

From smartwatch to psychopathology: longitudinally recorded digital phenotypes relate to psychopathology dimensions in patients with psychotic spectrum disorders

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Abstract

Background: Digital phenotyping refers to the objective measurement of human behavior via devices such as smartphones or watches and constitutes a promising advancement in personalized medicine. Digital phenotypes derived from heart rate, mobility, or sleep schedule data utilized in psychiatry to either diagnose individuals with psychotic disorders, or to predict relapse as a binary outcome. Machine learning models so far have achieved predictive accuracies that are significant but have not large enough for clinical applications. This could hinge on broad clinical definitions, which encompass heterogeneous symptom and sign ensembles, thus hindering accurate classification. The five-factor model for the Positive and Negative Symptom Scale (PANNS), which entails five independently varying dimensions, is thought to better capture symptom variability. Utilizing the specific definitions of this refined clinical taxonomy in combination with digital phenotypes could yield more precise results.

Objective: The present study aims to investigate potential links between digital phenotypes and each dimension of the five-factor PANNS model. We also assess whether clinical, demographic and medication variables confound said relations.

Methods: In the E-prevention study, heart rate, accelerometer, gyroscope and sleep schedule data were continuously collected via smartwatch for a maximum of 24 months, in 38 patients with psychotic spectrum disorders. Obtaining the mean and standard deviation for each patient-month, resulted in a database consisting of more than 740 monthly data points. A linear mixed model analysis was used to ascertain connections between monthly aggregated heart rate and mobility features and the 5 symptom dimension scores of PANNS, obtained during monthly clinical interviews.

Results: The positive symptom dimension was associated with increased sympathetic and decreased parasympathetic tone, while the negative dimension was mainly connected to decreased mobility during wakefulness. For the excitement/hostility and the depression/anxiety dimension we report an increase in motor activity during sleep while only excitement/hostility was related to increase in sympathetic heart activation and decreased sleep. The cognitive/disorganization dimension was related to decreased variability in sympathetic activation during wakefulness.

Conclusions: This study provides evidence that biological changes assessed by continuous measurement of digital phenotypes could be characteristic of specific symptom clusters rather than entire diagnostic categories of psychotic disorders. These results support the use of digital phenotypes not only as means for remote patient monitoring, but as concrete targets for biomarker research in psychotic disorders.

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Original Manuscript

From smartwatch to psychopathology: longitudinally recorded digital phenotypes relate to psychopathology dimensions in patients with psychotic spectrum disorders

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Abstract

Background: Digital phenotyping refers to the objective measurement of human behavior via devices such as smartphones or watches and constitutes a promising advancement in personalized medicine. Digital phenotypes derived from heart rate, mobility, or sleep schedule data utilized in psychiatry to either diagnose individuals with psychotic disorders, or to predict relapse as a binary outcome. Machine learning models so far have achieved predictive accuracies that are significant but have not large enough for clinical applications. This could hinge on broad clinical definitions, which encompass heterogenous symptom and sign ensembles, thus hindering accurate classification. The five-factor model for the Positive and Negative Symptom Scale (PANNS), which entails five independently varying dimensions, is thought to better capture symptom variability. Utilizing the specific definitions of this refined clinical taxonomy in combination with digital phenotypes could yield more precise results.

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increase in motor activity during sleep while only excitement/hostility was related to increase in sympathetic heart activation and decreased sleep. The cognitive/disorganization dimension was related to decreased variability in sympathetic activation during wakefulness.

Conclusions: This study provides evidence that biological changes assessed by continuous measurement of digital phenotypes could be characteristic of specific symptom clusters rather than entire diagnostic categories of psychotic disorders. These results support the use of digital phenotypes not only as means for remote patient monitoring, but as concrete targets for biomarker research in psychotic disorders.

Keywords: digital phenotype; sympathetic heart activation; parasympathetic heart activation; smartwatch; psychopathology dimension; schizophrenia; bipolar disorder.

Introduction

Psychotic spectrum disorders manifest in a variety of psychopathological symptoms and signs that vary across multiple time scales, ranging from hours or days (e.g. the development of positive symptoms in an acute psychotic or manic episode) to months or even years (e.g. the subtle increase of negative symptoms in remitted patients). In clinical practice, heterogeneous symptoms and signs are grouped in clusters to define categorical diagnoses of psychotic disorders (schizophrenia or bipolar disorder) that are used as invariant labels chronically attached to patients, guiding clinical decisions. The shortcomings of such an approach in capturing the dynamic nature of psychotic disorders have been widely recognized [1]. The dimensional approach to the definition of psychotic spectrum disorders introduced in DSM-V [2] is an attempt to account for the heterogeneity of psychopathology symptoms and signs in psychosis as well as their dynamic nature. Psychopathology dimensions are clusters of homogeneous symptoms and signs that vary independently within every patient and can follow a unique dynamic pattern in time, which can in turn be used to design optimal treatment strategies. Most currently used classes of medications already target specific psychopathological dimensions (antipsychotic medications targeting positive and manic symptoms, antidepressants targeting depressive symptoms) while new medications are being tested, targeting other dimensions such as cognitive symptoms [3].

The influence of the dimensional approach is also apparent in the redefinition of well-established clinical symptom assessment tools, such as the Positive and Negative Symptom Scale (PANSS) [4]. The original PANSS measured the positive and negative symptom scales and the general psychopathology scale, but recent work highlighted the effectiveness of a five-factor solution [5]. In a meta-analysis of 45 studies using factor analysis of PANSS [6] the authors propose a consensus of the five-factor solution for PANSS. The factors, following the pentagonal model for the dimensions of psychosis that has been adopted in DSM-V, include the positive factor (matching the

positive dimension), the negative factor (matching the negative dimension), the cognitive/disorganization factor (matching cognitive dimension), the depression/anxiety factor (matching the depression dimension) and the excitement/hostility factor (matching the mania dimension). The five-factor model of PANSS can serve as a useful clinical tool to quantitatively assess the psychotic symptom dimensions and their dynamic changes over time.

