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Spatial memory abilities and abnormal development of the hippocampal formation in Down syndrome

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SPATIAL MEMORY ABILITIES AND ABNORMAL DEVELOPMENT OF THE HIPPOCAMPAL FORMATION IN DOWN SYNDROME

by

Peter Anthony Mangan

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As members of the Final Examination Committee, we certify that we have read the dissertation prepared by Peter Anthony Mangan entitled SPATIAL MEMORY ABILITIES AND ABNORMAL DEVELOPMENT OF THE HIPPOCAMPAL FORMATION IN DOWN SYNDROME

and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy

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Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copy of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

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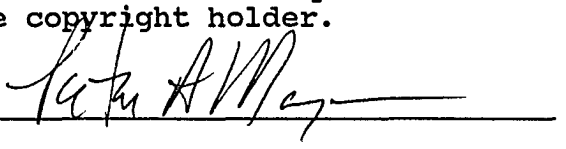
SIGNED: 

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ABSTRACT

The recent evidence concerning the nature of cognitive development in Down Syndrome (DS) suggests that it is different than normal development. The neuropathology seen in DS implicates a prenatal interruption of normal neural development as a possible basis for these differences. Since the hippocampal formation (HF) undergoes extensive postnatal maturation and is found to be abnormal in DS, it is proposed that cognitive deficits associated with DS would be most evident in tasks requiring hippocampal function. The performance of DS children at 16-18 months and 28-30 months of age was compared to that of age-matched control groups of normal children on two cognitive tasks requiring abilities that develop during the first postnatal year shown not to involve hippocampal function, response and cue learning tasks, and a task requiring abilities that develop during the second postnatal year shown to require hippocampal functioning, a place learning task. The results of this comparison show that the DS performed comparably on the nonhippocampal tasks but performed differently on the hippocampal task. The normal children's performance support the position that the ability to perform HF tasks develops during the second postnatal year while the performance of the older DS children suggest that this development does not

occur in DS. The specificity of the deficits to the hippocampal task was interpreted as indicative of a lack of HF development in DS.

INTRODUCTION

Down syndrome (DS) is one of the most common causes of mental retardation. It accounts for nearly one third of all mentally retarded individuals. Its incidence is approximately one in six hundred live births; in the United States, about seven thousand children per year are born with DS.

Dr. John Langdon Haydon Down has been credited with first recognizing this disorder as a discrete entity in his paper "Observation on an ethnic classification of idiots" (Down, 1866, 1877). Noting the mental deficits and the facial feature characteristics of the disorder, he provided the descriptive label of "mongoloid idiocy". Part and parcel of this label was Down's proposed cause, a cessation of early development, and his support of the dominant biological theory of development during the mid-part of the nineteenth century which held that "ontogeny recapitulated phylogeny". Higher animals including humans, progressed through developmental stages that represented, in order, the adult forms of early appearing animals. Thus they first appeared fishlike by developing gills, then progressed through a reptilian stage during which they developed three chambered hearts, and later, a lower mammalian stage developed during which they developed mammalian tails. This theoretical

construct was extended by many recapitulation theorists to propose that the development of humans progresses through stages during which higher races passed through stages representing the adults of more primitive races. Down concluded that since people with this disorder have the appearance of the "mongol" race, a race just beneath the "superior" caucasian race, their development must have been arrested during this earlier stage of development. This position was never widely accepted for two primary reasons: 1) the "mongoloid idiots" did not resemble members of the mongol race closely, and 2) it was difficult to explain the existence of mongoloid idiots who were also members of the mongol race (the mongol mongolian idiot) or were of another race considered to be inferior to the mongol race. While Down's theory was largely rejected, the term "mongoloid idiot" and the idea that these "unfinished children" resulted from arrested development have endured (for example see Shuttleworth, 1895; Thomson, 1907). Other proposed causes for this disorder included deficits in "maternal power" which was postulated to be the result of either maternal age or exhaustion caused by a long series of pregnancies (Shuttleworth, 1909), maternal syphilis (Sutherland, 1899), paternal alcoholism (Cafferata, 1909), thyroid deficiencies (Stoeltzner, 1919), or degeneration of the ovum due to maternal age (Jenkins, 1933).

The finding that DS is the result of a chromosomal aberration, while suspected as early as 1932 (Waalenburg, 1932) was not confirmed until 1959 (Jacobs et al, 1959; and LeJeune, Gautier, and Turpin, 1959a; 1959b). It is now known that DS is a genetic disorder arising through chromosomal non-disjunction during meiosis that usually results in a triplication (trisomy) of chromosome 21. Most frequently (92%-93%), this non-disjunction occurs during the first maternal meiotic division and results in a complete trisomy of the chromosome where all of the body's cells contain a third chromosome 21. Less frequently (2-3%), DS may involve a non-disjunction during later divisions of the zygote resulting in mosaic DS where only a proportion of the body's cells contain the third chromosome 21. A third possibility, one that is also relatively rare, is the triplication of only part of the twenty-first chromosome. This extra genetic material results from the translocation of a portion of chromosome 21 which then results in the triplication of portion of the longer arm of chromosome 21 (5-6%) (Cooper and Hall, 1988; Stratford, 1989). In the latter case, translocation of a specific segment of the chromosome, q22, suffices to cause DS (Smith and Warren, 1985).

In addition to the cognitive deficits that are characteristic of DS, the disorder involves deficits in a variety of biological systems. These include growth

retardation, hypotonia, heart defects, increased incidence of a specific form of leukemia, and neurological abnormalities which include the precocious development of Alzheimer's-type pathology in the central nervous system (McCoy and Epstein, 1987). Partly because of this wide range of defects, these cognitive and biological impairments have often been described in general, rather than specific terms. Thus, Lenneberg (1967) described DS as "a stretching" or delaying of the developmental timetable of a collection of simultaneously developing psychobiological processes, including sensory, motor, and cognitive functions. Later, Gibson (1978) described individuals with DS as having a slowed-down rate of development, and Metcalf and Stratford (1979) noted that while perceptual development of both children with DS and normal children could be described by a linear function, the function that described DS development had a smaller slope indicating similar but slower development. More recently, a longitudinal study of DS childrens' affective and cognitive development reported that while both were generally slower than that of normal children, the sequencing and organization of their development is not different (Cicchetti and Pogge-Hesse, 1982). The position that DS involves a generalized delay of development has been brought into question by data suggesting that various psychological functions, and their neurological

underpinnings, do not develop simultaneously, and that the deficits with DS may actually be associated with relatively "normal" development in some systems coupled with incomplete development in others. From this perspective neurological and cognitive development of individuals with DS would appear to be different from that of nonhandicapped individuals as opposed to simply being slower (see Morss, 1983, 1985; Nadel, 1986, 1988; Wishart, 1987, 1990).

Literature Review

Impaired cognitive functioning in DS has been an extensively studied. Understanding the nature of the impairment depends on how normal cognitive function and cognitive development are perceived. Cognitive functioning has been traditionally viewed as involving the activity of a central, general-purpose information processing system mediated by a unitary neural system (see Anderson, 1983); cognitive development in this view is simply the transition of a immature cognitive system to a more mature one. Any disruption or cessation in neurological development would be expected to result in general deficits in all cognitive domains. The position that cognition in general, and learning and memory in particular, reflect the activity of a unitary information processing system is not supported by recent studies (O'Keefe and Nadel, 1978; Olton, Becker, and

Handelmann, 1979; Sutherland and Rudy, 1989; Zola-Morgan, Squire, and Mishkin, 1982). These authors suggest that the ability to learn and remember information actually depends upon multiple cognitive functions each subserved by a different neural system. If cognitive function involves multiple semi-autonomous processing systems, or modules (Fodor, 1983), each mediated by a different neural system, a different picture of cognitive development emerges. While it is possible that these different modules and their underlying neural systems could mature synchronously, it is also possible, and as will be shown more probable, that individual modules have different maturation timecourses. This perspective is consistent with the view that the infant does not simply possess an immature central information processing system waiting for the proper experiences to mature, but possesses a cognitive system that is adapted to the needs of the infant at different periods of development. As the child physically matures, new cognitive needs arise and specific neural systems mature so that new cognitive abilities can develop to meet these needs. Disruption of neurological development within such a multimodal system should produce a rather different pattern of cognitive deficits than would be seen after disruption of a unitary cognitive system. Interruption or cessation of development in this type of a system would likely result in deficits in cognitive

functioning specific to those information processing modules that normally mature after the occurrence of the interrupting event. Thus cognitive deficits would be most severe in just those cognitive domains subserved by late developing modules; cognitive functions dependent upon early developing modules should be relatively intact.

These two theoretical concepts: (1) that cognitive development is characterized by the development of multiple cognitive skills and their underlying neural substrates and (2), that DS is characterized by relatively normal prenatal neural development coupled with abnormal postnatal development leads to an interesting hypothesis. If the cognitive deficits that characterize DS are the result of a disruption of normal neural development, and cognitive development involves the maturation of multiple information processing systems, then the development of cognitive function and the neural systems underlying these functions in infants with DS should be different than in the normal child. The purpose of the present study is to seek evidence that this is indeed the case: that the cognitive development of individuals with DS is qualitatively different in addition to being generally slow.

The first issue to be addressed is whether neuropathological examination of the DS brain has revealed abnormalities consistent with the position first suggested by

Down in 1866. Specifically, is there neuropathological evidence of an early interruption or cessation of neural development? If so, then a second question arises: Might the characteristic deficits in cognitive development observed in DS, traditionally attributed to generally slowed development, be better attributed to a selective lack of development of late developing brain structures?

Neuropathology, Neural Development, and DS

Neuropathology in DS

DS is characterized by a variety of neurological abnormalities including the development of Alzheimer's type neuropathologies in later life. From a morphological perspective, the DS brain has been shown to be of reduced weight, particularly in the cerebellum and brainstem; to be abnormally shaped, the DS brain being characteristically rounder and shorter with a smaller anterior-posterior circumference; and to have different convolutional patterns in the cortex, most noticeable in differences in the widths of the sulci and gyri, especially narrowing of the superior temporal gyri (Scott et al, 1983). Morphological differences in the hippocampal formation (HF), bilateral structures within the medial temporal lobes (figure 1), have also been reported. Sylvester (1983) compared the HF in twenty adult brains aged eighteen to seventy years to age-matched normal

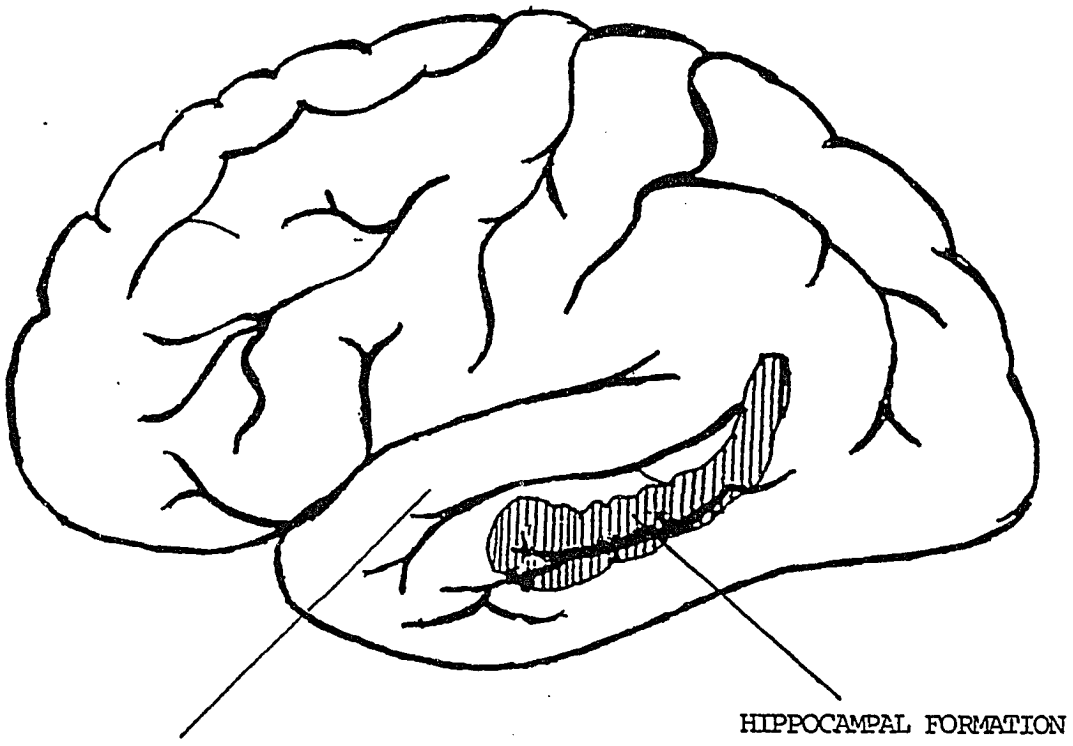


Figure 1. The location of the hippocampal formation and superior sulcus in the temporal cortex.

brains and reported difference in the size of two of the structures that make up the HF, the dentate gyrus and the hippocampus proper, the structures in the DS brains being nearly half the normal size.

Histological analysis has shown significant differences in the structure and density of neurons in areas of the cortex and cerebellum of the DS brain (Takashima et al, 1981; Wisniewski et al, 1985). An abnormal 20-50% reduction in the number of neurons in many layers of the cerebral and cerebellar cortex has been found, but without a corresponding reduction in cortical thickness (Wisniewski et al, 1986). This reduction is particularly evident in the granular layers which are populated by late maturing cells (Wisniewski et al, 1985). Surviving neurons show a reduced number of dendrites and dendritic spines with a 20-50% reduction in the number of synapses (Suetsugu and Mehraein, 1980). The surviving spines appear to be abnormally long and thin, much like spines that are normally seen in very early developmental stages, rather than having the short mushroom shape seen in mature dendritic spines (Marin-Padilla, 1976; Purpura, 1979; Takishima et al, 1981). These data suggest that the reductions in the number of neurons and the apparent immaturity of their processes may be due to a cessation, or premature arrest, of neural development (Nadel, 1986).

