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Research report

Panic disorder and agoraphobia: A direct comparison of their multivariate comorbidity patterns

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ABSTRACT

Background: Scientific debate has long surrounded whether agoraphobia is a severe consequence of panic disorder or a frequently comorbid diagnosis. Multivariate comorbidity investigations typically treat these diagnoses as fungible in structural models, assuming both are manifestations of the fear-subfactor in the internalizing–externalizing model. No studies have directly compared these disorders' multivariate associations, which could clarify their conceptualization in classification and comorbidity research.
Methods: In a nationally representative sample (N=43,093), we examined the multivariate comorbidity of panic disorder (1) without agoraphobia, (2) with agoraphobia, and (3) regardless of agoraphobia; and (4) agoraphobia without panic. We conducted exploratory and confirmatory factor analyses of these and 10 other lifetime *DSM-IV* diagnoses in a nationally representative sample (N=43,093).
Results: Differing bivariate and multivariate relations were found. Panic disorder without agoraphobia was largely a distress disorder, related to emotional disorders. Agoraphobia without panic was largely a fear disorder, related to phobias. When considered jointly, concomitant agoraphobia and panic was a fear disorder, and when panic was assessed without regard to agoraphobia (some individuals had agoraphobia while others did not) it was a mixed distress and fear disorder.
Limitations: Diagnoses were obtained from comprehensively trained lay interviewers, not clinicians and analyses used *DSM-IV* diagnoses (rather than *DSM*-5).
Conclusions: These findings support the conceptualization of agoraphobia as a distinct diagnostic entity and the independent classification of both disorders in *DSM-5,* suggesting future multivariate comorbidity studies should not assume various panic/agoraphobia diagnoses are invariably fear disorders.
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1. Introduction

Controversy has long surrounded the classification of panic disorder and agoraphobia. Issues of etiology, nosology, and treatment mark the complexity of the relationship between these disorders (see Goisman et al., 1994; Maier et al., 1991), which are associated with chronicity, significant distress, and impairment (Pollack and Smoller, 1995; Wittchen et al., 2010). Much of the scientific debate surrounding these disorders' classification reflects two mutually exclusive views. First, Klein (1980) posits that agoraphobia is a sequela of recurrent spontaneous panic attacks, which are the result of a biological defect (Klein and Gorman, 1987). This characterizes agoraphobia with recurring panic attacks as a severe subtype of panic disorder. Second, is a cognitive-behavioral perspective, largely developed by Marks (1987), which holds that agoraphobia is a separate diagnostic entity from panic disorder that may include concurrent panic attacks but may also present alone. In this view, panic attacks are conceptualized as nonspecific symptoms that can appear alongside several psychiatric illnesses.

Taken together, these opposing interpretations beg the following question: is agoraphobia a severe consequence of panic disorder or a frequently comorbid diagnosis? Individuals experiencing co-occurring panic disorder and agoraphobia report higher levels of panic symptom severity, lower rates of symptom remission, longer durations of illness episodes, and increased risk for the development of other comorbid mental disorders (Bruce et al., 2005; Pané-Farré et al., 2013). This suggests the presence of agoraphobia may be a proxy for panic severity, more social and occupational dysfunction, and greater levels of situational avoidance (Kessler et al., 2006; Nay et al., 2013), and may imply agoraphobia is not a separate entity. Another interpretation is agoraphobia has a direct impact on impairment (Kessler et al., 2006). That is, due to the positive relationship between comorbidity and harmful dysfunction, those with agoraphobia may report greater

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distress and impairment because it is a potential marker of substantial comorbidity with a broad range of severe psychopathology other than panic. Following such research, examining comorbidity patterns between agoraphobia and mental disorders other than panic disorder would be illuminating.

Consequences of the debate between these two conceptualizations of panic disorder and agoraphobia are also reflected in our classification systems' historical origins and its revisions, beginning with *DSM-III* (see Asmundson et al., 2014; Craske et al., 2010; Wittchen et al., 2010). The *DSM-IV-TR* (American Psychiatric Association, 2000) hierarchical classification of panic disorder over agoraphobia required an assessment of both, yielding diagnoses of panic disorder without agoraphobia (PD), panic disorder with agoraphobia (PD+AG), and agoraphobia without a history of panic disorder (AG). Under this rubric, a diagnosis of panic disorder was prioritized over agoraphobia despite any definitive pathognomonic evidence for conceptualizing agoraphobia as a residual of panic disorder. Even so, there is substantial empirical support for agoraphobia as an independent disorder, leading to a modified separation from PD in *DSM-5* (American Psychiatric Association, 2013). Now panic disorder and agoraphobia are defined as two separate, yet still associated, conditions. The remaining conceptual overlap is seen in both sets of these disorders' diagnostic criteria, which include symptoms of the other (this issue is reviewed in detail by Asmundson et al., 2014). This shift highlights the questionable nosological status of these diagnoses and illustrates the importance of systematic investigation to clarify their optimal classification and conceptualization.

