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Author(s): Bruce F. Pennington, Jennifer Moon, Jamie Edgin, Jennifer Stedron, Lynn Nadel

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The Neuropsychology of Down Syndrome: Evidence for Hippocampal Dysfunction

Bruce F. Pennington, Jennifer Moon, Jamie Edgin, Jennifer Stedron, and Lynn Nadel

This study tested prefrontal and hippocampal functions in a sample of 28 school-aged ($M = 14.7$ years, $SD = 2.7$) individuals with Down syndrome (DS) compared with 28 ($M = 4.9$ years, $SD = .75$) typically developing children individually matched on mental age (MA). Both neuropsychological domains were tested with multiple behavioral measures. Benchmark measures of verbal and spatial function demonstrated that this DS sample was similar to others in the literature. The main finding was a significant Group \times Domain interaction effect indicating differential hippocampal dysfunction in the group with DS. However, there was a moderate partial correlation ($r = .54$, controlling for chronological age) between hippocampal and prefrontal composite scores in the DS group, and both composites contributed unique variance to the prediction of MA and adaptive behavior in that group. In sum, these results indicate a particular weakness in hippocampal functions in DS in the context of overall cognitive dysfunction. It is interesting that these results are similar to what has been found in a mouse model of DS. Such a model will make it easier to understand the neurobiological mechanisms that lead to the development of hippocampal dysfunction in DS.

Although Down syndrome (DS) is both the “oldest” and most common genetic mental retardation (MR) syndrome, we know less about its neuropsychology than that of other MR syndromes, such as Fragile X syndrome (FXS) or Williams syndrome (WS). The goals of the present study were: (a) to better define the neuropsychological phenotype in DS by testing both prefrontal and hippocampal functions, potential dysfunction of which is suggested by what is known about brain structure in DS; and (b) to test whether this phenotype varies by age.

Understanding the development of the neuropsychological phenotypes in MR syndromes has important implications for theories of cognitive development, because an adequate theory should account for both typical and atypical development. Hence, the pattern of development in MR syndromes provides important tests of the universality of the predictions made by such theories, such as predictions about developmental sequences and the role of various cognitive processes in both developmental and individual differences in intelligence (see discussion in Pennington, 2002). In this study, we focused on two cognitive processes, prefrontally mediated executive functions and hippocampally

mediated long-term memory, that are likely to be important for understanding the development of MR, both in DS specifically and in MR syndromes generally.

DS was first described by Down (1866) well over a century ago, and its genetic basis—an extra chromosome 21—was discovered about 40 years ago (LeJeune, Gautier, & Turpin, 1959). DS occurs in 1 in 600 live births and accounts for close to 40% of cases of moderate or worse MR found in the general population. In what follows, we review what is known about genetics, brain development, and neuropsychology in DS to motivate the present study.

Genetics of DS

Most (about 94%) cases of DS are not familial. Instead, a parent with a normal chromosome number produces an offspring with an extra copy of chromosome 21 (trisomy 21) through a process called nondisjunction, which is failure of one of the paired chromosomes to separate in meiosis. Nondisjunction is more likely in mothers, especially older ones, than in fathers, because all of a mother’s eggs are present in an immature form before her birth. In contrast, new sperm are continually being produced by fathers across their reproductive lifespan. The small remainder of cases of DS are familial and reflect either translocation of an extra piece of the long arm of 21 to another chromosome or mosaicism.

Bruce Pennington, Jennifer Moon, Jamie Edgin, and Jennifer Stedron, Department of Psychology, University of Denver; Lynn Nadel, Department of Psychology, University of Arizona.

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Correspondence concerning this article should be addressed to Bruce F. Pennington, Department of Psychology, University of Denver, 2155 S. Race St., Denver, CO 80208. Electronic mail may be sent to bpenning@nova.psy.du.edu.

So, the genetic etiology of DS is due to an extra dose of the products of normal genes. Understanding this genetic etiology at the molecular level is a difficult task because it requires that we (a) have identified all the genes on chromosome 21; (b) know which of these are overexpressed, because other genes or epigenetic interactions may produce dosage compensation for some of the genes on 21; and (c) know which of the overexpressed genes are expressed early enough in development to cause a congenital disorder. To understand the etiology of the neurobehavioral phenotype in DS, we need to add a fourth constraint, namely, that the gene is expressed in brain, or at least affects brain development.

Recently, the physical map of chromosome 21 was completed (Hattori et al., 2000), and it appears that the number of genes is about 225, which is less than the size of the chromosome would predict (e.g., chromosome 22 is smaller than 21 but has about twice as many genes.) A majority of these 225 genes are in the DS region on the long arm of chromosome 21.

Work is now under way to determine which genes in the DS region meet the other criteria listed earlier to qualify as candidates for the etiology of the neurobehavioral phenotype in DS. Mouse models with trisomies of either single candidate genes or segments of the DS region have been constructed and are being tested for their neurological and neurobehavioral phenotype. Crnic and Pennington (2000) presented a review of this research, including some of the promising candidate genes that have already been identified. These include the amyloid precursor protein gene (APP), which is also implicated in Alzheimer's disease (AD); a glutamate receptor subunit gene (GRIK1); the human minibrain homologue (MNB); and neuronal intracellular adhesion molecule (DSCAM). Some of these genes are known to have localized effects on brain development. For instance, the APP gene influences the development of the hippocampus (Granhölm, Sanders, & Crnic, 2000).

In sum, the genetic etiology of DS is more complicated than that of FXS or WS because it involves many more genes. Recent advances in mapping the human genome and constructing mouse models have accelerated progress toward testing relations between specific genes and specific aspects of the neurobehavioral phenotype in DS. However, it is always possible that trisomy induces developmental instability in a general way and that we will not be able to trace specific phenotypic

features of DS back to extra doses of specific genes (Reeves, Baxter, & Richtsmeir, 2001).

Brain Development in DS

Nadel (1999) recently reviewed what is known about brain development in DS. Broadly speaking, it appears normal at birth and is invariably abnormal by adulthood, because virtually all adults with DS have developed some of the neuropathological features of AD disease by around age 35. In addition, by adulthood, the brain is clearly microcephalic, but differentially greater volume reductions occur in the hippocampus, prefrontal cortex, and cerebellum (Kesslak, Nagata, Lott, & Nalcioğlu, 1994; Lögdberg & Brun, 1993; Raz et al., 1995; Weis, 1991). What is much less clear from the existing data is when these aspects of abnormal brain development first appear in individuals with DS.

A wide range of studies have found no differences at birth between brains of individuals with and without DS (e.g., Schmidt-Sidor, Wisniewski, Shepard, & Sersen, 1990). Differences appear in the first few months of life and include delayed myelination, reduced growth of the frontal lobes, a narrowing of the superior temporal gyrus, diminished size of the brainstem and cerebellum, and a major reduction (20%–50%) in the number of cortical granular neurons (Nadel, 1999). However, these differences in brain development are not invariant across all cases. So several features of the adult brain phenotype begin to emerge in the first years of life. These include microcephaly and reduced volumes of the cerebellum and frontal lobes. However, evidence for hippocampal volume reduction in the first years of life has not been reported.

Less is known about brain development in children and adolescents with DS. One structural MRI study of adolescents (Jernigan, Bellugi, Sowell, Doherty, & Hesselink, 1993) found a pattern of results similar to that found in adults, that is, microcephaly and relatively smaller volumes of frontal cortex, hippocampus, and cerebellum. These investigators compared a small sample ($N = 6$) with DS with both normal chronological age (CA) controls ($N = 21$) and adolescents with WS ($N = 9$). Both of the groups with MR had overall microcephaly, but only the group with DS had a cerebellar volume reduction relative to age controls. In WS, despite microcephaly, the cerebellar volume was similar to that of age controls. There were also contrasts between the groups with DS and WS in the proportions of gray matter for several other structures. The group with DS had a smaller proportion

of anterior cortex and temporal limbic cortex, including the hippocampus (compared with both WS and controls). In contrast, posterior cortex, the lenticular nucleus, and the diencephalon were all proportionally larger in the group with DS compared with the other two groups.

