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How Chance, Environment, and Genes Determine Neurodevelopment

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Innate: How the Wiring of Our Brains Shapes Who We Are. Kevin J. Mitchell. Princeton, New Jersey: Princeton University Press, 2018, 293 pages, $29.95 hardcover

Most of us are perfectly comfortable hearing about biological bases of differences between species, but studies of biological bases of differences between people can make us uneasy. This can create difficulties for the scientist who wants to do research on the way genes influence neurodevelopment: if we identify genetic variants that account for individual differences in brain function, then it may seem a small step to concluding that some people are inherently more valuable than others. And indeed in 2019 we have seen calls for use of polygenic risk scores to select embryos for potential educational attainment (Parens, Appelbaum, and Chung, 2019). There has also been widespread condemnation of the first attempt to create a genetically modified baby using CRISPR technology (Normile, 2018), with the World Health Organization (2019) responding by setting up an advisory committee to develop global standards for governance of human genome editing.

Kevin Mitchell's book *Innate: How the Wiring of Our Brains Shapes Who We Are* is essential reading for anyone concerned about the genetics behind these controversies. The author is a superb communicator, who explains complex ideas clearly without sacrificing accuracy. The text is devoid of hype and wishful thinking, and it confronts the ethical dilemmas raised by this research area head-on. I'll come back to those later, but will start by summarising Mitchell's take on where we are in our understanding of genetic influences on neurodevelopment.

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Perhaps one of the biggest mistakes that we've made in the past is to teach elementary genetics with an exclusive focus on Mendelian inheritance. Mendel and his peas provided crucial insights into units of inheritance, allowing us to predict precisely the probabilities of different outcomes in offspring of parents through several generations. The discovery of DNA provided a physical instantiation of the hitherto abstract gene, as well as providing insight into mechanisms of inheritance. During the first half of the twentieth century it became clear that there are human traits and diseases that obey Mendelian laws impeccably: blood groups, Huntington's disease, and cystic fibrosis, to name but a few. The problem is that many intelligent laypeople assume that this is how genetics works in general. If a condition is inherited, then the task is to track down the gene responsible. And indeed, 40 years ago, many researchers took this view, and set out to track genes for autism, hearing loss, dyslexia and so on. Ben Goldacre's (2014) comment, "I think you'll find it's a bit more complicated than that," was made in a rather different context, but is a very apt slogan to convey where genetics finds itself in 2019. Here are some of the key messages that the author conveys, with clarity and concision, which provide essential background to any discussion of ethical implications of research.

Genes Are Not a Blueprint

The same DNA does not lead to identical outcomes. We know this from the study of inbred animals, from identical human twins, and even from studying development of the two sides of the body in a single person. How can this be? DNA is a chemically inert material, which carries instructions for how to build a body from proteins in a sequence of bases. Shouldn't two organisms with identical DNA turn out the same? The answer is no, because DNA can in effect be switched on and off: that's how it is possible for the same DNA to create a wide variety of different cell types, depending on which proteins are transcribed and when. As Mitchell puts it: "While DNA just kind of sits there, proteins are properly impressive — they do all sorts of things inside cells, acting like tiny molecular machines or robots, carrying out tens of thousands of different functions" (2012, p. 32). DNA is chemically stable, but messenger RNA, which conveys the information to the cell where proteins are produced, is much less so. Individual cells transcribe messenger RNA in bursts. There is variability in this process, which can lead to differences in development.

Chance Plays an Important Role in Neurodevelopment

Consideration of how RNA functions leads to an important conclusion: factors affecting neurodevelopment can't just be divided into genetic vs. environmental influences; random fluctuations in the transcription process mean that chance

also plays a role. Moving from the neurobiological level, Mitchell notes that the interpretation of twin studies tends to ignore the role of chance. When identical (monozygotic or MZ) twins grow up differently, this is often attributed to the effects of "non-shared environment," implying there may have been some systematic differences in their experiences, either pre- or post-natal, that led them to differ. But, such effects don't need to be invoked to explain why identical twins can differ: this can arise because of random influences at a very early stage of neurodevelopment.

Small Initial Differences Can Lead to Large Variation in Outcome

If chance is one factor overlooked in many accounts of genetics, development is the other. There are interactions between proteins, such that when messenger RNA from gene A reaches a certain level, this will increase expression of genes B and C. Those genes in turn can affect others in a cascading sequence. This mechanism can amplify small initial differences to create much larger effects.

