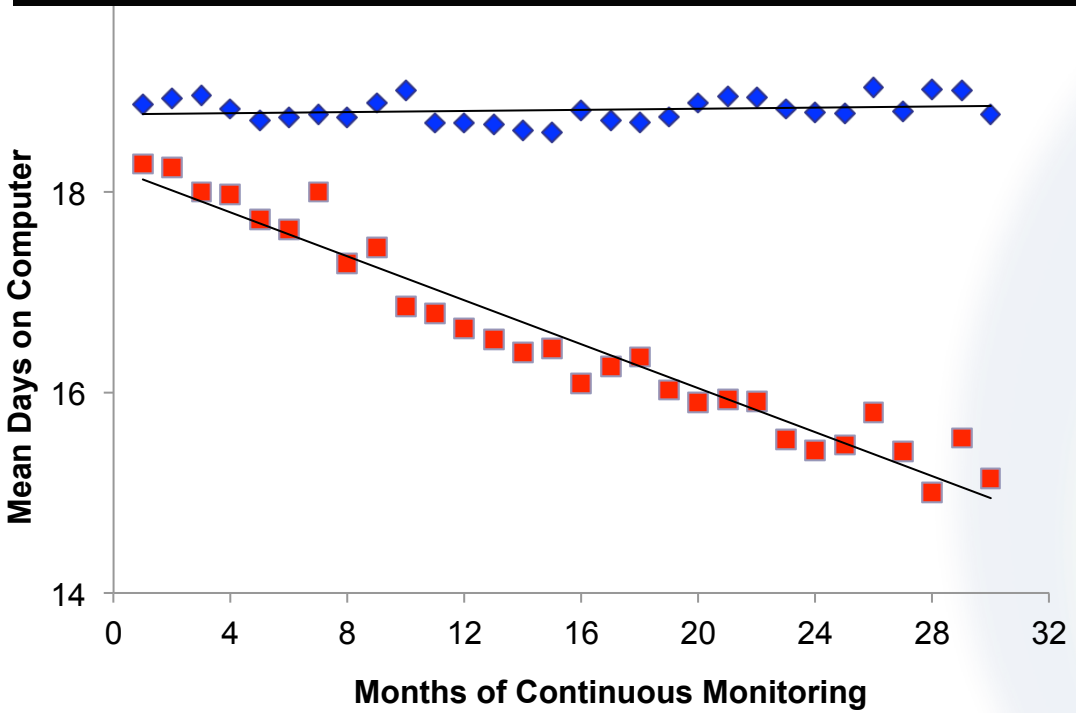
Every Day Cognition: Computer use changes over time in MCI (without formal cognitive tests)







- At Baseline: Mean 1.5 hours on computer/per day
- Over time:
  - Less use days per month
  - Less use time when in session
  - More variable in use pattern over time

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

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Dyad Analysis

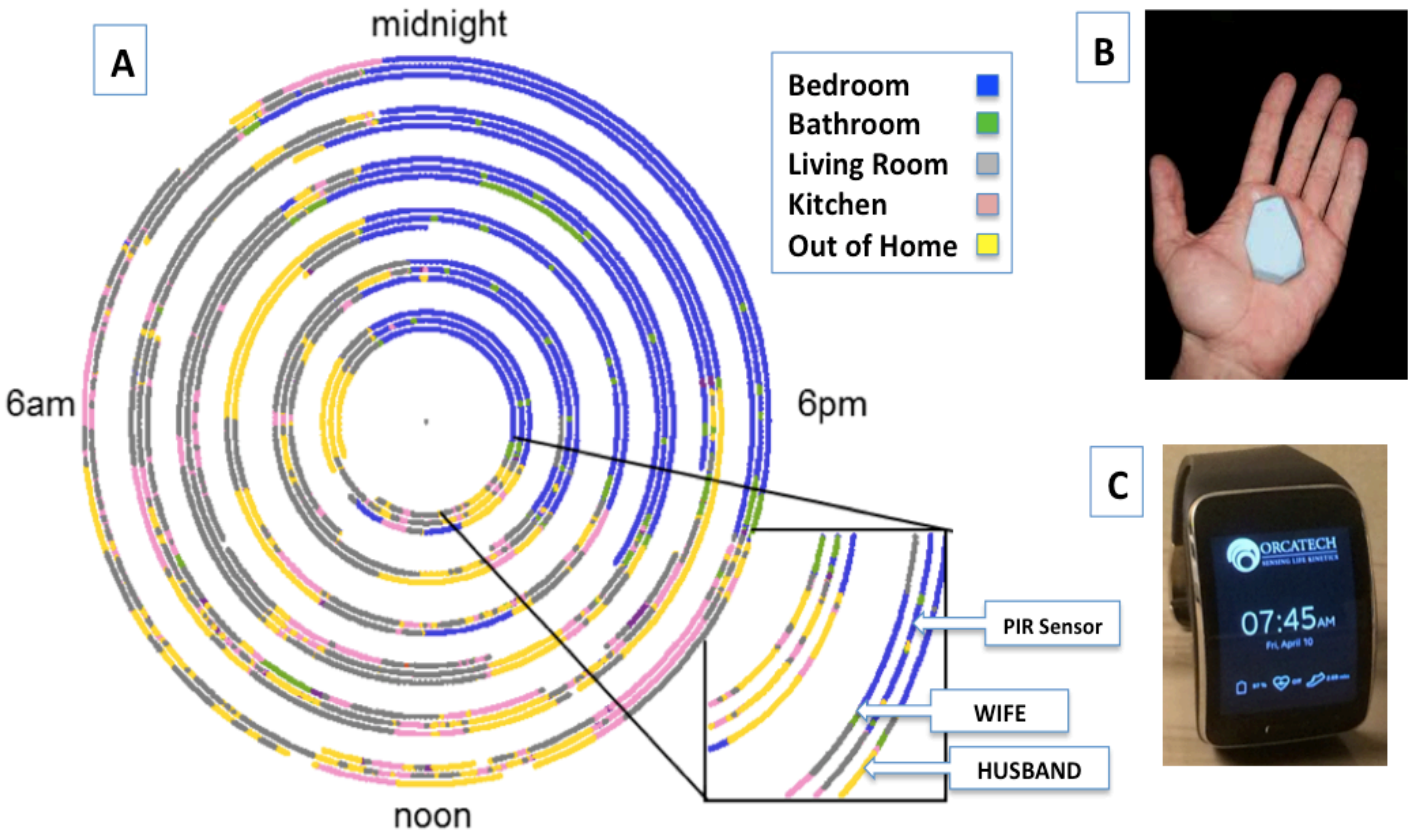

Figure. Spiral plot (**A**) depicting the within home location of a husband and wife plotted on a 24 hour clock for 6 consecutive days using a Bluetooth beacon system (**B -** photo of one of the beacons deployed around the home) paired with smartwatches (**C**) for individual localization. Each concentric circle outward depicts one day. In **A,** the colors represent where the person is located (see key). The outer trace is the husband, inner trace is the wife and middle trace is the activity of PIR sensors (see inset).

