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The dawn of cognitive genetics? Crucial developmental caveats

Gaia Scerif[1] and Annette Karmiloff-Smith[2]

[1]School of Psychology, University of Nottingham, Nottingham, UK; and Sackler Institute of Developmental Psychobiology, Cornell University, USA
[2]Neurocognitive Development Unit, Institute of Child Health, London, UK

Attempts to bridge genetics and cognition are rapidly coming to the forefront of cognitive neuroscience. It is therefore crucial to evaluate the current state of knowledge about disorders of known genetic origin as a way of assessing whether, and if so how, links between genotype and cognitive phenotype can be drawn, however indirect these links might be. We review recent empirical findings from research on genetic disorders at three levels of description – cognitive, neural systems, and cellular – that caution against simple genotype–phenotype mappings at all levels. Most importantly, interdisciplinary efforts to integrate human genetics and cognition will need to operationalize the mechanisms driving both typical and atypical developmental processes over time.

Introduction

The first decade of the 21st century was christened 'the dawn of cognitive genetics' ([1], p. 466). Indeed, the sequencing of the human genome and exciting advances in post-genomic technologies have led many researchers to raise the following question: can the function of specific genes be linked to specific cognitive-level processes? A variety of complementary approaches have been used to address this issue (see Table 1 for a synthesis of some commonly used methods, their merits and disadvantages). Within this context, developmental disorders of known genetic origin have provided unique naturally-occurring models to investigate the links between the function of genes and cognitive-level outcomes. Decreased or absent expression of a gene, A, accompanied by a deficit affecting a cognitive function, B, have been taken as evidence for the role of A in implementing B (e.g. [2–4]).

In this article, we review evidence that challenges, even in monogenic disorders, mappings between specific genes and the cognitive level of description when these ignore the developmental complexities of genetic influences on cognition (as originally proposed in [5]). This is because overlooking the role of developmental processes carries several implicit and potentially erroneous assumptions. First, if information is drawn solely from atypical adults, the association of the genetic dysfunction with a specific cognitive domain is implicitly accepted as 'static', with the empirically untested assumption that areas of impairment are equally affected along the whole developmental trajectory, from infancy to adulthood. Second, even when the research focus is solely adult cognition, concentrating primarily on domains that exhibit the most overt cognitive deficits assumes that the effects of the syndrome are selective to them, without affecting, even subtly, other functions and systems. Third, if developmental *relationships* between areas of cognitive impairment and proficiency are not investigated, one implicitly accepts not only simple mappings between genetic mutation and impairments, but also the independence of efficient and inefficient processes across development. None of these possibilities is in principle incorrect. However, accepting them *a priori* is an error, because it ignores the role of developmental change in determining adult phenotypic outcomes.

So, should all cognitive neuroscientists interested in genetics despair at the complexity of the task? We believe not, but with several caveats. The overall aim of the present article is first to suggest that genotype–phenotype mappings (see Glossary) must operationalize the early

Corresponding authors: Scerif, G. (Gaia.Scerif@nottingham.ac.uk), Karmiloff-Smith, A. (a.karmiloff-smith@ich.ucl.ac.uk).

Glossary

Down syndrome (DS): A sporadic disorder affecting approximately 1 in 600 births and in 95% of cases associated with trisomy of chromosome 21.
Fragile X syndrome (FXS): A familial disorder that affects approximately 1 in 4000 male and 1 in 6000 female births. In the vast majority of cases, it is associated with the silencing of a single gene, the Fragile X Mental Retardation Gene 1 (FMR-1), at Xq27.3.
Genotype: The combination of variants of a gene n the maternal and paternal chromosome at a particular locus.
KE family: Three-generation family, in which approximately half of the members are affected by severe oromotor dyspraxia (fine control of facial movement), accompanied by expressive and receptive language impairments. Affected members of the family carry a defective allele normally coding for a forkhead-domain transcription factor, FOXP2.
Phenotype: Characteristics associated with a particular genotype at multiple levels of description, from the molecular to the cellular, systems, cognitive and behavioural levels.
Phenylketonuria (PKU): Affects 1 in 10 000 births, associated with a mutation of the phenylalanine hydroxylase gene at 12q22-12q24.1, causing an imbalance in the ratio of phenylalanine to tyrosine.
Polymorphism: Multiple variants of a gene at a particular locus.
Transcription: The process by which messenger RNA is synthesized from DNA.
Translation: The process by which messenger RNAs (mRNAs) are read into particular amino acid sequences, eventually resulting in the production of proteins.
Williams syndrome (WS): A sporadic disorder affecting 1 in 20 000 births and associated with a hemizygous microdeletion of some 25 genes on chromosome 7q11.23.

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changes in neurocomputational properties that characterize genetic disorders and their potential effects on subsequent developmental trajectories – what we term 'neuroconstructivism' (see Table 2 for the broader theoretical viewpoint). Second, integrating evidence on atypical cognitive development with that from systems, molecular and computational developmental neuroscience has begun to provide such information (see [6,7,32] for excellent examples of such integrative research). We therefore focus our review on a small number of disorders of known genetic origin (henceforth, the shorthand of 'genetic disorders' will be used) that are well-defined at multiple levels of description, from cognitive processes, to neural systems and cellular properties, to genes, as we consider these to be important case studies making it possible to critically examine the notions of static, selective and developmentally independent deficits.

Cognitive processes: characteristics of atypical developmental change

Firstly, can earlier cognitive outcome be inferred from the adult phenotype? Several studies have now tested whether patterns of relative cognitive strength and weakness in adulthood hold in infants with genetic disorders, such as Williams syndrome and Down syndrome [8–11],

Table 1. Commonly used approaches for mapping genotype to cognitive phenotype, some of their merits and limitations[a]

