Review

Development itself is the key to understanding developmental disorders

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It is a truism that development involves contributions from both genes and environment, but theories differ with respect to the roles they attribute to each, which deeply affects the ways in which developmental disorders are researched. The strict nativist approach to abnormal phenotypes, inspired by adult neuropsychology and evolutionary psychology, seeks to identify impairments to domain-specific cognitive modules and studies the purported juxtaposition of impaired and intact abilities. The neuroconstructivist approach differs in several respects: (i) it seeks more indirect, lower-level causes of abnormality than impaired cognitive modules; (ii) modules are thought to emerge from a developmental process of modularization; (iii) unlike empiricism, neuroconstructivism accepts some form of innately specified starting points, but unlike nativism, these are considered to be initially 'domain-relevant', only becoming domain-specific with the process of development and specific environmental interactions; and (iv) different cognitive disorders are considered to lie on a continuum rather than to be truly specific. These alternative theoretical positions are briefly considered as they apply to Specific Language Impairment, and followed by a more detailed case study of a well-defined neurodevelopmental disorder, Williams syndrome. It is argued that development itself plays a crucial role in phenotypical outcomes.

All scientists studying normal and atypical development – from the staunchest Chomskyan nativist to the most domain-general empiricist – agree that development involves contributions from both genes and environment. The gulf between the theories lies in how genes and environment are claimed to contribute to developmental outcomes. At some level, of course, we all concur in the existence of some degree of innate specification. The difference in positions concerns how rich and how domain-specific the innately specified component is, whether development is the result of predetermined epigenesis[1] (mere triggering) or probabilistic epigenesis[1], and what happens when things go wrong. These differences in position influence the focus of the questions asked (nature or nurture, on the one hand, versus the mechanisms of progressive developmental change, on the other) and the way in which developmental disorders are studied.

Let's briefly take the example of language. For the staunch nativist, a set of genes specifically targets domain-specific modules as the end product of their epigenesis (e.g. a syntactic module[2], a morphological module[3], or a more narrowly pre-specified module for, say, canonical linkage rules in grammar[4]). Under this non-developmental view, the environment simply acts as a trigger for identifying and setting (environmentally-derived) native-tongue realizations of (pre-specified) parameters of universal grammar. The child is born innately expecting nouns, verbs, canonical linking rules, agreement between asymmetrical sentence elements, and so forth, but not yet knowing how they are realized in her/his native tongue[5]. The deletion, reduplication or mispositioning of genes is assumed to result in very specific impairments in the endstate[3–6]. For the empiricist, by contrast, much of the structure necessary for building language and the rest of the human mind is discovered directly in the structure of the physical and social environment.

These two extremes are not the only options, however. The neuroconstructivist approach to normal and atypical development fully recognizes innate biological constraints but, unlike the staunch nativist, considers them to be initially less detailed and less domain-specific as far as higher-level cognitive functions are concerned. Rather, development itself is seen as playing a crucial role in shaping

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phenotypical outcomes, with the protracted period of postnatal growth as essential in influencing the resulting domain specificity of the developing neocortex[7,8]. A clearer way to capture this idea is to specify that the interaction is not in fact between genes and environment. Rather, on the gene side, the interaction lies in the outcome of the indirect, cascading effects of interacting genes and their environments and, on the environment side, the interaction comes from the infant's *progressive* selection and processing of different kinds of input. For both the strict nativist and the empiricist, the notion of 'environment' is a static one, whereas development (both normal and atypical) is of course dynamic. The child's way of processing environmental stimuli is likely to change repeatedly as a function of development, leading to the progressive formation of domain-specific representations.

Most nativists interested in language argue that what is innately specified are *representations* of universal grammar. Other theorists recognize that knowledge representations *per se* are unlikely to be pre-specified in neocortex (although see Ref. 9 for an alternative, selectionist view of pre-specified representations). Rather than representational innateness, they opt for dedicated domain-specific mechanisms within innately specified modules, the presumed absence of which in a developmental disorder will inform about their specific function in normal development[10,11]. Such arguments seem to be heavily influenced by so-called evolutionary psychology[12]. According to this view, phylogenesis has led to increasing pre-specification for ontogenesis, such that there are genetically-coded responses to evolutionary pressures, leading, through relatively predetermined epigenesis, to hardwired circuitry for language, theory of mind, and other specific forms of higher-level cognitive processing. In this 'Swiss army knife' view of the brain, domain specificity is the starting point of ontogenesis, with development relegated to a relatively secondary role. A different view is that although evolution has pre-specified many constraints on development, it has made the human neocortex increasingly flexible and open to learning during postnatal development. In other words, evolution is argued to have selected for adaptive outcomes and a strong capacity to learn, rather than prior knowledge[7]. Within such a perspective, it is more plausible to think in terms of a variety of what one might call domain-relevant mechanisms that might gradually *become* domain-specific as a result of processing different kinds of input.

