The contribution of new technologies in the diagnosis and treatment of Parkinson's disease: The i-PROGNOSIS project

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Overview

- Introduction to Parkinson's Disease and digital biomarkers
- Overview of the i-PROGNOSIS project
- Early detection of symptoms of Parkinson's Disease
- Interventions for Parkinson's Disease patients

Parkinson’s Disease (PD)

One
of the commonest neurodegenerative diseases

1%
Of individuals over 60 years; **4%** over 75 years

Parkinson's Disease (PD)

Progressive
Subtle symptoms that go unnoticed

~2.2 M
Disability adjusted life years (DALYs)

Diagnosis

May take 10 years after disease onset

Prodromal PD
Hyposmia / Sleep disorder / Constipation / Anxiety / Depression

Motor symptoms

Stable PD
Predictable response to dopamine / No motor fluctuations

Impact on life quality

Daily activities are affected

Movement → Tremor, Bradykinesia

Walking → Slowness/Freezing of gait

Eating → Constipation

Talking → Hypophonia

Writing → Micrographia

Sleeping → REM behaviour disorder

Mood → Anxiety/Depression

Expression → Hypomimia

Digital biomarkers & endpoints

Definitions

Digital biomarker

Objective, quantifiable physiological or behavioural data collected and measured via digital (mobile) devices that are used to predict and/or assess a health-related outcome.

Digital endpoint

In clinical trials, a digital measurement (i.e., a digital biomarker) used to assess the effectiveness of an intervention, e.g., drug response, based on change.

Focus on digital biomarkers / endpoints measured with accessible devices in users' environment

Example of digital biomarkers

That can be captured with mobile & wearable devices

- Heart rate (variability)
- Number of Steps
- Time spent walking
- Total sleep time
- Blood oxygen saturation
- Blood pressure
- Inter-tap interval
- Skin temperature
- Gait speed
- Hand steadiness

Digital Biomarkers & PD

Benefits

+ Improve diagnosis

Enable population screening, including the earliest possible (prodromal stages), to accelerate clinical diagnosis

+ Remote monitoring

Important for patients in remote areas or in times of social distancing.

+ Monitor therapy response

Monitor ON-OFF periods, motor fluctuations and dyskinesias and fine-tune treatment

Technology enables new type of studies

Remote data- crowdsourcing studies

- Use of existing smartphone and wearable for study enrolment and data acquisition
- Remote electronic consent
- Large-scale participation and data collection

Technologies for PD assessment

Screening / assessment of

Motor symptoms
Tremors
Bradykinesia
Posture / balance problems
Gait impairment

Non-motor symptoms

Types of sensors

Inertial Measurement Unit (IMU)

Includes accelerometer and gyroscope - measures motion.

Microphone

Records sounds of interest, e.g., voice and biomedical sounds.

Heart rate sensor

Records heart rate (variability), usually via photoplethysmography.

Touchscreen

Provides coordinates, timing and pressure of touch events.

Camera

Capturing of still photos and videos - can be used for skeleton tracking.

Electrogastrograph

Records electrical activity from the abdominal area.

Approaches to symptom detection / assessment

Tremors

Key sensors: IMU (usually on wrist, finger or palm)

Rest tremor via smartwatch
Device: Wrist wearable (e.g. smartwatch)
Passive measurement: user wears smartwatch during the day
Monitoring Movement Disorders

Postural tremor via smartphone
Device: Smartphone
Passive measurement: user holds smartphone during phone call
Detecting Parkinsonian Tremor From IMU Data Collected in-the-Wild Using Deep Multiple-Instance Learning - IEEE Journals & Magazine

Rest tremor via smartphone
Device: Smartphone
Active measurement: user holds smartphone with hand at rest
Evaluation of smartphone-based testing to generate exploratory outcome measures in a phase 1 Parkinson's disease clinical trial

Bradykinesia

Key sensors: IMU (wrist), touchscreen, camera

Bradykinesia score via wrist wearable

Device: Wrist wearable / Sensor: IMU

Passive measurement: user wears the device during the day

Evaluation of the Parkinson’s KinetiGraph in monitoring and managing Parkinson’s disease

Finger tapping test on smartphone

Device: Smartphone / Sensor: Touchscreen / Data: timing of touch events

Active measurement: user taps alternately two touchscreen buttons

Evaluation of smartphone-based testing to generate exploratory outcome measures in a phase 1 Parkinson's disease clinical trial

Bradykinesia score from typing

Device: Smartphone / Sensor: Touchscreen / Data: keystroke dynamics

Passive measurement: users does routine typing on smartphone

Screening of Parkinsonian subtle fine-motor impairment from touchscreen typing via deep learning

Gait & Balance impairement

Key sensors: IMUs

Gait & balance features from multiple wearables on limbs and torso

Device: Wearable / Sensor: IMU

Passive measurement: user wears the device during the day

Potential of APDM mobility lab for the monitoring of the progression of Parkinson's disease

Gait monitoring with smart insoles

Device: Smart insole / Sensor: Touchscreen

Passive measurement: users wears shoes with smart insoles during ambulation

Wearable Solutions for Patients with Parkinson's Disease and Neurocognitive Disorder: A Systematic Review

Non-motor symptoms

Sleep measurement via wrist wearable
Device: Wrist wearable / Sensor: IMU
Passive measurement: user wears the device during sleep
Features: Total sleep time, sleep onset latency, sleep fragmentation index, wake after sleep onset
Sleep in Parkinson's Disease: A Comparison of Actigraphy and Subjective Measures