	Studied populations and recent review articles	Question addressed	Advantages	Limitations
Genetic manipulations in animal models of cognitive functioning	Clearly defined lines of experimental animals (e.g. rodents) for whom established behavioural measures exist [76].	What are the effects of single (or, more recently, multiple) gene mutations (e.g. gene silencing) on cognitive and behavioural markers compared with wild-type litter mates?	Precise control over the number and locus of manipulated genes allows systematic studies of the effects of defective genes.	(i) Functional homology of genes across species accepted for many, but not all genes of interest. (ii) Behavioural effects of genetic mutations often found only in specific lines, highlighting the importance of genetic background in modulating gene-specific effects.
Molecular genetics	Typically or atypically developing individuals characterized by different polymorphisms of a gene of interest [38].	How does cognitive performance vary for individuals characterized by different polymorphisms?	Allows testing the effects of variability of genes coding for proteins whose functions are relatively well understood (e.g. dopamine receptor types).	Selection of candidates genes is somewhat focused on well understood proteins, perpetuating interest in a set of proteins (but note advances in using data-driven approaches, e.g. in proteomics).
Quantitative behavioural genetics	Large samples of: (i) Monozygotic and dyzygotic twins [77]. (ii) Subgroups of interest (e.g. poorly functioning on the constructs of interest) [78,79].	What proportion of the variance of a given cognitive measure is explained by genetic variation? What are the additive or multiplicative effects of genetic variation on any cognitive measure?	Large samples mean that multiple factors affecting variability (genetic, shared and non-shared environments, etc.) can be assessed.	(i) Limited inferences can be drawn on individual cases. (ii) Amount of the variance on higher level cognitive measures accounted for by individual genes is usually exceedingly small.
Cognitive functioning in developmental disorders	Individuals with: (i) Monogenic disorders (involved gene known, e.g. [6]). (ii) Polygenic disorders (involved loci known, e.g. [3,16]). (iii) Behaviourally defined syndromes, for which genetic contributions are as yet unknown (although multiple candidate genes or loci may have been identified by linkage analysis).	How do individuals with a genetic disorder differ from comparison groups in terms of selected cognitive skills?	Allows pitting atypical groups to typical and atypical comparison groups either at discrete time points in development (cross-sectional designs), or over developmental time (longitudinal designs).	(i) Inferences that can be made from the comparison across groups depend on the correct choice of matching criteria, but the choice of matching criteria themselves affect the direction of group differences. (ii) Relatively small samples of individuals preclude interpretation of null findings (low statistical power). (iii) Restricted availability of sufficient individuals of various age groups limits drawing full developmental trajectories of performance.
Computational modelling	Neural networks designed to test distinct effects of various parameter settings on performance during and after training [24,60].	What changes in the parameters of a network alter its learning in a way that models cognitive functioning and its development in typical and atypical populations?	Clear definition of which computational properties or changes thereof best account for performance during and after training.	Not always easy to operationalize neural variables into meaningful parameters of neurobiologically plausible models.

[a]Divisions across approaches are somewhat arbitrary, and many researchers in the field use more than one. Advantages and limitations of each approach are also not mutually exclusive, with some overlap across categories.

Table 2. What is neuroconstructivism? Operationalization of different levels of description for disorders of known genetic origin, related empirical predictions and research strategies within this framework. (Adapted from [5].)[a]

Conceptualization and empirical predictions	Genetic level	Widespread and/or specific deficits depend on how early in prenatal development normal gene expression matters, and on how localized/stable throughout development are the molecular effects of the perturbation.
	Neural systems level	Perturbation to normal patterns of pre- and post-natal brain development; plasticity as a basic feature of both normal and atypical cortical development.
	Cognitive level	Modules develop by a process of gradual modularization; innate representations (rare at the cortical level) are distinct from differential developmental timing and low-level computational properties supporting learning.
	Environmental level	Environment is dynamic (changes as a function of infant's selection and processing of input).
	Behavioural level	Specific and general outcomes are both important; the later the gene expression, the more specific the impairment is likely to be.
Research strategies	Cause	Identify the timing of gene expression and interactions with other genetic and environmental events.
	Domain of study	Identify the lowest level of impairment and study its developmental effects on higher-level cognition re both proficiencies and impairments.
	Methodology	Devise tasks to differentiate overt behaviour from underlying cognitive processes; longitudinal brain imaging of both temporal and spatial changes; study changes in timing and structure of environmental input.
	Targeted populations	Study earliest possible markers of disorder in foetus and infancy; focus on differences *and* similarities across phenotypes.

[a]Relationships across levels of descriptions involve complex multi-level interactions throughout developmental time, rather than being unidirectional (e.g. from the genetic to the neural systems level alone).

fragile X syndrome [12–14], phenylketonuria [15] and others (see Glossary for definitions of syndromes).

Research focusing on the cognitive level for individuals with Williams syndrome (WS) has been particularly informative in this respect. The condition originally attracted much interest because of its strikingly uneven profile in the adult, with relative strengths in language and face processing and weaknesses in visuo-spatial cognition and numerical processing, and the related possibility of associating the deleted genes with selectively impaired cognitive domains ([3,4], but see [16]). However, infant studies revealed a rather different profile, with infants with WS showing grossly delayed vocabulary comprehension equivalent to infants with Down's syndrome (whose later language is delayed compared with adults with WS), and to that of much younger normal controls. By contrast, WS infants' ability to discriminate small quantities turned out to be similar to that expected given their chronological age, a finding that is very different from their serious numerical difficulties in adulthood [8]. By contrast, Down syndrome infants were extremely delayed on the same measure, despite the fact that adults with Down syndrome surpass the levels of WS adults in the numerical domain. This is certainly not to claim that early and late outcomes will necessarily differ. For example, in the domain of attention, infants, older children and adults with WS or fragile X syndrome (FXS) display consistent difficulties at all ages [9,12,13,17–20]. However, the language and number findings emphasize the need to investigate phenotypes empirically, not only in adulthood, but also at the outset of development, rather than inferring early profiles from the final outcomes. This is crucial when considering genotype—phenotype relations for genes that are expressed very early in embryonic and postnatal development.

Secondly, striking differences in functioning across domains have been documented in adults with genetic disorders, although these often occur in the context of overall cognitive delay. The issue of whether the cognitive architecture of genetic disorders can therefore be conceptualized as an ensemble of selectively impaired and intact modules, akin to those perhaps measured in individuals who suffered localized brain damage in adulthood, has been and remains a topic of hot debate [5,21–24]. The notion of a 'selective' deficit implies the impairment of a single process or domain and the preservation (i.e. normal functioning across time) of others. Crucially, the demonstration of selective deficits depends on the range and sensitivity of the measurements used within and outside the domain of primary interest [5,24]. Again, the case of Williams syndrome is particularly informative of this methodological challenge. Several studies across multiple laboratories have shown that, when examined in depth, language, an area of behavioural proficiency in adults with WS, is atypical in its various subcomponent processes, from vocabulary to syntax to pragmatics [25–28]. Similar subtle impairments hold for the ostensibly 'spared' face processing abilities in this clinical group [29]. An analogous example comes from the study of the KE family, whose affected members were initially described as having a selective grammatical impairment [30] (and see Glossary). Subsequent detailed neuropsychological assessment of verbal and non-verbal functioning revealed that oromotor dyspraxia (i.e. fine motor control of facial movements essential for language production) [31,32,33], and difficulties in the perception, production and timing of verbal *and* non-verbal sequential actions [34,35]

accompanied the striking expressive and receptive linguistic deficits in affected members. The proposals that either timing or articulatory difficulties, or the timing of rapid sequential actions have an impact on the development of phonological awareness and in turn affect the acquisition of multiple aspects of expressive and receptive language remain debated [36]. Nevertheless, even if these deficits proved to be unrelated, we note that their very co-existence suggests pleiotropic effects of the FOXP2 mutation and obviously questions the description of the condition as a *selective* speech and language disorder.

