

Chapter for *The Oxford Handbook of Down Syndrome and Development*

The Emerging Phenotype in Infants with Down Syndrome: Adaptations to Atypical Constraints

Hana D'Souza^{1,2} & Dean D'Souza³

¹Department of Psychology & Newnham College, University of Cambridge, Cambridge, UK

²School of Psychology, Cardiff University, Cardiff, UK

³Department of Psychology, City, University of London, London, UK

Address for correspondence: Hana D'Souza, Newnham College, University of Cambridge, Sidgwick Avenue, Cambridge, CB3 9DF, United Kingdom

E-mail: hd425@cam.ac.uk / dsouzah@cardiff.ac.uk

Reference:

D'Souza, H., & D'Souza, D. (in press). The emerging phenotype in infants with Down syndrome: Adaptations to atypical constraints. In J. Burack, J. Edgin, & L. Abbeduto (Eds.), *The Oxford Handbook of Down Syndrome and Development*. Oxford University Press. <https://doi.org/10.1093/oxfordhb/9780190645441.001.0001>

Abstract

The aim of this chapter is not just to present a selection of literature on early development in Down syndrome (DS), but to integrate findings from across disciplines within an overarching approach or framework. The approach we take is to view DS not as a collection of cognitive and motor deficits, nor as an assortment of relative strengths and weaknesses, but as a *functioning adaptive system albeit with a different start state (trisomy 21)*. According to this view, the emerging characteristics of DS are adaptations to atypical constraints, and thus serve an immediate functional purpose – but these early adaptations will in turn act as new developmental constraints, and some of them may exacerbate the divergence of the DS trajectories. In this chapter, we focus on the first few years after birth, because to understand how the DS phenotype gradually emerges, it is important to focus on early developmental constraints. We start by introducing DS as an adaptive system with trisomy 21, and how a developmental systems approach is needed to understand it. We continue by explaining how such an approach can be implemented in research. We then describe how trisomy 21 may constrain neural plasticity, which is likely to have cascading effects on the developmental process of specialization – contributing to less efficient information processing and atypical motor activity. We then discuss how young children with DS may adapt to these challenges within the context of the social environment. Finally, we point to future directions in theory, research, and intervention.

Keywords: Down syndrome, infancy, adaptive systems, developmental systems, neural plasticity, specialization, perception-action cycles, cognitive development, motor development, social development, intervention

Table of Contents

1	<i>Down syndrome: an adaptive system with a different start state</i>	5
2	<i>How to implement a developmental systems approach to study infants with DS</i>	9
3	<i>Trisomy 21 constrains neural plasticity</i>	11
4	<i>Neural plasticity constrains specialization</i>	16
5	<i>Specialization is driven by perception-action cycles</i>	20
5.1	Perceptual and attentional constraints on information sampling in infants with DS	20
5.2	Less efficient information processing in infants with DS	21
5.3	Less motor activity in infants with DS.....	24
6	<i>Perception-action cycles are embedded within social contexts</i>	30
6.1	Over-reliance on social agents as an adaptive strategy	30
6.2	Parental behaviour may matter more for infants with DS.....	33
7	<i>Future directions</i>	35
7.1	Embracing complexity	35
7.2	Diverging trajectories.....	40
7.3	Individual differences.....	41
7.4	Getting the interventions right.....	43
7.4.1	Behavioural interventions: Early enough? Intense enough?.....	44
7.4.2	Ready for pharmacological interventions?.....	46
8	<i>Conclusions</i>	47
9	<i>Acknowledgements</i>	48
10	<i>References</i>	48

“The study of Down’s syndrome has become a fractionated business, each discipline pressing exclusive views about mechanisms and management. The result has been a confusing array of books, pamphlets and technical articles about Down’s syndrome (close to 1000 published items to date on psychological matters alone) which mostly fail to enlighten.”

(Gibson, 1978, p. xi)

More than 40 years and over half a million academic papers and books later (Google Scholar), there seems to be an exponential tendency to review and meta-analyse findings in the Down syndrome (DS) field.¹ There is also growing recognition that DS is a multilevel, multisystem, neurodevelopmental disorder which needs to be understood by collating empirical findings across disciplines and across the lifespan (e.g., D’Souza, D’Souza, et al., 2017; D’Souza & Karmiloff-Smith, 2017). However, in order to understand these findings and move forward, it is necessary to cohere them into a single developmental story.

The aim of this chapter is not just to present a selection of the vast literature on DS, but to provide some clarity by integrating findings from across disciplines within an overarching approach or framework. The approach we take is to view DS not as a collection of cognitive and motor deficits, nor as an assortment of relative strengths and weaknesses, but as a *functioning adaptive system albeit with a different start state (trisomy 21)*. According to this view, the emerging characteristics of DS are adaptations to atypical constraints, and thus serve a functional purpose – and constrain later emerging skills. We focus on the first few years after birth, because to understand how the DS phenotype gradually emerges, it is

¹ In the past few years alone, there have been many reviews and meta-analyses in the DS field on topics such as paediatric brain development (Hamner et al., 2018), functional magnetic resonance imaging (fMRI) (Carbó-Carreté et al., 2020), the infant foundations of cognition (Fidler, Needham, et al., 2019), joint attention (Hahn et al., 2018), physical therapy (Ruiz-González et al., 2019), and memory (Godfrey & Lee, 2018), as well as a more general primer on DS (Antonarakis et al., 2020) and numerous reviews on neurobiological research and its implications for therapy (e.g., Lee et al., 2020; Stagni et al., 2018; Vacca et al., 2019; see also the collection edited by Dierssen, 2020).

important to focus on early developmental constraints (D'Souza & Karmiloff-Smith, 2016). We start by introducing DS as an adaptive system with trisomy 21, and how a developmental systems approach is needed to understand it. We continue by explaining how such an approach can be implemented in research. We then describe how trisomy 21 may constrain neural plasticity, which is likely to have cascading effects on the developmental process of specialization – contributing to less efficient information processing and atypical motor activity. We discuss how a young child may adapt to these challenges within their social environment. Finally, we point to future directions in theory, research, and intervention.

1 Down syndrome: an adaptive system with a different start state

Although the characteristics of DS vary across individuals in number and intensity (Dykens & Hodapp, 2001; Karmiloff-Smith et al., 2016), a widely accepted profile of DS has been described. In addition to general intellectual disability, the profile includes particular difficulties in motor ability, auditory processing, verbal short-term memory, and language ability (especially expressive language; e.g., Miller & Leddy, 1999); relative strengths in visuospatial processing and some aspects of social functioning (e.g., Cebula et al., 2010; Jarrold & Baddeley, 1997; Wishart & Johnston, 1990); and atypical motivation (Pitcairn & Wishart, 1994). However, most of what we know about this DS profile comes from studies of older children and adults. Yet, the DS profile only gradually *emerges* over developmental time (e.g., Fidler, 2005; Fidler et al., 2008; Will et al., 2018). Studying infants with DS therefore affords a window onto this process.

Because DS is diagnosed by genetic testing, it is tempting to assume that the emergence of the DS phenotype—with its loose assemblage of relative strengths and weaknesses—is under the control of *genetic* activity (e.g., trisomy 21). However, there is now ample evidence that control is distributed among multiple, diverse, interconnected, and

interdependent factors, many of which are external to the individual (for discussion, see D'Souza, D'Souza, et al., 2017). Therefore, DS is not a static *disorder* with deficits and areas of relative strengths, but an *adaptive system* with a different *start state*. Adaptive systems comprise manifold interdependent parts, which develop and give rise to new structures and functions by actively *adapting* to their environment. Each adaptive system begins from a slightly different start state, has a separate set of experiences, and thus develops different behaviours. But the behaviour of these systems, including those with trisomy 21, are *adaptations* – developmental processes in which the system maximizes its fit to the environment under internal and external constraints (Johnson, 2017). Moreover, while internal/external factors (e.g., genes) influence developmental processes, developmental processes (e.g., neural reorganisation) constrain the factors (e.g., genetic expression). In other words, development is produced by interacting factors across various levels (Fig. 1).

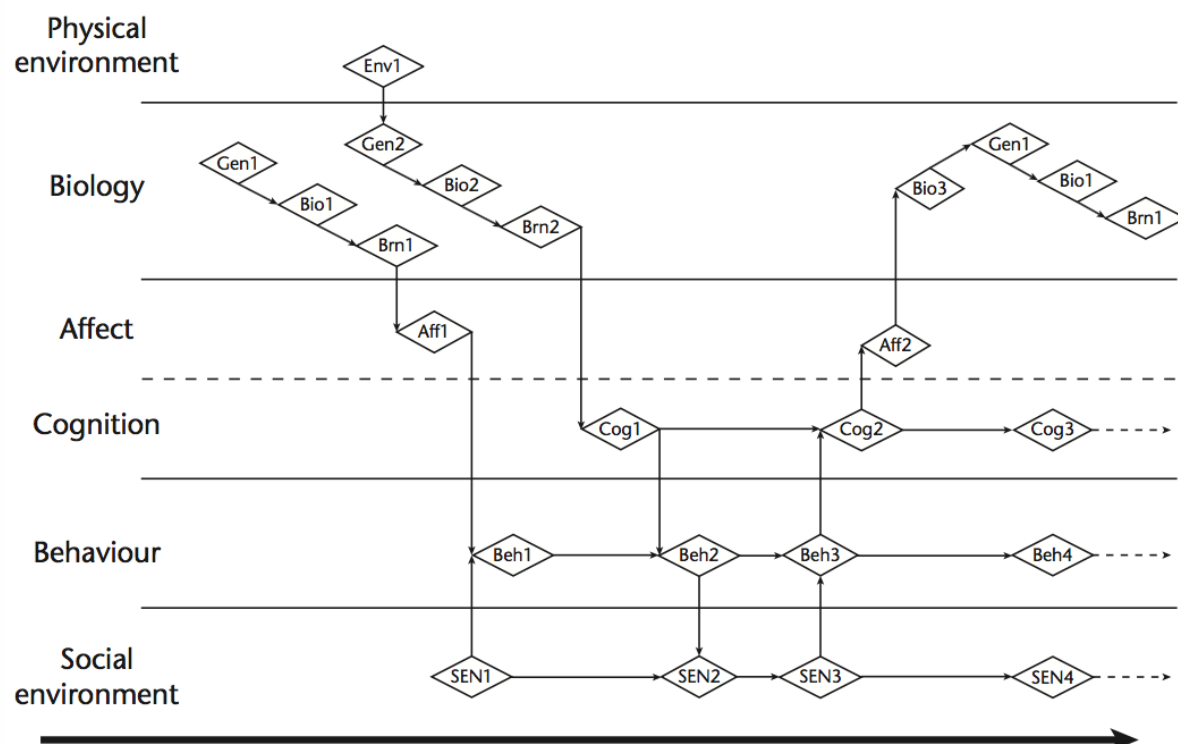


Figure 1. Illustration of cascading effects and the complexity of development across time (x-axis). Horizontal arrows = trajectories within a domain of functioning; diagonal arrows = causal pathways within levels of functioning; vertical arrows = effects between levels of functioning. Adapted from Moore & George (2015). Reproduced by permission of Taylor and Francis Group, LLC, a division of Informa plc.

Take language, for example. If language development were under the control of genetic activity and pre-programmed, then we would expect that damage to classic language areas in the brain would cause irrecoverable damage to the language system (see D'Souza & Karmiloff-Smith, 2011, 2016, for discussion). However, if control is distributed and language development is probabilistic, then we might expect that an adaptive system would have the flexibility to compensate for the injury. And, indeed, this is what seems to be the case; the literature is replete with examples of children with perinatal left-hemisphere brain damage who nevertheless acquire important age-appropriate language skills (e.g., Bates et al., 2001; see D'Souza & Karmiloff-Smith, 2016, for discussion). By the same token, in DS, language development has been shown to be a highly complex process that is contingent on multiple components, including nonverbal communication skills, motor skills, attentional abilities, face scanning, sleep, verbal short-term memory, visuospatial short-term memory, and family context (e.g., Chapman & Hesketh, 2001; D'Souza et al., 2015; D'Souza, D'Souza, Horváth, et al., 2020; D'Souza, D'Souza, Jones, et al., 2020; D'Souza, Lathan, Karmiloff-Smith, et al., 2020; Deckers et al., 2019; Edgin et al., 2015; Martin et al., 2009; Mason-Apps et al., 2018; Mundy et al., 1995).

The DS phenotype therefore seems to emerge through a cascade of interconnected and interdependent effects, which may reflect a more probabilistic than deterministic process (Gottlieb, 2007). According to this 'developmental systems'² perspective:

(1) At conception, the organism 'inherits' a wide range of interacting resources

(genes, chromatin marks, endosymbionts, nutrients, a family, society, etc. – the

² Like Ulrich (2010), we (e.g., D'Souza & D'Souza, 2019) use the phrase 'developmental systems' to refer to a cluster of (non-nativist) perspectives that share some (or all) of the core tenets of 'developmental systems theory' (Ford & Lerner, 1992; Oyama, 1985; Oyama et al., 2001) and that view neurocognitive and motor development as the emergent functions of a complex adaptive system constrained by an intricate web of interactions between manifold factors (Blumberg, 2017). These perspectives include connectionism (Bates et al., 1996; McClelland & Vallabha, 2009; Rosenblatt, 1958), dynamic systems theory (Thelen, 1992; Thelen & Smith, 1994), and neuroconstructivism (Westermann et al., 2007).

‘start state’), which affect, and are affected by, the infant’s development (Oyama, 1985).

- (2) The infant learns and develops through the *active* process of adapting its internal connectivity to the metrics of the external world (Buzsáki, 2006). Action is therefore at the heart of learning and development. It is an interactive process through which the conditions of the external world are also altered.
- (3) Neurocognitive and motor processes are not the sole products of our genes, but emerge through self-organized interactions among multiple factors (e.g., between the child and physical environment) across various levels (e.g., genes, brain, family, society) (Gottlieb, 1992; Lerner, 1978; also see Fig. 1).
- (4) Development is progressive; structures and systems that emerge at one point in time may constrain later-emerging structures and systems (Gottlieb, 1970, 2001). Hence, it is important to study constraints and adaptations early in development in order to understand later developmental processes.
- (5) Because development involves the interaction of diverse, interdependent factors over multiple timescales, it can be nonlinear (Buzsáki, 2004; McClelland & Vallabha, 2009; Rosenblatt, 1958; Schöner & Kelso, 1988). That is, small perturbations may result in large cascading effects, and large perturbations may have little or no effect on the developing system.

In other words, development is constrained (i.e., context-dependent and time-sensitive) and involves an active process of adapting to typical and atypical constraints. An understanding of how the DS phenotype emerges, therefore, necessitates an understanding of how the system adapts to constraints across time, and especially to constraints in early development, as these early adaptations may constrain the emergence of later adaptations.

2 How to implement a developmental systems approach to study infants with DS

Although the principles of developmental systems are widely acknowledged, they are not often reflected in our current research practices. This is not surprising given the complexity of human development. How might we go about implementing a developmental systems approach in our research practice? On the practical side, we need to collect large datasets and use advanced analytical techniques to reveal the patterns concealed within (*big data*). This requires time, resources, and the opportunity to test many participants many times and over many timescales (from moment-to-moment to longitudinally). But big data is not sufficient. Identifying patterns, trends, and associations is an important step, but it does not elucidate how emergent dynamics (e.g., object exploration) arise from the underlying mechanistic dynamics (e.g., neuronal firing). An interdisciplinary approach is needed to integrate the data in order to understand how the whole system functions and develops. This is because different levels of description (genetic, neural, behavioural, societal, etc.; see Fig. 1) constrain each other. For example, the firing of a neuron is partly constrained by activity at the genetic level (gene expression), while the expression of a gene in a neuron is partly constrained by the firing pattern of that neuron (Flavell & Greenberg, 2008; Leslie & Nedivi, 2011; Tyssowski et al., 2018). Causality thus appears to be multidirectional and distributed across levels in complex systems. Therefore, it is important to study interactions *between* levels, rather than each level in isolation.

How can we piece together the many interactions that occur across different timescales both within and between different levels? We need to bring together different methodologies which have been applied to the DS field: neurobiological methods (including animal modelling, induced pluripotent stem cells (iPSC) research, and post-mortem histology), human brain imaging, cognitive and behavioural experiments, observational studies, and computational modelling. Each method has its strengths and weaknesses. A

range of cutting-edge techniques can be used to probe mechanistic pathways by manipulating variables such as gene expression. However, these tend to involve mouse models or human cells that have been developed in a lab environment. They may therefore generate findings that are not directly applicable to humans and need to be interpreted with caution. On the other hand, a number of methods can be used directly with humans, but for ethical reasons these rarely involve manipulations that elucidate mechanistic causes. It is therefore challenging—perhaps even impossible—to investigate different levels of description using a single method or a single population in order to understand how levels interact and what processes give rise to the DS phenotype. But it is possible to piece together evidence from different studies, disciplines, and techniques, capitalizing on their different strengths. And it is only through converging evidence (consilience) that we can begin to make sense of the field.

In this chapter, we try to bind evidence from different levels into a coherent developmental story. This will mean that parts of this chapter will be suggestive rather than explicit, based on tentative rather than conclusive pieces of evidence. But these parts are far from trivial. We include them because they highlight links between levels that need exploring. Our hope is that binding evidence from different disciplines may help us to grasp the bigger picture and/or generate new hypotheses. We focus on the first few years after birth in DS because in order to understand how the DS phenotype gradually emerges, it is important to focus on early developmental constraints (see D'Souza, D'Souza, et al., 2017, for discussion). Of course, it would be interesting to study developmental trajectories from the earliest moment, from conception. But practical and technological limitations currently make it very difficult to study and integrate information on the different levels prenatally. Thus, we offer a compromise. In this chapter, we seek to link information from different levels at the earliest possible time in development that we believe this can currently be attempted: *infancy*.

We start at the level of the genes (because DS is diagnosed on this level) and then move ‘up’ the levels of organisation. It is important to note that this does not mean that the genetic level is more fundamental or important than the ‘higher’ levels (the word ‘hierarchy’ is a misnomer in this context).³ Another crucial point is that our use of the words ‘hierarchy’ and ‘levels’ do not imply unidirectional causality; the different levels constrain each other. Causality is distributed and multidirectional, and organisms adapt to the world through the feedback they receive from acting on it.

3 Trisomy 21 constrains neural plasticity

The genetics and neurobiology of DS have been extensively reviewed elsewhere (e.g., Dierssen, 2020; Stagni et al., 2018; Vacca et al., 2019). Here we focus on connections *between* the different levels of description to understand how they constrain each other. The start state of DS includes the presence of a partial or complete triplication of chromosome 21 (trisomy 21) (Reeves et al., 2001). Although chromosome 21 is the smallest human chromosome, making up only 1.5% of the human genome (Dierssen, 2012), the extra chromosome contributes to diffuse, widespread, and cascading atypicalities in brain and cognitive development. Not every gene on chromosome 21 is overexpressed in DS (Antonarakis, 2017), but dysregulation of genes such as *DYRK1A*, *APP*, *OLIG1*, *OLIG2*, and *RUNX1* is known to constrain cortical development (Sobol et al., 2019). For example, *DYRK1A* is involved in the production of an enzyme that regulates proteins involved in cell proliferation and differentiation (which, after cell migration, results in an accumulation of neurons in cerebral cortex by 20-21 weeks gestation) (Nakano-Kobayashi et al., 2017; Park et al., 2009; Stagni et al., 2016). This process is atypical in DS. For example, cell proliferation

³ We could have used the word ‘scales’ instead of ‘levels’, from small (genes) to large (society). We only use the word ‘levels’ because it is a familiar term and one could argue that structures such as the brain and society emerge from more basic layers of organisation such as atoms and molecules.

is reduced (Guidi et al., 2011; Larsen et al., 2008). Whereas typically developing (TD) fetuses at 19 weeks gestation were found to have ~10.4 billion neocortical cells (neurons and glia), fetuses with DS at 19 weeks gestation had only ~6.85 billion (Larsen et al., 2008). Moreover, neural progenitor cells in DS are less likely to acquire a neuronal phenotype and more likely to acquire an astrocytic phenotype (Stagni et al., 2018). More astrocytes in DS are likely to exacerbate overexpression of a gene located on chromosome 21 (*S100B*) whose product (the S100B protein) is secreted by astrocytes, and which, unless suppressed, impairs neurogenesis and induces neuronal cell death in DS (Chen et al., 2014). Consequently, the brain in DS develops both fewer neocortical cells than the TD brain and fewer neurons relative to overall brain cells (Stagni et al., 2018).