Gastrointestinal activity via smart belt to detect constipation
Device: Smart belt / Sensor: Microphone array / Data: Bowel sounds (BS)
Active measurement: user wears smart belt at rest
Features: No of BS / minute, Sound-to-sound interval
i-PROGNOSIS D3.5 - First version of SData analysis modules (Section 4.4

i-PROGNOSIS project

i-PROGNOSIS

Intelligent Parkinson's Disease Early Detection Guiding Novel Supportive Interventions

H2020 – Research and Innovation Action

2016 – 2020

11 partners

6 countries

~4M €

Project coordinator
Aristotle University of Thessaloniki

AGE Platform Europe

CERTH
CENTRE FOR RESEARCH & TECHNOLOGY HELLAS

COSMOTE

fMH

Fraunhofer IAIS

Karolinska Institutet

KING'S College LONDON

Microsoft
Microsoft | Innovation Center Ελλάς

plux

TECHNISCHE UNIVERSITÄT DRESDEN

01

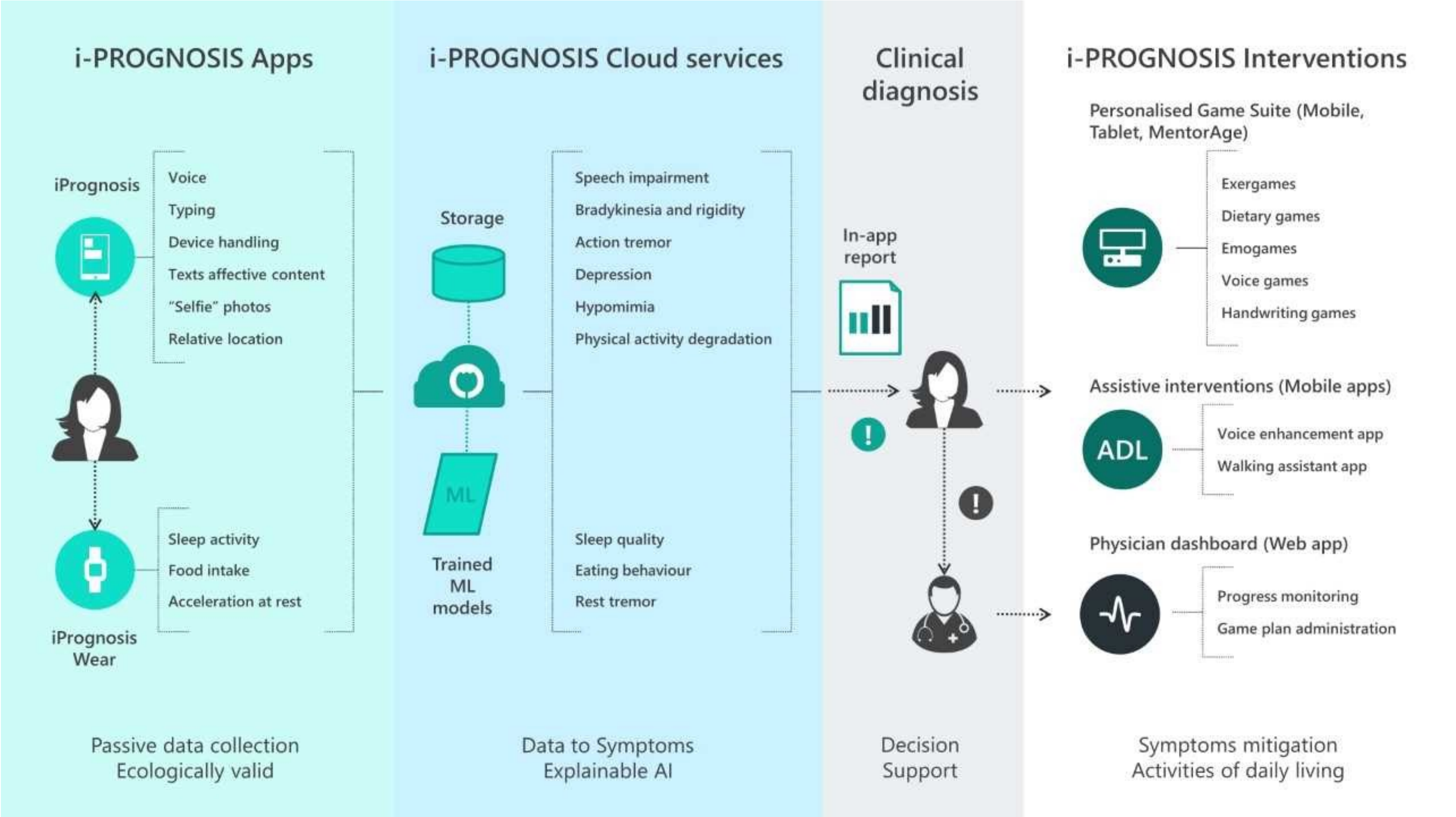
Early PD Detection

02

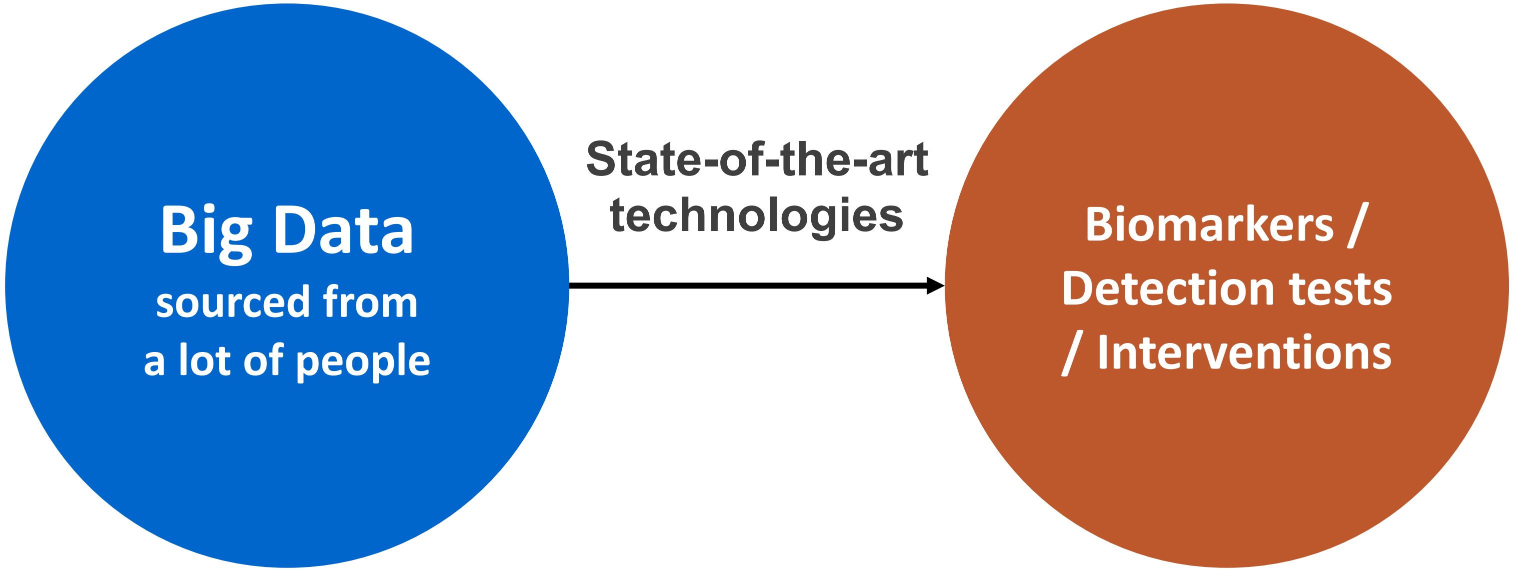
PD Support

i-PROGNOSIS Project Objectives

The i-PROGNOSIS concept



Main characteristics



PD Symptoms Detection

Source data from people

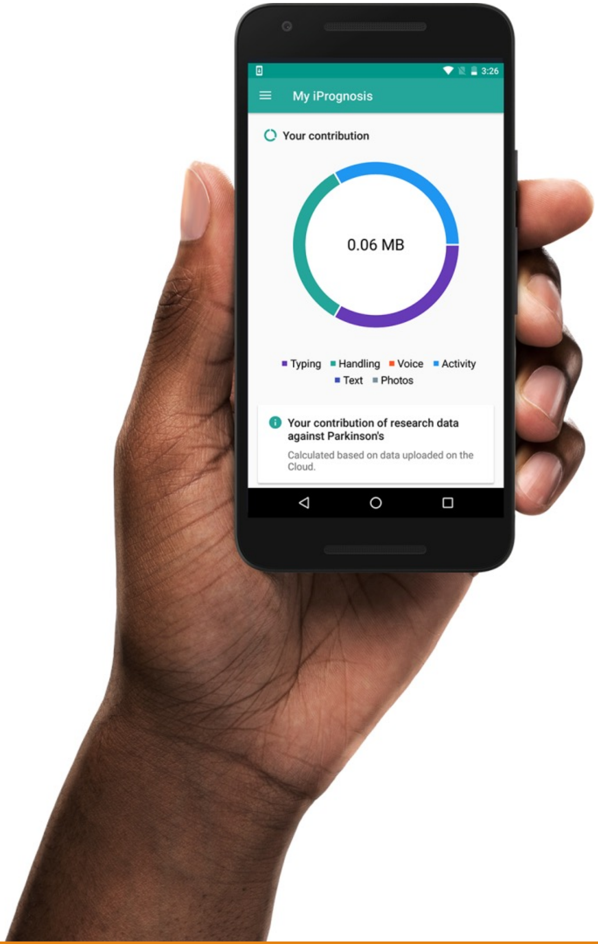
Unobtrusively

Via a dedicated mobile application

No user interaction required

<u>Target</u>

Build early PD detection tests



Sensors employed / Data captured

Smartphone

Detect early minor tremor that may relate to Parkinson's

- Accelerometer + gyroscope

Evaluate voice quality (hypophonia)

- Samples of voice during calls

Detect minor motor symptoms (rigidity and bradykinesia)

