Digital behavioural signatures reveal trans-diagnostic clusters of schizophrenia and Alzheimer's disease patients

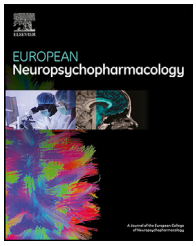
Kas, Martien J.H.; Jongs, Niels; Mennes, Maarten; Penninx, Brenda W.J.H.; Arango, Celso; van der Wee, Nic; Winter-van Rossum, Inge; Ayuso-Mateos, Jose Luis; Bilderbeck, Amy C.; l'Hostis, Philippe

Published in:
European Neuropsychopharmacology

DOI:
10.1016/j.euroneuro.2023.09.010

Publication date:
2024

European Neuropsychopharmacology 78 (2024) 3–12



www.elsevier.com/locate/euroneuro

Digital behavioural signatures reveal trans-diagnostic clusters of Schizophrenia and Alzheimer's disease patients

Martien J.H. Kas[a,*], Niels Jongs[a], Maarten Mennes[b], Brenda W.J.H. Penninx[c], Celso Arango[d], Nic van der Wee[e,f], Inge Winter-van Rossum[g], Jose Luis Ayuso-Mateos[h,i,j,k], Amy C. Bilderbeck[l], Philippe l'Hostis[m], Christian F. Beckmann[b,d], Gerard R. Dawson[n], Bernd Sommer[k], Hugh M. Marston[k,o]

[a] *Groningen Institute for Evolutionary Life Sciences, University of Groningen, Groningen, the Netherlands*
[b] *SBGneuro Ltd, Oxford, United Kingdom*
[c] *Department of Psychiatry and Amsterdam Neuroscience, Amsterdam UMC, Vrije Universiteit, Amsterdam, the Netherlands*
[d] *Donders Institute, Radboud University Medical Centre Nijmegen, the Netherlands*
[e] *Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, CIBERSAM, IiSGM, Universidad Complutense, School of Medicine, Madrid, Spain*
[f] *Department of Psychiatry, Leiden University Medical Center, the Netherlands*
[g] *Leiden Institute for Brain and Cognition/Psychiatric Neuroimaging, Leiden University Medical Center, the Netherlands*
[h] *Department of Psychiatry, University Medical Center Utrecht Brain Center, Utrecht University, Utrecht, the Netherlands*
[i] *Department of Psychiatry, Universidad Autónoma de Madrid, Madrid, Spain*
[j] *Centro de Investigación, Biomédica en Red de Salud Mental, CIBERSAM, Instituto de Salud Carlos III, Madrid, Spain*
[k] *Hospital, Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-Princesa), Madrid, Spain*
[l] *P1vital, Wallingford, Oxfordshire, United Kingdom*
[m] *Biotrial, Rennes, France*
[n] *Boehringer Ingelheim Pharma GmbH & Co KG, CNS Diseases Research, Biberach an der Riss, Germany*
[o] *Eli Lilly and Company, Windlesham, United Kingdom*

Received 12 June 2023; received in revised form 21 September 2023; accepted 25 September 2023

* Corresponding author.
E-mail address: m.j.h.kas@rug.nl (M.J.H. Kas).

https://doi.org/10.1016/j.euroneuro.2023.09.010

KEYWORDS
Digital phenotyping;
Clustering analysis;
Behaviour;
Neuro-imaging;
Psychiatry;
Neurology

Abstract
The current neuropsychiatric nosological categories underlie pragmatic treatment choice, regulation and clinical research but does not encompass biological rationale. However, subgroups of patients suffering from schizophrenia or Alzheimer's disease have more in common than the neuropsychiatric nature of their condition, such as the expression of social dysfunction. The PRISM project presents here initial quantitative biological insights allowing the first steps toward a novel trans-diagnostic classification of psychiatric and neurological symptomatology intended to reinvigorate drug discovery in this area. In this study, we applied spectral clustering on digital behavioural endpoints derived from passive smartphone monitoring data in a subgroup of Schizophrenia and Alzheimer's disease patients, as well as age matched healthy controls, as part of the PRISM clinical study. This analysis provided an objective social functioning characterization with three differential clusters that transcended initial diagnostic classification and was shown to be linked to quantitative neurobiological parameters assessed. This emerging quantitative framework will both offer new ways to classify individuals in biologically homogenous clusters irrespective of their initial diagnosis, and also offer insights into the pathophysiological mechanisms underlying these clusters.

1. Introduction

Currently, the diagnosis of neuropsychiatric disorders separates disorders into non-overlapping diagnostic categories, such as Schizophrenia and Alzheimer's disease. This separation is not based on underlying aetiologies, but on convention-based clustering of qualitative clinical symptoms. While these current diagnostic categories are sufficient to provide a basis for general clinical management, they fail to take into account the underlying neurobiology that gives rise to individual symptoms (Kas et al., 2007; Insel and Cuthbert, 2015). The ability to precisely link these symptoms to the underlying neurobiology would not only facilitate the development of better treatments, but would potentially also allows physicians to provide patients with a better understanding of the complexities and management of their illness. To realise this ambition, a paradigm shift is needed to raise awareness and to build an understanding of how neuropsychiatric diagnoses can be based on quantitative biological parameters. One of the main difficulties in the construction of biologically valid diagnoses is the lack of objective biomarkers with both translational and transdiagnostic value.

The PRISM project, funded through the Innovative Medicines Initiative 2 as a joint undertaking between the EU Horizon 2020 research and innovation framework and EFPIA, is pioneering the field in this respect and aims to develop a quantitative biological approach to the understanding and classification of neuropsychiatric diseases in order to accelerate the discovery and development of better treatments for patients (Kas et al., 2019). In this way, traditional symptom-based classifications will be deconstructed and replaced by a range of quantitative biological assessments using several analytical platforms to parse current heterogeneous syndromes into homogeneous, biology-based clusters.

