DIGITAL PHENOTYPING

TECHNOLOGIES FOR COLLECTION AND IDENTIFICATION OF DIGITAL BIOMARKERS IN NEUROLOGY AND MENTAL HEALTH

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Professor, Dept. of Health Technology, Technical University of Denmark

About me

Jakob E. Bardram

- Professor in **Digital Health** at **DTU Health Tech**
  – background in computer science, economics, and psychology
  – University of Aarhus (AU) & University of California at Irvine (UCI)
- Professor at AU and ITU before joining **DTU** in 2015
- Primary teaching & research areas
  – programming & **software** architecture (object-oriented)
  – **data** analysis (AI/ML)
  – **medical informatics** – electronic patient records, clinical logistics, standards
  – **mobile health** – psychiatry, neurology, diabetes, cardiology
- Entrepreneur
  – **co-founder** of 4 companies – e.g., Cetrea A/S and Monsenso A/S

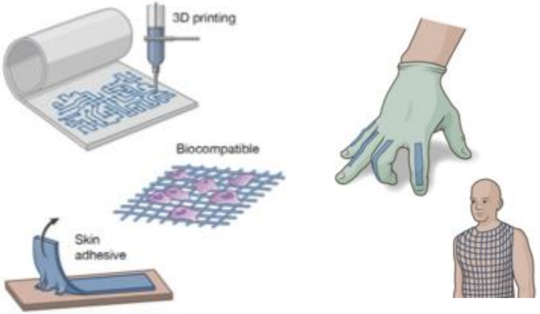
www.bardram.net

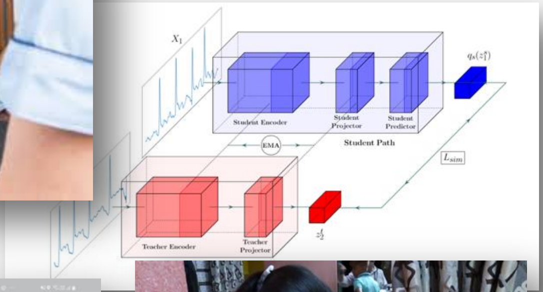
Digital Health at DTU Health Tech

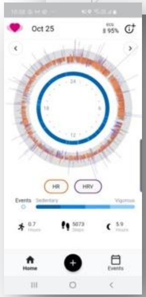
#1 Biocompatible and flexible electronics for wearable and implantable sensor technology

#2 Biomedical signal processing and health data science

#3 Personalized health technology and digital phenotyping







Outline

DIGITAL PHENOTYPING

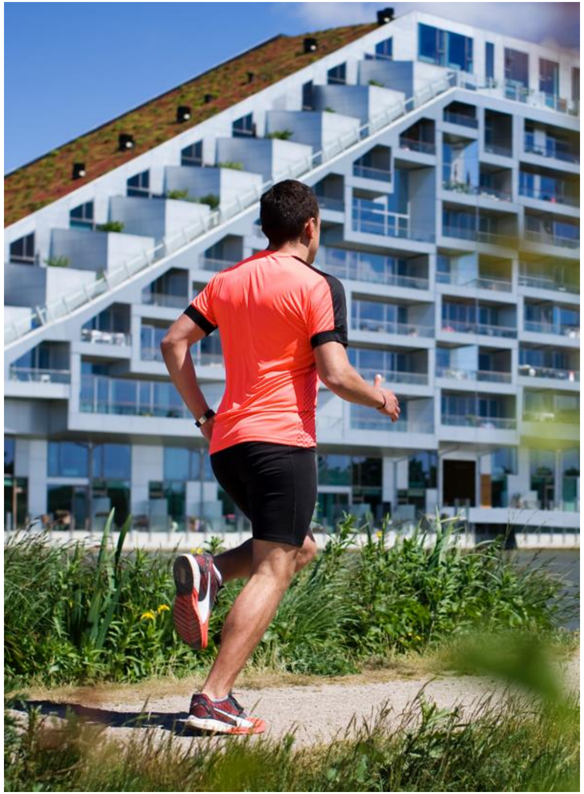
- Digital Phenotyping
- Digital Biomarkers

COPENHAGEN RESEARCH PLATFORM (CARP)

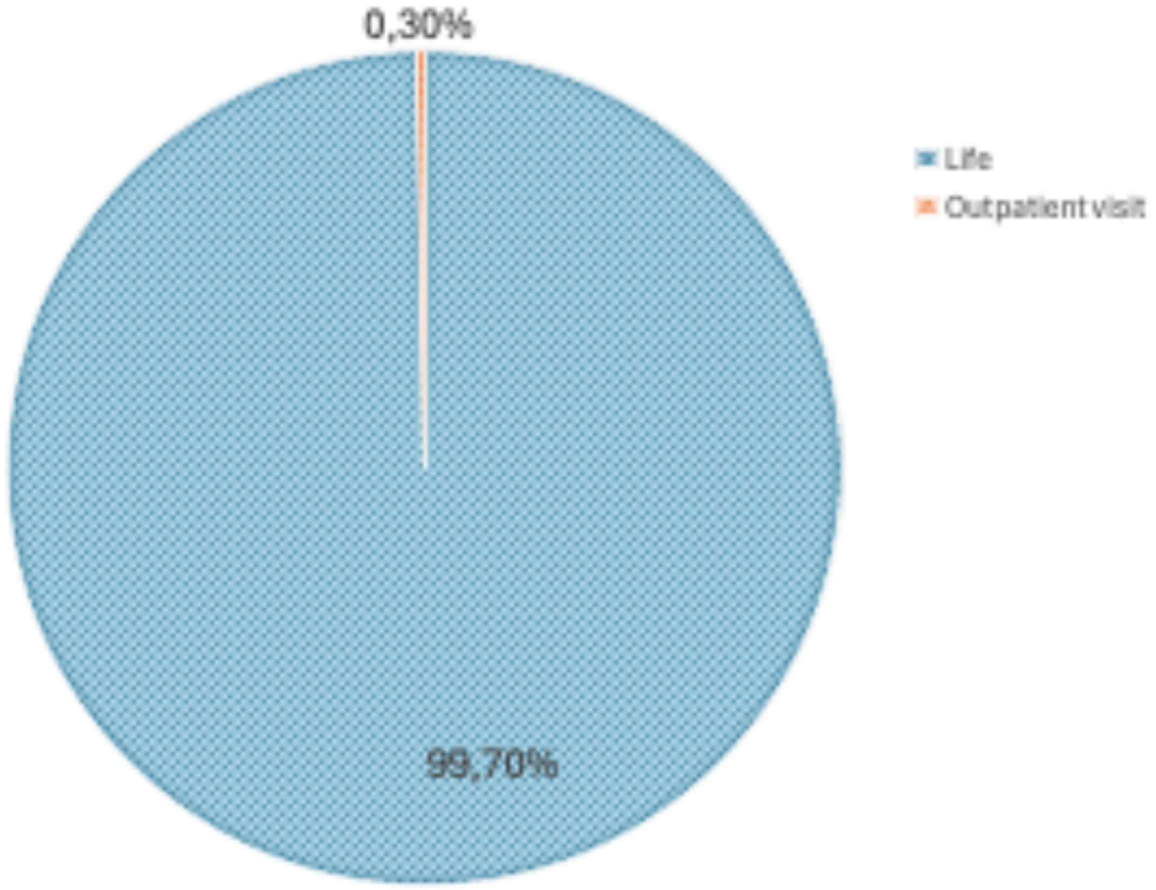
- Components
- Data collection | Devices | PRO | Cognition

