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Different approaches to relating genotype to phenotype in developmental disorders

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Abstract

In this paper we discuss the complex problem of relating genotype to phenotype and challenge the simple mapping of genes to higher-level cognitive modules. We examine various methods that have been used to investigate this relation, including quantitative genetics, molecular genetics, animal models, and in-depth psychological and computational studies of developmental disorders. Both single gene and multiple gene disorders indicate that the relationship between genotype and phenotype is very indirect and that, rather than identifying mere snapshots of developmental outcomes, the process of ontogenetic development itself must be taken into account.

Keywords: genotype, phenotype, Fragile X syndrome, Williams syndrome, mouse models, quantitative genetics, molecular genetics, computational models.

I. Introduction

The recent sequencing of the human genome provides the hope that substantial progress can now be made with respect to the relation between genes and cognition. However, many of the empirical tools at our disposal have serious limitations in uncovering the links between genotype and phenotype. In this article, our aim is threefold. First, we attempt to rule out overly simplistic theories of genotype-phenotype relations sometimes found in psychological literature. Second, we examine three current empirical approaches to investigating this relation. These approaches are quantitative genetics, molecular genetics, and animal models. Third, we stress the importance of the contribution of developmental computational neuroscience in building a realistic account of the way in which gene expression may affect the construction of the computational circuits that – via an extended process of development – give rise to the adult cognitive system.

We begin by identifying a trend in some disciplines to employ overly simple analyses of the relationship between genes and phenotypic outcomes, and in particular, to reduce this relationship to simple one-to-one mappings. Linguists, philosophers and even psychologists can often be found using the dangerous shorthand of "a gene (or set of genes) for X", where X is a purported higher-level cognitive module like face processing, grammar, number or the like. Claims abound in the psychological and linguistic literature about the specific contribution of genes to cognitive outcomes, as the following examples illustrate:

- [The human mind] is equipped with a body of genetically determined information specific to Universal Grammar (Smith & Tsimpli, 1995);

- It is uncontroversial that the development [of Universal Grammar] is essentially guided by a biological, genetically determined program (Wexler, 1996).
- The mind is likely to contain blueprints for grammatical rules... and a special set of genes that help wire [it] in place (Pinker, 1994).

We focus our quotations on the domain of language, because this is where much of the debate has centered. However, similar claims have been made with respect to number (Butterworth, 1999), to face processing (Bellugi et al., 1999; Rossen et al., 1994) and to other cognitive domains, as illustrated in the following quotation:

- These three abilites: to recognize numerosities, to detect changes in numerosity caused by adding or taking away from a collection, and ordering numbers by size, are the biologically basic numerical capacities, the ones that are embedded in our innate Number Module. (Butterworth, 1999).

Two issues are at stake: how direct the relation between genes and cognitive processes may be, and how specific. It is uncontroversial that a single gene product cannot construct cognition (although some appear tempted by this idea because the lack of a single gene product can sometimes impair cognition). The issue of directness relates to how precise a role any group of genes will have in determining the structure and content of any subsequent cognitive module. It is our contention that no combination of gene effects will alone determine a cognitive function. Necessarily, the environment plays a causal role in generating the ultimate cognitive structures, whether that environment constitutes the biochemical environment affecting cell differentiation, the prenatal nutritional environment affecting development of the

fetus, or the environment of the external world with which the individual interacts during the process of cognitive development. There obviously can be no direct link between genes and successful cognition.

The issue of specificity relates to the idea that genes, whether one or several, code for structures that are entirely specific to a particular cognitive domain. Consider, for example, the following quote:

- The grammar genes would be stretches of DNA that code for proteins, or trigger the transcription of proteins, in certain times and places in the brain, that guide, attract, or glue neurons into networks that, in combination with the synaptic tuning that takes place during learning, are necessary to compute the solution to some grammatical problem (like choosing an affix or a word) (Pinker, 1994, p. 322, italics added)

The deliberate stipulation that genes are "grammar" genes seems to serve the claim that these genes code for information specific to the domain of grammar. Without such a qualification, the above quote would simply read as a proposal that genes code for a brain that can learn language.

Our contention is that claims for such specificity are unwarranted given the empirical data and the prevalence of many-to-many mappings in relating genes to cognition. To the extent that genes are involved in the causal chain of several cognitive domains, it will be less likely that they code anything specific to a single domain. And they are unlikely given that spatial distributions of gene expression in the brain are rarely narrowly confined to subsequent areas of functional specialisation in the adult brain.

