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SPECIAL ISSUE - EDITORIAL

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Gene-environment interaction and the anxiety disorders

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In this Special Issue a number of leading anxiety researchers have critically reviewed attempts to discover replicable gene-environment interactions (G × E) for the anxiety disorders. They present cogent summaries of what is and what is not known about G × E for each of the anxiety disorders. They have also identified major stumbling blocks to progress, and offered practical suggestions for overcoming these challenges. Some illustrate strategies for better integrating epidemiological and experimental research to advance understanding. Together, they provide a splendid 'stocktake' of where the field currently is, as well as tantalising us with glimpses of what might be just over the horizon. By way of introduction to this series, we highlight several key issues confronting research seeking to model the complexity of nature–nurture interplay [44].

How best to conceptualise and measure the anxiety phenotype?

The anxiety disorders are the commonest class of mental disorder. The main groups of anxiety disorders identified in general population surveys are generalised anxiety disorder (GAD), post-traumatic stress disorder (PTSD), panic disorder and agoraphobia, social phobia, specific phobia and obsessive compulsive disorder (OCD). All, apart from specific phobias, feature strongly in clinical practice. The fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) provides a set of rules for identifying the category of each disorder, although it is clear that they are best represented as dimensions, the threshold that defines the category being an unstable convenience to allow clinicians to communicate easily with each other and determine that treatment is warranted. The threshold may not be ideal for research.

One way of examining the stability of these thresholds is to examine the correspondence when different definitions of the thresholds are used [46]. The text descriptions in ICD-10 and DSM-IV of GAD and PTSD describe similar constructs. Concordance should be very good and both classifications equally valid. In the Australian Survey of Mental Health and Well-Being, the percentage of people positive on either classification who were positive on both was not good; for GAD, it was only 41%, whereas the agreement in PTSD was only 32%. Clearly, different groups of people were being identified. However, the dissonance between the DSM and ICD classifications is not the issue. What is important is that quite small changes in words describing the same criteria can have a substantial effect on people being identified as cases. Researchers use, and often abbreviate, structured or semi-structured diagnostic instruments to identify disorders, but the problem is more complex. In DSM-IV, PTSD requires 25 pieces of information for six criteria, and GAD 25 pieces of information to satisfy the six criteria. ICD-10 is equally complex; for instance, GAD requires 34 pieces of information. Unless researchers are using the best level of structured diagnostic interviews, the identification of a disorder will be imprecise and the identification of the

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role of genes and environment in that disorder even less so.

Most anxiety disorders appear to be dimensional [11]. The inclusion criteria for all anxiety disorders specify either a count of the number of key symptoms above which the diagnosis is made and/or a duration of symptoms requirement. Taxometric analyses support dimensionality. In OCD, taxometric analysis favoured a dimensional model for most subtypes [10]. In GAD, results of a taxometric analysis provided evidence for the dimensionality of worry [41]. In PTSD, taxometric analysis converged on a dimensional solution that PTSD reflects the upper end of the stress response continuum [42]. In social phobia, taxometric analysis produced evidence of a dimensional latent structure [22]. Identification of the genes and environment associated with anxiety disorders might best refer to such dimensions for it is implausible that genes or the environment know about the threshold necessary to identify a category.

Are the individual anxiety disorders distinct? If this were the case then the rates of co-occurrence among these disorders would occur at chance levels. However, the rates of co-occurrence among these disorders are considerably higher than what would be expected [4, 33]. Epidemiological surveys using fully structured interviews show that half the people who meet criteria for one anxiety disorder also endorse symptoms that meet criteria for another mental disorder. Increasing numbers of current comorbid disorders are associated with increased disability, distress, neuroticism and service utilization [3], findings that are inconsistent with comorbidity being an artifact due to symptoms being common to other disorders, or an artifact of the fully structured diagnostic interview.

It has been suggested that such comorbidity rates could reflect the existence of higher order dimensions of psychopathology. A number of studies have examined this and found similar groupings of mental disorders [9, 17, 20, 23–26, 49]. A recent study [47] identified a hierarchical three-factor structure as the best fit to ten common DSM-IV disorders. This structure was characterized by *correlated* distress and fear factors, which were best considered as lower order facets of a broader internalizing factor [50] as well as an externalizing factor. The disorders that were characteristic of the distress factor were major depression, dysthymia, generalized anxiety disorder and post-traumatic stress disorder. The disorders that were characteristic of the fear factor were social phobia, agoraphobia, panic disorder and OCD.

This blurring of the diagnostic boundaries raises a problem for researchers wanting to identify genes or environment as risk factors for specific disorders; they may be, but they also may be risk factors for any disorder subsumed by the distress or fear factors or by any internalising disorder.