The DYRK1A enzyme is also involved in regulating proteins that form dendrites and dendritic spines (neuronal outgrowths that enable the neuron to receive signals from other neurons) (Park et al., 2009). Infants with DS present with spine dysmorphology and have less dendritic arborization and fewer dendrites/spines than TD infants (Becker et al., 1986; Benavides-Piccione et al., 2004; Purpura, 1975; Takashima et al., 1981; Wisniewski & Schmidt-Sidor, 1989). The abnormalities in spine morphology and cell proliferation may explain another finding: cortical lamination (the 7- to 10-week-long process through which the cortical neurons rearrange to form layers) is delayed and atypical in DS, and several cortical areas show underdeveloped gyral patterns (Golden & Hyman, 1994).

In sum, the altered expression of genes on chromosome 21 has cascading effects on brain development, including cell development and cortical organization (for summary, see Fig. 2). While the impact of the atypicalities in cortical lamination on the developing system is unclear, fewer dendritic spines should result in less input from other neurons, which, in combination with fewer neurons, would lead to reduced neural signalling. Fewer dendritic spines may also contribute to inhibitory predominance. For instance, while the most common

neurons (*principal cells*) excite each other via dendrites and dendritic spines, one family of neurons (*interneurons*) often control (inhibit) the activity of principal cells by targeting the cell body – i.e., bypassing dendrites and spines (Buzsáki, 2006). Interneurons may therefore have more influence on brain function in DS. Indeed, there is evidence of increased inhibitory (relative to excitatory) activity in mouse models of DS (for a review, see Contestabile et al., 2017).

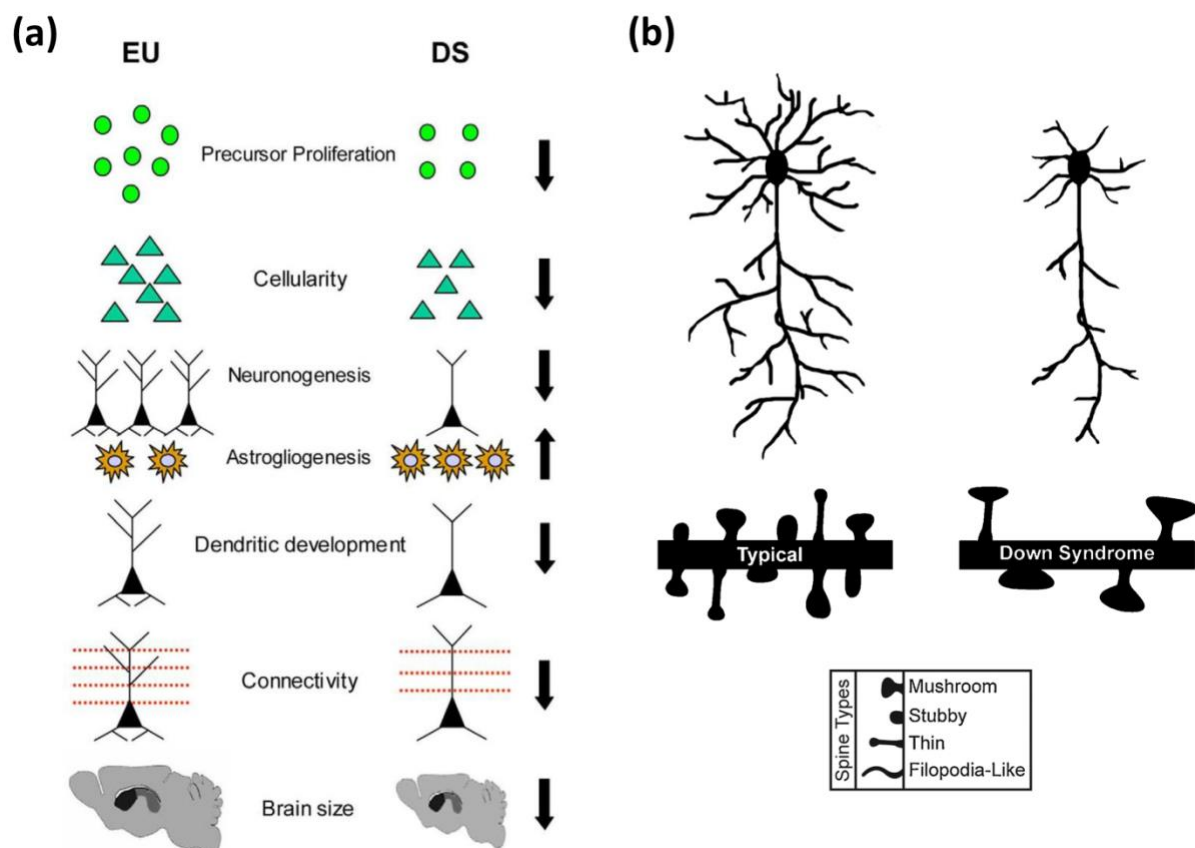


Figure 2. (a) Compared to typical development (EU = euploid mouse), a mouse model of DS (Ts65Dn) shows impairment in proliferation, reduced cellularity, decreased neurogenesis, increased astroglialogenesis, dendritic hypotrophy, reduced connectivity, and reduced brain size (as indicated by up/down arrows). Adapted from Bartesaghi et al. (2015); (b) Schematic representation of a neuron depicting atrophies in dendrite morphology in brains of individuals with DS (right) compared to TD individuals (left). Adapted from Kulkarni & Firestein (2012). The DS neuron contains fewer dendritic spines than the TD neuron. Also, dendritic spines in DS often have larger heads. Adapted from Phillips & Pozzo-Miller (2015). Image credit: Elsevier.

Inhibition is necessary for brain function. In its absence, sensory input generates similar widespread one-way patterns of activation (Buzsáki, 2006; Dichter & Ayala, 1987).

Interneurons can stabilise activity (through feedback loops), dampen activity (feedforward loops), and segregate activity (by suppressing the activity of some neurons and not others) (see Buzsáki, 2006, for discussion). However, brain function requires an appropriate balance between excitation and inhibition (Haider et al., 2006). Inhibitory predominance and reduced signalling in DS are likely to affect how the neurons in a system self-organise and optimize their functionality. To adapt to the world, neurons require some degree of flexibility (*plasticity*). They need to communicate with each other and connect to the external world in order to calibrate to it. Communication between neurons occurs via synapses between neurons, and most synapses are found on the neurons' dendritic spines. Synapses are thus the sites at which plasticity (learning) occurs at the level of the brain. As intimated above, learning involves both the flow of information (through excitatory connections) and control of that flow through inhibition to form coalitions or specialized subsystems of neurons. Plasticity enables the developing system to learn from and adapt to the environment, even in the face of extreme adversity such as brain injury. However, if neural communication in DS is constrained by lack of synaptic resources and over-inhibition, then flexibility (*synaptic plasticity*) and the ability of the system to adapt will be compromised (Buzsáki, 2006; see also Singer et al., 2019).

For learning to have a long-lasting effect (i.e., to be adaptive in the long term), it needs to be consolidated within the system. In the human brain, this process requires molecular and cellular stabilizing mechanisms. These stabilizing mechanisms include homeostatic negative feedback mechanisms (*homeostatic plasticity*) that are sensitive to, and regulate, the level of neural excitability (Turrigiano & Nelson, 2004). In this way, excitatory connections may lead to structural changes in post-synaptic material (e.g., dendritic spines) that are subsequently stabilized by genetic and molecular activity that is, in part, facilitated by inhibitory connections. We therefore speculate that inhibitory predominance in DS results

in over-regulation of neural excitability, further increasing the excitatory-inhibitory (E/I) imbalance and reducing the plasticity of the brain, and thus its capacity to adapt to the external world. This is consistent with the findings of a study that used single-cell-resolution intravital microscopy to monitor cortical tissue grafts derived from the skin fibroblasts of two individuals with DS (Real et al., 2018). Real and colleagues had reprogrammed the fibroblasts in vitro to form induced pluripotent stem cells (iPSCs), which were then differentiated into cortical neurons, labelled with fluorescent proteins (markers), and transplanted into the brains of mice. Longitudinal in vivo imaging of the markers revealed increased synaptic stability and reduced functional neural network activity (less oscillatory activity) in the DS neurons than in disomic clones without the extra copy of chromosome 21 (Real et al., 2018). Structural changes at the synapse were shown to be modifiable in three different DS mouse models (Tg, Ts65Dn, Dp1Yey) by inhibiting DYRK1A activity, which was associated with improved learning and memory (Nguyen et al., 2018).

Although this section of the chapter has described paths that branch out from trisomy 21 and overexpression of the *DYRK1A* gene through fewer neurons and synapses to inhibitory dominance and reduced plasticity, these paths are not unidirectional. As explained in the previous section, DS is a complex *adaptive* system. This means that the system and components of the system are constantly in flux, adjusting to new conditions. For example, while there is an initial paucity of early born neurons, increased production of later-born neurons has been described in a Ts65Dn mouse model (Chakrabarti et al., 2007). This could be the result of adaptive processes. However, complex adaptive systems are also *path-dependent*. This means that the timing of interactions can impact the developmental trajectory of the system. By the time the extra neurons have thickened the neocortical wall, the sparse connections between the early-born neurons may already have affected the process of neocortical lamination, a process that relies on spontaneous neural activity and is observed to

be both delayed and disorganised in DS (Golden & Hyman, 1994). To further illustrate the complexity of development, like most (if not all) parts of a complex adaptive system, the role of interneurons is not fixed: it is context dependent. For example, the major inhibitory neurotransmitter in the adult brain, γ -Aminobutyric acid (GABA), often acts through the chloride-dependent GABA type A (GABA_A) receptor. Intracellular chloride concentration is high prenatally and only drops during neonatal life (Cherubini et al., 1991). This means that many interneurons are initially excitatory and only switch to an inhibitory role later in development. It is possible that because neocortical lamination requires spontaneous neural activity, prenatal brain development requires more excitatory connections than inhibitory connections, while postnatal brain development requires an increase in inhibitory control to prune connections and hone neural networks through postnatal experience. The relatively late upsurge of neurogenesis in DS may therefore thicken the cortex but not necessarily correct important differences in early E/I ratios. Moreover, the postnatal structure (and thus contribution) of the GABAergic interneuron changes through interactions with the external environment (Donato et al., 2013), which highlights the complex interplay between the various levels. In sum, the path from genes to neural networks is not unidirectional; the developmental trajectory of the system is constrained by manifold interactions across levels of description and timing.

4 Neural plasticity constrains specialization

What may reduced synaptic plasticity mean for infants with DS? Early in typical development, the brain is characterized by overproduction of unspecified synaptic connections (Bourgeois, 2008; Greenough et al., 1987). Thus, patterns of activation in the infant brain are more diffuse than those in the adult brain. Brain activation becomes increasingly specialized (and thus more efficient) over developmental time through

interactions between various brain regions and the environment (Bates et al., 1996; Fair et al., 2007; Johnson, 2001, 2011). Indeed, the process of specialization has been identified in several developmental domains, including face perception (e.g., Pascalis et al., 2005), cognitive control (e.g., Crone, 2014), phoneme perception (e.g., Werker & Hensch, 2015), emotional reactivity and regulation (e.g., Somerville & Casey, 2014), and motor development (e.g., D'Souza, Cowie, et al., 2017).

In typical development, the number of synapses reaches its peak in early childhood (Huttenlocher, 1979; Huttenlocher & Dabholkar, 1997; Liu et al., 2012). Synapses are initially weak but some are strengthened through experience (Hebb, 1950). To reduce noise in the system and increase signal-to-noise ratio, unused synapses become weaker and are eventually pruned out (Colman et al., 1997; Navlakha et al., 2015; Sengpiel & Kind, 2002; Sretavan & Shatz, 1984). Whereas synaptogenesis provides the brain with plasticity (which enhances the influence of postnatal experience on neural circuitry), synaptic pruning stabilizes the experience-driven changes that occur when self-organizing neural circuitry specializes to its environment (Johnson, 2001, 2011). Fewer neurons and reduced synaptic plasticity in infants with DS are likely to lead to a worse signal-to-noise ratio. This may in turn make it more difficult for the DS brain to specialize to its environment (Rubenstein & Merzenich, 2003). Moreover, increased inhibition, sparser neurons/synapses, and spine dysmorphology may make excitatory synapses in DS more vulnerable during the pruning process. This is because pruning occurs through synaptic activity, and synaptic activity is constrained by inhibitory processes, the number of neurons/synapses, and spine morphology (Colman et al., 1997; Cowan, 1979). Indeed, the neuronal derivatives of trisomy-21-induced pluripotent stem cells (iPSCs) (the reprogrammed cells of two individuals with DS) showed less synaptic activity than an isogenic control that is disomic for human chromosome 21 (Weick et al., 2013). Furthermore, because inhibitory synapses are less affected by pruning

processes than excitatory synapses (De Felipe et al., 1997), pruning may further disrupt E/I imbalance (increase inhibitory predominance) in persons with DS. Indeed, the rate of pruning of inhibitory synapses is disrupted in Ts65Dn mouse models, resulting in an increase of inhibition (Mitra et al., 2012). Thus, reduced plasticity may make it more difficult for the DS brain to specialize in the same way or to the same extent as the TD brain.

The process of specialization also requires long-range connectivity between brain regions. This is because learning and development involve interregional interactions as well as intraregional refinement (Bassett & Sporns, 2017; Johnson, 2001, 2011). Interregional communication depends on axonal processes that can reach considerable distances in the brain and fast transmission. To establish fast transmission, axons are wrapped in a lipid-rich substance called myelin (Waxman, 1980). Traditionally considered to be modifiable only by damage, it now appears to participate in brain plasticity and be at least partly regulated by experience: brain imaging studies suggest that changes in white matter (which reflect changes in myelination) correlate with learning, and cellular studies reveal that myelination is modulated by neural activity (Almeida & Lyons, 2017; Fields, 2015; McKenzie et al., 2014; Mount & Monje, 2017). Myelination therefore plays an important role in brain plasticity and specialization. Yet, hypomyelination is observed early in development in DS, as demonstrated by a multi-region transcriptome analysis of myelin protein expression (Olmos-Serrano et al., 2016), histological examination (Ábrahám et al., 2012; Wisniewski & Schmidt-Sidor, 1989), magnetic resonance imaging (MRI) (Koo et al., 1992), and diffusion tensor imaging (DTI) (Gunbey et al., 2017). Moreover, a small near-infrared spectroscopy study found reduced long-range functional connectivity in infants with DS ($n = 5$) compared to 27 chronological age-matched term or late preterm and early term TD controls (Imai et al., 2014). Emerging evidence suggests that the dysregulated (genetic and molecular) signalling pathways that affect neuronal proliferation and differentiation also disrupt the process

through which progenitor cells differentiate into the cells that form myelin, oligodendrocytes (see Reiche et al., 2019, for review). Brain plasticity, neural connectivity, and specialization in DS may therefore be affected by hypomyelination as well as fewer neurons and fewer synapses.

Although functional communication within and between brain regions is atypical in young children with DS, the process of specialization has yet to be studied in these children (see Hamner et al., 2018, for a review of the sparse paediatric neuroimaging literature). There is, however, indirect evidence from the adult literature (for a review of functional magnetic resonance imaging (fMRI) studies in DS, see Carbó-Carreté et al., 2020). For example, brain activity during a passive listening task was studied in nine young adults with DS using fMRI (Reynolds Losin et al., 2009). While nine chronological age-matched TD comparison participants showed more activation (in classic receptive language areas) in response to language (forward speech) than non-language (backward speech) stimuli, the individuals with DS showed almost no difference in activation patterns between the two. The individuals with DS also showed a more diffuse brain response than the TD individuals, with greater activation in cingulate gyrus and parietal lobes. This suggests that the DS brain had not specialized for hearing speech, at least not to the same extent as the TD brain. Furthermore, Anderson et al. (2013) measured the brain activity of young adults with DS watching cartoons, and found that activity in adjacent brain regions was more synchronized than in TD participants matched on chronological age, while the opposite was true for distant brain regions. Diffuse local connectivity and reduced long-range connectivity is a hallmark of early brain development. As the brain specializes over developmental time, short-range connectivity decreases and long-range connections increase (Fair et al., 2007, 2009; Moraczewski et al., 2018). Therefore, Anderson et al.'s data suggest that the DS brain has not specialized to the same extent as the TD brain.

5 Specialization is driven by perception-action cycles

Specialization is not a passive process; the infant calibrates its internal operations to the external world by *actively* exploring (selecting, acting on) and sampling it (Buzsáki, 2006; Frankenhuys & Panchanathan, 2011; Held & Hein, 1963; Piaget, 1954). This is achieved through cycles of perceiving and acting (Edelman, 1987; Gibson, 1988; Gibson & Pick, 2000; Sporns & Edelman, 1993). As Ulrich (2010, p. 1871) explained:

“As newborns use their available eye muscle strength and control to attend to objects or people moving through their space, they push their systems, bit by bit, to go farther, to see more and longer. These repeated cycles of moving and perceiving the consequences lead, over time, to sufficient control of head and neck muscles to lift the head and eyes upward, leading to new, interesting things to explore. Their efforts have cascading effects, enabling more and longer movements through greater distances, toward objects, people, and sounds that attract them. Bit by bit, the foundation takes shape and expands for discovering new concepts, consistencies, and motor control.”

From this, it follows that if an infant is exposed to an atypical environment that hampers exploration, or its capacity to explore or sample the environment is limited (as may be the case in infants with DS), then the process of specialization will be affected and the infant would be more likely to develop atypically (Frankenhuys & Panchanathan, 2011; Johnson et al., 2015; Karmiloff-Smith et al., 2012).

5.1 Perceptual and attentional constraints on information sampling in infants with DS

In order for the organism to specialize, it must be able to sample information from the environment (Frankenhuys & Panchanathan, 2011). This process is constrained by the ability

to sense and perceive information. Early in development, DS is associated with perceptual difficulties in a number of modalities, including visual (John et al., 2004), auditory (Roizen et al., 1993), and tactile (Brandt, 1996). Furthermore, infants and toddlers with DS seem to struggle to integrate information from different modalities (multisensory/multimodal integration; D'Souza et al., 2016). Emerging evidence also points to lower responsivity in children with DS as reported by their caregivers on the Short Sensory Profile questionnaire (Bruni et al., 2010; Will et al., 2019). Taken together, it is possible that many infants with DS may not notice changes in the environment that TD infants would sample, learn about, and act on (e.g. Ulrich et al., 1997).

Even if young children with DS notice a change in the environment, there is evidence that they take longer than chronological and mental age-matched TD infants to orient their focus of attention towards it (D'Souza, D'Souza, Jones, et al., 2020). This means that they may sample less from (and learn less about) the environment than their TD peers. Furthermore, some fleeting events may be missed altogether, potentially involving a loss of some critical learning moments (e.g., the parent labelling an object). This is consistent with findings that faster attentional orienting is concurrently associated with better cognitive performance in 9-month-old infants with DS (Fidler, Schworer, Will, et al., 2019) and greater language ability in 15-month-olds (both with and without DS; D'Souza, D'Souza, Jones, et al., 2020).

5.2 Less efficient information processing in infants with DS

Once the infant has perceived and oriented to an external stimulus, they need to process the information more deeply. One of the earliest ways that infants process information sampled from their environment is through habituation. Habituation (a progressive reduction in response to a repeated stimulus) reflects the process through which an internal representation

of a familiar stimulus is gradually built up; the end triggers a switch in attention from the familiar stimulus to a novel one (Bremner & Fogel, 2004). If there is inhibitory predominance and a lack of neurons in the DS brain (and thus a lack of plasticity), it may take longer for the brain to build up sufficiently detailed representations – and thus take longer for it to habituate to stimuli in the external world. Indeed, this seems to be the case. Whereas ten TD foetuses during the final trimester of pregnancy habituated to repeated presentations of an auditory stimulus, atypical habituation was observed in two foetuses with DS (Hepper & Shahidullah, 1992). One of the foetuses with DS failed to habituate; the other showed a slower rate of habituation than all ten TD comparisons. Sadly, the foetus that failed to habituate did not survive long after birth, hinting at a link between habituation and developmental outcomes. Indeed, in typical development, infant habituation patterns are predictive of later-emerging cognitive functions such as language development (Bornstein & Tamis-LeMonda, 1989; Ruddy & Bornstein, 1982) and childhood intelligence (Bornstein & Sigman, 1986; Kavšek, 2004; McCall & Carriger, 1993; Rose et al., 1986). Furthermore, 106 neonates born at risk of intellectual delay (including DS) successfully habituated to a verbal stimulus, but oriented less to a novel stimulus and, later, less to the reappearance of the familiar stimulus than 37 TD neonates, indicating atypical information processing as early as 41 weeks (± 3 weeks) gestational age (Zelazo et al., 1989).

