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SPECIAL ISSUE

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Finding gene-environment interactions for phobias

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Abstract Phobias are common disorders causing a great deal of suffering. Studies of gene-environment interaction (G × E) have revealed much about the complex processes underlying the development of various psychiatric disorders but have told us little about phobias. This article describes what is already known about genetic and environmental influences upon phobias and suggests how this information can be used to optimise the chances of discovering G × Es for phobias. In addition to the careful conceptualisation of new studies, it is suggested that data already collected should be re-analysed in light of increased understanding of processes influencing phobias.

Key words gene · environment · interaction · phobia · twins

Finding gene-environment interactions for phobias

Despite having saved hard for her "trip of a life-time", a friend recently revealed that she was half-dreading her honeymoon because she knew that her new husband would spend the entire 11 h flight in a state of complete terror—a result of his lifelong fear of flying. Specific phobias are one of three main types of phobias highlighted in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders [1]. The other two are social phobia (characterised by high levels of anxiety resulting from exposure to social or performance situations) and agoraphobia (clinically significant levels of fear or avoidance of certain places or situations which are considered to be difficult or embarrassing from which to escape). Agoraphobia is often co-morbid with panic—and agoraphobics may fear places and situations in which they are concerned that they will not receive help if panicking. Unfortunately, these crippling disorders are common. Indeed, estimates from the national comorbidity survey—replication place anxiety disorders as the most common category of mental illness [21]. Of the anxiety disorders, phobias are known to be amongst the most commonly occurring difficulty [10, 21]. Phobias occur more frequently in females than males, may first appear early in life (especially with regards to specific phobias), and occur concurrently and longitudinally with certain internalising and externalising disorders [10, 21, 22]. In addition to considering phobias in terms of *diagnoses*, it is possible to examine specific fear *symptoms* and considering both approaches may be optimal when designing genetic studies [39]. Indeed, focusing upon a single measure of phobias may have limitations, as suggested by research demonstrating that information about fear and phobias assessed at personal interviews shows substantial unreliability [15].

This article addresses issues relevant to the aetiology of phobias. Specifically, there are now rich data estimating and describing genetic and environmental influences upon phobias. However, there have been few investigations of gene-environment interactions (G × E) in relation to phobias. Given that it is becoming increasingly clear that sensitivity to environmental insults is influenced by genotype and that

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this information is essential for understanding the complex pathways by which genes influence behaviour [33], this represents a sizeable limitation to knowledge with regards to the aetiology of phobias. In the hope of stimulating research into this area, this article describes what is known about genetic and environmental influences on phobias and discusses issues that need to be considered when designing studies investigating G × E for phobias.

Phobias and other anxiety disorders

When exploring genetic and environmental influences upon anxiety, researchers often combine different types of anxiety based on the findings that there is strong cross-sectional and longitudinal comorbidity between the different disorders and similarities between anxiety disorders in terms of mental health histories [10]. Furthermore, factor analyses suggest that different anxiety disorders share a common factor structure [23]. However, there are also reasons to examine phobias separately from other anxiety disorders. For example, factor analyses also suggest that within internalizing disorders it is possible to distinguish between generalized anxiety disorder (GAD) which can be grouped with depression; and a group comprising specific phobias, social phobias, panic and agoraphobia [23, 43, 44]. Furthermore, twin studies suggest that the genetic aetiology of specific phobias may differ from that of other anxiety disorders [13, 19]. In terms of developmental pathways, whereas most adult anxiety disorders are largely non-specific in terms of their history of anxiety disorders (they are preceded by a range of juvenile anxiety disorders), adults with specific phobias are unique in having a history of juvenile phobias but not other anxiety disorders [10]. This finding is consistent with prior research highlighting specificity within phobias: adolescent simple phobias predicted simple phobias in adulthood, whereas social phobias in adolescence predicted later social phobia [28]. Furthermore, selective serotonin reuptake inhibitors (SSRIs) are used to treat various anxiety disorders—but are not typically used in the treatment of specific phobias, due to their limited effectiveness. Hence, studies focusing exclusively upon phobias (as opposed to studies including phobias as part of a general anxiety scale) are the focus of this report.

Genetic and environmental influences

It has long-since been postulated that both genetic and environmental factors are important in the development of phobias. Indeed, Martin Seligman highlighted in an early paper the importance of environmental influences in the development of specific phobias by pointing out that a neutral stimuli (e.g. a horse) can become aversive when paired with an external negative event (e.g. receiving an electric shock) [35]. This early report also pointed out that it is easier to condition phobias towards certain stimuli (e.g. snakes) than others (e.g. flowers)-which may be due to a genetic predisposition to associate certain objects with fear (more recently, see [11] for a genetic study of fear conditioning).