While clinical definitions and taxonomies of psychotic disorders continue to be refined, sole reliance on phenomenology remains problematic [7]. The search for “biomarkers” related to psychotic disorder diagnosis is one of the most elusive research objectives in the field [8-9]. The term biomarker is defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” [10]. Perhaps an even more ambitious goal would be to monitor longitudinal biomarker variation to detect or predict changes in psychopathology dimensions, thus establishing a link between biological processes and clinical observations. An important advantage of longitudinal designs in biomarker research, when compared to case-control studies, is that repeated measures in time can lead to characteristic findings at the individual level. This could allow for early, case-specific clinical interventions, ensuring optimal outcome following the concept of personalized or precision medicine [11].

A promising advancement in personalized medicine is patient monitoring via digital phenotyping, which is defined as the moment-by-moment quantification of the individual-level human phenotype in-situ using data from smartphones, smartwatches and other personal digital devices [12]. These phenotypes include intermittent active data, requiring the participation of the individual (such as speech and video recording during a task or interview, question and answer surveys etc.) and continuous passive data that do not require participation of the individual such as physical activity (via accelerometer), heart rate (via photoplethysmography), spatial trajectories (via GPS) and light exposure (via camera) among others [13-14]. Passively recorded digital phenotypes

allow for truly continuous monitoring over large periods of time and thus have been utilized in recent studies to detect and predict relapse onset. The core idea is that during long periods of remission, or relative health, markers such as physical activity or heart rate form strong distinct patterns, characteristic for each individual. It is then postulated that during an acute episode of relapse, or even beforehand, abrupt, detectable pattern breaks may occur. Methodologically, features extracted from passively collected data are used to train machine learning models, such as anomaly detection models or neural networks, which then predict relapse as a binary outcome. Relapse could refer to a psychotic episode ([15-19], see [20] for a review), a mood episode [21-23], or a depressive episode ([24-26] see [27] for a review).

The main objective of the current study is to combine ideas and methodological concepts from the emerging field of digital phenotyping, with the dimensional approach for psychopathology. Instead of attempting to predict a binary outcome such as relapse, which is inherently diverse in its manifestations, we seek correlations between digital phenotypes and each of the five dimensions of PANSS. We use data from the e-Prevention project [28] in which heart rate and mobility data were continuously recorded via smartwatch, for up to 2 years. In a preliminary report [29], we used a subsample of the complete data set to show that specific phenotypes correlate with the positive and negative symptom scale scores of PANSS, as defined originally in [4]. Here, we use the complete e-Prevention database as well as the five-dimensional model of PANSS as described in [6]. We tested if longitudinal changes in each symptom dimension would correspond to digital phenotype variation. We also investigated the relation of the digital phenotypes and psychopathology dimensions to demographic clinical and medication variables recorded in the same patient group to test for their confounding effects on the relation of digital phenotypes to psychopathology dimensions.

Methods

Participants

The data for the current study were derived from the e-prevention study database, which included 38 patients with psychotic spectrum disorders (schizophrenia, schizoaffective and bipolar disorder). All patients were sequentially referred by their treating psychiatrists in remission and a diagnostic evaluation was performed at the intake interview by two trained psychiatrists using DSM-5 criteria. At the intake interview we recorded demographic data including age, gender, marital status, birthplace, occupation, educational level and Body Mass Index (BMI). Patients were screened for history of medical, neurological, psychiatric, and developmental disorders, family psychiatric history, birth complications and history of substance abuse (smoking, alcohol, cannabis, and other psychotropic substances) (Table 1). Verbal IQ scores were derived from the administration of the Vocabulary Test of Wechsler Intelligence Scales [30] (Table 1).

For each patient we recorded duration of psychotic disorder before entering the study for each patient and medications including antipsychotics, antidepressants, mood stabilizers and benzodiazepines (Table 1). Antipsychotic medication dosage was transformed into chlorpromazine equivalents [31]. Antidepressant medication dosage was transformed into fluoxetine equivalents [32]. Finally, benzodiazepine dosage was transformed into diazepam equivalents [33].

Each participant then provided written informed consent for participation in the study and monitoring of clinical and digital phenotypes, after being given a full description of the study design and objectives. Moreover, participants provided a separate consent form allowing the use of their personal data for the purposes of the e-Prevention research project in compliance with General Data Protection Regulation (GDPR, EU Regulation 2016/679). e-Prevention project study protocol and participant consent forms were reviewed and approved by the Ethics committee of the University Mental Health, Neurosciences and Precision Medicine Research Institute “COSTAS STEFANIS.”

Monthly clinical interviews

For the total duration of their participation in the e-Prevention patients agreed to visit the Psychiatry Department of Eginition University Hospital once every month for an evaluation during which psychopathology (Positive and Negative Syndrome Scale, PANSS) [4], Body Mass Index (BMI) and medication status (including equivalent transformed dosage of antipsychotics, antidepressants and benzodiazepines) were assessed among other clinical parameters [29]. The dimensional categorization of the PANSS scores [6] was used to derive the following 5-dimension scores: a) positive dimension, b) negative dimension, c) cognitive/disorganization dimension, d) depression/anxiety dimension, e) excitement/hostility dimension.

Digital phenotypes

The e-prevention data base includes digital phenotypes collected passively from patients via a commercial smartwatch (Samsung Gear S3, Samsung Group, South Korea). Patients agreed to wear the smartwatch for the total duration of the study, continuously day and night, excluding charging time and activities that might lead to hardware failure (taking a shower or swimming). Details about system architecture, smartwatch feature extraction and preprocessing are described in detail in our previous reports [28-29, 34-35].

Briefly, the accelerometer and gyroscope 3D signals were used to derive the Short Time Energy (STE) of their Euclidean norm over 5-minute time windows. For each 5-minute interval we derived a STE value the accelerometer that reflects translational motor activity (TMA) and from the gyroscope that reflects rotational motor activity (RMA).

Heart measurements via photoplethysmography included beats per minute (BPM) and intervals between successive pulses (PP intervals). PP intervals were processed for removal of artifacts and the count of the pre-processed PP intervals, named normal to normal intervals (NNIs) for each 5-minute window was derived. This measure of normalized heart rate is considered as a proxy of the sympathetic system heart activation (SHA, [36-37]). The series of PP interval values (in milliseconds) were used to calculate the root mean square of their successive differences

(RMSSD) for each 5-minute interval. The RMSSD is considered a proxy of parasympathetic heart activation (PHA, [38]).

