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CHAPTER THREE

Developmental Trajectories in Genetic Disorders

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Contents

Abstract

As the cognitive system develops over infancy and through childhood, profound changes in capacity and complexity occur. It is no surprise, then, that neurodevelopmental disorders of genetic origin are emergent over time. Characteristic cognitive profiles arise as neurodevelopmental

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constraints and multiple genetic and environmental factors influence an interactive network of developing systems. In order to construct a mechanistic understanding of this developmental process (both in the typically developing system and in those with additional, atypical constraints) it is necessary to take a developmental perspective. In this paper, we argue that a developmental trajectories approach is the most suitable framework within which to understand the highly complex, dynamic system that is the developing brain. The trajectories approach involves constructing algebraic functions linking performance on two measures, allowing a comparison of developmental change across typically and atypically developing groups. We advocate the use of brain measures to complement and extend our understanding of behaviorally measured cognitive change, on the basis that cognitive development is shaped by brain structure and function. We explore possible patterns of interaction between brain and behavioral trajectories, and give empirical examples of using the trajectories method with neurodevelopmental disorders of genetic origin. We conclude that this approach can offer a window onto how subtle neurocognitive anomalies in infancy can develop into the characteristic cognitive profiles seen in childhood and beyond, in those individuals with genetically determined developmental disorders.

1. Introduction

In this article, we argue that an understanding of the causes of genetic disorders is aided by characterizing those disorders in terms of developmental trajectories. This means following the pattern of abilities and disabilities in the child from infancy onwards, through early and mid-childhood, and into adolescence and adulthood. The *developmental trajectories approach* is a method of designing research studies that enables researchers and clinicians to identify the role that development plays in the origin of the cognitive strengths and weaknesses observed in the individual. In the following sections, we identify the key empirical effects that have motivated the use of the trajectories approach. We outline the explanations of developmental deficits that are emerging from the approach. We then describe the key tenets of the method, both as it is applied to studying behavior in children with developmental deficits and in characterizing brain development in these children. Finally, we illustrate the trajectories approach with three examples, drawn from studies of Williams syndrome (WS), Down syndrome (DS), autism, and dyslexia.

1. Why is Development Important?

Many developmental disorders associated with genetic conditions are characterized by learning disability. If this disability were global, so that cognitive development as a whole were slowed, and all aspects—perception, motor skills, language, social skills, reasoning—were equally delayed, one would infer that the condition had affected brain development as a whole. One might infer that, as a consequence, the brain did not have sufficient resources or power (or some equivalent property) to develop skills at the normal rate, and all processes occurred less efficiently. However, in many cases, while genetic disorders exhibit learning disabilities, they also show particular cognitive profiles of relative strengths and weaknesses. While there is always variability across individuals sharing a genetic condition (and little understanding of the source of that variability; see Thomas, Knowland, & Karmiloff-Smith, in press), the conditions frequently show a consistent pattern.

For example, in children with WS, there is a "hyper-social" personality profile, relatively good face recognition and language skills compared with overall mental age (MA), but relatively poor visuospatial skills (Donnai & Karmiloff-Smith, 2000; Farran & Jarrold, 2003; Mervis & Bertrand, 1997; Udwin & Yule, 1991). WS is a rare syndrome caused by a hemizygous microdeletion of 28 genes from chromosome 7 (Tassabehji, 2003) and is associated with learning disability. IQs range from 40 to 90, with the majority scoring between 55 and 69 (Mervis et al., 2000; Searcy et al., 2004). In children with DS, speech and language are impaired more than visuospatial processing skills, and major deficits have been observed in both short-term and long-term verbal memory (Carlesimo, Marotta, & Vicari, 1997; Fowler, 1990; Jarrold, Baddeley, & Hewes, 1999; Wang & Bellugi, 1994). DS is caused by the presence of three copies of chromosome 21 (Antonarakis, 1991) and is also associated with learning disability, with overall IQ levels ranging between 36 and 107 but declining significantly with age to between 40 and 70 (Roizen & Patterson, 2003; Wang, 1996). Autism is a common neurodevelopmental disorder characterized by impairments in social interaction, communication, and stereotypic behaviors (DSM-IV-TR [Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision], American Psychiatric Association, 2000). Autism is thought to have a strong genetic basis (Abrahams & Geschwind, 2008). The disorder is characterized in terms of a spectrum because both symptom severity and IQ level can vary widely (Caronna, Milunsky, & Tager-Flusberg, 2008).

What, then, is the origin of the particular cognitive profiles of these disorders? Why is social cognition a relative strength in WS but a weakness in autism? Why is visuospatial cognition a relative strength in DS but a

relative weakness in WS? The answer must lie in the different genetic causes of these disorders. In the 1980s and early 1990s, there was a hope that researchers would be able to make direct links between particular genes and particular parts of the cognitive profile: for instance, perhaps one of the genes deleted in WS might play a key role in the development of visuospatial skills but not other areas of cognition (Monaco, 1996; Pinker, 1994). This approach encountered two major difficulties, and together these led researchers to identify the need to characterize trajectories of development rather than simple snapshots of cognitive profiles.

2.1 A mismatch between the granularity of genetic effects and of cognitive fractionations

The first difficulty is that the genetic effects on brain development appear to be quite widespread, but the unevenness in the cognitive profiles can be quite fine-scaled. Let us take WS as an example. Structural studies of the WS brain, either at post mortem or using brain-imaging techniques, have indicated a range of abnormalities. These include reduced overall brain size, corpus callosum changes, a greater ratio than usual of anterior to posterior tissue, as well as differences in gyrification and sulcal depth in parietal, temporal, and occipital lobes (see Meyer-Lindenberg, Mervis, & Berman, 2006; Semel & Rosner, 2003, for reviews). Regional differences in gray matter volume have also been observed (although there is some inconsistency in the findings). Regional variations in gray matter include reductions in the intraparietal sulcus, around the third ventricle, and the orbitofrontal cortex (Meyer-Lindenberg et al., 2004), as well as increases in the medial prefrontal cortices, the anterior cingulate, insular cortex, and superior temporal gyrus (Reiss et al., 2004). The pattern is consistent with the idea that genetic mutations influencing development from the earliest stages do not produce focal consequences but widespread abnormalities in brain structure. As a consequence, the differences seem unlikely to specifically target neural networks responsible for individual behaviors.

The ambition of making direct links between particular genes and particular parts of the cognitive profile also relies on the assumption that genes target a particular level of cognitive granularity. For example, the WS cognitive profile includes relative strengths in language and face recognition but a relative weakness in visuospatial cognition. To make direct links from genes to the cognitive profile, the granularity of cognition would need to be at a level that differentiates a "language" component, a "visuospatial" component, and a "face recognition" component. However, as the behavioral evidence on the WS profile has accumulated, closer inspection has revealed that every one of these domains reveals more fine-grained levels of fragmentation (Brock, 2007; Semel & Rosner, 2003; Thomas, 2006).

Take the example of language. This domain is viewed as a relative strength in WS. However, within language, many finer fractions have emerged (see Semel & Rosner, 2003; Thomas, 2006, for reviews). Individuals with WS seem to be more advanced in grammar than pragmatics. But within grammar, more errors appear in morphosyntax (verb tense agreement, personal pronouns) than in syntax (complex sentence forms such as passives and conditionals). Even within syntax, there is greater difficulty with repeating certain types of sentence structure than others. Development is uneven within pragmatics too: there is relatively good performance in the "feeling" functions of communication (social sensitivity: e.g., making eye contact, sensitivity to nonverbal cues), which contrasts with problems in other areas such as greeting behaviors, topic maintenance, and question answering. In the domain of semantics, a relative strength in category concepts (e.g., animals vs. clothing) contrasts with problems understanding semantic relational concepts such as spatial-temporal terms. Even within category concepts, recent evidence has indicated differential naming problems across categories.

Fractionations are found in other areas of the WS cognitive profile showing relative strengths (see Semel & Rosner, 2003; Thomas, 2006). For example, children and adults with WS are noted for their sociability. However, within sociability, there is a fractionation between friendliness and success with adults, and disinterest or ineptness when interacting with peers. There is a fractionation between their sensitivity and understanding of others, and difficulty in respecting the private space of peers. Within the domain of memory, there are fractionations between relative skill in verbal memory (e.g., in digit span) and poor performance in visuospatial memory (e.g., Corsi span). Within verbal (phonological) memory itself, there is a fractionation between a strength in learning words but not in learning to read phonologically similar words. There is a strength in remembering semantically salient items like poems, stories, and songs over long periods, but not in learning or retaining facts over a few minutes. In musicality, in a few musically trained individuals in WS, there is a strength in composing, transposing, and performing music but a difficulty in reading music and playing instruments. In the domain of numeracy, children with WS reveal a weakness in understanding number concepts, but mental-age appropriate learning of the count sequence (Ansari et al., 2003).

Putting the brain and behavioral evidence together then, the first difficulty in making direct links between particular genes and particular parts of the cognitive profile in genetic disorders is that the effects on brain development appear to be fairly widespread, yet the cognitive effects appear to be fairly fine-grained. There is a mismatch in the granularity of cause and effect.

