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Transdiagnostic biomarker approaches to mental health disorders: Consideration of symptom complexity, comorbidity and context

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ABSTRACT

Depression is a multifaceted disorder characterized by heterogeneous symptom profiles and high rates of comorbidity with other commonly occurring mental illnesses. Considering the burden of mental health disorders and the lack of efficacy of available treatments, there is a need for biomarkers to predict tailored or personalized treatments. However, identifying reliable biomarkers for complex mental illnesses, such as depression, anxiety and PTSD, has been challenging, likely owing to the heterogeneity, comorbidity and differences in experiences and histories of individuals. For these reasons, taking a transdiagnostic approach, which identifies biomarkers that map onto shared symptoms/constructs across disorders could be most effective for informing personalized or precision medicine approaches in psychiatry. Transdiagnostic features of anxiety, depression and anhedonia have been examined in relation to brain activity and connectivity patterns. Neuroendocrine and inflammatory markers, which are altered in depression and other comorbid illness, such as post-traumatic stress disorder (PTSD), might be useful in differentiating transdiagnostic symptom profiles as well as treatment responses. Ultimately, biomarker research that looks beyond diagnostic categories and embraces the complexity of individuals' lives and experiences might be more effective in moving towards precision medicine in psychiatry.

1. Introduction

Precision medicine comprising targeted and personalized treatments based on an individuals' symptoms, biology, and experiences, has the potential to significantly improve outcomes among individuals with mental illnesses. Currently, response rates to first-line antidepressants range from 40 to 60%, and remission occurs in a minority of individuals with depression (30–45%; Rush et al., 2006; Trivedi et al., 2006). Moreover, large inter-individual differences occur in treatment response (Cipriani et al., 2018), such that, among individuals with comorbid illnesses or experiences of trauma, still lower rates of remission occur (Nanni et al., 2012; Saveanu et al., 2014). Thus, there is a clear need for biomarkers to predict which treatments will best serve affected individuals.

Precision medicine has existed for some time related to physical illnesses, such as in certain forms of cancer (e.g., Berger and Mardis, 2018). However, biosignatures relevant to mental illnesses, have largely been underdeveloped, likely owing to the difficultly in identifying *reliable* biomarkers for complex mental illnesses, such as depression. To address this need, the Research Domain Criteria (RDoC) introduced by the U.S. National Institutes of Mental Health focused on moving research beyond the constraints of traditional diagnostic approaches, instead considering transdiagnostic dimensions (i.e. fear, hopelessness, anhedonia symptoms/constructs that cut across many disorders) that could be validated at a biological level (Insel et al., 2010). Another dimensional approach, the Hierarchical Taxonomy Of Psychopathology (HiTOP), was similarly designed to address problems relating to arbitrary diagnostic boundaries such as heterogeneity and comorbidity, but also to be more immediately clinically relevant (Kotov et al., 2017). The primary difference between RDoC and HiTOP frameworks are the respective emphasis on more basic biological constructs (e.g., neurobiology) relative to more clinical characteristics. It is likely that these innovative approaches can inform each other to achieve a more comprehensive understanding of mental illnesses (Kotov et al., 2018). There have been advances in identifying transdiagnostic features of anxiety, depression and anhedonia that were related to resting-state functional MRI connectivity patterns (Mellem et al., 2020), whereas less headway was achieved in relation to peripheral blood-based biomarkers. Yet, there is ample reason to suppose that neuroendocrine and immune biosignatures can be identified across mental health disorders, such as depression and anxiety. Moreover,

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approaches that reflect the complexity of these multifaceted disorders could ultimately be more successful at informing individualized treatment strategies.

