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Chapter 2

A framework for assessing neuropsychiatric phenotypes by using smartphone-based location data

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ABSTRACT:
The use of smartphone-based location data to quantify behavior longitudinally and passively is rapidly gaining traction in neuropsychiatric research. However, a standardized and validated preprocessing framework for deriving behavioral phenotypes from smartphone-based location data is currently lacking.

Here, we present a preprocessing framework consisting of methods that are validated in the context of geospatial data. This framework aims to generate context-enriched location data by identifying stationary, non-stationary, and recurrent stationary states in movement patterns. Subsequently, this context-enriched data is used to derive a series of behavioral phenotypes that are related to movement.

By using smartphone-based location data collected from 245 subjects, including patients with schizophrenia, we show that the proposed framework is effective and accurate in generating context-enriched location data. This data was subsequently used to derive behavioral readouts that were sensitive in detecting behavioral nuances related to schizophrenia and aging, such as the time spent at home and the number of unique places visited.

Overall, our results indicate that the proposed framework reliably preprocesses raw smartphone-based location data in such a manner that relevant behavioral phenotypes of interest can be derived.
INTRODUCTION

The ability to objectively quantify different aspects of human behavior is essential for studies that aim to understand variations in human behavior and their underlying biological mechanisms. To date, such studies predominantly rely on subjective research methods such as in-person interviews, questionnaires and self- or proxy-rated measures. Subsequently, these behavioral phenotypic measures are used to examine interactions with an array of biological parameters, such as genotypes, brain activity patterns or structural brain data to study the biological underpinnings of the observed behavior. While such studies have led to numerous important insights, the current methods for behavioral phenotyping also have their limitations that preclude their objectivity. Most notably, these methods rely on the subject’s (or the subject’s proxy) account of behavior, and are invariably obtained post-hoc, i.e. questionnaire measures of behavior are virtually never real-time. Observational assessments are real-time, but they occur nearly always in a non-natural (e.g., clinical) setting.

As a consequence, current behavioral assessment methods are susceptible to a wide variety of method and response biases. These biases can cause systematic and random measurement errors, thereby impeding the validity and interpretation of findings. For example, when specific symptoms, such as cognitive dysfunction or lack of disease insight affect the subjective report of behavioral components, comparison between groups is severely hampered. Also, translational animal studies cannot use questionnaires, hence introducing additional divergence between animal and human assessments.

Recently, researchers have started to explore the utilization of smartphones as a more objective methodology to quantify human behavior. Contemporary smartphones are equipped among others with sensors such as a Global Positioning System (GPS), accelerometer, Bluetooth, Wi-Fi, microphone. These sensors can be used to collect a high-resolution trace of behavioral data, which can then be used to derive relevant behavioral markers. This method is increasingly referred to as “digital phenotyping” or “passive behavioral monitoring.” Recent studies are already starting to reveal the clinical potential of the approach in the context of neuropsychiatric research. The promise of this methodology is that the derived behavioral markers may provide unprecedented and unique insights into human behavior. Key features are 1) data is collected in real-time, 2) in the subject’s natural environment, and 3) without the need for any self- or proxy reporting, thereby addressing some of the most important challenges inherent to current behavioral research. Further adding to the appeal of using the smartphone is the relatively low-cost of this approach combined with the fact that the majority of people in western societies nowadays owns a smartphone.
One of the most frequently used smartphone sensors in passive behavioral monitoring is the so-called Global Positioning Sensor (GPS). The location data collected by this sensor primarily informs about the physical activity of participants but can also be used to explore different aspects of social behavior related to mobility. However, any single location data point in its raw state can only inform about the location in a two-dimensional space. In contrast, the analysis of multiple data points collected over time allows the inference of context. Contextualization, e.g., whether one is commuting between A and B, at home or visiting another location, is the basis for deriving relevant behavioral phenotypes from location data. This is acquired by a sequence of preprocessing procedures that enriches the raw location data. In addition, the process requires that a certain level of uncertainty in location data collected by smartphones is taken into account. Relevant behavioral phenotypes are subsequently derived by additional calculations on this context-enriched location data.

One major challenge in the utilization of smartphone-based location data for behavioral monitoring in research is the lack of a validated preprocessing framework to generate context-enriched location data. Previous studies that utilized smartphone-based location data\textsuperscript{9–11,14–16} to quantify behavior employed various generic preprocessing procedures that are not exclusively developed for location data. These methods are often not validated in context of location data and therefore often unable to deal with the uncertainty in location data. As a consequence, the use of these generic methods to preprocess location data might generate misleading behavioral phenotypes. In the present study, we (1) describe and evaluate the efficiency of a preprocessing procedure specifically developed for raw location data collected by smartphones, (2) describe a series of behavioral measures that are derived from these context-enriched location data, and (3) validate the sensitivity of the derived phenotypes in detecting behavioral nuances that are characteristic for specific populations samples (Figure 1).

