Objective habit metrics correlate to objective medication adherence: a retrospective study on 15,818 subjects from clinical studies

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Abstract

Background: Medication adherence, or how patients take their medication as prescribed, is a global public health issue. Improving medication-taking habit might be an effective way to improve medication adherence. However, habit is difficult to quantify, and conventional habit metrics are self-reported, with recognized limitations. Recently, several objective habit metrics have been proposed, based on objective medication-taking data.

Objective: Explore the correlation between objective habit metrics and objective medication adherence on a large dataset.

Methods: The MEMS® Adherence Knowledge Center, a database of anonymized electronic medication adherence data from ambulant subjects enrolled in past clinical studies, was used as the data source. Electronic medication adherence data from subjects following a once-daily regimen and monitored for 14 days or more were extracted. Two objective habit metrics were computed from each subject's medication intake history: standard deviation of the hour of intake and weekly cross-correlation. Objective medication adherence was computed usin15,818 subjects met the criteria. The two objective habit metrics were associated with the two objective adherence metrics (all p < 0.001). A lower daily or weekly variability in the timing of medication intakes is associated with a better medication adherence. However, no variability is not the norm. Among the numerous factors influencing medication adherence, habit strength is an important one.g the proportion of doses taken and the proportion of correct days.

Results: 15,818 subjects met the criteria. The two objective habit metrics were associated with the two objective adherence metrics (all p < 0.001). A lower daily or weekly variability in the timing of medication intakes is associated with a better medication adherence. However, no variability is not the norm. Among the numerous factors influencing medication adherence, habit strength is an important one.

Conclusions: Objective habit metrics are correlated to objective medication adherence. Such objective habit metrics can be used to monitor patients and identify those who may benefit from habit-building support. Clinical Trial: Not applicable

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Keywords: medication adherence; compliance; habit

Introduction

Medication adherence is defined as "the process by which patients take their medication as prescribed" [Error: Reference source not found]. Poor medication adherence is a global public health issue [1,Error: Reference source not found] and has important negative consequences on the personal level [3, 4, Error: Reference source not found, 5], but also at the societal level [3, 4, Error: Reference source not found]. Interventions aiming at improving medication adherence are abundant in the literature, but few have been shown to be effective across a population [4, 5]. Most medication adherence interventions have focused on structural factors outside of the individual (simplification of the regimen, refill reminders, *etc*.) or on behavior change interventions that target reflective/deliberative factors, such as patient education [6]. Since at least half of our daily behaviors are non-reflective, but rather automatic [7], interventions that target these habitual processes may be more successful than education or persuasion-based interventions. As a stronger medication-taking habit has been shown to be associated with a better medication adherence [3, 8, 11, Error: Reference source not found, Error: Reference source not found], some successful interventions have focused on improving habit [4, 12]. However, medication-taking habit, and habit in general, is difficult to quantify [7]. Conventional habit metrics are self-reported [Error: Reference source not found], with an important example being the self-reported habit index (SRHI) [13], a 12-item questionnaire. Another example is the self-reported behavioral automaticity index (SRBAI) [14], a 4-item subset of the SRHI. These and other self-reported indices suffer from common limitations associated with self-reported metrics, such as social desirability bias and poor patient recall [11]. In addition, a self-reported habit index requires someone to reflect on an automatic behavior, which is paradoxical [Error: Reference source not found, 14], although it may be possible for individuals to look back on their own behaviors and know that they were done automatically ("I just did that without really thinking about it") [14].

Medication-taking habit can also be assessed using objective medication-taking data [15]. Such data is collected using smart medication packages, which can take several forms: an electronic cap fitted on a medication bottle [15], an inhaler with a chip imbedded [11], a blister which detects when a pill is expressed out of a cavity, etc. The common feature to smart medication packages is that they passively timestamp each time a patient accesses their medication, thus providing objective data on when a patient takes their medication. This detailed information can be used to derive habit metrics quantifying the consistency of medication intake behavior over time [15, Error: Reference source not found]—the validity of which rests on the fact that habits are defined as context-stable responses to conditioned cues. Such habit metrics are objective and do not suffer from the limitations associated to self-reported habit.

Day-to-day consistency of the timing of medication intake is frequently used as an objective habit metric. It has been operationalized as the variance of the hour of intake [15], its standard deviation (SD) [16, 11], or the proportion of medication intakes occurring in a fixed-size window, for instance 2 [3, 25, 17], 3 [18, 19] or 4 hours [20].

