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Beyond diagnoses and total symptom scores: Diversifying the level of analysis in psychoneuroimmunology research

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Psychoneuroimmunology is a rapidly advancing field that investigates various immunological processes (at numerous levels of measurement) as risk factors, mechanisms, and sequelae of psychological phenomena. However, the majority of psychopathology-focused psychoneuroimmunology research to date has analyzed differences in immunological characteristics between those with vs. without a disorder (i.e., case-control studies), and/or relationships between immune markers and total scores on self-report symptom measures associated with a specific diagnostic category (e.g., depression). Although these approaches are important for studying psychopathology at the level which mental health is typically conceptualized (both in research and clinical work), there are inherent limitations to these methods that limit their utility in studying the associations between immune functioning and mental health. The example of inflammation and depression will be used throughout this viewpoint to illustrate these limitations and highlight arguments for diversifying the level of analysis of psychopathology in psychoneuroimmunology research.

1. The heterogeneity problem and assumption of symptom equivalence

One of the primary limitations of case-control studies is the heterogeneity problem (Feczko et al., 2019), which refers to how group difference designs implicitly assume each comparison group is homogenous in all domains relevant to the research question (i.e., no sample-dependent moderators of the associations analyzed). Although homogeneity is equally (if not more) unlikely for a sample of "healthy controls," the heterogeneity within current diagnostic criteria for Major Depressive Disorder (MDD) should serve as a major warning against this assumption for a sample of participants with depression. Currently, there are 227 different symptom profiles that would qualify for a diagnosis of MDD (Kendler, 2020), which is higher than the number of participants with depression included in many case-control studies.

One also must consider the assumption of symptom equivalence, which is relevant for both case-control designs and symptom total score methods. The assumption of symptom equivalence, which arises from the focus on latent factor models of psychopathology, holds that symptoms of a disorder are largely interchangeable/equivalent. In other words, it is symptom number, not symptom nature, that is relevant. Consider Participant A, who endorses depressed mood, anhedonia, psychomotor agitation, excessive guilt, and suicidal ideation. Then consider Participant B, who also endorses depressed mood, but then reports insomnia, fatigue, difficulty concentrating, and decreased appetite. Both have five symptoms and profiles that qualify for an MDD diagnosis and thus would be identical data points in these two study designs. However, it is plausible that these different symptom profiles might be associated with different risk factors and consequences. In fact, evidence suggests different depression symptoms have different risk factors (Fried et al., 2014), a perspective that some psychoneuroimmunologists are starting to incorporate into their research.

2. Analyzing deeper than diagnostic categories or total symptom scores

If not all depression symptoms have similar associations with an immunological risk factor, sampling variability in symptom profiles could account for some heterogeneity of effects (presence, direction, and size) seen in the literature using case-control designs or the total number/severity of symptoms. It also could explain why elevated peripheral inflammation is only seen in a subset of depressed participants (i.e., those with symptom profiles associated with inflammation; Raison and Miller, 2011). By focusing on smaller parts of the construct of depression (e.g., symptom subscales or individual symptoms) that are more homogenous in presentation than the disorder itself, it might be possible to generate more consistent results. This line of reasoning has inspired calls for the inflammatory phenotyping of depression (e.g., Dooley et al., 2018; Felger et al., 2018).

Analysis of psychopathology at more atomic levels of measurement also has the potential to result in transdiagnostic discoveries that can maximize relevance. For example, a finding that heightened inflammation is associated with decreased energy and sleeping problems (Fried et al., 2019) is as relevant for depression research as any other substantive topic involving sleeping issues or fatigue. Additionally, analyzing individual symptoms or symptom subscales can remove symptom variance unrelated to immune biomarkers of interest and increase power compared to analyzing all endorsed symptoms (e.g.,

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Moriarity et al., 2020). Clinically, the characterization of symptom profiles specifically associated with inflammation can help identify individuals for whom anti-inflammatory/immune-modulating treatments might prove beneficial and which symptoms should be expected to respond to these treatments. Finally, several theories (e.g., the network theory of psychopathology; Borsboom and Cramer, 2013) argue that symptoms cluster into syndromes due to causal associations between symptoms (e.g., sleeping problems and fatigue are both depression symptoms because one influences the other). If causal associations between symptoms are important for explaining the structure of psychopathology, knowledge of how abnormal immune processes influence specific symptoms/domains of symptoms is crucial for understanding how the immune system, brain, and behavior are interrelated. Even if these theories are not supported, diagnostic criteria are regularly re-evaluated, and it is important to know if immune processes are related to disorders themselves or specific criteria. As the understanding of psychopathology advances, lack of investigation at this level threatens the relevance of psychoneuroimmunology as a field.

3. Conclusion

We are not suggesting that case-control designs or analyzing total symptom scores are not important in psychoneuroimmunology. Variables composed of fewer indicators (especially single-item measures of individual symptoms) tend to have weaker reliability and, consequently, reduce statistical power. Therefore, symptom subscales might offer a balance between specificity of behavioral phenomena and the psychometric benefits of aggregate measures. Further, analyzing several symptoms or subscales rather than a total score or group comparison inflates Type-I error. And, as stated above, it is crucial to understand immune—behavior associations at the level that psychopathology is most frequently conceptualized in clinical settings. However, the case-control and total symptom score methods alone do not maximize the field's understanding of the association between the immune system and psychopathology. These approaches, which have predominated in the field, can inspire deeper thought into the association between immune and behavioral processes. Deeper thought invites more specific hypotheses, which promote the refinement of mechanistic and nosological theory. Increased specificity in study design and analytic choices could result in more consistent findings, streamlining the pipeline between research and advancement of classification, prevention, and treatment.

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