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J. Austin, 2016

Self-Report Data will Always be Needed...
...If captured on-line may provide measures of cognitive function

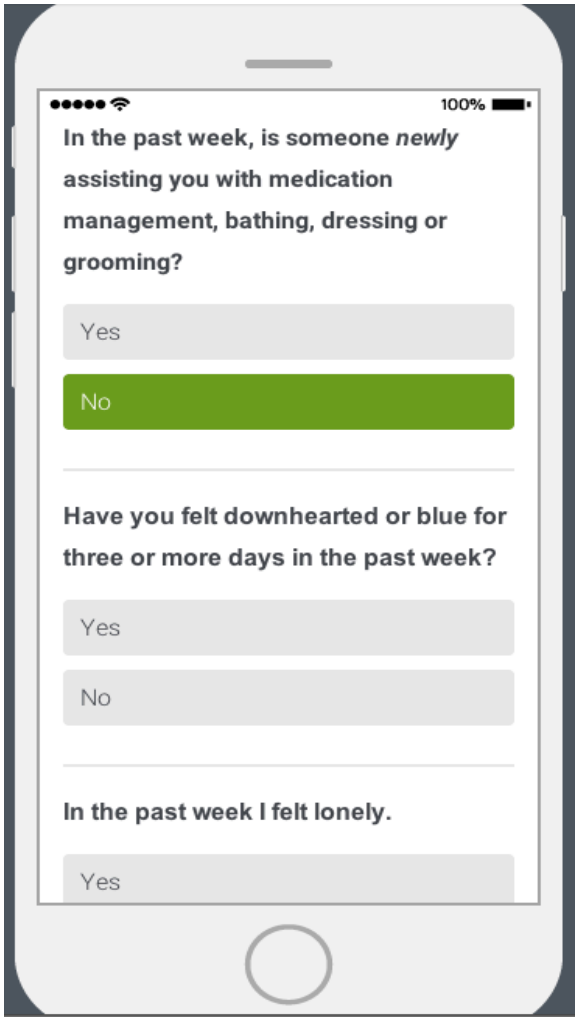

Figure 3: Screen shot showing questions presented for the weekly personal health and activity record (or PHAR) on a mobile device. "Yes" responses result in a drop-down menu that asks for further detail. The survey is tracked for timing of each item response and total time to complete the survey each week.

Seelye et al., Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 2015
Seelye et al., Alzheimer's Disease & Assoc. Disorders, 2015

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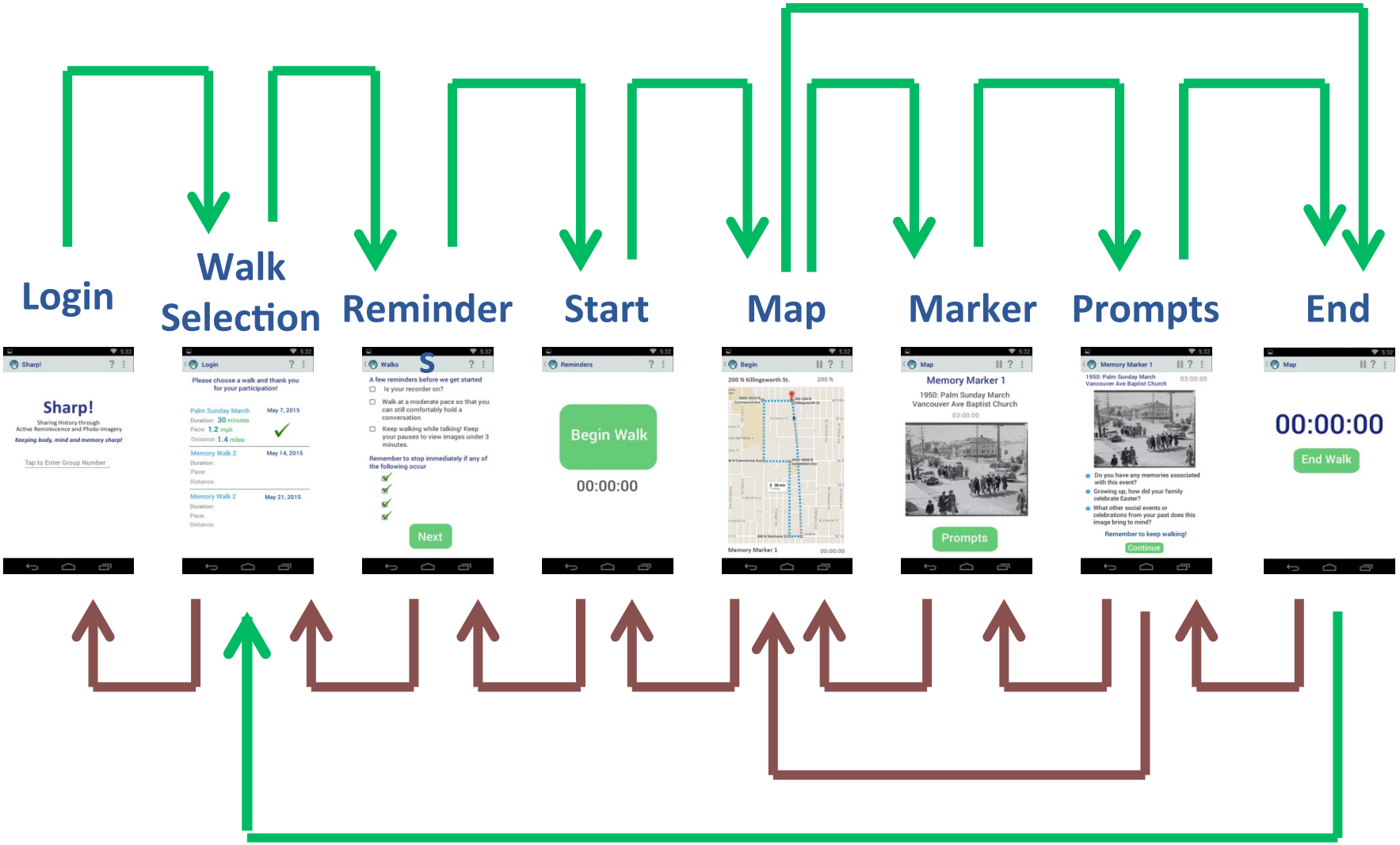
Some Use Cases...