These day-to-day consistency measures will penalize someone for having different routines on different days of the week (for instance, systematically taking their medication at 6 p.m. on weekdays and 10 p.m. on weekends). However, this feature might not be desirable if the cue for medication-taking (*e.g.* breakfast) is the same throughout the week, reflecting a good medication-taking habit. To overcome this limitation, Phillips *et al*. recently introduced another metric, called the weekly cross-correlation, based on the weekly consistency of intake timing [Error: Reference source not found]. In this metric, the medication intake timing of each day of a given week is compared to the corresponding day of the next week.

Recently also, Hoo *et al*. introduced a "pragmatic habit index" [11] empirically defined as the product of two variables: stability, measured as the SD of the hour of intake and frequency, measured as the proportion of prescribed doses taken. Introducing behavioral frequency in a habit index has been criticized [14], as it incorporates the dependent variable of interest (behavior frequency) in the predictors. Because the objective of the present work precisely is to test the correlation between habit metrics and adherence, the pragmatic habit index was not included.

In a recent paper [Error: Reference source not found], Phillips *et al*. used a dataset of 79 patients with type 2 diabetes, for which both self-reported and objective habit metrics were available. They found that only the weekly cross-correlation was correlated to self-reported habit measured using the SRBAI. In the same study, all objective habit metrics tested were correlated to objective medication adherence. The goal of the present article is to reproduce this latest finding on a much larger cross-pathology dataset, introduced in the next section.

Methods

Data

AARDEX Group's database, the MEMS® Adherence Knowledge Center was used as the data source. This database contains anonymized electronic medication adherence data from ambulant subjects enrolled in past clinical studies and whose medication adherence was electronically monitored using the Medication Event Monitoring System (MEMS®, AARDEX Group, Belgium). The following selection criteria were used: (1) once-daily medication with (2) a follow-up longer than 14 days.

Objective habit metrics

For each subject, two objective habit metrics were computed. Practical details and code explaining how to compute these metrics are presented in the appendix.
The first objective habit metric is the SD of the day-to-day hour of intake. The lower the SD, the more consistent a person is in the timing of their medication intakes. In the extreme case, when SD equals to 0 h, all intakes occur at exactly the same time of the day.
The second objective habit metric is the "weekly cross-correlation" introduced by Phillips *et al*. [Error: Reference source not found]. This metric compares each day of a given week with the corresponding day of the next week and quantifies whether intakes occurred around the same time on these two days.

Implementation adherence metrics

Medication adherence, more precisely its implementation component [Error: Reference source not found], was quantified as the proportion of correct days, that is, the proportion of days with exactly 1 intake. A second implementation metric was used, the proportion of doses taken. The proportion of doses taken was computed as the ratio between the total number of doses taken and the prescribed number of doses. In this work, since subjects were on a once-daily regimen, the prescribed number of doses was equal to the number of follow-up days.
The hypotheses were that: (1) SD of the day-to-day hour of intake would be negatively correlated to objective adherence (the more variable the hour of intake, the worse the adherence) ; (2) the weekly cross-correlation would be positively correlated to objective adherence (the more consistent the pattern of intakes, the better the adherence) and (3) the weekly cross-correlation would be more strongly correlated to objective adherence than the SD of the hour of intake.
Similarly to Phillips *et al*. [Error: Reference source not found], all dosing history data were compiled while patients were engaged with the monitored medication in the trial, therefore, non-initiation and non-persistence are not part of the adherence evaluation in this research.

Statistical analyses

Continuous variables were reported using medians and first and third quartiles. Categorical variables were reported using counts and proportions. Pairwise correlations between continuous variables were assessed using Spearman's rank correlation coefficient. Correlation coefficients were compared using their Fisher's Z-transformations then performing a z-test [21]. Analyses were performed using Python 3 [22].

Results

The selection criteria matched data from 15,818 subjects from the MEMS® Adherence Knowledge Center, who took part in 108 clinical trials. These trials enrolled a median of 59 subjects (Q1: 22, Q3: 169). Table 1 presents the characteristics of the population.

Table 1: population characteristics.

