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Publication Date

2023-08-01

DOI

10.1016/j.bbi.2023.06.002

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Peer reviewed

**This is a postprint of a paper published at
Brain, Behavior, & Immunity, please cite the
published version at
<https://doi.org/10.1016/j.bbi.2023.06.002>**

The Future is Dynamic: A Call for Intensive Longitudinal Data in Immunopsychiatry

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Conflict of Interest: The authors declare no conflicts of interest with respect to this work.

Funding: Daniel P. Moriarity and George M. Slavich were supported by grant #OPR21101 from the California Governor's Office of Planning and Research/California Initiative to Advance Precision Medicine. Additionally, Daniel P. Moriarity was supported by National Research Service Award F32 MH130149. These organizations had no role in planning, writing, editing, or reviewing this article, or in deciding to submit this article for publication.

Abstract

The long-term value of immunopsychiatry will be based on its ability to translate basic science into effective clinical interventions. In this article, we discuss a key obstacle to achieving this important translational goal—namely, the preponderance of studies that are cross-sectional, or that have months-to-years long follow-up periods. Immunopsychiatric processes such as stress, inflammation, and depression symptoms are inherently dynamic and fluctuate over hours, days and weeks. This fact suggests that higher-density data collection with only days between measurements is necessary to capture—with adequate resolution—the actual dynamics of these systems, determine optimal time lags with which to observe associations between variables of interest, and maximize the translational potential of these data. To illustrate these points, we use pilot data from our own intensive longitudinal immunopsychiatric study. We then conclude by making several recommendations for future research. By learning how to better use existing data for dynamically informative studies as well as collecting intensive longitudinal data, we believe immunopsychiatry will be much better positioned to advance our causal understanding of the interplay between the immune system and health.

Keywords: inflammation; psychoneuroimmunology; immunopsychiatry; intensive longitudinal designs; within-person effects; dynamic modeling

The last 50 years of psychoneuroimmunology have provided compelling data connecting a plethora of psychological and immunological processes, including psychiatric reactions to cancer treatment^{1,2}, regulation of emotions during acute immune responses³, interplay between social processes and immune biology⁴⁻⁶, inflammation and depression⁷, anti-inflammatory effects of psychotherapy^{8,9}, and early life adversity and inflammatory stress responses¹⁰ among others. The next era of psychoneuroimmunology, in turn, will involve translating this basic research into clinical benefit whenever possible. This goal is particularly salient for immunopsychiatry, the subfield of psychoneuroimmunology that examines bidirectional associations between immune functioning and mental health.

In this article, we demonstrate how the typical temporal design of immunopsychiatry studies is a critical limitation to the clinical translatability of extant data. We then argue that more frequent assessments are necessary to advance our causal understanding of the interplay between immunology, psychopathology, and behavior. This is not to say that longer follow-up periods do not have merit for certain processes that take longer to unfold, such as cyclic relationships, but that rather that the dearth of shorter follow-up periods in psychoneuroimmunology is an important weakness to address. To address these points, we first briefly introduce the concepts of Simpson's Paradox and ergodicity as motivating factors to consider research designs suited for within-person analysis. Second, we briefly summarize the current standards of longitudinal immunopsychiatric research. Third, we briefly review relevant psychometric and physiometric¹¹ properties (i.e., the measurement properties of biological variables^{11,12}) that underpin our call to improve study designs in immunopsychiatry. Fourth, we introduce the concept of intensive longitudinal designs and their potential methodological benefits in immunopsychiatry. Fifth, we present sample data from an ongoing intensive longitudinal immunopsychiatric study to concretely demonstrate several key

motivations for this work. Finally, we conclude with recommendations on how to use existing longitudinal data to advance our temporal understanding of these processes and advocate for the increased use of intensive longitudinal data in immunopsychiatry. Throughout this article, we use the association between inflammation and depression as a running example, but the core methodological considerations we recommend apply to all research linking psychological, immunological, and behavioral processes.