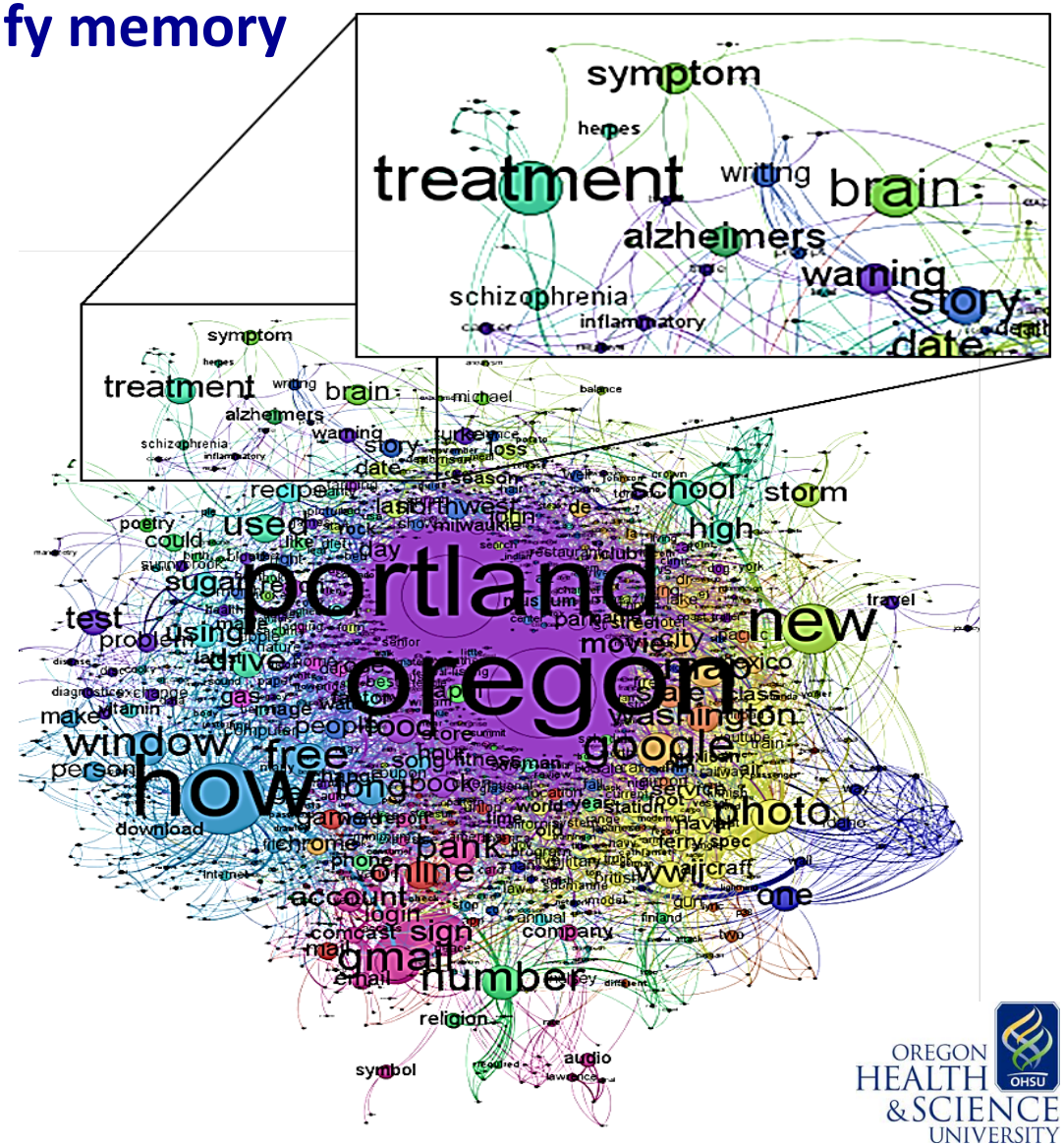


Applications Toward Advancing Clinical Care...

Internet searches to identify memory concerned patients

Dataset represents an average of 385 days of continuous computer search data (min 67 days, max 601 days) from 77 participants completing 8,899 searches (in Bing, Google and Yahoo)

