Down syndrome: A Genetic Disorder in Biobehavioral Perspective

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INTRODUCTION

How do genes translate into brains and thence to minds and behavior? Any answer to this question starts with development, and with two kinds of queries: (1) how do genes, in interactions with the environment, direct and constrain neural maturation; and (2) how do neural structures and systems give rise to mind and behavior? The study of neural, cognitive and behavioral development, an essential part of the answer to these questions has been greatly enriched by the careful examination of select cases of abnormal development. Following a tradition established in the l9th century in the study of language and other cognitive functions, insights into maturation can be gained through the study of infants and children whose development is distorted by a variety of genetic, epigenetic, or experience-driven abnormalities. In recent years this approach has benefitted from knowledge provided by new methods in both molecular and systems neuroscience. As a consequence, a field of study most properly termed "developmental cognitive neuroscience" is now emerging, bringing together the expertise of developmental psychologists, neuropsychologists, and developmental neuroscientists (cf. Tager-Flusberg, 1999b). This field offers the promise of shedding light on normal and abnormal development of both mind and brain. Thoughtful analysis of the consequences of abnormal development, and its neural underpinnings, should lead to new insights about normal mind-brain relations. These insights, in turn, provide the basis for thinking seriously about how genes translate into brains, minds and behaviors.

When one's interest includes an understanding of the role of genes in initiating the process of brain and cognitive development, Down syndrome has several unique features that make it an excellent model case. It is one of the most prevalent neurodevelopmental disorders, occurring in about 1 of 800 live births throughout the world. Individuals with Down syndrome probably comprise the majority of infants and children with mental retardation. Nearly all infants with Down syndrome have a known etiology and date of onset: a third chromosome

21 that is present at the outset. The exceptions, involving mosaicism, or translocation, account for about 5% of the total cases, and can be readily identified cytogenetically.

Notwithstanding the common starting point for those with full-blown trisomy-21, the range of outcomes is quite large. Thus, Down syndrome offers an interesting case study in the variability with which genotypes are translated into phenotypes. In contrast to what used to be assumed, the mental retardation observed in Down syndrome is not an across-the-board phenomenon; it manifests itself more severely in some areas of mental function than in others. As a consequence, Down syndrome offers an opportunity to link together a specific genetic abnormality to alterations in neural maturation and particular problems in cognitive development. In order to do this, we need data on neural and cognitive development in individuals with Down syndrome, and a clear understanding of the ways in which these differ from the normal case. To make the connection to genes, we would then need to explain how an extra chromosome 21 leads to the range of abnormal phenotypes observed in Down syndrome. I will have something to say about a possible strategy to make this connection at the end, but the bridge between genes and cognition is not the direct focus of this paper.

In what follows I review existing data about what is wrong, and what is right, in development in Down syndrome, and parallels between specific cognitive and neural defects will be drawn where possible (see Flórez, 1992, for an earlier review). Much of the work on individuals with Down syndrome has focused on their abilities in the domain of language, and there are a number of excellent recent reviews of this work (eg., Tager-Flusberg, 1999a). This review will focus instead on aspects of learning and memory in individuals with Down syndrome, in a framework provided by an analysis of the neural systems known to underlie various forms of learning and memory. I will suggest that difficulties in both the acquisition of information (learning), and the long-term storage and retrieval of information (memory) are a part of the phenotype of Down syndrome. It is

now clear that there are multiple forms of learning/memory, dependent upon dissociable neural systems (see Nadel, 1992, 1994 for recent reviews), and in many clinical syndromes, such as Down syndrome, Alzheimer's disease, Parkinsonism, and Huntington's chorea, impairments of learning and memory typically affect some, but rarely if ever all, of these forms of learning and memory. This paper begins with a review of what is known about the neural impairments associated with Down syndrome, and how these might impact various types of learning and memory. Following this, current knowledge about learning and memory in individuals with Down syndrome will be reviewed. The final section will include some thoughts about how we might be able to use Down syndrome to make the link between genes, brains and behavior.

I. Neural Sequellae of Down syndrome

What do we currently know of the precise neural sequellae of Down syndrome? Data to be reviewed below show that at birth it is often difficult to differentiate the brains of normal and Down syndrome individuals. Yet, both post-mortem studies and various, more recent, non-invasive neuroimaging studies, have demonstrated rather clear differences between these two groups as early as 6 months of age. Where do these differences come from, and what do they amount to?

