Using peripheral physiological markers for early detection of agitation in dementia

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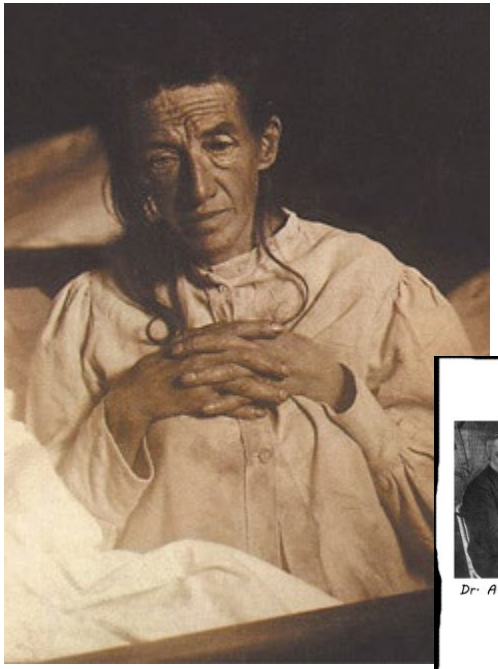
Disclosures

- Amer M. Burhan: received personal fees related to:
  - Serving on advisory board: Janssen Pharmaceutical, Avanir, and Eisai
  - Providing consultation to Atheneum Partners and HealthTechConnex
- Peer funded for brain stimulation (Brain Canada) and dementia trials (NIA/NIH, Alzheimer Drug Discovery Foundation, NRC/CIHR, Brain Canada and CABHI)
- Some of the peer funded trials will be discussed among other emerging therapeutics

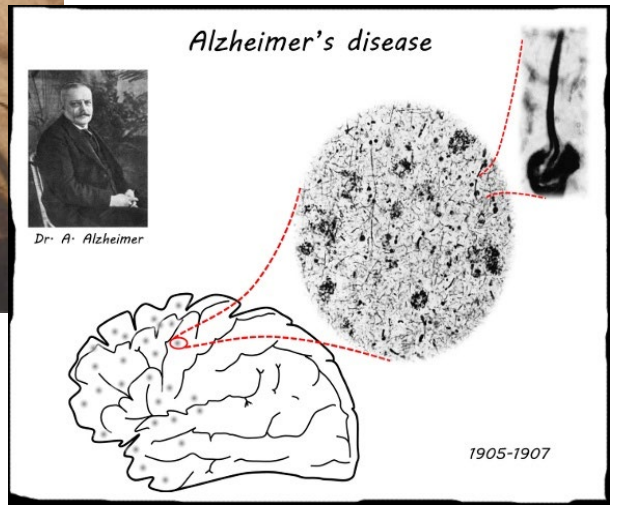
Auguste Deter

The “First” Patient

- 51-year-old woman who was experiencing problems with memory and language as well as various **psychological problems** such as disorientation and hallucinations.



