

What Does It Mean to Be Transdiagnostic and How Would We Know?

Deanna M. Barch, Ph.D.

Historically, the fields of psychiatry and psychology have focused research on traditional diagnostic categories. Furthermore, the vast majority of research studies investigating psychopathology focus on a single diagnostic category in any one study, typically comparing this single disorder group to some type of control group. However, psychopathology researchers have come to recognize that the boundaries between putatively distinct psychiatric disorders do not cleanly map to the complex configurations of human experience that manifest as mental illness. This recognition includes the understanding that some dimensions of disordered behavior cut across traditional diagnostic boundaries, and thus the biological factors that align with these dimensions also likely cut across traditional diagnostic boundaries. Hence, the past several years have seen a significant increase in the number of empirical and meta-analytic studies that have the goal of identifying neural, physiological, and/or psychological impairments that are present across putatively different diagnostic categories as opposed to those that might be specific to a particular diagnostic category (1–4).

In this issue of the *Journal*, McTeague and colleagues extend a series of meta-analytic studies focused on identifying common versus specific neural deficits across psychiatric disorders, with a meta-analysis focused on task activation during emotional processing in schizophrenia, bipolar disorder, major depression, anxiety disorders, and substance use disorders (5). If you do not consider the directionality of the activation differences (i.e., increased or decreased), the authors report finding that across disorders, “patterns of patient hyper- and hyporeactivity demonstrated abnormal activation in the amygdala, the hippocampal/parahippocampal gyri, the dorsomedial/pulvinar nuclei of the thalamus, and the fusiform gyri, as well as the medial and lateral dorsal and ventral prefrontal regions.” These findings build on previous elegant work from this group that examined structural differences demonstrating transdiagnostic patterns of reduced gray matter in the dorsal anterior cingulate (dACC) and the left and right insula across schizophrenia, bipolar disorder, depression, substance use disorders, obsessive-compulsive disorder, and other anxiety disorders (1). The authors hypothesized that this transdiagnostic pattern of reduced gray matter might contribute to impairments in cognitive control that are often found in many forms of psychopathology (6) and which may also be a transdiagnostic

risk factor (7). Consistent with this hypothesis, McTeague and colleagues reported finding in a meta-analysis of activation during cognitive control tasks (2) that individuals with schizophrenia, bipolar disorder, major depression, anxiety disorders, and substance use disorders showed transdiagnostic patterns of abnormal activation in the left prefrontal cortex, the anterior insula, the ventrolateral prefrontal cortex, the right intraparietal sulcus, and a part of the dACC that overlapped with the dACC region identified in their structural analyses.

These meta-analyses, as well as other empirical and meta-analytic work (e.g., 3, 4, 8–10), help advance and shape our understanding of the neural alterations that might be associated with broad risk factors for psychopathology, with additional etiological mechanisms potentially shaping the specific manifestations of mental illness for a particular individual. The findings converge nicely with a growing body of work identifying a general factor in structural models of psychopathology, often referred to as the “*p* factor” (e.g., 11–14). In fact, McTeague and colleagues have explicitly argued that their transdiagnostic findings might represent the neural correlates of such a *p* factor (6), an intriguing idea that could help lead to intervention or even prevention approaches that are quite broadly useful.

However, while the work from McTeague et al. is intriguing, it also raises the question of what we mean by transdiagnostic and how we should define and determine what neural or psychological impairments are transdiagnostic. A strong interpretation of “transdiagnostic” would suggest that all disorders in question should show significant differences from a designated control group in order to call the finding transdiagnostic, albeit potentially with graded severity. In their meta-analytic work, McTeague and colleagues have typically first looked at pooled analyses of “patients compared with controls” and then conducted follow-up analyses that were disorder specific. Significance in such pooled analyses can result from strong effects in a subset of diagnostic categories.

While the work from McTeague et al. is intriguing, it also raises the question of what we mean by transdiagnostic and how we should define and determine what neural or psychological impairments are transdiagnostic.