What does such a distinction entail? First we need to draw a distinction between domain-specific and domain-general mechanisms. Take, for example, inhibition. For the domain-general theorist, when the inhibitory mechanism is impaired, it will affect all systems across the board. By contrast, for the domain-specific theorist, the infant brain will contain, say, an inhibitory process *A* for theory-of-mind computations, an inhibitory process *B* for language-relevant computations, and yet another for sensorimotor development, and so forth. For this position, when the theory-of-mind inhibitory process is impaired, it will affect solely theory-of-mind computations, but leave intact linguistic, sensorimotor, and other domains. It is a subtly different distinction that I wish to draw between domain-relevant and domain-specific mechanisms. Unlike the domain-general theorist, this position does not argue for domain-general mechanisms simply applied across all domains. Rather, it suggests that biological constraints on the developing brain might have produced a number of mechanisms that do not start out as strictly domain-specific, that is, dedicated to the exclusive processing of one and only one kind of input. Instead, a mechanism starts out as somewhat more relevant to one kind of input over others, but it is usable – albeit in a less efficient way – for other types of processing too. This allows for compensatory processing and makes development channelled but far less predetermined than the nativist view. Once a domain-relevant mechanism is repeatedly used to process a certain type of input, it becomes domain-specific as a result of its developmental history[7,13]. Then, in adulthood, it can be differentially impaired. For example, a learning mechanism that has a feedback loop will be more relevant to processing sequential input than to processing static, holistic input. With time such a mechanism would become progressively dedicated to processing, say, sequentially presented linguistic input. In other words, rather than evolution providing pre-specified representations, this change in perspective places the mechanisms of progressive ontogenetic change on centre stage.

The implications for developmental disorders

The neuroconstructivist modification in perspective crucially influences the way in which atypical development is considered. In this approach, the deletion, reduplication or mispositioning of genes will be expected to subtly change the course of developmental pathways, with stronger effects on some outcomes and weaker effects on others. A totally specific disorder will, *ex hypothesis*, be extremely unlikely, thereby changing the focus of research in pathology. Rather than solely aiming to identify a damaged module at the cognitive level, researchers are encouraged to seek more subtle effects beyond the seemingly unique one, as well as to question whether successful behaviour (the presumed 'intact' part of the brain) is reached by the same processes as in normal development. This change in perspective means that atypical development should not be considered in terms of a catalogue of impaired and intact functions, in which non-affected modules are considered to develop normally, independently of the others. Such claims are based on the static, adult neuropsychological model which is inappropriate for understanding the dynamics of developmental disorders[14,15] (see Box 1).

The neuroconstructivist approach highlights how tiny variations in the initial state could give rise to domain-specific differences in endstates[7,13,15] (see Box 2). With a shift in focus from dissociations to cross-syndrome associations, disorders might turn out to lie on more of a continuum than commonly thought. Thus, two very distinct phenotypical outcomes could start with only slightly differing parameters but, with development, the effects of this small difference might be far reaching. This contrasts with the notion that a whole cognitive module is initially impaired. Rather, phenotypical outcomes could stem from small differences in one or more of the following parameters: developmental timing, gene dosage, neuronal formation, neuronal migration, neuronal density, biochemical efficiency affecting

Box 1. The postulates of the static adult neuropsychological model and its application to developmental disorders

- The method of double dissociation is used to identify specialized functions: Patient 1 has function A intact and function B impaired, whereas for Patient 2 the opposite obtains.
- This leads to the conclusion that the brain is organized into specialized circuits or modules which can be differentially damaged.

Thus far, the argument might be valid with respect to the fully-formed adult brain (although for arguments against the reduction of double dissociation to autonomy of modules, see Refs a,b; and for those against modularity of adult processing, see Ref. c). The subsequent conclusions are, in my view, open to serious challenge:

- Similar dissociations are found in certain developmental disorders.
- This leads to the conclusion that modules are innately specified in the human brain, with impaired genes mapped to impaired modules, alongside otherwise normal brain development.
- Developmental disorders are then explained in terms of the juxtaposition of damaged and intact sets of modules.

This ignores both the probabilistic dynamics of gene expression during embryogenesis and of progressive brain development during postnatal growth. When one considers the dynamics of development, the notion of the juxtaposition of spared and impaired higher-level cognitive processes is challenged, suggesting that in some developmental disorders, ostensibly 'intact' performance might turn out to be achieved through different cognitive processes (see Box 5).

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firing thresholds, variations in transmitter types, dendritic arborization, synaptogenesis, and pruning. The effects of alterations in these initial parameters might also vary in strength at different developmental periods[14]. Furthermore, some problems might stem from lack of connections between brain regions or between the two hemispheres[16,17]. In some cases, like Down syndrome, cognitive problems could stem from a failure to progressively specialize or modularize as a function of development, whereas in others specialization might occur too rapidly leaving less opportunity for environmental constraints to play a role in shaping the developmental outcome. These are all indirect and at a much lower level than the notion of direct damage to innately-specified cognitive modules invoked by strict nativists to explain developmental disorders. It is these subtle differences that are likely to explain the range of phenotypical outcomes that atypical development can display. Such differences might affect the resulting organism at multiple levels.

These multiple levels – brain volume, regional anatomy, brain chemistry, hemispheric asymmetry, the temporal patterns of brain activity, physical characteristics and cognitive/behavioural outcome – have recently been studied in some detail with respect to one neurodevelopmental disorder, Williams syndrome (see Boxes 3, 4 and 5). Consideration of the multiple two-way mappings from the biological to the cognitive levels leads to different hypotheses about so-called 'intact' abilities; that is, even where normal *behavioural* levels are found in a developmental disorder in a given domain, they might be achieved by different *cognitive* processes. This turns out to be the case for Williams syndrome, in which face processing and language are particularly proficient alongside other serious impairments, but the proficiency seems to be achieved through different cognitive processes (see Box 5).

