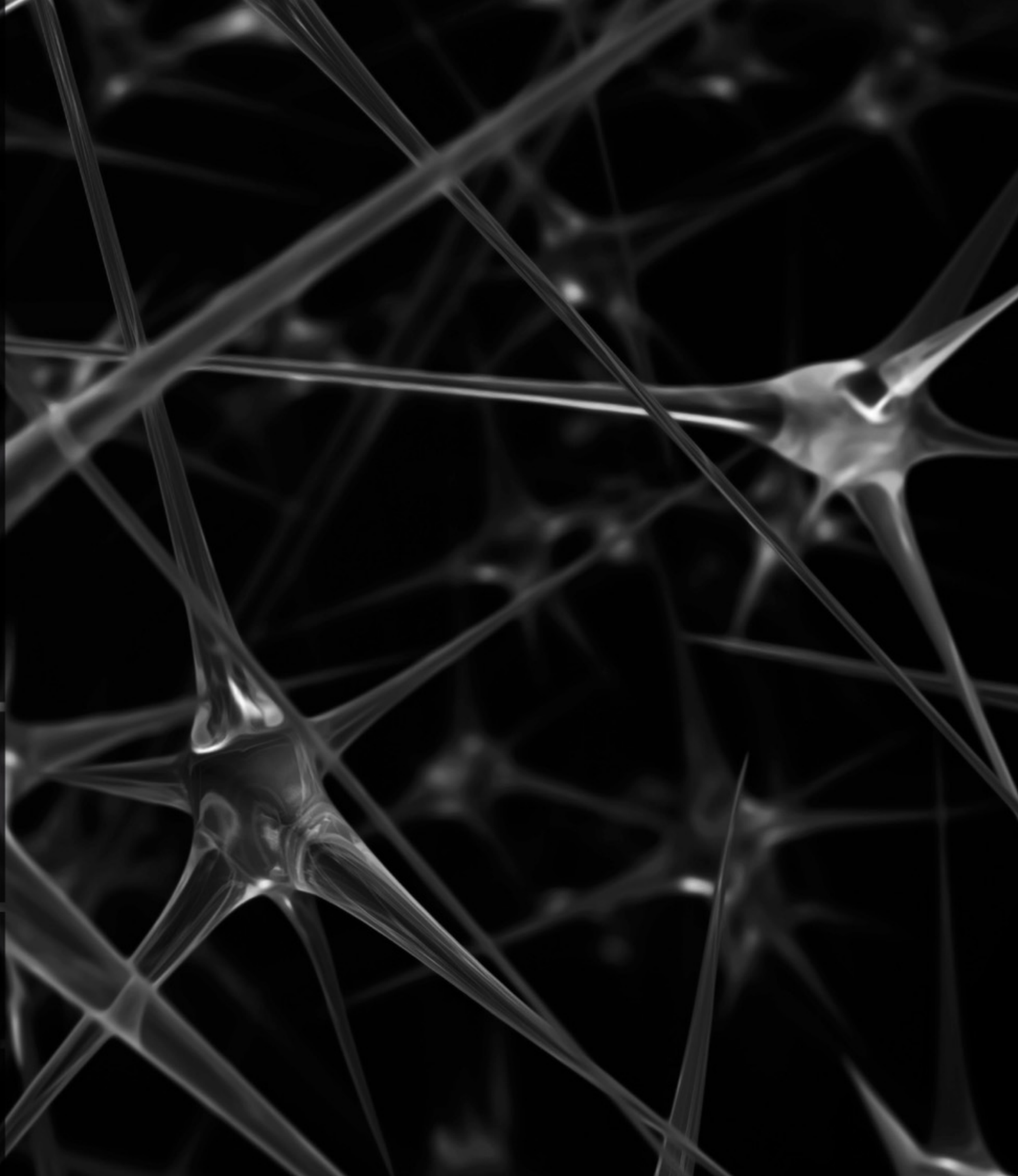
Starlab Neuroscience

Usage of Machine Learning in Brain Health

Aureli Soria-Frisch (PhD)

Director of Neuroscience BU

Starlab
Living Science



Outline

- Starlab, company context
- Overview: Machine Learning in Health applications
- Parkinsons' Decision Support System
- ADHD Digital Phenotypes
- Machine Learning for Consciousness Research
- Take home messages

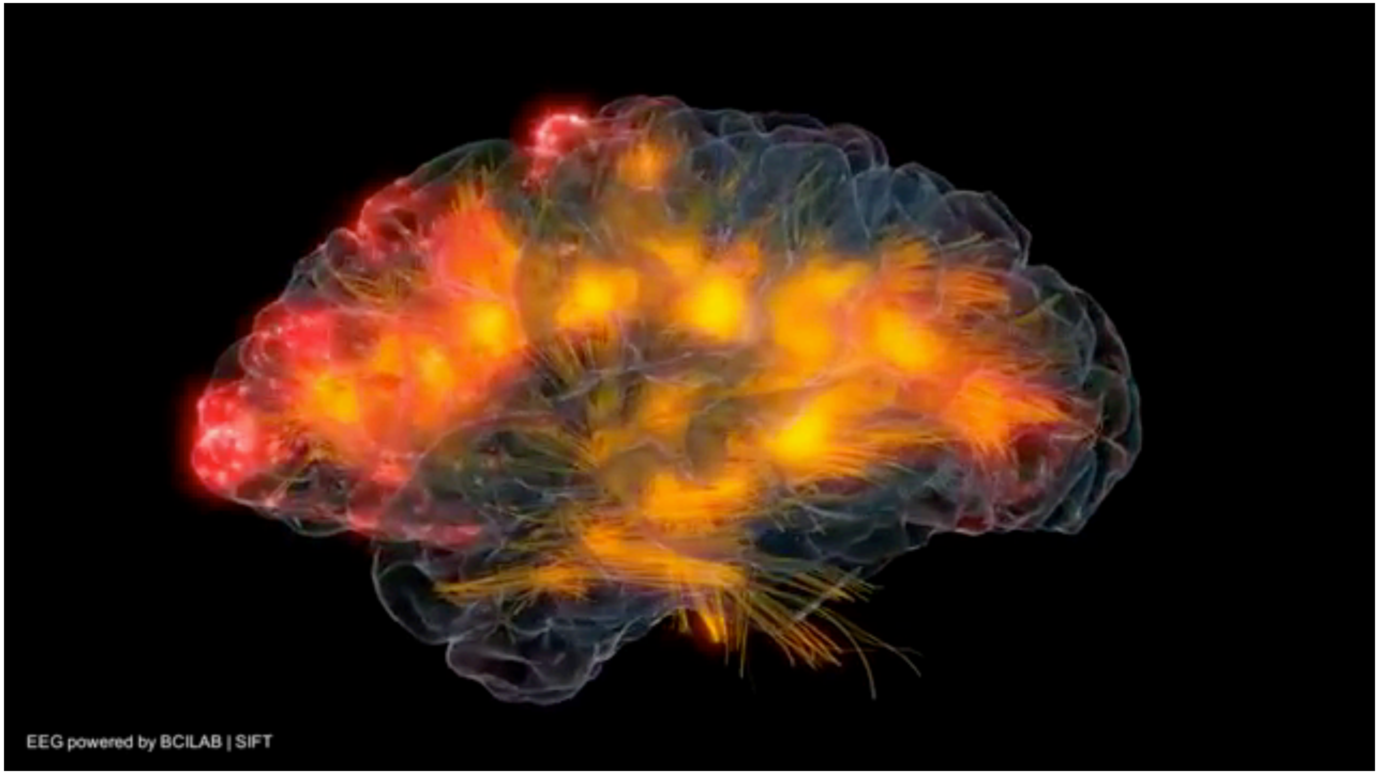
Starlab – Company Context

A private R&D company based in Barcelona (since 2000)

Transforming **Science** into **Technologies**

Developing new products and services with profound and **positive social impact**

The Electrical Brain



Neuroscape, UCSF ©
Mishra J., Gazzaley A., 2015
Trends in Cognitive Sciences

The need - subjective evaluation symptoms

BRAIN HEALTH

YOUR NEIGHBOR WITH EPILEPSY

(50M PATIENTS WORLDWIDE)

YOUR GRANDMA WITH ALZHEIMER'S

(90M PATIENTS WORLDWIDE)

YOUR FRIEND WITH DEPRESSION

(240M PATIENTS WORLDWIDE)

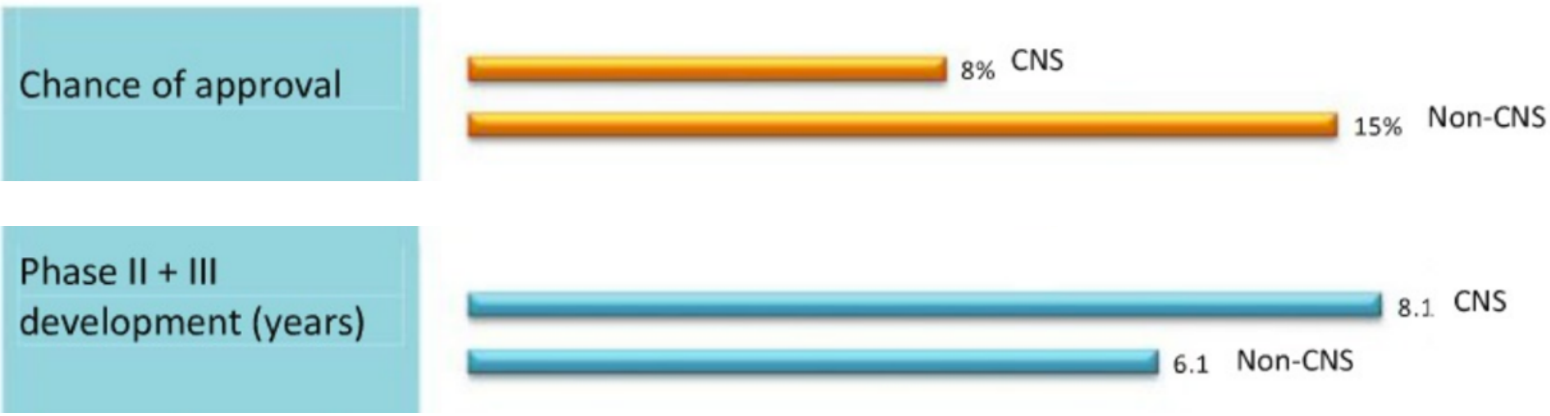
YOUR DAD WITH PARKINSONS

(5M PATIENTS WORLDWIDE)

@aurelisofr

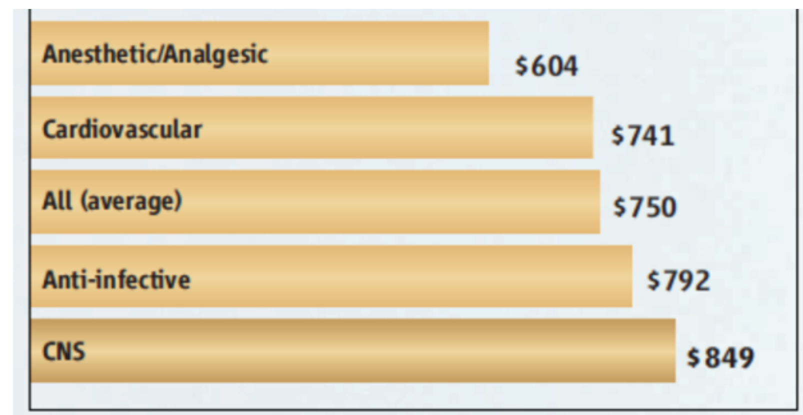
20% WORLD POPULATION

The need - CNS drug development costs



Source: Tufts Center for the Study of Drug Development, 2012

CNS HIGH RISK



Capitalized clinical development costs (in millions)

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Starlab - Research Program

AIMS•2•TRIALS

DIGITAL HEALTH

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

INNO BRAIN

NE neuroelectrics®

biomarker discovery

STIPED
Studying Consciousness in the electrical brain

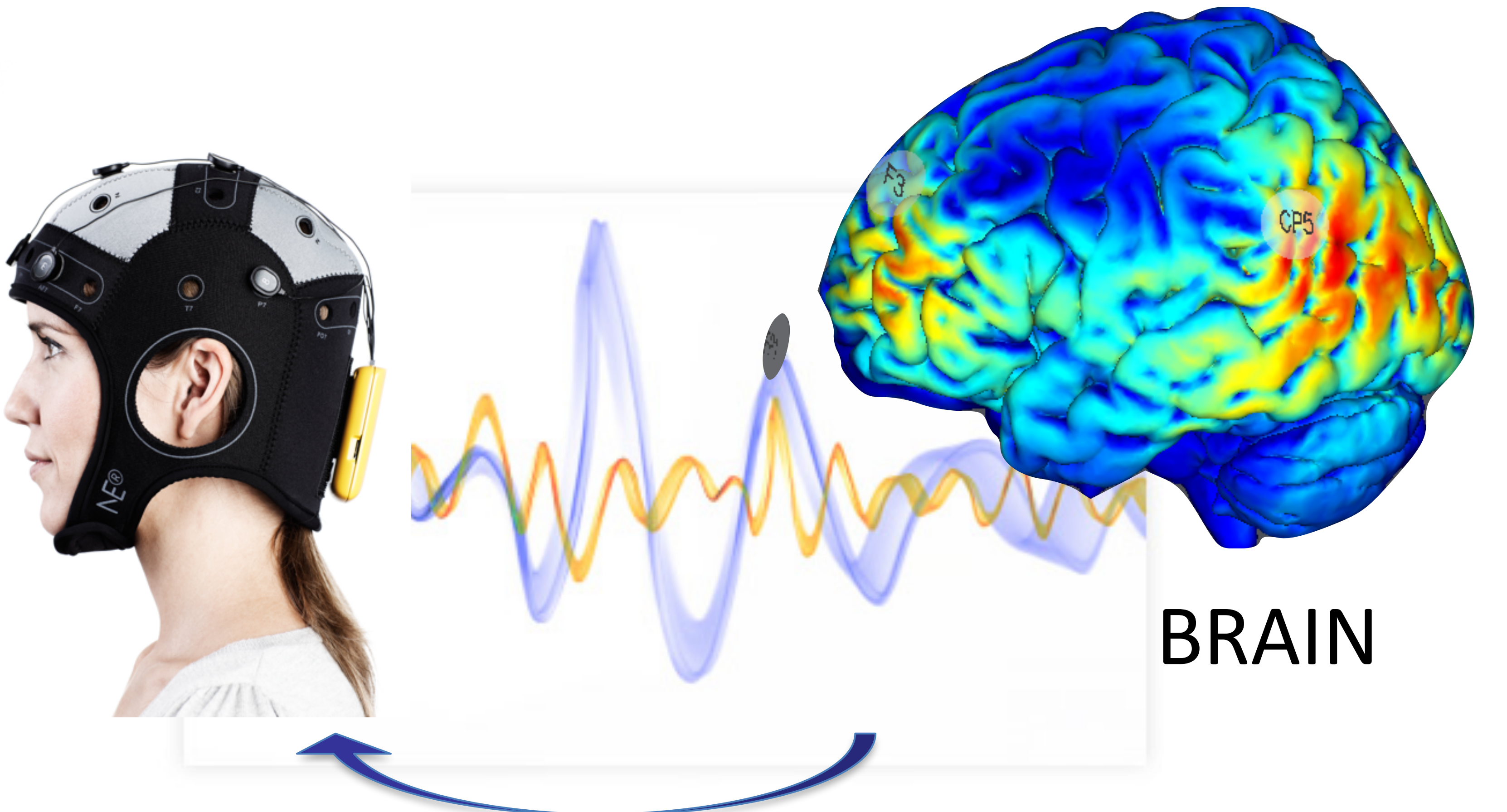
Starlab®

luminous

brain stimulation

hiVE
HYPER INTERACTION VIABILITY EXPERIMENTS

Starlab - Research Program on Biomarkers



Recording Electrical Activity

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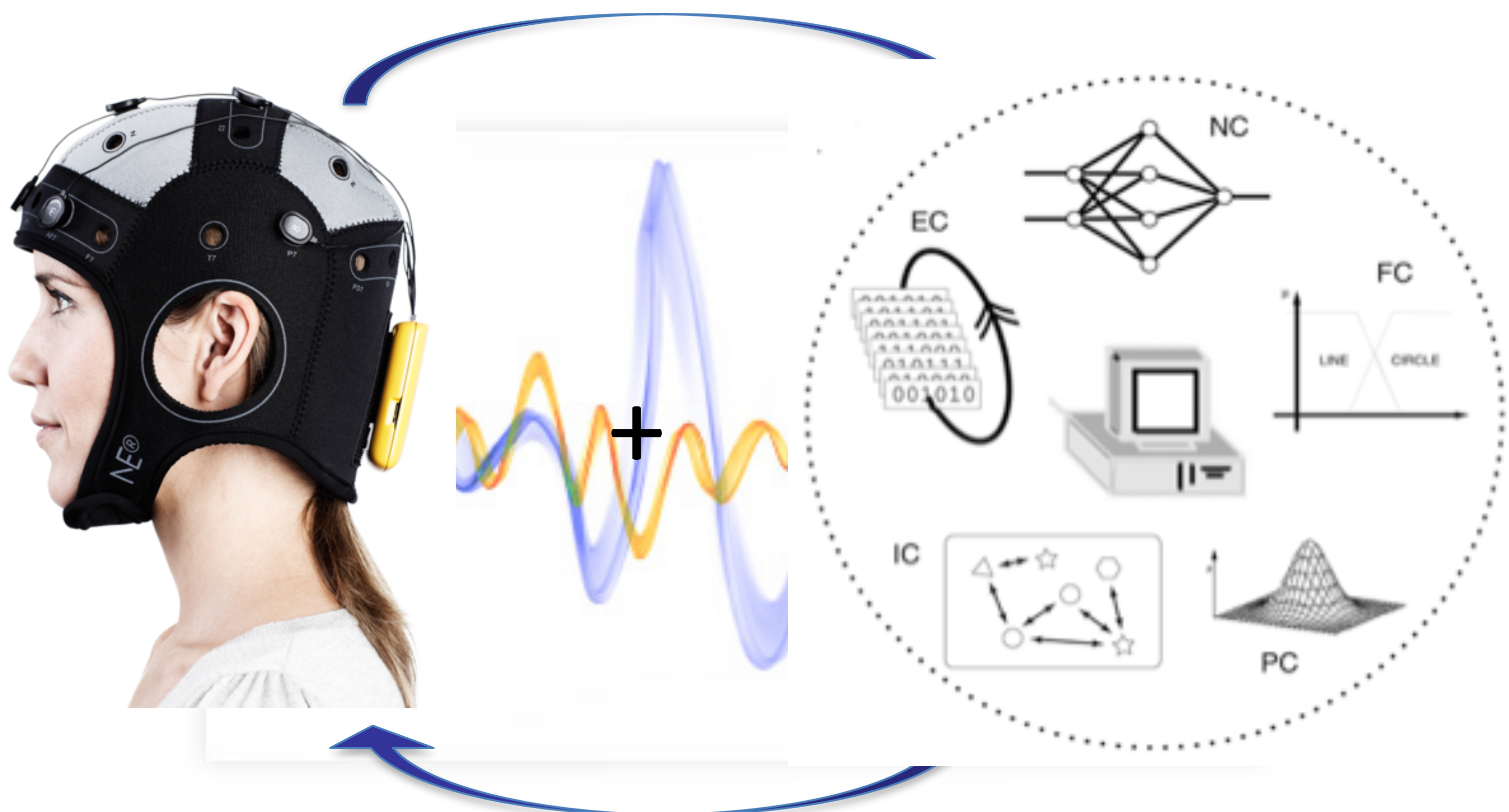
Starlab - Research Program on Biomarkers