Genetic is Not the Same as Heritable

Genetic variants that influence neurodevelopment can be transmitted in the DNA passed from parent to child leading to heritable disorders and traits. But many genetically-based neurodevelopmental disorders do not work like this; rather, they are caused by "de novo" mutations, i.e., changes to DNA that arise early in embryogenesis, and so are not shared with either parent.

We All Have Many Mutations

The notion that there is a clear divide between "normal people" with a nice pure genome and "disordered" people with mutations is a fiction. All of us have numerous copy number variants (CNVs), chunks of DNA that are deleted or duplicated (Beckmann, Estivill, and Antonarakis, 2007), as well as point mutations — i.e., changes in a single base pair of DNA. When the scale of mutation in "normal" people was first discovered, it created quite a shock to the genetics community, jamming a spanner in the works for researchers trying to uncover causes of specific conditions. If we find a rare CNV or point mutation in a person with a disorder, it could just be coincidence and not play any causal role. Converging evidence is needed. Studies of gene function can help establish causality; the impact on brain development will depend on whether a mutation affects key aspects of protein synthesis; but even so, there have been cases where a mutation thought to play a key role in disorder then pops up in someone whose development is entirely unremarkable. A cautionary tale is offered by Toma et al., (2018), who studied variants in *CNTNAP2*, a gene that was thought to be related to autism and

schizophrenia. They found that the burden of rare variants that disrupted gene function were just as high in individuals from the general population as in people with autism or schizophrenia.

One Gene–One Disorder Is the Exception Rather than the Rule

For many neurodevelopmental conditions, e.g., autism, intellectual disability, and epilepsy, associated mutations have been tracked down. But most mutations account for only a small proportion of affected individuals, and furthermore, the same mutation is typically associated with different disorders. Our diagnostic categories don't map well onto the genes.

This message is of particular interest to me, as I have been studying the impact of a major genetic change — presence of an extra X or Y chromosome — on children's development: this includes girls with an additional X chromosome (trisomy X), boys with an extra X (XXY or Klinefelter's syndrome) and boys with an extra Y (XYY constitution). The impact of an extra sex chromosome is far less than you might expect: most of these children attend mainstream school and live independently as adults. There has been much speculation about possible contrasting effects of an extra X versus extra Y chromosome. However, in general, one finds that variation within a particular trisomy group is far greater than variation between them. So, with all three types of trisomy, there is an increased likelihood that the child will have educational difficulties, language and attentional problems, and there's also a risk of social anxiety. In a minority of cases the child meets criteria for autism or intellectual disability (Wilson, King, and Bishop, 2019). The range of outcomes is substantial — something that makes it difficult to advise parents when the trisomy is discovered. The story is similar for some other mutations: there are cases where a particular gene is described as an "autism gene," only for later studies to find that individuals with the same mutation may have attention deficit hyperactivity disorder, epilepsy, language disorder, intellectual disability — or indeed, no diagnosis at all. For instance, Niarchou et al. (2019) published a study of a sample of children with deletion or duplication at a site on chromosome 16 (16p11.2), predicting that the deletion would be associated with autism, and duplication with autism or schizophrenia. In fact, they found that the commonest diagnosis with both conditions was attention deficit hyperactivity disorder, though rates of intellectual disability and autism were also increased. Fifty two percent of the cases with deletion and 37 percent of those with a duplication had no psychiatric diagnosis.

There are several ways in which such variation in outcomes might arise. First, the impact of a particular mutation may depend on the genetic background — for instance, if the person has another mutation affecting the same neural circuits, this "double hit" may have a severe impact, whereas either mutation alone would be innocuous. A second possibility is that there may be environmental factors that

affect outcomes. There is a lot of interest in this idea because it opens up potential for interventions. The third option, though, is the one that is often overlooked: the possibility that differences in outcomes are the consequence of random factors early in neurodevelopment, which then have cascading effects that amplify initial minor differences (see above).