Sleep/wake ratio (SWR) per day and the mean number of total steps per minute for each day as a measure of locomotive motor activity (LMA) were also recorded. To improve the robustness of these measurements we considered data only for days for which we have 18 or more hours of recorded data.

Our dataset included 740 patient months (minimum: 1 month, maximum 26 months, median: 11 months for each of the 38 patients). We excluded months for which less than 720 5-minute measurements of wake data, or less than 480 5-minute measurements of sleep data were collected. For each patient, we calculated the monthly mean and standard deviation for each digital phenotypes, separately for periods of wakefulness and sleep (except for SWR and LMA). These data are summarized in Supplementary Table 1, alongside data from clinical interviews regarding psychopathology or medication. We derived the following digital phenotypes for each participant, for every month:

- a) Mean and standard deviation of translational motor activity during wakefulness (W-TMA) and during sleep (S-TMA).
- b) Mean and standard deviation of rotational motor activity during wakefulness (W-RMA) and during sleep (S-RMA).
- c) Mean and standard deviation of sympathetic heart activation during wakefulness (W-SHA) and during sleep (S-SHA).
- d) Mean and standard deviation of parasympathetic heart activation during wakefulness (W-PHA) and during sleep (S-PHA).
- e) Mean and standard deviation of sleep wake ratio (SWR).
- f) Mean and standard deviation of locomotive motor activity (LMA).

Statistical analysis

Analysis of the relation of digital phenotypes to PANSS dimensions

We used Linear mixed effects (LME) model analysis to estimate the relation of each one of the 20 digital phenotypes (independent predictor) with each one of the 5 PANSS dimension scores (dependent variable) using SPSS 26 Software (IBM). LME analysis is suitable for the current dataset, since it includes different number of repetitions (months of follow up) for each participant. The analysis followed three steps as described below:

a) In the first step we perform an exploratory random intercept LME analysis, using the basic LME model in which each digital phenotype was entered as a fixed effect covariate predicting each PANSS dimension score (dependent variable) and participant was entered as a random intercept effect. This model is equivalent to a repeated measures analysis of variance assuming equal variance for repeated measures, for each participant. The maximum likelihood method was used to estimate the model. A total of 20 exploratory LME model analyses were performed for each PANSS dimension (one for each of 20 digital phenotypes). In those analyses with a p value < 0.05 we further checked for the effect size of predictor variable. We used marginal pseudo-R square value (R_m) provided in the coefficients of determination section of the SPSS results output to compute Cohen f^2 with the formula: $\text{Cohen } f^2 = R_m / (1 - R_m)$. We retained those results with a p value < 0.05 and effect size $f^2 \geq 0.01$.

b) The second step, which was a repeated measures LME analysis was performed only in those cases where the first step analysis resulted in significant effects. In this analysis each digital phenotype was included as a repeated measures factor with a first order autoregressive covariance matrix. This model assumes that the variance of the repeated measure factor within each participant varies across measurements in such a way that measurements that are closer together in time are more correlated than measurements further apart in time. The -2log likelihood difference between this model and the random intercept model of the first step analysis described above was used as a chi square value with

one degree of freedom to compute a p-value. If the p-value was lower than 0.05 this confirmed that the repeated measures extended model had a significantly better fit compared to the random intercept model.

c) The third step, a random slope LME analysis, was performed again only in cases where the first step analysis resulted in significant effects. We used either the first or the second step model (if it had a significantly better fit) and included the digital phenotype as a random effects factor with unstructured covariance. This model assumes that the relation of the independent factor (digital phenotype) and the dependent variable (PANSS dimension) is different among different subjects introducing a random slope effect. The -2-log likelihood difference between this extended model and the first or second step model was computed. This value was used as a chi square to compute a p-value with 1 degree of freedom and a p-value with 2 degrees of freedom. The final p-value was computed as:

$$\text{p-value} = \frac{1}{2} \text{p-value with one degree of freedom} + \frac{1}{2} \text{p-value with two degrees of freedom}$$

If the final p-value was lower than 0.05 this indicated that the random slope extended model had a better fit than the random intercept or repeated measures LME model.

Analysis of the effects of demographic clinical and medication variables on digital phenotypes and psychopathology dimensions and analysis of interactions

Random intercept LME models to test the effect of a set of demographic clinical and medication variables (Table 1) as independent predictor factors on each of the 20 digital phenotypes (dependent variables) as well as the 5 psychopathology dimensions of PANSS (dependent variables). We did not use more complex models with repeated measures and random slope variance components of the independent factor since all independent demographic and clinical variables were categorical with no random variation. The two medication variables (chlorpromazine and fluoxetine equivalents) were continuous covariates but again these variables did not have enough within subject variation and the use of repeated measure and random slope effects resulted in ill posed models that did not converge

to criterion. In the analysis we used 5 demographic and 6 clinical factors summarized in Table 1, excluding mood stabilizers due to heterogeneity in treatment and benzodiazepines because their use was only sporadic. We report those results with a p value < 0.05 and effect size $f^2 \geq 0.01$.

To test for interaction effects, we used the set of final models with significant effects of digital phenotypes on PANSS dimensions that were described in the previous section and added the demographic/clinical/medication variables that were significant in predicting both the digital phenotype and PANSS dimension, as independent predictors.

Results

Effects of digital phenotypes on PANSS dimensions

The results of the first step, exploratory analysis for relation of digital phenotypes to the PANSS dimensions using random intercept LME models, are presented in Table 2. Table 3 presents the results of the application of LME model selection for each of the five dimensions.

Higher positive symptom dimension scores were related to a higher mean sympathetic heart activation in wakefulness and sleep, and to a lower mean parasympathetic heart activation during sleep (Table 3). LME models including repeated measure as well as random slope effects had significantly better fits than the original random intercept models in all cases. Using these models the relation of parasympathetic heart activation during sleep to the PANSS positive dimension remained significant, while the relation of the sympathetic heart activation during wakefulness and during sleep to PANSS positive dimension became marginally significant (Table 3).

Increased negative symptom dimension scores were related to decreased mean translational motor activity and variability (SD), as well as decreased mean locomotive motor activity and decreased mean rotational motor activity during wakefulness. Table 2 presents the results of the application of LME model selection. The random slope LME models had significantly better fits than the original random intercept models in all cases. Using these models all the relations that selected in the first step analysis remained significant (Table 3).

