Digital phenotyping for psychiatry: accommodating data and theory with network science methodologies

D. M. Lydon-Staley\(^1\), I. Barnett\(^2\), T. D. Satterthwaite\(^3\) and D. S. Bassett\(^1,3,4,5,6\)

Abstract
Digital phenotyping is the moment-by-moment quantification of our interactions with digital devices. With appropriate tools, digital phenotyping data afford unprecedented insights into our transactions with the world and hold promise for developing novel signatures of psychopathology that will aid in diagnosis, prognosis, and treatment selection of psychiatric disorders. In this review, we highlight empirical work merging digital phenotyping data, and particularly experience-sampling data collected via smartphones, with network theories of psychopathology and network science methodologies. The intensive, longitudinal, and multivariate data collected through digital phenotyping designs provide the necessary foundation for the application of network science methodologies to parsimoniously test network theories of psychopathology, emphasizing causal interactions among psychiatric symptoms, as well as other phenotypes, across time.

Addresses
\(^1\) Department of Bioengineering, School of Engineering & Applied Science, University of Pennsylvania, Philadelphia 19104 USA
\(^2\) Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia 19104 USA
\(^3\) Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia 19104 USA
\(^4\) Department of Electrical & Systems Engineering, School of Engineering & Applied Science, University of Pennsylvania, Philadelphia 19104 USA
\(^5\) Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia 19104 USA
\(^6\) Department of Physics & Astronomy, School of Arts and Sciences, University of Pennsylvania, Philadelphia 19104 USA

Corresponding author: Bassett, D.S. (dsb@seas.upenn.edu)

Keywords
Digital phenotyping, Networks, Experience-sampling, Psychiatry, Psychopathology.

We live increasingly digital lives, with approximately 84% of American households containing at least one smartphone [1]. In our engagement with digital devices, we leave behind digital traces imbued with information about our cognitions, emotions, and behaviors. Digital phenotyping is the quantification of these rich, moment-to-moment data streams from sources as diverse as experience-sampling assessments on smartphones, wearable sensors that capture real-time physiological data, and our interactions with others captured via call and text logs [2]. With appropriate tools, these traces afford unprecedented insights into our transactions with the world and hold promise for developing novel signatures of psychopathology that will aid in the diagnosis, prognosis, and treatment selection of psychiatric disease.

Digital phenotyping enthusiasts highlight that, although much progress has been made in the collection of high-dimensional data, the challenge now shifts from data collection to data analysis techniques that can distill meaning from these data [3,4]. The data collected through digital devices are longitudinal, multivariate, and highly granular. These complex data have not been the typical purview of psychiatric and behavioral sciences and pose a challenge to researchers. We review recent work on the use of digital phenotyping in psychiatry, and in particular, the use of experience-sampling via smartphones, to highlight the utility of both network science methods and network theories of psychopathology for meeting the challenges and opportunities accompanying digital phenotyping data for understanding psychiatric disorders.

Network perspectives of psychopathology
Symptoms of psychiatric disorders tend to co-occur. This tendency for symptoms to cluster together is reflected in the traditional diagnosis of psychopathology. To obtain a classification of major depressive disorder according to the Diagnostics and Statistical Manual (DSM-V [51]), for example, a patient must present with five (or more) symptoms of a list of nine that include depressed mood, loss of interest or pleasure, insomnia, fatigue, and diminished ability to think or concentrate. Traditionally, symptom co-occurrence is explained by positing the existence of an underlying, latent disease entity that gives rise to groups of symptoms. Network perspectives of psychopathology present an alternative and complementary perspective. Specifically, network perspectives highlight the intuitive notion that...
For an unweighted and undirected graph, the matrix networks are represented with an adjacency matrix $A$. Once nodes and edges have been estimated, symptom parlance of graph theory, the symptom networks can be parsimoniously represented using nodes and edges. In the parlance of graph theory, each node represents a symptom of interest, and each edge between node $i$ and node $j$ indicates the presence (1) or absence (0) of an edge between node $i$ and node $j$. For a weighted graph, the element $A_{ij}$ takes on a value that corresponds to the strength of the association between node $i$ and node $j$. The adjacency matrix for an undirected graph is symmetric, but when causal relationships between symptoms can be identified, the result is a directed graph where the directions of associations between nodes is specified, and the adjacency matrix may not be symmetric. In this latter case, $A_{ij}$ represents the edge weight from node $j$ to node $i$. The adjacency matrix can be characterized using a well-developed and commonly used set of statistical measures that are mathematically defined and empirically calculated (see Fig. 1A–B for an overview of common measures).