EEG

Machine Learning

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Machine Learning in Health applications

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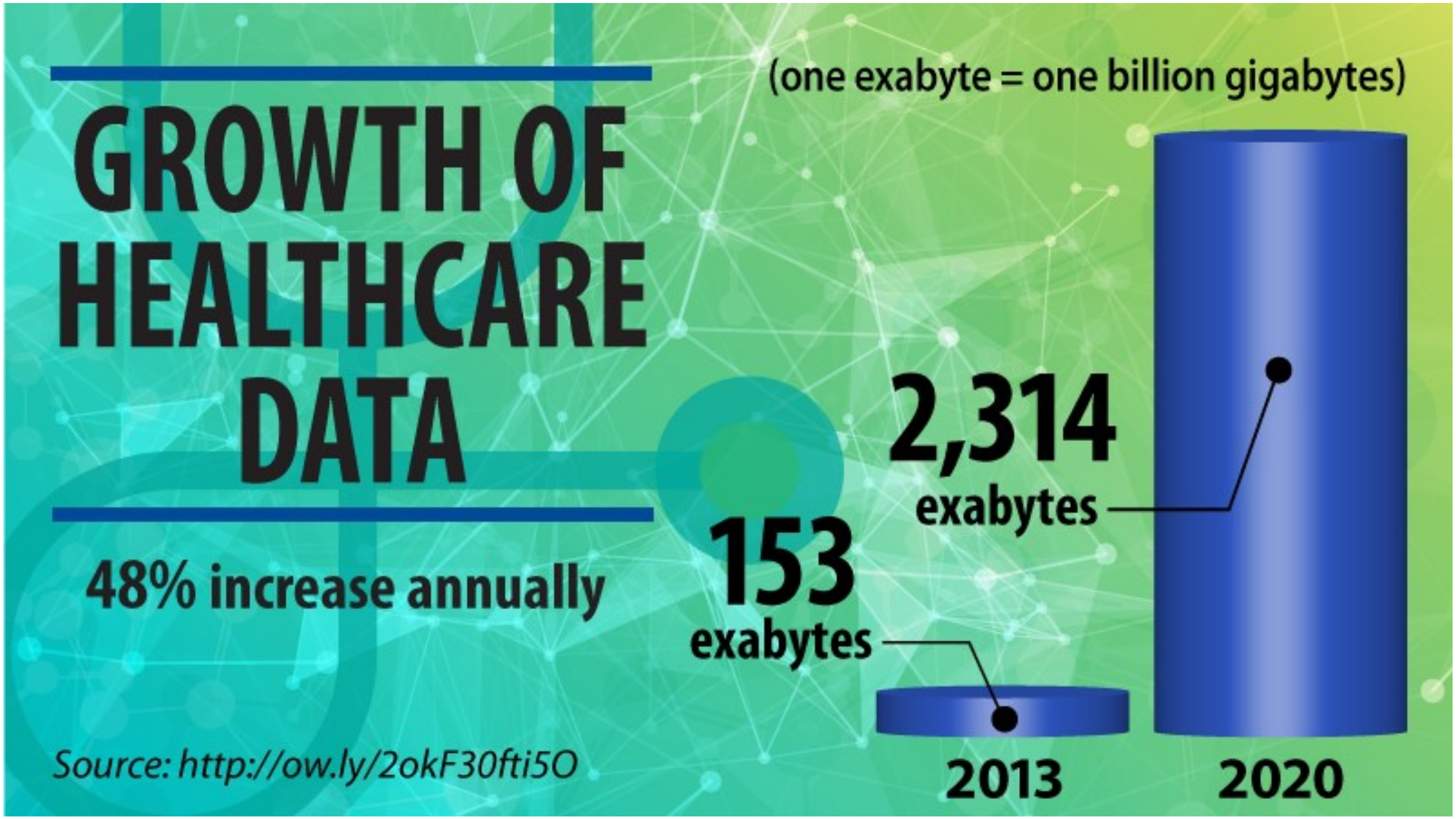
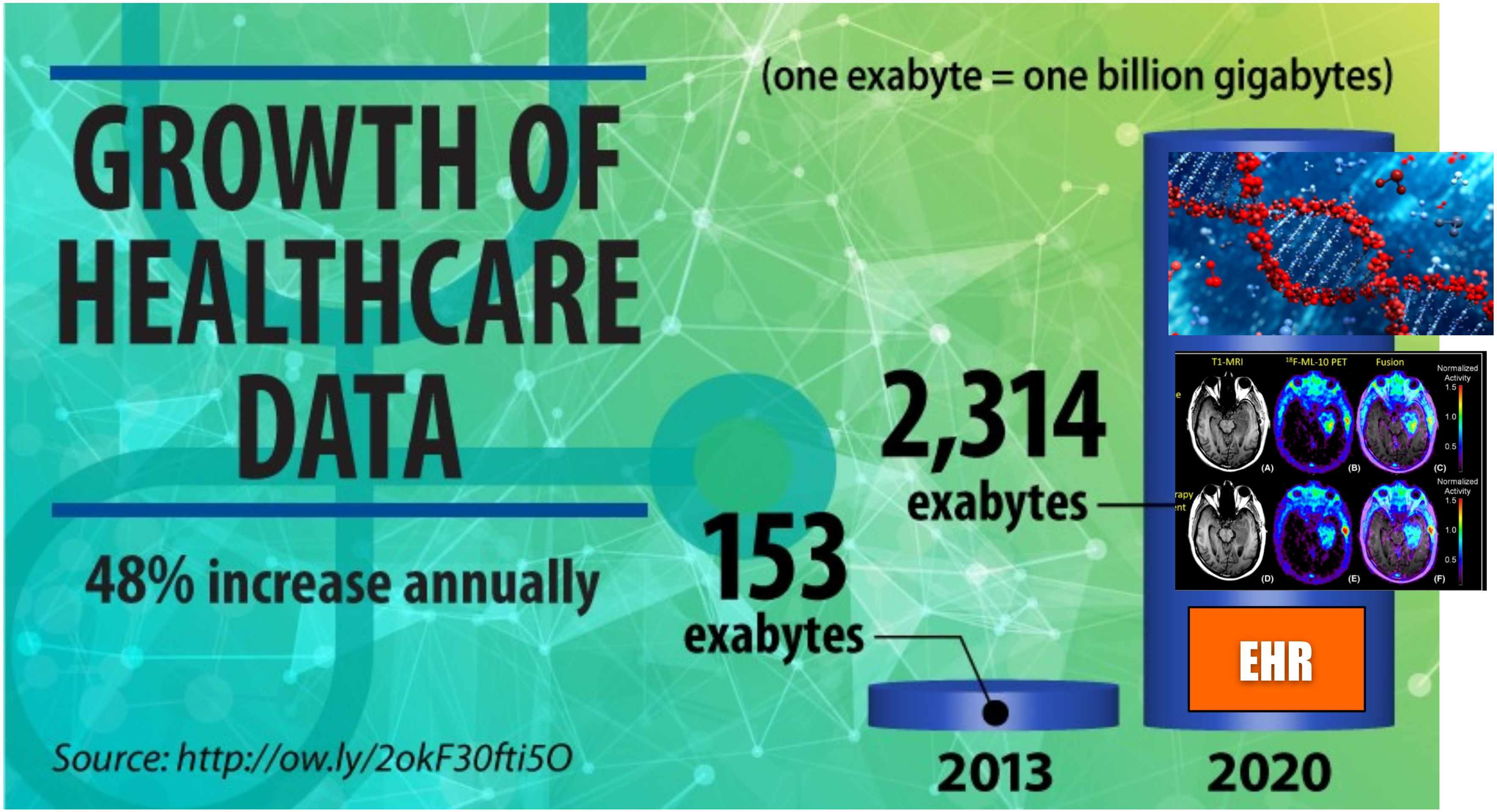
Health Industry



Health Industry



Roadmap Health Industry

FROST & SULLIVAN

About **80%** Healthcare Industry Participant believe 4 technologies namely **AI, Big Data Analytics, mHealth and Wearables** will be a game changer during 2019.

WHAT DOES IT MEAN FOR YOU?

AI for Healthcare IT application market to cross 1.7 billion by end of 2019 and projected to achieve a 68.5% CAGR from 2018-2022

AI IN HEALTHCARE

During 2019, more number of specialty-specific analytics solutions will gain prominence among providers. The healthcare data analytics market will cross $68 billion by 2020.

HEALTHCARE DATA ANALYTICS

During 2019, digital health technologies catering to out-of-hospital settings will grow by 30% to cross $25bn market globally. Key segments include RPM devices, Telehealth platforms, PERS, and mHealth.

DIGITAL HEALTH FOR OUT-OF-HOSPITAL SETTINGS

Access Actionable Intelligence

- AI Health IT Market and Growth Opportunities, Forecast to 2022
- AI for Medical Image Analysis- Companies-to-Action, 2018
- US Healthcare Data Analytics Market, Forecast to 2020
- Global Healthcare Data Analytics Companies-To-Action, 2017
- Vision 2025—Healthcare in the Smart Home
- Key Trends in Digital Health, Asia-Pacific, 2018
- Growth Opportunities in the US Telehealth Market, Forecast to 2021

Survey Question – Tell us ONE key technology, you believe, will have the most profound impact on the Healthcare industry during 2019?
Source: Frost & Sullivan Survey – Oct 2018 (n=244)

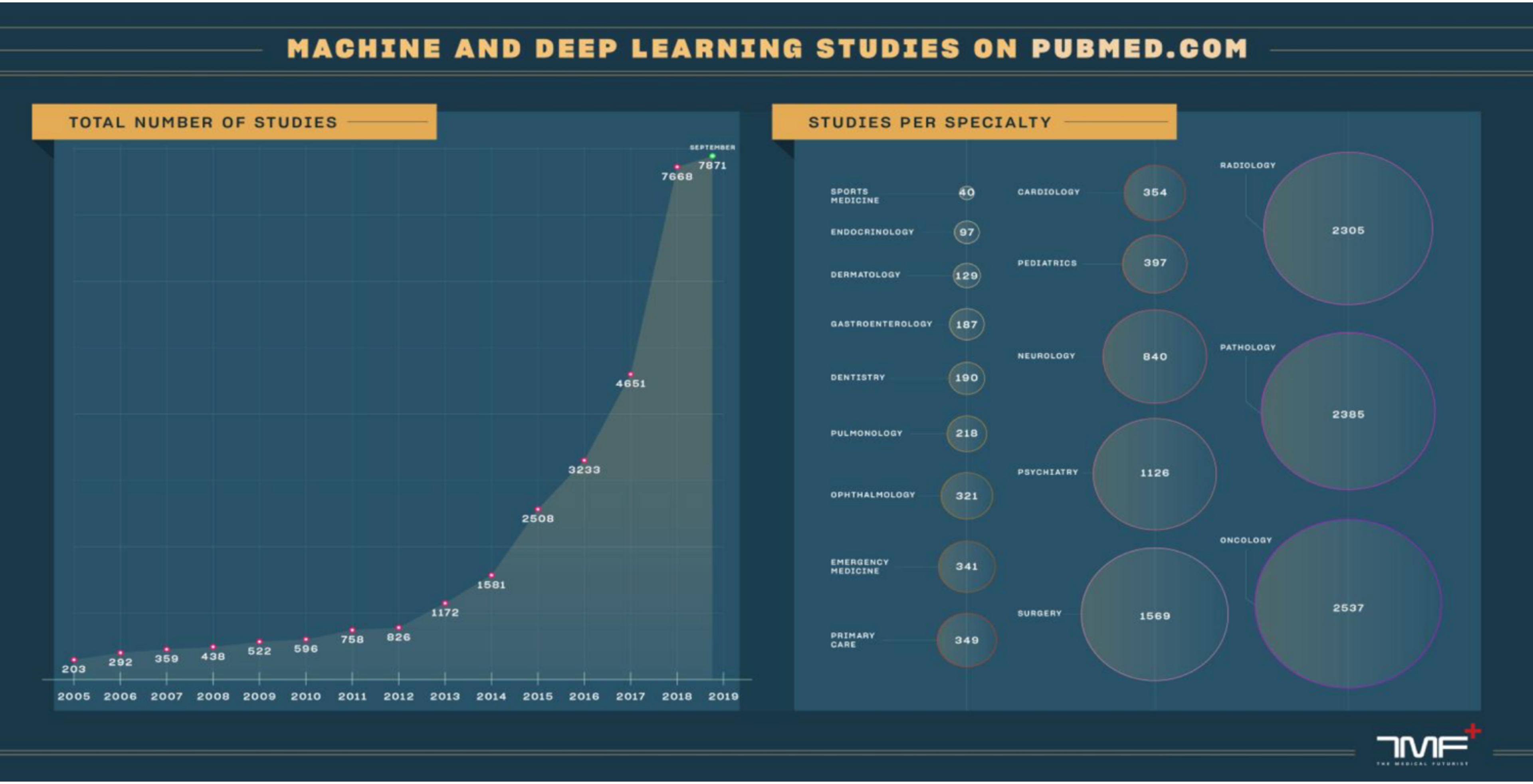
7

Throughout 2019, AI and machine learning will further evolve human and machine interaction. More specifically, AI will begin to see fruition, particularly in the imaging diagnostic, drug discovery, and risk analytics applications.