Higher cognitive/disorganization symptom dimension scores were associated with lower variability (SD) of sympathetic heart activation during wakefulness. The more complex step 2 and step 3 models were not significantly better compared to the step 1 model.

Increased scores in the depression/anxiety symptom dimension were related to elevated mean translational and rotational motor activity as well as their respective variability (SD) during sleep (Table 3). The more complex step 2 and step 3 models were not significantly better compared to the step 1 model.

Lastly, the increase in the excitement/hostility symptom dimension was associated with an increase in mean rotational motor activity and an increase in the variability (SD) of translational and rotational motor activity during sleep. There was also a relation between this symptom dimension and an increase in mean sympathetic heart activation during wakefulness and during sleep as well as a decrease in mean sleep wake ratio (Table 3). The more complex step 2 and step 3 models were not significantly better compared to the step 1 models, except for mean sympathetic heart activation during wakefulness. In that case the random intercept step 3 model had significantly better fit and was retained (Table 3).

Effects of demographic/clinical/medication variables

The results of the LME model analysis for the effects of demographic, clinical and medication variables on the digital phenotypes and on psychopathology dimensions are presented in supplementary Tables 2 and 3 respectively, while significant results with effect size $> .01$ are further elaborated in Tables 4 and 5.

We then investigated potential confounding effects of demographic, clinical and medication variables on the relations of digital phenotypes with PANSS dimensions (see methods). To be eligible for inclusion in this analysis, a potential confounder had to be significant in predicting both the digital phenotype (Supplementary Table 2) and the PANSS dimension (Supplementary Table 3).

To begin with, the effect of mean sympathetic activation during wakefulness (W-SHA(M)) on the positive dimension was tested with antipsychotic medication as a confounding covariate. The interaction LME model analysis showed a non-significant interaction of W-SMA(M) and antipsychotic medication on PANSS positive dimension ($t_{(95.6)} = -1.86$, $p = .065$) and significant effects of antipsychotic medication ($t_{(98.3)} = 2.56$, $p = .012$) and W-SHA(M) ($t_{(48)} = 2.32$, $p = .024$). The effect of mean sympathetic activation during sleep (S-SMA(M)) on the PANSS positive dimension was tested with antipsychotic medication as covariate. This LME model analysis showed

a non-significant interaction of S-SMA(M) and antipsychotic medication on PANSS positive dimension ($t_{(302.9)} = 1.08$, $p = .28$) and non-significant effects of antipsychotic medication ($t_{(297.8)} = -.18$, $p = .85$) and W-SHA(M) ($t_{(43.5)} = 1.2$, $p = .23$).

The effect of variability of translational motor activity during wakefulness (W-TMA(SD)) on the negative dimension of PANSS was tested with antipsychotic medication as a covariate. This LME model analysis showed a significant negative interaction of W-TMA(SD) and antipsychotic medication on PANSS negative dimension ($t_{(231.6)} = -3.15$, $p = .002$) and a significant effect of antipsychotic medication on PANSS score ($t_{(365.3)} = 3.98$, $p = .00008$) while the effect of W-TMA(SD) on PANSS negative dimension was not significant anymore ($t_{(49.4)} = -.84$, $p = .4$). The effect of mean rotational motor activity during wakefulness (W-RMA(M)) on the negative dimensions of PANSS was tested with gender as cofactor. This LME model analysis showed a non-significant interaction of W-RMA(M) and gender on PANSS negative dimension ($t_{(31)} = 1.1$, $p = .28$) while the effect of gender on PANSS score was significant ($t_{(65.9)} = 2.85$, $p = .006$) and the effect of W-RMA(M) on PANSS negative dimension was also significant ($t_{(34.1)} = -2.95$, $p = .006$). Finally, the effect of mean locomotive activity (LMA(M)) on the negative dimension of PANSS was tested with antipsychotic medication as covariate. This LME model analysis showed a significant negative interaction of LMA(M) and antipsychotic medication on PANSS negative dimension ($t_{(93.1)} = -2.08$, $p = .04$) and a significant effect of antipsychotic medication on PANSS negative dimension ($t_{(271.2)} = 2.67$, $p = .008$) while the effect of LMA(M) on PANSS negative dimension was not significant ($t_{(34.8)} = -.88$, $p = .38$).

Discussion

Digital phenotypes and psychotic symptom dimensions

In the current study we investigated the potential relation of continuously recorded digital phenotypes to the monthly variation of psychotic symptom dimensions measured with PANSS. We observed significant relations between psychotic symptomatology and digital phenotypes, by applying the dimensional model comprised of five symptom dimensions (positive, negative, cognitive/disorganization, depression/anxiety and excitement/hostility). Notably, each symptom dimension was associated with a different set of digital markers, providing further evidence for the applicability of the dimensional model.-

Positive and excitement/hostility dimension symptoms were related to increased sympathetic heart activation in wakefulness and sleep. In our preliminary report [29], we showed that increased sympathetic activity in wakefulness and sleep was related to the PANSS positive symptom scale score. Present results corroborate these initial findings in the sense that items from the PANSS original positive scale score are included in these two symptom dimensions (positive and excitement/hostility). A novel finding of this study was the specific relation of the positive symptom dimension to decreased parasympathetic heart activation in sleep that was not shared with any other symptom dimension (Figure 1). The lack of universality of this relation across symptom dimensions is of particular interest given the vast body of literature ascertaining a connection between decreased vagal tone and schizophrenia and other psychotic disorders ([39-42], see [43-44] for a review). It is conceivable that decreased parasympathetic activation could be linked solely to the existence or exacerbation of positive symptomatology rather than the entire range of symptoms characterizing psychotic disorders, although this hypothesis requires further testing.

Increased negative dimension scores were related to decreased motility during wakefulness overall, marked by a decrease in translational and rotational motor activity, a decrease in the variability of translational motor activity and a decrease in locomotor activity (Figure 1). A decrease

in motility would be the expected overt behavior accompanying increased negative symptomatology [45-46]. It should be noted that in our preliminary report we did not detect a relation of motility to the negative symptom scale score of PANSS. In that report we observed that increased original PANSS negative scale scores were linked to decreased parasympathetic activation during wakefulness and increased sleep wake ratio, findings which are in line with the literature cited above. While these effects were also detected in the current study (Supplementary Table 2), they were excluded from further analysis due to their very small effect size (Cohen $f^2 < .01$). This discrepancy between studies could be attributed to the different definitions of the original negative PANNS scale and the negative symptom dimension. Another plausible explanation could be that negative symptoms evolve much slower in time and a longer period of observation would be needed to detect a robust relation to digital phenotypes measuring behavior.

