

Patterns of comorbidity among mental disorders: a person-centered approach

Uma Vaidyanathan^{a,*}, Christopher J. Patrick^a, William G. Iacono^b

^aDepartment of Psychology, Florida State University, Tallahassee, FL 32306, USA

^bDepartment of Psychology, University of Minnesota, Minneapolis, MN 55455, USA

Abstract

Objective: Comorbidity poses a major challenge to conventional methods of diagnostic classification. Although dimensional models of psychopathology have shed some light on this issue, the reason for interrelationships among dimensions is unclear. The current study employed an alternative approach to characterizing patterns of comorbidity among common mental disorders by modeling them instead as clusters by using latent class analysis (LCA).

Method: Latent class analyses of *Diagnostic and Statistical Manual of Mental Disorders* diagnoses from two nationally representative epidemiological samples—the National Comorbidity Survey and National Comorbidity Survey–Replication datasets—were undertaken.

Results: Within each dataset, LCA yielded 5 latent classes exhibiting distinctive profiles of diagnostic comorbidity: a fear class (all phobias and panic disorder), a distress class (depression, generalized anxiety disorder, dysthymia), an externalizing class (alcohol and drug dependence, conduct disorder), a multimorbid class (highly elevated rates of all disorders), and a few-disorders class (very low probability of all disorders). Whereas some disorders were relatively specific to certain classes, others (major depression, posttraumatic stress disorder, social phobia) appeared to be evident across all classes. Profiles for the five classes were highly similar across the two samples. When bipolar I disorder was added to the LCA models, in both samples, it occurred almost exclusively in the multimorbid class.

Conclusions: Comorbidity among mental disorders in the general population appears to occur in a finite number of distinct patterns. This finding has important implications for efforts to refine existing diagnostic classification schemes, as well as for research directed at elucidating the etiology of mental disorders.

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The phenomenon of comorbidity poses a serious challenge to traditional psychiatric classification systems such as the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and the *International Classification of Diseases* (ICD), which conceptualize mental disorders as discrete pathologic conditions. Factor analytic studies have characterized observed co-occurrence among common mental disorders in terms of two correlated but distinct factors of internalizing (subsuming two interrelated subdimensions of “fear” and “anxious-misery”) and externalizing (antisocial and addictive disorders) [1]. However, the basis of the moderately large correlation between factors of internalizing and externalizing (ie, the sources of overlap between disorders in one domain and the other) remains unclear [1–7].

A complementary approach to understanding comorbidity that might help shed light on this issue is latent class analysis

(LCA)—that is to say, if the same set of disorders that are modeled as dimensions [1–3] are modeled instead as clusters or groups, the disorders might reveal reasons for the correlations among dimensions. In other words, if one imagines diagnostic data as falling along a Cartesian coordinate system, the axes of that system would represent the orthogonal forms of those dimensions; and the classes would reflect “hotspots” of activity along those dimensions. Modeling data in this manner would help reveal what people who had comorbid internalizing and externalizing disorders look like. Is there a particular pattern to their profiles? Are there certain disorders that are more likely to “link” the dimensions? With this aim in mind, the current study used LCA to characterize patterns of comorbidity exhibited by individuals in two large-scale epidemiological cohorts: the National Comorbidity Survey (NCS) and the National Comorbidity Survey–Replication (NCS-R) sample. If comorbidity in such clusters or groups of individuals occurred in stable patterns, the number of latent classes revealed by LCA using this particular set of disorders

* Corresponding author.

E-mail address: uma@psy.fsu.edu (U. Vaidyanathan).

and their configural profiles should replicate across the two epidemiological samples used in the current study.

Previous research has shown that bipolar disorder tends to co-occur frequently with both internalizing and externalizing disorders [8–10]. However, its position in dimensional models of psychopathology is relatively less clear, as it appears to be correlated equally with the fear, anxious-misery, and externalizing dimensions [10]. As a particular strength of the LCA method is that it is relatively unaffected by assumptions of multivariate normality, linearity, or homogeneity [11,12], it can be used to analyze more severe and rarer forms of psychopathology such as bipolar disorder, which are usually not included in factor analytic models because of their low prevalence rates [1,2]. Thus, as data regarding bipolar I disorder were available in both the NCS [13] and NCS-R [14], these were added to the LCA models to assess their place in conjunction with internalizing and externalizing psychopathology. These analyses were more exploratory in nature; the relationship between bipolar I disorder and other forms of psychopathology in classification systems is still a much-debated issue [15,16].

1. Method

1.1. Participants

The NCS and NCS-R are two nationally representative surveys (N = 8098 and 9282, respectively) of mental health diagnoses conducted in the United States between 1990–1992 and 2001–2002, respectively, with response rates of 82.6% and 70.9%. Subjects in both surveys consist of non-institutionalized participants (NCS age range, 15–54 years; NCS-R age range, 18–99 years). Further details regarding the recruitment, consent, and sampling strategy have been documented elsewhere [17–21].

1.2. Assessment of mental disorders

Lifetime diagnoses were used for all analyses of both the NCS and NCS-R datasets. Diagnoses for the two datasets are based on the World Mental Health Survey Initiative Version of the World Health Organization Composite International Diagnostic Interview (CIDI) [22], a structured interview protocol. The version used in the NCS yielded *DSM, Revised Third Edition (DSM IIIR)* [23] diagnoses; and the version used in the NCS-R yielded *DSM, Fourth Edition DSM IV* [24] diagnoses. Further details regarding the assessment procedures for each sample are reported elsewhere [17,19]. Given that the central aim of the study was to characterize patterns of comorbidity, nonhierarchical diagnoses were used.