Neuropathological evidence of this apparent early interruption or premature arrest of late developing neurons is particularly evident in layers II and IV of the entorhinal cortex, which normally have large populations of granular cells (Wisniewski et al, 1986), the dentate gyrus, also normally rich in granule cells (Suetsugu and Mehraein, 1980), the granular layers of the visual cortex (area 17) (Wisniewski et al ,1984), and the granule cell layer of the cerebellum (Scott et al, 1983).

The aforementioned findings of abnormalities in late maturing areas of the DS brain are indicative of a possible interruption of neural development in DS. They do not, however, provide information about the nature or the timing of this proposed interruption of neural development. Developmental differences between the normal brain and the DS brain have only recently been described.

Normal Neurological Development

Early mammalian neural development involves a predominantly prenatal period of neurogenesis. This period of neuronal proliferation and migration is followed by a period of synaptogenesis, the growth of neuronal processes and synaptic connections. This period of synapse development begins prenatally but is maximal postnatally (Cowan, 1979). In humans, this period of optimal synapse formation lasts

until approximately 24 months, when a maximum number of neurons and synapses have developed (Huttenlocher, 1979). The proliferative and growth stages of general neuronal development are followed by a period of selective or programmed cell death and synaptic degeneration during which time excess synapses and connections are eliminated. The result of this period of development is that by early adolesence the total number of neurons and synapses is estimated to be reduced by approximately 40-50% (Heumann and Leuba, 1983; Wisniewski, Laure-Kamionowska, Wisniewski, 1985).

Neural Development of Neocortex

In the neocortex, the neurons in the deepest layer, layer six, are generated first. The neurons of subsequent layers are then generated and migrate through the existing layers until they reach their destinations above the previously formed cortical layers. The neurons found in the first cortical layer migrate through all five previously formed layers to take their position closest to the cortical surface. Thus the order of neurogenesis in the neocortex is determined by where a particular neuron will be located when mature, and not by cell size. Synaptogenesis, however, does appear to be related to cell size. The large pyramidal cells found predominantly in layers III and V develop lengthy

processes and synaptic connections before the horizonal cells of layer I or the stellate or granular cells that predominate in layers II and IV.

Neural Development of the HF and Cerebellum

In contrast to the aforementioned pattern of development in the neocortex, is the extensive postnatal proliferation of granule cells in the cerebellum and the dentate gyrus of the HF in a number of species (Bayer and Altman, 1987; Eckenhoff and Rakic, 1988; Rakic et al, 1986; Rodier, 1984). Autoradiographic studies of hippocampal development in all altricial species studied thus far have shown that the generation of neurons in the HF of the mouse (Angevine, 1965), rat (Altman, 1963; Schlessinger, Cowan, and Gottleib, 1978, Stanfield and Cowan, 1988), rabbit (Gruneau et al, 1982), and monkey (Eckenhoff and Rakic, 1988; Rakic and Nowakowski, 1981) differs from that seen in neocortical development.

The generation of the pyramidal cells of the hippocampus proper occurs early during the same prenatal period as neocortical neurons. In humans, the first pyramidal cells appear to align themselves into what will become the hippocampus at 10 weeks with further proliferation continuing through the prenatal period (Gilles, 1983). The generation of the granule cells that make up the dominant

cell layer of the dentate gyrus is remarkably different. These cells are produced by a two stage process of neuronal proliferation.

The first granule cells that migrate to the dentate gyrus are generated in the ventricular zone during the same time period as neocortical and hippocampal pyramidal neurons (Stanfield and Cowan, 1979; Bayer, 1980; Rakic and Nowakowski, 1981). However, a second proliferative zone, referred to as the sub-ventricular zone, develops later in the prenatal period (Eckenhoff and Rakic, 1988). While both these zones produce neurons during the prenatal period, the later developing subventricular zone has been shown to continue to generate granule cells that migrate to the dentate gyrus postnatally (Stanfield and Cowan, 1988; Eckenhoff and Rakic, 1988). In the rat, the generation of these cells is essentially complete by three weeks of age (Seress and Ribak, 1990). In monkey, granule cell generation appears to be more predominantly a prenatal function, but newly generated cells have been identified as late as the onset of puberty (Eckenhoff and Rakic, 1988). In humans, up to twenty percent of the granule cells of the dentate gyrus are formed postnatally with proliferation continuing as late as six months, and immature granule cells, with incomplete dendritic development have been observed in brains of children fifteen months of age (Seress, 1991). Rakic and

Nowakowski (1981) noted that while the length of the periods of cell generation differed between primates and rat, the order and the ratio of duration of the periods of cell generation in the two species was very similar. This constancy of developmental order and ratio duration is consistent with the position of stability of function of the HF during evolution, i.e., the HF does not underlie different cognitive functions in different species.

In their neurobiological approach to infantile amnesia, Nadel and Zola-Morgan (1984) used such neuroanatomical data and behavioral data, as well as assumptions about the age of normal weaning in different species, to extrapolate an age of twenty-four months as the likely time when the human HF should be approximating adult levels of functioning.

Neural Development in DS

Prenatal Neural Development

Evidence that the neurological abnormalities in DS are due to a premature arrest of neural development and not a general slowness in development has been supported by findings that most indices of neuronal maturation are predominantly normal in the prenatal DS brain. Brooksbank et al (1989) compared postmortem tissue from the cerebral cortex of DS and control fetuses, nineteen to twenty-four weeks

gestation, using four biochemical measures of maturation. These included concentrations of neural cell adhesion molecules (N-CAM), choline acetyltransferase (ChAT), gangliosides, and seven major classes of lipid. These markers of maturation were used because differences in concentrations are either indicative of maturational processes (N-CAM and gangliosides), differences between adult DS and normal adult brains (ChAT), or for both of these reasons (lipid concentrations). No indication of a maturational abnormality was found in any of the markers studied save one class of lipid where an elevated level of polyunsaturated fatty acid was detected. The authors concluded that there was no evidence of major retardation of neuronal development being detected in the DS brains during this period, a period very near to the peak proliferation of neurons in the human forebrain. This lack of neuronal growth retardation has also been reported in studies of the morphology of neurons in the visual cortex. No abnormalities were found in cell distribution, number of dendrites, or number of dendritic spines in pre-term DS brain's unlike post-term DS brains that showed abnormal spines in the youngest (forty weeks gestation) and abnormal numbers of neurons, dendrites, and spines in older tissue (one to twelve months postnatal) (Takashima et al., 1981). Similarly, Wisniewski, Schmidt-Sidor, and Shepard, (1987a) reported

normal brain maturation in fetuses between fifteen and twenty-two weeks. Petit et al (1984) reported similar findings in brains twelve to forty weeks gestational age, but noted that there appeared to be more abnormal synaptic development in the older brain tissue.

Postnatal neural development.

In contrast to the prenatal developmental data, postnatal development of the DS brain has been seen to be clearly abnormal. Head circumference and brain weight, shown to be within normal limits at birth, have been shown to have a lower growth curve between birth and five years of age (Wisniewski, Schmidt-Sidor, and Sersen, 1987). Myelination, also normal during the prenatal period, has been found to be reduced in the postnatal DS brain by Wisniewski and Schmidt-Sidor (1989). More importantly, this study reported that a correlation was found between the reduction in myelination in specific brain structures and delays in reaching developmental milestones (see Wisniewski and Schmidt-Sidor, 1989).

Prenatal Development and Postnatal Neuropathology

The pattern of abnormalities found in the adult DS brain is consistent with the expected effects of an interruption of neural development commencing during the latter part of the prenatal period. An interruption of

neural development at this time would have a major impact on the later stages of the neuronal proliferation and migration; stages that include the generation and migration of neurons destined for brain structures undergoing extensive postnatal development. It would also severely disrupt synaptogenesis; a process that has begun to accelerate during this period. Additionally, since neuronal survival is, at least in part, dependent upon the efficacy of neural connections, late developing neurons having relatively few and immature connections would be most susceptible to elimination (Cowan et al., 1984; Clark, 1985). Thus, one would expect to find the reduction in the number of neurons and neural processes as well as a lack of maturity in dendrites and synaptic connections mentioned above.

That late developing neurons are most susceptible to elimination has been shown in studies involving the pattern of cellular death of the granule cells in the dentate gyrus of the rat. It was found that later developing neurons were more likely to be eliminated through programmed cellular death than those developing earlier (Gould, Wooley, and McEwen, 1991). Since the neurons making up the granular layers of the neocortex and the granule cells of the dentate gyrus and cerebellum are known to mature later than other cells, the reduction in the number of neurons in these areas

in the DS brain is quite likely to be the result of a selective elimination of these late maturing neurons.

Possible Mechanisms of Interrupted Development

The aforementioned neuropathological findings are consistent with the view that a cessation of neurological development occurs in DS, but why this cessation occurs is not understood. Possible candidates for this early cessation mechanism have only recently been identified in studies investigating the causes of inheritable forms of Alzheimer's disease. The connection between DS and Alzheimer's disease has been extensively studied as a result of findings that the brains of all individuals with DS who live past thirty-five years of age show Alzheimer's type neuropathology. The neuropathology seen in brains with Alzheimer's disease and adult DS brains has been frequently described as resulting from an early acceleration or exaggeration of degenerative processes which occur in varying degrees during the normal aging process (see Ball, Shapiro, and Rapoport, 1986; Cutler et al, 1985; Mann, Yates, and Marcyniuk, 1984; Miniszek, 1983). Of particular interest has been the discovery of the over-expression of different proteins whose gene locus has been assigned to the twenty-first chromosome. These include cell membrane proteins found in the brains of neonates with

DS, adults with Alzheimer's disease, and to a lesser extent in normal adult brains, but not in normal neonate brains, and amyloid proteins found in the amyloid plaques seen in adults with Alzheimer's disease or DS. The conclusion drawn from these results is that genetic defects involving genes located on the twenty-first chromosome result in familial types of Alzheimer's disease and the triplication of these defects contributes to the early developmental abnormalities associated with DS (Takashima et al, 1990; Tanzi et al., 1987; St. George-Hyslop et al., 1987). Although additional research is required, the over-expression of these and probably other proteins emerge as likely causes of an arrest of neural development.

Arrested Neural Development and Cognitive Ability in DS

Could this proposed premature arrest of neuronal development and its subsequent effect on the maturation of specific brain structures be involved in the dysfunctional cognitive development seen in DS? Further, are these deficits of a general nature, as predicted by the traditional central processing model of cognition; or are there specific deficits which can be correlated with the lack of maturation in particular neurological systems/structures, as would be predicted by the multiple systems (modular) model of cognition?

The extensive cell loss in many cortical areas suggests that cognitive deficits in DS would be of a general nature even from a modular model of cognition perspective, but a number of factors suggest that cognitive abilities requiring the function of the HF may be more adversely affected by an early cessation of neural development: (1) the significant numbers of the main cells of a part of the HF, the granule cells of the dentate gyrus, are still being produced during this proposed late prenatal interruption of neural development, a time when nearly all cells in the cortex have been born and have migrated to their final destinations; and (2), recent light and electron microscopic studies of the rat hippocampus and dentate gyrus have reported that other small cells, the basket cells, which function as inhibitory interneurons in these two structures, undergo extensive postnatal development that precedes the appearance of adult-like electrical activity in the hippocampus during the third postnatal week (Lang and Frotscher, 1990; Seress, Frotscher, and Ribak, 1989; Seress and Ribak, 1990). The third postnatal week is the same period in which these animals have been shown to perform tasks known to be dependent upon hippocampal maturation (Carew and Rudy, 1988).

The preponderance of neuropathological evidence is indicative of a prenatal period of predominantly normal

neural development that is followed by a period of disrupted development during the later stages of prenatal that continues through postnatal life. The result of this disruption is the characteristic patterns of neuropathology seen in DS brains. This leads to the question of whether there exists a specific pattern of cognitive deficits associated with DS in which: 1) severe cognitive deficits more prevalent in late developing cognitive abilities, 2) these severe deficits more than an additive effect of the accumulation of deficits in earlier appearing abilities, and 3) these deficits are related to identifiable developmental abnormalities.

The Nature of Cognition, Cognitive Development, and DS

Early investigations of the cognitive impairments associated with DS provide little evidence for determining when individuals with DS are selectively effected by a disruption of development. Perhaps the most critical reason for this lack of relevant data was the general practice of institutionalizing children with DS at very young ages, often directly following birth. These unnatural, and in most situations quite impoverished, environments made comparisons of cognitive ability with nonhandicapped children raised in family environments difficult and generated results of questionable merit. Deficits seen in these studies could be

attributed to the effects of poor environment as well as to the genetic flaw in DS. Adherence to home and community-based rearing have greatly increased the validity of more recent research on individuals with DS, and have begun to alter our understanding of their cognitive capacities. Of particular importance has been research reporting qualitative differences between DS and normally-developing individuals, as well as quantitative impairments of general cognitive function.

The Multiple Systems Approach to Cognition

While there is little evidence from the study of DS for the existence of the multiple cognitive systems previously mentioned, considerable evidence from other areas of cognitive science provides support for a multiple systems theory of cognition. As briefly mentioned previously, one approach, involving the nature of learning and memory, argues for the existence of multiple memory systems. Memory, defined as the capacity for acquiring, storing, and retrieving information about our experiences and the consequences of our behavior, allows us to make use of experiences in that we can use it to recognize familiar objects and events, to predict events, return to positive locations while avoiding negative places; but it also allows us to acquire skills, habits or procedures.