Atypical habituation has also been described in infants with DS using electroencephalography (EEG), a measure of neurophysiological activity in the brain. Whereas TD 6- and 12-month-old infants who were presented with a repetitive auditory stimulus showed neural habituation through a progressive decrement in the amplitude of their auditory evoked responses (AER) (Barnet et al., 1971), 6- and 12-month-old infants with DS did not show this pattern of neural habituation; which was also not observed among one-month-olds, either with or without DS (Barnet et al., 1971). These data hint that the ability to

process auditory information changes over the first half year of postnatal life in typical development, but less so (or not at all) among infants with DS. Atypical neural habituation in the auditory domain has also been identified in studies of older children with DS (Díaz & Zurrón, 1995; Seidl et al., 1997), supporting the notion that infants with DS are slower at building internal representations of auditory stimuli. Similar findings have also been reported in the visual domain. For example, using a visual oddball paradigm in which one face was presented for 80% of the trials and another face for 20% of the trials to measure face discrimination and EEG in 6-month-old infants, Hill Karrer and colleagues (1998) found that attenuation of brain activity in response to the repetitive face stimuli (habituation) was more gradual in the infants with DS than in chronological age-matched TD participants.

Less efficient or slower habituation mechanisms in infants with DS, which is consistent with difficulties in building internal representations, may help to explain a core characteristic of DS – experiencing more difficulty in processing verbal information than visual information. In a familiar environment, an infant is unlikely to need the same level of representational detail to be able to discriminate between naturally occurring visual stimuli than between auditory stimuli. For example, during social interaction a child may not need to discriminate every featural change it observes in the body or face of an interacting social agent, but it would need to discriminate featural changes in any accompanying speech stream. Furthermore, key physical properties of speech can change rapidly over the duration of an utterance. This makes speech discrimination a challenging task.

If habituation is less efficient or slower in DS, an infant with DS would require more exposure to a stimulus in order to form an internal representation of it. This dovetails with the finding that infants with DS are relatively slow at disengaging attention from a visual stimulus in order to redirect attention to a novel stimulus (D'Souza, D'Souza, Jones, et al., 2020). They may require more time to build up an internal representation of a visual stimulus

and are thus slower at switching attention to other stimuli. Rather than being an impairment, the long disengagement latency might therefore be a useful adaptation: infants with DS might benefit more by *not* shifting attention quickly. There is always a trade-off, however. By spending more processing time on a single stimulus, the infant with DS is spending less time exploring the environment.

5.3 Less motor activity in infants with DS

Information sampling is not a passive process. It usually involves motor activity. Indeed, motor activity has been proposed to be at the core of early development (Piaget, 1952; Thelen & Smith, 1994; Von Hofsten, 2004). Even young infants actively select aspects of their environment to focus on by moving their eyes, reaching towards people and objects, and locomoting to new locations. TD infants generate a large amount of activity. By 3.5 months, TD infants experience 3-6 million eye movements (Johnson et al., 2003). Around the first year of life, TD infants spend about half of their day manipulating objects (Karasik et al., 2011). Between 12 and 19 months, TD toddlers produce around 14,000 steps per day (in terms of distance, this is equivalent to walking the length of 46 American football fields) and fall around 100 times per day (Adolph et al., 2012). TD children therefore generate what seems to be an extensive amount of motor activity to develop their skills to adult-like levels. Because the DS brain is characterised by fewer neurons, inhibitory predominance, and a poor signal-to-noise ratio, it may require even more motor activity to adapt its neural circuitry to the external world than the TD brain. Yet, from very early on, infants with DS produce less spontaneous motor activity than TD infants of the same chronological age (Mazzone et al., 2004). Motor activity in infants with DS also differs from that of the TD infants in terms of intensity and complexity. Infants with DS produce more low-intensity and less high-intensity spontaneous leg motor activity than TD infants of the same chronological age (McKay &

Angulo-Barroso, 2006). They also produce fewer complex leg movements (i.e., kicking patterns; Ulrich & Ulrich, 1995) in comparison to TD infants matched on chronological age and TD infants matched on motor age.

Why do we see these differences in motor activity? Motor ability relies on the interactions of multiple subsystems (Thelen & Smith, 1994), many of which are atypical in infants with DS. Reduced motor activity in DS is likely to be a consequence of perceptual difficulties, atypical neural constraints, and an adaptive response to muscular and skeletal differences, including low muscle tone (hypotonia), joint laxity, and hypermobility (Block, 1991; Cardoso et al., 2015; Cowie, 1970; Lott, 2012; Ulrich & Ulrich, 1993). Furthermore, common health-related issues may also play a role, including congenital heart disease (Alsaied et al., 2016; Pfitzer et al., 2017) and sleep difficulties (Hauck et al., 2018; McKay & Angulo-Barroso, 2006). A combination of these constraints may make it more challenging for the developing system with DS to generate motor activity. Thus, the developing system may end up producing less motor activity, which would lead to fewer experience-dependent changes, impacting the system's developmental trajectory. Indeed, individual differences in early motor activity has been linked to the development of motor milestones in DS. Infants who are more active than the mean at 2 or 3 months of age achieve several prone and sitting skills earlier (Hauck et al., 2020). Furthermore, intensity of leg kicks predicts onset of walking in DS, as infants who show more high-intensity leg motor activity at around 12 and 14 months of age start walking earlier than those who show less of this activity (Lloyd et al., 2010). Although one explanation may be that those children whose starting state is more typical tend to produce more motor activity and reach their developmental milestones earlier, a randomized controlled study suggests that facilitating early motor experience has a positive effect on the emergence of later motor skills (Ulrich et al., 2001). Specifically, Ulrich and colleagues (2001) showed that infants with DS who underwent a home-based stepping

training intervention achieved independent walking by an average of 101 days earlier than infants with DS who were not part of this intervention. This suggests that despite their particular genetic and neurocognitive constraints, the infants with DS were able to benefit from the extra motor activity, altering their developmental pathways.

Motor activity in DS does not only differ from typical development in onset and intensity, but also in the type of strategies employed to reach a particular motor state. ‘Symmetrical’ strategies have been observed across a range of contexts in DS. For example, some children with DS use a symmetrical strategy (i.e., they move their limbs symmetrically along the body midline) to lift themselves up from a prone position into a sitting position, which involves doing the splits (Lydic & Steele, 1979). Infants and toddlers with DS have also been reported to use a symmetrical strategy when rising up from the floor into a standing position; they tend to simultaneously use both hands and both feet to provide maximal support (Lautenslager, 1995). A symmetrical strategy for locomotion—bottom shuffling—has also been described in DS (Robb, 2015). Although atypical, these symmetrical strategies seem to be adaptive strategies employed to compensate for hypotonia and hypermobility of joints (Åkerström & Sanner, 1993; Kugel, 1970) and/or reduced posture reactions (balance and self-righting; Haley, 1986).

Though adaptive (it is likely to be more adaptive, e.g., to be able to sit up by ‘doing the splits’ than not to sit up at all), these symmetrical strategies are likely to constrain the type of activity and experiences that the developing system can generate in the future, taking the system down a different developmental path. Reliance on symmetrical strategies may lead to less sensorimotor experience with differentiated limbs. Consequently, regular use of symmetrical strategies may impact motor behaviour in situations when the strategies are not adaptive, such as when postural stability is provided by a seat (for an example in TD infants, see Corbetta & Bojczyk, 2002). In other words, if infants with DS regularly use symmetrical

strategies as adaptations, they may subsequently have difficulties decoupling their limbs in situations when it would have been possible and advantageous to do so. This may potentially affect the development of motor skills that require asymmetrical strategies, such as intermanual coordination (e.g., using one hand to hold a jar while the other hand twists the lid of the jar). This is consistent with behavioural findings in school-aged children and adults with DS which show that, although they face many motor challenges, intermanual coordination is particularly challenging for this population (Ringebach et al., 2002; Spanò et al., 1999).

Early motor ability not only constrains future motor ability, but also impacts how infants explore and interact with the world around them, such as how they engage with objects. Differences in self-generated activity have been observed in the emergence of reaching for objects. De Campos and colleagues (2013) followed infants with DS and TD infants monthly, with a first assessment at the age of 4 months. As expected, the majority of TD infants were able to reach at the age of their first assessment (i.e., at 4 months; Spencer et al., 2000). They subsequently showed a gradual increase in number of reaches. The age at which the infants started reaching was a better predictor of later reaching behaviour than chronological age. This suggests that reaching behaviour is dependent on experience rather than on chronological age (Carvalho et al., 2008). This conclusion is in line with the proposal that TD infants act and select aspects of their environment as a function of their current level of abilities (Kidd et al., 2012; Rovee-Collier & Cuevas, 2009). TD infants spontaneously repeat their actions and, in so doing, practise new emerging skills (Adolph et al., 2012). De Campos et al. (2013) observed the same trend in infants with DS, with an increasing number of reaches after onset of reaching (even though reaching onset was delayed). However, the average number of reaches and subsequent object exploration was lower in the infants with DS. Thus, the children with DS both started reaching later and practised their actions less

frequently than the TD infants. Although some developmental delay may be expected, it is not obvious why the infants with DS produced less reaching. Less repetition may be due to the actions being more taxing to infants with DS compared to TD infants. Emerging motor actions, such as reaching in young infants, requires the coordination of many motor, perceptual, and cognitive resources (Berger et al., 2019; Boudreau & Bushnell, 2000; for a review, see Berger et al., 2018). Whereas in TD infants many of these resources are freed as movements become automatized over development (Berger et al., 2018) and as the motor system becomes specialized (D'Souza, Cowie, et al., 2017), these processes are possibly delayed in DS. Thus, motor performance may be drawing on diverse (and already limited) resources in DS for a longer developmental period. The adaptive response to taxing motor actions may be to produce less of them. Taken together, even though the exact reasons are unclear, infants with DS engage less with their physical environment than TD infants.

Less motoric engagement with the environment is likely to negatively impact the development of other domains in infants with DS. Several studies in TD infants have demonstrated cascading effects of the motor domain on other domains. Independent sitting and visual-manual exploration in 4.5- to 7.5-month-olds were found to be related to infants' 3-dimensional object completion abilities (Soska et al., 2010). Crawling experience was found to increase sensitivity to optic flow information for balance (Campos et al., 2000) as well as mental rotation abilities (Schwarzer et al., 2013). Motor development was also found to be associated with social development. Training 3-month-old infants to manipulate and reach for objects affects their visual exploration of social agents (Libertus & Needham, 2010, 2011). Furthermore, the transition from crawling to walking was found to change interactions between infants and their caregivers, increasing opportunities for more advanced social interactions (Clearfield et al., 2008; Karasik et al., 2011, 2014). This could potentially

contribute to the positive association between walking and language development (Walle & Campos, 2014).

If different domains (e.g., motor and social development) are interconnected and interdependent, then a deficit in one domain (e.g., motor) may have cascading effects on other domains (e.g., social). However, this does not mean that a particular domain provides the necessary and sufficient conditions for the development of other domains (Campos et al., 2000; Iverson, 2010). For example, even though vision and locomotion may be associated with language development in TD children, it is clearly possible for a child to develop language even when they are unable to see or locomote. The components of the system would adapt to the constraints; an alternative pathway would emerge. However, due to other constraints such as reduced brain plasticity, an infant with DS may have fewer alternative pathways available to them than an infant with no or fewer atypical constraints. Thus, identifying *early* atypicalities in motor development in DS may be important because of their potential cascading effects on other domains. Indeed, there is some emerging evidence that such cascading effects may be operating in DS. Yamauchi and colleagues (2019) observed motor abilities to be positively associated with both cognitive and language abilities in 1- to 3-year-olds with DS. This association strengthened with increasing age. Furthermore, onset of walking was suggested to facilitate both cognitive and language development in DS (Yamauchi et al., 2019). Even though longitudinal and intervention studies are needed to further probe these cascades in DS, the study supports the idea that early atypicalities in the motor domain may cascade onto cognitive and language development in DS. This may be an important focus of research, as infants with DS show particularly pronounced difficulties in motor development early in life (e.g., Carr, 1970; Harris, 1981; LaVeck & LaVeck, 1977). Indeed, motor development in DS seems to be delayed even when compared to mental age-

matched children with developmental delays (Fidler et al., 2008). This may result in a unique set of cascading effects, potentially contributing to a DS-specific developmental trajectory.

6 Perception-action cycles are embedded within social contexts

As young infants improve their motor skills, they can reach further, move their bodies faster, and explore places and objects they could not before. But they do not do this in isolation; perception-action cycles are embedded within social contexts and are consequently constrained by interactions with parents, siblings, peers, and other social agents (Adolph & Hoch, 2019). For example, social agents are often useful sources of information and infants integrate social information to guide their perception-action cycles (Karasik et al., 2016; Tamis-LeMonda et al., 2008). In the following section, we discuss how the perception-action cycles may interact with social contexts in the infant with DS. Could one adaptive response to motor difficulties and less efficient information processing in infants with DS be an over-reliance on social agents?

6.1 Over-reliance on social agents as an adaptive strategy

At birth, visual acuity and the ability to physically interact with the external world is limited. This constrains the type of information that neonates can perceive and makes them largely dependent on their caregivers for visual input. What kinds of visual scenes do their caregivers create for them? A study using head-mounted cameras demonstrated that these mostly comprise their caregivers' faces (Fausey et al., 2016). As the infants' motor abilities develop, however, they take a more active role manipulating objects and locomoting – with their visual input shifting from faces to hands and objects (Fausey et al., 2016). If infants with DS present with motor delay and put their emerging motor abilities to use less than TD controls, then the nature of their visual input will likely change less over developmental time than for

TD infants. Perhaps this could partly explain the findings that, even though mutual gaze with a caregiver is initially slower to develop in infants with DS, it remains high over the first year of life whereas declines are seen among TD infants (Berger & Cunningham, 1981; Carvajal & Iglesias, 2000). In another observational study, 6- and 9-month-old infants with DS spent almost half of their time looking at their caregiver during free play, which was nearly twice as much as TD infants of the same chronological age (Gunn et al., 1982). If infants with DS receive more visual input of their caregiver, this might bias them to over-rely on this source of information. This may over time contribute to relative strengths in other social domains, such as joint attention (for a metaanalysis, see Hahn et al., 2018).

The possible social bias is in line with observations that imitation abilities are relatively strong in children with DS (Nielsen & Hudry, 2010; Vanvuchelen et al., 2011). As John Langdon Down (1867) noted in early work on DS, individuals with DS seem to possess “considerable power of imitation, even bordering on being mimics” (p. 122). Even though imitation often has negative connotations, it may in fact be a very successful adaptive strategy for individuals with DS, as social agents are often useful and trustworthy sources of information. Hence, by imitating social agents, infants with DS may achieve goals that they would not easily accomplish through other means. Imitating others may be easier than generating and initiating novel ideas and actions. In support of this hypothesis, Wright and colleagues (2006) found that toddlers with DS use imitative strategies to solve cognitive tasks, even when it would be more appropriate for them to use different cognitively driven strategies. So, they seem apt at copying what they see around them rather than generating their own actions.

Further evidence in support of this hypothesis comes from a study of children with DS interacting with their TD sibling. The children with DS often adopted the role of ‘learner’, while their sibling took on the role of ‘teacher’ or ‘manager’ (Stoneman et al.,

1987), irrespective of who was older (Abramovitch et al., 1987). Furthermore, children with DS were less likely to initiate interaction and more likely to imitate their sibling than vice versa (Knott et al., 1995). This asymmetry in interactions may again be an adaptive strategy in DS, but it could nevertheless further exacerbate an over-reliance on others.

Over-reliance on others is likely to hinder the development of independent behaviour. Indeed, toddlers with DS at 21 months of mental age showed significantly more help-seeking behaviour during an object retrieval task than both TD children of the same mental age and a group of children with developmental disabilities of mixed or unknown aetiology (Fidler et al., 2005). Furthermore, lower levels of task persistence and higher levels of off-task behaviour in children with DS have been reported (Landry & Chapieski, 1989; Pitcairn & Wishart, 1994; Ruskin et al., 1994; Vlachou & Farrell, 2000). For example, 4-year-olds with DS have been found to engage in more off-task 'party pieces' or charming behaviour to socially engage the experimenter compared to chronological and mental age-matched TD groups (Pitcairn & Wishart, 1994). Anecdotally, during our testing sessions, young children with DS often attempt to terminate more challenging tasks by clapping to indicate that the tasks have somehow been completed. We rarely observe this behaviour in children with other neurodevelopmental disorders. These are certainly very creative and charming adaptive strategies to ending challenging or less engaging tasks. If reinforced, it is not inconceivable that these behaviours could steer developmental trajectories. Seeking help and ending tasks may be adaptive in the short term, but if it occurs at the expense of practising solving problems, then it may reduce skill development and independence in the long term. This is consistent with the finding that, later in life, individuals with disabilities are more likely to

select easier problems to solve, seek help from others, and demonstrate less satisfaction when working on problems (for a review, see Bybee & Zigler, 1998).⁴

Although children with DS are often considered to be highly social, neither their sociability nor their over-reliance on social agents necessarily mean that they interact optimally with social agents. For example, Krakow and Kopp (1982) found that 19- to 38-month-old toddlers with DS spent less time socially oriented (e.g., engaging their caregiver in play, handing toys to their mother, seeking assistance) and also less time exploring their environment (e.g., looking around at other people and/or distant toys) than mental age-matched TD children. That poses the question of what they were doing during those interactions: 50% of the toddlers with DS engaged in stereotypic activity such as throwing toys and 75% of them spent time totally unoccupied (e.g., staring into space) (Krakow & Kopp, 1982). The fact that the toddlers with DS demanded less interaction from their caregivers than did the TD children suggests that over-reliance on external sources of information does not imply expertise in social interaction (see Cebula et al., 2010, for a review). Rather, less self-generated, exploratory, and social behaviours place a demand *on the caregiver* to initiate social exchanges and provide opportunities for exploration and learning.

6.2 Parental behaviour may matter more for infants with DS

If infants with DS are less likely to explore their environment and initiate social exchanges, then their caregivers may take a more active role. Even though findings on parenting styles in DS are mixed (for a review, see Daunhauer et al., 2017), a number of observations of parent-child interaction have revealed that parents of children with DS are more directive than

⁴ However, this may be highly constrained by the level of society and change with changing societal attitudes towards people with disabilities (Shogren et al., 2017).

parents of TD children matched on chronological age (Soukup-Ascencao et al., 2016), mental age (Cielinski et al., 1995; Schworer et al., 2018; Venuti et al., 2009), or both (Roach et al., 1998). This is not dissimilar to observations in the study of children with DS interacting with their TD sibling (see above; Stoneman et al., 1987). There is some evidence that parenting style is associated with individual differences in the DS phenotype. For example, Gilmore and colleagues (2009) compared children with DS (and their mothers) to TD children matched on mental age (24-36 months) (and their mothers). The children were presented with a problem-solving task, and the ensuing parent-child interactions were observed. Although mothers of children with DS are often reported to be more directive, maternal style did not significantly differ across groups in this study, and mothers in both groups used similar verbal strategies (Gilmore et al., 2009). However, whereas maternal style was unrelated to task persistence in the TD children, greater persistence when working independently on a challenging task was observed in the children with DS whose mothers were more supportive of their autonomy (Gilmore et al., 2009). This suggests that parenting style may have more impact on children with DS than on TD children of the same mental age.

Of course, causal relationships cannot be inferred from correlational studies. The development of persistence in children with DS may be driven by parenting style. Alternatively, children who are more dependent on others may be more likely to elicit directive parenting behaviour than children who are more independent. In addition, persistence may emerge through interactions among multiple diverse factors, of which internal motivation and parenting style are only two among many. Regardless of how it emerges, persistence in early childhood is associated with persistence in early adolescence in DS (Gilmore & Cuskelly, 2009).

If children with DS are less active and their caregivers are more directive, then learning and development in DS may be largely driven by the caregiver's selection of tasks.