- Touchscreen typing dynamics

Evaluate facial motion and reveal possible masked-face

- Selfies

Sensors employed / Data captured

Smartwatch

Detect minor tremor at rest

- Accelerometer + gyroscope

Track eating behavior in order to detect eating disorders

- Accelerometer + gyroscope

Identify sleep quality in order to detect sleep disorders

- Accelerometer + gyroscope + heart rate

Sensors employed / Data captured

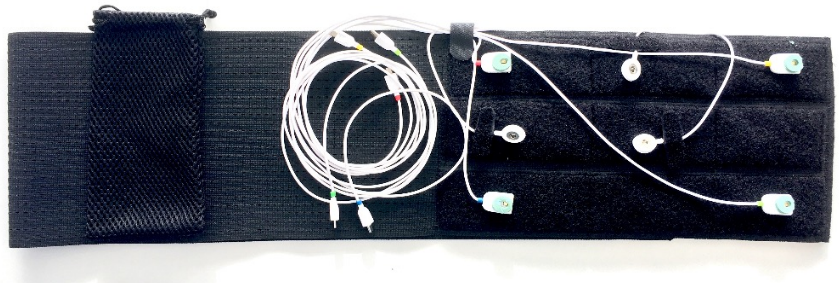
IoT – smart belt

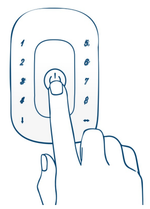
It can sense your bowel sounds

- Microphones
- Detect **bowel motility** and **gastrointestinal disorders**

It can sense your gastric myoelectrical activity

- Adhesive electrodes
- Capture EGG and detect **gastrointestinal disorders**



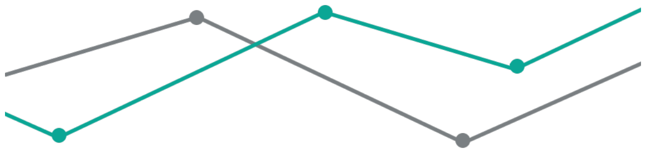


Big Data and Machine Learning

Sensed data alone provide little information.

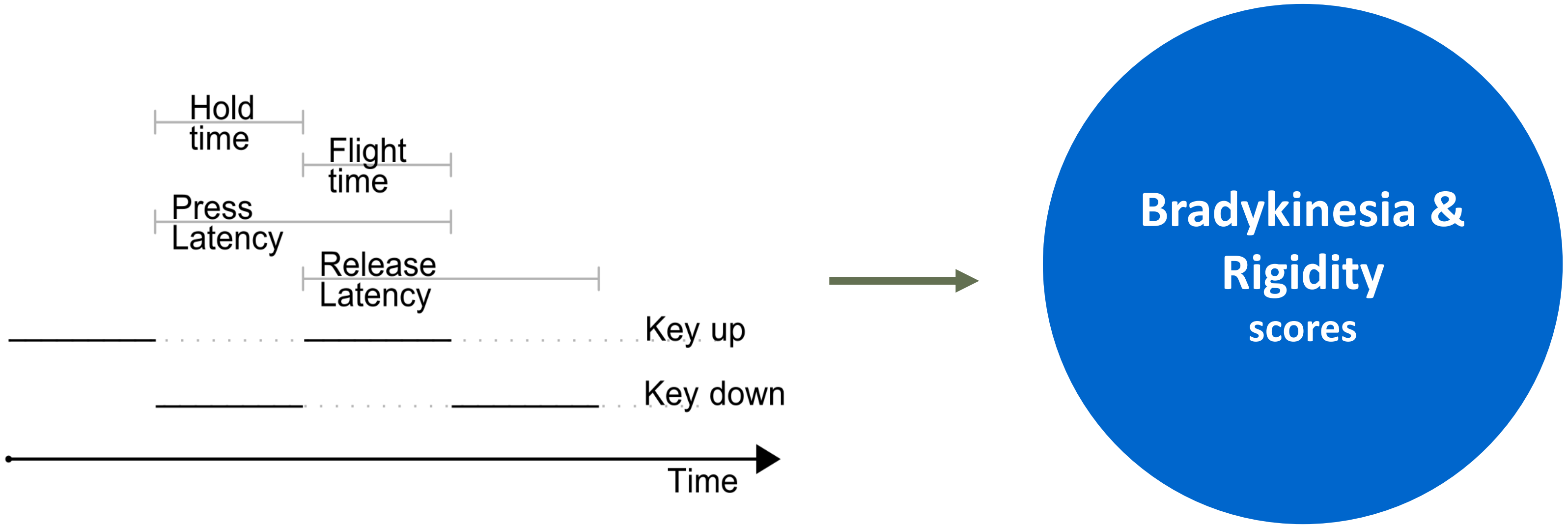
The important things lie hidden and processing / learning algorithms come to the rescue.

Hidden trends in measurements, characteristics of the signals and more can come to light through algorithmic processing and provide information about changes