Simpson's Paradox and Ergodicity

Much social and behavioral research, psychoneuroimmunology included, attempts to identify population-level truths about associations of interest by testing between-person differences. Despite this fact, many key psychobiological processes of interest involve within-person *change* (e.g., Does this medication decrease symptoms? Does regular exercise improve immune health?). This is problematic, as much of what is observable at a population level in the social and medical sciences might not generalize to subgroups (i.e., *Simpson's Paradox*¹³) or individuals¹⁴. Consider the following example from Ref¹⁵. At a group-level, experienced typers are both faster and make fewer errors than non-experienced typers. However, if you look at data across time for any given person, the faster someone types, the more likely they are to make errors. This lack of group-to-individual generalizability is referred to as a *nonergodic process*. Conversely, *ergodicity processes* are both equivalent between groups and individuals (i.e., homogeneous) and have constant means and variances overtime (i.e., stationary)¹⁶. These are widely considered to be unrealistic assumptions for psychological processes,^{14,16,17} which, by extension, renders them unrealistic for immunopsychiatric processes. Consequently, we advocate for the importance of conducting intensive longitudinal data collection as one key way to facilitate immunopsychiatric research that can adequately capture key within-person processes.

Current Longitudinal Immunopsychiatric Study Designs

A key limitation to the translational value of current immunopsychiatry studies rests on the frequency of their data collection and the resulting ability of those data to characterize the dynamics of the biopsychosocial systems they represent. Indeed, most immunopsychiatry studies use cross-sectional data, with the rest most commonly using longitudinal data collected in assessment lags of 6 months or longer. In a recent meta-analysis of longitudinal studies of the associations between inflammatory proteins and depression, for example, only 3 of the 38 studies included (8%) had follow-up lengths of less than 1 year, and no studies (0%) had a follow-up length of less than 6 months¹⁸. A second meta-analysis had a median follow-up length of 5 years¹⁹.

Indeed, many frequently cited longitudinal studies on the relation between two key constructs in immunopsychiatry—namely, inflammatory biology and depression—have assessment lags ranging from 5-12 years (e.g., Refs ²⁰⁻²³). Critically, meta-analyses of longitudinal studies have consistently found substantial heterogeneity between studies for the effect size between inflammatory proteins and depression^{18,19}, underscoring the likelihood that one or more unaccounted factors are influencing observed effect sizes. Although follow-up duration was not a significant predictor of the interleukin (IL)-6 → depression association or C-reactive protein (CRP) → depression association in Ref. ¹⁸ (tumor necrosis factor (TNF)- α was not included in the meta-regression and Ref. ¹⁹ did not test follow-up duration as a meta-regression predictor)—we posit that one factor affecting effect sizes in longitudinal immunopsychiatric research is the variability in, and long duration of, the assessment lags.

It is widely accepted that the size of an effect depends on the time interval assessed^{24,25}; however, very little research²⁶ has investigated the temporal specificity of the inflammation →

depression association in search of optimal time lags (i.e., when the effect size would be the largest). Ref. ²¹ found that temporal specificity of these associations differed by sex. Specifically, higher IL-6 and TNF- α predicted greater increases in depression symptoms at longer time lags for females, but for males, higher IL-8 predicted greater decreases in depression at longer time lags. Although not explicitly testing depression symptoms, results from a study measuring affect 5 times per day for 14 days leading up to a blood draw suggest that the association between negative affect and inflammation was stronger when affect and inflammation were measured closer in time²⁷. Contrasting the two studies' statistical methodology, it is plausible that the discrepant results are influenced by Ref. ²¹ predicting depression change scores—therefore, longer periods of time would be associated with greater likelihood of measurable variability in depression symptoms.

The lack of thorough evaluation of temporal specificity and optimal time lags is particularly problematic considering that time lags in psychological research are often biased toward being too long, leading to attenuated effect sizes^{28,29}. Research also suggests that fields should initially risk over-sampling, instead of under-sampling, until optimal time lags are determined³⁰. This is especially important when multiple parts of the system (e.g., different inflammatory proteins) might have different optimal time lags with a given outcome³⁰.

