CHAPTER 7

Human and mouse model cognitive phenotypes in Down syndrome: implications for assessment

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Abstract: The study of cognitive function in Down syndrome (DS) has advanced rapidly in the past decade. Mouse models have generated data regarding the neurological basis for the specific cognitive profile of DS (i.e., deficits in aspects of hippocampal, prefrontal, and cerebellar function) and have uncovered pharmacological treatments with the potential to affect this phenotype. Given this progress, the field is at a juncture in which we require assessments that may effectively translate the findings acquired in mouse models to humans with DS. In this chapter, we describe the cognitive profile of humans with DS and associated mouse models, discussing the ways in which we may merge these findings so as to more fully understand cognitive strengths and weaknesses in this population. New directions for approaches to cognitive assessment in mice and humans are discussed.

Keywords: cognitive assessment; mouse phenotype; pharmacological intervention; Down syndrome; mouse models; medial temporal lobe function; prefrontal function; cerebellum.

Introduction

The study of cognitive function in Down syndrome (DS), the most common genetic cause of intellectual disability (ID), has advanced rapidly in the past decade. We now know that DS results in a specific cognitive phenotype in humans (Fidler and Nadel, 2007; Pennington et al., 2003; Vicari, 2006) and that this cognitive profile can be reliably measured with validated and well-replicated cognitive assessments (Edgin et al., 2010a). In general, individuals with DS present variable deficits in learning, memory, and language with global levels of cognitive function in the range of ID (i.e., IQ < 70) (Lott and Dierssen, 2010).

The study of cognitive deficits in DS has benefited substantially from the use of mouse models, which have provided data highlighting the neural mechanisms that may underscore cognitive

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difficulties. These advances have generated several targets for interventions to ameliorate the cognitive deficits. Recent findings using such models have shown that aspects of the associated cognitive deficits can be modified through pharmacological agents and environmental enrichment (Fernandez et al., 2007; Guedj et al., 2009; Martinez-Cue et al., 2002; Roper et al., 2006; Salehi et al., 2009).

The mouse has proven to be an especially useful model organism, not only because of the general mammalian and genetic similarities with humans (Crnic and Pennington, 2000), but also more specifically because many of the protein-coding genes currently identified on human chromosome 21 (HSA21) are conserved on mouse chromosomes (MMU) 10, 16, and 17 (Pletcher et al., 2001). While most of the research to date has been carried out with the Ts65Dn mouse (Davisson et al., 1990), models that more closely approximate the genetic basis of DS in humans have recently been developed, involving triplication of different chromosomal regions. These include a "transchromosomic" (trans-species aneuploid) model containing nearly the entire HSA21, "Tc1" (O'Doherty et al., 2005) and a

more recent model syntenic for all regions of HSA21 orthologs on mouse 16, 17, and 10, "Dp (16)1Yey/+, Dp(17)1Yey/+, Dp(10)1Yey/+" (Yu et al., 2010). Other models have been developed to test the importance of segments of genes included in the triplication, such as the DS "critical" region (e.g., Ts1rhr; Olson et al., 2004a). While the newer models have been developed to contain more complete segments of HSA21 (or mouse orthologs), there are still no "perfect" models of the human case. For instance, Tc1, which could have replicated more closely the genetic alteration, results in mosaicism. Table 1 displays the current models in use and the extent of their genetic alteration (i.e., both in terms of mouse and HSA structure). The Ts65Dn model has been the most widely used in studies of behavioral outcomes as well as tests of pharmacological interventions; we review the data for this model in detail throughout the chapter, adding the findings from newer models that include a more complete representation of the genes on HSA21 where relevant. Beyond offering testable mechanisms of drug treatment in this population, mouse models that prove sensitive to the same treatment as humans may also help us understand

Table 1. Mouse models of Down syndrome and descriptions of their genetic alteration

Mouse model	Mouse chromosomes affected	HSA21 syntenic regions
Ts65Dn (Davisson et al., 1990)	MMU16, subcentromeric region of MMU17	Region spanning from *Mrpl39* to *Zfp295*; MMU 17 trisomic region not syntenic to any HSA21 region
Ts1Cje (Sago et al., 1998)	MMU16	Region spanning from 21q22.1 to 22.3
Ts1Rhr (Olson et al., 2004a)	MMU16	"Down Syndrome Critical Region" (DSCR); spanning from *cbr3* gene to *mx2* gene on chr21 (~21q22.2–22.3)
Ts1Yah (Pereira et al., 2009)	MMU17	*Abcg1-U2af1* telomeric region
Tc1 (O'Doherty et al., 2005)	N/A	Most of HSA21 inserted through microcell-mediated chromosome transfer; regions inserted bound by markers CXADR and D21S1922, and IFNAR1 and RUNX1
Dp(16)1Yu (also see Ts1Yu, Dp(16)1Yey) (Li et al., 2007)	MMU16	Large region spanning from 21q11.2 to 22.3
Dp(16)1Yey/+, Dp(17)1Yey/+, Dp(10)1Yey/+ (Yu et al., 2010)	MMU16, MMU17, MMU10	Distal portion of 21q22.3 (MMU10); proximal portion of 21q22.3 (MMU17); region spanning from 21q11.2 to 22.3 (MMU16)

the reasons for treatment success, the projected time course of treatment effects, and in the identification of biomarkers to establish treatment efficacy.

Given that hypothesis-based drug treatment in humans with DS is ongoing, the field urgently requires cognitive measures that bridge findings between mouse models and humans with DS. The success of animal-tested interventions in humans with DS rests on two central assumptions, (1) that particular drugs may affect mice and humans in essentially the same way, by targeting the same neural systems, and (2) that the neural systems so targeted play similar functional roles in mice and humans, such that the drugs will have a substantial impact on cognitive function in the human. Beyond these assumptions, it is also critical for the measures used in both species to have adequate reliability, validity, and sensitivity to detect effects. While it is often difficult to have measures in both species that tap similar constructs (i.e., demonstrate construct validity), maximizing this characteristic in measures may help to support translation of the findings. Therefore, in order to maximize success of interventions based on animal model work, the tests administered in humans and mice should be as directly comparable as possible. Our primary goal in this chapter is to facilitate the translation of findings from the mouse model to humans with DS. To do so, we (1) detail the specific profile of cognitive and neurological deficits in humans with DS, (2) detail findings regarding brain and behavioral deficits in the range of mouse models, and (3) discuss ways to merge these findings so as to more fully understand cognitive function in DS and measure the outcome of clinical trials in the future.

While theories regarding ID syndromes have sometimes posited that the various IDs include similar core cognitive deficits (e.g., a common impairment in working memory; Cornoldi and Vecchi, 2003; Crnic and Pennington, 2000), the bulk of the evidence supports the view that each syndrome has its own unique profile of cognitive strengths and weaknesses (Edgin et al., 2010b;

Nadel, 1999; Vicari et al., 2005). Basic neuroscience work has also shown that multiple learning and memory systems exist within the brain (e.g., Nadel, 1994), with dissociations in cognitive processes apparent even within single brain systems, such as the hippocampus (e.g., CA3/dentate gyrus vs. CA1/subiculum functions). We assume that taking such dissociations into account will prove essential in detailing the unique profile of spared and impaired cognitive abilities in ID syndromes and that this will have critical implications for behavioral and pharmacological intervention. Therefore, our discussion focuses on neurocognitive dissociations that are apparent in humans with DS and animal models.

The importance of a developmental approach

While our understanding of the DS cognitive phenotype has advanced rapidly in the past 10 years, we still are lacking an understanding of the developmental trajectory of these cognitive deficits. The large majority of studies conducted to date have measured cognitive outcomes in adult mice and older children or adult humans. Interventions, with a few exceptions (Moon et al., 2010; Roper et al., 2006), have also been conducted with adult mice.

There are a number of problems with assessing the cognitive and behavioral phenotype in individuals with DS, or any other developmental disability, at one "snapshot" in time, and then comparing that snapshot to data generated in adults without any developmental disability or experimental animals with lesions. First, we have substantial evidence that the cognitive profile in individuals with DS evolves across the lifespan, demonstrating periods of slowing in development or decline. Data collected at a single time point will not reflect the complexity of these transitions. Similarly, even when patterns of behavior appear exactly the same, the underlying brain bases of these behaviors may differ across developmental periods or in different populations (e.g., DS vs.

typically developing controls). A recent example of this point comes from a study showing that pediatric brain injuries may result in what appear to be "prefrontal" impairments, no matter the site of the lesion (Jacobs et al., 2011). This study suggests that end-state impairments that appear specific to a region (e.g., frontal lobe) may actually result from injury or dysfunction in any of several regions that are part of a network including the prefrontal cortex. In this case, improper construction of networks of connectivity may cause the deficit rather than dysfunction restricted to one region alone (e.g., in this case, the prefrontal cortex). With this kind of information about networks in hand, one would suggest a rather different treatment than if the outcome was examined at one point in development (i.e., a treatment supporting connectivity vs. a treatment to enhance PFC function). Keeping this complexity of the developmental process in mind, we also review the available findings from early development in humans with DS and in mouse models.