Are some developmental disorders truly specific?

Despite the arguments in the previous section, some developmental disorders (e.g. autism[18,19], Asperger syndrome[20], dyslexia[21], Turner's syndrome[22], Specific Language Impairment[14]) appear at first sight to involve very specific deficits at the cognitive level. Autism, for example, is argued to be the result of impairment of the domain-specific mechanism of metarepresentation, dedicated solely to the processing of social stimuli[10,19] – a deficit in the so-called 'theory-of-mind' module. When other, non-social impairments are noted, they are explained either in terms of secondary effects[10] or of an additional, unrelated cognitive impairment[23], with other parts of the brain assumed to be intact. A similar approach has been taken with respect to Specific Language Impairment (SLI). This phenotype suggests, by its very name, a specific linguistic deficit alongside otherwise intact intelligence, as if grammar developed in total isolation of the rest of the growing brain. Researchers differ as to what they claim the specific deficit to be: the inability to make canonical links from grammar to semantics[4], feature blindness with respect to morphology[3,24], and so forth (for comprehensive reviews, see Refs 14,25). The common suggestion, however, is that there is a specific genetic underpinning to the derivation of certain grammatical rules, which is impaired in these forms of SLI but leaving the rest of development intact.

It is clear that disorders like autism and SLI have a genetic origin and that evolutionary pressures have contributed to whatever is innately specified. This is a truism. The question is whether, on the one hand, the deficit results from damage to a domain-specific starting point at the cognitive level, as a result of evolution specifying dedicated processing systems for grammar, theory of mind and so forth, or whether, on the other hand, evolution has specified more general constraints for higher-level cognition and there is a more indirect way for genetic defects to result in domain-specific outcomes as a function of development.

The case of SLI (Ref. 14) shows how this second alternative might hold. Developmental timing plays a crucial role. If, early on, the infant's processing of fast auditory

Box 2. Single and multiple gene disorders, but no Swiss army knives

A report in the press recently heralded the discovery of a specific gene for hearing. The Science article[a] on which it was based, however, illustrates how indirect the effects of the gene are. Geneticists studying eight generations of a Costa Rican family found a 50% incidence of acquired deafness, with onset around age 10 and complete deafness by age 30. A single gene mutation was identified, with the last 52 amino acids in the gene's protein product misformed, and the first 1,213 amino acids formed correctly. This gene produces a protein that controls the assembly of actin. Actin organizes the tiny fibres found in cell plasma which determine a cell's structural properties, such as rigidity. Because the genetic impairment is tiny and the protein functions sufficiently well to control the assembly of actin in most parts of the body, no other deficits are observable. However, it turns out that hair cells are especially sensitive to loss of rigidity, such that even this tiny impairment has a huge effect on them, resulting in deafness. In other words, what might look like a specialized gene for a complex trait like hearing is, on closer examination, very indirect – hearing is dependent on the interaction of huge numbers of genes, one of which affects the rigidity of hair cells and has cascading effects on the others. A 'gene for hearing' might be a convenient shorthand, but it could be a very misleading one, impeding the researcher from seeking to understand the probabilistic dynamics of development.

A second illustration comes from a computational model of the development of the ventral and dorsal pathways of visual cortex. There are several things we know about these pathways. First, they operate on somewhat different time schedules in early infancy: infants track novel objects (dorsal pathway) before they can categorize them (ventral pathway). Second, double dissociations exist in adult brain damage, such that patients can locate objects without being able to identify them, or vice versa[b]. This has led some neuropsychologists to argue that the two pathways must be innately specified. But is this conclusion necessary? Their specialization in adulthood could have emerged from development itself. A computational model illustrates how this might occur[c]. A simple three-layer feedforward network was used. At the hidden layer, two channels were fed with identical input (see Fig.). The only difference was the speed with which activation levels changed (channel A rapidly, channel B slowly). Despite processing identical inputs, channel A progressively came to represent where objects were (mimicking the dorsal pathway in the brain), whereas channel B came to represent what each object was (ventral pathway). These functions were not pre-specified in the network but emerged from its developmental history, caused by a small difference in a starting state parameter. Thus, when neuropsychologists find dissociations in brain-damaged adults in visual form agnosia, this does not mean that the 'where' and 'what' pathways are necessarily pre-specified in the infant neocortex for spatio/temporal information versus form/colour/shape information. A small difference simply in firing thresholds (which might be innate) could give rise to such specialized functions indirectly, via the gradual processing during early infancy of differences between moving versus static stimuli. And a lack of such a difference in firing thresholds could result in domain-specific abnormality in one of these pathways. Again, the shorthand of talking about innate 'where' and 'what' pathways could be seriously misleading. They might only *become* what they are after processing the input. This leads to an important speculation: domain-specific outcomes might not even be possible without the process of development itself.

