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Building a replicable and clinically-impactful immunopsychiatry: Methods, phenotyping, and theory integration

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ABSTRACT

Immunopsychiatry is a subfield of psychoneuroimmunology that integrates immunological and psychopathological processes with promise for improving the classification, identification, and treatment of psychopathology. Using research on the relationship between inflammation and depression as a running example, this mini-review will discuss three areas of work that should be emphasized in future research to maximize the replicability and clinical impact of the field: 1) methodology with respect to planning data collection and statistical analyses with measurement properties and conceptually important sources of variance in mind, 2) characterizing inflammatory phenotypes of psychopathology, and 3) the integration of inflammatory processes into robust, extant psychosocial theoretical frameworks of psychopathology risk. Consistent, parallel growth in all three areas will ensure immunopsychiatry research is replicable, contributes to understanding of how (and for whom) the immune system is associated with psychiatric symptoms, and increases the flexibility and power of personalized treatment planning.

1. Introduction

Immunopsychiatry is a subfield of psychoneuroimmunology that integrates immunological and psychopathological processes with promise for improving the classification, identification, and treatment of psychopathology. Inflammation, part of the immune system's response to illness and injury, is gaining evidence as a transdiagnostic risk factor for psychopathology (Michopoulos et al., 2016; Moriarity et al., 2020a,b,c; Rosenblat et al., 2014). In particular, much work has studied the relationship between inflammation and depression, which will be the focus of this mini-review to provide focus, although the future directions described herein are broadly generalizable.

Inflammation can induce “sickness behaviors” (e.g., fatigue, social withdrawal, anhedonia), many of which overlap with depression symptoms (Dantzer et al., 2008). There is converging evidence from experimentally-administered endotoxin (Dantzer and Kelley, 2007; Watkins and Maier, 1999), behavioral reactions to immunotherapy and vaccinations (Capuron et al., 2001, 2002; Kuhlman et al., 2018), and natural fluctuations in inflammatory proteins (Moriarity et al., 2020a) that inflammation could play a causal role in the pathogenesis of depression. In fact, the relationship might be bidirectional (Huang et al., 2019; Moriarity et al., 2020a,b,c). Additionally, inflammation might be a viable adjunctive treatment target (Nettis et al., 2021). Importantly, there are many ways to target inflammation, including psychosocial interventions, medication, and behavioral activation (although these approaches vary in the specificity with which they target inflammation, Euteneuer et al., 2017; Raison et al., 2013; Shields et al., 2020), providing treatment flexibility. However, elevated inflammation is not observed in all depressive episodes (Raison and Miller, 2011) and increases in inflammation do not invariably lead to increases in symptoms (Capuron et al., 2004). Further, there is inconsistency in observed effects between inflammatory proteins and depression symptoms (e.g., CRP; Horn et al., 2018; Mac Giollabhui et al., 2020), obfuscating the translation from research to practice. Thoughtful future research is needed to determine how, and for whom, inflammation plays a role in the pathophysiology of depression. This review will describe three future directions that I believe can maximize the replicability, efficiency, and clinical impact of immunopsychiatry (Fig. 1). Specifically, advancing methodology, characterizing inflammatory phenotypes of psychiatric disorders, and the integration of inflammation into established psychosocial theories of risk and resilience (Table 1).

2. Methodology

Methodology should complement both the theory and variables under study. For example, pathophysiological pathways to depression

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Fig. 1. Daniel Moriarity. Daniel Moriarity's research aims to elucidate the bidirectional relations between psychopathology (with a focus on affective disorders) and inflammation. Throughout his graduate career he has developed three intersecting lines of work in an effort to maximize the clinical impact of his research as well as contribute to how the field conceptualizes and tests these relationships. Substantively, his work investigates the relationships between inflammation and psychopathological characteristics in naturalistic and experimental settings. In particular, he is interested in the role cognitive vulnerabilities have in modulating the pathway from stress, thru immunology, to behavior, which inspired the immunocognitive model described in this review. Further, he has two more methodologically-oriented research aims. First, he seeks to contribute to precision medicine through the characterization of inflammatory phenotypes of psychopathology by utilizing multiple levels of measurement (e.g., total symptom score vs. subscales vs. individual symptoms and inflammatory composites vs. individual proteins) in his work. Second, he investigates physiometrics (the measurement properties of biological variables) and advocates for their importance in immunopsychiatry and biological psychiatry as a whole. By leveraging this information, he believes it is possible to improve the replicability of biological psychiatry and create a more efficient research—practice pipeline. Daniel completed his undergraduate education at Elmira College, was a post-bacc with Dr. Andres De Los Reyes at the University of Maryland-College Park, and began his clinical psychology Ph.D. in 2015 in Dr. Lauren Alloy's Mood and Cognition Lab at Temple University. He completed his clinical training at Temple University's Psychological Services Center, the Adult Anxiety Clinic of Temple, and Drexel's Center City Behavioral Health Clinic (which specialized in working with clients with comorbid HIV and psychiatric disorders). He looks forward to starting his clinical internship at McLean Hospital in July 2021.