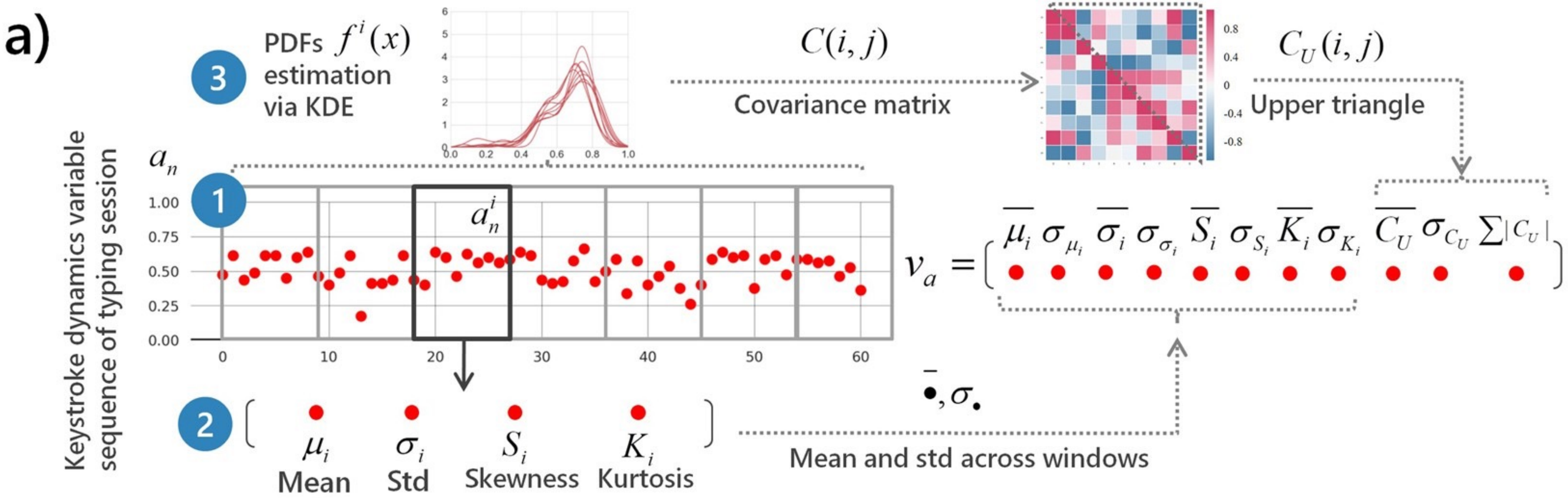
Keystroke dynamics analysis

Keystroke dynamics analysis



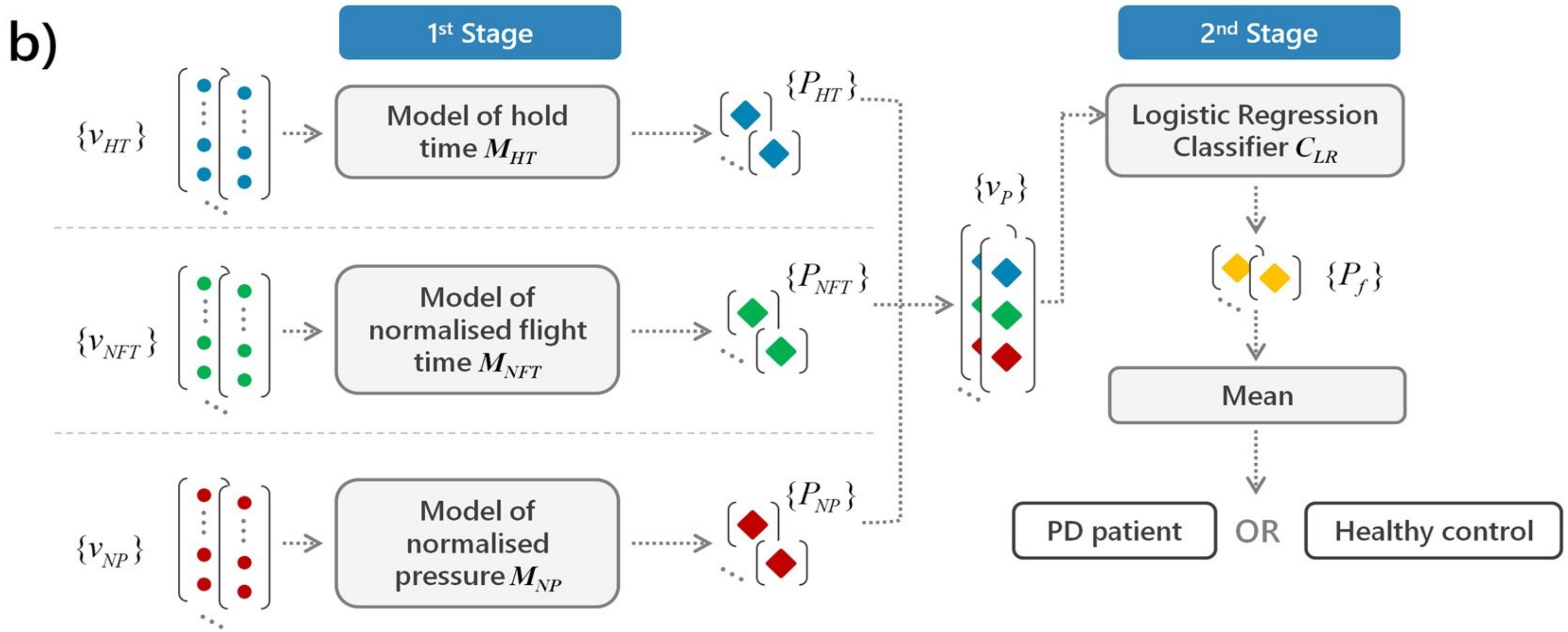
Hold Time: the time when each key is sustained pressed; Flight time: the time between a key release until the pressing of the next one; Press Latency: the time between the pressing of a key until the pressing of the next one; Release Latency: the time between the release of a key until the release of the next one.

Approach



Given a keystroke dynamics variable sequence a_n, $a \in \{HT, NFT, NP\}$: (1) The sequence is split in subsequences a_{ni} using 15-seconds non-overlapping time windows; (2) For each subsequence, the first- up to fourth-order statistical moments (mean μ_i, standard deviation σ_i, kurtosis K_i, and skewness S_i) of the elements are computed; (3) The probability density function (PDF) $f_i(x)$ of each subsequence is estimated through kernel density estimation (KDE) and the matrix of sample covariance $C(i, j)$ between the PDFs of all subsequences is calculated. Feature vectors v_a representing each typing session are formed by the mean $\bar{\bullet}$ and standard deviation (std) $\sigma_\bullet$ of the moments extracted in (2), across time windows (subsequences), and the mean, std and sum of absolute values of the upper triangle $C_U(i, j)$ of the covariance matrix calculated in (3).