- Courtesy of J. Austin



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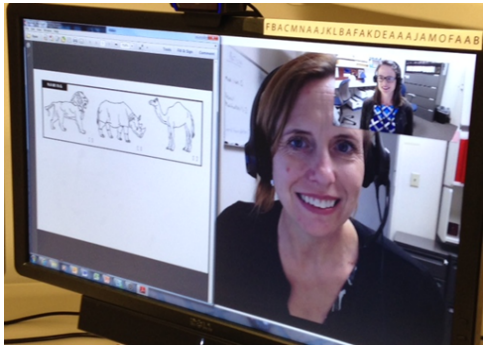
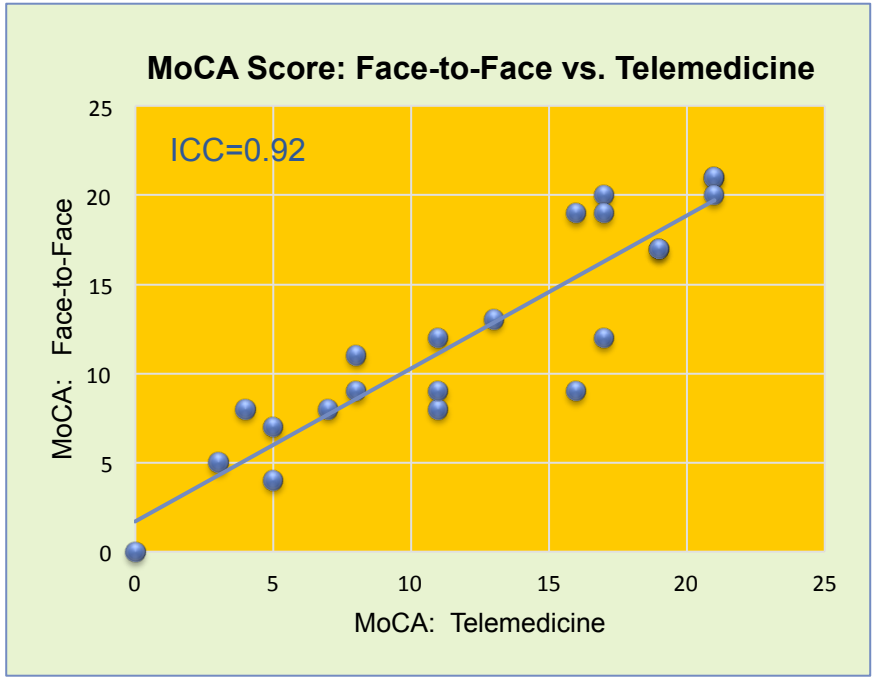
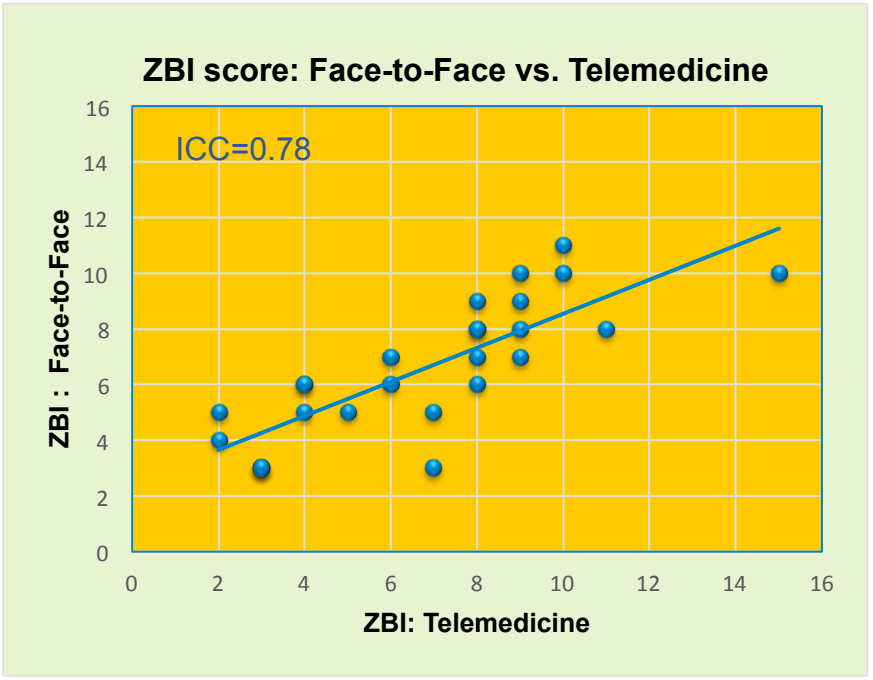
Teledementia Care: Direct to Home

Alzheimer's Care via Telemedicine for Oregon (ACT-ON) Phase I: Establishing the Reliability of Telemedicine-based Measures (PIs – A. Lindauer and D. Erten-Lyons)







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Oregon Health Authority

Lindauer, AAN, 2016

OREGON ORH OFFICE OF RURAL HEALTH

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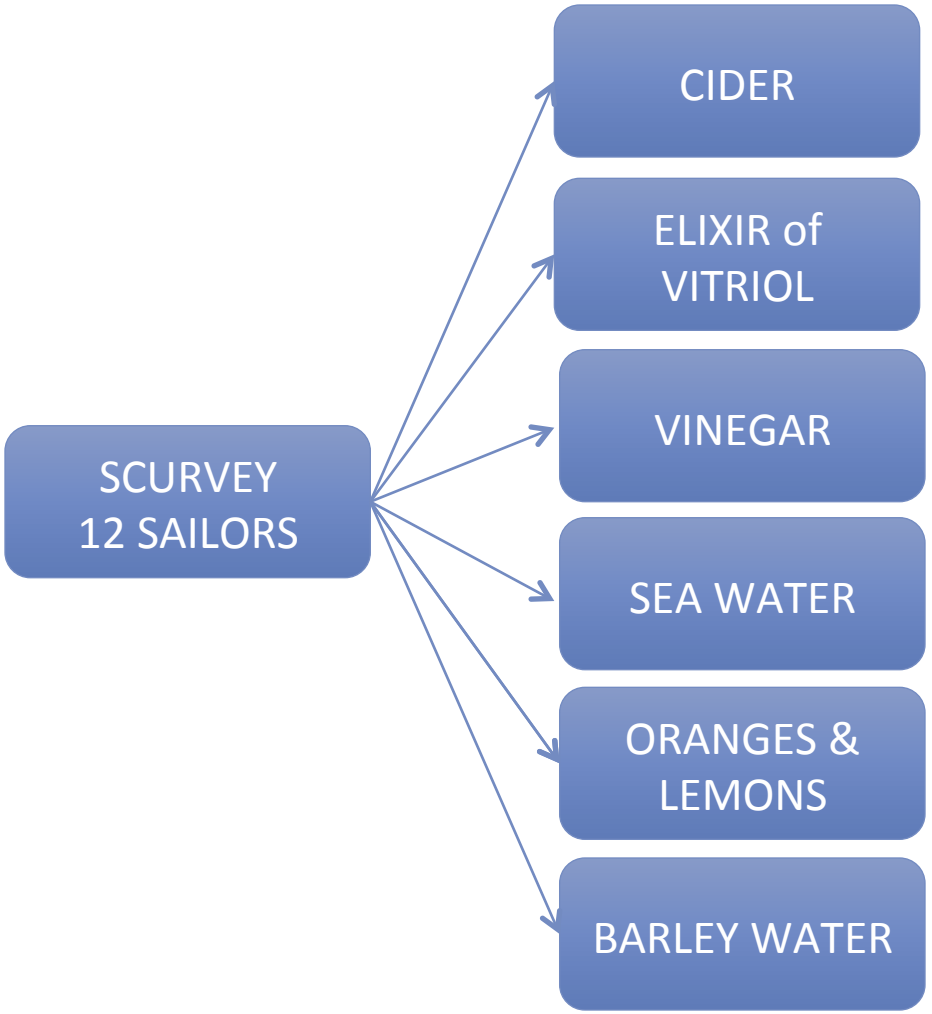
Advancing Clinical Trials...

The First RCT ?