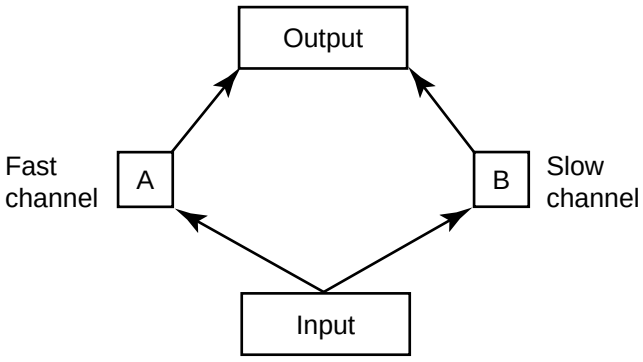

Fig. A simple three-layer feedforward network model of specialization in neural pathways. (See text for details.)

These two examples highlight the importance of giving serious consideration to very indirect causes of albeit very specific outcomes.

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transitions is even slightly delayed in maturation, then certain aspects of grammar might, with development, emerge as more impaired than others. Grammatical disorders would then be the indirect, developmental effect of a subtle, initial acoustic deficit. Such a position is supported by the fact that training solely at the acoustic level has been shown to have positive repercussions at the grammatical level[26]. However, some adolescents and adults with SLI do not display a processing deficit[3,4,25]. It is none the less possible that by later childhood or adulthood, an initial deficit in acoustic processing which had a huge effect at one point in development might no longer be detectable (owing, for example, to subsequent long-term compensation or to ceiling effects and the lack of sufficiently subtle measures; S. Rosen, pers. commun.), but its early effects could continue to have a significant impact. This stresses the importance of developmental timing in understanding developmental disorders. Although atypical processing of fast auditory transitions might not turn out to be the final cause of SLI, this view aptly illustrates how a less pre-specified approach to language can result in a language-specific representational impairment through the process of development itself. This is why a truly developmental approach is so crucial.

The neuroconstructivist account modifies the way a developmental disorder like SLI will be studied. It suggests that focus must be placed on at risk populations in early infancy, before the onset of language, and longitudinally thereafter, to ascertain whether the timing of subtle developmental processes is out of synchrony and grows in importance as the child starts to process more complex linguistic input. Furthermore, the neuroconstructivist approach predicts that because of the way genes interact in their developmental expression, we should seek co-occurring, more subtle impairments which might have nothing to do with language. In fact, it has been shown that people with language-related deficits, such as SLI or dyslexia, often display an impairment (albeit lesser) in various forms of motor control such as balance[27]. This indicates that we

Box 3. Williams syndrome: genetic and brain levels

Williams syndrome (WS) is caused by a microdeletion on the long arm of chromosome 7 at q.11,23 (Refs a,b). The genes on the deleted area have not all been identified, but they include:

- the elastin gene (*ELN*), not expressed in the brain, and thought to cause the vascular abnormalities;
- the *Limkinase1* gene (*LIMK1*) expressed in the brain, and claimed to cause the spatial deficits;
- the gene for DNA replication factor C2 (*RFC2*), and syntaxin1A (*STX1A*) which affects the way chemicals are released in the brain;
- the *frizzled* gene (*FZD3*), affecting the way in which cells signal to one another during development.

All patients with classic WS are hemizygous for *ELN*, *LIMK1*, *STX1A* and *RFC2*. While these discoveries seem to offer a neat mapping between genes and particular phenotypical outcomes, our recent study challenges these conclusions[c]. Three patients were identified with hemizygotic *ELN* and *LIMK1* deletions, two of whom also had *RFC2* deletions and one the *STX1A* deletion. However, none had the facial dysmorphology, the mental retardation or the specific spatio-constructive problems typical of people with Williams syndrome. The explanation of the WS phenotype clearly cannot be sought in simple gene/outcome mappings, but lies at the level of developmental timing and downstream effects of the complex interaction between all the deleted genes and the rest of the developing organism.

At the brain level, WS has been mainly described in terms of adult brains[d]. No work has yet been done on the developing infant brain. Some important discoveries about the fully-formed adult brain include:

- the WS brain is 80% of normal volume
- the total cerebral grey matter is significantly reduced
- there is abnormal layering, orientation, clustering and size of neurones
- the anterior regions are smaller than in normal controls but larger than in Down syndrome brains
- the dorsal hemispheres show cortical malformation
- the cerebrum is particularly small
- the limbic structures of the temporal lobe are small but proportionally similar to normal controls
- the frontal cortex displays a near normal proportional relation with posterior cortex, although both are reduced in size

Although limbic structures and frontal cortex are both proportionally similar in WS compared with normal brains, their functions show very different levels of impairment, with socio–affective behaviour being relatively good[e] and executive functions being particularly impaired[f]. Thus, the existence of normal anatomical proportions cannot be used to infer normal functions in the domains that they subserve in normal adults.

Our study using magnetic resonance spectroscopy has shown that brain biochemistry is also atypical in people with WS (Ref. g). Significant correlations were found between abnormal brain chemistry in the cerebellum and various neuropsychological tests, including Verbal and Performance IQ, British Picture Vocabulary Scale, and Ravens Progressive Matrices. The strongest correlation was with very poor results on a task measuring speed of processing, suggesting decreased neuronal efficiency in WS.