Brain development in DS

Brain development is a dynamic process: in DS this seems to involve a sequence of relative declines across childhood and into adulthood. Shortly after birth, the brains of individuals with DS appear to be within the normal range in terms of major structural indices (i.e., brain size, shape, lobular proportions, and neurotransmitter development; Bar-Peled et al., 1991; Brooksbank et al., 1989; Flórez et al., 1990; Pazos et al., 1994; Schmidt-Sidor et al., 1990; Wisniewski and Schmidt-Sidor, 1989). By 6 months of age differences in brain structure are clearly apparent (Engidawork and Lubec, 2003; Golden and Hyman, 1994; Schmidt-Sidor et al., 1990; Wisniewski and Kida, 1994).

Neuropathological evidence demonstrates foreshortening of the frontal lobes, narrowing of the superior temporal gyrus, and diminished size of the cerebellum and brainstem in infants with DS (Benda, 1971; Blackwood and Corsellis, 1976;

Crome et al., 1966). Additionally, structural differences in the medial temporal lobes (MTL), prefrontal cortex, and cerebellum have also been observed in studies using magnetic resonance imaging later in development and into adulthood (Menghini et al., 2011; Nadel, 2003). This pattern of neurological development corresponds well with patterns of cognitive deficits found in humans and mice with DS.

Nadel (1986) suggested that the pattern of findings of brain dysfunction in DS described above is suggestive of compromised development in late-developing systems. The prefrontal cortex, hippocampus, and cerebellum are regions with relatively protracted neural development, including postnatal generation of neurons and synapses, and myelination of the tracts connecting these regions and the rest of the brain persisting into later childhood. Recent evidence suggests that there may be dissociations in the developmental trajectory of functional subregions within these structures as well, and that the later developing components are again at greatest risk. It remains unclear why having an extra copy of HSA21 differentially affects late-developing structures, but the pattern of differences in brain structure and function observed in these regions seems relatively well established in both humans and mouse models.

Given this background, we focus on dysfunction in the MTL, cerebellum, and prefrontal cortex as well as on language impairments. It is, of course, difficult to build a bridge between findings of language deficits in the human and behavior in the mouse. However, ability of the mice to hear and learn in comparison to their healthy littermates is interesting to discriminative association learning. Given the extent of language impairments in DS, this set of skills demands attention when testing the effects of interventions, even though direct parallels cannot be made with animal models. Our discussion of data addressing cognitive and neurological differences in DS will predominantly focus on findings in children and young adults, given that declines associated with

Alzheimer's disease (AD) are prevalent in older adults and can complicate the interpretation of the cognitive profile (Lott and Dierssen, 2010).

MTL functions

The cognitive functions of the MTL have been extensively studied in humans and animal models of DS (Crnic and Pennington, 2000; Pennington et al., 2003; Uecker et al., 1993), and this brain region has been identified as the target of several potential drug agents in mouse (Fernandez et al., 2007; Guedj et al., 2009; Salehi et al., 2009). The MTL contains several distinct areas, each of which may serve a specialized role in mnemonic processing and, as evidence has recently suggested, aspects of perception (Bussey and Saksida, 2005; Nadel and Hardt, 2011). Figure 1 shows the various MTL regions and their interactions. Figure 2 displays the functional regions of the hippocampal circuit itself.

The hippocampus is a site of convergence of information from multiple sources, including the dorsal and the ventral visual streams (Ungerleider and Mishkin, 1982). Within these processing streams, representations of visual information become increasingly more complex moving from the periphery to the center, with perhaps the most complex representations being processed in the hippocampus (e.g., objects in specific contexts). Evidence suggests that one role of the hippocampus is to orthogonalize these representations of episodic contexts, using uniquely varying details of events to do so.

The majority of evidence suggests that the different regions in the hippocampus and surrounding MTL are specialized to process differing types of input (Kesner and Goodrich-Hunsaker, 2010). One specialization comes from the segregation of object and spatial information routed into the hippocampus via the entorhinal cortex. Object information is processed in the ventral visual stream,

Fig. 1. Schematic diagram of the connectivity between regions of the medial temporal lobe system. Adapted from Nadel and Hardt (2011).
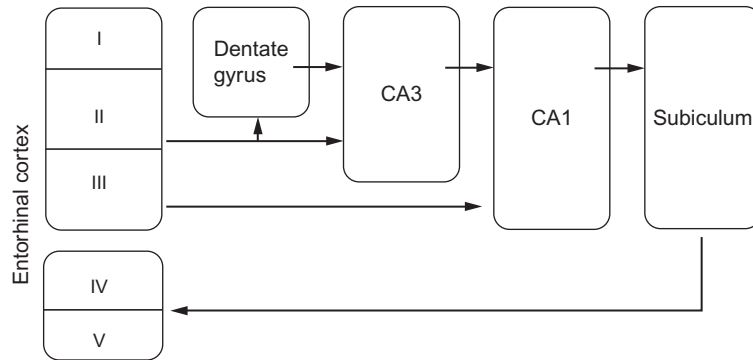
Fig. 2. Schematic diagram of the hippocampus proper and circuits originating from the entorhinal cortex. Inputs from the entorhinal cortex (EC) to hippocampus travel through the dentate gyrus and CA3 (the preforant path) or directly to CA1.

including the perirhinal cortex, which projects predominantly to the lateral entorhinal cortex, and hence to the hippocampus. The perirhinal cortex is specifically involved in the processing of objects with highly overlapping features (i.e., in resolving feature ambiguity). Monkeys with perirhinal lesions are impaired at discriminating morphed pairs of stimuli, particularly when featural overlap between the pairs is high (Bussey et al., 2003). In contrast, hippocampally lesioned monkeys are unimpaired on this task (Saksida et al., 2006). The role of the perirhinal cortex differs from the object processing undertaken by the fusiform gyrus in the temporal lobe, which allows for view independent recognition of single distinct objects and faces. Forming a set of inputs into the hippocampus that are primarily spatial in nature, the parahippocampal cortex encodes spatial locations or visual scenes, and receives direct projections from the dorsal visual stream (Sommer et al., 2005). Within the hippocampus, the dentate gyrus and CA3 are involved in memory tasks that require spatial pattern separation (Bakker et al., 2008) and the CA1 and the subiculum have been shown to be involved in novelty detection and spatial navigation (Kesner and Goodrich-Hunsaker, 2010). Other functional dissociations have been noted in the hippocampus, including variation in the number and size of place-sensitive fields along the septotemporal axis (i.e., dissociations in dorsal and ventral hippocampus; Jung et al., 1994).

The evidence linking these areas to distinct information processing functions derives from studies of adult patients with lesions, intact adults studied with neuroimaging methods, or animal work. Developmental disorders such as DS do not reveal such sharply defined distinctions. Deficient processing in the MTL regions projecting to the hippocampus likely leads to a degradation of the representations processed by these regions. Therefore, deficits in the mnemonic functions of the MTL could arise from dysfunction specific to the hippocampus proper *or* from impairments at any point in this pathway (e.g., Zola-Morgan et al., 1989). Given this possibility, our review of MTL dysfunction in humans with DS and mouse models considers not only findings relating to the function of the hippocampus itself but also tasks that may tap MTL inputs into the hippocampus. We focus on nonverbal tasks as the findings from measures of verbal memory are difficult to interpret, given deficits in auditory short-term memory (STM) and language function (Pennington et al., 2003).

Early dorsal and ventral visual stream processing

Dendritic abnormalities (in branching, length, spine density, and arborization) have been observed in various brain areas within DS (see Dierssen and Ramakers, 2006 for a review). In the cortex, studies of dendritic branching have

suggested the possibility of deficits early in the visual stream in DS. An analysis of dendritic arborization in visual cortex showed a greater number of branches than typical in early infancy in humans with DS (i.e., less than 6 months), with decreases to lower than normal levels after 2 years (Becker et al., 1986). The finding of greater branching of dendrites has been replicated in other areas of cortex and may reflect altered connectivity patterns in the associated circuits, which ultimately results in reductions in dendritic arborization.

Despite these findings, the few behavioral studies examining early visual stream function have failed to observe defects. For instance, individuals with DS have been shown to perform at the level of mental age (MA) matched controls on tasks requiring immediate memory for spatial locations across several studies (i.e., CANTAB Spatial Span or CORSI blocks; Pennington et al., 2003; Visu-Petra et al., 2007; Edgin et al., 2010a), suggesting spared function of the dorsal visual stream, at least in relation to MA controls. In another study, Fidler et al. (2006) found that 2–3-year-old children with DS showed no deficits in relation to MA-matched infants on the visual reception scale of the Mullen Scales of Early Learning, which included tasks of basic visuo-motor and perceptual ability (e.g., visual tracking and scanning of objects and simple visual discriminations). In an eye-tracking study, Brown et al. (2003) showed that 2–3year-olds with DS were unimpaired at visual tracking and integration when compared to children with William's syndrome, and to MA, and chronological age (CA) matched controls.

