Invited Commentary on Patho-Genetics of Posttraumatic Stress Disorder

Recent advances in molecular genetics have simplified sample collection and lowered the cost of genotyping, and subsequently have led to a drastic increase in the number of psychiatric genetic investigations. Increased attention to genetic factors in the etiology of posttraumatic stress disorder (PTSD) and other psychiatric conditions has also followed. The paper by Dr. Domschke provides a brief overview of the genetic investigations on PTSD to date, and serves as a great starting point for a reader new to this area of investigation. The purpose of this commentary is to highlight a few central issues, developments, and limitations, in this line of research. This article, nor the article by Dr. Domschke, are not meant to provide an exhaustive review of either the literature on genetics of PTSD, or on genetically informed research methodologies, but instead aims at highlighting key findings and issues that are central to the conduct of state of the science genetic studies. The interested reader is referred to review articles on genetics of PTSD (e.g., Cornelis et al. 2010, Afifi et al. 2010), more detailed articles on genetics for social scientists (Dick et al. 2011), and methods texts (Neale et al. 2008).

Although recent years have seen an exponential increase in the number of studies examining the influence of candidate genes on PTSD diagnosis and symptomatology, the majority of studies have been characterized by relatively low rates of PTSD with apparent inconsistencies in gene-associations linked to marked differences in methodology. It is clear that the genetic association-PTSD literature is limited in a number of ways. There are very few genetic association studies of PTSD compared to other disorders such as major depression that have similar heritability estimates. Similarly, very few candidate genes, which are then selected from a limited number of theoretically relevant neurobiological pathways, have been targeted in genetic studies of PTSD. The sample sizes of the available studies are relatively small and are limited in the variability within trauma exposure type and duration. Extant studies evidence many of the challenges common to trauma research including control group trauma exposure, comorbidity in both case and control groups, influences on likelihood of exposure to trauma, time since index trauma, and number/type/timing of trauma(s) experienced. The combination of important methodological differences and relatively few comprehensive studies make interpretation of findings across studies difficult – observed findings may indicate specificity of real genetic effects or may simply reflect design limitations. Finally, an overview of the available literature points to many conflicting results, and inconsistencies are likely the result of sample and design differences and highlight the need to address such differences in future genetic-PTSD research. Given that the costs associated with high throughput genotyping have decreased with technological advancements, GWAS has become a relatively more feasible option for examining gene-PTSD relations, however, such investigations need to be adequately powered. Such studies take an agnostic approach, rather than the theoretically-based gene selection process employed in candidate gene studies, and compare frequencies of hundreds of thousands of SNPs across the entire genome of cases to those of controls. GWAS are especially powerful when genetic variations with appreciable frequency in the population at large, but relatively low penetrance, are the major contributors to genetic susceptibility to common diseases. Large, carefully-planned GWAS with sufficient power and replication would provide a unique opportunity to identify key variants underlying the disorder. Furthermore, future research utilizing global "omics" platforms (e.g., investigation of the methylom) provide promise for unraveling the complex ways in which genes and environment interact for this key anxiety disorder.

Two other conceptual issues are key to mention for this line of research, both falling under the broad category of "*gene-environment interplay.*" These issues are particularly important to consider for disorders such as PTSD that are contingent on an environmental event. Gene-environment interplay involves investigating the relationships between various genetic and environmental factors as they relate to a particular phenotype and includes two primary approaches: gene-environment interaction and gene-environment correlation. *Gene-environment interactions* (GxE) can be thought of in terms of the genetic variation modifying the relationship between environmental exposure (e.g., a traumatic event) and the phenotype (e.g., PTSD), or the environment modifying the effect of genetic variation on an outcome. *Gene-environment correlation* (rGE), on the other hand, refers to the extent to which individuals create and influence their own environments). In other words, rGE reflects the passive and active ways in which an individual's genotype influences their subsequent environment. Controlling for rGE and GxE in molecular studies of PTSD is crucial to moving the field forward.

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