One means of investigating construct validity is to embed variables of interest within a broader network and assess convergent and discriminant associations with other variables (Cronbach and Meehl, 1955). For psychopathological constructs, this includes investigations of disorders' comorbidity patterns. Therefore, examining convergent and discriminant patterns of comorbidity for agoraphobia and panic disorder to ascertain the (dis)similarity of these diagnoses may be informative. Epidemiological studies suggest that these phenomena can, but do not necessarily, manifest comorbidly: lifetime prevalence estimates are 1.2–4.2% for PD, .5–1.8% for PD+AG, .2–1.6% for AG (Grant et al., 2006; Kessler et al., 2005, 2006; Nay et al., 2013; Wittchen et al., 2010, 2008). Moreover, Eaton et al. (1994) found 50% of individuals with panic disorder had no history of agoraphobia, and others suggest more than 50% of agoraphobia cases have no history of panic disorder as defined by both *DSM-III* (Angst and Dobler-Mikola, 1985; Joyce et al., 1989; Weissman et al., 1985) and *DSM-IV* (Wittchen et al., 2008). With regard to comorbidity with other mental disorders, higher rates of comorbidity are seen in AG (97%) and co-occurring PD+AG (100%) than in PD (80%) (Kessler et al., 2005, 2006).

1.1. Multivariate comorbidity and transdiagnostic factors

The bivariate comorbidity patterns discussed above provide an informative, but limited, pair-wise perspective on diagnostic construct validity. In contrast, multivariate comorbidity patterns can provide important evidence about these diagnostic constructs' possible independence by investigating how agoraphobia and panic disorder relate to numerous common mental disorders *simultaneously*. To our knowledge, no multivariate comorbidity studies have focused explicitly on contrasting panic disorder and agoraphobia, which leaves the question of their potentially informative multivariate comorbidity patterns unresolved.

Latent variable modeling of multimorbidity among common mental disorders has converged on a structure with two transdiagnostic factors: *internalizing* and *externalizing* (Eaton et al., 2012, 2015; Kessler et al., 2011a, 2011b; Krueger, 1999; Krueger and Eaton, 2015; Slade and Watson, 2006; Vollebergh et al., 2001). The internalizing factor represents comorbidity among mood and anxiety disorders, and the externalizing factor represents comorbidity among impulsivity-related disorders such as substance use and antisocial personality disorder (ASPD). While internalizing can be modeled as a unitary factor, multiple studies have replicated a bifurcated structure, wherein higher-order internalizing subsumes two lower-order comorbidity factors: *distress* (indicated by major depressive disorder [MDD], dysthymic disorder, generalized anxiety disorder [GAD], etc.) and *fear* (indicated by social phobia, specific phobia, posttraumatic stress disorder, etc.) (Eaton et al., 2013b; Kim and Eaton, in press; Krueger, 1999; Slade and Watson, 2006; Vollebergh et al., 2001). Moreover, multiple studies have now established the latent internalizing–externalizing model as being invariant across gender, race/ethnicity, and the adult lifespan, both in cross-sectional age groups followed over time and in individuals followed longitudinally (see Eaton et al., 2015, 2010; Krueger and Markon, 2006).

Among PD, PD+AG, PD+/−AG, and AG diagnoses, little information is available regarding their saturation by latent transdiagnostic factors, and thus their optimal placement in the internalizing–externalizing structure. All four diagnostic combinations have been modeled in the structural literature as indicators of internalizing or fear (Eaton, 2014; Eaton et al., 2013a; Keyes et al., 2013; Krueger and Markon, 2006; Miller et al., 2012; Rodriguez-Seijas et al., 2015b; Slade and Watson, 2006; Vollebergh et al., 2001). Such models reflect a tenuous assumption that these four manifestations are invariably fear disorders, which no study has tested. Some structural psychopathology studies have modeled only AG, PD, or PD+AG; other studies have modeled panic disorder without regard to agoraphobia (PD+/−AG). The issue is complicated by skip-out rules in many datasets, biased towards a temporally primary role of panic attacks and panic-like symptoms.

Directly exploring each diagnostic construct's association to latent transdiagnostic factors of psychopathology has marked implications for structural research—particularly in models requiring *a priori* assignment of disorders to latent factors (e.g., confirmatory factor analysis (CFA))—and may also inform classification. For instance, PD has potential as a marker of distress: although panic attacks are fear-based paroxysmal episodes, evidence points to elevated risk of subsequent depression regardless of whether panic is active or in remission (Kessler et al., 1998). This leads us to question whether the consequences associated with panic attacks (e.g., generalized and longstanding apprehension and worry) are better reflected as distress as compared to fear. In contrast, there is evidence that AG is more specifically associated with anxiety disorders, especially phobias (Asmundson et al., 2014; Wittchen et al., 2010).

1.2. The current study

A direct comparison of these four diagnostic constructs' multivariate comorbidity patterns informs two questions: (1) How do panic disorder and agoraphobia, alone and in combination, relate to other common mental disorders? Such analyses have the potential to inform these constructs' classification by considering their patterns of convergent and discriminant relations. (2) How best should transdiagnostic comorbidity structural models treat various forms of panic disorder and agoraphobia? A multivariate comorbidity investigation may also inform classification by embedding these diagnoses in a broader network, allowing for examination of potential (cross-)loadings that have been historically assumed rather than empirically adjudicated.

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