A Mutation May Create General Developmental Instability

Many geneticists think of effects of mutations in terms of the functional impact on particular developmental processes. In the case of neurodevelopment, there is interest in how genes affect processes such as neuronal migration (movement of cells to their final position in the brain), synaptic connectivity (affecting communication between cells) or myelination (formation of white matter sheaths around nerve fibres). Mitchell suggests, however, that mutations may have more general effects, simply making the brain less able to adapt to disruptive processes in development. Many of us learn about genetics in the context of conditions like Huntington's disease, where a specific mutation leads to a recognisable syndrome. However, for many neurodevelopmental conditions, the impact of a mutation is to increase the variation in outcomes. This makes sense of the observations outlined above: a mutation can be associated with a range of developmental disabilities, but with different conditions in different people.

Sex Differences in Risk for Neurodevelopmental Disorders Have Genetic Origins

There has been so much exaggeration and bad science in research on sex differences in the brain, that it has become popular to either deny the existence of differences, or attribute differences to varying environmental experiences of males and females. Mitchell has no time for such arguments. There is ample evidence from animal studies that both genes and hormones affect neurodevelopment: Why should humans be any different? But he adds two riders: first, although systematic sex differences can be found in human brains, they are small enough to be swamped by individual variation within each sex. So if you want to know about the brain of an individual, its sex would not tell you very much. And second, different does not mean inferior.

Mitchell argues that brain development is more variable in males than females and he cites evidence that, while average ability scores are similar for males and females, males show more variation and are overrepresented at the extremes of distributions of ability. The over-representation at the lower end has been recognised for many years and is at least partly explicable in terms of how the sex chromosomes operate. Many syndromes of intellectual disability are X-linked, which means they are caused by a mutation of large effect on the X chromosome. The mother of an affected boy often carries the same mutation but shows

no impairment: this is because she has two X chromosomes, and the effect of a mutation on one of them is compensated for by the unaffected chromosome. The boy has XY chromosome constitution, with the Y being a small chromosome with few genes on it, and so the full impact of an X-linked mutation will be seen. Having said that, many conditions with a male preponderance, such as autism and developmental language disorder, do not appear to involve X-linked genes, and some disorders, such as depression, are more common in females, so there is still much we need to explain. Mitchell's point is that we won't make progress in doing so by denying a role for sex chromosomes or hormones in neurodevelopment.

Mitchell moves into much more controversial territory in describing studies showing over-representation of males at the other end of the ability distribution: e.g., in people with extraordinary skills in mathematics. That is much harder to account for in terms of his own account of genetic mechanisms, which questions the existence of genetic variants associated with high ability. I have not followed that literature closely enough to know how solid the evidence of male over-representation is, but assuming it is reliable, I'd like to see studies that looked more broadly at other aspects of cognition of males who had spectacular ability in domains such as maths or chess. The question is how to reconcile such findings with Mitchell's position — which he summarises rather bluntly by saying there are no genes for intelligence, only genes for stupidity. He does suggest that greater developmental instability in males might lead to some cases of extremely high functioning, but that is at odds with his general view that instability generally leads to deficits, not strengths. I'd be interested in studies of these exceptional high achievers to look at their skills across a wider range of domains. Is it really the case that males at the very top end of the IQ distribution are uniformly good at everything, or are there compensating deficits? It's easy to think of anecdotal examples of geniuses who were lacking in what we might term social intelligence, and whose ability to flourish was limited to a very restricted ecological niche in the groves of academe. Maybe these are people whose specific focus on certain topics would have been detrimental to reproductive fitness in our ancestors, but who can thrive in modern society where people are able to pursue exceptionally narrow interests. If so, we can predict that at the point in the distribution where exceptional ability has a strong male bias, we should expect to find that the skill is highly specific and accompanied by limitations in other domains of cognition or behaviour.

It Is Difficult to Distinguish Polygenic Effects from Genetic Heterogeneity

In the early 1900s, there was criticism of Mendelian genetics because it maintained that genetic material was transmitted in quanta, and so genetics seemed not to be able to explain inheritance of continuous traits such as height, where the child's phenotype may be intermediate between those of parents. Reconciliation

of these positions was achieved by Ronald Fisher, who showed that if a phenotype was influenced by the combined impact of many genes of small effect, we would expect correlations between related individuals in continuous traits. This polygenic view of inheritance is thought to apply to many common traits and disorders. If so, then the best way to discover genetic bases for disorder is not to hunt through the genome looking for rare mutations, but rather to search for common variants of small effect. The problem with that is that on the one hand it requires enormous samples to identify tiny effects, and on the other it's easy to find false positive associations. The method of the Genome Wide Association has been developed to address these issues, and has had some success in identifying genetic variants that have little effect in isolation, but which in aggregate play a role in causing disorder.

