Intersecting Dimensions of Cognitive and Neuropsychiatric Symptoms: Embarking on a New Era of Clinical Neuropsychological Research

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A new era of scientific exploration has arrived in the neuropsychiatric arena, one in which the clinical neuropsychological community is well poised to ensure optimistic and promising outcomes (Parsons and Duffield, 2019). Driven by a need to better inform neuropsychiatric diagnoses and treatment development (Sansilow, Ferrante, Pacheco, Rudorfer and Morris, 2019), this new era was born out of the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) Framework (Cuthbert and Insel, 2013; Cuthbert, 2020). The NIMH RDoC framework is a research classification system that seeks to integrate multiple units of analyses (e.g., behavioral outcomes, neuroimaging data, genetic information) to inform the understanding of underlying neural systems responsible for behavior. With the rich history of uncovering and establishing brain and behavior relationships, clinical neuropsychology can make substantial contributions to this new era of neuropsychiatric classification and treatment development (Parsons & Duffield, 2019).

Most, if not all, neuropsychiatric diagnoses are comprised of multiple heterogeneous symptoms, which unfortunately diminishes diagnostic classification accuracy and ultimately limits effective therapeutics. Major depressive disorder is commonly highlighted as one such example of a heterogeneous

diagnosis (Ballard et al., 2018), though it is not alone. Indeed, other neuropsychiatric illnesses such as bipolar disorder, schizophrenia, Parkinson disease, and Alzheimer disease can be parsed into discrete symptomatological domains including mood, motor, and cognitive symptoms (Habes et al., 2020; Schrag et al., 2019; Tamminga et al., 2014). With expertise that spans multiple units of analysis to integrate including behavioral observations, neurocognitive metrics, neuroimaging and neurophysiology data, and genetic variables, clinical neuropsychologists and the clinical neuropsychological field can play meaningful roles in furthering our understanding of these symptomatological domains and their intersectionality.

The articles in this special issue of *Neuropsychology Review* exemplify this new era of research as they highlight studies that apply neurocognitive scientific approaches to advance the understanding of brain and behavior relationship through the multidimensional spectrum of neuropsychiatric illnesses across the adult lifespan. The articles focus on multiple diagnostic dimensions including neurodegenerative disease, cerebrovascular aging, and psychosis, as well as multiple investigative tools such as neuroimaging and non-invasive brain stimulation.

Five of the articles in this issue identify neurocognitive deficits that cut across neuropsychiatric illnesses or across severity levels within a disorder. The systematic review by Green et al. summarizes the results of studies that use data-driven clustering methods to delineate cognitive subtypes among adults with schizophrenia, schizoaffective disorder, or bipolar disorder. Their review highlights the inconsistencies in the literature using unsupervised clustering approaches, but nonetheless identifies a severe cognitive deficit subtype across cluster solutions in the reviewed studies.

Dotson et al. examine cognitive control functions across the lifespan to examine associations with subthreshold and clinical depressive symptoms. Their meta-analysis shows that both subthreshold and clinically significant depressive

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symptoms are associated with poorer performance across different aspects of cognitive control including inhibition, cognitive flexibility, and planning. This association is stronger in studies that included a sample with an older mean age. Interestingly, the relationship is also stronger in adults who were taking antidepressant medications.

Langenecker et al. examine components of a specific cognitive control function—inhibition—across the mood disorder spectrum. Their review suggests that there is a complex relationship between inhibitory control accuracy and interference resolution speed across mood disorders that is dynamic across the lifespan. As pointed out in their article, inhibitory control and emotion regulation overlap in their underlying neural circuitry. Thus, these overlapping neuronetworks provide important targets for therapeutic interventions such as repetitive transcranial magnetic stimulation (rTMS).

The review by Yang et al. directly addresses the benefits of non-invasive brain stimulation therapies on cognitive and neuropsychiatric symptoms. They review the use of rTMS and transcranial direct current stimulation (tDCS) to modulate impulsivity across multiple neuropsychiatric disorders. They find that while rTMS had no impact on impulsivity, tDCS had a small, though clinically unmeaningful, modulatory effect on impulsivity. This highlights that unique brain stimulation treatments, depending on the dosing and treatment strategy, could have differential clinical and cognitive effects.

Seabury et al. provide a narrative review and theoretic overview of the literature on memory impairment in individuals at high risk for psychosis and incorporated multiple units of analysis through examination of both the cognitive and neuroimaging literature. Specifically, they examine the utility of verbal memory as a predictor of conversion to psychosis as well as the neurobiological underpinnings of verbal memory deficits in high risk individuals. They find that the premorbid phase of psychosis is characterized by memory impairment, which was predictive of future conversion to psychosis. Functional magnetic resonance imaging studies show greater activation of memory-related regions during memory retrieval among high-risk individuals who later developed a psychotic disorder, although the effect is not observed across all studies.

Lamar et al. similarly review neuroimaging studies to identify brain changes that cut across both medical and neuropsychiatric conditions. They review the overlap in neuroanatomical profiles associated with cardiovascular risk factors and Alzheimer's disease (AD) as a way of offering more relevant targets for investigating ways to reduce the growing AD epidemic. Their systematic review identifies 23 gray matter, subcortical, and white matter regions commonly associated with both cardiovascular risk factors and AD. As the population ages worldwide, this knowledge is essential for better characterizing, preventing, and treating dementia.

The meta-analysis by Hudon et al. also addresses this important topic. They identify studies examining behavioral and

psychological predictors of subsequent cognitive decline in cognitively intact middle-aged and older adults. They examine a spectrum of cognitive outcomes, including a decline in cognitive test scores, diagnosis of mild cognitive impairment, and a diagnosis of AD or other type of dementia. Depression and sleep duration predict cognitive decline, which supports the need to assess behavioral and psychological symptoms in cognitively intact older adults to identify those who are at risk for cognitive decline.

Together, articles in this special issue highlight the advances that can be made in our understanding of neuropsychiatric disorders when dimensions of behavior and the spectrum of symptom severity levels are considered. The articles also support the notion that examining intersecting dimensions of neurocognitive and neuropsychiatric symptoms can aid in identifying risk factors for disorders as well as neurobiological targets for the refinement of current and development of new therapeutics.

Putting together this special issue has been an incredible opportunity to collaborate with wonderful colleagues across the globe. We are thankful to the authors for their excellent contributions, the reviewers for their thoughtful reviews and recommendations, and to the editors and journal personnel for their support and guidance. We hope this special issue will inform scientists across the globe on the importance of examining not only discrete diagnoses, but also symptoms and behaviors across spectrums through multiple units of analyses to fully establish the neural bases for symptom expression and behavioral function across the lifespan.

Note from the Editors-in-Chief: In the preparation of this special issue Drs. Rosemary Fama and Sallie Baxendale were Action Editors for the manuscript Dotson, V.M., McClintock, S.M., Verhaeghen, P. et al. Depression and Cognitive Control across the Lifespan: a Systematic Review and Meta-Analysis. *Neuropsychol Rev.* (2020). <https://doi.org/10.1007/s11065-020-09436-6>

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