Patterns of Heterotypic Continuity Associated With the Cross-Sectional Correlational Structure of Prevalent Mental Disorders in Adults

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**IMPORTANCE** Mental disorders predict future occurrences of both the same disorder (homotypic continuity) and other disorders (heterotypic continuity). Heterotypic continuity is inconsistent with a view of mental disorders as fixed entities. In contrast, hierarchical-dimensional conceptualizations of psychopathology, in which each form of psychopathology is hypothesized to have both unique and broadly shared etiologies and mechanisms, predict both homotypic and heterotypic continuity.

**OBJECTIVE** To test predictions derived from a hierarchical-dimensional model of psychopathology that (1) heterotypic continuity is widespread, even controlling for homotypic continuity, and that (2) the relative magnitudes of heterotypic continuities recapitulate the relative magnitudes of cross-sectional correlations among diagnoses at baseline.

**DESIGN, SETTING, AND PARTICIPANTS** Ten prevalent diagnoses were assessed in the same person twice (ie, in 2 waves separated by 3 years). We used a representative sample of adults in the United States (ie, 28 958 participants 18-64 years of age in the National Epidemiologic Study of Alcohol and Related Conditions who were assessed in both waves).

**MAIN OUTCOMES AND MEASURES** Diagnoses from reliable and valid structured interviews.

**RESULTS** Adjusting for sex and age, we found that bivariate associations of all pairs of diagnoses from wave 1 to wave 2 exceeded chance levels ($P < .05$) for all homotypic (median tetrachoric correlation of $\rho = 0.54$ [range, 0.41-0.79]) and for nearly all heterotypic continuities (median tetrachoric correlation of $\rho = 0.28$ [range, 0.07-0.50]). Significant heterotypic continuity was widespread even when all wave 1 diagnoses (including the same diagnosis) were simultaneous predictors of each wave 2 diagnosis. The rank correlation between age- and sex-adjusted tetrachoric correlation for cross-sectional associations among wave 1 diagnoses and for heterotypic associations from wave 1 to wave 2 diagnoses was $\rho = 0.86$ ($P < .001$).

**CONCLUSIONS AND RELEVANCE** For these prevalent mental disorders, heterotypic continuity was nearly universal and not an artifact of failure to control for homotypic continuity. Furthermore, the relative magnitudes of heterotypic continuity closely mirrored the relative magnitudes of cross-sectional associations among these disorders, consistent with the hypothesis that both sets of associations reflect the same factors. Mental disorders are not fixed and independent entities. Rather, each diagnosis is robustly related to other diagnoses in a correlational structure that is manifested both concurrently and in patterns of heterotypic continuity across time.

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n developmental studies of both adaptive and maladaptive behavior, 2 types of continuity in behavior over time are distinguished. When a behavior predicts itself at a later time in the same individual, the term homotypic continuity is used; in contrast, heterotypic continuity applies when a behavior predicts a different form of behavior in the same individual at a later time.1,2 In the present study, we use the concepts of homotypic and heterotypic continuity to interrogate the basic nature of psychopathology during adulthood. If heterotypic continuity among diagnoses of mental disorders is common, then that would further disconfirm the increasingly untenable view of mental disorders as fixed and independent entities.3 Rather, widespread heterotypic continuity would argue for a reconceptualization of psychopathology as phenomena that are subject to “changing manifestations”4 and "phenotypic plasticity.”5

Previous studies have documented both homotypic6-11 and heterotypic continuity12-19 in common forms of psychopathology during childhood and adolescence. There has been little study of heterotypic continuity of mental disorders during adulthood, however.7,20 This is an important omission because it is possible that heterotypic continuity is limited to periods when developmental changes are rapid.21 Therefore, we assess heterotypic continuity in a longitudinal study of a representative cohort of adults. Our first goal is to determine if heterotypic continuity is an artifact of homotypic continuity. In these analyses, heterotypic continuity will be demonstrated only when disorder X at time 1 (X1) predicts disorder Y at time 2 (Y2) when disorder Y at time 1 (Y1) is controlled.11 These analyses ensure that X1 does not predict Y2 solely because X and Y are correlated at both time points.