An immediately obvious difference is that the brains of individuals with Down syndrome are typically smaller than those of age-matched controls, at least after 6 months of age. One possibility that has been given insufficient attention in the past is that this difference is a consequence of the fact that Down syndrome individuals have smaller bodies. That is, the differences in brain size could be a matter of allometry. This possibility, added to the fact that there is no clear relation between brain size and "intelligence" in any event, suggests that the

mental retardation observed in Down syndrome results from something other than gross differences in brain size.

Although the brains of Down syndrome individuals are indeed smaller overall, some brain areas are disproportionately affected. This differential impact is not predicted by allometry, and presumably offers important clues about how trisomy 21 brings about the mental retardation so characteristic of Down syndrome. Before evaluating these clues another caveat is important: the probability that brain development is influenced by experience. If this is true, and there are increasing reasons from basic neurobiological studies to believe that it is, then the study of the brains of individuals with Down syndrome who have recently come to post-mortem evaluation might be quite misleading. Most of these individuals did not benefit from the kinds of early stimulation regimes that are now available and indeed prevalent, and that might have a direct impact on brain development. This is at present a highly speculative but very important area; such brain plasticity is one of the best hopes for bringing about significant improvements in the prospects of individuals with Down syndrome. At this time we do not know, from a theoretical or empirical perspective, the extent to which experience can cause changes in normal brain development. We do not know whether normal possibilities for brain plasticity exist in individuals with Down syndrome. We do not know the extent to which changes in brain development promoted by specific stimulation regimes can translate into meaningful behavioral and cognitive improvements, although there is some indication that environmental enrichment can improve learning in a mouse model of Down syndrome (Martinez-Cué et al., 2002). We do not know which kinds of changes would be beneficial and which not. Obviously, there is a great deal we do not know in this area, and very little that we can be certain of, except that further research on these issues is of the utmost importance. While one does not wish to raise false hopes, it is important to stress that we now know the brain to be much more malleable than was previously thought.

With these caveats registered, what can we say about nervous system development and function in Down syndrome? Data bearing on this question come from a number of sources; for present purposes we emphasize what is known about neural development, but some discussion of neural function in adolescents and adults helps to illuminate and flesh out the developmental story. It is important to begin with a discussion of what the nervous system is like at or before birth, to get a sense of the starting point. We then discuss what the nervous system is like as the individual with Down syndrome develops through childhood, adolescent and into adult life. It has been clear for some time that as individuals with Down syndrome reach "old age", signs of neuropathology emerge much earlier than in the normal population. This fact may help us understand some of the developmental abnormalities observed in Down syndrome.

Information about neural function and development comes from three primary sources: neuroanatomical studies of brains from individuals with Down syndrome who died at various ages, neurophysiological studies of the dynamic properties of the brains of individuals with Down syndrome at various ages, and neuroimaging studies of the metabolic activity of the brains of individuals with Down syndrome, typically in adulthood.

A. Early Development

A number of early studies point to the already-noted conclusion that the brain of an individual with Down syndrome at or shortly before birth is in many respects indistinguishable from the brain of a normal individual (Brooksbank etal., 1989; Wisniewski & Schmidt-Sidor, 1989; Schmidt-Sidor etal. 1990; Florez etal. 1990; Bar-Peled etal. 1991; Pazos etal. 1994). Normal values were reported for brain and skull shape, brain weight, proportion of specific cerebral lobes, size of cerebellum and brain stem, and the emergence of most neurotransmitter systems. The idea that relative normalcy exists at birth is potentially of the greatest significance, since it seems to create the opportunity to do something

about the not-yet-created differences that quite clearly do emerge during the period right after birth.