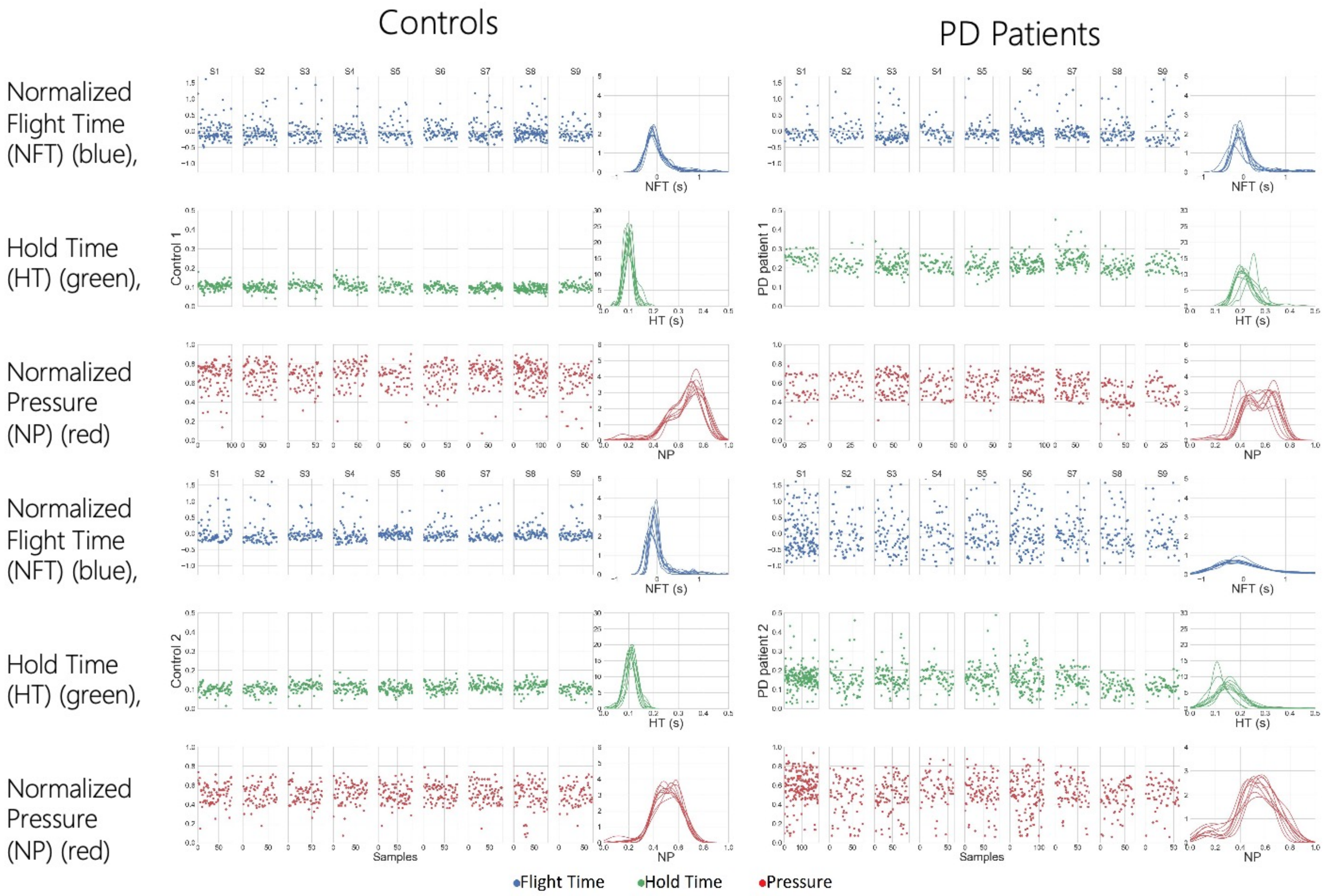
Approach



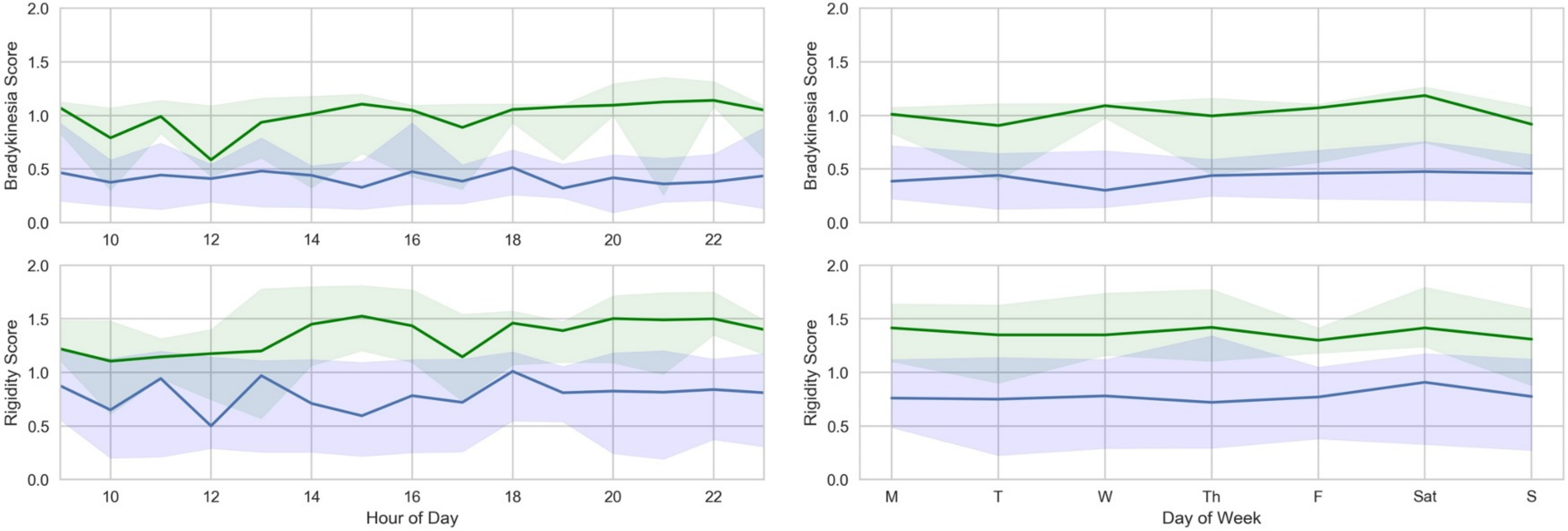
The proposed two-stage multi-model pipeline for classifying subjects as PD patients or healthy controls: (1st Stage) Feature vector sets {v_a} of a given subject, with each vector representing a typing session, serve as input to three trained models M_a, each one dedicated to a keystroke dynamics variable, $a \in$ {*NFT*, *HT*, *NP*}. Models M_a yield three prediction probabilities P_a which are then grouped in new feature vectors v_P; (2nd Stage) Feature vector set {v_P} serves as input to a Logistic Regression classifier C_{LR} that outputs the final classification probabilities {P_f} denoting whether each typing session belongs to a PD patient or a healthy control. Finally, the mean of prediction probabilities P_f is used to categorise the subject as PD patient or healthy control