2.2 Cognitive profiles may not be constant over time

The second difficulty stems from the issue of when one can identify the cognitive profile of a given genetic disorder. A battery of observational or cognitive tests only offers a snapshot of the profile. If snapshots at younger ages were to demonstrate the same profile right back into infancy, we might conclude that the underlying causes of the profiles were present from the start and this would encourage more direct links between early brain development and the later cognitive profile. However, there are practical difficulties in using this putative method to investigate the origins of the uneven profiles. Behavioral tests are often only appropriate over a certain age range. If we want to examine a given behavior in an 18-month old versus a 4-year old versus a 12-year old, we may have to use different tests. This in turn creates the risk that differences in cognitive profiles at different ages may arise from the different tasks we are using. Moreover, tests have different levels of sensitivity in their relation to cognitive processes. If individuals are given a long time to generate their response in, say, pointing to the correct picture out of a set of four that corresponds with a target word (a standard way to assess receptive vocabulary), it is possible the individual may use a different strategy to get to the correct answer. The behavior may look the same even though the process is different. So there might be concerns whether our behavioral measures are necessarily telling us about the nature of the underlying cognitive processes.

Additional concerns stem from the fact that many of the behaviors we are measuring from infancy onwards are products of experience-dependent learning processes. There is no vocabulary or grammar system at 6 months. At 18 months, there might be a small vocabulary in typical development, but still little in the way of grammar. Visuospatial skills are often assessed using puzzle-building tasks (such as block design or pattern construction). Yet visuospatial construction requires a combination of visual perception, planning, and motor control that is not apparent until early childhood. The earlier one moves in generating snapshots of the cognitive profile, the more one is in fact tapping "proto" or seed versions of the systems measured at later ages. Conversely, the later one moves in generating the snapshot, the more one must consider the contribution of the learning process to that cognitive profile.

Perhaps the greatest challenge, however, would be if the cognitive profile observed at different ages in a given disorder were different (and this did not arise from problems of measurement). Such an occurrence would make it very much harder to make direct links between a (fixed) genetic mutation and a (changing) cognitive profile. Data are only starting to accumulate on the cognitive profiles of infants with genetic disorders. But there is already evidence suggesting profiles can change. For example

in WS, when the "proto" systems for vocabulary and number in toddlers were compared with the developed systems in adulthood, the relative patterns were different (Paterson, Brown, Gsodl, Johnson, & Karmiloff-Smith, 1999). For numerosity judgments, individuals with WS did well in infancy but poorly in adulthood, whereas for language, they performed poorly in infancy but well in adulthood.

Together, these challenges prompted a different approach to explaining the origins of cognitive profiles, one that shifted the emphasis on development itself (Karmiloff-Smith, 1998).

3. Developmental Trajectories

The response to these two difficulties was to place the process of development at the heart of explanations of developmental deficits. Recent theoretical approaches propose that many of the observed behavioral fractionations in developmental disorders are the consequences of cognitive development acting on a neonatal brain that has been constructed with (perhaps subtly) altered initial neurocomputational biases. This theoretical framework has been called *neuroconstructivism* (Elman et al., 1996; Karmiloff-Smith, 1998; Karmiloff-Smith & Thomas, 2003; Mareschal & Thomas, 2007; Sirois, Spratling, & Thomas et al., 2008; Westermann et al., 2007; Westermann, Thomas, & Karmiloff-Smith, in press). Neuroconstructivism is a general theory about cognitive development. *Constructivist* theories of development argue that there is a progressive increase in the complexity of representations, which enables new competences to develop based on earlier, simpler ones. *Neuroconstructivism* argues that this increase in representational complexity is realized in the brain by a progressive elaboration of functional cortical structures.

From the perspective of neuroconstructivism, an uneven cognitive profile is viewed as follows. At a given point in time, the pattern of relative strengths and weaknesses is the result of complex processes of development, attenuating, or exaggerating initial low-level neurocomputational differences. In terms of brain development, the usual emergence of an interactive network of neural systems may be perturbed by several factors. These include (1) the differing effect of the atypical computational biases on the ability of various areas to process the signal with which they are provided, by virtue of the initial large scale input–output connectivity of the brain; (2) anomalies in the emergence of specialized circuits through pruning or competition; (3) compensatory changes during interactions between different brain regions; and (4) the atypical subjective environment to which the individual with the disorder is exposed and indeed evokes in caregivers and peers (Mareschal & Thomas, 2007).

To construct and test theories within the neuroconstructivist framework, it is not sufficient to identify the cognitive profile that stabilizes in late childhood or early adulthood. Instead, researchers need to trace the development of abilities over time, potentially tracing back behavioral deficits to their origins in particular developmental stages in infancy. The developmental trajectories approach involves constructing algebraic functions linking task performance and age, thereby allowing developmental change to be compared across typically and atypically developing groups. Research designs of this sort require three conditions to be met (1) both typical and atypical groups are followed longitudinally as one or more abilities develop, or a cross-sectional design is employed which spans this range; (2) developmentally sensitive tasks are used, that is, tasks that can capture graduations of performance as the ability improves, rather than suffering from floor or ceiling effects. These measures should be sufficiently sensitive that they stand a chance of revealing atypical underlying processes, be it in areas of weakness or strength; and (3) there are grounds to believe that the task(s) used bear on the same cognitive processes across the age and ability range under consideration. Lastly, given that neuroconstructivism views functional brain development as a constraint on cognitive development, measures of brain structure and function are viewed as offering complementary evidence to behavioral studies.

3.1 Developmental relations

One distinction that has been widely used in the study of developmental disorders is that between delayed and atypical (sometimes deviant or different) development. In delayed development, the behavior of an older child with a developmental disability appears to resemble that of younger typically developing (TD) children. Particularly in the case of genetic disorders with learning disability, general delay is expected and not taken to be the marker of the particular disorder. Empirically, researchers assess whether some particular skill is atypical or delayed by attempting to gauge the general developmental stage that the cognitive domain in question has reached and then assess whether the skill level is in line with that stage.

There are shortcomings to this approach. For example, there is currently no good theory of the mechanisms that cause delay; and the fact that cognitive domains can be delayed to different extents appears itself a marker of atypicality. We return to these points later. For current purposes, however, the idea that delay can be diagnosed for a given behavior by gauging the developmental stage of the system is predicted on an assumption. The assumption is that cognition develops in *functional blocks*. A given behavior is generated from a particular block. For example, one might assume that a vocabulary test elicits behavior generated by the *language block*. A separate measure can then be used to assess the

developmental stage of the wider block. Test batteries like the British Abilities Scale (BAS; Elliot, Smith, & McCulloch, 1997) or the Differential Abilities Scale (DAS; Elliot, 2007) output a "verbal mental age." Delay in this case would be diagnosed if the observed performance on the target behavior (vocabulary knowledge) resembled the performance of TD children at the same developmental stage, that is, whose chronological ages (CAs) matched the verbal mental ages of the children with the disorder according to the BAS or DAS.

When applied to a group of children with a disorder who are in a narrow age range, this translates into a research design in which the children are compared to two TD control groups. One control group is matched to the disorder group on CA, while the other control group is matched on MA. If the disorder group is worse than the CA group, then there is a deficit. If the disorder group differs from the MA control group, the underlying processes are viewed as atypical. If the disorder group does not differ from the MA group, then the underlying processes are deemed as only to be delayed.

In the trajectories approach, delay is diagnosed by constructing trajectories that link task performance with MA, rather than CA. If task performance is in line with a given standardized measure, then plotting the disorder group's data according to each participant's MA should "normalize" the atypical trajectory—that is, move the trajectory to lie on top of the typically developing trajectory. In our example, if the scores on the vocabulary test for the disorder group were plotted against verbal mental age on the BAS or DAS, the same trajectory would be observed as when plotting the vocabulary test score against CA in the TD group.

Crucially, however, this approach—deriving the developmental relations between different cognitive abilities—is a much more general one. It need not rely on the assumption that cognition develops in blocks. Trajectories can be plotted between any pair of abilities, rather than just between task performance and standardized test score. Such relations reveal the abilities that are developing in harness, but also offer an insight into possible causal interactions between components of the cognitive system across development. And they offer a window onto how these causal processes may be different in developmental disorders.

4. Types of Trajectory: Behavior and Brain

4.1 Behavior

Adopting a developmental trajectories approach, to define relationships between variables, can incorporate the use of a number of related analytical techniques, including analysis of covariance, hierarchical regression,

and structural equation modeling. Employing linear analytical methods to capture relationships between behavioral measures demonstrates two fundamental ways in which trajectories can differ. First, performance level at the point of onset (intercept), that is the youngest point of measurement, can differ from the TD onset. Second, the rate of change and direction (gradient) after the point of onset can differ from the typical trajectory. In this case the relationship between typical and atypical performance differs over time in a linear, or nonlinear, fashion.

Differences in these two parameters result in six general ways in which developmental trajectories can deviate from the typical path (Thomas et al., 2009). (1) A group difference at the intercept, but with similar gradients thereafter, indicates that the disorder group shows a developmental delay in performance. (2) Comparable performance at the intercept, but with differing gradients, suggests that the development of the disorder group follows a typical path up to the youngest point of measurement, but deviates after that point. This deviation may be linear or nonlinear, for example, the disorder group may show slower rate of change, thus diverging from the TD trajectory. (3) Differences in both intercept and gradient suggest that the behavior shows both a late onset in the disorder group and a differential rate once it has started to emerge. (4) The disorder group can show a premature asymptote, or (5) a zero trajectory, either of which may be revealing the developmental constraints of the system, such that only so a certain level of performance can be achieved. (6) There may be a systematic relationship between the variables of interest for one group but not the other, which indicates that the groups are using different systems to achieve behavioral output.