2. The problem: heterogeneity and comorbidity

Mental health disorders, such as MDD, generalized anxiety disorder (GAD), and post-traumatic stress disorder (PTSD) have high rates of comorbidity with one another (Kessler et al., 2008; Slavich and Auerbach, 2018). In fact, almost 50% of individuals with MDD have had one or more anxiety disorders in their lifetime (Kessler et al., 2015), and 44% of Canadian Armed Forces personnel with MDD will have PTSD in their lifetime (Sareen et al., 2021). Moreover, within diagnostic categories, such as MDD, symptoms are highly heterogeneous, such that individuals can present vastly different combinations of symptoms to meet diagnostic criteria (Fried, 2015), which can complicate diagnosis and treatments. Biomarker research has largely focused on specific diagnostic categories including differences in symptoms expressed in relation to particular biological processes (Majd et al., 2019). While this is a good strategy it is also important to consider that the comorbidities that exist between disorders makes it difficult to discern key features of any particular illness.

In addition, multiple subtypes of depression exist (Ahmed et al., 2018; Insel et al., 2015) whose biological basis is poorly understood. Depressive subtypes including melancholic depression (e.g. anhedonia, loss or appetite/weight, insomnia), atypical depression (e.g. increased eating, sleeping, etc.), dysthymia (e.g. persistent low-grade depression), and seasonal depression vary in their etiology and symptoms (Harald and Gordon, 2012), however, it is unclear if these conditions can be differentiated according to neurobiology. Through functional magnetic resonance imaging (fMRI), four depressive subtypes were identified according to distinct whole-brain patterns of abnormal functional connectivity in resting-state networks, and these profiles mapped onto differences in depressive symptomatologies. Thereby helping to identify subtypes of individuals that would benefit most from repetitive transcranial magnetic stimulation (rTMS) (Drysdale et al., 2017). Moreover, homogenous depressive subtypes that mapped onto structural alterations of the anterior insular cortex were found in young people and have also been seen in an adult sample (Toenders et al., 2020). Subtyping studies such as these reflect the vast heterogeneity that exists within diagnostic categories, which will continue to be important for informing personalized treatment. It might also be profitable to examine biomarkers that not only reflect heterogeneity but also the comorbidities and shared features/constructs across disorders, which necessarily requires a transdiagnostic approach.

Constructs related to depressive symptoms, such as anhedonia and cognitive deficits, cut across many diagnostic boundaries (McTeague et al., 2017; Nusslock and Alloy, 2017). Identifying transdiagnostic symptom profiles that occur or cluster together across disorders is an important first step (Lee et al., 2018); however, in order to inform targeted or personalized treatments it is necessary to also differentiate symptoms clusters based on their biological substrates (Anisman et al., 2018). In a truly transdiagnostic approach, robust subtypes of mental health symptom profiles evident across MDD, panic disorder, and PTSD revealed distinct and meaningful associations in cognition, brain activity (e.g. electroencephalography (EEG) recordings), and observable real-world function (Grisanzio et al., 2018). Despite the promising findings using this approach, few studies have applied a transdiagnostic method to examine neuroendocrine and inflammatory biomarkers across multiple mental health disorders.

3. Stress and inflammatory transdiagnostic biomarkers

Stressful experiences can cause prolonged dysregulation of hypothalamic-pituitary-adrenal (HPA) axis functioning resulting in altered glucocorticoids (e.g. cortisol) and immune messaging molecules (cytokines). Dysregulation of neurobiological pathways that occur following stressor encounters are similarly altered in several mental health disorders, and may be causally related to the pathogenesis of depression (e.g. Audet et al., 2013; see reviews in Anisman et al., 2018). In this regard, depressed individuals frequently display elevated peripheral cortisol levels (Pariante and Lightman, 2008), but this is not apparent among all depressed individuals, being more common in melancholic depression than among individuals with atypical depressive disorder, which is characterized by normal or low cortisol profiles (Gold & Chrousos et al., 2002; Juruena et al.,. 2018). Although these data suggest that elevated HPA axis functioning might be a biomarker for specific depressive features, disturbed glucocorticoid activity is also dysregulated in other psychological conditions, including those that are highly comorbid with depression, such as PTSD (Yehuda et al., 2005).