To achieve these goals, we collected location data by using a passive behavioral monitoring application called BEHAPP\textsuperscript{6,17} in three different samples. First, we collected data in a relatively small sample of healthy individuals (sample 1; n = 10) to optimize and evaluate the efficiency of the preprocessing procedures. Subsequently, these optimized preprocessing procedures were applied on data obtained in two additional samples (samples 2 and 3; n = 193 and n = 42 respectively) to generate context-enriched location data (Figure 1c). The context-enriched location data from sample 2 and 3 was used to derive a set of six behavioral phenotypes that relate to several basic aspects of mobility and daily activities. Samples 2 and 3 were selected based on specific phenotypes (ageing and schizophrenia, respectively) known to be associated with certain behavioral characteristics, including rela-
tive changes in mobility patterns. Increasing age (sample 2) is characterized, for example, by a deterioration of the skeletal and muscular system which is known to impede mobility\textsuperscript{18}. For this reason, we expected a relative decrease in mobility as a function of ageing. For schizophrenia (sample 3) it is known that the negative symptoms, which include decreased social engagement\textsuperscript{19} and initiative\textsuperscript{20,21}, are associated with decreased mobility patterns\textsuperscript{10}. Therefore, we expect mobility patterns to be affected in some of the derived phenotypes (e.g., time spent at home and visiting new places) for our sample of patients with schizophrenia relative to their age- and sex matched controls.

In summary, we propose a preprocessing framework on smartphone-derived location data to allow contextualization and the inference of mobility-related phenotypes. Subsequently, we evaluated whether the smartphone-derived phenotypic measures of mobility were sufficiently sensitive to detect differences relative to controls and accordance with expectations given the impact of age or the presence of schizophrenia.

Figure 1 | Overview experiments and utilization of the samples. (A) Sample 1 is used to develop and evaluate the preprocessing procedure used to contextualize raw location data collected by smartphones. (B) Samples 2 and 3 are used to validate the sensitivity of the derived behavioral readouts in detecting sample specific deviations of behavior. (C) Visualization of preprocessing procedure used to derive context-enriched location data. The raw location data (left figure) contains limited behavioral information and requires preprocessing to extract contextual information. Location data plotted over time combined with contextual information as derived by the preprocessing procedure (right figure). In this figure we can easily identify several stay points with repeated visits over time, the home location and travel patterns. This information is used to derive behavioral phenotypes such as the number of places visited (red and green), amount of home stay (blue) and the frequency of traveling (grey).
METHODS

Participants

We recruited three different samples of participants to develop and evaluate the efficiency of the preprocessing framework (sample 1) and validate the sensitivity of the derived behavioral phenotypes (samples 2 and 3, supplementary Table 1) in detecting sample-related behavioral changes. The data in sample 2 and 3 was collected with approval from the concerned institutional ethics review boards and written informed consent was provided by all subjects.

Sample 1: Data from 10 healthy participants was used to evaluate the efficiency of the preprocessing framework used to generate context-enriched location data. These participants (6 males; 4 females) with an average age of 33.2 ± 13.74 verbally agreed to collect location data over a period of 2 weeks (14 days). After the data collection period, participants were asked to manually confirm the output of the preprocessing procedures. We obtained a complete and detailed confirmation of output in 5 out of 10 participants. The remaining 5 participants provided confirmation that was limited to the home location, as identified by using their smartphone data.

Sample 2: We recruited 193 healthy participants without any neurological or psychiatric condition that might affect the data collection or the derived phenotypes. We used these participants to validate the sensitivity of the behavioral phenotypes in detecting age-specific differences. This group (81 males; 112 females) with an average age of 57.48 ± 14.71 years agreed to collect location data for 14 days with their own smartphone. Age was arbitrarily binned in three categories, namely <35 years (n = 21), 35 to 65 years (n = 103) and 65 to 90 years (n = 69) years to account for variations in the behavioral phenotypes. The greater part of the subjects in the 65 to 90 bin were recruited through hersenonderzoek.nl (www.hersenonderzoek.nl). These participants provided self-assessed information regarding the presence of a psychiatric condition and cognitive impairments. The remaining participants were screened on the absence of any neurological disease or psychiatric condition affecting the CNS, which is associated with cognitive impairment.

Sample 3: We recruited 21 individuals with a clinically confirmed diagnosis of schizophrenia (SZ) and 21 age- and gender matched healthy controls (HC). Sample 3 was used to assess the sensitivity of the behavioral phenotypes in detecting differences in social behavior between those with and without schizophrenia. Patients with SZ and controls were recruited as part of the ongoing Psychiatric Ratings using Intermediate Stratified Markers (PRISM) project21 and the Social Cognition and Imaging in Psychiatry (SCIP) study. SZ diagnoses were confirmed during recruitment by using the Comprehensive Assessment of Symptoms and History22.
(CASH) questionnaire. The average age of this group (34 males, 8 females) was 31.78 ± 8.91. All participants provided written informed consent to collect at least 14 days of location data. Data collection in 3 out of the 42 participants failed due to smartphone compatibility problems.