In sum, the adult brain phenotype in DS is characterized by both general (microcephaly) and specific (frontal lobes, hippocampus, and cerebellum) volume reductions, some of which may emerge earlier in development than others.

Neuropsychology of DS

What is known about the brain phenotype in DS leads one to predict both overall neuropsychological dysfunction and more specific deficits on measures of prefrontal, hippocampal, and cerebellar functions. Because different aspects of the brain phenotype appear to emerge at different points in development, one would also predict different developmental trajectories for different domains of dysfunction. Specifically, one would predict that hippocampal dysfunction may appear later in development than dysfunction in the other domains (Nadel, 1986). We next examine whether existing cognitive data support these hypotheses.

We begin with areas of cognitive development that have been thoroughly studied, including the level and trajectory of IQ, speech and language functions, verbal short-term memory (STM) and visuoconstructive functions, and we conclude with the few studies of hippocampal functions (i.e., allocentric spatial cognition and explicit long-term memory) in DS. To our knowledge, there are no previous studies of a range of prefrontal functions in DS, such as planning, set shifting, inhibition, and nonverbal working memory.

Level and Trajectory of IQ

DS does not prescribe a particular IQ but instead exerts a powerful, downward main effect on the IQ distribution. IQ in DS is also influenced by other genetic and environmental factors, just as it is in normally developing children. For instance, there is a positive correlation between parental IQ and the IQ of individuals with DS, and part of this relation is very likely genetic, just as in children without MR.

In contrast to normally developing children, there is a progressive IQ decline in DS beginning in the first year of life. In other words, the ratio of mental age (MA) to CA is not constant (Hodapp & Zigler, 1990). By adulthood, IQ is usually in the moderately

to severely retarded range (IQ = 25–55), with an upper limit on MA of approximately 7 to 8 years (Gibson, 1978), though a few individuals with DS have IQs in the normal range (Epstein, 1989). The trajectory of IQ in adulthood is also different in DS because of the increased risk of early onset AD; consequently, IQ declines much sooner in adulthood in DS than it would in normal aging (Epstein, 1989).

Little is known about the etiology of this virtually linear decline in IQ in the early development of individuals with DS. Determining the brain bases of the IQ trajectory in DS could illuminate the relations between normal brain and cognitive development. More specifically, either microcephaly or dysfunction in specific structures (i.e., prefrontal cortices, hippocampus, or cerebellum) could conceivably reduce IQ in DS and affect its trajectory, but each in different ways. Each of these specific structures helps mediate general cognitive processes that operate across content domains. Hence, dysfunction in each could be expected to have a general effect on cognitive development.

Speech, Language, and Verbal STM

Speech, language, and verbal STM have been extensively studied in DS and are probably the most well-documented aspect of its cognitive phenotype besides IQ. They also decline early and thus contribute to the IQ decline, because IQ tests partly measure language development. This speech and language profile contrasts markedly with what is observed in FXS and WS, a finding that potentially limits the causal role for some speech and language processes in explaining MR across syndromes.

Several areas of speech and language development are delayed below MA expectations in DS. Specifically, articulation (Fowler, Gelman, & Gleitman, 1994; Hulme & Mackenzie, 1992), phonology (Rondal, 1993), vocal imitation (Dunst, 1990), mean length of utterance, and expressive syntax (Fowler et al., 1994) are all below the expected MA level.

The development of verbal STM lags behind MA in DS (Hulme & Mackenzie, 1992). This well-replicated deficit may help explain some of the speech and language difficulties found in DS, as a number of researchers have suggested for the syntactic deficit (Chapman, 1999; Fowler, 1998; Marcell & Weeks, 1988). This relation makes sense both theoretically and empirically. Theoretically, comprehending syntactic relations requires temporary memory storage of the words in a phrase. Empirically, there are consistent moderate correlations between measures of verbal STM and language

measures in groups both with developmental disabilities and with typical development. For instance, verbal STM is a relative strength in WS, as is language, and the two are moderately correlated ($r_s = .47-.69$, with CA partialled; Mervis, Morris, Bertrand, & Robinson, 1999). Although there are clear articulatory delays in individuals with DS, Hulme and Mackenzie (1992) showed that slower articulation was not responsible for their verbal STM deficit. The authors proposed that children with DS were not rehearsing the to-be-remembered information in the articulatory loop. Consistent with the position taken here, they also suggested that deficits in verbal STM may play an important causal role in MR.

Hence, the verbal STM deficit in DS likely helps explain the language deficit, which in turn contributes to the IQ deficit. But we do not know the brain basis of the verbal STM deficit in DS.

Visuoconstructive Functions

Certain spatial abilities are a strength relative to MA in DS. For instance, Silverstein, Legutski, Friedman, and Tayakama (1982) found that a group with DS outperformed a group with non-DS MR individually matched on CA and MA on several drawing and other visuoconstructive tasks from the Stanford-Binet Intelligence Scale. This relative strength in DS contrasts with a relative weakness on similar tasks in WS (Wang & Bellugi, 1994; Wang, Doherty, Rourke, & Bellugi, 1995).

Hippocampal Functions

There are a few studies of hippocampal functions in individuals with DS, all of which find deficits. Mangan (1992) studied preschool (16 to 30 months old) children with DS and CA controls on three spatial tasks, one of which (place learning and recall) tapped hippocampal functions. The group with DS performed worse than CA controls on the learning portion of all three tasks but were severely and selectively impaired only on the delayed recall probes for the place-learning tasks. However, there was not an MA control group in this study.

Carlesimo, Marrotta, and Vicari (1997) tested implicit (stem completion) and explicit verbal memory (word-list learning and prose recall) as well as explicit nonverbal memory (Rey's Figure Form B) in adolescents with DS ($N = 15$) and MA controls ($N = 30$). They found similar verbal priming in all three groups for the stem-completion tasks. For the two explicit tasks, the group with DS was signifi-

cantly worse than the other two groups in learning but not differentially impaired in delayed recall or recognition. In fact, the DS group improved on recognition trials relative to their recall performance. These authors interpreted their results as supporting a hippocampally mediated deficit in episodic memory in DS, one that particularly affects encoding and retrieval. However, verbal memory tests are problematic in individuals with DS because of their well-documented language and verbal STM deficits. Therefore, it would be valuable to test nonverbal long-term memory (LTM) in individuals with DS, using a task that does not depend on visuomotor skills.

Three studies of adults with DS have found marked LTM deficits (Caltagirone, Nocentini, & Vicari, 1990; Devenny, Hill, Patxot, Silverman, & Wisniewski, 1992; Ellis, Woodley-Zanthos, & Dulaney, 1989). For instance, Ellis et al. (1989) examined nonverbal LTM using pictures in a book. Their group with DS was impaired at both recognizing pictures and remembering their locations, a result that is consistent with hippocampal dysfunction. However, a subset of the group with DS performed very well on this task.

In sum, previous LTM research has supported hippocampal dysfunction in DS. However, there are only two studies in nonadult samples, and both of these have methodological shortcomings. So, more work is needed to determine whether hippocampal dysfunction occurs before adulthood in individuals with DS and, if so, how early it occurs.

Goals of the Study

The main goal of the current study was to test whether neuropsychological development in DS is most consistent with prefrontal, hippocampal, or generalized dysfunction. As discussed earlier, these hypotheses derive from what is known about the development of brain structures in DS. The criterion for relatively specific dysfunction was performance below an MA comparison group on multiple measures of that neuropsychological domain (a CA comparison group would provide a less useful test of specific dysfunction because the DS group would perform below CA level on all measures correlated with IQ). Hence, it was possible to find evidence for (a) both the hippocampal and prefrontal hypotheses, (b) only one of the hypotheses, or (c) neither of the hypotheses. In this last case, the group with DS would be at MA level on both prefrontal and hippocampal measures, supporting the hypothesis of generalized rather than specific dysfunction.

There were two secondary goals. One was to begin to test the developmental trajectory of both (a) specific prefrontal or hippocampal deficits, if there were any; and (b) benchmark features of the cognitive phenotype, such as deficits in language and verbal STM. A final goal was to test for relations between neuropsychological measures and benchmark features.