Regarding the cognitive/disorganization symptom dimension, a significant, negative relation with the variability of sympathetic activation during wakefulness was observed. (Figure 1). In a related review [38], no studies examining potential HRV disruptions in mental processes such as attention or memory are cited. There are, however, two studies [47-48] in which social functioning is linked to a lower LF/HF ratio, indicative of an imbalance in autonomic regulation (higher SNS activity or lower PSNS activity). While results are not directly comparable, due to differences in both the independent and dependent variables used, the alignment concerning autonomic dysregulation in this broader area of symptoms warrants further investigation.

The two mood related dimensions (depression/anxiety and excitement/hostility) were related to increased rotational motor activity and its variability as well as elevated translational motor activity during sleep. The depression/anxiety dimension was also related to a higher variability of translation motor activity during sleep. These findings are in line with established clinical observations, namely that increased motility is indicative of restless sleep, which in turn is characteristic of both depression and manic episodes [49-51]. Finally, the excitement/hostility dimension showed a unique negative

relation to sleep wake ratio, confirming that these symptoms are accompanied by less sleep (Figure 1).

Interactions among digital phenotypes, clinical/demographic/medication factors and psychopathology dimensions

The main objective of the current study was to investigate the relations of digital phenotypes to psychopathology dimensions as well as demographic/clinical/medication variables. Importantly, it could be hypothesized that these relations are confounded by demographic/clinical/medication factors. If that were true, there should exist a direct connection among digital phenotypes and demographic/clinical/medication variables and among psychopathology dimensions and demographic/clinical/medication variables simultaneously. While demographic variables were related to digital phenotypes (mainly RMA and PHA), very few relations were detected between clinical variables and digital phenotypes. To conclude, the observed relations were generally not confounded by demographic or clinical factors.

Another finding with significant implications is that only two digital phenotypes varied significantly with diagnosis. The standard deviation of rotational motor activity during wakefulness was larger for patients diagnosed with bipolar disorder compared to those with schizophrenia and the standard deviation of parasympathetic heart activation during sleep was larger for patients with schizophrenia compared to those with bipolar disorder. If one compares these findings with the results concerning the relation of psychopathology dimensions to digital phenotypes it is evident that digital phenotypes were more successful at dissociating the different psychopathology dimensions of psychotic disorders than the categorically defined syndromes of schizophrenia and bipolar disorder. These results further cement the dimensional model of psychosis [52].

As far as interaction effects among the three sets of variables (digital phenotypes, demographic/medication factors, psychopathology dimensions) are concerned, the only ones

involving all sets of variables were those including antipsychotic medication and not antidepressant medication. Considering the significance of the link between sympathetic heart activation and the positive symptom dimension, we highlight that there was no significant interaction between sympathetic heart activation and antipsychotic medication in predicting positive symptom dimension, conclusively ruling out antipsychotic medication as a potential confounder. The same cannot be stated for the relation between decreased motility and negative symptoms. Significant interaction effects indicate that the observed reduction in motility is in part mediated by the effect of increased antipsychotic medication.

Limitations

One potential limitation of the current study is the small to medium sample size of patients. We believe though that this limitation is countered by the long observation time for each patient that allowed for a substantial amount of data collected for each patient. This resulted in a large database of digital phenotype and psychopathological estimation data (about 700 data points) that increased the power for detecting significant effects.

Another limitation of the current study was that our analysis was not sensitive to the time evolution of digital phenotypes and its potential significance in predicting psychopathology. Although digital phenotypes were measured continuously in time, we implemented a coarse-grained approach for all analyses, where data from the entire month preceding each psychopathology measurement were collapsed into a single mean and variance value for each phenotype. It could be hypothesized that more subtle phenotype variation in time, evolving over days or weeks, could have significant effects in predicting psychopathological changes.

Conclusions

The present study adds to the mounting evidence in favor of the five-factor model of PANNS, which

can capture symptom profile heterogeneity, as well as symptom variation in time. Crucially, each psychopathology dimension was associated with a different set of digital markers, while those relations were not confounded by demographic or clinical variables. This finding constitutes a preliminary indication that biological changes such as decreased parasympathetic activity, could underlie a narrower group of symptoms, rather than the entire psychotic disorder spectrum as assumed till now. Another important detail is that both behavioral markers and symptom severity vary in time, which seems inherently conflicting with static diagnostic labels and explains why only 2 of 19 utilized markers correlated with diagnosis. Lastly, we highlight the potential of smart devices (e.g. watches or phones) and digital phenotypes not only as remote monitoring tools, but also as valuable research targets in the quest for objective markers in psychotic disorders.

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Table 1: Demographic, clinical and medication data of the patients in the e-prevention database

Demographic			
Age	Mean = 30.5 years	SD = 7.3years	Range: 19-45years
Age category	(18-30y): 50%	(31-45y): 50%	
Gender	Male: 68.4%	Female:31.6%	
Marital status	Single:84.2%	Married:15.8%	
Birth Place	Urban:89.5%	Rural:10.5%	
Occupation	Unemployed: 44.7%	Employed:42.1%	Student: 13.2%
Education	Mean: 13.4 years	SD: 2.2 years	Range: 9-18years
Education category	(<=12y): 63.2%	(>12y):36.8%	
Verbal IQ	Mean: 97	SD:13.8	Range:70-120
Verbal IQ category	(>=70 and <=100): 52.6%	(>100 and <=120):47.4%	
Body Mass Index	Normal (<25):34.2%	Overweight (25-30):44.7%	Obese (>30):21.1%
Clinical			
Diagnosis	Schizophrenia N=21	Schizoaffective N = 2	Bipolar N = 15
Diagnostic category	(Schizophrenia): 55.3%	(Affective): 39.5%	
Disorder Duration	Mean = 7.3years	SD =6.4 years	Range:0-23years
Duration category	(<= 5 y): 50%	(> 5 y):50%	
Family History	Yes:52.6%	No:47.4%	
Birth Complications	Yes:28.9%	No:71.1%	
Alcohol use	Yes:36.8%	No:63.2%	
Smoking	Yes:68.4%	No:31.6%	
Medication			
Antipsychotics	Yes:89.5%	No:10.5%	
Chlorpromazine eq.	Mean:518.6	SD:481.4	Range:0-2000
Antidepressants	Yes:44.7%	No:55.3%	
Fluoxetine eq.	Mean:8.1	SD:13.5	Range:0-60
Benzodiazepines	Yes:18.4%	No:81.6%	
Diazepam eq.	Mean: 0.9	SD:4.8	Range:0-40
Mood Stabilizers	Yes:52.6%	No:47.4%	

This table presents the demographic, clinical and medication data collected for the 38 patients of the e-prevention database used for the current analysis.