http://thebrain.mcgill.ca

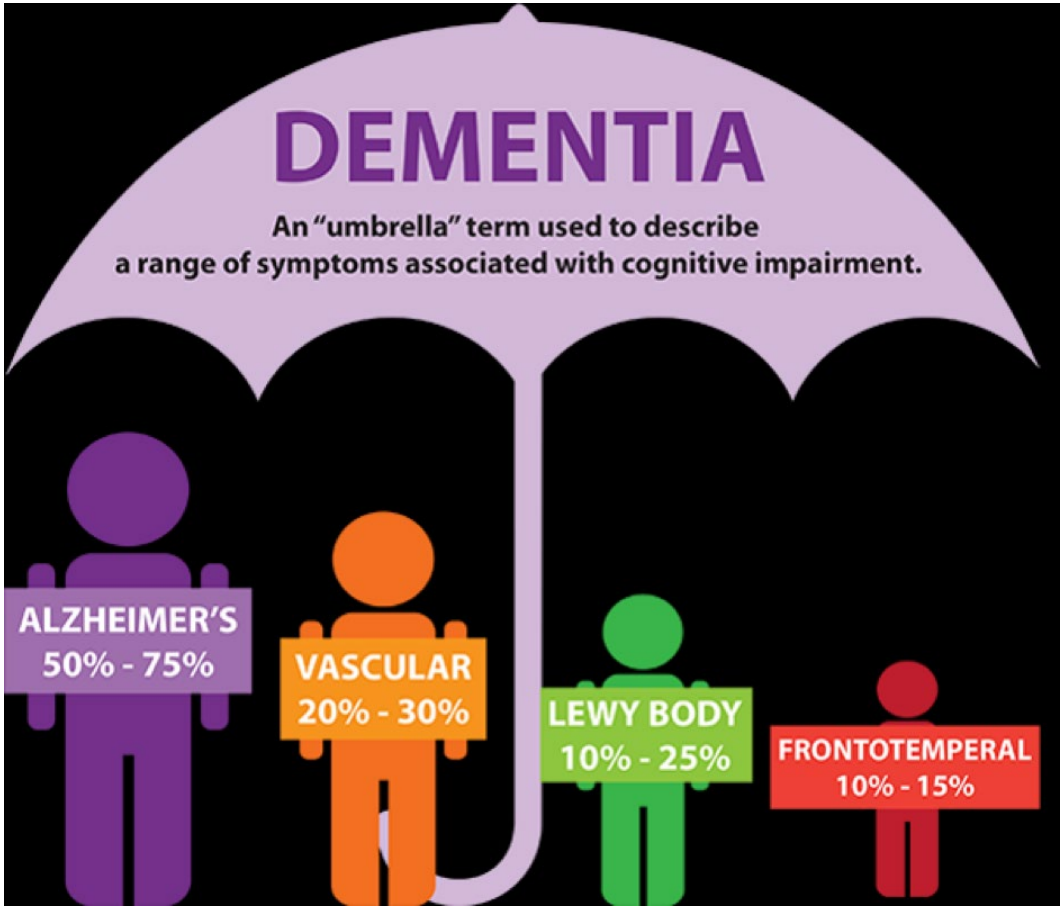


http://www.niu.sav.sk/research-groups/

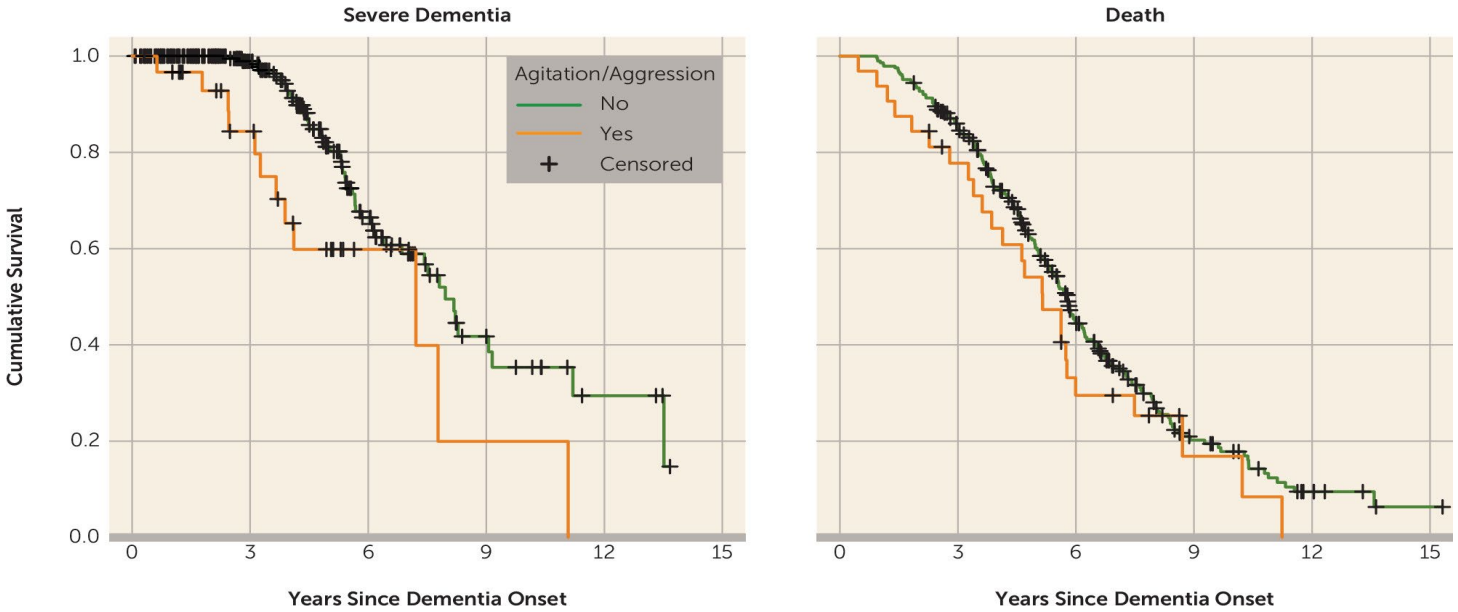
Agitation in Dementia

- Reported in up to 50 % of patients with AD, 40 % with FTD, 40% VaD, and 30% LBD
- Tends to be in moderate to advanced stages of the illness
- Important care and prognostic implications

Carrarini et al Front Neurol. 2021



http://www.dfwsheridan.org/types-dementia, accessed 27/01/2019



- Psychiatric symptoms (Psychosis and agitation/aggression) are associated with over 2 times the risk for progression to **severe dementia**
- Psychiatric symptoms (psychosis, affective, and agitation/aggression) are associated with 1.5-2 times the increase risk of **death!!!**

Peters et al Am J of Psychiatry 2015

Effect of Psychiatric/Behavioral Symptoms on Family Burden

- Higher psychiatric/behavioral symptoms correlated with higher family burden especially:
    - Psychosis, anxiety, restlessness, nighttime behavior, disinhibition, eating behavior
- That was more predictive of burden than cognitive impairment!

Allegri et al Neuropsychr Dis Treat 2006

International Psychogeriatric Association Definition of Agitation!

- Excessive **motor activity**, **verbal or physical aggression** associated with **emotional distress**
- Severe enough to cause disability
- Not solely explainable on cognitive, psychiatric, medical or substance related issues

Cummings et al 2015

Measuring Change in IPA Agitation

- In an attempt to identify “minimal clinical important differences” in agitation, the IPA agitation items where mapped on Neuropsychiatric Inventory-clinician (NPI-C), and the Cohen-Mansfield Agitation Inventory (CMAI).
- NPIC-IPA: agitation/aggression, irritability, disinhibition and aberrant motor seems to perform best

De Mauleon et al 2020

IPA Agitation Definition NPI-C Derivation (NPI-C-IPA)

Patient Name: _____ Date:_____

Caregiver Name: _____ Location:_____

Instructions: Please rate the frequency and severity of behaviors subject (S) has exhibited in the past **4 weeks.**
Please rate frequency: **1 = Rarely** (less than once per week); **2 = Sometimes** (about once per week); **3 = Often** (several times per week but less than every day); **4 = Very Often** (once or more per day).

Please rate severity: **1 = Mild** (symptoms present but seem harmless and produce little distress in the patient); **2 = Moderate** (symptoms are distressing and disruptive); **3 = Severe** (symptoms are very disruptive and are a major source of behavioral disruption; if PRN medications are prescribed, their use signals that the symptoms are of marked severity).

Excessive Motor Activity

	Absent	Frequency				Severity			Clinical Impression			
1. Does (S) seem restless in general?	0	1	2	3	4	1	2	3	0	1	2	3
2. Does (S) pace nervously or angrily, in a way that differs from general wandering?	0	1	2	3	4	1	2	3	0	1	2	3
3. Does (S) pace or move in a wheelchair without apparent purpose?	0	1	2	3	4	1	2	3	0	1	2	3
4. Does (S) rummage around opening and unpacking drawers and closets?	0	1	2	3	4	1	2	3	0	1	2	3
5. Does (S) repeatedly put on and take off clothing?	0	1	2	3	4	1	2	3	0	1	2	3
6. Does (S) have repetitive activities or "habits" that he/she performs over and over (e.g., wiping off the table, opening and closing doors)?	0	1	2	3	4	1	2	3	0	1	2	3
7. Does (S) engage in repetitive activities such as handling buttons, picking, wrapping string, etc.?	0	1	2	3	4	1	2	3	0	1	2	3
8. Does (S) fidget excessively, seem unable to sit still, or bounce his/her feet or tap his/her feet a lot?	0	1	2	3	4	1	2	3	0	1	2	3
9. Does (S) perform self-stimulating behaviors such as rocking, rubbing or moaning?	0	1	2	3	4	1	2	3	0	1	2	3
10. Does (S) move with no rationale purpose, seemingly oblivious to his/her needs or safety?	0	1	2	3	4	1	2	3	0	1	2	3

