Uncovering Potential Mechanisms of the Relationship Between Structural Deficits and General Psychopathology

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The psychopathology factor (p factor) has reconceptualized the way we think about the organization of psychopathology. The classification of psychopathology has undergone substantial advancement with the use of hierarchical modeling, which defines an overarching general factor representing the symptoms that are common or shared across all disorders, as well as subfactors for specific types of symptoms (1–3). Hierarchical modeling of psychopathology symptoms represents an important advance over the traditional case-control approach that was previously ubiquitous throughout the field. In contrast to traditional diagnostic categories, hierarchical modeling embraces comorbidity, includes symptom severity spanning the continuum from health to disorder, captures the dimensional nature of the data, and has the potential to assess the full spectrum of mental health symptoms. Case-control studies that exclude cases based on comorbidity to achieve “pure” samples result in prototypical cases that are not generalizable. In addition, using clinical thresholds to retain patients at the extreme ends of the spectrum leads to ascertainment bias (2). The dimensional nature of factors obtained through hierarchical modeling is more consistent with the actual presentation of mental health symptoms in the general population.

In recent years, there has been a surge in studies examining the neurobiological correlates of the p factor. In the current issue of Biological Psychiatry: Global Open Science, Romer and Pizzagalli (4) link structural alterations associated with the p factor to executive functioning. In particular, they test the hypothesis that individual differences in executive functioning may explain the relationship between structural deficits and higher scores on general psychopathology. Participants included 130 healthy control subjects who did not meet the criteria for any DSM diagnosis and 142 patients who met the criteria for schizophrenia, bipolar I disorder, or attention-deficit/hyperactivity disorder. Romer and Pizzagalli (4) replicated their prior work showing that greater psychopathology symptoms were associated with reduced gray matter volume in the visual association cortex, but they did not replicate this association in the cerebellum-thalamo-cerebro-cortical circuit. A whole-brain analysis revealed that greater general p factor scores were related to decreased fractional anisotropy in the genu of the corpus callosum, among other areas. The authors then demonstrated that higher p factor scores were linked to executive functioning deficits measured with a general factor of executive functioning based on performance across 13 tests of working memory, shifting, and inhibition. The authors tested two indirect path models focusing on the two regions with relationships with both the p factor and executive functioning. Specifically, they tested the paths of 1) visual association cortex gray matter volume → executive functioning → psychopathology and 2) genu of the corpus callosum fractional anisotropy → executive functioning → psychopathology and found both indirect paths to be significant. The authors concluded that executive functioning may be one mechanism that contributes to the relationship between the p factor and structural deficits (4).

These findings invite the following questions: What are the causal mechanisms that underlie the p factor? Does the p factor reflect executive functioning deficits or something else? Now that several studies have demonstrated an association between structural deficits and general psychopathology, there are increasing efforts on the part of researchers to show what is “causing” these relationships. For example, is it the case that structural deficits lead to greater executive functioning deficits, and this in turn leads to greater general psychopathology? Uncovering such causal mechanisms is central to understanding what the p factor reflects—otherwise it remains a statistical byproduct devoid of meaning. Some suggest that the p factor simply reflects global impairment across otherwise unrelated symptoms, whereas others posit specific hypotheses about the meaning of the p factor. This commentary will focus on 5 potential processes that may underlie the p factor and drive the relationship between structural deficits and general psychopathology. As shown in Figure 1, the mechanisms underlying the p factor are likely multifaceted, which each accounting for only a small part of the variance. There is also likely to be substantial overlap in the implicated brain regions, as many processes will rely on the same neural systems.

Romer and Pizzagalli (4) suggest that the p factor may partly reflect impairment in executive functioning. Executive functioning deficits could be an important contributing factor underlying the relationship between smaller gray matter volume and greater psychopathology. But as seen in their results, only a small amount of the variance is accounted for by executive functioning. Other work shows that those with higher levels of general psychopathology not only fair poorly on measures of executive function such as attention, working memory, inhibition, and flexible thinking, but also perform worse on tasks of processing speed and visual motor coordination, as well as showing lower overall IQ (1). This suggests that the first
potential mechanism may point to broad deficits in cognitive reserve (5) rather than being specific to executive functioning.