If caregivers do have more impact on developmental processes in infants with DS as compared to TD children, then the beliefs that parents hold about their children are likely to affect children with DS more than TD children. Yet, obtaining a ‘true’ picture of an infant’s current level of abilities if that infant has DS may be more challenging because infants with DS often present with an uneven profile with particular difficulties in the motor domain. This may make it more difficult for the caregiver to evaluate their child’s developmental level and provide them with an appropriate amount and level of challenges – both of which are required for optimal learning (akin to a *zone of proximal development*; Vygotsky, 1978). Indeed, even though a group of children with DS at 18 and 24 months of mental age did not show any differences in task-directed behaviour as compared to TD children of the same mental age, Glenn and colleagues (2001) found that their parents rated them as scoring lower on object-oriented play and general competence. This is consistent with evidence from young children with motor delay (Wang et al., 2013). The potential mismatch between what the parent believes their child is capable of and what the child is actually capable of may further exacerbate the child’s difficulties. Thus, even though an immediate adaptive response to the more passive behaviours of infants with DS may be more directive behaviour in the caregiver, in the long term it may be more beneficial for the caregiver to encourage the child with DS to take a more active role; stimulate them to generate, plan, and initiate actions; and steer them away from relying on others for motivation and self-control (Glenn et al., 2001).

7 Future directions

7.1 Embracing complexity

It is clear from the previous section that more research on infants with DS is needed in order to understand their development. The question is: what *type* of research? Most research (including our own) comprises group comparisons between DS and TD (and/or other

neurodevelopmental disorders). Sometimes it consists of associations between variables within a particular DS group. When planning the studies, we often think: *If only we could measure more variables, we would finally understand how infants with DS develop.* So we try to collect more information about the infants and their environment longitudinally (e.g., infant chronological age, infant mental age, health comorbidities, parental education, parenting style, sibling age, sleep patterns, family income, vocabulary size, memory abilities, attentional abilities, motor abilities); and when possible manipulate variables in order to understand their role in development. Thus, we study DS by first decomposing the system into separate units (the variables), and then by measuring/manipulating these units in order to understand their contribution to the system. In doing so, we are assuming that the system is *complicated but understandable as the sum of its parts*. Metaphorically, it is like trying to understand how fabric is made by cutting it into pieces, and then trying to reconstruct how each fibre fits together. But by taking apart the fabric, we no longer see how the fibres are *plaited*. Yet the structure and functional properties of a fabric (e.g., its strength, breathability, warmth) are contingent on how the individual fibres are woven together. Likewise, the structure and functional properties of a living system are contingent on how the individual units interact with each other. This is because the living system is not *complicated* but *complex* (for the importance of this distinction, see Den Hartigh et al., 2017).

Complex systems cannot be understood by studying their parts in isolation; complexity emerges through dynamic multicausal interactions between interdependent, always-adapting components. It is very difficult—perhaps even impossible—to study all these interactions as the system adapts to and changes its environment over developmental time. But it is something to strive for – because it may not be possible to understand complex adaptive systems by breaking them down to their component parts, assigning each part a function, and then recomposing the system in a linear fashion. Embracing complexity

necessitates a study of *interactions* (between and within different levels) as they unfold moment-by-moment. Such an approach has provided unexpected insights into typical development (as we demonstrate below using the example of word learning) and thus we believe it is a very promising avenue for understanding how infants with DS develop.

As discussed in earlier sections, action-perception cycles are at the core of early development (Piaget, 1952; Thelen & Smith, 1994; Von Hofsten, 2004) and these are deeply embedded in social context (Adolph & Hoch, 2019). In fact, one of the most common contexts in which the developing child actively learns is parent-child interaction. During this free-flowing activity, parents direct or react to their child, while their child—who is often surrounded by interesting objects and in pursuit of their own goals—directs, reacts to, or ignores the activity of their parent. How do children learn in this rich (and thus potentially confusing) context? Traditional developmental research has been unable to answer this question, because it has predominantly used methods that require young children to sit and look at a computer screen (Fig. 3a). However, some studies now consider the child's embodied experiences in interaction with their parent by measuring gaze using head-mounted cameras/eye-trackers (Suarez-Rivera et al., 2019; Yoshida & Smith, 2008; Yu & Smith, 2012, 2013, 2016) (Fig. 3c). This technology allows researchers to investigate the dynamic interplay between various components of parent-child interaction (Fig. 3e)—eye movements (visually selecting an object), hand movements (grasping an object), and speech (describing a grasped object)—which work together to form optimal learning moments in TD infants/toddlers (Yu & Smith, 2012).

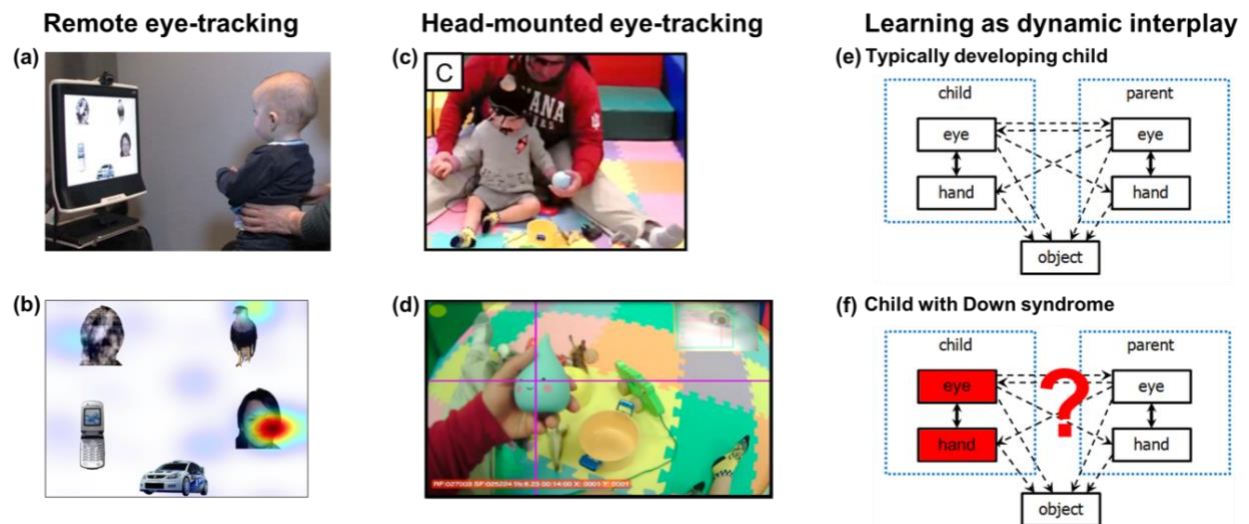


Figure 3. Comparison of (a) a remote eye-tracking setup with (c) a head-mounted eye-tracking setup. The remote eye-tracking setup allows researchers to track (b) the position of the eyes on a screen. Head-mounted eye-tracking enables researchers to record (d) the moment-by-moment gaze allocation of a child and a parent during naturalistic interaction, which captures (e) the dynamic interplay of various components in learning. Little is currently known about how learning unfolds moment by moment in (f) children with DS who often have perceptual, attentional, and motor difficulties. Image credit: (a) provided by Birkbeck Babylab; (b) modified from *Task Engine - Face Popout* (n.d.); (c) and (d) modified from Slone et al. (2018); (e) and (f) modified from Yu & Smith (2013).

Research on the interplay between different components of parent-child interaction (eyes, hands, speech) has been challenging fundamental assumptions about many aspects of early development, most notably word learning and language development in TD children. For example, from an adult's perspective it seems impossible for a child to learn the label for a single object in a cluttered visual scene containing multiple objects (the 'referential ambiguity' problem; see Quine, 1960), yet researchers who take into account the children's perspective find that the problem of referential ambiguity disappears during parent-child interaction (Samuelson & McMurray, 2017; Yu & Smith, 2012). For example, Pereira and colleagues (2014) used a head-mounted camera to record gaze data from TD toddlers (16-25 months) as they played with novel objects, and as the parent spontaneously named them. They found that toddlers' allocation of attention is highly constrained by their hands/arms. Due to their limited reach, single objects often fill the toddler's field of view. Parents are sensitive to these moments and often provide labels for the object during them, eliminating

the problem of referential ambiguity. In other words, in naturalistic settings, toddlers are not trying to learn labels by deducing what their caregivers are referring to; optimal word learning moments emerge from an interplay between eye movements (visually selecting an object), hand movements (grasping an object), and parental sensitivity (naming a grasped object) (Yu & Smith, 2012). This insight would have been missed had the variables been measured and analysed separately.

How is this moment-by-moment learning constrained in infants with DS? We are currently investigating this question, but can make some predictions based on the DS literature. Infants with DS present with a number of perceptual, attentional, and motor difficulties that may limit the occurrence of optimal word learning moments (Fig. 3f). For example, infants with DS spend less time handling objects during parent-child interaction than TD infants of the same mental age (Legerstee & Weintraub, 1997). This is likely to reduce the number of optimal naming opportunities that a parent would have – and require the parent to be particularly sensitive and responsive to the child if they are to co-create a sufficient number of optimal learning moments. As a parent may experience more difficulty in evaluating and reacting appropriately to the needs of a child with DS than a TD child (see the previous section [6.2]), even if a child with DS were to hear the same number of tokens of a word, it may not occur during optimal learning moments. Furthermore, even if the child were to hear the word during an optimal learning moment, other processes necessary for word learning are often atypical in DS. As we mentioned above, reduced neural plasticity and atypical information processing may mean that infants with DS require more repetition than is typically necessary (for a computational model showing an atypical associative learning mechanism in DS, see Tovar et al., 2018). Also sleep, which plays an important role in learning and memory (and thus in word learning), develops atypically in DS (D'Souza, D'Souza, Horváth, et al., 2020; Edgin et al., 2015; for discussion of other constraints on

language learning in DS, see D'Souza, D'Souza, et al., 2017). To understand how infants with DS learn, it is thus necessary to embrace complexity and employ multiple methodologies (neuroimaging, head-mounted eye-tracking, movement sensors, etc.) across different timescales, with both the infant and their social partners as they interact in naturalistic settings. This approach could help us to understand why infants with DS diverge in their trajectories from TD infants and whether there is a DS-specific pathway.

7.2 Diverging trajectories

As infants with DS get older, they seem to progressively diverge from their TD peers. For example, a decline in standardized cognitive and motor scores in DS, relative to TD children, was found in Carr's landmark longitudinal study of children who were tested at 6 weeks, 6 months, 10 months, 15 months, and 24 months of age (Carr, 1970).⁵ This decline was particularly steep from 10 to 15 months of age. In other words, as children with DS develop, their standardized scores fall further behind those of their TD peers. This divergence is particularly pronounced for their areas of relative difficulties, giving rise to the classic profile associated with DS. Carr (1970) reported that from 6 months of age, mean standardized motor score was lower than mean standardized cognitive score in DS. A deceleration of development with increasing chronological age in DS has also been found in other studies, as has the finding that motor standardized scores lag behind cognitive standardized scores (Harris, 1981; LaVeck & LaVeck, 1977). Increased divergence over developmental time has also been found in expressive language, another area of relative difficulty in DS. While expressive language ability was at an appropriate level for almost 50% of 22-month-old children with DS given their mental age and receptive language ability, this was the case for only 21% of them two years later (Miller, 1992).

⁵ These children have been followed across the lifespan (e.g., Carr & Collins, 2018).

In order to understand why the trajectories of infants with DS diverge from those of TD infants, as well as how a DS-specific phenotype might emerge, the interactions of various constraints require longitudinal investigations across a range of domains. These investigations may benefit from comparing different disorders, as many constraints are unlikely to be specific to DS. In fact, it is likely that different disorders share similar constraints in early development, but particular clusters of constraints, or their intensity or co-occurrence, or the timing of the interactions between them, may increase the likelihood that disorder-specific phenotypes emerge. The converse may also apply: different constraints may give rise to similar phenotypes through common adaptations (Johnson, 2017; Oliver et al., 2000). For this reason, a multi-level, cross-syndrome, developmental approach to studying disorders is needed.

7.3 Individual differences

Although a DS-specific phenotype has been described (see above), individual differences in DS are vast on all levels of description (genetic, cellular, brain, cognition, behaviour, social context; for examples, see Karmiloff-Smith et al., 2016). Large variability can already be detected early in development, including in the domains that at the group level have been identified as areas of relative difficulty. In the gross motor domain, while the average age of walking in TD children is 13 months and the age ranges from 9 to 17 months, most children with DS learn to walk between 18 and 36 months of age – with some DS children unable to walk even at 4 years of age (Palisano et al., 2001; see also Winders et al., 2019 for variability in motor development in DS). In the expressive language domain, in one longitudinal study of expressive vocabulary size in children with DS, the lowest-scoring child was nonverbal at 36 months, while the expressive vocabulary size of the highest-scoring child was close to the normal range (243 words; Zampini & D’Odorico, 2009). When the same children were

assessed 6 months later, the nonverbal child remained nonverbal, while the child with the most developed language had doubled their expressive vocabulary size to nearly 500 words.

The fact that large variability exists in DS raises the question of whether it is possible to identify a single DS-specific profile. In other words, to what extent can the classic DS profile be applied to all young children with DS, when the individual differences seem so vast? Indeed, Tsao and Kindelberger (2009) identified four distinct cognitive profiles for children with DS between 6 and 11 years of age. Subgroups seem to be possible to detect even in infants with DS. Fidler, Schworer, Prince, and colleagues (2019) observed visual, manual, and oral exploration in 9-month-old infants with DS and found that they could differentiate between two subgroups: ‘Active’ and ‘Passive’. Subgrouping with a wider range of domains in younger children with DS may therefore be a fruitful approach – albeit a challenging one, as it would require large sample sizes with children of similar chronological age, ideally followed longitudinally at the same timepoints.

Although individual differences are often averaged out in DS studies in order to ‘extract’ general developmental mechanisms, the individual differences themselves afford a window onto these mechanisms. For example, on the genetic level, while variability in the genetic origin of DS has been proposed to contribute to variation in the phenotype (e.g., mosaicism; for a review, see Papavassiliou et al., 2015), the contribution of genetic background effects (i.e., all the genes that infants with DS inherit from their parents) has received less focus. Would a child’s genetic background have very little effect on the developmental path cleaved out by trisomy 21? Or can variation in this genetic background contribute to variation in the emerging DS phenotype? In older adults, variation in the apolipoprotein E (*APOE*) gene on chromosome 19 is related to variation in Alzheimer’s disease (AD), both in individuals with DS (who are already at high risk for AD) and in the general population (Prasher et al., 2008; van der Lee et al., 2018). Interestingly, the *e4* allele

of *APOE* (*APOE e4*) that relates to increased AD risk later in life is associated with an attentional *advantage* in early development in DS (D'Souza, Mason, et al., 2020), potentially through variation in myelination (Dean et al., 2014). Can these small but early differences in attentional abilities constrain the emergence of higher-level functions such as language in DS (D'Souza, D'Souza, et al., 2017; Karmiloff-Smith, 1998)? Indeed, we found that infants and toddlers (either with or without DS) with better attentional abilities demonstrate better language abilities than those whose attentional abilities are worse (D'Souza, D'Souza, Jones, et al., 2020). These findings dovetail with the perspective that higher-level functions (like language) gradually emerge through manifold interactions across levels and developmental time (roughly, from variation in genes, through variation in attention, to variation in language⁶). Although these studies are correlational, when taken together they illustrate how individual differences might be an important focus of research. A mechanistic understanding of the within-syndrome heterogeneity may thus provide us with greater power to predict outcomes and tailor interventions to individuals.

7.4 Getting the interventions right

If we view the DS phenotype as an adaptive response to atypical constraints, and take into consideration the fact that its divergence from the typical path becomes increasingly pronounced over time, with increases in individual differences over time too, it becomes apparent that early interventions are likely to have the most impact. Therefore, rather than building interventions around later emerging relative strengths and weaknesses, a more useful strategy might be to alter constraints early in development to improve the child's present and future quality of life. This does not mean that interventions should aim to steer the child back

⁶ One might then expect to find a relationship between *APOE e4* and language ability (for some suggestive analysis, see Thomas et al., 2020).

towards the typical path, a process that might be neither possible nor desirable. It means that interventions should alter constraints to ensure that the system does not adapt in ways that might make life more difficult later on. Because development is constrained by factors across many interconnected domains, the most successful interventions are likely to be the ones that target multiple domains simultaneously.

7.4.1 Behavioural interventions: Early enough? Intense enough?

The need for behavioural therapy programs to maximize developmental outcomes in infants with DS has been recognized across domains (e.g., speech and language therapy, physiotherapy, occupational therapy). It is crucial that these start early enough in development. For example, consider motor development, one of the earliest difficulties reported in DS. As we outlined above, motor abilities constrain how infants interact with their environment, and difficulties in this area may have cascading effects on other domains such as social and language development. Therefore, infants must be engaged early in actively moving their bodies to build muscle strength and minimize motor delay. This is likely to increase self-driven exploration. Although it is difficult to establish the frequency and intensity of therapy required to significantly improve muscle strength and motor control in infants with DS, from what is known about TD infants, self-driven practice is extensive in typical development, as toddlers produce around 14,000 steps per day (Adolph et al., 2012). Young children with DS will likely require even more repetitions considering their reduced neural plasticity. How could such high-intensity intervention be feasibly delivered to infants with DS? Due to limited resources, the most viable pathway for delivering high intensity therapy is through engaging the caregivers. Ulrich and colleagues implemented this approach in a series of studies using a portable paediatric treadmill (Fig. 4a) to develop trunk and leg control and strength in DS. Caregivers held their infants upright on a mini-treadmill for 8

minutes a day, 5 days a week. This amounted to an upper limit of about 960 steps per training session. This may be well short of the amount of activity spontaneously generated by TD children, yet, this intervention was shown to reduce delay in walking onset in DS by an average of 3 months (Ulrich, 2010; Ulrich et al., 2001). A more individually tailored version of this intervention, with the addition of small weights, led to even greater gains, bringing forward walking onset by 5 months (Angulo-Barroso et al., 2008; Ulrich et al., 2008). Although this may not seem much from the perspective of adult timescales, walking provides children with a very different set of experiences (Karasik et al., 2014), and every month spent not walking affects how the infant with DS interacts with the world, which may have cascading effects on other developing domains and alter the child's developmental trajectory (Yamauchi et al., 2019).



Figure 4. (a) Infant stepping during treadmill training. Photo provided by D. A. Ulrich. (b) Modified ride-on car which 'grows' with the child. Adapted from Hospodar et al. (2020). Image credits: (a) D. A. Ulrich; (b) reproduced by permission of Taylor & Francis.

As the treadmill intervention demonstrated, therapies that are tailored to the needs of the individual seem to provide the largest effect. In the motor domain, a number of possible interventions have been developed which can be applied to different developmental stages, scaffolding development one step at a time. These include 'Tummy Time' (Wentz, 2017), 'Kick and Drive Gym' (Lloyd & Ulrich, 2006), 'sticky mittens' (Libertus et al., 2015; but cf. Corbetta et al., 2016), 'Playskin Lift' (Lobo et al., 2016), and 'Go Baby Go' (Hospodar et al., 2021; Logan et al., 2017). When appropriate, a combination of these interventions may

facilitate outcomes. For example, the treadmill may enable infants with DS to achieve a number of steps, or the type of step, they would not otherwise be able to self-generate, but it does not provide aspects of locomotion such as visual flow or the experience of reaching new people and objects. This is something that ‘Go Baby Go’, a modified ride-on car, can provide. As the child grows, the car can be adjusted to ‘grow’ with them, from seated, to standing, to walking (see Fig. 4b). This provides an experience that would be enjoyable and sufficiently challenging for the child to self-generate locomotion but not too challenging that it becomes discouraging. Therefore, a combined intervention utilising both the motorized treadmill and self-generated ride-on car might enhance intervention gains.

It may also be advantageous to combine different types of interventions across domains. For example, as we discussed earlier in this chapter, motor activity is embedded in social interaction. Indeed, Ulrich (2010) notes that parents often reported enjoying treadmill intervention time, as it provided them with ‘face time’ to spend in interaction with their infants. Therefore, as long as it is not too demanding on the child, one approach might be to integrate movement therapy with other types of therapies (e.g., speech and language therapy), rather than targeting each domain in separate sessions.

7.4.2 Ready for pharmacological interventions?

The principle of behavioural intervention is to capitalise on brain plasticity by increasing stimulation. However, as noted above, plasticity itself is reduced in infants with DS.

Therefore, preclinical research has often focused on identifying pharmacological targets for altering neural constraints (for a review, see the collection edited by Dierssen, 2020).