Finally, we highlight a further problem for accounts of cognitive performance in genetic disorders that ignore developmental trajectories in linking genes and adult cognition. They carry the implicit assumption that the patterns of behaviour observed in adulthood are not the result of atypical interactions across cognitive processes through developmental time. This is a related but distinct issue from the importance of investigating cognitive functioning from infancy. Whereas the latter emphasizes the need to investigate the ontogenetic origins of later strengths or weaknesses within each domain, the former draws the focus on potential *interactions* and *compensations* across processes over developmental time. There are multiple ways in which such interactions can alter the course of development. First, the normal temporal relationships between processes across domains can be offset in genetic disorders. Indeed, longitudinal studies indicate that language development in WS follows an early atypical trajectory in its relative timing in comparison with other cognitive milestones, the vocabulary spurt preceding the onset of exhaustive sorting and pointing following the onset of vocabulary (reviewed in [37]). However, the simple observation that the timing of developmental milestones is atypical does not warrant a tight functional relationship between these asynchronies. Second, measures of cognitive functioning across domains can vary in their contribution to processes of interest in normal development as opposed to genetic disorders. For example, in WS the normal relationships between triadic attention (caregiver-to-infant-to-object) and vocabulary development do not hold, suggesting that apparently proficient performance is supported by different cognitive processes from the typical case [37]. WS infants tend to fixate on adults and fail to disengage from their face when this would help learning about the referent of adults' attention (see [10] and Box 1 for further examples). A third way in which asynchronies across processes could play a role in phenotypic outcome is the following: a 'simply delayed' process at a particular time in development could give rise to later deviance [5,60].

In summary, current empirical data, neurocomputational models and theoretical arguments stress the key role of including a truly developmental account when attempting to make mappings between genotype and cognitive phenotype. They also caution against the popularly used shorthand of 'genes for' high-level cognitive processes. By contrast, understanding the mechanisms by which genetic variation warps low-level neurocomputational properties at the systems and cellular level is vital. It is to these changes that we now turn.

Box 1. Genetic disorders and developmental interactions across cognitive domains

Whereas areas of manifest selective impairment in adults with genetic disorders have received much attention, potential atypical relationships *across* cognitive skills over developmental time need to receive as much empirical focus. For example, Williams syndrome (WS) is characterized by relative strengths in language and face processing, but weaknesses in visuo-spatial cognition and number. Ansari and colleagues [65] showed that children with Williams syndrome achieve competence in reciting the counting sequence, but their full understanding of cardinality is severely delayed and only reaches that of much younger children with equivalent visuo-spatial skills. Crucially, verbal abilities predict variability in cardinality understanding in WS, whereas visuo-spatial measures are predictive of variability in this important aspect of numerical representations in typically developing children. These results underline how ostensibly simple 'delayed' functioning in WS is actually associated with predictors of variability that deviate from the normal case. Atypical relationships across domains can have even subtler characteristics. Understanding spatial language is particularly challenging for adults and children with WS, a finding that is predicted by their poor visuo-spatial skills. Interestingly, relational but non-spatial aspects of language (for example, comparatives such as 'lighter than' or 'darker than') also turn out to be more difficult than expected given their grammatical competences [66].

Findings such as these highlight subtle interactions across cognitive processes and question their developmental independence, but do not as yet explain why these interactions occur. Could there be common mechanisms underlying these relationships across domains? For example, difficulties in abstracting the relational characteristics of the surrounding perceptual environment might account for deficits in all of the following: spatial and non-spatial relational language [66], abstract representations crucial for number development [65,67] and a difficulty with second-order relational features of faces, that is, their configurations [29,45]. Difficulties at this level of computation might also lead to the establishment of atypical processing strategies (for example, a focus on first-order perceptual features, as opposed to the relational aspects of stimuli). Suggestions such as these remain speculative, especially because cross-domain relationships are rarely tested longitudinally. However, they shift the focus away from apparent islets of ability or deficit to the possibility of *interactions* across processes. In turn, they generate novel questions about the potential computational mechanisms that drive them to co-occur through development.

Systems neuroscience: atypical functional neuroanatomy

Associations between particular polymorphisms (see Glossary) and specific cognitive processes tend to be characterized by small effect sizes, and this might depend on the fact that our conceptualization of high-level cognitive processes is not always constrained stringently by advances in neuroscience. Goldberg and Weinberger [38] propose that phenotypes that are more closely related to the functioning of neural systems (such as activity in functional magnetic resonance imaging tasks) might hold better promise for relationships with gene expression. This has indeed been the strategy followed successfully by several researchers investigating adults with genetic disorders, but developmental studies are scarce in this respect. This scarcity is due in part to limitations associated with testing atypically developing children,

but also to difficulties in interpreting atypical performance, given disagreement as to what drives *normal* functional brain development across domains (reviewed in [39]). Consider, for example, the developmental changes in the functioning of posterior cortical regions involved in face processing, such as the fusiform face area: is their development driven by a maturational time-schedule, or is their specialization for face processing highly dependent on experience-driven interactions with other cortical areas? Answers are still debated [39]. As another example, the dorsal stream is involved in the control of action in the adult and its functions are often relatively more affected in genetic disorders than ventral stream skills. However, the normal timescale of dorsal functional development in comparison with that of ventral pathways and their segregation through development is still debated, making the developmental selectivity of dorsal deficits and their high incidence in developmental disorders difficult to assess (reviewed in [40]).