Mitchell, however, has a rather different approach. At a time when most geneticists were embracing the idea that conditions such as schizophrenia and autism were the result of the combined effect of the tiny influence of numerous common genetic variants, Mitchell (2012) argued for another possibility — that we may be dealing with rare variants of large effect, which differ from family to family. In *Innate*, he suggests it is a mistake to reduce this to an either/or question: a person's polygenic background may establish a degree of risk for disorder, with specific mutations then determining how far that risk is manifest.

This is not just an academic debate: it has implications for how we invest in science, and for clinical applications of genetics. Genome-wide association studies need enormous samples, and collection, analysis, and storage of data are expensive. There have been repeated criticisms that the yield of positive findings has been low and they have not given good value for money. In particular, it's been noted that the effects of individual genetic variants are minuscule, can only be detected in enormous samples, and throw little light on underlying mechanisms (Turkheimer, 2012, 2016). This has led to a sense of gloom that this line of work is unlikely to provide any explanations of disorder or improvements in treatment.

An approach that is currently in vogue is to derive a Polygenic Risk Score, which is based on all the genetic variants associated with a condition, weighted by the strength of association. This can give some probabilistic information about likelihood of a specific phenotype, but for cognitive and behavioural phenotypes, the level of prediction is not impressive. The more data are obtained on enormous samples, the better the prediction becomes, and some scientists predict that Polygenic Risk Scores will become accurate enough to be used in personalised medicine or psychology. Others, though, have serious doubts. A thoughtful account of the pros and cons of Polygenic Risk Scores is found in an interview that Ed Yong (2018) had with Daniel Benjamin, one of the authors of a recent study reporting on Polygenic Risk Scores for educational attainment (Lee et al., 2018). Benjamin suggested that predicting educational attainment from genes is a non-starter, because prediction for individuals is very weak. But he suggested

that the research has value as we can use a Polygenic Risk Score as a covariate to control for genetic variation when studying the impact of environmental interventions. However, this depends on results generalising to other samples. It is noteworthy that when the Polygenic Risk Score for educational attainment was tested for its ability to explain within-family variation (in siblings), its predictive power dropped (Lee et al., 2018).

It is often argued that knowledge of genetic variants contributing to a Polygenic Risk Score will help identify the functions controlled by the relevant genes, which may lead to new discoveries in developmental neurobiology and drug design. However, others would question whether Polygenetic Risk Scores have the necessary biological specificity to fulfil this promise (Reimers, Craver, Dozmorov, Bacanu, and Kendler, 2018). Furthermore, recent papers have raised concerns that population stratification means that Polygenetic Risk Scores may give misleading results: for instance, we might be able to find a group of SNPs (single nucleotide polymorphisms) predictive of "chopsticks-eating skills," but this would just be based on genetic variants that happen to differ between ethnic groups that do and don't eat with chopsticks (Barton, Hermisson, and Nordborg, 2019).

I think Mitchell would in any case regard the quest for Polygenic Risk Scores as a distraction from other more promising approaches that focus on finding rare variants of big effect. Rather than investing in analyses that require huge amounts of big data to detect marginal associations between phenotypes and SNPs, his view is that we will make the most progress by studying the consequences of mutations. The tussle between these viewpoints is reflected in two articles that appeared at the end of 2017. Boyle, Li, and Pritchard (2017) queried some of the assumptions behind genome-wide association studies, and suggested that most progress will occur if we focus on detecting rare variants that may help understand the biological pathways involved in disorder. Wray, Wijmenga, Sullivan, Yang, and Visscher (2018) countered by arguing that while exploring for de novo mutations is important for understanding severe childhood disorders, this approach is unlikely to be cost-effective when dealing with common diseases, where genome-wide associations with enormous samples is the optimal strategy. In fact, the positions of these authors are not diametrically opposed: it is rather a question of which approach should be given the most resources. The discussion involves more than just scientific disagreement: reputations and large amounts of research funding are at stake.