might differ for circulating vs. neural inflammation (e.g., plasma cytokines vs. neural mechanisms). Additionally, decisions about which variables to measure must be informed by the biological-plausibility of proposed pathways. It is also critical to emphasize that inflammatory proteins are sensitive to technical details (e.g., differences in storage temperature) as well as participant-level differences such as diet, exercise, and sleep. Thus, researchers should standardize data collection procedures, sample storage, and participant preparation (e.g., fasted blood draws taken at the same time) to avoid unnecessary measurement error. Fortunately, the measurement of many inflammatory proteins is incredibly precise (relative to most psychological variables) and it is common for some key measurement properties (e.g., coefficients of variation) to be reported. However, there is a dearth of understanding about several key measurement properties of inflammation that are germane to standard study designs in immunopsychiatry. As we review in Moriarity and Alloy (2021), this could impose meaningful limitations on study design, analysis planning, and result interpretation.

Table 1
Key future directions and action items.

Future Direction	Action Items:
Methodology	1. Standardize inflammation data collection, storage, and processing procedures (e.g., time of blood draw, fasted samples, store all samples at the same temperature) 2. Increase investigation of measurement properties of immunological variables that are germane to immunopsychiatry designs (e.g., temporal stability, temporal specificity, dimensionality for aggregate measures) 3. Leverage knowledge of these measurement characteristics to plan data collection and analysis 4. Utilize statistical approaches that isolate theoretically-relevant variance to increase precision of inferences
Phenotyping	1. Diversify the level of psychopathological measurement (e.g., diagnostic cases, total scores, subscales, individual symptoms) to identify which level of measurement has the most robust associations with immunology 2. Similarly, explore the possibility for specific inflammatory proteins/processes to have differential relationships with psychopathology
Theory Integration	1. Increase conceptual and empirical work placing immunological processes in the context of established psychosocial risk frameworks for psychopathology (e.g., rumination, social stress) 2. Extend promising integrated etiological models to clinical research to establish maximally-comprehensive treatment plans

In addition to data collection procedures, measurement error is impacted by modeling strategies (e.g., individual indicators vs. aggregates). It is common for several inflammatory proteins to be tested independently, which invites concerns about multiple comparisons. Additionally, this approach induces a disconnect between how theories are typically described (i.e., inflammation generally) and how they are tested (i.e., individual proteins), which influences theory advancement and treatment development (e.g., should any anti-inflammatory medication improve symptoms or are ideal treatments protein-specific?). These concerns are underscored by questions about the extent to which individual proteins have adequate specificity/sensitivity to the broader construct of inflammation to be considered "biomarkers" of inflammation (Konsman, 2019). Alternatively, appropriate use of composite variables can reduce the error-to-signal ratio by aggregating theoretically-relevant shared variance. In light of these considerations, some researchers have used inflammatory composite variables created using the sum of a set of standardized proteins (e.g., Moriarity et al., 2020a,b,c). However, the use of composites uninformed by first investigating dimensionality is problematic. Assuming unidimensionality when a process is multidimensional risks increasing measurement error and obscuring nuanced relationships if different components (e.g., pro-vs. anti-inflammatory processes) have different associations with outcomes of interest.