Our second goal is to test a strong prediction derived from emerging hierarchical-dimensional models of psychopathology.5-22-27 Cross-sectional studies of correlations among mental disorders show that subgroups of disorders load on broad second-order factors of psychopathology defined by their patterns of correlations. Some studies modeled 2 second-order domains of psychopathology (internalizing and externalizing), whereas other studies divided the internalizing domain into correlated fears and distress subdomains.23,24,28,29 Twin studies indicate that the cross-sectional correlations among mental disorders reflect a hierarchical combination of both broadly shared and disorder-specific etiologic influences.25,30,31 This supports a hierarchical-dimensional conceptualization in which different forms of psychopathology are correlated with the extent to which they share etiologic influences.22-25 A number of direct and indirect ways in which sharing of etiologic influences could occur have been described by Krueger and Markon.22

Although hierarchical-dimensional models of psychopathology were derived from cross-sectional data,24-25 substantial homotypic continuity of second-order factors of psychopathology (internalizing and externalizing,26 or fears, distress, and externalizing27) has been documented during adulthood, including a report of homotypic continuity in the National Epidemiologic Study of Alcohol and Related Conditions (NESARC).34 These studies provide evidence of the homotypic stability of second-order domains of psychopathology during adulthood. In the present study, we examine the heterotypic continuity among specific disorders within and between second-order domains of psychopathology.

We derive a strong prediction regarding heterotypic continuity from our hierarchical-dimensional model of psychopathology to subject this model to possible refutation.35 We predict that the relative magnitudes of cross-sectional phenotypic associations among different mental disorders at time 1 will be duplicated in the relative magnitudes of heterotypic associations from time 1 to time 2. If the relative extent to which disorder X1 predicts Y2 closely mirrors the relative magnitude of their cross-sectional correlation at time 1 (X1 and Y1), this would be consistent with the hypothesis that the same shared propensities that give rise to correlations among multiple mental disorders at time 1 also underlie the heterotypic continuities between those disorders over time. That is, if X1 and Y1 are highly correlated at time 1 partly because they share etiologic influences, the same shared etiologic influences on diagnosis X1 at time 1 would be expected to increase the likelihood of diagnosis Y2 at time 2. Support for this hypothesis would be seen both in a significant rank-order correlation between cross-sectional and heterotypic correlations overall and in greater heterotypic continuity within than across second-order domains. Failure to confirm this prediction would require either substantial modification or rejection of the hierarchical-dimensional model.

Methods

Data on diagnoses are from the first and second wave of NESARC. In wave 1, structured diagnostic interviews were conducted with 43 093 adults representative of the noninstitutionalized civilian population of the United States. Participants gave written informed consent and were financially compensated, and the study received ethical review and approval from the US Census Bureau and the US Office of Management and Budget. One person per household was randomly selected, but adults 18 to 24 years of age were oversampled at a 2.25:1 ratio. African American and Hispanic households were oversampled, achieving 19.1% non-Hispanic African American and 19.3% Hispanic households. The sample was weighted in all analyses to adjust for probabilities of selection, nonresponse, the selection of one person per household, and oversampling. Once weighted, the data were representative of the US population.36 Participation was 81.0% in wave 1, and 3 years later, 34 653 (86.7%) of wave 1 participants were reinterviewed in wave 2. The present analyses were conducted on the 28 958 individuals who were 18 to 65 years of age in wave 1 and assessed in both waves.

Measures

The reliable37 and valid38-40 Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV37 was administered in person. The 12-month DSM-IV diagnostic categories used in these analyses are major depression, dysthymia, social phobia, specific phobia, generalized anxiety disorder, agoraphobia/panic disorder, antisocial personality disorder, to-
Bivariate cross-sectional tetrachoric correlations were first presented, followed by tetrachoric correlations. Models were estimated and tested in continuous variables. The residual correlation among the latent, they were specified in the model as being regressed on all desired adjustors; the residual correlation among the latent continuous variables is then interpreted as an adjusted tetrachoric correlation. The 2 hypotheses were tested using adjusted tetrachoric correlations. The magnitudes of the bivariate heterotypic correlations are substantially correlated with the relative magnitudes of bivariate cross-sectional correlations in wave 1 using the Spearman rank correlation.