However, translating preclinical research to human clinical trials presents some serious challenges (Lee et al., 2020; Zhu et al., 2019). One of them involves a lack of available tools that can accurately measure intervention-related changes across domains in individuals with

DS (d'Ardhuy et al., 2015; Hedge et al., 2018). This is especially the case for studies involving infants and young children (D'Souza et al., 2021; Lee et al., 2020). Yet, obtaining accurate measurements across domains is crucial, as some pharmacological interventions (e.g., fluoxetine) have been suggested even for foetuses with DS (Bartesaghi et al., 2015; Guedj et al., 2014; Guidi et al., 2014; for an ethical discussion, see de Wert et al., 2017).⁷ As discussed above, because the developing system is highly interconnected, altering the chemical properties of one part may have unpredictable and widespread effects on the entire system. For example, it has been suggested that SSRI medications, which include fluoxetine, may have detrimental effects in pregnancy, including increased risk of heart defects, brain and craniofacial abnormalities, neonatal seizures, and changes in neurodevelopment and behaviour (for review, see Ortega-Alves & Urato, 2016). Therefore, high quality outcome measures are needed both to capture domains in which gains would be expected (such as improved learning) and to reliably measure any negative effects a pharmacological intervention may have.

8 Conclusions

Compared to many other neurodevelopmental disorders, DS is often diagnosed—and therefore can be studied—very early in development. This provides us with a unique window onto early developmental processes. Rather than describing DS as a static assemblage of relative strength and difficulties, we have emphasized the importance of viewing DS as an adaptive system with a different start state (i.e., trisomy 21). We have argued that trisomy 21 has cascading effects on the adapting system, such as how it processes information and explores the environment. This may in turn lead to adaptations such as over-reliance on social

⁷ A pilot feasibility trial of perinatal fluoxetine treatment at the University of Texas was proposed in 2014 (as mentioned in Martínez Cué & Dierssen, 2020) but has yet to share any findings.

agents. These adaptations may be useful in the short term, but they are likely to constrain the emergence of functions later in development. Taking a developmental perspective may therefore help us to understand how the DS phenotype emerges, and what the best intervention approaches are likely to be.

9 Acknowledgements

HD is the Beatrice Mary Dale Research Fellow, supported by Newnham College (University of Cambridge) and the Isaac Newton Trust. Our work is further supported by the Waterloo Foundation and the Baily Thomas Charitable Fund.

10 References

- Ábrahám, H., Vincze, A., Veszprémi, B., Kravják, A., Gömöri, É., Kovács, G. G., & Seress, L. (2012). Impaired myelination of the human hippocampal formation in Down syndrome. *International Journal of Developmental Neuroscience: The Official Journal of the International Society for Developmental Neuroscience*, *30*(2), 147–158.
<https://doi.org/10.1016/j.ijdevneu.2011.11.005>
- Abramovitch, R., Stanhope, L., Pepler, D., & Corter, C. (1987). Influence of Down's syndrome on sibling interaction. *Journal of Child Psychology and Psychiatry*, *28*(6), 865–879. <https://doi.org/10.1111/j.1469-7610.1987.tb00675.x>
- Adolph, K. E., Cole, W. G., Komati, M., Garciaguirre, J. S., Badaly, D., Lingeman, J. M., Chan, G. L. Y., & Sotsky, R. B. (2012). How do you learn to walk? Thousands of steps and dozens of falls per day. *Psychological Science*, *23*(11), 1387–1394.
<https://doi.org/10.1177/0956797612446346>
- Adolph, K. E., & Hoch, J. E. (2019). Motor Development: Embodied, Embedded, Enculturated, and Enabling. *Annual Review of Psychology*, *70*(1), 141–164.

<https://doi.org/10.1146/annurev-psych-010418-102836>

Åkerström, M. S., & Sanner, G. (1993). Movement patterns in children with Down's syndrome: A pilot study. *Physiotherapy Theory and Practice*, 9(1), 33–41.

<https://doi.org/10.3109/09593989309036484>

Almeida, R. G., & Lyons, D. A. (2017). On Myelinated Axon Plasticity and Neuronal Circuit Formation and Function. *Journal of Neuroscience*, 37(42), 10023–10034.

<https://doi.org/10.1523/JNEUROSCI.3185-16.2017>

Alsaied, T., Marino, B. S., Esbensen, A. J., Anixt, J. S., Epstein, J. N., & Cnota, J. F. (2016). Does Congenital Heart Disease Affect Neurodevelopmental Outcomes in Children with Down Syndrome? *Congenital Heart Disease*, 11(1), 26–33.

<https://doi.org/10.1111/chd.12322>

Anderson, J. S., Nielsen, J. A., Ferguson, M. A., Burbach, M. C., Cox, E. T., Dai, L., Gerig, G., Edgin, J. O., & Korenberg, J. R. (2013). Abnormal brain synchrony in Down syndrome. *NeuroImage: Clinical*, 2, 703–715. <https://doi.org/10.1016/j.nicl.2013.05.006>

Angulo-Barroso, R., Burghardt, A. R., Lloyd, M. C., & Ulrich, D. A. (2008). Physical activity in infants with Down syndrome receiving a treadmill intervention. *Infant Behavior and Development*, 31(2), 255–269.

<https://doi.org/10.1016/j.infbeh.2007.10.003>

Antonarakis, S. E. (2017). Down syndrome and the complexity of genome dosage imbalance. *Nature Reviews Genetics*, 18(3), 147–163. <https://doi.org/10.1038/nrg.2016.154>

Antonarakis, S. E., Skotko, B. G., Rafii, M. S., Strydom, A., Pape, S. E., Bianchi, D. W., Sherman, S. L., & Reeves, R. H. (2020). Down syndrome. *Nature Reviews Disease Primers*, 6(1), 9. <https://doi.org/10.1038/s41572-019-0143-7>

Barnet, A. B., Elizabeth, Ohlrich, S., & Shanks, B. L. (1971). EEG Evoked Responses to Repetitive Auditory Stimulation in Normal and Down's Syndrome Infants.

Developmental Medicine & Child Neurology, 13(3), 321–329.

<https://doi.org/10.1111/j.1469-8749.1971.tb03269.x>

Bartesaghi, R., Haydar, T. F., Delabar, J. M., Dierssen, M., Martinez-Cue, C., & Bianchi, D. W. (2015). New Perspectives for the Rescue of Cognitive Disability in Down Syndrome. *Journal of Neuroscience*, 35(41), 13843–13852.

<https://doi.org/10.1523/JNEUROSCI.2775-15.2015>

Bassett, D. S., & Sporns, O. (2017). Network neuroscience. *Nature Neuroscience*, 20(3), 353–364. <https://doi.org/10.1038/nn.4502>

Bates, E., Elman, J., Johnson, M. H., Karmiloff-Smith, A., Parisi, D., & Plunkett, K. (1996). *Rethinking Innateness*. The MIT Press. <https://doi.org/10.7551/mitpress/5929.001.0001>

Bates, E., Reilly, J., Wulfeck, B., Dronkers, N., Opie, M., Fenson, J., Kriz, S., Jeffries, R., Miller, L., & Herbst, K. (2001). Differential effects of unilateral lesions on language production in children and adults. *Brain and Language*, 79(2), 223–265.

<https://doi.org/10.1006/brln.2001.2482>

Becker, L. E., Armstrong, D. L., & Chan, F. (1986). Dendritic atrophy in children with Down's syndrome. *Annals of Neurology*, 20(4), 520–526.

<https://doi.org/10.1002/ana.410200413>

Benavides-Piccione, R., Ballesteros-Yáñez, I., de Lagrán, M. M., Elston, G., Estivill, X., Fillat, C., Defelipe, J., & Dierssen, M. (2004). On dendrites in Down syndrome and DS murine models: A spiny way to learn. *Progress in Neurobiology*, 74(2), 111–126.

<https://doi.org/10.1016/j.pneurobio.2004.08.001>

Berger, J., & Cunningham, C. C. (1981). The development of eye contact between mothers and normal versus Down's syndrome infants. *Developmental Psychology*, 17(5), 678–689. <https://doi.org/10.1037/0012-1649.17.5.678>

Berger, S. E., Harbourne, R. T., Arman, F., & Sonsini, J. (2019). Balancing act(ion):

Attentional and postural control strategies predict extent of infants' perseveration in a sitting and reaching task. *Cognitive Development*, 50, 13–21.

<https://doi.org/10.1016/J.COGDEV.2018.12.001>

Berger, S. E., Harbourne, R. T., & Horger, M. N. (2018). Cognition–Action Trade-Offs Reflect Organization of Attention in Infancy. *Advances in Child Development and Behavior*, 54, 45–86. <https://doi.org/10.1016/BS.ACDB.2017.11.001>

Block, M. E. (1991). Motor development in children with Down syndrome: A review of the literature. *Adapted Physical Activity Quarterly*, 8(3), 179–209.

<https://doi.org/10.1123/apaq.8.3.179>

Blumberg, M. S. (2017). Development evolving: the origins and meanings of instinct. *Wiley Interdisciplinary Reviews: Cognitive Science*, 8(1–2), e1371.

<https://doi.org/10.1002/wcs.1371>

Bornstein, M. H., & Sigman, M. D. (1986). Continuity in mental development from infancy. *Child Development*, 57(2), 251–274. <https://doi.org/10.2307/1130581>

Bornstein, M. H., & Tamis-LeMonda, C. S. (1989). Maternal responsiveness and cognitive development in children. *New Directions for Child and Adolescent Development*, 1989(43), 49–61. <https://doi.org/10.1002/cd.23219894306>

Boudreau, J. P., & Bushnell, E. W. (2000). Spilling thoughts: configuring attentional resources in infants' goal-directed actions. *Infant Behavior and Development*, 23(3–4), 543–566. [https://doi.org/10.1016/S0163-6383\(01\)00059-5](https://doi.org/10.1016/S0163-6383(01)00059-5)

Bourgeois, J. P. (2008). Handbook of Developmental Cognitive Neuroscience. In C. A. Nelson & M. Luciana (Eds.), *Handbook of developmental cognitive neuroscience*. The MIT Press. <https://doi.org/10.7551/mitpress/7437.001.0001>

Brandt, B. R. (1996). Impaired tactual perception in children with Down's syndrome. *Scandinavian Journal of Psychology*, 37(3), 312–316. <https://doi.org/10.1111/j.1467->

9450.1996.tb00663.x

- Bremner, J. G., & Fogel, A. (2004). *Blackwell Handbook of Infant Development*. Blackwell Publishing Ltd. <https://doi.org/10.1002/9780470996348>
- Bruni, M., Cameron, D., Dua, S., & Noy, S. (2010). Reported Sensory Processing of Children with Down Syndrome. *Physical & Occupational Therapy In Pediatrics*, 30(4), 280–293. <https://doi.org/10.3109/01942638.2010.486962>
- Buzsáki, G. (2004). Large-scale recording of neuronal ensembles. *Nature Neuroscience*, 7(5), 446–451. <https://doi.org/10.1038/nn1233>
- Buzsáki, G. (2006). *Rhythms of the Brain*. Oxford University Press. <https://doi.org/10.1093/acprof:oso/9780195301069.001.0001>
- Bybee, J., & Zigler, E. (1998). Outerdirectedness in individuals with and without mental retardation: A review. In E. Zigler & D. Bennett-Gates (Eds.), *Handbook of mental retardation and development* (pp. 165–205). Cambridge University Press.
- Campos, J. J., Anderson, D. D. I., Barbu-Roth, M. A., Hubbard, E. M., Hertenstein, M. J., & Witherington, D. (2000). Travel broadens the mind. *Infancy*, 1(2), 149–219. https://doi.org/10.1207/S15327078IN0102_1
- Carbó-Carreté, M., Cañete-Massé, C., Peró-Cebollero, M., & Guàrdia-Olmos, J. (2020). Using fMRI to Assess Brain Activity in People With Down Syndrome: A Systematic Review. *Frontiers in Human Neuroscience*, 14, 147. <https://doi.org/10.3389/fnhum.2020.00147>
- Cardoso, A. C. das N., Campos, A. C. de, Santos, M. M. dos, Santos, D. C. C., & Rocha, N. A. C. F. (2015). Motor performance of children with Down syndrome and typical development at 2 to 4 and 26 months. *Pediatric Physical Therapy : The Official Publication of the Section on Pediatrics of the American Physical Therapy Association*, 27(2), 135–141. <https://doi.org/10.1097/PEP.0000000000000120>

- Carr, J. (1970). Mental and motor development in young mongol children. *Journal of Mental Deficiency Research*, *14*(3), 205–220. <https://doi.org/10.1111/j.1365-2788.1970.tb01116.x>
- Carr, J., & Collins, S. (2018). 50 years with Down syndrome: A longitudinal study. *Journal of Applied Research in Intellectual Disabilities*, *31*(5), 743–750. <https://doi.org/10.1111/jar.12438>
- Carvajal, F., & Iglesias, J. (2000). Looking Behavior and Smiling in Down Syndrome Infants. *Journal of Nonverbal Behavior*, *24*(3), 225–236. <https://doi.org/10.1023/A:1006693121491>
- Carvalho, R. P., Tudella, E., Caljouw, S. R., & Savelsbergh, G. J. P. (2008). Early control of reaching: Effects of experience and body orientation. *Infant Behavior and Development*, *31*(1), 23–33. <https://doi.org/10.1016/j.infbeh.2007.06.001>
- Cebula, K. R., Moore, D. G., & Wishart, J. G. (2010). Social cognition in children with Down's syndrome: challenges to research and theory building. *Journal of Intellectual Disability Research*, *54*(2), 113–134. <https://doi.org/10.1111/j.1365-2788.2009.01215.x>
- Chakrabarti, L., Galdzicki, Z., & Haydar, T. F. (2007). Defects in Embryonic Neurogenesis and Initial Synapse Formation in the Forebrain of the Ts65Dn Mouse Model of Down Syndrome. *Journal of Neuroscience*, *27*(43), 11483–11495. <https://doi.org/10.1523/JNEUROSCI.3406-07.2007>
- Chapman, R. S., & Hesketh, L. (2001). Language, cognition, and short-term memory in individuals with Down syndrome. *Down Syndrome Research and Practice*, *7*(1), 1–7. <https://doi.org/10.3104/reviews.108>
- Chen, C., Jiang, P., Xue, H., Peterson, S. E., Tran, H. T., McCann, A. E., Parast, M. M., Li, S., Pleasure, D. E., Laurent, L. C., Loring, J. F., Liu, Y., & Deng, W. (2014). Role of astroglia in Down's syndrome revealed by patient-derived human-induced pluripotent

stem cells. *Nature Communications*, 5, 4430. <https://doi.org/10.1038/ncomms5430>

Cherubini, E., Gaiarsa, J. L., & Ben-Ari, Y. (1991). GABA: an excitatory transmitter in early postnatal life. *Trends in Neurosciences*, 14(12), 515–519. [https://doi.org/10.1016/0166-2236\(91\)90003-d](https://doi.org/10.1016/0166-2236(91)90003-d)

Cielinski, K. L., Vaughn, B. E., Seifer, R., & Contreras, J. (1995). Relations among sustained engagement during play, quality of play, and mother-child interaction in samples of children with Down syndrome and normally developing toddlers. *Infant Behavior and Development*, 18(2), 163–176. [https://doi.org/10.1016/0163-6383\(95\)90046-2](https://doi.org/10.1016/0163-6383(95)90046-2)

Clearfield, M. W., Osborne, C. N., & Mullen, M. (2008). Learning by looking: Infants' social looking behavior across the transition from crawling to walking. *Journal of Experimental Child Psychology*, 100(4), 297–307. <https://doi.org/10.1016/j.jecp.2008.03.005>

Colman, H., Nabekura, J., & Lichtman, J. W. (1997). Alterations in synaptic strength preceding axon withdrawal. *Science*, 275(5298), 356–361. <https://doi.org/10.1126/science.275.5298.356>

Contestabile, A., Magara, S., & Cancedda, L. (2017). The GABAergic Hypothesis for Cognitive Disabilities in Down Syndrome. *Frontiers in Cellular Neuroscience*, 11, 54. <https://doi.org/10.3389/fncel.2017.00054>

Corbetta, D., & Bojczyk, K. E. (2002). Infants return to two-handed reaching when they are learning to walk. *Journal of Motor Behavior*, 34(1), 83–95. <https://doi.org/10.1080/00222890209601933>

Corbetta, D., Williams, J. L., & Haynes, J. M. (2016). Bare fingers, but no obvious influence of “prickly” Velcro! In the absence of parents' encouragement, it is not clear that “sticky mittens” provide an advantage to the process of learning to reach. *Infant Behavior and Development*, 42, 168–178. <https://doi.org/10.1016/j.infbeh.2015.05.001>

- Cowan, W. M. (1979). The Development of the Brain. *Scientific American*, 241(3), 112–133.
<https://doi.org/10.1038/scientificamerican0979-112>
- Cowie, V. (1970). *A study of the early development of mongols*. Pergamon.
- Crone, E. A. (2014). Cognitive control and affective decision making in childhood and adolescence. In M. S. Gazzaniga & G. R. Mangun (Eds.), *The cognitive neurosciences* (5th ed., pp. 23–32). MIT Press.
- d’Ardhuy, X. L., Edgin, J. O., Bouis, C., de Sola, S., Goeldner, C., Kishnani, P., Nöldeke, J., Rice, S., Sacco, S., Squassante, L., Spiridigliozzi, G., Visootsak, J., Heller, J., & Khwaja, O. (2015). Assessment of Cognitive Scales to Examine Memory, Executive Function and Language in Individuals with Down Syndrome: Implications of a 6-month Observational Study. *Frontiers in Behavioral Neuroscience*, 9, 300.
<https://doi.org/10.3389/fnbeh.2015.00300>
- D’Souza, D., & D’Souza, H. (2019). Emergent and constrained: Understanding brain and cognitive development. *Journal of Neurolinguistics*, 49, 228–231.
<https://doi.org/10.1016/j.jneuroling.2018.04.011>
- D’Souza, D., D’Souza, H., Horváth, K., Plunkett, K., & Karmiloff-Smith, A. (2020). Sleep is atypical across neurodevelopmental disorders in infants and toddlers: A cross-syndrome study. *Research in Developmental Disabilities*, 97, 103549.
<https://doi.org/10.1016/J.RIDD.2019.103549>
- D’Souza, D., D’Souza, H., Johnson, M. H., & Karmiloff-Smith, A. (2015). Concurrent Relations between Face Scanning and Language: A Cross-Syndrome Infant Study. *PLOS ONE*, 10(10), e0139319. <https://doi.org/10.1371/journal.pone.0139319>
- D’Souza, D., D’Souza, H., Johnson, M. H., & Karmiloff-Smith, A. (2016). Audio-visual speech perception in infants and toddlers with Down syndrome, fragile X syndrome, and Williams syndrome. *Infant Behavior and Development*, 44, 249–262.

<https://doi.org/10.1016/j.infbeh.2016.07.002>

D'Souza, D., D'Souza, H., Jones, E. J. H., & Karmiloff-Smith, A. (2020). Attentional abilities constrain language development: A cross-syndrome infant/toddler study. *Developmental Science*, 23(6), e12961. <https://doi.org/10.1111/desc.12961>

D'Souza, D., D'Souza, H., & Karmiloff-Smith, A. (2017). Precursors to language development in typically and atypically developing infants and toddlers: The importance of embracing complexity. *Journal of Child Language*, 44(3), 591–627. <https://doi.org/10.1017/S030500091700006X>

D'Souza, D., & Karmiloff-Smith, A. (2011). When modularization fails to occur: A developmental perspective. *Cognitive Neuropsychology*, 28(3–4), 276–287. <https://doi.org/10.1080/02643294.2011.614939>

D'Souza, D., & Karmiloff-Smith, A. (2016). Why a developmental perspective is critical for understanding human cognition. *Behavioral and Brain Sciences*, 39, e122. <https://doi.org/10.1017/S0140525X15001569>

D'Souza, H., Brady, D., Wiseman, F. K., Good, M. A., & Thomas, M. S. C. (2021). Aligning cognitive studies in mouse models and human infants/toddlers: The case of Down syndrome. In M. S. C. Thomas, D. Mareschal, & V. Knowland (Eds.), *Taking development seriously: A Festschrift for Annette Karmiloff-Smith: Neuroconstructivism and the multi-disciplinary approach to understanding the emergence of mind* (pp. 213–238). Routledge. <https://doi.org/10.4324/9780429445590-16-16>

D'Souza, H., Cowie, D., Karmiloff-Smith, A., & Bremner, A. J. (2017). Specialization of the motor system in infancy: from broad tuning to selectively specialized purposeful actions. *Developmental Science*, 20(4), e12409. <https://doi.org/10.1111/desc.12409>

D'Souza, H., & Karmiloff-Smith, A. (2017). Neurodevelopmental disorders. *Wiley Interdisciplinary Reviews: Cognitive Science*, 8(1–2), e1398.