Pathology, number of subjects (proportion)	
Hypertension	4,737 (30 %)
Osteoporosis	3,353 (21 %)
Viral hepatitis	2,005 (13 %)
Hypercholesterolemia	1,246 (8 %)
Angina	968 (6 %)
AIDS	754 (5 %)
Depression	561 (4 %)
Diabetes	549 (3 %)
Reversible airways obstruction	397 (3 %)
Heart failure	334 (2 %)
ADHD	301 (2 %)
Colorectal polyp	192 (1 %)
Others	421 (3 %)
Follow-up duration, median (Q1 – Q3)	168 days (60 – 365)
Proportion of correct days, median (Q1 – Q3)	93.3 % (83.7 % - 97.7 %)
Proportion of doses taken, median (Q1 – Q3)	100.0 % (93.7 % - 101.8 %)
SD hour of intake, median (Q1 – Q3)	1.7 hour (1.0 – 2.7)
Weekly cross-correlation, median (Q1 – Q3)	0.54 (0.38 – 0.69)

Figure 1 presents the distributions and pairwise plots for the four variables of interest: proportion of correct days and proportion of doses taken as two objective measures of adherence, and SD of the hour of intake and weekly cross-correlation as two objective habit metrics. Table 2 presents the associated correlation coefficients. All correlations were statistically significant (all $p < 0.001$).

Figure 1: Pairwise relationships between the four variables of interest: two objective adherence metrics: proportion of correct days (number 1) and proportion of doses taken (number 2) and two objective habit metrics (numbers 3 and 4). Off-diagonal panels contain scatter plot for each pair of variables; on-diagonal panels show a histogram of the distribution of single variables.