The measurement of change is most reliably achieved through repeated longitudinal assessment such that individual variation across ages cannot confound effects of developmental change, especially in the case of developmental disorders where individual variation can be substantial. Cross-sectional designs offer an approximation of this model, and, as an efficient validation, longitudinal follow-ups can be taken. (See http://www.psyc.bbk.ac.uk/research/DNL/stats/Thomas_trajectories.html for worked examples of simple linear trajectory analyses.)

4.2 Brain

Just as developmental trajectories can be used to describe the relationship between any two behavioral variables, so they can describe how measures of brain structure or function vary in relation to age, behavioral measures or other brain measures, to describe neurodevelopmental trajectories. Using brain measures as the dependent variable maintains the same philosophy of considering the dynamics of change, rather than time-point

specific profiles, that behavioral trajectories maintain, but arguably extends the flexibility of the approach by opening up the potential for cross-technique and cross-measure comparisons.

Shaw, Gotgay, and Rapoport (2010) recently reviewed their considerable work in this area by describing the trajectory shapes observed with this method of analysis, and illustrated each with data from a developmental disorder. Just as with behavioral measures, a primary distinction is made between differences of intercept and gradient. The first trajectory described is a rightward shift along the *X*-axis, in which gradient and shape are maintained but a difference between groups is seen at the intercept. That is to say, the developmental disorder trajectory is delayed with reference to the typical trajectory. Shaw et al. (2007) found this delayed trajectory when using structural imaging to measure changes in cortical thickness over development in children with and without attention deficit hyperactivity disorder (ADHD). The point of maximal thickness, where increase in cortical thickness through childhood gives way to thinning in adolescence, was delayed in children with ADHD compared to their typically developing peers, although gradients of change were comparable. This was especially true in the prefrontal cortex, though the order in which cortical regions matured remained the same as the controls. This pattern of developmental delay in neurotrajectories is interesting since tracing the origin of neural differences back to infancy is, in some respects, a more direct method than building trajectories using behavioral measures. So long as the brain measure taken can be applied to very young children, there is no need here to use different measures more appropriate to infant testing to chart the early emergence of an ability. In the case of Shaw's participants, children who later show ADHD may either be born with reduced cortical thickness or may show a delay in the initial increase in thickness.

In terms of gradient differences, Shaw et al. give the example of brain volume change in infants later diagnosed with autism. These infants show normal head size and brain volume at birth (normal intercept), followed by a period of unusually rapid growth (steeper gradient), plateauing by late childhood to realign with their typically developing peers (see Redcay & Courchesne, 2005 for a review). However, recent modeling work from our lab (Thomas, Knowland, & Karmiloff-Smith, submitted) has raised the possibility that the increased brain volumes observed might in fact be tapping a risk factor for the disorder rather than a direct cause. The research indicates that a proto-measure of IQ (or parental IQ) may tap this risk factor. If so, a trajectories approach can help elucidate the issue by evaluating whether a plot of brain volume against the IQ measure in at-risk infants normalizes the observed atypical trajectory. In addition, the use of unaffected siblings as controls may become increasingly important,

especially in disorders of genetic origin, but without genetic diagnoses such as autism.

A final example from Shaw et al. illustrates the imposition of a developmental constraint on change. In adolescence, individuals with child onset schizophrenia do not show the typically observed (Giedd et al., 1999) increase in cortical white matter volume (Gogtay, 2008). That is to say, the typical trajectory of white matter increase from early childhood through to adulthood is seen to asymptote in those with child onset schizophrenia.

When considering brain measures, we can think more directly about developmental constraints, in terms of neurophysiology, rather than the more abstract relations between behavior and brain mechanisms. Nevertheless, making causal links back to the behavioral level can be just as challenging. For example, a current challenge in the charting of neurotrajectories is that brain measures are, in some ways, more general than behavioral measures due to the resolution of imaging instruments. This means that finding the fine-scale anomalies that impact on behavioral change in developmental disorders is, *in vivo* at least, currently unfeasible.

4.3 Combining behavioral and brain trajectories

The use of trajectories to chart change over time on brain and behavioral measures reveals the same basic patterns of divergence from typical development. However, the conclusions we can draw from each method are, at this stage, somewhat different. The question at this juncture is how best to combine developmental trajectories at different levels of description in the most informative way. The aim of developmental neurocognition is to understand the complex interplay between genes, neuroanatomy, neurophysiology, and cognition. The benefit of using a trajectories approach in order to study these relationships is that researchers can plot the impact of change over time from one level to another. Given the example of a developmental delay in cortical thickening in ADHD (Shaw et al., 2007), by additionally taking a behavioral measure of, say, inhibitory control, we can plot not only cortical thickness against CA to determine the nature of the neuroanatomical delay, but then plot cortical thickness against the behavioral measure to see if the trajectory normalizes. The TD group here provides a template of the relationship you would expect between brain measure and behavioral output, such that if the ADHD group still differs, in terms of intercept or gradient, we can infer that a deviant relationship exists between the variables. In this case the disorder group may be using an alternative route to achieve a given behavior, or may switch routes in the event of some neuroanatomical/neurophysiological asymptote being reached. This means that trajectories may differ in terms of brain but not behavioral measures. Indeed one group may not

show a consistent relationship, while the other does. In this case we can assume that the brain parameter being measured is either constraining or supporting behavioral performance for one group, while the other is using an alternative route to behavioral output.

We are also able to ask about the timing of developmental impacts. For example, in the case of child onset schizophrenia, what is the temporal relationship between the silencing of white matter increase and the onset of symptoms? How does the timing of gene expression result in these changes? Pinter, Eliez, Schmitt, Capone, and Reiss (2001) examined cortical growth rates in children with DS and found that some areas grow as normal and others show deviation. Such work, with syndromes where we understand both genetic cause and cognitive profiles, is a vital step to understanding the flow of genetic impact.

Interpretation of brain-to-behavior relationships can be especially difficult, as frequently we see a many-to-many relationship. That is, many brain areas are involved in driving complex behaviors and each brain area is involved in many behaviors. So it is unlikely that any individual brain-to-behavior mapping will reveal the full story of a behavioral symptom (see conceptual example, below). As we slowly begin to understand the role played by, for example, neuroanatomical markers such as the point of maximal cortical thickness, then changes in relation to behavior over time will become clearer. In the next section, we set out a conceptual example of inferences that may be made from brain and behavioral trajectories.

4.4 A conceptual example of types of developmental relation and causal inferences

Figure 3.1 shows a model system containing two developing cognitive mechanisms. Potentially, each mechanism might drive a separate behavior, A and C. However, the mechanisms might jointly drive a behavior B. While we might assess the development of the two mechanisms using behavioral tests, there may also be ways to assess their development using brain measures. Here are some possible developmental relations, and inferences one might make about causal mechanisms.

If there were a reliable trajectory when behavior A were plotted against behavior C, one could infer either there was a causal relation between mechanisms 1 and 2, or both relied on a common causal mechanism 3. If in a disorder, both behaviors A and C were equally delayed, both mechanisms could be equally impaired (e.g., by poor processing conditions), or both could rely on a common mechanism that was impaired. An uneven delay in the two behaviors might imply that both mechanisms were impaired in a common property X, but that property X was more important for the development of one mechanism than the other.

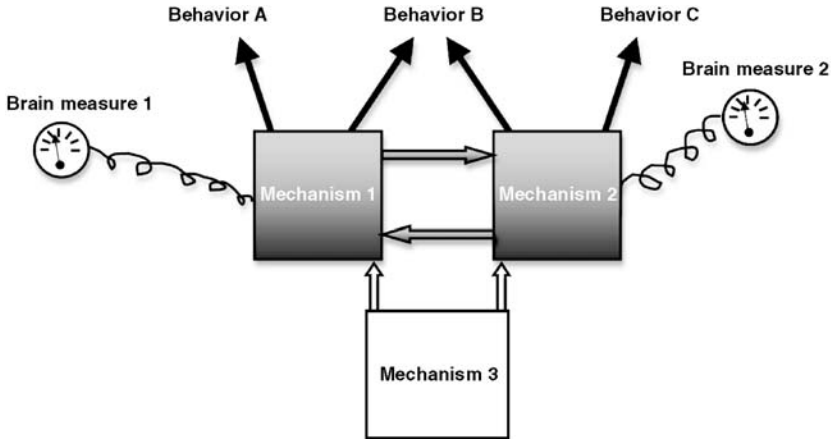

Figure 3.1 A conceptual example of how developmental relations between behaviors may be used to infer causal relations between underlying mechanisms. Boxes depict cognitive mechanisms (usually implemented in networks of brain regions). Gray and white arrows indicate possible causal relationships. Solid arrows indicate possible behaviors driven by the cognitive mechanisms. Gauges indicate the possibility of independently measuring the operation of the mechanisms via functional brain-imaging methods.

If a causal link existed between the mechanisms (1 relied on 2 for its development and vice versa), then any initial deficit observed in behavior A should later spread to behavior C (or vice versa). The developmental relation should increase over time, with both behaviors impaired. Conversely, a causal relation may allow for compensation. An initial deficit in behavior A but not behavior C may be followed developmentally by deficits in neither. The developmental relation should increase, but now with both behaviors in the normal range. Brain-based measures would be required to show that mechanism 1 still had an underlying deficit.