Even studying functional activity in adults with genetic disorders brings intriguing findings to bear on the issue of selectivity. Atypical patterns of activity during tasks that display overt behavioural impairment are well documented. Adults with fragile X syndrome, for instance, display reduced modulation of activity of distributed prefrontal and parietal networks during stimulus-response interference [41] as well as in tasks requiring arithmetic manipulations [42], and finally across frontostriatal circuits when required to inhibit responses [43]. Affected family members of the KE family activate atypically motor and language related areas of the brain during both overt and covert verb generation tasks [44]. However, it is crucial to note that atypical neural processing also characterizes areas of behavioural *proficiency* in genetic disorders. For example, even though people with WS exhibit good face recognition skills on some standardized behavioural tasks, early electrophysiological markers of configural processing of faces suggest that they do not process them normally nor differently from non-faces, contrasting with the gradual specialization for faces seen in the general population [45]. Neuroimaging data also point to atypical face processing: individuals with WS recruit wider frontal areas when engaged in face and eye-direction processing, whereas controls rely on the activation of posterior face-related areas [46]. Integrating across these and other studies of functional activity in genetic disorders reveals that multiple regions are activated atypically across domains, including both those that exhibit overt behavioural deficits for the syndrome of interest, and domains in which these individuals are relatively proficient. Intriguingly, in the case of single-gene disorders characterized by a variable degree of expression of the affected genes, studying patterns of functional activation also makes it possible to investigate whether variability in activity correlates with gene expression. This is the case for women with FXS, who express variable levels of FMRP, depending on their patterns of X-chromosome inactivation. This variability allows an examination of the correlations between FMRP expression and functional activation. Activity in task-relevant areas turns out to be correlated with FMRP expression [41–43]; see Figure 1).

In summary, relationships between genetic defects and brain dysfunction hold exciting promise. However, truly developmental questions remain unexplored and the selectivity of the deficits to areas normally supporting affected cognitive processes has been questioned. Furthermore, intriguing correlational findings have only recently been complemented with more detailed mechanistic accounts. These involve a deeper understanding of the cellular and molecular levels at which genetic disorders affect neural functioning, and a better grasp of how these effects vary regionally.

Cellular and molecular level: changes in neurocomputational properties

Interpreting the developmental effects of genetic dysfunction at the molecular level is a particularly difficult enterprise when multiple genes are involved. The task is relatively easier in disorders associated with single-genes, such as those affecting members of the KE family or individuals with fragile X syndrome (FXS). Disruption of FOXP2, a gene coding a forkhead-domain transcription factor, differentiates affected from unaffected members of the KE family [6]. Expression of the gene (or its homolog across species) increases through embryonic and foetal development in mouse and human cortical plate, basal ganglia, thalamus, inferior olive and cerebellum [7], as well as in the homolog of the thalamus and striatum of songbirds [47]. Teramitsu and colleagues point out that, across species, these structures are part of circuits crucial to the *development* and *learning* of the timing of complex

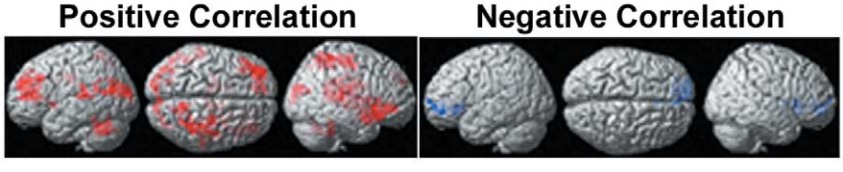

Figure 1. Women with fragile X syndrome (FXS) performed a task requiring them to inhibit some responses in certain trials (mixed 'go–nogo' blocks), in contrast with blocks in which they responded on every trial ('go' blocks). Compared with a control group, they achieved a similar degree of accuracy and speed but showed abnormal patterns of activation in areas related to inhibitory control. Widespread significant positive correlations ($p<0.001$, corrected) between FMRP expression and activation were found bilaterally for the cerebellar hemispheres and vermis, putamen, ventral prefrontal cortex, superior and middle occipital gyri, and middle temporal gyrus. Activity in left dorsolateral prefrontal cortex and angular gyrus, as well as right caudate, striatum, insula, hippocampus and precuneus was also positively correlated with FMRP expression. By contrast, bilateral ventromedial prefrontal activation was negatively correlated with FMRP expression, because of greater activation in the go than in the mixed go–nogo condition with increases in FMRP expression. These findings suggest that FMRP may be involved in the modulation of activity in such areas, although the mechanisms underlying such changes or different modulatory effects across areas remain unclear. (Reproduced with permission from [43]; medial correlations not shown here.)

motor sequences, rather than purely innate orofacial behaviours such as feeding. The case of the KE family, therefore, illustrates how disrupted gene expression across a restricted number of structures can affect learning mechanisms that might subsequently affect language development as well as other skills.

Even more intriguing is the case of genes that are much more ubiquitously expressed than FOXP2. Fragile X syndrome is associated with the silencing of a single gene, whose protein product, FMRP, is expressed throughout cortex and is involved in the regulation of multiple cascading processes leading to activity-dependent changes in dendritic spine morphology across cortex. And yet FXS is characterized by an uneven cognitive profile, with relative strengths in receptive vocabulary and visuoperception, and weaknesses in attention and spatial cognition. This poses an interesting developmental conundrum: how does the silencing of a protein with ubiquitous functions nonetheless result in an uneven phenotypic profile? Relative regional differences in gene expression can account for some, but not all, neural and cognitive differences across domains. We have proposed that overt deficits are likely to be more apparent for certain processes than others, because the neural changes associated with fragile X syndrome are more *relevant* to the neurocomputational requirements that are crucial for the development of these functions compared with others [13,48]. Analogous suggestions have been made to account for the correlations between FMRP expression and functional activity in women with FXS [43], as well as to interpret the dissociation in performance on tasks tapping magnocellular and parvocellular pathways projecting from the thalamus to cortex, as well as first- and second-order motion [49,50] (see Box 2 for further details).

By differentiating domain-relevant from domain-specific neurocomputational properties, we introduce the idea that a more generalized change in the developing system can result in deficits that are most overtly measurable in some domains and yet also subtly affect others [5]. This is not to say that specific effects on cognitive processes are impossible. Rather, such considerations pinpoint the necessity to continue to investigate empirically the presumed stability and selectivity of deficits across developmental time, while also providing a mechanistic account of *why* they should occur. For example, Diamond and colleagues [15] reasoned that in phenylketonuria, another single gene disorder, specific dopaminergic projections to prefrontal cortex should be more vulnerable to damage because of their high-dopamine turnover. Having proposed this, they tracked cognitive development longitudinally in individuals with treated PKU from infancy onwards and found consistent but subtle deficits in executive functions compared with recognition memory. The selectivity of these deficits is still highly debated [51], with the timing of exposure to elevated phenylananine seeming to contribute to differences in outcome [52]. Nonetheless, this truly developmental perspective is precisely the type of approach we are advocating.