1.3. Statistical analyses

Latent class analysis models incorporating the design of the complex datasets including weighting, clustering, and stratification were carried out using the Latent Gold 4.5 software package [25]. To account for the complex sampling

design of the NCS and NCS-R datasets, models were estimated using weighted data, while controlling for stratification and clustering. Participants within each sample were assigned varying weights to adjust for survey nonresponding, variation in probability of selection within and between households, and differences across successive phases of surveying, and to approximate the distribution of major demographic variables in the US population. This weighting procedure resulted in adjusted sample sizes (ie, “weighted ns”; see below) for each sample. Models specifying from 2 to 10 classes were compared. Model fit was assessed using the Bayesian information criterion (BIC) [26] and the Akaike information criterion (AIC) [27]. Both AIC and BIC are model selection indices that balance model fit and parsimony, but penalize model complexity to different degrees. When comparing models, generally, lowest values of both, or a scree-plot-like test (ie, where AIC and BIC values begin to level off), may be used to determine optimal model fit [28,29]. Each model was run with 50 starting values to avoid problems with local maxima [30].

Four different sets of LCA models were examined including the following sets of disorders:

1. Mental disorders commonly used in structural models of epidemiological studies [1–3]: Disorders targeted for these LCA analyses consisted of conditions diagnosed most frequently in the general population: specific phobia, social phobia, agoraphobia, panic disorder, posttraumatic stress disorder (PTSD), major depressive disorder, generalized anxiety disorder (GAD), dysthymia, alcohol dependence, drug dependence, and conduct disorder. Separate models of these disorders were examined in both the NCS and NCS-R.
2. Next, LCA models for both samples were rerun after adding diagnoses of bipolar disorder.¹ In each case, profiles obtained from optimal LCA solutions were compared with the models obtained in the previous step.

Although the NCS and NCS-R contain 8098 and 9282 participants, respectively, targeted subsets of each were used to provide full representation of disorders of interest that

¹ A clinical reappraisal study by Kessler et al [13] of the diagnoses of bipolar I disorder collected in the NCS noted that only a particular form of manic episodes (those that entailed euphoria, grandiosity, and decreased need for sleep) could be validly assessed with the CIDI and that analyses that used the broader definition of bipolar I disorder that was provided with the dataset might lead to false positives. Thus, we used only this set of manic episodes in our analyses, rather than the diagnostic data provided for bipolar I disorder as a whole. However, we refer to these as *bipolar I disorder* throughout the remainder of the article for the sake of consistency with the bipolar I disorder diagnosis used from the NCS-R dataset. With regard to the NCS-R diagnosis of bipolar I disorder, because there was concern about overestimation of bipolar I disorder again by the CIDI, the diagnostic algorithm for bipolar I disorder was recalibrated after data collection [31]. Consequently, we used this more stringent version of the bipolar I disorder variable that was provided with the NCS-R dataset.

Table 1

Bayesian information criterion (BIC) and Akaike Information Criterion (AIC) values for LCA models with classes ranging from 2 to 10 for NCS subsample ($N = 5877$) and NCS-R subsample ($N = 2980$)

No. of classes	NCS: INT and EXT disorders		NCS-R: INT and EXT disorders		NCS: INT, EXT, and bipolar I disorders		NCS-R: INT, EXT, and bipolar I disorders	
	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC
2	36 245.48	36 091.86	16 739.16	16 601.17	36 489.39	36 322.42	17 127.18	16 977.19
3	35 817.59	35 583.83	16 622.61	16 412.62	36 066.20	35 812.41	17 012.32	16 784.33
4	35 660.46	35 346.56	16 592.92	16 310.94	35 913.46	35 572.84	16 972.16	16 666.17
5	35 515.29	35 121.24	16 588.74	16 234.76	35 761.90	35 334.46	16 978.32 ^a	16 594.33
6	35 556.84	35 082.64	16 621.62	16 195.64	35 812.70	35 298.43	17 014.53	16 552.55
7	35 605.47	35 051.13	16 696.94	16 198.96	35 861.43	35 260.33	17 094.66	16 554.68
8	35 663.87	35 029.39	16 770.71	16 200.74	35 930.38	35 242.46	17 173.70	16 555.73
9	35 733.12	35 018.49	16 849.27	16 207.31	36 006.53	35 231.79	17 257.67	16 561.70
10	35 808.01	35 013.24	16 924.57	16 210.60	36 090.67	35 229.11	17 344.03	16 570.07

Best-fitting model for each sample is in boldface. INT indicates internalizing; EXT, externalizing.

^a Bootstrap likelihood ratio test indicates significant difference from 4-class model.

were present in both samples, to verify if results replicated across both samples. In particular, PTSD, antisocial behavior in the form of conduct disorder, and alcohol and drug problems were available only for subsamples of the NCS and NCS-R. Posttraumatic stress disorder was assessed in 5877 and 5692 participants of the NCS and NCS-R, respectively. Similarly, in the NCS-R, alcohol and drug problems were assessed only in the subsample with 5692 subjects. Diagnoses of antisocial personality disorder were not a part of the publicly available dataset; however, lifetime diagnoses of conduct disorder were available for a subsample of the NCS-R ($n = 3197$), ranging from 18 to 44 years of age. In summary, to permit direct comparison of findings across the two samples, LCAs were performed using subsamples of participants from the NCS and NCS-R (unweighted/weighted $Ns = 5877/5877$ and $3197/2980$, respectively) who had been assessed for conduct disorder, PTSD, and substance use problems, along with other disorders of interest.

Following determination of the best-fitting LCA model in each subsample, parameter estimates of probability of diagnoses for specific disorders, along with standard errors, were compared across classes. Because estimated probabilities for diagnoses of certain disorders were zero or almost zero in some cases, it was not possible to calculate relative indices such as odds ratios or relative risk ratios. As an alternative to this, 95% confidence intervals (CI = estimated value $\pm [1.96 \times \text{standard error of estimate}]$) are presented for the estimated probabilities of being diagnosed with a particular disorder among individuals in each of the LCA classes.