Statistical Analyses

Data were analyzed at the US Census Bureau with the permission of the National Institute on Alcohol Abuse and Alcoholism. Because NESARC used complex probability sampling, all analyses were weighted proportionally to the inverse of sampling probability, adjusted for nonresponse, to accurately represent the population, and standard errors and tests accounted for the complex stratified and clustered sampling design. The 2 hypotheses were tested using adjusted tetrachoric correlations. Tetrachoric correlations adjusted for age in wave 1 and sex were estimated using linear structural equation models for binary data. In these models, a binary manifest variable is construed as a dichotomized version of a latent normal variable. For any pair of variables to be correlated, they were specified in the model as being regressed on all desired adjustors; the residual correlation among the latent continuous variables is then interpreted as an adjusted tetrachoric correlation. Models were estimated and tested in Mplus version 6.1. Bivariate correlations are first presented for cross-sectional associations in wave 1 and for homotypic continuities from wave 1 to wave 2 to aid interpretation of the analyses addressing 2 goals:

Goal 1 (heterotypic continuity, controlling for homotypic continuity) is to conduct a strict test of the existence of heterotypic continuity during adulthood. To do so, tetrachoric correlations between all wave 1 and wave 2 diagnoses were estimated pairwise, diagnosis by diagnosis, each time controlling the other 9 wave 1 diagnoses, including the same diagnoses in wave 1 as in wave 2, in addition to sex and age in wave 1.

The same diagnosis was included as a predictor to ensure that heterotypic predictions are not simply an artifact of the uncontrolled homotypic continuity of persistent disorders. The other 9 wave 1 diagnoses were included to estimate the unique heterotypic continuity of each diagnosis controlling for all other assessed diagnoses.

Goal 2 (correlation of cross-sectional and heterotypic associations) is to test the prediction that the relative magnitudes of bivariate heterotypic correlations are substantially correlated with the relative magnitudes of bivariate cross-sectional correlations in wave 1 using the Spearman rank correlation.

Results

To facilitate interpretation, the results displayed in Figures 1, 2, and 3 are grouped by the 3 second-order domains of fears, distress, and externalizing disorders identified in previous studies, including wave 1 of NESARC. Cross-sectional tetrachoric correlations among all pairs of the 10 diagnoses in wave 1, adjusted for age and sex (Figure 1), ranged from $p = 0.22$ to 0.75 (median, $p = 0.38$) (all $P < .001$). Figure 2 presents the bivariate homotypic and heterotypic tetrachoric correlations between all pairs of diagnoses from wave 1 to wave 2, adjusted for sex and wave 1 age. Correlations for homotypic continuities in Figure 2 were all significant at $P < .001$, ranging from moderate ($p = 0.41$ for specific phobia) to large ($p = 0.79$ for tobacco dependence). The magnitudes of the bivariate heterotypic continuities in Figure 2 ranged considerably from $p = 0.07$ (wave 1 alcohol dependence to wave 2 specific phobia) to $p = 0.50$ (wave 1 generalized anxiety disorder to wave 2 major depression). All bivariate heterotypic correlations were significant at $P < .05$, except for the prediction of wave 2 other substance dependence from wave 1 specific phobia.
Figure 2. Bivariate Tetrachoric Correlations (SE) for Prospective Homotypic and Heterotypic Continuities From Wave 1 Diagnoses to Wave 2 Diagnoses in NESARC, Adjusted for Sex and Age in Wave 1

Figure 3 presents the homotypic and heterotypic tetrachoric correlations among all pairs of diagnoses from wave 1 to wave 2, adjusted for sex, age in wave 1, and the 9 other wave 1 diagnoses. Even in these strict tests, significant heterotypic continuity was nearly universal within second-order domains. Each wave 1 diagnosis in the distress domain accounted for significant independent variance in the prediction of each of the other distress diagnoses in wave 2, and each wave 1 diagnosis in the fears domain independently predicted each of the other fears diagnoses in wave 2. Similarly, heterotypic continuity was universal in the externalizing domain, except wave 1 other substance dependence did not predict wave 2 tobacco dependence.