<https://doi.org/10.1002/wcs.1398>

D'Souza, H., Lathan, A., Karmiloff-Smith, A., & Mareschal, D. (2020). Down syndrome and parental depression: A double hit on early expressive language development. *Research in Developmental Disabilities, 100*, 103613. <https://doi.org/10.1016/j.ridd.2020.103613>

D'Souza, H., Mason, L., Mok, K. Y., Startin, C. M., Hamburg, S., Hithersay, R., Baksh, R. A. A., Hardy, J., Strydom, A., & Thomas, M. S. C. (2020). Differential Associations of Apolipoprotein E ϵ 4 Genotype With Attentional Abilities Across the Life Span of Individuals With Down Syndrome. *JAMA Network Open, 3*(9), e2018221. <https://doi.org/10.1001/jamanetworkopen.2020.18221>

Daunhauer, L. A., Schworer, E., & Howshar, M. (2017). Parenting Matters: Parent–Child Interactions in Down Syndrome and Recommendations for Future Research. *International Review of Research in Developmental Disabilities, 53*, 1–43. <https://doi.org/10.1016/BS.IRRDD.2017.08.003>

de Campos, A. C., da Costa, C. S. N., Savelsbergh, G. J. P., & Rocha, N. A. C. F. (2013). Infants with Down syndrome and their interactions with objects: Development of exploratory actions after reaching onset. *Research in Developmental Disabilities, 34*(6), 1906–1916. <https://doi.org/10.1016/j.ridd.2013.03.001>

De Felipe, J., Marco, P., Fairén, A., & Jones, E. G. (1997). Inhibitory synaptogenesis in mouse somatosensory cortex. *Cerebral Cortex, 7*(7), 619–634. <https://doi.org/10.1093/cercor/7.7.619>

de Wert, G., Dondorp, W., & Bianchi, D. W. (2017). Fetal therapy for Down syndrome: an ethical exploration. *Prenatal Diagnosis, 37*(3), 222–228. <https://doi.org/10.1002/pd.4995>

Dean, D. C., Jerskey, B. A., Chen, K., Protas, H., Thiyyagura, P., Roontiva, A., O'Muircheartaigh, J., Dirks, H., Waskiewicz, N., Lehman, K., Siniard, A. L., Turk, M.

- N., Hua, X., Madsen, S. K., Thompson, P. M., Fleisher, A. S., Huentelman, M. J., Deoni, S. C. L., & Reiman, E. M. (2014). Brain Differences in Infants at Differential Genetic Risk for Late-Onset Alzheimer Disease. *JAMA Neurology*, *71*(1), 11–22. <https://doi.org/10.1001/jamaneurol.2013.4544>
- Deckers, S. R. J. ., Van Zaalen, Y., Van Balkom, H., & Verhoeven, L. (2019). Predictors of receptive and expressive vocabulary development in children with Down syndrome. *International Journal of Speech-Language Pathology*, *21*(1), 10–22. <https://doi.org/10.1080/17549507.2017.1363290>
- Den Hartigh, R. J. R., Cox, R. F. A., & Van Geert, P. L. C. (2017). Complex versus Complicated Models of Cognition. In L. Magnani & T. Bertolotti (Eds.), *Springer Handbook of Model-Based Science* (pp. 657–669). Springer. https://doi.org/10.1007/978-3-319-30526-4_30
- Díaz, F., & Zurrón, M. (1995). Auditory evoked potentials in Down's syndrome. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *96*(6), 526–537. [https://doi.org/10.1016/0013-4694\(95\)00080-I](https://doi.org/10.1016/0013-4694(95)00080-I)
- Dichter, M. A., & Ayala, G. F. (1987). Cellular mechanisms of epilepsy: a status report. *Science*, *237*(4811), 157–164. <https://doi.org/10.1126/science.3037700>
- Dierssen, M. (2012). Down syndrome: The brain in trisomic mode. *Nature Reviews Neuroscience*, *13*(12), 844–858. <https://doi.org/10.1038/nrn3314>
- Dierssen, M. (2020). Preclinical Research in Down Syndrome: Insights for Pathophysiology and Treatments. In M. Dierssen (Ed.), *Progress in Brain Research* (Vol. 251). Elsevier. [https://doi.org/10.1016/S0079-6123\(20\)X0002-1](https://doi.org/10.1016/S0079-6123(20)X0002-1)
- Donato, F., Rompani, S. B., & Caroni, P. (2013). Parvalbumin-expressing basket-cell network plasticity induced by experience regulates adult learning. *Nature*, *504*(7479), 272–276. <https://doi.org/10.1038/nature12866>

- Down, J. L. H. (1867). Observations on an Ethnic Classification of Idiots. *Journal of Mental Science*, 13(61), 121–123. <https://doi.org/10.1192/bjp.13.61.121>
- Dykens, E. M., & Hodapp, R. M. (2001). Research in mental retardation: Toward an etiologic approach. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 42(1), 49–71. <https://doi.org/10.1017/S0021963001006540>
- Edelman, G. M. (1987). *Neural Darwinism: The theory of neuronal group selection*. Basic Books.
- Edgin, J. O., Tooley, U., Demara, B., Nyhuis, C., Anand, P., & Spanò, G. (2015). Sleep Disturbance and Expressive Language Development in Preschool-Age Children With Down Syndrome. *Child Development*, 86(6), 1984–1998. <https://doi.org/10.1111/cdev.12443>
- Fair, D. A., Cohen, A. L., Power, J. D., Dosenbach, N. U. F., Church, J. A., Miezin, F. M., Schlaggar, B. L., & Petersen, S. E. (2009). Functional brain networks develop from a “local to distributed” organization. *PLoS Computational Biology*, 5(5), e1000381. <https://doi.org/10.1371/journal.pcbi.1000381>
- Fair, D. A., Dosenbach, N. U. F., Church, J. A., Cohen, A. L., Brahmbhatt, S., Miezin, F. M., Barch, D. M., Raichle, M. E., Petersen, S. E., & Schlaggar, B. L. (2007). Development of distinct control networks through segregation and integration. *Proceedings of the National Academy of Sciences*, 104(33), 13507–13512. <https://doi.org/10.1073/pnas.0705843104>
- Fausey, C. M., Jayaraman, S., & Smith, L. B. (2016). From faces to hands: Changing visual input in the first two years. *Cognition*, 152, 101–107. <https://doi.org/10.1016/j.cognition.2016.03.005>
- Fidler, D. J. (2005). The emerging Down syndrome behavioral phenotype in early childhood. *Infants & Young Children*, 18(2), 86–103. <https://doi.org/10.1097/00001163->

200504000-00003

- Fidler, D. J., Hepburn, S. L., Mankin, G., & Rogers, S. J. (2005). Praxis skills in young children with Down syndrome, other developmental disabilities, and typically developing children. *American Journal of Occupational Therapy, 59*(2), 129–138. <https://doi.org/10.5014/ajot.59.2.129>
- Fidler, D. J., Most, D. E., Booth-LaForce, C., & Kelly, J. F. (2008). Emerging Social Strengths in Young Children With Down Syndrome. *Infants & Young Children, 21*(3), 207–220. <https://doi.org/10.1097/01.IYC.0000324550.39446.1f>
- Fidler, D. J., Needham, A. W., & Schworer, E. (2019). Infant foundations in Down syndrome: early constraints on cognitive skill acquisition. *International Review of Research in Developmental Disabilities, 56*, 41–65. <https://doi.org/10.1016/BS.IRRDD.2019.06.008>
- Fidler, D. J., Schworer, E., Prince, M. A., Will, E. A., Needham, A. W., & Daunhauer, L. A. (2019). Exploratory behavior and developmental skill acquisition in infants with Down syndrome. *Infant Behavior and Development, 54*, 140–150. <https://doi.org/10.1016/J.INFBEH.2019.02.002>
- Fidler, D. J., Schworer, E., Will, E. A., Patel, L., & Daunhauer, L. A. (2019). Correlates of early cognition in infants with Down syndrome. *Journal of Intellectual Disability Research, 63*(3), 205–214. <https://doi.org/10.1111/jir.12566>
- Fields, R. D. (2015). A new mechanism of nervous system plasticity: activity-dependent myelination. *Nature Reviews Neuroscience, 16*(12), 756–767. <https://doi.org/10.1038/nrn4023>
- Flavell, S. W., & Greenberg, M. E. (2008). Signaling Mechanisms Linking Neuronal Activity to Gene Expression and Plasticity of the Nervous System. *Annual Review of Neuroscience, 31*(1), 563–590. <https://doi.org/10.1146/annurev.neuro.31.060407.125631>

- Ford, D. H., & Lerner, R. M. (1992). *Developmental systems theory: An integrative approach*. Sage Publications, Inc.
- Frankenhuis, W. E., & Panchanathan, K. (2011). Individual differences in developmental plasticity may result from stochastic sampling. *Perspectives on Psychological Science*, 6(4), 336–347. <https://doi.org/10.1177/1745691611412602>
- Gibson, D. (1978). *Down's syndrome: the psychology of mongolism*. Cambridge University Press.
- Gibson, E. J. (1988). Exploratory behavior in the development of perceiving, acting, and the acquiring of knowledge. *Annual Review of Psychology*, 39(1), 1–42. <https://doi.org/10.1146/annurev.ps.39.020188.000245>
- Gibson, E. J., & Pick, A. D. (2000). *An ecological approach to perceptual learning and development*. Oxford University Press.
- Gilmore, L., & Cuskelly, M. (2009). A longitudinal study of motivation and competence in children with Down syndrome: early childhood to early adolescence. *Journal of Intellectual Disability Research*, 53(5), 484–492. <https://doi.org/10.1111/j.1365-2788.2009.01166.x>
- Gilmore, L., Cuskelly, M., Jobling, A., & Hayes, A. (2009). Maternal support for autonomy: Relationships with persistence for children with Down syndrome and typically developing children. *Research in Developmental Disabilities*, 30(5), 1023–1033. <https://doi.org/10.1016/J.RIDD.2009.02.005>
- Glenn, S., Dayus, B., Cunningham, C., & Horgan, M. (2001). Mastery motivation in children with Down syndrome. *Down's Syndrome, Research and Practice*, 7(2), 52–59. <https://doi.org/10.3104/reports.114>
- Godfrey, M., & Lee, N. R. (2018). Memory profiles in Down syndrome across development: a review of memory abilities through the lifespan. *Journal of Neurodevelopmental*

Disorders, 10(1), 5. <https://doi.org/10.1186/s11689-017-9220-y>

Golden, J. A., & Hyman, B. T. (1994). Development of the Superior Temporal Neocortex Is

Anomalous in Trisomy 21. *Journal of Neuropathology & Experimental Neurology*,

53(5), 513–520. <https://doi.org/10.1097/00005072-199409000-00011>

Gottlieb, G. (1970). Conceptions of prenatal behavior. In L. R. Aronson, E. Tobach, D. S.

Lehrman, & J. S. Rosenblatt (Eds.), *The Significance of Biology for Human*

Development: A Developmental Psychobiological Systems View Development and evolution of behavior (pp. 111–137). Freeman.

Gottlieb, G. (2001). *Individual Development and Evolution*. Psychology Press.

<https://doi.org/10.4324/9781410604422>

Gottlieb, G. (2007). Probabilistic epigenesis. *Developmental Science*, 10(1), 1–11.

<https://doi.org/10.1111/j.1467-7687.2007.00556.x>

Greenough, W. T., Black, J. E., & Wallace, C. S. (1987). Experience and brain development.

Child Development, 58(3), 539–559. <https://doi.org/10.2307/1130197>

Guedj, F., Bianchi, D. W., & Delabar, J.-M. (2014). Prenatal treatment of Down syndrome.

Current Opinion in Obstetrics and Gynecology, 26(2), 92–103.

<https://doi.org/10.1097/GCO.0000000000000056>

Guidi, S., Ciani, E., Bonasoni, P., Santini, D., & Bartesaghi, R. (2011). Widespread

Proliferation Impairment and Hypocellularity in the Cerebellum of Fetuses with Down

Syndrome. *Brain Pathology*, 21(4), 361–373. [https://doi.org/10.1111/j.1750-](https://doi.org/10.1111/j.1750-3639.2010.00459.x)

[3639.2010.00459.x](https://doi.org/10.1111/j.1750-3639.2010.00459.x)

Guidi, S., Stagni, F., Bianchi, P., Ciani, E., Giacomini, A., De Franceschi, M., Moldrich, R.,

Kurniawan, N., Mardon, K., Giuliani, A., Calzà, L., & Bartesaghi, R. (2014). Prenatal

pharmacotherapy rescues brain development in a Down's syndrome mouse model.

Brain, 137(2), 380–401. <https://doi.org/10.1093/brain/awt340>

- Gunbey, H. P., Bilgici, M. C., Aslan, K., Has, A. C., Ogur, M. G., Alhan, A., & Incesu, L. (2017). Structural brain alterations of Down's syndrome in early childhood evaluation by DTI and volumetric analyses. *European Radiology*, *27*(7), 3013–3021. <https://doi.org/10.1007/s00330-016-4626-6>
- Gunn, P., Berry, P., & Andrews, R. J. (1982). Looking behavior of Down syndrome infants. *American Journal of Mental Deficiency*, *87*(3), 344–347. <http://www.ncbi.nlm.nih.gov/pubmed/6217747>
- Hahn, L. J., Loveall, S. J., Savoy, M. T., Neumann, A. M., & Ikuta, T. (2018). Joint attention in Down syndrome: A meta-analysis. *Research in Developmental Disabilities*, *78*, 89–102. <https://doi.org/10.1016/J.RIDD.2018.03.013>
- Haider, B., Duque, A., Hasenstaub, A. R., & McCormick, D. A. (2006). Neocortical network activity in vivo is generated through a dynamic balance of excitation and inhibition. *Journal of Neuroscience*, *26*(17), 4535–4545. <https://doi.org/10.1523/JNEUROSCI.5297-05.2006>
- Haley, S. M. (1986). Postural Reactions in Infants with Down Syndrome. *Physical Therapy*, *66*(1), 17–22. <https://doi.org/10.1093/ptj/66.1.17>
- Hamner, T., Udhmani, M. D., Osipowicz, K. Z., & Lee, N. R. (2018). Pediatric Brain Development in Down Syndrome: A Field in Its Infancy. *Journal of the International Neuropsychological Society*, *24*(9), 966–976. <https://doi.org/10.1017/S1355617718000206>
- Harris, S. R. (1981). Effects of neurodevelopmental therapy on motor performance of infants with Down's syndrome. *Developmental Medicine & Child Neurology*, *23*(5), 477–483. <https://doi.org/10.1111/j.1469-8749.1981.tb02021.x>
- Hauck, J. L., Felzer-Kim, I. T., & Gwizdala, K. L. (2020). Early Movement Matters: Interplay of Physical Activity and Motor Skill Development in Infants With Down

Syndrome. *Adapted Physical Activity Quarterly*, 37(2), 160–176.

<https://doi.org/10.1123/apaq.2019-0012>

Hauck, J. L., Zott, G. R., Felzer-Kim, I. T., & Adkins, C. M. (2018). A comparison of low-intensity physical activity, growth, and sleep behavior in 6-month old infants. *Infant Behavior and Development*, 53, 18–24. <https://doi.org/10.1016/J.INFBEH.2018.09.013>

Hebb, D. O. (1950). Hebb, D. O. The organization of behavior: A neuropsychological theory. New York: John Wiley and Sons, Inc., 1949. 335 p. \$4.00. *Science Education*, 34(5), 336–337. <https://doi.org/10.1002/sce.37303405110>

Hedge, C., Powell, G., & Sumner, P. (2018). The reliability paradox: Why robust cognitive tasks do not produce reliable individual differences. *Behavior Research Methods*, 50(3), 1166–1186. <https://doi.org/10.3758/s13428-017-0935-1>

Held, R., & Hein, A. (1963). Movement-produced stimulation in the development of visually guided behavior. *Journal of Comparative and Physiological Psychology*, 56(5), 872–876. <https://doi.org/10.1037/h0040546>

Hepper, P. G., & Shahidullah, S. (1992). Habituation in Normal and Down's Syndrome Fetuses. *The Quarterly Journal of Experimental Psychology Section B*, 44(3–4), 305–317. <https://doi.org/10.1080/02724999208250617>

Hill Karrer, J., Karrer, R., Bloom, D., Chaney, L., & Davis, R. (1998). Event-related brain potentials during an extended visual recognition memory task depict delayed development of cerebral inhibitory processes among 6-month-old infants with Down syndrome. *International Journal of Psychophysiology*, 29(2), 167–200. [https://doi.org/10.1016/S0167-8760\(98\)00015-4](https://doi.org/10.1016/S0167-8760(98)00015-4)

Hospodar, C. M., Sabet, A., Logan, S. W., Catena, M. A., & Galloway, J. C. (2021). Exploratory analysis of a developmentally progressive modified ride-on car intervention for young children with Down syndrome. *Disability and Rehabilitation: Assistive*

Technology, 16(7), 749–757. <https://doi.org/10.1080/17483107.2019.1710773>

Huttenlocher, P. R. (1979). Synaptic density in human frontal cortex — Developmental changes and effects of aging. *Brain Research*, 163(2), 195–205.

[https://doi.org/10.1016/0006-8993\(79\)90349-4](https://doi.org/10.1016/0006-8993(79)90349-4)

Huttenlocher, P. R., & Dabholkar, A. S. (1997). Regional differences in synaptogenesis in human cerebral cortex. *The Journal of Comparative Neurology*, 387(2), 167–178.

[https://doi.org/10.1002/\(sici\)1096-9861\(19971020\)387:2<167::aid-cne1>3.0.co;2-z](https://doi.org/10.1002/(sici)1096-9861(19971020)387:2<167::aid-cne1>3.0.co;2-z)

Imai, M., Watanabe, H., Yasui, K., Kimura, Y., Shitara, Y., Tsuchida, S., Takahashi, N., & Taga, G. (2014). Functional connectivity of the cortex of term and preterm infants and infants with Down's syndrome. *NeuroImage*, 85, 272–278.

<https://doi.org/10.1016/j.neuroimage.2013.04.080>

Iverson, J. M. (2010). Developing language in a developing body: the relationship between motor development and language development. *Journal of Child Language*, 37(2), 229–261. <https://doi.org/10.1017/S0305000909990432>

Jarrold, C., & Baddeley, A. D. (1997). Short-term memory for verbal and visuospatial information in Down's syndrome. *Cognitive Neuropsychiatry*, 2(2), 101–122.

<https://doi.org/10.1080/135468097396351>

John, F. M., Bromham, N. R., Woodhouse, J. M., & Candy, T. R. (2004). Spatial Vision Deficits in Infants and Children with Down Syndrome. *Investigative Ophthalmology & Visual Science*, 45(5), 1566–1572. <https://doi.org/10.1167/iovs.03-0951>

Johnson, M. H. (2001). Functional brain development in humans. *Nature Reviews Neuroscience*, 2(7), 475–483. <https://doi.org/10.1038/35081509>

Johnson, M. H. (2011). Interactive specialization: A domain-general framework for human functional brain development? *Developmental Cognitive Neuroscience*, 1(1), 7–21.