There is evidence, however, that some changes begin to emerge as early as 22 weeks gestational age (eg., Schmidt-Sidor etal. 1990; Wisniewski & Kida, 1994; Golden & Hyman, 1994; Engidawork & Lubec, 2003), and it is clear that by the age of 6 months a number of important differences are already obvious. Some of these differences are expressed in terms of the proportion of individuals with Down syndrome who show abnormal values, rather than in terms of a uniform abnormality in all instances. This is of importance, as it highlights the variability in this population sharing the genotypic feature of trisomy 21[1]. One quite noticeable difference concerns a postnatal delay in myelination (Wisniewski, 1990), global at first but then manifested primarily in nerve tracts that are myelinated especially late in development, such as the fibers linking the frontal and temporal lobes. This delay is observed in about 25% of infants with Down syndrome who come to post-morten analysis between the ages of 2 months and 6 years. Delayed myelination has also been observed in a study employing magnetic resonance imaging on a single infant (18 months of age) with Down syndrome (Koo et al., 1992). While not underestimating the impact of this myelination delay, it is certainly worth noting that in all cases myelination is within normal range at birth, while in 75% of the cases it is within normal range throughout early development. Becker etal. (1986) showed that dendritic arborizations in visual cortex of individuals with Down syndrome were paradoxically greater-than-normal early in infancy, but then considerably less-than-normal by the age of 2 years. They speculate that the initial overabundance might result from a compensatory response to the absence of adequate synapse formation, but the basic point remains that by early childhood there is an impoverishment in neocortex.

[1] It seems entirely probable that for most characteristics, including mental functions, there is a "normal" distribution of values - a typical bell curve - in both normally developing infants and infants with Down syndrome.

Neuropathological differences after 3-5 months of age include a shortening of the fronto-occipital length of the brain that appears to result from a reduction in growth of the frontal lobes, a narrowing of the superior temporal gyrus (observed in about 35% of cases), a diminished size of the brain stem and cerebellum (observed in most cases) and a significant reduction (20-50%) in the number of cortical granular neurons (see Benda, 1971; Crome, Cowie & Slater, 1966; Blackwood & Corsellis, 1976). Notwithstanding these differences, however, the overall picture at birth or shortly thereafter is one of only modest abnormalities, although individuals with Down syndrome tend to fall towards the bottom of the normal range (or outside it) on most measures.

Investigations of neural function, as opposed to structure, in early infancy suggest some abnormalities: there is evidence of either delayed or aberrant auditory system development (Jiang etal. 1990) that might contribute to the widespread hearing disorders observed in Down syndrome. Obviously, such a disorder, if organic, could be related to many of the subsequent difficulties seen in the learning of language. Hill Karrer et al. (1998) have reported delayed development of cerebral inhibition using visual event related potentials (ERP) in a visual recognition memory paradigm. There is also evidence of a more widespread abnormality in EEG coherence (McAlaster, 1992) that seems to reflect the generally impoverished dendritic environment (cf. Marin-Padilla, 1976). This difference, like many of the others, emerges only sometime after birth. It appears that this effect is predominant in posterior, rather than anterior, brain regions, and in the left, more than the right, hemisphere.

B. Later Development and Adulthood

The evidence of neuropathological sequellae in Down syndrome is more extensive for the middle stage of life. Data from both post-mortem studies and from studies of brain function in select populations, indicate that the changes

beginning to emerge early in life become more prominent and prevalent by early adolescence.

There have been relatively few studies of brain function in adolescents and young adults with Down syndrome, and the existing data are somewhat equivocal. Devinsky etal. (1990) reported relatively normal EEG alpha activity in young adults (< 40 years of age), while Schapiro etal. (1992) reported relatively normal brain metabolism in a similar group, using positron emission tomography (PET) measures of glucose uptake and regional blood flow. They did report some disruption of normal neuronal interactions between the frontal and parietal lobes, possibly including the language area of Broca. Overall, they concluded that in younger subjects with Down syndrome cerebral atrophy does not generally extend beyond what would be predicted by the smaller cranial vault and stature of these subjects. On the other hand, in those cases where dementia can be observed in younger subjects, there are clear signs of abnormal cerebral atrophy and metabolic deficiencies. Enlargement of the ventricles is a standard sign in these cases. In an earlier study looking at glucose uptake these investigators found abnormal interactions between the thalamus and neocortex, in particular the temporal and occipital lobes, speculating that there might be a problem with "directed attention" as a result (Horwitz etal. 1990).

A PET study of 7 young adults with Down syndrome (mean age 28 years) without dementia (Haier etal., 1995) confirmed previous findings that overall cortical glucose metabolic rate is higher in subjects with Down syndrome (and in other mentally retarded subjects) than in normal controls. This seemingly paradoxical increase is typically interpreted as a sign of "inefficiency".[2] When one looks at specific areas more closely, there are decreases in metabolic rate in medial frontal and medial temporal lobes in the Down syndrome subjects, and some evidence of dysfunction in the basal ganglia.

