Gene–Environment Interplay and Individual Differences in Behavior

Ina Anreiter[1,2], H. Moriah Sokolowski[3], and Marla B. Sokolowski[1,2]

ABSTRACT— Individuals of the same species display remarkable variation in behavior, even in identical contexts. Increasing complexity in behavioral phenotypes brings with it an increase in individual variation in the manifestation of those phenotypes, and human behavior undoubtedly stands at the pinnacle of complexity. In this article, we discuss current knowledge of gene–environment interplay and how the complex interactions of genes, experiences, epigenetics, and developmental timing give rise to individual differences in behavior.

Questions about why humans and other animals vary in their behavior have occupied our thoughts for centuries (Logan & Johnston, 2007). Discussions concerning contributions to variation in behavior began with disagreements around the nature–nurture dichotomy (Burkhardt, 2005; Kruuk, 2003). Nature is akin to genes (G) and nurture to the environment (E). Early psychologists who typically studied aspects of nurture in the laboratory believed that infants were born with a blank slate and that their experiences (E) wrote on this slate and generated individual differences in behavior (Pinker, 2002; Watson, 1913). Biologists and early ethologists who observed and quantified animal behavior in their natural habitats argued that variation in behavior arises from nature (genes) and called these behaviors instinctive or innate (Lorenz, 1981; Tinbergen, 1951). The history of research that followed for the most part resulted in geneticists controlling but not manipulating environmental influences on behavior and psychologists not considering genetic predispositions and their contributions to individual differences in behavior. However, these early ideas about a nature–nurture dichotomy proved to be incorrect. Indeed, sources of variation in behavior are neither due to genes or environments alone. As more data were collected, the debates about there being a nature–nurture dichotomy were confirmed to be nonsensical, along with the deterministic thinking that this dichotomy provoked. Had the present article been written for a genetics audience we would have urged them to consider the importance of the environment (experiences) during development and adulthood and how the environment shapes behavioral variation. Because this article is written for researchers in psychology/neuroscience and education, we emphasize the inclusion of genetic predispositions and their interplay with experiences as important for understanding behavioral variation. In either case, the aim is to understand concepts around gene–environment interplay so that they can be incorporated into research, practice, and everyday thinking. In particular, we introduce the Mind, Brain, and Education (MBE) community to the concept of gene–environment interplay and suggest that it become incorporated into discussions aiming to bridge neuroscience and education.

EARLY EFFORTS TO INTEGRATE GENETICS AND ENVIRONMENTAL CONTRIBUTIONS TO BEHAVIORAL DIFFERENCES

Biometricians who used statistical approaches to make their arguments replaced the nature–nurture dichotomy with a G + E model. In this case, one could take the amount of variation in a behavioral trait that was attributed to genes and add it to the variation attributed to the environment and this alone would predict individual differences in behavior.

[1]Department of Ecology and Evolutionary Biology, University of Toronto
[2]Child and Brain Development Program, Canadian Institute for Advanced Research (CIFAR)
[3]Department of Psychology, Brain and Mind Institute, The University of Western Ontario

Address correspondence to Marla B. Sokolowski, Department of Ecology and Evolutionary Biology, University of Toronto, 25 Willcocks Street, Toronto, Ontario, M5S 3B2 Canada; e-mail: marla.sokolowski@utoronto.ca

This additive model led to broad sense heritability measures (reviewed in M. B. Sokolowski & Wahlsten, 2001) that continued the tradition of gene–environment determinism by partitioning the variance into genetic and environmental sources of variation. Heritability consisted of the proportion of variance of a trait (e.g., IQ, aggression, smoking) that was attributable to genetic variation among individuals in a population. There are many excellent critiques of heritability measures in the literature (e.g., Wahlsten & Gottlieb, 1997). Although these measures were developed and effectively used by quantitative geneticists for agricultural research to predict responses to selection (Falconer & Mackay, 1996), they have misled our thinking about the origins of our differences for decades because they have been interpreted from a genetic determinism framework. It is important to keep in mind that heritability measures are population measures that cannot predict an individual's traits. In addition, the idea that the effect of G and E could be simply added together to explain individual differences in a trait propelled deterministic thinking into the scientific and public domain, because it implied that if something is heritable (i.e., in the genes), it is not modifiable or flexible. This presumed inverse relationship between heritability and plasticity led people to believe that experience could not modify traits that are influenced by genes (M. B. Sokolowski & Wahlsten, 2001).