2. Results

2.1. Identification of comorbidity patterns using LCA

For the LCA models with just internalizing and externalizing disorders, in both the NCS and NCS-R samples, a 5-class model fit best according to BIC and AIC (Table 1; note

that AIC values level off after 5 classes for both models). For the LCA models with bipolar disorder, whereas the NCS revealed a 5-class solution again, in the NCS-R, the BIC indicated a 4-class model, while the AIC suggested a 5-class model. To reconcile this discrepancy, we examined bivariate residuals (BVRs) among disorders in this model [25] and used the bootstrap likelihood ratio test (BLRT) [32] to formally assess the statistical significance of adding an extra class. Bivariate residuals indicate the strength of association between pairs of disorders, after accounting for those modeled by the latent classes; the presence of large BVRs in a model indicates that the model is not adequately capturing such associations. The BLRT evaluates the difference in log-likelihoods between two models by comparing it to an empirically estimated difference distribution generated by bootstrapping. An examination of BVRs among disorders in the 4-class model revealed several large significant associations among the internalizing disorders, suggesting that the 4-class model was not adequately accounting for all relationships among these disorders. Similarly, the BLRT indicated that the additional fifth class significantly improved model fit to data ($P < .0001$ with 500 replication samples).² Thus, given the weight of this evidence, the 5-class model was chosen as the best model in this set of LCA models as well.

2.2. Characterizing the latent classes

Inspection of the profiles for the NCS and NCS-R 5-class LCA models (Figs. 1–4) revealed the following. Class 1, the largest of the five classes, showed extremely low probabilities of diagnosis of any disorder. Class 2 was composed of individuals with modal diagnoses of phobias (all types) and panic disorder (to a lesser extent) in conjunction with depression. Class 3 consisted predominantly of subjects diagnosed with depression in conjunction with dysthymia and also GAD. Class 4 was distinguished by a high

² The 4-class solution of this particular NCS-R model collapsed the fear and distress classes into a larger internalizing class.

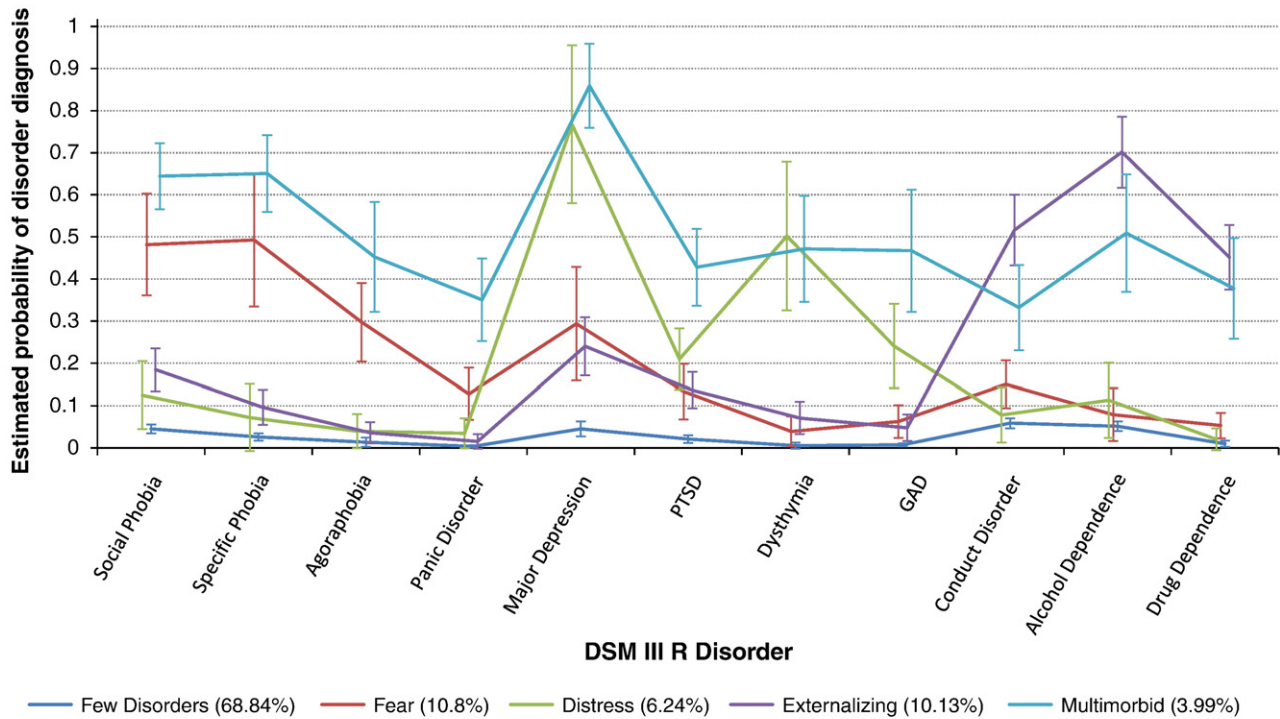


Fig. 1. Profiles of parameter estimates for latent classes derived from best-fitting 5-class LCA model with internalizing and externalizing disorders within the NCS subsample ($N = 5877$).

