

# Passing Down Psychopathology

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Researchers have long known that, much like physical traits, characteristics of mental health and mental illness can be passed down through family trees, moving from one generation to the next. Longitudinal studies and new forms of genetic analysis are helping shed light on intergenerational continuity and transmission of psychopathology.

At the inaugural International Convention of Psychological Science, held this past March in Amsterdam, the Netherlands, APS James McKeen Cattell Fellow Michael E. Lamb (University of Cambridge, United Kingdom), APS Fellow Jay Belsky (University of California, Davis), APS Fellow Marinus H. van IJzendoorn (Leiden University and Erasmus University Rotterdam, the Netherlands), Deborah M. Capaldi (Oregon Social Learning Center), and Michael J. Meaney (McGill University, Canada) came together in a symposium chaired by APS Board Member Annette Karmiloff-Smith (Birkbeck, University of London, United Kingdom) to discuss research examining the intergenerational transmission of psychopathology.

Belsky proposes that parent psychopathology influences children's environmental experiences — for example, by exposing them to marital conflict, parental stress, or poor parenting behaviors. These environmental experiences then contribute to the development of psychopathology in children; however, not all children are equally susceptible to these environmental influences. Differences in temperament, psychological reactivity, and genotype can lead children to be more or less sensitive to — and therefore more or less affected by — these environmental influences. Children who are more sensitive to their environments are thought to be more malleable than are less sensitive children. While these malleable children are disproportionately influenced by negative environmental influences, such as poor parenting, they also disproportionately benefit from environmental support and enrichment, which means they might be particularly responsive to therapeutic interventions.

One of the questions surrounding the implications of these types of studies is how they will impact the development of new interventions. In answering this question, Belsky says, “I don't think we're there yet”; however, knowing more about the types of children who are the most susceptible to — and the most influenced by — positive and negative environmental factors may help researchers and practitioners create treatments for targeted groups.

Psychological scientist Deborah M. Capaldi has real-world experience with the type of longitudinal research often needed to truly understand the transmission of psychopathology across generations. Her involvement with the Oregon Youth Study (OYS), a prospective examination of the intergenerational associations in psychopathology, has helped shed light on how this type of transfer occurs.

The OYS began in 1983, with researchers examining risk and protective factors for antisocial, delinquent, and substance-use behaviors in 9-year-old boys. These children were considered second-generation (G2) participants in the study, while their parents were considered first-generation (G1). The

researchers followed the boys as they matured, collecting data on their romantic relationships and partner interactions. The study, now in its third generation (G3), is examining substance use, depression symptoms, and conduct problems in the children of the G2 participants.

Capaldi and her colleagues have identified parenting behaviors as a mediator of problem behavior from one generation to another. “It has long been assumed that many of our parenting behaviors are learned from our parents, but most evidence for this is retrospective,” says Capaldi. The OYS was able to take a prospective look at this relationship, examining intergenerational and partner influences on fathers’ negative discipline.

Researchers found a direct link between poor and harsh disciplinary practices of G1 parents and poor parenting displayed by G2 fathers. In addition, the risk behaviors and negative parenting practices of G2 fathers’ partners also influenced the fathers’ poor discipline practices. The way G2 parents treat their own children therefore seems to be influenced by the way their parents treated them and also by the behavior of their partners.

“Intergenerational associations are complex and occur through a number of mechanisms,” Capaldi said. Although these associations exert moderate influences, they do not tell the whole story, as new families have two parents who are in a dynamic relationship and influence each other’s behavior.

As a specialist in biological psychiatry, Michael J. Meaney seeks to understand the relationship between early childhood adversity and later chronic health problems, asking, “Why is it that experience over the first years of life would be translated and ... biologically embedded so as to influence health over the entire life span?”

Meaney believes that epigenetic factors — “the biochemistry of the way genes regulate the conversion of DNA to RNA” — mediate this relationship. Modifications of DNA influence the activity of the genes but do not alter their function.

The different types of cells in the body all have the same basic template, yet the genome does not operate the same way in every cell. Methylation (i.e., the addition of methyl groups to DNA) is one of the most common processes through which the activity of different parts of DNA is altered: Parts of the genome that are methylated become silenced, thereby defining which genes are operative within each cell.

Methylation allows similarly structured cells in our bodies to perform different functions. In addition, environmental influences can alter DNA methylation, leading to gene-expression changes that can be quite stable over time, extending the impact of an environmental event over a person’s life span.