The PRISM project aims to demonstrate that quantitative biological parameters of shared symptom domains across three neuropsychiatric disorders (Schizophrenia, Alzheimer's disease and Depression) can be used to create novel biologically meaningful clusters. These neuropsychiatric disorders share part of their symptomatology, in particular social withdrawal (Peralta et al., 1992; Reichman and Negron, 2001; Winograd-Gurvich et al., 2006; Porcelli et al., 2019) and specific cognitive deficits (i.e., working memory, sensory processing and attention deficits) (Weintraub et al., 2012; Millan et al., 2012; McIntyre et al., 2013; Lepage et al., 2014; Gilmour et al., 2019; Danjou et al., 2019). With Schizophrenia, Depression and Alzheimer's disease patients, amongst others, known to commonly exhibit social deficits, it was decided to focus on Schizophrenia and Alzheimer's as being the most neurobiologically dissimilar and hence offering the best chance of finding different clusters. Schizophrenia is a neurodevelopmental disorder, with a strong genetic component and typically characterised by the emergence of psychotic symptoms in adolescence or early adulthood (Kahn et al., 2015; Insel, 2010; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Alzheimer's disease is a neurodegenerative disorder characterised by an impairment in cognitive functioning that emerges in later life and by the presence of amyloid plaques in the brain (Scheltens et al., 2016; Frere and Slutsky, 2018). As Schizophrenia and Alzheimer's disease typically emerge at different ages, the single strongest discriminative parameter may simply prove to be age. Therefore, to remove age as a confounding factor in the analysis, age-matched healthy control subjects were included in the study as well.

The basic concept of the PRISM clinical study is to define a set of quantifiable biological parameters for social withdrawal and cognitive deficits in order to cluster Schizophrenia and Alzheimer's disease patients into biologically ho-

mogenous patient groups that transcend clinical labels. Selected patients have subsequently been assessed in a clinical deep phenotyping study (for clinical protocol specifications, see (Bilderbeck et al., 2019)). Methods, instruments, and inclusion/exclusion criteria for this clinical deep phenotyping study have been selected and implemented based on scientific, feasibility, and ethical considerations obtained during consensus meetings between project partners, external scientific, ethical and clinical advisory panel members, as well as based upon input from patient/family organisations and regulators (Bilderbeck et al., 2019). The quantitative assessments in Schizophrenia and Alzheimer's disease patients focus on social dysfunction (Porcelli et al., 2019), sensory processing (Danjou et al., 2019), as well as on working memory and attention (Gilmour et al., 2019).

Recent studies have shown that passive remote smartphone monitoring can provide digital behavioural endpoints related to social functioning that are able to differentiate between patients and controls (Jongs et al., 2020; Muurling et al., 2022). Based on these endpoints (e.g., total phone calls, unique stay points, home stay time), novel insights in objective and real-world environment measures of individual social communication and exploration behaviour can be obtained (Eskes et al., 2016). To address whether these digital behavioural features can provide meaningful transdiagnostic clustering, a subgroup of PRISM study subjects installed the Behapp smartphone app on their phones that subsequently monitored smartphone activities in the background (without active involvement of the subjects) (Jagesar et al., 2021). In this study, we applied spectral clustering on the behavioural endpoints derived from the Behapp smartphone app collected in a subgroup of Schizophrenia and Alzheimer's disease patients, as well as age matched healthy controls, as part of the PRISM clinical study.

2. Experimental procedures

2.1. Subjects

Eligible patient and healthy control participants were identified via patient cohort registers and clinical programs affiliated with the participating centres (VUMC (Amsterdam, the Netherlands), LUMC (Leiden, the Netherlands), UMCU (Utrecht, the Netherlands), CIBERSAM (Madrid, Spain)). Patient participants were selected to differ by level of social functioning (high vs. low), according to their researcher-rated score on a subset of items from the WHODAS-2 (social withdrawal) scale. Low social functioning was defined as a score ≤ 10, whereas high social withdrawal was denoted by a score ≥ 11.

Key inclusion criteria for patients included an absence of social withdrawal due to external circumstances or disease-unrelated disabilities (e.g. lack of access to transport, lack of mobility, facial disfigurement), and right-handedness/ambidextrousness. Alzheimer's disease patients were additionally required to fall between the ages of 50 and 80 (inclusive), meet the National Institute on aging and the Alzheimer's Association (NIA-AA) criteria for probable AD and have an MMSE score of 20 to 26 (inclusive). Schizophrenia patients were required to fall between the ages of 18 and 45 (inclusive), meet the DSM-IV diagnosis of Schizophrenia with at least one confirmed psychotic episode but a maximum of 10 years disease duration since diagnosis and be on stable doses of medication for at least 8 weeks prior to screening. According to the exclusion criteria for patients, patients were excluded if they presented very severe disease symptoms (e.g. a score of ≥ 22 on the 7-item PANSS positive symptom factor for schizophrenia, or a score < 20 on the MMSE for Alzheimer's disease). Furthermore, they were excluded if they had a current DSM-IV diagnosis of Major Depressive Disorder as assessed by the MINI or scored ≥ 16 on the QIDS-SR16, suffered from drug or alcohol dependence within the three years prior to screening or had any contraindications for MRI studies.

Healthy control participants were required to fall into the same two age brackets as the patient groups and to be right handed or ambidextrous, and were excluded if they had a past or current diagnosis of an Axis-I psychiatric disorder as determined by the MINI, mild depressive symptoms as indicated by a score of 5 on the QIDS-SR16, or any contraindications for MRI studies. For complete inclusion/exclusion criteria, see (Bilderbeck et al., 2019).

2.1.1. Ethical approval and informed consent

Participants were recruited between July 2017 and March 2019 from five different recruiting sites across Spain (Hospital General Universitario Gregorio Marañón and Hospital Universitario de La Princesa) and the Netherlands (University Medical Center Utrecht, VU University Medical Center Amsterdam and Leiden University Medical Center). The study was approved by the Ethics Review Board of all participating centers: University Medical Center Utrecht, VU University Medical Center Amsterdam, Leiden University Medical Center, Hospital General Universitario Gregorio Marañón and Hospital Universitario de La Princesa. All participants provided verbal and written consent prior to participation and were considered sufficiently competent to participate by researcher and caregivers.