These situations depend on the ability to tap the development of a single process with a single behavioral measure. However, all behaviors may be like B, combining the actions of several underlying cognitive mechanisms. In this case, if behavior B were impaired, it would require brain measures to localize the source of the deficit: behavioral measures would not be sufficiently precise.

Developmental relations might differ between TD and disorder groups. If a reliable relation were found between behavior A and behavior C in typical development but not in the disorder group, this implies either that there is a deficit to one of the mechanisms in the disorder group, or no causal relation exists between the mechanisms during development. Finally, if behaviors A and C correlate in the disorder group but not in

typical development, this might imply a widespread deficit impacting on both mechanisms, or that a novel causal relation exists (for instance, that there is a deficit in one mechanism and the other is being used atypically to drive behavior; or a deficit in one mechanism is serving as a limiting factor on the development of the other).

This conceptual example indicates how developmental relations between behavioral measures may be used to infer causal relationships between cognitive mechanisms. However, such schematics are limited. This is because the schematic is not in itself a developmental model (Thomas, 2005a). It does not explain where the mechanisms come from. It does not include the possibility that the arrows may alter across development. For example, what if a behavior needs to be driven by two mechanisms early in development, but can be supported by a single mechanism later? Perhaps also our brain mechanisms may offer different windows on to cognitive mechanisms at different ages.

4.5 The importance of understanding mechanism

Ultimately, theoretical progress in understanding the course of development in genetic disorders depends on our gaining insight into details of the mechanisms. The key issue is how cognitive processes and representations can change to drive more complex behavior. To gain these insights, diagrams of possible causal relations must be replaced by formal, computational models, which capture the processes underlying behavior and the mechanisms driving changes of behavior (Mareschal & Thomas, 2007). Such models are able to explore the conditions under which early deficits might spread across a cognitive system, or situations when compensation might occur, and how this depends on the global architecture of the cognitive system (Baughman & Thomas, 2008). Computational models allow a more detailed investigation of the constraints that shape normal development, and how alterations in those constraints might lead to developmental deficits as the system attempts to acquire its target cognitive domain (Thomas & Karmiloff-Smith, 2002, 2003). Models allow flesh to be put on the bones of a term like "compensation" (Thomas, 2005b, c): under what conditions can an early deficit be compensated for, so that a cognitive profile will become less uneven with age? Will there remain any markers of that compensation at the behavioral level? Not only do computational models of development offer greater theoretical precision but also they hold out the prospect that models of deficits can be used to predict behavioral interventions that will remediate those deficits (Poll, in press). We next turn to examine the use of developmental trajectories in different settings and the way in which brain and behavioral measures can be used in conjunction to enrich the trajectory approach.

4.6 Three examples illustrating the use of the trajectory approach

In this section, we consider three examples that illustrate the use of trajectory methods to characterize developmental deficits. The first example considers the development of semantic knowledge in WS, and demonstrates both how the disorder profile can alter with age, and the importance of the particular behavioral task used to assess an underlying ability. The second example considers the development of face recognition, and demonstrates the use of cross-syndrome comparisons with the trajectories approach, contrasting WS with DS and autism. The third example considers audiovisual processing in developmental dyslexia, and illustrates the use of more sensitive measures of brain function to tap the development of typical and atypical cognitive processes.

4.7 Lexical semantic knowledge in ws

A notable feature of WS is the relative strength of language skills compared to visuospatial skills (although language itself can be quite delayed; see Thomas, Karaminis, & Knowland, 2010; see also Brock, 2007, for a review of research on language abilities in WS). The sophistication of productive vocabulary can seem particularly surprising compared to overall mental age, and compared to other disorders with learning disability, such as DS. One question that has been considered is whether underlying semantic knowledge is necessarily in step with productive vocabulary ability in the syndrome. Purser, Thomas, Snoxall, Mareschal, and Karmiloff-Smith (in press) investigated knowledge of word meanings (lexico-semantic knowledge) using the developmental trajectories approach, with particular reference to the type of task used to assess this knowledge. The domain of animals was chosen to make the tasks as easy as possible for participants with WS, because it has been shown that individuals with WS as young as 10 have comparable basic knowledge in this area to verbal-MA-matched controls (Johnson & Carey, 1998). Verbal mental age was assessed via the British Picture Vocabulary Scale (BPVS; Dunn et al., 1997). This is a receptive vocabulary test where participants are asked to pick which of four pictures goes with a target word in order to demonstrate knowledge of the word's meaning.

An understanding of word meanings was assessed in two different ways. The first method employed a definitions task in which participants were asked to define words (e.g., "What is an elephant?"). The second method employed a novel categorization task, which involved sorting toy animals into semantic categories (e.g., participants were asked questions such as "Which live in the sea?" and "Which lay eggs?"). This second task was designed to avoid the meta-cognitive demands of the definitions task: to perform well on a definitions task, children have to know what a

definition is, and also understand that the implicit requirement is for them to list the semantic features or attributes of the target concept in descending order of salience and diagnosticity (in this case, the features that stand out for the animal and set it apart from the other animals). Performance on the definitions task was assessed based on how many correct features the individual produced for each animal, while performance on the categorization task was assessed by how many animals were correctly sorted into the probed categories. Purser et al. then constructed developmental trajectories linking performance on each task with verbal mental age, separately for a group of TD children and a group of children and adolescents, and adults with WS.

Figure 3.2, left panel, shows the two groups' performance on the definitions task. The WS group's performance began at a level appropriate for vocabulary age, but then the TD group improved more steeply than the WS group. The gradients of the trajectories rather than the intercepts differed. Individuals with WS found it increasingly hard to produce the type of word definition that is expected of higher levels of vocabulary ability. In the categorization task (right panel), the WS group's performance developed at a similar rate to that of the TD group, but was markedly poorer than predicted by vocabulary age across the range of ability. Here the intercepts of the trajectories differed, but not the gradients. This pattern of results suggests that individuals with WS have a lower level of lexico-semantic knowledge than expected given their receptive vocabulary, although this knowledge increases with advancing vocabulary age at a similar rate to that seen in typical development. The demands of accessing this knowledge via definitions, however, led to a divergence from typical development at higher ability levels.

Of potential importance is the implication that receptive vocabulary tests like the BPVS might *overestimate* lexico-semantic knowledge in individuals with WS. Other more general tests might be recommended

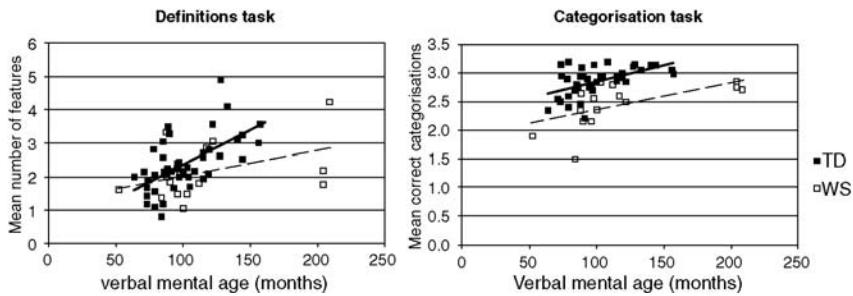

Figure 3.2 Left panel: Mean number of features given by participants in the definitions task, plotted against verbal mental age in years. Right panel: Mean number of correct categorizations plotted against verbal mental age in years. TD: typically developing, WS: Williams syndrome. Data from Purser et al. (in press).

to assess language ability in this population. For our purposes, the study highlights the fact that some differences between groups are stable across development while others change depending on the age that is considered. The disparity in lexico-semantic knowledge between WS and typical development was stable across development, while the meta-cognitive demands of the definitions task increasingly disadvantaged the WS group at higher ability levels.

4.8 Cross-syndrome studies of the development of face recognition

Face recognition is a crucial skill in development of social cognition. TD children demonstrate a characteristic shift in the information they use to recognize faces as they get older, moving from the use of information about individual features (eyes, nose, mouth) to information about the spatial arrangement of these features, known as configural information (Carey & Diamond, 1977; Mondloch, Le Grand, & Maurer, 2002). One way to verify this shift is to turn the face upside-down. The ability to perceive configural information is disrupted by inverting faces, but the ability to perceive information about features is much less disrupted by inversion. If children shift to using configural information to recognize faces, they will be increasingly hampered by inversion, and this is what is observed (Mondloch et al., 2002).

Anomalies in face recognition have been identified in several genetic developmental disorders. Individuals with WS are noted for their relatively strong face recognition abilities compared to overall MA. However, several studies have suggested that relatively good face recognition behavior is achieved by atypical underlying cognitive processes, in particular, the preferential use of information about features rather than configurations (Deruelle, Mancini, Livet, Cassé-Perrot, & de Schonen, 1999; Karmiloff-Smith et al., 2004; Mills et al., 2000). The atypical behavioral evidence is complemented by findings from a small number of functional brain-imaging studies indicating anomalous brain activation during face recognition (Grice et al., 2001; Mobbs et al., 2004).

Studies of high-functioning children with autism have pointed toward perceptual processing that relies on detailed information (Shah & Frith, 1983). The same appears to hold for face recognition, where a reliance on features has been observed (Langdell, 1978). Other behavioral anomalies have been noted, including reduced attention to faces during infancy and deficits in the recognition of emotional expressions (see Annaz et al., 2009, for review). Atypical functional brain activation has also been found during face recognition (e.g., Koshino et al., 2008). Little research, however, has focused on low-functioning children with autism to investigate the impact of learning disability on face recognition.