However, in early studies of the visual–spatial processing of global and local elements of a visual display, Wang et al. (1995) presented data suggesting individuals with DS had an abnormal tendency toward globally oriented visual perception. When asked to reconstruct elements of a hierarchical visual display, with one letter—say an "X"—being constructed out of many smaller "Os," they would focus on the global features of

the display (the X) with less attention paid to the local features (the Os).

In a subsequent study examining the perception of global and local details in DS, Edgin, J. O. and Pennington, B. F. (unpublished data) examined global and local perception using two tasks: (1) the Navon figures and (2) a task described by Banks and Prinzmetal (1976) in which children have to detect a letter (either a T or an F) that is embedded within a visual display with varying global and local features (see Fig. 3). Twenty-four children with DS (mean age 14.9 years) were compared to 24 MA-matched controls. Results showed that children with DS were equally focused on the global and local levels when reproducing the drawings and showed better reproduction of detail at the local level than MA controls. Results on the Banks and Prinzmetal task were also in line with the usual pattern of data in the typical population, with measured biases at both the local and global levels (see Fig. 3).

Taken together, these data suggest integrity in the early stages of both dorsal and ventral visual stream processing. While more work could be conducted in this area, these findings suggest that the inputs into the medial temporal lobe from these processing streams may be intact. Therefore, memory dysfunction is likely to originate not from dysfunction in primary visual function processes but from differences in the hippocampus or surrounding MTL.

MTL in humans with DS

Magnetic resonance imaging studies have shown consistent evidence for reductions in gray matter density in the hippocampus in children and young adults with DS (Menghini et al., 2011; Pinter et al., 2001). Alterations in MTL microstructure are also apparent, with levels of dendritic branching in the temporal cortex, CA1, CA2, and CA3 in the hippocampus particularly affected in patients with DS (Ferrer et al., 1990; Takashima et al., 1989). White et al. (2003) also
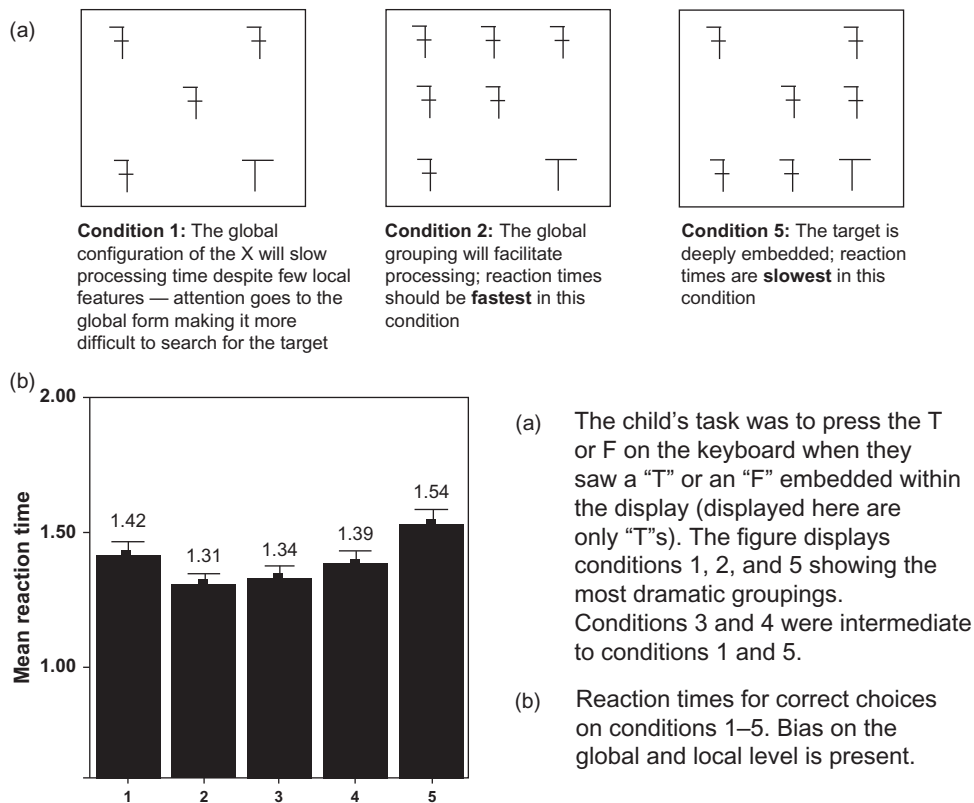
(a)

Condition 1: The global configuration of the X will slow processing time despite few local features — attention goes to the global form making it more difficult to search for the target

Condition 2: The global grouping will facilitate processing; reaction times should be **fastest** in this condition

Condition 5: The target is deeply embedded; reaction times are **slowest** in this condition

(b)

(a) The child's task was to press the T or F on the keyboard when they saw a "T" or an "F" embedded within the display (displayed here are only "T"s). The figure displays conditions 1, 2, and 5 showing the most dramatic groupings. Conditions 3 and 4 were intermediate to conditions 1 and 5.

(b) Reaction times for correct choices on conditions 1–5. Bias on the global and local level is present.

Fig. 3. Banks and Prinzmetal Task (1976) and results in 24 individuals with DS.

found reductions in gray matter density in non-demented adults with DS, including specific reductions in CA2 and CA3. A recent as yet unpublished study (Abraham, H. et al., personal communication) demonstrated not only reduced hippocampal volume in DS, but also an indication of some regional differences, with the dentate gyrus being more affected than other areas. There was a hint in this work that specific reductions in neurogenesis might be responsible for this impact on the dentate gyrus and on hippocampal volume overall. In addition, the onset of myelination was delayed in DS relative to controls, particularly so in the dentate gyrus. It is of interest to note that in both controls and DS, myelination occurs later in dentate gyrus than in other parts of the hippocampus (Arnold and Trojanowski, 1996; Contestabile et al., 2007).

Data on MTL-related neuropsychological measures in humans with DS are presented in Table 2. Uecker et al. (1993) provide a comprehensive review of early research suggesting behavioral deficits on MTL tasks in those with DS. Described in detail in this review, Mangan (1992) carried out one of the first investigations of the integrity of hippocampal functions. CA-matched control infants and infants with DS were tested on three related spatial tasks, one of which, a place-learning task, assessed the state of function of the hippocampal system. Two other spatial tasks included in the study could be solved without engagement of the hippocampus, involving

Table 2. Studies of MTL tasks in humans with DS

Study	Findings	MTL region implicated
Mangan (1992)	Toddler with DS<CA on place–learning task DS=CA on response learning (make a specific body turn), cue learning (approach a specific cue)	CA1
Carlesimo et al. (1997)	DS<ID<MA on word list learning, prose recall, reproduction of a complex figure	general MTL function
Pennington et al. (2003)	DS<MA on CANTAB PRM	perirhinal
	DS<MA on CANTAB PAL	CA3/dentate gyrus
	DS<MA on virtual maze	CA1
	DS<MA on everyday episodic memory	General
Vicari et al. (2005)	DS<MA on visual-object patterns	Perirhinal cortex, CA3/dentate gyrus
	DS=MA on learning of visual-spatial material	
Visu-Petra et al. (2007)	DS<MA on CANTAB PAL, PRM, SRM[a]	CA3/dentate gyrus, perirhinal
	DS=MA on CANTAB SSP and SWM	Parahippocampal spared
Edgin et al. (2010a)	DS<MA on CANTAB PAL	CA3/dentate gyrus, perirhinal
	DS=MA on virtual maze	CA1 spared

[a]Authors note the presence of significant floor effects; MA, mental age match; CA, chronological age match; ID, intellectual disability match.

either response learning (make a specific body turn) or cue learning (approach a specific cue). In all three tasks, the child searched for a toy hidden under a pie-plate, using a place, response, or cue strategy. After viewing the hiding of the toy, the infants were removed from the apparatus for a delay interval and then were given a "memory" test. On the critical memory probes, children with DS performed similarly to typical children on the response and cue tasks but were severely impaired on the place task. These findings point to deficits in functions of the hippocampus. However, MA-matched controls were not used in this

study, making the findings somewhat difficult to interpret. See Table 3 for a comparison of controls used in studies of animals and humans with DS.

In another study examining dissociations in mnemonic processing in DS versus other IDs, Carlesimo et al. (1997) found impairments in explicit memory in the context of spared implicit memory (e.g., intact word stem and visual priming). Explicit memory deficits were apparent on word list learning and prose recall as well as in the reproduction of a complex figure over a delay. However, it is difficult to further define the specific functions of the MTL tapped by these tasks, given their language demands as well as the possibility that deficits on the complex figure

Table 3. Studies of prefrontal tasks in humans with DS

Experimental type	Control type	Comparison value
Human	Mental age (MA)-matched control (TD children 3–6 years; IQ-matched same-age individuals with other ID)	*Benefits*: controls for effects of IQ on cognitive performance. *Limitations*: developmental or phenotype-specific confounds may be present
	Chronological age (CA)-matched control (TD same-age individuals; IQ-matched same-age children with other ID)	*Benefits*: controls for effects of age and experience on cognitive differences observed. *Limitations*: IQ or phenotype-specific confounds may be present
Mouse model	Wild type (euploid)	*Benefits*: controls for developmental period of the mouse. *Limitations:* Not able to determine whether or not deficits result from global or specific dysfunction

TD: typically developing.

reproduction could reflect dysfunction in a number of brain regions.