<https://doi.org/10.1016/j.dcn.2010.07.003>

- Johnson, M. H. (2017). Autism as an adaptive common variant pathway for human brain development. *Developmental Cognitive Neuroscience, 25*, 5–11.
<https://doi.org/10.1016/j.dcn.2017.02.004>
- Johnson, M. H., Jones, E. J. H., & Gliga, T. (2015). Brain adaptation and alternative developmental trajectories. *Development and Psychopathology, 27*(2), 425–442.
<https://doi.org/10.1017/S0954579415000073>
- Johnson, S. P., Amso, D., & Slemmer, J. A. (2003). Development of object concepts in infancy: Evidence for early learning in an eye-tracking paradigm. *Proceedings of the National Academy of Sciences, 100*(18), 10568–10573.
<https://doi.org/10.1073/pnas.1630655100>
- Karasik, L. B., Tamis-LeMonda, C. S., & Adolph, K. E. (2011). Transition from crawling to walking and infants' actions with objects and people. *Child Development, 82*(4), 1199–1209. <https://doi.org/10.1111/j.1467-8624.2011.01595.x>
- Karasik, L. B., Tamis-LeMonda, C. S., & Adolph, K. E. (2014). Crawling and walking infants elicit different verbal responses from mothers. *Developmental Science, 17*(3), 388–395. <https://doi.org/10.1111/desc.12129>
- Karasik, L. B., Tamis-LeMonda, C. S., & Adolph, K. E. (2016). Decisions at the Brink: Locomotor Experience Affects Infants' Use of Social Information on an Adjustable Drop-off. *Frontiers in Psychology, 7*, 797. <https://doi.org/10.3389/fpsyg.2016.00797>
- Karmiloff-Smith, A. (1998). Development itself is the key to understanding developmental disorders. *Trends in Cognitive Sciences, 2*(10), 389–398. [https://doi.org/10.1016/S1364-6613\(98\)01230-3](https://doi.org/10.1016/S1364-6613(98)01230-3)
- Karmiloff-Smith, A., Al-Janabi, T., D'Souza, H., Groet, J., Massand, E., Mok, K., Startin, C., Fisher, E., Hardy, J., Nizetic, D., Tybulewicz, V., & Strydom, A. (2016). The importance of understanding individual differences in Down syndrome. *F1000Research,*

5, 389. <https://doi.org/10.12688/f1000research.7506.1>

Karmiloff-Smith, A., D'Souza, D., Dekker, T. M., Van Herwegen, J., Xu, F., Rodic, M., &

Ansari, D. (2012). Genetic and environmental vulnerabilities in children with neurodevelopmental disorders. *Proceedings of the National Academy of Sciences*, *109*(Supplement 2), 17261–17265. <https://doi.org/10.1073/pnas.1121087109>

Kavšek, M. (2004). Predicting later IQ from infant visual habituation and dishabituation: A

meta-analysis. *Journal of Applied Developmental Psychology*, *25*(3), 369–393. <https://doi.org/10.1016/J.APPDEV.2004.04.006>

Kidd, C., Piantadosi, S. T., & Aslin, R. N. (2012). The Goldilocks Effect: Human Infants

Allocate Attention to Visual Sequences That Are Neither Too Simple Nor Too Complex. *PLoS ONE*, *7*(5), e36399. <https://doi.org/10.1371/journal.pone.0036399>

Knott, F., Lewis, C., & Williams, T. (1995). Sibling Interaction of Children with Learning

Disabilities: A Comparison of Autism and Down's Syndrome. *Journal of Child Psychology and Psychiatry*, *36*(6), 965–976. <https://doi.org/10.1111/j.1469-7610.1995.tb01343.x>

Koo, B. K., Blaser, S., Harwood-Nash, D., Becker, L. E., & Murphy, E. G. (1992). Magnetic

resonance imaging evaluation of delayed myelination in Down syndrome: a case report and review of the literature. *Journal of Child Neurology*, *7*(4), 417–421. <https://doi.org/10.1177/088307389200700417>

Krakov, J. B., & Kopp, C. B. (1982). Sustained attention in young Down syndrome children.

Topics in Early Childhood Special Education, *2*(2), 32–42. <https://doi.org/10.1177/027112148200200208>

Kugel, R. B. (1970). Combatting retardation in infants with Down's syndrome. *Children*,

17(5), 188–192.

Kulkarni, V. A., & Firestein, B. L. (2012). The dendritic tree and brain disorders. *Molecular*

and Cellular Neuroscience, 50(1), 10–20. <https://doi.org/10.1016/j.mcn.2012.03.005>

Landry, S. H., & Chapieski, M. L. (1989). Joint Attention and Infant Toy Exploration:

Effects of Down Syndrome and Prematurity. *Child Development*, 60(1), 103.

<https://doi.org/10.2307/1131076>

Larsen, K. B., Laursen, H., Græm, N., Samuelsen, G. B., Bogdanovic, N., & Pakkenberg, B.

(2008). Reduced cell number in the neocortical part of the human fetal brain in Down

syndrome. *Annals of Anatomy - Anatomischer Anzeiger*, 190(5), 421–427.

<https://doi.org/10.1016/J.AANAT.2008.05.007>

Lauteslager, P. E. M. (1995). Motor Development in Young Children with Down Syndrome.

In A. Vermeer & W. E. Davis (Eds.), *Physical and motor development in mental*

retardation (pp. 75–98). Karger. <https://doi.org/10.1159/000424520>

LaVeck, B., & LaVeck, G. D. (1977). Sex differences in development among young children

with Down syndrome. *The Journal of Pediatrics*, 91(5), 767–769.

[https://doi.org/10.1016/S0022-3476\(77\)81037-8](https://doi.org/10.1016/S0022-3476(77)81037-8)

Lee, S. E., Duran-Martinez, M., Khantsis, S., Bianchi, D. W., & Guedj, F. (2020). Challenges

and Opportunities for Translation of Therapies to Improve Cognition in

Down Syndrome. *Trends in Molecular Medicine*, 26(2), 150–169.

<https://doi.org/10.1016/J.MOLMED.2019.10.001>

Legerstee, M., & Weintraub, J. (1997). The integration of person and object attention in

infants with and without Down syndrome. *Infant Behavior and Development*, 20(1), 71–

82. [https://doi.org/10.1016/S0163-6383\(97\)90062-X](https://doi.org/10.1016/S0163-6383(97)90062-X)

Lerner, R. M. (1978). Nature, Nurture, and Dynamic Interactionism. *Human Development*,

21(1), 1–20. <https://doi.org/10.1159/000271572>

Leslie, J. H., & Nedivi, E. (2011). Activity-regulated genes as mediators of neural circuit

plasticity. *Progress in Neurobiology*, 94(3), 223–237.

<https://doi.org/10.1016/J.PNEUROBIO.2011.05.002>

Libertus, K., Joh, A. S., & Needham, A. W. (2016). Motor training at 3 months affects object exploration 12 months later. *Developmental Science, 19*(6), 1058–1066.

<https://doi.org/10.1111/desc.12370>

Libertus, K., & Needham, A. (2010). Teach to reach: The effects of active vs. passive reaching experiences on action and perception. *Vision Research, 50*(24), 2750–2757.

<https://doi.org/10.1016/j.visres.2010.09.001>

Libertus, K., & Needham, A. (2011). Reaching experience increases face preference in 3-month-old infants. *Developmental Science, 14*(6), 1355–1364.

<https://doi.org/10.1111/j.1467-7687.2011.01084.x>

Liu, X., Somel, M., Tang, L., Yan, Z., Jiang, X., Guo, S., Yuan, Y., He, L., Oleksiak, A., Zhang, Y., Li, N., Hu, Y., Chen, W., Qiu, Z., Pääbo, S., & Khaitovich, P. (2012).

Extension of cortical synaptic development distinguishes humans from chimpanzees and macaques. *Genome Research, 22*(4), 611–622. <https://doi.org/10.1101/gr.127324.111>

Lloyd, M. C., Burghardt, A., Ulrich, D. A., & Angulo-Barroso, R. (2010). Physical activity and walking onset in infants with Down syndrome. *Adapted Physical Activity Quarterly, 27*(1), 1–16. <https://doi.org/10.1123/apaq.27.1.1>

Lloyd, M. C., & Ulrich, D. A. (2006). Oral and Poster. *Journal of Sport and Exercise Psychology, 28*(s1), S23–S198. <https://doi.org/10.1123/jsep.28.s1.s23>

Lobo, M. A., Koshy, J., Hall, M. L., Erol, O., Cao, H., Buckley, J. M., Galloway, J. C., & Higginson, J. (2016). Playskin Lift: Development and Initial Testing of an Exoskeletal Garment to Assist Upper Extremity Mobility and Function. *Physical Therapy, 96*(3), 390–399. <https://doi.org/10.2522/ptj.20140540>

Logan, S. W., Feldner, H. A., Bogart, K. R., Goodwin, B., Ross, S. M., Catena, M. A., Whitesell, A. A., Zefton, Z. J., Smart, W. D., & Galloway, J. C. (2017). Toy-Based

- Technologies for Children with Disabilities Simultaneously Supporting Self-Directed Mobility, Participation, and Function: A Tech Report. *Frontiers in Robotics and AI*, 4, 7. <https://doi.org/10.3389/frobt.2017.00007>
- Lott, I. T. (2012). Neurological phenotypes for Down syndrome across the life span. *Progress in Brain Research*, 197, 101–121. <https://doi.org/10.1016/B978-0-444-54299-1.00006-6>
- Lydic, J. S., & Steele, C. (1979). Assessment of the Quality of Sitting and Gait Patterns in Children with Down's Syndrome. *Physical Therapy*, 59(12), 1489–1494. <https://doi.org/10.1093/ptj/59.12.1489>
- Martin, G. E., Klusek, J., Estigarribia, B., & Roberts, J. E. (2009). Language characteristics of individuals with Down syndrome. *Topics in Language Disorders*, 29(2), 112–132. <https://doi.org/10.1097/TLD.0b013e3181a71fe1>
- Martínez Cué, C., & Dierssen, M. (2020). Plasticity as a therapeutic target for improving cognition and behavior in Down syndrome. In M. Dierssen (Ed.), *Progress in Brain Research (Vol. 251)* (pp. 269–302). <https://doi.org/10.1016/bs.pbr.2019.11.001>
- Mason-Apps, E., Stojanovik, V., Houston-Price, C., & Buckley, S. (2018). Longitudinal predictors of early language in infants with Down syndrome: A preliminary study. *Research in Developmental Disabilities*, 81, 37–51. <https://doi.org/10.1016/j.ridd.2017.12.021>
- Mazzone, L., Mugno, D., & Mazzone, D. (2004). The general movements in children with Down syndrome. *Early Human Development*, 79(2), 119–130. <https://doi.org/10.1016/j.earlhumdev.2004.04.013>
- McCall, R. B., & Carriger, M. S. (1993). A Meta-Analysis of Infant Habituation and Recognition Memory Performance as Predictors of Later IQ. *Child Development*, 64(1), 57–79. <https://doi.org/10.1111/j.1467-8624.1993.tb02895.x>

- McClelland, J. L., & Vallabha, G. (2009). Connectionist Models of Development: Mechanistic Dynamical Models with Emergent Dynamical Properties. In J. P. Spencer (Ed.), *Toward a Unified Theory of Development Connectionism and Dynamic System Theory Re-Consider* (pp. 3–24). Oxford University Press.
<https://doi.org/10.1093/acprof:oso/9780195300598.003.0001>
- McKay, S. M., & Angulo-Barroso, R. M. (2006). Longitudinal assessment of leg motor activity and sleep patterns in infants with and without Down syndrome. *Infant Behavior and Development*, 29(2), 153–168. <https://doi.org/10.1016/J.INFBEH.2005.09.004>
- McKenzie, I. A., Ohayon, D., Li, H., Paes de Faria, J., Emery, B., Tohyama, K., & Richardson, W. D. (2014). Motor skill learning requires active central myelination. *Science*, 346(6207), 318–322. <https://doi.org/10.1126/science.1254960>
- Miller, J. F. (1992). Lexical development in young children with Down syndrome. In R. Chapman (Ed.), *Processes in Language Acquisition and Language Disorders* (pp. 202–216). Mosby Year Book.
- Miller, J. F., & Leddy, M. (1999). Verbal fluency, speech intelligibility, and communicative effectiveness. In J. F. Miller, M. Leddy, & L. A. Leavitt (Eds.), *Improving the communication of people with Down syndrome* (pp. 81–91). Brookes Publishing Co.
- Mitra, A., Blank, M., & Madison, D. V. (2012). Developmentally altered inhibition in Ts65Dn, a mouse model of Down syndrome. *Brain Research*, 1440, 1–8.
<https://doi.org/10.1016/J.BRAINRES.2011.12.034>
- Moore, D. G., & George, R. (2015). ACORNS: a tool for visual modelling of causes and outcomes in neuro-developmental disorders. In J. van Herwegen & D. M. Riby (Eds.), *Neurodevelopmental Disorders: Research Challenges and Solutions* (pp. 93–113). Psychology Press.
- Moraczewski, D., Chen, G., & Redcay, E. (2018). Inter-subject synchrony as an index of

functional specialization in early childhood. *Scientific Reports*, 8(1), 2252.

<https://doi.org/10.1038/s41598-018-20600-0>

Mount, C. W., & Monje, M. (2017). Wrapped to Adapt: Experience-Dependent Myelination.

Neuron, 95(4), 743–756. <https://doi.org/10.1016/J.NEURON.2017.07.009>

Mundy, P., Kasari, C., Sigman, M., & Ruskin, E. (1995). Nonverbal communication and early language acquisition in children with Down syndrome and in normally developing children. *Journal of Speech and Hearing Research*, 38(1), 157–167.

<https://doi.org/10.1044/jshr.3801.157>

Nakano-Kobayashi, A., Awaya, T., Kii, I., Sumida, Y., Okuno, Y., Yoshida, S., Sumida, T., Inoue, H., Hosoya, T., & Hagiwara, M. (2017). Prenatal neurogenesis induction therapy normalizes brain structure and function in Down syndrome mice. *Proceedings of the National Academy of Sciences*, 114(38), 10268–10273.

<https://doi.org/10.1073/pnas.1704143114>

Navlakha, S., Barth, A. L., & Bar-Joseph, Z. (2015). Decreasing-Rate Pruning Optimizes the Construction of Efficient and Robust Distributed Networks. *PLOS Computational Biology*, 11(7), e1004347. <https://doi.org/10.1371/journal.pcbi.1004347>

Nguyen, T. L., Duchon, A., Manousopoulou, A., Loaëc, N., Villiers, B., Pani, G., Karatas, M., Mechling, A. E., Harsan, L.-A., Limanton, E., Bazureau, J.-P., Carreaux, F., Garbis, S. D., Meijer, L., & Herault, Y. (2018). Correction of cognitive deficits in mouse models of Down syndrome by a pharmacological inhibitor of DYRK1A. *Disease Models & Mechanisms*, 11(9), dmm035634. <https://doi.org/10.1242/dmm.035634>

Nielsen, M., & Hudry, K. (2010). Over-imitation in children with autism and Down syndrome. *Australian Journal of Psychology*, 62(2), 67–74.

<https://doi.org/10.1080/00049530902758613>

Oliver, A., Johnson, M. H., Karmiloff-Smith, A., & Pennington, B. (2000). Deviations in the

emergence of representations: a neuroconstructivist framework for analysing developmental disorders. *Developmental Science*, 3(1), 1–23.

<https://doi.org/10.1111/1467-7687.00094>

Olmos-Serrano, J. L., Kang, H. J., Tyler, W. A., Silbereis, J. C., Cheng, F., Zhu, Y., Pletikos, M., Jankovic-Rapan, L., Cramer, N. P., Galdzicki, Z., Goodliffe, J., Peters, A., Sethares, C., Delalle, I., Golden, J. A., Haydar, T. F., & Sestan, N. (2016). Down Syndrome Developmental Brain Transcriptome Reveals Defective Oligodendrocyte Differentiation and Myelination. *Neuron*, 89(6), 1208–1222.

<https://doi.org/10.1016/j.neuron.2016.01.042>

Ortega-Alves, M. V., & Urato, A. (2016). Making Sense Out of the Controversy: Use of SSRIs in Pregnancy. *Current Obstetrics and Gynecology Reports*, 5(3), 225–233.

<https://doi.org/10.1007/s13669-016-0173-z>

Oyama, S. (1985). *The ontogeny of information*. Cambridge University Press.

Oyama, S., Griffiths, P., & Gray, R. D. (2001). *Cycles of contingency: Developmental systems and evolution*. MIT Press.

Palisano, R. J., Walter, S. D., Russell, D. J., Rosenbaum, P. L., Gémus, M., Galuppi, B. E., & Cunningham, L. (2001). Gross motor function of children with Down syndrome:

Creation of motor growth curves. *Archives of Physical Medicine and Rehabilitation*, 82(4), 494–500. <https://doi.org/10.1053/apmr.2001.21956>

Papavassiliou, P., Charalsawadi, C., Rafferty, K., & Jackson-Cook, C. (2015). Mosaicism for trisomy 21: A review. *American Journal of Medical Genetics Part A*, 167(1), 26–39.

<https://doi.org/10.1002/ajmg.a.36861>

Park, J., Song, W.-J., & Chung, K. C. (2009). Function and regulation of Dyrk1A: towards understanding Down syndrome. *Cellular and Molecular Life Sciences*, 66(20), 3235–

3240. <https://doi.org/10.1007/s00018-009-0123-2>

- Pascalis, O., Scott, L. S., Kelly, D. J., Shannon, R. W., Nicholson, E., Coleman, M., & Nelson, C. A. (2005). Plasticity of face processing in infancy. *Proceedings of the National Academy of Sciences*, *102*(14), 5297–5300.
<https://doi.org/10.1073/pnas.0406627102>
- Pereira, A. F., Smith, L. B., & Yu, C. (2014). A bottom-up view of toddler word learning. *Psychonomic Bulletin and Review*, *21*(1), 178–185. <https://doi.org/10.3758/s13423-013-0466-4>
- Pfitzer, C., Helm, P. C., Rosenthal, L.-M., Berger, F., Bauer, U. M. M., & Schmitt, K. R. (2017). Dynamics in prevalence of Down syndrome in children with congenital heart disease. *European Journal of Pediatrics*, *177*(1), 107–115.
<https://doi.org/10.1007/s00431-017-3041-6>
- Phillips, M., & Pozzo-Miller, L. (2015). Dendritic spine dysgenesis in autism related disorders. *Neuroscience Letters*, *601*, 30–40.
<https://doi.org/10.1016/j.neulet.2015.01.011>
- Piaget, J. (1952). *The origins of intelligence in children*. W W Norton & Co.
- Piaget, J. (1954). *The construction of reality in the child*. Basic Books.
- Pitcairn, T. K., & Wishart, J. G. (1994). Reactions of young children with Down's syndrome to an impossible task. *British Journal of Developmental Psychology*, *12*(4), 485–489.
<https://doi.org/10.1111/j.2044-835X.1994.tb00649.x>
- Prasher, V. P., Sajith, S. G., Rees, S. D., Patel, A., Tewari, S., Schupf, N., & Zigman, W. B. (2008). Significant effect of APOE epsilon 4 genotype on the risk of dementia in Alzheimer's disease and mortality in persons with Down syndrome. *International Journal of Geriatric Psychiatry*, *23*(11), 1134–1140. <https://doi.org/10.1002/gps.2039>
- Purpura, D. P. (1975). Normal and Aberrant Neuronal Development in the Cerebral Cortex of Human Fetus and Young Infant. In N. A. Buchwald & M. A. B. Brazier (Eds.), *Brain*

Mechanisms in Mental Retardation (Vol. 18, Issue 18, pp. 141–169). Elsevier.

<https://doi.org/10.1016/B978-0-12-139050-1.50014-8>

Quine, W. (1960). *Word and Object*. MIT Press.

Real, R., Peter, M., Trabalza, A., Khan, S., Smith, M. A., Dopp, J., Barnes, S. J., Momoh, A.,

Strano, A., Volpi, E., Knott, G., Livesey, F. J., & De Paola, V. (2018). In vivo modeling of human neuron dynamics and Down syndrome. *Science*, *362*(6416), eaau1810.

<https://doi.org/10.1126/science.aau1810>

Reeves, R. H., Baxter, L. L., & Richtsmeier, J. T. (2001). Too much of a good thing:

mechanisms of gene action in Down syndrome. *Trends in Genetics*, *17*(2), 83–88.

[https://doi.org/10.1016/S0168-9525\(00\)02172-7](https://doi.org/10.1016/S0168-9525(00)02172-7)

Reiche, L., Küry, P., & Göttle, P. (2019). Aberrant Oligodendrogenesis in Down Syndrome:

Shift in Gliogenesis? *Cells*, *8*(12), 1591. <https://doi.org/10.3390/cells8121591>

Reynolds Losin, E. A., Rivera, S. M., O'Hare, E. D., Sowell, E. R., & Pinter, J. D. (2009).

Abnormal fMRI activation pattern during story listening in individuals with Down syndrome. *American Journal on Intellectual and Developmental Disabilities*, *114*(5),

369–380. <https://doi.org/10.1352/1944-7558-114.5.369>

Ringenbach, S. D., Chua, R., Maraj, B. K. V, Kao, J. C., & Weeks, D. J. (2002). Bimanual

coordination dynamics in adults with Down syndrome. *Motor Control*, *6*(4), 388–407.

<https://doi.org/10.1123/mcj.6.4.388>

Roach, M. A., Barratt, M. S., Miller, J. F., & Leavitt, L. A. (1998). The structure of mother–

child play: Young children with Down syndrome and typically developing children.