An example from the animal literature is helpful to clarify the above point. The *foraging* gene influences a number of behavioral traits. Rover and sitter allelic variants of the *Drosophila foraging* gene differ in a number of behavioral and metabolic phenotypes. For example, rovers move more, eat less, and are leaner than sitters. However, despite the strong genetically based differences in rovers and sitters, these traits are themselves modifiable by the environment (Anreiter, Vasquez, Allen, & Sokolowski, 2016; Burns et al., 2012; Kaun et al., 2007). When the nutritional environment is modified with a period of food deprivation in early life, rovers become sitters (Kaun et al. 2007). This shows that the nutritional environment interacts with the *foraging* gene to generate changes in behavior. In an olfactory-based learning paradigm, sitters are better at associating an odor with a reward, but only when they are trained and tested in a group. In contrast, rovers can learn and remember when trained and tested alone or in groups (Kohn et al., 2013). In this case, the social context affects the plasticity of traits that have a known genetic underpinning. Although there is a long reach from early life to adulthood, early-life experience can also affect later-life outcomes. For example, rover and sitter flies differ in risk taking during food search, with rovers taking more risks, but both rovers and sitters increase their risk taking if they experience nutritional deprivation in early life (Burns et al., 2012). Similarly, a genetic variant (at the level of the DNA sequence) in the human *foraging* gene *PRKG1* affects how sensitive mothers are to their infants (i.e., maternal sensitivity), but this is dependent on the mother's history of abuse and neglect as a child (H. M. Sokolowski et al., 2017). Mothers of one genotype are well buffered against early adversity, whereas mothers of the alternative genotype are more vulnerable. The aforementioned examples using studies of the *foraging* gene clearly show that genetic predispositions to behave a certain way are flexible and modifiable by experience.

From the perspective of the environment, individuals can experience the same environment differently. Twin studies have been particularly useful to help conceptualize the different ways that individuals experience their environments (Ashbury & Plomin, 2014). Historically, twins provide us with a natural experiment because identical (monozygotic [MZ]) twins share 100% of their genes (DNA), while fraternal (dizygotic [DZ]) twins have only half of their genes in common. Heritability of behavior in twin studies is calculated by comparing how similar identical twins are to how similar nonidentical twins are. Correlation analyses are used to define similarity (a score of 1.0 indicates no differences between MZ and DZ twins and 0.0 indicates no similarities). Twin studies are particularly useful from the perspective of understanding how the environment contributes to behavioral variation. In twin studies, behavior geneticists divide the environment (the nongenetic influences) into two parts: the shared environment (SE) and the nonshared environment (NSE). Within the NSE, experiences can be objectively nonshared or subjectively nonshared. For example, in school-age twins, experiences that fall into the objectively nonshared category might be choosing different types of friends, one twin breaking an arm, or one twin being chosen for a theater production, while the other did not audition because he/she was on the track team. The perceived or subjectively nonshared environment could occur around there being a divorce in the family. For example, when only one twin was exposed to a particularly bad argument between the parents, or when one twin may be more or less sensitive to the change in the family or more close to the parent that has left. This would make the experience of the same divorce in the family (an objective experience) different for each child (a subjective experience) (Ashbury & Plomin, 2014). In this way, twin studies have been helpful in partitioning variance attributable to heredity and to environments. An important point here is that, undeniably, some environmental effects are hidden within heritability estimates through gene–environment interplay (discussed further below).

Twin studies have shown that educational traits, including reading, writing, and educational attainment, fit a genetic model of many genes each with small additive effects contributing to the variation in each of these traits. Currently, however, the identification of gene variants (e.g., single-nucleotide polymorphisms [SNPs]) involved in these multifaceted educational phenotypes is challenging, as each

genetic variant will comprise a very small proportion of the variance (0.5% at most). Notably, educational traits are normally distributed in populations and classrooms, and do not fall into dichotomous categories (e.g., reading abilities comprise a full range). Consequently, it makes sense to develop approaches to education that maximize each child's potential rather than aim at bringing all children up to a given and often arbitrarily chosen level of attainment. From the perspective of gene–environment interplay, "genes do not operate independently of experience and therefore educators need not fear genes as being deterministic. Instead teachers should think of themselves as drawing out a child's genetic potential rather than writing haphazardly on a mythical blank slate" (Ashbury & Plomin, 2014, p. 145).