Pennington et al. (2003) reported deficits in relation to MA controls on several tasks that may map onto the function of the MTL, including immediate memory for patterns (CANTAB Pattern Recognition Memory, PRM), binding between object and location (CANTAB PAL), spatial memory through navigation (a virtual Morris water maze, MWM; Morris, 1984), and list learning across four trials. The group with DS also showed impairment on one ecological episodic memory measure (e.g., remembering what they did in the last testing session). Many findings of Pennington et al. (2003) were replicated by Visu-Petra et al. (2007) in a study that also showed deficits on the CANTAB PAL and PRM tests in relation to MA-matched controls. Together, these findings suggest deficits on tasks dependent on MTL structures adjacent to the hippocampus (Heuer and Bachevalier, 2011), such as visual recognition memory, as well as on tasks dependent on the hippocampus proper (i.e., spatial navigation relying on CA1/subiculum).

However, in one of the largest samples tested on neuropsychological measures to date (Edgin et al., 2010a), we did not replicate one of the deficits suggesting involvement of the CA1/subiculum circuitry. This study measured MTL, prefrontal, and cerebellar function in 74 children and young adults. Individuals with DS showed clear deficits on an object in place memory task in comparison to MA controls (i.e., CANTAB PAL), but performance on a test of spatial memory with navigation (the c–g arena) was not impaired.

Similarly, other studies seem to suggest greater deficits in some MTL regions than others (Ellis et al., 1989). For instance, Vicari et al. (2005) found that a group of 15 individuals with DS were more impaired on a task tapping visual-object long-term memory than on a task tapping memory for spatial locations, which was completed at the level of MA-matched controls. However, this finding is difficult to interpret in the context of the MTL model presented here, because the tasks assessing spatial memory did not necessarily involve allocentric spatial representations or spatial navigation, as did the virtual arena task utilized in Pennington et al. (2003) and Edgin et al. (2010a). Further, not all studies have shown differences in performance on object and spatial memory tests (CANTAB PRM vs. CANTAB SRM (Spatial Recognition Memory); Visu-Petra et al., 2007). The latter note that the CANTAB SRM test showed substantial floor effects, which could have obscured any differences.

In recent work in our laboratory, 11 children with DS and a matched sample of 11 MA controls were tested on their recognition of single objects displayed on a white background or in varying contexts after a 5-min delay (i.e., objects in congruent and incongruent contexts, see Fig. 4, e.g., stimuli and results). This task had been linked to the parahippocampal cortex in adults in a recent imaging study (Hayes et al., 2007). Individuals with DS displayed striking impairments across all conditions, including the recognition of single objects and objects embedded in a context. Again, these findings implicate multiple regions of the MTL, in addition to the hippocampus itself.

Given that a large number of treatment studies target the function of the hippocampus and MTL for neurocognitive intervention in DS, it is important to establish the impact of these deficits on the broader profile of cognitive and behavioral development. Pennington et al. (2003) reported an association between hippocampal measures (a composite score) and both adaptive behavior and language, including expressive and receptive syntax. Edgin et al. (2010b) also replicated the association between the CANTAB PAL and adaptive behavior. The composite used by Pennington et al. (2003) summed the scores of tests likely tapping the function of both the hippocampus proper (e.g., c–g arena and CANTAB PAL) and the surrounding MTL (e.g., CANTAB
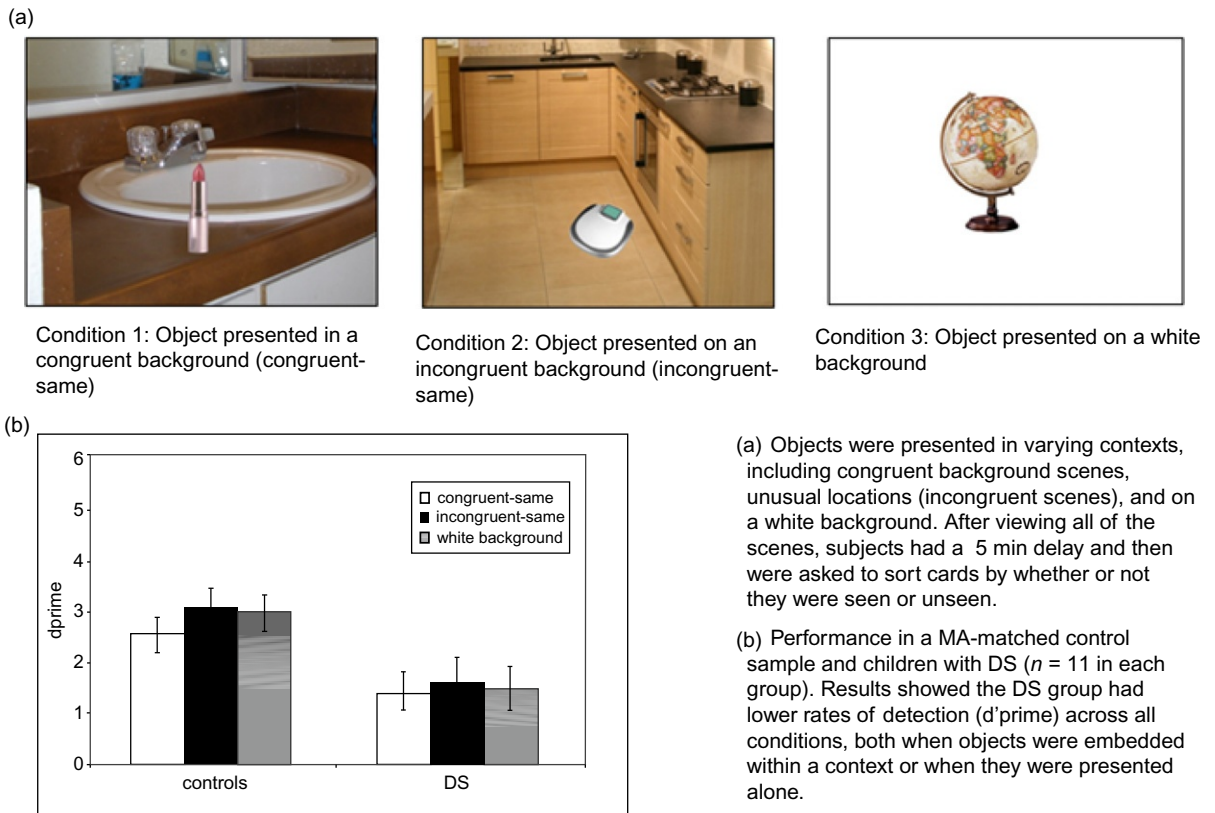
(a)

Condition 1: Object presented in a congruent background (congruent-same)

Condition 2: Object presented on an incongruent background (incongruent-same)

Condition 3: Object presented on a white background

(b)

(a) Objects were presented in varying contexts, including congruent background scenes, unusual locations (incongruent scenes), and on a white background. After viewing all of the scenes, subjects had a 5 min delay and then were asked to sort cards by whether or not they were seen or unseen.

(b) Performance in a MA-matched control sample and children with DS (n = 11 in each group). Results showed the DS group had lower rates of detection (d'prime) across all conditions, both when objects were embedded within a context or when they were presented alone.

Fig. 4. Memory for objects in context and on a white background in individuals with DS and controls.

PRM). In a recent reanalysis of these data (Fernández, A., Nadel, L., & Edgin, J. O. unpublished), we examined how each specific memory measure from Pennington et al. (2003), including auditory STM, may predict language outcomes. In this analysis, auditory and pattern STM (i.e., CANTAB PRM) were related to both expressive and receptive syntax scores. However, hippocampal tests did not relate beyond the influence of STM impairments. This pattern was different from MA controls, for whom auditory and spatial STM related to expressive and receptive syntax and one hippocampal test related to expressive syntax. Future studies should aim to understand the brain basis of STM impairments in DS in order to better target treatments.

While more research is clearly needed to clarify this body of work on MTL deficits in DS, these findings do suggest that individuals with DS are impaired on tasks dependent upon functions of MTL processing streams. The data point to deficits in recognition memory, which may depend upon areas adjacent to the hippocampus proper, as well as deficits on tasks tapping functions of the hippocampus itself. However, little research has been conducted with paradigms capable of determining which specific MTL structures are implicated. Many tasks that have

been utilized in past work, such as the reproduction of a complex figure, are too diverse in their cognitive demands to determine the neural basis of any observed deficit. Recent work has identified tasks that tap the functions of specific MTL subregions (Bakker et al., 2008; Bussey et al., 2003), which could provide a basis for more targeted batteries of assessments in humans and animal models. Given that successful pharmacological modification of MTL deficits may depend on targeting specific regions (e.g., perirhinal vs. CA1), this direction could be an important next step in neuropsychological work with humans with DS.