CASES

- Psychology
- Psychiatry
- Neurology

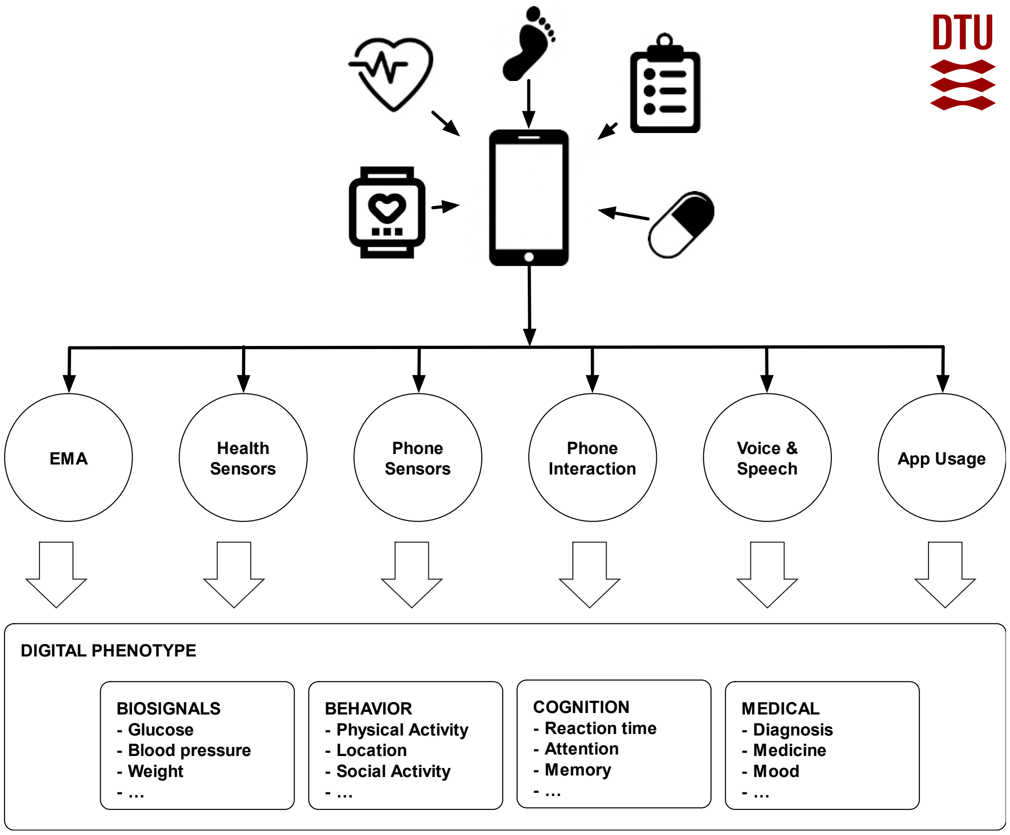


Digital Phenotyping

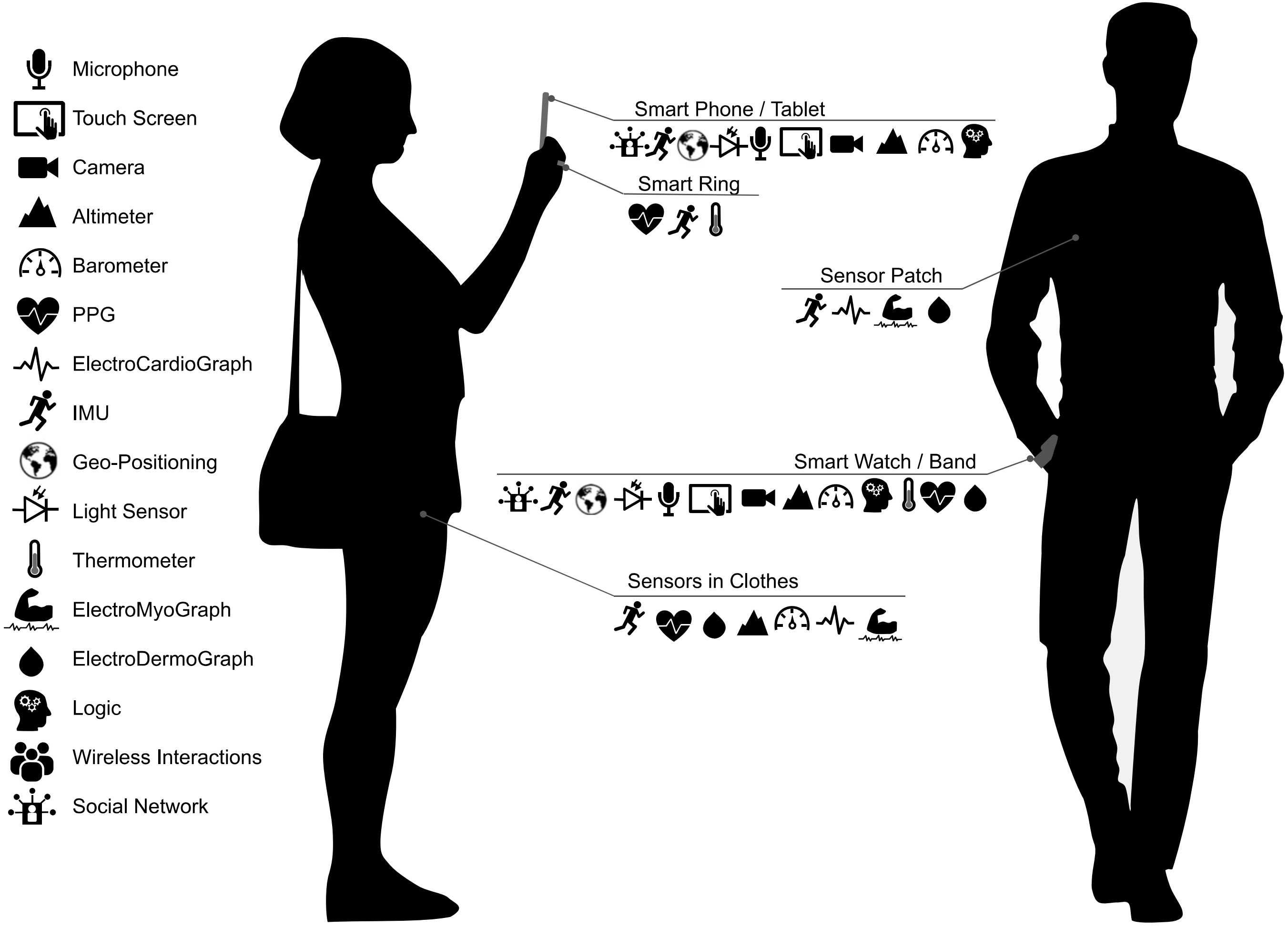

0,30%
99,70%
Life
Outpatient visit

Digital Phenotyping

- **Continuous**
  – 24/7, longitudinal, everywhere
- **Ambulatory**
  – "in-the-wild", at home, daily life, ...
- **Unobtrusive**
  – consumer / everyday technology
  – mobile & wearable sensing
- **Large N's**
  – large-scale deployment
  – "cheap" technology
- **Inference & Insights**
  – behavior, cognition, health, ...
  – based on health data science (AI/ML)



- JP Onnela & SL Rauch (2016). Harnessing Smartphone-Based Digital Phenotyping to Enhance Behavioral and Mental Health. *Neuropsychopharmacology*. 41(7): 1691–1696.
- SH Jain, BW Powers, JB Hawkins & JS Brownstein (2015). The digital phenotype. *Nat Biotech*, 33(5), 462–463.
- TR Insel (2017). Digital phenotyping: Technology for a new science of behavior. *JAMA*, *318*(13), 1215–1216.



Kourtis, L. C., Regele, O. B., Wright, J. M., & Jones, G. B. (2019). Digital biomarkers for Alzheimer's disease: the mobile/wearable devices opportunity. *NPJ digital medicine*, *2*(1), 9.

Biomarkers & Digital Biomarkers

- **Biomarker** [1]
  - a defined characteristic
  - that is measured as an **indicator** of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions
  - e.g., **blood pressure**
- **Digital biomarker** [2]
  - a characteristic or set of characteristics
  - collected from **digital health technologies**,
  - that is measured as an **indicator** of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.
  - e.g., **location entropy** extracted from the phone's GPS as an early indicator of depression
  - e.g., **cardiovascular features** extracted from wearable devices to identify atrial fibrillation

1. U.S. Food and Drug Administration. Patient-Focused Drug Development: Collecting Comprehensive and Representative Input. Final guidance document.

2. Vasudevan, S., Saha, A., Tarver, M.E. *et al.* Digital biomarkers: Convergence of digital health technologies and biomarkers. *npj Digit. Med.* **5**, 36 (2022).

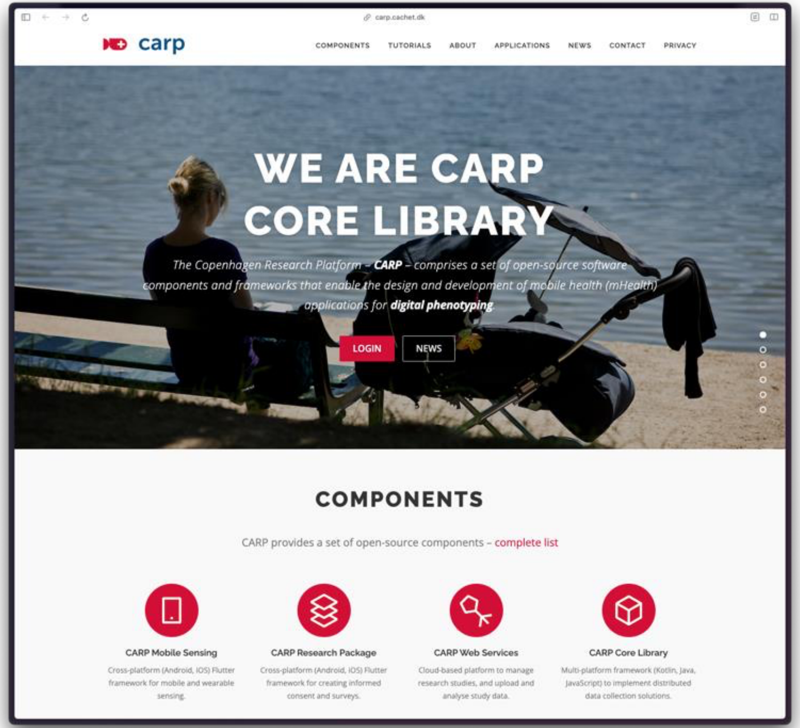
The Copenhagen Research Platform (CARP)