Recent investigators have identified at least two classes of memory. Each class consists of different modules with each module implicated in the processing and storage of different forms of information and (see Schacter, 1987; Squire, 1987; Tulving, 1985). It has also been proposed that different types of memory are dependent on the functioning of different neural systems (Mishkin, 1982; O'Keefe and Nadel, 1978; Squire, 1987). While investigators disagree as to how different mnemonic functions should be classified and described, memory for events and the effects of those events are usually classified as one type of memory and the acquisition of what has been referred to as implicit skills, habits, or procedural information is classified as another (Mishkin, Malamut, and Bachevalier, 1984; O'Keefe and Nadel, 1978; Squire, 1982). This position is supported by studies of human amnesics as well as results reported from studies of various animal models of human amnesia. This research has shown that the two forms of memory can be dissociated through selective lesions of neural structures (Mishkin, Malamut, and Bachevalier, 1984; O'Keefe and Nadel, 1978; Schacter, 1987; Squire, 1987; Zola-Morgan and Squire, 1985). Bilateral removal of the medial temporal lobes in humans, including the HF causes what appears initially to be global and profound amnesia (Scoville and Milner, 1957). Further study of the behavioral effects of these lesions demonstrates that the

memory deficits are more circumscribed as they appear to only be related to deficits in explicit or declarative memory. Deficits included the inability to remember events, their location, and facts acquired during the events, but not skills, procedures, and other implicit forms of knowledge (Corkin, 1965; Cohen and Squire, 1980; Schacter, 1987). Thus, amnesic patients showed minimal deficits in implicit or procedural memory, maintaining the ability to learn and retain complex skills, but showed severe deficits in explicit or declaratory memory being unable to acquire information about events and the context in which events occur.

Development of Multiple Cognitive Systems

The emergence of the multiple systems model of cognition is paralleled by current theories of cognitive development which challenge the traditional Piagettian theory. Piaget and proponents of his theory contend that cognitive development involves a series of systematic reorganizations of cognition which occur from interactions between individuals and their environment. This theoretical position identifies two basic charactertistics of cognition and cognitive development: 1) there is a unitary cognitive system; and 2) the development of this single system is discontinuous, the system developing through stages of reorganization such that each stage of development produces

a cognitive system that is qualitatively and quantitatively different than previous stages (see Piaget, 1952; 1954; 1970).

Opposing theorists dispute both these contentions. They contend that cognitive development is characterized by the continuous development of a cognitive system made up of multiple cognitive domains, and while there exist general learning principles (or constraints on how knowledge is acquired) common to all domains, there also exist constraints on the acquisition of knowledge which are specific to each domain (e.g. Keil, 1981, 1988). Critical to the continuous development theories are findings indicating that when task requirements are quantitatively reduced, children are able to perform cognitive tasks at ages significantly before Piagettian theory proposes. Recent research in normal human cognitive development has provided data which more accurately describe the changes in cognition that occur during early development. This has been accomplished by reducing the response requirements of the tasks so as to reduce the possibility that an apparent lack of ability being the result of physical rather than cognitive deficits. Examples include Rovee-Collier, Paterson, and Hayne's (1985) work that challenges previous literature describing infants as having poor memory skills, Gelman's (1982) work demonstrating that infants have a more sophisticated concept of numerosity than

previously reported, and Gibson & Spelke's (1983) work suggesting that the development of visual perception is well advanced during early infancy.

These results have been interpreted as evidence that: 1) Piaget's stages of development are an artifact of the difficulty of his tasks and not an indication of the nature of childrens' cognitive system, and 2) the appearance of early cognitive abilities is indicative of a continuous increase in, or an elaboration of, pre-existing and perhaps innate abilities specific to different cognitive domains.

Cognitive Development in DS

Investigation of cognitive development in individuals with DS has provided evidence supporting the concept that the cognitive deficits seen in infants with DS involves more than a general slowness to develop. Thompson et al. (1984) have reported differences in affective behavior development, Jones (1976) has reported finding differences in the development of communication skills, and Morss (1983, 1985) has reported differences, as well as delays, in learning a series of object permanence tasks. Morss concluded from the analysis of error patterns and strategies observed in DS subjects in his longitudinal study of learning in six tasks that infants with DS not only learn object permanence tasks more slowly; they learned the tasks "differently". He postulated that

perhaps the general mental retardation seen in DS is a secondary effect of differences in development of specific cognitive skills. These findings of differences in cognitive development are similar to the aforementioned findings of selective differences in neurological development in that they suggest that development in DS is different than normal rather than merely slow.

As discussed earlier, evidence consistent with a early disruption of neurogenesis and synaptogenesis in DS has been reported in areas of visual cortex, motor cortex, the cerebellum, the HF, and the entorhinal cortex. Can specific cognitive deficits be identified in the infant with DS that are consistent with abnormal development of these neuroanatomical structures? Some support for such a relationship has been provided by investigators studying differences in visual perception and skills requiring sensorimotor integration. Stratford (1979; 1980) and Stratford and Metcalfe (1981) reported differences in the development of visual perceptual skills presumably related to differences in neurophysiologic function of the visual cortex, and studies of sensorimotor abilities have reported deficits consistent with differences found in the development of the cerebellum and motor cortex (e.g.: Frith and Frith, 1974; Anwar,1981 and 1981b; Kerr and Blais, 1985).

These data appear to support the existence of specific differences in cognitive development correlated with the differences in neural development observed to accompany DS. Three important caveats need to be kept in mind, however, when attempting to describe the cognitive abilities and inabilities of children in general, and, to an even greater extent, when attempting to compare cognitive abilities of children with DS to those of nonhandicapped children.

The first caveat concerns the general problem of determining whether differences in task performance between very young children of different ages are the result of differences in cognitive abilities or physical abilities. Cognitive development during the first two postnatal years occurs at an accelerated rate when compared to development during later periods of development. During this period of rapid development, physical development is proceeding at such an accelerated rate that tasks designed to measure the development of cognitive skills at one age may not be viable at another age because of the physical limitations of younger children. This period of rapid physical development includes the rapid growth and maturation of the human central nervous system that occurs prenatally or within the first few postnatal years. This accelerated rate of development, and the nature of the question being addressed, necessitate the

use of cognitive tasks on which successful performance is dependent on the maturation of specific brain areas, but at the same time is independent of physical differences between the age groups being studied.

The second caveat involves the extreme diversity in the abilities of DS children; this is not usually found in normal children or in children with other mental handicaps of known etiology. Individuals with DS may function at near normal levels of cognitive ability or may be severely mentally handicapped (Melyn and White, 1973; Morgan, 1979). This variability in functioning includes the wide variation in age at which these children reach different developmental milestones. While the mean ages at which DS children reach developmental milestones such as walking unassisted, being toilet trained, speaking single words, and speaking phrases and sentences are later than that of nonhandicapped peers, some children with DS actually reach these milestones weeks or months earlier than their nonhandicapped peers. Thus the age range for reaching these milestones extends beyond both extremes of the normal range of development (Melyn and White, 1973).

The third caveat is specific to testing children with mental retardation in general and children with DS in particular. It has recently been shown that the cognitive ability of these children may be underestimated because the

tests include measurement procedures which do not accurately reflect cognitive ability. Wishart (1987) and Wishart and Duffy (1990) have proposed that earlier studies have underestimated the cognitive abilities of children through the use of single session testing and the use tests validated on much younger (mental age matched controls) nonretarded children. In the earlier study, children 3 to 5 years of age with DS showed increased ability on three Piagetian infant search tasks over multiple testing sessions. Due to the nature of the tasks, these increases were unlikely to be a result of new learning. It was also shown that while the DS children did not perform as well as chronologically age matched controls, the older nonhandicapped children also made errors on the tasks. These are tasks that infants less than 2 years of age find easy. If nonhandicapped children make errors on infant tests, then it is quite probable that factors other than slow cognitive development may partially explain poor performance of DS children on these type of tests (Wishart, 1987). In the second study, children six-months to five years were tested on four Piagettian tasks previously established as forming a developmental hierarchy. A child who could perform task three would be expected to successfully perform tasks one and two, but may not be able to perform task four, while a child who performed task four would be expected to successfully perform all tasks. The

performance of the DS children did not follow this hierarchical pattern. First the children's performance showed instability; the children would correctly perform the task during one session and fail during another. Second, many of the older children successfully performed task 3 while failing to perform tasks 1 and 2, tasks on which considerably younger children were successful during at least one of two testing sessions. The authors concluded that the characteristic pattern of cognitive deficits seen in DS is possibly the result of a variety of factors including the motivation to perform and deficits in the consolidation of learning rather than the result of a general delay of development (Wishart and Duffy, 1990).

In order to identify the nature of the relationship between the development of cognitive deficits and the neuroanatomical abnormalities seen in DS , it is necessary that the above factors be accounted for in the experimental design. Experimental tasks utilized to measure specific cognitive abilities have to be designed such that differences in performance on the tasks are the result of the cognitive ability under consideration and not the result of differences in motivation, physical abilities, or other extraneous factors.

Psychobiological Approaches to Cognitive Development

Investigators interested in the process of cognitive development in human infants have provided new insights into the increased competency of infants and young children largely through the reduction of task requirements of existing experimental paradigms. The use of these new tasks has illustrated the extensive qualitative, as well as quantitative, development that occurs at these ages. Few of these studies have attempted to identify changes in the neural systems which may underlie early cognitive development. While these redesigned tasks have been simplified and the task requirements reduced, they remain either too complex to attribute change in performance to maturation of specific neural structures, or involve cognitive processes for which the underlying neural underpinnings are unknown. A different approach to understanding human development, that taken by developmental psychobiologists, directly addresses the nature of the relationship between cognitive development and neural development of humans by measuring changes in cognitive abilities for which the underlying neural systems have been substantially identified.

The Development of Spatial Memory

The development of the ability to perform three different types of what the animal literature has generally referred to as "spatial memory" tasks has received extensive investigation. This has occurred because the ability to perform each type of task has been shown to depend upon the function of different neural systems. Successful performance on these three tasks depends upon three different mnemonic abilities. Response learning involves memory for the location of a reward by associating the location with a particular motor response. Cue learning that involves the association of a location with a specific cue or landmark. Place learning involves memory for the spatial relationship between the reward location and multiple cues in the environment.

The advantage of these three tasks is that they have been extensively used in memory research and substantial data exists, at least from the study of nonhumans, suggesting that the maturation of specific neural structures underlies successful performance on these spatial memory tasks. Additionally, the different periods of maturation of these neural structures is also correlated with differences in the ontogeny of these spatial memory abilities.

A major problem with this psychobiological approach to human memory development has been the differences in

experimental paradigms and terminology used in nonhuman and human development research. These differences have made comparisons between the study of spatial memory in animals and what has been referred to in the human development literature as "spatial knowledge" somewhat difficult. Nevertheless, these two bodies of literature have produced similar findings. A critical factor in this discussion is the contrast between behaviors identified which require spatial knowledge and those which do not. Spatial knowledge involves the memory of spatial relationships between objects and the deduction of new spatial relationships between these objects, a definition consistent with what the animal literature frequently refers to as place learning. "Spatial" behaviors not requiring place knowledge include navigation toward a cue or single landmark, described as cue learning in animal studies, and navigation dependent upon the memory of a specific and successful motor response, previously described as response learning in animal studies (Landau and Spelke, 1984). Another common finding in these two bodies of literature is that the ontogeny of these different kinds of memory and the development of their underlying neural systems in humans and nonhumans is similar. Both human and nonhuman infants can perform tasks not requiring place knowledge comparatively early, prior to twelve months of age in humans, while behaviors employing place knowledge appear to develop

later, perhaps as late as twenty-four months of age in humans. Likewise, the development of the underlying neural systems have been shown to have a similar timetable.

Ontogeny of Spatial Memory and Neural Development

Thus far, this discussion has emphasized the existence of neural systems and structures underlying different cognitive functions. This emphasis is not meant to imply that these cognitive functions are entirely localized to a particular brain structure, or that neural systems are so different as to preclude the sharing of neural components. What is implied by the use of the term "different" is that different combinations of brain structures and their connections comprise the different neural systems and that these systems develop at different times. With this in mind, this discussion will focus on the roles that the development and function of four different areas of the brain - regions of the prefrontal cortex, neostriatum, inferior temporal cortex, and medial temporal cortex - play in each of the three types of spatial memory function. Furthermore, it will be shown that the late development of place learning is the result of extensive postnatal development within a corticolimbic system that includes the HF, a structure not part of the corticostriatal systems underlying the other two types of memory.

Development of Response Learning

At its simplest level, a response learning task that requires an organism to learn that a specific motor response will locate a goal requires a minimum of two mnemonic abilities; first the organism must remember that a reinforcing event, a reward, is associated with a goal. This goal could be an end of a maze arm, an underwater platform, a cover over a food well, or a box. Secondly the organism must maintain a memory for the response that resulted in the successful reaching of the goal.

The first mnemonic ability is necessary for all three of the spatial memory tasks and most likely develops shortly after birth. Infants quickly learn to associate reward events with particular behaviors, objects, or people (Piaget and Inhelder, 1969). The development of the second ability - associating the location where a reward can be found with a learned response - has been extensively studied in humans and nonhumans using a wide variety of experimental paradigms. While all of these paradigms require response learning, they differ greatly in task complexity and the age at which they first appear. Nonspatial response learning, for example learning that kicking one's foot will make a mobile move, appears within two or three months of birth (Rovee-Collier et al, 1985). Response learning that involves a spatial component, such as learning to move or reach in a

specific egocentric direction, on the other hand, has been shown to appear later in the first postnatal year.

Piaget (1936/54) first proposed that the use of response strategies by infants explains the A-not B error shown by infants less than twelve months of age. The A-not B error is a consistent error that infants less than twelve months of age make on a special version of the delayed response (DR) task. In this task, infants are shown an object being hidden under one of two identical covers, their vision is occluded briefly, and they are asked to retrieve the object from under the cover. After a series of trials where the object is always hidden under the same cover, the object is placed under the other cover with the infant watching, the infant's vision is briefly occluded, and the infant is then asked to retrieve it. Most infants will search under the cover that was first used instead of under the cover where they saw the object hidden. Piaget suggested two reasons for this error. The first was the lack of a concept of object permanence when an object is out of sight, and the second was the infants' egocentric notion of space, the location of the object being recorded in terms of the infants movements.