MTL evidence from mouse models

Mouse models have added invaluable information to our understanding of the mechanisms of MTL dysfunction as well as potential treatments targeted at modifying the function of this region. For instance, models have revealed neuropathology in the MTL, including abnormalities of hippocampal long-term potentiation (LTP), long-term depression (LTD), and excessive inhibition in the dentate gyrus (Kleschevnikov et al., 2004; Siarey et al., 1997 and see Chapter 10). Data from Ts65Dn (see Chapter 9) show robust evidence for involvement of the dentate gyrus/CA3 (preforant) pathway, including extensive loss of granule cells in the dentate gyrus and disruptions of synaptic function in CA3 (Hanson et al., 2007; Insausti et al., 1998; Lorenzi and Reeves, 2006). In addition to evidence regarding involvement of dentate gyrus and CA3, a recent study evaluating gene expression in the Ts65dn (Ginsberg et al., 2012) found differences in the gene expression profiles of CA1 neurons and across regions. It is important to note that gene expression among the two types of samples taken from each group (i.e., CA1 neurons vs. regional dissections) differed within the groups as well as within the postmortem tissue samples taken from humans with AD and human controls.

Recent targeted attempts to remedy these specific hippocampal deficiencies have been successful in reversing MTL-dependent memory deficits with pharmacological and environmental interventions in mouse models (Fernandez et al., 2007; Guedj et al., 2009; Martinez-Cue et al., 2002; Salehi et al., 2009). For instance, Braudeau et al. (2011) demonstrated that Ts65Dn mice treated with an α5-selective GABA inverse agonist (3-(5-methyl-isoxazol-3-yl)-6-[(1-methyl-1,2,3-triazol-4-yl)methyloxy]-1,2,4-triazolo[3,4-a]phthalazine, also known as α51A) showed improved acquisition of the platform location and decreased thigmotaxis on the MWM task, as well as improvements in the ability to discriminate between novel and familiar objects in the novel object recognition (NOR) task. Regarding environmental enrichment, Chakrabarti et al. (2011) recently showed that both short- and long-term exposure to enriched conditions (including a larger colony cage with a running wheel and various "toys") restored hippocampal cell proliferation and neurogenesis within the dentate gyrus of Ts65Dn mice to levels comparable to those observed in control (unenriched euploid) mice. Increased cell proliferation and neurogenesis was also observed in the forebrain subventricular zone, though the results were a bit more selective: these effects were only seen with long-term (4 weeks) enrichment, with more robust increases found in female mice than in males. Ultimately, treatment approaches for DS will be multimethod, and therefore, moving forward, approaches that test the joint influence of environmental stimulation and drug therapy could be particularly revealing.

Seregaza et al. (2006), Roubertoux and Carlier (2010), and Das and Reeves (2011) have reviewed the cognitive phenotype across the various DS models. Similar to humans, Ts65Dn mice that have been screened for blindness do not display visual or sensory motor deficits, with spared performance on simple cued learning tasks (Crnic and Pennington, 2000). Reeves et al. (1995) reported hippocampal-dependent deficits in the Ts65Dn, showing that affected mice took longer to reach

the hidden platform than wild-type mice on the MWM. Ts65Dn have also shown impairments on a broad range of MTL dependent tasks, including context fear conditioning (CFC), spontaneous alternation in a T-maze, NOR, and nesting behavior (Das and Reeves, 2011; Gardiner, 2010; Shamloo et al., 2010). While many of these tasks might tap CA1/subiculum due to their navigational components, the deficit in NOR provides the closest mapping onto the deficits in the human on tasks such as CANTAB PRM or PAL which assess recognition memory or the pattern separation functions relating to the dentate gyrus/CA3 pathway.

However, in one study utilizing immediate measures of spatial or object novelty, there was no noticeable difference between older Ts65Dn and wild-type mice (Hyde and Crnic, 2002), suggesting immediate recognition memory is not impaired in the Ts65Dn, in contrast to the PRM deficits seen in humans (Pennington et al., 2003). Das and Reeves (2011) also note that object in place tasks have not been found to be impaired across two models (Ts1Cje and Ts65Dn), which is in sharp contrast to the well-replicated deficits on object in place measures in humans (i.e., CANTAB PAL).

While the Ts65Dn findings suggest MTL impairments broadly, MTL findings have not been consistent across models (reviewed in detail in Das and Reeves, 2011). For instance, the Ts1Rhr and Ts1Yah did not show MWM deficits, and the Tc1 only displayed MWM and NOR deficits with a short delay. Also, in Tc1, LTP was disrupted at 1h, but not disrupted in the long term. Therefore, the Tc1 shows less evidence for task impairment in the long term, with some evidence of deficits in recognition memory (NOR) and STM (Morice et al., 2008; O'Doherty et al., 2005). The Dp(16)1Yey/+, Dp(17)1Yey/+, Dp(10)1Yey/+ model that includes all mouse orthologs of Has21 showed MWM deficits, but in the context of slower swimming speed (Yu et al., 2010). Dp(16)1Yey/+, Dp(17)1Yey/+, Dp

(10)1Yey/+ mice did, however, exhibit deficits on contextual fear conditioning and CA1 LTP was altered. Given the inconsistency of findings across models and various studies, it seems important that both human and rodent studies also include a consistent set of measures, including measures targeted toward specific aspects of MTL function.

Merging mouse and human MTL findings

Research in both species using more consistently administered, comprehensive batteries of tests that dissociate MTL function is clearly needed. Given the consistent findings of object in place deficits in humans with DS, more work should be done using similar measures in mice. Two studies suggest that mouse models do not show deficits on these tasks (Fernandez and Garner, 2007; Fernandez and Garner, 2008), but given the consistent presence of this deficit in humans, more work in the mouse is warranted. Further, to our knowledge, no study has explored tasks specifically related to perirhinal cortex in DS mouse models, including immediate tests of visual discrimination in conditions of high feature ambiguity. Given that the cognitive profile in the human is suggestive of the involvement of MTL structures adjacent to the hippocampus, it is necessary to explore the function of these regions in more detail.

While MTL functions are impaired in humans and seem relevant to developmental gains in other areas (i.e., language and adaptive behavior), these findings were examined mostly later in development. More developmental work is needed in both species to determine the pattern of deficits in early development and the impact of such deficits on learning across time. This developmental work is essential if we are to target those systems that would have the maximum impact in supporting cognitive development across childhood in DS.

Prefrontal functions

The prefrontal cortex, and particularly, the working memory functions associated with this region, has been shown to be highly important for cognitive function, academic achievement, and behavior in typical and atypical cognitive development (Alloway, 2009; Robinson et al., 2003). The prefrontal cortex mediates a variety of functions, including our ability to juggle incoming information, plan everyday tasks, and successfully adapt to the changing demands of the external environment. As with the MTL, the prefrontal cortex subserves a number of arguably distinct functions. These functions (often grouped under the label "executive functions, EF") include (1) the ability to hold information in mind and manipulate it (i.e., working memory), (2) the ability to inhibit actions for which a response tendency has been established (i.e., inhibitory control), and (3) the ability to flexibly switch between response sets (set-shifting).

In evidence suggesting distinct cognitive processes in typical adults, Miyake et al. (2000) utilized a latent variable approach to show that the three EF factors—working memory, inhibitory control, and set-shifting—are intercorrelated but separate. Friedman et al. (2008) also showed that these factors shared common variance but were differentially heritable in a behavioral genetics study. Given these results, Miyake has argued that there are distinct components of prefrontal function that may benefit from an overarching process, such as executive attention (Baddeley, 1986; Engle et al., 1999; Norman and Shallice, 1986).

The executive factors found by Miyake and colleagues are consistent with the cognitive profile of adult patients with differing prefrontal lesions, which suggests dissociations in the behavioral profile based on the location of the lesion within the frontal lobe. While frontal lesions can result in a diverse set of outcomes, often differing substantially based on the background of the patient, there appear to be two main subtypes. Mesulum (2002) describes them as follows: (1) a frontal abulic syndrome involving a loss of initiative, creativity, and concentration and (2) a frontal disinhibition syndrome which, in sharp contrast, involves behavioral excess, impulsivity, and lack of forethought. Patients with frontal abulic syndrome often have lesions to anterior frontal cortex. In contrast, patients with frontal disinhibition syndrome have damage to the orbital and medial frontal cortex including areas connecting to the striatum, which has been shown to be involved in inhibitory control across a number of studies (Durston et al., 2002). Working memory, on the other hand, has been shown to relate to dorsolateral prefrontal cortex, with the anterior cingulate also recruited on tasks requiring the resolution of conflicting stimuli (i.e., set-shifting tasks) (D'Esposito et al., 1995). The two prefrontal syndrome subtypes roughly correspond to the dissociated EF from Miyake et al. (2000), relating to reduced working memory and attentional capacity versus deficits in inhibitory control.

There is, however, some debate in the literature regarding the separability of these component processes of prefrontal function, especially early on in development. For instance, recent findings have suggested that in very young children executive processes may be unitary and that only during the course of development do they become dependent on somewhat separate neural mechanisms (Wiebe et al., 2010). Given the altered maturation of the PFC in DS, one might imagine global delays in most PFC-driven cognitive functions. However, given that these functions come to rely on separate neural mechanisms over development, individuals with DS may show a mixed profile of spared and impaired prefrontal functions.