GENE–ENVIRONMENT INTERPLAY AND DEVELOPMENT

As statistical models advanced, other components, such as gene by environment interaction terms (G×E), were added to the previous gene–environment model. Animal research confirmed that G×E was of critical importance for understanding behavioral variability (M. B. Sokolowski & Wahlsten, 2001). Nevertheless, with the advent of molecular biological techniques that can elevate statistical correlations to the level of causation, it became clear that the relationship between genes and the environment is more nuanced than G×E. Genetic predispositions and environmental exposure interact at many levels to guide child development. Neither genes or environment or even statistical gene–environment interactions (G×E) are sufficient to explain all the interindividual variability in life trajectories. The dynamic complexity of environmental and biological factors that lead to specific developmental outcomes has led researchers to the term gene–environment interplay (Caspi & Moffitt, 2006; Boyce et al., 2012). Gene–environment interplay expands on the idea of G×E interactions by describing a reciprocal relationship between G and E (Rutter, 2007). As a child develops, genes are listening to the environment and respond to the child's experiences in a reciprocal way. Below, we discuss gene–environment interplay in the context of G×E correlations and G×E interactions, genetic predispositions, and environmental exposures, as well as other contributing factors such as epigenetics and developmental time constraints.

GENE–ENVIRONMENT CORRELATIONS

One of the earlier theories of how genotypes and environments correlate highlights the false dichotomy between genetic determinism and naïve environmentalism mentioned above (Plomin, DeFries, & Loehlin, 1977). This theory states that genotypic differences affect phenotypes through passive, evocative, and active gene–environment correlations. Passive gene–environment correlations happen when individuals who are genetically more similar are more likely to mate. In this scenario, children are genetically more related to their parents, and as a consequence, genetically more similar caregivers provide the environment for their child. This means that the child's genetics will correlate with the child's environment. Evocative gene–environment correlations refer to the notion that an individual's genes influence the way that others respond to that individual. For example, a child who is taller might be treated differently than a shorter child. Active gene–environment correlations refer to the idea that an individual's genes influence the individual's selective attention to different aspects of the environment. This may make the individual more likely to seek out certain experiences across the life span (for a detailed description of gene–environment correlation, see Plomin et al., 1977). Active gene–environment correlations may explain why some students gravitate to one activity in the classroom, whereas others prefer another. Respecting this diversity of interests and providing a range of experiences in the classroom will embrace this diversity of interests and abilities and aid in having each child reach their potential. Importantly, this means that the latest science on gene–environment interplay does not support a one-size fits all approach to learning. Furthermore, it has been suggested that the relative importance of these three kinds of gene–environment correlations changes across developmental time (Scarr & McCartney, 1983). Specifically, the passive kind may be most salient in infancy, whereas evocative and active gene–environment correlations become more important during later childhood and adolescence; however, these hypotheses require testing using longitudinal study designs (Scarr & McCartney, 1983). Although gene–environment correlations are not sufficient to fully explain variation in childhood developmental outcomes, they make important contributions to our understanding of gene–environment interplay.

GENETIC PREDISPOSITIONS

When discussing twin studies above, we mentioned that genetic contributions to reading and writing fit a genetic model of many genes each with very small effect sizes. We return to this subject by discussing approaches to investigate genetic and environmental contributions to individual differences in behavior. We know the most about genetic predispositions from studies of disease phenotypes. There are many examples of genetic mutations affecting development, and the size of the effects range from very small to very large. The most drastic examples are of specific single gene

mutations causing impaired development, such as Tay-Sachs disease (Lacorazza, Flax, Snyder, & Jendoubi, 1996), or Cornelia de Lange syndrome (Krantz et al., 2004). Nevertheless, these examples are relatively rare, and genetic variants (also called polymorphisms) associated with developmental outcomes in humans usually have small, additive effects that are environment-dependent.