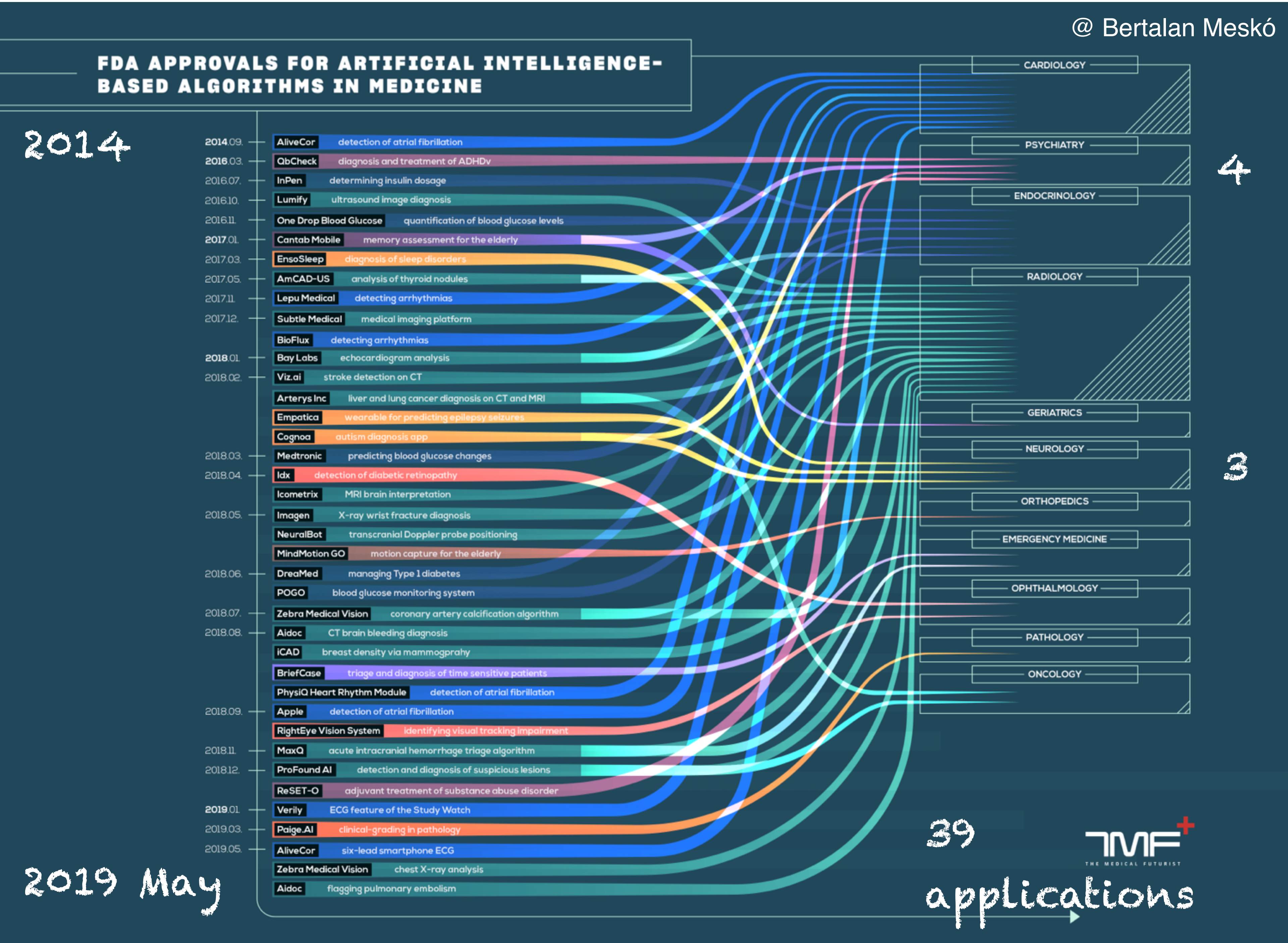
https://www.forbes.com/sites/reenitadas/2018/11/13/top-8-healthcare-predictions-for-2019/#

Health AI Publications

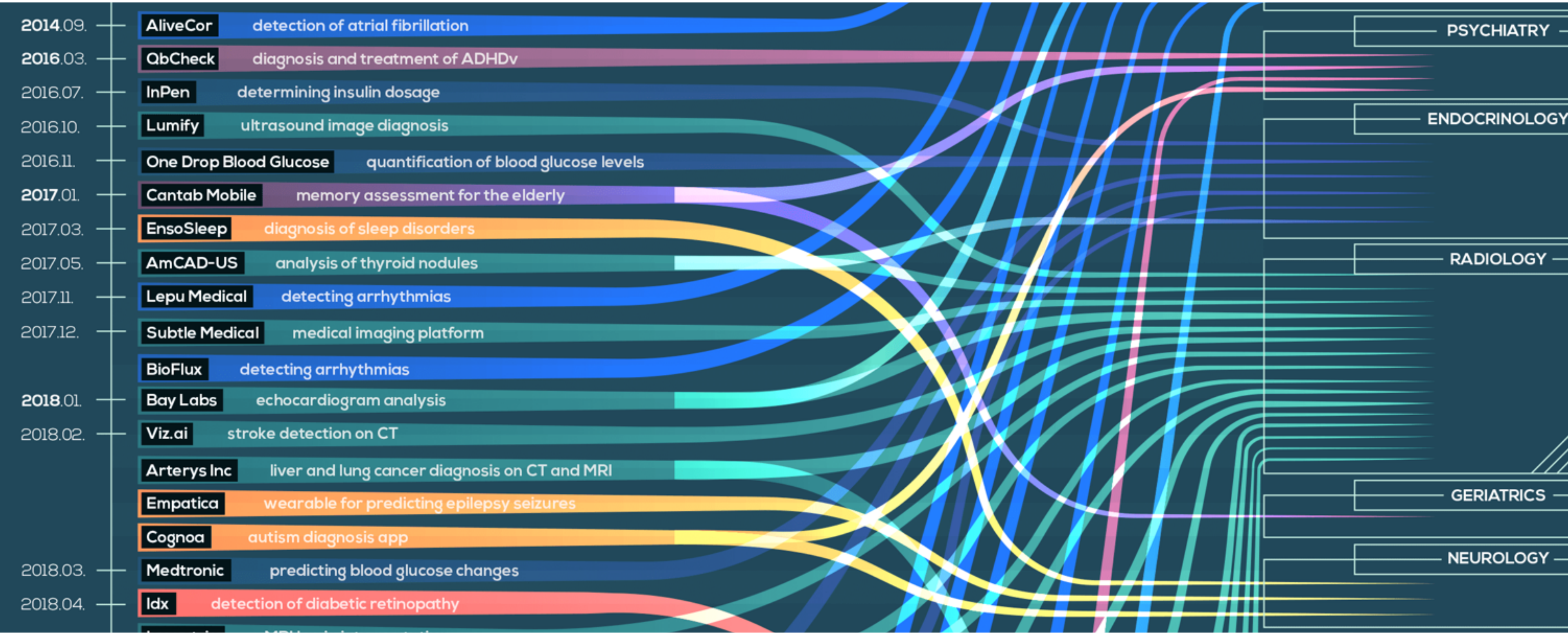
@ Bertalan Meskó
The Medical Futurist



Machine learning in Health (top 6 specialities): Neurology, Psychology, and Pathology


@ Bertalan Meskó
FDA APPROVALS FOR ARTIFICIAL INTELLIGENCE-BASED ALGORITHMS IN MEDICINE
2014
2014.09. AliveCor detection of atrial fibrillation
2016.03. QbCheck diagnosis and treatment of ADHDv
2016.07. InPen determining insulin dosage
2016.10. Lumify ultrasound image diagnosis
2016.11. One Drop Blood Glucose quantification of blood glucose levels
2017.01. Cantab Mobile memory assessment for the elderly
2017.03. EnsoSleep diagnosis of sleep disorders
2017.05. AmCAD-US analysis of thyroid nodules
2017.11. Lepu Medical detecting arrhythmias
2017.12. Subtle Medical medical imaging platform
BioFlux detecting arrhythmias
2018.01. Bay Labs echocardiogram analysis
2018.02. Viz.ai stroke detection on CT
Arterys Inc liver and lung cancer diagnosis on CT and MRI
Empatica wearable for predicting epilepsy seizures
Cognoa autism diagnosis app
2018.03. Medtronic predicting blood glucose changes
2018.04. Idx detection of diabetic retinopathy
Icometrix MRI brain interpretation
2018.05. Imagen X-ray wrist fracture diagnosis
NeuralBot transcranial Doppler probe positioning
MindMotion GO motion capture for the elderly
2018.06. DreaMed managing Type 1 diabetes
POGO blood glucose monitoring system
2018.07. Zebra Medical Vision coronary artery calcification algorithm
2018.08. Aidoc CT brain bleeding diagnosis
iCAD breast density via mammograhy
BriefCase triage and diagnosis of time sensitive patients
PhysiQ Heart Rhythm Module detection of atrial fibrillation
2018.09. Apple detection of atrial fibrillation
RightEye Vision System identifying visual tracking impairment
2018.11. MaxQ acute intracranial hemorrhage triage algorithm
2018.12. ProFound AI detection and diagnosis of suspicious lesions
ReSET-O adjuvant treatment of substance abuse disorder
2019.01. Verily ECG feature of the Study Watch
2019.03. Paige.AI clinical-grading in pathology
2019.05. AliveCor six-lead smartphone ECG
Zebra Medical Vision chest X-ray analysis
Aidoc flagging pulmonary embolism
2019 May
CARDIOLOGY
PSYCHIATRY
ENDOCRINOLOGY
RADIOLOGY
GERIATRICS
NEUROLOGY
ORTHOPEDICS
EMERGENCY MEDICINE
OPHTHALMOLOGY
PATHOLOGY
ONCOLOGY
4
3
39
applications
TMF
THE MEDICAL FUTURIST

Roadmap in Digital Brain Health



18% FDA approved AI applications: Neurology, and Psychology

↑

Biological Psychiatry: From subjective diagnosis to data-driven diagnosis

Digital Markers: Purpose?

nature neuroscience

Review Article | Published: 23 February 2017

Building better biomarkers: brain models in translational neuroimaging

Choong-Wan Woo, Luke J Chang, Martin A Lindquist & Tor D Wager

Digital Markers: Purpose?

Building better biomarkers: brain models in translational neuroimaging

- Risk assessment, conversion prediction and early detection
- Differential diagnosis and subtyping
- Predicting treatment outcome

Digital Markers: Purpose?

Building better biomarkers: brain models in translational neuroimaging

- **Risk assessment, conversion prediction and early detection**
- Differential diagnosis and subtyping
- Predicting treatment outcome

Starlab Neuroscience

Parkinsons' Decision Support System

Starlab Living Science

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DSS – Rationale

onset average
age 60 years

develop
RBD

Healthy
subjects

time

REM Behavior Disorder (RBD)

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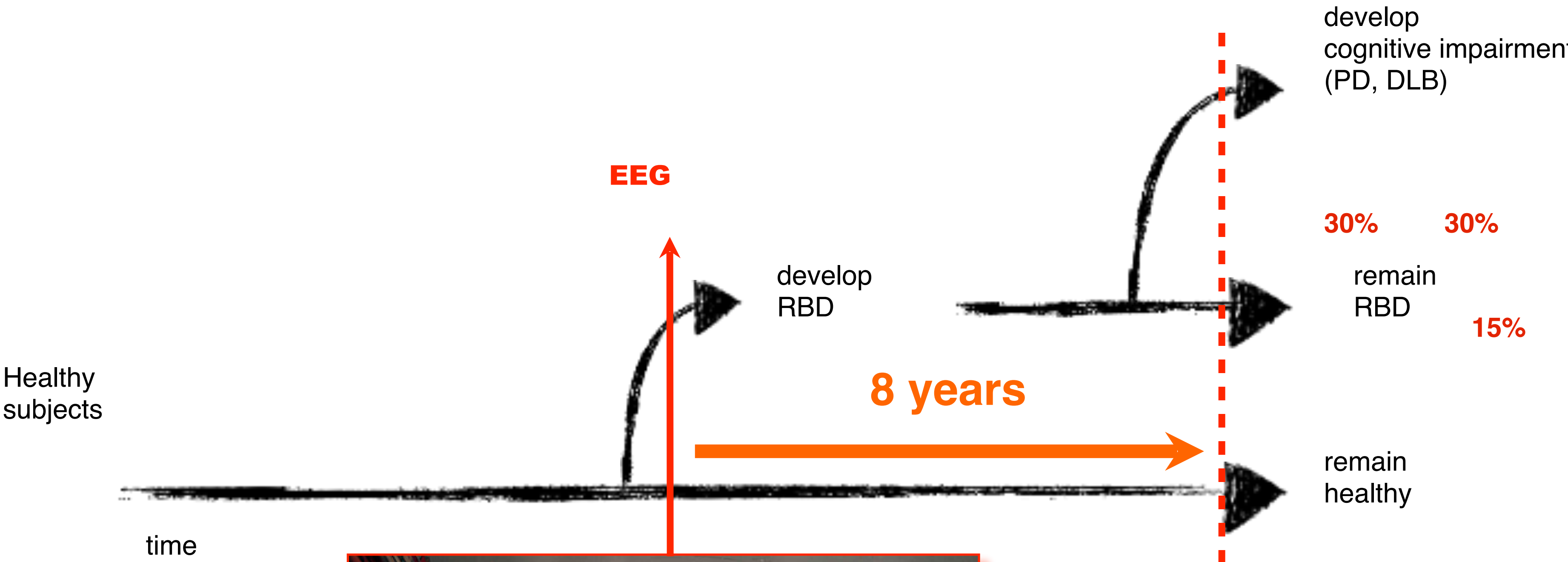
DSS – Background



REM Behavior Disorder (RBD)

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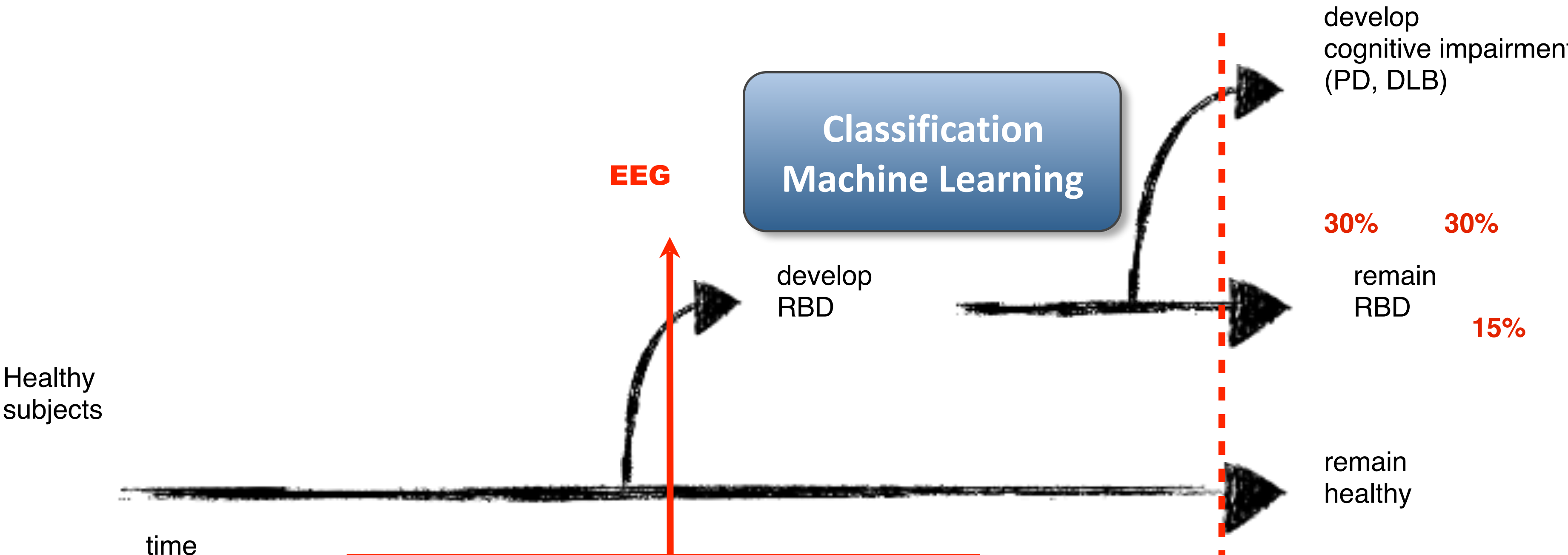
DSS – Background



REM Behavior Disorder (RBD)

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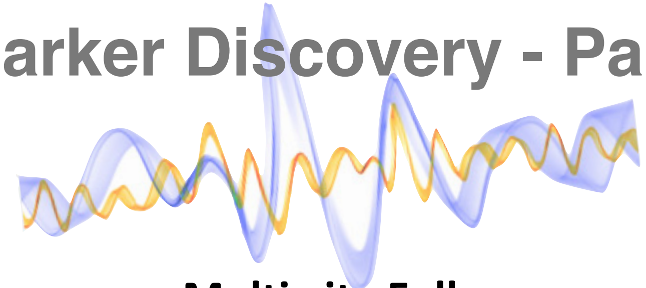
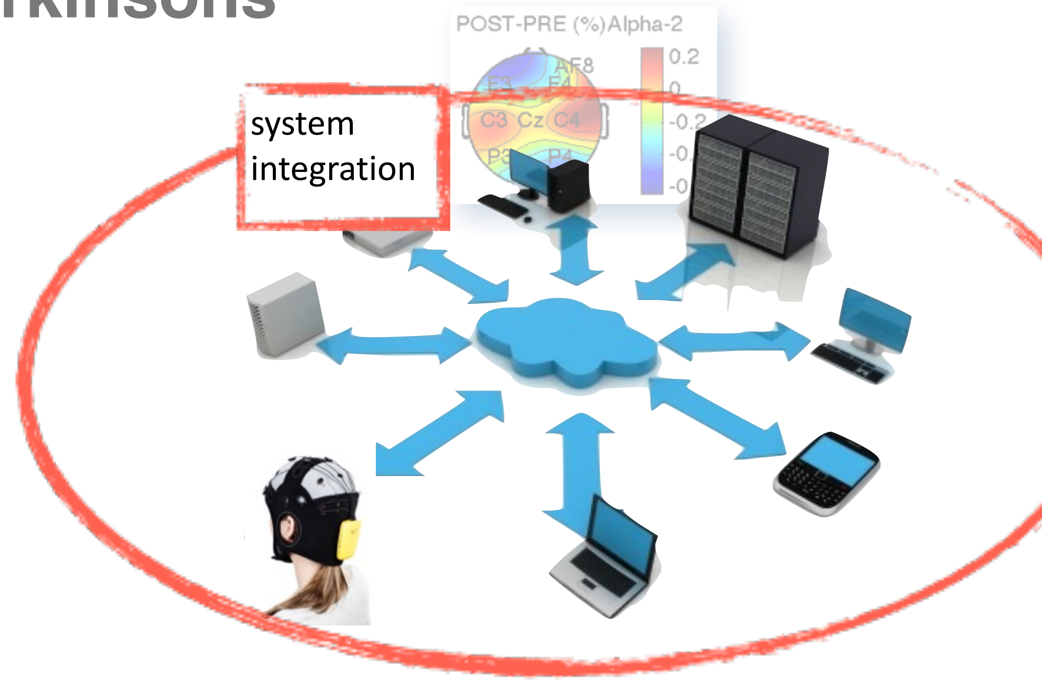
RIAA – finished 2014