Hence, a key issue is whether findings from pooled analyses should be called transdiagnostic if they seem primarily to reflect impairment in one disorder and not others. For example, in the article in this issue, McTeague and colleagues describe both dorsomedial thalamus and amygdala as showing disturbances across disorders. However, in the disorder-specific analyses (see Figure 3 in the article and Figure S2 in the online supplement), the dorsomedial thalamus appears to show similar deficits across disorders, while the amygdala does not, with alterations present in nonpsychotic disorders but not in psychotic disorders. The dorsomedial thalamus would thus seem to fit a strong definition of transdiagnostic, while the amygdala would not. Analogously, in their cognitive control meta-analysis, McTeague et al. found hypoactivation in the left and right insula and the left prefrontal cortex in the pooled patient analysis (2). Analyses examining psychotic and nonpsychotic patients separately indicated shared reductions in the right insula but not in the left prefrontal cortex, with the latter clearly present in the schizophrenia patients and much less so in other diagnostic groups, especially bipolar disorder and major depression. Again, by the strong definition outlined above, the right insula hypoactivation would be transdiagnostic, but the left prefrontal hypoactivation would not.

As another example in the literature, Janiri et al. (3) examined converging task-related functional MRI activation deficits across a range of cognitive, social, and emotion tasks in major depression, bipolar disorder, posttraumatic stress disorder, and other anxiety disorders. They separately examined hypo- and hyperactivation and found three regions with converging hypoactivation (prefrontal/insula, inferior parietal, and putamen). The prefrontal and parietal regions showed no significant differences across diagnostic categories, while the putamen did, with the majority of the effect being accounted for by bipolar disorder (72.17%). They go on to suggest that all three regions showed transdiagnostic effects, but one might argue that the putamen effect was instead more specific to bipolar disorder. In work on functional connectivity, Ma et al. (4) demonstrated reduced modularity in schizophrenia, bipolar disorder, and major depression, with each group showing a significant difference from control subjects, a finding that they described as transdiagnostic and which fits the strong definition outlined above. At the same time, Ma et al. also found deficits more specific to schizophrenia, which they interpret as disorder specific. Strong distinctions between features that are transdiagnostic and those that are disorder specific are critical, as they will inform our search for general risk factors as distinct from those mechanisms that interact with transdiagnostic features to shape differential expression of psychopathology.

Analogous issues arise in a different type of transdiagnosis approach, such as examining whether a particular symptom or behavior dimension relates to a particular neurobiological factor “transdiagnostically.” Similar to the argument for diagnostic categories, strong claims about transdiagnostic relationships would seem to require demonstrating that

such dimensional relationships hold within diagnostic categories as well as across diagnostic categories, or at least that the dimensional relationships do not differ across diagnostic groups (e.g., no interactions with group). For example, Sharma et al. (10) examined the relationship between anhedonia (reduced reward responsivity) as measured by the Behavioral Activation Scale and resting-state functional connectivity across major depression, bipolar disorder, schizophrenia, and psychosis risk. In a pooled analysis of all participants, they found that reduced reward responsivity was associated with altered connectivity involving the nucleus accumbens, the default mode network, and the cingulo-opercular network. Critically, they then examined these relationships within each disorder and found that the same pattern held across diagnostic categories, although the statistical significance was not clear. Given the similarity across groups, it seems well justified to describe this finding as transdiagnostic, as the authors do (see also Kebets et al. [8] for a similar approach with connectivity). Sheffield et al. (9) examined relationships between general cognition function in relation to the global efficiency of the cingulo-opercular network in a sample of individuals with bipolar disorder, schizophrenia, and schizoaffective disorder and healthy control subjects. They found that the relationships did differ significantly across groups, with a significantly weaker relationship in the control group, but no significant differences across patient groups. This result is also transdiagnostic, although Sheffield et al. should have also examined the significance of the relationship *within* each group as well demonstrating no significant differences across patient groups.

Another key issue in identifying transdiagnostic impairments or relationships is consideration of the similarity or differences in the directionality of effects across diagnostic groups. Neural alterations can take different forms, such as increased or decreased activation, increased or decreased connectivity, or even more or less gray matter volume. Finding that alterations across diagnostic categories converge on the same region regardless of directionality is important and helps in identifying common circuits relevant to understanding psychopathology as a whole. However, the specific form of such alterations is critical in terms of understanding mechanisms and potential treatments, and thus must be taken into consideration when defining something as transdiagnostic. In the article in this issue, McTeague et al. start with analyses that combined hypo- and hyperactivation differences, and then split by the direction of the difference. When directionality is examined, the selectivity of the left amygdala hyperactivation to nonpsychotic disorders is even clearer (see Figure 4, Figure S14). Furthermore, the deficit in the dorsomedial thalamus shows quite different patterns in psychotic disorders (specifically schizophrenia) and nonpsychotic disorders (anxiety and depression), but hypoactivation in the former and hyperactivation in the latter (see Figure 4, Figure S14). For the thalamus, both patterns converge on this nucleus with projections to the prefrontal

cortex, but the differential directions suggest important differences in the mechanisms that are likely contributing to such impairments. McTeague et al. provide some discussion of these differences in direction, but overall the findings are described as providing evidence of convergence across disorders, potentially missing an opportunity to highlight the likelihood that differential mechanisms may be contributing across forms of psychopathology.