Genome-wide association analysis is an approach used to identify genetic variants that associate with trait variation. Genome-wide association studies (GWAS) associate variation in the phenotype with a set of genetic variants (usually SNPs). SNPs are distributed throughout the genome (the entire DNA sequence in humans) and GWAS identifies SNPs that statistically differ between individuals with different phenotypes. Often, these SNPs mark a large region in the human genome that encompasses hundreds of genes, any one of which might be associated with variation in the trait of interest. Many GWAS studies have been carried out on major human diseases. The advantage of GWAS is that it is an unbiased approach that relies on phenotype rather than the genotype. What this means is that there are no prespecified candidate genes or regions of interest that are associated with trait variation. This makes GWAS a noncandidate gene approach that avoids missing important genetic contributions due to *a priori* assumptions. Nevertheless, GWAS identifies SNPs associated with the trait, but does not address whether the genetic variants found are causal to the trait variation. Confounders that can contribute to population stratification, such as sex, age, geography, and ethnic background, have to be adjusted for in GWAS, and significance values have to be corrected for multiple comparisons. There are usually millions of SNPs tested for association, making it necessary to adjust the *p*-value threshold of significance for multiple comparisons to avoid "random" significant hits. The downside of this multiple comparison correction is that SNPS with very small contributions (small *p*-values) can be easily missed. Finally, to assess reproducibility, significant SNPs need to be validated in an independent cohort. In general, SNPs found in GWAS have very small predictive value, but when validated can contribute to understanding the genetic pathways underlying variation in a trait. Often the predictive value of a SNP is so small that several SNPs are used to assemble polygenic (multiple gene) risk scores with higher predictive value. In general, however, the reported associated variants are not likely to be causal variants because they mark an associated region of DNA that spans hundreds of genes, making it difficult to biologically interpret the genes that emerge from GWAS. To assess causality, genetic variants identified in GWAS have to be tested independently, but this approach is costly.

As the prices for next generation sequencing have come down, large human genetics consortia have begun to use GWAS to identify genes important to complex phenotypes. Using GWAS, over 700 genes were found to be linked to intellectual disability (Vissers, Gilissen, & Veltman, 2016), and 107 genes were been associated with risks for autism spectrum disorder (ASD) (De Rubeis et al., 2014). More recently, Yuen et al. (2017) identified new genes that contribute to ASD. Nevertheless, it has been difficult to find genetic determinants for some complex human disorders. Although major depressive disorder has high heritability from twin studies (40%–50%), it has been notoriously difficult to identify the genes that drive it (Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium et al., 2013), most likely because the genes involved have such small individual effects that they are hard to detect. A recent study that identified 15 genetic loci associated with depression used over 300,000 individuals (Hyde et al., 2016), illustrating the large sample sizes needed to detect genes of small effects. Importantly, none of the genes involved in these complex disorders have been shown to be deterministic, or the sole cause for these disorders. Some of the difficulty in pinpointing the genetic contributions to these disorders comes from methodological problems with GWAS. GWAS often lack replication, meaning that a gene associated with a given phenotype in one study often does not correlate with that same phenotype in other studies (Torrico et al., 2017). The lack of replication in GWAS is probably due to a combination of insufficient sample sizes, inappropriate statistical methods, lack of control for population stratification, variability in how phenotypes are measured, and unaccounted for GxE interactions (Heid et al., 2009; Kraft, Zeggini, & Ioannidis, 2009; Moonesinghe, Khoury, Liu, & Ioannidis, 2008). GWAS studies also suffer from the problem that individual genes or SNPs cannot account for much of the heritability of diseases, behaviors, and other phenotypes predicted from twin studies (Maher, 2008). This most likely relates back to the findings in the animal literature that most phenotypes are driven by complex G×G, G×E interactions, and G–E correlations, rather than by single genes. Furthermore, when disease-correlated SNPs fall outside of gene-coding regions, they are often assumed to affect the gene with the closest proximity, while in truth they might be affecting the expression of a more distant gene (Thakurela, Sahu, Kumar, Garding, & Tiwari, 2015). Additionally, from the perspective of the present discussion, little is known about genetic differences and individual variation in normal human development that is not linked to a disease phenotype.

G×E interactions could help explain much of the reproducibility problem of GWAS mentioned above, as the significant correlation of genes with phenotypes might often be dependent on environmental factors. Nevertheless, effectively teasing apart G×E interactions in GWAS is challenging. Methods are being developed that will enable researchers to include quantitative measures of the

environment and multifaceted measures of risk in GWAS (e.g., Soave et al., 2015), and combinations of genetic variants that pass threshold can be assembled to generate a polygenic risk score that can be used to further assess risk. An example of this in the social science literature is described for a GWAS on educational attainment, which used almost 300,000 individuals along with a replicate sample of over 100,000 individuals. They found 74 genome-wide significant loci associated with the number of years of schooling completed, a proxy for educational attainment. Together, a polygenic score accounted for approximately 20% of the variation between individuals in this highly environmentally related trait (Okbay et al., 2016).