Prefrontal function in humans with DS

Table 4 displays the findings from studies of prefrontal function in DS. Impairments in prefrontal function have been found in some, but not all,

Table 4. Studies of prefrontal tasks in humans with DS

Study	Findings
Inhibition	
Kopp et al. (1983)	DS<MA on reward delay latency
Pennington et al. (2003)	DS=MA on stopping task
Lanfranchi et al. (2010)	DS<MA on stroop type task–day/night version
Edgin et al. (2010a)	DS=MA on inhibition phase of modified dots task
Edgin et al. (2011)	DS normal range on BRIEF inhibition, emotional control
Raitano Lee et al. (2011)	Toddlers with DS normal range on BRIEF inhibition, emotional control
Set-shifting	
Zelazo et al. (1996)	DS<MA on DCCS
Edgin (2003)	DS<WS on DCCS
Rowe et al. (2006)	DS<ID on weigl color-form sort test
Lanfranchi et al. (2010)	DS<MA on rule shift card and modified card sorting test
Working memory	
Pennington et al. (2003)	DS=MA on CANTAB spatial working memory and counting span task
Lanfranchi et al. (2004)	DS<MA on verbal and visuospatial tasks
Lanfranchi et al. (2010)	DS<MA on verbal and visuospatial dual tasks
Visu-Petra et al. (2007)	DS<MA on CANTAB Spatial WM
Edgin et al. (2010a)	DS<MA on working memory phase of modified dots task

MA, mental age match; ID, intellectual disability match; DCCS, dimensional change card sorting task.

studies; our early work involving the administration of a large battery of executive function tasks yielded one of the negative results (Pennington et al., 2003). However, most recent research has found deficits, with the majority of studies showing specific deficits in working memory and attention (Brown et al., 2003; Edgin et al., 2010a; Lanfranchi et al., 2004; Lanfranchi et al., 2010; Visu-Petra et al., 2007) and set-shifting (Edgin, 2003; Lanfranchi et al., 2010; Rowe et al., 2006; Zelazo et al., 1996), with less

consistent impairments found on tasks requiring inhibitory control. These findings are consistent with structural imaging evidence showing reductions in gray matter volumes in the frontal cortex and cingulate gyrus (White et al., 2003).

In Rowe et al. (2006), young adults with DS were impaired on a range of prefrontal measures. However, after control for differences in verbal memory and psychomotor speed, only measures of attention and set-shifting were significant. In a large sample, Edgin et al. (2010a) also confirmed deficits in working memory and set-shifting in comparison to MA-matched controls, with impairments found on the CANTAB intra-dimensional/extra-dimensional set-shifting task as well as the working memory phase of a directional Stroop task (the Modified "Dots" task; Davidson et al., 2006). Edgin et al. did not, however, find impairments on the phase of the task requiring only inhibitory control. Parent report of everyday EF on the Behavioral Rating Inventory of Executive Function (BRIEF) suggests that ratings of working memory and set-shifting are more impaired than ratings of inhibitory and emotional control, both in younger (ages 4–10 years; Raitano Lee et al., 2011) and older children with DS (ages 7–25 years; Edgin et al., 2011).

It is of interest to note that the Pennington et al. (2003) study, which produced a null result, included measures of planning, inhibition, and working memory, but no set-shifting assessments. Edgin (2003) retested a group of individuals from the Pennington et al. (2003) study on a set-shifting task in which children initially sorted multidimensional cards (i.e., a red rabbit and a blue boat) by one category (i.e., the "Dimensional Change Card Sorting," DCCS task; Zelazo, 2006). After several trials in which they completed sorting by that category, they were asked to sort cards by the other dimension. School-age children and young adults with DS showed substantial deficits on this measure in relation to a matched sample of individuals with William's syndrome. While they performed the initial sorting of

the cards with near perfect performance, they were impaired when required to shift their response to the next dimension. These findings replicate earlier findings of Zelazo et al. (1996) in which adults with DS showed more errors when sorting to a second dimension in comparison to a MA-matched control sample. Taken together, these findings consistently point to more impairment on set-shifting and working memory measures as compared to measures of inhibitory control.

Given this pattern, Raitano Lee et al. (2011) hypothesized that individuals with DS may show dissociated deficits, with "cool" EF tasks such as working memory showing greater impairment than EF tasks with an emotional or inhibitory control component ("hot" EF). While "hot" EF has not been specifically measured in past studies of DS beyond parent ratings of emotional control, this could be an interesting avenue of research, given the pattern of findings reported here. A "hot" versus "cool" distinction would suggest dysfunction in the dorsolateral rather than ventromedial prefrontal cortex (Metcalfe and Mischel, 1999; Zelazo, 2006) and is also consistent with findings showing relatively preserved amygdala volumes in DS (Pinter et al., 2001).

One important next step is to determine the profile of prefrontal functions in DS, especially in young children and assess the ways in which these processes may underscore cognitive difficulties across domains. At least one study suggests that the pattern of dissociation described in older children may evolve over time. In contrast to the majority of results in older children, toddlers with DS did show difficulties in inhibitory control when presented with an attractive reward, displaying a shorter latency to touch the rewards than MA-matched controls (Kopp et al., 1983). Therefore, it is quite possible that very young children with DS do "grow out" of prefrontal difficulties relating to inhibitory control while deficits in attention, working memory, and set-shifting tend to persist. Given that the targets of certain pharmacological interventions are the attentional and executive systems (i.e., LDOPS;

Salehi et al., 2009), an important step will be to clarify the profile of these functions across development.

Prefrontal function in DS mouse models

In comparison to mouse model work on the MTL, there are far fewer studies examining the profile of prefrontal functions. However, there are neuropathological mechanisms that could influence both hippocampal and prefrontal function, and the bulk of studies that have been conducted show clear differences on prefrontal tasks. It has been noted that one of the most pronounced neuropathological features in the Ts65Dn mouse model of DS is the degeneration of cholinergic basal forebrain (CBF) neurons. CBF neurons have two major projection systems, including (1) projections to the hippocampus from the medial septal nucleus and (2) projections from the nucleus basalis to the frontal cortex (Moon et al., 2010). In mouse models, these neurons are intact at birth but show atrophy by 6 months of age. Another potential neurobiological target gleaned from mouse models is the locus coeruleus, whose early degeneration has been shown to lead to underdevelopment of the noradrenergic inputs to the frontal cortex and hippocampus (Salehi et al., 2009).

Indeed, Ts65Dn mice do display some behaviors that suggest difficulties with frontal function. For instance, they have documented deficits in spatial working memory (Escorihuela et al., 1995), a higher overall activity level (e.g., repetitive jumping), and lower levels of anxiety, with these differences apparent in both their home cage and a novel environment (Coussons-Read and Crnic;, 1996; Turner et al., 2001). Tc1 mice (Morice et al., 2008) have deficits in reversal learning, which could be analogous to the human tests of set-shifting. In a detailed examination of attentional behavior using a novel set of tests, Moon et al. (2010) showed that attentional deficits in Ts65Dn could be improved with prenatal choline supplementation. The mice performed a series of tasks requiring that they poke their

nose into one of five holes based on the appearance of a light cue from one of the holes. Successful responses resulted in a liquid reward. In various versions of the task, difficulty was varied to ascertain the mouse's level of attention. On a baseline visual discrimination task, a light from one hole was illuminated after 2s. The light remained on until the mouse responded or until 32s had elapsed. For the first two attention tasks, the task was identical except for cue duration. The mouse was required to make a response to a light from one of the five holes, but the light was present for only 1 or 2s. Another two attention tasks added a variable precue delay, placing greater demands on sustained attention. The final task was the Reward Omission task, in which some trials were unrewarded and the mouse's emotional response to the absence of an expected reward (i.e., activity level through jumping) was recorded. Collectively, these tests likely assess the range of prefrontal cortical functions in humans, including inhibitory control, working memory, and sustained attention.

Consistent with the information reported for humans, the test assessing simple visual discrimination was not significantly different in the Ts65Dn. However, all the tests of sustained attention yielded deficits in the Ts65Dn mouse, with some rescue of function after choline supplementation in pregnancy. The authors also reported significantly increased activity levels in Ts65Dn mice after errors on the task. This overreaction to making an error could reflect impaired "hot" executive function, as discussed above. Therefore, unlike humans with DS, mouse models seem to show uniform impairments across a variety of executive tasks.

Merging mouse and human prefrontal function findings

While data from humans suggest dissociations in the profile of prefrontal functions, the findings in the mouse models suggest overall impairment. Given that the profile of executive function deficits may change across development, it is possible that the dissociation between tasks tapping inhibitory control and other EFs reflects a maturational change that is simply not achieved in the mouse models before the onset of neurodegeneration around 6 months (Granholm et al., 2000). Another explanation may relate to cross-species differences in the structure of the frontal cortex. The prefrontal cortex has been shown to be less structurally segregated in the rodent as compared to the primate and human (i.e., less well-developed dorsolateral prefrontal cortex), a fact that could explain less differentiated functional outcomes associated with dysfunction in this region in the mouse (Preuss, 1995).