Table 2: Random intercept LME model analysis of the relation of PANSS symptom dimensions to digital phenotypes

Digital phenotype	Positive	Negative	Cognitive/ Disorganization	Depression / Anxiety	Excitement / Hostility
W-TMA(M)	.863	.00036(.018)	.169	.106	.373
W-TMA(SD)	.547	.00069(.014)	.166	.201	.191
S-TMA(M)	.717	.037(.004)	.075	.005(.017)	.098
S-TMA(SD)	.772	.913	.201	.012(.015)	.002(.031)
W-RMA(M)	.940	.001(.016)	.454	.142	.652
W-RMA(SD)	.590	.014(.006)	.731	.238	.759
S-RMA(M)	.902	.913	.085	.001(.022)	.030(.013)
S-RMA(SD)	.714	.070	.316	.005(.017)	.001(.029)
W-SHA(M)	.0003(.021)	.453	.109	.342	.021(.013)
W-SHA(SD)	.100	.661	.0004(.013)	.500	.593
S-SHA(M)	.00007(.05)	.474	.059	.402	.001(.044)
S-SHA(SD)	.329	.728	.008(.006)	.045(.008)	.088
W-PHA(M)	.222	.028(.007)	.386	.092	.522
W-PHA(SD)	.641	.947	.161	.051	.518
S-PHA(M)	.0008(.021)	.407	.8	.155	.122
S-PHA(SD)	.217	.509	.385	.350	.232
LMA(M)	.499	.00037(.016)	.078	.073	.934
LMA(SD)	.463	.018(.003)	.012(.003)	.632	.609
SWR(M)	.208	.002(.006)	.975	.862	.007(.013)
SWR(SD)	.538	.870	.804	.458	.205

This table presents the results of the first step analysis of the relation of digital phenotypes to PANSS dimension scores using the random intercept only linear mixed effects (LME) models. The p value of the fixed effect is shown for each analysis and Cohen f^2 is shown in parentheses only in the cases where the p value was significant ($<.05$). The significant results with $p <.05$ and $f^2 \geq .01$ that were selected for further analysis are marked in bold.

Table 3: Final LME model selection for the relation of digital phenotypes to PANSS dimensions

Digital phenotype	Estimate (SD)	t (df)	P	LME model comparison step 1: random intercept, step 2: repeated measures, step 3: random slope
Positive Dimension				
W-SHA(M)	.017(.009)	1.9 (35.1)	.069	step 2 v step 1 $X^2 = 33.4$, $P < .00001$ step 3 v step 2 $X^2 = 17.9$, $P = .00007$
S-SHA(M)	.016 (.009)	1.9 (33.7)	.062	step 2 v step 1 $X^2 = 16.1$, $P = .00006$ step 3 v step 2 $X^2 = 37.5$, $P < .00001$
S-PHA(M)	-.014 (0.04)	-3.3 (570.7)	.0008	step 2 v step 1 $X^2 = .4$, $P = .53$ step 3 v step 1 $X^2 = 5.1$, $P = .36$
Negative Dimension				
W-TMA(M)	-.375(.119)	-3.1(22.1)	.005	step 2 v step 1 $X^2 = .1$, $P = .75$ step 3 v step 1 $X^2 = 10.9$, $P = .0026$
W-TMA(SD)	-.291(.121)	-2.4(20)	.026	step 2 v step 1 $X^2 = 1.9$, $P = .17$ step 3 v step 1 $X^2 = 11.8$, $P = .0016$
W-RMA(M)	-.00045 (.00016)	-2.8(22.9)	.01	step 2 v step 1 $X^2 = 1.6$, $P = .2$ step 3 v step 1 $X^2 = 7.2$, $P = .017$
LMA(M)	-.00023 (.00009)	-2.44(17.2)	.026	step 2 v step 1 $X^2 = 3.7$, $P = .054$ step 3 v step 1 $X^2 = 23$, $P < .00001$
Cognitive/Disorganization Dimension				
W-SHA(SD)	-.029(.008)	-3.5(574.5)	.0004	step 2 v step 1 $X^2 = 1.8$, $P = .18$ step 3 v step 1 $X^2 = 3.7$, $P = .105$
Depression/Anxiety Dimension				
S-TMA(M)	1.49(0.529)	2.8(564.4)	.005	step 2 v step 1 $X^2 = 1.8$, $P = .18$ step 3 v step 1 $X^2 = 3.7$, $P = .105$
S-TMA(SD)	.475(.187)	2.53(551.6)	.012	step 2 v step 1 $X^2 = 0.7$, $P = .4$ step 3 v step 1 $X^2 = 2.4$, $P = .21$
S-RMA(M)	.003(.001)	3.2(564.5)	.001	step 2 v step 1 $X^2 = 1.4$, $P = .24$ step 3 v step 1 $X^2 = 2.5$, $P = .2$
S-RMA(SD)	.001(.00026)	2.8(569.2)	.005	step 2 v step 1 $X^2 = .2$, $P = .65$ step 3 v step 1 $X^2 = 2.5$, $P = .2$
Excitement/Hostility Dimension				
S-TMA(SD)	.548(.172)	3.2(469.7)	.002	step 2 v step 1 $X^2 = .7$, $P = .4$ step 3 v step 1 $X^2 = 2.5$, $P = .2$
S-RMA(M)	.002(.001)	2.18(497)	.03	step 2 v step 1 $X^2 = 2.7$, $P = .1$ step 3 v step 1 $X^2 = 4.7$, $P = .063$
S-RMA(SD)	.001(.00024)	3.2(507.7)	.001	step 2 v step 1 $X^2 = 1.6$, $P = .2$ step 3 v step 1 $X^2 = 1.1$, $P = .43$
W-SHA(M)	.017(.009)	1.92(20.28)	0.069	step 2 v step 1 $X^2 = 1.7$, $P = .19$ step 3 v step 1 $X^2 = 13.2$, $P = .0008$
S_SHA(M)	.013(.004)	3.2(368.2)	.001	step 2 v step 1 $X^2 = 1.1$, $P = .29$ step 3 v step 1 $X^2 = 4.7$, $P = .062$
SWR(M)	-.601(.222)	-2.7(562)	.007	step 2 v step 1 $X^2 = .2$, $P = .16$ step 3 v step 1 $X^2 = 1$, $P = .6$

