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Neurobehavioral Aspects of Multidimensional Psychopathology

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Despite the many ways modern psychiatric classification systems have advanced since DSM-III was introduced in 1980, the etiology and biological basis of most disorders remains unknown. This is no doubt due in part to the fact that there is little reason to expect that expert opinion regarding disorder definition, uninformed by biology, will necessarily lead to biological insights. It is also due in part to the fact that disorder comorbidity is the rule rather than the exception (1), a phenomenon that complicates success if the goal is to identify biological factors that contribute uniquely to only one disorder. This lack of progress has led to interest in alternative approaches to characterize the structure of psychiatric disorders.

An alternative approach that has met with considerable success involves developing empirically derived, symptom-based dimensions that capture the phenotypic covariance shared across commonly comorbid disorders (2, 3). One such prominent dimension captures the covariance among disorders that fall into the externalizing spectrum, which includes childhood disruptive disorders like attention deficit hyperactivity disorder (ADHD) and conduct disorder (CD), as well as antisocial personality disorder and substance use disorders (4-6). Past research with genetically related individuals has shown that the covariance among these disorders is captured by a highly heritable latent externalizing trait that is passed on from parent to child (7-9). The latent trait is hypothesized to reflect an underlying biological vulnerability to behavioral disinhibition predisposing individuals to develop one or more of the facet disorders comprising the externalizing spectrum (10). Specific genetic and environmental influences determine how many and which facets of externalizing develop in any given person. While these genetically informed studies point to the likely importance of biological mechanisms, the nature of any underlying pathophysiology shared across disorders or specific to just one is unspecified. The international IMAGEN Consortium report by Castellanos-Ryan et al. (11) in this issue takes an important step to fill this knowledge gap. Their work represents a monumental undertaking to examine how measures of personality, neuropsychological performance, and brain function yield neurobehavioral configurations that differentiate externalizing vulnerability from its facet disorders and the facet disorders from each other.

Consistent with expectations from past research, a hierarchical model comprising a latent externalizing factor and two component facets, capturing childhood disruptive behavior and substance use, best characterized the covariance among externalizing behaviors. What is

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new are findings that a constellation of cognitive ability, neuropsychological performance, personality trait, and fMRI BOLD response measures was differentially associated with the three aspects of the model. Delay discounting deficits, reflecting sensitivity to short term rewards, were found for all three model components. The externalizing factor, which captures the phenotypic commonality across all the externalizing symptoms, was characterized by impulsive decision making and brain dysfunction associated with disinhibition. This profile may thus characterize the biological core underlying the genetic predisposition for externalizing. Substance use, largely defined by alcohol misuse, could be differentiated from this factor and the childhood disruptive symptom facet through association with high sensation seeking and deviant frontal brain activation in anticipation of reward, which together are suggestive of a deficit in reward processing. The childhood disruptive facet, defined primarily by symptoms of ADHD and CD, was uniquely associated with low intelligence, go/no-go task commission errors, and weak brain activation in the frontal cortex. In addition, impulsive action and choice was associated with this facet, producing a combination pointing to poor frontal executive control. These two distinct profiles for the substance use and childhood disruptive facets indicate what neurobehavioral factors, in addition to those associated with the general predisposition to externalizing, may be important to the differential development of each facet. Here we have the strongest biological evidence provided to date attesting to the construct validity of an empirically derived, multifaceted dimensional model that has already received considerable support from over a decade of twin, family, and adoption research. In addition, Castellanos-Ryan et al. build on existing psychophysiological endophenotype research which has been able to document biological commonality across all externalizing disorders (12) but has provided little insight into the possible pathophysiological processes unique to each.

Strengths of this study are many. With a general population sample of 1778 European adolescents, it is one of the largest neuroimaging investigations ever undertaken, important for an area of research that has been criticized for false discoveries emanating from small sample studies (13). Establishing valid associations between behavioral and neural measures is challenging because, as the Castellanos-Ryan et al. supplementary tables illustrate, and as has been noted previously (3), effect sizes can be expected to be small. Without a sample of this magnitude, it would have been difficult to provide an adequate test of the relevance of the measures examined to the components of the hierarchical model they evaluated. Girls, who are typically underrepresented in studies of externalizing behavior, comprised slightly over half the sample. Resource-demanding brain measures, such as those derived from the two MRI sessions each subject completed in this study, are to be valued because they are so difficult to obtain. Participants were seen at the key age of 14, old enough to evidence externalizing behaviors, but young enough to be largely unaffected by the consequences of manifest disorder and significant substance abuse. These youths thus provide a glimpse of premorbid pathophysiological vulnerability.