The environment (and G×E) can and should be included at the genome-wide level. Polimanti et al. (2017) performed a genome-wide study to address risk for alcohol use in two independent cohorts ($N = 16{,}361$ and $N = 8{,}084$), taking into account lifetime trauma; individuals were scored dichotomously as exposed or unexposed. Their study is called a GEWIS, which stands for a gene-by-environment genome-wide interaction study. They found a significant gene-by-trauma interaction effect on alcohol misuse in the African American subjects in their study. Interestingly, in this study, the *PRKG1* gene (discussed previously in a G×E candidate gene context) was the only gene that passed significance threshold and did so in the two independent cohorts. *PRKG1* is a cyclic guanosine monophosphate (cGMP)–dependent protein kinase known to be an important modifier of behavior in the animal literature.

ENVIRONMENTAL EXPOSURES AND G×E INTERACTIONS

Another type of association analysis uses candidate genes to correlate variants in specific genes to variation in a particular trait. (Examples are provided in the next paragraph.) G×E studies of this type use specific genetic variants of a candidate gene and correlate this to an environmental measure such as early adversity (e.g., H. M. Sokolowski et al., 2017). Nominated candidate genes often come from the animal literature and it is important to know enough about the human trait to erect a hypothesis about a particular candidate gene. Results of analyses such as these for behavioral and psychiatric phenotypes have been inconsistent, difficult to replicate, and are heavily influenced by assumptions around candidate genes. As mentioned above, GWAS is exploratory and not hypothesis-driven, whereas the candidate gene approach is hypothesis-driven. Candidate gene and G×E studies have come under heavy scrutiny in the past decade for lack of reproducibility (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Duncan, Pollastri, & Smoller, 2014; Karg, Burmeister, Shedden, & Sen, 2011; Risch et al., 2009; Rutter, 2010). Studies can fail to replicate G×E interactions because of lack of standardization of environmental and phenotypic assessment, statistical methods, and study designs (Dunn et al., 2011). Improved phenotyping, better environmental measures, bigger sample sizes, more informed study designs, and replication in independent populations will help to uncover more meaningful G×E interactions in the future. G×E interactions show that genetic risk factors should be seen as predispositions and do not determine a given developmental outcome. As mentioned above, it is timely to include E and G×E in genome-wide studies.

Experience affects development in many ways, especially in the early years, throughout pregnancy and childhood and also in adolescence. Prenatal nutrition and emotional stress can lead to life-long effects on physical and psychological health (Ozanne, Lewis, Jennings, & Hales, 2004; Vickers, Breier, Cutfield, Hofman, & Gluckman, 2000). Perceived socioeconomic status (SES), which is a result of factors such as income, education, social status, poverty, and social stratification, constitutes a major source of stress that clearly affects biological and psychological development (Goodman, Huang, Schafer-Kalkhoff, & Adler, 2007). Children from mothers that were stressed during pregnancy are at increased risk for attention-deficit/hyperactivity disorder, conduct disorder, and impaired cognitive development (Talge, Neal, & Glover, 2007). This increased risk for behavioral disorders might be linked to altered brain structure and function in children and adults exposed to high levels of stress (Buss et al., 2012; Chetty et al., 2014; Harker, Raza, Williamson, Kolb, & Gibb, 2015). The effects of adverse environments on biology are largely mediated through the hypothalamic-pituitary-adrenal (HPA) axis, the human stress response system (Maniam, Antoniadis, & Morris, 2014). For instance, maternal separation affects HPA axis function, resulting in cognitive impairment, anxiety, and depression later in life (Aisa, Tordera, Lasheras, Del Río, & Ramírez, 2007; Champagne, Francis, Mar, & Meaney, 2003; Vargas, Junco, Gomez, & Lajud, 2016). More recently, the early-life environment has been shown to also play an important role in the development of the immune system and regulation of inflammation throughout life (Coe, Lubach, & Shirtcliff, 2007; McDade, Borja, Largado, Adair, & Kuzawa, 2016; Miller et al., 2009). Both HPA axis regulation and inflammation have been linked to metabolic syndrome and obesity, establishing a connection between early-life environment and later physical health outcomes. Nevertheless, exposure to an adverse environment does not always result in the same health outcome. There is individual variability in how susceptible we are to the biological and psychological consequences of environmental exposure. G×E interactions have been shown for a variety of environmental factors. DNA polymorphisms in HPA axis