This table presents the results for the final linear mixed model (LME) model analysis selected after the three-step process described in the methods section. Selected models of digital phenotypes predicting each PANSS dimension score are grouped for each PANSS dimension. In each model we present the estimated coefficient for the digital phenotype and its corresponding standard error (SE), the t-value and degrees of freedom (df) for the fixed effect of the digital phenotype and the p value

for this fixed effect. In the last column we present the X^2 and corresponding p value for the comparison of the -2log-likelihood of the different models at each step of the analysis (see methods section). Step1: random intercept only, step2: repeated measures random intercept and step3: random slope model.



Table 4A: Significant effects of demographic and clinical variables on digital phenotypes

	Mean (SE)	Mean (SE)	Mean (SE)	t (df) or F(df)	P
W-RMA(M)	Female: 4354.6(394.6)	Male: 3202.8(259.9)		2.44(36.3)	.02
W-RMA(SD)	Schizophrenia: 4066.3(326.4)	Bipolar: 5260.6(397.1)		2.32(37)	.026
S-RMA(SD)	Female: 1065.1(119.1)	Male: 717.9(78.5)		2.43(36.2)	.02
W-SHA(M)	Smoking: 369.5(3.4)	Non-Smoking: 350.6(4.8)		3.18(36)	.003
S-SHA(M)	Smoking: 285.3(9.1)	Non-Smoking: 308.9(6.4)		2.12(36.5)	.041
W-PHA(M)	Married: 305(12.1)	Single: 275.4(5.3)		2.47(37.7)	.03
W-PHA(M)	Rural birthplace: 245.2(14.7)	Urban birthplace: 284(34.7)		2.49(38.2)	.017
W-PHA(M)	Unemployed: 272.8(7.1)	Employed: 294.1(7)	Student: 257.4(12.4)	4.19(36.2)	.023
W-PHA(SD)	Unemployed: 92.7(1.6)	Employed: 87.3(1.4)	Student: 95.7(1.6)	5(33.1)	.013
W-PHA(SD)	Education <=12years: 92.7(1.3)	Education > 12years: 87(1.6)		2.7(33.4)	.01
W-PHA(SD)	Normal weight: 89(1.4)	Overweight: 90.9(1.3)	Obese: 87.6(1.5)	7.2(602)	.0001
S-PHA(SD)	Female: 69.8(3.7)	Male: 81.3(2.5)		2.6(35.1)	.014
S-PHA(SD)	Schizophrenia: 82.7(2.77)	Bipolar: 72.9 (3.25)		2.3(34.8)	.028
LMA(SD)	Married: 1712.9(371.7)	Single: 2638.3(157.4)		2.29(38.1)	.027
SWR(M)	Female: .729(.078)	Male: 1.01(.053)		3(34.5)	.005
SWR(M)	Married: 0.639(.115)	Single: 0.974(.049)		2.67(38.4)	.011
SWR(M)	Rural birthplace: 1.2(.147)	Urban birthplace: .89(.05)		2.09(40.3)	.043
SWR(M)	Duration <= 5years 1.06(.062)	Duration > 5years .786(.063)		3.08(36.3)	.004
SWR(SD)	Female: .32(.058)	Male: .501(.044)		2.5(30.3)	.019
SWR(SD)	Married: .226(.087)	Single: .474(.038)		2.6(28.1)	.015

This table presents the results of linear mixed model analyses for the significant effects of demographic and clinical factors on digital phenotypes that also had effect size >.01 (selected from supplementary table 2). The LME model estimated mean and standard error of the mean (SE) for each value of the factor are presented in columns 2, 3,4, the t or F value (factors with 3 levels) for the fixed effect and its corresponding degrees of freedom (df) are presented in column 5 and finally the p value for the fixed effect is presented in column 6.

Table 4B: Significant effects of antipsychotic medication on digital phenotypes

	Estimate (SE)	t (df)	P
W-TMA(SD)	-.001(.00016)	3.62(633)	.0003
W-RMA(SD)	-.402(.151)	2.66(628)	.008
W-SHA(M)	.005(.002)	2.99(612)	.003
S-PHA(SD)	.004(.002)	1.97(.519)	.049
LMA(M)	-.61(.25)	2.41(598)	.016
SWR(M)	.00015(.00005)	3.5(441.5)	.0005

This table presents the results of the selected linear mixed model analyses of the significant effects of antipsychotic medication on digital phenotypes that also had effect size $> .01$ (selected from supplementary table 2). The LME model estimated mean and standard error of the mean (SE) for the antipsychotic medication (chlorpromazine equivalents) are presented in column 2 the t value for the fixed effect and its corresponding degrees of freedom (df) are presented in column 3 and finally the p value for the fixed effect is presented in column 4.