Static network measures capture snapshots of symptom networks. Symptom network dynamics at the core of the network approach to psychopathology can be elucidated by extending static graphs to dynamic graphs (also referred to in some literature as temporal networks [9]). A common approach is to create multiple adjacency matrices by applying a sliding window across smaller sections of the digital phenotyping time series to construct a series of time-ordered graphs. This ordered graph ensemble then forms the basis for analyses focused on capturing changes in network organization across time ([10]; Fig. 1C).

Empirical research review

The network perspective of psychopathology coupled with network science methodologies has been applied to a range of psychopathologies to date, including major depressive disorder [11], schizotypal personality disorder [12], and tobacco withdrawal [13]. Broadly, two types of networks are encountered in the literature, distinguished by the ways in which their edges are estimated: cross-sectional networks and temporal networks. In the former, networks are based on symptom ratings collected at one time point per individual. The edges typically represent partial correlations between ratings of individual symptom severity, highlighting associations between two variables after conditioning on all other variables in the network [14]. Such cross-sectional networks provide insights into the co-occurrence of symptoms and may be used to generate hypotheses about putative causal associations among symptoms, with the implicit causal assumption that two symptoms are correlated because the experience of one (e.g., sleep problems) leads to the experience of another (e.g., fatigue).

Results from cross-sectional symptom networks, however, may not generalize to temporal networks [15]. Cross-sectional networks provide insights into interindividual variation, or variation between or across people, rather than intraindividual variation, or variation within a person over time [16]. The increasingly feasible collection of temporally dense data streams made possible by digital phenotyping allows for the capture of fluctuations in symptoms within persons across time. These time series data allow the creation of temporal networks that capture within-person associations among symptoms across time. Temporal fluctuations in the symptoms of neuropsychiatric disorders have been captured via smartphone assessment, and temporal networks have been estimated using a range of analytic approaches. Lag-one vector autoregressive models (VARs [17]) are a promising and commonly used approach. In VAR models, each symptom is regressed on
all other symptoms, including itself, at the previous time point. Variations on VARs include information about contemporaneous and lagged symptom associations to capture symptom interactions that may be occurring on timescales shorter than the length between two measurement occasions [18]. Less common are unified structural equation modeling approaches, implementing automatic procedures to estimate individual, group, and subgroup symptom networks by iteratively adding and pruning significant edges until excellent model fit is achieved [19].

In line with the network perspective’s emphasis on symptom interactions, temporal networks highlight substantial temporal associations among symptoms. This line of research is providing insights into the person-specific structure and dynamic organization of psychopathology (e.g. Ref. [20]). Once constructed, symptom networks are increasingly interrogated using network statistics to provide parsimonious descriptions of symptom network organization. Centrality indices are often estimated on symptom networks (Fig. 1B). For example, Fisher et al. [20] calculated the strength centrality (the sum of the edge weights associated with a given node) of nodes in person-specific, temporal symptom networks estimated from experience-sampling data of 21 descriptors of mood and anxiety symptomatology reported 4 times a day across 30 days. Intuitively, symptoms with high centrality can tend to have strong connections to many other nodes (degree centrality) and connect otherwise disparate nodes to one another (betweenness centrality). As such, these central symptoms are theorized to be particularly influential in the development and maintenance of mental disorders [21].
(but see Refs. [22,23] for recent work highlighting potential limitations of using centrality estimates to inform intervention).