regulators such as 5HTTLPR interact with early-life stress to determine psychophysiological outcomes (Cicchetti, Rogosch, Sturge-Apple, & Toth, 2010; Kaufman et al., 2006; Qiu et al., 2015; Roy, Hu, Janal, & Goldman, 2007; Uher & McGuffin, 2010). Adversity might have heightened effects on individuals with genetic risk alleles, but positive environments can prevent the developmental consequences of carrying a risk allele. The misleading metaphor that DNA is a genetic blueprint that maps out development can lead to misguided thinking that interventions could not change individuals with certain genetic predispositions.

EPIGENETIC EMBEDDING OF ENVIRONMENTAL EXPOSURE

Research over the past decade has shown that environmental exposures can leave epigenetic marks on DNA that affect the function of genes and molecular pathways. In this context, epigenetic regulation is receiving increasing attention as the molecular mechanism by which experience is embedded in to our biology in the long term (Boyce et al., 2012; Boyce & Kobor, 2015). In some cases, these epigenetic changes are thought to last a lifetime, or even pass on to the next generation. One of the first studies on the epigenetic embedding of experience showed that rat pups that experience low maternal care have epigenetic changes at the glucocorticoid receptor, a gene important in HPA axis regulation. These changes are acquired during the first weeks of life and persist into adulthood, but are absent in pups that were cross fostered with a high maternal care mother (Weaver et al., 2004). Low maternal care in rats also negatively affects other HPA regulators and neuroplasticity (Chetty et al., 2014; Murgatroyd et al., 2009; Roth, Lubin, Funk, & Sweatt, 2009) through epigenetic mechanisms. In humans, similar epigenetic changes in HPA axis genes, caused by early-life stress, are associated with depression and diminished responsiveness to antidepressant treatment in adolescents (Levine, Worrell, Zimnisky, & Schmauss, 2012; McGowan et al., 2009; Nieratschker et al., 2014; Oberlander et al., 2008; Romens, McDonald, Svaren, & Pollak, 2014). Other early-life exposures, such as early-life SES and nutrition, can also leave lifelong epigenetic signatures on the DNA that have been associated with psychological and physical health outcomes in adulthood (Borghol et al., 2012; Drake et al., 2012; Heijmans et al., 2008; Lam et al., 2012; McGowan et al., 2009; Mehta et al., 2013; Tehranifar et al., 2013; Terry et al., 2008; Xu et al., 2013; Yehuda & Bierer, 2009).

Studies of child development, disease, and resilience have mostly focused on genetic variability as a "predisposing" factor and on epigenetic embedding as a mechanism for integrating environmental information (G+E model). Nevertheless, some recent studies show that genotypic differences can interact with epigenetic processes, resulting in individual responses to environmental factors (Anreiter, Kramer, & Sokolowski, 2017; Klengel et al., 2013; Okhovat, Berrio, Wallace, Ophir, & Phelps, 2015). This adds a new level of complexity to biological processes and highlights the need for including genetic by epigenetic analysis as well as genome by epigenome-wide analyses in developmental research.

The question of whether environmentally induced epigenetic marks are passed to subsequent generations is still heavily debated. Both human and model organism studies have shown that some epigenetic marks induced in the parents are still present in the offspring (Ashe et al., 2012; Carone et al., 2010; Dias & Ressler, 2014; Ost et al., 2014). But when a parent is exposed to an experience, their offspring is indirectly exposed as well, through the developing gametes. And in a pregnant mother, the subsequent two generations are simultaneously exposed to the same environment as the mother, because the egg that will produce the grandchild is already developing within the fetus. This means that studies on transgenerational epigenetic inheritance must span over multiple generations, and even then, a recurring cycle of de novo deposition of epigenetic marks, instead of direct inheritance of these marks is hard to exclude. Because of this, empirical evidence for transgenerational epigenetic inheritance is scarce, with a few studies suggesting its occurrence in model organisms, but none in humans (for review, see Heard & Martienssen, 2014). Epigenetics research also struggles with other methodological challenges. For instance, DNA methylation patterns vary more widely between different tissues in a single person than in the same tissue in different people (Jiang et al., 2015). This means that questions regarding the functionality of DNA methylation need to be directed at a specific tissue, and the tissues of most interest to child development (e.g., brain) are not readily accessible. In sum, we know that epigenetic regulation undoubtedly plays an important role in child development, but the field is still in its infancy, and more research is needed to fully understand the role of epigenetics in development.