While direct conditioning has been the most influential theory of fear acquisition, other pathways are also important. Indeed, Rachman proposed three main pathways to fear conditioning involving direct conditioning; vicarious acquisition and informational/instructional acquisition [31]. Each of these pathways has received support from various sources (e.g. for a test of the informational/instructional pathways see [6]). Although traditional theories have tended to emphasise the importance of experience in the development of phobias, a fourth, complementary, non-associative route also needs to be acknowledged (for a review see [30]). Non-associative theories of fear acquisition emphasise that evolutionary-relevant fears (such as fears of snakes and heights) can appear with minimal or no learning.

Evidence that both genetic and environmental factors are important in explaining individual differences in phobias is provided by data from twin studies. These studies compare similarity between monozygotic twins who are genetic clones, and dizygotic twins who share on average half of their segregating genes (for further discussion of twin methodology see [29]). Results of studies have shown that phobias are more likely to co-occur in monozygotic than dizygotic twins.

Studies focusing upon children have found significant genetic influence upon fears and specific phobias examined in terms of symptoms [42] and disorders [2, 24]. Similarly, studies of adult twins have highlighted the importance of genes influencing specific phobias (e.g. [15, 17, 38]), social phobias (e.g. [15, 17, 38]) and agoraphobia (e.g. [15, 17, 38]).

In addition to distinguishing genetic and environmental influences, most twin studies also distinguish *shared environmental influences* (those that make family members alike) and *nonshared environmental influences* (those that make family members differ). Nonshared environment appears to have a robust influence on phobias (e.g. [2, 17, 20]). However, research has produced mixed results with regards to shared environmental influence. For example, one study of children highlighted shared environmental influence on phobias [24] whereas another did not find this type of influence to be significant [2]. Similarly, there have been mixed results from studies of adults—with a study of males revealing possible shared environmental influence on agoraphobia and social phobia but not specific phobia [17]. A further report showed negligible shared environmental influence on panic-phobia in males

but a more modest influence on females [20]. The distinction between shared and nonshared environmental influences is relevant to studies of G × E. Indeed, most twin analyses do not estimate G × E and if positive interactions between genetic and shared environmental influences are present but ignored they artificially inflate estimates of genetic influence. In contrast, positive interactions between genetic and nonshared environmental influence are estimated as nonshared environmental influence [32].

Studies of both children and adults have highlighted differences between the sexes in terms of the magnitude of influences on different types of phobias (e.g. [20, 24]). Further studies have also revealed that some of the genes influencing phobic disorders may differ between males and females. For example, a study of over 3,000 adult twin pairs found that exactly the same set of genes influenced animal fears in both males and females [14]. In contrast, for agoraphobia, situational phobia and blood/injury phobia there was some genetic overlap although different genes also influenced these traits in males and females separately. Hence, the impact of sex differences appears to vary across phobia subtype. To add further complexity, sex differences have also been found in the magnitude of influences accounting for stability of symptoms. Specifically, one study found that, for males, genes account for 73% of the stability of panic-phobic symptoms over a mean 14-month period, as compared to 24% for females [20]. Genetic and environmental influences clearly differ by phenotype and sex and these variables therefore need to be considered when planning G × E studies for phobias.

Twin studies have also increased understanding of comorbidity. For example, a twin study of different phobias in males revealed that genetic risks were partly common and partly specific across different types of phobias [17]. Studies examining the overlap between different types of anxiety have also highlighted an overlap between genes influencing different types of anxiety (for a study of anxiety-related behaviours in pre-school twins see [5]), although such studies have also suggested that the aetiology of specific phobias may be largely distinct from that of other anxiety disorders [13, 19]. In addition to providing information about the co-occurrence of anxiety disorders, studies of comorbidity examine different types of disorders. For example, those with phobias are at increased risk of major depressive disorder [12] and comorbidity between the two types of illness appears to be influenced by genetic and environmental influences to different degrees depending upon the type of phobia being examined in association with depression [18, 26]. Longitudinal associations between phobias and depression have also been reported and genetic decomposition of this association in a sample of over 600 female twin pairs revealed that genetic influences on depression after 14 years of age reflect liability to symptoms of phobias before the age of 14, whereas shared environmental influences on depression before 14 years of age influenced phobias after the age of 14 [36] highlighting the role of development in the complex links between phobias and depression. Twin studies of co-occurring traits are useful when planning studies of G × E, as strong correlations between the influences (e.g. genes) on different traits (e.g. depression and phobias) suggest that once a specific influence on one trait (e.g. depression) has been identified, this same influence may also be a good candidate to explore in models of G × E with regards to the co-occurring trait (e.g. phobias).