Developmental time – or what Elman and collaborators called 'chronotopic constraints' [53] – seems to play a crucial role, even in monogenic disorders. For example, FMRP is highly expressed in both adult and foetal brain tissues, but it interacts with multiple proteins and mRNAs [54–56]. In adult cerebellum and cerebral cortex, FMRP and two of these proteins are co-localized. In the foetus, as in the adult, FMRP is located in cytoplasm but one of the collaborating proteins is strongly expressed in foetal nucleus [57]. Thus FMRP is likely to collaborate with different sets of proteins in undifferentiated foetal neurones from those it interacts with in differentiated adult neurones. FOXP2 also co-localizes differently with collaborating proteins through development [47]. These complex interactions suggest that a single gene dysfunction can initiate cascading effects on cellular, systems and

Box 2. Single genes but uneven outcomes: focus on neurocomputations

Examining relationships between low-level molecular properties and uneven cognitive profiles is currently easier in monogenetic disorders. Fragile X syndrome (FXS) is the most common form of inherited mental retardation and it is associated with the silencing of a single gene, FMR1 [68]. Its protein product, FMRP, is crucial for the refinement of dendritic spine morphology [69,70] as, in response to the stimulation of metabotropic glutamatergic receptors, it modulates the translation of multiple mRNAs (see Glossary), many of which are in turn necessary for regulating activity-dependent synaptic changes across the brain [71,54]. Despite relative regional differences in expression (cortically and subcortically), FMRP is expressed ubiquitously across the brain, and its loss is associated with altered dendritic spine morphology through *all* neocortical areas examined so far. And yet, FXS is characterized by an uneven outcome in the cognitive profile. What could underlie ubiquitous effects at one level of description and relative differences at another? To find an answer requires the examination of low-level neural changes associated with FXS and their cascading effects over time on neurocomputational properties. Dendritic spines are the point at which glutamatergic neurones make synaptic contact with dendrites integrating inputs on pyramidal neurones [72], and they increase in density dramatically from primary visual cortex (V1) to parietal cortices, and similarly from premotor to prefrontal cortex for both human and non-human primates [73]. Furthermore, different cortical areas show heterochronous dendritic changes through development: faster in lower visual cortices and slowest in prefrontal cortex [74]. Thus, although ubiquitous, the structural and functional changes that are associated with FXS might be more relevant to the development and computational requirements of certain neurocomputational circuits than others. Given the role of activity-dependent synaptic changes in establishing neural networks across the developing cortex and the crucial roles of the multiple proteins with which FMRP normally interacts [55], it is likely that numerous cortical circuits will develop atypically to some extent. However, some cognitive domains and processes within each domain might have less reliance on the changed computational properties, and thus might develop to show less overt impairment in the phenotypic outcome [13,39]. Intriguingly, a similar argument might extend beyond cortex to thalamocortical projections [49]. Complex dendritic spine morphology is most relevant to those functions that rely on integration on large dendritic trees [49]. This is a crucial property of magnocellular (M) neurones in LGN, whereas parvocellular (P) neurones are less reliant on this property (see Figure I on following page for an illustration of these differences, and see Box 2 in [5] for a similar example on deafness). As the two systems are not fully segregated across development, the relationships between their developing functions needs to be studied. Importantly, although the most overt effects appear to be on M-pathway functions, there might be residual effects on the development of P-pathway functions. Certainly, recent evidence reveals difficulties in second-order form tasks, as well as first and second-order motion discrimination [50].