Copenhagen Research Platform – CARP

Large-scale data science platform for digital phenotyping and mobile health technology

- **Open-source programming framework**
  - components & frameworks for the design of mHealth applications
  - used to create disease-specific solutions
  - developed and shared with research & industry partners (open source)

- **“Out-of-the-Box” Study Hosting**
  - CARP instance hosted @DTU Computerome (HPC)
  - GDPR compliant for Danish researchers
  - configurable study setup
  - standard participant phone app
  - large-scale analysis of data



carp.dk

CARP Components

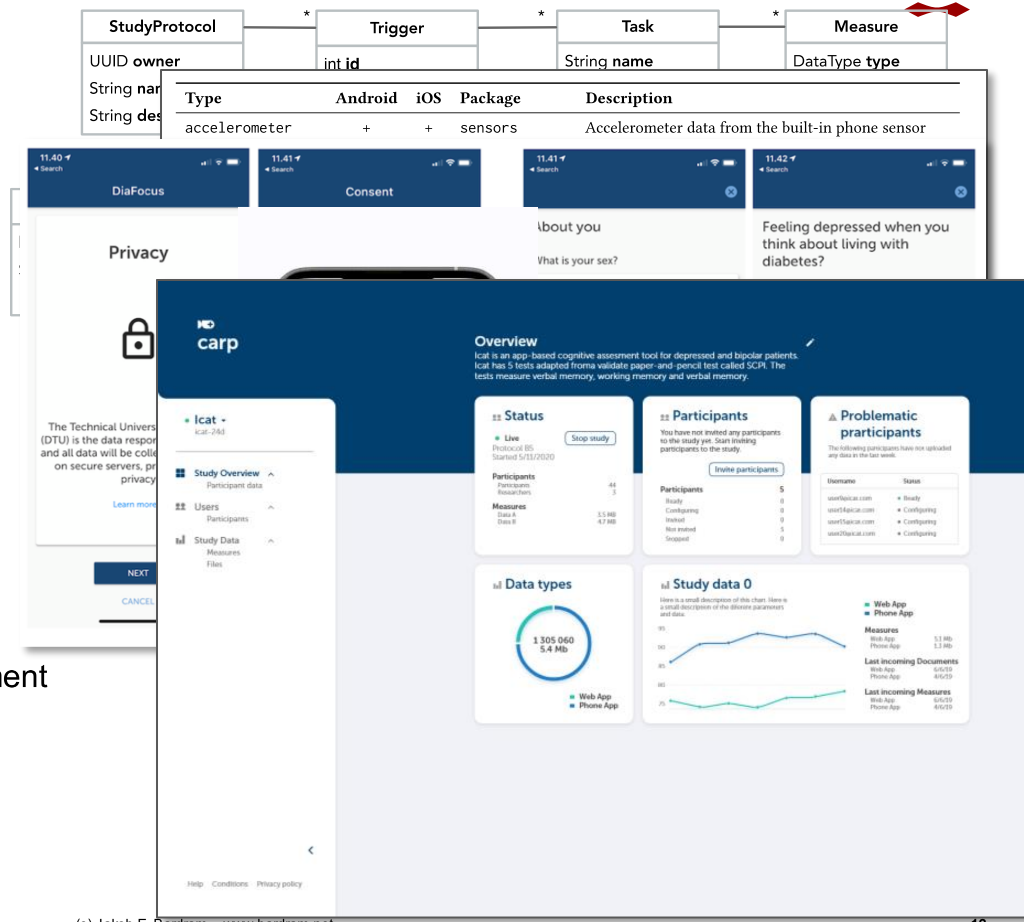
CARP Core
- domain model and standards

CARP Mobile Sensing (CAMS)
- mobile & wearable sensing framework

CARP Research Package
- informed consent & survey framework

CARP Cognition Package
- cognitive test framework incl. 14 pre-made tests

CARP Web Services (CAWS)
- cloud-based infrastructure for data management



Data Collection

Physiological
- weight, height, ...
- ECG, HR, HRV, blood pressure...
- Blood glucose

Behavioral
- physical activity (steps, movement, ...)
- social activity (communication, calendar, messaging, ...)
- phone usage (screen, connectivity, ...)

Contextual
- location (geo-position, geofence, ...)
- weather, air quality

Patient-Reported
- surveys
- ecological momentary assessments (EMA)
- audio & video

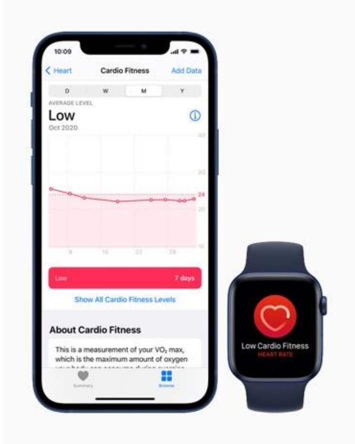
Cognition
- 8 Neurocognitive domains
- 14 validated gold-standard cognitive tests

Plug-in Model for Devices

- Movisens (activity, ECG, EDA)
- Nokia Bell Labs eSense (noise, activity)
- Polar Sense & H10 (HR/ECG)
- Empatica E4 (HR, GSR, activity)
- Dexcom (CGM)

- Apple Health
- Google Health Connect

- Dexcom (CGM)
- Garmin (activity, sleep, HR, ...)
- Fitbit (activity, sleep, HR, BP, ECG, weight,
- Withings (activity, sleep, HR, BP, ECG, weight, ...)

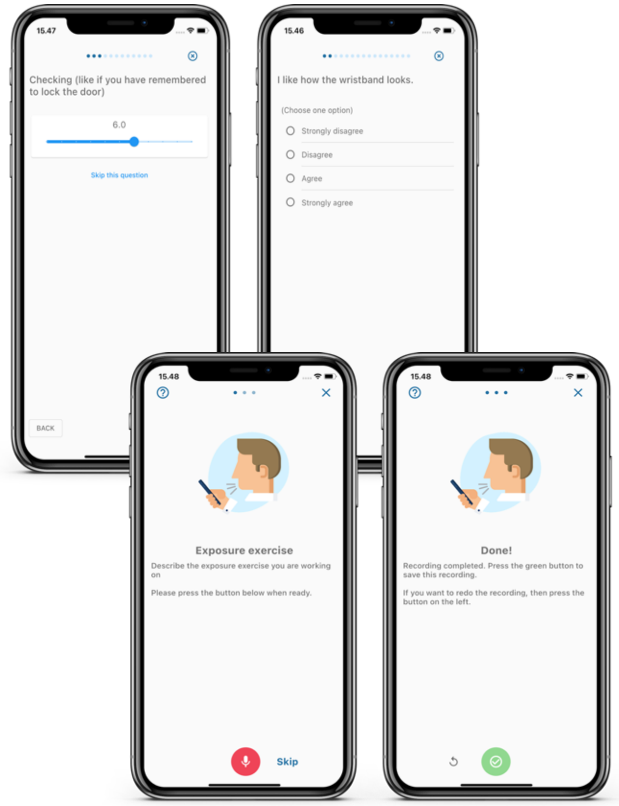


Patient Reported Data (PRO)

- Informed Consent

- Questionnaires / Surveys
- Ecological Momentary Assessment (EMA)

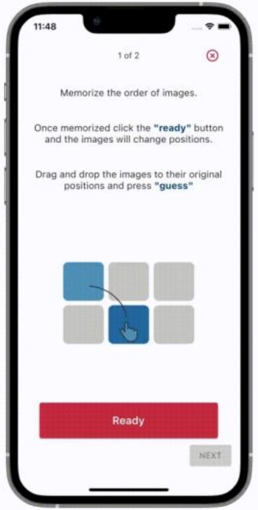
- Image Capture
- Audio Recording
- Video Recording