However, it is important to understand the origin of claims that postulate direct, specific, one-to-one mappings between genes and cognition. Such claims are usually made on the basis of two important sources of data: adult neuropsychology and developmental disorders. At first blush, these data often seem to point to independently functioning cognitive modules (identified by cognitive neuropsychology in the adult) that can be selectively impaired or preserved in genetic developmental disorders. On the basis of these data, it is not uncommon to find statements like the following:

- Overall, the genetic double dissociation is striking, suggesting that language is both a specialisation of the brain and that it depends on generative rules that are visible in the ability to compute regular forms. The genes of one group of children [Specific Language Impairment] impair their grammar while sparing their intelligence; the genes of another group of children [Williams syndrome] impair their intelligence while sparing their grammar. (Pinker, 1999, p. 262).

In this paper, we argue that such direct mapping between genes and higher-level cognitive outcomes is highly questionable. Genes are likely to affect much lower-level mechanisms than 'grammar'. In the following section, we look at various methods available to establish relations between genes and behaviour, illustrated with the specific example of FragileX syndrome. We then briefly present our in-depth cognitive and computational studies of another developmental disorder, Williams syndrome, to illustrate a developmental neuroconstructivist approach to genotype/phenotype relations.

- **Methods for relating genotype to phenotypic outcome**

IIa. Quantitative genetics

IIa.i The Method

Epidemiological studies of human genetics focus on discovering the extent to which genetic and environmental factors influence individual differences in a particular trait. These can involve physical traits such as height and weight, personality traits such as aggressiveness and altruism, or cognitive traits such as intelligence, novelty seeking and memory. Researchers pinpoint a trait for which there is interesting population variation, e.g., IQ, and then search for a correlating genetic variation in the population under study. Of course, the discovery that something is highly heritable, i.e., influenced by genes, does not mean that the trait is not also strongly influenced by environmental factors.

There are two types of possible genetic influence: additive, in which the effects of each gene are simply accumulated to influence the final trait, and non-additive, where gene effects are multiplicative. Although multiplicative effects are far more likely, heritability estimates are normally based only on additive genetic variance (see discussion in Thapar & McGuffin, 2000). Note that the heritability calculations are relevant at the population level, not at the individual level. Thus, for example, a statement that trait X (e.g., IQ) has a heritability estimate of 50% does not imply that 50% of any particular person's IQ is explained by their genes. Rather, the figure refers to the proportion of the variation of IQ in the population as a whole that can be imputed to genetic effects. It is also important to recall that children not only inherit half of each of their parents' genes, they are also exposed to environments that are moulded by their parents' genetic makeup and by the children's own influence on their environments. Such indirect effects are known as genotype-environment

correlations, and illustrate that evidence of heritability does not in itself implicate direct or specific causal relations between genes and cognitive traits.

In methodological terms, researchers studying heritability employ huge sample sizes in the general population and focus on family, twin and adoption methods with smaller numbers. Of course, while stating that something "runs in families" may indicate a genetic influence, this conclusion cannot be taken for granted, because environment may be a causal factor, either alone or together with susceptible genes. It turns out to be rare that a specific cognitive trait can be explained by a single genetic variation in the population. Rather, cognitive traits typically involve complex patterns of inheritance involving many genes, each accounting for quite a tiny percentage of the behavioural variance, e.g., as little as 1 or 2% (Plomin, DeFries, McClean & McGuffin, 2001), in combination with environmental factors.

In an attempt to separate the influence of genes and environment, researchers have used twin and adoption methods, comparing monozygotic (MZ) and dyzygotic (DZ) twins, either reared together or apart. If the MZ twin pairs reared apart show a higher correlation than DZ twin pairs, this usually indicates a genetic influence. However, even in this case caution is warranted because adoption is often into similar families as those of the original parent. Note, too, that some environmental factors have an influence on twins that make them more similar (the shared environment), whereas others exaggerate the difference between twins (the non-shared environment).

IIa.ii Developmental disorders: evaluating the quantitative genetics approach

Turning now to developmental disorders, it is true that if one of a pair of MZ twins – whether reared together or apart – develops autism or dyslexia, the other twin

is at greater risk than in the case of DZ twins. This suggests a genetic component to the disorders. Interestingly, however, the risk is far from being 100%. Heritability figures based on MZ twins for autism and dyslexia are 60% and 65% respectively (Plomin, DeFries, McClean & McGuffin, 2001), suggesting that environmental factors play an important role. Noteworthy, too, is the fact that concordance rates for schizophrenia are much higher when MZ twins have shared the same placenta (Davis, Phelps & Brancha, 1995). So environmental factors such as prenatal nutrition also play a significant part in determining the extent to which genetic risk factors are actually expressed. Indeed, genes and environment have an interactive influence, such that particular environments can exaggerate genetic differences (Rutter, 2000). But within disorders such as dyslexia and autism, mere heritability estimates are far from telling us which of the mutated genes are responsible for the elevated risk. Rather, at this stage, we simply know that genetic factors are implicated. With other genetic syndromes, the likelihood of both MZ twins having the disorder is much closer to 100%, as for instance in Williams syndrome and Down syndrome. However, even in the latter case, the much greater heritability does not mean that we can automatically relate mutation of specific genes directly to phenotypic traits.