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[2] Although this interpretation of inefficiency makes intuitive sense, it does make one pause for a moment in thinking about results from all PET studies, in which increases in activity are usually interpreted as signs of normal, not inefficient, function.

Two recent studies (Pinter et al., 2001a; Kates et al., 2002) provide more specific information. Pinter et al. used high-resolution MRI methods to analyze brain structure in 16 youngsters (mean age 11.3 years) with Down syndrome. After correcting for overall brain volume, hippocampal, but not amygdala volume reductions were seen in this group. This result confirms some earlier work using lower resolution MRI methods (Jernigan et al., 1993). Kates et al. looked at a group of 12 children (all males, mean age 5.94 years) with Down syndrome, and compared them to children with Fragile-X, developmental language delay, or typical development. The children with Down syndrome had smaller brain volumes than any of the others, with previously unreported reductions in parietal cortex as well as the oft-reported reductions in the temporal lobe. Pinter et al. (2001b), on the other hand, note the relative preservation of parietal cortex.

Overall, the evidence from the study of subjects in mid-life is not yet conclusive. While there are clear problems in some cases, with some evidence for localized neuropathology, the general picture is quite diffuse. This, however, is not the case when one looks at studies focused on somewhat older subjects.

For some time it has been clear that neuropathology resembling that seen in Alzheimer's disease (AD) is prevalent in individuals with Down syndrome (DS) after the age of about 35 years. A large number of studies have concentrated on this issue, documenting the ways in which the neuropathology seen in Down syndrome is similar to, or different from, that seen in Alzheimer's disease. A very important fact emerging from the past 10 years of careful study, is that while virtually 100% of individuals with Down syndrome show neuropathology similar to that associated with Alzheimer's disease, less than 50% show the dementia invariably seen with AD. This uncoupling of the neuropathology from the dementia has of course occasioned considerable interest, with an initial emphasis on attempts to determine if there might be subtle differences between the cases of DS and AD that could explain the dissociation observed in DS but not in AD. It has not proven possible to point to any difference that could be said,

with confidence, to account for this fact (eg., Cork, 1990). Recently, H. Wisniewski (personal communication) has shown that there is a critical difference between DS and AD with regard to the nature of the amyloid deposits found in the plaques characteristic of the neuropathology common in these two syndromes. Dementia is only observed when insoluble amyloid, which causes the formation of fibrous tangles, is present. This type of amyloid is rarely seen in DS until after 50 years of age, regardless of the extent of gross neuropathology.

Five recent papers provide an up-to-date view on the neuropathology observed in adults with Down syndrome (Weis, 1991; Kesslak etal., 1994; Raz etal., 1995; Lögdberg & Brun, 1993; Aylward etal., 1999). Weis (1991) applied stereological techniques in combination with magnetic resonance imaging scans to estimate the size of various brain regions in a group of 7 adults (30-45 years of age) with Down syndrome. The volume of the whole brain was smaller in subjects with Down syndrome. When the data were normalized and then considered as a ratio of the volume of the cranial cavity, specific differences were observed in cortex and white matter overall, with a not-quite-significant difference in cerebellum ($p < .06$). The second study (Kesslak et al., 1994) looked at 13 adults with Down syndrome, using MRI to assess the size of various brain regions. Two additional subjects with clinically diagnosed dementia were also studied. The main findings in the group without dementia were a decrease in the size of the hippocampus and neocortex, and a paradoxical increase in the size of the parahippocampal gyrus. No significant differences were observed in the superior temporal lobe, the middle and inferior temporal lobes, the lateral ventricles, or cortical or subcortical areas. In these Down syndrome subjects there were only two significant age-related changes: with aging, ventricle size increased and hippocampal size decreased. In the two subjects with dementia, there was considerable brain atrophy and an enlargement of the ventricles; in general a picture similar to that observed in Alzheimer's disease, but absent in the subjects with Down syndrome who were not clinically demented, even those as old as 51 years of age.