At a higher topological scale, network density (Fig. 1A) is often used as a summary measure to test the hypothesis that densely connected networks impact the development and course of psychiatric disorders. Across a range of studies, participants with densely interconnected symptom networks with many and strong edges among symptoms show greater vulnerability to developing psychopathology relative to participants with less-dense networks [24,25]. Notably, these same participants are also more likely to be experiencing more severe symptoms of psychopathology [26]. Moreover, symptom network density is associated with psychopathology above and beyond traditionally used survey instruments. For example, dense emotion networks with strong temporal associations within and between emotions from day to day are associated with the experience of more symptoms of depression above and beyond a commonly used, one-time assessment of emotion dysregulation [27], underscoring the added value of the network approach in studies of psychopathology.

Networks of relatively high density are interpreted as reflecting self-perpetuating symptom networks, in which spirals of reinforcing symptoms reverberate through symptom networks. Although network density provides a parsimonious description of the symptom network structure and shows expected associations with psychopathology, applications of impulse response analysis to symptom networks are emerging and provide a stronger match to network theory’s emphasis on activated symptoms spreading through networks. Once networks have been constructed, impulse response analysis simulates a sudden increase in a network symptom (a ‘shock’ in impulse response analysis terms), matching the network perspective’s hypothesized symptom activation from a source outside of the symptom network. The propagation of this sudden increase through the network is modeled with an emphasis on how symptom activation impacts the duration and magnitude of activation of other symptoms in the network over a horizon of several time points. Notably, open-source software capable of automated impulse response analysis is now available [28], and studies using this analytic framework to capture how the spread of symptom activity through symptom networks may inform patient-specific insights into psychopathology are beginning to emerge [29].

One such study [30] merged person-specific network analysis and impulse response analysis to test the extent to which the duration of the experience of sadness after a simulated impulse or ‘shock’ to sadness is extended in depression due to changes in the dynamic interplay among nodes within the socio-emotional network within which sadness resides. Person-specific networks, characterizing the interplay among a range of emotion and interpersonal behaviors across time (including shame, anger, sadness, pride, and self-esteem), were estimated using data from a sample of 150 persons who completed three 21-day measurement bursts of intensive experience-sampling spaced at approximately even intervals over 1 year. A simulated impulse was sent to the sadness node, and the evolution of the network was computed over 150 time steps. By simulating the evolution of the network after an initial impulse, the time taken for the activity of the sadness node to return to equilibrium after perturbation was quantified for each participant at each measurement burst. Results indicated that sadness took longer to return to equilibrium in participants reporting higher levels of depressive symptoms. Furthermore, recovery time for sadness was longer than usual for an individual during bursts within which depressive symptoms were higher than usual for that individual. The findings are in line with proposals that depression, and potentially psychopathology in general, is associated with a network structure that facilitates the propagation of symptom activity through the network in a way that leads to spirals of reinforcing symptoms and highlights the suitability of impulse response analysis for testing these proposals.

Studies with even more highly intensive sampling protocols suggest the predictive value of symptom network structure for identifying changes in the severity of psychopathology. In a striking case study, 1474 momentary reports of cognitive and affective states were collected over the course of 239 days in an individual with a history of major depressive disorder undergoing gradual discontinuation of antidepressant medication [31]. A sliding window approach was taken to construct multiple symptom networks throughout the experiment. Clinically relevant shifts in the experience of depressive symptoms, leading to resumption of antidepressants, were preceded by changes in the network structure, including more and stronger connections (i.e. increases in symptom network density; Fig. 1A) between symptoms (including mental unrest, negative affect, and worry). The study’s results support the broader notion that changes in symptom networks may act as warning signs for changes in the severity of psychopathology.