Methods

Participants

There were two groups of participants in this study: children with DS and a control group of typically developing children individually matched on MA. Altogether, there were 33 children with DS between the ages of 11 and 19 years who were recruited with the help of a Denver-area DS association, but 5 of these could not be matched to an MA control participant, as discussed later. Of these 33 children with DS, the large majority (96%) carried the full trisomy 21 mutation. One child (4%) carried a chromosome 21 translocation. Medical complications, including coronary malformations, thyroid problems, gastrointestinal problems, or hearing and vision problems commonly accompany DS, and because we were seeking a DS sample that was representative of the syndrome, we did not exclude participants on the basis of medical complications, provided the children were able to complete the battery of cognitive tests. Consistent with the DS population as a whole, approximately 60% of our children had a history of coronary malformations, the majority of which required surgical intervention; 25% had a history of medically treated thyroid problems; 75% had vision problems, generally corrected with glasses; and 55% had a history of hearing problems. In addition, 4 children had a history of at least one seizure and 1 child had a history of successfully treated leukemia. Given this

high rate of medical complications, children in the DS group had spent considerably more time under medical care than the typically developing children.

We were unable to match 5 of our DS participants because of their low scores on the Differential Abilities Scale (DAS). They were at floor on several subtests, and their MA estimate was below the lower age limit for many of our neuropsychological measures. Indeed, these 5 children had extreme difficulty completing these tasks.

The remaining 28 of the DS participants were matched individually to younger typically developing children. The typically developing children, with CAs between 3 and 6 years, were recruited from a list of volunteers available through the University of Denver. Each participant with DS was matched to a control participant on the basis of MA, as determined by performance on the core tests from the School-Age version of the DAS (Elliott, 1990). The estimated mental age of both groups was 4.5 years.

Group comparisons between the DS and control populations indicated that the mean parental education for the two samples was equivalent (maternal education: DS $M = 15.23$ years, MA control $M = 15.64$ years; paternal education: DS $M = 15.68$ years, MA control $M = 15.42$ years). The groups also showed equivalent distributions for gender and ethnicity. Of course, the DS participants had significantly higher CAs and, correspondingly, more years of education than the typically developing children (see Table 1).

To test for developmental differences on various measures, the samples were split into older and younger groups ($n = 14$ pairs each). The mean age ($M = 16.98$ years, $SD = 1.29$) in the older group with DS was about 5 years greater than the mean age in the younger group with DS ($M = 12.39$ years, $SD = 1.52$). For the MA controls, this age difference was inevitably smaller (older $M = 5.14$ years, $SD = .76$; younger $M = 4.69$ years, $SD = .70$).

Table 1
Description of Samples

Measure	No. Pairs	Down syndrome		MA control ^a	
		<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
DAS composite score ^b	28	264.68	51.58	264.11	51.30
Chronological age (years)	28	14.68	2.72	4.92	.75
Gender (% Male)	28	40%		50%	
Ethnicity ^c	28	89%		89%	

^aMA controls are control participants matched on mental age.

^bComposite score represents the sum of nonstandardized scores across the six core DAS subtests.

^cEthnicity measure represents the percentage of children of European origin.

Procedure

The entire study required four 2-hour sessions, during which time the children completed the measures described in the next section. Each child was seen individually by a trained evaluator. The tests were presented in a fixed order to allow adequate time for delay trials on a number of the measures. Participants were given encouragement and small rewards throughout the test sessions, and families were given \$20 per test session.

Measures

The measures can be divided into four conceptual categories (Table 2). To ensure that our sample was representative of the DS population more generally, both descriptive measures of adaptive behavior and general intellectual ability and benchmark measures were included. Previous research, reviewed earlier, has consistently found below-MA performance in groups with DS on verbal measures, in particular verbal STM and syntax, but relatively preserved performance on some nonverbal measures (e.g., spatial span). We included benchmark measures of verbal STM, spatial span, syntax, and receptive vocabulary. The final two conceptual categories were neuropsychological, that is, measures of hippocampal or prefrontal functions. Several criteria were employed to select these measures. First, each

measure had to tap the core neuropsychological function associated with each brain region. For the hippocampus, this core function is the storage of episodic information in LTM. For the prefrontal cortices, this core function is the holding of information in active or working memory to guide action selection. Second, the measures within a domain needed to differ in their surface characteristics to provide multiple converging tests of the hypothesis of a deficit in the core neuropsychological function associated with that domain. Third, we sought measures for which there was brain imaging or lesion data that validated the measure as being either hippocampal or prefrontal; this requirement was met for most of the measures. Fourth, the measure had to be developmentally appropriate for the samples studied. Fifth, to avoid the potential confound of the well-known verbal STM and language deficits in DS, the majority of the measures were nonverbal. Finally, to permit cross-species comparisons, some of the measures were selected because analogues or variants existed that could be used in animal models of DS.

Descriptive Measures

To assess adaptive functioning, we asked parents to complete the Scales of Independent Behavior-Revised (SIB-R; Bruininks, Woodcock, Weatherman, & Hill, 1996), a checklist-style rating scale designed to assess functional independence and adaptive functioning. This measure has four subtests—Motor, Social/Communication, Personal Living Skills, and Community Living Skills—and yields an overall Broad Independence score. The SIB-R has good split-half reliability on its cluster scores for this age range (10–19 years) with intercorrelations ranging from .78 to .98 ($M = .92$). Bruininks et al. (1996) established the measures' validity by demonstrating expected age changes in the scores and by showing that these scores discriminate individuals with severe disabilities from age peers without disabilities.

General intellectual ability was evaluated with the School-age Version of the DAS. The DAS offers a wide range of possible scores at the lower end of the IQ distribution, and for this reason it is often used in studies with developmentally delayed children. The measure yields indices of Verbal Ability, Nonverbal Reasoning Ability, and Spatial Ability, in addition to an overall General Conceptual Ability (GCA) score. The DAS has excellent reliability with an internal consistency score of .95 for the School-Age Level Core (Sattler, 2001). Test-retest reliability scores were

Table 2
Measures Administered

Descriptive measures
SIB-R (completed by parent)
DAS
Benchmark measures
PPVT-III
CANTAB Spatial Span
TROG
CELF
DAS Recall of Digits
Hippocampal measures (all require long-term memory)
NEPSY List Learning
Virtual Morris water maze
CANTAB Pattern Recognition
CANTAB Paired Associates Learning
Ecological Memory Questionnaire
Prefrontal measures (all require working memory)
CANTAB Stockings of Cambridge
NEPSY Verbal Fluency
NEPSY Design Fluency
Stopping Task
CANTAB Spatial Working Memory
Counting Span Task

also good with mean stability quotients ranging from .90 to .95 for GCA, .86 to .88 for the Verbal Ability cluster, .82 to .83 for the Nonverbal Reasoning cluster, and .85 for the Spatial Ability cluster. In addition, the DAS has been shown to be a valid measure of general intelligence, with the GCA correlating highly with other measures of IQ ($M r = .76$) and with academic achievement ($M r = .60$). In particular, the GCA on the DAS is correlated highly ($r = .85$) with the Full Scale Intelligence Quotient score on the Wechsler Intelligence Scale for Children—Third Edition (WISC—III).

Benchmark Measures

Benchmark measures included measures of: (a) receptive and expressive syntax, and (b) verbal and nonverbal STM. The Test for Reception of Grammar (TROG) (Bishop, 1983) evaluated receptive syntax skills. Children were first given a brief vocabulary screen to establish comprehension of the words used in the test. The measure proceeded with 80 four-choice items, and for each item, the child was required to select a picture that corresponded to a phrase or sentence spoken by the evaluator. In each case, selection of the correct response required successful interpretation of the grammatical structure presented in the sentence. For example, the child was asked to point to the picture in which "the dog is chased by the boy." Distractor pictures included those in which the dog chases the boy, hence testing comprehension of grammar. The measure yielded a score reflecting the number of items answered correctly out of the 80 items presented. The TROG has an average internal consistency score of .77 across the ages of 4 to 9 years (Bishop, 1983).