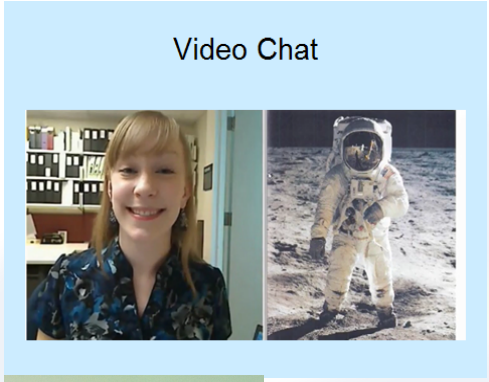
James Lind, 1774



cancergrace.org: S. Ramalingham

RCT to Increase Social Interaction in MCI Using Home-based Technologies (PI: H. Dodge)

- 6 week RCT of daily 30 min video chats
- 89% of all possible sessions completed; Exceptional adherence – *no drop-out*
- Intervention group improved on executive/ fluency measure.
- MCI participants spoke 2985 words on average while cognitively intact spoke 2423 words during sessions; better discrimination of MCI than conventional tests (animal fluency and delayed list recall)



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

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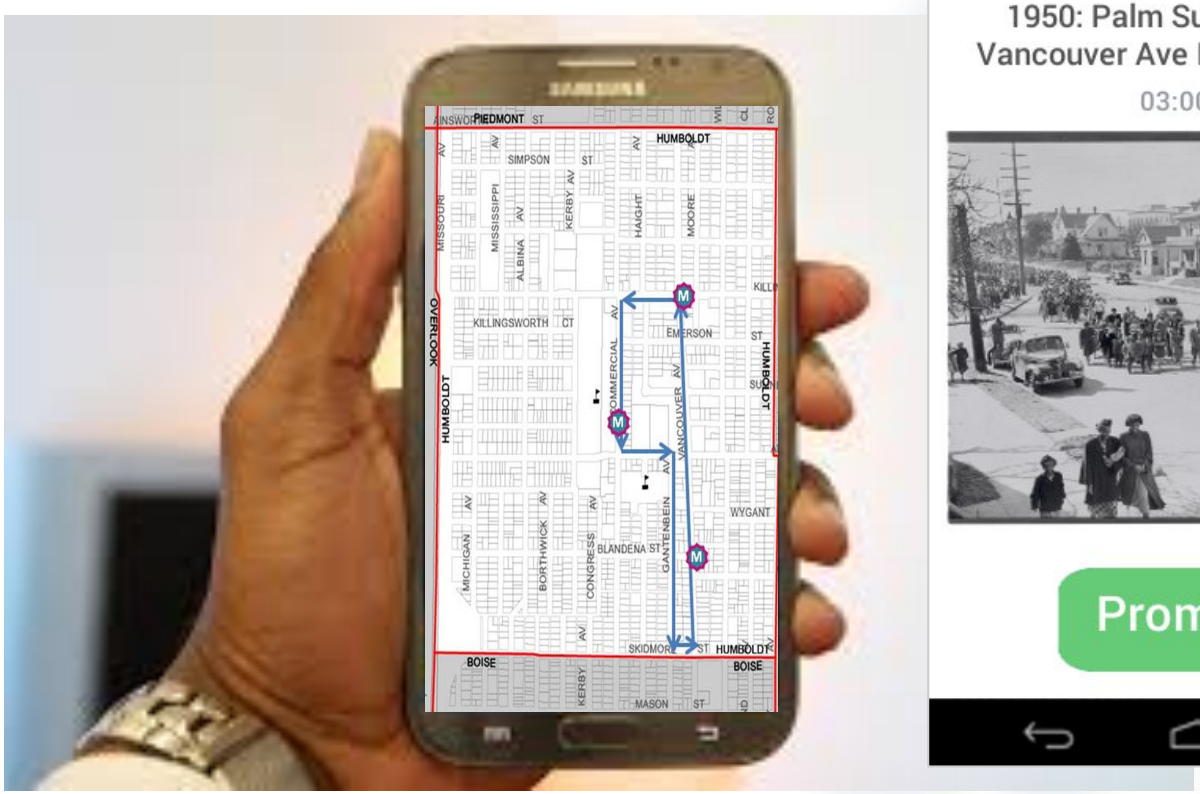
SHARP: *Multi-modal Brain Health Program*