This physiometric information is not only central to designing and analyzing future observational studies, but would also facilitate the development of interventions. Specifically, knowing the ideal time lag after which intervening on inflammation should improve depression symptoms (i.e., establishment of a temporal phenotype) will guide clinical expectations for time-to-improvement as well as selecting which immune mechanisms to target. For example, if two inflammatory processes have comparable effect sizes and side effect profiles, but one has a

shorter optimal time lag to improvement in depression symptoms, the process with the shorter time-to-improvement would be a preferable treatment target.

Immunopsychiatric Processes are Dynamic

Consideration of the temporal dynamics of immunopsychiatric processes is critical to optimizing study design. Dormann and Griffin²⁸ demonstrate that temporal stability, the effect a variable has on itself over time, is a key factor in determining the optimal time lag between variables. Several immunopsychiatric theories hypothesize that inflammation is a mediator linking stress and depression^{31,32}; therefore, efforts to quantify the causal relations between these variables must consider their stability. Before describing the following examples, we would like to reiterate that, formally, *stability* in this context refers to autoregressive effects (e.g., the effect of a variable on itself between time points); however, the following examples will use other approximations of temporal stability that are more common in the literature and/or might be more intuitively interpretable for most readers (e.g., re-test reliability, which is the correlation between two measurements at different points in time).

Meta-analytic evidence suggests that the most widely used self-report measure of stress, the Perceived Stress Scale, only has acceptable retest reliability*¹ over about 6 weeks³³. This is notably shorter than the standard assessment lag of immunopsychiatry studies; consequently, it is plausible that many longitudinal studies have underestimated the effect that stress has on immune functioning. Similarly, certain core features of depression, such as sad mood, feature fairly low stability, even in people with current Major Depressive Disorder³⁴. Further, different depression

*¹ It is important to note that stability differs from retest reliability in that stability refers to the effect of a variable on itself, but multiple factors (including stability) can influence the retest reliability of a variable. Therefore, citations incorporating retest reliability are useful, but imperfect examples of how temporal dynamics influence optimal time lags

symptoms feature different stabilities³⁴. For example, in an ecological momentary assessment (EMA) study that assessed depression symptoms 5 times per day for 12 days, “low mood” was the least stable, whereas “wish to die” was the most temporally stable²⁹. This result underscores the critical importance of temporally informed methodology to characterize inflammatory phenotypes of depression^{35–39}. In this context, we believe intensive longitudinal data may provide even greater benefits for modeling immunological data than it does for self-report measures.

The temporal dynamics and stability of immune functioning vary at both the protein (e.g., C-reactive protein vs. IL-8) and process level (e.g., acute phase response) across a variety of scenarios (e.g., basal levels over months or years⁴⁰, diurnal fluctuations across a day⁴¹, responses to acute stress⁴²). Consider Ref.⁴⁰, which tested the short-term (i.e., 120 minutes) and long-term (i.e., 18-month) reliability of seven inflammatory proteins measured using saliva samples. The reliability over just 120 minutes ranged from $.51 \leq r \leq .81$. In contrast, the reliability over 18 months, which is much more representative of standard psychoneuroimmunology research, was much lower, ranging from $.04 \leq r \leq .32$.

Considering these temporal dynamics might be critical for refining theory about how, and which facets of, immunology influence mental health (and vice-versa). This possibility is consistent with evidence that temporal features such as time of day of injury influence inflammatory responses to injury and length of hospital stay⁴³. Digging deeper, it is well known that acute inflammatory reactions to stress, illness, and injury are themselves highly dynamic and involve a series of upregulations, migrations, and downregulations of various processes and proteins in what is commonly referred to as the *inflammatory cascade*^{44,45}. The complexity of these dynamics is impossible to integrate into analyses, and consequently theory, using traditional approaches in immunopsychiatry. The inability to consider these nuances, already appreciated as

critical to understanding recovery from physical injury and illness, might be a significant obstacle in the clinical translation of immunopsychiatry. Further, it is important to consider that the temporal dynamics of stress, the immune system, and depression symptoms might interact to determine optimal time lags.