The Word Structure subtest from the Clinical Evaluation of Language Fundamentals (CELF-3) was used to evaluate expressive syntax. In this test, the child completed a sentence based on the examiner's spoken model. The evaluator showed the child a picture and used a target construction in a spoken sentence. Another picture was used to elicit the same construction from the child in a new, but related, context. For example, one item showed two pictures of a girl getting a present and the present that she got. The experimenter said, "The girl is getting a present. This is the present that the girl _____." The child must have understood the pattern of syntax presented by the experimenter to complete the sentence with the correct construction. Constructs evaluated included possessive

nouns and pronouns, regular and irregular plurals, derivation of nouns and adjectives, regular and irregular past tense, demonstrative pronouns, comparative and superlative, future tense, subjective pronouns, and reflexive pronouns. Both the Preschool (Wiig, Secord & Semel, 1992) and the School-Age (Semel, Wiig & Secord, 1995) versions of the test were administered to avoid floor and ceiling effects. The total score across both versions was used in statistical analyses. The CELF-3 Word Structure subtest has an internal consistency score ranging from .80 to .82 between the ages of 6 to 8 years, and the test-retest reliability correlation for the subtest is $r = .76$. The CELF-3 is a discriminating measure of language disorder in children, matching school diagnoses of language disorder 71.3% of the time. The CELF-3 also correlates well with the WISC—III Verbal IQ, $r = .75$ (Semel et al., 1995).

To evaluate verbal STM, participants completed the Recall of Digits subtest from the DAS. Although the Recall of Digits subtest is included among the DAS subtests, it was not used in calculations of Verbal Ability, Nonverbal Reasoning Ability, or Spatial Ability index scores. On this measure, the child was presented with a list of orally presented single-digit numbers at a rate of two digits per s and asked to repeat those numbers back in the same order to the evaluator. The task was administered in blocks of five trials that advanced in difficulty from two numbers per sequence up to nine numbers per sequence. The child reached ceiling and the task ended after they incorrectly repeated at least four trials in a block.

Neuropsychological Measures

Hippocampal function. These included both measures of verbal and visual LTM, as well as a measure of ecological memory. As a measure of verbal LTM, participants completed a test of supraspan word learning, the NEPSY List Learning Test, which has excellent reliability, $r = .91$ (Korkman, Kirk, & Kemp, 1998). In terms of validity, imaging studies suggest the involvement of the posterior hippocampus in this type of supraspan learning task (Fernandez et al., 1998), and other researchers have demonstrated impairments in list-learning ability in patients with degeneration or damage to the hippocampus (Hermann et al., 1996; Koehler et al., 1998). In the NEPSY List Learning Test children were orally presented with a list of 15 words by the evaluator. After the presentation of the entire word list, the child was instructed to recall as many words as

possible. The target list was presented five times in succession, and each time the child was prompted to recall the list. After the fifth presentation of the target list, an interference list, containing 15 new words, was presented. The child was instructed to recall words from the interference list, after which he or she was prompted to recall the words from the target list. After a 30-min delay filled with other tasks, the evaluator returned to the list-learning task, again prompting the child to recall the words on the target list. Because the list-learning portion of the task gave us the largest sample of supraspan learning (vs. the single-trial immediate- or delayed-recall conditions) a score reflecting the total number of words recalled across the five learning trials was used in these analyses.

To test spatial LTM, we used a computer-generated virtual Morris water maze task (Thomas, Aut, Laurance, Nadel, & Jacobs, 2001) adapted from the water maze task used in animal models of memory and learning, in which animals used contextual cues in the environment to remember the location of a submerged platform. Maintaining this kind of spatial map requires intact LTM skills; animals with lesions to the hippocampus are generally not able to use spatial cues to create this kind of spatial map.

The human version of the water maze task we used involved a computer-generated, virtual arena analogous to the circular tank used in the animal model of the task. The circular arena was enclosed within a low-lying brick wall (all of the features described here were part of the virtual environment). Beyond this wall and visible to the participant were walls that had distinct objects (e.g., a door, a picture frame, a leaf, a globe) meant to represent objects in the environment that the child could use to orient himself or herself to find a target hidden on the floor of the arena, much like the mouse would use environmental cues to find the hidden platform.

The target object in the virtual arena was a blue square, presented to the child as a "blue rug." The child moved around the virtual arena using a joystick. Each participant was given an opportunity to practice on trials where the target was visible (i.e., the child could see the blue rug somewhere in the arena and was instructed to move to the rug and "stand" on it). All of the children appeared able to use the joystick, and they had little difficulty initiating goal-directed movements toward the target. After the fourth practice trial, the target rug became invisible to the child, and he or she was instructed to move around the arena until the target was found. When the child moved the joystick across the hidden target, the target immediately

became visible, the child was not able to move beyond the bounds of the target (i.e., the joystick no longer allowed the child to move off of the blue rug), and a sound was presented as a reward for finding the target. At this point in the task, the child was told that the target would continue to be invisible on future trials but that it would be located in the same place each time. The child was not given specific instructions to use the contextual cues provided in the arena to help find the target. After five test trials, the child was presented with a "probe trial." On this trial, the target was not, in fact, present, although the child did not know this. As a consequence, however, the child could not trigger the target and end the trial. Instead, he or she was forced to continue searching for the target throughout the duration of the session (90 s). During that time, the computer recorded where the child searched for the target. The variable of interest was the amount of time the child spent looking for the target in the correct quadrant of the arena (the northeast quadrant). If the participant successfully used the cues available in the virtual environment to develop a spatial map of the arena, he or she should spend the majority of the probe trial searching in the correct quadrant.

Two additional LTM measures were drawn from the Cambridge Neuropsychological Test Automated Battery (CANTAB), which used a touch screen to record participant responses. Two tests of nonverbal memory were selected for the present investigation: the Pattern Recognition Memory and Paired Associates tests.

The CANTAB Pattern Recognition Memory test presented the child with a series of two blocks of 12 abstract visual patterns, shown sequentially in the center of the computer screen. The patterns were designed so that they could not easily be given verbal labels, and each pattern was shown for 3 s. On each of the 12 recognition trials, two patterns were presented: one from the series that the participants had already seen and another novel pattern. Each participant was instructed to select the pattern that he or she had already seen. This same procedure was repeated with a second block of 12 new patterns. Luciana and Nelson (1998) used the Pattern Recognition Memory task in typically developing children as young as 4. The investigators reported that even 4-year-old participants were able to complete the task at a level significantly better than chance, and they demonstrated a trajectory of improving performance from 4 years of age to 7 years of age. In addition to being a suitable task for use in children, the Pattern Recognition Memory task has also been found to be reliable. Lowe & Rabbitt (1998) reported

a test-retest correlation of .84 for this measure. In another study, the test-retest reliability correlation was .72 for the number correct on the measure (CeNeS Ltd., 1999).

The Paired Associates test requires participants to learn associations between an abstract visual pattern and its location. Miller, Munoz, and Finmore (1993) found that humans with damage to the hippocampus showed significantly impaired performance on a paired-word associates task. In addition to these findings on similar versions of this task, the CANTAB Paired Associates test has been used as a reliable detector of AD, in which it has been found to detect the disorder with 98% accuracy 18 months before a formal diagnosis (Swainson et al., 2001). The authors claimed that the test was specific to the first affected areas in the disease, primarily the hippocampus and surrounding cortex.

On this task the participant was presented with a number of white squares, or "boxes," arranged in a circle around an empty central space. When the trial began, each of the boxes was "opened" in turn to reveal what was underneath. In some cases, the space underneath the box was empty. In others, a unique pattern was presented. Each of the boxes was opened in a randomized order until the child had looked under every one. Next, a single pattern was presented in the center of the screen and the child was instructed to touch the box where that pattern had been shown during the presentation phase of the trial. The task increased in difficulty from one to eight patterns. The number of patterns for which the child could remember the correct location on the first presentation of each trial (the first score) gave the index of memory that was used in the analyses. Lowe and Rabbitt (1998) reported a test-retest correlation of .68 for the first score and .86 on the trials to success on the measure. In addition, CeNeS Ltd. (1999) reported test-retest reliability quotients of .87 and .68, respectively, for the stages completed and total errors on the measure.

To create a hippocampal composite, the previously described main dependent measure from each of these four tasks was converted to a *z* score (using all participants) and an average *z* score was computed for each participant.