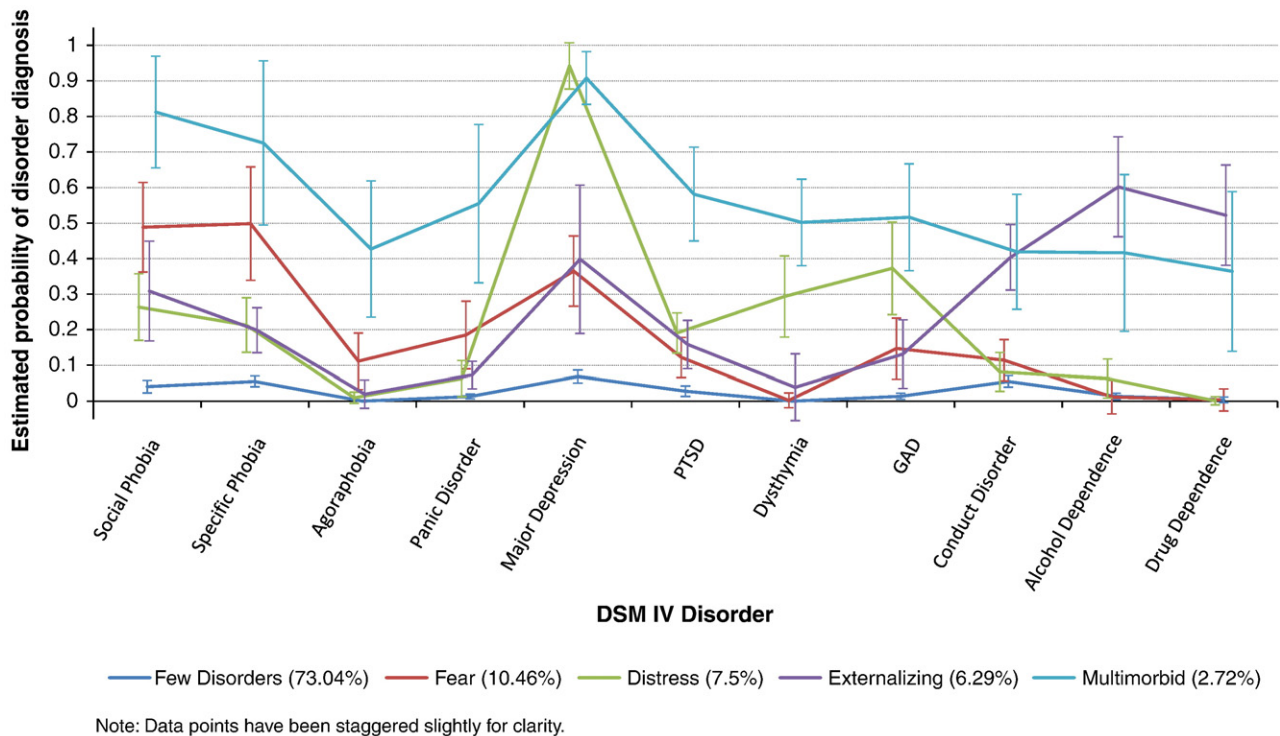
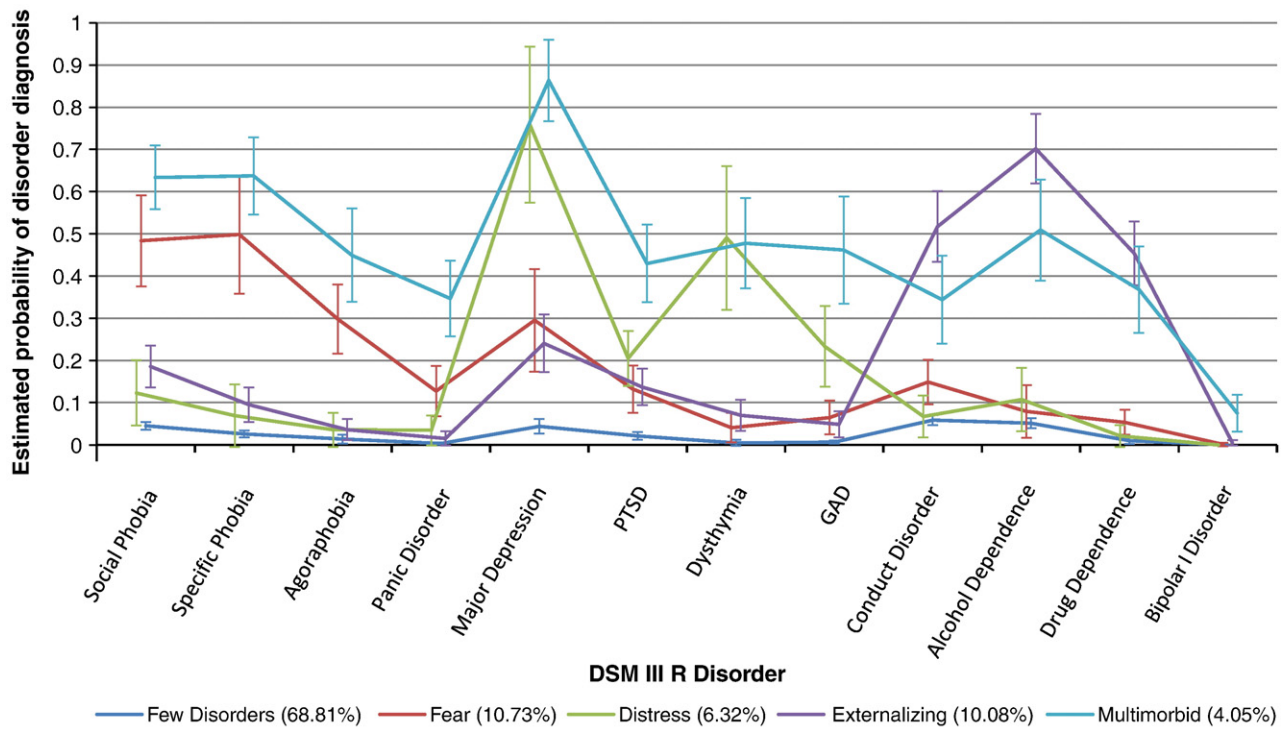
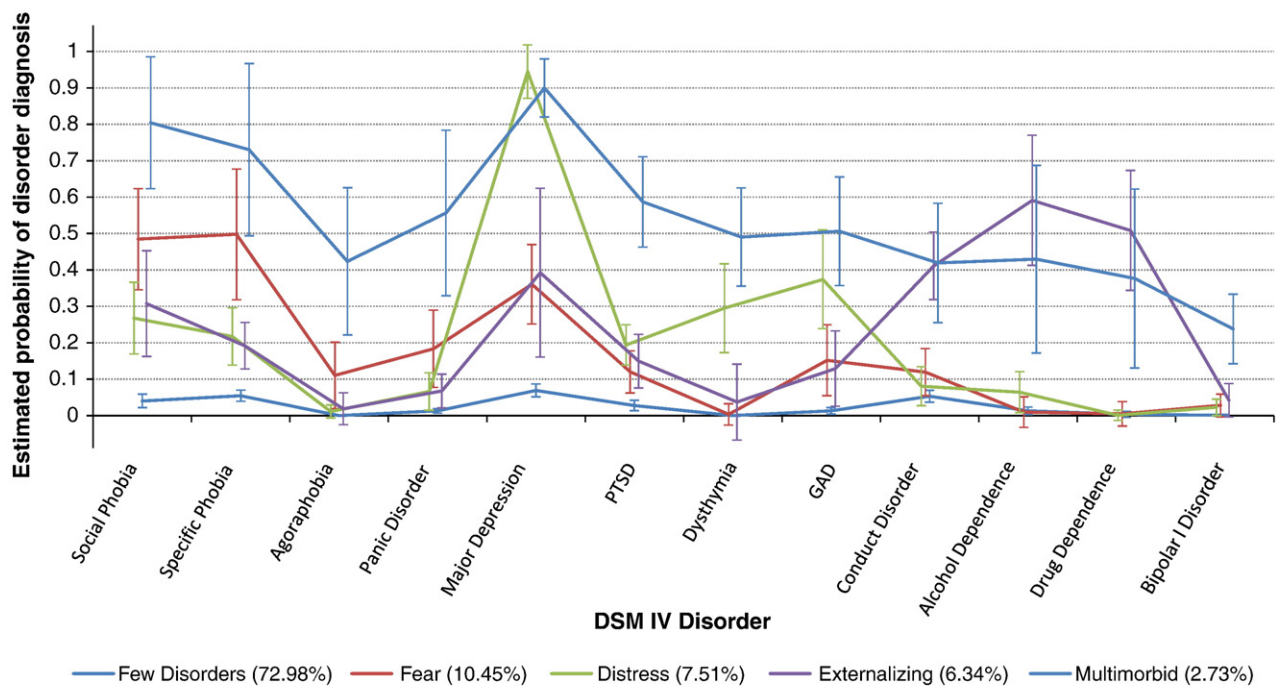