The first proposed explanation for the A-not B error has been successfully challenged by the findings that under many circumstances infants demonstrate a knowledge of object

permanence (e. g., Ramsey and Campos, 1978). The second explanation still appears to be relevant. Analysis of the errors made by infants at nine months of age on a version of the task where the infant or the testing table was rotated 180 degrees after the infant is shown the object being hidden, indicated that the infants' errors were due to response perseveration. They remembered and continued to perform the response that had previously been successful (Bremner, 1978; Bremner and Bryant, 1977). Diamond (1991) reported similar findings when human infants were tested longitudinally on DR tasks between the ages of seven and a half and twelve months. The younger infants appeared to have better memory for a response that resulted in a successful retrieval of a toy than for the memory of where they saw the toy being hidden. When the location where the toy was hidden changed so that retrieval required a new response, the younger children still tended to reach to the previously rewarded location. This occurred even with a two week interval between testing sessions. As the infants became older, they were able to successfully perform the tasks at progressively longer delays. Apparently, they became better at deciding which type of memory should be used to successfully retrieve the toy.

The preponderance of evidence indicates that the ability to perform simple DR tasks with short delays begins

between seven and eight months of age. This ability becomes progressively more sophisticated until twelve months of age, at which time the characteristic errors associated with response perseveration rarely occur even with lengthy delays.

The performance of nonhuman primates on the A-not B and other versions of DR tasks following different brain lesions has identified two extensively interconnected brain structures whose maturation underlies increased ability to perform these DR tasks. Adult monkeys with lesions limited to the dorsolateral area of the prefrontal cortex (figure 2) are impaired on the Piagetian A-not B tasks and other DR tasks. Monkeys with these lesions, but not with lesions of inferior temporal cortex or HF, like human infants, continued to search in the previously rewarded place on the A-not B task and made numerous errors on DR tasks despite seeing a food reward hidden (Bachevalier and Mishkin, 1984; Diamond and Goldman-Rakic, 1989).

Deficits in performance, similar to those observed with the prefrontal lesions, on comparable DR tasks have also been reported after lesions in areas of the neostriatum, (figure 2) particularly if specific parts of the head of the caudate nucleus are involved (O'Berg and Divac, 1979; Rolls and Williams, 1987). This pattern of behavioral deficits and the extensive reciprocal connections between these two brain areas implicate both structures in a response learning

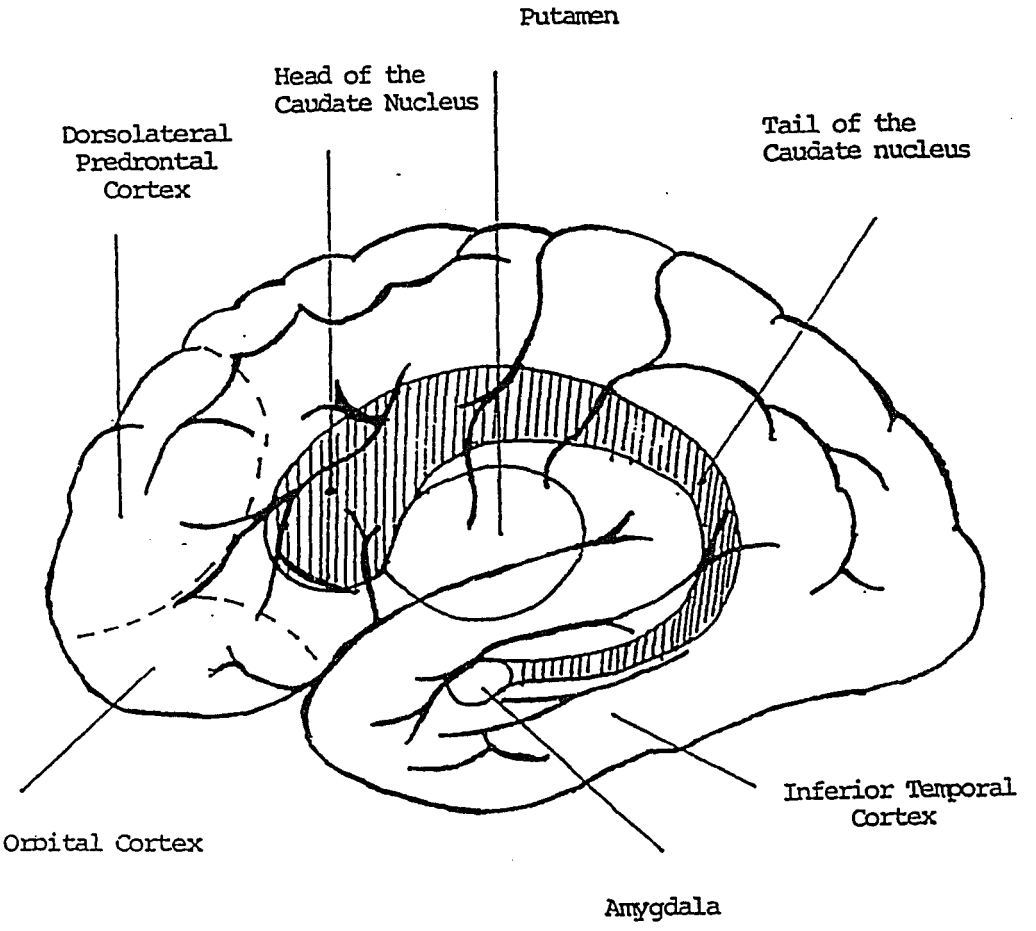


Figure 2. Location of caudate nucleus (head and tail), amygdala, dorsolateral and orbital areas of prefrontal cortex, and inferior temporal cortex in the human brain.

system.

The functional relationship between the two is less clear. One possibility is that the maturation of the prefrontal cortex and it's connections with neostriatum results in an elaboration of an earlier existing neostriatal system. This hierarchical relationship is supported, neuroanatomically, by evidence that the caudate nucleus reaches all neurological developmental markers including adult levels of synaptic density earlier than the prefrontal cortex (Brand and Rakic, 1984). Behaviorally, this relationship is suggested by an increase in the ability to perform more complex tasks with longer delays in close correlation with the maturation of the prefrontal cortex. When tested prior to normal prefrontal maturation, neither intact infant monkeys nor infant monkeys with prefrontal lesions are impaired in performing simple DR tasks with two second delays; tasks on which adults with prefrontal lesions are impaired (Alexander and Goldman, 1978, Goldman, 1971). Thus the learning of DR tasks with short delays does not rely on a mature prefrontal cortex.

The importance of prefrontal maturation has been demonstrated in more recent studies. Infant monkeys with lesions to dorsolateral prefrontal cortex made prior to maturation of the prefrontal cortex showed learning deficits when tested at four and a half to six months of age. These

deficits occurred on the more difficult A-not B task, even with two second delays, and on other DR tasks with delays of five to ten seconds (Diamond and Goldman-Rakic, 1989).

The above neuroanatomical and behavioral data from both human and animal studies supports the ability of human infants less than one year of age to locate a hidden object by utilizing a learned response. It also appears evident that the ability to perform tasks with increasing complexity and delays is associated with the maturation of a corticostriatal neural system that includes the dorsolateral area of the prefrontal cortex and areas within the head of the caudate nucleus. This ability does not appear related to the maturation of the late developing structures within the corticolimbic system, structures making up the HF (Diamond and Goldman-Rakic, 1989).

Development of Cue Learning

Cue learning by human infants less than twelve months of age has been demonstrated by experimental paradigms involving spatial orienting skills. During these tasks, the infant is either placed in the center of the room and taught to anticipate the occurrence of a repeated event by looking at the location in which the event will occur, or placed at a table and shown a toy being hidden in a covered well. The

infant is then turned to face in a different direction or moved to the opposite side of the table so that use of a response strategy will lead to search errors. The general findings of the orienting studies has been that infants, as young as six months, could accurately anticipate the location of the event if a highly salient and contiguous landmark made the location distinctly different from other possible targets. In the absence of such a landmark, infants could also successfully perform the task if a previously learned response continued to be a correct response (Acredolo, 1978; McKenzie et al, 1984; Rieser, 1979). Acredolo (1988) has proposed that the use of a salient landmark is not based upon the use of spatial relationships between a landmark and an event, but is based upon associating the location of an event with a landmark. The ability to "appreciate" the spatial relationships between a landmark and an event when they are not contiguous begins to develop later, between nine and thirteen months (Acredolo, 1988). In studies where infants saw a toy hidden, were moved to a new location, and then permitted to search for the toy, it has been shown that when the well covers were different colors and the location of the toy was associated with one color cover and not the other, infants eight or nine months of age produced fewer reponse perseveration errors (Bremner, 1978; Goldfield and Dickerson, 1982).

The age at which infants can perform cue learning tasks and the neural system underlying this performance on different tasks depends upon the complexity of the task requirements. Those tasks that require only the learning of an association between a single cue and a goal appear early. This variation has been frequently used with humans as well as nonhumans and usually involves an environment where only one cue is available to the subject (e. g. Acredolo, 1978; Carew and Rudy, 1988; Parker and Walley, 1989).

A second and later developing ability involves the learning of a visual discrimination. Instead of merely learning a simple association between goal and cue, the subject is also required to discriminate which one of at least two cues is associated with the goal. The neural system that underlies visual discrimination learning has been extensively studied in nonhuman primates. Lesions of three interconnected brain regions or of their connections in adult animals have resulted in visual discrimination deficits, implicating these structures in a corticostriatal visual memory system. This system appears to include parts of the inferior temporal lobes (Brown, Rosvolt, and Mishkin, 1963; Mishkin, 1982), parts of the tail of the caudate nucleus (Divac, Rosvold, and Szwarebart, 1967; Oberg and Divac, 1978), and orbital cortex in the prefrontal lobes (Voytko, 1985)(figure 2). Since lesions to the HF do not result in

similar deficits and infant animals demonstrate competency on these tasks prior to HF maturity, the HF does not appear to have a role within this system.

A logical conclusion from the behavioral and neuroantomical data presented above is that the early maturation of two neural systems underlie the comparatively early competence shown by infants on cue learning and response learning tasks. The question now becomes whether the third spatial memory ability is later to develop and is correlated with the late development of a third neural system.

Development of Place Learning

Place learning, requiring spatial knowledge (Landau and Spelke, 1984) or cognitive mapping skills (O'Keefe and Nadel, 1978), is much more complex than either cue or response learning. While it still requires that an association be remembered between a location and a reinforcing event, place learning requires remembering the location of the event in terms of the spatial relationships between the event location and the array of cues in the environment. This is opposed to the simple acquisition of an association between the location of a reinforcing event with a particular cue or associating the location with a learned motor program. Place learning can occur when no single cue

or response is sufficient to locate the event, but to do this requires the integration of different cognitive abilities. While place learning has been shown to be multimodal and not limited to visual memory ability, spatial knowledge has been reported with blind children and animals, most studies have used visual tasks on which the use of visual information dominates other sensory information. An analysis of these visual tasks requiring place learning identifies two important aspects of place learning not evident in the other types of memory. First is the need for a sophisticated visual recognition system. An individual needs to be able to remember objects that it has seen. Second is the need to be able to perceive the spatial relationships between the goal location and environmental cues. That this form of memory develops later than the other two is supported by studies of children's search behavior and the performance of nonhuman subjects on different spatial tasks.

DeLoache and Brown (1983) compared the search behavior of different aged children in a large familiar environment and determined that children less than twenty-six months of age required a landmark that was directly linked to the target location to be successful. During each trial, the child watched a toy being hidden in one of four identical boxes placed in the center of a room of their home, they were then removed from the room, and then returned after a delay

and asked to find the toy. The hiding place of the toy changed on each trial. Children in the twenty-two to twenty-four month group performed at chance levels unless a salient landmark served as a contiguous cue. Similar results were reported when children were tested using variations of the eight-arm maze. Children at twenty-four months of age performed at chance levels and only children at forty-eight months were able to perform at adult levels. These data suggest that the ability to employ place strategies develops well after twenty-four but prior to forty-eight months of age (Aadland, Beatty, and Maki, 1985; Foreman, Arber, and Savage, 1984). While the above studies are supportive of late development of this type of spatial memory, they indicate that its development is later than predicted by the HF maturation theory of Nadel and Zola-Morgan (1984). The lack of performance by the children may have been a result of the sizable memory load required by the tasks, or of the large amount of visual information that the children had to process during the single brief exposure to the target.

In a recent study, it was found that when the memory load is reduced from eight places to only one place and children were given additional opportunities to learn the location of the toy through multiple searches, children at twenty-four months of age were successful on spatial memory tasks requiring place knowledge (Mangan and Nadel, 1989). To

determine when prior to twenty-four months this spatial memory ability develops, groups of children fourteen to sixteen months of age and twenty-four to twenty-six months of age were tested on two spatial tasks. The first task required that children locate a toy hidden in one of eight identical boxes arranged in a circle within a familiar room. Each possible target had one or more proximal cues. In the second task, children were tested on a circular platform with eight holes cut near the edge. A white curtain two and a half feet tall was built around the platform to occlude all proximal cues. The closest cue visible from within the testing apparatus was approximately fifteen feet away. The children were required to search for a toy hidden in one of the holes. For each child, the toy was always hidden in the same location. Both experimental tasks involved visuospatial perception and spatial memory components. During the learning trials, each child had their vision briefly occluded while the toy was hidden. They remained in the testing area between trials. Trials continued until they located the toy on the first try on two consecutive trials.

During a "memory probe", the child saw the toy being hidden in the same place and was then removed from the test area for one and a half minutes. The toy was removed, and the child was returned to the test area to look for it. The first two places searched were recorded. All the children

were able to learn both the proximal and the distal cue tasks when no memory ability was required, and performance in the task requiring memory for a proximal cue did not differ between groups. Both groups reliably limited their search to the correct location.