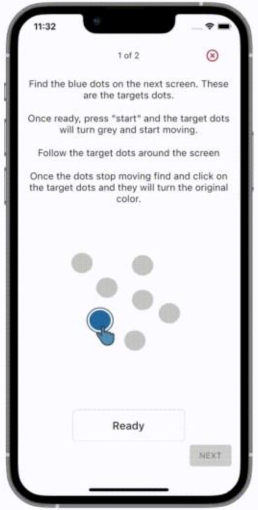
Cognition

- 14 validated gold-standard cognitive tests

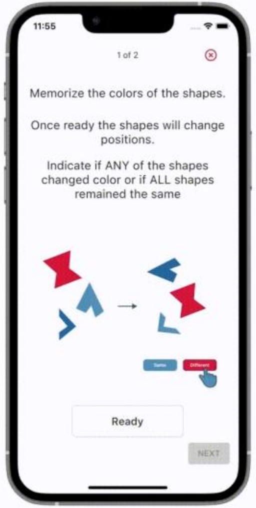
- 8 Neurocognitive domains
  - Sensation
  - Perception
  - Motor skills and construction
  - Attention and concentration
  - Memory
  - Executive functioning
  - Processing speed
  - Language and verbal skills



Picture Sequence Memory



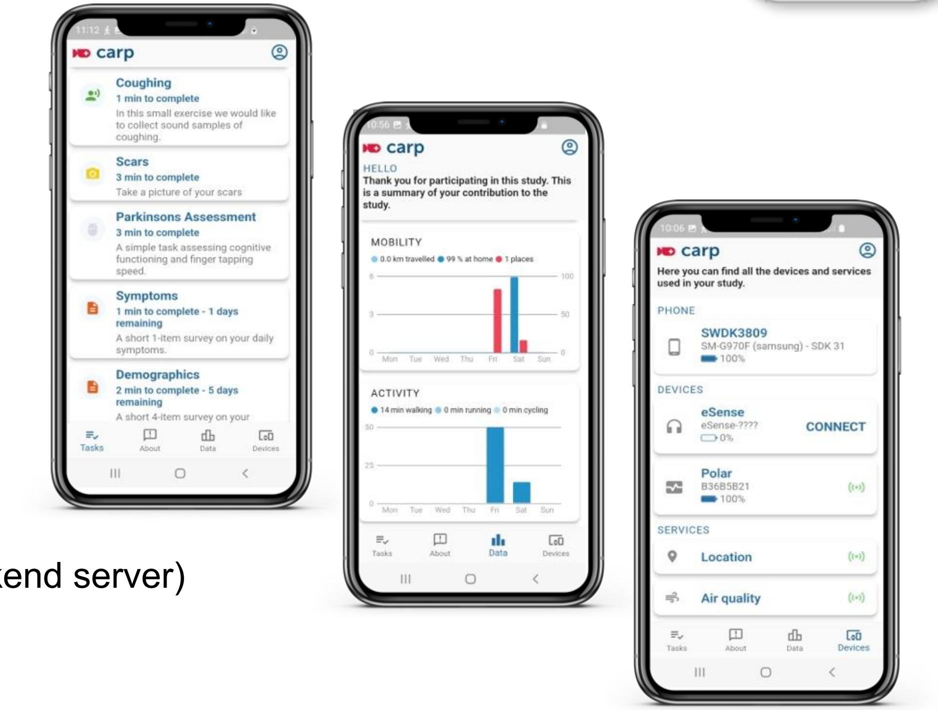
Multiple Object Tracking



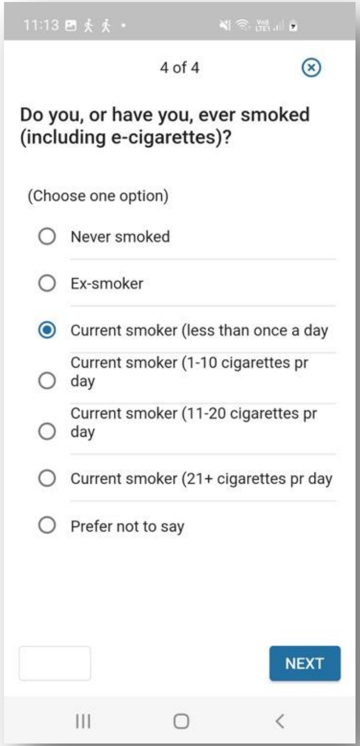
Visual Array Change

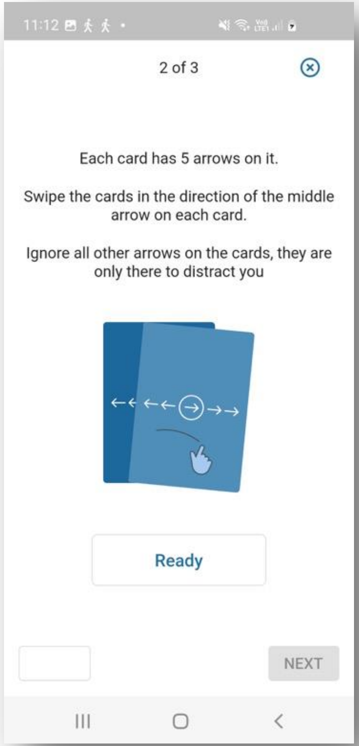
“CARP Studies” App (standard, out-of-the box)

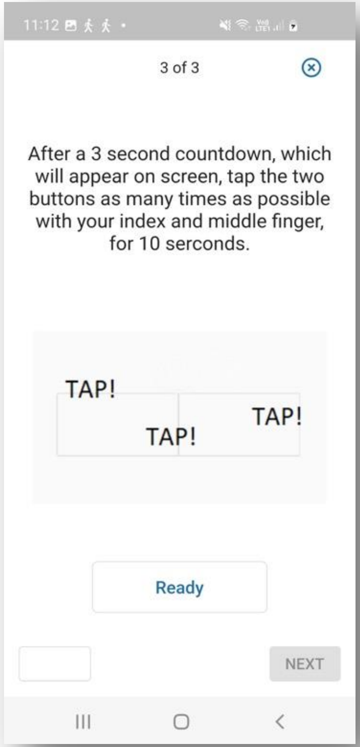
- Triggering of **user tasks**
  - surveys, cognitive tests, EMAs, ...
  - notifications
- **Sensor** data collection
  - on-board mobile sensing
  - wearable devices
- Informed Consent (**eConsent**)
- On-going study **information**
- **Internationalization** (DA, EN, ES, FR, ...)
- **Cross-platform** (Android & iOS)
- Infrastructure-independent (**upload** data to any backend server)
- **Available** in Apple & Google App Stores



Clinical Outcome Assessment / Digital Biomarker







Clinical Outcome Assessment / Digital Biomarker

Table 2. Hypothetical example of assessing hand function using a smart phone[a].

Concept being measured	Type of measure
Tasking a study participant to complete a structured tapping exercise on the smart phone for measuring location of the tap and time delays between taps for identifying signal for an early sign of a neurological disorder	Digital biomarker
Tasking a study participant to complete a structured tapping exercise on the smart phone for measuring the study participant's functional ability	COA – Performance outcome
Physical function questionnaire that asks a study participant about hand-related activities of daily living	COA – Patient-reported outcome
Clinician observing a study participant complete a hand exercise and grading the participant's performance	COA – Clinician-reported outcome
Life partner reporting observations of spouse doing certain hand-related functions	COA – Observer-reported outcome

[a]These are theoretical examples. The authors do not assert that hand tapping would be a measure of hand function/dexterity without appropriate evaluation of the analytical and clinical evidence.

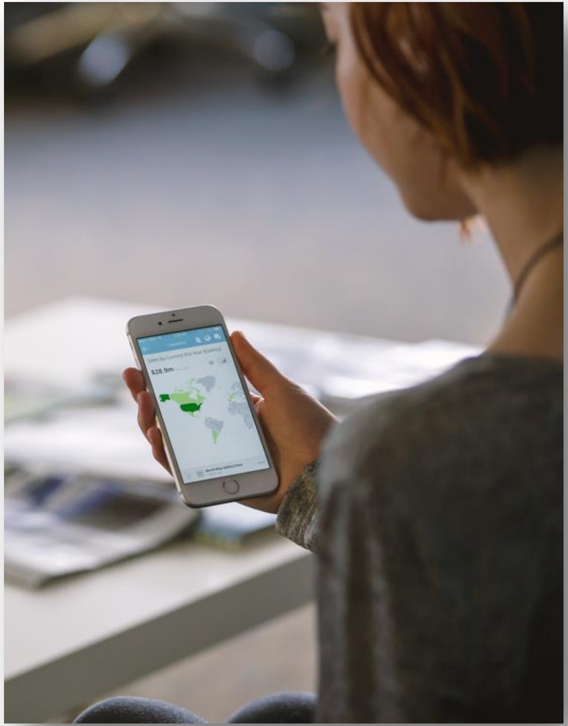
Vasudevan, S., Saha, A., Tarver, M.E. *et al.* Digital biomarkers: Convergence of digital health technologies and biomarkers. *npj Digit. Med.* **5**, 36 (2022).