Table 5A: Significant effects of demographic and clinical variables on psychopathology dimensions

	Mean (SE)	Mean (SE)	Mean (SE)	t (df) or F(df)	P
Negative	Female: 13.4(1.19)	Male: 16.8(.81)		2.33(37.7)	.025
Negative	Urban birthplace: 15(.67)	Rural birthplace: 21.7(2)		3.24(39)	.002
Negative	Employed: 13.5(1)	Unemployed: 17.2(.97)	Student: 17.7(1.8)	4.18(37.7)	.023
Negative	Schizophrenia: 17.3(.87)	Bipolar: 14.2(1)		2.28(36.01)	.028
Cognitive / Disorganization	Employed: 9.2(.67)	Unemployed: 12.12(.65)	Student: 11.24(1.2)	5.06(37.7)	.011
Cognitive / Disorganization	Verbal IQ ≤ 100: 11.82(.62)	Verbal IQ > 100: 9.38(.7)		2.6(36)	.013
Cognitive / Disorganization	Schizophrenia: 11.59(.56)	Bipolar: 9.4(.66)		2.53(36.1)	.016
Depression / Anxiety	Verbal IQ ≤ 100: 6.5(.42)	Verbal IQ > 100: 7.92(.48)		2.24(35.9)	.031
Depression / Anxiety	Schizophrenia: 6.44(.39)	Bipolar: 8.53(.47)		3.42(36.1)	.002
Excitement/ Hostility	Schizophrenia: 6.1(.3)	Bipolar: 7.45(.38)		2.97(36.1)	.005
Excitement/ Hostility	Birth complications: 7.46(.38)	No birth complicat.: 5.99(.32)		2.2(38.2)	.034

This table presents the results of linear mixed model analyses for the significant effects of demographic and clinical factors on psychopathology dimensions that also had an effect size > .01 (selected from supplementary table 3). The LME model estimated mean and standard error of the mean (SE) for each value of the factor are presented in columns 2, 3, 4, the t or F value (factors with 3 levels) for the fixed effect and its corresponding degrees of freedom (df) are presented in column 5 and finally the p value for the fixed effect is presented in column 6.

Table 5B: Significant effects of medication on psychopathology dimensions

	Estimate (SE)	t (df)	P
Antipsychotic			
positive	.002(.0002)	9.06(654.8)	<.00001
negative	.001(.0003)	2.31(670.5)	.021
Cognitive/ disorganization	.0008(.0002)	21.8(669.8)	<.00001
Antidepressant			

Excitement/Hostility	-.038(.01)	15.5(465.4)	<.00001
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This table presents the results of the selected linear mixed model analyses of the significant effects of antipsychotic medication on psychopathology dimensions (selected from supplementary table 3). Effect sizes are $>.01$ except for the effect on negative dimension ($f^2 = .006$). The LME model estimated mean and standard error of the mean (SE) for the antipsychotic medication (chlorpromazine equivalents) are presented in column 2 the t value for the fixed effect and its corresponding degrees of freedom (df) are presented in column 3 and finally the p value for the fixed effect is presented in column 4.

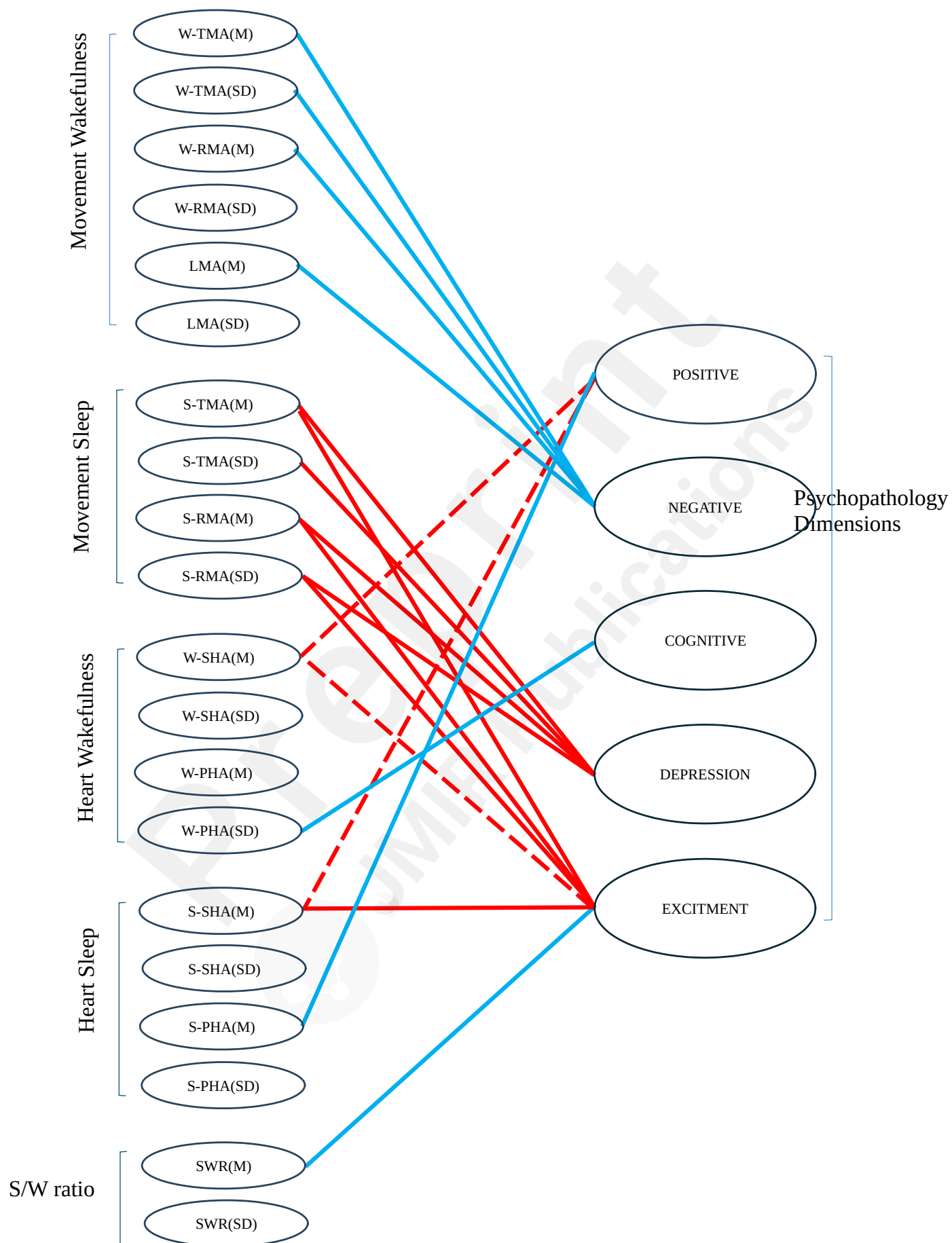




Figure 1: A line diagram showing significant relations between digital phenotypes (left) and psychopathology dimensions. Positive relations are presented with red color lines and negative relations with blue lines. Solid lines indicate significant relations while dashed lines indicate marginally significant relations.



Supplementary Files