**Expanding symptom networks**

The network perspective joined with digital phenotyping data provides a powerful and parsimonious framework for modeling and quantitatively characterizing the interconnected nature of symptoms in psychopathology. Many opportunities for expanding the study of symptom networks with utility in understanding psychopathology remain. We highlight two opportunities. Once constructed, symptom networks can potentially provide information on causal relations among symptoms. A common interpretation of the resulting networks is that nodes with high centrality may be prime targets for
intervention. However, we caution against informing treatment with node-level information extracted from symptom networks constructed using the commonly applied methods because important node-level attributes, such as mean symptom levels, which are typically included in other modeling approaches to psychopathology, are absent in the current network approaches [32]. We anticipate that future efforts will overcome this limitation by retaining information relating to symptom severity in addition to the covariance among symptoms in the symptom network structure. We suggest annotated graphs as one possible way of joining both sources of information. Annotated graphs can be used to extend the adjacency matrix representation of intersymptom associations by incorporating information on symptom severity via a vector of dimension $N \times 1$. The annotated graph structure may then be characterized by extensions of common graph analysis tools [33,34]. One possibility is to perform community detection on annotated symptom networks to detect groups of symptoms that are both densely interconnected and have similar levels of symptom severity. Capturing both intersymptom associations and information on individual symptom severity will maximize the information that symptom networks can provide in treatment settings.

We anticipate that a second major advancement will come in the form of elements that are included under the purview of symptoms in symptom networks. Symptom networks to date have largely incorporated previously defined phenotypes (e.g. depressed mood, fatigue) as collected via experience-sampling. Digital phenotyping, in addition to capturing subtle dynamics in phenotypes believed to be important in disease [2], is also facilitating discovery of novel phenotypes that may signal meaningful changes in psychiatric states. Notably, these phenotypes can be collected passively, with limited input from patients. For example, social responsiveness can be estimated through call or text logs on the basis of how quickly a person returns a missed call or text. Changes in these sociability phenotypes are observed in patients with schizophrenia in the days leading up to relapse and hospitalization [35]. Other metrics of passive data coverage include time to first view of a prompted survey and time to complete a survey once viewed. These metrics are associated with future survey scores for a variety of symptom domains in patients with schizophrenia [36]. Although psychiatry has little existing theoretical frameworks within which to accommodate these novel phenotypes, early work indicates that they are meaningfully related to psychiatric states. In addition, the unobtrusive, constant, and continuous nature of smartphone data collection enables frequent symptom measurement, producing the type of data required for the analysis approaches used in network science to date (including both impulse response analysis and sliding window approaches to capture change in network dynamics). This ease of collection of highly granular measurements over long periods of time makes digital phenotyping studies ideal for these kinds of analyses.

Conclusions

The increasingly feasible quantification of moment-to-moment changes in phenotypes is affording unprecedented insights into the ebb and flow of psychiatric symptoms during the course of daily life. The use of network perspectives of psychopathology and network science tools is providing a powerful framework within which to accommodate digital phenotyping data and to capture dynamic symptom networks, the structures of which are implicated in the development and course of psychiatric disorders.

Acknowledgements

D.S.B. and D.M.L. acknowledge support from the John D. and Catherine T. MacArthur Foundation, the Alfred P. Sloan Foundation, the ISI Foundation, the Paul Allen Foundation, the Army Research Laboratory (W911NF-10-2-0022), the Army Research Office (Bassett-W911NF-14-1-0679, Grafton-W911NF-16-1-0474, DCIST- W911NF-17-2-0181), the Office of Naval Research, the National Institute of Mental Health (2-R01-DC-009209-11, R01-MH107235, R21-MMH-106799), the National Institute of Child Health and Human Development (1R01HD086888-01), National Institute of Neurological Disorders and Stroke (R01 NS099348), and the National Science Foundation (BCS-141502, BCS-1430087, NSF PHY-1554488 and BCS-1631550). T.D.S. was supported by R01MH113550, R01MH107073, R21MH106799, the AE Foundation, and the Lifespan Brain Institute at Penn/CHOP.

Conflict of interest

Nothing declared.

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest


This study made use of impulse response function analysis to examine the impact of physical activity, stress experience, and affect on each other using experience sampling assessments collected across 30 days.


Making use of experience sampling data collected 4 times a day over 30 days, this study created person-specific networks describing symptom dynamics across time in 40 individuals with generalized anxiety disorder, major depressive disorder, or comorbid generalized anxiety disorder and major depressive disorder.


This study presents a case experiment in which a patient with a history of major depressive disorder monitored his experiential states (n = 1474 observations across 239 days) and depressive symptoms over the course of antidepressant discontinuation. A clinically relevant change in the severity of depressive symptoms was preceded by increased density of symptom networks created using the time series of the momentary states.