2.2. Clinical protocol

The PRISM clinical study comprised an exploratory investigation of three groups: Alzheimer's Disease patients, schizophrenia patients and healthy control participants. Participants were assessed on a vast array of validated neuroimaging, neuropsychological and neurophysiological assessments of cognitive, attentional and sensory processing.

After initial contact with the research team, interested individuals were provided with the PIS and ICF, and given the opportunity to provide oral/email consent to be contacted by phone for telephone/email pre-screening. The pre-screening was designed to assess the likelihood that participants would be eligible for the study based on a subset of their demographic and clinical data, including the five items from the WHODAS-2 scale. The aim of the pre-screening was to reduce participant burden, especially for patients who would have been found ineligible for the study at screening.

Eligible participants attended their study centre on three assessment days. Assessment day 1 included further screening, collection of questionnaire measures, behavioural testing, a blood draw and optional installation of a smartphone application for the remote collection of sociability and social exploration data (Behapp service (Jagesar et al., 2021); www.Behapp.com). Assessment days 2 and 3 each included an MRI and EEG neuroimaging session, during which various structural and functional scans were acquired. Follow-up activities consisted of continued Behapp app data collection and remote completion of a short set of social withdrawal questionnaires near the end of the follow-up period (+42 days from assessment day 1). A flow diagram of the clinical study protocol is provided in Fig. 1.

2.2.1. Data collection

The final sample for the PRISM clinical study consisted of 165 participants: 52 Alzheimer's Disease patients, 56 schizophrenia patients, 29 younger and 28 elderly healthy controls. In this study,

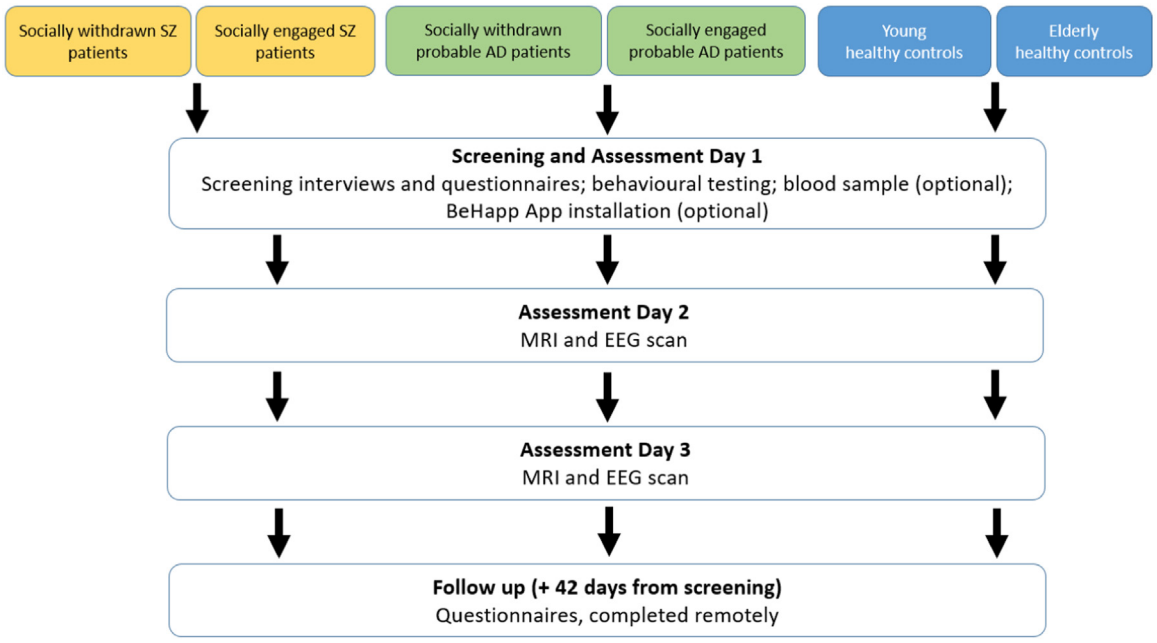


Fig. 1 Schematic representation of the PRISM clinical study protocol. SZ = Schizophrenia; AD = Alzheimer's Disease.

Table 1 Characteristics of the PRISM subsample for this study.

	AD = 20	SZ = 14	Young HC = 11	Old HC = 14
N male	13	8	7	9
N female	7	6	4	5
N White	19	12	10	14
Age	65.55, SEM = 2.66	31.21, SEM = 1.64	27.55, SEM = 1.60	66.71, SEM = 1.73
Years in education	14.75, SEM = 1.03	14.93, SEM = 0.79	17.36, SEM = 0.66	17.00, SEM = 1.27

AD = Alzheimer's Disease; SZ = Schizophrenia; HC = healthy controls; SE = standard error of the mean.

data from 59 participants was used. This number was lower than the actual number of participants in the study due to various reasons (e.g., Behapp participation in the clinical study was optional; at the time of the study, Behapp was only available for Android phones; for that reason, participants with an iPhone did not participate in this part of the study). The demographic characteristics of the sample for the present study in terms of gender, ethnicity, age and years in education can be visualised in Table 1.

Participants who consented to the remote collection of sociability data via Behapp were given the option of installing the app on their personal Android smartphone. Participants were encouraged to allow follow-up data collection for 28 days (4 weeks) from assessment day 1, to allow for the collection sufficient data for meaningful analysis, but they were free to choose to discontinue Behapp data collection at any time whilst continuing with other aspects of the study. Whilst installed, the Behapp app passively monitored smartphone activities, including frequency, duration and diversity of events, such as incoming and outgoing phone calls (with number encryption), SMS usage, and social media activities (e.g., WhatsApp and Facebook events), to provide an objective measure of sociability and social exploration in a longitudinal daily-life manner. No content (e.g., from calls or messages) was collected. In the case of each participant, each one of these longitudinal endpoints was condensed into a cumulative measure, representing the total count of observed events throughout the follow-up period. To accommodate variations in the duration of follow-up among participants, these consolidated measures were subsequently normalized by dividing them by the individualized follow-up durations of each participant.