Fig. 2. Profiles of parameter estimates for latent classes derived from best-fitting 5-class LCA model with internalizing and externalizing disorders within the NCS-R subsample ($N = 2980$).



Note: Data points have been staggered slightly for clarity.

Fig. 3. Profiles of parameter estimates for latent classes derived from best-fitting 5-class LCA model with internalizing and externalizing disorders and bipolar I disorder within the NCS subsample ($N = 5877$).



Note: Data points have been staggered slightly for clarity.

Fig. 4. Profiles of parameter estimates for latent classes derived from best-fitting 5-class LCA model with internalizing and externalizing disorders and bipolar I disorder within the NCS-R subsample ($N = 2980$).

prevalence of externalizing disorders (conduct disorder, alcohol dependence, drug dependence) in conjunction with lesser elevations on certain other disorders including depression. The fifth and final class was composed of subjects who demonstrated high levels of both internalizing (fear, distress) and externalizing (antisocial, substance-related) psychopathology, in addition to bipolar I disorder. Given these disorder profiles, we labeled the five classes as follows: *few-disorders*, *fear*, *distress*, *externalizing*, and *multimorbid*.

2.3. Disorders common across classes

As Figs. 1–4 illustrate, besides showing marked elevations in disorders most distinct to their class, individuals in the fear, distress, and externalizing classes also showed elevated prevalence of certain other disorders. In particular, across the two participant samples, depression, PTSD, and social phobia occurred in all three of these classes at high rates (>10% probability, in all cases). Notably, marked elevations in prevalence rates for *all* disorders were evident in the highly multimorbid class, with the prevalence of some disorders (panic disorder and PTSD, in particular) higher in this class than in any other class across both samples.

3. Discussion

The current work provides a quantitative-descriptive characterization of patterns of lifetime comorbidity among common mental disorders exhibited by individuals in two large-scale epidemiological samples. Within each sample, LCA revealed five classes with contrasting disorder profiles that were highly similar across the two samples. The classes included a “few-disorders” class with low probabilities of diagnoses of all disorders and four classes showing elevated probabilities of particular lifetime disorders. Whereas sample size and replication across two different nationally representative datasets collected a decade apart from each other represent significant strengths of the current study, weaknesses include the fact that diagnoses were determined by interviews administered by laypersons, that lifetime diagnoses were based on retrospective recall, and that each sample consisted only of noninstitutionalized subjects. In addition, certain disorders (PTSD in both the NCS and NCS-R; conduct disorder and substance use disorders in the NCS-R) were assessed on a follow-up basis in selected subsets of participants who met criteria for other diagnoses in an initial assessment. Thus, it is possible that such disorders showed evidence of greater comorbidity because they were selectively associated with classes exhibiting some other diagnosable form of psychopathology.

Nonetheless, despite these limitations, the results are in accordance with previous research that has examined comorbidity using dimensional models in general community or twin samples [1,2,33]. In parallel with the models specified in these studies, distinct patterns of comorbidity were evident among individual participants in the current study, reflecting

systematic coherency among fear-related disorders (social and specific phobia; agoraphobia; and, to a lesser extent, panic disorder); among disorders entailing high levels of distress and dysphoria (GAD, dysthymia, and major depression); and among disorders involving deficient impulse control (conduct disorder, alcohol dependence, and drug dependence). Notably, the fear, distress, and externalizing classes were each characterized by high levels of a core group of two to three disorders. This pattern of results indicates that these latent classes do not reflect subsets of individuals who differ simply in overall severity of mental illness, but rather distinct groups of individuals prone to differing combinations of disorders. In addition, and more importantly, a class emerged that has not been identified in dimensional models—namely, the “multimorbid” class. Across both samples, this class emerged as the smallest of the five classes; and it was clearly associated with the greatest overall severity of psychopathology, in terms of high probabilities of endorsement for all disorders. In addition, what distinguished this class from other classes was the markedly elevated rates of bipolar I disorder relative to all other classes.

