Implications of the Hierarchical Structure of Psychopathology for Psychiatric Neuroimaging

Supplemental Information

Description of Internalizing and Externalizing Factors

Achenbach provided the original labeling of internalizing and externalizing to describe two second-order factors of psychopathology that arise in children and adolescents (1). The choice of labels was rooted in a theoretical model that emphasizes whether an individual's maladaptive symptoms are directed at others (such as antisocial behavior in externalizing) or one's self (such as anxiety or depression in internalizing). However, the labels are increasingly used atheoretically when applied to the empirically-derived, second-order factors of psychopathology. The second-order internalizing factor receives high loadings from first-order dimensions including major depressive disorder and dysthymia, and all anxiety disorders. By contrast, the second-order externalizing factor has heavy loadings from attention-deficit/hyperactivity disorder (ADHD), conduct disorder and oppositional defiant disorder, along with antisocial personality disorder/psychopathy and substance use disorders (with the precise composition depending upon the first-order domains or diagnoses being assessed, which varies between adults and children because of the age-dependent nature of these symptoms and diagnoses).

One way to understand the importance of these second-order factors is to consider the extent to which variance in the higher-order factor can explain variance in the first-order factors. Critically, the second-order factors of internalizing and externalizing disorders explain a substantial part of the variance in first-order dimensions of psychopathology (2-5). For instance, in the Tennessee Twin Study, the externalizing factor explained 68-82% of the variance in

attention problems, hyperactivity-impulsivity, oppositional defiant and conduct disorder problems in children and adolescents (4).

Alternate Models of Second-Order Factors

While the 2-factor internalizing-externalizing model has been repeatedly replicated and consistently explains a large proportion of phenotypic variance of prevalent forms of psychopathology (2-5), there are some variations in the precise second-order structure that emerges across studies. Krueger and Markon (6) conducted a meta-analytic FA on studies, covering a cumulative total of 23,000 adults, and observed that a 2-factor model with internalizing and externalizing factors fit the data adequately, but the best-fitting model was a 3-factor model with an externalizing factor, and a division of internalizing into separate distress and fear factors. The distress factor included major depressive disorder, generalized anxiety disorder and dysthymia, while the fears factor included specific phobia, social phobia (social anxiety disorder), and panic-agoraphobia. Figure 2A in the body of the paper shows a similar 3-factor solution in the nationally representative NESARC sample of adults (7, 8).

Some studies suggest that the externalizing factor also can be divided into two factors, one involving ADHD and oppositional defiant disorder and a separate factor of substance use disorders (9, 10). However, the most consistent model has not been fully established, particularly in terms of the loading of antisocial/conduct symptoms, which likely reflects differences in the samples and the particular symptom domains studied, especially when contrasting studies of children vs. adults.

An additional distinct, but important, second-order factor reflecting psychotic experiences has been demonstrated in analyses that include less prevalent forms of

psychopathology (11). While not measured in most of the above-mentioned studies, the dimension clearly warrants attention in any attempt to comprehensively understand the substrates of the full structure of psychopathology. We note that although the optimal number and nature of second-order factors of psychopathology has not yet been settled, this issue does not necessarily need to be resolved in order to apply second-order factor scores as variables of interest in neurobehavioral research.

Methodological Questions Regarding the General Factor

Since our initial demonstration that a general factor can be observed in studies of the structure of psychopathology (8), there have been multiple replications and extensions of this finding in children, adolescents and adults (12-17). Effects have been seen using both dimensional data and categorical diagnoses. Bonifay, Lane and Reise (18) recently raised some potential concerns to applying bifactor models that warrant consideration. In particular, it is possible that bifactor models overfit the data in a way that biases them to fit better than a correlated (oblique) factors model under some circumstances. More work is needed to understand and address such issues, but as Bonifay et al. noted, and we (19) have previously noted, the critical issue is less about small differences in statistical fit than *scientific utility*. That is, the general factor of psychopathology will only be a useful construct if it possesses unique external correlates that are important (e.g., improves prediction of future mental health outcomes) and/or makes it easier to identify the nonspecific and specific etiologies and psychobiological mechanisms of psychopathology. The general factor has already been shown to preferentially correlate with specific risk factors and behavioral variables (19, 20), but far more remains to be learned.