The third study (Raz et al., 1995) looked at 25 adults, 13 with Down syndrome, also using MRI. Most critically, their results were adjusted for body size, so they took into account differences resulting simply from allometry. The authors found that a number of brain regions were smaller in the Down syndrome subjects, including the hippocampal formation, the mammillary bodies, and parts of the cerebellum and cerebral hemispheres. They also replicated the increase in size of the parahippocampal gyrus observed by Kesslak et al. (1994). There was some shrinkage of other brain regions, including the dorsolateral prefrontal cortex, the anterior cingulate cortex, the pericalcarine cortex, the inferior temporal and parietal cortex, and the parietal white matter. No differences at all were observed in orbito-frontal cortex, pre- and post-central gyri, and the basal ganglia. The fourth study (Lögdberg & Brun, 1993) applied morphometric analyses to the brains of 7 subjects with Down syndrome (mean age of 25.3 years), and demonstrated a significant decrease in gyri in the frontal lobe. Finally, Aylward et al. (1999) used high-resolution MRI to show a selective hippocampal volume reduction in adults.

These observed changes confirm earlier reports of decreased volume of cerebellum (Jernigan & Bellugi, 1990), and of decreased dendritic spines and volume in hippocampus (Ferrer & Gullotta, 1990). There have also been reports of neuropathology in the amygdala (Mann & Esiri, 1989; Murphy etal. 1992), in particular in those subregions most closely associated with the hippocampus (Murphy & Ellis, 1991), but the more recent findings that controlled for overall brain volume (Pinter et al. 2001a) cast some doubt on these data.

The earliest neuropathological changes with aging in Down syndrome seem to appear in parts of the hippocampal formation, especially the entorhinal cortex, but also involving the dentate gyrus, CA1 and the subiculum (Mann & Esiri, 1989; Hyman, 1992). There is extensive cell loss in the locus coeruleus (Mann etal. 1990), a brainstem nucleus that projects to the hippocampal formation; this was most noticeable in cases of severe dementia.

In sum, there are widespread signs of neuropathology in older subjects with Down syndrome, but there is selectivity nonetheless, in terms of where signs are seen first, and where they are most prominent. In this regard, changes in hippocampal formation (Ball & Nuttal, 1981, Sylvester, 1983; Ball etal. 1986), temporal lobe in general (Deb etal. 1992; Spargo etal. 1992), prefrontal cortex (Logdberg & Brun, 1993; Kesslak etal., 1994) and cerebellum (Cole etal. 1993) stand out.

Work with animal models of Down syndrome is quite consistent with this picture, and adds some measure of confidence to the conclusions drawn from the human data. The trisomy-16 mouse (Ts-16) has generally been viewed as a plausible model of Ts-21 in humans (eg., Holtzman et al., 1995). These animals, however, do not survive birth, and study of the postnatal neural and behavioral consequences of this trisomy has awaited the development of a partial Ts-16 mouse that survived into adulthood, and that had triplicates of most of the human chromosome 21 genes. Recently, this goal has been accomplished with the development of Ts65Dn mice (Davisson et al., 1993). Recent behavioral work with these mice, using a variety of paradigms, is highly consistent with the idea that damage in the hippocampus is an important part of the syndrome (Coussons-Read and Crnic, 1996; Escorihuela et al., 1995; Hyde & Crnic, 2001; Hunter et al., 2003). In these studies, the Ts65Dn mice showed behavioral profiles highly similar to those observed after experimental damage in the hippocampus in mouse and rat studies. Thus, the Ts65Dn mice were hyperactive, defective in spatial and context discrimination learning, but normal in other forms of learning not dependent upon the hippocampus. The development of new kinds of partially trisomic mice, with triplication restricted to other segments of the critical chromosomes, should help greatly in unraveling the relation between the genetic defect and neural dysfunction.

Overall, study of neuropathology in early and later life points to certain regions of the cortex, including most prominently the temporal lobe[3] and the hippocampal formation (Wisniewski etal, 1986), the prefrontal cortex, and the cerebellum. In analyzing learning and memory difficulties we should be particularly alert to changes that reflect problems with these neural systems. While there is a substantial and growing literature dealing with the hippocampal system and prefrontal cortex in Down syndrome, the possible role of the cerebellum has been generally downplayed. Given the persistent abnormalities observed in this structure closer examination of its role in the behavioral and cognitive phenotype in Down syndrome should be a high priority for the future.

