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The Genetics of Personality/Psychopathology: A Brief Review of Constructs, Results, Approaches and Implications.

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Abstract

Psychiatric "conditions" are part of the personality sphere and not discrete "disorders". All personality traits are significantly influenced by many genes of very small effect. The personality traits that imply dysfunction are positively correlated, implying a general "p" factor. The brain is a "kludgy" organ due to the way it evolved. It is likely that explanations of psychopathology will also be "kludgy". Nevertheless, current research suggests that we are making sure but slow progress.

Keywords

Personality, Psychopathology, Genes, Quantitative genetics, Molecular genetics, Heritability, Twins, GWAS

"We shall never, probably, disentangle the inextricable web of affinities between the members of any one class; but when we have a distinct object in view, and we do not look to some unknown plan of creation, we may hope to make sure but slow progress" (Darwin, 1859, p. 434)

Introduction

This chapter selectively reviews recent work on the genetics, both quantitative and molecular, of personality/psychopathology. We use the conjunction 'personality/psychopathology' because one often-useful way to think of "psychiatric disorders" is as extremes of continuously measured (not necessarily normally-distributed) personality traits (Pettersson et al., 2014). Put simply, we treat psychopathology as part of the personality "trait sphere" (Cattell, 1943; Markon, Chmielewski, & Miller, 2011). We do not deny that there may be some specific, rare behavioral traits that are discrete classes (Norris, Marcus, & Green, 2015), but most currently offered examples do not hold up to closer scrutiny (Haslam, Holland, & Kuppens, 2012) and proof of existence of a taxon is a very difficult enterprise (Wilmot, 2015).

A Brief Exposition on Psychometric Traits and Quantitative Genetic Methods.

Quantitative measures of personality and psychopathology abound. Some instruments make use of brief statements describing a person's rather general psychological status, the *Minnesota Multiphasic Personality Inventory* (MMPI: Tellegen et al., 2003;

Trumbetta, Bolinskey, & Gottesman, 2013) being a prime example. Other measures make use of specific symptom counts gathered by interview, such as the *Diagnostic Interview Schedule* (Robins, Cottler, Bucholz, & Compton, 1995). Scores and scales can be derived in many ways (Simms, 2008) and the number of different scales derived from different combinations of items from the single MMPI item pool runs into the hundreds. Scales can also be constructed at several levels (facet, trait, higher-order factor) depending on the intended use (Condon, 2014). All such scales show evidence of genetic influence. This is usually quantified using heritability estimates. Until modern genotyping technology became available in the early 2000's such estimates were based on kinship studies for humans and breeding studies for other organisms. The heritability estimates for personality and psychiatric traits constitute standards against which estimates of genetic influence based on aggregating estimates of effects of individual genetic units (alleles) using modern genotyping techniques are compared. Currently the latter estimates fall far short of the former, leading to the so-called "puzzle" of "missing heritability" (Nolte et al., 2017). In reality, what we have is not missing heritability but a new level of analysis and the new questions this always raises. There is now consensus that complex traits/diseases such as personality and psychopathology are highly polygenic, influenced by many genes of very small effect (Chabris, Lee, Cesarini, Benjamin, & Laibson, 2015), with some genes contributing positively and others contributing negatively, sometimes even for the same trait in different individuals. In addition, the same genes may well contribute differently to different traits, and different genes often fill the same biological roles. As Wray and Maier (2014) pointed out:

"Consideration of these factors can quickly lead to philosophical musings of the definition of disease, since even for a single genetic disease under a polygenic model of disease, each individual could carry a unique portfolio of risk loci. In the genomics era, a disease definition may be at the pathway level, whereby a single genetic disease considers different portfolios of risk loci impacting the same pathway, or, more practically, the class of individuals who respond to the same treatment." (p. 225).