In the memory task that required memory for the targets relationship with distal cues, a difference was found between groups during the memory probe. The older children's performance was similar to their performance on the proximal condition; they were quite successful in locating the target where the toy should have been. The younger childrens' performance, however, fell to chance levels. While they limited their search to the correct side of the platform, they appeared unable to make any further discrimination about the correct location. These results suggest that the younger children were not able to remember the spatial layout of the environment, and were not employing a place strategy. Their ability to limit search to the correct side of the platform suggests that they could have been using a single cue or a scene, which defined the correct side, but could not use the spatial relationships of the cues to determine which of four choices on that side was correct (Mangan and Nadel, 1990).

While these data are consistent with the late development of cognitive mapping or place learning, they do not elucidate the specific maturational changes in the brains

of the subjects which occurred at these ages. Noninvasive techniques for measuring the kinds of maturational changes being proposed are not currently available.

Lesion, developmental, and neurophysiological studies of nonhuman subjects on tasks requiring place learning have produced similar evidence of a relatively late shift to place learning. These studies have also identified a putative corticolimbic system as the neural basis for this cognitive ability.

Ungerleider and Mishkin (1982) have argued for two parallel visual pathways that process two types of information required for place learning, object recognition and visuospatial perception. They propose the existence of an "occipitotemporal" pathway made up of connections between occipital cortex and temporal cortex and an "occipito-parietal" pathway, consisting of interconnections between different areas of occipital cortex and posterior areas of the parietal lobes. The occipitotemporal pathway performs a specialized role in various visual discrimination abilities such as pattern detection and object recognition while the occipitoparietal pathway is critical for the perception of spatial relationships of objects in the environment (figure 3).

The dissociation of the two functions of these pathways has been supported by lesion studies of inferior

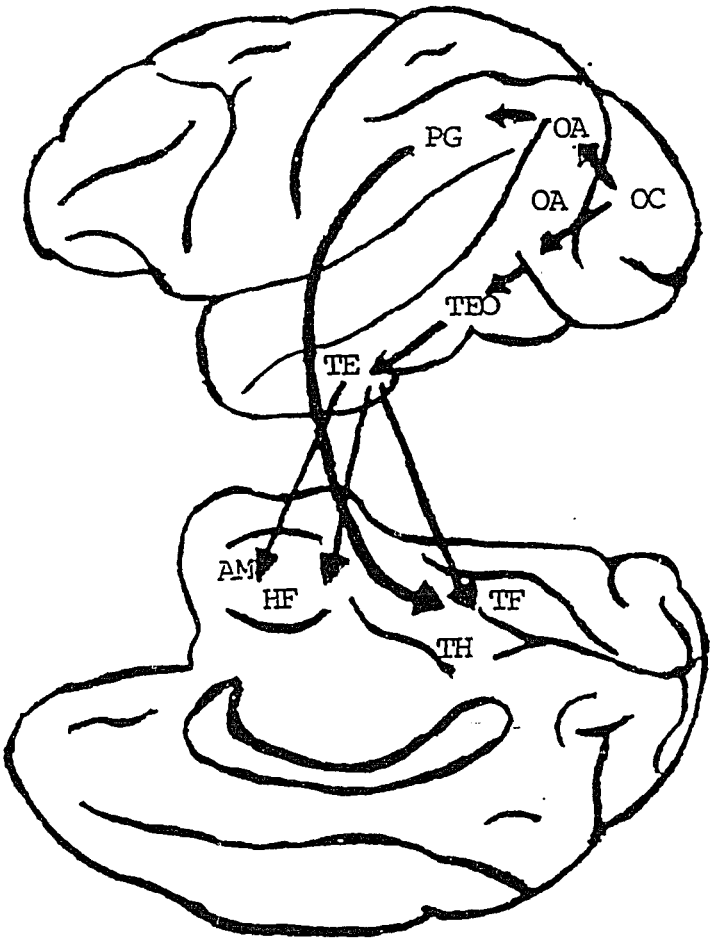


Figure 3. The left hemisphere of a rhesus monkey showing the occipitotemporal pathway that underlies object recognition memory (OC - OA - TEO - TE - HF and AMG) and the occitoparietal pathway that underlies memory for spatial relationship between objects (OC - OA - PG - TF, TH - HF). OC and OC - areas of occipital cortex; TEO and TE - areas of inferior temporal cortex; Pg - posterior parietal cortex; TF and TH - areas of the medial temporal cortex; and HF - hippocampal formation; AMG - amygdala.

parietal cortex or inferior temporal cortex. Lesions limited to inferior temporal cortex consistently produce visual discrimination and object recognition deficits in humans and nonhuman primates (see Mishkin, 1982; Mishkin, Ungerleider, and Macko, 1983 for reviews). Lesions limited to the inferior parietal cortex of humans or to the posterior parietal cortex in other primates produce deficits in various aspects of visuospatial perception. Reported deficits from lesions in human subjects include an inability to attend to stimuli in the visual field contralateral to the lesion (Pierrot-Deseilligny, Gray, and Brunet, 1986), a decrease in visually guided reaching or pointing ability (Mountcastle et al, 1984), a reduced ability to accurately perceive relative size and/or distances of objects in space, disruption of the ability to use maps or follow routes, and deficits in memory formation and maintenance of previously formed memories (Andersen, 1987). The more precise lesions of posterior parietal cortex performed on monkeys produce visuospatial perception deficits comparable to those seen in humans. Pohl (1973) and Mishkin, Lewis, and Ungerleider (1982) for example demonstrated that lesions of PPC produced severe deficits in the ability of monkeys to perform spatial, but not object discrimination tasks. Petrides and Iverson (1979) reported deficits in route following, and a number of researchers have

reported contralateral visual field neglect similar to that seen after lesions of the IPL in humans (Andersen, 1987).

The behavioral and neuroanatomical data presented above provide compelling evidence for the existence of two pathways, each processing different visual information, but provides little information about mechanisms by which the pathways eventually connect. Ungerleider and Mishkin (1982) did not propose a specific location or structure where these pathways converge, but they suggested the HF as a likely candidate. This position is supported by the HF's role in spatial memory and object recognition, and by the extensive connections between the HF, cortex adjacent to the HF, the parahippocampal region, and regions in the inferior parietal and inferior temporal lobes (see van Hoesen, 1982; and Witter et al, 1989 for reviews).

Studies of the HF of nonhumans (e. g. O'Keefe, 1979; O'Keefe and Nadel, 1978) have provided evidence of its importance in learning a number of spatial memory tasks, and its central role in certain forms of spatial cognition. O'Keefe and Nadel (1978) have suggested that the HF mediates the development of "cognitive maps" which among other important functions are assumed to be critical for the storage of knowledge about objects and their location in the environment. In their cognitive map theory of hippocampal function, a theory supported largely by findings from the

study of individual neurons in the rat HF that respond as "place units" and by research involving maze learning of rats, O'Keefe and Nadel (1978) contend that the HF plays a central role in the construction of internal representations or "cognitive maps" of the world. These maps serve as substrates for the development of memory for events, the location of these events, and the recognition of the spatial relationships between locations. Without a functional HF, these maps cannot be constructed and place learning does not occur. This theory is supported by numerous studies in which place cells, in the rat HF are seen to be maximally active when the animal moves in a particular place in an environment (O'Keefe, 1976; O'Keefe and Conway, 1980; O'Keefe and Speakman, 1987). Additional support for this theory is provided by behavioral data showing that animals with HF lesions, unlike intact animals are: (1) unable to use distal cues required during place learning tasks, being able to perform spatial tasks accurately only if a contiguous cue is associated with the goal or a previously learned response will lead to the goal, and (2) fail to reinitiate exploratory behavior when the location of objects in a familiar environment is changed (Means and Douglas, 1970; Morris, 1981; Morris et al, 1982; Okaichi, 1987; O'Keefe and Nadel, 1978; Parker and Whalley, 1988).

Behavioral data from studies of HF development in rodents has generally confirmed the postnatal development of the HF. Rat pups have been shown to undergo a transition in their ability to do place learning at around twenty-one days of age, the same time that the aforementioned neuroanatomical studies reported the HF to reach adult levels of maturation. Animals less than twenty days of age had difficulty locating a hidden platform in a water maze using the relationships among distal cues, but had little difficulty if a proximal cue was present. By twenty days, animals had begun to use distal cues and by twenty-three days they were quite proficient at using them. When compared with the performance of twenty-eight day old rats with delays of twenty-four hours between sessions, however, the twenty-three day rats showed retention deficits (Carew and Rudy, 1988; Rudy, Stadler-Morris, and Albert, 1987). This is indicative of a transition to the use of a place strategy during the latter part of the third postnatal week with the ability to retain spatial information continuing to improve during the fourth postnatal week. The possibility that the late maturation of the granule cells of the dentate gyrus underlies this transition is supported by the negative impact of X-irradiation exposure on the growth of these neurons and in cognitive mapping abilities. By using levels of X-ray exposure that destroy developing neurons but leave mature

neurons intact, Bayer et al (1973) was able to selectively damaged the granule cell layer of the dentate gyrus in infant rats. Behavioral testing of the irradiated animals as adults revealed spatial memory deficits that were attributed to the blocking of normal development of the dentate gyrus. Thus, the pattern of spatial memory development in young rats is similar to that seen in human infants, and this pattern is related to maturation of the HF and more specifically to the maturation of granule cells within the dentate gyrus.

Summary

The preceding discussion draws upon findings from a diverse group of neuroscientific and psychological fields of research to support the hypothesis that an interruption of neural development during the late prenatal period underlies the pattern of cognitive deficits that characterize DS. First, the neuropathology found in DS is consistent with an interruption of development at this time. Postmortem examination of both DS adult and children have revealed that areas of the brain known to undergo extensive postnatal development have reduced numbers of neurons, with the processes of the neurons that are found resembling those of immature neurons. The prenatal period, however, is remarkable for a comparative lack of neuropathology. Second, data was presented suggesting that cognitive development in

DS is different from normal development as opposed to simply being slower than normal, and that the differences in cognitive development are generally consistent with the abnormal neuropathological findings. Cognitive deficits in DS children are found in those cognitive domains subserved by neural systems showing extensive cell loss and other neuronal abnormalities. Finally, it was proposed that recent developmental psychobiological findings, particularly in the development of learning and memory, provide a means by which the level of functioning of different brain structures can be determined using behavioral measures. The major advantage of this approach in studying cognitive development being that performance on the different tasks designed to measure cognitive function is dependent upon the maturation of specific neural systems.

In the present study, three spatial memory tasks modeled after tasks used to measure spatial cognition in nonhumans were adapted for use with young human subjects. The tasks were administered to two groups of children with DS and two age matched normal control groups. The specificity of the neural systems underlying the performance of these tasks and their development permits the evaluation of the hypothesis that: (a) spatial memory deficits are a characteristic of DS, and (b) these spatial memory deficits

are specific to those tasks sensitive to abnormal HF development or HF lesion.

METHODS

Three experimental conditions were designed to determine whether DS children of one and two years of age would perform differently than their age matched nonhandicapped peers on three spatial tasks. One experimental condition required late developing spatial memory skills as defined by cognitive mapping theory and the other two required the two previously described early developing spatial memory skills. The experimental conditions were also designed to determine whether any differences in performance between groups were a result of memory deficits, deficits in prerequisite skills such as visuospatial perception, or differences in noncognitive factors such as motivation.

Subjects

Four groups of subjects participated in this study and were all tested on all three spatial tasks. The first two groups included children with DS, five children age sixteen to twenty months at the beginning of the study and five children age twenty-six to twenty-eight months at the beginning of the study. All DS children were ambulatory although two of the younger subjects ambulated primarily by creeping on their hands and knees (1). The second two groups of children included five age matched nonhandicapped peers

all functioning within normal limits as indicated by scores on the Bayley Scales of Infant Development. These two groups of children were recruited by speaking to parents of children in local preschools or by the parents of the DS children participating in the study and the staff of the preschool were testing was conducted.

Apparatus/Equipment

Testing was conducted at a preschool serving developmentally delayed children and their parents. The children with DS and their parents met for two hours a week with teachers and therapists and also received in-home assistance as well. The preschool was operated by the Arizona Department of Economic Security-Division of Developmental Disabilities.

The same testing apparatus was used for all experimental conditions and was a modification of the hole board apparatus designed by Barnes (1979) to test hippocampal function in rats. The hole board apparatus was designed to take advantage of rats natural preference to avoid bright lights. It consisted of a brightly lit circular platform with holes drilled along the edge of the platform. A variety of objects surrounded the platform to serve as visual cues. One hole led to a dark box while the others were blocked. A typical procedure called for a rat to be released from a box placed in the center of the platform. After a period of

immobility, the rat would explore the platform and find the hole through which it could escape the bright light. The rats learned to go directly to the escape hole presumably by using the cues located around the platform. The "hole board" designed for this study differed from that used with rats (besides the obvious difference in size) in that two sets of holes were cut into the platform. The use of two sets of holes was designed to provide additional information about spatial behavior in these two populations and which is presented in the discussion. The inner circle consisted of four holes, each equidistant from adjacent holes, and two and a half feet from the center of the platform. These holes were the ones in which the childrens' reward was hidden during all experimental conditions.

An outer circle consisting of six holes, each equidistant from adjacent holes, was made eight inches from the edge of the platform. Within each hole was placed a stainless steel bowl in which the reward could be placed. The platform measured twelve feet in diameter and was constructed of three quarter inch particle board covered with carpet devoid of any discernible pattern. Holes in the carpet were cut to match the location of the holes in the platform, but were only two inches in diameter so that an object placed in the holes was not visible to a child unless the child went to the hole to look. The platform was placed

on an outside cement porch such that no visual cues were within five feet of the platform (figure 4). A variety of small toys and/or food were used as the reward for which the children searched. The choice of reward was determined by the preference of the child and varied for each testing session.