Finally, it is worth stressing that quantitative genetics can only report on variability. Its methods are unable to investigate the relation between genes and cognition where there is little or no allelic variability in genes or in cognitive outcomes.

IIb. Molecular genetics

IIb.i The Method

The second approach we discuss targets the identification of specific genes. A candidate gene approach is used when genetic variation can be traced back to the protein function for which a particular gene codes. One especially well-known example is the case of variant alleles found in the number of 16 amino acid repeats in the so-called dopamine D4 receptor (D4DR). In general, people vary as to whether they have 2, 4 or 7 repeats, and this difference has been implicated in behaviours like novelty seeking (Benjamin et al., 1996). Differences in repeats impact on dopamine binding, so this neurotransmitter variation could implicate allelic differences contributing to variation in phenotypic outcome.

However, even when a single gene is implicated in a disorder, there is no simple mapping to phenotypic outcome. This is because in most cases, the gene's effect is widespread, having many cognitive (and physical) effects. To illustrate this point, let us consider the example of FragileX syndrome.

IIb.ii Example of a molecular genetics approach to genotype/phenotype relations: FragileX

FragileX syndrome is one of the most common forms of inherited mental retardation, with a prevalence of 1 in 4,000 males and 1 in 6,000 females (de Vries et al., 1997). Clinically the syndrome presents with variable levels of ability, ranging from mild to severe mental retardation, with abnormal facial features (prominent jaw and large ears), subtle connective tissue abnormalities and macroorchidism in males. However, the physical morphology is often less diagnostic of the syndrome than the individual's cognitive profile (Turk, 1998). The cognitive profile in late childhood and adulthood is characterised by weaknesses in attention (Munir, Cornish &

Wilding, 2000), in visuospatial cognition (Cornish, Munir & Cross, 1999), in short-term memory and sequential information processing, alongside (relative) strengths in language, long-term memory and holistic information processing (Freund & Reiss, 1991). In addition, many individuals with FragileX display hyperactive/attention deficit disorder, hyperacusis and autistic-like behaviours (Hagerman & Cronister, 1996).

FragileX is interesting in the current context because, in addition to a characteristic phenotypic outcome, the underlying genetic anomaly is also reasonably well understood. It will become clear that despite knowledge of both the genotype and the adult phenotype, a cognitive developmental perspective is still essential in order to uncover the complex developmental relationship between genotype and phenotype in this disorder. This is because an understanding of the molecular, cellular and system pathophysiology of the syndrome points to experience-dependent synaptic plasticity as critical in determining phenotypic outcome (Churchill, Grossman, Irwin, Galvez, Klintsova, Weiler, & Greenough, 2002, current special issue).

This has implications for understanding the syndrome at the cognitive level. First, given that experience and learning are key factors in shaping the structure of the brain, the effects on cognition must be understood in the context of a dynamically developing cognitive system, rather than merely in terms of the relation of the anomalous genotype to the adult phenotype. Focus on the adult system alone will not help us understand how restrictions in low-level synaptic plasticity could result in the pattern of deficits seen. Instead, we must consider the way in which normal developmental processes would be warped if cognitive development were attempted with a system whose plasticity is restricted.

Second, given the role of this type of synaptic plasticity in establishing neural networks across the developing brain, all circuits in which this low-level process is involved will develop atypically to some extent. However, some cognitive domains may rely less crucially on this particular low-level property, and they will thus display less overt impairment. In other words, as with other syndromes, development itself will be a crucial factor in governing atypical phenotypic outcome across and within domains of both relative strength and weakness (Karmiloff-Smith, 1998).

Let us consider the underlying genetic anomaly in FragileX, and how this alters low-level neural properties. The vast majority of cases of FragileX Syndrome are due to an expansion of the CGG repeat in the untranslated 5' region of the FragileX Mental retardation-1 (FMR1) gene. Among normal individuals, this CGG repeat is highly variable in length and content. The normal repeat size varies from 7 to 60, with 30 repeats being the level most commonly found in the general population. In most affected Fragile X individuals, CGG repeats are massively expanded, ranging from more than 200 repeats up to several thousands (Jin & Warren, 2000). This results in silencing of the FMR1 gene. The lack of expression of the Fragile X Mental Retardation Protein (FMRP) is the sole genetic contribution to the Fragile X phenotype (Verkerk et al., 1991).