Another potential mechanism for the association of greater structural abnormalities with higher p factor scores is emotion dysregulation. Specifically, Carver et al. (6) posit that emotional impulsivity, or being highly reactive to emotions, may be central to general psychopathology. The premise here is that behavior is governed by two competing systems: an associative system and a deliberative system. While the deliberative system takes information into account before deciding on a course of action, the associative system is thought to be reflexive and quick. The associative system is what gives rise to impulsive responsiveness to emotions (6). Evidence in support of this hypothesis comes from a study showing that both general psychopathology and a dysregulation profile suggest that emotional dysregulation is central to the general vulnerability for psychopathology (7). Thus, a key mechanism for brain–behavior relationships may be that structural deficits lead to greater psychopathology symptoms across a broad range of disorders. Importantly, both executive functioning and emotion regulation processes may rely on similar neural systems, suggesting that these processes may be overlapping rather than independent from each other.

Negative emotionality has also been proposed to underlie the p factor. Negative emotionality refers to the tendency to experience and react with negative emotions and is common across many psychological disorders. Research suggests there is a high degree of overlap between negative emotionality, or neuroticism, and general psychopathology. For example, in a large cross-sectional twin study, negative emotionality was shown to be highly correlated with the general factor of psychopathology (6). However, this study did not measure negative emotionality using a broadband measure. A more recent study of 695 preadolescent children revealed that the general factor of neuroticism showed substantial overlap with the p factor (9), supporting the association between negative emotionality and general psychopathology. In terms of brain–behavior relationships, perhaps abnormal structural development influences key structures for the processing of negative emotions, which then increases the risk of developing psychopathology symptoms.

An additional hypothesized mechanism underlying the p factor is thought dysfunction. Proposed by Caspi and Moffitt (5), the idea is that disordered form and content of thought underlies many psychological disorders, from rumination in depression to delusions in psychosis. Specifically, Caspi and Moffitt (5) define disordered thought processes as those that are illogical, unfiltered, tangential, reality-distorted, and reality-distorting cognitions. They suggest that disordered thought is a core functional mechanism underlying the p factor. There is some evidence to support this. In addition to internalizing and externalizing symptoms, thought disorder is frequently found to be a subfactor in hierarchical models of psychopathology and in some samples, the thought disorder factor has shown the strongest correlations with the p factor (1). Thus, it is possible that structural brain deficits may lead to impairments in thought processes, which in turn may manifest as different types of psychopathology.

These four potential mechanisms for explaining the relationship between structural differences and psychopathology have been outlined in prior work (5). To this we can add a fifth potential mechanism: deficits in reward/punishment sensitivity. Individuals vary in their sensitivity to reward and punishment. Reward sensitivity, or the degree to which behavior is motivated by rewarding stimuli, is thought to be regulated by the behavioral activation system. Conversely, punishment sensitivity involves a behavioral pattern that is characterized by using risk assessment to avoid negative outcomes and is regulated by the behavioral inhibition system. Alterations in reward and punishment sensitivity have been implicated in many psychological disorders. There is emerging evidence for the role of reward sensitivity in explaining brain–behavior relationships. For example, Sharma et al. (10) examined reward responsiveness in a transdiagnostic sample consisting of those with depression, bipolar disorder, schizophrenia, and/or psychosis risk, as well as healthy control subjects (10). They found that reduced reward responsivity across diagnoses was associated with decreased functional connectivity between the nucleus accumbens and both the default mode network and the cingulo-opercular network (10). Thus, altered reward processing may represent another potential mechanism underlying the p factor. However, while this study was transdiagnostic, it did not model the general factor of psychopathology or examine brain structure, suggesting areas for future work.

Taken together, there are several promising constructs to test as possible mechanistic pathways that may clarify the link between neural deficits and general psychopathology. Brain–behavior relationships likely involve multiple
mechanisms interacting in complex ways, representing exciting avenues for future work.

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