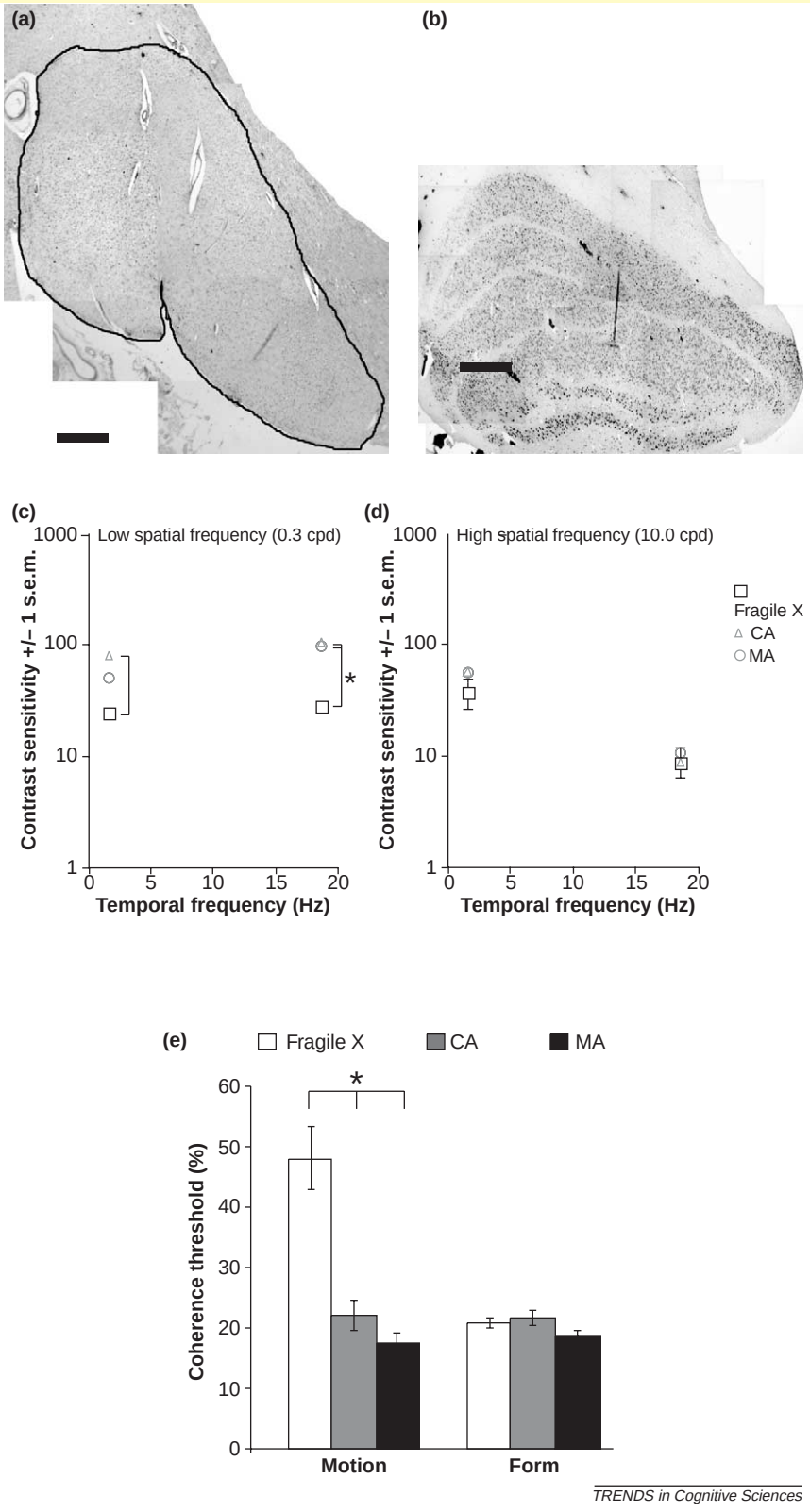

Figure I. In normal brains, FMRP is more highly (but not exclusively) expressed in magnocellular (M) neurones of the lateral geniculate nucleus (LGN) of the thalamus than in parvocellular (P) neurones. In FXS, the LGN has a highly atypical alaminar structure with smaller homogeneously sized cells **(a)** compared with the normal brain **(b)** in which darker and lighter layers show the segregation of M and P cells, respectively. This is accompanied by a weakness in tasks that tap M-cell function, such as contrast sensitivity for low spatial frequency gratings modulated at either low or high temporal frequency **(c)**, in comparison with P-cell function, such as high spatial frequency gratings modulated at either low or high temporal frequency **(d)**. People with FXS also show a higher motion threshold than normal controls (CA and MA), but a global form threshold within the normal range **(e)**. (Adapted with permission from [49].)

cognitive functions that vary across developmental time. A better understanding of regional differences in developmental timing of gene expression as well as longitudinal data on structure-function relationships will allow further integration of molecular and systems neuroscience.

Conclusion and future directions

Integrating a developmental approach with information on processes of change at the systems and molecular levels is producing more detailed mechanistic accounts of atypical development. Available evidence suggests that direct mappings between genes and the adult cognitive phenotype will not suffice beyond being a (rather misleading) short-hand for far more dynamic interactions over developmental time.

The issues discussed here also stress that precision has become paramount: what do cognitive psychologists and neuroscientists mean when they refer to multiple and heterogeneous mechanisms of developmental change at the cognitive and neural levels of description? The study of genetic disorders reveals how crucial it is to operationalize the meaning of 'pure selective deficits' in the context of *developmental* disorders of genetic origin and the constraints under which they would occur. Although one should not deny *a priori* the logical possibility of the existence of selective deficits, they are empirically dubious and computationally highly unlikely [24,58–63]. Effects of low-level processes on multiple domains seem a far more plausible outcome. Those domains for which these low-level processes are most relevant (in terms of the computational requirements) will be most overtly affected, but subtle effects will also be probably detectable in other domains [5]. Clearer predictions can be derived from a deeper understanding of the neural and computational requirements of various cognitive processes, how they change through typical development, and how they can be atypically affected at the outset of development. Computational modelling provides a powerful tool in this respect [53,58–63]. To provide testable hypotheses across levels of description (and entice all neuroscientists to do so), models of typically and atypically developing processes will need to be informed by our growing knowledge of common neural properties as well as their regional differences (e.g. [64]).

More generally, disorders of known genetic origin can, if studied within an integrated, cross-disciplinary framework, serve as a vital tool for the study of developmental cognitive neuroscience (see also Box 3). This will require investigating the neurocomputational properties that sustain the development of cognitive processes as well as how they are altered in atypically developing systems [53]. Although this might seem a daunting research enterprise, it is one that is increasingly within reach, as genetics and proteomics uncover the molecular and cellular processes involved in systems cognitive neuroscience, and as cognitive and neural processes are studied throughout the course of development from its very onset onwards.

Box 3. Questions for future research

Atypical cognitive processes

- Will longitudinal designs allow us to study reliably atypical developmental trajectories and interacting cognitive processes (across and within domains)?
- Can the growing knowledge of neurocomputational properties studied by cognitive neuroscientists be integrated further with the study of typical and atypical cognitive development?

Systems, cellular and molecular neuroscience in genetic disorders

- Genes code for interacting proteins that vary in expression across developmental time. Precisely how does the timing of specific gene expression vary in human development, and how does expression vary at the cortical and subcortical levels?
- Animal models continue to play an important role in the study of human genetic disorders, because understanding protein expression at a detailed mechanistic level can in the main only be achieved through these models. Can meaningful cross-species homologies in behavioural tasks be designed? Do developmental changes in the behavioural phenotype of knockout animals mirror those observed in humans, or does this only hold for adult animals? What would the significance of differences be for our evaluation of *developmental* animal models of disorders?
- The study of the developmental changes in interactions across neural circuits will require techniques that are still in their infancy: diffusion tensor imaging is beginning to make possible the tracking of changes in structural connections and eventually their overlay with functional information in normal development. Will it be possible to apply the combination of these techniques to atypically developing brains?

Computational neuroscience and genetics

- Neurocomputational models need to be physiologically plausible to aid the investigation of genotype–cognitive phenotype mappings, by integrating the multiple and heterogeneous mechanisms driving development at the cellular and systems levels. Can differences in the normal computational properties of neurones across cortical and subcortical areas be modelled successfully to subsequently enhance our understanding of atypical brain development?

All disciplines

- As well as revealing cross-syndrome differences, disorders of known genetic origin are characterized by striking similarities at multiple levels of description (for example, relative weaknesses in visuo-spatial cognition and attention, fronto-parietal abnormalities, dendritic spine abnormalities [40,75]). Does this imply that there are multiple pathways to similar behavioural and cognitive outcomes? At what levels do associations and dissociations of deficit emerge?