The concept of heritability is often misunderstood. Heritability is *not* an intrinsic feature of a trait or condition. Without going into details, heritability provides an estimate of the relative importance of genetic and environmental influences on trait variation in the very broadly construed overall environmental conditions experienced by the particular *population* under study. It is a population statistic involving relative proportions of variance, with no relevance to mean trait levels in that population, to any particular individuals within that population, or to absolute magnitudes of population variance (which also can and do vary from sample to sample). Most studies of genetic influence have involved populations living in what might be called average expectable environments or normal ranges of environments in so-called 'developed' nations. Consequently findings reported apply to those environments and may not apply to more extreme or qualitatively different environments. High heritability does not imply genetic determination. Johnson, Penke and Spinath (2011) provide a thoughtful discussion of numerous misconceptions regarding heritability.

Quantitative Genetic Analysis of Measures of Personality/Psychopathology

Recently, Polderman, et al. (2015) carried out a meta-analysis of the heritability of human traits (physical and psychological) based on fifty years of twin studies (1958-2012; among 3,404 traits, 764 studies of traits labeled 'Psychiatric' and 1,774 traits, 280 studies of traits labeled 'Temperament and Personality Functions'). Meta-analysis is intended to hone in on 'the' size of some quantitative factor, so this study was in some ways misuse of the technique. Even individual traits do not have intrinsic heritabilities, and, even if they did, there would be no reason to suspect that groupings of different traits should have similar or the same heritabilities. Still, the results offer a comprehensive catalog of the ranges of heritabilities commonly observed across many different traits.

This catalogue suggests considerable consistency for human traits. Across the Personality/Psychiatric category, Polderman, et al. (2015) reported an average heritability (h^2) of .41 and a common (shared) family environmental influence (c^2) of .16 for females and values of .41 and .17 for males. Due to the large sample sizes, the standard errors of these estimates were tiny. Separate compilations by sex were very similar for all human trait categories. But such overall averages, or even within-trait category averages, cannot tell us much that really matters. What would be of primary importance in understanding their relevance to the underlying transactions between genetic and environmental influences on trait development would be the sample-to-sample and study-to-study variances in these statistics and any specific genetic factors and/or environmental circumstances that contributed systematically to these variances. If these were small, we

would infer something quite different about consistency of manifestation of genetic similarities than if they were large. The study did not offer any information about this.

The compilations in the Polderman, et al. (2015) paper were also limited in focusing on samples of twins reared together. Estimates of genetic and environmental variance components from such studies rely on specific assumptions about degrees of genetic and environmental relationships between mono- and dizygotic co-twins, independence of genetic and environmental influences, and degrees to which twins and their environments can be considered typical of those of much more commonly-occurring singleton births. A good way to check their validities is to estimate the same quantities in samples from the same populations with different degrees of genetic and environmental relationships, though doing this is rare. One place where it has been done, however, is Minnesota. Table 1 provides a summary of results from two large Minnesota projects making use of the *Multidimensional Personality Questionnaire* (Tellegen & Waller, 2008).

Table 1 about here

Besides 1,252 monozygotic twins and 1,263 dizygotic twins reared together (MZT, DZT individuals) the Finkel and McGue (1997) study included 495 parents, 333 siblings, 1,690 spouses and 535 adult offspring of the twins. Estimates of genetic and environmental variance components using the MZT and DZT correlations in these data were very consistent in aggregate with those from the monozygotic twin correlations in the Minnesota Study of Twins Reared Apart (MISTRA) (Segal, 2012). The monozygotic twin reared apart (MZA) correlation directly estimates heritability though it relies on

somewhat different (though no less specific) assumptions (Bouchard, Lykken, McGue, Segal, & Tellegen, 1990). This consistency suggests that the assumptions underlying both study designs do not distort the estimates.

In contrast with Polderman et al.'s (2015) summaries for a mixture of psychopathological and more ordinary personality characteristics, which reported some common family environmental influences, the Minnesota MPQ results with 'normal-range' personality traits suggested very modest, if any, such influences. This has been typical of normal-range personality results. Perhaps measures of psychopathology contain more such influence than measures of normal-range personality. The heritability of major depression, no matter how it is assessed, however, is generally reported to be about .40 with very little common environmental influence (Flint & Kendler, 2014). A recent large twin study replicated the absence of common environmental influences for its full sample (heritability of .52), but application of more sophisticated statistical methods suggested that heritabilities differed by sex, with males showing common environmental influences of .22 and heritability of .35, and females showing values of .01 and .54 (Molenar et al., 2016). This study demonstrated that quantitative genetic methods continue to evolve, that individual estimates can deviate considerably from the Polderman et al. reported averages, and that many findings in the field should be considered tentative.