Finally, to evaluate memory for everyday events, the examiners asked each child to respond to a number of ecological memory questions on each of the 3 testing days. There were 18 items in all, including parents' names, meals in the last 24 hr, the time they got up that morning and went to bed the previous night, their birthday, the experimenter's name, and the activity they did in the last testing

session. We asked parents to answer independently the same questions, and we compared child and parent responses to determine accuracy.

Prefrontal function. There were six measures in this domain covering a range of executive functions: (a) planning (CANTAB Stockings of Cambridge), (b) verbal fluency, (c) nonverbal fluency, (d) inhibition (a "stopping" task), (e) spatial working memory, and (f) verbal working memory. All six measures tapped the core prefrontal function of holding information in active memory to guide action selection but did so in different ways. Unlike the hippocampal measures, none of the prefrontal measures required delayed recall of episodic information.

The Stockings of Cambridge task is analogous to the Tower of London (TOL) task. Cerebral blood flow patterns associated with performance on the TOL task show involvement of the dorsal prefrontal cortex in successful execution of the task (Rowe, Owen, Johnsrude, & Passingham, 2001). Planning impairments on the TOL task were also noted in human patients with frontal lobe dementia and in patients with lesions to the frontal lobes (Carlin et al., 2000).

In the Stockings of Cambridge task, the participant was shown two displays containing three colored balls. The displays were presented in such a way that they could be perceived as stacks of colored balls held in stockings or socks that are suspended from a beam. The two displays were presented one above another, with the display at the top of the screen provided as a model. The display at the bottom of the screen was the child's display, and each participant was instructed to move the balls in his or her display so that the arrangement of balls in the three "socks" matched the arrangement provided in the model at the top of the screen. Similar to the TOL task, the child must plan ahead to recreate the model display in a minimum number of moves. The balls may be moved one at a time by touching the required ball, then the position to which it should be moved. There were two-, three-, four-, and five-move problems. The number of moves taken by the participant was recorded as a measure of planning ability. A trial was terminated when the participant took more than twice the number of moves required to recreate the model, and the entire task was terminated when three consecutive trials were failed (i.e., terminated). Luciana and Nelson (1998) found that 4-year-old children used significantly more moves to solve problems than did older children. Older children demonstrated a linear increase in problem-solving ability illustrated by an increase in ability to solve

difficult problems and to solve them in the most efficient manner.

Fluency tasks have also been cited as benchmark measures of prefrontal function. Elfgren and Risberg (1998) reported regional cerebral blood flow augmentations in the frontal lobes in response to both verbal- and design-fluency tasks. In the current investigation, we used both the Verbal Fluency task and the Design Fluency task from the NEPSY Developmental Neuropsychological Assessment battery. The NEPSY Verbal Fluency task has a reliability of 0.74 from ages 5 to 12, and the Design Fluency task has a reliability of .59 in this same age range (Kemp, Kirk, & Korkman, 2001).

The NEPSY Verbal Fluency task required the participant to generate as many words as possible within each of two semantic categories (animals and foods/drinks) in 1 min. Because of the limited literacy skills of our typically developing children, the phonemic fluency condition (generate words that begin with *F* and *S*) was not used.

Each trial of the NEPSY Design Fluency task presented participants with an array of five dots and asked them to make a design, using straight lines, that connected two or more of the dots. Two versions of the task were presented, one in which the dot arrays were "ordered," resembling the configuration for the number 5 seen on dice, and another in which the dot arrays were presented in a less ordered configuration. The dependent measure was the total number of designs created across both versions of the test.

Extensive research also highlights the role of the prefrontal cortex in the ability to inhibit unwanted actions or cognitions. The Stopping task (Logan, Cowan, & Davis, 1984; Logan, Schachar, & Tannock, 1997) was included in the research battery as a prefrontal measure of inhibition. In this computerized task the child saw one of two letters flash on the screen, either an *X* or an *O*. Two keys were clearly designated on the keyboard, one marked with an *X* label and another with an *O* label. Participants learned to press the *X* key when they saw the letter *X* and the *O* key when they saw the letter *O*. Participants were instructed to press the keys corresponding to the letter stimuli, but they received an additional instruction to inhibit all responses if a short tone was presented in conjunction with the letter stimuli. Failure to inhibit the key-press response when the sound stimulus was presented generated an inhibition score that was used in the research analyses.

Analogous to a prefrontally sensitive self-ordered pointing task developed by Petrides and Milner

(1982), the CANTAB Spatial Working Memory test required participants to search under a series of colored boxes to locate a "blue token" hidden underneath one of the boxes. The first trial presented three boxes with three hidden tokens. When participants found the first token, they were instructed that the token would never be found in the same location more than one time, and they must search under the remaining boxes to find more tokens. To complete the task in the most efficient manner, then, participants had to ignore boxes where the tokens had been found previously. When a participant found all of the tokens within a trial, a new trial began. The colors and positions of the items changed with each new trial. The difficulty level increased across trials, with an initial presentation of three boxes and subsequent trials of four, six, or eight boxes under which the child had to search.

To complete the task successfully, the child had to keep track of the spatial locations where the token was previously found, update this information as new targets were found, and inhibit incorrect responses (i.e., looking under boxes where a target had already been found). These processes are thought to be central to working-memory abilities (Pennington, Bennetto, McAleer, & Roberts, 1995), and this task has been found to activate regions in the brain thought to contribute to spatial working memory, including the dorsal and ventral regions of the prefrontal cortex (Owen, Doyon, Petrides, & Evans, 1996; Robbins, 2000). Performance on this task was assessed by recording the number of times children returned to a box that had already been opened without finding a token (within errors), number of times children returned to a box in which they had found a token previously (between errors), and by a strategy score that measured how efficiently children used a strategy that was apparent to success on this task (i.e., starting in a similar place on each search). A recent study of test-retest reliability using the CANTAB battery found that the Spatial Working Memory task had a reliability of 0.68 for the total errors (Lowe & Rabbitt, 1998).

The Counting Span task (Case, Kurland, & Goldberg, 1982) is a verbal working memory measure similar to a sentence span task. The child was presented with a set of cards, each containing a randomly distributed array of blue and yellow dots. Beginning with the first card in the set, the child was instructed to count aloud the number of yellow dots on the card. When the child finished with one card, the next card in the set was presented and the child was again instructed to

count the number of yellow dots. After all of the cards in the set had been presented, the child was asked to recall, in temporal order, the number of yellow dots that appeared on each of the cards in the set. The task increased in difficulty as more cards were added to the sets (two to six cards per set). Performance on the task was assessed by recording the number of card sets completed successfully.

To compute a prefrontal composite, again the main dependent measure was converted to a z score and each participant's average z score across tasks was computed.

Results

The results will be presented in four sections, concerned respectively (a) descriptive measures, (b) benchmark measures, (c) neuropsychological measures, and (d) relations among measures. The main analyses in the first three sections compare the group with DS with MA controls. Because increasing deficits with age have been documented for IQ and language measures in groups with DS, we also tested whether this was the case in the present sample, using the age subgroups described earlier. Finally, we tested relations among measures in the group with DS using regression analyses. Specifically, we tested how the composite measure of each neuropsychological domain, hippocampal and prefrontal, relates to three developmental outcomes: MA, adaptive behavior, and language (i.e., syntax).

Descriptive Measures

Table 1 shows that the two groups were similar on the MA matching variable (nonstandardized composite score on the DAS). Hence, the group with DS ($M = 14.68$ years, $SD = 2.72$) was inevitably older than the MA control group ($M = 4.92$ years, $SD = .75$; $t(56) = 18.43$, $p < .001$). The groups were also similar in gender distribution, $\chi^2(2, N = 56) = .65$, ns ; parental education, $t(45) = -0.086$, ns ; and ethnicity, $\chi^2(2, N = 56) = .00$, ns .