WS and autism therefore seem similar in a reliance on feature information in face recognition, despite contrasting styles of social engagement versus social disengagement. Much less research has been carried out on face recognition in DS, with some evidence of difficulties in recognizing emotional expressions (Williams, Wishart, Pitcairn, & Willis, 2005; Wishart & Pitcairn, 2000; Wishart, Cebula, Willis, & Pitcairn, 2007). Nevertheless, there have been suggestions that individuals with DS exhibit a global style in visuospatial processing (e.g., Bellugi et al., 1999). This would imply a greater emphasis on configural information in face recognition, which would contrast with the pattern observed in WS and autism.

Annaz (2006) employed a trajectories approach to investigate the development of face recognition in children with autism, WS, and DS between the ages of 5 and 12 (see Annaz, Thomas, & Karmiloff-Smith, in preparation; Annaz, Karmiloff-Smith, Johnson, & Thomas, 2009). The autistic group was split into high-functioning and low-functioning children, based on the Childhood Autism Rating Scale (Schopler, Reichler, & Rochen, 1993). Annaz adapted the technique of Mondloch et al. (2002) to focus on children's sensitivity to featural or configural changes in faces. Children had to detect these differences in faces presented either in upright or inverted orientations. Overall face recognition ability was assessed using the Benton face recognition task (Benton, Hamsher, Varney, & Spreen, 1983). This task involves matching black and white photographs of faces presented in different orientations. On each trial, the participant is required to choose 3 faces from an array of 6 that match a target face.

Figure 3.3 plots cross-sectional developmental trajectories for TD children and each of the disorder groups. There are four trajectories plotted against CA: detecting featural changes in upright faces, detecting featural changes in inverted faces, detecting configural changes in upright faces, and detecting configural changes in inverted faces. The plot for TD children demonstrates four characteristics: performance improved with age; configural changes were overall harder to detect than featural changes; inverting faces made the task harder; and while the ability to detect configural changes in upright faces improved rapidly, there was no corresponding increase when faces were inverted. In comparison, the most startling finding for the disorder groups was that not only did every disorder demonstrate differences from the typical profile but also the pattern for every disorder was *different*. For high-functioning children with autism, there was no evidence of an inversion effect. For low-functioning children, performance improved more slowly with age than for the high-functioning group, and for faces with featural changes, surprisingly the younger low-functioning children performance better when these faces were inverted. Both WS and DS groups performed

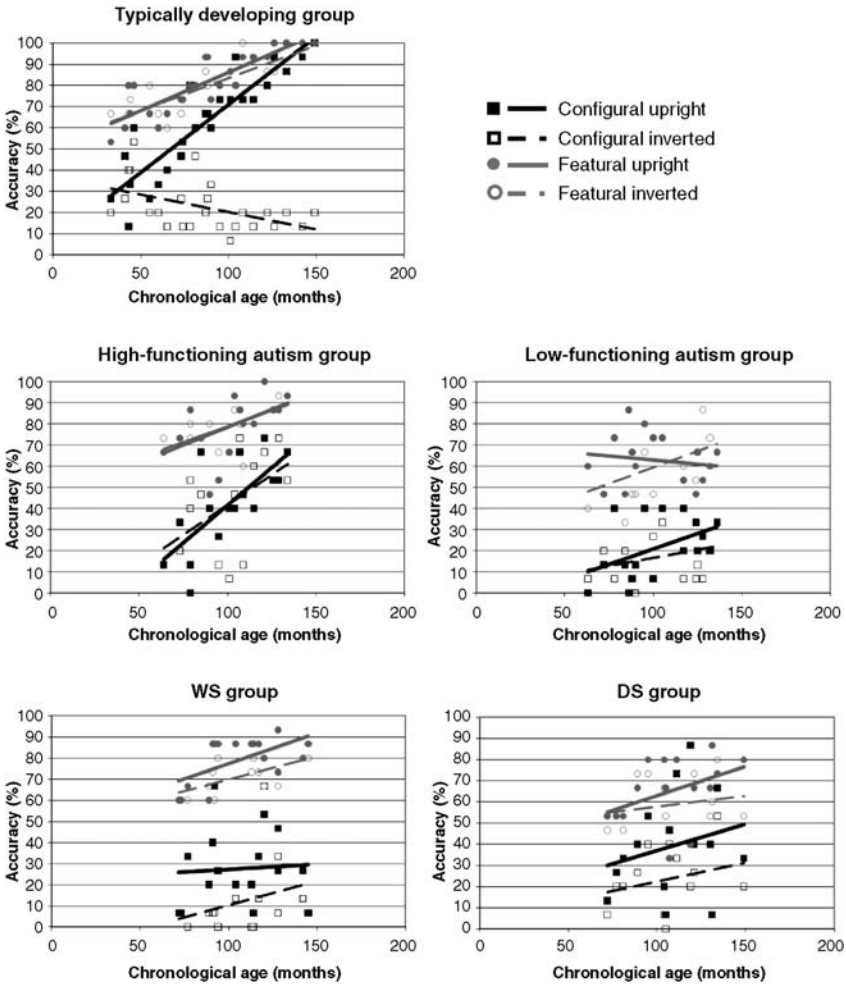

Figure 3.3 Cross-syndrome comparison in the ability to detect featural versus configural changes in faces. Panels show accuracy for typically developing children (N = 25, 3–12 years of age), children with WS (N = 15, 5–12 years of age), children with DS (N = 15, 6–13 years of age), high-functioning children with autism (N = 16, 5–11), and low-functioning children with autism (N = 17, 5–11). Data from Annaz (2006) and Annaz, Thomas, and Karmiloff-Smith (2011).

better on detecting featural rather than configural changes, though the advantage was larger in WS than DS. While the WS group showed improvement with increasing age, the DS group did not.

One might argue that some of these differences between disorder groups emerge because the children had different levels of impairment in face recognition. Figure 3.4 plots the developmental relation between

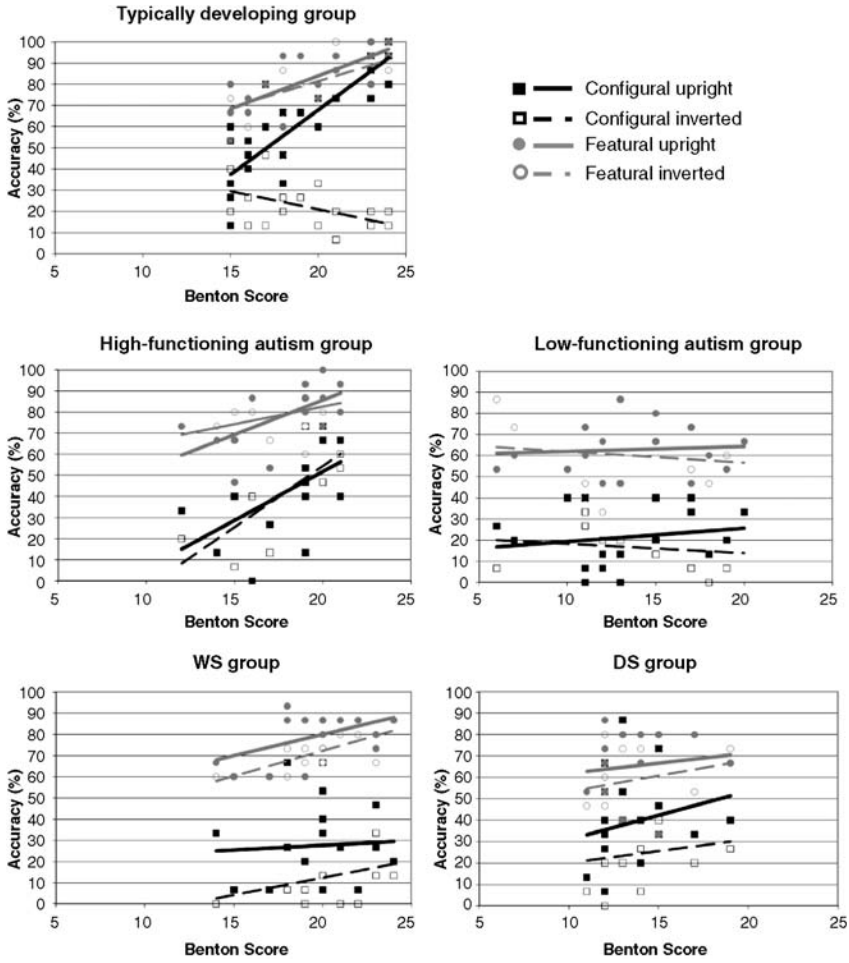

Figure 3.4 Data from Fig. 3.3, with performance plotted against raw score on the Benton face recognition test (Benton et al., 1983).

task performance and the score on the Benton face recognition test. Recall, if anomalies are due to the developmental stage of the face recognition system, plotting this developmental relation should transform the trajectories to resemble the TD profile. Although the trajectories are shifting to the left or right depending on each group's level of performance, the results remain the same. Thus, even controlling for the level of face recognition ability, all four disorder groups exhibited atypical patterns, and all were different.