Greenough and collaborators (e.g., Greenough, Klintsova, Irwin, Bates & Weiler, 2001, Churchill, Grossman, Irwin, Galvez, Klintsova, Weiler, & Greenough, 2002, current special issue) present strong evidence for a role of FMRP in processes underlying morphological synaptic changes in response to glutamatergic stimulation. They suggest that FMRP is not necessary for initial neuronal outgrowth, but is crucial for the refinement of dendritic spine morphology, a crucial neural correlate of changes

linked to both development and learning. Let us look briefly at development to understand how dynamic and complex this role may be.

FMRP is highly expressed in both adult and fetal brain tissues (Devys et al., 1993). Early in fetal development, FMR1 gene expression is high throughout the brain, particularly high in the hippocampus, cerebellum and nucleus basalis (Devys et al., 1993). The levels are considerably greater than in the adult. FMRP does not act in isolation: it interacts with at least two proteins that are very similar to it in structure (Zhang et al., 1995). In human adult cerebellum and cerebral cortex, FMRP and these proteins are co-localised. However, in the fetal brain they are not: FMRP is located in the cytoplasm as in the adult, whereas one of the two collaborating proteins is also strongly expressed in the fetal nuclei (Tamanini et al., 1997). This suggests that the collaborative functions of FMRP may vary from undifferentiated fetal neurons to differentiated adults neurons. Furthermore, the pathway in which FMRP plays a role, triggered by stimulation of the metabotropic glutamate receptors type 1, is more active in young animals than in adults (e.g., Flavin, Daw, Gregory & Reid, 1996), pointing to the possibility of differential roles of FMRP functioning (and malfunctioning) across developmental time.

Therefore, the important role of FMRP in experience-dependent plasticity can only be properly understood within a truly developmental context. The complex interaction of FMRP with other proteins across development suggests that the silencing of the FMR1 gene alone initiates a series of imbalances that have cascading effects on other elements of the developmental pathway at differing times in development.

In the next section, we discuss the advantages and disadvantages of animal models as an increasingly prevalent tool for understanding such complex cascades. In

addition, we review the loss-of-function approach with the example of knockout mouse models of FragileX syndrome itself.

IIc. Animal models

IIc.i The Method

Selective breeding of natural traits and the creation of transgenic animals (e.g., mice that have had genes knocked out, or altered so that gene products are under- or over-expressed) allow scientists to study the effects of genetic change at different stages of embriogenesis and postnatal development. Transgenic models (altering the genetic makeup of a species) have hitherto mainly concentrated on rodents, in particular the mouse. This is because the mouse breeds very rapidly and shows a high degree of evolutionary conservatism of many developmentally important genes. Conservation of specific genes across species does not necessarily mean, of course, that sequence or timing of gene expression are equivalent in mice and man (Fougerousse et al., 2000). Moreover, murine embriogenesis and postnatal life are considerably shorter than in the human case, with experience-dependent processes playing a much greater role in specifying the micro-circuitry of the human neocortex. Thus, developmental processes may play a much greater role in specifying the phenotypic outcome in the human than in equivalent mouse models.

Induced changes in an animal's genetic makeup can be produced in several ways (Flint, 1996; Heinz, 2000; Hunter, Nolan & Brown, 2000; Kempermann, Kuhn, & Gage, 1997), the main examples of which are: selective breeding of naturally occurring traits, selective breeding of animals exposed to radiation, drugs, specific diets, enriched or impoverished environments, or breeding of animals in whom specific genes have been knocked out or under/over-expressed. Selective breeding of

normal variation in traits capitalises on naturally occuring individual differences of a particular trait. For example, a group of animals may be divided into those with high novelty exploration and those with low exploratory behaviour. The groups are then interbred separately across a number of generations until the offspring all display the group trait. This experimental group then undergoes a number of genetic and behavioural tests. The other strategy is to modify the amount of a particular gene product or the product itself, and then to assess the effect of the mutagenesis on the animal's responses in behavioural tasks.