My dissertation (Moriarity et al., 2021a,b,c) compared this "a priori" approach (assuming all proteins are equally associated with a unidimensional inflammatory construct) to an empirically-identified factor structure of eight proteins (C-reactive protein (CRP), interleukin (IL)-6, IL-8, IL-10, tumor necrosis factor-α (TNF-α), fibrinogen, E-selectin, and intercellular adhesion molecule (ICAM)-1)) using a "bass-ackward" factor analysis (Goldberg, 2006). This analysis supported a hierarchical factor structure with two first-order factors (Factor-A = CRP, IL-6, and fibrinogen; Factor-B = TNF-α, IL-8, IL-10, ICAM-1, and IL-6), and one higher-order general inflammation factor. E-selectin was not substantively associated with any factor. Confirmatory factor analyses conducted in two other datasets universally supported the use of the empirically-identified composites over the "a priori" composite. However, model fit indices (metrics describing how well data correspond to a

statistical model) diverged on whether the empirically-identified structure fit the data better than the proteins modeled individually (without a latent variable). Thus, these results should primarily be interpreted as a warning that creating composites without investigating dimensionality can increase measurement error. Given the diverse functions of individual proteins, composites should only be used after careful consideration of biological plausibility. When the composites were recreated in a longitudinal dataset (which only had five of the proteins available in the other datasets), none of the individual proteins, the "a priori" factor, or the empirically-identified general inflammation factor predicted depression symptoms. However, both empirically-identified first-order factors predicted depression symptoms, but in opposite directions, underscoring the dual threats for false negatives resulting from a) falsely assuming unidimensionality and b) failure to aggregate theoretically-relevant shared variance across multiple individual proteins.

Measurement error from any source drives down the maximum observable true effect size between variables. For illustration, consider the formula for the maximum observable true correlation between two variables as a function of reliability: $r_{xy}(\max) = \sqrt{(r_{xx}r_{yy})}$ in which r_{xy} represents the maximum observable true correlation between variables x and y, r_{xx} represents the reliability of variable x, and r_{yy} represents the reliability of variable y (Davidshofer and Murphy, 2005). A perfect correlation of 1 only is possible when the reliability of both x and y are also 1 (i.e., measured without error). Thus, increased measurement error results in an average downward bias across studies, increasing the chance for false negatives and trivial effect sizes.

Descriptive studies on the short-term (i.e., same session) reliability of inflammatory proteins can inform data collection to reduce measurement error. For example, investigations of short-term reliability can be used in combination with the Spearman-Brown prophecy formula to estimate the number of samples that should be aggregated for a single day's inflammation measurement to reach a specified reliability threshold (note that this approach collapses within-person variability across the day and should not be used when acute changes are of interest, Shields et al., 2019). Importantly for longitudinal studies, reduction of measurement error increases confidence that lack of perfect temporal stability between two occasions represents true within-person change as opposed to the influence of measurement error at multiple time points.

Another key measurement property for longitudinal studies is temporal specificity, the degree to which the strength of a relationship between two variables changes over time. The duration between observations in longitudinal studies of inflammation and depression is extremely variable, ranging from days or weeks (e.g., Graham-Engeland et al., 2018) to over a decade (Gimeno et al., 2009). Our group found that higher CRP consistently predicted increases in depression symptoms in a community sample of adolescents, but the relationships between TNF-α, IL-6, and IL-8 and change in symptoms varied by time to follow-up and sex (Moriarity et al., 2019). Specifically, higher TNF-α predicted greater increases in symptoms at <1 months for males and between 13 and 31 months from baseline for females, higher IL-6 predicted greater increases in symptoms between 13 and 31 months from baseline for females, and higher IL-8 predicted fewer depression symptoms at 31 months from baseline for males. Consequently, discrepancies in time-to-follow-up might be partially responsible for some of the heterogeneity seen in the longitudinal literature and could be an important methodological consideration when designing future studies.

It is also important to consider how isolating theoretically-relevant variance from variables can improve the quality of research. Consider that variables measured multiple times have three sources of variance (differences between people, differences within people over time, and error). Ideally, studies of inflammatory risk for depression should test how change in inflammation predicts change in symptoms, necessitating the isolation of within-person variability. Although some studies have examined within-person effects of inflammation on depression symptoms via experimental (Eisenberger et al., 2010) or quasi-experimental (Kuhlman et al., 2018) designs, many theories of inflammatory risk for depression describe naturally-occurring shifts in resting inflammatory profiles (e.g., Slavich and Irwin, 2014). Because it is unclear whether acute inflammatory reactions and non-acute shifts in concentrations of proteins are equally associated with depression, observational data are necessary. Falkenström et al. (2017) describes how to isolate within-person variance in observational data by subtracting a participant's average level of a variable from each individual time-point, removing the average differences between participants. These "person--centered" predictors can highlight potentially causal relationships in observational data by isolating within-person change, controlling for between-person differences. Additionally, the person-centered predictors cannot be confounded by unchanging participant characteristics. Our group used this approach to test for bidirectional, potentially causal, effects between inflammatory proteins and depression symptoms in an observational study of adolescents (Moriarity et al., 2020a). Results found significant within-person effects of TNF-α and IL-10 predicting increases in a dysphoria subscale and within-person effects of dysphoria on TNF-α, IL-10, and IL-6, providing the strongest evidence to date for causal relationships between naturally-occurring fluctuations in inflammatory proteins and depression symptoms, consistent with evidence from experimental and quasi-experimental designs. Future work focusing on within-person effects is necessary to maximize the clinical utility of immunopsychiatry.