Verbal Aggression

	Absent	Frequency				Severity			Clinical Impression			
1. Is (S) verbally abusive or does he/she use lewd or threatening language?	0	1	2	3	4	1	2	3	0	1	2	3
2. Does (S) make verbal sexual advances?	0	1	2	3	4	1	2	3	0	1	2	3
3. Does (S) make frequent verbal outbursts?	0	1	2	3	4	1	2	3	0	1	2	3
4. Does (S) have a bad temper, flying "off the handle" easily over little things?	0	1	2	3	4	1	2	3	0	1	2	3
5. Is (S) argumentative and difficult to get along with?	0	1	2	3	4	1	2	3	0	1	2	3
6. Is (S) insulting to others?	0	1	2	3	4	1	2	3	0	1	2	3
7. Does (S) openly express conflict with friends, family and/or staff?	0	1	2	3	4	1	2	3	0	1	2	3
8. Is (S) overly critical of others?	0	1	2	3	4	1	2	3	0	1	2	3

Physical Aggression

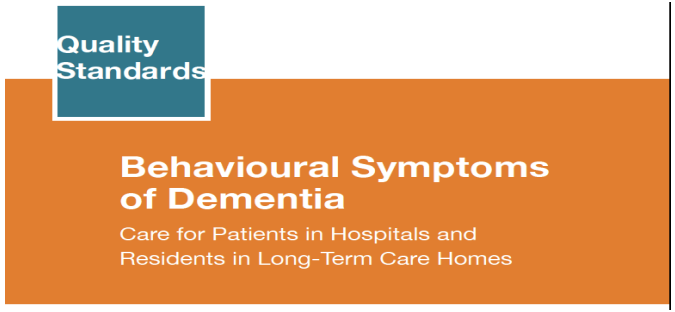
	Absent	Frequency				Severity			Clinical Impression			
1. Is (S) uncooperative or resistive to help from others?	0	1	2	3	4	1	2	3	0	1	2	3
2. Does (S) aggressively try to leave the residence or get to a different place (e.g., room)?	0	1	2	3	4	1	2	3	0	1	2	3
3. Does (S) attempt to hurt or hit others?	0	1	2	3	4	1	2	3	0	1	2	3
4. Does (S) slam doors, kick furniture, and throw things?	0	1	2	3	4	1	2	3	0	1	2	3
5. Does (S) grab, push or scratch others?	0	1	2	3	4	1	2	3	0	1	2	3
6. Is (S) intrusive, such as taking others' possessions or entering another's room inappropriately?	0	1	2	3	4	1	2	3	0	1	2	3
7. Does (S) take things from others?	0	1	2	3	4	1	2	3	0	1	2	3

Adapted from the Neuropsychiatric Inventory - Clinician ©Jeffrey L. Cummings

How do we detect emotional distress reliably and timely?

De Mauleon et al 2020

Quality Statements



- Comprehensive assessment
- Individualized plan of care
- Individualized non-pharmacological intervention
- Standards for psychotropic medication use (4 statements)
- Other: Mechanical restraints, informed consent, specialized inter-professional team, provider and caregiver training, care environment, transition in care

https://www.hqontario.ca/Blog/tag/agitation

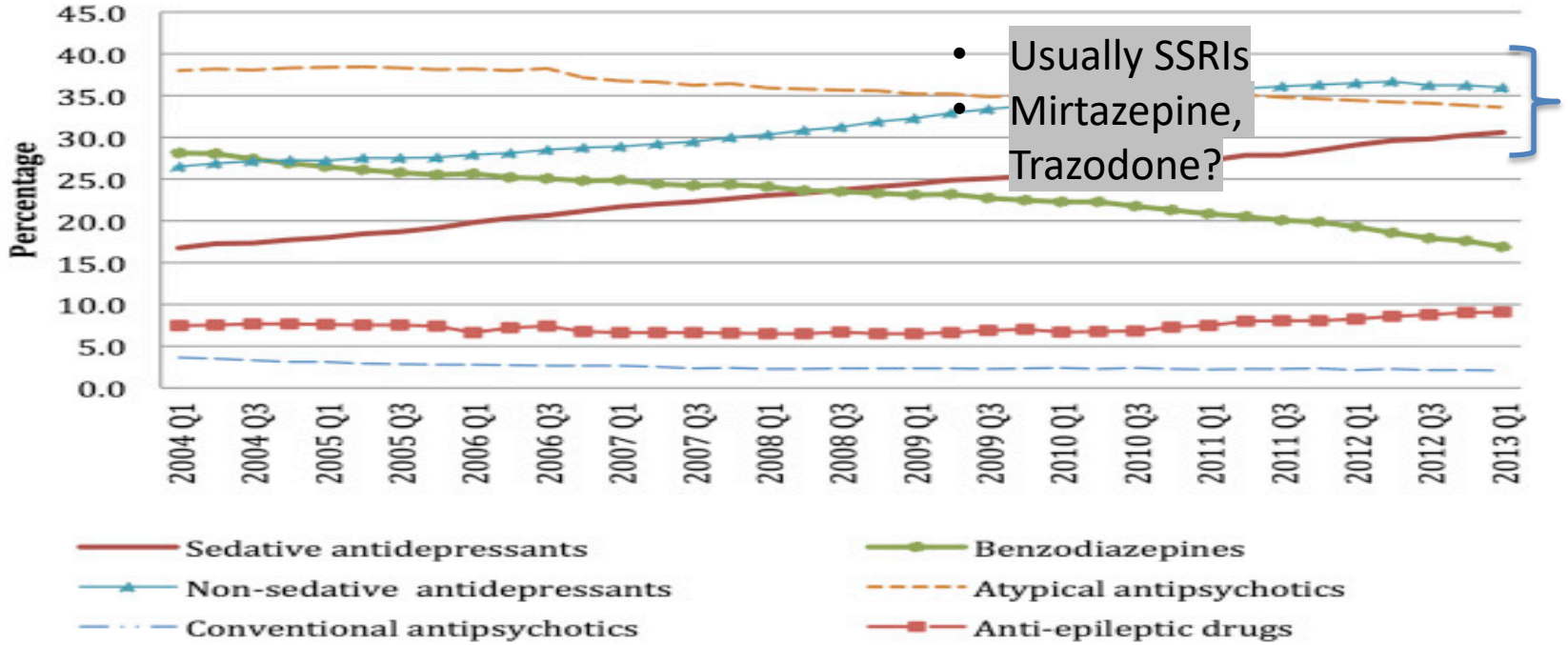
Non-Pharmacological Interventions

- Patient-Centered Care framework
- Music therapy (white noise and individualized music)
- Doll therapy (need to consider the individual's history)
- Activity-based interventions to counter boredom (live socialization)
- Sensory interventions (e.g. aromatherapy, bright light, fresh air, rocking chairs)
- Evolving technology based interventions (e.g. VR)

Pharmacological Interventions

- Antipsychotics
- Antidepressants: SSRIs and Trazodone
- Anticonvulsants
- Benzodiazepines
- Other emerging therapies