Procedure

Testing of the four groups of children was conducted over a six month period with each child being tested in multiple sessions for each of the three experimental conditions if necessary. Testing was completed for each child within a three month period. Testing for each child consisted of a maximum of two testing sessions given on the same day each week. Each child was tested under all three conditions with the order of presentation counterbalanced between subjects. When a child successfully performed under one condition, they shifted to the next condition during the next testing session. If they were unable to correctly perform the task, they were retested on that task during following sessions until they were successful or they had attempted a maximum of six testing sessions, at which time they moved on to the next condition. The location of the reward changed after each session whether the child was successful or not. This was done to reduce the possibility of the child learning the location of the reward over

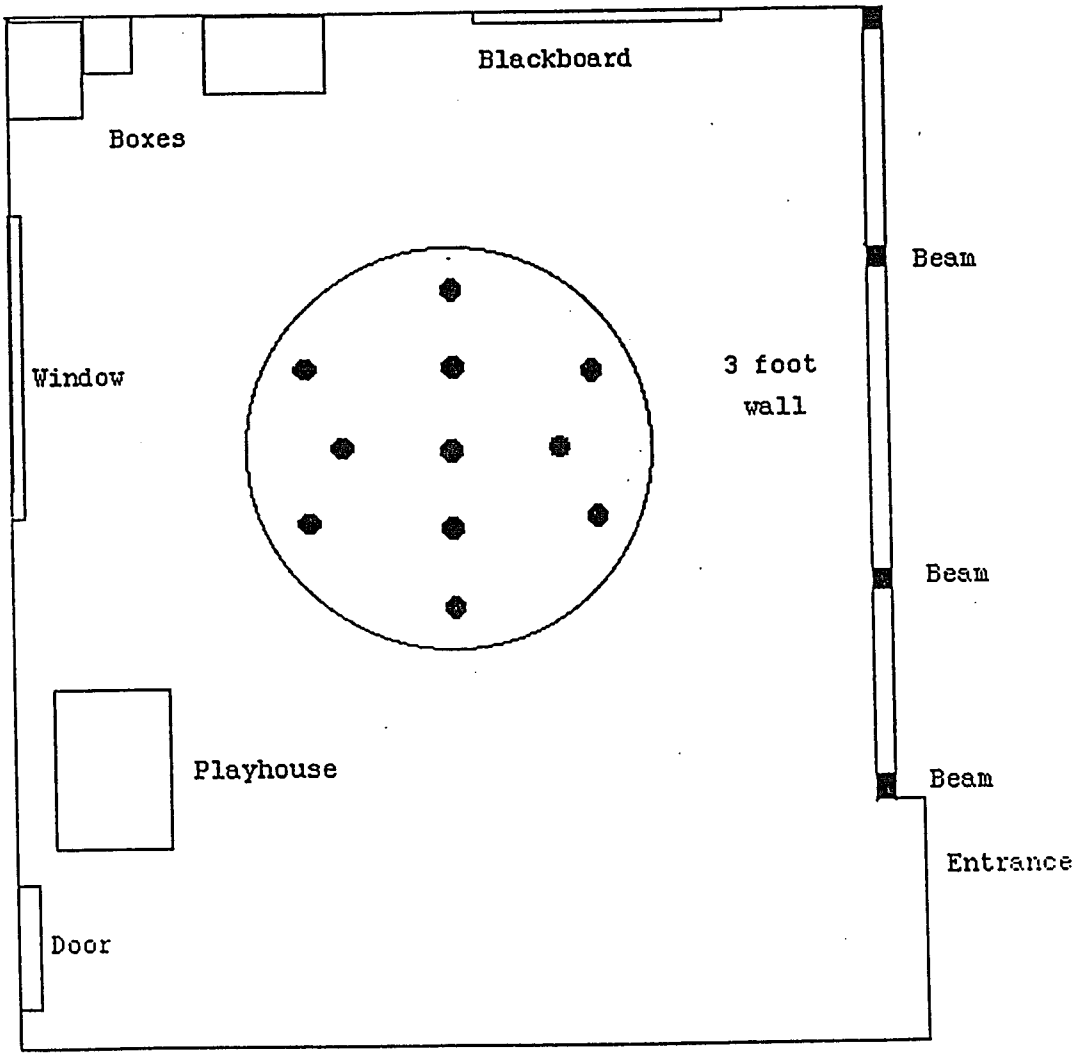


Figure 4. A diagram of the testing environment showing the spatial arrangement of the holes in the platform and the location of cues visible from the platform.

repeated testing sessions.

Testing sessions for all three experimental conditions and all subjects consisted of three parts: a familiarization period, a training period, and a memory probe. The familiarization period enabled the children to become comfortable with the testing apparatus and experience some of the task demands. Each child was shown a toy or piece of cookie or cracker being placed in a hole and then was asked to find it. If the child showed no interest, a different item was used until the child went to the hole and removed the item. This period gave the children experience in searching and identified items that each child found reinforcing. The time required for the familiarization period was greatly decreased during later testing sessions when it was realized that toys were more reinforcing during the first sessions of the day, and food more reinforcing shortly before snack time. The training period began immediately after the familiarization period and a memory probe followed a successful training period for all testing sessions. The procedure employed during the training period differed from the training period normally used with rats in that the procedure frequently used with the hole board designed for rats requires the rat to continue to search until it finds the hole that leads to the box. In this study, it was decided to not require the child to use this

type of a trial and error strategy to locate their reward because it has been shown that DS children do not perform well under these circumstances (Duffy and Wishart, 1987). The children were prevented from experiencing repeated failures by showing them where the reward was hidden after one unsuccessful search. By reducing the number of errors and the length of time between reinforcement, it was felt the DS children would perform better.

Response Learning Condition

The training trials during the response learning condition consisted of a variation of a spatial delayed response task. Each child was shown a reinforcing object being placed in one of the four holes nearest to the center of the platform. With their vision occluded, they were then moved to an area ninety degrees to the left or right of the target hole located just outside the inner circle of holes. The child was then placed facing the center of the platform and walked to the center of the platform facing straight ahead so that turning ninety degrees in one direction would position them to walk to the hidden reward. The child was then asked to search for the reward. The child was praised when it was located (2), and allowed to play with it, or eat it if edible. If the child did not locate the correct hole on the first attempt, they were taken back to the center, turned in the right direction, and shown the correct

location. The reward was always hidden in the same location for each child and the child was always placed in the same location so that the child's turning in the same direction and moving the same distance would succeed in locating the desired object. A different hiding location was chosen for each child. The training trials ended when the child located the reward at the first location searched on two consecutive searches. If the child refused to search for three consecutive trials, the testing session was stopped and a refusal to search was recorded. A refusal to search was defined as no attempt to search for a minimum of ten seconds. The maximum number of training trials permitted during any one testing session was set at ten, however, no child from any group attempted more than eight trials before being successful or quitting.

Upon reaching criterion on the training trials, a memory probe was begun by showing the children the reward being placed in the hole again, removing them from the apparatus, and providing them with a distracting activity for approximately one minute. The child was then returned to the task and asked to search for the reward. To determine whether children exhibited response learning a score of one was assigned for a correct search and a zero for an unsuccessful search. Other data recorded included the number of testing sessions required before successful performance

occurred, and number of trials required to reach criterion during the successful test period.

Cue Learning Condition

The basic procedure in the cue learning condition was the same as in the response learning condition with a few important exceptions. Covers of different colors (purple, blue, and yellow) were placed over each hole. The choice of color for all holes was random with the exception of the cover for the target hole which was different from all the others. Thus the uniqueness of the color served as the cue. The children were also shown the reward being hidden, but were moved to different locations on the platform and asked to search rather than always beginning their search from the same location. The changing the child's starting place made the use of a learned response an ineffective strategy. With these exceptions, the familiarization period, the training period, and memory probe were conducted as reported for the response learning condition. Scoring was also similar in that a 1 was given for a correct search and a 0 for an incorrect search. The number of sessions conducted and the number of trials to criterion during the successful training period was recorded.

Place Learning Condition

The procedure employed during the place learning condition was designed to measure the same spatial abilities in the four groups of children that Barnes (1979) was measuring in rats: the ability to locate a specific place when neither eliciting a learned response or locating a single cue would lead to finding the rewarding location. Successful performance on this task required learning and then memory for the spatial relationship between multiple cues and the rewarded location.

The set up of the apparatus and the procedure during the place learning condition was the same as the response learning condition. The difference between this place learning task and the response learning task and the task used with rats was that the starting positions from where the children began their search were pseudorandomly located on the edge of the platform for each trial instead of always starting from the same place. In the rat studies, the starting point was the center of the platform. This prevented the possibility of a child avoiding using a place learning strategy by learning to locate the reward by remembering that the reward was located in a hole located between them and a single cue outside the apparatus. The children were required to learn where the target was in

relationship to multiple cues in the environment instead of in relationship to themselves or a single cue.

The familiarization and training periods were conducted as reported above for the other learning conditions. The memory probe was done differently. It involved showing the children the reward being hidden in the same hole as during the training trials, taking them from the platform as on the other two tasks, but while they were gone the toy was removed. When returned to the platform, the first two places searched were recorded. A score of 3 was given for a correct search, a two for a search in an adjacent hole, a one for a search in the opposite hole, and a zero for a search in one of the outside holes. The child's final score was the total of the two searches. The score of zero for a search in the outside circle was given because this type of search indicates that the child had not remembered the spatial relationship of the most proximal cues, the spatial arrangement of the holes themselves. As with the previous tasks, the number of sessions and the number of trials to criterion of the successful training period was recorded.

Footnotes

(1) All of the younger group of DS children and their parents had been participating in an early intervention program for at least six months and the older children for at least fourteen months.

(2) Originally a successful search required that the child retrieve the reward from the hole, but because younger subjects were sometimes reluctant to reach in or uncover the hole, what constituted a successful search was expanded to include going over to the correct hole and pointing at it.

RESULTS

Table 1 provides a summary of the results obtained for the four experimental groups under each experimental condition. The results obtained for individual subjects is presented in the Appendix. The spatial delayed response learning, cue learning, and place learning results were subjected to between group analysis. The number of trials to criterion during the training trials preceding a memory test and the number of testing sessions required for a successful memory test were analyzed for each task in order to assess possible differences in learning not evident from performance on the memory probes alone.

Response Learning Condition

All subjects in all four groups were able to successfully locate the rewarded location during the memory probe that followed successful training trials, demonstrating that all groups were able to perform the spatial delayed response task. Differences were observed in the number of trials required to learn the correct response during the training period and in the number of testing sessions required to perform the task successfully. An analysis of variance (2 X 2, age X DS or control) of the number of trials needed on the successful trial period revealed a significant

Table 1

Task performance as a function of group membership and experimental condition

Experimental condition		Group membership			
		DS1	DS2	C1	C2
Response task	Sessions	2.8	1.8	1.2	1.0
	Trials	5.8	4.0	4.6	3.0
Cue task	Sessions	2.8	2.2	1.4	1.2
	Trials	5.4	4.4	4.6	2.8
Place task	Sessions	2.7*	3.4	1.8	1.2
	Trials	7.3*	6.8	7.6	4.0
	Probe	2*	2.6	4.0	5.2

Note. The values represent group means except for probe scores which represent the combned score of both searches during the memory probe.

* Includes data from only the three subjects who were able to successfully perform the place task.

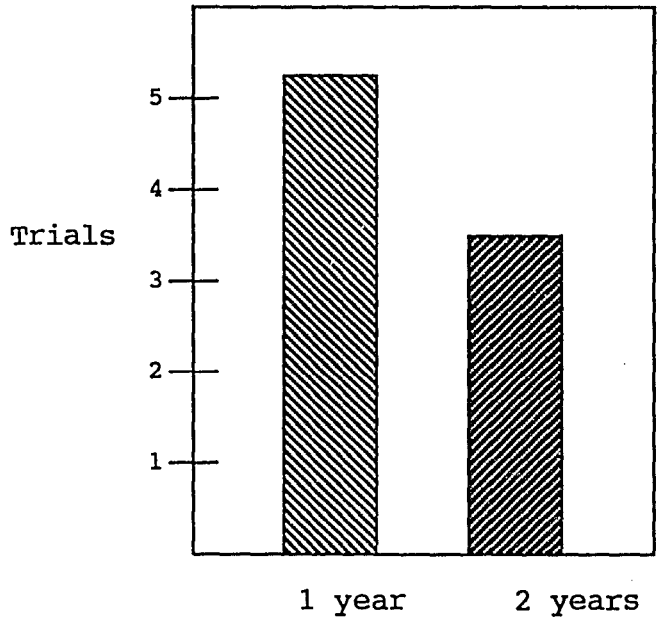
main effect for whether the child had DS or was a member of a control group (F (1, 16) = 9.09; $P < .01$); the DS children required more trials than the age matched controls ($\bar{X}ds = 4.9$; $\bar{X}c = 3.8$). A significant main effect was also revealed for the effects of age (F (1, 16) = 23.27; $P < .001$); the older children required fewer trials than the younger children ($\bar{X}1 = 4.7$; $\bar{X}2 = 3.5$). This indicates that the DS children required more trials than their age matched controls (see figure 5).

A similar ANOVA with number of testing sessions required for successful performance of the task as the dependent measure revealed a significant main effect only for whether the children were DS or control (F (1, 16) = 9.29; $P < .01$). The DS children required more testing sessions than the controls to successfully perform the task ($\bar{X}ds = 2.3$; $\bar{X}c = 1.1$).

