Genes, Environment and Psychopathology: Understanding the Causes of Psychiatric and Substance Use Disorders

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This book describes the hypotheses, methods, analyses and results of the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPSUD), a study designed to disentangle the genetic and environmental contributions to psychiatric and substance use disorders. Started 20 years ago, VATSPSUD followed an unselected population through time, administering up to four interviews to twins and their family members at approximately 1- to 3-year intervals. Over 10,000 individuals have been interviewed, including over 400 complete twin pairs of each sex combination. The interviews included standard psychological and psychopathogical assessments which can lead to allocation of diagnoses for psychiatric disorders. Also included were a wide range of questions giving information on demographics, childhood experiences, substance (caffeine, alcohol, tobacco and illicit drugs) use and family history of psychiatric disorders or substance abuse. In this way, a substantial body of data has been collected on a population cohort that differs significantly from clinically derived psychiatric cohorts. The classic twin design, in which the comparison of monozygotic (MZ, identical) and dizygotic (DZ, fraternal) twins gives a handle on genetic versus shared environment effects, is enhanced by the wealth of information on environmental risk factors, some of which are measured prior to diagnosis of a psychiatric or substance disorder.

The authors Kenneth Kendler and Carol Prescott are both highly respected researchers in their fields. Kendler is the Banks Distinguished Professor of Psychiatry and Professor of Human Genetics at Virginia Commonwealth University (VCU). Although acknowledging the many contributions of others, he is undoubtedly the driving force of VATSPSUD, instrumental in its design and maintaining the pace to see it through to completion (although with such a wealth of information there will always be more to do and to add). Carol Prescott is Professor of Psychology at the University of Southern California but worked at VCU from 1992 to 2005 as co-director of VATSPSUD specializing in the substance use and abuse aspects of the project. Both have received special prizes from professional societies of psychiatry acknowledging the value of VATSPSUD and the foresight with which it was conceived and productivity that has been delivered.

The book is divided into five sections. The first 'Background' section lays out the motivation for the VATSPSUD, the study cohorts it encompasses and the questionnaires administered. The attention to detail seen throughout the study is demonstrated by checks on validity of the representativeness of the sample, reliability of self-reported zygosity status and interviewer reliability. The section concludes with an introduction to path analysis and structural equation modeling used throughout the book.

The second section examines the evidence provided by VATSPSUD for genetic risk that may underlie internalizing disorders (major depression, anxiety disorders and phobias) and externalizing disorders (antisocial behavior and substance abuse). The third section goes on to examine the evidence for environmental risk factors considering separately the impact of childhood experiences and of stressful life events in adulthood on adult psychopathology. The fourth section is entitled 'a closer look at genetic and environmental influences' and looks for evidence of the way genetic and environmental factors interact.

In this way, the authors build up an overall picture based on solid foundations. Wherever possible they address potential points of criticism by formulating a hypothesis and collecting data to address it. With this attention to detail, the book sets a fine example to students and researchers for rigor in scientific method. For example, chapter 6 is dedicated to addressing the underlying assumptions of their twin methodology. An important assumption is that of equal common environment for MZ and DZ twins. Many researchers are happy to acknowledge the assumption and continue. Instead, Kendler and Prescott (and their many warmly acknowledged collaborators) ensured that questions about degree of shared environment

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(friends in common, perception as being seen as an individual or as one member of a pair, parental treatment) were included in questionnaires and could be used in analysis. It is widely recognized that physical attractiveness influences a wide range of social interactions and therefore some critics have suggested that the greater physical resemblance between MZ twins may cause resemblance for psychological traits. This criticism was formulated into a hypothesis and a specific experimental measure taken (a score of pair resemblance from photographs) which could be included as a covariate in analyses. In most situations, the equal common environment assumption was shown to be upheld. Similarly, most of chapter 12 is dedicated to issues dealing with unreliability of measurements and how this has been investigated using test-retest measurements and multiple-rater methods (using individual and co-twin responses). It is certainly hard to fault their scientific method: at every step they willingly point out the limitations of their study and it seems that no turnable stone has been left unturned.

By considering first genetic risk factors and then environmental risk factors the authors take on the role of first psychiatric geneticists and subsequently epidemiologists, demonstrating that both have been right in their respective approaches but that the self-imposed barriers between them are artificial. These barriers reflect partially the different schools of learning traditionally followed by the different study fields but also reflect the type of study sample collected and available to each. Psychiatric geneticists tend to collect study samples of clinically presented subjects and have enriched their collections by focusing on families with many affected individuals with little regard to concurrent environmental risk factors. In contrast, epidemiologists may collect prospective study samples noting contributions of environmental risk factors to disease liability but with no indication of the possibility of the contribution of genetic risk if family members have not been included in the study design. Here lies the true power of the VATSPSUD study as both genetic and environmental risk factors can be estimated concurrently from the same data set, pulling together the divergent fields into one of psychiatric genetic epidemiology. In considering the concurrent estimation of genetic and environmental risk factors, the authors argue strongly against the independence and additivity of these risk factors, in favor of a much more complex etiology so that 'these two broad classes of factors are 'woven' together into a complex fabric to determine an individual's overall level of risk' with genetic risk factors influencing the exposure to environmental risk factors.