Inflammatory factors, such as C-reactive protein (CRP) and pro-inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, may also be elevated in MDD patients (Haapakoski et al., 2015; Osimo et al., 2019). However, not all depressed individuals exhibit high levels of inflammation (Jokela et al., 2016; Majd et al., 2019). Once again, the ties between inflammation and depression may only be present in a subpopulation or 'subtypes' of depression. In fact, associations between CRP and other depressive symptoms, such as anhedonia and concentration, were no longer significant after controlling for neurovegetative symptoms, such as sleep and eating profiles (Jokela et al., 2016; Majd et al., 2019). These findings suggest that neurovegetative symptoms of depression might be most closely tied to inflammation. Furthermore, elevated CRP was not unique to depression having been observed among individuals with generalized anxiety disorders (Costello et al., 2019) and PTSD (Lindqvist et al., 2017).

Clinical trials revealed that anti-inflammatory treatments could diminish depressive symptoms (Köhler-Forsberg et al., 2019). But such effects might only be apparent among patients in whom inflammation was present, making it that much more important to identify which patients might benefit most from this treatment option. We recently applied a hierarchical clustering approach to identify transdiagnostic depressive and anxiety symptom subtypes at a neurobiological level. Six distinct symptom clusters of individuals were identified that significantly differed based on symptom dimensions and inflammatory profiles. Specifically, CRP levels were elevated in the cluster of individuals that expressed higher neurovegetative symptoms, but not among those with high levels of anhedonia or physical (somatic) anxiety features (Franklyn et al., 2021). These data looked beyond diagnostic categories and focused on specific symptomatologies and biological correlates to potentially inform tailored and personalized treatments.

Cortisol profiles, inflammatory factors, including cytokine levels are also dysregulated among individuals with PTSD compared to healthy individuals (Lindqvist et al., 2017; Yehuda et al., 2005). Like depression, the presentation of PTSD is heterogeneous as factors including the type of trauma, early-life adversity, age, sex and genetics can all influence the development, heterogeneity and severity of PTSD (Campbell-Sills et al., 2021; Yehuda et al., 2015). These factors were explored to create subtypes, including a threat-reactivity profile, a dysphoric profile and a high-symptom profile that differed according to symptomatology, heterogeneity and progression of PTSD (Campbell-Sills et al., 2021). One specific subtype known as dissociative PSTD (Lanius et al., 2012), in which the usual symptoms are accompanied by depersonalization and derealization symptoms, is included in the DSM-5. While individuals with this subtype often display high PTSD symptom severity, less is known about the neuroendocrine and inflammatory profiles of dissociative PTSD (van Huijstee and Vermetten, 2018). To address this gap, our team at the University of Ottawa Institute of Mental Health Research (IMHR) and the Royal Ottawa Mental Health Centre have been developing a biosignature for the dissociative PTSD subtype among past and present Canadian Armed Forces (CAF) members who had been actively deployed. While this project is ongoing, preliminary data suggested that individuals with dissociative PTSD display higher plasma CRP levels

(Jarkas et al., 2021), and altered event related potentials (ERP) in response to trauma based stimuli compared to those with non-dissociative PTSD (Staff et al., 2021). Once again, identifying a biosignature that integrates multiple biological systems to characterize the PTSD subtypes could inform tailored or personalized treatments. Moreover, considering the high rates of comorbidity between PTSD and depression among armed forces personnel and veterans (Sareen et al., 2021), this project also included members with MDD without PTSD present to explore transdiagnostic associations between symptom profiles and peripheral biomarkers in the presence or absence of comorbid conditions.