**Data collection**

The location (GPS) data used for this study was collected by the BEHAPP\textsuperscript{23} application. BEHAPP is a passive behavioral monitoring application for Android that collects data by utilizing the embedded sensors in participants own smartphones. BEHAPP is developed by the University of Groningen and is used for scientific research that aims to provide objective, quantitative and longitudinal measures of human (social) behavior to classify mental health disorders based on digital behavioral profiles, develop digital biomarkers to study disease progression and treatment efficacy, and identify early indicators of disease that allow prediction of disease onset, relapse and remission.

The location data collected by BEHAPP for a single participant is defined as a four-dimensional matrix $C$ and holds the latitude and longitude, their corresponding time-stamps and accuracy indicators of the coordinates. Therefore, a single geospatial coordinate $i$ is defined as $C_i = \{\text{lat}_i, \text{lng}_i, t_i, \text{acci}\}$ where $i = 1, 2, \ldots, p$. The accuracy of smartphone-based location data is rarely 100% exact and is irregular over time due to sensor noise and environmental factors. The accuracy of a coordinate is described in terms of their confidence in meters. This confidence is interpreted as the 68% probability that the true location is within the radius of the circle around the observed coordinate. Coordinates that exceeded an accuracy of 350 meters were excluded from further computations. An example of smartphone-based location data is given in supplementary Table 2, in this example the third record accommodates the most accurately observed coordinate.

**Preprocessing procedures**

The primary aim of our preprocessing procedure is to differentiate between stationary and non-stationary states, and cluster those stationary states that are recurrent over time. Examples of stationary states include being at home, visiting a relative or being at work. Movements within these stationery states are still considered stationary. Traveling from work to home or from work to a supermarket are examples of non-stationary states. We identified these stationary states by employing a stay point detection algorithm\textsuperscript{24} on raw location data that is filtered on accuracy. This stay point detection algorithm requires two parameters, a distance parameter $\theta_d$, and a time threshold parameter $\theta_t$. These threshold parameters $\theta_t$ and $\theta_d$ were fixed at 60 minutes for $\theta_t$ and 350 meters for $\theta_d$. With these parameters,
a single stay point is detected by the algorithm if a group of geospatial coordinates remains stationary for 60 minutes within an area of 350 meters.

A set of \( v \) stationary states for a single subject is denoted as \( S = \{ s_1, s_2, \ldots, s_v \} \), where a distinct stationary state is defined as \( s_j = \{ t_j^a, t_j^d, \text{lat}_j, \text{lng}_j \} \). Here, \( t_j^a \) and \( t_j^d \) contain the arrival and departure time for stationary state \( j \), \( \text{lat}_j \) and \( \text{lng}_j \) hold the coordinates for stationary state \( j \). The coordinates for stationary state \( j \) are obtained by taking the average of the latitude and longitude of the coordinates that belong to stationary state \( j \). The efficiency of the stay point detection algorithm in correctly identifying stationary states was evaluated with the afore mentioned parameters by analyzing the user confirmed output of the algorithm. User confirmed output was provided by 5 of the 10 participants from sample 1 (supplementary Table 1).

Recurrent stationary states over time are clustered by using a density-based clustering \(^{25}\) (DBSCAN) approach which groups stationary states that are close in space. Two stationary states are considered close in space if directly reachable by a pre-specified distance. DBSCAN requires two parameters; a minimum number of points needed to establish a cluster (\( \text{MinPt} = 2 \)), and an \( \epsilon \) parameter. The \( \epsilon \) parameter defines the maximum space of the neighborhood for a single stationary location and is crucial for clustering locations. A new cluster is established if two stay points are directly reachable by the distance as defined by \( \epsilon \). This distance between stationary states is defined by the haversine distance function which calculates the distance between a pair of coordinates denoted in latitude and longitude. By using this distance function, a distance matrix \( V \) of size \( v \times v \) with pairwise distances between all observed stationary states was generated and used as input for the DBSCAN algorithm. The output of this approach was used to assign each stationary state to a cluster of recurrent stationary locations. These clusters of recurrent stationary locations are denoted by \( \text{cl}_j = \{ \text{cl}_{i_1}, \text{cl}_{i_2}, \ldots, \text{cl}_j \} \) where \( \text{cl}_j \) is the cluster index for stationary location \( j \).

We used the data collected in sample 1 to perform an optimization experiment to find the optimal \( \epsilon \) value that maximizes the performance of DBSCAN. For a range of \( \epsilon \) values between 10 and 600 meters the accuracy (Adjusted Rand Index) of DBSCAN was assessed by comparing the user grouped stationary locations with the clustered stationary states. User grouped stationary locations were again provided by 5 of the 10 subjects from the sample 1. The \( \epsilon \) value with the highest accuracy was chosen as the final parameter for DBSCAN and was used to derive behavioral phenotypes from the preprocessed location data.