Developmental Psychology, *34*(1), 77–87. <https://doi.org/10.1037/0012-1649.34.1.77>

Robb, J. (2015). The Delayed Walker. In B. Joseph, J. Robb, R. T. Loder, & I. Torode (Eds.),

Paediatric Orthopaedic Diagnosis (pp. 249–256). Springer India.

https://doi.org/10.1007/978-81-322-2392-4_25

- Roizen, N. J., Wolters, C., Nicol, T., & Blondis, T. A. (1993). Hearing loss in children with Down syndrome. *The Journal of Pediatrics*, *123*(1), S9–S12.
[https://doi.org/10.1016/S0022-3476\(05\)81588-4](https://doi.org/10.1016/S0022-3476(05)81588-4)
- Rose, D. H., Slater, A., & Perry, H. (1986). Prediction of childhood intelligence from habituation in early infancy. *Intelligence*, *10*(3), 251–263. [https://doi.org/10.1016/0160-2896\(86\)90019-X](https://doi.org/10.1016/0160-2896(86)90019-X)
- Rosenblatt, F. (1958). The perceptron: A probabilistic model for information storage and organization in the brain. *Psychological Review*, *65*(6), 386–408.
<https://doi.org/10.1037/h0042519>
- Rovee-Collier, C., & Cuevas, K. (2009). Multiple memory systems are unnecessary to account for infant memory development: An ecological model. *Developmental Psychology*, *45*(1), 160–174. <https://doi.org/10.1037/a0014538>
- Rubenstein, J. L. R., & Merzenich, M. M. (2003). Model of autism: Increased ratio of excitation/inhibition in key neural systems. *Genes, Brain and Behavior*, *2*(5), 255–267.
<https://doi.org/10.1034/j.1601-183X.2003.00037.x>
- Ruddy, M. G., & Bornstein, M. H. (1982). Cognitive correlates of infant attention and maternal stimulation over the first year of life. *Child Development*, *53*(1), 183–188.
<https://doi.org/10.1111/j.1467-8624.1982.tb01306.x>
- Ruiz-González, L., Lucena-Antón, D., Salazar, A., Martín-Valero, R., & Moral-Munoz, J. A. (2019). Physical therapy in Down syndrome: systematic review and meta-analysis. *Journal of Intellectual Disability Research*, *63*(8), 1041–1067.
<https://doi.org/10.1111/jir.12606>
- Ruskin, E. M., Kasari, C., Mundy, P., & Sigman, M. (1994). Attention to people and toys during social and object mastery in children with Down syndrome. *American Journal on Mental Retardation*, *99*(1), 103–111. <http://www.ncbi.nlm.nih.gov/pubmed/7946251>

- Samuelson, L. K., & McMurray, B. (2017). What does it take to learn a word? *Wiley Interdisciplinary Reviews: Cognitive Science*, 8(1–2), e1421.
<https://doi.org/10.1002/wcs.1421>
- Schöner, G., & Kelso, J. A. (1988). Dynamic pattern generation in behavioral and neural systems. *Science*, 239(4847), 1513–1520. <https://doi.org/10.1126/science.3281253>
- Schwarzer, G., Freitag, C., Buckel, R., & Lofruchte, A. (2013). Crawling is Associated with Mental Rotation Ability by 9-Month-Old Infants. *Infancy*, 18(3), 432–441.
<https://doi.org/10.1111/j.1532-7078.2012.00132.x>
- Schworer, E., Fidler, D. J., Lunkenheimer, E., & Daunhauer, L. A. (2018). Parenting behaviour and executive function in children with Down syndrome. *Journal of Intellectual Disability Research*, 63(4), 298–312. <https://doi.org/10.1111/jir.12575>
- Seidl, R., Hauser, E., Bernert, G., Marx, M., Freilinger, M., & Lubec, G. (1997). Auditory evoked potentials in young patients with Down syndrome. Event-related potentials (P3) and histaminergic system. *Cognitive Brain Research*, 5(4), 301–309.
[https://doi.org/10.1016/S0926-6410\(97\)00008-6](https://doi.org/10.1016/S0926-6410(97)00008-6)
- Sengpiel, F., & Kind, P. C. (2002). The role of activity in development of the visual system. *Current Biology*, 12(23), R818–R826. [https://doi.org/10.1016/S0960-9822\(02\)01318-0](https://doi.org/10.1016/S0960-9822(02)01318-0)
- Shogren, K. A., Wehmeyer, M. L., & Singh, N. N. (2017). *Handbook of Positive Psychology in Intellectual and Developmental Disabilities*. Springer International Publishing.
<https://doi.org/10.1007/978-3-319-59066-0>
- Singer, W., Sejnowski, T. J., & Rakic, P. (2019). *The neocortex*. The MIT Press.
<http://cognet.mit.edu/book/neocortex>
- Slone, L. K., Abney, D. H., Borjon, J. I., Chen, C., Franchak, J. M., Percy, D., Suarez-Rivera, C., Xu, T. L., Zhang, Y., Smith, L. B., & Yu, C. (2018). Gaze in Action: Head-mounted Eye Tracking of Children’s Dynamic Visual Attention During Naturalistic

Behavior. *Journal of Visualized Experiments*, 141, e58496.

<https://doi.org/10.3791/58496>

Sobol, M., Klar, J., Laan, L., Shahsavani, M., Schuster, J., Annerén, G., Konzer, A., Mi, J., Bergquist, J., Nordlund, J., Hoeber, J., Huss, M., Falk, A., & Dahl, N. (2019).

Transcriptome and Proteome Profiling of Neural Induced Pluripotent Stem Cells from Individuals with Down Syndrome Disclose Dynamic Dysregulations of Key Pathways and Cellular Functions. *Molecular Neurobiology*, 56(10), 7113–7127.

<https://doi.org/10.1007/s12035-019-1585-3>

Somerville, L. H., & Casey, B. J. (2014). Emotional reactivity and regulation across

development. In M. S. Gazzaniga & G. R. Mangun (Eds.), *The Cognitive Neurosciences* (5th ed., pp. 731–739). MIT Press.

Soska, K. C., Adolph, K. E., & Johnson, S. P. (2010). Systems in development: Motor skill acquisition facilitates three-dimensional object completion. *Developmental Psychology*, 46(1), 129–138. <https://doi.org/10.1037/a0014618>

Soukup-Ascencao, T., D'Souza, D., D'Souza, H., & Karmiloff-Smith, A. (2016). Parent-child interaction as a dynamic contributor to learning and cognitive development in typical and atypical development. *Infancia y Aprendizaje*, 39(4), 694–726.

<https://doi.org/10.1080/02103702.2016.1221054>

Spanò, M., Mercuri, E., Randò, T., Pantò, T., Gagliano, A., Henderson, S., & Guzzetta, F. (1999). Motor and perceptual-motor competence in children with Down syndrome:

Variation in performance with age. *European Journal of Paediatric Neurology*, 3(1), 7–14. <https://doi.org/10.1053/ejpn.1999.0173>

Spencer, J. P., Vereijken, B., Diedrich, F. J., & Thelen, E. (2000). Posture and the emergence of manual skills. *Developmental Science*, 3(2), 216–233. <https://doi.org/10.1111/1467-7687.00115>

- Sporns, O., & Edelman, G. M. (1993). Solving Bernstein's problem: A proposal for the development of coordinated movement by selection. *Child Development*, *64*(4), 960–981. <https://doi.org/10.1111/j.1467-8624.1993.tb04182.x>
- Sretavan, D., & Shatz, C. J. (1984). Prenatal development of individual retinogeniculate axons during the period of segregation. *Nature*, *308*, 845–848. <https://doi.org/10.1038/308845a0>
- Stagni, F., Giacomini, A., Emili, M., Guidi, S., & Bartesaghi, R. (2018). Neurogenesis impairment: An early developmental defect in Down syndrome. *Free Radical Biology and Medicine*, *114*, 15–32. <https://doi.org/10.1016/J.FREERADBIOMED.2017.07.026>
- Stagni, F., Giacomini, A., Emili, M., Trazzi, S., Guidi, S., Sassi, M., Ciani, E., Rimondini, R., & Bartesaghi, R. (2016). Short- and long-term effects of neonatal pharmacotherapy with epigallocatechin-3-gallate on hippocampal development in the Ts65Dn mouse model of Down syndrome. *Neuroscience*, *333*, 277–301. <https://doi.org/10.1016/J.NEUROSCIENCE.2016.07.031>
- Stoneman, Z., Brody, G. H., Davis, C. H., & Crapps, J. M. (1987). Mentally retarded children and their older same-sex siblings: Naturalistic in-home observations. *American Journal on Mental Retardation*, *92*(3), 290–298.
- Suarez-Rivera, C., Smith, L. B., & Yu, C. (2019). Multimodal parent behaviors within joint attention support sustained attention in infants. *Developmental Psychology*, *55*(1), 96–109. <https://doi.org/10.1037/dev0000628>
- Takashima, S., Becker, L. E., Armstrong, D. L., & Chan, F. (1981). Abnormal neuronal development in the visual cortex of the human fetus and infant with Down's syndrome. A quantitative and qualitative golgi study. *Brain Research*, *225*(1), 1–21. [https://doi.org/10.1016/0006-8993\(81\)90314-0](https://doi.org/10.1016/0006-8993(81)90314-0)
- Tamis-LeMonda, C. S., Adolph, K. E., Lobo, S. A., Karasik, L. B., Ishak, S., &

- Dimitropoulou, K. A. (2008). When infants take mothers' advice: 18-month-olds integrate perceptual and social information to guide motor action. *Developmental Psychology, 44*(3), 734–746. <https://doi.org/10.1037/0012-1649.44.3.734>
- Task Engine - Face popout. (n.d.). Retrieved June 30, 2020, from <https://sites.google.com/site/taskenginedoc/task-packages/face-popout>
- Thelen, E. (1992). Development as a dynamic system. *Current Directions in Psychological Science, 1*(6), 189–193. <https://doi.org/10.1111/1467-8721.ep10770402>
- Thelen, E., & Smith, L. B. (1994). *A dynamic systems approach to the development of cognition and action*. MIT Press.
- Thomas, M. S. C., Ojinaga Alfageme, O., D'Souza, H., Patkee, P. A., Rutherford, M. A., Mok, K. Y., Hardy, J., & Karmiloff-Smith, A. (2020). A multi-level developmental approach to exploring individual differences in Down syndrome: genes, brain, behaviour, and environment. *Research in Developmental Disabilities, 104*, 103638. <https://doi.org/10.1016/j.ridd.2020.103638>
- Tovar, Á. E., Westermann, G., & Torres, A. (2018). From altered synaptic plasticity to atypical learning: A computational model of Down syndrome. *Cognition, 171*, 15–24. <https://doi.org/10.1016/J.COGNITION.2017.10.021>
- Tsao, R., & Kindelberger, C. (2009). Variability of cognitive development in children with Down syndrome: Relevance of good reasons for using the cluster procedure. *Research in Developmental Disabilities, 30*(3), 426–432. <https://doi.org/10.1016/J.RIDD.2008.10.009>
- Turrigiano, G. G., & Nelson, S. B. (2004). Homeostatic plasticity in the developing nervous system. *Nature Reviews Neuroscience, 5*(2), 97–107. <https://doi.org/10.1038/nrn1327>
- Tyssowski, K. M., DeStefino, N. R., Cho, J.-H., Dunn, C. J., Poston, R. G., Carty, C. E., Jones, R. D., Chang, S. M., Romeo, P., Wurzelmann, M. K., Ward, J. M., Andermann,

- M. L., Saha, R. N., Dudek, S. M., & Gray, J. M. (2018). Different Neuronal Activity Patterns Induce Different Gene Expression Programs. *Neuron*, *98*(3), 530-546.e11. <https://doi.org/10.1016/J.NEURON.2018.04.001>
- Ulrich, B. D. (2010). Opportunities for early intervention based on theory, basic neuroscience, and clinical science. *Physical Therapy*, *90*(12), 1868–1880. <https://doi.org/10.2522/ptj.20100040>
- Ulrich, B. D., & Ulrich, D. A. (1993). Dynamic Systems Approach to Understanding Motor Delay in Infants With Down Syndrome. In G. J. P. Savelsbergh (Ed.), *Advances in Psychology* (Vol. 97, pp. 445–459). Elsevier. [https://doi.org/10.1016/S0166-4115\(08\)60963-2](https://doi.org/10.1016/S0166-4115(08)60963-2)
- Ulrich, B. D., & Ulrich, D. A. (1995). Spontaneous leg movements of infants with Down syndrome and nondisabled infants. *Child Development*, *66*(6), 1844–1855. <https://doi.org/10.1111/j.1467-8624.1995.tb00969.x>
- Ulrich, B. D., Ulrich, D. A., Angulo-Kinzler, R., & Chapman, D. D. (1997). Sensitivity of infants with and without Down syndrome to intrinsic dynamics. *Research Quarterly for Exercise and Sport*, *68*(1), 10–19. <https://doi.org/10.1080/02701367.1997.10608862>
- Ulrich, D. A., Lloyd, M. C., Tiernan, C. W., Looper, J. E., & Angulo-Barroso, R. M. (2008). Effects of Intensity of Treadmill Training on Developmental Outcomes and Stepping in Infants With Down Syndrome: A Randomized Trial. *Physical Therapy*, *88*(1), 114–122. <https://doi.org/10.2522/ptj.20070139>
- Ulrich, D. A., Ulrich, B. D., Angulo-Kinzler, R. M., & Yun, J. (2001). Treadmill training of infants with Down syndrome: evidence-based developmental outcomes. *Pediatrics*, *108*(5), e84. <https://doi.org/10.1542/peds.108.5.e84>
- Vacca, R. A., Bawari, S., Valenti, D., Tewari, D., Nabavi, S. F., Shirooie, S., Sah, A. N., Volpicella, M., Braidy, N., & Nabavi, S. M. (2019). Down syndrome: Neurobiological

- alterations and therapeutic targets. *Neuroscience & Biobehavioral Reviews*, 98, 234–255. <https://doi.org/10.1016/J.NEUBIOREV.2019.01.001>
- van der Lee, S. J., Wolters, F. J., Ikram, M. K., Hofman, A., Ikram, M. A., Amin, N., & van Duijn, C. M. (2018). The effect of APOE and other common genetic variants on the onset of Alzheimer's disease and dementia: a community-based cohort study. *The Lancet Neurology*, 17(5), 434–444. [https://doi.org/10.1016/S1474-4422\(18\)30053-X](https://doi.org/10.1016/S1474-4422(18)30053-X)
- Vanvuchelen, M., Feys, H., & De Weerd, W. (2011). Is the good-imitator-poor-talker profile syndrome-specific in Down syndrome?: Evidence from standardised imitation and language measures. *Research in Developmental Disabilities*, 32(1), 148–157. <https://doi.org/10.1016/J.RIDD.2010.09.010>
- Venuti, P., de Falco, S., Esposito, G., & Bornstein, M. H. (2009). Mother-child play: Children with Down syndrome and typical development. *American Journal on Intellectual and Developmental Disabilities*, 114(4), 274–288. <https://doi.org/10.1352/1944-7558-114.4:274-288>
- Vlachou, M., & Farrell, P. (2000). Object Mastery Motivation in Pre-school Children with and without Disabilities. *Educational Psychology*, 20(2), 167–176. <https://doi.org/10.1080/713663715>
- Von Hofsten, C. (2004). An action perspective on motor development. *Trends in Cognitive Sciences*, 8(6), 266–272. <https://doi.org/10.1016/j.tics.2004.04.002>
- Vygotsky, L. S. (1978). *Mind in Society: The Development of Higher Psychological Processes*. Harvard University Press.
- Walle, E. A., & Campos, J. J. (2014). Infant language development is related to the acquisition of walking. *Developmental Psychology*, 50(2), 336–348. <https://doi.org/10.1037/a0033238>
- Wang, P.-J., Morgan, G. A., Hwang, A.-W., & Liao, H.-F. (2013). Individualized Behavioral

Assessments and Maternal Ratings of Mastery Motivation in Mental Age-Matched Toddlers With and Without Motor Delay. *Physical Therapy*, 93(1), 79–87.

<https://doi.org/10.2522/ptj.20120068>

Waxman, S. G. (1980). Determinants of conduction velocity in myelinated nerve fibers.

Muscle & Nerve, 3(2), 141–150. <https://doi.org/10.1002/mus.880030207>

Weick, J. P., Held, D. L., Bonadurer, G. F., Doers, M. E., Liu, Y., Maguire, C., Clark, A., Knackert, J. A., Molinarolo, K., Musser, M., Yao, L., Yin, Y., Lu, J., Zhang, X., Zhang, S.-C., & Bhattacharyya, A. (2013). Deficits in human trisomy 21 iPSCs and neurons.

Proceedings of the National Academy of Sciences, 110(24), 9962–9967.

<https://doi.org/10.1073/pnas.1216575110>

Wentz, E. E. (2017). Importance of Initiating a “Tummy Time” Intervention Early in Infants With Down Syndrome. *Pediatric Physical Therapy*, 29(1), 68–75.

<https://doi.org/10.1097/PEP.0000000000000335>

Werker, J. F., & Hensch, T. K. (2015). Critical Periods in Speech Perception: New Directions. *Annual Review of Psychology*, 66(1), 173–196.

<https://doi.org/10.1146/annurev-psych-010814-015104>

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

<https://doi.org/10.1111/j.1467-7687.2007.00567.x>

Will, E. A., Caravella, K. E., Hahn, L. J., Fidler, D. J., & Roberts, J. E. (2018). Adaptive behavior in infants and toddlers with Down syndrome and fragile X syndrome.

American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 177(3), 358–368. <https://doi.org/10.1002/ajmg.b.32619>

Will, E. A., Daunhauer, L. A., Fidler, D. J., Raitano Lee, N., Rosenberg, C. R., & Hepburn, S. L. (2019). Sensory Processing and Maladaptive Behavior: Profiles Within the Down

- Syndrome Phenotype. *Physical & Occupational Therapy In Pediatrics*, 39(5), 461–476.
<https://doi.org/10.1080/01942638.2019.1575320>
- Winders, P., Wolter-Warmerdam, K., & Hickey, F. (2019). A schedule of gross motor development for children with Down syndrome. *Journal of Intellectual Disability Research*, 63(4), 346–356. <https://doi.org/10.1111/jir.12580>
- Wishart, J. G., & Johnston, F. H. (1990). The effects of experience on attribution of a stereotyped personality to children with Down's syndrome. *Journal of Intellectual Disability Research*, 34(5), 409–420. <https://doi.org/10.1111/j.1365-2788.1990.tb01551.x>
- Wisniewski, K. E., & Schmidt-Sidor, B. (1989). Postnatal delay of myelin formation in brains from Down syndrome infants and children. *Clinical Neuropathology*, 8(2), 55–62. <http://www.ncbi.nlm.nih.gov/pubmed/2524302>
- Wright, I., Lewis, V., & Collis, G. M. (2006). Imitation and representational development in young children with Down syndrome. *British Journal of Developmental Psychology*, 24(2), 429–450. <https://doi.org/10.1348/026151005X51257>
- Yamauchi, Y., Aoki, S., Koike, J., Hanzawa, N., & Hashimoto, K. (2019). Motor and cognitive development of children with Down syndrome: The effect of acquisition of walking skills on their cognitive and language abilities. *Brain and Development*, 41(4), 320–326. <https://doi.org/10.1016/J.BRAINDEV.2018.11.008>
- Yoshida, H., & Smith, L. B. (2008). What's in View for Toddlers? Using a Head Camera to Study Visual Experience. *Infancy*, 13(3), 229–248.
<https://doi.org/10.1080/15250000802004437>
- Yu, C., & Smith, L. B. (2012). Embodied attention and word learning by toddlers. *Cognition*, 125(2), 244–262. <https://doi.org/10.1016/j.cognition.2012.06.016>
- Yu, C., & Smith, L. B. (2013). Joint Attention without Gaze Following: Human Infants and

Their Parents Coordinate Visual Attention to Objects through Eye-Hand Coordination.

PLoS ONE, 8(11), e79659. <https://doi.org/10.1371/journal.pone.0079659>

Yu, C., & Smith, L. B. (2016). The Social Origins of Sustained Attention in One-Year-Old Human Infants. *Current Biology*, 26(9), 1235–1240.

<https://doi.org/10.1016/j.cub.2016.03.026>

Zampini, L., & D'Odorico, L. (2009). Communicative gestures and vocabulary development in 36-month-old children with Down's syndrome. *International Journal of Language & Communication Disorders*, 44(6), 1063–1073.

<https://doi.org/10.1080/13682820802398288>

Zelazo, P. R., Weiss, M. J., Papageorgiou, A. N., & Laplante, D. P. (1989). Recovery and dishabituation of sound localization among normal-, moderate-, and high-risk newborns: Discriminant validity. *Infant Behavior and Development*, 12(3), 321–340.

[https://doi.org/10.1016/0163-6383\(89\)90042-8](https://doi.org/10.1016/0163-6383(89)90042-8)

Zhu, F., Nair, R. R., Fisher, E. M. C., & Cunningham, T. J. (2019). Humanising the mouse genome piece by piece. *Nature Communications*, 10(1), 1845.

<https://doi.org/10.1038/s41467-019-09716-7>