4. Considering context and experiences

To understand the high degree of comorbidity between common mental health disorders and the neurobiological similarities that can exist across diagnoses, consideration of upstream shared risk and/or protective factors might be advantageous. Among military personnel or veterans, deployment-related traumatic events can have cumulative effects with earlier childhood traumas that greatly increase the risk of PTSD (Afifi et al., 2021). In the general population, one in three Canadians have experienced some form of childhood trauma, which has been associated with approximately *three* times greater likelihood of being diagnosed with depression or anxiety and *four and a half* times greater likelihood to develop PTSD (Afifi et al., 2014). This risk was exponentially greater when considering cumulative trauma experiences. For example, individuals who experienced three different types of childhood trauma, were approximately *five* times more likely to develop depression and *fifteen* times more likely to develop PTSD (Afifi et al., 2014). Accordingly, earlier trauma is considered a powerful transdiagnostic risk factor for multiple mental illnesses (McLaughlin et al., 2020). If childhood trauma exposure is associated with elevated risk for virtually all commonly occurring mental illnesses, this begs the question as to why some individuals are more likely to develop one form of illness relative to another?

This question seems particularly relevant when considering that many biological systems, such as altered HPA axis and inflammatory processes that are dysregulated in depression and other mental health disorders are similarly disturbed following trauma experiences (Danese and Baldwin 2017; Slavich and Irwin, 2014). In fact, although inflammatory markers are associated with depression, once childhood trauma was controlled for, this relation was greatly diminished (Lu et al., 2013). In a preliminary study, we observed that while depressive symptoms did not relate to IL-6 levels, childhood trauma scores were positively associated with adult levels of this cytokine (Franklyn and McQuaid, 2020). Similarly, individuals with depression and a history of childhood trauma displayed elevated inflammatory levels compared to controls, an effect not found among depressed individuals with no history of childhood trauma (Danese et al., 2008; Watt et al., 2020). These data highlight the possibility that childhood trauma and inflammatory processes are linked to mental health disorders in a subset of individuals (Danese and Lewis, 2017). Although a recent meta-analysis indicated that retrospective studies were compromised by multiple methodological issues, there was robust evidence that elevated CRP was associated with childhood trauma in prospective studies (Kerr et al., 2021). Furthermore, depressed individuals who have a history of childhood trauma were more likely to display recurrent depressive episodes and treatment resistance (Nanni et al., 2012), revealing practical treatment implications of identifying subtypes of individuals based on trauma histories that might inform precision medicine.

These data broadly highlight the importance of considering an individual's life experiences that could influence biological developmental trajectories that affect mood symptoms and perhaps the efficacy of specific treatments. Taking a narrow perspective could explain the inconsistencies in biomarker research that exist, which impede the identification of robust biomarkers or biosignatures in commonly occurring mental health disorders. Lessons from genetic studies revealed the importance of considering childhood trauma experiences through Gene x Environment interactions in understanding depressive symptoms (McQuaid et al., 2013, 2016a). Indeed, numerous studies have pointed to epigenetic changes related to early-life experiences in the occurrence of depression and anxiety (Farrell et al., 2018). It is now understood that although the contribution of individual gene variants is small, current evidence indicates that genome-wide influences on MDD can vary with stressful life experiences (Kendall et al., 2021). In this regard, a large-scale genome-wide study showed strong associations between polygenic risk scores and major depression among individuals exposed to childhood trauma and socioeconomic adversity (Shen et al., 2020). Conversely, social support/social cohesion was accompanied by reduced relations with polygenic risk scores and MDD among individuals who had encountered significant stressors (Choi et al., 2020; Kendall et al., 2021). Evidently, interactions exist between genetic factors and childhood trauma, socioeconomic adversity, and social support in risk of MDD.