The investigation is longitudinal, and includes an age-16 follow-up assessment documenting that externalizing behaviors show developmental continuity during a maturational period characterized by pronounced increase in social deviancy. Because the project is ongoing, we can look forward to extensions of the current study as these teenagers grow older, passing through the age of risk for the development of externalizing spectrum disorders, providing

opportunity to examine how effects strengthen and change as manifest psychiatric disorder and substance abuse emerge.

Relying on traditional granting mechanisms, with their budget and funding period constraints, this project would never have been launched due to the great expense of executing a longitudinal study with extensive behavioral and complicated neurocognitive assessments carried out on thousands of individuals. The IMAGEN consortium, collecting harmonized data across eight sites, highlights the payoff to be garnered from such efforts, hopefully encouraging the formation of more large-scale multi-site collaborations.

Although this study is guided by a reasonable set of hypotheses, the IMAGEN project has many elements, and many decisions were made to structure this study, process the data, and analyze the variables selected for this report. In addition, despite the several interesting results that were obtained, some predicted effects were not evident, and the exact pattern of obtained findings would be difficult to predict *a priori*. To a certain extent, this study is discovery based, and like other discovery-based projects involving complicated data sets, follow-up confirmation of the findings will be required. To facilitate molecular genetic investigation, the multi-national European sample was deliberately selected to achieve ethnic homogeneity, leaving unanswered how generalizable the results might be to other ethnicities and cultures.

This ground breaking report falls short of uncovering the neural basis of externalizing. However, it represents an important initial step toward achieving this goal, and provides a heuristic for how we can supplement research with DSM/ICD to carve the nature of psychopathology at its biological joints.

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References

1. Vaidyanathan U, Patrick CJ, Iacono WG. Patterns of comorbidity among mental disorders: a person-centered approach. Compr Psychiatry. 2011; 52(5):527–35. [PubMed: 21111407]
2. Haslam N, Holland E, Kuppens P. Categories versus dimensions in personality and psychopathology: a quantitative review of taxometric research. Psychol Med. 2012; 42(5):903–20. [PubMed: 21939592]
3. Patrick CJ, Venables NC, Hicks BM, Nelson LD, Kramer MD. A construct-network approach to bridging diagnostic and physiological domains: Application to assessment of externalizing psychopathology. J Abnorm Psychol. 2013; 122(3):902–16. [PubMed: 24016026]
4. Krueger RF, Hicks BM, Patrick CJ, Carlson SR, Iacono WG, McGue M. Etiologic connections among substance dependence, antisocial behavior, and personality: modeling the externalizing spectrum. J Abnorm Psychol. 2002; 111(3):411–24. [PubMed: 12150417]
5. Kendler KS, Prescott CA, Myers J, Neale MC. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. Arch Gen Psychiatry. 2003; 60(9):929–37. [PubMed: 12963675]
6. Young SE, Stallings MC, Corley RP, Krauter KS, Hewitt JK. Genetic and environmental influences on behavioral disinhibition. Am J Med Genet. 2000; 96(5):684–95. [PubMed: 11054778]

7. Hicks BM, Foster KT, Iacono WG, McGue M. Genetic and environmental influences on the familial transmission of externalizing disorders in adoptive and twin offspring. JAMA psychiatry. 2013; 70(10):1076–83. [PubMed: 23965950]

8. Hicks BM, Krueger RF, Iacono WG, McGue M, Patrick CJ. Family transmission and heritability of externalizing disorders: a twin-family study. Arch Gen Psychiatry. 2004; 61(9):922. [PubMed: 15351771]

9. Bornovalova MA, Hicks BM, Iacono WG, McGue M. Familial transmission and heritability of childhood disruptive disorders. Am J Psychiatry. 2010; 167(9):1066–74. [PubMed: 20634367]

10. Iacono WG, Malone SM, McGue M. Behavioral disinhibition and the development of early-onset addiction: common and specific influences. Annu Rev Clin Psychol. 2008; 4:325–48. [PubMed: 18370620]

11. Castellanos-Ryan N, Struve M, Whelan R, Banaschewski T, Barker GJ, Bokde AL, et al. Neural and Cognitive Correlates of the Common and Specific Variance Across Externalizing Problems in Young Adolescence. Am J Psychiatry. 2014

12. Iacono WG, Malone SM, McGue M. Substance use disorders, externalizing psychopathology, and P300 event-related potential amplitude. Int J Psychophysiol. 2003; 48(2):147–78. [PubMed: 12763572]

13. Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, et al. Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci. 2013; 14(5):365–76. [PubMed: 23571845]