Biomarker Discovery - Parkinsons'



Multi-site Followup

- 1 Years
- 7 partners, 6 countries
- further development of Machine Learning based biomarkers



automate knowledge generation

Integrated platform for electrophysiology data analytics from acquisition to biomarker performance

EEG biomarker discovery for Parkinson's

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FOR PARKINSON'S RESEARCH

System architecture

EEG → Classification Machine Learning

EEG data → subject score

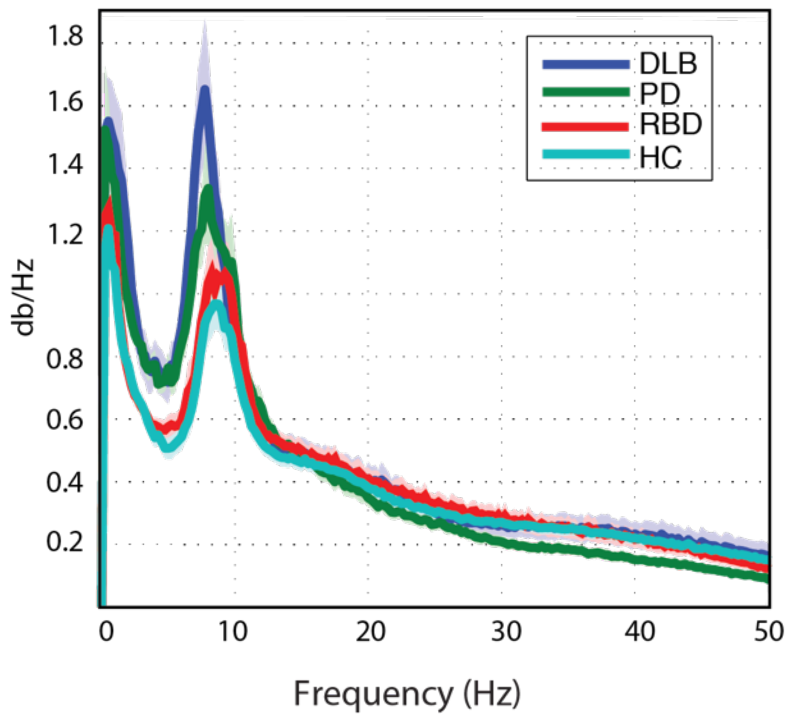
feature extraction — feature selection — classification — averaging

real value in [-1, 1]

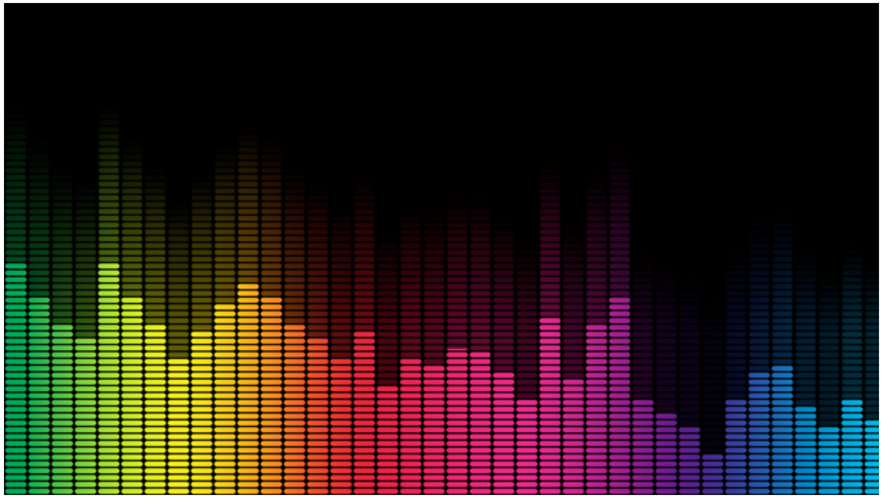
- diagnosis:
  HC vs RBD+PD+DLB
- prognosis:
  RBD vs PD+DLB
- prognosis: PD vs DLB

EEG features – starting point

A visualization of the EEG features analyzed suggests that there may be a potential use as a classification tool:



FFT of channel T3 for different groups (shadow areas = STE).



Features -> Power per Frequency Band

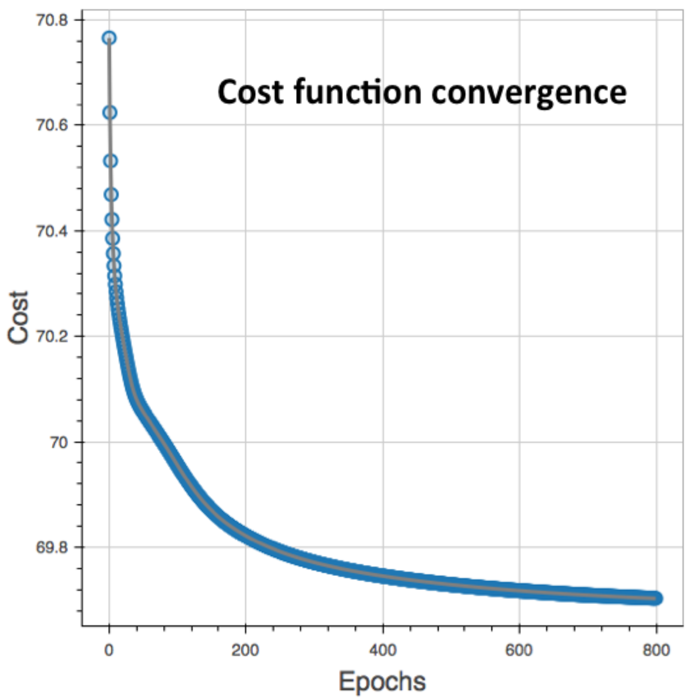
Number features = 14 channels x 13 freq bands

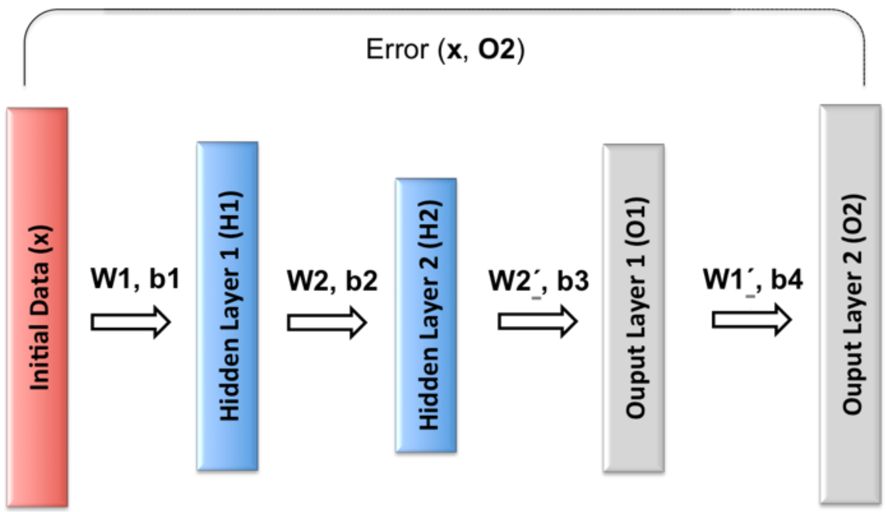
Number features = 182

Feature selection – Classical vs Deep Autoencoders

LPSO Validation, SVM Class

- Classical: Filter, Wrapper
- Deep Autoencoder





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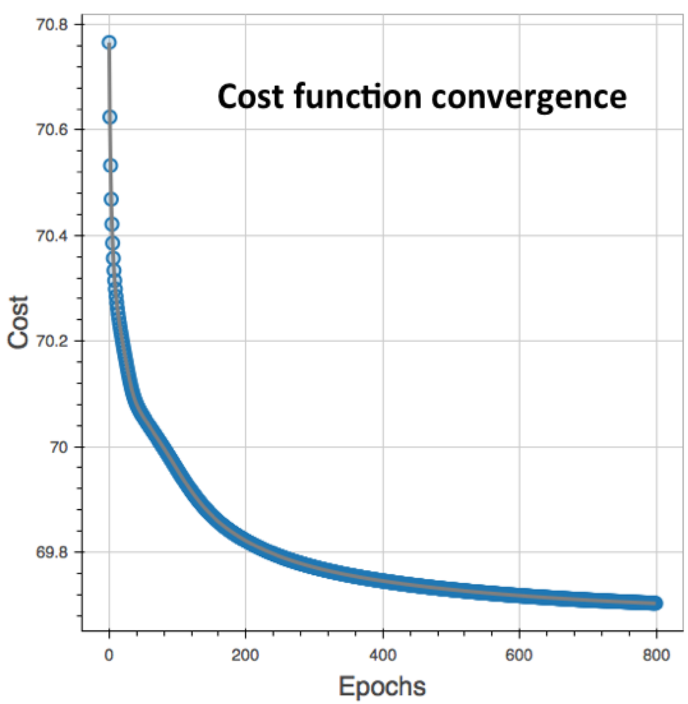
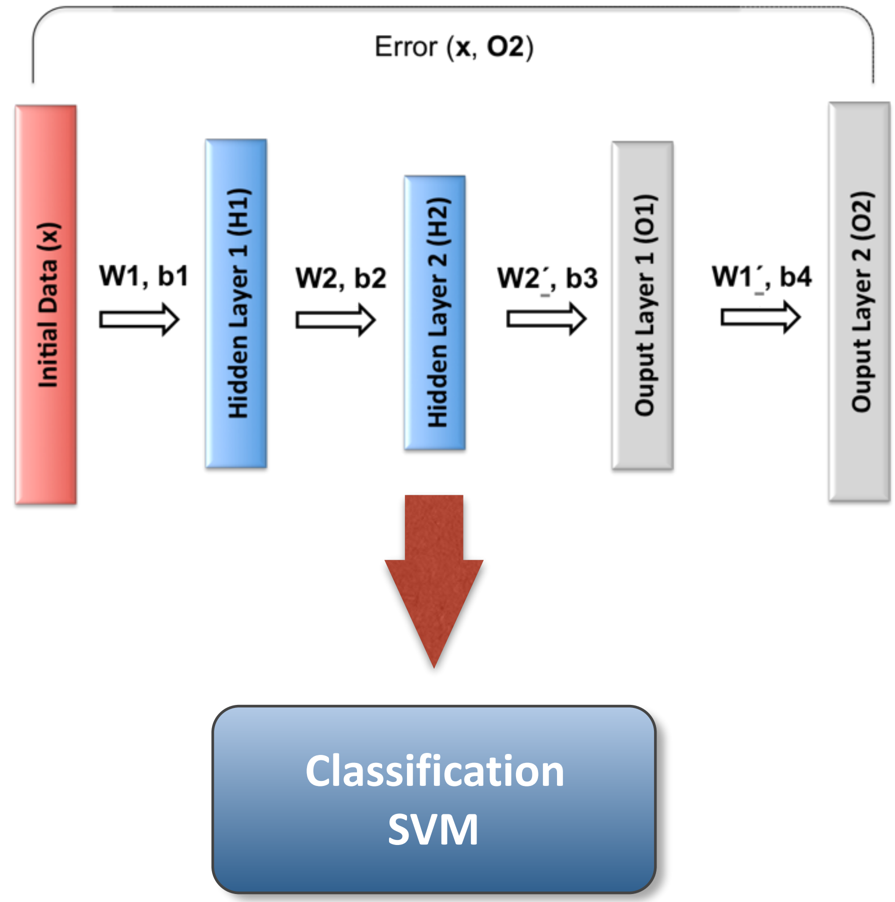
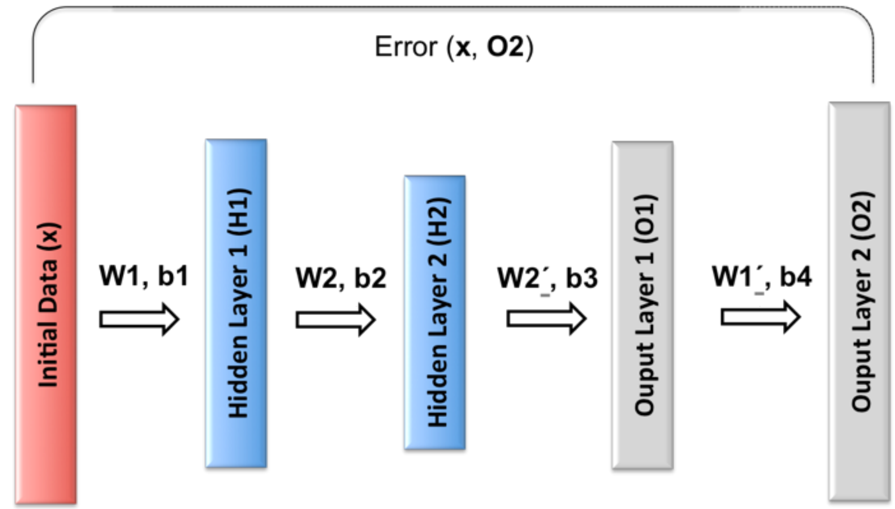


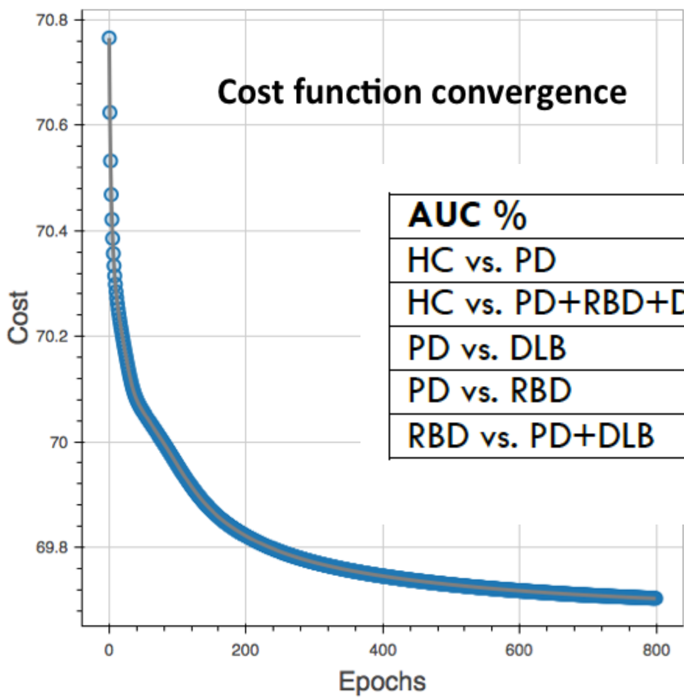


Feature selection – Classical vs Deep Autoencoders



LPSO Validation, SVM Class

- Classical: Filter, Wrapper
- Deep Auto (H1 200 nodes, H2 80 nodes)



AUC %	Wrapper	Filtering	Deep Auto-encoder
HC vs. PD	63	76	76
HC vs. PD+RBD+DLB	63	71	72
PD vs. DLB	57	48	67
PD vs. RBD	67	68	71
RBD vs. PD+DLB	66	76	76

Table 7 AUC achieved with SVM classification.