Ethical Implications

And so we come to the ethical issues around modern genetics. I hope I have at least convinced readers that in order to have a rational analysis of moral questions in this field, one needs to move away from simplistic ideas of the genome as some kind of blueprint that determines brain structure and function. Ethical issues which are quite hard enough when things are deterministic are given a

whole new layer of complexity when we realise that there's a large contribution of chance in most relationships between genes and neurodevelopment.

But let's start with the simpler and more straightforward case where you can reliably predict how a person will turn out from knowledge of her genetic constitution. There are then two problematic issues to grapple with: (1) if you have knowledge of genetic constitution prenatally, under what situations would you consider using the information to select an embryo or terminate a pregnancy, and (2) if a person with a genetically-determined condition exists, should she be treated differently on the basis of that condition?

Some religions bypass the first question altogether, by arguing that it is never acceptable to terminate a pregnancy. But, if we put absolutist positions to one side, I suspect most people would give a range of answers to question 1, depending on what the impact of the genetic condition is: termination may be judged acceptable or even desirable if there are such severe impacts on the developing brain that the infant would be unlikely to survive into childhood, be in a great deal of distress or pain, or be severely mentally impaired. At the other extreme, terminating a pregnancy because a person lacks a Y chromosome seems highly unethical to many people, yet this practice is legal in some countries, and widely adopted even when it is not (Hvistendahl, 2011). These polarised scenarios may seem relatively straightforward, but there are numerous challenges because there will always be cases that fall between these extremes.

It is impossible to ignore the role of social factors in our judgements. Many hearing people are shocked when they discover that some Deaf parents want to use reproductive technologies to select for Deafness in their child (Mand, Duncan, Gillam, Collins, and Delatycki, 2009), but those who wish to adopt such a practice argue that Deafness is a cultural difference rather than a disability.

Now let's add chance into the mix. Suppose there is a genetic condition that makes it more likely that a child will have learning difficulties or behaviour problems, but the range of outcomes is substantial; the typical outcome is mild educational difficulties, and many children do perfectly well. This is exactly the dilemma facing parents of children who are found on prenatal screening to have an extra X or Y chromosome. In many countries parents may be offered a termination of pregnancy in such cases, but it is clear that whether or not they decide to continue with the pregnancy depends on what they are told about potential outcomes (Jeon, Chen, and Goodson, 2012).

Like Kevin Mitchell, I don't have easy solutions to such dilemmas, but like him, I think that we need to anticipate that such thorny ethical questions are likely to increase as our knowledge of genetics expands — with many if not most genetic influences being probabilistic rather than deterministic. The science fiction film *Gattaca* portrays a chilling vision of a world where genetic testing at birth is used to identify elite individuals who will have the opportunity to be astronauts, leaving those with less optimal alleles to do menial work — even though prediction is

only probabilistic, and those with "invalid" genomes may have desirable traits that were not screened for. The *Gattaca* vision is bleak not just because of the evident unfairness of using genetic screening to allocate resources to people, but because a world inhabited by a set of clones, selected for perfection on a handful of traits, could wipe out the diversity that makes us such a successful species.

There's another whole set of ethical issues that have to do with how we treat people who are known to have genetic differences. Suppose we find that someone standing trial has a genetic mutation that is known to be associated with aggressive outbursts. Should this genetic information be used in mitigation for criminal behaviour? Some might say this would be tantamount to letting a criminal get away with antisocial behaviour, whereas others may regard it as unethical to withhold this information from the court. The problem, again, becomes particularly thorny because association between genetic variation and aggression is always probabilistic. Is someone with a genetic variant that confers a 50 percent increase in risk of aggression less guilty than someone with a different variant that makes them 50 percent less likely to be aggressive? Of course, it could be argued that the most reliable genetic predictor of criminality is having a Y chromosome, but we do not therefore treat male criminals more leniently than females. Rather, we recognise that genetic constitution is but one aspect of an individual's make-up, and that factors that lead a person to commit a crime go far beyond their DNA sequence.

As we gain ever more knowledge of genetics, the ethical challenges raised by our ability to detect and manipulate genetic variation need to be confronted. To do that we need an up-to-date and nuanced understanding of the ways in which genes influence neurodevelopment and ultimately affect behaviour. *Innate* provides exactly that.

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