Digital Phenotyping in Neuroscience

#1 **MONARCA** – Digital Biomarkers in Bipolar Disorder

#2 **ICAT** – Internet-based Cognitive Assessment

#3 **Neuropathy Tracker** – Assessment of Neuropathy



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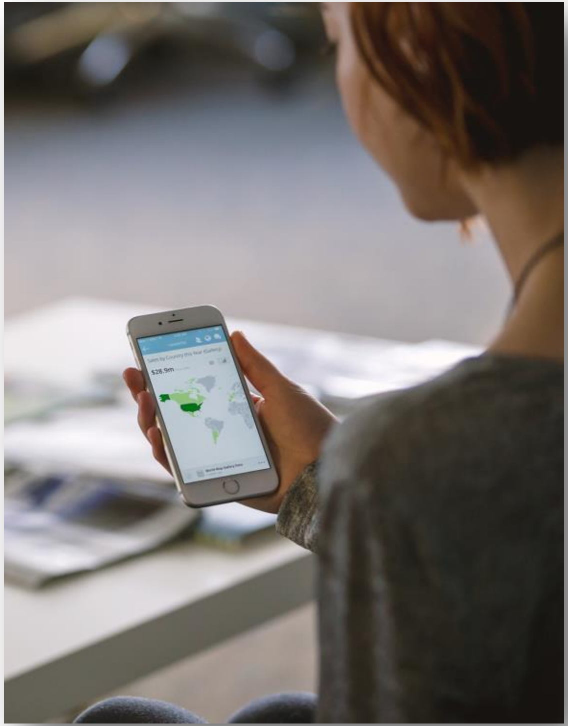
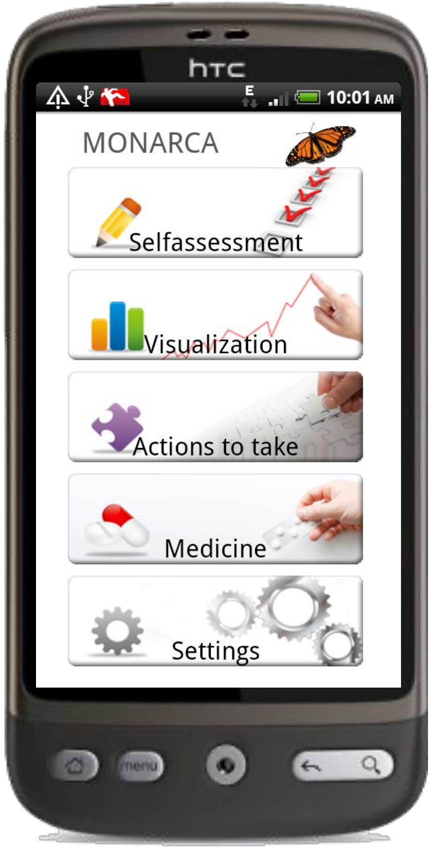


MONARCA Project

- **Bipolar disorder** (manio-depressive)
- EU STREP project | **2010**-2014 | 13 partners
- **Copenhagen** team
  - Psychiatric Center Copenhagen (RegionH)
  - IT University of Copenhagen

- **MONARCA system**
  - **Self-assessment** – mood | sleep | stress | medicine | …
  - **Auto-assessment** – physical activity | mobility | social activity | phone usage
  - **Feedback** – visualizations | medication | actions-to-take | triggers | early-warning-signs | impact factors
  - **Mood forecast** – predict mood for next 5 days



Bardram, J. E., Frost, M., Szántó, K., Faurholt-Jepsen, M., Vinberg, M., & Kessing, L. V. (2013, April). Designing mobile health technology for bipolar disorder: a field trial of the MONARCA system. In *Proceedings of the SIGCHI conference on human factors in computing systems* (pp. 2627-2636).

Double Loop

JE Bardram, MM Frost (2018). Double-loop health technology: enabling socio-technical design of personal health technology in clinical practice. In *Designing Healthcare That Works* (pp. 167-186). Academic Press.

Clinical Validation

- Clinical **STUDY**
  - N=61 | 6 m | 19 m
  - HDRS-17 (depression) and YMRS (manic)
  - 400+ clinical ratings (monthly)

- **RESULTS**
  - significant correlations between YMRS
  - significant correlatio clinical ratings on both HDRS
    - especially when gro ffective states' (3 states)

"Smartphones provide an **easy** and **objective** way to monitor illness activity and could serve as an **electronic biomarker** for depressive and manic symptoms in patients with bipolar disorder."

Table 2. Correlations between self-monitored data[a] collected using smartphones and depressive and manic symptoms measured using the HDRS-17 and YMRS, respectively[b]

	Unadjusted			Adjusted[c]		
	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value
Mood (scale: −3 to +3)						
HDRS-17	−0.055	−0.067 to −0.042	<0.001	−0.058	−0.071 to −0.045	<0.001
HDRS-17 sub-item 1 (mood)	−0.38	−0.45 to −0.30	<0.001	−0.38	−0.46 to −0.31	<0.001
YMRS	0.39	0.016–0.062	<0.001	0.039	0.017–0.062	<0.001
YMRS sub-item 1 (mood)	0.38	0.24–0.53	<0.001	0.38	0.24–0.53	<0.001
Sleep (hours/night)						
HDRS-17	−0.017	−0.048 to 0.014	0.28	−0.02	−0.052 to 0.011	0.21
YMRS	−0.047	−0.088 to −0.005	0.027	−0.047	−0.088 to −0.006	0.026
Acti						
[illegible]	−0.037	−0.053 to −0.020	<0.001	−0.042	−0.059 to −0.025	<0.001
[illegible]	0.047	0.022–0.072	<0.001	0.048	0.023–0.072	<0.001
[illegible]						
[illegible]	047	0.029–0.065	<0.001	0.046	0.027–0.064	<0.001
[illegible]	12	−0.013 to 0.033	0.34	0.012	−0.013 to 0.037	0.35

milton Depression Rating Scale–17 item; YMRS = Young Mania Rating Scale.
ere analyzed for the current day and three days before ratings with the HDRS-17 and YMRS, as
mptoms over the last four days.
ge and sex.

Table 5. Correlations between automatically generated objective data [a] collected using smartphones and *affective states* according to the HDRS-17 and YMRS presented as categorical data [b], respectively[c]

	Unadjusted			Adjusted[d]		
	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value
Incoming calls (no./day)						
Asymptomatic versus mania	0.95	0.076–1.82	0.033	0.97	0.10–1.84	0.029
Duration incoming calls (sec/day)						
Asymptomatic versus hypomania	729.51	334.87–1124.13	<0.001	768.10	374.34–1161.86	<0.001
Outgoing calls (no./day)						
Asymptomatic versus hypomania	2.09	0.38–3.80	0.016	2.08	0.37–3.80	0.017
Duration outgoing calls (sec/day)						
Asymptomatic versus moderate to severe depression	452.17	149.56–754.78	0.003	421.57	111.55–731.60	0.008
Asymptomatic versus hypomania	623.15	173.63–1072.67	0.007	641.53	190.41–1092.65	0.005
Outgoing text messages (no./day)						
Asymptomatic versus mania	4.14	−0.38 to 8.67	0.073	4.42	−0.10 to 8.95	0.055

CI = confidence interval; HDRS-17 = Hamilton Depression Rating Scale–17 item; YMRS = Young Mania Rating Scale.
[a]Averages of the smartphone data were analyzed for the current day and three days before ratings with the HDRS-17 and YMRS, as these rating scales address symptoms over the last four days.
[b]Scores on the HDRS-17 or YMRS ≤ 7 were defined as asymptomatic. Scores on the HDRS-17 or YMRS from 7 to 14 were defined as mild depression or hypomania. Scores on the HDRS-17 or YMRS ≥ 14 were defined as moderate to severe depression or mania.
[c]Analyses including all study participants; total N = 61.
[d]Adjusted for age and sex.