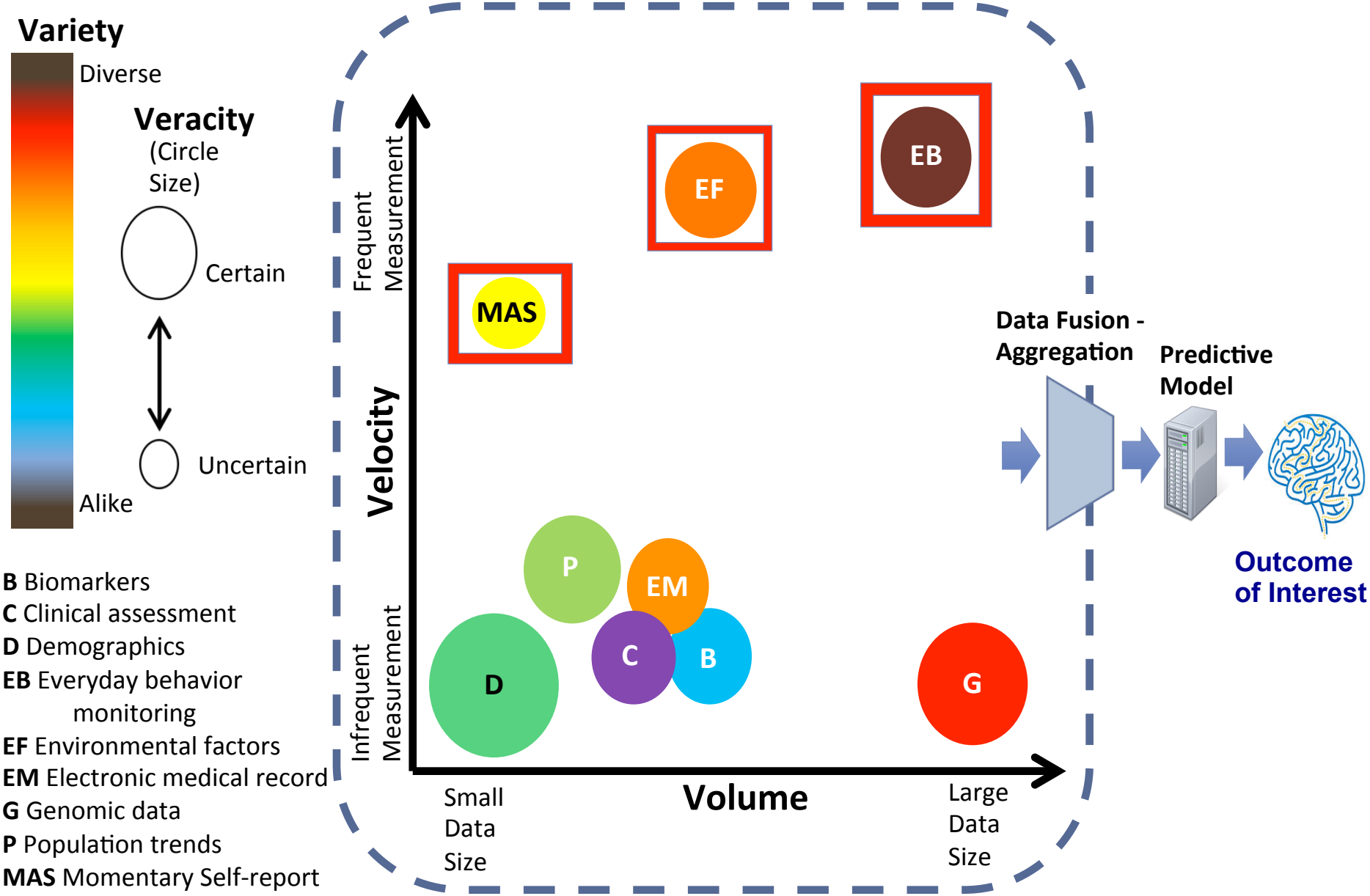
PI: Raina Croff

M	T	W	Th	F
Group Walking + Reminiscence 45 minutes	Health Education Session 30 minutes	Group Walking + Reminiscence 45 minutes	Memory Session 30 minutes	Group Walking + Reminiscence 45 minutes

In-home technology to monitor social engagement



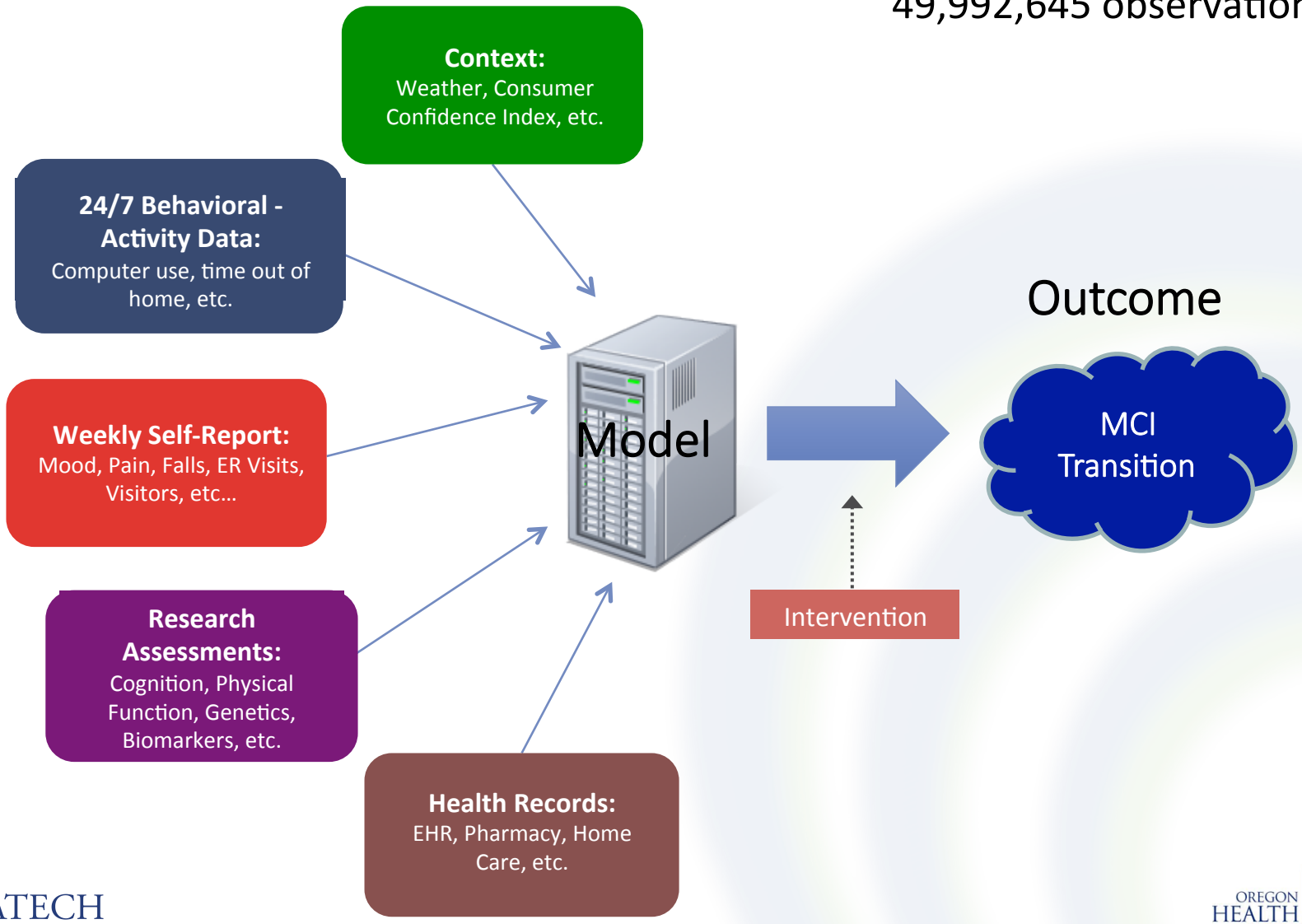
Predictive Modeling Using Multi-Dimensional Data



B Biomarkers
C Clinical assessment
D Demographics
EB Everyday behavior monitoring
EF Environmental factors
EM Electronic medical record
G Genomic data
P Population trends
MAS Momentary Self-report

Predictive Modeling Using Multi-Dimensional Data:
High dimensional data fusion model predicting MCI