Cue Learning Condition

As was the situation with the spatial delayed response, all four groups of children were successful on the cue learning trials required to correctly perform during the training period and in the number of testing sessions required to perform the task successfully. Two similar analysis of variance (2 X 2, age X DS or control) were performed with number of sessions and number of trials in the successful training period as dependent measures.

a. 1 year old vs 2 year old



b. controls vs ds

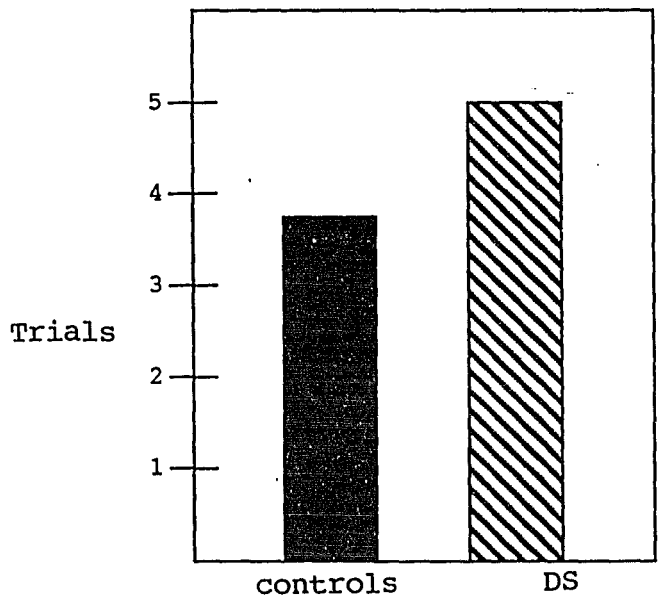


Figure 5. Mean number of trials required during the successful testing session of the response learning task; a) one year old group versus two year old group, b) DS children and normal controls.

The ANOVA of the number of trials revealed a significant interaction ($F(1, 16) = 17.20$; $P < .001$, a main effect for age ($F(1, 16) = 9.53$; $P < .01$) older children requiring fewer trials than younger children ($\bar{X}2 = 3.6$; $\bar{X}1 = 5.0$), and a main effect for DS or control ($F(1, 16) = 7.16$; $P < .05$) the group of children with DS requiring more trials than the control group ($\bar{X}ds = 4.9$; $\bar{X}c = 3.6$). A posthoc pairwise comparison of the group means was made using Tukey's HSD. The test ($HSD = 1.32$, $P < .05$) revealed significant differences between the performance of the older group of control children and the two DS groups indicating that the interaction was largely the result of the ease with which the older control group performed the task ($\bar{X}c2 = 2.8$; $\bar{X}c1 = 4.6$; $\bar{X}ds2 = 4.4$; $\bar{X}ds1 = 5.4$) (see figure 6).

The second ANOVA with the number of testing sessions required for successful performance as the dependent variable revealed a significant effect only for whether the group had DS or was a control group ($F(1, 16) = 9.93$; $P < .01$). The DS subjects required more testing sessions the control subjects ($\bar{X}c = 1.3$; $\bar{X}ds = 2.5$).

Place Learning Condition

The performance of the subjects on the place learning task was different than that on the other two tasks. While all groups were able to learn the cue and response task and accurately perform during a memory probe, two of the younger

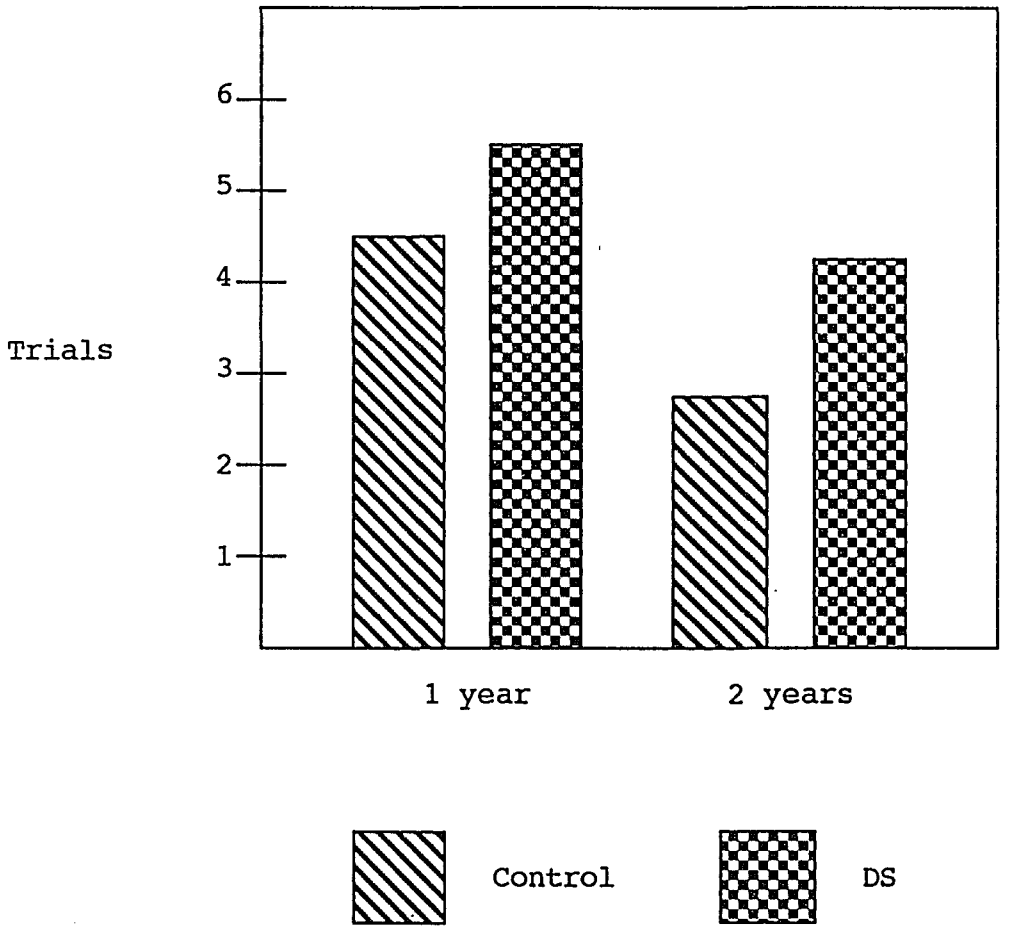


Figure 6. Mean number of trials required by the experimental groups during the successful testing session of the cue learning task showing the interaction between age and DS or control.

DS children could not reach criterion during the training trials over six testing sessions of the place learning task. Whether this failure to reach criterion was the result of a learning deficit or a motivational deficit is difficult to determine. Both subjects were tested during the six sessions, but all sessions ended before they attempted the maximum trials allowed because of their refusal to continue. Whether they could have succeeded on the task if they performed on all possible trials remains speculative.

Analysis of variance (2 X 2 ANOVA, age X DS or control) of performance during the memory probe of those subjects who succeeded during the training period revealed only a significant main effect for DS or control ($F(1, 14) = 23.321$; $P < .001$) the controls performed more accurately than the DS groups ($\bar{X}c = 4.6$; $\bar{X}ds = 2.4$) (see figure 7). The effect of age on performance was not statistically significant probably because of the poor performance of the older DS group. Their performance was similar to the performance of the younger DS group and was poorer than either of the two control groups ($\bar{X}ds2 = 2.6$; $\bar{X}ds1 = 2.0$; $\bar{X}c1 = 4.0$; $\bar{X}c2 = 5.2$). Nor was the effect of any interaction between age and Ds vs control significant. This lack of a significant interaction is not consistent with the prediction that the control children would show increased spatial memory ability with age while the DS childen would not. However,

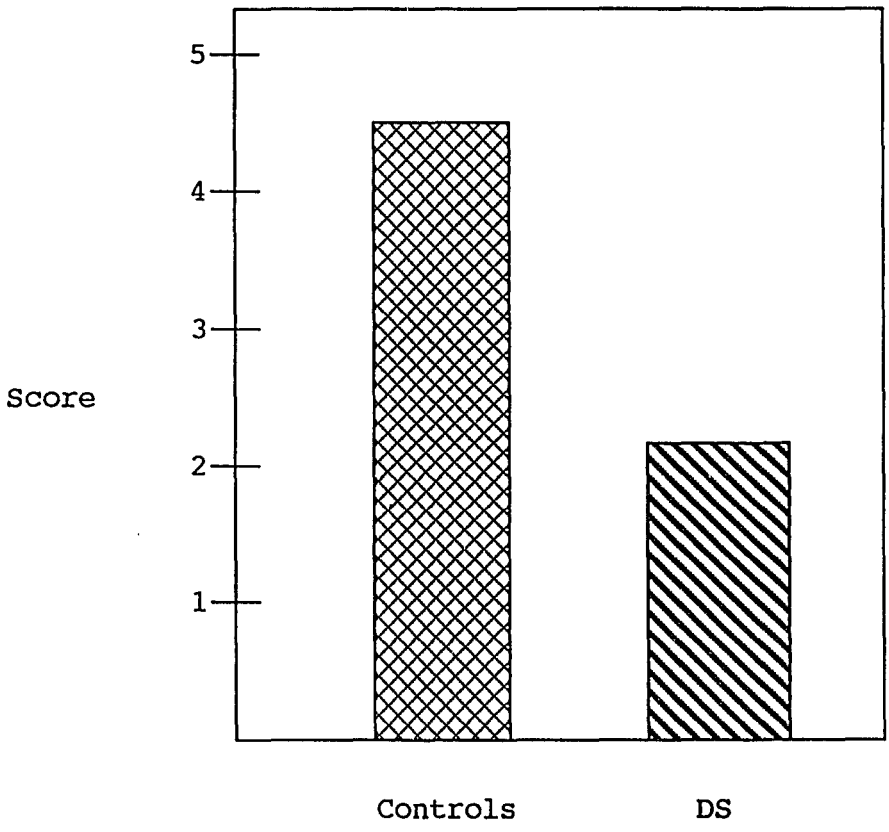


Figure 7. Mean score on the memory probe of the place learning condition showing the difference between the DS children and the normal controls.

the lack of a significant age difference does not support the opposing position that both the DS and normal children demonstrated a similar increase in spatial memory ability as a function of age. Looking at the group means, the lack of a significant interaction most likely resulted from the unexpectedly high scores of the younger control group. Thus, the lack of a significant increase may have been the result of insufficient statistical power, or the result of the younger children, who were approaching two years of age, having an improved ability to remember spatial information. Since only one of the two year old DS children searched in the correct hole on any one of their two searches and three of the five younger control group children searched in the correct hole on one of their two searches, post hoc binomial tests were run to determine whether either of these groups performed above chance levels. The analysis showed that the younger control group performed significantly above chance ($Z = 2.22$; $P < .05$) while the older DS children did not. This supports the latter possibility that the lack of a significant interaction resulted from the improving ability of the younger children. This possiblity is also supported by differences in the search strategies used by the different groups of childrens.

During the memory probe, differences were observe in the search strategy used by the DS children and those used by

the two control groups. Whereas both groups of control subjects, even during inaccurate searches, limited most of their searches to the general area where the target hole was located, the DS children did not. They adopted a trial and error strategy that involved searching the holes closest to their starting point. This was consistent even for DS children who had been previously tested under the cue or response learning conditions, only the inside holes were used in these tasks also. Thus, these children seem unable to remember the basic layout of the platform and that the reward was always in an inside hole. Whether the nonhandicapped children were able to use the previous experience acquired in other experimental conditions is unclear; the small numbers of subjects and small amount of variability in performance preclude statistical analysis. However the possibility that the memory of previous experiences accounted for part of the increased accuracy of the nonhandicapped children cannot be excluded.

DISCUSSION

A common frustration expressed by many parents of DS children who reach three or four years of age is the realization that their children have and will continue to have moderate to severe limitations in cognitive ability. This follows their early optimism based upon the childrens' ability to reach many developmental milestones prior to two years of age. As preschoolers, the gap between their child's development and normal children becomes larger and the parents begin to fully realize that even early intervention and great effort may not eliminate developmental disabilities and may only reduce the magnitude. The results of this study provides one possible reason for this series of events.

Cognitive development in DS: Slow or different?

The major findings of this study are: (1) DS children were slower than age matched nonhandicapped children in that they required more trials and/or testing sessions to learn all three tasks; and (2) the DS children demonstrated memory abilities which were different from normal children. The DS children performed similarly to the normal children on the memory probes of the response and cue learning tasks while displaying severe deficits during the place learning condition. These findings are consistent with the neuropathology found in the DS brain, and consistent with the

proposed cause of this neuropathology; an interruption of neural development during brain development. The memory deficits shown by the children with DS were specific to the task demanding hippocampal function, supporting the hypothesis that this brain structure, because of its extensive postnatal maturation, is more adversely affected by an early interruption of neural development.

However, the increased difficulty during the acquisition or training trials of all tasks by the DS children indicates that hippocampal dysfunction cannot account for all differences seen between DS children and normal children on these tasks. While all subjects were able to locate a hidden reward using the information acquired during training and maintained during the one minute delay on the response learning and cue learning tasks, differences were observed in the duration of the training period needed to solve the task. The difficulty the children with DS, particularly the younger group, had in learning the tasks, indicated by the significantly larger number of testing sessions (cue learning) or both testing sessions and training trials (response learning) to reach criterion, suggests that since the ability to perform both these tasks normally develops during the latter half of the first postnatal year, the children with DS were slow to develop these abilities. This interpretation is in agreement the conclusions of

earlier studies of DS in which it was reported that older DS children failed to perform as well as mental age matched controls on infant Piagetian object permanence tasks. It is also in agreement with studies showing that the learning of these tasks can be greatly accelerated to nearly normal levels given intense and repetitive training (Pasnak and Pasnak, 1987). Closer analysis of the actual behavior of the children learning the tasks suggests that this conclusion does not present the whole story.

A major difference between the tasks utilized in this study and previous studies of object permanence knowledge in DS is that these tasks were performed in comparatively large space. Instead of being seated in a chair and reaching to displace a cover in order to retrieve a reward, the normal object permanence procedure, the children were required to ambulate a minimum of two and a half feet to obtain the reward. The primary purpose of this change was to more closely approximate tasks used in animal studies and to make the physical demands of the tasks more comparable to those required by the place learning task. It also allowed better differentiation between lack of ability to perform and the lack of motivation to perform. Wishart (1987, 1990) has reported that in the standard object permanence task, the reaching behavior of DS children is sometimes difficult to interpret. In her studies, the children would frequently

reach with a sweeping motion that would dislodge both the cover over the reward and the cover over the nonrewarded location. Under these circumstances, it was difficult to determine whether they did this because they did not know where the reward was, were adopting an easier strategy of locating the reward (uncovering both possible locations at the same time), or simply indicating they no longer wanted to "play the game".