A second issue is interpretational: essentially, what is the meaning of the orthogonal externalizing and internalizing (or fears and distress) factors once they have had all their shared variance removed? These orthogonal factors are critically different from the correlated oblique internalizing and externalizing factors that have traditionally been studied. Statistically, we may assume that they will have greater specificity (as they explain a narrower slice of the variance once the common variance is accounted for). However, that does not necessarily clarify how to conceptualize or interpret the orthogonal factors relative to the existing body of research.

The Neurobiology of Orthogonal Second-Order Factors

The potential differences in conceptualizing the orthogonal second-order externalizing and internalizing factors in the bifactor model from the broader versions of these factors in a correlated oblique model have specific implications for understanding the neurobiological substrates of psychopathology. Unfortunately, almost all of the existing data regarding neurophysiological correlates of internalizing and externalizing factors have been derived from studies that either did not measure other second-order dimensions beyond their target internalizing or externalizing dimension, or did not include a general factor.

Shanmugan et al. (21) provides a notable exception. The authors performed a bifactor analysis on data from the GOASSESS screening interview (22), which in addition to the general factor, produced four orthogonal factors that they labelled behavioral (which corresponds to the externalizing factor), anxious-misery (corresponding to the distress factor), fears, and psychosis. While the general factor was associated with hypoactivations in multiple brain regions during the study's working memory task, analysis of the four second-order orthogonal factors showed differential patterns of associations that were distinct from those arising in relation to the general

factor. This was particularly true for the behavioral and anxious-misery factors which showed broad associations with BOLD activity beyond those seen for the general factor. Specifically, the behavioral factor was associated with hypoactivations in a frontoparietal network, as well as hypoactivations in the cerebellum, thalamus and left anterior insula. These data indicate that there is a pattern of hypoactivation related to this factor that is specific to the behavioral (externalizing) domain in youth and is not simply a reflection of general psychopathology. In contrast to the general factor and the behavioral factor, the anxious-misery factor was associated with hyperactivation within multiple frontal regions, the dorsal anterior cingulate cortex and the anterior insula. It may be speculated that these specific anxious-misery hyperactivations would have been obscured by the nonspecific patterns of hypoactivation associated with the general factor, if the general factor were not accounted for in the analyses.

It is worth noting that in the Shanmugan study, the psychosis and fears factors showed only restricted patterns of association. The paucity of specific associations to psychosis and fears factors may relate to several features of the study, including the subject population (which had relatively low levels of thought disorder symptoms), or the task (which may not be particularly relevant to symptoms of phobia), but they make clear that at least in this large study, the pattern of associations was far greater at a nonspecific level. These data suggest that if either a first-order dimension (or diagnostic category). or even a second-order dimension, was studied in isolation without consideration of a general factor, any observed hypoactivations would have been misattributed as reflecting a more specific level than is accurate.

Network Models and Etiological Heterogeneity Within a Hierarchical Approach

The idea that different psychobiological mechanisms act at different levels of the symptom hierarchy may also be considered in relation to recent developments in the network science of psychopathology (23, 24). In a network, a perturbation in any of multiple connected nodes can spread to proximal nodes within a community, with the level of spreading determined by the strength of connections between nodes. This suggests that there may be an interchangeability of starting nodes within a narrow or first-order symptom dimension, which may make it difficult to disentangle etiologies or neural substrates of closely related symptoms at the lower levels of the symptom hierarchy. Graph theory network characterization also suggests that some symptoms may be particularly important for linking different symptom communities. By extension, this suggests that some neural mechanism may be uniquely important for understanding cases with broad symptom pictures. For instance, convergent with prior research (25), network analysis of externalizing symptoms suggests the importance of impulsivity as linking different symptoms communities (26). As such, research on the neural correlates of impulsivity may be particularly informative as a guide for where to look for one of the higher-order mechanisms. The convergence of findings regarding the anterior cingulate's role in cognitive control (or lack thereof) (27, 28), and its emergence in neuroimaging studies across a range of psychopathology (21, 29-31) is at a minimum consistent with this perspective.