Conclusion:
Autoencoders outperform traditional feature selection but large computational cost

Performance evaluation LPO

DLB vs PD
-BandPower features-

	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	Ave AUC
S1	0.08	0.00	0.47	0.01	0.02	0.22	0.00	0.00	0.16	0.07	0.86	0.40	0.19
S2	0.94	0.47	1.00	0.90	0.67	0.91	0.07	0.06	0.96	0.72	0.98	0.91	0.72
S3	0.99	0.79	1.00	0.96	0.78	0.94	0.00	0.05	0.98	0.92	0.98	0.95	0.78
S4	0.40	0.19	0.66	0.25	0.23	0.51	0.03	0.06	0.57	0.37	0.86	0.56	0.39
S5	0.96	0.52	1.00	0.95	0.72	0.92	0.08	0.11	0.96	0.62	0.98	0.94	0.73
S6	0.81	0.11	0.98	0.54	0.36	0.82	0.00	0.00	0.95	0.40	0.98	0.79	0.56
S7	0.98	0.70	1.00	0.95	0.74	0.94	0.11	0.15	0.98	0.88	0.98	0.93	0.78
S8	0.95	0.57	1.00	0.91	0.65	0.91	0.01	0.19	0.97	0.69	0.98	0.91	0.73
S9	1.00	0.98	1.00	1.00	0.96	0.99	1.00	1.00	1.00	1.00	1.00	1.00	0.99
S10	1.00	0.99	1.00	1.00	0.96	0.98	0.73	0.99	1.00	1.00	1.00	1.00	0.97
S11	0.26	0.05	0.41	0.30	0.15	0.26	0.00	0.03	0.21	0.04	0.57	0.38	0.22
S12	1.00	0.93	1.00	0.97	0.83	0.96	0.02	0.38	0.99	0.96	0.98	0.98	0.83
S13	0.51	0.10	0.90	0.26	0.22	0.68	0.04	0.04	0.76	0.38	0.97	0.72	0.47
S14	0.99	0.90	1.00	0.98	0.85	0.96	0.45	0.50	0.99	0.95	0.99	0.97	0.88
Ave AUC	0.78	0.52	0.89	0.71	0.58	0.78	0.18	0.25	0.82	0.64	0.94	0.82	0.66

performance evaluation at individual level through LPSO [Airola et al 2010]:

- evaluate performance with small data sets
- AUC computation without representing the ROC space - AUC Wilkoxon
- keep balance in the training (wrt LOSO)

Performance evaluation

N=118

	Scoring system					Decision system	
	AUC Wilkoxon	AUC ROC averaging	Acc	Sens	Spec	*Ave Acc*	*Acc Global Norm.*
HC vs. PD	88	88.22	94.19	88	100	61	68
HC vs. rest	76	76.26	88.01	76	100	68	68
LBD vs. PD	70	70.73	85.17	70	100	70	72
RBD vs. PD	80	80.07	89.93	80	100	66	77
RBD vs. PD+LBD	75	75.39	87.39	75	100	71	73

performance measure depends on the validation procedure and further normalization of scores - not always specified in the literature

Performance evaluation

N=118

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RBD vs. PD	80	80.07	89.93	80	100	66	77
RBD vs. PD+LBD	75	75.39	87.39	75	100	71	73

performance measure depends on the validation procedure and further normalization of scores - not always specified in the literature

Outperforming Classifiers

N=212

	AUC (optimal accuracy)	APP 1	APP 2
PD diagnosis	HC vs. PD	82 (91)	55 (77)
PD/DLB prognosis	PD vs. DLB	62 (81)	63 (82)
PD prognosis	PD vs. RBD	69 (84)	78 (89)
Conversion prognosis	RBD vs. PD+DLB	73 (87)	82 (91)
RBD diagnosis	HC vs. rest	73 (86)	-
	Average	72 (86)	69 (85)

- Validated in a larger data set (212 vs 118) in yellow
- Improved performance in a larger data set for conversion prognosis by going from spectral features to connectivity features (in red)

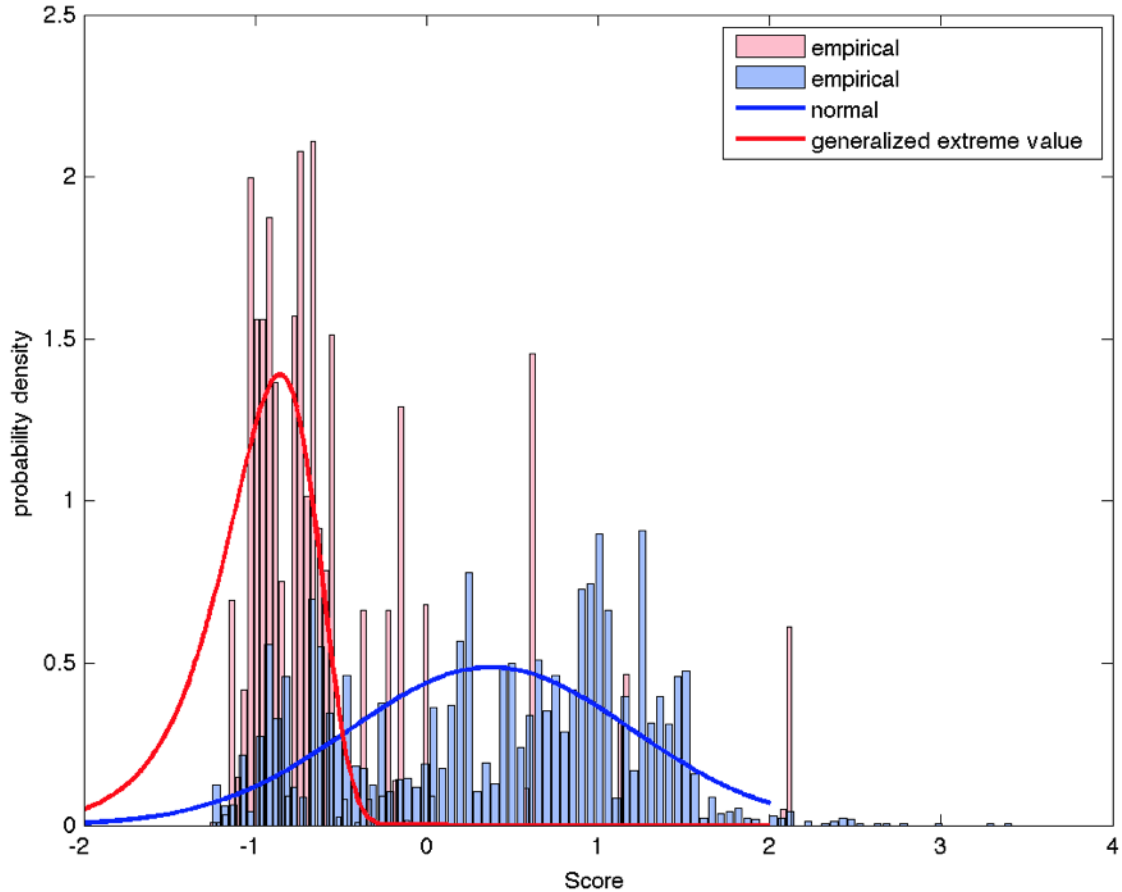
Classifier Scores as Biomarkers – Effect Size

AUC (optimal accuracy)	APP 1	APP 2

Conversion prognosis

RBD vs PD+DLB

AUC 0.82
Accuracy 91%
Effect size 0.75



Classification scores can be used as any other biomarker

Decision Support System - deployment

Clinical Translation and its problems

Decision Support System - deployment

Clinical Translation and its problems

Starlab Neuroscience

ADHD Digital Markers

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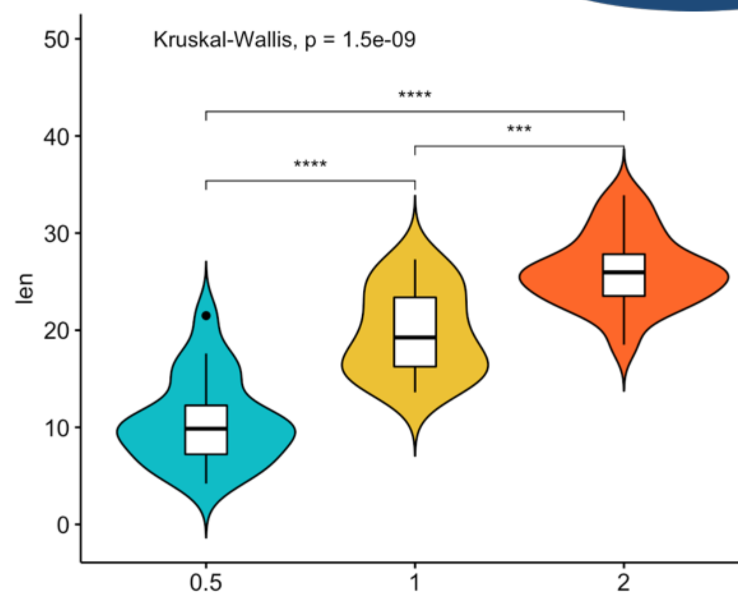
Digital Markers – ADHD data-driven diagnosis

approx. 22%
misdiagnosis



Digital Phenotypes – ADHD

Building better biomarkers: brain models in translational neuroimaging

- Risk assessment, conversion prediction and early detection
- **Differential diagnosis and subtyping**
- Predicting treatment outcome

Starlab Neuroscience

Echo State Networks for EEG connectivity analysis

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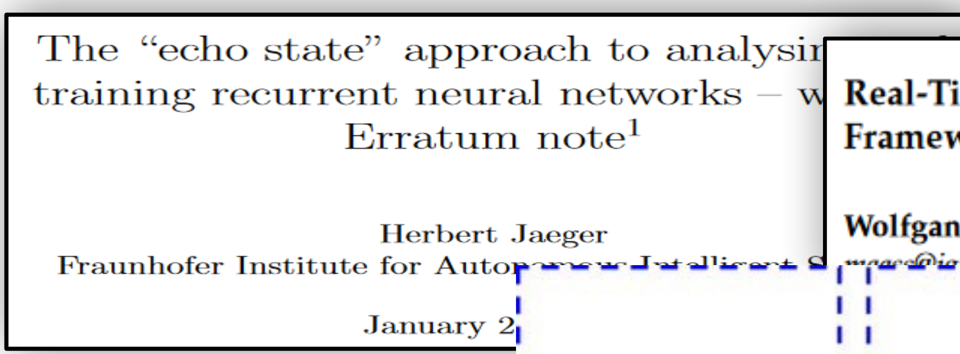
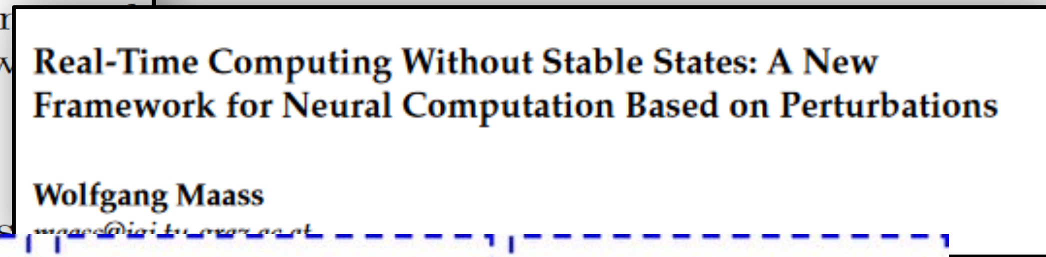
Recurrent Neural Networks - Echo State Networks



The "echo state" approach to analysin
training recurrent neural networks – w
Erratum note[1]

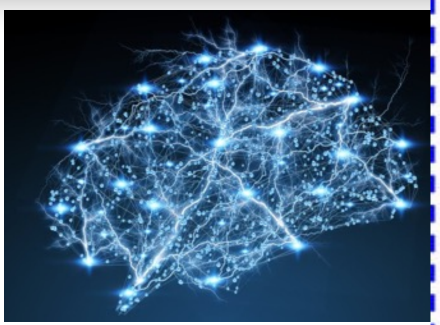
Herbert Jaeger
Fraunhofer Institute for Auton

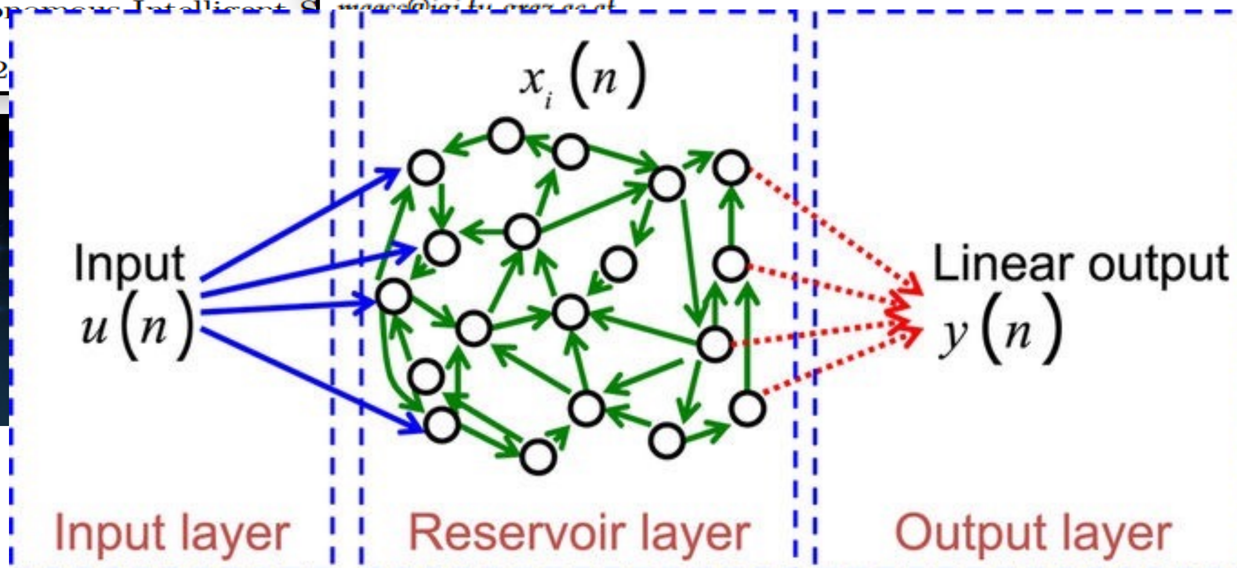
January 2



Real-Time Computing Without Stable States: A New Framework for Neural Computation Based on Perturbations

Wolfgang Maass





Recurrent Neural Networks - Echo State Networks

The "echo state" approach to analysin
training recurrent neural networks – w
Erratum note[1]

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Real-Time Computing Without Stable States: A New Framework for Neural Computation Based on Perturbations

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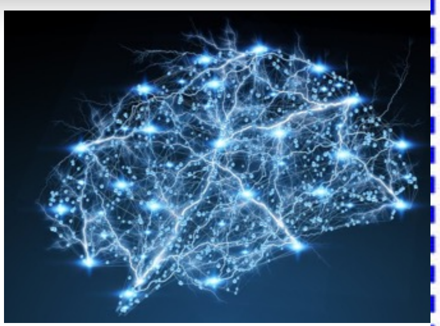
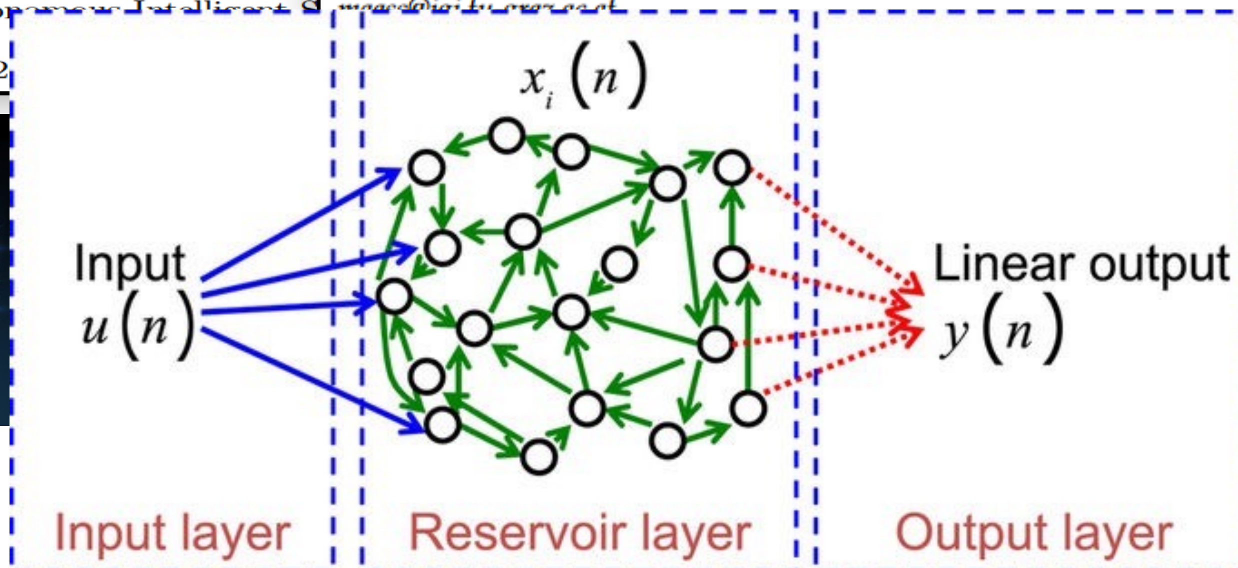
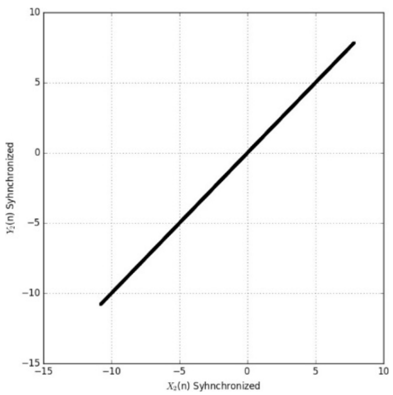


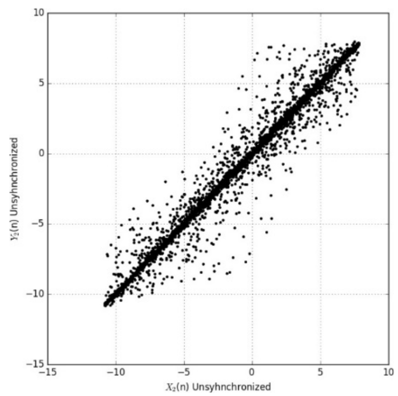


Hypothesis:
Recurrent neural networks and in particular Echo State Networks are able to detect complex chaotic synchronization between **temporal series**.