II. Learning and Memory in Individuals with Down syndrome

In considering the learning and memory abilities of individuals with Down syndrome two major concerns must be taken into account: first, learning and memory must be considered as involving a number of separate systems; and second, attention must be paid to the abilities of individuals at various stages of life. I will focus largely on the medial temporal lobe, in particular the hippocampus, which plays a critical role in memory and seems disproportionately affected in Down syndrome. The evidence for this is now quite clear in older subjects, if only suggestive in younger subjects. Work with animal models, as we have seen, supports this view. The hippocampal system is involved in spatial cognition in particular, flexible learning in general, and the normal consolidation of what has already been learned, and we should therefore expect selective difficulties with these aspects of learning (Nadel & O'Keefe, 1974; O'Keefe & Nadel, 1978; Nadel, 1994). It is known that this system is not crucial for much learning about categories and concepts, nor is it necessary for skill learning, hence we should expect relatively normal performance in these domains. The prefrontal cortex, also affected in Down syndrome, appears to be

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[3] In an intriguing study of perceptual capacity, Bihrle etal. (1989) have shown that adolescents with Down syndrome are considerably more impaired in analysis of local features as compared to global features. This result strongly points to the inferotemporal cortex, and perhaps more precisely to the dorsal region (see Horel, 1994, for an analysis of the role of this area in local vs. global perception).

particularly important in executive function, but also plays an as yet ill-defined role in episodic memory. We do not have as clear a picture of the precise functions of the cerebellum, another brain region prominently affected in subjects with Down syndrome. There is some evidence to suggest that it is involved in motor skills, and other indications that it might be critical in the acquisition of conditioned responses, for example the so-called nictitating membrane response. We will see below that there is some evidence that this form of conditioning is indeed impaired in older subjects with Down syndrome.

A. Early Learning

In general, infants with Down syndrome show relatively normal abilities in learning and memory (but see Hepper & Shahidullah, 1992, for a report of impaired habituation in 2 fetuses with Down syndrome). It is essential to understand, however, that this does not mean that either they, or indeed normally-developing infants, have the full adult range of learning and memory abilities at birth. In fact, this is not the case, since some parts of the brain mature postnatally, and the forms of learning and memory dependent on them are not available until some time after birth. The medial temporal lobe, and particularly the hippocampus, as well as parts of the cerebellum, are included in this category. The fact that these late-developing structures are apparently particularly at risk in Down syndrome is probably of considerable importance (see Nadel, 1986). Although there is insufficient evidence to be certain about the exact ages, there is little doubt that in humans, as in most other animals, the hippocampus is not fully functional until many months after birth, and perhaps as long as 16-18 months (see Nadel & Zola-Morgan, 1984; Nadel & Willner, 1989). This means that the kinds of learning and memory that are dependent upon this system are not available to infants.

In an early series of studies, Ohr & Fagen (1991, 1993) looked at the ability of infants to acquire behaviors based on learning about the contingencies between their own movements (leg-kicking) and reinforcement. They reported that 3-month old infants with Down syndrome were entirely normal at this task, including initial learning, acquisition speed, and retention. In a later report, (Ohr & Fagen, 1994) they showed that 9 month-old infants with Down syndrome were impaired, as a group, in learning about the contingency between arm movements and reinforcement. However, they noted that some infants with Down syndrome were able to learn. They concluded that there is a relative decline in conditionability in infants with Down syndrome compared to normally developing infants after 6 months. This is in agreement with the general picture emerging from studies of brain maturation, which also show relative normalcy at birth but increasing abnormality after 6 months.

Mangan (1992) tested control infants and infants with Down syndrome on a variety of spatial tasks, one of which, a place-learning task, was designed especially to assess the state of function of the hippocampal system. It is known that this place-learning task does not emerge in normal development until about 18 months of age, which matches current estimates of when the hippocampus itself becomes functional (Mangan & Nadel, 1990). Two other spatial tasks were utilized, one involving response-learning, where the child had to make a consistent body-turn, and the other involving cue-learning, where the child had to approach a specific cue. In all three tasks the child was searching for a toy hidden in a hole. After learning, the infants were removed from the apparatus for a delay interval, then were given a "memory" test. Mangan tested children at the age of 16-20 months on the response and cue tasks and at the age of 26-30 months on the place task. He found that children with Down syndrome were somewhat impaired in the learning of all three tasks, although they did manage to learn them all. On the critical memory probes, children with Down syndrome performed similarly to the normal children on the response and cue tasks but were severely impaired on the place task. This pattern of results is consistent

with diffuse, but mild, neuropathology combined with much more extensive pathology localized to the hippocampus.