Introduction to Intensive Longitudinal Data

As we have already alluded to, one strategy for addressing these methodological challenges involves collecting intensive longitudinal data. Intensive longitudinal data refer to frequent data collection at a small time scale, typically once every few days to multiple times per day. This methodology has facilitated advancements in the understanding of both how processes unfold in individuals (i.e., idiographic analyses^{46,47}) as well as individual differences in within-person processes (i.e., change)^{48,49} in the psychological sciences.

Intensive longitudinal data can also reduce measurement error induced by recall/memory bias in traditional, retrospective self-report data (i.e., measuring affect daily for a week instead of asking participants to report how they felt the past week⁵⁰) and can maximize ecological validity⁵¹. For an example that is particularly relevant to psychoneuroimmunology, one study found that only momentary (collected hourly) and daily assessments of stress predicted cortisol, which is widely considered the primary stress hormone and is a potent contributor to anti-inflammatory processes; in contrast, retrospectively reported stress levels—both across the past month and even just the previous 4 days—was unassociated with cortisol⁵². For constructs that are not highly stable over months or years, intensive longitudinal data methods enable the collection and analysis of data at timescales that more precisely complement how psychobiological systems naturally interact—maximizing the opportunity for causally, and thus clinically, relevant research.

Further, many outcomes of interest in immunopsychiatry—including psychosocial

processes, immune biology, and mental health—are multiply determined and thus can have complicated trajectories that feature non-linear fluctuations. A scientist's ability to characterize these trajectories is inherently restricted by the number of observations taken in a given study: one time point cannot reveal change; two time points can only reveal an increase or decrease; three time points can only detect increases, decreases, or a singular quadratic effect (increase then decrease or decrease then increase); and so forth. Truly, even if the actual temporal dynamics are known, they cannot be represented in the data if the frequency of assessment is insufficient (for an strong empirical example featuring simulated emotion dynamics, see Ref⁵³). Consequently, we argue that the field of immunopsychiatry would benefit greatly from studies with both much shorter time lags and greater numbers of repeated observations per participant. Below, we present data from the first wave of an intensive longitudinal immunopsychiatric study to illustrate the benefits of this approach.

Mental Health & Immunodynamics of Social Stress (Project MHISS)

Preliminary data from an intensive longitudinal immunopsychiatric study, Project MHISS, provide an illustrative example of the notable benefits of using high frequency assessments. Project MHISS uses the transition to college for first-year college students to model biopsychosocial changes that occur in response to a naturally occurring social stressor. Participants in this study complete daily self-reports of stress (measured using the Perceived Stress Scale⁵⁴) and depression symptoms (measured using the Inventory of Depression and Anxiety Symptoms-II⁵⁵), and provide blood samples over 22 days. Participants' first full day on campus is the 7th day of the protocol. Blood samples will not be immunoassayed until the end of data collection to limit batch effects; however, our preliminary analyses of the stress and symptom data from the first wave of data collection illustrate the benefits of collecting intensive

longitudinal data for immunopsychiatry.

Determining the shape of the temporal unfolding of predictors and outcomes is a crucial step in longitudinal modeling of risk and resilience processes (for more information, see Case 4: “The Problem of Shape” in Ref⁵⁶). Therefore, it is best to visualize trajectories of variables of interest before determining statistical modeling approaches (e.g., should there be a non-linear effect of time?). Consider Figure 1, which plots the trajectories of depression symptoms and perceived stress across the 22-day protocol. Note the red lines, which illustrate the trajectories if data were only collected on the three primary events of the study: study start, 7th day move-in, and study end. Both depression symptoms and stress appear to be on steady downward trajectories throughout the study. However, by overlaying the blue lines, which depict the daily data, a much more dynamic picture emerges.