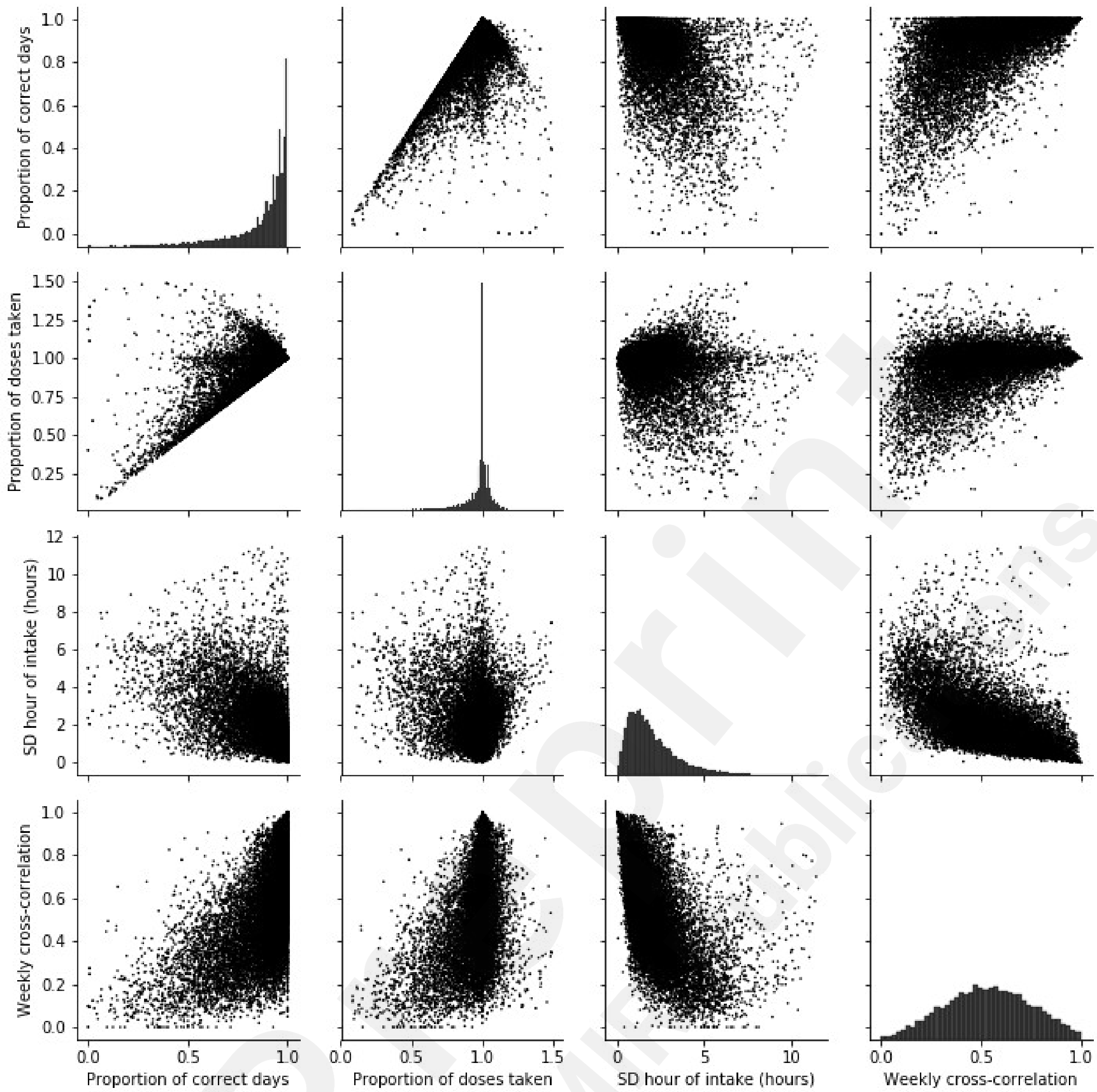

Table 2: Spearman correlation coefficients between two objective habit metrics (rows) and two objective adherence metrics (columns).

		Objective adherence	
		Proportion of correct days	Proportion of doses taken
Objective habit	SD hour of intake	-0.62	-0.09
	Weekly cross-correlation	0.55	0.32

The comparison of the Spearman correlation coefficients presented in Table 2 showed that the SD of the hour of intake is more strongly correlated to the proportion of correct days than the weekly cross-correlation is ($p < 0.001$). On the other hand, the weekly cross-correlation is more strongly correlated to the proportion of doses taken than the SD of the hour of intake is ($p < 0.001$).

Discussion

The correlation between the SD of the hour of intake and objective adherence (proportion of correct days or proportion of doses taken) has a negative sign, indicating that, as expected under hypothesis number 1, the smaller the SD hour of intake, the higher the adherence. Such a significant and negative correlation has previously been reported on a smaller population [Error: Reference source not found].

The weekly cross-correlation is positively correlated to objective adherence, meaning that the more consistent a person's medication intake pattern is from week to week, the higher their medication adherence. Such a correlation has also been previously observed on a smaller population [Error: Reference source not found]. Hypothesis number 2 is thus also verified.

The weekly cross-correlation was more strongly correlated to adherence measured as the proportion of doses taken than the SD of the hour of intake was, but the conclusion was reversed when adherence was measured using the proportion of correct days. Hypothesis number 3 is thus only true if adherence is measured using the proportion of doses taken.

Over 700 reported determinants of adherence have been reported [23]. Among all these determinants, habit strength seems to be an important one, as it explained over 30 % of the variance in medication adherence, computed as the proportion of correct days, in the present study (data not shown).

A question related to the present work is whether people use time-based cues for taking their medications [8]. To answer this question, the proportion of subjects having 95 % of their intakes in a 1-hour window was computed. Only 3.6 % of subjects met this criterion. In a previous study [8], 21.7 % of subjects reported taking their medication at a specific time of the day. These numbers mean that a minority of patients rely on cues triggered by the clock and take medication at the same time every day. This finding might explain why reminders for medication adherence sent at a specific time of the day can be ineffective [24].

Few studies have studied how well objective habit metrics for medication adherence correlate with conventional self-reported habit metrics. SD or other metrics of day-to-day consistency were found to correlate with self-reported habit in two studies [15, 16], but not in a third one [Error: Reference source not found]. Weekly cross-correlation was found to correlate with self-reported habit in one study [Error: Reference source not found].

Conclusion

Objective habit metrics can be computed from electronic medication intake data. These habit metrics do not suffer from the biases of self-reported habit metrics. In this study, we assessed whether objective habit metrics were correlated to objective medication adherence in a large database of subjects enrolled in past clinical trials.

The two objective habit metrics tested in this work were correlated to the two objective adherence metrics. These four pairwise correlations all imply that a lower variability in the pattern of medication intakes, be it day-to-day or week-to-week, is correlated to a higher medication adherence. However, no variability is not the norm.

Objective habit metrics allow to better identify patients who might-benefit from habit-building support. If a patient uses electronic monitoring, the habit metrics can even be automated and computed in real-time, directly reflecting habit changes and allowing timely intervention. In addition, some effective interventions for medication adherence are based on developing or improving habits [4]. In such settings, electronic monitoring can be used to assess the effect of the habit-building intervention in real-time [26].

Acknowledgements

Not applicable.

Conflicts of Interest

AP is an employee of AARDEX Group. BV is a shareholder of AARDEX Group.