The contribution of social relationships and support on mental health cannot be overstated (Audet et al., 2014; Santini et al., 2015). In our own work (and that of others), social support effectively buffered mood and cortisol responses to stressors (Heinrichs et al., 2003; McQuaid et al., 2016b). Likewise, children were less likely to develop trauma-related mental health disturbances if they had high levels of social support (Trickey et al., 2012). Moreover, prospective studies demonstrated that among individuals with depression, risk of relapse was reduced if they joined one or more social groups (Cruwys et al., 2013). Conversely, feelings of loneliness was a strong longitudinal predictor of depression (Cacioppo et al., 2006) and was dose-dependently linked to anxiety and depressive symptoms (McQuaid et al., 2021). While the biological pathways in which social relationships affect mental health are not well delineated, inflammatory processes might be involved. In this regard, we observed that poor social ties were related to higher plasma TNF-α levels and lower levels of the anti-inflammatory cytokine IL-10 (Ysseldyk et al., 2018). A meta-analyses indeed indicated that social isolation and loneliness were marked by elevated inflammation (Smith et al., 2020), whereas social support was linked to lower levels of the inflammatory markers CRP and IL-6 (Uchino et al., 2018). While speculative, it is possible that social support serves to protect against the negative impacts of stressors on mental health by buffering the impact of cytokines. In essence, just as trauma can be considered a transdiagnostic risk factors for the development of multiple mental health disorders, social support can serve as a protective factor (McLaughlin et al., 2020). Clearly, understanding the neurobiology of mental health symptomologies ought to integrate social determinants of health to obtain a better understanding of the transdiagnostic factors involved.

5. Considerations and future directions

Targeted or personalized treatments in psychiatry require reliable clinically relevant biomarkers. To achieve this goal, biomarker studies that embrace the complexity of disorders, capturing the vast heterogeneity of symptoms and/or high rates of comorbidities might be more efficacious at informing personalized treatments. Working from existing transdiagnostic frameworks, namely RDOC and HiTOP, and recognizing the complementary strengths of these approaches, could inform significant advances for precision medicine in psychiatry (Michelini et al., 2021). This is particularly relevant as each approach has various advantages/disadvantages, such that some RDoC dimensions could lack clinical context, and HiTOP dimensions might not easily allow for biological differentiation. In this regard, HiTOP could inform the RDoC initiative by identifying key clinical dimensions to examine on a biological level (Kotov et al., 2018). As indicated earlier, there have been promising studies identifying trandiagnostic symptom subtypes based on brain recordings (Grisanzio et al., 2018), however, similar work examining symptom subtypes across diagnoses in relation to blood-based peripheral biomarkers are needed. These data could expand the findings of

clinical trials, which revealed that lower levels of CRP prior to treatment among individuals with MDD resulted in better response to SSRI's (Miller et al., 2017).

To highlight the importance of environments using a transdiagnostic approach to biomarker research, we emphasized experiences of trauma and social support as strong risk and protective factors for multiple mental health disorders. Of course, many other social determinants, such as living in poverty (Miller et al., 2020) and experiencing racial discrimination (Matheson et al., 2016, 2019), can act as chronic stressors to impact mental health and neurobiological factors. Other social determinants, such as culture may be critical when applying a precision medicine approach (Gone and Kirmayer, 2020; Matheson et al., 2018). Consideration of culture allows for a deeper understanding of culturally-relevant approaches to healing and resiliency as well as historical events (collective trauma) to properly contextualize the mental health of various populations. This is especially relevant, for example, when considering Indigenous wellness and the intergenerational impacts of harmful government assimilation policies (McQuaid et al., 2017).

Together, the ideal precision medicine model for complex multifaceted mental illnesses requires integrated methods that combine multiple sources of data comprising not just the consideration of clinical, and biological information, but also individuals' diversity of experiences (Lydiard and Nemeroff, 2019). Furthermore, it is unlikely that single biomarkers will be sufficient to guide tailored treatments, a more comprehensive profile combining multiple biomarkers to create a 'biosignature' will be more fruitful. Ultimately, biomarker research that breaks down diagnostic barriers and embraces the complexity of individuals' lives and realities may be ideal to move precision medicine in psychiatry forward.

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Declaration of competing interest

The author has no conflicts of interest to declare.

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