The psychopathology "*p*" factor.

One of the most interesting and perplexing problems in psychiatric diagnosis has been the common occurrence of comorbidity (Bebbington, 2015; Moffitt et al., 2010), the apparent appropriateness of multiple psychiatric diagnoses for many patients. Recently the categorical approach to psychopathology that generates this comorbidity has yielded to a more empirical, quantitative, scale-based factor approach (Lahey, Krueger, Rathouz, Waldman, & Zald, 2017) that articulates 'dimensions' or 'axes' along which dispositional vulnerabilities vary subject to underlying genetic and environmental influences. Under this newer model comorbidity arises because these psychopathological dimensions or axes are themselves inter-related (correlated). Caspi et al. (2013) and Krueger and Markon (2014) have argued that, parallel to the *g* factor in cognitive abilities, there is a general *p* factor in psychopathology. As with the *g* factor, the existence of a general *p* factor does not negate the importance of more specific, lower-order factors in addressing important scientific and applied problems such as variations in efficacies of psychopharmacological agents and behaviorally-based treatments among patients exhibiting similar clinical features. The suggested *p* factor does not fully explain either overall rates of comorbidity or their tendencies to involve some groupings of disorders more than others; residuals specific to individual scales or diagnoses also offer explanation. Caspi, et al. studied symptoms gathered from longitudinal interviews while Krueger and Markon studied multiple independent replications of cross-sectional questionnaire data, but their resulting models were very similar. Their *p* factors contributed directly to two major factors both groups labeled Internalizing (*Int*) and Externalizing (*Ext*). Both projects also found evidence for a thought-disorder factor, but it tended to collapse into the other domains. We ignore this important but unresolved issue

here. There is now a wide consensus regarding the validity and utility of the *p* factor (Kim & Eaton, 2017; Kotov et al., 2017). A symptom/network theory consistent with the *p* factor has been put forward by Borsboom (2017, p. 7) and by McNally's group (Jones, Heeren, & McNally, 2017).

Molecular Genetics: Genome-Wide Association Studies (GWAS) and "Missing Heritability"

Given pervasive evidence of genetic influence on personality/psychopathology-related traits, their impact on people's lives, and burgeoning availability of cost-effective technology to examine the genomes of large samples of people directly, there is high interest in identifying the specific genetic variants that contribute to these traits. The method most commonly used in recent years to do this has been the Genome-Wide Association Study (GWAS). A GWAS correlates hundreds of thousands of single-nucleotide polymorphisms (SNPs, sequences of DNA varying relatively frequently in human populations) with the traits or diagnostic measures of interest across the genomes of population samples often running into the tens and even hundreds of thousands. Results from these studies have overwhelmingly fed the emerging consensus that these traits are influenced by very large numbers of genes with very small effect sizes and that the same genes influence or are involved in many different disorders. This is consistent with the notion that the diagnostic psychopathological categories are in reality dimensional (Lee, Vattikuti, & Chow, 2016). Typically, the associations (links between the SNPs or nearby genes and the traits) suggested in these studies involve genes

expressed in the brain, suggesting plausible biological mechanisms (Hibar et al., 2015; Lee & McGue, 2016), though effect sizes for individual genes are always so small that the possibility that any indicated biological mechanism is necessary to cause the trait or condition is very remote.