The PRISM clinical study involved 4 MRI data collection sites (3 using Philips Ingenia 3T-scanners and one using a Siemens Prisma 3T-scanner) in two countries (The Netherlands and Spain). The basic BOLD parameters were standardized between the different scanners and advanced shims were performed at all sites. Behavioural task data was collected using the P1vital® ePRO system. Tasks were completed online via a personalized account which researchers created for participants. The ePRO system is built to high, industry-regulation standards, and site staff was provided with training and materials to ensure standardized data collection procedures across sites (Bilderbeck et al., 2019).

2.3. Statistical analysis

2.3.1. Participant inclusion in current analysis

Within the full PRISM dataset we had access to Behapp endpoint data for 75 participants for whom we had derived endpoints available. We removed participants who had more than 10 missing endpoints and removed endpoints where more than 5 participants missed data. This resulted in inclusion of 59 participants (19 AD, 14 SZ, and 26 HC) and 62 endpoints. Remaining missing endpoints were replaced with the mean value for that endpoint in the avail-

able participants. Finally, each endpoint score was converted to a z-score by subtracting its mean and dividing by its standard deviation across the population.

2.3.2. Clustering approach

To obtain subgroups of participants exhibiting a similar profile of Behapp endpoint scores we applied spectral clustering on a participant by participant correlation matrix. This matrix is calculated across all endpoints and illustrates how similar the endpoint profile (i.e., all endpoints) of each participant is to the endpoint profile of each other participant in the population. We used Pearson Correlation as the measure of similarity. For further clustering we rescaled the similarity matrix to a 0–1 range.

We choose to apply spectral clustering as our initial clustering approach. This is an unsupervised clustering method indicating that we do not make use of available diagnostic labels to decide on the number of clusters that should be retrieved by the algorithm. Instead we use data-driven criteria to decide on the most likely number of clusters. Note that this number is typically validated using (out-of-sample) cross-validation, however, in light of the current data exploration we have not implemented such cross-validation. To inform ourselves about the potential number of clusters present in our dataset we assessed the silhouette metric and a principal component decomposition of the similarity matrix.

Based on the silhouette metric a solution with 2 or 3 clusters would yield the best possible separation. This was further confirmed by a PCA decomposition on the similarity matrix in order to estimate the underlying intrinsic dimensionality of the data. That the first 4 principal components cumulatively explained 80 % of the variance in the data. In terms of the percent of explained variance per component we observed a first inflection point ('elbow') at component number 3. Based on these metrics we obtained a 3-cluster solution.

2.3.3. Cluster characterization

To investigate how the resulting clusters related to available clinical and demographic variables we assessed the distribution of diagnostic labels among the clusters, the relationship with participant age, and the relationship with participant sex. In addition, we characterised each of the clusters in terms of the scores on the Behapp endpoints and tentatively named each profile based on the distribution of participant z-scores across endpoints.

2.3.4. Relationship with imaging derived endpoints

To assess the relationship between the cluster solution and endpoints derived from the imaging modalities present in PRISM, we implemented group-analyses using cluster-membership as group-identifiers (instead of diagnostic label). Given the exploratory nature of these analyses and the limited number of participants we assessed effects at a significance level of $p < 0.05$ without further correction for multiple comparisons. Group-level 1-factor ANOVA models were applied to endpoint data residualized for the effects of AGE, SEX, and SITE. The factor group comprised three levels corresponding to each participant's cluster membership. Table 2 lists the unimodal endpoints that were assessed and the modality they were derived from. Here, we assessed the effect of cluster membership on multi-modal components derived through linked-ICA (Groves et al., 2011) based on simultaneous decomposition of whole-brain endpoints derived from the T1 (volume, area, thickness), EEG, and resting fMRI (Default mode network, and seed-based networks derived for nucleus accumbens, anterior cingulate cortex, amygdala, and medial prefrontal cortex).

3. Results

Behapp passive remote behavioural monitoring through the smartphone of subjects allowed us to define behavioural profiles of objectively assessed individual levels of social functioning. Based on 62 BEHAPP endpoints (e.g., total in- and outgoing phone calls and chats, GPS signal-derived unique visits of places, home stay time), novel insights in objective and real-world environment measures of individual social communication and exploration behaviour were obtained. This analysis revealed three discriminable clusters (indicated as the green "hot spots" in Fig. 2A), importantly, as Fig. 2Band C illustrate, these clusters did not show a 1-to-1 mapping to the initial diagnostic groups and were not driven by participant age. Relating the 3-group cluster solution to multimodal components derived across structural, functional, and EEG neuroimaging endpoints yielded a significant effect of cluster for one of the multimodal components (Fig. 2D). This component was driven by between-participant differences in brain anatomy endpoints including volume, cortical surface area, and cortical thickness. These initial findings indicate that multimodal quantitative neuroimaging measures are associated with specific social profiles that transcend the initial clinical diagnosis (Fig. 2D).

We characterised each of the clusters in terms of the scores on Behapp endpoint classes (outgoing calls, incoming calls, social diversity, communication, social media usage, phone usage, location diversity, travelling, home stay). Each of these classes were built on a variety of Behapp endpoint features functionally related to a class, as indicated in Table 3. This profile showed the average score for each class score across the participants in each cluster. We tentatively characterized each profile based on the distribution of participant z-scores across classes. Cluster 1 is related to high levels of communication, as participants in this profile score higher than the population on call- and text-related endpoints, have a highly diverse social network, yet lower on travel-related classes, such as location diversity and travelling. In contrast, cluster 2 is related to reduced social interactions, with lower scores on call-and other communication-related classes, and by increased home stay time. Finally, participants in cluster 3 show a mixed distribution of classes with lower home stay time and increased usage of social media (Fig. 3).

4. Discussion

The PRISM project set out to use an unbiased approach to exploring a number of inter-related issues in neuropsychiatry (Kas et al., 2019). Across the range of data collected the project is clearly demonstrating that quantitative parameters offer both practical and differentially informative alternatives and/or adjuncts to traditional subject and/or qualitative assessment. By taking social dysfunction as a transdiagnostic domain (Porcelli et al., 2019) the project is providing new insights into the nature, quantification and biology of this poorly understood area. This focus has also allowed an illustration that by utilising a transdiagnostic approach unexpected commonalities and differences can identified adding, it is believed, novel colour to our understanding of these disorders. Taken together the merit and practicality of a true trans-diagnostic, biology-driven classification system for use across psychiatry and neurology is emerging.