Despite being matched on MA, the group with DS ($M = 472.91$, $SD = 77.58$) had a significantly higher total raw score on the SIB-R than the MA control group ($M = 374.96$, $SD = 76.93$; $t(36) = 3.91$, $p < .001$). Because the group with DS was almost 10 years older than the MA control group, they had much longer to learn adaptive behaviors. There was also a significant group by domain interaction across the subscale raw scores

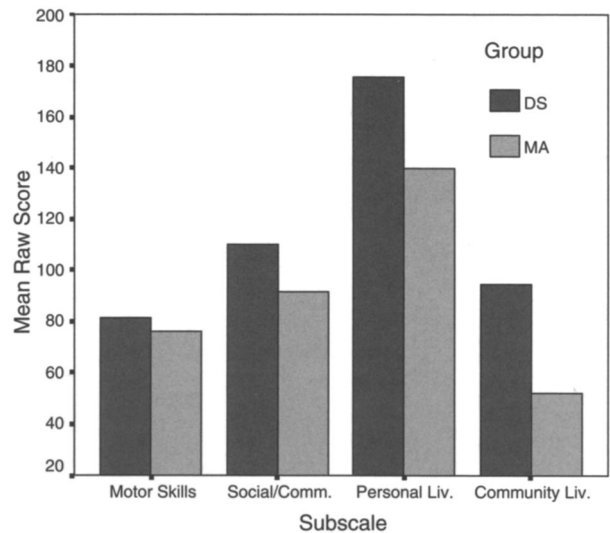


Figure 1. Group by subscale differences on the SIB-R.

of the SIB-R, $F(2,36) = 12.64$, $p < .001$. As can be seen in Figure 1, the groups did not differ significantly on the raw Motor Skills score, $t(36) = 1.65$, $p > .10$, but they did show significant differences on the subscales measuring Social/Communication Skills, $t(36) = 3.67$, $p < .01$; Personal Living Skills, $t(36) = 3.51$, $p < .01$; and Community Living Skills, $t(36) = 4.22$, $p < .001$, with the DS group earning higher scores than the MA controls in each case.

Nonetheless, as expected, the mean age quotient score on the SIB-R was significantly lower for the DS group, $M = 58.84$, $SD = 19.27$, $range = 8-87$, than for the MA control group, $M = 115.79$, $SD = 12.47$, $range = 93-146$; $t(36) = -10.81$, $p < .001$. In fact, the two distributions of these age quotient scores were nonoverlapping. The mean score for the DS group fell well below the cutoff of 70 required for a diagnosis of MR, and 79% of the participants with DS fell below this cutoff.

We next turn to age group differences within the DS group on these descriptive measures. The DAS IQ score did not differ by age group, old: $M = 47.5$, $SD = 3.4$; young: $M = 48.5$, $SD = 3.9$; $t(25) = -.68$, ns . On the SIB-R, the mean age quotient score of the older group, $M = 48.3$, $SD = 17.9$, was not significantly lower than that of the younger group, $M = 55.9$, $SD = 21.3$; $t(26) = -.99$, ns .

Benchmark Measures

Table 3 shows how the groups compared on the benchmark verbal and spatial measures. They performed similarly on receptive vocabulary

(PPVT-III) and spatial STM (CANTAB Spatial Span) measures. Consistent with previous results, the group with DS performed significantly worse than the MA control group on measures of both receptive syntax, TROG: $t(54) = -4.44$, $p < .001$, $d = 1.20$; and expressive syntax, CELF: $t(52) = -3.93$, $p < .001$, $d = 1.10$; and verbal STM, DAS Digits: $t(52) = -3.74$, $p < .001$, $d = 1.02$. The effect size (d) of these differences were all greater than 1.0, indicating a robust effect. Hence, this sample with DS was generally similar to previous samples on these benchmark measures.

We next consider age group differences for these benchmark measures. For the PPVT-III, older children with DS ($M = 53.2$, $SD = 16.4$) had similar IQ scores to younger children with DS ($M = 57.0$, $SD = 13.2$, $t(23) < 1.0$, *ns*). We also had longitudinal data on the PPVT-III for a subset ($n = 16$) of the DS sample, with an average test-retest interval of 1.5 years. The IQ scores on both occasions were similar, Time 1: $M = 55.8$, $SD = 15.1$; Time 2: $M = 57.0$, $SD = 16.4$; $t(15) < 1.0$. So, there was no evidence for an age decline on the PPVT-III, whether evaluated cross-sectionally or longitudinally.

Because the age norms for the remaining benchmark measures did not cover all of the participants, we examined age differences by means of 2 (age group) \times 2 (diagnosis group) ANOVAs of raw scores. In these models, evidence for an age group difference is provided by an Age \times Diagnosis interaction effect. There were robust age main effects for all measures except spatial span (see Table 4), indicating that the older group performed significantly better than the younger group. Specifically, the age main effects were as follows: Digits: $F(1, 50) = 4.77$, $p < .05$; TROG: $F(1, 52) = 5.92$, $p < .05$; CELF: $F(1, 50) = 4.59$, $p < .05$; and Spatial Span: $F(1, 50) = .31$, *ns*. However, there were no age by diagnosis interactions, all $F_s < .1$, except for Digits where $F(1, 50) = 1.17$, *ns*. In sum, consistent with earlier studies, there were robust deficits in the DS

group on these language measures, but no evidence that these deficits increased across this age range.

Neuropsychological Measures

In this section we begin with an overall test of whether the group with DS exhibited a differential deficit in the hippocampal or prefrontal domains, then examine age group differences on these domains, and finally analyze each neuropsychological measure individually.

To test the main hypotheses of hippocampal, prefrontal, or generalized dysfunction, a Group \times Composite mixed-model ANOVA was performed on the previously described hippocampal and prefrontal composites. As seen in Figure 2, this analysis found a highly significant Group \times Composite interaction effect, $F(2,52) = 39.22$, $p < .001$. The group with DS was significantly worse than the MA control group on the hippocampal composite, DS: $M = -.31$, $SD = .68$; MA: $M = .27$, $SD = .54$; $t(54) = -3.52$, $p < .01$, whereas they were nonsignificantly better on the prefrontal composite, DS: $M = .094$, $SD = .59$; MA: $M = -0.14$, $SD = .40$; $t(52) = 1.73$, $p > .09$. This interaction effect supports the hippocampal hypothesis.

We also examined age effects on each composite with 2 (age group) \times 2 (participant group) ANOVAs. Similar to the benchmark measures, there were robust main effects of age, with older participants performing better than younger participants, hippocampal composite: $F(1, 52) = 11.42$, $p < .01$; prefrontal composite: $F(1, 50) = 16.12$, $p < .001$. But there were no Age \times Group interactions ($F_s < .1$), providing no evidence of age declines in these DS participants.

Hippocampal Measures

Children in the DS group tended to learn fewer words on the Nepsy List Learning task than did the MA control group across the five learning trials,

Table 3
Down Syndrome and Mental Age (MA) Control Group Differences on Benchmark Measures

Measure	No. Pairs	Down syndrome		MA controls	
		M	SD	M	SD
PPVT-III (no. correct)	28	83.04	27.98	81.43	12.98
Spatial Span (length of span)	26	2.88	1.51	2.69	1.16
TROG (no. correct)	28	42.50	15.61	58.54	11.02
CELF (% correct)	27	.39	.26	.61	.14
Recall of Digits (no. correct)	27	10.78	4.47	15.37	4.57

Table 4
Age Group Differences in Performance on Neuropsychological Measures Within the Group (DS)

Measure	Older DS children (<i>n</i> = 14)		Younger DS children (<i>n</i> = 14)	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Benchmark Measures				
TROG (Total correct)	46.75	16.82	34.94	13.54
CELF (proportion correct)	.43	.29	.31	.18
Spatial Span (# items remembered)	2.88	1.63	2.47	1.66
Recall of Digits (# items correct)	12.06	5.17	8.12	3.53
Hippocampal Measures				
Nepsy List Learning (total recall across 5 trails)	28.19	10.33	17.12	9.96
Morris water maze (% time in NE quadrant)	.17	.10	.16	.11
Pattern Recognition (No. patterns recognized)	7.20	2.40	7.30	1.70
Paired Associates Learning (No. patterns placed correctly)	4.00	1.67	2.75	2.02
Prefrontal Measures				
Stockings of Cambridge (No. solved in min. moves)	5.60	2.32	3.47	2.13
Verbal Fluency (No. words generated)	22.69	9.42	16.18	7.41
Design Fluency (No. designs generated)	14.19	4.13	10.06	5.72
Stopping Task (% correct inhibitions)	0.64	0.18	0.69	0.18
Counting Span (No. items correct)	2.69	2.18	1.06	1.06
Spatial Working Memory (Between errors)	72.81	16.30	71.76	12.50