As can be seen from Figure 1, both perceived stress and depression symptoms decrease throughout the first week but spike on students’ first days on campus. After moving onto campus, both stress and symptom levels decrease and stabilize for about a week before spiking again, potentially due to missing friends and family from home or adjustment to the start of classes. Interestingly, during these last few days of the study the trajectories for depression symptoms and stress diverge, with symptoms decreasing slightly and stabilizing while stress remained slightly elevated (relative to the first week on campus).

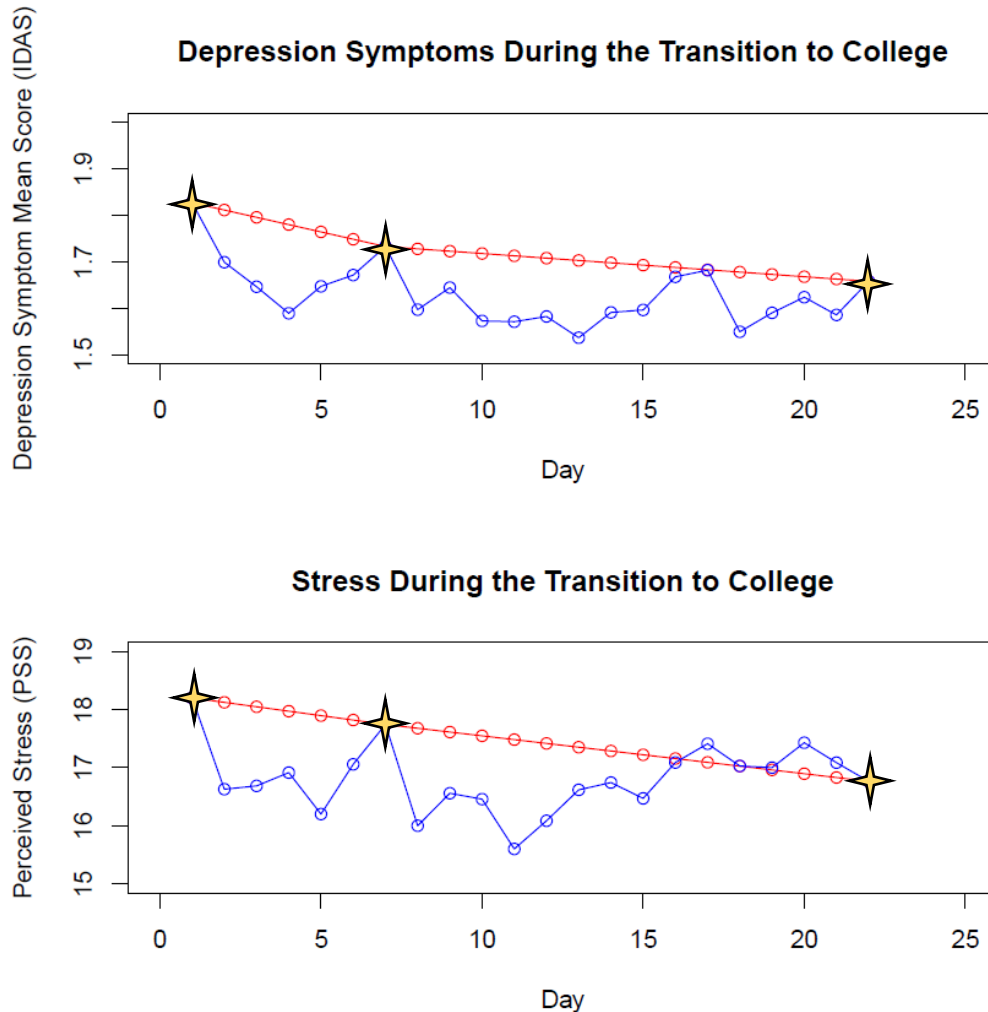


Figure 1. Trajectories of Depression Symptoms and Stress During the Transition to College. Stars indicate the three primary events of the study—namely, study start, moving onto campus, and study end. The red lines illustrate the trajectories of depression symptoms and stress if data were only collected and analyzed at these event time points. The blue lines illustrate the actual daily fluctuations in depression symptom and stress data throughout the study. Note: IDAS = Inventory of Depression and Anxiety Symptoms; PSS = Perceived Stress Scale.