In one epigenetic study, Meaney and colleagues examined maternal licking in rats, finding that adult animals raised by high- compared with low-licking mothers showed substantial differences in stress response, neurological development, metabolism, and learning and memory. They found that a social event (maternal licking behavior) led to intracellular changes in certain populations of brain cells, which created opportunities for DNA methylation remodeling. Differences in the activity of the hypothalamic–pituitary–adrenal axis are linked to a wide range of physiological outcomes.

While many epigenetic studies examine an individual gene site, scientists need to survey the entire genome to “fully understand variability across phenotype,” Meaney said. A birth-cohort study, of which Meaney is a part, is doing just that by looking at the methylation status not of one gene but of almost 500,000 individual sites across the genome. Findings from this study have indicated that variation in methylation at these 500,000 sites occurs primarily in response to gene–environment interactions, suggesting that environmental influences on the epigenome are moderated by genotype.

Another researcher interested in examining genetic impacts on the intergenerational transmission of psychopathology is Marinus van IJzendoorn, who uses genome-wide association studies (GWAS) and genome-wide complex trait analysis (GCTA) to examine the genetic transmission of behavior problems. GWAS look at common genetic variants in a large number of people to see whether any specific variant is associated with a specific phenotypic trait, such as aggressive behavior.

GCTA, a relatively new method, takes into account information gained in a GWAS but also “considers commonalities between pairs of unrelated individuals on the level of the gene and on the level of the phenotype,” says van IJzendoorn. Gene-level and phenotype-level similarities are correlated, giving researchers an estimate of the contribution of variability in single nucleotide polymorphisms (SNPs) to the heritability of certain traits, such as child behavior problems.

Van IJzendoorn’s ongoing GWAS and GCTA studies examining aggression and child behavior problems, and his current epigenetic studies examining the influence of parental smoking on birth weight and the influence of prenatal maternal psychopathology on the epigenome, are producing promising results, in particular in the area of attention problems in children.

Nevertheless, “it might be that [these] genetic and epigenetic searches for behavior-problem explanations are a search for needles in a haystack,” says van IJzendoorn. “We may have to conclude that main genetic and main epigenetic effects are really elusive and quite small,” requiring experimental rather than correlational studies, the inclusion of the environment in scientific inquiries, a better assessment of phenotypes, and of course, replication.

Michael E. Lamb, a developmental psychologist, does not do research on intergenerational transmission and came to this panel as a psychological scientist “who is a consumer of this research rather than a generator of it.” According to Lamb, researchers have long known that psychopathology can be transmitted across generations, and early research on this topic focused on the influence of genetics or on the influence of parenting and the environment (i.e., the nature vs. nurture debate).

It was not until the 1950s that scientists recognized that it was the interaction of genes and environment that was important, rather than the influence of genes or environment alone. And not until the turn of the century did studies examining gene  $\times$  environment emerge. “These studies have, I think, fundamentally altered our conception of, and our understanding of, some of these gene–environment interactions,” Lamb said.

As a group, most of these studies have used a candidate-gene approach (i.e., they focused on one specific allele and looked at its relation to different types of outcomes). Often, the chosen candidate gene of these earlier studies was a neurotransmitter coding gene or a gene associated with the production, degradation, or transmission of neurotransmitters.

As candidate-gene studies have made their way into the literature, their conclusions have been criticized by developmental psychopathologists. One main concern with such studies is that they focus on single genetic alleles, while many researchers believe that psychopathology is polygenic in nature — that is, it involves many different genes rather than just one.

While debates rage around the replicability, reliability, and appropriateness of candidate-gene studies, a new type of study — the GWAS used by researchers such as van IJzendoorn — is coming to the fore. Lamb said that GWAS have shown that the majority of psychopathic conditions being studied are, as expected, polygenic in nature, often involving thousands of genes. Another revelation from these types of studies is that many of the genes that were the subject of candidate-gene-association studies — genes associated with neurotransmitters — have not been identified as correlates of psychopathology in GWAS.

Both candidate-gene studies and GWAS, Lamb also noted, explain very small amounts of variance, suggesting that researchers have yet to identify many of the key factors explaining developmental variation. Further complicating matters, according to Lamb, is that the theoretical approaches of GWAS and GCTA conflict somewhat with the theoretical approaches often used in developmental psychopathology.

“Most of developmental psychology has embraced a dynamic-systems-theory approach,” says Lamb.

In contrast, many gene–environment studies conceptualize genetic and environmental factors from a static, rather than a dynamic, viewpoint, making it difficult to embed findings from these types of studies within a dynamic understanding of developmental issues.

Although studies such as the ones mentioned above have provided exciting new insights into the transmission of psychopathology, much work remains in order for researchers to gain a full understanding of the genetic and environmental influences and interactions that lead to continuity and discontinuity in the intergenerational transmission of psychopathology.