2.1. Phenotyping

Unless inflammation has an equal relationship with all symptoms of depression, sampling variability in symptom profiles could drive inconsistency in results. Depression is an extremely heterogenous phenotype with 277 different symptom profiles diagnosable as Major Depressive Disorder (Kendler, 2020) and a growing body of evidence indicates that not all cases or symptoms of depression are associated with inflammation (Capuron and Miller, 2004; Dooley et al., 2018; Lamers et al., 2018; Majd et al., 2020; Milaneschi et al., 2020; Raison and Miller, 2011). Consequently, the field's reliance on case-control studies and total scores from questionnaires limits the replicability and utility of immunopsychiatry by failing to account for differential relationships between inflammation and specific symptoms. We (Moriarity and Alloy, 2020) outline these considerations in more detail and advocate for increased variety in the level of symptom measurement analyzed in immunopsychiatry to determine at what level (e.g., diagnosis, total scores, subscales, discrete symptoms), effects are largest and most replicable. Although this section focuses on the heterogeneity of depression due to the prevalence of studies using aggregate symptom measures, it is important to highlight that inflammation is also multi-faceted and different components might have differential relationships with depression (Felger and Miller, 2020).

Initial support for the replicability of associations between CRP and individual depression symptoms using network analysis (used to investigate unique, pairwise associations in multivariate data) was found in our recent replication attempt of Fried et al. (2019), which found that higher CRP was specifically associated with increased fatigue, changes to sleeping patterns, and changes in appetite in a large, clinically-enriched, Dutch sample. Across several different models, the CRP—fatigue and CRP—changes in appetite associations were replicated in a larger American population-based sample (Moriarity et al., 2021b), which is consistent with theorized neurovegetative presentations of inflammation-associated depression (Majd et al., 2020). Importantly, both studies suggest that CRP—depression associations might differ across samples due to sampling variability when these symptoms are aggregated with symptoms unassociated with CRP. This also underscores the possibility that specific symptom presentations might be indicative of clients for whom anti-inflammatory adjunctive treatments might be viable (Nettis et al., 2021), advancing the personalized treatment of depression.

Further, the structure of depression symptoms might differ in those

with elevated inflammation compared to those without. Our team (Moriarity et al., 2021a) found that CRP moderated the symptom structure of nine depression symptoms at all levels of analysis (global, symptom-level, and symptom-symptom level), indicating that ideal measurement practices for depression in groups with elevated inflammation might differ from the general population. Interestingly, one of the analyses found that global connectivity (the degree to which all symptoms are associated with one another) was higher in the elevated CRP group. Higher global connectivity has been associated with treatment-resistant depression (van Borkulo et al., 2015), as has elevated inflammation (Sluzewska et al., 1997), indicating that greater symptom connectivity might partially account for inflammation-associated differences in disease course. Future longitudinal research is necessary to test whether these phenotypic differences have clinical implications.

2.2. Theory integration

Most immunopsychiatry research on depression has focused solely on inflammation alone or in interaction with other biological risk factors. Although this is important, there is a dearth of research integrating inflammation into extant psychosocial etiological models, despite many theories describing inflammation as a mediator between stress and psychopathology (e.g., Slavich, 2020; Slavich and Irwin, 2014). Improved integration of immunological and psychosocial risk factors would advance theory and increase the clinical impact of immunopsychiatry. For example, given the sensitivity of inflammation to psychosocial interventions (often small-moderate in size, Shields et al., 2020), identifying inflammation-modulating psychological/behavioral treatment targets offers a way to target this biological mechanism without the associated cost, risk, or stigma of medication. Conversely, understanding that inflammation mediates the relationship between a difficult to target psychosocial risk factor (e.g., social stress, treatment-resistant rumination) and symptoms offers an alternative biological target, maximizing flexibility in treatment administration. Further, fully characterizing the modulators of a risk pathway promises to augment intervention efforts via a maximally comprehensive treatment plan.