Of course the next step is to infer what developmental processing constraints are different in each disorder; and by virtue of their variation

in genetic disorders, what constraints must operate to shape typical development. This is a stern challenge, which requires the integration of data from multiple disciplines (see Annaz et al., 2009, for one attempt to draw such conclusions). Overall, the current example illustrates how cross-syndrome comparisons can reveal the unique contribution of a given disorder to the behavioral profile, rather than characteristics of task performance that stem from learning disability *per se*.

4.9 The use of brain measures to complement behavioral measures: audiovisual integration and developmental dyslexia

Dyslexia is a common neurodevelopmental disorder characterized by a level of attainment in reading and spelling below that expected given nonverbal IQ and environmental opportunity. The specific learning difficulty in this case does not, by definition, extend to a general learning deficit, but the principle of a specific, emergent, cognitive profile as a result of genetic influence, remains. Dyslexia is highly heritable, as confirmed by behavioral genetic studies (Gayán & Olson, 2001; Ziegler et al., 2005), and molecular genetic work (e.g., Chapman et al., 2004) has identified a number of candidate genes (see Schumacher, Hoffman, Schmal, Schulte-Korne, Nothen, 2007, for a review).

Dyslexia is associated with various cognitive and perceptual processing deficits. One such deficit is the processing of stimuli in noise (Sperling, Lu, Manis, & Seidenberg, 2005, 2006), including speech-in-noise (Ziegler, Pech-George, George, & Lorenzi, 2009). Work in our lab (Knowland, Dick, Karmiloff-Smith, & Thomas, in preparation) is currently investigating whether children with dyslexia can help compensate for this weakness by using visual speech cues to bootstrap their auditory perception of speech-in-noise. Such cues are known to be highly useful for adults (e.g., Grant & Seitz, 2000). Using a trajectories approach, here, allows us to consider the changing use of visual cues as speech processing abilities develop. TD children between 5 and 12 years of age, and children with developmental dyslexia between 7 and 12 years of age, were asked to respond to spoken sentences in either low or high noise, with or without visual support. A visual-only condition was also included. Children showed improvement with age on all conditions except visual-only. However, in the high-noise condition, the difference between performance with visual support and without visual support did not increase with age. That is, young children benefited from visual cues as much as their older peers. Furthermore, no differences were found in either the onset or rate of change between the TD and dyslexia groups when plotted against either CA or nonverbal IQ. Figure 3.5 shows the difference between performance with and without

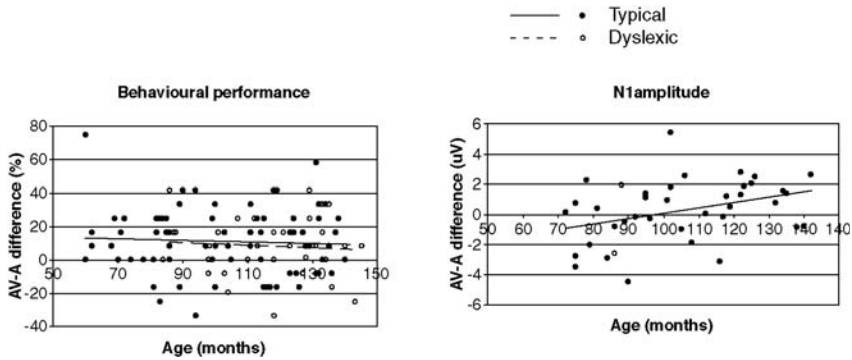

Figure 3.5 Data showing the use of visual speech cues in typically developing children and children with developmental dyslexia. The left-hand panel shows the difference between percentage correct scores on a speech in noise task with versus without the availability of visual speech cues, for the TD ($N = 74$) and dyslexia ($N = 37$) groups. The right-hand panel shows the difference in *N*100 amplitude when listening to speech with versus without visual speech cues, for the TD group ($N = 38$) plus two children with dyslexia.

visual support for the two groups, in trajectories linking task performance and age.

To complement this work, we have developed a trajectory of neural changes in TD children associated with the use of visual speech cues. Event-related potential (ERP) studies with adults show that the availability of visual speech cues modulates parameters of auditory waveforms associated with the processing of speech (Pilling, 2009; van Wassenhove, Grant, & Poeppel, 2005). One such modulation is the amplitude of the auditory *N*100, a negative going voltage deflection peaking around 100 ms after stimulus onset. We investigated the change in this modulation over developmental time, with TD children between 6 and 11 years. Children were asked to watch videos of a woman saying concrete nouns either with or without visual cues, while we recorded their ERPs.

While children between these ages had, behaviorally, not shown any developmental change in the advantage of visual speech cues, we did nonetheless observe neural changes over this period. The timing and amplitude of auditory components was seen to alter, but also the difference between *N*100 amplitude, when visual cues were available compared to not available, increased over developmental time. Figure 3.5 shows the voltage difference between the *N*100 amplitude for conditions with and without visual cues, plotted against age.

This example demonstrates the use of brain measures to determine whether neural changes are occurring that may result in behavioral

changes more subtle than those currently being observed. In this case, the behavioral measure taken was fairly coarse, yet a developmental change in neural correlates predicts that subtle changes in how visual speech cues alter auditory perception are occurring. However, it also highlights how cautious we need to be when making assumptions about neural correlates and what brain measures actually mean. We are assuming that the modulation of the *N*100 brain voltage component represents the extent to which an individual is using visual speech cues. Yet the complexity of the ERP response leaves open a number of other possible options, including developmental changes in the synchronicity of the neural sources underlying auditory ERP components.

To illustrate how this trajectory could be used as a basis for comparison with developmental groups, two 7-year-old children with developmental dyslexia were tested. As shown in Figure 3.5, these two children did not show modulation of the *N*100 outside that which would be expected given their age. If replicated in a larger sample, such a result would suggest that children with dyslexia do not differ from TD children in the use of visual speech cues either behaviorally or neurally. The finding of a null result, in terms of group differences, is interesting here, as it illustrates how low-level deficits in one domain do not necessarily translate into atypical developmental constraints at a higher level. In this case, a deficit in the integration of simple auditory and visual stimuli, as shown in dyslexia (e.g., Virsu, Lahti-Nuuttila, & Laasonen, 2002), does not translate to a problem using visual cues to help process a more complex auditory signal such as speech.

5. Discussion

We need to understand the mechanisms of developmental change in order to understand how cognitive processes can show deficits over development; in order to appropriately intervene when such deficits appear; and in order to appreciate how typical cognition emerges over developmental time. Traditional ways of investigating cognition over childhood, using groups of children at different ages, can impose or conceal patterns of change. The developmental trajectories approach is a method of data collection and analysis that allows researchers to adopt a truly developmental perspective, and encourages thinking about data in terms of a dynamic system. By following profiles, as initial small differences unfold, and as components interact in changing ways over time, genuine developmental relations and constraints can be revealed. The trajectories approach requires certain conditions to be met: measures need to be developmentally sensitive; they need to target skills that take time

to develop but which are believed to be driven by the same processes across age; and performance should be measured in samples with a broad age/ability range.

Neurodevelopmental disorders with known genetic origins may provide a particularly useful window onto the mechanisms of cognitive development. WS, for example, has been cited as providing vital insights into the relationship between the genes on chromosome 7, known to be deleted in the disorder (Tassabehji et al., 2005), and aspects of the cognitive profile seen in this disorder (Meyer-Lindenberg et al., 2006). However, even in this case, work remains far from linking levels of explanation, both as a result of the many-to-many relationship between brain areas and behavior discussed above, and also the extent to which this relationship is further complicated by the many-to-many relationship between genes and the development of brain areas.

Tracing genetic abnormalities to high-level cognitive differences and deficits in developmental disorders is a challenge that will require multiple disciplinary methods to address. We believe that a key part of building up this picture in the future will be played by the tracing of developmental trajectories at multiple levels of explanation. Charting developmental change of cognitive abilities, as measured by behavior, by functional and structural brain indices, by genetic expression and by changing environmental input, will allow us to understand the influences of multiple factors over time. This in turn will allow us to determine when and how to intervene to minimize cognitive deficits and behavioral disadvantages. The role of environmental change is particularly neglected and may prove important in terms of how interactions with the environment exaggerate or attenuate the effects of initial impairments.

The linking of behavior with indexes of brain function and structure is an achievable step in this direction and offers the considerable advantage of specifying the neural origins of observed behavior across disorders. One instance where this is particularly valuable is in the case of general intellectual disability, where it is common to see a pattern of delay and premature asymptote in ability levels. We still do not have a good mechanistic understanding of what causes this familiar pattern (see Thomas et al., 2009; Thomas, Karaminis, & Knowland, 2010), or indeed whether there is a single cause across different disorders showing the same poor performance. Indeed, computational modeling suggests impairments in several different neurocomputational parameters can cause similar looking patterns of poor development (Thomas & Karmiloff-Smith, 2003). Taking brain measures across development and comparing disorder types could help untangle the similarities and differences between the causes of cognitive deficits. So while general intellectual deficits are not currently taken as a marker for a particular disorder, with the aid of targeted brain measures, aspects of that general deficit could illuminate disorder-specific markers.

However, caution must be applied when making assumptions about the nature or specificity of neural correlates. Often brain measures can be interpreted in multiple ways depending on the context. For example, total brain volume correlates with IQ in TD individuals, and smaller brain volume in WS (Reiss et al., 2000) seems to support this association. However, brain volume is *increased* early in development in those with autism, arguing against a simple relationship with intelligence. Researchers are only beginning to construct mechanistic accounts that would help explain these anomalies (see Thomas et al., submitted). Simple relationships between brain and behavior are elusive. Indeed, in principle, atypical brain activation need not necessarily imply atypical cognitive processes at all, due to the availability of alternative pathways to behavioral success.