A great deal of work on learning within the language domain has been carried out in children with Down syndrome (see Rondal, 1994). There is little question that difficulties in the acquisition of language can be quite severe, particularly in the phonological and syntactic domains (see Tager-Flusberg, 1999b; Vicari et al. 2002; Thordardottir et al. 2002), but there are also cases where language capacity is within normal range, or even at the upper end of that range. Infants with Down syndrome show many of the normal features of pre-language behavior, including babbling and imitation, although there are some subtle but possibly important differences between Down syndrome and normally-developing infants in this regard (Lynch etal., 1990; Oller & Siebert, 1988; Steffens etal., 1992). Sigman and her colleagues (Sigman, 1999; Mundy etal. 1988) have shown deficits in the use of nonverbal requests in young children with Down syndrome. Similar deficits in requesting behavior have been seen in other studies, including one assessing verbal requests (Beeghly et al., 1990), but a number of studies have failed to detect a deficit (eg., Greenwald & Leonard, 1979). Vocalization appears to be under contingent control in infants with Down syndrome (Poulson, 1988), and their ability to acquire words seems normal as well, although slow (Hopmann & Nothnagle, 1994). While it is hard to pinpoint the precise defect at the root of the typical language problem, there is little to suggest that the difficulty is primarily one of learning or memory. Sigman (1999) stresses defective requesting behavior, less-than-optimal caregiver behavior, and diminished capacity to initiate joint attention as precursors to language problems. Tager-Flusberg (1999b) focuses on auditory working memory, which certainly could account for the observed phonological defects. The fact that disproportionate difficulties are observed in grammatical development is consistent with the idea that learning and memory problems are not at the root of language defects in Down syndrome. Nor can the language defect be simply a function of mental retardation. Children with Down syndrome and Williams

syndrome (another genetic disorder) can show equal retardation yet differ considerably in terms of language capabilities. As the focus of this review is on learning and memory, it will not consider the acquisition of language in any further detail.

Young children develop notions about the continuing existence and properties of objects in a characteristic fashion. Children with Down syndrome have typically been shown to acquire this basic object concept more slowly than normal (eg., Rast & Meltzoff, 1995), but with extensive training they can acquire it at more or less the same time as normally-developing infants (Wishart, 1993). However, a different kind of problem emerges in this task situation: instability of acquisition. Although the typical subject with Down syndrome solved various levels of the tasks used to assess the object concept at ages not very far from the norm, performance after acquisition could be highly variable and apparently beset by motivational difficulties. These problems, if representative of the learning style of children with Down syndrome, are extremely important in thinking about effective intervention. The results of Wishart's studies using standard intelligence test batteries suggest that they are indeed representative. Test-retest reliability was very low because successes gained in one test might not appear upon retest, as soon as 2 weeks later. New skills show up, only to disappear shortly thereafter. One could speculate that evidence of such "rapid forgetting" is consistent with damage in the hippocampal formation, but considerably more data are required before this conclusion can be accepted.

The motivational difficulties and developmental instabilities observed in Wishart's work strongly suggest that young children with Down syndrome are not merely delayed in mental development, but actually follow a somewhat different path. As Wishart (1993) points out, this view "has the substantial merit of being consistent with data from the neurosciences showing Down syndrome to be associated with fundamental differences in the morphology and functioning of the brain" (p. 392).

To summarize the situation in infants and children: there is evidence of relatively normal learning of certain types, especially in the youngest subjects. The kinds of learning that appear normal fall into the category often referred to as "procedural": simple conditioning, for example, and deferred imitation (Rast & Meltzoff, 1995). There is also evidence for some highly specific learning deficits, which typically emerge only some months or even years after birth. The evidence is consistent with a specific problem in the hippocampal formation spatial cognitive system.

The learning and memory problems that begin to emerge in late infancy become considerably more noticeable as the infant grows to childhood and adolescence. While much of our knowledge for this period comes from the learning of language, there is information available about other kinds of learning and memory. One major point to be stressed from these language learning data has less to do with the inability of children with Down syndrome to acquire words, or linguistic constructions, or other non-verbal material, and more to do with their inability to "stabilize" the information that they do manage to acquire. Wishart (1993) and Fowler (1988) stress this point, which might reflect, among other factors, impairments in memory consolidation, another function of the hippocampal system.