49,992,645 observations



Austin et al. 2015

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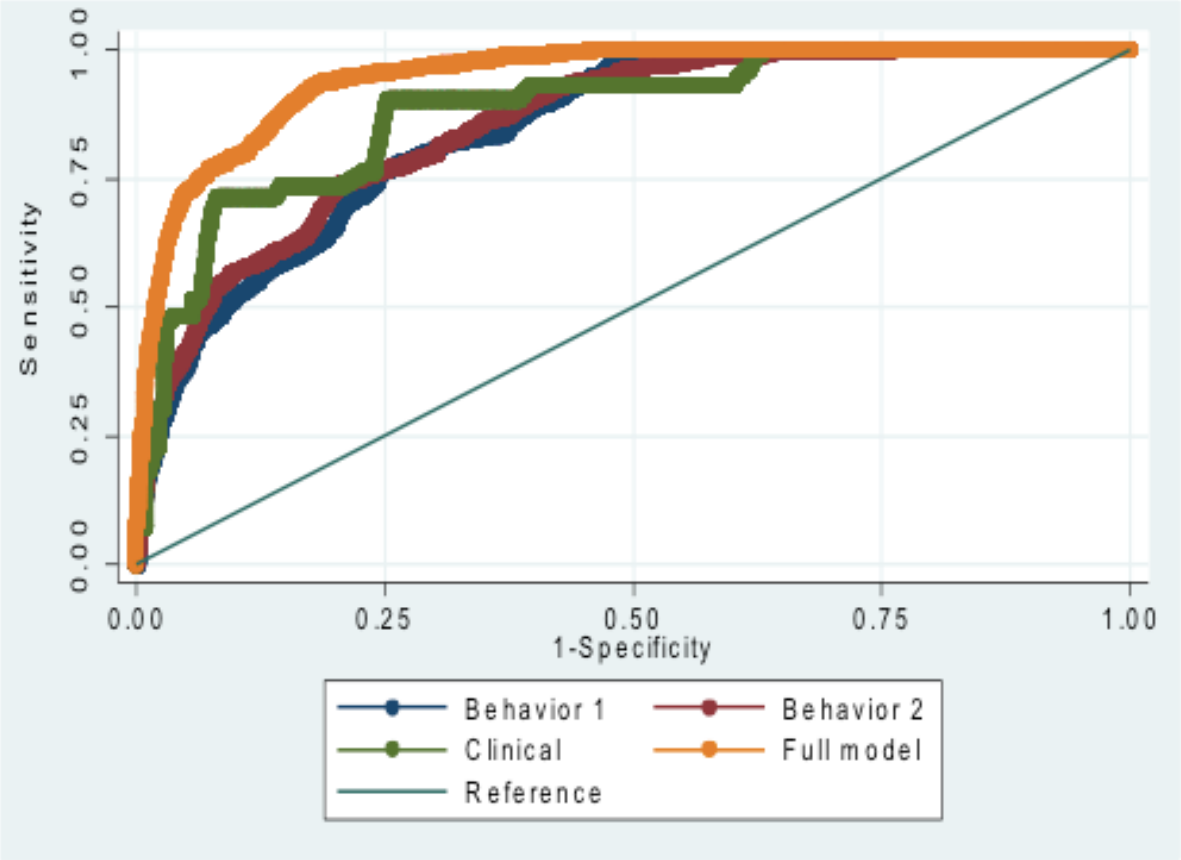
Predicting MCI Transitions: Sensitivity Analysis

- 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)

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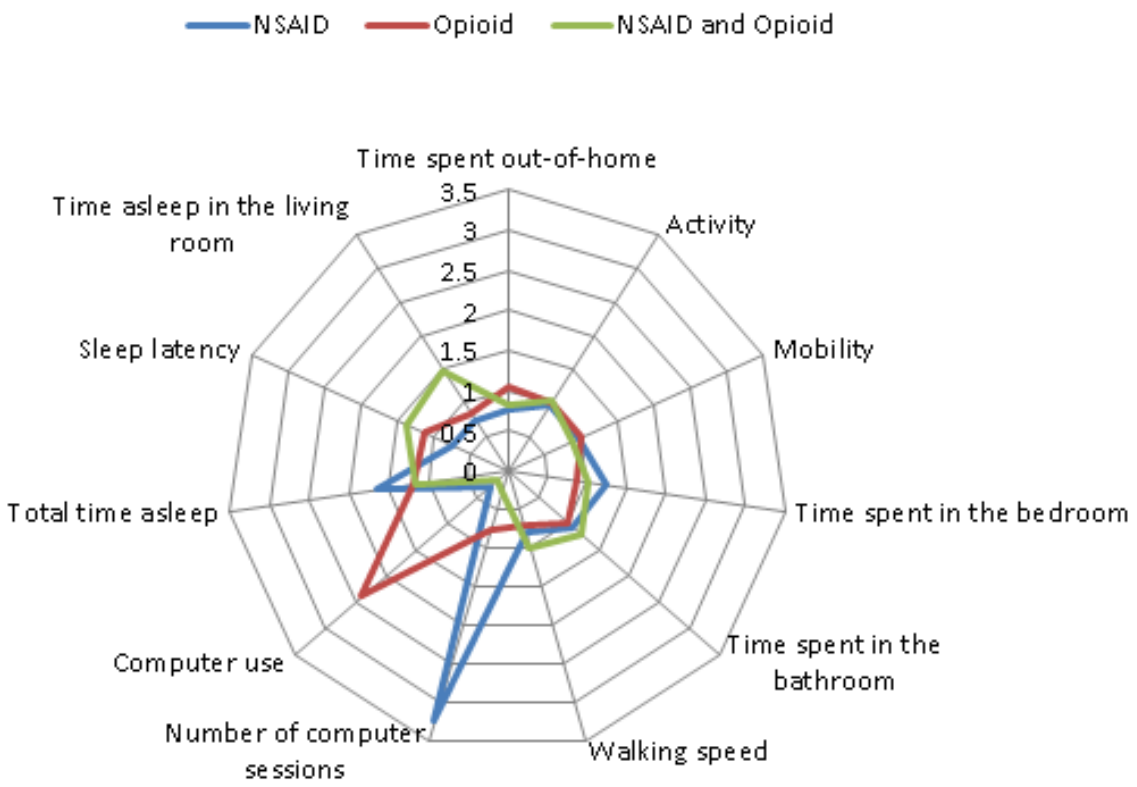
Identifying Drug Class Effects: *Drug Action Behavioral Fingerprinting*

Example of analgesics



	NSAID	Opioid	Both
Sensitivity (%)	94.9	65.9	67.4
Specificity (%)	99.9	98.6	99.6
Positive Predictive Value (%)	99.7	82.6	86.1
Negative Predictive Value (%)	99.7	96.6	98.9
Correctly Classified (%)	99.6	95.6	98.6

Logistic regression models treated as classifiers (and model fit statistics)