IIc.ii Example of a mouse model of a developmental disorder: FragileX

In human brain development, the lack of FMR1 transcription has widespread effects. FMR1 knockout mice display some of the cognitive and behavioural characteristics of the human syndrome (Churchill, Grossman, Irwin, Galvez, Klintsova, Weiler, & Greenough, 2002, current special issue), like hyper-reactivity to stimuli (Chen & Toth, 2001) and difficulties with visuospatial spatial learning and working memory. However, these deficits are specific to certain strains of knockout mice only, pointing to genetic background effects (Dobkin et al., 2000). Again, this serves to undermine the notion of simple one-to-one mappings from a single gene dysfunction to phenotype, even when simply considering rodents.

Irwin et al. (2001) found that the morphology of dendrites in knockout mice was atypical and resembled immature cortex or the effects of sensory deprivation, with a large number of long and thin spines as opposed to the thicker and shorter ones characteristic of adulthood and rearing in rich environments. Post-mortem studies of a small number of humans with FragileX syndrome have confirmed the atypical

dendritic morphology suggested by the mouse models in all cortical tissues sampled (Hinton et al., 1995, Irwin et al., 2001).

Churchill et al. (2002, current issue) discuss similarity and differences between murine and human data. The extent of the dendritic abnormality is more limited in knockout mice than in humans. Furthermore, in contrast with human data, the effects on spine morphology are transient in rodents, being most marked at 1 week of age, but disappearing at 4 weeks of age (Nimchinsky, Oberlander & Svoboda, 2001). Churchill et al. explain these important cross-species differences in terms of the divergent developmental timing between human and rodent, as well as different levels of environmental stimulation to which humans and laboratory mice are exposed. Both arguments suggest that, as in the human case, work with mouse models requires an approach that takes into account changes over developmental time and dynamic interactions between developing mice and their environment.

IIc.iii Strengths and weaknesses of mouse models

One of the obvious advantages of mouse models is that the human and murine genomes are very similar, so that many human genes have mouse counterparts. Since mice breed very rapidly and plentifully, linkage analysis is often faster than in humans and provides a smaller candidate region than in the human genome. Many organ systems of mouse and man are also very similar, so that expression analysis of known or candidate genes can be done in the laboratory with the justified expectation that this will be similar in the human case. A particular advantage is that scientists can study gene expression throughout murine embriogenesis and early postnatal life which makes it possible to chart where and when a mutant gene is expressed.

However, as specific genes in humans are mapped to specific genes in mice, there is an unfortunate tendency to take the static unit of a gene as a valid theoretical construct. Yet the gene only has meaning within the complex dynamics of development involving multiple gene-gene/gene-environment interactions (Gerhart & Kirschner, 1997; Keller, 2000). Differences in the developmental trajectories of various species are just as important as similarities in the structure of their genes, since function derives from development over time. As mentioned earlier, in contrast to the shorter period of murine embriogenesis and postnatal life, the formation and consolidation of much of the micro-circuitry of the human neocortex takes place postnatally. In consequence, the importance of the external environment in shaping gene expression and brain structure/function is likely to be greater in the human case than in the mouse. Thus, while human genes have many orthologues in the mouse, expression patterns in terms of both spatial and time-dependent processes differ significantly between the two species (Fougerousse et al., 2000). Although specific genes may be similar, interactions between genes as well as with the internal and external environments may be different. Even identical single genes may have different functions across different species within the development of the total organism. Many knockout models of genes expressed in the brain have resulted in no obvious behavioural consequences of any kind, supporting the view of genetic redundancy (Keverne, 1997), which may not be the same in mice and man. It is quite possible that while one copy of a gene knocked out in the mouse has no effect, the presence of both alleles is vital for normal human development. Alternatively, the deletion of a gene in the mouse may be lethal, whereas haploinsufficiency (i.e., the presence of a single copy of a gene rather than both alleles) may be tolerated in the human case. Equally, environmental conditions and training can alter the way in

which genes are expressed. In sum, generalisations from mouse to man need to be examined with great caution, and there are no simple mappings between genes and outcome at any level of analysis.

Another factor relevant to the problems of generalising from mouse to man is the fact that the mouse repertoire of measurable behaviour is limited and even then, not always empirically investigated to the full. When exploring something equivalent to intelligence, most researchers focus on the mouse's spatial memory in the water maize. How comparable are enhanced murine behaviours in the water maize (which is not even a natural environment for the mouse) to improvements in, say, human memory in all its multiple forms? Other measurements less often used, but perhaps more homologous to human behaviour, might be speed of mental processing or motor reaction time. In other words, good genetics require an accurate and detailed characterisation of cognitive outcome, what one might call "good phenotypics"!