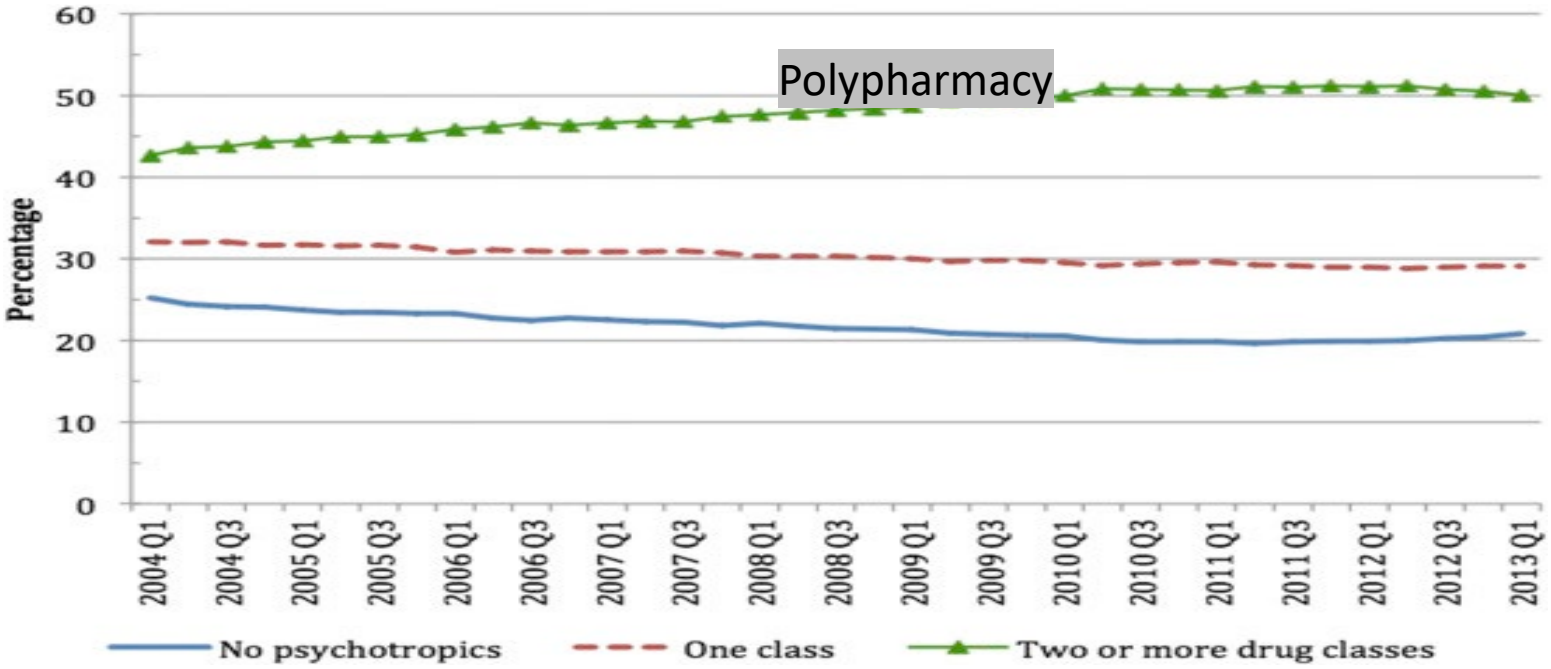
Psychotropic Medications Use in LTC!



- Usually SSRIs
- Mirtazepine, Trazodone?

Vasudev et al (Burhan) 2015

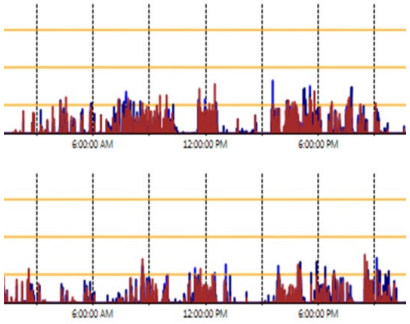
Psychotropic Medications Use in LTC!



Vasudev et al (Burhan) 2015

ACTIGRAPHY MEASURE OF AGITATION

Wrist-mounted wGT3x+ activity monitor (Actigraph, Pensacola, FL ®)



ActiLife accelerometer data output

- There is evidence that actigraphy has the potential to be a feasible measure to detect and monitor agitation in dementia
- A study by Nagels et al was published 2006-2007 that suggested utility of actigraphy and correlation with nurses observation
- We wanted to follow-up and evaluate the utility of actigraphy in detecting agitation in institutionalized setting

Khan et al 2018, Nagels et al 2006 and 2007

STUDY 1: KINGSTON ONTARIO

- We reported on a cohort-observational study of actigraphy and agitation measures in a cohort of LTC and tertiary care hospital centre in Kingston Ontario Canada.
- 20 participants with AD, 16 males, average age 74.3, average MMSE 11.6, average total CMAI 46.7
- High agitation and low agitation groups (CMAI below or above 50)
- We found significant difference in actigraphy pattern between high and low agitation groups
- Most actigraphy measures significantly correlated with CMAI and NPI, but not physically aggressive behavior

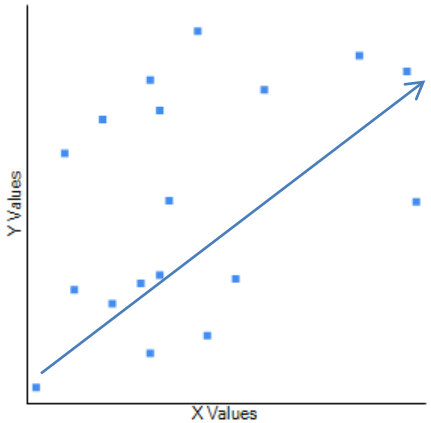
Knuff….(Burhan) et al AJGP 2019

EXTENSION STUDY: LONDON ONTARIO

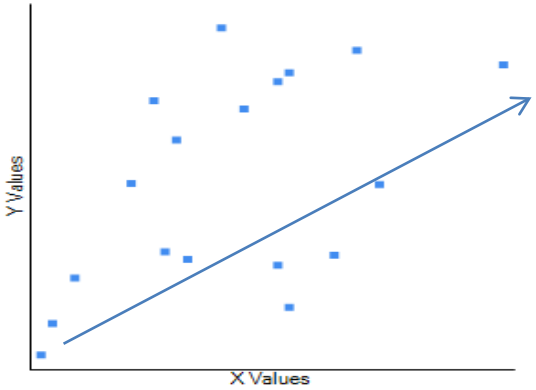
- We conducted a second study, similar design in London Ontario, Canada
- 20 patients with AD+, average age 81, average MMSE 6.3, NH unit and hospital dementia unit.
- Actigraphy was tolerated with at least 36 hours of recording, lost 2 devices (patients not included)
- Significant moderate correlation between actigraphy measure of motor activity and total CMAI, specifically physical non-aggressive behavior