The results presented in Figure 3 also revealed less consistent but still widespread heterotypic continuities from diagnoses in 1 second-order domain to diagnoses across second-order domains, even when homotypic continuity and the heterotypic associations of all other wave 1 diagnoses were controlled for. There was a notable pattern to these cross-domain heterotypic continuities: The significant independent heterotypic associations more commonly involved distress diagnoses as either the predictor or as the predicted diagnosis. The 3 wave 1 distress diagnoses accounted for significant independent variance in the prediction of wave 2 fear diagnoses in 7 of 9 tests of association. Similarly, wave 1 fear diagnoses were found to independently predict wave 2 distress diagnoses in 6 of 9 tests, and wave 1 externalizing diagnoses predicted wave 2 distress diagnoses in 6 of 12 tests. In contrast, the wave 1 fear diagnoses only accounted for significant independent variance in wave 2 externalizing diagnoses in 2 of 12 tests.

Given this conservative evidence of widespread heterotypic continuity during adulthood, we tested the prediction derived from hierarchical-dimensional models of psychopathology that the varying magnitudes of bivariate heterotypic continuities from wave 1 to wave 2 will mirror the extents of cross-sectional correlations among the wave 1 disorders. Note that the heterotypic associations of diagnoses X and Y across waves generate 2 heterotypic correlations for each pair of disorders (X1 with Y2 and Y1 with X2), in contrast to the single cross-sectional correlation of X1 and Y1. The rank-order correlation of the cross-sectional tetrachoric correlations adjusted for age and sex for cross-sectional associations among wave 1 diagnoses with the heterotypic tetrachoric correlations adjusted for age and sex for predictions from wave 1 to wave 2 diagnoses was $\rho = 0.86$ ($P < .001$) (Figure 4).

Discussion

The present findings reveal widespread heterotypic continuity among mental disorders in a representative sample of adults. The tests of heterotypic continuity reported in Figure 3 were highly conservative, controlling not only for homotypic continuity but heterotypic continuity with every other wave 1 diagnosis. The results of these strict tests are important in 2 ways. First, they reveal that widespread heterotypic prediction of future diagnoses is not an artifact of uncontrolled homotypic continuity. Second, these tests reveal that each wave 2 diagnosis is independently predicted by multiple wave 1 diagnoses. Consider one example: Agoraphobia/panic disorder in wave 2 is not only significantly predicted by the same diagnosis in wave 1,
it also is independently predicted by 6 other wave 1 diagnoses, each of which explained from 1.0% to 3.6% of the residual variance in wave 2 agoraphobia/panic disorder, after controlling all other predictors. Thus, a network of multiple significant homotypic and heterotypic continuities allows agoraphobia/panic disorder in wave 2 to be predicted based on knowledge of all wave 1 diagnoses. To varying degrees, the same is true of all other wave 2 diagnoses.

The present findings also confirmed a key prediction derived from hierarchical-dimensional models of psychopathology. The relative magnitudes of heterotypic associations among different diagnoses from time 1 to time 2 clearly recapitulate the relative magnitudes of their cross-sectional associations at time 1. These findings are consistent with the hypothesis that the same shared etiologic factors that give rise to patterned correlations among multiple mental disorders at time 1 also give rise to heterotypic continuities over time.