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References

1 Pinker, S. (2001) Talk of genetics and vice versa. *Nature* 413, 465–466
2 Wexler, K. (1996) The development of inflection in a biologically based theory of language. In *Towards a Genetics of Language Acquisition* (Rice, M.L., ed.), pp. 113–144, Erlbaum
3 Bellugi, U. *et al*. (1999) Bridging cognition, the brain and molecular genetics: Evidence from Williams syndrome. *Trends Neurosci.* 22, 197–207
4 Morris, C.A. *et al*. (2003) GTF2I hemizygosity implicated in mental retardation in Williams syndrome: genotype–phenotype analysis of five families with deletions in the Williams syndrome region. *Am. J. Med. Genet.* 123A, 45–59
5 Karmiloff-Smith, A. (1998) Development itself is the key to understanding developmental disorders. *Trends Cogn. Sci.* 2, 389–398
6 Lai, C.S. *et al*. (2001) A forkhead-domain gene is mutated in a severe speech and language disorder. *Nature* 413, 519–523
7 Lai, C.S. *et al*. (2003) FOXP2 expression during brain development coincides with adult sites of pathology in a severe speech and language disorder. *Brain* 126, 2455–2462

8 Paterson, S.J. *et al*. (1999) Cognitive modularity and genetic disorders. *Science* 286, 2355–2358
9 Brown, J.H. *et al*. (2003) Spatial representation and attention in toddlers with Williams syndrome and Down syndrome. *Neuropsychologia* 41, 1037–1046
10 Mervis, C.B. *et al*. (2003) Attentional characteristics of infants and toddlers with Williams syndrome during triadic interactions. *Dev. Neuropsychol.* 23, 243–268
11 Paterson, S.J. (2001) Language and number in Down syndrome: the complex developmental trajectory from infancy to adulthood. *Downs Syndr. Res. Pract.* 7, 79–86
12 Scerif, G. *et al*. (2004) Visual search in typically developing toddlers and toddlers with fragile X or Williams syndrome. *Dev. Sci.* 7, 118–130
13 Scerif, G. *et al*. To look or not to look? Typical and atypical development of oculomotor control. *J. Cogn. Neurosci.* (in press)
14 Bailey, D.B., Jr. *et al*. (2001) Variability in FMRP and early development in males with fragile X syndrome. *Am. J. Ment. Retard.* 106, 16–27
15 Diamond, A. (2001) A model system for studying the role of dopamine in the prefrontal cortex during early development in humans: Early and continuously treated phenylketonuria. In *Handbook of Developmental Cognitive Neuroscience* (Nelson, C.A. and Luciana, M., eds), pp. 433–472, MIT Press
16 Donnai, D. and Karmiloff-Smith, A. (2000) Williams syndrome: From genotype through to the cognitive phenotype. *Am. J. Med. Genet.* 97, 164–171
17 Cornish, K. *et al*. (2001) Differential impact of the FMR-1 full mutation on memory and attention functioning: a neuropsychological perspective. *J. Cogn. Neurosci.* 13, 144–151
18 Wilding, J. *et al*. (2002) Further delineation of the executive deficit in males with fragile-X syndrome. *Neuropsychologia* 40, 1343–1349
19 Cornish, K. *et al*. (2004) Attention and language in fragile X. *Ment. Retard. Dev. Disabil. Res. Rev.* 10, 11–16
20 Cornish, K. *et al*. (2004) Annotation: Deconstructing the attention deficit in fragile X syndrome: a developmental neuropsychological approach. *J. Child Psychol. Psychiatry* 45, 1042–1053
21 Bishop, D.V. (1997) Cognitive neuropsychology and developmental disorders: Uncomfortable bedfellows. *Q. J. Exp. Psychol. A* 50, 899–923
22 Temple, C.M. (1997) Cognitive neuropsychology and its application to children. *J Child Psychol. Psychiatry* 38, 27–52
23 Baron-Cohen, S. (1998) Modularity in developmental cognitive neuropsychology: evidence from autism and Gilles de la Tourette syndrome. In *Handbook of Mental Retardation and Development* (Burack, J.A. *et al*., eds), Cambridge University Press
24 Thomas, M.S.C. and Karmiloff-Smith, A. (2002) Are developmental disorders like cases of adult brain damage? Implications from connectionist modelling. *Behav. Brain Sci.* 25, 727–750
25 Thomas, M.S.C. *et al*. (2001) Past tense formation in Williams syndrome. *Lang. Cogn. Process.* 16, 143–176
26 Vicari, S. *et al*. (2002) Language acquisition in special populations: a comparison between Down and Williams syndromes. *Neuropsychologia* 40, 2461–2470
27 Volterra, V. *et al*. (2003) Early linguistic abilities of Italian children with Williams syndrome. *Dev. Neuropsychol.* 23, 33–58
28 Temple, C.M. *et al*. (2002) Lexical skills in Williams Syndrome: a cognitive neuropsychological analysis. *J Neurolinguist.* 15, 463–495
29 Karmiloff-Smith, A. *et al*. (2004) Exploring the Williams syndrome face processing debate: The importance of building developmental trajectories. *J. Child Psychol. Psychiatry* 45, 1258–1274
30 Gopnik, M. and Crago, M.B. (1991) Familial aggregation of a developmental language disorder. *Cognition* 39, 1–30
31 Vargha-Khadem, F. *et al*. (1995) Praxic and nonverbal cognitive deficits in a large family with a genetically transmitted speech and language disorder. *Proc. Natl. Acad. Sci. U. S. A.* 92, 930–933
32 Vargha-Khadem, F. *et al*. (1998) Neural basis of an inherited speech and language disorder. *Proc. Natl. Acad. Sci. U. S. A.* 95, 12695–12700
33 Watkins, K. *et al*. (2002) Behavioural analysis of an inherited speech and language disorder: comparison with acquired aphasia. *Brain* 125, 452–464
34 Alcock, K. *et al*. (2000) Oral dyspraxia in inherited speech and language impairment and acquired dysphasia. *Brain Lang.* 75, 17–33
35 Alcock, K. *et al*. (2000) Pitch and timing abilities in inherited speech and language impairment. *Brain Lang.* 75, 34–46
36 Fisher, S.E. *et al*. (2003) Deciphering the genetic basis of speech and language disorders. *Annu. Rev. Neurosci.* 26, 57–80
37 Laing, E. *et al*. (2002) Atypical development of language and social communication in toddlers with Williams syndrome. *Dev. Sci.* 5, 233–246
38 Goldberg, T.E. and Weinberger, D.R. (2004) Genes and the parsing of cognitive processes. *Trends Cogn. Sci.* 8, 325–335
39 Johnson, M.H. (2001) Functional brain development in humans. *Nat. Rev. Neurosci.* 2, 475–483
40 Braddick, O. *et al*. (2003) Normal and anomalous development of visual motion processing: motion coherence and 'dorsal-stream vulnerability'. *Neuropsychologia* 41, 1769–1784
41 Tamm, L. *et al*. (2002) fMRI study of cognitive interference processing in females with fragile X syndrome. *J. Cogn. Neurosci.* 14, 160–171
42 Rivera, S. *et al*. (2002) Functional brain activation during arithmetic processing in females with fragile X Syndrome is related to FMR1 protein expression. *Hum. Brain Mapp.* 16, 206–218
43 Menon, V. *et al*. (2004) Frontostriatal deficits in fragile X syndrome: relation to FMR1 gene expression. *Proc. Natl. Acad. Sci. U. S. A.* 101, 3615–3620
44 Liegeois, F. *et al*. (2003) Language fMRI abnormalities associated with FOXP2 gene mutation. *Nat. Neurosci.* 6, 1230–1237
45 Grice, S.J. *et al*. (2001) Disordered visual processing and oscillatory brain activity in autism and Williams syndrome. *Neuroreport* 12, 2697–2700
46 Mobbs, D. *et al*. (2004) Anomalous brain activation during face and gaze processing in Williams syndrome. *Neurology* 62, 2070–2076
47 Teramitsu, I. *et al*. (2004) Parallel FoxP1 and FoxP2 expression in songbird and human brain predicts functional interaction. *J. Neurosci.* 24, 3152–3163
48 Karmiloff-Smith, A. *et al*. (2002) Different approaches to relating genotype to phenotype in developmental disorders. *Dev. Psychobiol.* 40, 311–322
49 Kogan, C.S. *et al*. (2004) Differential impact of the FMR1 gene on visual processing in fragile X syndrome. *Brain* 127, 591–601
50 Kogan, C.S. *et al*. (2004) Integrative cortical dysfunction and pervasive motion perception deficit in fragile X syndrome. *Neurology* 63, 1634–1639
51 Luciana, M. *et al*. (2004) A preliminary report on dopamine system reactivity in PKU: acute effects of haloperidol on neuropsychological, physiological, and neuroendocrine functions. *Psychopharmacology (Berl.)* 175, 18–25
52 Antshel, K.M. and Waisbren, S.E. (2003) Timing is everything: executive functions in children exposed to elevated levels of phenylalanine. *Neuropsychology* 17, 458–468
53 Elman *et al*. (1996) *Rethinking Innateness: A Connectionist Perspective on Development*, MIT Press
54 Brown, V. *et al*. (2001) Microarray identification of FMRP-associated brain mRNAs and altered mRNA translational profiles in fragile X syndrome. *Cell* 107, 477–487
55 Beckel-Mitchener, A. and Greenough, W.T. (2004) Correlates across the structural, functional, and molecular phenotypes of fragile X syndrome. *Ment. Retard. Dev. Disabil. Res. Rev.* 10, 53–59
56 Hoogeveen, A.T. *et al*. (2002) Fragile X syndrome, the Fragile X related proteins, and animal models. *Microsc. Res. Tech.* 57, 148–155
57 Tamanini, F. *et al*. (1997) Differential expression of FMR1, FXR1 and FXR2 proteins in human and brain testis. *Hum. Mol. Genet.* 6, 1315–1322
58 Karmiloff-Smith, A. and Thomas, M. (2002) Developmental disorders. In *The Handbook of Brain Theory and Neural Networks* (2nd Edn) (Arbib, M.A., ed.), pp. 292–294, MIT Press
59 Karmiloff-Smith, A. *et al*. (2003) Double dissociations in developmental disorders: Theoretically misconceived, empirically dubious. *Cortex* 39, 161–163
60 Thomas, M.S.C. and Karmiloff-Smith, A. (2003) Modelling language acquisition in atypical phenotypes. *Psychol. Rev.* 110, 647–682
61 Karmiloff-Smith, A. and Thomas, M.S.C. (2003) What can developmental disorders tell us about the neurocomputational constraints that shape development? The case of Williams syndrome. *Dev. Psychopathol.* 15, 969–990
62 Karmiloff-Smith, A. (1992) *Beyond Modularity: A Developmental Perspective on Cognitive Science*, MIT Press