Getting a handle on the 'E' in G × E for the anxiety disorders

Theories about the etiology of anxiety disorders vary by disorder category and in terms of the importance placed on conditioning processes for acquisition (e.g., [27, 30, 37, 38]). This issue is nontrivial in the context of attempts to uncover G × E for the anxiety disorders. If a key role for conditioning is upheld, then selection of environmental risk factors should be relatively straightforward, involving directly or vicariously experienced trauma, or the transmission of information about such dangers. If the more biologically-based theories (many of which allow for some form of conditioning or learning) are correct, then identification of appropriate environmental risks will require consideration of a broader range of stimuli than are usually considered. An illustration of this conundrum comes from Kendler et al. [18] who tested three stress-diathesis hypotheses for phobias (agoraphobia, social phobia and specific phobia) in a large twin sample, and found no support in any of the three tests. They concluded that their findings were "compatible with nonassociative models, which postulate the vulnerability to phobias is largely innate and does not arise directly from environmental experiences. The stress-diathesis model may not be an appropriate paradigm for phobic disorders" (p. 242).

Others have also questioned the *necessary* role of trauma in the development of at least some fears and anxieties (e.g., [13, 28, 35]). In contrast, robust environmental risk factors have been identified for GAD (e.g., [19, 31]), and for PTSD [21, 48], which, by definition, requires a traumatic precipitant [1]. The picture is less clear for OCD and social phobia, despite many promising leads (e.g., [36, 39]). Thus, determining the 'E' in G × E for some, if not all, anxiety disorders may not be as straightforward as is often assumed. Progress toward uncovering G × E for the anxiety disorders may depend in part upon greater precision around the true nature of the environmental risk. In this regard, closer integration of epidemiology with neuroscience offers exciting possibilities that leverage the complementary strengths of both approaches for understanding how environmental risk operates in the context of genetic variability (see [7]).

Assuming plausible environmental risk factors have been identified, it will be important to establish their independence from gene effects, i.e. passive, active or evocative gene-environment correlation [16, 34]. That is, environmentally-mediated risk cannot always be assumed, despite use of ostensibly environmental measures. This assumption requires checking, and there are a range of methods available for doing this [45].

Measuring the environment is not easy. Although self-report is cheap and practical, problems with accuracy and recall bias [12] emphasise the value of multisource data collection for mitigating error inherent in any single assessment method. Wherever possible, multiple and complementary measures of environment risk should be obtained. This 'belt and braces' approach permits triangulation [43] and provides a more complete picture of the environmental risk spectrum, as different sources provide different but equally valid information about environmental risk exposures. Laboratory testing will often be a useful adjunct, notwithstanding the challenges to ecological validity when extrapolating from controlled laboratory settings [29]. Cumulative estimates of risk are likely to provide greater purchase on 'E' than single risk factor approaches (e.g. [15]), as risk often accumulates over long periods and aggregates across multiple risk factors.

Good sampling and measurement are crucial in studies of G × E. Ideally, general population samples should be assessed because they represent the full range of both environmental risk exposure and genetic variation. High quality measurement on multiple occasions significantly increases the likelihood of detecting G × E, while reducing the sample size required for detection [51]. Further, some G × E may rely on 'critical' periods or exhibit latency effects, hence the desirability of a lifecourse or developmental perspective [5]. Interrogating existing databases (cf. [40]) represents a prudent and cost-effective strategy, particularly if data about proximal risk factors are available. Here it is important to recognise that the main value of distal (or downstream) risk factors lies in 'setting the scene' for proximal risk factors to exert their influence—distal risk factors (e.g. low socioeconomic status) by themselves are unlikely to provide robust indices of environmental risk in G × E research.

And the 'G' in G × E?

Selection of genes for tests of G × E hypotheses should be guided by hypothetico-deductive principles. Ideally, there should be some evidence, albeit only circumstantial at times, suggesting that candidate genes are related to both the environmental risk factor *and* to the outcome of interest (e.g., [6, 8]). There should also be some evidence of a biological pathway or mechanism consistent with the G × E hypothesis. A number of other considerations are important for framing G × E hypotheses, and the interested reader is referred to [32] for a review of these strategies.

So, how should we proceed?

Hymen [14] asked "can neuroscience be integrated into the DSM-V?" He concluded that it was probably premature to bring neurobiology into the formal classification of mental disorders. However, he thought it was not too early to use neurobiology as a central tool to rethink the current approach. We think that it is not too early to recruit environmental factors, identified prospectively, as another tool to rethink the current approach. But how should this be done? Each of the papers in this series reference many findings. How could we know which is likely to be replicated and become a fact? Neither meta-analysis nor data consolidation strategies like the Cochrane Collaboration are sufficient for this task. Hymen argues for committees to adjudicate. Andrews et al. [2] did something similar. They used a group of researchers to identify 'facts'—the stubborn findings that regularly recur, discarding unreplicated findings and replicated findings that had been successfully challenged. The resulting restricted set of stubborn findings informed theory and additional research. They were fortunate to be working with a dimensional disorder with few disputed boundaries. Research in the anxiety disorders will be more difficult as account is taken of whether the stubborn findings refer to the disorder category, the disorder dimension, the disorder stress or fear factor, or to internalising disorders in general. We live in exciting times. At such times, it is important to get the questions we are asking, and answering, clear.

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