We previously reported evidence based on cross-sectional twin data that phenotypic correlations among common dimensions of psychopathology in children and adolescents at one point in time are primarily due to highly pleiotropic genetic influences, whereas environmental influences are mostly specific to each dimension of psychopathology. By adding the dimension of time, the present prospective analyses suggest the further hypothesis that the underlying pleiotropic liabilities are relatively unchanging but often give rise to changing symptomatic

### Figure 3. Tetrachoric Correlations (SE) [z Scores] Between Each Wave 1 and Wave 2 Diagnosis, Simultaneously Adjusted for Sex, Wave 1 Age, and All Other Wave 1 Diagnoses in NESARC

<table>
<thead>
<tr>
<th>Wave 1 Diagnoses</th>
<th>Wave 2 Diagnoses</th>
<th>Distress</th>
<th>Fears</th>
<th>Externalizing</th>
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<tr>
<td></td>
<td></td>
<td>MDD</td>
<td>DYS</td>
<td>GAD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SPP</td>
<td>SOC</td>
<td>AGP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>APD</td>
<td>TOB</td>
<td>ALC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SUB</td>
<td></td>
<td></td>
</tr>
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<td>Distress</td>
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<td></td>
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<tr>
<td>MDD</td>
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<td>0.24 (0.02)</td>
<td>0.11 (0.02)</td>
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<td>[3.47]</td>
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<td>0.27 (0.03)</td>
<td>0.03 (0.03)</td>
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<td>[6.14]</td>
<td>[8.14]</td>
<td>[0.95]</td>
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<tr>
<td></td>
<td>[6.03]</td>
<td>[0.36]</td>
<td>[4.14]</td>
<td>[4.95]</td>
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<tr>
<td>AGP</td>
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<td>0.15 (0.03)</td>
<td>0.18 (0.03)</td>
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<td>[6.15]</td>
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<td>[4.44]</td>
<td>[6.11]</td>
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<td>Externalizing</td>
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<td></td>
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</tr>
<tr>
<td>APD</td>
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<td>0.07 (0.03)</td>
<td>0.08 (0.03)</td>
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<td>[0.04]</td>
<td>[2.12]</td>
<td>[2.69]</td>
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<td>0.15 (0.04)</td>
<td>0.09 (0.02)</td>
<td>0.11 (0.02)</td>
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<td>[5.51]</td>
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<td>0.06 (0.04)</td>
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<td>[3.61]</td>
<td>[0.10]</td>
<td>[1.14]</td>
<td>[1.34]</td>
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<tr>
<td>SUB</td>
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<td>-0.11 (0.13)</td>
<td>0.09 (0.06)</td>
<td>0.05 (0.07)</td>
</tr>
<tr>
<td></td>
<td>[0.31]</td>
<td>[-0.87]</td>
<td>[1.17]</td>
<td>[1.37]</td>
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</table>

Tetrachoric correlations for homotypic associations are in bold; prospective associations within the same second-order class of mental disorders (distress, fears, or externalizing) are displayed in shading. AGP indicates agoraphobia and panic disorder; ALC, alcohol dependence; APD, antisocial personality disorder; DYS, dysthymia; GAD, generalized anxiety disorder; MDD, major depressive disorder; SOC, social phobia; SPP, specific phobia; SUB, other substance dependence; and TOB, tobacco dependence.

*P < .001.
*P < .05.
*P < .10.
manifestations over time, perhaps due to changing environmental influences.

An incidental finding regarding the relative magnitudes of homotypic and heterotypic predictions of some wave 2 diagnoses is notable in this context. Although we did not conduct formal statistical tests, Figures 2 and 3 show that bivariate heterotypic continuities are generally smaller than homotypic continuities for the same diagnosis. In the distress domain, however, bivariate heterotypic continuities rival the homotypic continuities. Indeed, generalized anxiety disorder in wave 1 heterotypically predicts dysthymia in wave 2 as well as it predicts itself homotypically. This suggests substantial shifting across diagnostic boundaries among the distress diagnoses over time, perhaps more than among diagnoses in other domains.

The robust pattern of widespread heterotypic continuity observed in the present analyses supports future studies of hierarchical-dimensional models and other models that view psychopathology as subject to change from one form of psychopathology to another over time. These models have strong implications for how shared and disorder-specific aspects of etiology and psychobiological mechanisms should be studied, and argue for further study of transdiagnostic approaches to the treatment of psychopathology, which focus less on the specific presenting symptoms and more on broad domains of dysfunction hypothesized to underlie changing symptoms.