Table 2 List of the unimodal endpoints that were assessed as part of the clinical protocol in PRISM.

Modality	Endpoint	N	Notes
EEG Visit 2	various	3234	111 unique endpoints were extracted, of those certain endpoints were collected from 58 electrodes; also included in Linked-ICA analysis
Anatomical MRI	volume	134	total volume for 134 regions of the brain derived via Freesurfer segmentation; also included in Linked-ICA analysis
	thickness	70	cortical thickness for 70 regions along the grey matter surface of the brain derived via Freesurfer segmentation; also included in Linked-ICA analysis
	area	70	surface area for 70 regions along the grey matter surface of the brain derived via Freesurfer segmentation; also included in Linked-ICA analysis
BOLD Resting State	DMN	1	whole brain map of the default mode network derived via dual regression (Filippini et al., 2009); included in Linked-ICA analysis only
	seed-maps	26	whole brain seed-based functional connectivity maps, one for each of the masks provided for the task-based analysis endpoint extraction; Whole-brain seed-based networks derived for nucleus accumbens, anterior cingulate cortex, amygdala, and medial prefrontal cortex included in Linked-ICA analysis
BOLD FEP	mean z-score in region	36	average z-score within the regions provided by the data champions; average scores were extracted for all provided contrasts; N contrasts = 6; N regions = 6
BOLD VMWM	mean z-score in region	32	average z-score within the regions provided by the data champions; average scores were extracted for all provided contrasts; N contrasts = 4; N regions = 8
BOLD MSID	mean z-score in region	36	average z-score within the regions provided by the data champions; average scores were extracted for all provided contrasts; N contrasts = 4; N regions = 9
BOLD NBACK	mean z-score in region	21	average z-score within the regions provided by the data champions; average scores were extracted for all provided contrasts; N contrasts = 7; N regions = 3
DWI	FA, MD, MO	20	diffusion metrics extracted for 20 white-matter tracts; FA: Fractional anisotropy; MD: Mean Diffusivity; MO: Mode of anisotropy
ASL	CBF	120	cerebral blood flow in 120 regions of the brain
FERT (Behaviour)	various	47	
Hinting Task (Behaviour)		1	Total Score
DSST (Behaviour)	various	3	
EEfRT (Behaviour)	various	7	
CPT (Behaviour)	various	9	
BOLD FEP (Behaviour)	various	12	
BOLD VMWM (Behaviour)	various	4	
BOLD MSID (Behaviour)	various	147	
BOLD NBACK (Behaviour)	various	30	

Table 3 Composition of BEHAPP classes on the basis of BEHAPP endpoint features.

BEHAPP endpoint classes				
location diversity	**Travelling**	**Phone usage**	**Communication**	**Social diversity**
Total amount of minutes spent in a stationary state.	Day and night distribution of activity based on the distance from home.	Number of times a phone usage events was registered.	Entropy of the usage time of communication apps.	Number of contact-id's with a single outgoing call.
Total number of stay points. Stay points are defined as being stationary for 60 min within an area of 350 m.	Number of trajectories that represent the movement between two stay points.	Total time of entertainment apps usage*.	Mean usage time of communication apps.	Most frequent contact-id divided by the number of unique contact-id's.
Number of places that are visited once.	Day and night distribution of activity based on raw location data.	Total count of news apps usage*.	Total count of communication apps usage*.	Normalized entropy for incoming and outgoing calls when using the count. Values range from 0 to 1. 1 indicates that the number of calls are uniformly distributed over the contact-id's.
Total number of places visited. Based on WiFi data.	Day and night distribution of activity based on the unique stay points.	Total time of phone usage.	Total time of communication apps usage*.	Average repetition per contact for outgoing, incoming and missed calls.
Volume of the minimum bounding box.	Total distance travelled in kilometres.	Number of times phone usage events are registered between 24:00 pm and 05:00 am.	Total number of calls.	Normalized entropy for incoming and outgoing calls over time. Values range from 0 to 1. 1 indicates that the time spend calling with different contact-id's is uniformly distributed.
Number of unique MAC addresses found via WiFi.	Standard deviation of the duration of trajectories in minutes.	Total time of news apps usage*.	Total number of calls with a duration longer than 0 s.	Number of contact-id's with a single incoming call.
Area of a minimum bounding box	Standard deviation of the length of trajectories in kilometres.	Total count of entertainment apps usage*.	Total time whatsapp used.	Number of unique contact-id's for missed calls.
Number of unique places visited.	Maximum distance from home.		Total duration of all communication events*.	Number of unique contact-id's for outgoing calls.
Normalized entropy for the time spent at different locations.	Average length of a trajectory in kilometres.		Number of times WhatsApp opened.	Number of unique contact-id's.
Area of operation in km^2.	Total amount of time spent travelling in minutes.			Number of unique contact-id's for incoming calls.
Average duration of visits in minutes.	Average distance from home.			Number of contact-id's that are contacted once.
	Average duration of a trajectory in minutes.			
	Radius of gyration based on the mass of the data.			
	Radius of gyration from home location.			
	Total number of location observations.			

BEHAPP endpoint classes			
Outgoing call	**Incoming call**	**Home stay**	**Social Media**
Total duration of outgoing calls.	Total duration of incoming calls.	Time spent at home.	Total count of social media apps usage.
Total number of no responses on outgoing calls.	Total number of missed calls.		Total time of social media apps usage.
Total number of outgoing calls.	Total number of incoming calls.		

* Classification of apps is according to listing of the google play store.