Developmental trajectories supply researchers with a powerful tool. Tracing cognitive deficits back to their developmental origins in infancy or early childhood furnishes researchers with the best opportunity to understand causal mechanisms, with the potential to inform clinicians about when and how to intervene to best support development.

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REFERENCES

Abrahams, B. S., & Geschwind, D. H. (2008). Advances in autism genetics: on the threshold of a new neurobiology. *Nature Reviews Genetics*, *9*(5), 341–355.

Annaz, D. (2006). The development of visuospatial processing in children with autism, Down syndrome, and Williams syndrome. Unpublished PhD thesis. University of London.

Annaz, D., Karmiloff-Smith, A., Johnson, M. H., & Thomas, M. S. C. (2009). A cross-syndrome study of the development of holistic face recognition in children with autism, Down syndrome and Williams syndrome. *Journal of Experimental Child Psychology*, *102*, 456–486.

Annaz, D., Thomas, M. S. C., & Karmiloff-Smith, A. (in preparation). The development of configural and featural face processing in children with autism, Williams syndrome, and Down syndrome: Varieties of atypicality? Manuscript in preparation.

Ansari, D., Donlan, C., Thomas, M. S. C., Ewing, S. A., Peen, T., & Karmiloff-Smith, A. (2003). What makes counting count? Verbal and visuo-spatial contributions to typical and atypical number development. *Journal of Experimental Child Psychology*, *85*, 50–62.

Antonarakis, S. E. (1991). Parental origin of the extra chromosome in trisomy 21 as indicated by analysis of DNA polymorphisms. *New England Journal of Medicine*, *324*, 872–876.

Baughman, F. D., & Thomas, M. S. C. (2008). Specific impairments in cognitive development: A dynamical systems approach. In B. C. Love., K. McRae, and V. M. Sloutsky, (Eds.), *Proceedings of the 30th Annual Conference of the Cognitive Science Society* (pp. 1819–1824). Austin, TX: Cognitive Science Society.

Benton, A., Hamsher, K., Varney, N. R., & Spreen, O. (1983). *Benton test of facial recognition*. New York: Oxford University Press.

Brock, J. (2007). Language abilities in Williams syndrome: a critical review. *Development and Psychopathology*, *19*, 97–127.

Carey, S., & Diamond, R. (1977). From piecemeal to configurational representation of faces. *Science*, *195*(4275), 312–314.

Carlesimo, G. A., Marotta, L., & Vicari, S. (1997). Long-term memory in mental retardation: evidence for a specific impairment in subjects with Down's syndrome. *Neuropsychologia*, *35*, 71–79.

Caronna, E. B., Milunsky, J. M., & Tager-Flusberg, H. (2008). Autism spectrum disorders: Clinical and research frontiers [review]. *Archives of Disease in Childhood*, *93*, 518–523.

Chapman, N. H., Igo, R. P., Thomson, J. B., Matsushita, M., Brkanac, Z., & Holzman, T., et al., (2004). Linkage analyses of four regions previously implicated in dyslexia: Confirmation of a locus on chromosome 15q. *American Journal of Genetics part B: Neuropsychiatric Genetics*, *131*, 67–75.

Deruelle, C., Mancini, J., Livet, M., Cassé-Perrot, C., & de Schonen, S. (1999). Configural and local processing of faces in children with Williams syndrome. *Brain and Cognition*, *41*, 276–298.

Donnai, D., & Karmiloff-Smith, A. (2000). Williams syndrome: From genotype through to the cognitive phenotype. *American Journal of Medical Genetics: Seminars in Medical Genetics*, *97*, 164–171.

Dunn, L. M., Whetton, C., & Burley, J. (1997). *British Picture Vocabulary Scale II.* Windsor, UK: NFER-Nelson.

Elliot, C. D. (2007). Differential Ability Scales-II (DAS-II)San Antonio, TX: Pearson.

Elliot, C. D., Smith, P., & McCulloch, K. (1997). *British Ability Scales Second Edition (BAS II).* London: NFER-Nelson.

Elman, J. L., Bates, E. A., Johnson, M. H., Karmiloff-Smith, A., Parisi, D., & Plunkett, K. (1996). *Rethinking innateness: A connectionist perspective on development.* Cambridge, MA: MIT Press.

Farran, E. K., & Jarrold, C. (2003). Visuo-spatial cognition in Williams syndrome; Reviewing and accounting for the strengths and weaknesses in performance. *Developmental Neuropsychology*, *23*, 175–202.

Fowler, A. (1990). Language abilities in children with Down syndrome: Evidence for a specific syntactic delay. In D. Cicchetti, and M. Beeghly, (Eds.), *Down Syndrome: A Developmental Perspective* (pp. 302–328). Cambridge, UK: Cambridge University Press.

Gayán, J., & Olson, R. K. (2001). Genetic and environmental influences on orthographic and phonological skills in children with reading disabilities. *Developmental Neuropsychology*, *20*, 483–507.

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., & Zijdenbos, A., et al., (1999). Brain development during childhood and adolescence: A longitudinal MRI study. *Nature Neuroscience*, *2*, 861–863.

Gogtay, N. (2008). Cortical brain development in schizophrenia: Insights from neuroimaging studies in childhood-onset schizophrenia. *Schizophrenia Bulletin*, *34*, 30–36.

Grant, K. W., & Seitz, P. F. (2000). The use of visible speech cues for improving auditory detection of spoken sentences. *Journal of the Acoustical Society of America*, *108*(3), 1197–1208.

Grice, S. J., Spratling, M. W., Karmiloff-Smith, A., Halit, H., Csibra, G., & de Haan, M., et al., (2001). Disordered visual processing and oscillatory brain activity in autism and Williams syndrome. *NeuroReport*, *12*, 2697–2700.

Jarrold, C., Baddeley, A. D., & Hewes, A. K. (1999). Genetically dissociated components of working memory: Evidence from Down's and Williams syndrome. *Neuropsychologia*, *37*, 637–651.

Johnson, S. C., & Carey, S. (1998). Knowledge enrichment and conceptual change in folkbiology: Evidence from Williams syndrome. *Cognitive Psychology*, *37*, 156–200.

Karmiloff-Smith, A. (1998). Development itself is the key to understanding developmental disorders. *Trends in Cognitive Sciences*, *2*, 389–398.

Karmiloff-Smith, A., & Thomas, M. S. C. (2003). What can developmental disorders tell us about the neurocomputational constraints that shape development? The case of Williams syndrome. *Development and Psychopathology*, *15*, 969–990.

Karmiloff-Smith, A., Thomas, M., Annaz, D., Humphreys, K., Ewing, S., & Brace, N., et al., (2004). Exploring the Williams syndrome face processing debate: The importance of building developmental trajectories. *Journal of Child Psychology and Psychiatry*, *45*, 1258–1274.

Knowland, V. C. P., Dick, F., Karmiloff-Smith, A., & Thomas, M. S. C. (in preparation). *Audio-visual integration and developmental disabilities in reading*. Manuscript in preparation.

Koshino, H., Kana, R. K., Keller, T. A., Cherkassky, V., Minshew, N., & Just, M. A. (2008). fMRI investigation of working memory for faces in autism: Visual coding and underconnectivity with frontal areas. *Cerebral Cortex*, *18*, 289–300.

Mareschal, D., & Thomas, M. S. C. (2007). Computational modeling in developmental psychology. *IEEE Transactions on Evolutionary Computation (Special Issue on Autonomous Mental Development)*, *11*(2), 137–150.

Mervis, C. B., & Bertrand, J. (1997). Developmental relations between cognition and language: Evidence from Williams syndrome. In L. B. Adamson, and M. A. Romski, (Eds.), *Research on communication and language disorders: Contributions to theories of language development* (pp. 75–106). New York: Brookes.

Mervis, C. B., Robinson, B. F., Bertrand, J., Morris, C. A., Klein-Tasman, B. P., & Armstrong, S. C. (2000). The Williams syndrome cognitive profile. *Brain and Cognition*, *44*, 604–628.

Meyer-Lindenberg, A., Kohn, P., Mervis, C. B., Kippenhan, S., Olsen, R. K., & Morris, C. A., et al., (2004). Neural basis of genetically determined visuospatial construction deficit in Williams syndrome. *Neuron*, *43*, 623–631.

Meyer-Lindenberg, A., Mervis, C. B., & Berman, K. F. (2006). Neural mechanisms in Williams syndrome: a unique window to genetic influences on cognition and behaviour. *Nature Reviews Neuroscience*, 7, 379–392.

Mills, D., Alvarez, T., St. George, M., Appelbaum, L., Bellugi, U., & Neville, H. (2000). Electrophysiological studies of face processing in Williams syndrome. *Journal of Cognitive Neuroscience*, *12*(Suppl.), 47–64.

Mobbs, D., Garrett, A. S., Menon, V., Rose, F. E., Bellugi, U., & Reiss, A. L. (2004). Anomalous brain activation during face and gaze processing in Williams syndrome. *Neurology*, *62*, 2070–2076.

Monaco, A. P. (1996). Human genetics: Dissecting Williams syndrome. *Current Biology*, *6*(11), 1396–1398.