Example

- Controls exhibit similar behaviour across all variables.
- Differentiations in the behaviour of PD patients when compared to each other, as well as healthy subjects.
- PD Patient 1 exhibits similar values to controls in terms of NFT and NP, but clearly higher HT values.
- PD Patient 2 produced more wide-spread values for all keystroke dynamics variables in comparison to controls



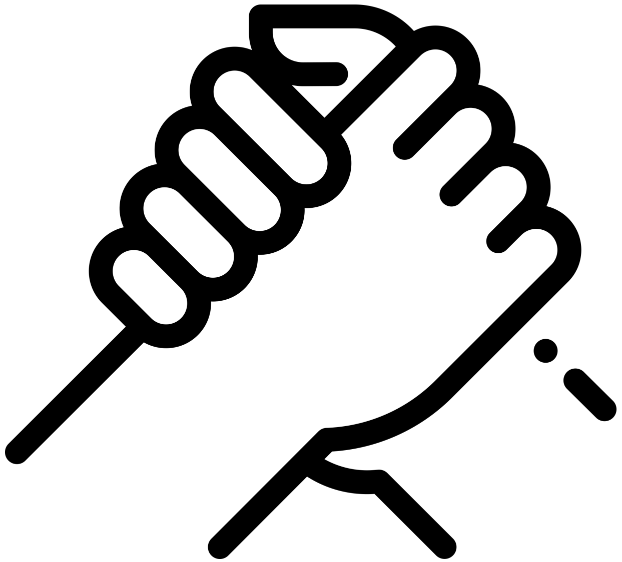
Response of the estimated indices across time



PD (green); Controls (blue)

Interventions

Interventions



Personalized Game Suite (PGS)

Targeted Nocturnal Intervention (TNI)

Assistive interventions

PGS adaptation algorithm

Personalised Game Suite

Serious games

Electronic games designed for a primary purpose other than pure entertainment

Gamification – the disguise of tasks and activities into game playing in order to encourage engagement

Personalised Game Suite (PGS)