Exploring ESN Capabilities

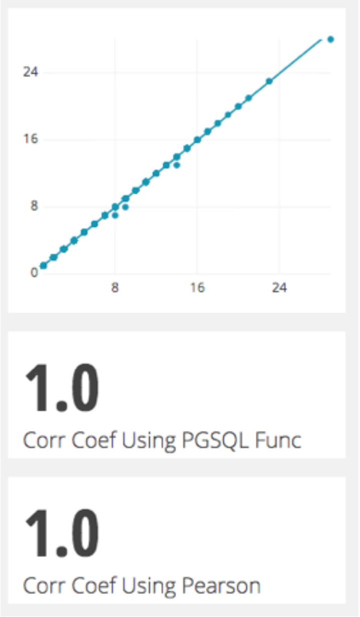


Synchronzed

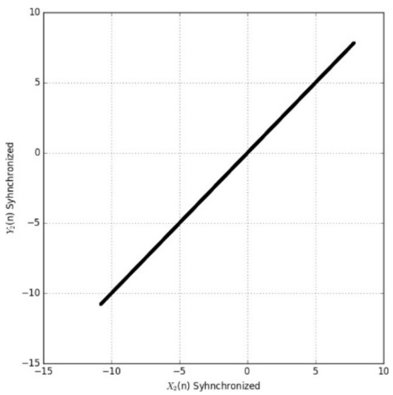


Unsynchronized

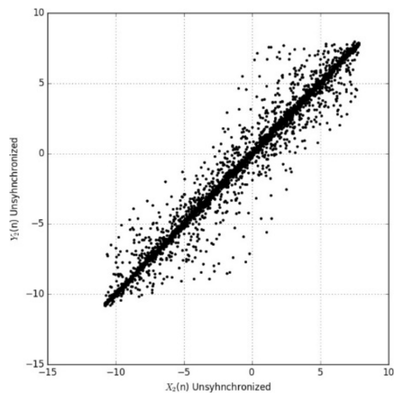
Correlational Analysis



Exploring ESN Capabilities

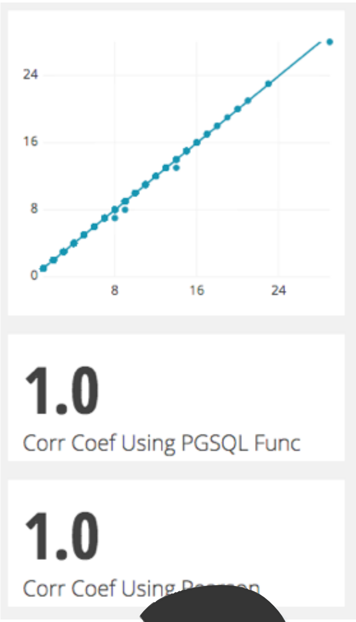


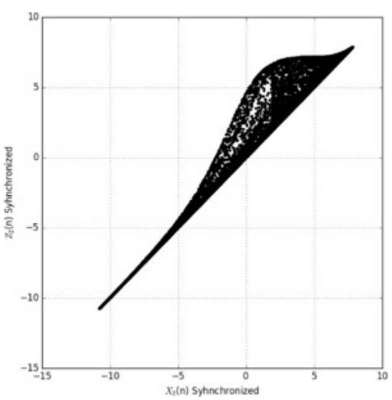
Synchronzed



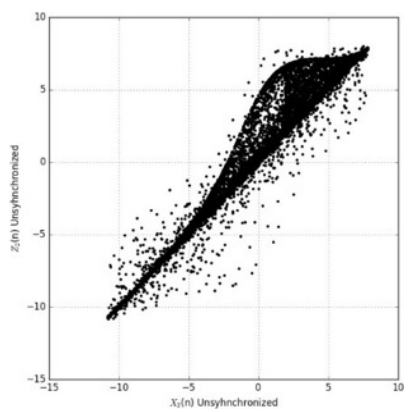
Unsynchronized

Correlational Analysis

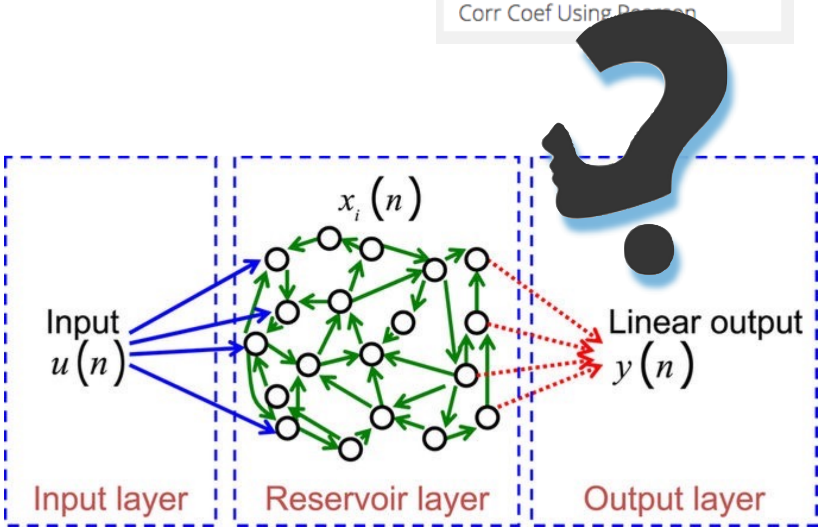




Generalized Synchronzation



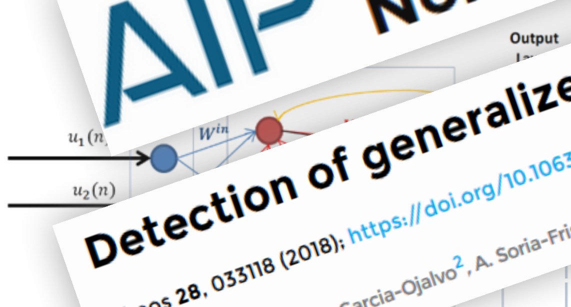
Unsynchronized



Exploring ESN Capabilities

We have constructed a continuous temporal signal consisting of a seri... synchronized sequences interleaved with unsynchronized on... varying ‘g’ factor

Regression m... ...ate bet... ...s

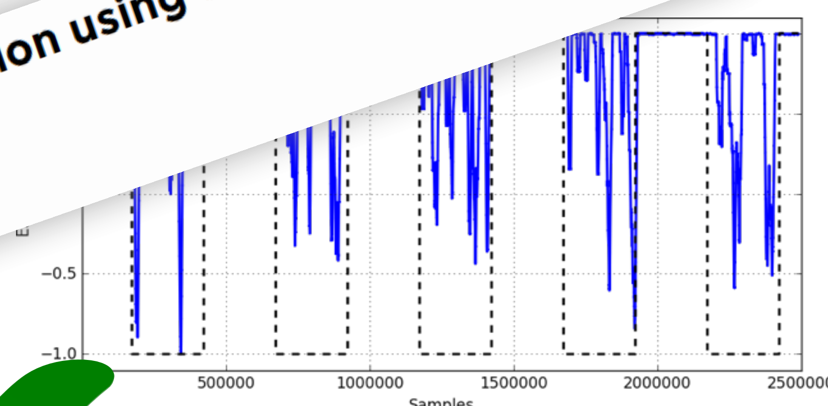


AIP Chaos: An Interdisciplinary Journal of Nonlinear Science

Detection of generalized synchronization using echo state networks

Chaos 28, 033118 (2018); https://doi.org/10.1063/1.5010285

D. Ibáñez-Soria[1,a)], J. García-Ojalvo[2], A. Soria-Frisch[1], and G. Ruffini[1,3]



If well parameterized ESN are capable of detecting changes in GS between two temporal time series even in the presence of high noise levels

Starlab Neuroscience

Echo State Networks as a Marker Generator

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Living Science

Background Data-Set

51 children aged 7-11

	ADHD (n = 21)	Control (n = 30)
Age in years	M 9.6 (SD 1.4)	M 9.3 (SD 1.5)
Male/Female	14 / 7	13 / 17
ADHD C/I	12 / 9	-
Medication (Yes/No)	6 / 15	-

ADHD Inclusion Criteria:

- Clinically diagnosed according to DSM-IV.
- Not having comorbidity problems of mental retardation, autism, bipolar or psychotic disorders, history of epileptic seizures or any other relevant medical disorder.
- Refrain 48h prior to the EEG assessment

Healthy Controls Inclusion Criteria:

- Not having any psychopathology diagnosis, neither mental retardation or learning disorders
- Not showing behavioral problems nor learning difficulties
- Not having major family problems that could interfere with their participation in the study

ESN-Based ADHD Biomarkers

Arousal: Psychological state of characterizing activation level wrt stimuli

Hypo-arousal Theory: The hypo-arousal theory is based on the principle that ADHD population looks for self-stimulation in order to achieve normal arousal levels through excessive activity.

Eyes Closed:

- Low arousal
- Low attention

Eyes Open:

- Normal arousal
- Normal attention

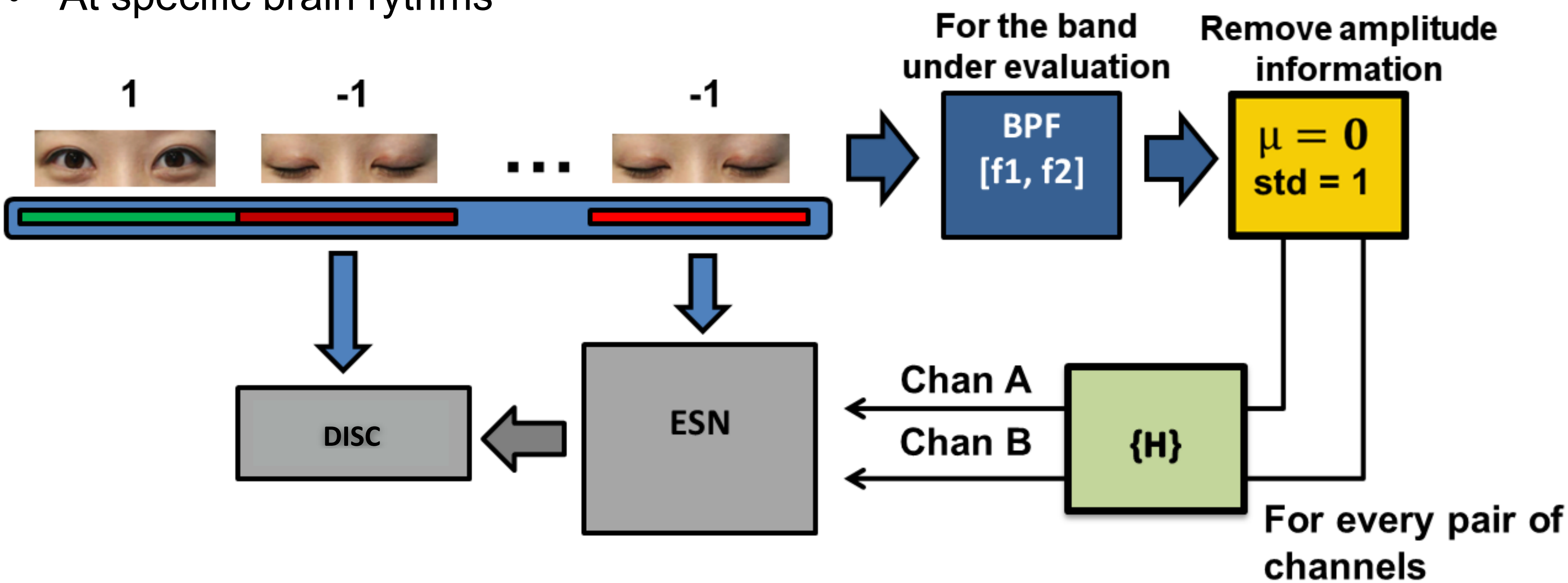
Hypothesis

Arousal alterations in the EEG comparing low arousal states with respect to normal arousal may be altered in the ADHD population

ESN-Based ADHD Biomarkers

ESN-based novel approach aiming at quantifying within subject dynamical differences between resting EO and EC

- Complex synchronization and non-stationary patterns change
- Between pairs of channels
- At specific brain rythms



ESN-Based ADHD Biomarkers

	DCI							
	θ_1	θ_2	α_1	α_2	β_1	β_2	γ_1	γ_2
C3	**				*			
Cz	**				**	*		
C4	**				*	**		
F3	**				**			
Fz	**				**			
F4	**				**	*		

Wilcoxon Ranksum (5%)

- Statistically significant differences in low theta and beta in every electrode

ESN-Based ADHD Biomarkers

	DCI							
	θ_1	θ_2	α_1	α_2	β_1	β_2	γ_1	γ_2
C3	**				*			
Cz	**				**	*		
C4	**				*	**		
F3	**				**			
Fz	**				**			
F4	**				**	*		

Wilcoxon Ranksum (5%)

- Statistically significant differences in low theta and beta in every electrode

	DCI							
	θ_1	θ_2	α_1	α_2	β_1	β_2	γ_1	γ_2
C3								
Cz	*							
C4	*							
F3	*							
Fz								
F4								

Bonferroni-Holm Correction

- Statistically significant differences in low theta at C4, Cz and F3

ESN-Based ADHD Biomarkers

	DCI							
	θ_1	θ_2	α_1	α_2	β_1	β_2	γ_1	γ_2
C3	**				*			
Cz	**				**			
C4	**							
F3	**							
Fz	[illegible]				**			
F[illegible]								

Wilco[illegible] [illegible]ksum (5%)

[illegible]gnificant [illegible]nces in [illegible] and be[illegible]

Psychiatry Research

ELSEVIER

Hypoarousal non-stationary ADHD biomarker based on echo-state networks

D. Ibanez-Soria[1], A. Soria-Frisch[1], J. Garcia-Ojalvo[2], Jacobo Picardo[3], Gloria García-Banda[3], Mateu Servera[3], Giulio Ruffini[1,4]

Bonferroni-H[illegible]

- Statistically sig[illegible] differences in l[illegible]eta at C4, Cz and F3

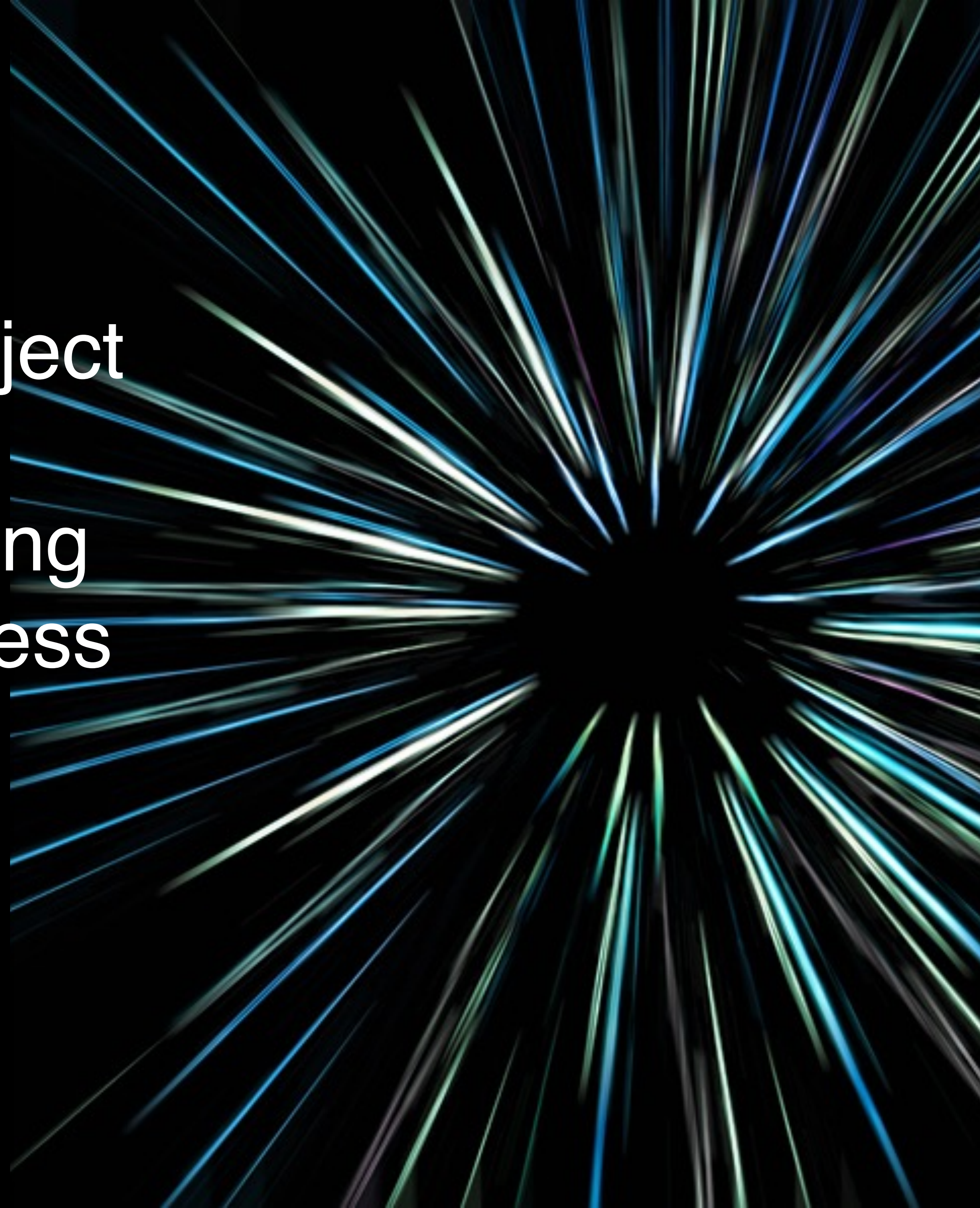
	DCI							
	[illegible]1	θ_2	α_1	α_2	β_1	β_2	γ_1	γ_2
C3								
Cz	*							
C4	*							
F3	*							
Fz								
F4								