Apart from theoretical difficulties in extrapolating from the mouse to the human case, there are also methodological issues to be resolved in mouse models. It becomes clear that results from mouse studies cannot be taken at face value unless replicated numerous times across different conditions. This has been particularly evident when results differ even across ostensibly identical conditions. Crabbe and his colleagues set up a comparison of results from three different laboratories with serotonin neurotransmitter knockout mice (Crabbe, et al., 1999). Each laboratory had identical strains of mice, with the experiments starting at the same time, on the same day and under the same laboratory conditions, using the same mouse feed and the same battery of post-mutagenesis behavioural tests (including the water maize). The results were surprising. Compared to wild type littermates, one laboratory's mice showed more activity in the maize, the second laboratory less activity, and the third

no difference in activity. These results can only be explained by minute differences in handling, in the odour of the handlers, or in the composition of the water supply. Recall that the strains used in each of the three laboratories were identical and thus individual differences across groups were similar, so cannot explain the empirical disparities here. If such tiny differences such as handling or water composition can affect whether or not the serotonin knockout has an effect on subsequent behavioural outcome, considerable caution must be exercised when extrapolating from the mouse model to the human case.

Finally, we return to a more general issue to which we alluded in our Introduction. There can be dangerous slippage when reporting on mouse models and extrapolating to the human case. Terms such as gene X contributes to outcome Y (one of many indirect causes) become easily translated into X causes Y (the only direct cause). The fact that complex systems like human intelligence can be easily disrupted by deficiencies in a single gene does not validate the opposite claim that the normal function of the gene is solely responsible for the phenotypic trait.

In conclusion, there is no denying that animal models of the genetics of human behaviour have greatly advanced our understanding of gene expression and brain development in developmental disorders. However, it is essential to recognise that behavioural outcome is far removed from gene expression, that there is a reciprocal and dynamic relationship between genes, environment and behaviour, and that extrapolations to the human case from even closely related species must be made with considerable caution.

III. Genes and cognition: how plausible are direct relations?

The developmental disorder, FragileX, has attracted a lot of attention from cognitive neuroscientists because as a single gene disorder it promised to present a relatively simple case of direct gene/cognition mapping. For example, Kaufmann, Abrams, Chen and Reiss (1999) found correlations between FMRP expression and IQ. Menon, Kwon, Eliez, Taylor, and Reiss (2000) investigated correlations between FMR1 gene expression and brain activation measured using functional magnetic resonance imaging during a working memory task. Both measures of FMR1 gene expression correlated with activity in the right inferior frontal, middle frontal gyrus (left and right) and supramarginal gyrus (left and right, parietal lobe), but not with activity in the left inferior frontal gyrus and superior parietal lobe.

There are, however, a number of reasons to be cautious in interpreting such otherwise intriguing correlations. First, clear correlations between protein expression and cognitive functioning are not unequivocally found even in this well understood syndrome. For example, Cornish, Munir and Cross (1999) found no evidence of a correlation between activation ratio (i.e., proportion of FMR1 genes that are not silenced) in young girls with Fragile X and their spatial performance (for further evidence, see Cornish, Munir & Cross, 2001). Second, understanding the neurophysiology of FMRP expression suggests that even robust correlations only represent markers of indirect cascading events, rather than of one-to-one mappings. Thirdly, the Kaufmann et al. and Menon et al. studies did not focus on <u>developmental</u> differences in correlations between FMRP expression and cognition across participants, despite the complex role of FMRP in the process of development itself. However, when Bayley et al. (2001) examined the development of 53 young children

with the syndrome (23-98 months), they found that FMRP expression accounted for a small but significant variance in the level, but not the rate of development. Correlations between FMRP expression and cognition thus received weak support, but crucially suggested the involvement of other factors in understanding early development in FragileX syndrome.

So how directly does FMRP expression affect cognition? Firstly, FMRP is involved in experience-dependent plasticity, a core process in development and learning. Therefore approaches to cognition in FragileX syndrome must encompass a developmental picture. Secondly, despite higher FMRP concentration in certain areas, FMRP is expressed ubiquitously in the typically developing brain. Thus, FragileX syndrome should be characterised by effects on the development of the whole brain. In conclusion, all cognitive domains are likely to have developed atypically to some extent, and the focus on certain domains of very apparent deficit should never overshadow atypicalities, however subtle, in others. In sum, even in a single gene disorder, direct genotype-phenotype mappings are highly questionable. And such reasoning applies equally to developmental disorders caused by mutations of multiple genes and their cascading effects on the developing system.