Multi-diagnosis Case-control Designs

An alternative approach for dealing with the hierarchical nature of psychology involves simultaneously studying individuals with different diagnoses and matched controls in the same study. This may be described as a multi-diagnosis case-control design in that it still uses a case-

control methodology, but allows for greater heterogeneity of the diagnostic groups. The advantage of this design is that it avoids some of the methodological confounds that can compromise the interpretation of cross-study comparisons in meta-analytic or systematic review approaches. It may be noted that there has been a tradition of including a secondary patient group in certain domains of psychopathology research, including neuroimaging studies. However, the goal of including the second diagnostic groups was typically to rule out potential general effects, rather than to identify them. Far fewer studies have used a multi-diagnoses case-control design to explicitly identify the neural correlates of higher-order factors. Bjork et al. (32) report a rare example of this sort of multi-diagnosis case-control study in which they had adolescents with different externalizing disorders perform a monetary incentive delay task. Cases with any externalizing disorder showed significantly elevated ventral striatal activation during reward notification. However, conclusions are tempered by an extremely small sample size (n =12 cases and 12 matched controls), and studies with far larger sample sizes will be necessary if such designs are to address the relative magnitude of correlates at different levels of a symptom hierarchy.

The multi-diagnoses case-control design can also be applied restricting the types of cases to a single 2nd order domain. However, given the correlational structure of 2nd order domains, it may prove useful to include diagnostic groups from multiple 2nd order dimensions. Hägele et al. (33) provide an example of this type of multi-diagnoses case-control study in adults. They observed a modest, but statistically significant, transdiagnostic correlation of dimensional self-report measures of anxiety and depression with reward anticipation BOLD responses in the right ventral striatum across a sample that included both controls and cases with alcohol dependence, major depressive disorder, bipolar disorder and ADHD. This sort of multi-diagnoses case-control

approach can also be applied retrospectively to pre-existing data if the same neuroimaging and assessment measures have been used across originally independent (single) case control studies. Unfortunately, the frequent use of slightly different variants of tasks or imaging parameters may provide a confound in implementing such analyses across existing data sets. To maximize these possibilities, researchers should be urged to adopt protocols that optimize the future harmonization of data, even when they are only focused on a single disorder.

Arguably, even in case-control studies with a single diagnostic group, the inclusion of measures tapping transdiagnostic features can allow for assessment and statistical control of key transdiagnostic dimensions or functional constructs. However, we note that when these measures are correlated with the expression of the diagnosis, it may be difficult, if not impossible, to dissociate the diagnosis from the transdiagnostic characteristics of interest. For instance, if we only have healthy controls and patients with social anxiety disorder, we will expect there to be a high correlation between a trait measure of negative affect and the diagnosis of social anxiety disorder. If these correlations are high enough (which is not unrealistic to expect), we will not be able to see different patterns of associations between diagnosis and our transdiagnostic measure. As a consequence, we will not be able to determine whether the diagnosis or the negative affect construct drove observed effects. We have a far greater ability to dissociate transdiagnostic features from diagnostic group membership when there are individuals who are not in the target group who nevertheless possess high levels of the transdiagnostic feature. In our current example, inclusion of patients with major depressive disorder would result in participants with high negative affect but not the diagnosis of social anxiety disorder, thus lowering the correlation between the social anxiety disorder diagnosis and negative affect in the sample as a whole. As a consequence, the multi-diagnosis case-control design shows substantial advantages over

traditional single-diagnosis case-control designs (although it nevertheless retains some of the already noted limitations of these traditional case-control designs, such as the use of unrepresentative samples).

Supplemental References

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