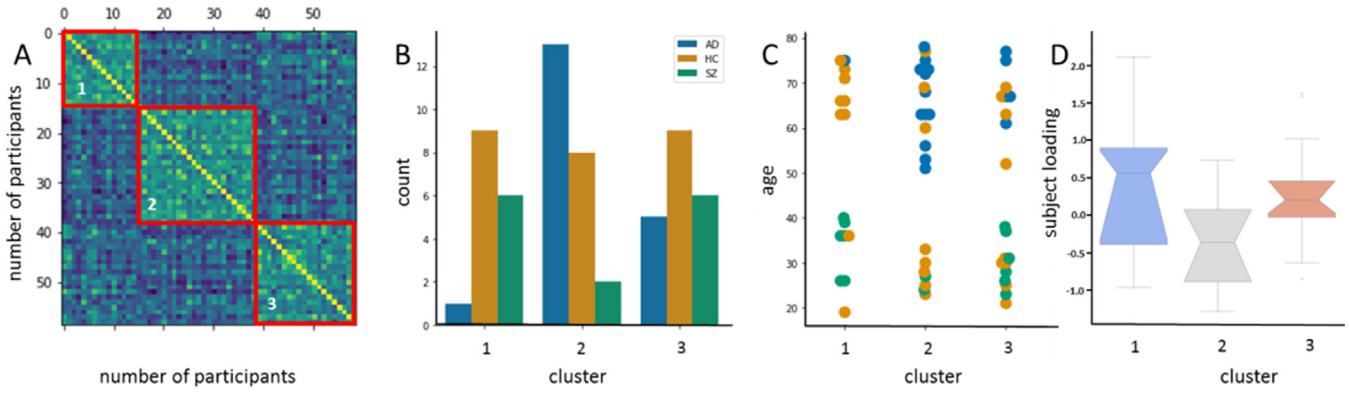


Fig. 2 Illustration of Behapp clustering results. (A) Re-ordered similarity matrix for BEHAPP smartphone data obtained across all participants with completed Behapp data ($N = 59$) after applying spectral clustering with $n = 3$ clusters. The matrix illustrates how similar the endpoint profile (i.e., all endpoints) of each participant is to the endpoint profile of the other participants in the population. Pearson correlation was used as the measure of similarity. (B) The three identified clusters showed an approximately equal distribution of Healthy Controls (HC) and schizophrenia (SZ) patients over the 3 clusters, while Alzheimer's disease (AD) patients were overrepresented in the second cluster. (C) Age was not a determining factor in the clustering solution. (D) The 3-group cluster solution entered into a multimodal analysis including structural, functional, and EEG neuroimaging endpoints yielded a significant effect of cluster for one of the multimodal components, loading primarily on brain volume, cortical thickness and curvature. These initial findings indicate that multimodal quantitative neuroimaging measures are associated with specific social profiles that transcend the initial clinical diagnosis.

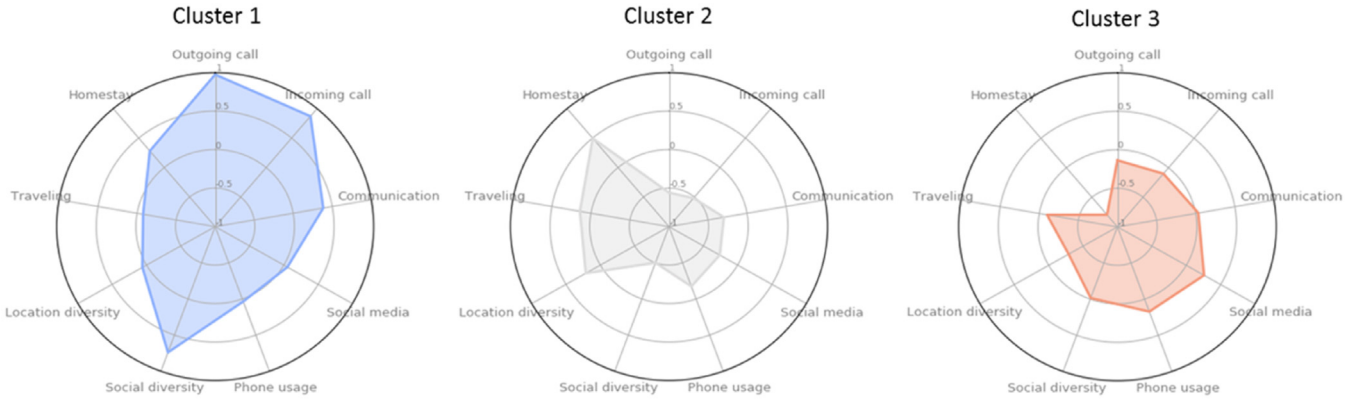


Fig. 3 Behapp endpoint profile for each of the three clusters. Spectral clustering analysis on Behapp endpoint profiles revealed three distinct clusters. For each cluster, mean cluster scores for Behapp endpoint classes (e.g., travelling, social diversity) are plotted relative to cohort mean scores (= score 0).

In the present study the data collected from the deployment of the Behapp, a passive smartphone App, has been concentrated on (Jagesar et al., 2021). The data collected within the unique framework of the PRISM project provides a compelling, first empirical demonstration of the unbiased identification of potentially novel, meaningful, biological phenotypes. With three clear groupings in the profile of the subjects; Healthy Controls, Alzheimer and Schizophrenic patients, along with major potential contributory factors; such as age and sex, a realistic null hypothesis would be that one or a small collection of these factors would be the most convincing driver for first order clustering. This though was not the case with the clustering, based on behavioural profiles using the smartphone app endpoint measures, revealing three distinct "social profiles" each containing healthy controls, as well as Schizophrenia and Alzheimer's disease patients. In the first cluster which is principally made up of schizophrenic patients, healthy controls both young and old, and a few Alzheimer patients there is no evidence of unusual overall social media or App usage. Further, their amount of travel is close to the mean for the whole cohort while the time spent at home is only marginally above the mean. However, there is strong evidence that these individuals have a diffuse and well curated social network sustained through the use of their smartphones. Individuals in this cluster seem to have a prosocial profile with a relatively broad social network and active social engagement (as reflected by the high levels of in- and out-coming calls, as well as their high level of social diversity). The second cluster which again contains both young and old healthy controls