M Faurholt-Jepsen, M Vinberg, M Frost, EM Christensen, JE Bardram, LV Kessing. Smartphone data as an electronic biomarker of illness activity in bipolar disorder. *Bipolar Disorders*. 17(1): 2015

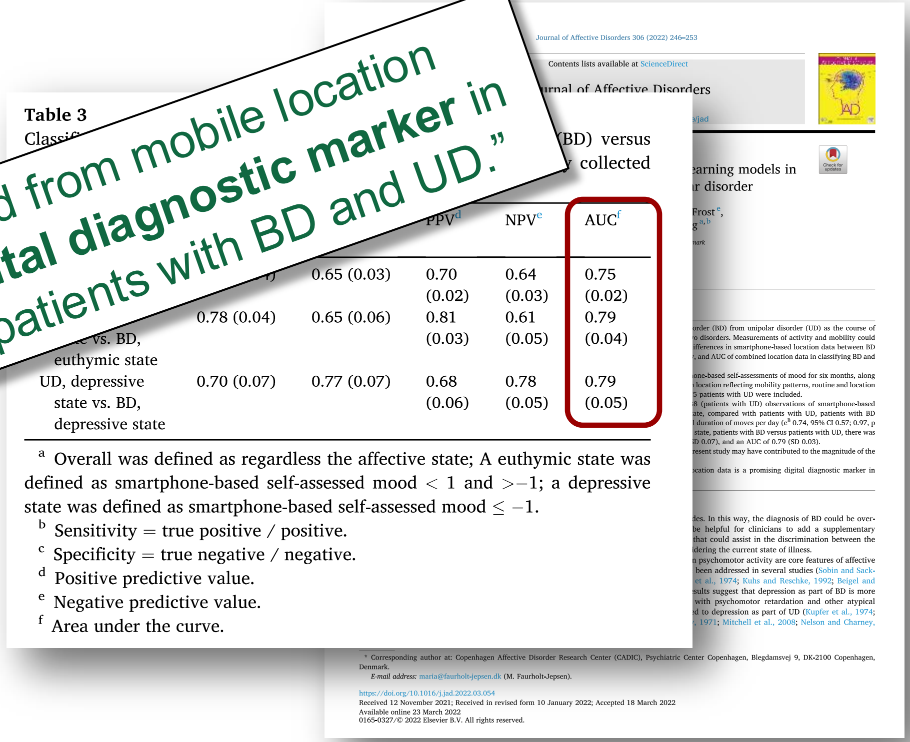
Classification Affective Disorders from Mobility Patterns

- Classification of affective disorders based on mobility patterns
  – bipolar disorder (mania-depression)
  – unipolar disorder (depression)

- T = 6 months
- N = 65 (BD) | N = 75 ...

- Mobility Features
  – no. stops
  – duration stops
  – ...
  – location entropy

"**Mobility patterns** derived from mobile location data are a promising **digital diagnostic marker** in discriminating between patients with BD and UD."



M Faurholt-Jepsen, J Busk, DA Rohani, M Frost, M Tønning, JE Bardram, LV Kessing (2022). Differences in mobility patterns according to machine learning models in patients with bipolar disorder and patients with unipolar disorder. *Journal of Affective Disorders*, *306*, 246-253.

Classification – Voice & Mood (2016 & 2021)

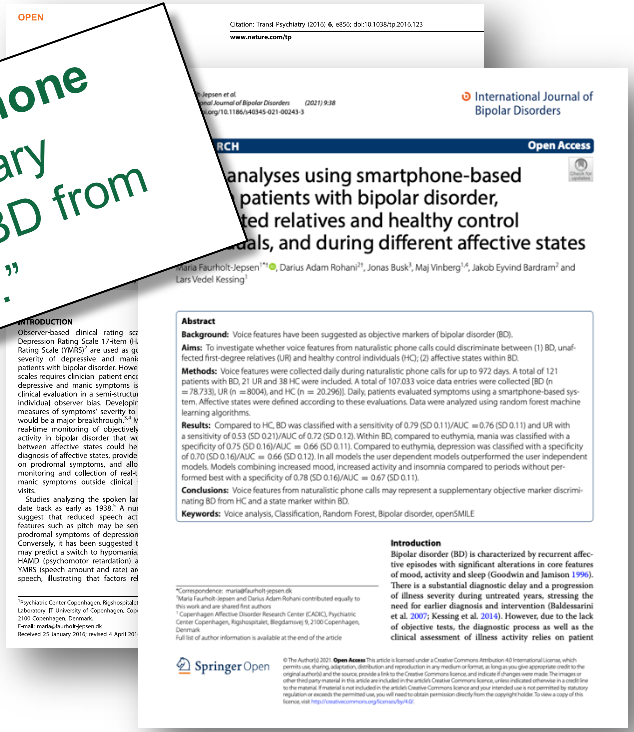
Collection of voice features in naturalistic setting

- N=180 | 972 days
- clinical rating :: HDRS-17 (depression) an
- openSMILE (emolarge)

Classification results

- depressive state : 7
- manic state : 75% (0
- HC vs. bipolar : 79%

"Voice features from **naturalistic phone calls** may represent a supplementary **objective marker** discriminating BD from HC and a state marker within BD."



M Faurholt-Jepsen, J Busk, M Frost, M Vinberg, EM Christensen, O Winther, JE Bardram, LV Kessing (2016,). Voice analysis as an objective state marker in bipolar disorder. *Transl Psychiatry.* Macmillan Publishers Limited.

M Faurholt-Jepsen, DA Rohani, J Busk, M Vinberg, JE Bardram, LV Kessing (2021). Voice analyses using smartphone-based data in patients with bipolar disorder, unaffected relatives and healthy control individuals, and during different affective states. International Journal of Bipolar Disorders, 9, 1-13.

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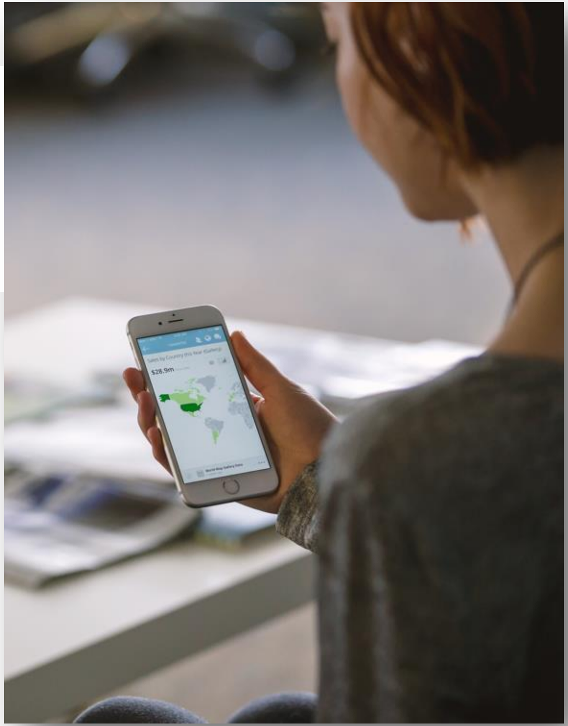


ICAT – Internet-based Cognitive Assessment Tool

- Based on the Screen for Cognitive Impairment (**SCIP**) in Psychiatry
  – clinically administered
  – paper-based & manual scoring
- **ICAT Vision**
  – patient self-administered
  – large-scale deployment (national s
  – useful across many health domain
- **ICAT Technology**
  – browser-based (scalable)
  – automatic speech recognition & scoring
  – study & participant management using CARP

SCREEN FOR COGNITIVE IMPAIRMENT IN PSYCHIATRY (SCIP)
Scot E. Purdon, Ph.D., Clinical Professor of Psychiatry, University of Alberta; spurdon@ualberta.ca
© 2005 Purdon Neuropsychological Labs Inc., Edmonton, Alberta, Canada

1. List Learning T
presentation. For the 1
I want you to repeat ba
at a pace of about 3 sec
am going to read the li
many words as you ca

Received: 5 September 2017 | Revised: 21 November 2017 | Accepted: 15 December 2017
DOI: 10.1111/bdi.12595

REVIEW

WILEY BIPOLAR DISORDERS

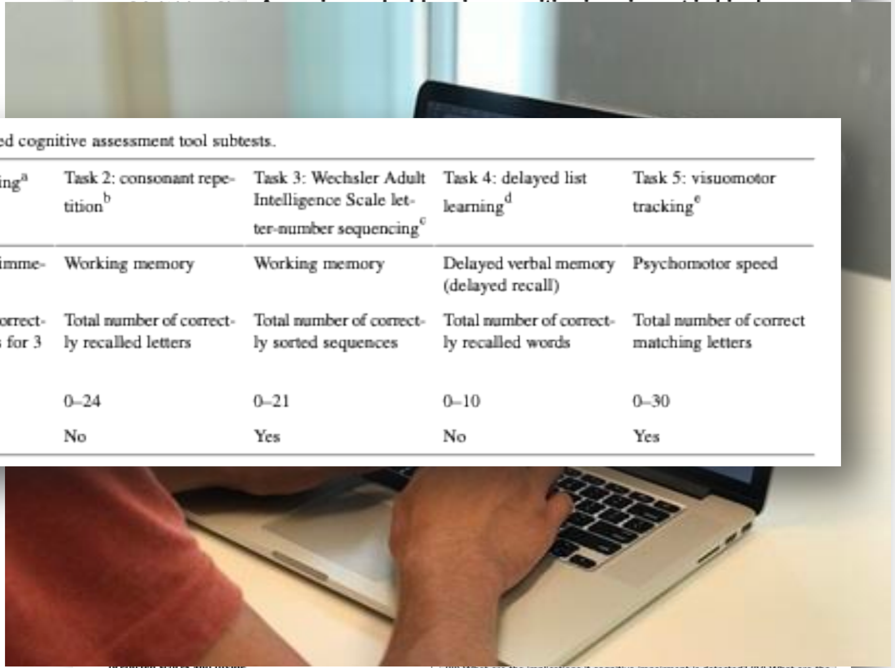


Table 1. Description of the internet-based cognitive assessment tool subtests.