63 Bates, E. and Elman, J.L. (1993) Connectionism and the study of change. In *Brain Development and Cognition: A Reader* (Johnson, M., ed.), pp. 623–642, Blackwell
64 Spratling, M.W. and Johnson, M.H. (2004) A feedback model of visual attention. *J. Cogn. Neurosci.* 16, 219–237
65 Ansari, D. *et al*. (2003) What makes counting count? Verbal and visuo-spatial contributions to typical and atypical number development. *J. Exp. Child Psychol.* 85, 50–62
66 Phillips, C.E. *et al*. (2004) Comprehension of spatial language terms in Williams syndrome: evidence for an interaction between domains of strength and weakness. *Cortex* 40, 85–101
67 Ansari, D. and Karmiloff-Smith, A. (2002) Atypical trajectories of number development: a neuroconstructivist perspective. *Trends Cogn. Sci.* 6, 511–516
68 O'Donnell, W.T. and Warren, S.T. (2002) A decade of molecular studies of fragile X syndrome. *Annu. Rev. Neurosci.* 25, 315–338
69 Greenough, W.T. *et al*. (2001) Synaptic regulation of protein synthesis and the fragile X protein. *Proc. Natl. Acad. Sci. U. S. A.* 98, 7101–7106
70 Huber, K.M. *et al*. (2002) Altered synaptic plasticity in a mouse model of fragile X mental retardation. *Proc. Natl. Acad. Sci. U. S. A.* 99, 7746–7750
71 Bear, M.F. *et al*. (2004) The mGluR theory of fragile X mental retardation. *Trends Neurosci.* 27, 370–377
72 Nimchinsky, E.A. *et al*. (2002) Structure and function of dendritic spines. *Annu. Rev. Physiol.* 64, 313–353
73 Elston, G.N. (2003) Cortex, cognition and the cell: new insights into the pyramidal neuron and prefrontal function. *Cereb. Cortex* 13, 1124–1138
74 Huttenlocher, P.R. (2002) *Neural Plasticity: The Effects of the Environment on the Development of the Cerebral Cortex*, Harvard University Press
75 Kaufmann, W.E. and Moser, H.W. (2000) Dendritic anomalies in disorders associated with mental retardation. *Cereb. Cortex* 10, 981–991
76 Flint, J. (2003) Animal models of anxiety and their molecular dissection. *Semin. Cell Dev. Biol.* 14, 37–42
77 Plomin *et al*. (2001) *Behavioural Genetics*, 4th Edn, Freeman
78 Plomin, R. and McGuffin, P. (2003) Psychopathology in the post-genomic era. *Annu. Rev. Psychol.* 54, 205–228
79 Bishop, D.V.M. (2002) Motor immaturity and specific speech and language impairment: Evidence for a common genetic basis. *Am. J. Med. Genet.* 114, 56–63