The culmination of the arguments developed through the first four sections comes together in the aptly named section 5 'Bringing it all together' with chapter headings which highlight the complex interplay between genetic and environmental risk factors: chapter 13, 'The genetics of the environment', chapter 14, 'Genetic control of exposure to risk factors', chapter 16, 'Genetic control of sensitivity to the environment'. For example, genetic risk factors, influencing, say, novelty seeking, can lead us to environmental situations more inducive of stressful life events. These stressful life events, in turn, may lead to expression of specific genetic risk factors to depression that are not observable in nonstressful situations.

The pinnacle of the thesis developed throughout the books is presented in Chapter 17 'Integrative models' in which the authors cast aside any thoughts of 'too hard' and present a 'rough draft' integrative model for major depression separately for each sex. In this model 18 predictor variables are used to predict incidence of major depression in the last year. The variables are organized into five developmental tiers: (1) childhood (genetic risk factors, disturbed family environment, childhood sexual abuse, early parental loss), (2) early adolescence (neuroticism, low self-esteem, early-onset anxiety, conduct disorder), (3) late adolescence (low educational attainment, lifetime traumas, low social support, substance misuse), (4) adulthood (divorce, history of major depression), (5) past year (past-year marital problems, total difficulties and dependent and independent stressful lifetime events). The results are presented as a complex path diagram. Up until this chapter all path diagrams are fairly easy to interpret for those not familiar with structural equation modeling (SEM), as the diagrams are first presented as a model which is discussed in the text and then redrawn to show analysis results with paths labeled with a number representing the percentage of the total variance attributable to each path. Therefore, checking that contributions sum to 100 confirms understanding for the reader. The path diagram of the integrative model is a quantum leap in complexity as the path arrows are now labeled with partial regression coefficients, and a check that the sum of the product of the squared coefficients through each path is unity is not a back-of-the-envelope calculation. The complexity, of course, is a reflection of reality and the authors are at pains to break down the complexity and urge the reader to persevere while they explain the diagram step by step, redisplaying it five times with different paths highlighted and discussed. The complexity of this final diagram highlights the true power of SEM. SEM is the standard method of analysis in behavioral genetics and the simple models of the earlier chapters can be equivalently expressed in a linear mixed model framework with results expressed in variance-covariance or correlation matrices, an approach perhaps more transparent to a wider genetics and statistics audience. On the

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other hand, the authors have presented a complete volume of complex statistical analysis that is explained with clarity using no more than a handful of equations, an approach which allows the reader to focus on the phenotypes and underlying risk factors and opens the readership to the widest possible audience of academics, students and professionals.

The discussion of the integrative model concludes that major depression is a 'complex, multifactorial disorder, the liability to which is influenced by a broad array of risk factors that act at different stages of development'. The integrative model is presented as a first draft and the authors are cautious in their interpretation or over-interpretation of the results estimated from a data set, which although large in human study terms, is small for the number of parameters included in the model. None-the-less, integrative models derived independently for females and then males are in surprisingly good agreement, suggesting that genetic and environmental risk factors operate in similar ways in the sexes, despite the higher incidence of depression in women. The value of the integrative model is that for the first time a model has been presented with evidence all drawn from a single data set as opposed to literature review or speculation. Having demonstrated the complexity, the authors offer no indication as to whether they believe resources should be allocated to the collection of data sets that would allow a more robust draft of the integrative model to be compiled. While tackling the integrative model thus far has been useful, will building a more refined and accurate model add to the ultimate aims of prevention, diagnosis and treatment of psychiatric and substance disorders?

Since the book argues a theme through the first four sections it is perhaps not easy to 'dip in' to the book and pull out the correct take-home message. Those just interested in the punch line could turn straight to chapter 18, 'Conclusions', in which four central themes and eight minor themes set out in the introduction are discussed in turn. In fact, this chapter is perhaps a good starting point for all readers as it demonstrates the overall value of the VATSPSUD study and provides motivation for progressing through the foundation stones in sections 1 to 3 into the complexity of sections 4 and 5. Only one page is dedicated to 'VATSPSUD and the New Molecular Genetics', but the length of this section should not undermine the importance of its message. Genetic linkage and association studies have made surprisingly little headway in the identification of causal variants in many complex human diseases including psychiatric disorders. The vast majority of human subject collections are clinically derived with little or no indicators for environmental risk factors based on the view that causal variants will have sufficient effect size to break through any environmental masking. The results of VATSPSUD suggest that genetics and environment must be considered together and that continuous endophenotypes may be more useful than dichotomous diagnoses for identification of causal variants. The rate-limiting factor may well be the availability of suitable study samples.

The contribution of VATSPSUD to the psychiatric community cannot be understated. The authors and their collaborators must be congratulated not only for the initiation of the project, but for seeing it through and for communicating the results in a clear, thoughtful and timely way. It is hard not to be overwhelmed by the shear volume of work that underlies this book. Acknowledgments include two full pages of names of researchers, project managers, interviewers, database managers and statisticians on top of the twin family participants. Publications total 179 peer reviewed papers of which Kenneth Kendler is first author on approximately one half. The book is the icing on the cake, bringing together the wealth of knowledge gained from VATSPSUD into a single volume. It is clear throughout the book that there have been critics of VATSPSUD and of the approaches taken by twin family researchers in general. These criticisms have been taken seriously and are discussed throughout the book. It is often easier to criticise than 'to do'. It is hard to imagine that even critics could not be impressed with what VATSPSUD has achieved. This book is a gift to all those willing to embrace the underlying complexity of psychiatric disorders and substance abuse.

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