Task features	Task 1: list learning[a]	Task 2: consonant repetition[b]	Task 3: Wechsler Adult Intelligence Scale letter-number sequencing[c]	Task 4: delayed list learning[d]	Task 5: visuomotor tracking[e]
Measure	Verbal memory (immediate recall)	Working memory	Working memory	Delayed verbal memory (delayed recall)	Psychomotor speed
Scoring criteria	Total number of correctly recalled words for 3 trials	Total number of correctly recalled letters	Total number of correctly sorted sequences	Total number of correctly recalled words	Total number of correct matching letters
Score range	0–30	0–24	0–21	0–10	0–30
Practice test	No	No	Yes	No	Yes

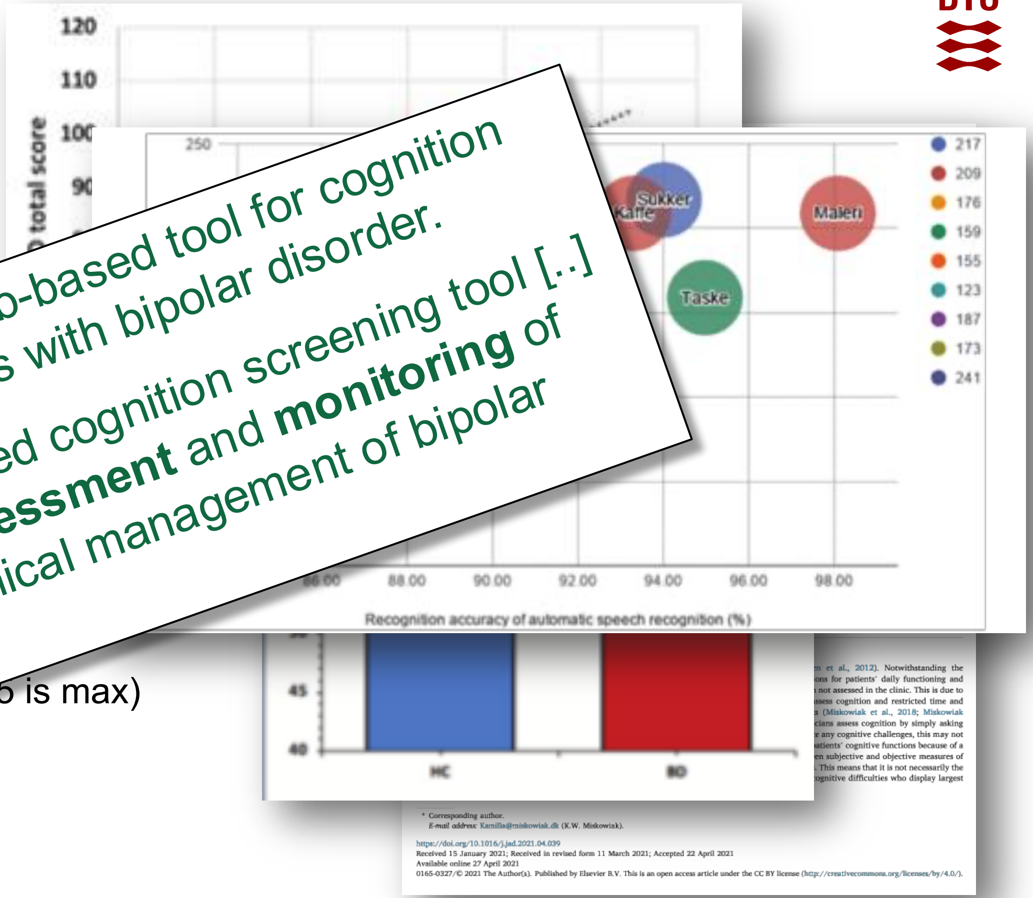
VLT_I= (__-23.59)/2.87. V
14.26)/2.25. Global index is

(III) What are the implications if cognitive impairment is detected? (IV) What are the treatment perspectives? Key recommendations are that clinicians: (I) formally screen cognition in partially or fully remitted patients whenever possible, (II) use brief,

Hafiz, P., Miskowiak, K. W., Kessing, L. V., Jespersen, A. E., Obenhausen, K., Gulyas, L., ... & Bardram, J. E. (2019). The internet-based cognitive assessment tool: system design and feasibility study. *JMIR formative research*, *3*(3).

Validation Study

- **Study**
  - 35 HC | 35 BD
  - SCIP vs. ICAT
  - in-clinic assessment
  - validation | spe
- **Results**
  - scores : ρ = 0.72,
  - speech : ρ = 0.91,
  - usability : M=4.1 (SD … e (5 is max)



"ICAT is a [...] **valid** web-based tool for cognition assessment in patients with bipolar disorder.

[...] a novel web-based cognition screening tool [..] for **large-scale assessment** and **monitoring** of cognition in the clinical management of bipolar disorder."

Miskowiak, K. W., Jespersen, A. E., Obenhausen, K., Hafiz, P., Hestbæk, E., Gulyas, L., ... & Bardram, J. E. (2021). Internet-based cognitive assessment tool: sensitivity and validity of a new online cognition screening tool for patients with bipolar disorder. *Journal of Affective Disorders*, *289*, 125-134.

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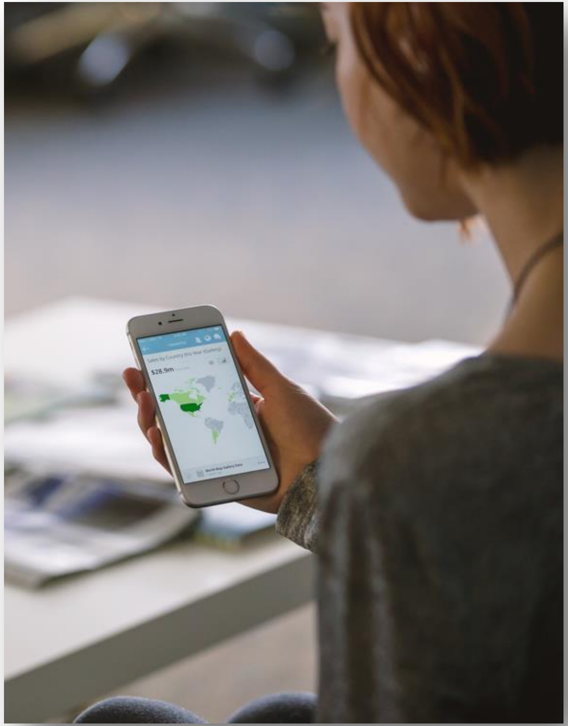
#3 **Neuropathy Tracker** – Assessment of Neuropathy



Neuropathy Tracker

- **Peripheral neuropathy**
  - common complication of diabetes or cancer treatment
  - early detection and treatment are crucial
  - done in the clinic using paper-and-pen tool(s)
- **Vision**
  - patient-administered, “at-home” assessment
  - screening | diagnosis | treatment monitoring
  - early detection
- **Technology**
  - “Custom” designed and implemented using the CARP software components
  - Using patients’ own phones and accessories