Burhan, Knuff, and Seitz Alzheimer & Dementia 2020

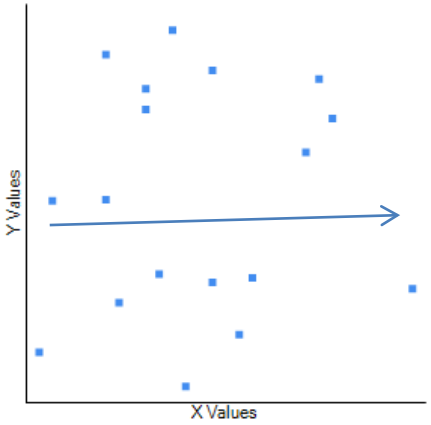
CORRELATION BETWEEN ACTIGRAPHY AND CMAI CLINICIAN RATING



24-hour actigraphy correlation with **physical** agitation: *r*(18)=49, *p*=.03



24-hour actigraphy correlation with **total** CMAI: *r*(18)=51, *p*=.02



24-hour actigraphy correlation with **verbal** agitation: *r*(18)=.06, *p*= ns

Role of Multi-Sensory Devices?

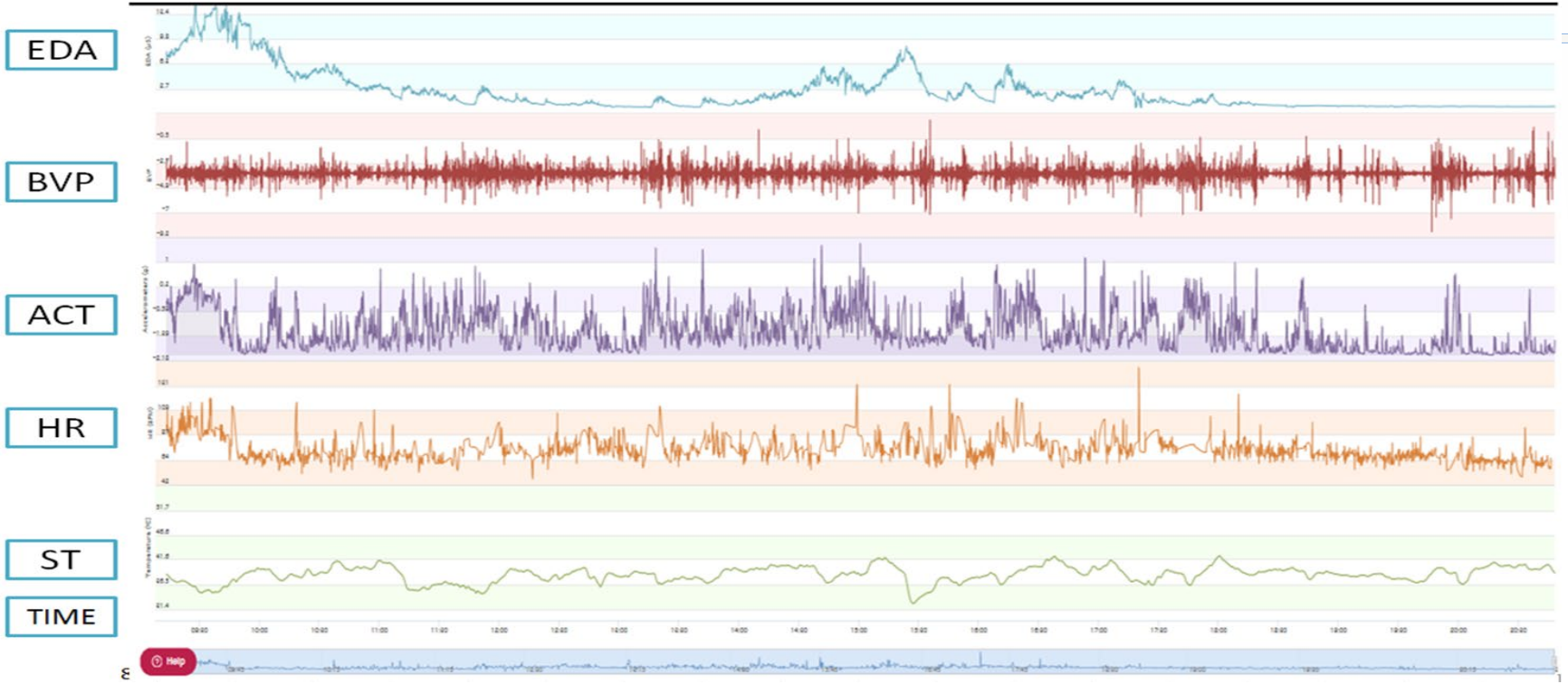
- Observational study (parallel with ongoing clinical trial)
- Six patients with severe Dementia and frequent Agitation episodes
- Wristband Empatica4 for

  EDA, BVP, ACT, HR, ST
- Research team

  (clinicians, researchers,

  AI expert)