Mondloch, C. J., Le Grand, R., & Maurer, D. (2002). Configural face processing develops more slowly than featural face processing. *Perception*, *31*, 553–566.

Paterson, S. J., Brown, J. H., Gsodl, M. K., Johnson, M. H., & Karmiloff-Smith, A. (1999). Cognitive modularity and genetic disorders. *Science*, *286*, 2355–2358.

Pilling, M. (2009). Auditory event-related potentials (ERPs) in audiovisual speech perception. *Journal of Speech, Language and Hearing Research*, *52*, 1073–1081.

Pinker, S. (1994). *The Language instinct*. London: Penguin books.

Pinter, J. D., Eliez, S., Schmitt, J. E., Capone, G. T., & Reiss, A. L. (2001). Neuroanatomy of Down Syndrome. A high resolution MRI study. *American Journal of Psychiatry*, *158*, 1659–1665.

Poll, G. (in press). Increasing the odds: Applying emergentist theory in language intervention. *Language, Speech, and Hearing Services in Schools*.

Purser, H. R. M., Thomas, M. S. C., Snoxall, S., Mareschal, D., & Karmiloff-Smith, A. (2010). 2012, (in press). Definitions versus categorisation: Assessing the development of lexico-semantic knowledge in Williams syndrome. *International Journal of Language and Communication Disorders*, eprint ahead of publishing: Posted online on August 18, 2010. (doi:10.3109/13682822.2010.497531).

Redcay, E., & Courchesne, E. (2005). When is the brain enlarged in autism? A meta-analysis of all brain size reports. *Biological Psychiatry*, *58*, 1–9.

Reiss, A. L., Eckert, M. A., Rose, F. E., Karchemskiy, A., Kesler, S., & Chang, M et al., (2004). An experiment of nature: brain anatomy parallels cognition and behavior in Williams Syndrome. *The Journal of Neuroscience*, *24*(21), 5009–5015.

Reiss, A., Eliez, S., Schmitt, E., Straus, E., Lai, Z., & Jones, J., et al., (2000). Neuroanatomy of Williams Syndrome: A high-resolution MRI study. *Journal of Cognitive Neuroscience*, *12*, 65–73.

Roizen, N. J., & Patterson, D. (2003). Down's syndrome. *Lancet*, *36*, 1281–1289.

Schumacher, J., Hoffman, P., Schmal, C., Schulte-Korne, G., & Nothen, M. (2007). Genetics of dyslexia: The evolving landscape. *Journal of Medical Genetics*, *44*, 289–297.

Searcy, Y. M., Lincoln, A. J., Rose, F. E., Klima, E. S., Bavar, N., & Korenberg, J. R. (2004). The relationship between age and IQ in adults with Williams syndrome. *American Journal on Mental Retardation*, *109*, 231–236.

Semel, E., & Rosner, S. R. (2003). *Understanding Williams syndrome: Behavioral patterns and interventions*. Mahwah, NJ: Lawrence Erlbaum Associates, Publishers.

Shah, A., & Frith, U. (1983). An islet of ability in autistic children. *A research note, Journal of Child Psychology and Psychiatry*, *24*, 213–220.

Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J. P., & Greenstein, D. K et al., (2007). Attention deficit/hyperactivity disorder is characterised by a delay in cortical maturation. *Proceeding from the National Academy of Sciences of the United States of America*, *104*, 19649–19654.

Shaw, P., Gotgay, N., & Rapoport, J. (2010). Childhood psychiatric disorders as anomalies in neurodevelopmental trajectories. *Human Brain Mapping*, *31*, 917–925.

Schopler, E., Reichler, R., & Rochen, B. (1993). *The childhood autism rating scale*. Los Angeles: Western Psychological Services.

Sirois, S., Spratling, M., Thomas, M. S. C., Westermann, G., Mareschal, D., & Johnson, M. H. (2008). Précis of neuroconstructivism: How the brain constructs cognition. *Behavioral and Brain Sciences*, *31*, 321–356.

Sperling, A. J., Lu, Z. L., Manis, F. R., & Seidenberg, M. S. (2005). Deficits in perceptual noise exclusion in developmental dyslexia. *Nature Neuroscience*, *8*, 862–863.

Sperling, A. J., Lu, Z. L., Manis, F. R., & Seidenberg, M. S. (2006). Motion-perception deficits and reading impairment. *Psychological Science*, *17*, 1047–1053.

Tassabehji, M. (2003). Williams–Beuren syndrome: A challenge for genotype–phenotype correlations. *Human Molecular Genetics*, *15*, 229–237.

Tassabehji, M., Hammond, P., Karmiloff-Smith, A., Thompson, P., Thorgeirsson, S. S., & Durkin, M. E., et al., (2005). GTF2IRD1 in craniofacial development of humans and mice. *Science*, *310*, 1184–1187.

Thomas, M. S. C. (2005a). Plotting the causes of developmental disorders. *Trends in Cognitive Sciences*, *9*(10), 465–466.

Thomas, M. S. C. (2005b). Constraints on language development: Insights from developmental disorders. In P. Fletcher, and J. Miller, (Eds.), *Language disorders and developmental theory* Philadelphia, PA: John Benjamins.

Thomas, M. S. C. (2005 c). Characterising compensation. *Cortex*, *41*(3), 434–442.

Thomas, M. S. C. (2006). Williams syndrome: Fractionations all the way down? *Cortex*, *42*, 1053–1057.

Thomas, M. S. C., Annaz, D., Ansari, D., Serif, G., Jarrold, C., & Karmiloff-Smith, A. (2009). Using developmental trajectories to understand developmental disorders. *Journal of Speech, Language, and Hearing Research*, *52*, 336–358.

Thomas, M. S. C., Karaminis, T. N., & Knowland, V. C. P. (2010). What is typical language development? *Language, Learning & Development*, *6*, 162–169.

Thomas, M. S. C., & Karmiloff-Smith, A. (2002). Are developmental disorders like cases of adult brain damage? Implications from connectionist modelling. *Behavioral and Brain Sciences*, *25*(6), 727–788.

Thomas, M. S. C., & Karmiloff-Smith, A. (2003). Modeling language acquisition in atypical phenotypes. *Psychological Review*, *110*(4), 647–682.

Thomas, M. S. C., Knowland, V. C. P., & Karmiloff-Smith, A. (submitted). Explaining the mechanisms of developmental regression in autism and the broader phenotype: A neural network modelling approach. Manuscript submitted for publication.

Thomas, M. S. C., Knowland, V. C. P., & Karmiloff-Smith, A. (in press). What causes variability in the severity of developmental disorders? A neurocomputational account using the example of developmental regression in autism. In E. Davelaar (Ed.), *Proceedings of the 12th Neural Computation and Psychology Workshop.* World Scientific.

Udwin, O., & Yule, W. (1991). A cognitive and behavioural phenotype in Williams syndrome. *Journal of Clinical and Experimental Neuropsychology*, *13*, 232–244.

Van Wassenhove, V., Grant, K., & Poepel, D. (2005). Visual speech speeds up the processing of auditory speech. *Proceeding of the National Academy of Sciences of the United States of America*, *102*(4), 1181–1186.

Virsu, V., Lahti-Nuuttila, P., & Laasonen, M. (2002). Crossmodal temporal processing acuity impairment aggravates with age in developmental dyslexia. *Neuroscience Letters*, *336*, 151–154.

Wang, P. P. (1996). A neuropsychological profile of Down syndrome: Cognitive skills and brain morphology. *Mental Retardation and Developmental Research Reviews*, *2*, 102–108.

Wang, P. P., & Bellugi, U. (1994). Evidence from two genetic syndromes for a dissociation between verbal and visual-spatial short-term memory. *Journal of Clinical Experimental Neuropsychology*, *16*, 317–322.

Westermann, G., Mareschal, D., Johnson, M. H., Sirois, S., Spratling, M. W., & Thomas, M. S. C. (2007). *Neuroconstructivism. Developmental Science*, *10*(1), 75–83.

Westermann, G., Thomas, M. S. C., & Karmiloff-Smith, A. (2010). Neuroconstructivism. In U. Goswami (Ed.), *Handbook of Childhood Cognitive Development, Second edition. (pp. 723–748). Oxford, UK: Wiley-Blackwell.*

Williams, K. R., Wishart, J. G., Pitcairn, T. K., & Willis, D. S. (2005). Emotion recognition by children with Down syndrome: Investigation of specific impairments and error profiles. *American Journal on Mental Retardation*, *110*, 378–392.

Wishart, J. G., Cebula, K. R., Willis, D. S., & Pitcairn, T. K. (2007). Understanding of facial expressions of emotion by children with intellectual disabilities of differing aetiology. *Journal of Intellectual Disability Research*, *51*, 552–563.

Wishart, J. G., & Pitcairn, T. K. (2000). The recognition of identity and expression in faces by children with Down syndrome. *American Journal of Mental Retardation*, *105* (6), 466–479.

Ziegler, A., König, I. R., Deimel, W., Plume, E., Nothen, M., & Propping, P., et al., (2005). Developmental dyslexia—Recurrence risk estimates from a German bi-center study using the single prob and sib pair design. *Human Heredity*, *59*, 136–143.

Ziegler, J. C., Pech-George, C., George, F., & Lorenzi, C. (2009). Speech perception in-noise deficits in dyslexia. *Developmental Science*, *12*, 732–745.