Limitations
Like nearly all studies of adult psychopathology in population-based samples, the structured diagnostic interview in NESARC used skip patterns to route the interview away from questions about further symptoms as soon as it was impossible for the individual to meet diagnostic criteria for that disorder. For example, individuals who did not report either dysphoria or anhedonia were not asked about other symptoms of major depression. This means that counts of all symptoms of each disorder could not be used in these analyses. Because persons with subthreshold symptoms of at least some disorders are at increased risk for the same and other mental disorders in the future, it would have been preferable to study symptom counts. Although this may have changed the estimates of homotypic and heterotypic continuity somewhat, it seems unlikely that it would have changed the pattern of findings. Nonetheless, longitudinal studies of large population-based samples of adults (using instruments that yield symptom counts) are needed to fully understand the structure of psychopathology over time.

Future Directions
Studies are needed to test at biological levels the hypothesis of hierarchical-dimensional models that broadly shared (ie, pleiotropic) genetic influences on psychopathology, and the biopsychological processes they influence, are an important source of the hierarchical structure of psychopathology. Although sex and age were controlled for in the present analyses, we did not test the possible moderation of homotypic and heterotypic continuity by demographic factors. Because previous studies of youth found evidence for moderation of continuity by sex, this is an important topic for future research.

Such future biological studies of etiology and pathophysiology based on the hierarchical-dimensional model of psychopathology will inform the Research Domains Criteria project. This project is based on the assumption that nominal diagnostic categories do not capture the fundamental and often heterogeneous underlying biopsychological mechanisms of dysfunction that lead to psychopathology. This is both because dysfunction in any of several mechanisms can give rise to the symptoms of each diagnosis and because each mechanism of dysfunction underlies multiple diagnoses. Thus far, the present findings have been discussed in terms of their implications for etiologies and mechanisms that are broadly shared by multiple dimensions. The same patterned correlations also suggest hypotheses regarding the heterogeneity of etiologies and mechanisms within each category or dimension of psychopathology emphasized in the approach of the Research Domains Criteria project. Consider genetic influences on the diagnosis of agoraphobia as an example. Each individual who meets criteria for agoraphobia could be influenced by any combination of genetic variants that are specific to only agoraphobia, genetic variants pleiotropically associated with risk for any internalizing disorder, and highly pleiotropic genetic variants associated with risk for any common form of psychopathology. As a result, the symptoms of different persons who meet diagnostic criteria for agoraphobia could be influenced by different combinations of these different sets of genetic variants. This may create an intractable heterogeneity of genetic influences and related mechanisms in studies that do not separate such putative hierarchical sets of genetic influences. The most informative biological studies of psychopathology, therefore, will examine genetic and environmental influences at multiple levels in the hierarchical organization of psychopathology and link those influences to the specific psychobiological domains identified in the Research Domains Criteria project model.

Conclusions
Each mental disorder in the first wave of this study significantly predicted each of the other diagnoses 3 years later (heterotypic continuity) in nearly every instance, adjusting for sex and age. This heterotypic continuity was widespread even when the other wave 1 diagnoses (including the same diagnosis to control homotypic continuity) were simultaneous predictors of each wave 2 diagnosis. Furthermore, the relative magnitudes of heterotypic continuity closely recapitulated the relative magnitudes of cross-sectional correlations among mental disorders in wave 1, consistent with the hypothesis that both sets of associations reflect the same underlying factors. These findings suggest that mental disorders are not fixed and independent entities. Rather, prevalent mental disorder diagnoses are robustly related in ways that can be seen in the patterns of both concurrent correlations and heterotypic continuity over time.
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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Lahey.
Critical revision of the manuscript for important intellectual content: All authors.
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Obtained funding: Zald.
Administrative, technical, or material support: Hakes.
Study supervision: Lahey, Zald.

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