Finally, several studies have investigated brain activation in WS, particularly with respect to their domains of relative proficiency (language and face processing; see Box 5)[h]. Event-related potentials of individuals with WS show abnormal patterns for both face processing and language. More importantly, such patterns are found at no age across normal development, suggesting aberrant rather than delayed development in WS (Ref. h). Neither do people with WS show the progressive hemispheric asymmetries typical of normal development[h]. Furthermore, infants with WS spend far more time than controls focused on faces and language[i], suggesting that more of the developing brain might be devoted to processing such inputs.

In sum, brain volume, brain anatomy, brain chemistry, hemispheric asymmetry, and the temporal patterns of brain activity are all atypical in people with WS. How could the resulting cognitive system be described in terms of a normal brain with parts intact and parts impaired, as the popular view holds[j,k]? Rather, the brains of infants with WS develop differently from the outset, which has subtle, widespread repercussions at the cognitive level (see Box 5).

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might not be dealing with an initially language-specific impairment, but a deficit that turns out to be more detrimental to spoken and/or written language over developmental time (i.e. caused by an earlier language-relevant deficit), but that also gives rise to (weaker) problems in other areas. There is unlikely to be such a thing as impaired 'genes for reading' or 'genes for grammar'. Rather, genetic impairments lead to a disruption in probabilistic epigenesis pushing individuals onto different developmental pathways which eventually result in reading or grammatical deficits[26–28].

The neuroconstructivist approach would seek the initial disruption in innate mechanisms such as level of firing

Box 4. Clinical characteristics of the Williams syndrome phenotype

Williams syndrome (WS) is a rare genetic disorder that occurs in 1 in 20,000 live births. Its clinical features[a] include dysmorphic facies (see Fig. A–C), congenital heart and renal disorders due to a narrowing of the large arteries, musculo-skeletal abnormalities, growth retardation, hyperacusis, and infantile hypercalcaemia. The physical abnormalities are accompanied by moderate to severe mental retardation, a specific personality profile, very poor visuospatial constructive skills and relatively good language and face processing abilities (see Box 5).

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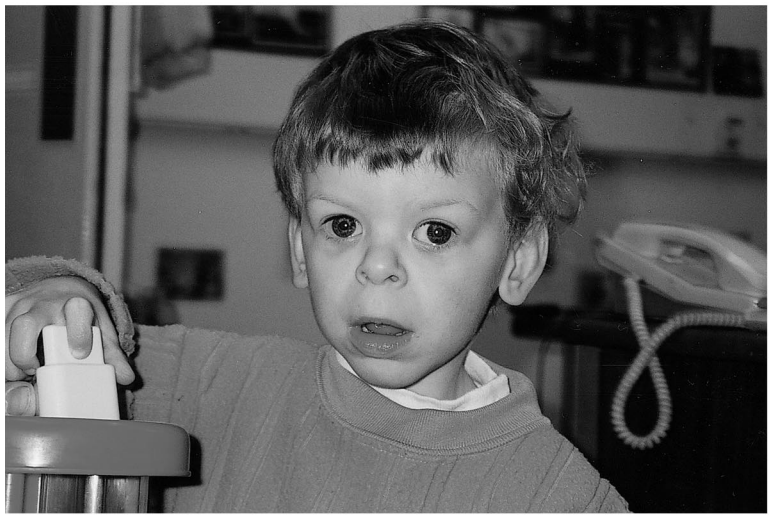
A



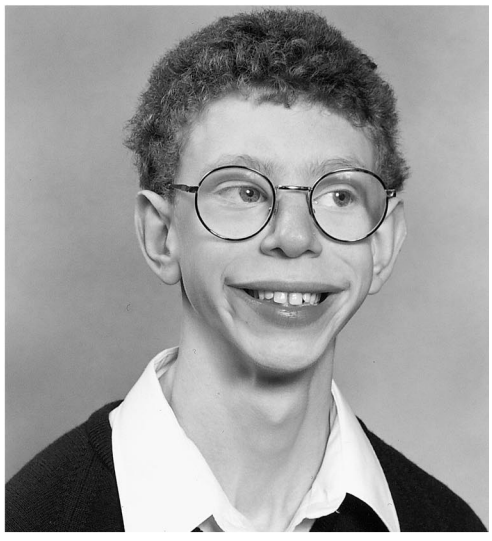
M.S., aged 2 yrs

Fig. The typical facial dysmorphology in WS, illustrated in three patients (photographs reproduced with permission of parents), aged 2 years, 10 years and 18 years, respectively. To be noted are the full cheeks, flared nostrils, wide mouth, full lips, pointed ears, and dental irregularities.

B

L.S., aged 10 yrs

C



R.D., aged 18 yrs

thresholds, differences in inhibition, and so forth. These are clearly at a lower-level, less richly domain-specific form than is commonly invoked by strict nativists who argue for innately specified representations of universal grammar. Neuroconstructivists would seek domain-relevant computational biases and the effects of differential developmental timing[7]. This is because we hypothesize that, rather than bringing greater pre-specialization to neocortex, evolution has provided the human neocortex with a greater and more varied capacity to learn via the process of development itself[29]. This clearly requires innate constraints but, because of the unusually slow period of human postnatal brain development, the child's gradual processing of different types of input is likely to have a strong influence on the way in which neocortex structures itself.