Further, it is important to highlight that change is a process that happens within- individuals over time. Visualizations and analyses at the group level (i.e., “nomothetic”) might obscure important nuances at individual level (i.e., “idiographic”). Consider Figure 2, which visualizes the depression symptom trajectories for the participant with the most variability (blue line) and the participant with the least variability (red line) in depression scores over the course of the study. Whereas the red line shows consistently negligible depression symptoms

(regardless of timepoint), the blue line shows (a) much more change over time, (b) notably higher peak symptoms relative to Figure 1's group-based plots, and (c) a different trajectory than that suggested by Figure 1's group-based plots. Specifically, the group-based plots (Figure 1) reveal that depression symptoms were highest at the start of the study. However, this individual's depression symptoms consistently fluctuated throughout data collection and peaked during the last week of the study. Critically, this lack of group-to-individual generalizability has inspired some researchers to call for more idiographic approaches in human subjects research¹⁴, giving rise to new methods that combine idiographic and nomothetic approaches such as group iterative multiple model estimation (GIMME)⁵⁷. Proponents of these approaches highlight that many of the processes health scientists aspire to understand, such as disease detection, prevention, and treatment, all happen within specific individuals and argue that an overreliance on methods that aggregate across individuals obscures nuance that is critical for successfully translating basic research to clinical impact.

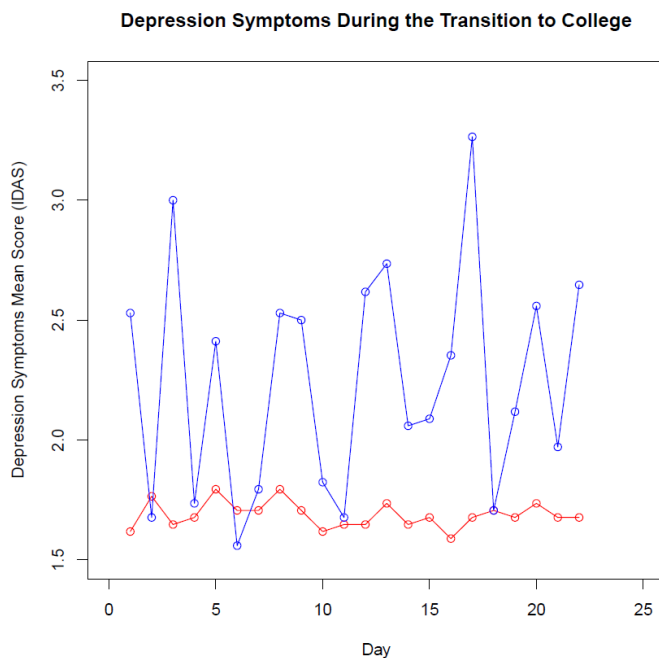


Figure 2. Individual Depression Symptom Trajectories. The trajectories for the participant with the greatest variability (blue line) and the participant with the least variability (red line) in depression symptoms. Note: IDAS = Inventory of Depression and Anxiety Symptoms.

Recommendations for Moving Forward

To help immunopsychiatry become a more temporally informed science, we conclude with several recommendations. First, existing longitudinal datasets—regardless of the duration between measurement occasions—should be leveraged to advance our temporal understanding of how immunopsychiatric variables change in isolation and in relation to one another over time. Examples include psychometrics^{11,12} such as temporal stability/reliability (e.g., retest reliability, intraclass correlation coefficients, stability estimates from a variable predicting itself over time²⁸) and temporal specificity/optimal time lags to detect an association between two variables. It is important that this descriptive work specifies the timescale of the data tested to avoid general statements about stable/unstable or reliable/unreliable measures.