DEVELOPMENTAL TIME CONSTRAINTS

Many aspects of child and brain development are governed by temporal constraints, known as critical or sensitive periods. Critical periods are windows of plasticity where the brain is more sensitive to experience (Takesian & Hensch, 2013). These windows occur at different times in early development and shape the function of the developing brain (Kobayashi, Ye, & Hensch, 2015; Perani et al., 2011; Werker & Hensch, 2015). The onset and closure of critical periods is both genetically and environmentally influenced, and some research indicates that critical periods can be reopened even after closure (Gervain et al., 2013). This is important because

it means that experiences affect development differently, depending on when during development they happen. For instance, maternal nutrient deficiency during the Dutch winter famine of 1944–1945 had specific long-term consequences at different stages in human pregnancy (Ravelli et al., 1998; Ravelli, van der Meulen, Osmond, Barker, & Bleker, 1999). This also means that interventions targeted to a specific cognitive skill might prove more (or less) effective, depending on the age of the target group of children. Further research into developmental time constraints will prove useful in designing interventions. Although the biological basis of critical periods is not fully understood, research shows that certain factors can shift or reopen critical periods (Peña, Werker, & Dehaene-Lambertz, 2012; Werker & Hensch, 2015). This has led to the suggestion that the developmental time constraints for cognitive functions are often governed by flexible sensitive periods, rather than unchangeable critical periods. It is also important to consider critical periods in the study of gene–environment interplay and epigenetics, because a specific G×E interaction may be more important during a discrete period, and experiences might only result in epigenetic marks during these time periods.

PHENOTYPE MEASUREMENTS

The large body of research described above has identified biological mechanisms that underpin how the interplay between an individual's genetics and their environment affects certain phenotypes. Nevertheless, the term phenotype has a broad definition (i.e., "observable characteristics or traits" (Charney, 2016), and when it comes to taking the leap from biological research to education, it is especially important to consider the usefulness of different phenotype measures. Phenotypic outcome measures can include lower biologically specific level of analysis, such as gene (RNA/protein) expression or synaptic plasticity (Reaume & Sokolowski, 2011), or higher behaviorally broad level of analysis, such as coarsely measured educational outcomes (Belsky et al., 2016; Okbay et al., 2016). Some common examples of phenotypic outcome measures include specific cognitive tasks (Savitz, Solms, & Ramesar, 2006), emotional regulation (Canli, Ferri, & Duman, 2009), personality traits (Rimfeld, Kovas, Dale, & Plomin, 2015) and, more recently, patterns of neural activation (Liu et al., 2009; Peper, Brouwer, Boomsma, Kahn, & Hulshoff Pol, 2007). In view of this broad definition of the term *phenotypes*, researchers have evaluated the effect of gene–environment interplay on phenotypes at many different levels of analysis. This large body of research has made strides toward a major goal of genetic research—to establish and understand the connections between genetic variations, the environment, and phenotypic outcome measures. However, there are ongoing debates about which genetic methodology and analysis method is optimal (Charney, 2016) and which phenotypic measures are best. For example, multiple studies have used various genetic methodologies to explore the link between genetics and educational attainment (Belsky et al., 2016; Okbay et al., 2016; Shakeshaft et al., 2013). However, the "phenotype" educational attainment has been operationally defined in many different ways, such as years of education (Okbay et al., 2016), highest degree completed (Belsky et al., 2016), and score on a U.K. nationwide examination (Rimfeld et al., 2015; Shakeshaft et al., 2013). It is also possible to study the link between genetics and certain components of education attainment such as mathematics (Chen et al., 2017; Wang et al., 2014) or reading (Christopher et al., 2016; Davis et al., 2014; Gialluisi, Guadalupe, Francks, & Fisher, 2016). It is unclear whether these different measurements of educational attainment are all tapping into the same phenotype, or instead measuring distinct components of behavior. Phenotypic measurement inconsistencies have also been reported for genetic studies of psychiatric disorders (Szatmari et al., 2007). Additionally, it remains unclear which levels of analyses are best suited to measure behavior and whether it is sufficient to measure a single level of analysis when examining phenotypic outcomes. We argue that researchers from different fields (such as geneticists, psychologists, and educators), interested in understanding child development, life trajectories, and developmental outcomes, need to work together to identify the most informative phenotypes. As the field progresses, most researchers concur that gene–environment interplay and phenotypic outcomes should be assessed using multiple methods at numerous time points during development. More consistency among methods of assessment is also needed. Furthermore, longitudinal studies, in addition to cross-sectional studies, are critical for analyzing developmental trajectories. Finally, replication of entire studies across more than one population is critical for assessing the significance of the study.