Box 5. Williams syndrome: the resulting cognitive–behavioural phenotype

Classic Williams syndrome (WS) has been characterized along the following lines (for more details, see Refs a–c):

- IQs mainly in the 50s (range: 45–87)
- serious deficits in spatio-constructive skills, but spatio-perceptual skills as would be predicted by Mental Age
- serious deficits in numerical cognition
- serious deficits in problem solving and planning
- intact syntactic capacities alongside aberrant semantics
- intact face processing capacities
- relatively spared social cognition skills.

The above conclusions stemmed mainly from standardized tests used to assess intact and impaired functions, an approach inspired theoretically by the adult neuropsychological model of deficit. However, even in cases where behavioural scores are equivalent to chronologically matched controls, it is essential to go beyond behavioural success and study the underlying cognitive processes in detail[d,e]. For example, our study of face-processing capacities of people with WS (Ref. e) showed that, although their scores were equivalent to normal controls, the way in which they solved the task was different. Whereas normal controls used predominantly configural (holistic) processing, the subjects with WS reached their good scores by using predominantly componential (feature-by-feature) processing. In other words, different *cognitive* processes led to similar *behavioural* outcomes. The notion that WS displays a normal, intact face-processing module is thereby challenged. None the less, the neuroconstructivist view could accept that people with WS might have developed a face-processing module. However, it would be argued that, rather than simply being triggered, such a module – like the normal face-processing module – is the result of a developmental process of modularization, but emerging in this case from an atypical ontogenetic pathway.

A similar story obtains for WS language acquisition. Several studies now suggest that neither syntax nor semantics is entirely normal in WS, despite earlier claims to the contrary. First, there is a discrepancy between vocabulary Mental Age (MA) and syntactic MA, the former being considerably higher[f]. Second, high vocabulary scores in WS patients camouflage the fact that they learn the lexicon in a somewhat different way from normally developing children[g]. Third, they show dissociations within syntax itself, with problems in forming agreement between elements in phrase structure, difficulties in processing embedded relative clauses and subcategorization frames (the distinction between transitive and intransitive verbs), and so forth[f,h,i]. Furthermore, even when language is fluent, Williams syndrome cannot be used to claim, as some have[j], that syntax develops independently of cognition. The use of IQ scores is very misleading in this respect. To state that a person has fluent language but an IQ of 51 indeed appears theoretically surprising and could lead to the conclusion that syntax develops in isolation from the rest of the brain. But to state that the same person has fluent language and an MA of 7 yrs changes the conclusion. In other words, those people with WS who have relatively fluent language might indeed have low IQs, but their MAs in non-verbal cognition, although seriously behind their chronological age, are usually well over 5, the age at which most language has been acquired in normally developing children.

In sum, not only are brain anatomy, brain chemistry, and temporal brain processes atypical, but Williams syndrome also displays an abnormal cognitive phenotype in which, even where behavioural scores are equivalent to those of normal controls, the cognitive processes by which such proficiency is achieved are different.

Our ongoing longitudinal behavioural and brain-imaging studies of atypical infants (with Janice Brown, Sarah Paterson, Marisa Gsödl, Michelle de Haan, Mark Johnson and others) already point to important differences in the initial state of WS patients compared with controls. The atypical groups' patterns are not one of juxtaposition of intact and impaired functions, as different end states might suggest. Interestingly, too, although WS linguistic performance ends up resembling normal language far more than Down syndrome performance, our preliminary results with infants show how important it is to distinguish the cognitive level from the behavioural level (see Box 6). Fluent linguistic behaviour might stem from different processes at the cognitive level of description. Our initial results suggest that Down syndrome language comprehension has a delayed but relatively normal developmental pathway in infancy, whereas WS language development seems to be deviant from the outset. It is only by focusing studies of developmental disorders at their roots in early infancy that we will ultimately be able to chart longitudinally the varying developmental pathways that progressively lead to different phenotypical outcomes.