Taken together, however, these findings suggest some avenues for future research, including (1) a more detailed analysis of frontal function in humans with DS and mouse models, given that these impairments are present and could have a substantial influence on learning in multiple domains; (2) an analysis of the profile of EFs across development (i.e., does the pattern shift from global to dissociated impairment?); and (3) the development of tests, in both the mouse and the human, that measure these functions in a specific manner. The measures of Moon et al. (2010) are a step in the right direction and utilize paradigms that could be quite similar in mice and humans. Given the evidence for set-shifting difficulties in humans with DS, it will be important to develop a close analog of those measures as well.

Cerebellum

The cerebellum is one of the most affected neural structures in DS (Pinter et al., 2001), with behavioral deficits found in this domain in both mouse models and humans (Frith and Frith, 1974; Olson et al., 2004b). Traditional measures of cerebellar function have been extensively studied in humans with DS, particularly aspects of motor control (Table 5). Eyeblink conditioning is one of the purest measures of cerebellar function available

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Table 5. Studies of cerebellar tasks in humans with DS

Study	Findings
Frith and Frith (1974)	DS no improvement on rotor tracking task after 5 min test. DS slower than ID and MA on a finger tapping task
Rast and Harris (1985)	DS<CA in Motor Assessment of Infants task
Connolly and Michael (1986)	DS<ID on gross motor and fine motor skill composite scores on the Bruininks Oseretsky Test of Motor Proficiency
Woodruff-Pak et al. (1994)	Older DS (m=47.7) <younger DS (m=27.6), ID (fragile X) <CA on eye blink classical conditioning task
Latash et al. (2002)	DS<CA on both maximal single- and multifinger force production tasks and multifinger tasks
Stedron (2004)	DS<MA on rhythmic finger tapping, DS=MA on eye blink conditioning
Virji-Babul et al. (2006)	DS<MA on complex perceptual discriminations of point-light displays of human action
Lam et al. (2009)	DS<CA (slower) on Fitts' task
Edgin et al. (2010a)	DS<MA on finger sequencing, DS=MA on visuomotor precision, reaction time

MA, mental age match; CA, chronological age match.

(McCormick and Thompson, 1984). However, eyeblink conditioning has led to inconsistent results in the DS literature, with deficits found in older adults but not younger children (Stedron, 2004; Woodruff-Pak et al., 1994). As seen in Table 5, complex motor tasks, such as finger sequencing or rhythmic finger tapping, have been shown to be impaired in humans with DS, suggesting deficits in specific aspects of motor control governed by the cerebellum.

While early work on the cerebellum focused on its role in motor coordination, it is now clear that this structure has a broad range of functions, including links with language, visuospatial cognition, and working memory (Stoodley and Schmahmannm, 2009). The cerebellum is a highly modularized structure, forming separate loops between its various lobules and specific cortical and subcortical regions. Recent studies have shown that the lobes of the cerebellar hemispheres may show differing developing trajectories, with more protracted development in the inferior portions (lobules VI–VII) than anterior sections (lobes I–V) (Tiemeier et al., 2010). While the anterior portion of the cerebellar hemispheres shows associations with motor tasks, the inferior lobes of the cerebellum are more closely related to aspects of higher-level cognition, including prefrontal function and auditory memory (Marvel and Desmond, 2010). Given the robust nature of language and verbal STM deficits in DS (Edgin et al., 2010b), an examination of nontraditional links between the cerebellum and cognitive processes may be particularly important in this syndrome. Equally important will be more detailed neuroimaging studies of this structure in humans with DS, ideally using a similar approach to the study of Tiemeier et al. (2010) in which variation in subregions was closely examined in typically developing children.

Cerebellum in mouse models

A summary of the physiological cerebellar profile for selected mouse models is found in Table 6. In the Ts65Dn, overall cerebellar volume is reduced to 88.1% of the volume observed in euploid, with significant reductions in both granule and Purkinje cell density (Baxter et al., 2000). As can be seen in the table, very few studies have examined the morphological development of individual cerebellar lobules. Given the data in the humans suggesting functional segregation by subregion, this analysis may be an important step forward in understanding cerebellar profiles in the mouse.

Table 6. Differences in cerebellar phenotype among mouse models of DS

Mouse model	Normalized cerebellar volume (compared to euploid)	Granule cell density	Purkinje cell density	Lobular density
Dp(16)1Yey/+, Dp(17)1Yey/+, Dp(10)1Yey/+(Yu et al., 2010)	N/M	N/M	N/M	N/M
Dp(16)1Yu (also see Ts1Yu, Dp (16)1Yey) (Li et al., 2007)	N/M	N/M	N/M	N/M
Ts65Dn (Baxter et al., 2000)	88.1%	76%	89.5%	Midline 81.7%, parasagittal section 80.6% of euploid
Ts1Cje (Olson et al., 2004b)	88.8%	91.2%	98.3%	N/M
Ts1Rhr (Olson et al., 2007)	95%	102%	101%	N/M
Ts1Yah (Pereira et al., 2009)	N/M	N/M	N/M	N/M
Tc1 (Moldrich et al., 2007; O'Doherty et al., 2005)	N/M	84–85%	N/M	Lobe VIII reported to be reduced to approximately 84% of wild type

N/M, not measured.

Cerebellar function in mouse models has historically been assessed through motor tasks such as the rotarod, observations of posture and gait (Crawley, 2007), and adapted eyeblink conditioning paradigms (Chen et al., 1996). Despite global reductions in volume in the Ts65Dn, mixed results have been observed when these animals were tested on motor skills tasks assessing functions typically associated with the cerebellum in mice, with some studies actually finding enhanced function, while others found impairment (Baxter et al., 2000; Costa et al., 1999; Hyde et al., 2001). In comparison, the Tc1 model displays significant deficits on tasks such as the rotarod and static rod as well as a significantly different exploratory behavior profile in an open-field exploration environment (Galante et al., 2009). However, studies of the physiological cerebellar profile of Tc1 have indicated a granule cell density reduction that, while significant, is less than the reduction observed in Ts65Dn (85% vs. 76%; Moldrich et al., 2007). Further, certain aspects of Purkinje cell function are not significantly impaired relative to euploid mice (Galante et al., 2009), suggesting that the motor deficits found in Tc1 may correspond to specific cerebellar impairments.

Merging human and mouse cerebellar findings

Given these results it is clear that this region shows substantial morphological differences in both humans and mouse models. However, the behavioral findings have not been consistent in either species. One reason for inconsistencies in outcome may be because of the complex nature of this structure and its cognitive correlates. Because of the extensive connections between the cerebellum, subcortical, and cortical structures, it is difficult to find tasks that tap only "cerebellum." Another piece of evidence regarding this point comes from our recent work, in which we found a substantial correlation between measures of cerebellar and prefrontal function on the Arizona Cognitive Test Battery (Edgin et al., 2010a). Given mounting indications that there are substantial links between cerebellum and higher-level cognition, it may be

too simplistic to continue to assess the global function of this region solely with motor-based outcome assessments.

The linguistic brain

Difficulties with language are a central feature of the cognitive profile in DS. Therefore, it will be important for us to be able to accurately assess language function when interventions are developed for humans. Similar to the domains of neuropsychological function already reviewed, language functions in DS are not uniformly impaired. In this case, however, we cannot lean on mouse model research to help us define the specific domains of language functions compromised in DS.

Children with DS appear to show deficits in language production from an early age. The pattern of language impairment includes a longer transition period from babbling to words, reduced intelligibility of speech, and less word production and word variety resulting in a shorter mean length of utterance (Abbeduto et al., 2007; Berglund et al., 2001; Chapman et al., 1998). When tested in receptive vocabulary, individuals with DS have been shown to perform at the level of MA controls. However, not all studies have suggested this pattern is consistent throughout development. For instance, in a longitudinal study following 17–19-month-old children with DS in comparison to typically-developing 9-month-olds during a 14–21-month period, Cardoso-Martins et al. (1985) found that vocabulary development in DS lagged behind the children's level of cognitive development. Therefore, language is one additional domain in which we could use an understanding of developmental progressions in order to better target treatments.

The majority of studies in older children suggest specific impairment in morphosyntactic capacities (i.e., grammar development; Abbeduto et al., 2007). Morphology concerns aspects of language that convey meaning, such as words and affixes. Morphosyntax involves the way in which these units of speech, or morphemes, are combined together to convey meaning. It is in this area of language that one sees the most dramatic impairments in DS.

In typical development and the development of those with DS, research on the neurological underpinnings of language processing has highlighted the involvement of a number of brain regions. Research using fMRI has expanded the regions implicated in the phonological processing and lexical-semantic aspects of language beyond what were formerly known as "Broca's" and "Wernicke's" areas (inferior frontal, and superior temporal gyri) to include the angular gyrus, certain prefrontal regions (inferior, superior, and portions of the middle frontal gyri along with part of the anterior cingulate), some temporoparietal regions (Binder et al., 1997), as well as parts of the cerebellum and basal ganglia (Booth et al., 2007).