Physiological parameters

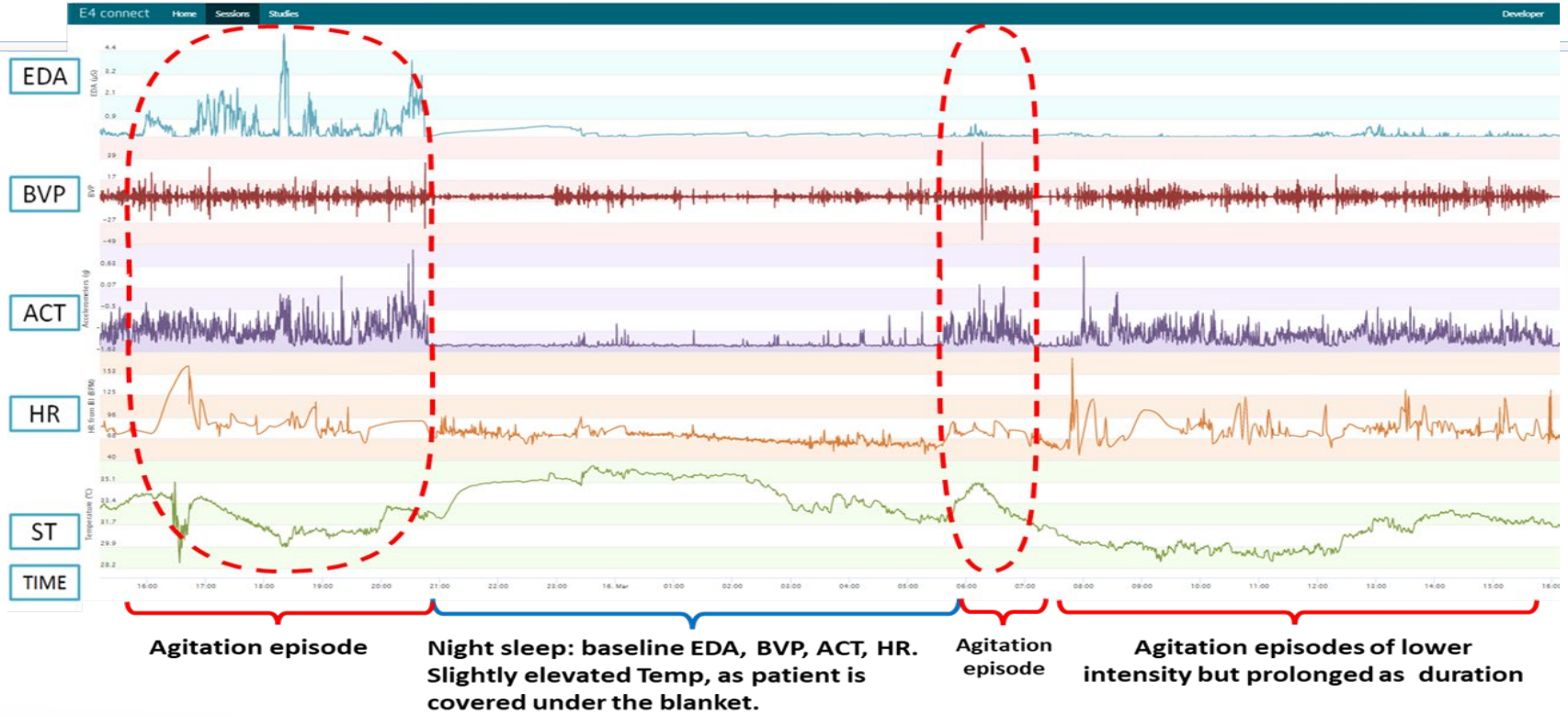


Graphical representation of physiological paramenters upon uploading them from the E4 on the designated laptop (EDA – electroderamal activity; BVP – blood volume pressure – the raw data for calculation of Heart Rate Variability; ACT – actigraphy, HR – heart rate/ pulse; ST – skin temperature, TIME – real time).

Observational chronological notes

WEEK: 1 (REC 1 of 1) DATE: 15-03-21	26 HOURS CLOCK	DATE	TIME	PLACE	SLEEP/ AWAKE	BVC SCORE	DOS	PRN (0 - no; 1 - yes)	ACTIVITY/ INTERVENTION/ ASSESMENT	PAINAD SCORE
Recording hrs: 26	1	15/03/2021	3:00 PM	Day Area	Awake		Calm	0		
Time: 2:55' pm	2	15/03/2021	4:00 PM	Day Area	Awake		Irritable	0	Restless/pacing	3
PARTICIPANT: XX	3	15/03/2021	5:00 PM	Day Area	Awake	4	Irritable	0	Restless/pacing	
*BVC: BROSET VIOLENCE CHECKLIST	4	15/03/2021	6:00 PM	Day Area	Awake		Irritable	0	Patient ambulating in day area, vocalizing loudly and gesticulating at a co-patient.	
	5	15/03/2021	7:00 PM	Day Area	Awake		Irritable	0		
	6	15/03/2021	8:00 PM	Day Area	Awake		Irritable	0		
	7	15/03/2021	9:00 PM	Day Area	Awake		Irritable	1		
	8	15/03/2021	10:00 PM	Bedroom	Awake	1	Calm	0		
	9	15/03/2021	11:00 PM	Bedroom	Sleeping			0		
	10	16/03/2021	12:00 AM	Bedroom	Sleeping			0		
	11	16/03/2021	1:00 AM	Bedroom	Sleeping			0		
	12	16/03/2021	2:00 AM	Bedroom	Sleeping			0		
	13	16/03/2021	3:00 AM	Bedroom	Sleeping			0		
	14	16/03/2021	4:00 AM	Bedroom	Sleeping			0		
	15	16/03/2021	5:00 AM	Bedroom	Sleeping			0		
	16	16/03/2021	6:00 AM	Bedroom	Awake		Irritable	0	Restless/pacing	
	17	16/03/2021	7:00 AM	TV Lounge	Awake		Calm	0		
	18	16/03/2021	8:00 AM	TV Lounge	Awake			0		
	19	16/03/2021	9:00 AM	Day Area	Awake		Irritable	0		
	20	16/03/2021	10:00 AM	Day Area	Awake		Irritable	0	Participating in activities	
	21	16/03/2021	11:00 AM	Day Area	Awake		Calm	0		
	22	16/03/2021	12:00 PM	Day Area	Awake		Calm	0		
	23	16/03/2021	1:00 PM	Day Area	Awake		Calm	0		
	24	16/03/2021	2:00 PM	Day Area	Awake		Irritable	0	Restless/pacing, Calling out for somebody (first name stated)	
	25	16/03/2021	3:00 PM	Day Area	Awake		Irritable	0	Restless/pacing	
	26	16/03/2021	4:00 PM	Day Area	Awake		Irritable	0	Restless/pacing	

Agitation recorded by Empatica4 (and



Example of data analysis:

1. Does average Heart Rate correlate with irritability?

2 Variables:	STATE_1 HR_VALUE

Simple Statistics

Variable	N	Mean	Std Dev	Sum	Minimum	Maximum
STATE_1	1735627	0.03306	0.17880	57385	0	1.00000
HR_VALUE	1735627	78.34838	19.16718	135983564	43.80000	209.37000

Pearson Correlation Coefficients, N = 1735627
Prob > |r| under H0: Rho=0

	STATE_1	HR_VALUE
STATE_1	1.00000	0.06228 <.0001
HR_VALUE	0.06228 <.0001	1.00000

STATE_1 = {('Irritable'=1), ('Calm' = 0)};

❖ Strong correlation between Average Heart Rate and Irritability

Probability modeled is STATE_1=1.