ExerGames

Improve physical activity, reduce the presence of tremor

DietaryGames

Affect the nutritional status

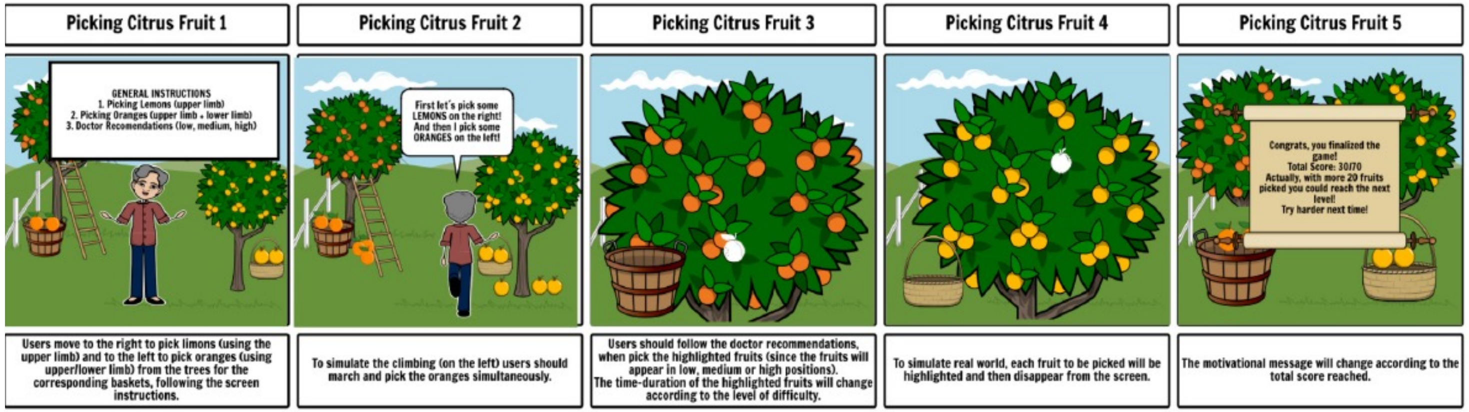
EmoGames

Expressive face encouragement

H/V Games

Enhance handwriting and voice patterns

Co-creation of PGS



Warming-up game

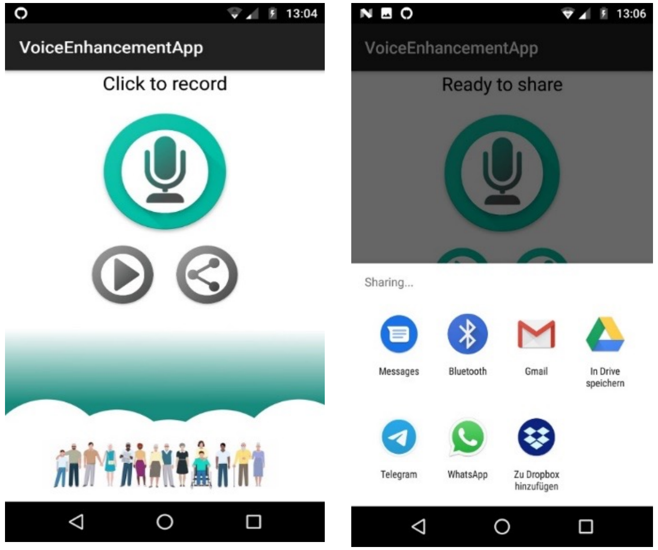
“Fishing” game

Assistive interventions

Assistive Interventions

Voice enhancement

- Smartphone and/or desktop application
- Produces an enhanced version of a voice message
- The user can reproduce voice message or share it via social media apps/email etc.
- Offline processing
- 5 sec. to process 150 sec. recording



Unprocessed **Processed**

Assistive Interventions

Gait rhythmic guidance

- Smartwatch application for Wear OS smartwatches
- Non-invasive mitigation of freezing of gait (FoG) episodes

Target: Mitigation of Freezing-Of-Gate (FOG)

FOG - sudden inability to generate effective stepping and forward progression despite the intention to do so

How: Rhythmic stimulation is the playback of external short-length sounds, such as metronome beats, and haptic feedback, via localised vibrations

Real-time gait pattern analysis module

- Identifies gait velocity, stride frequency and step frequency
- Modulates the playback frequency of the stimuli ty

Assistive Interventions

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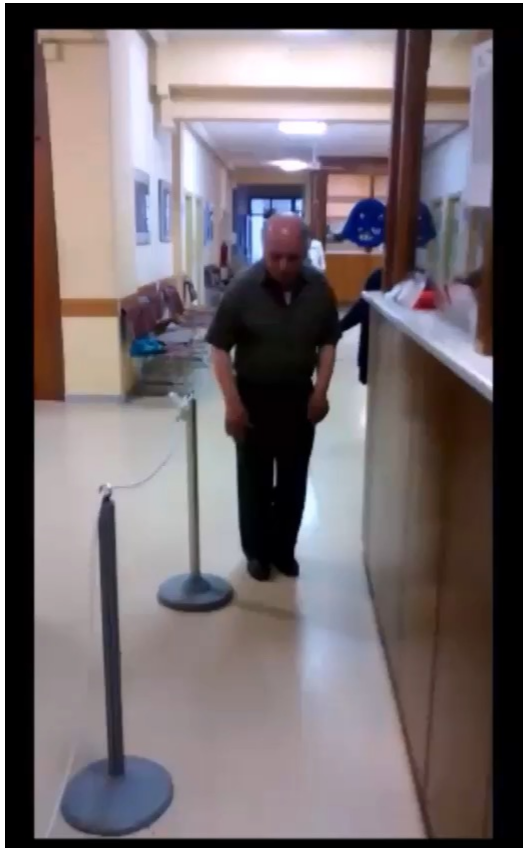


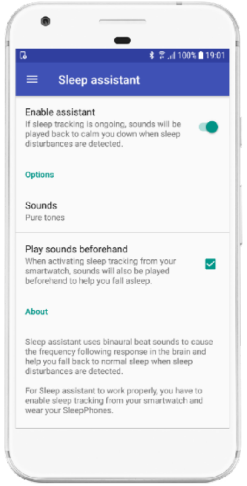
Targeted Nocturnal Intervention

Sleep tracking

Based on smartwatch IMU and heart rate data.

Data processing and sounds playback

Online data processing on smartphone and sound playback triggering



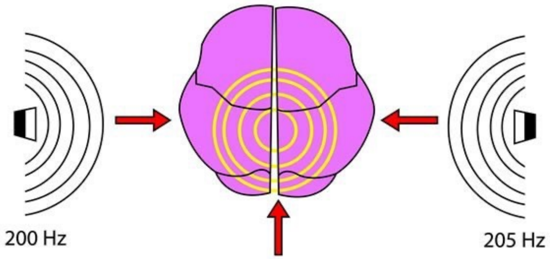
Sound streaming to headphones

Streaming over Bluetooth to headphones worn by the user.

Type of sound→Binaural beat

What is it

Such tones can be further embedded in regular music or sounds.



Why exploit it

Frequency following response (FFR) in the human brain, i.e., the brain produces electrical activity in the same frequency as the frequency difference.

Interesting fact: Untreated PD patients may not perceive binaural beats, but as drug treatment progresses, the ability is reinstated.

Oster, G. (1973). Auditory beats in the brain. *Scientific American, 229*(4), 94-103.