Perseverative cognitive response styles are an established transdiagnostic risk factor/treatment target for psychopathology (Johnson et al., 2008). They also can exacerbate the physiological impact of stress by increasing the magnitude and duration of the biological stress response (Brosschot et al., 2005, 2006). The immunocognitive model of psychopathology (Moriarity et al., 2018) posits that perseverative responses to negative affect amplify the association between other stress-modulating characteristics (e.g., anxiety, reward sensitivity) and symptoms via their impact on immunological physiology. Our team (Moriarity et al., 2018) found that rumination (the tendency to passively focus on negative affect) amplified the risk anxiety symptoms conferred for changes in IL-6 in a longitudinal adolescent sample. Further, increases in IL-6 mediated the relationship between baseline anxiety and increases in depression symptoms, a relationship that was amplified by rumination. These results suggest that rumination might indirectly increase risk for depression secondary to anxiety via changes in IL-6.

The synergistic effect of rumination with arousal-related characteristics on inflammation and psychopathology is not restricted to anxiety and depression. Inspired by work finding that reward sensitivity (the strength of reward processing/approach motivation) is associated with heightened negative affect in response to stressors (Harmon-Jones, 2003) and inflammation (Chat et al., 2021), we also tested rumination as a moderator of the relationship between reward drive (the reward sensitivity facet involving intensity of goal pursuit) and inflammatory reactivity to a performance-based social stressor (Moriarity et al., 2020a). Results indicated that both rumination and higher perseverative cognitive response style profiles (i.e., rumination/(problem solving + distraction)) interacted with high reward drive to predict greater increases in IL-6 post-stressor. Further, problem solving and distraction (non-perseverative response styles) buffered the association between high reward drive and increases in IL-6 post-stressor. A second study extended this work to test the interaction between reward sensitivity and rumination in predicting i) resting levels of inflammatory proteins and ii) change in depression and hypo/mania symptoms (Moriarity et al., 2020a) in young adults. Parallel interactions were found predicting inflammatory and mood outcomes: 1) high reward responsiveness interacted with high rumination on positive affect to predict increases in (hypo)manic symptoms and higher IL-8, 2) low reward responsiveness interacted with high brooding on negative affect to predict increases in depression symptoms and higher CRP. Importantly, these parallel interactions suggest conditional pathways via rumination that might explain how abnormal reward sensitivity is associated with both inflammation (Chat et al., 2021) and mood psychopathology (Alloy et al., 2016). Moving forward, immunopsychiatry should prioritize the conceptualization and testing of etiological models integrating psychosocial and immunological risk factors to identify for whom inflammatory abnormalities are most likely to be a pathophysiological characteristic (e.g., individuals high in rumination) and to support the development of maximally-comprehensive treatment plans.

3. Conclusion

Immunopsychiatry holds substantial promise for the advancement of depression research. There is strong theoretical rationale for the association between inflammation and depression symptoms via sickness behaviors theory (Hart, 1988), converging evidence from animal and human studies (e.g., Dooley et al., 2018; Laugeray et al., 2011), findings that inflammation is sensitive to both psychosocial and medication-based interventions (Raison et al., 2013; Shields et al., 2020), and inflammation has initial support as a useful adjunctive treatment target for depression (Nettis et al., 2021). However, both the immune system and many psychiatric disorders (e.g., depression) are extremely multi-faceted, complex constructs. To maximize the replicability and clinical impact of this field, careful attention needs to be paid to methodology/measurement properties (Moriarity and Alloy, 2021), characterizing inflammatory phenotypes of psychopathology (Moriarity and Alloy, 2020), and integration of immunology into robust, extant psychosocial frameworks (e.g., response styles theory; Moriarity et al., 2018; Nolen-Hoeksema and Morrow, 1991). Parallel growth in all three areas (summarized in Table 1) will ensure immunopsychiatry research is replicable, contributes to understanding how (and for whom) the immune system is associated with psychiatric symptoms, and increases the flexibility and power of personalized treatment planning.

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Declaration of competing interest

None.

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