Starlab Neuroscience

LUMINOUS®

H2020 FET project

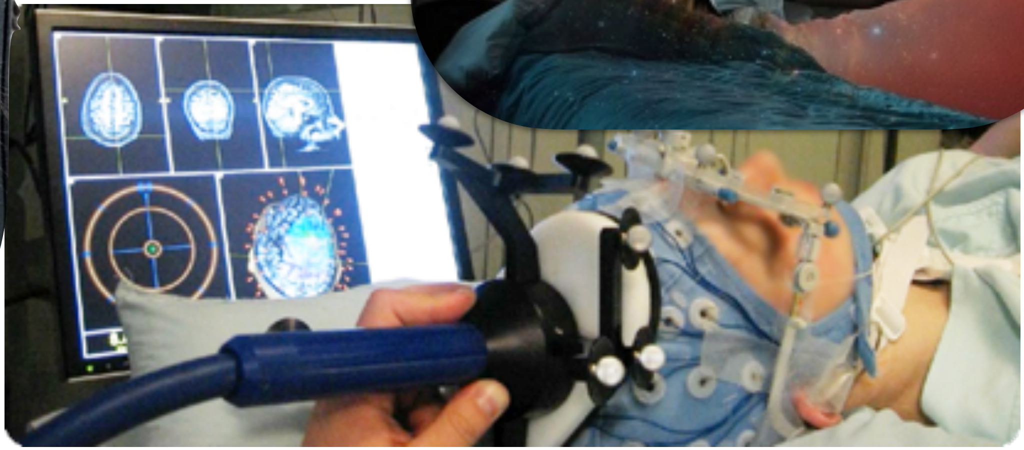
Machine Learning for Consciousness Research



Aureli Soria-Frisch (PhD)
Project Coordinator

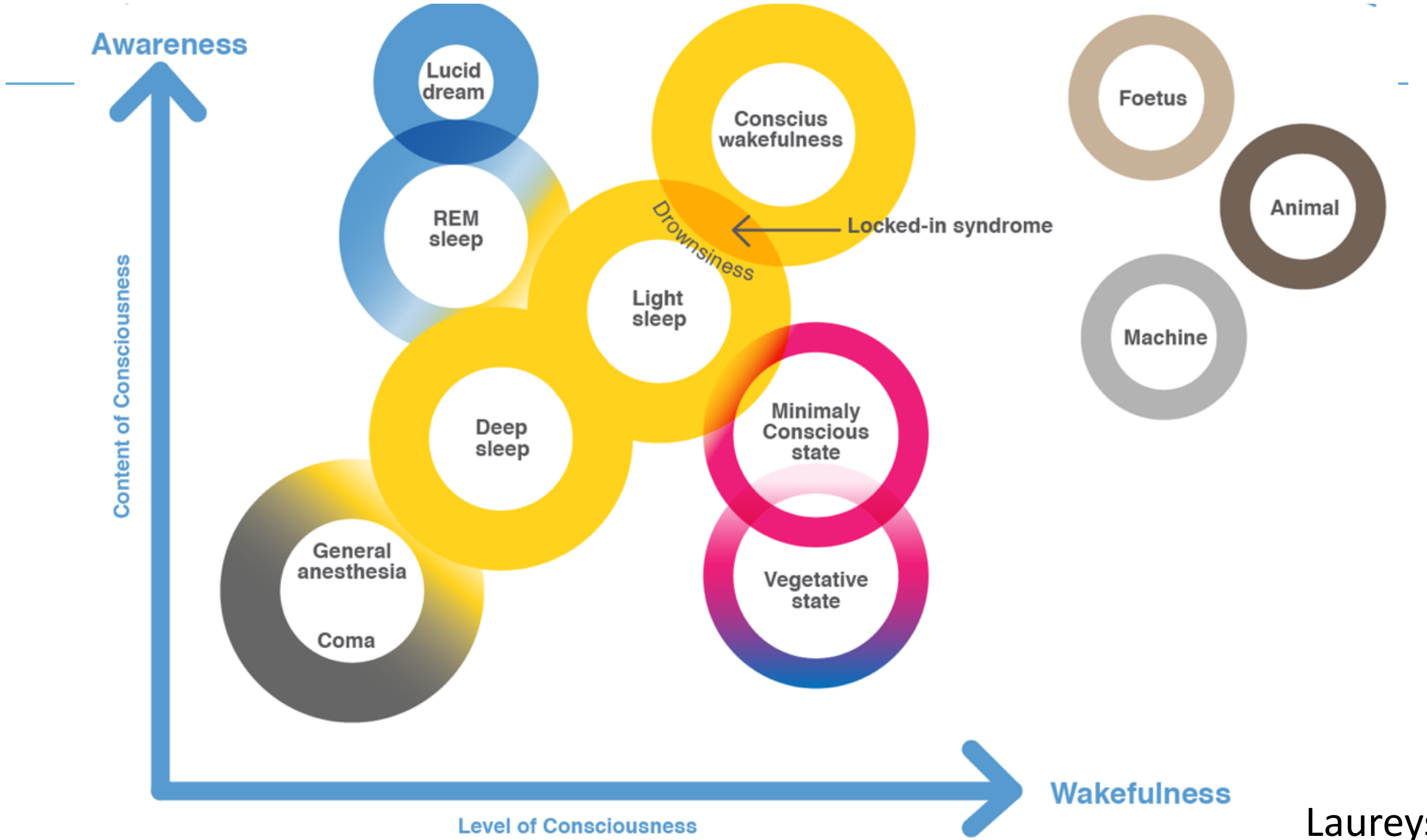
03/17/2019

Consciousness will someday be electromagnetically measured and altered, and that the associated needed insights will prove crucial to the development cognitive



Luminous project

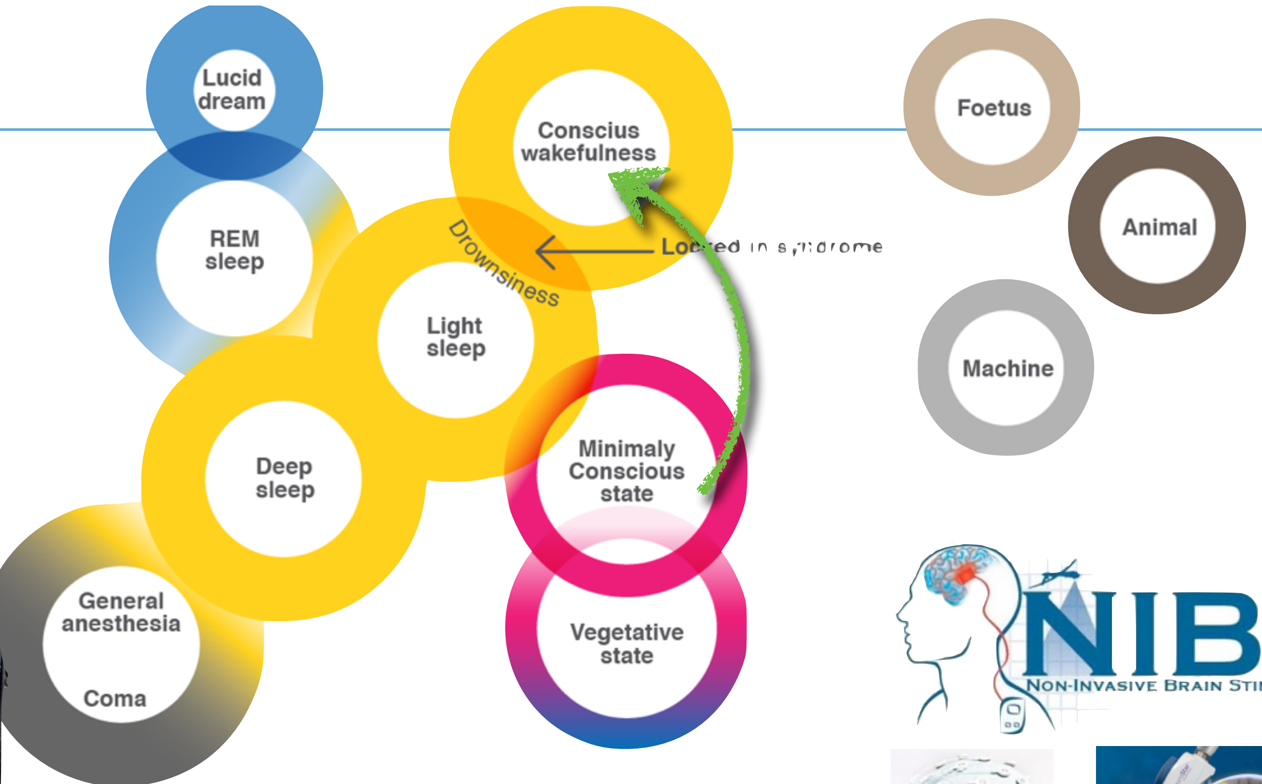
Studying Consciousness in the Electrical Brain



Laureys 2005

Luminous project

Changing Consciousness in the Electrical Brain?



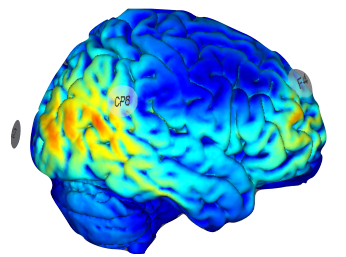
NIBS
NON-INVASIVE BRAIN STIMULATION

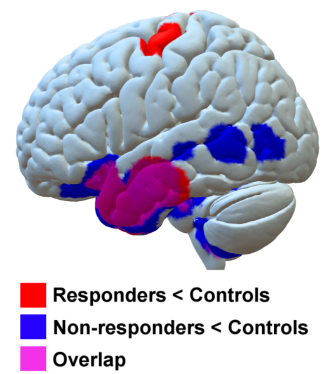
Non-Invasive Brain Stimulation

Coma patients treatment

based on electrical stimulation

NIBS
NON-INVASIVE BRAIN STIMULATION



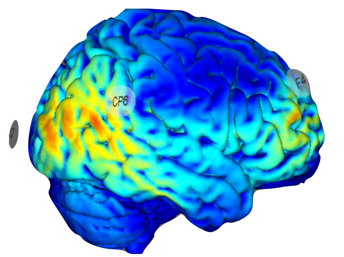


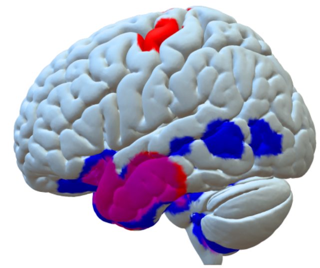
CHU de Liège
LIÈGE université
COMA SCIENCE GROUP
GIGA CONSCIOUSNESS

6/46 responders to treatment

Coma patients treatment

based on electrical stimulation





Responders < Controls
Non-responders < Controls
Overlap

6/46 responders to treatment

Can we predict who will respond positively?

Digital Markers – Minimal Conscious State

Building better biomarkers: brain models in translational neuroimaging

- Risk assessment, conversion prediction and early detection
- Differential diagnosis and subtyping
- **Predicting treatment outcome**
  - **brain measures to predict who will respond to a particular treatment**

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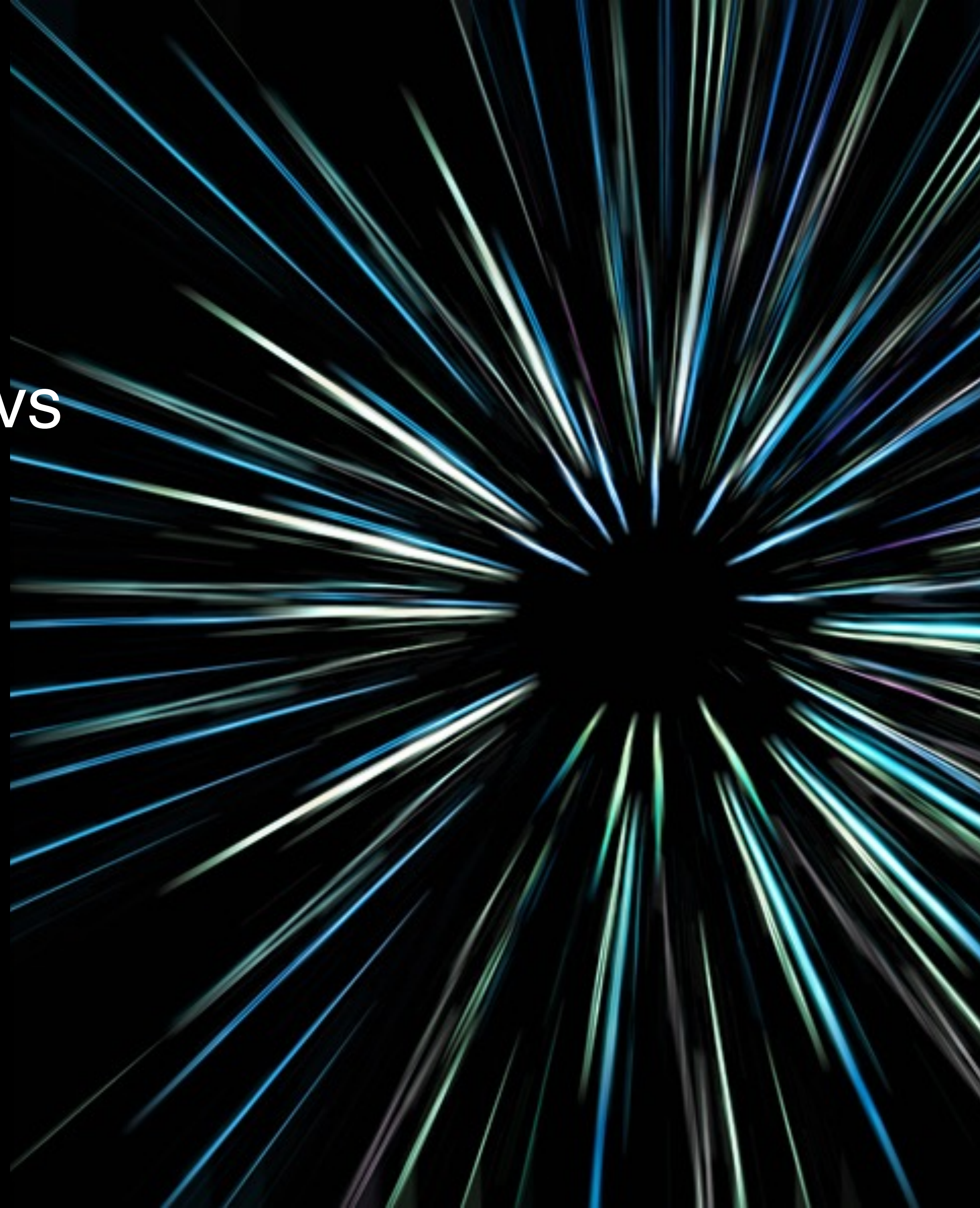
TCS responders vs non-responders: EEG-based ML

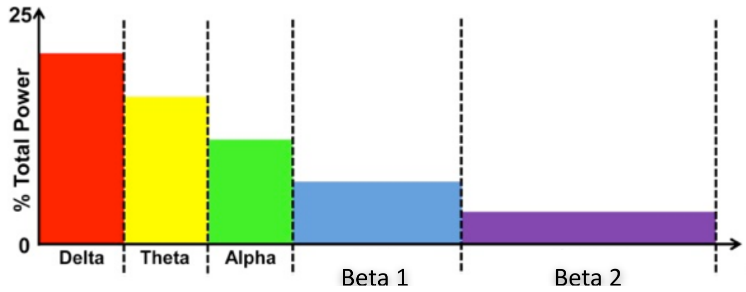


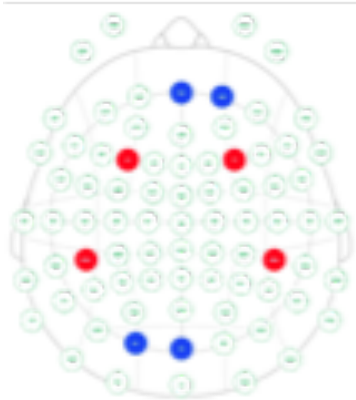
Aureli Soria-Frisch (PhD)
Project Coordinator