Genetic models have also been used to shed light on links between phobias and cognitive dimensions and one study reported a strong genetic correlation between fear of negative evaluation (a cognitive construct central to social phobia) and social anxiety related personality traits [40]. It may be fruitful to measure cognition (in addition to phobias) in G × E models as it is possible that cognitive style mediates some of the genetic risk on phobic symptoms. Measuring cognitions central to phobias may therefore allow testing of theories underlying the development and maintenance of these difficulties. Furthermore, certain central cognitive aspects of phobias may be more directly influenced by genes than the symptoms of phobias themselves. Such "endophenotypes" for phobias need to be proposed and tested empirically (for further discussion of endophenotypes in genetic research see [9]).

There has been extensive debate concerning the adequacy of the twin methodology. Critics of twin research claim that the assumptions underlying the methodology are unfounded and so estimates provided by studies employing twin methodology are inaccurate. Twin researchers justify assumptions made and point out that this is amongst the best methodologies available whilst emphasising the need for cautious general interpretation of estimates from twin data (see [29] for further discussion of this topic). Although it is beyond the scope of this review to represent this highly charged debate, it is important to mention criticisms, which have focused upon phobias. One such criticism concerns generalizability. In order to extrapolate results from twin studies to the non-twin population, it must be assumed that twins are similar to non-twins. However, this is not necessarily the case for phobias—as one study including both twin and sibling pairs revealed higher levels of heritability for panic-phobia when focusing upon twins exclusively than when including non-twins [20]. Other studies have emphasised similarities between twins and non-twins, however, and the prevalence rate for psychiatric disorders is similar in twins and non-twins [37]. Despite criticisms, twin studies have revealed a great deal about genetic and environmental influences on phobias. Together with early conditioning studies which suggest that phobias may arise from genetic propensities which are expressed fol-

lowing exposure to certain environmental stimuli, twin studies have stimulated hypotheses concerning G × E for phobias.

Finding G × Es for phobias

The finding from twin studies that environmental factors are influential (albeit to varying degrees) sits well with clinical observations that patients with phobias often report early traumatic experiences associated with their phobias. However, such observations may not demonstrate purely "environmental" influences on phobias as it is known that genes may influence both *exposure* and *sensitivity* to environmental insults. Imagine for example that a child has genes associated with high levels of behavioural inhibition. Perhaps these genes influence the way in which the child interacts with unfamiliar animals—and the awkward stroking of a dog may lead to the child being bitten (an example of gene-environment correlation, rGE). Based on the child's genetic propensity, this environmental trauma may make this child (as compared to certain other children) particularly vulnerable for developing a dog phobia (an example of G × E).

There is little evidence of rGE and G × E for phobias. However, one study explored the possibility of a stress-diathesis model for phobias in 7,500 twin pairs [16]. The authors examined whether phobic individuals who reported higher levels of environmental stress (e.g. experiencing a severe trauma) had a lower genetic loading (i.e. were phobias were less heritable in this sub-group?) as compared to those who reported lower levels of environmental stress (e.g. observing a trauma occurring to another or experiencing a mild trauma). The results did not support the stress-diathesis model and the authors proposed that this is most likely because the model is not applicable to phobias and instead argue that vulnerability to phobias may be largely innate without the need for environmental experiences.

An alternative suggestion of these null results concerns the measure of the environment—which could have been inappropriate. While the authors point out that this explanation is unlikely given the adequate reliability and validity of their assessment of stress—the issue of how best to conceptualise the environment is of central importance when designing studies of G × E. For example, it is important to decide upon the optimum aspect of the environment on which to focus—and there are distinctions between "negative life events" influencing anxiety and depression, with "threat" events associated with anxiety and "loss" events associated with depression (e.g. [7]). Additionally, there may be differences between anxiety disorders with regards to environmental influences. For example, while elevated rates of abuse have been reported in individuals with different types of anxiety disorders, two studies suggest that there may be a particularly strong association between abuse and panic as compared to certain other anxiety disorders [34, 41]. Further still there are likely to be distinctions between different types of phobias in terms of environmental influences. For example, Kendler and colleagues [16] identified differences in the mode of acquisition of different types of phobias. Whereas experiencing a trauma was identified as the mode of acquisition for 48% of participants with *animal fears*, it accounted for just 23% of cases of *social fears*.