Non-stationary states are identified by using the inverse of the output as generated by the stay point detection algorithm. This approach defines all the geospatial coordinates between two consecutive stationary states as non-stationary when a set of conditions is satisfied. We used a heuristic-based rule to exclude trajec-
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tories that do not exceed a minimum of 20 coordinates. We consider it unlikely, that trajectories with less than 20 coordinates are a good representation of the transition between two consecutive stay points. A set of trajectories is denoted as $TR = \{tr_1, tr_2, ..., tr_{n_{tr}}\}$ and contains $n_{tr}$ trajectories. A single trajectory is denoted as $tr = \{t_j^d, t_{j+1}^a, COR_{tr}\}$ where $t_j^d$ denotes the departure time at stay point $j$ and $t_{j+1}^a$, the arrival time at the consecutive stay point $j + 1$. The corresponding set of geospatial coordinates for a single trajectory is denoted as $COR_{tr} = C[t_j^d t_{j+1}^a]$. The accuracy of this approach is depended on the performance of the stay point detection algorithm as described above. So, a highly accurate stay point detection algorithm directly translates into accurate trajectories.

**Smartphone-based behavioral phenotypes**

Here we describe the behavioral phenotypes that are derived from the context-enriched location data. This context-enriched location data is extracted from the raw location data by using the optimized preprocessing procedure described above. The described phenotypes are proven to be sensitive in detecting behavioral nuances related to neuro-psychiatric disorders\(^9,11\).

**Count-based phenotypes:** Smartphone-based behavioral phenotypes such as the number of places visited, number of unique places visited, and the number of trajectories are directly derived from the context-enriched location data. So, with the definitions given above, the number of places visited is equal to $v$, the number of unique places visited to the unique values in $cl$ and the number of trajectories is equal to $n_{tr}$.

For sample 3, these count-based phenotypes are adjusted for the length of the data collection period by using simple linear regression. This linear model is fitted by using:

$$\hat{y} = \beta_0 + \beta_0 x_{\text{period}}$$

where $y$ is the count-based phenotype and $x_{\text{period}}$ the length of the data collection period. The adjusted phenotype is then defined as the residuals added to the average of the count-based phenotype:

$$\hat{y} + (\hat{y} - y).$$

**Home Stay:** Home stay is defined as the total amount of time observed at home during the data collection period. For this behavioral phenotype, it is crucial to correctly identify those geospatial coordinates that reside with the actual home location $H$. In order to achieve this, we defined a heuristic-based rule that estimates the home location from a set of clustered stationary locations (see preprocessing procedures). This heuristic-based rule estimates the home location by selecting those three clustered stationary locations with the most hours observed at night.
(between 00:00 AM and 06:00 AM). Subsequently, the most frequently visited stationary location of these three is considered the home location \(H\).

The total amount of home stay \(HS\) is defined by the sum of the hours observed at the estimated home location \(H\),

\[
HS = \sum_{j|c=H}^{1} (t_j^d - t_j^a),
\]

and measures the total time observed at home. The percentage of home stay is defined by the amount home stay divided by the sum of the total time spent at stationary locations:

\[
HSP = \frac{HS}{\sum_{j}(t_j^d - t_j^a)}.
\]

This percentage of home stay is favorable over the total amount of home stay if the length of the data collection period varies between subjects such as in the SZ sample (sample 3).

We evaluated this heuristic rule by comparing the home locations provided by the 10 subjects from group 1 with the estimated home locations. The accuracy of this rule in estimating the correct home location is expressed in percentage correctly estimated home locations. For the groupwise comparisons in sample 2 and 3, observations with less than 35% (8.4 hours a day) of home stay were removed from further analysis since it is unlikely that the derived amount of home stay is calculated by using the correct home location.

**Normalized entropy:** The normalized entropy\(^{26}\) measure is calculated by using the percentage of time spent at different clusters of stationary locations and is defined by:

\[
ENT = -\frac{\sum_{l} \log_{10}(p_l)}{\log_{10}(N_{cl})},
\]

where each \(l = 1,2,...,N_{cl}\) refers to a clustered set of stationary locations, and where \(N_{cl}\) is the observed number of clusters. \(p_l\) denotes the percentage of time spent at location cluster \(l\). This readout measures the degree of variability in stay time over the clustered stationary locations. Higher normalized entropy values indicate more uniformly distributed stay times across clusters and lower values are observed when the stay times are focused around a single cluster. Because of this, the normalized entropy is expected to be negatively associated with the percentage of home stay.

**Diurnal movement:** Diurnal movement (DM) measures the regularity in daily movement patterns. Subjects with stable daily movement patterns score higher on this phenotype compared to subjects with irregular daily movement patterns\(^{9,11}\). The DM measure is calculated by using the using the Lomb-Scargle periodogram\(^{27}\). The Lomb-Scargle periodogram is used to determine the power within a 24 ±
0.5-hour cycle for the distance between the home location $H$ and the observed stationary locations. The distance between the home location $H$ and a single stationary location $j$ is again defined by haversine distance function. The power spectral density (PSD) of these distances for a $24 \pm 0.5$-hour period is estimated and averaged by the $K$ frequencies in the $24 \pm 0.5$ cycle by applying

$$P_d = \sum_{t} psd(f_t)/K$$

Where $psd(f_t)$ is the PSD of the data at time bin $t$ that is within a $24 \pm 0.5$-hour period bin.