IV. Genes and cognition: An indirect approach

IV.a The computational level

Let us assume that we have actually discovered "a gene (Y) for X", where presence or absence of gene Y accounts for variability in behaviour X in a developmental disorder (or presence/absence of gene Y accounts for variation of behaviour X in a mouse model; or different alleles of gene Y account for variation in behaviour X in the normal population). The product of gene Y cannot alone be responsible for the

cognitive processes underlying behaviour X. Instead, gene Y will likely be part of a group of genes that code for molecular processes that construct the brain, in an overall process that itself relies on activity-dependent changes to construct micro-circuitry, and perhaps even macro areas of functional specialisation in the adult cognitive system. What can it mean, then, that gene Y correlates with behaviour X?

In order to answer this question, we must turn to an intermediate level of description, one that falls in between the low-level properties of the brain (such as the synaptic plasticity discussed in the case of FragileX), and the high-level behaviours that, in the human at least, very often only consolidate after a protracted period of post-natal development. The cognitive level imports computational principles from biological circuits and builds them into more abstract models that can make contact with the cognitive phenomena of interest. Since development is a key contributor to the causal pathway between genetic mutation and cognitive deficit, it is essential that models studying genotype-phenotype relations are truly developmental in nature. Research carried out over the last fifteen years with the connectionist modelling paradigm provides just such a framework within which to examine disruptions to or variations within trajectories of cognitive development (for reviews, see Elman, Bates, Johnson, Karmiloff-Smith, Parisi & Plunkett, 1996; Thomas & Karmiloff-Smith, in press a).

Connectionist models are computational systems loosely based on principles of neural information processing. They comprise simple processing units connected together into networks. Each processing unit has associated with it an activation level, analogous to the firing rate of a neuron. Units facilitate or inhibit the activity of their neighbours depending on the strength of the connection between the units. In models of cognitive development, initial computational architectures are exposed to an

environment (internal or external, depending on their level within the system). Using a learning algorithm, the network changes its structure (in terms of connectivity patterns or strengths) to encode cognitive domains, and to learn mappings corresponding to appropriate behaviours.

In extending these models to account for patterns of atypical development or individual variation, it is important to note that connectionist networks incorporate a range of initial computational constraints. These affect both the types of problem that the system can learn and the way in which learning will take place (Thomas & Karmiloff-Smith, in press a, in press b, 2001). These constraints include the architecture of the network, its learning algorithm, its activation dynamics, and the representations it uses to encode the cognitive domain. In generalizing these models to atypical development (including disorders of a specifically genetic origin), it is assumed that the underlying biological anomaly serves to change the initial computational constraints of the learning system. When the system then undergoes a process of development using these constraints, the outcome can be a system showing behavioural impairments. However, impairments are not a necessary outcome, since not all problem domains will weigh equally heavily on all computational constraints within the system: some domains may be reasonably successfully acquired even in an atypical system. In this case, the only way to show that such an apparently "intact" cognitive system was atypical would be to probe the fine-grained characteristics of its processing.

IV.b Example of the indirect approach to a multi-gene disorder: Williams syndrome

We illustrate this approach with regard to a particular disorder that has been the focus of much research in our laboratory. This is the genetic disorder known as Williams syndrome (WS). WS is a rare neurodevelopmental disorder occurring in approximately 1 in 20,000 live births, caused by a deletion of 16 genes on chromosome 7q11.23 (Tassabehji et al., 1999). It results in specific physical, cognitive, and behavioural abnormalities, with relatively good verbal, face processing and social skills alongside deficient visuospatial, numerical and problem-solving abilities (Donnai & Karmiloff-Smith, 2000; Mervis et al., 1999; Paterson et al., 1999). Some researchers have characterised WS as a juxtaposition of impaired and intact mental capacities (Rossen et al., 1994), where language, face processing, and social skills are viewed as the intact components, and number, problem solving and visuo-spatial cognition the impaired components.

Part of the research interest in this disorder stems from the fact that the underlying genetic basis is becoming increasingly well understood (Donnai & Karmiloff-Smith, 2000). While some researchers have attempted to link specific genes in the deleted region to specific behavioural deficits (e.g., Bellugi et al., 1999), detailed investigation of the supposedly intact abilities has revealed that in every case, the cognitive processes appear atypical and to be subserved by atypical neural processes. For example, face recognition was initially reported as a 'spared' ability in WS, on the basis that scores on standardised tests fell within the normal range (Bellugi, Wang, & Jernigan, 1994; Udwin & Yule, 1991). However, closer examination of the items within the standardised tests on which individuals with WS performed well, and those on which they performed poorly, suggested that their