Model Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	504143.49	498701.78
SC	504155.86	498726.51
-2 Log L	504141.49	498697.78

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	5443.7139	1	<.0001
Score	6731.9161	1	<.0001
Wald	6557.2566	1	<.0001

Analysis of Maximum Likelihood Estimates

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-4.4610	0.0146	93750.0723	<.0001
HR_VALUE	1	0.0134	0.000165	6557.2566	<.0001

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	
HR_VALUE	1.013	1.013	1.014

❖ A unit increase on Average HR increases the likelihood of irritability

2. Does average increase in heart rate and irritability correlate with clinically recorded Aggression?

STATE_1 = {('Irritable'=1), ('Calm' = 0)};
TYPE_OF_AGRESSION_1 = { ('Physical', 'Verbal') = 1, else 0}

Response Profile		
Ordered Value	TYPE_OF_AGRESSION_1	Total Frequency
1	1	115200
2	0	1620427

Probability modeled is TYPE_OF_AGRESSION_1=1.

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Analysis of Maximum Likelihood Estimates					
Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-0.6934	0.0180	1476.3996	<.0001
STATE_1	1	3.5032	0.00987	126006.988	<.0001
HR_VALUE	1	-0.0304	0.000247	15199.3736	<.0001

Odds Ratio Estimates			
Effect	Point Estimate	95% Wald Confidence Limits	
STATE_1	33.223	32.586	33.872
HR_VALUE	0.970	0.970	0.971

Model Fit Statistics		
Criterion	Intercept Only	Intercept and Covariates
AIC	847530.19	718276.37
SC	847542.56	718313.48
-2 Log L	847528.19	718270.37

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	129257.818	2	<.0001
Score	252592.284	2	<.0001
Wald	127053.284	2	<.0001

❖ **Strong indication that a unit decrease in average heart rate and state of irritability have an impact on aggression**

Where Does this Leaves Us?

- The physiological signature of emotional distress that may predict irritability (emotional distress?) and aggression is promising, but needs further validation as a biomarker to make it useable at point of care

- Wearable multi-sensors to monitor patients with severe dementia and frequent agitation episodes in tertiary care settings are **feasible** but needs further refinement

- Possible use of camera synchronized with multi-sensory device to improve **"time-stamp"** for behavioral episodes

Collaboration with Ontario Tech Scientists

Dr. Khalid Elgazzar

– Canada Research Chair in the Internet of Things, Associate Professor, Ontario Tech University

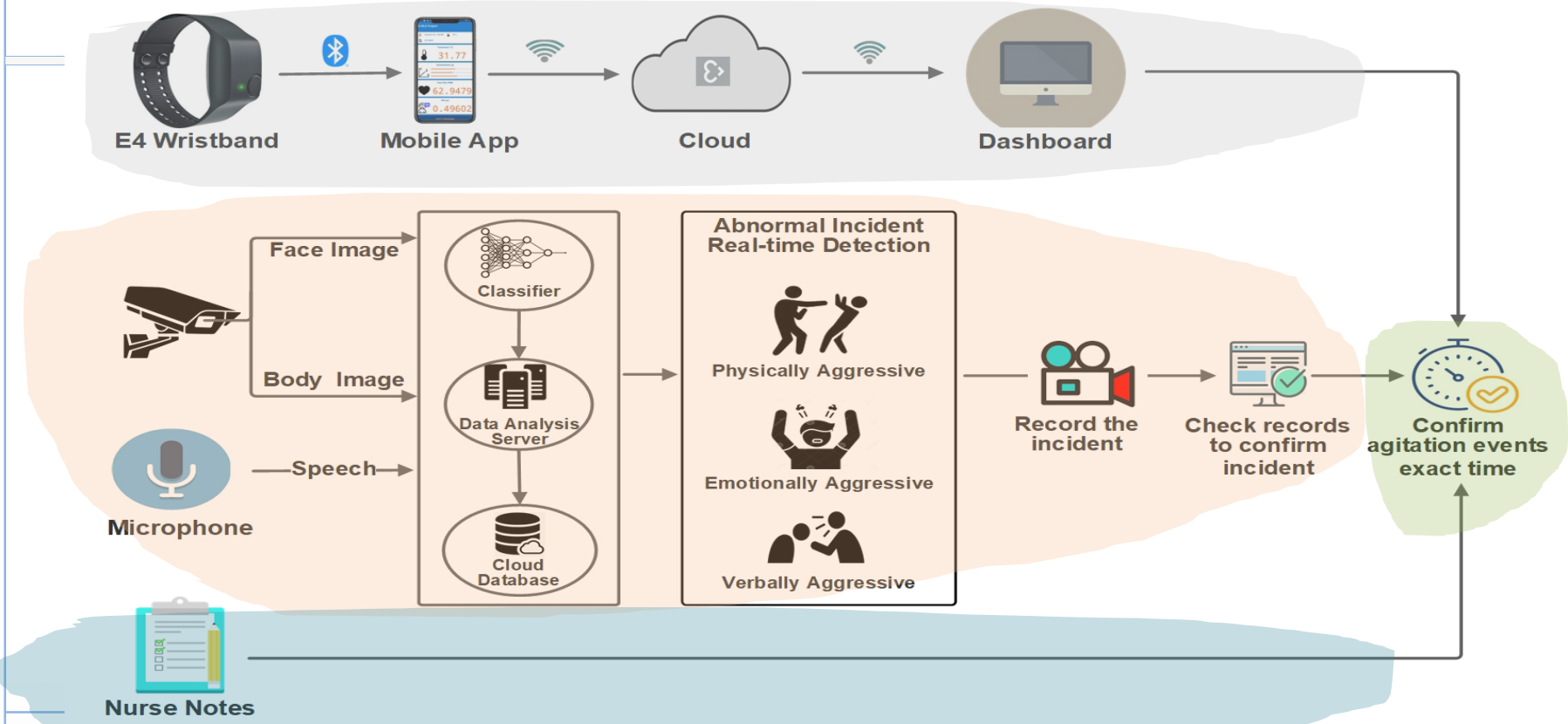
Will present on the next chapter of this work!