With regard to the current findings, it is worth noting that three prior studies have undertaken LCAs of *DSM*-based disorders and have reported optimal solutions ranging from 6 to 8 latent classes [34–36]. Although some commonalities in results are evident across these investigations, direct comparisons are difficult because different sets of disorders and differing time referents (eg, lifetime vs 12-month diagnoses) were used in these studies. In addition, the purpose of the current study was to examine psychopathology from a complementary modeling perspective rather than to make a decisive statement on the structure of psychopathology (eg, identify a definitive number of classes). Thus, we made a series of a priori decisions that guided our approach in terms of the disorders and time referents used in the current analyses, with the aim of using our findings to provide additional insight into the nature of comorbidity underlying internalizing and externalizing psychopathology.

3.1. Overlap between internalizing and externalizing domains of psychopathology

In addition to providing converging evidence for distinct domains of psychopathology marked by excessive fear or pervasive distress (internalizing disorders) or by deficient impulse control (externalizing disorders), the current work also sheds new light on a key unanswered question emerging from dimensional-structural studies: What accounts for the overlap between internalizing and externalizing disorders, reflected in moderate-to-high correlations among factors and subfactors in dimensional models of comorbidity?

The current findings point to two systematic sources for this overlap. One of these pertains to elevated rates within the fear, distress, and externalizing classes of what might be termed *cross-class disorders*—that is, disorders evident at elevated rates (exceeding estimated probabilities of

diagnosis of .1) in each of these classes. This set of disorders included major depression, social phobia, and PTSD. The other source consists of a distinctive subgroup of individuals exhibiting heightened rates of all disorders from both the internalizing and externalizing domains—that is, the multimorbid class. Across the two study samples, individuals in this class showed (1) high rates of all phobic disorders (agoraphobia as well as social and specific phobias)—comparable to or higher than those evident in the fear class—along with markedly higher rates of panic disorder; (2) rates of depression, dysthymia, and GAD comparable to those observed in the distress class, along with the highest rates of PTSD compared with all classes; and (3) rates of conduct disorder, alcohol dependence, and drug dependence that substantially exceeded rates in other classes aside from the externalizing class. These observations, by highlighting major ways in which individuals in the fear, distress, and externalizing classes manifest particular disorders characteristic of other classes, suggest ways to account for the overlap that exists between internalizing and externalizing domains.

3.2. Homogeneity and heterogeneity of disorders

The current findings have implications for traditional conceptions of mental disorders as discrete, etiologically coherent entities. In line with findings from previous structural modeling studies [1–3], common mental disorders were found to co-occur reliably in distinctive patterns, consistent with the idea of shared etiologic underpinnings to differing disorders [37,38]. As noted above, however, for the four comorbid classes in both the NCS and NCS-R, heightened rates of disorders characteristic of other classes were also evident, with one particular set of disorders (ie, depression, social phobia, and PTSD) elevated across classes. Although somewhat speculative, this raises the possibility that mechanisms governing manifestations of particular disorders vary according to what class they occur in, that is, as a function of the overall pattern of affiliated comorbidity.

Consider, for example, major depression, which emerged as one of the three most prevalent diagnoses in all five classes across both samples. Although at odds with the traditional idea of depression as a coherent entity, further consideration reveals deeper ties to the extant literature. Long-standing debates exist regarding depression subtypes; and a number of schemes have been proposed including unipolar vs bipolar, episodic vs chronic, and reactive vs endogenous. The occurrence of depression in the context of differing patterns of comorbidity may indicate variability in the nature and etiology of depressive syndromes. Thus, whereas recurrent depression in the context of dysthymia and GAD may reflect a core dysphoric liability, episodes of depression in the context of chronic antisocial behavior and substance abuse may reflect the cumulative impact of adverse consequences over time. Indeed, in this context, it is worth noting that there have been recent calls to demarcate

melancholia as a distinct mood disorder from major depression in the upcoming version of the *DSM* [39]. A similar argument can be made with regard to the syndrome of PTSD, which has been conceptualized as including both internalizing and externalizing variants [40,41].

More broadly, these cross-class disorders may reflect characteristic output pathways along which psychological discomfort tends to be expressed in most individuals. In support of this notion, rates for these particular disorders were elevated even within the few-disorders class in both samples. This suggests that these disorders may be more indicative of general distress or difficulty in dealing with adverse life events. For example, symptoms of depression represent a natural reaction to loss or defeat, symptoms associated with PTSD (eg, persisting distress and wariness) are common following exposure to extreme stressors, and discomfort in situations involving social performance or evaluation is normative in the population. Thus, although our findings indicate groups of individuals with a preponderance of problems in distinct domains (possibly implying specific underlying vulnerabilities or diatheses along each of these lines), such individuals may be prone to greater levels of psychological discomfort in general, resulting in elevated rates of these common disorders across all classes identified in the current study.

3.2.1. Bipolar I disorder and internalizing and externalizing psychopathology

An interesting feature of our results pertains to the multimorbid class in the current study, which exhibited high rates of all relatively common disorders used in the LCA models, as well as bipolar I disorder. These results fit with data indicating that bipolar I disorder shows substantial comorbidity with internalizing and externalizing disorders of differing types [8,9]. However, what is particularly noteworthy about this class is that it suggests that the presence of high levels of internalizing *and* externalizing disorders appears to be associated with more than just either kind of psychopathology.