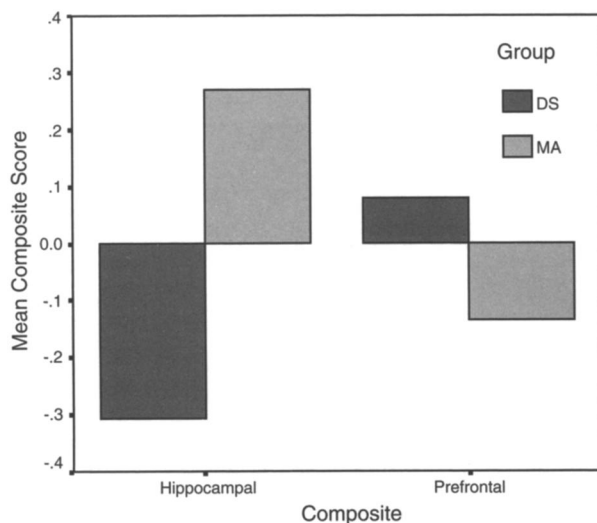


Figure 2. Group differences on neuropsychological composites.

$t(54) = -1.92, p < .07$. On the Morris water maze task, the DS group spent significantly less time, $t(34) = -2.50, p < .05$, searching for the target object in the correct quadrant than did the MA controls. As a group, the DS participants also had greater difficulty recognizing a previously presented pattern on the CANTAB Pattern Recognition test than did the MA control group, $t(52) = -2.05, p < .05$. Finally, the DS group performed more poorly than the MA control group on the CANTAB Paired Associates Learning task, $t(31) = -2.41, p < .05$. In sum, the DS group demonstrated poorer performance across all four of the hippocampal measures evaluated (see Table 5).

However, children with DS ($M = 11.65, SD = 4.73$) did not differ from the MA controls ($M = 10.79, SD = 2.5$) on the Ecological Memory Index, $t(27) = .58, ns$. To understand this null result, we

Table 5
Down Syndrome and Mental Age (MA) Control Group Differences on Neuropsychological Measures

Measure	No. Pairs	Down syndrome		MA controls	
		<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Hippocampal measures					
Nepsy List Learning (total recall across 5 trials)	28	21.39	11.04	26.71	9.64
Morris water maze (% time in NE quadrant)	18	.17	.09	.30	.21
Pattern Recognition (no. Patterns recognized)	27	7.26	2.01	8.52	2.47
Paired Associates Learning (no. patterns placed correctly)	26	3.38	2.02	4.54	1.36
Prefrontal Measures					
Stockings of Cambridge (no. solved in min. moves)	21	4.95	1.72	5.19	1.44
Verbal Fluency (no. words generated)	27	20.19	8.94	16.78	6.47
Design Fluency (no. designs generated)	27	12.70	5.01	10.33	5.53
Stopping Task (% correct inhibitions)	13	.66	.19	.56	.13
Counting Span	28	1.93	1.84	1.68	1.36
Spatial Working Memory	28	71.39	14.98	68.36	15.17

examined performance on two individual items—examiner’s name and the activity participants did in the last testing session—that were learned (or not learned) during the experiment. Many of the other items (parents’ names, birthday, bedtime, wake-up time, and usual breakfast) would have been known before the experiment and might tap semantic rather than episodic memory. For memory of what they did in a previous testing session, the control group’s mean of 95.0% ($SD = 15.8\%$) was significantly greater than the DS group’s mean of 68.8% ($SD = 41.2\%$), $t(41) = 2.60$, $p < .001$. It is interesting that there was a trend for an opposite result for memory of the examiner’s name. The group with DS had a mean of 81.3% ($SD = 32.3\%$) compared with a mean of 60.5% ($SD = 42.7\%$) in the control group, $t(41) = 1.81$, $p = .08$. In sum, although the Ecological Memory Index overall did not find group differences, analysis of these two individual items did. Of these two items, only remembering what occurred in a previous testing session clearly requires episodic memory, because the examiner’s name is a single piece of information, not an episode. Hence, the results on the Ecological Memory Index suggest that although children with DS gradually acquire semantic information from their everyday

lives, they have more trouble remembering unique episodes.

We next turn to an examination of age group differences on individual hippocampal measures, which were examined with 2×2 ANOVAs, just as were the other measures discussed earlier (Table 4). It is not surprising that these results generally mirrored the results for the hippocampal composite. There were main effects of age on most individual hippocampal measures, Morris: $F(1, 40) = .02$, *ns*; NEPSY List: $F(1, 52) = 5.04$, $p < .05$; Pattern Recognition: $F(1, 50) = 2.17$, $p = .15$; Paired Associates: $F(1, 48) = 14.61$, $p < .001$, but no Group \times Age interactions ($F_s < 1.0$). The one exception was Pattern Recognition, $F(1, 50) = 2.45$, $p = .12$, where there was a trend toward such an interaction. Examination of the cell means reveals that older participants with DS ($M = 7.2$, $SD = 2.4$) did not perform better than younger participants ($M = 7.3$, $SD = 1.7$), whereas older MA controls ($M = 9.5$, $SD = 2.1$) did outperform younger controls ($M = 7.6$, $SD = 2.5$).

In sum, although there was a robust hippocampal deficit in the overall group with DS, we only have evidence for an increasing hippocampal deficit on one of the four hippocampal measures (Pattern Recognition).

Table 6
Regression Analyses

Model	Variable	R ²	F change
MA = Age+EF+Memory	Age	.34	14.68**
	EF	.33	27.25***
	Memory	.12	14.92**
MA = Age+Memory+EF	Age	.34	14.68**
	Memory	.37	34.32***
	EF	.08	70.16**
SIB-R = Age+EF+Memory	Age	.36	15.32**
	EF	.08	3.77 ⁺
	Memory	.05	2.38
SIB-R = Age+Memory+EF	Age	.36	15.32**
	Memory	.12	5.48*
	EF	.02	0.89
Syntax = Age+EF+Memory	Age	.17	5.90*
	EF	.40	25.38***
	Memory	.04	3.03 ⁺
Syntax = Age+Memory+EF	Age	.17	5.90*
	Memory	.27	13.50**
	EF	.17	11.63**

Note. MA = mental age, EF = executive functions (prefrontal) composite, SIB-R = adaptive behavior measure.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

⁺ $p < .10$.

Prefrontal Measures

In contrast to the hippocampal measures, there were no significant group differences on individual measures of prefrontal function (see Table 5). Performance by the two groups was comparable on the CANTAB Stockings of Cambridge task, $t(40) = -.49$, $p > .10$; the NEPSY Verbal Fluency task, $t(52) = 1.60$, $p > .10$; the NEPSY Design Fluency task, $t(52) = 1.65$, $p > .10$; the Stopping task, $t(24) = 1.54$, $p > .10$; the Spatial Working Memory task, $t(54) = .75$, $p > .10$; and the Counting Span task, $t(54) = .57$, $p > .10$. On five of six measures, participants in the DS group tended to perform better than the MA control participants, although the group differences were not significant.

We next turn to an examination of age group differences on individual prefrontal measures (Table 4). These were likewise analyzed with 2×2 ANOVAs, and the results generally mirrored the results for the prefrontal composite. There were main effects of age on most individual prefrontal measures: Stockings, $F(1, 38) = 6.90$, $p < .05$; Verbal Fluency, $F(1, 50) = 2.02$, $p = .16$; Design Fluency, $F(1, 50) = 6.23$, $p < .05$; Stopping, $F(1, 22) = .03$, ns ; Spatial Working Memory, $F(1, 52) = .03$, ns ; and Counting Span, $F(1, 52) = 7.25$, $p < .05$, with older participants

outperforming younger participants. But there were no significant Age \times Group interactions, all $F_s < 1.0$, except for Stockings, $F(1, 38) = 1.96$, ns .