Second, existing data should be combined with analytic strategies that isolate within-person variance that can yield stronger inferences about change compared to between-person variance. One such methodology is the use of person-centered predictors, which separate each individual's average levels of a variable (i.e., between-person variance) from their fluctuations overtime (i.e., within-person variance). For a more in-depth overview of this methodology, see Ref⁵⁸, and for an example of this methodology in psychoneuroimmunology research, see Ref⁷. Another relevant technique is the use of latent change score models, which estimate both latent change scores (i.e., the change in the “true score” between time points) and latent growth factors (i.e., the constant change across all measurement occasions). For guides and tutorials on latent change score models, see Refs^{59,60}, and for an example of this technique in psychoneuroimmunology research, see Ref.⁶¹.

Finally, we recommend the collection of intensive longitudinal data for highly dynamic psychoneuroimmunological variables. Typically, intensive longitudinal designs for

psychological data involve using web- or app-based surveys that are scheduled to prompt participants to complete self-report measures at pre-specified times, which is often referred to as EMA or experience sampling methods (ESM) (see Ref ⁶² for an introduction to a special section on EMA and ESM approaches). Frequent assessment of immune variables, in turn, can be done in several ways. First, standard venipuncture blood draws can be used. The benefits of this methodology are that it (a) is comparable to most psychoneuroimmunology studies, (b) might result in more consistent data collection and storage than alternatives due to the involvement of trained phlebotomists and blood draws being done in a laboratory setting, and (c) results in larger blood-volumes than microsampling procedures (described below), which allow for the assessment of more analytes with a single sample. However, high-intensity venipuncture blood draws would (typically) require frequent trips to a laboratory, thus significantly increasing burden for both participants and research staff. Additionally, it is not uncommon for some participants to have a strong aversion to needles, which can hurt and/or bias study recruitment efforts.

To address these limitations of standard venipuncture blood draws, some companies have developed micro-sampling devices that enable remote blood draws and which, in turn, permit less-invasive, high intensity immune assessment. Compared to standard venipuncture procedures, the micro-sampling devices have the benefits of typically being self-administered, removing the need to schedule in-person study visits and thus greatly reducing participant and research staff time and burden. This approach also has some limitations, such as logistical challenges including, but not limited to, shipping costs (for sending devices to and/or from participants), the lack of a controlled lab setting and associated confidence that proper blood draw procedures are followed, and potential variability in how samples are stored and/or handled

before arriving to the lab for storage and analysis.

In weighing the pros and cons of these two approaches, for Project MHISS, we elected to use the latter method and achieved a 91% compliance rate for blood draw measurement for participants who completed the study, thus demonstrating its feasibility. Once data are collected, one particularly suitable and highly flexible statistical approach to analyzing intensive longitudinal data is dynamic structural equation modeling. The following references can serve as useful starting points for readers interested in learning more about this approach⁶³⁻⁶⁵. Additionally, differential time varying effect models can be useful in large intensive longitudinal datasets to identify optimal time lags between variables⁶⁶.

In the end, data collected at longer timescales can be useful in some instances and, in fact, such data may be important for modeling certain associations that take longer to unfold or that have cyclic or bidirectional effects. In such circumstances, readers might want to consider the potential value of measurement-burst designs⁶⁷, which combine both intensive longitudinal and longer scale assessments. Our final recommendation, therefore, is to make sure your study design and assessment frequency map on well to the hypothesized model you seek to test, taking into careful consideration knowledge about the rates at which each relevant variable can be expected to change over time.

Conclusion

In conclusion, what we have tried to highlight here is that there is presently a large disconnect between the months-to-years long follow-up periods typically seen in immunopsychiatry and what is known about the dynamics and stability of key constructs that are central to this field, including stress, immune functioning, and psychopathology, which change (sometimes quite substantially) in individuals over short amounts of time. Only by investing in

high-density data will immunopsychiatry be able to determine what measurement frequency is ideal to maximize the translational value of this work. By learning how to better use existing data for research on temporal dynamics as well as collecting intensive longitudinal data, immunopsychiatric researchers will be much better positioned to advance our causal understanding of the interplay between the immune system, mental health, and the other psychological and behavioral outcomes, thus greatly enhancing the clinical and public benefit of the field as a whole.

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