but a predominance of Alzheimer versus Schizophrenic patients stay at home more and do use their phones less. However, they also show normal travel in terms of amount and complexity. It is therefore a little surprising that their social networks, even allowing for the lower use of the phone are so impoverished, for instance in- and out-coming calls are well below the cohort mean. In addition, based on their low social diversity in contact, their social network seems to be less diverse than for those individuals belonging to cluster 1. This would suggest that this cluster is more introverted and social impoverished a hypothesis that needs to be explored further. The Third cluster made up of the most even spread of patients and healthy controls use their smart phones a little more than normal and have an averagely complex and curated social network. They do not though stay at home but also do not appear to have a complex life away from home. This pattern is the most difficult to interpret but could perhaps infer a group of individuals who "follow" society rather than engage with it (e.g., go from home to work and back home again), again a hypothesis that could be easily tested going forward. Thus, in this initial analysis in a subgroup of Schizophrenia and Alzheimer's disease patients, and their matched controls, a quantitative digital clustering of three distinct social signatures was identified. Further studies will be necessary to properly understand how these clusters can provide clinical relevance, however, it provides a novel basis for quantifying behavioural differences in a transdiagnostic manner and for stratification of patient groups based on digital phenotypes that may have a biological basis. Hopefully, in the future, this will not only improve clinical trial outcomes (via new digital stratification biomarkers and/or digital endpoints for social functioning), but could also provide a basis for personalized treatments on the basis of these different biotypes (Insel and Cuthbert, 2015; Kas et al., 2019).

As these novel findings provide innovative ways of clustering patients with real world quantitative digital measures irrespective of their traditional diagnosis, we have to take the limitations of the present study into account. First, the sample sizes per patient group are still relatively small, and an independent replication would be important to further expand on these findings, which we are currently pursuing in the ongoing PRISM2 project. Second, the inclusion and exclusion criteria for patient recruitment for the study do, for example, preclude participation of early onset and severely affected schizophrenia and Alzheimer patients, making these findings relevant to a selected population. Thirdly, participants with severe cognitive decline or mental illness may have difficulties to interact with their phone, however, this may be more problematic for smartphone-base ecological monetary assessments than for passive monitoring that requires no active interaction with the smartphone from the participants. Furthermore, changes in phone usage due to mental illness or cognitive decline (e.g., changes in communication and/or movement) is also part of what we want to measure, as they may be reflecting early signs of relevant changes in social behaviour. Finally, participation to the smartphone component of the PRISM study was optional and only possible for Android users, which may have introduced a bias in our sample. Subsequent studies with larger sample sizes, less restrictions on type of smartphone and expansion of the breadth of the psychiatric and neurological spectrum will be relevant to both replicate and generalize the present findings.

The present clustering on behavioural profiles using smartphone app endpoint measures revealed three distinct social profiles each containing healthy controls, as well as Schizophrenia and Alzheimer's disease patients. This provisional finding demonstrates the potential for novel and/or alternative nosologies to emerge. Further, as these are quantitatively derived, they offer the opportunity for testable hypotheses to be formed and investigated rapidly. In a subsequent study, these behavioural profiles were coupled to other quantitative parameters collected in the study, such as the neuro-imaging data and revealed associations with these clusters. In this way, we are providing evidence for new ways of classifying cohorts and to develop a growing understanding of the associated phenotypes underlying these classifications. These new classifications will then be based on quantitative biological measures underlying the social behavioural profiles rather than the traditional clinical diagnostic framework. Together, we hope that this novel approach will contribute to the acceleration of developing new treatments with high efficacy and provide solutions to the growing public health challenges of psychiatry and neurology.

Role of funders

The PRISM project (www.prism-project.eu) leading to this application has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115916. This Joint Undertaking receives support from the European Union's Horizon 2020 Research and Innovation Programme and EFPIA. This publication reflects only the authors' views neither IMI JU nor EFPIA nor the European Commission are liable for any use that may be made of the information contained therein.

Contributors

NJ and MJK designed the criteria for developing the digital outcome measures. BP, CA, NvdW, IWvR, GRD, ACB, Pl'H, BS, HM, and MJK designed the PRISM clinical study protocol. BP, CA, NvdW, IWvR, JLAM, Pl'H, ACB, GRD, and MJK were involved in the implementation, execution and/or patient recruitment and assessments of the clinical study. MM and CFB performed the statistical analysis on the neuroimaging data and for the spectral clustering analyses. The Behapp smartphone service was developed in the research group of MJK. MJK wrote the first version of the manuscript. All authors reviewed the manuscript prior to submission and their feedback was implemented to the final version of the manuscript.

Conflict of interest

MK has received (non-related) research funding from Novartis during the conduct of the study. MM is employee and CFB is director and shareholder of SBGneuro Ltd. CA has been a consultant to or has received honoraria or grants

from Acadia, Angelini, Gedeon Richter, Janssen Cilag, Lundbeck, Minerva, Otsuka, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion and Takeda. BP has received (non-related) research funding from Jansen Research and Boehringer Ingelheim during the conduct of the study. ACB and GRD were fully employed by P1Vital during the conduct of the study. BS was fully employed by Boehringer Ingelheim during the conduct of the study. HM was fully employed by Eli Lilly and Company during the conduct of the study. All other authors declare no conflict of interests.

Acknowledgements

The PRISM project (www.prism-project.eu) leading to this application has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115916. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. This publication reflects only the authors' views neither IMI JU nor EFPIA nor the European Commission are liable for any use that may be made of the information contained therein.

References

Bilderbeck, A.C., Penninx, B.W.J.H., Arango, C., van der Wee, N., Kahn, R., Winter-van Rossum, I., Hayen, A., Kas, M.J., Post, A., Dawson, G.R., 2019. Overview of the clinical implementation of a study exploring social withdrawal in patients with schizophrenia and Alzheimer's disease. Neurosci. Biobehav. Rev. 97, 87–93.

Danjou, P., Viardot, G., Maurice, D., Garcés, P., Wams, E.J., Phillips, K.G., Bertaina-Anglade, V., McCarthy, A.P., Pemberton, D.J., 2019. Electrophysiological assessment methodology of sensory processing dysfunction in schizophrenia and dementia of the Alzheimer type. Neurosci. Biobehav. Rev. 97, 70–84.