recognition of faces proceeded atypically. Specifically, individuals with WS were better at recognising faces which could be identified by single features than those which required computation of configurations of features; control participants showed no such distinction (Karmiloff-Smith, 1997). Subsequent experimentation with artificially created stimuli confirmed this difference (Humphreys, Ewing & Karmiloff-Smith, 2001) Although Jones et al. (1995; cited in Bellugi et al., 1999) reported a correlation between WS performance on standardised face recognition tasks and the volume of grey matter in inferior posterior medial cortex, electrophysiological brain imaging studies have indicated anomalous underlying processing. Mills et al. (2000) found reduced sensitivity in event related potential waveform components to inverted faces compared to normal faces in WS, as well as an absence of the progressive developmental pattern of right hemisphere localisation found in typically developing controls. Moreover, based on a detailed analysis of gamma frequencies in waveforms during face recognition, Grice et al. (2001) revealed patterns consistent with atypical processes of perceptual grouping in their participants with WS. In short, when examined in detail, a superficially intact ability turned out to be associated with quite atypical cognitive and brain processes.

A similar story can be told for language, another aspect of the WS cognitive profile often referred to as intact. The apparent successful acquisition of language in the face of low IQ has been adopted by some to motivate claims for the developmental independence of language from general cognition (Pinker, 1994). Once more, however, detailed investigation has demonstrated atypicalities in many areas of language, including vocabulary, grammar, pragmatics, and the precursors to language development in infants (Karmiloff-Smith et al., 1997; Paterson et al., 1999; see Thomas & Karmiloff-Smith, 2001, for a review). For instance, Thomas et al.

(2001) demonstrated that the developmental trajectory of acquisition of morphology (learning how to change word forms to modify their meanings) in WS was not only delayed but displayed qualitative differences compared to controls. Other studies have suggested a difficulty in acquiring items that violate grammatical regularities also (Clahsen & Almazan, 1998; Zukowski, 2001).

Importantly, for verbal morphology, much work exists demonstrating how connectionist computational models can account for the trajectory of development in normal children. These models use neural networks to learn the relation between verb stems, their meanings and their inflected forms. Perhaps a model with atypical computational constraints might account for the WS profile of development. But which constraints should we alter?

A growing body of literature suggests that the relative balance between the use of phonological information (i.e., the sounds of words) and semantic information (i.e., their meaning) may be different in WS. Once more, evidence for atypical brain processes has been uncovered. Using an event related potential paradigm, Neville, Mills and colleagues found that individuals with WS had activation responses to auditory stimuli that were less refractory and more excitable than those found in controls, a difference which did not extend to the visual modality (Neville, Holcomb, & Mills, 1989; Neville, Mills, & Bellugi, 1994). Neville et al. (1994) suggested that the hypersensitivity of the auditory system may be related to atypical language development in WS.

More generally, we are beginning to have an explanation that in WS, genetic influences operate to affect the trajectory of development via an alteration in the relative quality or accessibility of different types of information that normally enable successful language development in children. Here is an example illustrating the

indirect route through which genes are likely to impairments. However, for this particular domain, the empirically evidence is sometimes contradictory and a clear theory has yet to emerge. In order to clarify the viability of different theoretical accounts, Thomas & Karmiloff-Smith (2001) employed a connectionist model of the typical development of inflectional morphology. They systematically compared existing hypotheses by altering the initial computational constraints of the model in line with each account, and examining its adequacy in accounting for the WS data. The model was able to rule as unlikely some explanations (e.g., that in WS inflectional morphology is acquired purely on the basis of word sounds), and to point to more viable explanations (word sounds are represented atypically; there are problems integrating information about a word's sound and its meaning). In addition, the model demonstrated for the first time precisely how different computational constraints interact in a developmental system: the atypical trajectory found in WS may arise from more than one altered constraint.

Concluding comments

In this paper we have explored genotype/phenotype relations, particularly in regard to two syndromes in which both genes and behavioural outcomes are well documented. Whether a single gene disorder, as in the case of FragileX, or a contiguous multiple gene disorder, as in the case of Williams syndrome, the relations between genotype and phenotype were shown to be very indirect and complex. Even in the case of supposedly intact abilities, we found that detailed empirical investigation revealed atypical cognitive and brain processes underlying a superficially preserved ability.

This supports the idea that from a low-level consideration of how genes contribute to the developmental process, it is unlikely that we will find specific outcomes in terms of impaired and preserved cognitive modules. Computational models of development form an intermediate level at which hypotheses may be generated concerning the link between low-level neurocomputational differences and high-level cognitive outcomes. This is an explanatory strategy that respects the inevitable indirectness of the causal relation between genotype and phenotype and takes seriously the process of development itself.

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