In sum, there is neither evidence for an overall prefrontal deficit (relative to MA controls) in this group with DS, nor evidence for a decline with age in prefrontal functions.

Relations Among Measures

Table 6 presents the results of regression analyses that examined how well the hippocampal and prefrontal composites predicted individual differences within the group with DS on three measures of developmental outcome: mental age on the DAS, adaptive behavior, and language (i.e., syntax, because the other two language measures, verbal STM and PPVT-III, overlapped with verbal IQ). If hippocampal dysfunction is the main cause of retarded development in individuals with DS, the hippocampal composite should be a much stronger predictor of individual differences on these measures than the prefrontal composite. Thus, we conducted three hierarchical regression analyses, one for each domain of development (MA, adaptive behavior, and language). In each analysis, we first entered CA and then forced the entry of either the hippocampal or prefrontal composite to evaluate which accounted for the most unique variance in the domain of development being examined. Before discussing the results, it is important to note that the hippocampal and prefrontal composites were moderately correlated within the group with DS ($r = .54$, $p < .01$), even with CA partialled out. Hence, measures of these two neuropsychological domains are not totally independent. Although each domain differs in its core neuropsychological function (LTM vs. working memory), they must share some other unknown cognitive components. This cognitive overlap makes these regression analyses a conservative test of the contribution of each neuropsychological domain to the three outcomes.

As can be seen in Table 6, different composites have different predictors. Age, entered first, predicted more variance in adaptive behavior than the two neuropsychological composites combined, whose individual contribution was often not statistically significant. This result is consistent with the group difference on this variable, on which the older DS group performed better than the younger MA controls. In contrast, about 45% of the variance in the other two outcomes, MA and syntax, was predicted by the combination of the two neuropsychological variables, after the prediction of age was accounted

for. It is interesting that the contribution of age to individual differences in syntax in the group with DS was only 17%, about half of its contribution to the other two outcome variables. For MA, the hippocampal composite (R^2 change = .12) accounted for more unique variance than the prefrontal composite (R^2 change = .08). In contrast, for syntax, the prefrontal composite (R^2 change = .17) accounted for almost 4 times as much unique variance as the hippocampal composite (R^2 change = .04), a result that might be explained by the role of working memory in syntactic processing. Hence, both neuropsychological domains contributed to developmental outcome, but in different ways. The hippocampal composite was particularly related to MA, whereas the prefrontal composite was more strongly related to syntax.

Discussion

The main goal of this study was to test whether neuropsychological development in DS is characterized by hippocampal dysfunction, prefrontal dysfunction, or both (generalized dysfunction). The main finding was specific hippocampal dysfunction, as supported by a significant Group \times Domain interaction effect. The group with DS performed worse than MA controls on each hippocampal measure but not on any of the prefrontal measures. This converging pattern of results across measures in each domain provides fairly strong evidence for a dissociation in DS between two neuropsychological functions, hippocampally mediated LTM and prefrontally mediated working memory.

However, hippocampal dysfunction was not totally specific. This group with DS was below CA levels on a wide range of other measures (MA, adaptive behavior, language, spatial cognition, and prefrontal functions). In addition, there was a moderate partial correlation ($r = .54$, controlling for CA) between the hippocampal and prefrontal composites in the group with DS, and both composites contributed unique variance to the prediction of two measures of developmental outcome: MA and syntax. So, hippocampal dysfunction is not the only source of abnormal development in DS. In addition, we need to analyze whether the LTM deficit in DS is in encoding, storage, or retrieval.

We found very little evidence for cognitive decline across the age range considered here. Both older and younger participants with DS performed similarly, relative to MA controls. The one exception was a trend toward an increasing deficit with age on one hippocampal measure (Pattern Recognition). So, we

have little evidence that hippocampal dysfunction increases across this mainly adolescent age range. Hence, more research is needed with both younger and older samples than the present research to pinpoint when hippocampal dysfunction begins in DS and when it accelerates (presumably in adulthood). We also need research directly comparing the developmental timing of declines in various domains: MA, language, and hippocampal functions.

Although acquired etiologies, such as anoxia, can produce hippocampal damage and resulting amnesia in childhood (Vargha-Khadem et al., 1997), just as such etiologies do in adults, an amnesic profile is rare among developmental disabilities (Pennington, 1991). The only other known neurodevelopmental disorder with hippocampal dysfunction is schizophrenia (Cornblatt, Green, & Walker, 1999). Among MR syndromes that have been studied, DS is the only one that exhibits hippocampal dysfunction. However, our mostly null results on the ecological memory measure indicate that the amnesia in DS is less severe than that produced by acquired etiologies in children (e.g., the patients in Vargha-Khadem et al., 1997, were impaired on ecological memory), although many of our ecological memory items (e.g., mother's name) depended on overlearned semantic memories rather than episodic memory. Perhaps more problems in children with DS would be detected on a better ecological memory measure. In FXS, LTM functions are a relative strength (Bennetto, Pennington, Porter, Taylor, & Hagerman, 2001). Although a hippocampal hypothesis of autism has been proposed (Bachevalier, 1991; DeLong, 1992), LTM measures in non-MR samples with autism are essentially normal (Bennetto, Pennington, & Rogers, 1996; Minshew, & Goldstein, 1993). Why hippocampal dysfunction is relatively rare among developmental disabilities is an important question.

The present results converge with recent results from a mouse model of DS, which exhibited declines with age on measures of LTM (Hyde & Crnic, 2001). But we do not know how early in development this or other changes in the hippocampus occur in humans with DS. This and another study (Carlesimo et al., 1997) provided behavioral evidence of hippocampal dysfunction by adolescence, consistent with the structural MRI finding of reduced hippocampal volumes in a small sample of adolescents with DS (Jernigan et al., 1993).

Potential limitations of this study include a relatively restricted age range; the possibility that specific prefrontal deficits in the DS group could be found on other, more developmentally appropriate measures; problems inherent to a design comparing

an older group with MR with a younger MA control group; and the cognitive complexity (and overlap) of the prefrontal and hippocampal measures used here.

The last two limitations merit further discussion. A CA control group was not used because it is a foregone conclusion that a group with a mean IQ around 50 will perform significantly worse than CA controls on all measures correlated with IQ. It is noteworthy that greater age allows people with DS to outperform MA controls on adaptive behavior (Figure 1), so some aspects of development are dissociable from mental age. The specificity of the neuropsychological profile found here can be tested further by comparing groups with different MR syndromes (e.g., DS and WS), matched on age and IQ, on prefrontal and hippocampal measures. We are currently conducting such a study. However, even without such data, previous studies reviewed earlier of hippocampal and prefrontal functions in other MR syndromes indicated there is some specificity to the profile found here for the DS group.

Standard neuropsychological measures of prefrontal and hippocampal functions, such as those used here, are cognitively complex and have overlapping cognitive components, as demonstrated by the moderate partial correlation of 0.54 between the prefrontal and hippocampal composites. Moreover, the prefrontal cortex and hippocampus are known to interact in cognitive processing (e.g., Mitchell, Johnson, Raye & D'Esposito, 2000), so their functions are not independent. Nonetheless, the measures of each domain used in this study were selected to tap the core neuropsychological function of their domain and most were validated by previous functional neuroimaging or lesion studies. Our finding of a consistent dissociation between domains, despite the different surface characteristics of measures within a domain, is hard to explain unless there is a cognitive difference between the measures used for each domain.

The hypothesis of specific hippocampal dysfunction in DS can be further tested by: (a) cognitive experiments that manipulate a single cognitive component uniquely associated with each brain region, (b) functional neuroimaging studies of each brain region in individuals with DS, or (c) a study that combines these two approaches. Neural network models of the prefrontal cortex and hippocampus have identified cognitive operations, activation-based working memory, and context binding, respectively, that are unique to each structure (O'Reilly & Munakata, 2000), thus allowing such experiments. Clearly, more work is needed to

rigorously test the hippocampal hypothesis of DS that is supported by the current results.

In addition, future studies of DS are needed to determine (a) how early in development specific hippocampal dysfunction appears in humans with DS and (b) which other brain structures (e.g., cerebellum) contribute to the neuropsychology of DS.

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