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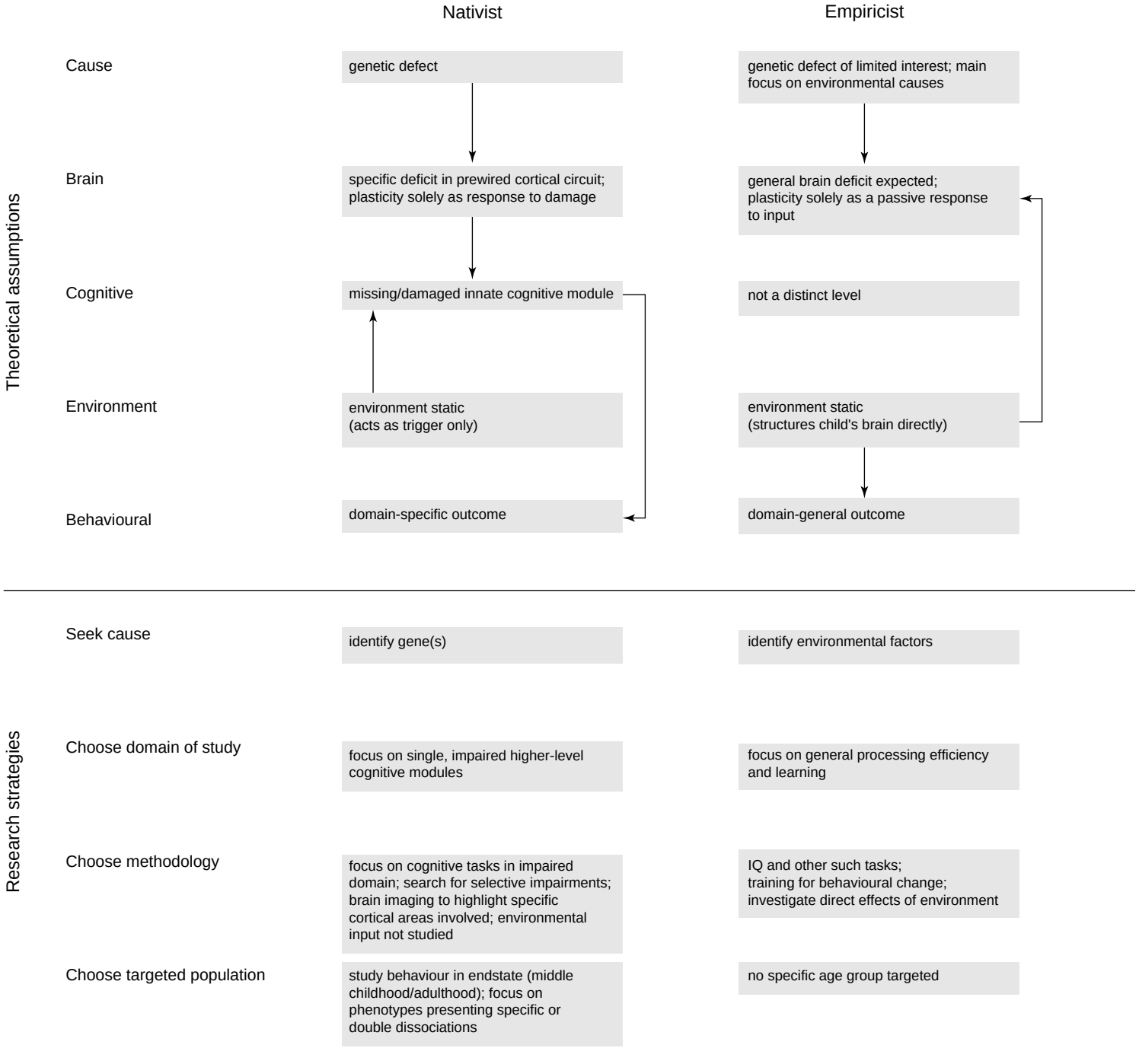
Conclusions

One of the major problems with very specific accounts of developmental disorders of higher-level cognition is that so far no gene (or set of genes) has been identified that is expressed solely in a specific region of neocortex (see Ref. 30 for discussion). Yet, such theories claim that neocortex is

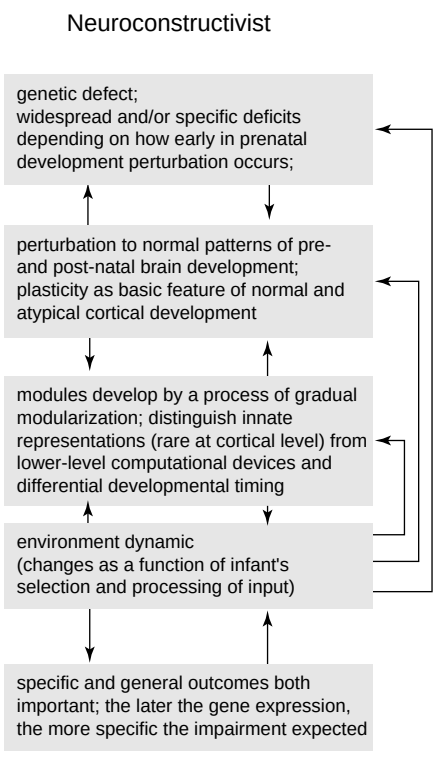
Box 6. Models of developmental disorders of known genetic aetiology

The figure illustrates how the neuroconstructivist approach differs in its theoretical assumptions and resulting research strategies from both the nativist and empiricist accounts. Boxes and arrows are clearly not the most appropriate notation for a dynamic system, but the current representation hopefully captures some of the essential differences between neuroconstructivism and the other two theories. At the cognitive level, the neuroconstructivist approach stresses the difference between innate representations (invoked by most nativist linguists) and much lower-level innate computational and timing constraints from which representations progressively emerge as a function of development and of interaction with different types of



pre-specified for functions such as theory of mind or language and that this is why they can dissociate in adulthood. This is the basis for most brain imaging studies. Some authors go as far as claiming that epigenetic selection acts on preformed synaptic substrates and that to learn is to stabilize pre-existing synaptic combinations and to eliminate the surplus[31]. By contrast, current knowledge suggests that genes that are expressed in neocortex tend to do so throughout most regions, resulting in a similar six-layer structure and a similar overall pattern of intrinsic connectivity[30]. Combinations of neuroanatomical features, cortical layers and brain cytoarchitectural regions are found to be remarkably

environmental input. The multiple interactions between all levels, invoked by the neuroconstructivist approach, highlight why it is essential to start studies of developmental disorders in early infancy and then to trace the subsequent processes of development itself.