As noted earlier, there are marked differences between quantitative estimates of heritability based on twin studies and GWAS estimates, the so-called "missing heritability". The GWAS methods assume additive effects. Genes underlying GWAS markers form "genetic interaction networks" (Shorter et al., 2015, Figure 4, provides a nice example), and Mackay (2014) has shown "that additivity can be an emergent property of underlying genetic epistatic and interaction networks" (p. 22). Under these models, traits manifested by the simulated networks appear to be additive, but the underlying processes that were used to generate them involve epistatic and interactive aspects. Adding interaction terms to equations based on weighting associations identified in GWAS studies could make their estimates of genetic variance more consistent with those from quantitative genetic studies. There has been modest success in this area using pathway polygenic risk scores (PPRS) that weight the individual genes according not to the strengths of their statistical associations with the trait but according to the relative importance of the biological pathways they implicate. Genome-wide polygenic scores (GPS) are now approaching effect sizes found in some of the social and biological sciences (Bouchard, 2007; Selzam et al., 2016) though they involve such large numbers of individual genetic markers that most of them did not reach statistical significance in

any sample and they tell us little more than do family-based 'traditional' quantitative genetic studies

Genes and Biological Pathways (Mechanisms)

The long-term goal of understanding how genes influence complex phenotypic personality traits will require specifying precisely how particular genes transact with environments to influence development of the mechanisms/pathways underlying traits. All the traits discussed here are also clearly influenced by environments. Studies of model organisms offer many examples of dependence of genetic expression on environmental circumstances, so understanding the natures of these gene-environment transactions in trait development and expression is critical[ii]. Two theories of psychopathology offer examples of attempts to accomplish this, the "Feinberg Hypothesis" involving neural mechanisms and the Vascular Hypothesis involving pathophysiology. We chose these two examples not to pit them against each other but to emphasize that there are very likely multiple causal mechanisms influencing any existing *p* factor and they are likely biologically heterogeneous. Some causal mechanisms probably involve neural networks but co-existing ones may influence systems that support very general bodily functions (e.g., blood vessels, hormones, etc.). For example, genes influencing Well-Being (sometimes considered reversed *Int*) are expressed in the central nervous system as well as in adrenal and pancreatic tissues (Okbay et al., 2016). Genes and environments may also become linked through repeated environmental exposures (self-selected or otherwise; passive or active gene-environment correlation).

Moreover, just like *g*, *p* could be emergent rather than latent, which requires a very different theoretical framework within which to understand genetic influences (van der Maas et al., 2006).

The Feinberg Hypothesis suggests that schizophrenia is in part caused by a fault in the synaptic pruning normally occurring during adolescence. This is the critical period during which symptoms often first appear (Feinberg, 1982-1983). Progressive cortical thinning, as psychosis develops, has been observed (Cannon et al., 2015), and genes involved in this thinning have now been associated with schizophrenia (Sekar et al., 2016) as well as bipolar disorder (Hanford, Nazarov, Hall, & Sassi, 2016). There is also evidence that *de novo,* newly-appearing, mutations influence genetic risk for schizophrenia by influencing synaptic networks (Fromer, 2014).

The Vascular Hypothesis posits that abnormalities in genetic polymorphisms that regulate inflammatory responses interfere with "exquisitely precise regulation of the delivery of energy and oxygen required for normal brain function" (Hanson & Gottesman, 2005). A corollary of this hypothesis is that environmental agents trigger inflammatory responses. Inflammatory influences on the brain, measured via retinal imaging, have now been related to both the *p* factor and IQ (Meier et al., 2013; Shalev et al., 2013). Genes regulating inflammatory response (among others) have also been related to risk of schizophrenia (Andreassen, Harbo, & Wang, 2015).

Potential involvement in specific personality/psychopathology traits of the pathophysiological mechanisms underlying these hypotheses can be investigated in considerable detail (Ruzzo & Geschwind, 2016). Even if these mechanisms influenced behavior in only individual patients and only to small degrees, they would be causal mechanisms in the fundamental sense of the word. There may well be many co-existing mechanisms of this sort, each influenced by numerous genes, and the particular ones involved may differ among traits. Methods facilitating discovery and roles played by genes underlying complex traits are rapidly proliferating (Gamazon et al., 2015; Potkin, van Erp, Ling, Macciardi, & Xie, 2016; Wang et al., 2016).

The Feinberg and Vascular hypotheses were proposed before GWAS came into regular use. GWAS have merely offered evidence potentially consistent with them. Moreover, the manner in which they have done so suggests rather strongly that it is not any particular genes that matter in generating psychopathologies, but genes' aggregate involvement in emergent processes that somehow send biological pathways 'off-course', with the 'somehow' remaining a wide-open space in which environmental input is important. In addition, though we know many so called "risk genes" are expressed in the human brain, we do not know the neuronal subtypes influenced by those genes (Lake et al., 2016).