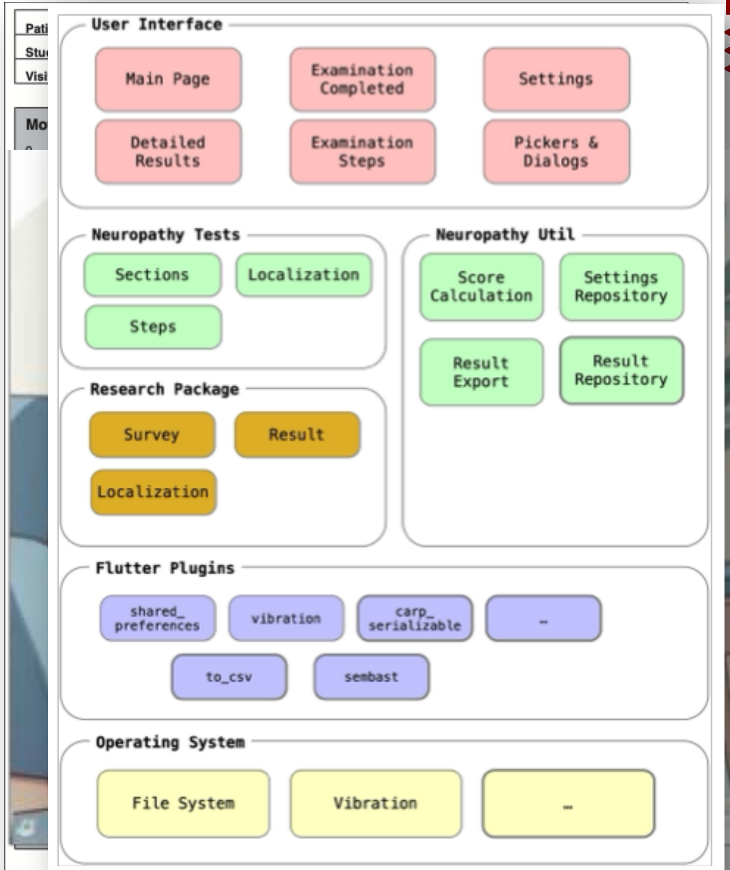
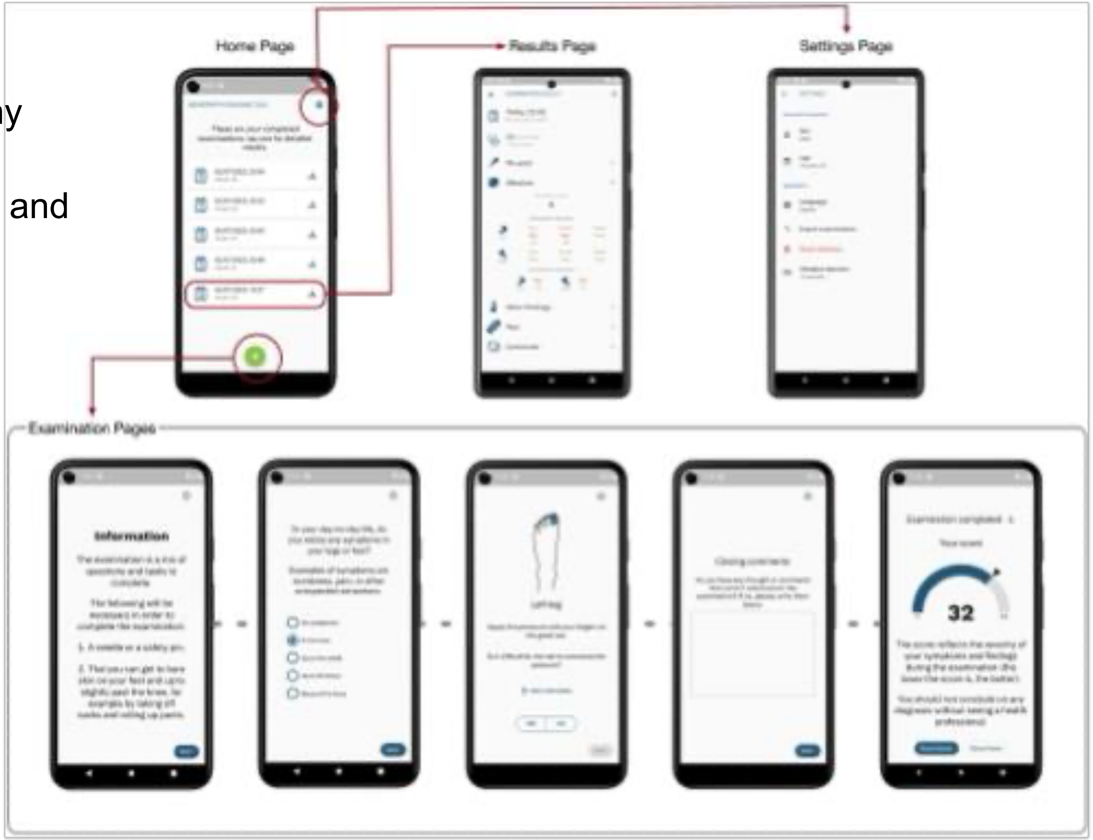


Fig 7. Software architecture. Software architecture diagram of the Neuropathy Tracker comprising of (i) UI components (red) as shown in Figs 3 to 6; (ii) business logic components (green); (iii) Research Package (RP) components (orange); (iv) Flutter plugins (blue), and (v) the phone’s operating system services (yellow).

Bardram, J. E., Westermann, M., Makulec, J. G., & Ballegaard, M. (2025). The Neuropathy Tracker—A mobile health application for ambulatory and self-administred assessment of neuropathy. *PLOS Digital Health*, *4*(2).

User-Centered Design

- involving neurologists, patients, and healthy subjects
- ensuring a high degree of **clinical validity** and **usability**



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Feasibility Study

- Comparing to “Golden Standard”
  – Total Neuropathy Score clinical (TNSc) done by clini
- N=17 neuropathy patients
- Self-assessment in the clinic

- **Results**
  – ρ = 0.86, p < 0.0
  – Bland-Altman Plo

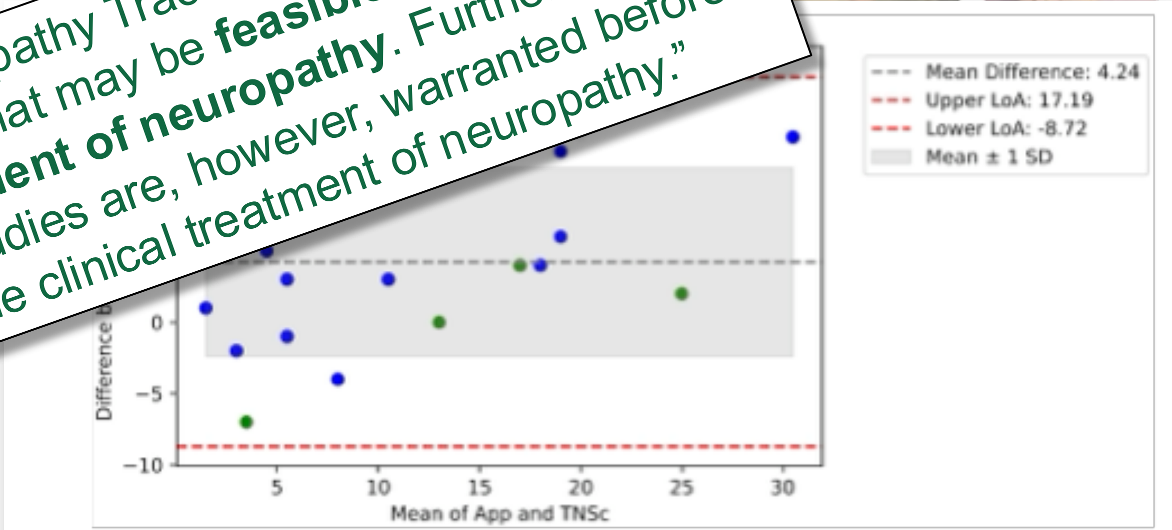

Fig 10. Concurrent validity. A Bland-Altman plot with the differences between the Neuropathy Tracker ("App") and TNSc measures on the y-axis and their means on the x-axis. The plot includes horizontal lines for the mean difference and the limits of agreement (LoA) and is color-coded by sex (green = male, blue = female).

“The [...] Neuropathy Tracker presents a stable mHealth tool that may be **feasible for ambulatory self-assessment of neuropathy**. Further clinical validation studies are, however, warranted before it is used in the clinical treatment of neuropathy.”

Bardram, J. E., Westermann, M., Makulec, J. G., & Ballegaard, M. (2025). The Neuropathy Tracker—A mobile health application for ambulatory and self-administred assessment of neuropathy. *PLOS Digital Health*, *4*(2).

Digital Phenotyping in Neuroscience

#1 **MONARCA** – Digital Biomarkers in Bipolar Disorder

#2 **ICAT** – Internet-based Cognitive Assessment

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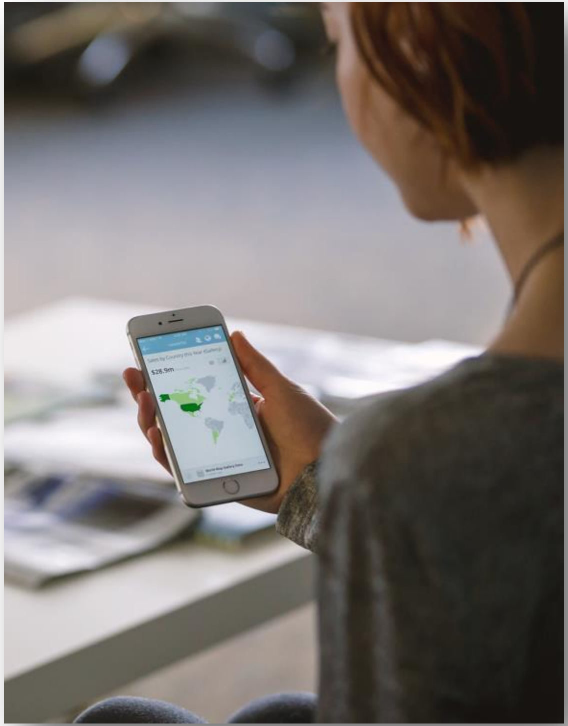

Interested in **Digital Phenotyping** and using CARP as part of a research project?

Just reach out...

Questions?

Funding Acknowledgement

cachet | Copenhagen Center for Health Technology

Innovationsfonden

novo nordisk fonden

Bagger-Sørensen Fonden