The power $P_d$ is calculated for the normalized distances between the home location and the stationary locations and is considered the final measure of DM. By using these normalized distances, the DM measure becomes insensitive to outliers and the distance traveled.

**Statistical analysis groupwise comparisons**

For sample 2 we used a one-way ANOVA with a Tukey post hoc test to study the association between the age bins and the derived behavioral phenotypes. In order to approach normality for the derived phenotypes we used a log transformation on those phenotypes that deviated from normality. Visual inspection of each phenotype was performed to assess normality.

For the SZ sample (sample 3) we performed a Poisson generalized linear model with a Tukey post hoc test to study the difference between the SZ and their controls on the number of stay points, trajectories and the number recurrent stay points. For the remaining phenotypes (percentage of home stay, normalized entropy and diurnal movement) we used a one-way ANOVA with a Tukey post hoc test to evaluate the difference between SZ and controls. For both sample 2 and 3 the assumptions of the used statistical methods were checked prior to analysis.

Prior to analyzing the phenotypes in sample 2 and 3 we adjusted the count-based phenotypes for the length of data collection by using the residuals of a linear model. In addition, the effect of gender was also assessed for sample 1 and 2 on each phenotype by using a t-test and the results revealed a non-significant effect of gender and was therefore, not included in any further analysis.

**RESULTS**

**Preprocessing procedures (sample 1)**

The preprocessing procedure serves 1) to enrich raw smartphone-based location data with contextual information by identifying non-stationary and stationary
states and 2) to identify clusters of the latter that are recurrent over time. User confirmed validation of stationary states from five subjects collected over a period of 2 weeks showed that the accuracy (percentage correct) of the stay point detection algorithm\(^2\) in correctly identifying stationary states is \(94\% (\mu) \pm 8\% (sd)\). The accuracy of the algorithm ranged between 100% and 95% for four out of five subjects (95%, 95%, 98%, 100%). The performance of the algorithm was substantially less for one subject with an accuracy of 81%. Closer inspection revealed that the collected location data from this subject was relatively more precise (Figure 2a). The precision of geospatial coordinates is denoted by their confidence in meters. This confidence is interpreted as the 68% probability that the true location is within a specific range of proximity to the measured coordinates. The average confidence of this subject was with 24.9 meters considerably lower than the 129.3, 108.9, 46.1 and 167.7 meters that were observed for the remaining four subjects. Somewhat counter intuitively, the higher level of precision of GPS data in this subject led to a relatively lower accuracy of the stay point detection algorithm. These results suggest that the current definitions of the algorithm parameters (see methods) tend to be more favorable on relative less precise GPS raw data.

The density-based clustering\(^2\) (DBSCAN) approach aimed at identifying recurrent stationary locations as a single entity. Our results revealed that by considering locations within a range of 150 meters (\(\varepsilon\) parameter; Figure 2b) as a single entity, 87% ± 13% of the stationary locations with corresponding contextual meanings were correctly clustered together. This accuracy is defined as the percentage of stationary locations with corresponding contextual meaning correctly clustered together.

**Count-based phenotypes (samples 2 and 3)**

Count-based behavioral phenotypes such as the number of places visited in total, unique places visited and trajectories, are directly derived from the preprocessed location data.

For sample 2 (ageing; \(n = 193\)), these count-based behavioral phenotypes revealed (Figure 3A, 3B and 3C) significant differences between the middle aged (35 – 65 years) to elderly (65 – 90 years) subjects and the younger (< 35 years) subjects. We found that relative to the younger group, middle aged and elderly subjects visited significant fewer places per day (young: 4.04 ± 2.26; middle: 2.76 ± 1.69; elderly: 2.41 ± 1.35) and traveled significant less on a daily basis (young: 2.10 ± 1.22; middle: 1.06 ± 0.84; elderly: 0.99 ± 0.82). With regard to the number of unique places visited, we found no difference between the elderly subjects and the other two age groups (young: 1.20 ± 1.13; middle: 1.02 ± 0.63; elderly: 0.94 ± 0.58).
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For sample 3 (Schizophrenia (SZ); n = 42), these phenotypes showed that relative to the age- and sex matched healthy control (HC) subjects the SZ subjects visited significantly fewer places (HC: 43.35 ± 23.72; SZ: 34.55 ± 19.44) (Figure 4a). In addition to this, our results also showed that SZ subjects visited significantly less unique places (HC: 15.25 ± 6.16; SZ: 11.44 ± 6.18; Figure 4b) and traveled significantly less often (HC: 25.25 ± 20.70; SZ: 15.00 ± 12.99; Figure 4c).

**Home Stay (samples 1, 2 and 3)**

To estimate the amount of home stay we used a heuristic-based rule (i.e. pre-defined rule) to identify the home location from a set of clustered stationary states as identified by the preprocessing procedure. We evaluated the accuracy of this heuristic-based rule by using the user confirmed clustered stationary states as provided by the subjects from sample 1. The results of this evaluation revealed that with an accuracy of 100% all home locations were correctly identified. Subsequently, we used this rule to infer the home location in sample 2 and 3, and subsequently, to determine the amount of home stay.