Closing Thoughts from an Evolutionary Perspective: Complexity as a Consequence of "Descent with Modification".

Four large facts stand out from the body of research we have briefly reviewed. First, all complex traits are heritable. Second is pervasive co-morbidity, both at the phenotypic and molecular levels. Third, these traits are influenced by a very large number of genes of very small effect. Finally, there is pleiotropy/epistasis, individual genes having multiple influences and interacting with other genes, in simultaneous transaction with the environment. How do these facts intermesh with evolutionary processes? Nature is a tinkerer and the brain is not an elegantly designed and optimized adaptive machine. The brain is made up of multiple layers of more recently evolved systems overlaid on older systems (Allman, 2000, Chap. 3; Panksepp, 2011). This creates problems of coordination among systems, but also a level of redundancy that can maintain phenotypic function despite disruption of individual operative pathways. Jacob (1977) likened the human brain to a jet engine (cortex) mounted on an old horse cart (subcortical regions) and noted, "It is not surprising, …. that accidents, difficulties, and conflicts, can occur" (p. 1166). Consequently, complex biological organisms and their brains lie somewhere between "design" and "bricolage" (Wilkins, 2007). That 'somewhere' is a "kluge", a less-than-elegant mechanism, but "good enough" (Marcus, 2008), at least for some period of time in some environments. Systems biology and analysis of modular networks (Sporns & Betzel, 2016) are being used to explicate brain networks. The connectome project's goal, for example, is to identify and map the networks that underlie brain disorders (Fornito, Zalesky, & Breakspear, 2015). It has recently indicated that the human cerebral cortex is structurally more complex than previously believed, articulating 97 new areas as well as the previously known 83 (Glasser et al., 2016). These networks are also likely kludgy. Weiss and Buchanan (2011) summarized the situation as follows;

"Much of life seems to be characterized by ad hoc, ephemeral, contextual probabilism without proper underlying distributions. To the extent that this is true, causal effects are not asymptotically predictable, and new ways of understanding life may be required." (p. 761).

Turkheimer (2016) came to a similar "gloomy" conclusion for behavioral traits.

"What we will see instead is a proliferation of small, diverse, contingent findings that do not accumulate into coherent scientific theories. These will not be robust findings with large effect sizes; they will be the signature of a complex problem being addressed at the wrong level of analysis. They will be the keyless sidewalk under the genomic streetlight." (p. 28).

We do not disagree that the problem is complex and we may need "new ways of understanding life". We, however, side with Darwin and "hope to make sure but slow progress". There is no reason to doubt that how genes influence the multi-various pathways (networks/structures, etc.) that underlie "traits" can be worked out[iii]. The various solutions will be messy (kludgy). One consequence of this messiness is that a given value on any particular trait (e.g., IQ) is likely to be achievable via different genetic and environmental pathways (equifinality) due to unique portfolios of loci living in unique environments. In an important sense any individual gene per se may or may not be involved, its role depending on a variety of other things (contextual probability). From

this point of view, the status of every individual on every trait is to some extent emergent.

Legends

Table 1: Heritability estimates from a multiple group design by gender and intraclass correlations for monozygotic and dizygotic twins reared apart (MZA, DZA) and reared together (MZT, DZT).

Note: The DZA and DZT samples include both same sex and opposite sex twins. The data were derived from multiple tables in multiple studies conducted in Minnesota.

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[i] Prof. Gottesman passed away on June 29th, 2016 before the completion of this manuscript.

[ii] The focus of this chapter has precluded discussion of the complexities introduced by both environmental influences and development. These topics have been dealt with elsewhere (Bouchard, 2016; Johnson, 2014).

[iii] Most of these pathways will be initially worked out using lower animals where powerful experimental manipulations can be implemented and causal mechanisms explicated (Kukekova, Temnykh, Johnson, Trut, & Acland, 2012; Shorter et al., 2015).