Agitation: From Detection to Perdition

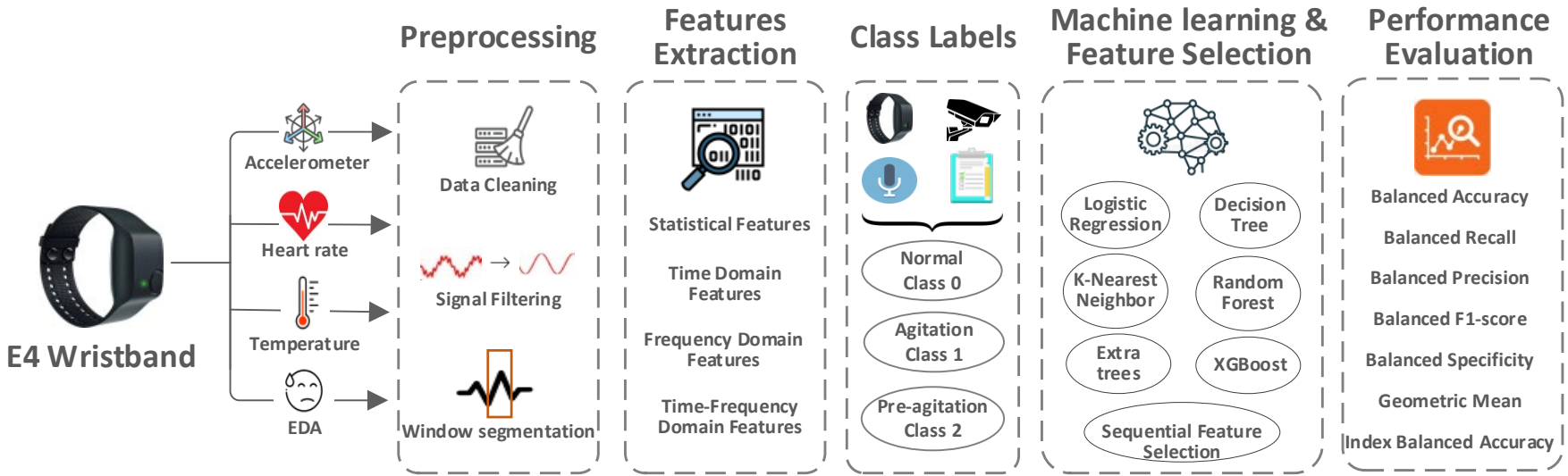
- We were able to **detect** agitation but not **predict** it
- Wearable devices are a source of agitation to some patients
- Clinical staff are not around the patients 24/7

Taking Agitation Detection to the Next Step

Using Audio and Video to Make Better Detection



Physiological Markers Classification



Testing Machine Learning Techniques

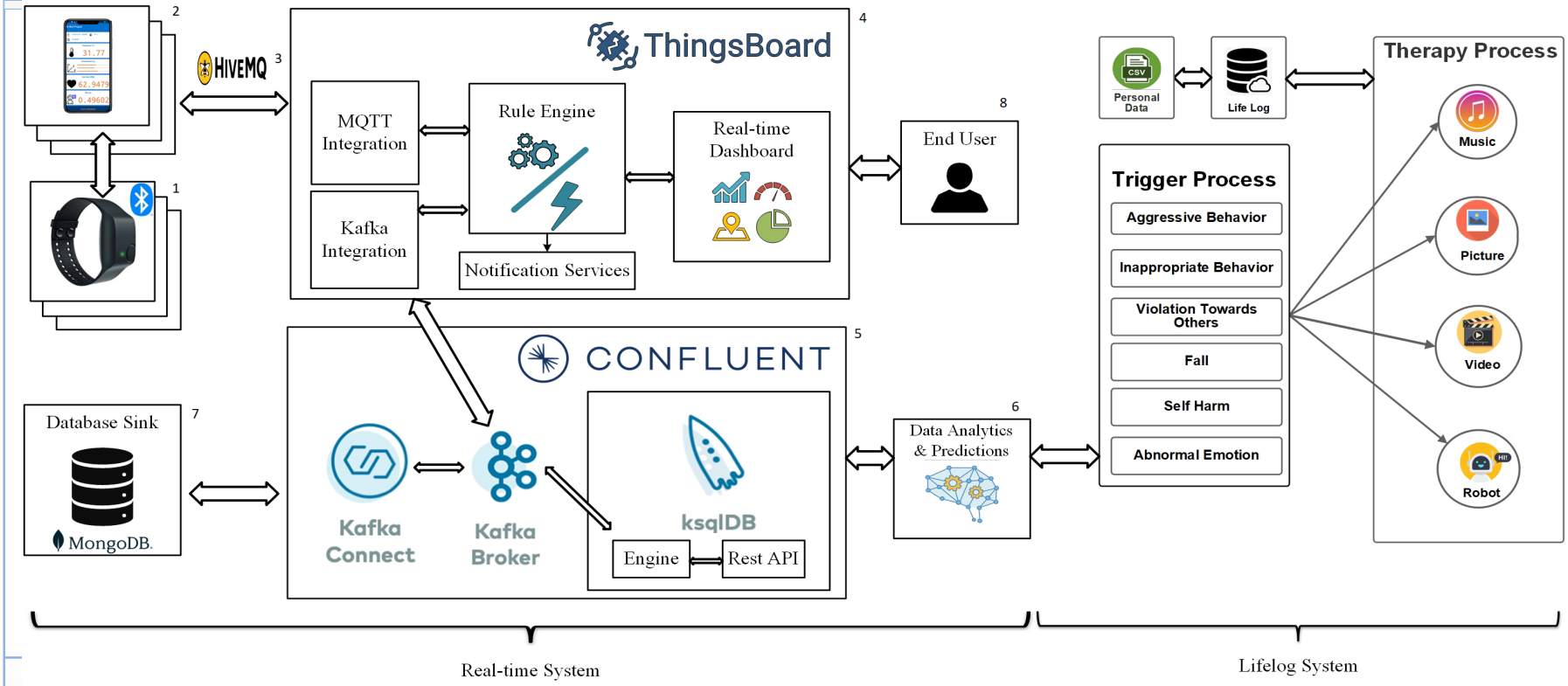
Classification model	Balanced accuracy
Logistic Regression Classifier	80.803 %
Decision Tree Classifier	63.839 %
K-Neighbors Classifier	80.103 %
Random Forest Classifier	90.657 %
XGB Classifier	95.479 %
Extra Trees Classifier	87.822 %

Processing More Patients

Classification model/ performance evaluation	Balanced Accuracy	Balanced Precision	Balanced Recall	Balanced Specificity	Balanced F1-score	Geometric Mean	Index Balanced Accuracy
Random Forest Classifier	92.63 %	98.69 %	98.70 %	88.56 %	98.67 %	93.43 %	88.17 %
XGB Classifier	94.13 %	98.78 %	98.79 %	90.36 %	98.77 %	94.43 %	89.93 %
Extra Trees Classifier	94.15 %	98.85 %	98.85 %	89.47 %	98.82 %	93.99 %	89.16 %

From Prediction to Intervention

Personalized Non-pharmacological Interventions



Wait for next update!

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- Patients and families
- Ontario Shores clinical teams on GDU and GTU
- Dr. Abeer Badawi
- Dr. Samira Choudhury
- Dr. Aurelia Soltan, MD, MPH, PhD
- Mervin Blair, PhD, C. Psych
- StaN study team

Fondation Brain Canada Foundation

CENTRE FOR AGING + BRAIN HEALTH INNOVATION

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Discussion!