identify timing of gene expression and interactions with other genetic and environmental events

identify lowest level of impairment and study its developmental effects on higher-level cognition re both proficiencies and impairments

devise tasks to differentiate behaviour from cognitive processes; longitudinal brain imaging of both temporal and spatial changes; study changes in timing of environmental input

study earliest possible markers of disorder in foetus and infancy; focus on differences and similarities across phenotypes

similar in all regions of the brain from birth to 72 months. In other words, for quite some time the developmental patterns of different cytoarchitectural regions are indistinguishable from one another[32]. A single set of instructions might structure the different areas of neocortex, leaving the interaction with different environmental inputs to influence specific forms of synaptogenesis and dendritic arborization. In fact, neocortical specialization has already been shown to be very progressive across developmental time[33]. So if there is early genetic impairment, then it could be relatively widespread in the developing neocortex, even though its effects might be surprisingly differential in outcome. To be biologically and developmentally plausible, we must go beyond the more obvious deficit to seek far subtler effects on other aspects of the developing system. Even if future research were to uncover a specific regional pattern of neocortical gene expression – which is not ruled out by the position developed in this paper – the neuroconstructivist approach would force a reinterpretation of the meaning of localized gene expression, encouraging researchers to take serious account of the developmental time course. The systemic properties of ontogenesis and the developmental effects of the interconnectedness of brain regions, together with a structuring rather than merely triggering role for environmental input, would still be likely to result in a cascade of subtle deficits rather than a single, higher-level one.

Because both normal and abnormal development is progressive, a change of focus is essential in future research into pathology. Rather than concentrate on the study of disorders solely at their end state in school-aged children and adults, which is most commonly the case, it becomes essential to study disorders in early infancy, and longitudinally, to understand how alternative developmental pathways might lead to different phenotypical outcomes. Furthermore, if we accept that behavioural outcomes could stem from different cognitive processes, then matching control groups on the basis of behavioural scores, rather than underlying processes, might also be open to challenge.

One essential step towards a deeper understanding of developmental disorders is to model their various manifestations. In an important contribution to the field, Morton and Frith devised a structural framework for causal modelling within which to explore a variety of theories concerning different abnormal phenotypes[34]. Work of this nature is crucial in developing more constrained theories of developmental disorders. The authors present their discussion in terms of a framework rather than the embodiment of a particular theory. However, the 55 different models that they explore are all unidirectional in their causal chains, and so do not capture the basic assumptions of the neuroconstructivist approach. The figure in Box 6 illustrates how the neuroconstructivist approach differs from both the nativist and empiricist approaches to developmental psychopathology. It pinpoints the various theoretical assumptions discussed in this paper and the different research strategies to which they lead.

The complex dynamics of both normal and atypical development indicate, in my view, that the neuroconstructivist approach is the most viable theoretical framework within which to explore developmental disorders. These must be approached from early infancy onwards, and simultaneously at multiple levels: the genetic, the brain in its spatial and temporal dynamics, the cognitive, the environmental and the behavioural, as well as stressing the multiple two-way rather than unidirectional chains that interact all the way from genetic causes through to ultimate

Outstanding questions

- Some argue that evolution has provided the human cortex with increasingly detailed pre-specification prior to ontogenetic development. To what extent can the ontogenetic data be accounted for in terms of evolution selecting for less specific factors, such as increased neocortical plasticity and a greater range of learning mechanisms, to ensure adaptive outcomes rather than prior knowledge? Is it more useful to entertain the possibility that the highest level of evolution is to pre-specify simply a number of domain-relevant mechanisms which, after processing specific aspects of the environment, *become* increasingly domain-specific, that is, specialized, during ontogenesis? How might this change our perspective on developmental disorders?
- What can we learn about subtle differences in the environmental input to atypically developing infants and children? In this respect, is it useful to replace the static notion of 'environment' by that of the 'child's progressive processing of environmental input'? To what extent does the infant/child contribute to its own subsequent brain specialization by selecting aspects of its environment to attend to at different times in development?
- How influential is subcortical specialization in the structuring of neocortex?
- Are developmental disorders really specific, or do they lie on a continuum, with seeming dissociations due to relatively small differences in developmental timing, gene dosage, neuronal formation, neuronal migration, neuronal density, biochemical efficiency affecting firing thresholds, variations in transmitter types, dendritic arborization, synaptogenesis, and pruning?
- Just as modularity theorists can show that specific disorders also predict more general impairments, so non-modularity theorists can show that dynamic systems predict dissociations that do not reduce to autonomous modules. Is the double-dissociation method necessarily the right tool for furthering our knowledge of developmental disorders?
- If we do discover a truly specific disorder of higher-level cognition with no other subtle impairments, how could this be explained without violating what is known about the probabilistic epigenetics of biological development? Can one region of neocortex develop abnormally with no effects on any other region?
- How do acquired developmental disorders differ from genetically-based disorders?
- If we take development seriously, is atypical ontogenesis necessarily a window on the structure/functioning of the normal mind/brain, as seems to be taken for granted by many of those studying developmental disorders?

behavioural outcomes. This is because the dynamics of development itself are the key to understanding developmental disorders.

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