Showing that deficits are present within each disorder, or that a relationship with a dimension of behavior or psychopathology relates within as well as across disorders, is certainly a high bar for defining a transdiagnostic conclusion. Such a definition will be much more likely to be challenged by statistical power considerations and will require adequate sample sizes within as well as across diagnostic groups. In my own research, I have used this criterion much of the time, but not always, and will need to “up my game” accordingly. Strong and actionable claims about transdiagnostic impairments and transdiagnostic relations require such a definition. Further, this high bar is necessary if we are to shift our conception of the structure of psychopathology and put significant focus and effort into understanding transdiagnostic factors that may contribute to a broader risk for psychopathology. This research direction may engender novel and important new avenues for intervention and prevention that are much more widely applicable than more traditional disorder-specific approaches to treatment, but it will require a solid evidence base upon which to build.

AUTHOR AND ARTICLE INFORMATION

Departments of Psychological and Brain Sciences, Psychiatry, and Radiology, Washington University, St. Louis.

Send correspondence to Dr. Barch (dbarch@wustl.edu).

Dr. Barch has received support from NIH and NIMH.

Accepted March 3, 2020.

Am J Psychiatry 2020; 177:370–372; doi:10.1176/appi.ajp.2020.20030243

REFERENCES

1. Goodkind M, Eickhoff SB, Oathes DJ, et al: Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry* 2015; 72:305–315
2. McTeague LM, Huemer J, Carreon DM, et al: Identification of common neural circuit disruptions in cognitive control across psychiatric disorders. *Am J Psychiatry* 2017; 174:676–685
3. Janiri D, Moser DA, Doucet GE, et al: Shared neural phenotypes for mood and anxiety disorders: a meta-analysis of 226 task-related functional imaging studies. *JAMA Psychiatry* (Epub ahead of print, October 30, 2019)
4. Ma Q, Tang Y, Wang F, et al: Transdiagnostic dysfunctions in brain modules across patients with schizophrenia, bipolar disorder, and major depressive disorder: a connectome-based study. *Schizophr Bull* 2019; sbz111
5. McTeague LM, Rosenberg BM, Lopez JW, et al: Identification of common neural circuit disruptions in emotional processing across psychiatric disorders. *Am J Psychiatry* 2020; 177:411–421
6. McTeague LM, Goodkind MS, Etkin A: Transdiagnostic impairment of cognitive control in mental illness. *J Psychiatr Res* 2016; 83:37–46
7. Goschke T: Dysfunctions of decision-making and cognitive control as transdiagnostic mechanisms of mental disorders: advances, gaps, and needs in current research. *Int J Methods Psychiatr Res* 2014; 23(suppl 1):41–57
8. Kebets V, Holmes AJ, Orban C, et al: Somatosensory-motor dysconnectivity spans multiple transdiagnostic dimensions of psychopathology. *Biol Psychiatry* 2019; 86:779–791
9. Sheffield JM, Kandala S, Tamminga CA, et al: Transdiagnostic associations between functional brain network integrity and cognition. *JAMA Psychiatry* 2017; 74:605–613
10. Sharma A, Wolf DH, Ciric R, et al: Common dimensional reward deficits across mood and psychotic disorders: a connectome-wide association study. *Am J Psychiatry* 2017; 174:657–666
11. Caspi A, Moffitt TE: All for one and one for all: mental disorders in one dimension. *Am J Psychiatry* 2018; 175:831–844
12. Caspi A, Houts RM, Belsky DW, et al: The p factor: one general psychopathology factor in the structure of psychiatric disorders? *Clin Psychol Sci* 2014; 2:119–137
13. Michelini G, Barch DM, Tian Y, et al: Delineating and validating higher-order dimensions of psychopathology in the Adolescent Brain Cognitive Development (ABCD) study. *Transl Psychiatry* 2019; 9:261
14. Kotov R, Krueger RF, Watson D, et al: The Hierarchical Taxonomy of Psychopathology (HiTOP): a dimensional alternative to traditional nosologies. *J Abnorm Psychol* 2017; 126:454–477