In one of the earliest studies taking into account the multiple forms of learning and memory, Carlesimo et al. (1997) reported a selective impairment in Down syndrome. Subjects with Down syndrome were tested on a variety of "implicit" (or procedural) and "explicit" (or episodic) memory paradigms, including word stem completion, list learning and prose recall. Robust priming effects were seen in the Down syndrome group, comparable to that observed in controls indicating that implicit memory was intact. However, deficits were observed in both explicit memory tasks. Performance on these kinds of explicit memory paradigms has been linked to functions of the hippocampal system, hence the

defects suggest differential impairment in hippocampal function and thereby converge with the data from study of spatial cognition.

In a series of recent studies my colleagues and I have tested several different groups of individuals with Down syndrome on a range of tasks designed to directly assess the function of specific brain systems. This "cognitive neuropsychological" approach often uses tasks first developed in animal models, where the critical underlying brain circuits can be identified and carefully studied in invasive experiments. We started with a focus on three brain systems identified by the neuropathological data, much of which was discussed above: the hippocampal system, the prefrontal cortex, and the cerebellum. We developed a set of tasks that could, collectively, tell us something about how these brain systems are faring.

In the first set of studies (Pennington et al. 2003) we found evidence of specific hippocampal dysfunction in our sample of 28 adolescents, using mental age matched controls. We found little evidence of prefrontal dysfunction in a battery of nonverbal tasks. Subsequent pilot work, however, suggested that verbal tasks might yield a different result, and indeed that is what we are now seeing (Moon et al., in preparation). We have been testing two new groups of individuals with Down syndrome, a young group and an old group. Using verbal tasks to explore the prefrontal cortex, we found in both our young and old groups strong signs of dysfunction in both the hippocampal and prefrontal systems. Deficits were observed in a range of tasks, although verbal mediation was necessary to bring out the prefrontal effect. Taken as a whole, our studies show that particular problems emerge in the memory domains subserved by the hippocampal system and the prefrontal system. The latter impairment appears to be linked to the use of verbal test materials. The impairment in hippocampal function could in principle reflect problems in any of the structures of the hippocampal region; a recent study of two neuropsychological paradigms (delayed non-matching to sample and visual paired comparison) dependent on parahippocampal and perirhinal regions, however, suggests that these areas are

functioning appropriately, and that the impairment is more likely to reflect improper development of the hippocampus itself (Dawson et al. 2001).

The prefrontal cortex, as noted already, plays an important role in a wide range of functions, including episodic/explicit memory and working memory. We have already seen that episodic memory is impaired in individuals with Down syndrome. There has been extensive research on working memory in this population, and clear deficits have been observed in a number of studies (Varnhagen et al. 1987; Laws, 1998; Marcell & Weeks, 1988; Jarrold et al., 2000, 2002). However, this impairment seems to be limited to verbal information, as impairments are minimal in visuospatial domains. The deficit appears to be neither a motor nor articulatory problem (Kanno & Ikeda, 2002), and may relate to the so-called phonological loop (Laws, 2002).

Thus, several forms of data indicate that specific impairments in prefrontal cortex and the hippocampal system are an important part of the phenotype of Down syndrome. This suggests a framework for research in the future: what is it about an extra chromosome 21 that leads to particular impairments in the function of these two brain systems?

IV. Conclusions

Learning and memory are disrupted in Down syndrome, and progress is being made in defining exactly what the deficit is. Most indications suggest that the impairment is not spread across all learning and memory systems equally, but instead selectively impacts only some systems. There is at this time clear evidence implicating the forms of learning and memory dependent upon the hippocampus; strong evidence implicating the prefrontal cortex is also available. No doubt other impairments will be found, most probably including the cerebellum, or parts of the cerebellum. This research has provided a reasonably clear picture of which aspects of improper neural development might be

responsible for the particular features of the mental retardation seen in Down syndrome. This neural phenotype, or neurotype, results in some way from trisomy 21.

How do we go from this kind of knowledge to an understanding of the linkages between genes and the neural and cognitive phenotype emerging in these studies of Down syndrome? The strategy my colleagues and I have been pursuing goes something like this: (1) identify as carefully as possible the neural and cognitive phenotype in humans with Down syndrome; (2) create mouse models that triplicate only some of the genes on human chromosome 21, aiming to isolate just those genes that are responsible for the specific features of the phenotype. Nobody should be fooled by the seeming simplicity of only having to take two steps. Each of these enterprises is complex and littered with blind alleys, but some persistence might pay big rewards. Not least, careful analysis of how trisomy 21 leads to the specific pattern of improper neural development seen in Down syndrome might shed considerable light on how genes are ultimately translated into brains and behavior in the case of normal development.

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