We used the amount of home stay per day to evaluate the association between home stay and increasing of age in sample 2. Our results revealed that the ob-

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**Figure 2 | Evaluation and optimization preprocessing procedure.** (A) Accuracy of the geospatial coordinates for each participant represented by the confidence in meters (colored in 25% quantiles). The confidence of each geospatial coordinate is interpreted as the 68% probability that true location is within the distance in meters. (B) Adjusted Rand Index for each epsilon value combined with the standard error. The optimal $\epsilon$ value is 150 meters with an Adjusted Rand Index of 0.87, this point is marked by the arrowed line.
Figure 3 | Behavioral phenotypes based on geospatial data for different age groupings. (A) Comparison of the number of places visited for three age bins showed that relative to the <35 the 35-65 (p = 0.012) and 65-90 (p < 0.001) group visited significant fewer places [F(2,190) = 7.14, p = 0.001]. (B) Number of unique places visited revealed non-significant differences for the three age bins [F(2,190) = 0.98, p = 0.378]. (C) Comparison of the number of trajectories revealed that number of trajectories was higher for the <35 relative to the 35-65 (p = 0.002) and 65-90 (p < 0.001) group [F(2,190) = 7.64, p < 0.001]. (D) Percentage of home stay is gradually and significantly increasing (p = 0.027, p = 0.017) with age [F(2,161) = 4.06, p = 0.019]. (E) Comparison of the normalized entropy measure revealed lower scores for the 35-65 (p < 0.001) and 65-90 (p < 0.001) group [F(2,190) = 12.03, p < 0.001]. (F) For the diurnal movement measure we did not find any significant differences. However, noteworthy is the difference in variance between the age groups which seems to increase by age [F(2,190) = 1.96, p = 0.144].
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Figure 4 | Behavioral phenotypes based on geospatial data for SZ and HC subjects. (A) Comparison of the number of places visited* for SZ and HC subjects showed that HC subjects visited significant more places [$\chi^2(1) = 18.813, p = <0.001$]. (B) HC subjects visited significant more unique places* [$\chi^2(1) = 10.289, p = 0.001$]. (C) Comparison of the number of trajectories* showed that HC subjects travel significant more than SZ subjects [$\chi^2(1) = 25.837, p < 0.001$]. (D) Percentage of home stay revealed that SZ subjects spent significant more time at home compared to HC’s [$\chi^2(1) = 7.3878, p = 0.006$]. (E) The results of the normalized entropy measure revealed that SZ subjects tend to spent significantly more time on a small set of stationary locations [$\chi^2(1) = 4.1058, p = 0.04$]. (F) Comparison of the diurnal movement measure revealed a non-significant difference between SZ and HC subjects. (*Counts are adjusted for the number of days data collected).
served amount of home stay per day is significantly less in the younger subjects relative to the middle and elderly aged groups (young: 12.95 ± 2.67; middle: 15.15 ± 3.46; elderly: 15.25 ± 3.42; Figure 3d). The observed amount of home stay between the middle (35-65) and elderly aged (65-90) did not differ significantly.

For sample 3, we used the same heuristic-based rule to estimate the percentage of home stay. Our results revealed that subjects diagnosed with SZ on average spent 15% (i.e. 3.6 hours) more time at home as compared to HC’s (HC: 65% ± 18%; SZ: 80% ± 15%; Figure 4a).

**Normalized entropy (samples 2 and 3)**

Normalized entropy quantifies the variability of time spent at different stationary states. Lower scores are observed on this measure when stay times are restricted to a small set of stationary states. Higher scores are observed when the time spent at different stationary states is more uniformly distributed across these stationary states. Given this definition, we found, as expected, a negative association between the normalized entropy measure and the percentage of home stay (Figure 5, $r(191) = -.72, p < .001$). This strong association is explained by the fact that spending more time at home leaves less time to visit other locations.

For the three age groups (sample 2), our results revealed significant differences relative to the younger subjects (<35). The results indicated greater inequality in the time spent across different stationary locations between the younger subjects and the middle and elderly aged subjects (Figure 3E). For the younger group we observed an average normalized entropy of 0.52 ± 0.09 vs an average of 0.39 ± 0.14 and 0.36 ± 0.14 for the 35-60 and 60-90 groups, respectively.

The normalized entropy was also significantly different between SZ patients and age- and sex-matched HC’s (sample 3; Figure 4E). It revealed a greater inequality in the time spent across different stationary locations for subjects diagnosed with SZ. The normalized entropy measure was on average 0.13 points higher in the HC group (HC: 0.51 ± 0.21; SZ: 0.38 ± 0.18).

**Diurnal movement (sample 2 and 3)**

The regularity in movement patterns is measured by the diurnal movement phenotype. Higher scores on this behavioral phenotype are observed in subjects with a repetitive and regular movement pattern within a 24-hour period over a consecutive assessment of multiple days (including weekday and weekend). Results revealed that the regularity in movement patterns is similar for the three age groups (7.25 ± 1.40 vs 6.68 ± 1.38 vs 6.51 ± 1.69) (Figure 3F).
We observed a small difference in the regularity of movement patterns between SZ and HC; (HC: 7.25 ± 1.67; SZ: 7.13 ± 1.47; Figure 4F) respectively. However, this difference was not statistically significant.