3.2.2. Understanding comorbidity from multiple perspectives

A final important point concerns how to interpret and understand the phenomenon of comorbidity using results from previous factor analytic work and from the current study. As noted earlier, the purpose of the current study was to provide a complementary descriptive perspective on psychopathology by examining how comorbidity could be understood when examined as clusters of persons occurring along dimensions of psychopathology. Results from the current study suggest that certain forms of psychopathology, that is, major depression, social phobia, and PTSD, appear to “link” the dimensions, beyond the contribution of a multimorbid class. Thus, these findings could be interpreted from a purely mathematical-statistical point of view, without attributing a deeper meaning to the latent classes we found in the current study.

Alternatively, if one were to interpret the model used in the current study in the spirit of the latent variable model that was used, then the results might support the existence of latent classes of mental disorders. For example, as proposed by Jablensky [42], it could be hypothesized that the classes obtained in the current study are “syndromes” reflecting “facets of the same clinical entity.” If one were to draw analogies from this perspective to medical disorders, applying a structural model to symptoms such as fever and headaches that are common to differing disorders such as bacterial meningitis and influenza would yield correlated “fever” and “headache” factors. This would not mean that meningitis and influenza are the same, nor would it mean that the fever and headache symptoms are unimportant. On the contrary, it is valuable to know both what general disorder is present so that the appropriate broadband treatment can be applied (eg, antibiotics, antivirals, or other medication) and what individual symptoms (eg, fever) require in terms of focal treatment. Thus, information from both levels (ie, both the individual symptoms and how they cluster together) is important to understand and treat the disorder. A similar case can be made for psychopathological syndromes as well.

A third alternative, as noted by Jaspers [43] and more recently suggested by Maj [44], is that psychopathology may indeed be “intrinsically heterogeneous,” with “true diseases” (such as general paresis), which have clear boundaries among themselves and with normality; ‘circles’ (such as manic-depressive insanity and schizophrenia), which have clear boundaries with normality but not among themselves; and ‘types’ (such as neuroses and abnormal personalities), which do not have clear boundaries either among themselves or with normality.” Indeed, results from the current study support such an interpretation as well in that bipolar disorder only appears to intersect with extremes of internalizing and externalizing psychopathology (ie, the multimorbid class). Future research is doubtless required to understand what the true nature of psychopathology may be [45].

In this context of attempting to understand interrelations among psychopathology from differing perspectives, it is worth noting that there has been a recent effort to develop a “metastructure” of mental disorder clusters for the upcoming version of the *DSM (Psychological Medicine, December 2009 special issue [16,46–50])*. However, a point acknowledged by contributing authors [46] and highlighted in accompanying commentaries [51–53] was that further empirical evidence is required to support a move in this direction. Results from the current study could contribute to such efforts from the perspective of latent variable modeling. However, alternative methods to understanding comorbidity other than latent variable modeling [54] have been proposed as well. Thus, it remains to be seen which approach will prove most useful with regard to nosological considerations of psychopathology.

In conclusion, our analyses importantly extend prior work by suggesting some possible reasons for overlap among differing dimensions of psychopathology. Ultimately, re-

search that incorporates findings from multiple perspectives regarding interrelations among differing mental disorders is likely to contribute most to understanding, remediation, and prevention of disorders of this type.

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References

- [1] Krueger RF. The structure of common mental disorders. *Arch Gen Psychiatry* 1999;56:921–6.
- [2] Vollebergh WAM, Iedema J, Bijl RV, de Graaf R, Smit F, Ormel J. The structure and stability of common mental disorders: the NEMESIS study. *Arch Gen Psychiatry* 2001;58:597–603.
- [3] Slade T, Watson D. The structure of common DSM-IV and ICD-10 mental disorders in the Australian general population. *Psychol Med* 2006;36:1593–600.
- [4] Fu Q, Heath AC, Bucholz KK, Nelson E, Goldberg J, Lyons MJ, et al. Shared genetic risk of major depression, alcohol dependence, and marijuana dependence: contribution of antisocial personality disorder in men. *Arch Gen Psychiatry* 2002;59:1125–32.
- [5] Koenen KC, Fu QJ, Lyons MJ, Toomey R, Goldberg J, Eisen SA, et al. Juvenile conduct disorder as a risk factor for trauma exposure and posttraumatic stress disorder. *J Trauma Stress* 2005;18:23–32.
- [6] Kim-Cohen J, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. *Arch Gen Psychiatry* 2003;60:709–17.
- [7] Subbarao A, Rhee SH, Young SE, Ehringer MA, Corley RP, Hewitt JK. Common genetic and environmental influences on major depressive disorder and conduct disorder. *J Abnorm Child Psychol* 2008;36:433–44.
- [8] Krishnan KRR. Psychiatric and medical comorbidities of bipolar disorder. *Psychosom Med* 2005;67:1–8.
- [9] Simon NM, Otto MW, Wisniewski SR, Fossey M, Sagduyu K, Frank E, et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry* 2004;161:2222–9.
- [10] Watson D. Rethinking the mood and anxiety disorders: a quantitative hierarchical model for DSM-V. *J Abnorm Psychol* 2005;114:522–36.
- [11] Magidson J, Vermunt JK. Latent class models. In: Kaplan D, editor. *Handbook of quantitative methodology*. London: Sage; 2004. p. 175–98.
- [12] McCutcheon AL. *Latent class analysis*. Newbury Park (CA): Sage; 1987.
- [13] Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. *Psychol Med* 1997;27:1079–89.
- [14] Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RMA, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2007;64:543–52.
- [15] Goldberg DP, Andrews G, Hobbs MJ. Where should bipolar disorder appear in the meta-structure? *Psychol Med* 2009;39:2071–81.
- [16] Carpenter WT, Bustillo JR, Thaker GK, van Os J, Krueger RF, Green MJ. The psychoses: cluster 3 of the proposed meta-structure for DSM-V and ICD-11. *Psychol Med* 2009;39:2025–42.
- [17] Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM-III-R

- psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994;51:8-19.
- [18] Kessler RC, Merikangas KR. The National Comorbidity Survey Replication (NCS-R): background and aims. *Int J Methods Psychiatr Res* 2004;13:60-8.
- [19] Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005;62:593-602.
- [20] Kessler RC, Berglund P, Chiu WT, Demler O, Heeringa S, Hiripi E, et al. The US National Comorbidity Survey Replication (NCS-R): design and field procedures. *Int J Methods Psychiatr Res* 2004;13:69-92.
- [21] Wittchen H-U. Reliability and validity studies of the WHO-Composite International Diagnostic Interview (CIDI): a critical review. *J Psychiatr Res* 1994;28:57-84.
- [22] World Health Organization. International classification of diseases, 10th revision (ICD-10). Geneva, Switzerland: World Health Organization; 1992.
- [23] American Psychiatric Association. Diagnostic and statistical manual of mental disorders, revised third edition. Washington, DC: American Psychiatric Association; 1987.
- [24] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.
- [25] Vermunt JK, Magidson J. Technical guide to Latent Gold 4.5. Belmont (MA): Statistical Innovations Inc.; 2007.
- [26] Schwarz G. Estimating the dimension of a model. *Ann Stat* 1978;6:461-4.
- [27] Akaike H. A new look at the statistical model identification. *IEEE Trans Automatic Control* 1974;19:716-23.
- [28] Sclove SL. Application of model-selection criteria to some problems in multivariate analysis. *Psychometrika* 1987;52:333-43.
- [29] Bradshaw CP, Buckley JA, Ialongo NS. School-based service utilization among urban children with early onset educational and mental health problems: the squeaky wheel phenomenon. *Sch Psychol Q* 2008;23:169-86.
- [30] Goodman LA. Exploratory latent structure analysis using both identifiable and unidentifiable models. *Biometrika* 1974;61:215-31.
- [31] Revised algorithm for bipolar spectrum. 2007. http://www.icpsr.umich.edu/CPES/diagnostics/DSM-IV_Mania.pdf.
- [32] McLachlan GJ, Peel D. Finite mixture models. New York: John Wiley; 2000.
- [33] 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;60:929-37.
- [34] Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005;62:617-27.
- [35] Kessler RC. The prevalence of psychiatric comorbidity. In: Wetzler S, Sanderson William C, editors. *Treatment strategies for patients with psychiatric comorbidity*. New York, (NY): John Wiley & Sons; 1997. p. 23-48.
- [36] Sullivan PF, Kendler KS. Typology of common psychiatric syndromes. an empirical study. *Br J Psychiatry* 1998;173:312-9.
- [37] 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;111:411-24.
- [38] Mineka S, Watson D, Clark LA. Comorbidity of anxiety and unipolar mood disorders. *Annu Rev Psychol* 1998;49:377-412.
- [39] Parker G, Fink M, Shorter E, Taylor MA, Akiskal H, Berrios G, et al. Issues for DSM-5: whither melancholia? The case for its classification as a distinct mood disorder. *Am J Psychiatry* 2010;167:745-7.
- [40] Miller MW, Greif JL, Smith AA. Multidimensional personality questionnaire profiles of veterans with traumatic combat exposure: externalizing and internalizing subtypes. *Psychol Assess* 2003;15:205-15.
- [41] Miller MW, Kaloupek DG, Dillon AL, Keane TM. Externalizing and internalizing subtypes of combat-related PTSD: a replication and extension using the PSY-5 scales. *J Abnorm Psychol* 2004;113:636-45.
- [42] Jablensky A. The syndrome—an antidote to spurious comorbidity? *World Psychiatry* 2004;3:24-5.
- [43] Jaspers K. General psychopathology. Baltimore, (MD): Johns Hopkins University Press; 1913.
- [44] Maj M. 'Psychiatric comorbidity': an artefact of current diagnostic systems? *Br J Psychiatry* 2005;186:182-4.
- [45] Kendell R, Jablensky A. Distinguishing between the validity and utility of psychiatric diagnoses. *Am J Psychiatry* 2003;160:4-12.
- [46] Andrews G, Goldberg DP, Krueger RF, Carpenter WT, Hyman SE, Sachdev P, et al. Exploring the feasibility of a meta-structure for DSM-V and ICD-11: could it improve utility and validity? *Psychol Med* 2009;39:1993-2000.
- [47] Sachdev P, Andrews G, Hobbs MJ, Sunderland M, Anderson TM. Neurocognitive disorders: cluster 1 of the proposed meta-structure for DSM-V and ICD-11. *Psychol Med* 2009;39:2001-12.
- [48] Andrews G, Pine DS, Hobbs MJ, Anderson TM, Sunderland M. Neurodevelopmental disorders: cluster 2 of the proposed meta-structure for DSM-V and ICD-11. *Psychol Med* 2009;39:2013-23.
- [49] Goldberg DP, Krueger RF, Andrews G, Hobbs MJ. Emotional disorders: cluster 4 of the proposed meta-structure for DSM-V and ICD-11. *Psychol Med* 2009;39:2043-59.
- [50] Krueger RF, South SC. Externalizing disorders: cluster 5 of the proposed meta-structure for DSM-V and ICD-11. *Psychol Med* 2009;39:2061-70.
- [51] First MB. Reorganizing the diagnostic groupings in DSM-V and ICD-11: a cost/benefit analysis. *Psychol Med* 2009;39:2091-7.
- [52] Jablensky A. A meta-commentary on the proposal for a meta-structure for DSM-V and ICD-11. *Psychol Med* 2009;39:2099-103.
- [53] Wittchen HU, Beesdo K, Gloster AT. A new meta-structure of mental disorders: a helpful step into the future or a harmful step back to the past? *Psychol Med* 2009;39:2083-9.
- [54] Cramer AOJ, Waldorp LJ, van der Maas HLJ, Borsboom D. Comorbidity: a network perspective. *Behav Brain Sci* 2010;33:137-50.