BRIDGING THE GAP

For two decades, researchers have discussed whether the field of neuroscience can inform education (e.g., Ansari & Coch, 2006; Bowers, 2016; Bruer, 1997; Gabrieli, 2016; Howard-Jones et al., 2016). This idea has garnered a great deal of support and led to a large group of international researchers developing the new field Mind, Brain, and Education (MBE). Skeptics of this idea have highlighted problems with this new field (Bowers, 2016; Bruer, 1997). However, proponents of the field of MBE have tirelessly highlighted flaws in these arguments and proposed novel ways to bridge the gap between neuroscience and education (Ansari & Coch, 2006; Gabrieli, 2016; Howard-Jones et al., 2016).

Bruer (1997) pointed out that directly applying neuroscience research to classroom practices has been challenging and unsatisfying. He suggests that this link is "a bridge to far" (Bruer, 1997). Researchers responded to this by highlighting that the link between neuroscience and education need not be a direct link; instead, the field of MBE creates multiple researcher–practitioner links for collaborations to facilitate engaging in discussions about the learning brain (Ansari & Coch, 2006). Recently, this debate has reemerged with Bowers (2016) stating that there is no instance in which neuroscience research informs education beyond psychology. Teams of researchers responded to this criticism (Gabrieli, 2016; Howard-Jones et al., 2016). Specifically, Howard-Jones et al. (2016) highlighted that the expectation that neuroscience must directly influence education is a misinterpretation of the goal of the field of MBE. Critically, the defenders of the field of MBE argue that the link between neuroscience and education is bidirectional. Leading experts from the field of MBE suggest that infrastructure should be put in place to support interdisciplinary training that promotes bidirectional collaborations between neuroscientists and educational researchers and educators (Ansari & Coch, 2006; Ansari, Coch, & De Smedt, 2011; Howard-Jones et al., 2016). Furthermore, these researchers reason that brain and behavioral levels of analysis should not be pitted against each other, as they are complementary levels of analysis that should be examined simultaneously (Howard-Jones et al., 2016).

In line with this idea, we suggest that the field of MBE should extend to include measures of gene–environment interplay. Gene–environment interplay is a critical level of analysis for understanding MBE. We recognize that building the intellectual bridge to form the link between neuroscience and education took time and extensive collaborative discussions. Therefore, we predict and encourage a forthcoming debate regarding the link between gene–environment interplay, neuroscience, and education. These intellectual ongoing debates have ultimately strengthened the field of MBE by forcing researchers to deeply consider the best approaches for forging collaborations between researchers across multiple disciplines and practitioners. We propose that the first goal toward including gene–environment interplay in the field is to work with educators to reconceptualize the false dichotomy between nature and nurture. Only then, can we forge collaborations to better understand the link between gene–environment interplay, neuroscience, and education.

CONCLUSION

Research exploring the link between gene–environment interplay and educational outcomes holds promise to improve the current education system. Specifically, this research can deepen our understanding of individual differences in children across development. This work has the potential to help educators better understand students' responses to the educational environment. Additionally, it may be useful for informing researchers and practitioners on mechanisms that underlie children's individual differences in response to educational intervention programs. This comprehensive understanding can be used to forge new collaborations to improve current educational practices. Ultimately, incorporating gene–environment interplay into the field of MBE will provide researchers and practitioners with a more holistic understanding of the individual and plastic developmental trajectories of children throughout their education.

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