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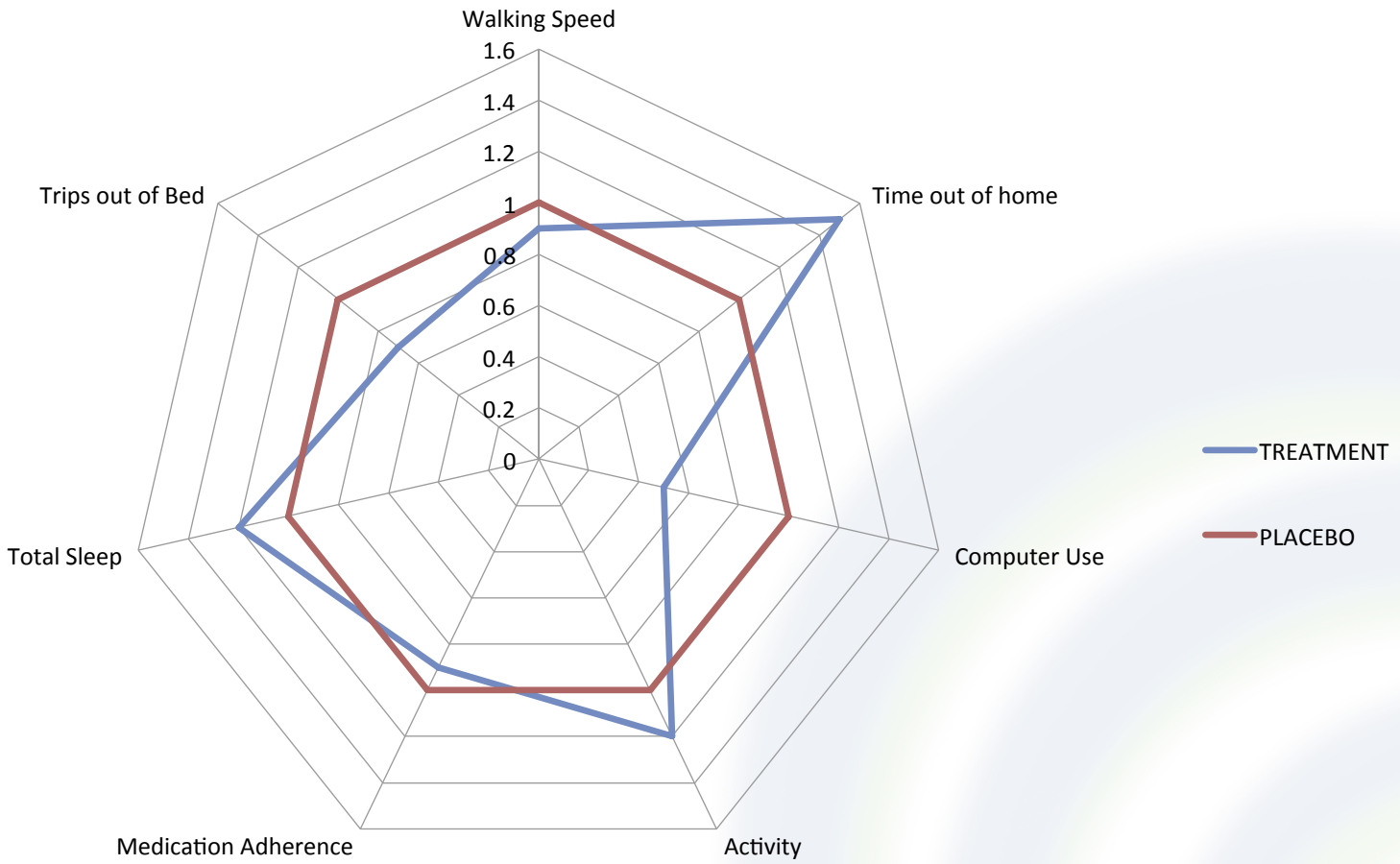
Observation period: July, 2011 – March, 2014; 66,172,380 observations

Behavioral Fingerprinting by Treatment Status



Values are odds ratios. 1 is the reference value, and is 'normalized' to placebo.

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Transforming Clinical Trials with High Frequency, Objective, Continuous Data: "Big Data" for Each Subject

MCI Prevention Trial – Sample Size Estimates

	Current Method	Continuous Measures	
	LM Delayed Recall*	Computer Use**	Walking Speed**
SAMPLE SIZE TO SHOW 50% EFFECT	688	10	94
SAMPLE SIZE TO SHOW 40% EFFECT	1076	16	148
SAMPLE SIZE TO SHOW 30% EFFECT	1912	26	262
SAMPLE SIZE TO SHOW 20% EFFECT	4300	58	588

Dodge, et al., PLoS One, 2015

- Reduces required sample size and/or time to identify meaningful change.
- Reduces exposure to harm (fewer needed/ fewer exposed)
- More precise estimates of the trajectory of change; allows for *intra-individual* predictions.
- Provides the opportunity to substantially improve efficiency and inform go/no-go decisions of trials.

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New Generation High Efficiency Clinical Trials

Traditional Trial Enrichment:
Stratification according to increased risk of AD.
Does not predict who progresses

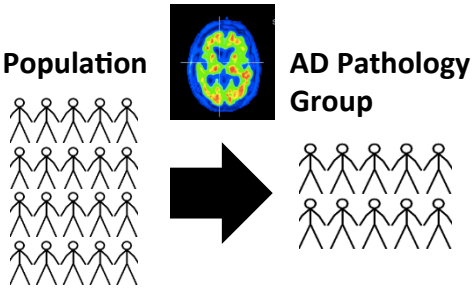
Further Enrichment:
Stratification according to who will progress.
Can predict who progresses

Efficient Longitudinal Assessment:
Continuously assessed objective measures.
Detects *individual* relevant change rapidly

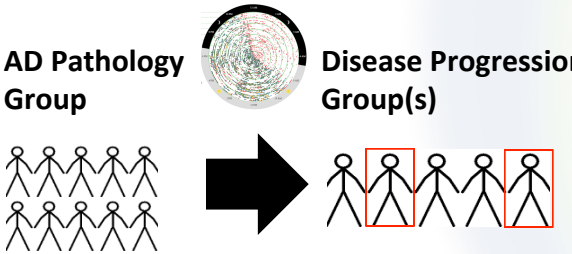
Biomarker Enrichment
Imaging, CSF, Plasma, Genetics, other risk factors

Behavioral Phenotype Enrichment
Sleep hygiene, Time out of home, etc…

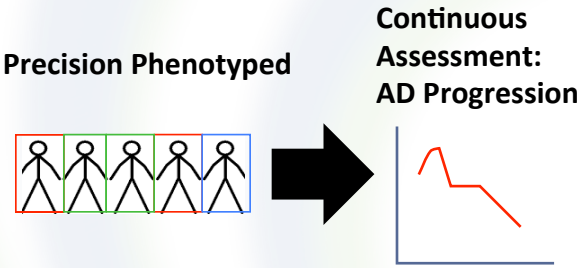
Continuous Assessment
Computer use, Walking speed, Activity, Mobility, etc…



6 months



2-3 months



6 months

Acknowledgements

"The smallest act of kindness is worth more than the grandest intention."

- Oscar Wilde

Profound Thanks to My Amazing Colleagues and the Research Volunteers

Funders

Robert Wood Johnson Foundation

Thank You!

"This really is an innovative approach, but I'm afraid we can't consider it. It's never been done before."

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