A recent structural neuroimaging study in individuals with DS (Menghini et al., 2011) suggested that receptive morphosyntax was related to the gray matter density of the cerebellum, while productive morphosyntax related to the gray matter density of the inferior and middle temporal gyrus. Another recent functional neuroimaging study reported differences in regional activation between individuals with DS and typically developing age-matched controls during passive story listening. Losin et al. (2009) noted that individuals with DS showed almost the identical pattern of activation when listening to the words of stories read forward or backward, unlike a sample of CA-matched controls that showed more activation in classic receptive language areas (i.e., superior and middle temporal gyri) in the forward condition. Further, individuals with DS did not show activation in these language areas but had greater activation in the cingulate gyrus and parietal lobes, suggesting either a compensatory strategy or the engagement of more diffuse neural mechanisms. While the neurological profile underlying these deficits is quite complex, it is clear that core neuropsychological functions such as those supported by the MTL,

prefrontal cortex, and cerebellum may also play a role in this important cognitive domain.

Although mice are not considered a "linguistic" species, recent research has suggested that there are certain behaviors in mice that might help us to better understand language in humans. One behavior that has received some attention, in this regard, is mouse ultrasonic vocalization (USVs), with some studies showing that DS mouse models as well as mouse models of other disorders with communicative deficits are altered in this behavior (Holtzman et al., 1996). Holtzman et al. found that USV behavior was delayed by 4 days in Ts65Dn mouse pups, and there have been a number of studies indicating specific pup and adult USV irregularities in mice with alterations in genes such as FOX P2 and oxytocin gene OXT (i.e., implicated in language and social behavior) as well as neuroligin-4 and neuroligin-3, which have been associated with autism spectrum disorder (ASD; see Fischer and Hammerschmidt, 2011 for review). While it is important to note that USVs are delayed in the Ts65Dn, these vocalizations do not map onto the specific language impairments observed in humans with DS (i.e., morphosyntax). They may instead be more reflective of the animal's drive to communicate. In mouse models of autism, this may be a good proxy for communication impairments, but in DS, USVs are not likely to be as useful.

In addition to USVs, previous studies have indicated that auditory learning tasks (i.e., oddball discrimination) can be completed in mice. In one such task (Peiffer et al., 2003), mice are presented with a pattern of two-tone auditory sequences separated by constant intervals. During the sequence presentation, a startle-eliciting stimulus (a white noise burst producing an acoustic startle reflex in mice) interrupts one of the between-sequence intervals. In the uncued (control) condition, a control two-tone (high/low) sequence is presented repetitively prior to the startle-eliciting stimulus, while in the cued (oddball) condition, an oddball (low/high) sequence is inserted as a "cue" for the startle-eliciting stimulus amongst the high/low sequences. The acoustic startle reflex of the mice is recorded in each condition, and it is expected that if the mice are able to discriminate the oddball sequence, then their startle reflex should be significantly attenuated in the cued condition relative to the uncued condition. Using this reflex modification paradigm, Peiffer et al. (2003) were able to find significant oddball detection differences among male BXSB/MpJ mice with cortical ectopias resembling the pathology seen in dyslexia, which suggests that it may be useful for assessing auditory processing deficits in relation to neurodevelopment.

Other paradigms used in rodents have made use of auditory "go/no-go" tasks, in which rodents are rewarded for responding to short tone sequences containing an oddball tone in contrast to sequences of identical tones. Differences on this task correlate with age-related changes in the primary auditory cortex of rats (de Villers-Sidani et al., 2010). Given these results, it is possible that the addition of auditory learning tasks could allow for the testing of the effects of drugs on multiple neural systems and some additional aspects of the DS phenotype prior to trials in humans.

Recommendations for cognitive assessment moving forward

Using data generated in mouse models of DS, in the past 5 years several drug targets have been identified for cognitive intervention (see Chapter 10 for additional details). Many of these pharmacological agents are currently being tested or will go to trial in humans in the coming years. Returning to our assumptions regarding the bridge between animal models and human work, we can expect success in this transfer only to the extent that the cognitive processes affected in the mouse and the human are as similar as possible. Further, given that some important behaviors (e.g., language or adaptive behavior) cannot be measured in the same way in mice, we want to be certain that the neurological processes

modified by any drug will have an effect on important cognitive domains in humans with DS. Based on the data reviewed here, we recommend the following research directions moving forward: (1) better definition of the phenotype in both mice and humans; (2) examination of the functional subregions of affected neural systems; (3) work on cross-species assessment batteries that are targeted at specific neural structures; (4) a closer examination of developmental profiles, rather than just isolated snapshots, in both species; (5) a definition of the impact of compromised neural structures on the broader cognitive profile, including outcomes, such as language and adaptive behavior; (6) a better recognition of the role of interactions across brain systems that may be important in explaining the profile (i.e., the presence of cerebellar–prefrontal interactions); and (7) the joint exploration of the influence of environmental stimulation and pharmacotherapy on cognitive outcomes.

While there have been considerable advances in our knowledge of the cognitive phenotype in both species, we still require more precise definition of the cognitive deficits relating to impaired function in the MTL, prefrontal cortex, and cerebellum, including any dissociations in the function of subregions of these areas. The data reviewed here suggest that dissociations in cognitive functions do exist in humans (i.e., specific language and prefrontal profile), but the findings are less clearly differentiated in mice. In humans, there is evidence for deficits on tasks that tap both the hippocampus proper and the surrounding MTL. The findings in mice clearly show deficits in hippocampal-dependent memory, with mixed evidence for short-term recognition memory impairments. While the profile of prefrontal function is clearly differentiated by domain in older children with DS, the findings in mice seem more uniform, albeit the number of studies examining prefrontal function are fewer in number. The findings regarding cerebellar function show similar inconsistencies in outcomes, with most studies of motor control in humans showing deficits and studies in mice not always showing dsyfunction. We also reviewed the pattern of language deficits in individuals with DS, noting clear dissociations in impairment, with syntax being the strongest area of impairment. While there is no direct analog of syntax in mice, we review some methods to test auditory processing that might prove useful. Moving forward, the development of assessment batteries that can be easily completed in both humans and mice will be essential. In addition, more work is required to understand the neurological status of the specific subregions of affected brain structures. For instance, given that the cerebellum is so highly modularized, it is important to understand the morphology of the specific lobules of the human and mouse cerebellum. As can be seen in Table 6, very little work has been done along these lines to date.

One problem with currently administered cognitive tests is that the tasks are too complex to target specific structures. For instance, the MWM and the human variant (i.e., the computer generated arena) tap a complex set of skills. In the mouse, performance can be affected by swim speed. Similarly in humans, the task is operated by a joystick control, a method that can lead to perseverative responding. Tasks should be developed that are simple as possible in their cognitive demands. However, this goal may not always be fully realized, and thus, statistical control for extraneous demands will often be necessary.

Another need is a clarification of the inconsistencies in measured behavior across both humans and mouse models. Some of the differences between mouse and human studies are difficult to intrepret because measures have differed across studies. As much as we need to develop consistent measures for humans, mice of various genetic alterations also need to be tested on the same paradigms. Further, studies of pharmacological intervention in mice will be better placed to make claims about how these drugs may affect the human if they utilize more than one measure of function (i.e., expanding beyond the MWM), including measures from a broader

range of affected cognitive domains. Further, while the Ts65Dn is the most easily utilized and well-understood model, it cannot be ignored that the cognitive profile in this model may differ from the newer models carrying the full trisomy.

As emphasized earlier, there has been little work describing the longitudinal development of the cognitive profile in DS. An understanding of this trajectory is essential in targeting treatments to affect the primary source(s) of cognitive deficits in DS. The evidence reviewed here suggests that the functions targeted by pharmacological treatment (i.e., hippocampal-dependent memory, medial- temporal lobe, and prefrontal function) may have some influence in the broader cognitve profile when measured at a single time point in later childhood, but more work is needed to understand the progression of these deficits across development. Some surprises may be found if we examine this trajectory closely, such as the potential for the cerebellum to play a role in the development of verbal memory deficits or language dysfunction.

Closing remarks

In summary, our understanding of the cognitive profile and neuropathological mechanisms associated with DS has advanced rapidly in the past decade, leading to tests of pharmacological interventions for cognitive rehabilitation that are increasing in number. Crosstalk between studies of cognition in humans and mice is indeed possible, and essential, to maximize the possibility that drugs may positively affect humans at trial. It is necessary that cross-species comparisons are conducted with care to ensure continued development of drug treatments in this population. In our work, we have shown that cognitive assessment can indeed be valid and reliable in humans with DS (Edgin et al., 2010a). Now, we require additional test development resulting in measures that are targeted toward specific neurological structures and can be administered across a range of ages.

Only through a more complete understanding of the developmental profile of cognitive function in DS will we be able to target early cognitive deficits in a way that could have the greatest impact in changing the developmental trajectory for each individual.

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