Abbreviations

SRHI: self-reported habit index
SRBAI: self-reported behavioral automaticity index
SD: standard deviation
MEMS®: Medication Event Monitoring System

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Supplementary Files

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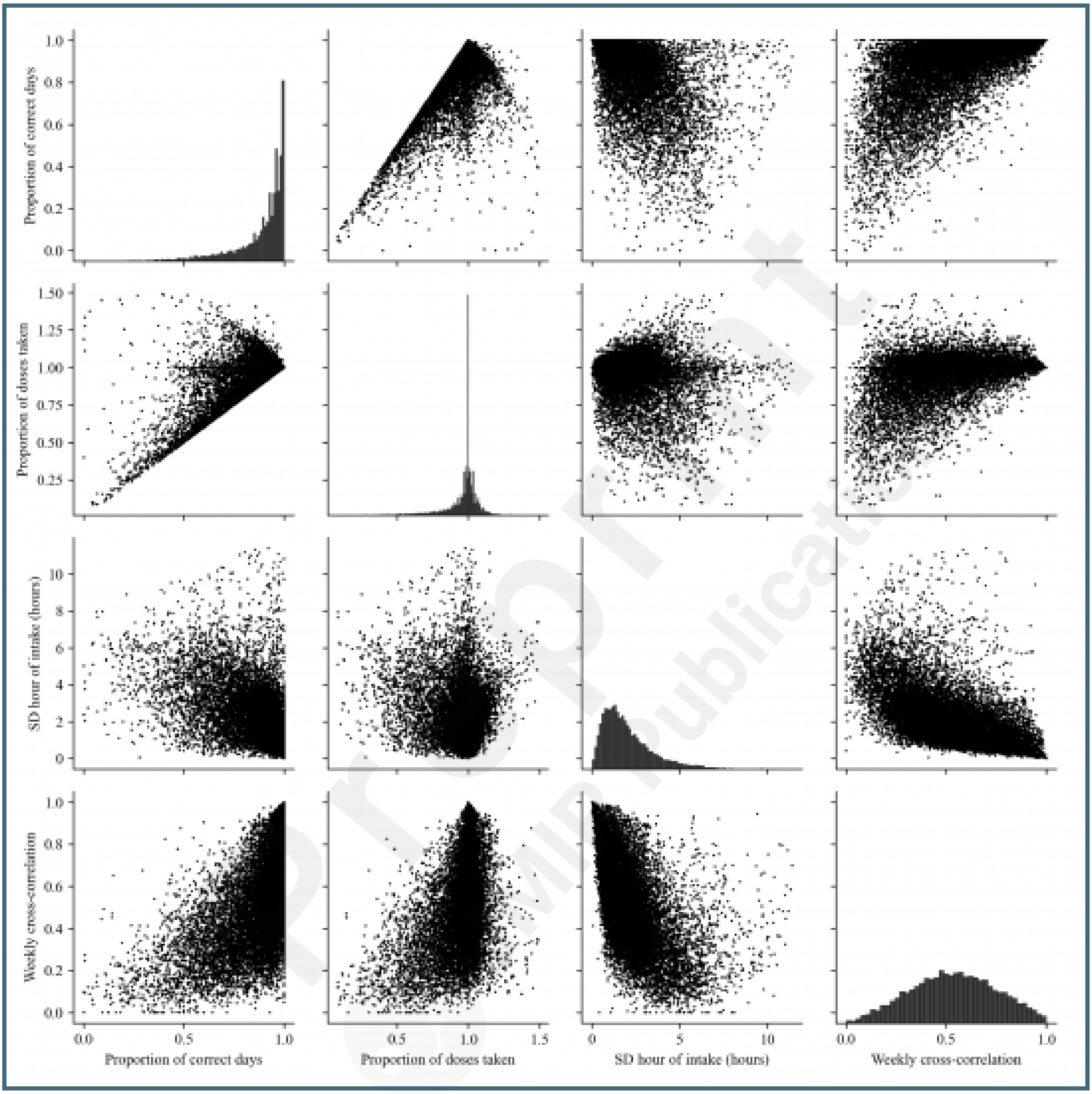
Proportion of correct days
Proportion of doses taken
SD hour of intake (hours)
Weekly cross-correlation
1.0
0.8
0.6
0.4
0.2
0.0
1.50
1.25
1.00
0.75
0.50
0.25
10
8
6
4
2
0
0.0
0.5
1.0
1.5
5

Multimedia Appendixes

Objective habit strength metrics.
URL: http://asset.jmir.pub/assets/e551d7d61516a0d58dd0e4e8eeef578e.docx