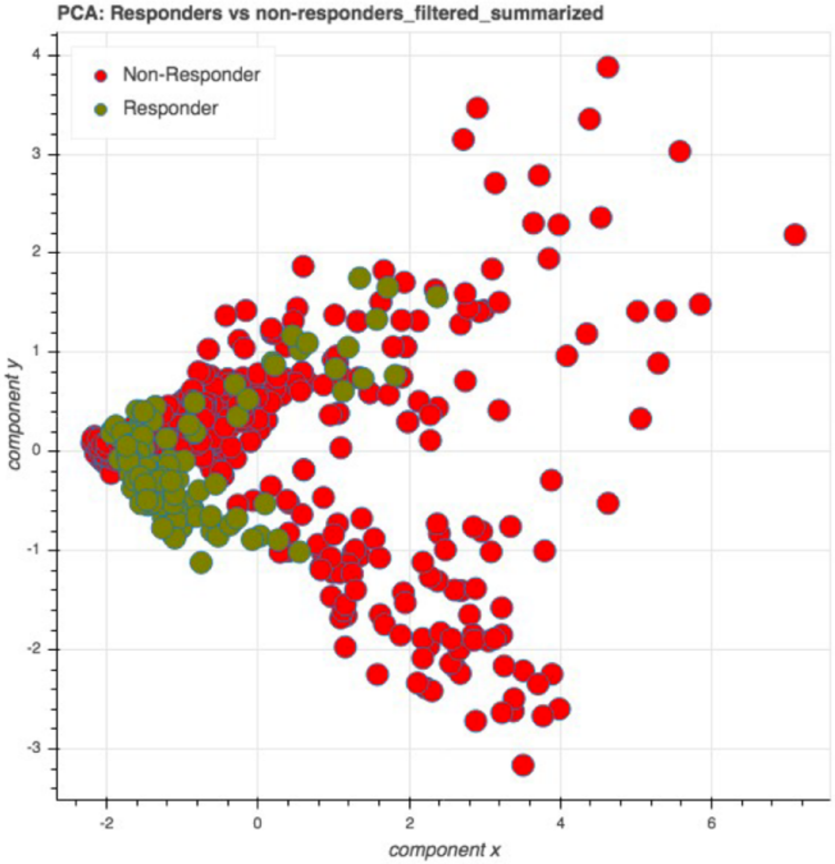
03/17/2019

EEG biomarkers - visualisation RBP feature

Relative Band Power







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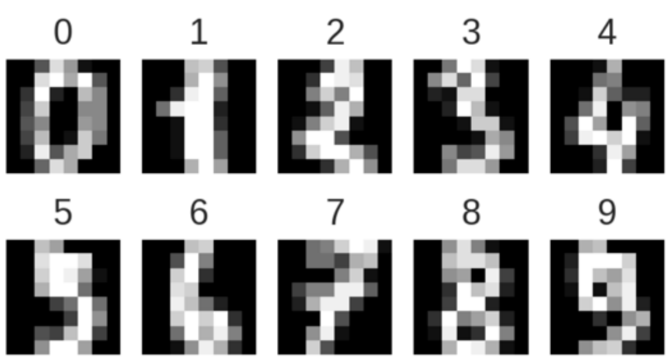
EEG biomarkers - visualisation RBP feature

t-distributed stochastic neighbour embedding (t-SNE)

iterative minimisation of KL measure
between distribution of distances in original
and projected spaces

example MNIST



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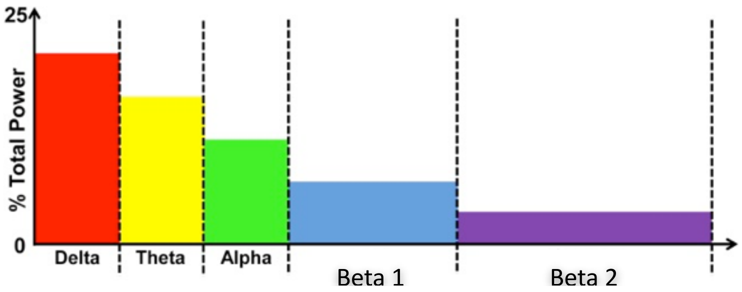
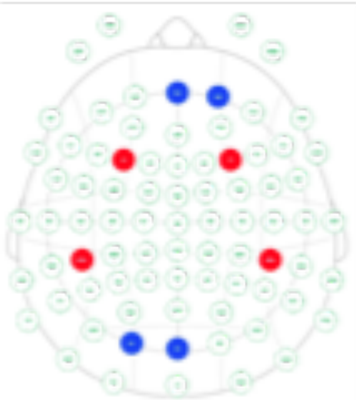
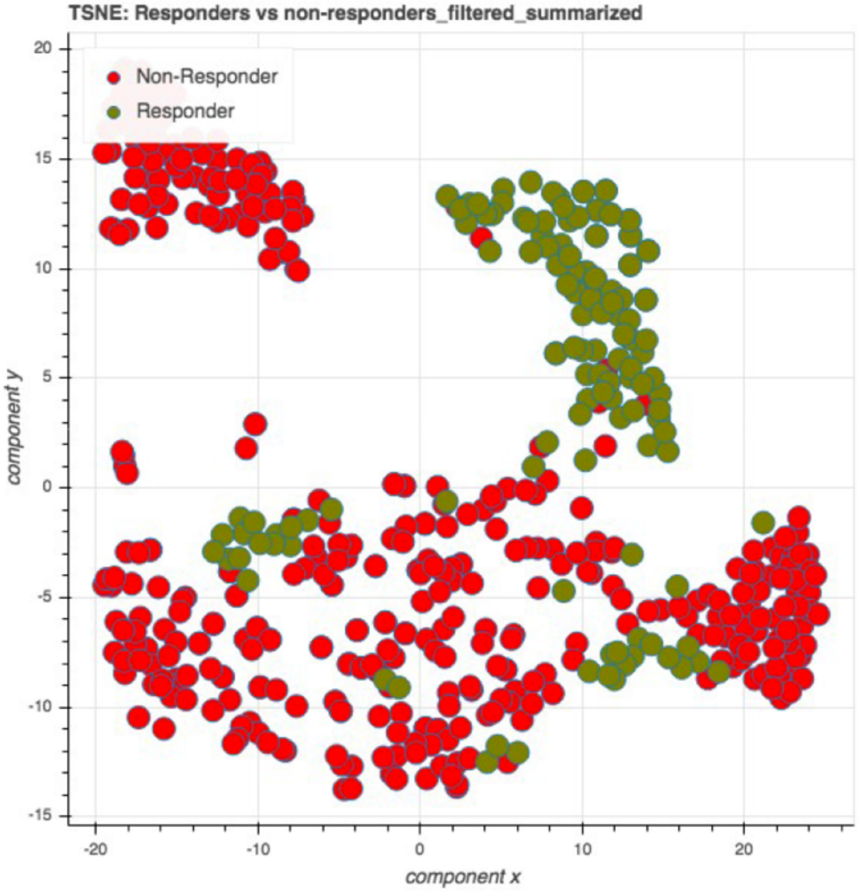
EEG biomarkers - visualisation RBP feature

Relative Band Power







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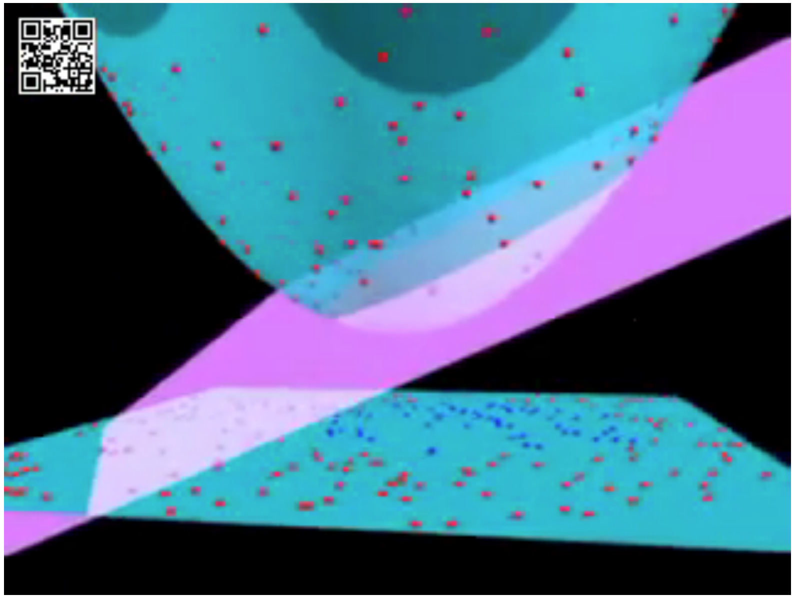
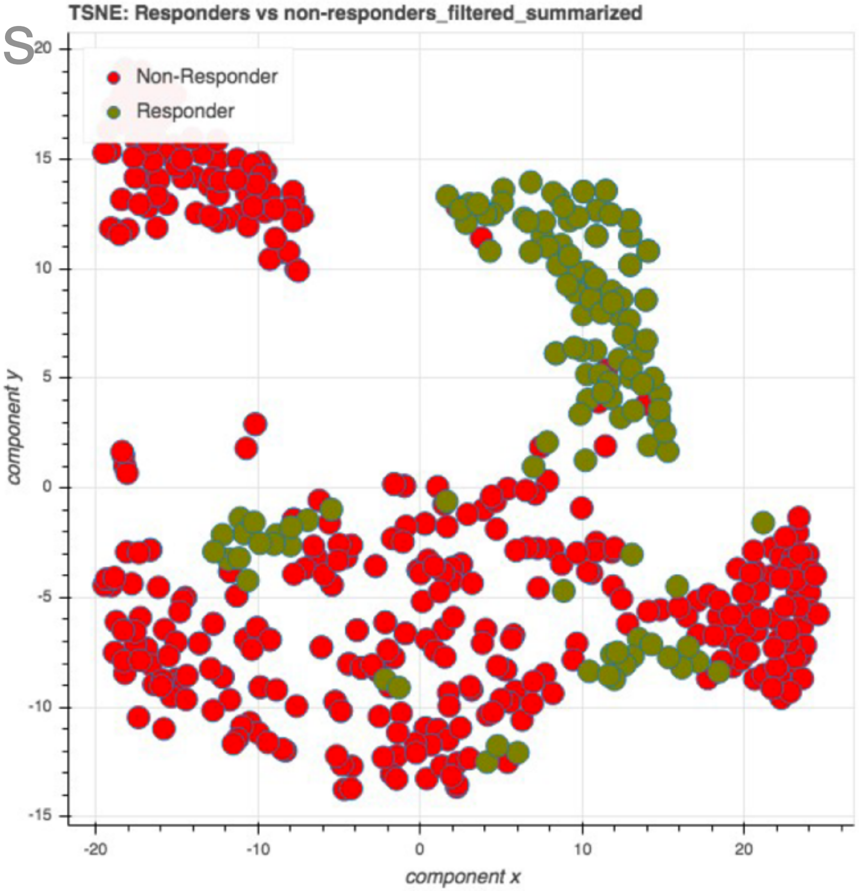
EEG biomarkers - classifiers

Support Vector Machines

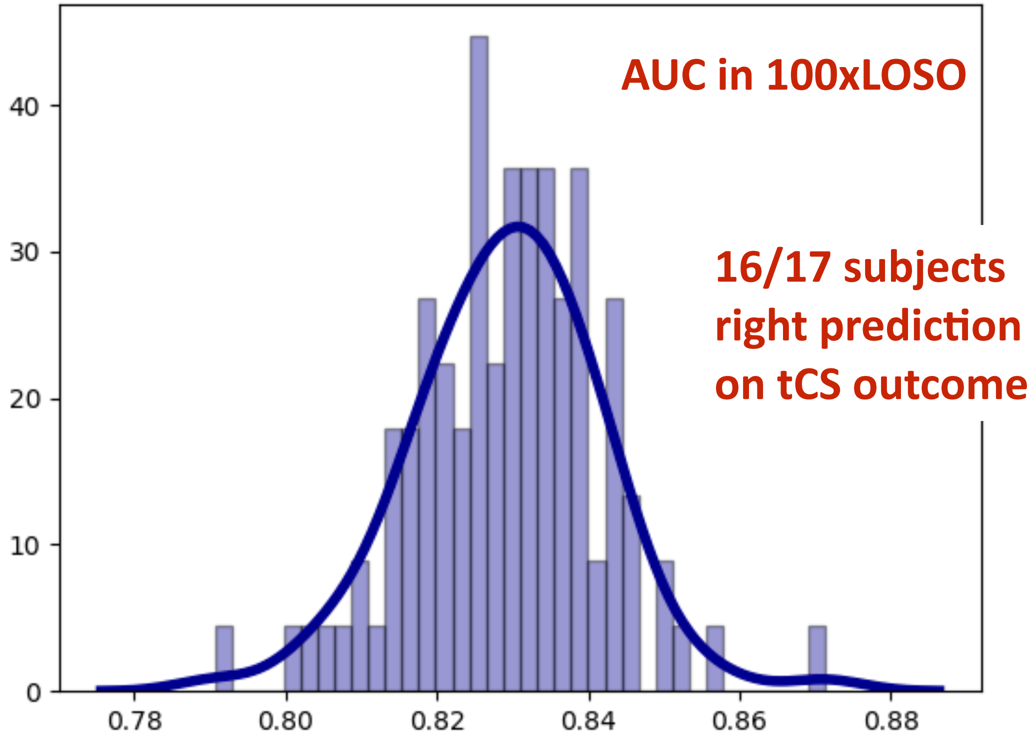




EEG biomarkers - performance evaluation

Crossfold validation

- Area Under the Curve (AUC)
- Acc in subject classification at Equal Error Rate (EER) operation point
- Leave-One Subject Out (LOSO)
- 100 x LOSO



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Take home messages

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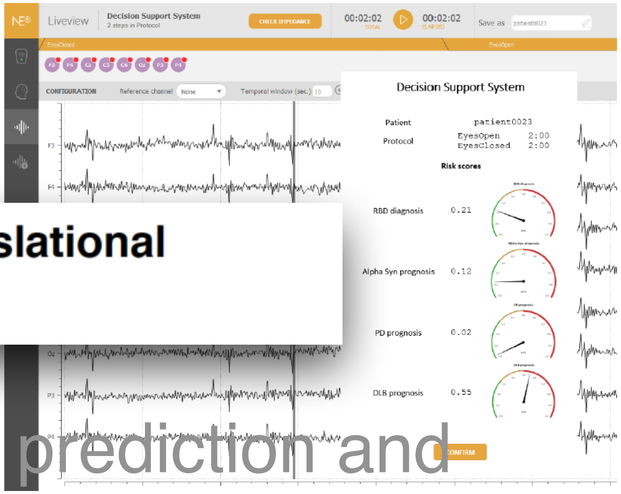
Applications ML as Digital Markers



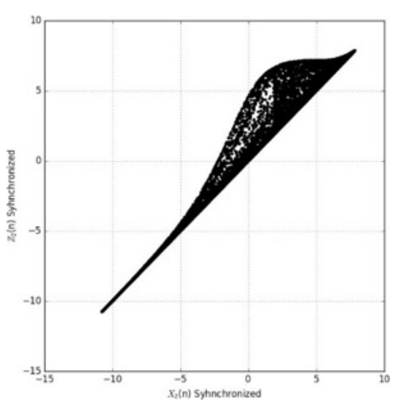
Building better biomarkers: brain models in translational neuroimaging

- Risk assessment, conversion prediction and early detection - Parkinsons

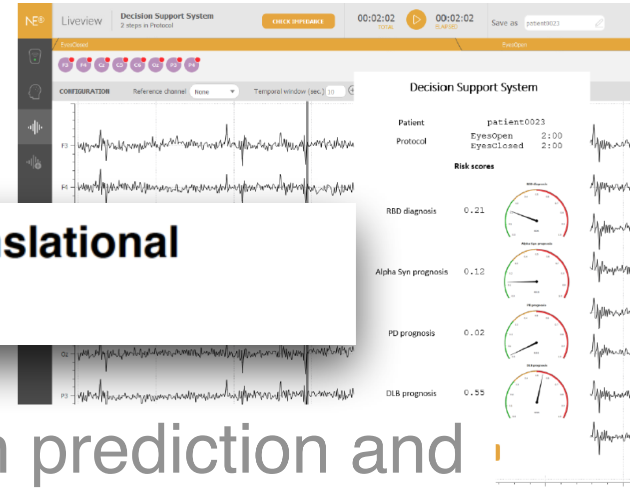
Applications ML as Digital Markers

Building better biomarkers: brain models in translational neuroimaging

- Risk assessment, conversion early detection - Parkinsons
- Differential diagnosis and subtyping - ADHD

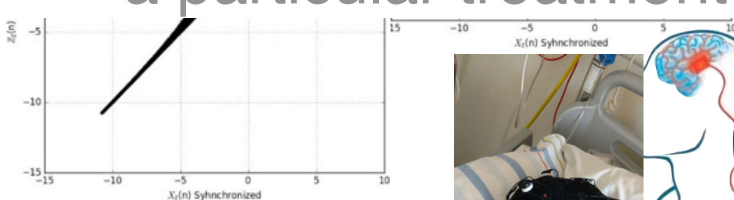


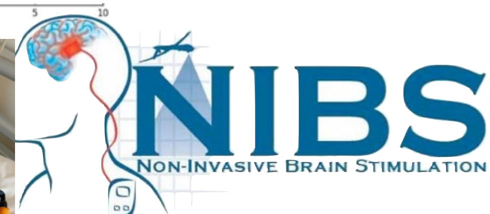
Applications ML as Digital Markers

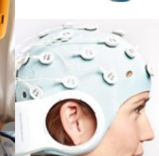


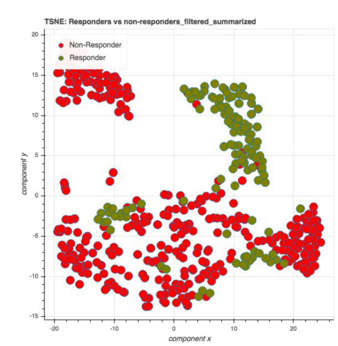
Building better biomarkers: brain models in translational neuroimaging

- Risk assessment, conversion prediction and early detection - Parkinsons
- Differential diagnosis and subtyping - ADHD
- Predicting treatment outcome
  - brain measures to predict who will respond to a particular treatment - tCS in DoC









Thanks

Eleni Kroupi

Marta Castellano

Aureli Soria-Frisch

Giulio Ruffini

Andrés Rojas

David Ibáñez


THANKS!
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