In addition to consideration of the optimal environmental phenotype to measure in G × E models, the *timing* of environmental experiences also needs to be considered. First, the impact of certain life events may vary with age. For example, being bitten by a dog may represent a more traumatic experience for a young child who has not yet developed the cognitive capacity to deal with this event, as compared to an adult. A further consideration concerns latent inhibition, which refers to a phenomenon whereby being pre-exposed to a neutral stimulus results in subsequent difficulty when attempting to condition that stimulus to be aversive. This theory would explain increased susceptibility of dog phobia in a bitten child as compared to a bitten adult by pointing to greater neutral exposure to dogs in adults as compared to children. As environmental events associated with phobias may have occurred early in life care needs to be taken when measuring events that have occurred a long time ago. In particular, use of prospective longitudinal data eliminates the need for retrospective reporting, which is notoriously unreliable. Research also suggests that phobias may develop as an acute reaction to an event—and genetic moderation of response to experimental manipulations of the environment (e.g. requesting patients with social phobia to give a public presentation; using novel paradigms to eliciting an acute response in "real-time") is therefore likely to be scientifically important. Ethical considerations in relation to eliciting or inducing stress in participants suggests that animal studies are likely to continue being used in order to establish responses to certain environmental manipulations (e.g. classical conditioning studies of phobias).

In addition to environmental explanations for the lack of evidence for G × E for phobias, a further explanation could be that previous studies have not assessed genetic influence appropriately. For example, sample size must be considered in order to ensure appropriate power to identify the interactions being sought. While previous studies employ large sample sizes and are therefore appropriate with regards to this issue [16], these studies have *estimated* as opposed to *measured* genetic influence, and the latter approach has obvious advantages. Consequently, in addition to identifying statistical G × E, studies of other phenotypes have begun to examine associations

between *specific genes* and environmental factors (e.g. the short allele of the 5-HTT promoter polymorphism has been associated with greater sensitivity to life events in the development of depression, [4]). When designing studies of G × E for phobias, researchers should capitalise upon what is already known about specific genes linked with phobias in order to select candidate genes to examine in models of G × E. For example, there have been associations between phobias and the *val/val* genotype of the catechol-*O*-methyltransterase (COMT) Val158Met polymorphism [25] and with genes involved in thyroid hormone receptor function [27]. Candidate genes may also come from other types of studies, such as twin studies of comorbidity—as knowledge of strong genetic overlap between disorders suggests that once a gene has been associated with one disorder it may also be associated with the comorbid disorder.

Conclusion

Twin studies have been essential in advancing understanding of genetic and environmental influences on phobias—although previous research is limited in that it largely ignores associations between genes and the environment. Studies of G × E inevitably involve measurement of three components: genes; the environment; and phobias. Given developing knowledge of all three, it is increasingly likely that *novel studies* utilising this knowledge and designed to identify G × E for phobias will succeed.

In addition to the careful conceptualisation of new studies designed to find G × Es for phobias, researchers may also benefit from *re-examining data, which have already been collected*. Indeed, distinctions between phobias and other types of anxiety suggest that it may be beneficial to regroup data already collected in order to focus upon: (1) specific types of phobias (rather than anxiety as a whole); (2) environmental factors which have been directly linked to phobias (rather than more general measures of stress); and (3) genes that have been associated with phobias (rather than more generally with anxiety). This approach is likely to be particularly fruitful in light of continuous growth in knowledge of genes and environmental factors linked to phobias.

In order to develop a more comprehensive understanding of phobias, it may also be worthwhile acknowledging other disciplines. Twin studies have already used important information provided by cognitive psychologists to increase understanding of the aetiology of phobias. Furthermore, reviews have stressed the mutual benefit of combining gene-environment interactions and neuroscience in psychiatry [3]. For example, based partly on G × E findings that genetic influence on a trait may only appear following a stressful experience, one study explored an association between a specific polymorphism and a brain response, finding that the 5-HTT candidate gene is associated with individual differences in amygdala responsiveness to social anxiety provocation in patients with social phobia [8]. In turn, such findings provide inspiration to researchers developing studies of G × E for phobias.

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