**DISCUSSION**

The availability of objective and real-world behavioral phenotypes represents a fundamental change in our ability to study variation in human behavior. Here, we propose a framework to process raw smartphone collected geospatial data. We demonstrate that objective behavioral phenotypes of human behavior can be derived that are clinically relevant and are effective in detecting behavioral nuances consistent with expectation in specific population samples. This framework provides an important next step in the era of digital phenotyping, namely that of systematic pre-processing and validating passively monitored longitudinal raw data sets to deliver biologically relevant behavioral phenotypes of interest.

The sensitivity and usability of these behavioral phenotypes in detecting behavioral deviations is dependent on the efficiency of the preprocessing procedures. We demonstrate the efficiency of a two-step preprocessing procedure that utilizes a set of methods that are validated in the context of geospatial data. Evaluation of this framework in terms of efficiency revealed an overall high accuracy in detecting stationary, non-stationary and recurrent stationary states correctly. We show that the stay point detection algorithm is able to detect stationary and non-stationary states with relatively high efficiency. Despite the relatively small size of

![Figure 5](image-url) | Normalized entropy measure plotted against the amount of home stay per day. The dashed line represents the linear model that was used to test the association between normalized entropy and the amount of home stay ($\beta = -0.57, p < 0.001$). These results suggest that lower scores on the normalized entropy measure is correlated with increased home stay ($r(191) = -0.72, p < .001$).
sample 1 (n = 10), these results are in accordance with earlier findings that demonstrated the efficiency of this same algorithm in accurately detecting stationary and non-stationary states from smartphone-based location data. Importantly, we found that the efficiency of the stay point detection algorithm is dependent on the interaction between the parameters as used by the algorithm and the precision of the collected geospatial coordinates. Our results suggest that under the current conditions the algorithm was less efficient on location data with relatively high precision. These findings indicated that the choice of these parameters should depend on the precision of the data that is used as input for the algorithm.

In addition, we used density-based clustering (DBSCAN) with an optimized set of parameters to identify recurrent stationary states with identical entities. We showed that with these optimized parameters we were able to identify recurrent stationary states with high accuracy (87%). This finding is consistent with results of earlier work that demonstrated the efficiency of the DBSCAN in clustering stationary states with identical entities together. It is important to bear in mind that this approach remains relatively limited when it comes to differentiating between two distinct stationary states that are close in space. This limitation is due to the range parameters in DBSCAN that takes into account the variability in coordinates for stationary states with an identical entity. As a consequence, stationary states with distinct entities that are close in space are likely to be identified as a single entity due to the uncertainty that is introduced by this range parameter.

Overall, our results suggest that the proposed preprocessing steps (stay point detection and DBSCAN clustering) are efficient and reliable in detecting stationary and recurrent stationary states. Given that non-stationary states are defined as the inverse of stationary states, our results also provide evidence that non-stationary states are effectively identified by these preprocessing procedures.

We utilized these stationary and non-stationary states to formulate a set of behavioral phenotypes, which subsequently proved to be sensitive in detecting important behavioral nuances in our population samples. In the sample that included subjects across a wide age range (sample 2), our results revealed changes in these phenotypes that are likely associated with processes of aging. For example, relative to the younger subjects, we found that the middle and elderly aged subjects visited fewer places, traveled less and spent more time at home. Our findings did not reveal a difference between the middle and elderly aged subjects. We had expected a difference in mobility patterns, since the elderly group could be hypothesized to have a weaker fitness due to age-related physical changes in the skeletal and muscular system and elderly could be expected to be less active since they most often have retired from work. The difference between the results and these initial expectations are likely related to the fact that we did not
take into account that the elderly group is likely to be more active due to retirement, while the context of work in the middle-aged group is likely associated with a higher frequency of sedentary lifestyle due to employment status, which is in accordance with earlier findings. Arguably, one could still expect differences in certain aspects of mobility that were not captured by the phenotypic endpoints measured in the current study.

In addition, we found significant differences between SZ and HC subjects. For instance, we showed that subjects diagnosed with SZ significantly visited fewer unique places, traveled less and spent more time at home as compared to their age- and gender-matched controls. These significant differences may be indicators of reduced social behavior and may relate to the known diminished social functioning in the SZ group and other psychiatric disorders. These findings are comparable to an earlier location data based phenotype of decreased exploratory behavior in patients with depression who are also known to suffer from social withdrawal. Alternatively, these findings could also be driven by a different attitude of patients with schizophrenia towards smartphones (e.g., averse due to paranoid tendencies) or cognitive impairments that cause patients to leave their smartphone at home. Therefore, while our findings are consistent with what is known about social behavior in schizophrenia, alternative explanations exist which are unrelated to the social functioning of a patient. Additional studies addressing parallel social functioning and smartphone monitoring assessments are needed to extend the validation of digital measures of social behavior in these patient cohorts.