Eskes, P., Spruit, M., Brinkkemper, S., Vorstman, J., Kas, M.J., 2016. The sociability score: app-based social profiling from a healthcare perspective. Comput. Human Behav. 59. doi:10.1016/j.chb.2016.01.024.

Filippini, N., MacIntosh, B.J., Hough, M.G., Goodwin, G.M., Frisoni, G.B., Smith, S.M., Matthews, P.M., Beckmann, C.F., Mackay, C.E., 2009. Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. Proc. Natl. Acad. Sci. USA 106, 7209–7214.

Frere, S., Slutsky, I., 2018. Alzheimer's disease: from firing instability to homeostasis network collapse. Neuron 97, 32–58.

Gilmour, G., Porcelli, S., Bertaina-Anglade, V., Arce, E., Dukart, J., Hayen, A., Lobo, A., Lopez-Anton, R., Merlo Pich, E., Pemberton, D.J., Havenith, M.N., Glennon, J.C., Harel, B.T., Dawson, G., Marston, H., Kozak, R., Serretti, A., 2019. Relating constructs of attention and working memory to social withdrawal in Alzheimer's disease and schizophrenia: issues regarding paradigm selection. Neurosci. Biobehav. Rev. 97, 47–69.

Groves, A.R., Beckmann, C.F., Smith, S.M., Woolrich, M.W., 2011. Linked independent component analysis for multimodal data fusion. Neuroimage 54, 2198–2217.

Insel, T.R., Cuthbert, B.N., 2015. Brain disorders? Precisely. Science 348, 499–500.

Insel, T.R., 2010. Rethinking schizophrenia. Nature 468, 187–193.

Jagesar, R.R., Vorstman, J.A., Kas, M.J., 2021. Requirements and operational guidelines for secure and sustainable digital phenotyping: design and development study. J. Med. Internet Res. 23. doi:10.2196/20996.

Jongs, N., Jagesar, R., van Haren, N.E.M., Penninx, B.W.J.H., Reus, L., Visser, P.J., van der Wee, N.J.A., Koning, I.M., Arango, C., Sommer, I.E.C., Eijkemans, M.J.C., Vorstman, J.A., Kas, M.J., 2020. A framework for assessing neuropsychiatric phenotypes by using smartphone-based location data. Transl. Psychiatry 10, 211.

Kahn, R.S., Sommer, I.E., Murray, R.M., Meyer-Lindenberg, A., Weinberger, D.R., Cannon, T.D., O'Donovan, M., Correll, C.U., Kane, J.M., van Os, J., Insel, T.R., 2015. Schizophrenia. Nat. Rev. Dis. Prim. 1, 15067.

Kas, M.J.H., Fernandes, C., Schalkwyk, L.C., Collier, D.A., 2007. Genetics of behavioural domains across the neuropsychiatric spectrum; Of mice and men. Mol. Psychiatry 12. doi:10.1038/sj.mp.4001979.

Kas, M.J., Penninx, B., Sommer, B., Serretti, A., Arango, C., Marston, H., 2019. A quantitative approach to neuropsychiatry: the why and the how. Neurosci. Biobehav. Rev. 97, 3–9.

Lepage, M., Bodnar, M., Bowie, C.R., 2014. Neurocognition: clinical and functional outcomes in schizophrenia. Can. J. Psychiatry. 59, 5–12.

McIntyre, R.S., Cha, D.S., Soczynska, J.K., Woldeyohannes, H.O., Gallaugher, L.A., Kudlow, P., Alsuwaidan, M., Baskaran, A., 2013. Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. Depress. Anxiety 30, 515–527.

Millan, M.J., Agid, Y., Brüne, M., Bullmore, E.T., Carter, C.S., Clayton, N.S., Connor, R., Davis, S., Deakin, B., DeRubeis, R.J., Dubois, B., Geyer, M.A., Goodwin, G.M., Gorwood, P., Jay, T.M., Joëls, M., Mansuy, I.M., Meyer-Lindenberg, A., Murphy, D., Rolls, E., Saletu, B., Spedding, M., Sweeney, J., Whittington, M., Young, L.J., 2012. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. Nat. Rev. Drug Discov. 11, 141–168.

Muurling, M., Reus, L.M., de Boer, C., Wessels, S.C., Jagesar, R.R., Vorstman, J.A.S., Kas, M.J.H., Visser, P.J., 2022. Assessment of social behavior using a passive monitoring app in cognitively normal and cognitively impaired older adults: observational study. JMIR Aging 5, e33856.

Peralta, V., de Leon, J., Cuesta, M.J., 1992. Are there more than two syndromes in schizophrenia? A critique of the positive-negative dichotomy. Br. J. Psychiatry 161, 335–343.

Porcelli, S., Van Der Wee, N., van der Werff, S., Aghajani, M., Glennon, J.C., van Heukelum, S., Mogavero, F., Lobo, A., Olivera, F.J., Lobo, E., Posadas, M., Dukart, J., Kozak, R., Arce, E., Ikram, A., Vorstman, J., Bilderbeck, A., Saris, I., Kas, M.J., Serretti, A., 2019. Social brain, social dysfunction and social withdrawal. Neurosci. Biobehav. Rev. 97, 10–33.

Reichman, W.E., Negron, A., 2001. Negative symptoms in the elderly patient with dementia. Int. J. Geriatr. Psychiatry 16 (Suppl 1), S7–11.

Scheltens, P., Blennow, K., Breteler, M.M.B., de Strooper, B., Frisoni, G.B., Salloway, S., Van der Flier, W.M., 2016. Alzheimer's disease. Lancet 388, 505–517.

Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511, 421–427.

Weintraub, S., Wicklund, A.H., Salmon, D.P., 2012. The neuropsychological profile of Alzheimer disease. Cold Spring Harb. Perspect. Med. 2 a006171–a006171.

Winograd-Gurvich, C., Fitzgerald, P.B., Georgiou-Karistianis, N., Bradshaw, J.L., White, O.B., 2006. Negative symptoms: a review of schizophrenia, melancholic depression and Parkinson's disease. Brain Res. Bull. 70, 312–321.