It is important to emphasize that we used age and neuropsychiatric disease status to demonstrate that the location-based derived behavioral phenotypes are sufficiently sensitive to detect behavioral nuances characteristic to specific populations. While our results evidently demonstrate this sensitivity, it also suggests the importance of taking into account demographical factors when using these phenotypes for groupwise comparisons. Demographical factors such as age, employment status, living in a rural or urban area, or disability status have the potential to affect the derived phenotypes. For example, employment status and living in a rural area might affect the distance travelled and factors such as age have an effect on the number of places visited and the amount of time spent at home as showed in this manuscript. Without the availability of subjects matched on the basis of several demographical factors, the ability to compare these phenotypes between different populations/groups is limited and might lead to wrong conclusions.

It is also noteworthy that the interpretation of the derived phenotypes is limited to the definition of how the stationary locations are identified here. While we have
showed that the stay point detection algorithm\textsuperscript{24} as used here is accurate in detecting stationary locations, the movement within stationary locations (i.e. buildings) is not registered by this approach. With regard to the derived phenotypes this indicates that the movement within stationary locations is not taken into account by the derived phenotypes. This restricts the behavioral interpretation of these phenotypes and is therefore, limited to the definition of a stationary location. This inability to detect movement within stationary locations is due to the constraint that smartphone-based location data solely reflects movement with a degree of uncertainty and provides a rough estimation of the true location. Additional smartphone sensors such as the accelerometer could potentially be utilized to quantify movement with stationary locations and enrich the information used to derive phenotypes.

We expect that passive monitoring strategies have an important potential for both research and clinical care related to human behavior and mental health. For research, implementation of these methods will generate behavioral data that is unlike any of the currently existing data in this field in terms of their objective nature, their high resolution and their acquisition in a natural, real world setting. There is also clinical potential; we speculate that objective measures of mobility can provide, at least theoretically, clinically relevant insights in a patient’s physical exercise and may also be related to their level of social engagement. Accuracy of the latter may be improved by combining GPS data with other data retrievable from smartphones related to communication (e.g. frequency of phone calls or texting). Further research is required to validate these potential clinical applications of passive monitoring strategies. Future directions of research should also explore to what extent changes individual passive monitoring data patterns may be used to identify transitions in mental health status; for instance someone recovering from a depressive mood episode may be showing a gradual increase in mobility. Another example may be the detection of decrease in social interaction through passive monitoring a possible early warning signal for an impending recurrent psychotic episode in an individual diagnosed with schizophrenia.

In sum, we propose a framework to derive digital quantitative measures of human mobility that can be assessed in a longitudinal and objective manner in the real-world environment. Following preprocessing raw smartphone location data, human behavioral phenotypes have been developed, validated through user confirmation, and successfully applied to assess the effects of ageing and schizophrenia on these measures. We suggest that provided data is adequately processed, digital phenotyping has the potential to provide a new entry into the quantitative and more objective assessment of behavior in humans, allowing to expand our knowledge of the biological mechanisms that drive these behaviors.
For neuropsychiatric disorders, this is the first step towards a scalable and more objective measure of behavior, which will be a critical step forward to improve our understanding of mental illness.

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Conflict of Interest:
Dr. Arango. has been a consultant to or has received honoraria or grants from Acadia, Angelini, Gedeon Richter, Janssen Cilag, Lundbeck, Otsuka, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion and Takeda.
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SUPPLEMENTARY MATERIALS

Supplementary Table 1 | Overview of the characteristics per group and in which part of the study the data was used.

|          | n   | Age     | Gender | Data collection period | Development preprocessing procedures | Validation phenotypes |
|----------|-----|---------|--------|------------------------|--------------------------------------|-----------------------|
| Group 1  | 10  | 33.2 (sd = 13.74) | 6 M; 4 F |                         |                                      | ✓                     |
| Group 2  | 192 | 55.47 (sd = 14.71) | 81 M; 112 F | 13 days               |                                      | ✓                     |
| Group 3  | 42  | 31.78 (sd = 8.91)  | 34 M; 8 F | 14 or 42 days          |                                      | ✓                     |

Supplementary Table 2 | Example of geospatial coordinates collected by smartphones. The latitude and longitude provide information about the actual location, time provides some contextual and temporal information about this actual location. The accuracy values inform about the reliability of the observed location. In this example the third observation is the most reliable in terms of accuracy.

| Latitude  | Longitude | Time      | Accuracy(m) |
|-----------|-----------|-----------|-------------|
| 53.24149  | 6.537214  | 14:49:15  | 48.000      |
| 53.24086  | 6.537754  | 15:00:26  | 128.000     |
| 53.24136  | 6.537314  | 15:00:47  | 20.006      |
| 53.24118  | 6.536491  | 15:56:58  | 48.000      |
| 53.24088  | 6.536467  | 15:57:00  | 32.000      |
| 53.24081  | 6.536918  | 15:57:16  | 32.000      |