The use of our testing apparatus made the interpretation of their searching behavior less difficult. First, the distance between the holes in the platform prevented children from searching in multiple locations at the same time; and secondly, a differentiation could be made between a search error (looking in the wrong location) and a failure to search. If the child moved toward and looked in the wrong location, a search error was recorded; if the child refused to move toward a hole and look or if the child engaged in a non-task behavior such as attempting to leave, a refusal to search was recorded. Using this information, the need for more trials to reach criterion was most likely the result of finding the task more difficult, perhaps as a result of delayed development as indicated by the older DS children's performance being more like the normal control groups. The reason for the need for more testing sessions is less clear.

The need for more testing sessions by the DS children to learn the tasks was consistent for all three experimental conditions. This did not occur simply because they could not solve the tasks within the maximum number of trials permitted, a result that would be expected if they simply found the tasks difficult. All unsuccessful testing sessions ended as a result of the child's refusal to continue to search, not because they completed all the trials. Since all DS children were eventually successful on the response learning and the cue learning tasks, it is clear that motivational factors affected performance on these tasks. The inability of two of the DS children to learn the place learning task is more difficult to interpret. Whether their lack of performance resulted from a lack of ability or a lack of motivation to learn a task they found difficult cannot be determined from the data. An explanation of the response and cue learning results is that perhaps DS children, in addition to differences in the cognitive abilities being considered here, also differ from normal children in motivational factors, tolerance of frustration, or other factors involving temperament.

Probably the result of an inappropriate extension of early studies comparing institutionalized DS children with other institutionalized mentally retarded children, DS children have been generally considered to be more "easy

going", more friendly, more affectionate, and more willing to please than other children (see Domino et al, 1964; Johnson and Abelson, 1969; Silverstein, 1964). This popular stereotype is consistent with characteristic differences in temperament, but these "characteristic" differences in temperament between DS children and normal children were not evident in the behaviors of the groups of children participating in this study. The behavior of the children participating in this study was clearly at variance with this stereotypical image, and the parent's description of their child's overall personality also did not support this stereotype. Both the DS children and the normal children could be friendly and cooperative, but the DS children, in particular, could be very persistent and uncooperative when they did not want to participate or when insisting that they perform a task according to their own rules. An example of the latter behavior were children who would walk to where their reward was hidden, point at it, and wait until the experimenter or their mother retrieved it for them, instead of retrieving it themselves. Two parents of the older group of DS children expressed their dismay that their children did not appear to have the natural immunity to the "terrible twos" they had hoped their children would have. In addition to this anecdotal information, the existence of differences in temperament has also been challenged by studies that have

reported finding more differences in temperament between individual children with DS than differences between groups of DS children and normal children (Huntington and Simeonsson, 1987). Thus, it is unlikely that the refusal to search behavior is a result of a characteristic difference in temperament.

A more likely explanation for the need for more testing sessions involves the difficulty of the task and subsequent loss of interest in the task. Since the DS children found these tasks to be more difficult than the normal children, they may have become frustrated with the task sooner than the normal children and became discouraged or lost interest. A consistent outward expression of frustration was not obvious in the DS childrens' behavior. However, recent findings that DS children generally exhibit a flatter affect could account for the lack of intense signs of frustration (Huntington and Simeonson, 1987; Sroufe and Cicchetti, 1976). The difficulty they have in performing well on tasks where frequent failures occur during the learning process (Duffy and Wishart, 1988) suggest the inability to quickly solve the task may have contributed to refusals to search. The need for more testing sessions also appears to result from the DS children finding the tasks more difficult than the normal children, again suggesting a slower rate of development.

Thus far, a good case has been presented for general cognitive deficits in DS being the result of slow development. Their performance on memory probes, however, illustrates the proposed effects of differential development. Unlike the performance during the training trials, the difference between the search behavior of the two groups of older children during the memory probes of the place learning condition and the cue and response conditions strongly supports distinct differences in memory capabilities.

The most common strategy employed by children in all four of the groups during the training trials was to first search in holes which were close to their starting position. This was followed by limiting their search to a particular area of the platform, either the inner part or one particular side. Finally they determined which of the holes in that area held the reward. On the memory probe, the children in the older control group performed nearly perfectly. All of them walked over to the correct area and looked in the correct hole on at least one of their two searches, and all but one child searched in the correct hole on the first search. Two of the children who looked in the correct hole only to find the toy missing, demonstrated surprise at not finding it, looked in it again, and when not finding it, searched in the hole with their hand. The children in the younger control group, while not able to perform as well as

the older group, limited their search to the general area of the platform that had held the toy. The DS children, on the other hand, demonstrated a greater deficit for memory of the location. They reverted back to the strategy of looking in the holes that were close to them. Two of the children clearly indicated that while they understood what they were to do, they had no idea where to search. When asked where the toy or cookie was hidden these two children raised both their hands over their heads, shrugged their shoulders, and made a face that provided a clear indication that they did not know where to look. They began a their trial and error search only after further encouragement.

The memory deficits shown on the place learning task are interpreted here as support for differential cognitive development in DS. A case could be made, however, that these deficits could also be explained by delayed development in DS. Since DS children were slow to acquire the abilities to perform the cue learning task and the response learning task, both which normally appear during the second half of the of the first postnatal year, perhaps they are also just slow to develop place learning abilities. Two observations argue against this interpretation. First, the older group of DS children were able to accurately perform the place learning task when they remained on the platform and a delay of seconds was involved; severe deficits were evident only after

the children were removed from the platform for a one minute delay. These deficits were not evident on either of the other two tasks. Second, the DS childrens' performance on the memory probe was not simply less accurate than the normal children it was very different. They appeared to use none of the spatial knowledge learned during the training trials and reverted back to a less efficient strategy of trial and error. If DS children were simply delayed in their ability to solve a place learning task, their search behavior would be similar to the younger group of normal children, though perhaps less accurate. In this study, this did not appear to be the case. The cognitive deficits were specific to memory, specifically memory that clearly requires the development, maintenance, and later use of an internal representation of space, indicating a difference in development rather than a simple delay in development.

A second argument could be made that the difference in the performance was not due to differences in development, but a result of the DS children being unable to perform the task because of the excessive length of the delay. Perhaps if a shorter delay was used, performance would improve. While it may be possible that if the delay was reduced to ten or fifteen seconds, the DS children may have performed more accurately, this argument does not address the issue as to why the negative effects of the one minute delay would be

specific to the place learning memory probe and not affect the others. A slowness in the development of a general memory system would predict that performance on the memory probes to be similar. Findings of deficits specific to memory of place is inconsistent with this prediction.

The specificity of the memory deficits to place learning, and presumably to hippocampal function, while supportive of abnormal neural development within this structure adds support to the proposed existence of differential cognitive development in individuals with DS. DS is not characterized by only a slowness of cognitive development, but also differential development. That this differential development includes the maturation of the HF formation has important implications for understanding the problems these individuals have in learning and suggesting ways in which they might be more effectively taught.

Implications of a Lack of HF Development in DS

This study investigated several forms of spatial memory because of the preponderance of neurophysiological, neuroanatomical, and neurobehavioral evidence of the neural basis for these kinds of memory. However, deficits in spatial memory certainly cannot by themselves explain the amnesia experienced by individuals with hippocampal lesions, nor can they explain the mental retardation characteristic of DS. The memory deficits of amnesic patients, such as the

extensively studied HM, involve much more than deficits in "spatial abilities".

Hippocampal Function in Humans

HF function, at least in humans and other primates, is probably not limited to place learning. O'Keefe and Nadel (1978), while stressing the critical role of the HF in spatial mapping, recognized that the function human hippocampal system was involved in more than spatial memory. They proposed that this system, referred to as the locale system, could also be used to represent verbal as well as spatial information. "For both these forms, the locale system will be shown to be central to a particular form of memory: that concerned with the representation of experiences within a specific context" (O'Keefe and Nadel, 1978; Nadel, 1991). This proposal suggests that the amnesia resulting from lesions that include the HF result from the disruption of a system that underlies spatial memory and related forms of explicit or declarative memory. Damage to the HF prevents the memory of the spatial relationship of a location with cues in the environment, but it also prevents the memory of events by preventing the development of a representation of the event within the context in which it occurred.

It has been speculated that hemispheric specialization may underlie these two forms of mental

representations. The right HF having a special role in spatial memory formation and the left HF having a role in mapping verbal information (Nadel, 1991). This is supported by recent findings that the right HF does play a specialized role in spatial memory abilities defined by cognitive mapping theory (Piggott and Milner, 1990; Smith and Milner, 1981, 1989). Despite the knowledge that amnesic patients with left temporal lobe lesions, including damage to the left HF, exhibit memory deficits for verbal information, the left HF has not received much attention. The possibility that it is necessary for some aspect of language has not been sufficiently explored to confirm it's role in the development of verbal representations (Frisk and Milner, 1991, Milner. 1967; Nadel, 1991, O'Keefe, 1991).

Perhaps future study will show that the memory component that hippocampal maturation adds to the neural systems which underlie place learning is also needed for a related form of verbal memory. A proposal consistent with this perspective proposes that the HF plays a critical role in memory consolidation, the ability to form longlasting and stable memories of events and experiences (Squire, Cohen, and Nadel, 1984; Squire, 1987). Memories may not be permanently stored in the HF and perhaps the HF is not necessary for the retrieval of established memories, but its function is necessary for experiences, events, and the context in which

these events occurred to be consolidated into more permanent memory storage.

The previously mentioned neurobiological explanation of infantile amnesia of Nadel and Zola-Morgan (1984) provides a developmental view of this position. They propose that the maturation of the HF during the second postnatal year underlies the ability for adults to remember events that occur after this period while preventing them from remembering events that occurred prior to HF maturation. This is not to say that early memories may not exist in some form; only that the adult memory system is so different from that of the infant it is unable to retrieve them. The impaired maturation of the HF in children with DS who exhibited performance deficits on the hippocampal task suggests that HF abnormalities may make a significant contribution to the cognitive deficits characteristic of DS.

Cognitive Dedicits in DS Result from Different as Well as Slow Development

Morss (1983) proposed that the general pattern of slow development shown by individuals with DS might be the result of "certain handicaps in the learning process associated with cognitive development"; and concluded that "retardation in achievement would thus be seen as a secondary and not a primary effect." Both Morss (1983; 1985) and Wishart (1990) have suggested that one of these handicaps

involves difficulties in the learning process, specifically in the consolidation of what has been learned. This study of spatial memory ability of children with DS supports this position, and more importantly, suggests abnormal development of the HF as a basis of these deficits.

Conclusion

The psychobiological paradigm used in this study was effective in identifying HF involvement in the cognitive deficits that characterize DS. However, two issues currently being debated in the learning and memory literature have an impact on the validity of this paradigm with human children.

The advantage of a psychobiological approach that utilizes hippocampal tasks found in rat studies instead of those used with primates may not appear to be intuitively obvious given the comparatively large phylogenic distance between humans and rats. However, when the nature of the hippocampal primate tasks is considered, the preference for the spatial tasks becomes apparent. The task that has become the hallmark of those studying the HF in the primate, the Delayed Non-Matching to Sample (DNMS) task, has a number of drawbacks that precluded its use in this study. First, as Nadel (1991) has stated, these tasks are "highly artificial" and "have no analogue to normal primate behavior in the real world". Hippocampal lesions cause deficits on these tasks, but since we do not know what memory function the HF is

performing during these tasks, or even if its function on these tasks involves memory, it is difficult to determine exactly what is being affected by the lesion. Secondly, and more importantly, is the extreme difficulty monkeys have in learning the DNMS task. Intact monkeys normally require hundreds of trials to learn this task. If DS children do not perform well on tasks which entail trial and error learning as reported by Duffy and Wishart (1987), it is unlikely that performance on the DNMS task which requires many such trials and errors would provide a good measure of the DS childrens' performance.

The cognitive mapping theory of O'Keefe and Nadel, which served as a basis for this study, has been frequently criticized for holding that the HF is preferentially concerned with spatial memory (see Eichenbaum et al, 1989; Rawlins, 1985; Squire, Shimamura, and Amaral, 1989; Sutherland and Rudy, 1989). Their insistence that the HF memory system is best characterized by spatial information processing continues to be a contested issue (see for example, Hippocampus, 1(3), 221-292, 1991). However, whatever the resolution of this debate may be, it will have little impact on the conclusions reached in this study. The debate centers on whether the HF is preferentially concerned with spatial information, not whether it is concerned with spatial information. Therefore, it is unlikely that the

deficits in spatial memory abilities shown by the DS children were not the result of a lack of hippocampal development, only that perhaps it may not be the only memory system affected. When performing similar tasks, the accuracy of the search behavior of children less than two years of age and DS children nearly three years of age was similar to that of very young rodents and adult rodents with hippocampal lesions This supports the contention that the human HF develops comparatively late (when compared to neocortical structures), and that its development is more adversely affected by an early disruption of neural development in DS. The implication of these findings for DS is that the developmental delays and deficits characteristic of DS are not of a purely general nature; they also include memory deficits specific to the functions of the HF.

Appendix A

Table A-1
Individual scores as a function of group membership and experimental condition

	Response task		Cue task		Place task		
Subjects	Ts	Tt	Ts	Tt	Ts	Tt	Pr
DS1							
1	1	6	3	5	6	-	-
2	3	7	2	6	6	-	-
3	5	5	4	5	4	8	(1-2) 3
4	2	6	1	7	2	6	(0-1) 1
5	3	5	1	7	2	8	(0-2) 2
DS2							
1	1	4	3	4	4	8	(0-3) 3
2	2	5	1	5	4	7	(2-1) 3
3	2	4	2	3	5	7	(0-2) 2
4	3	4	3	4	3	6	(2-0) 2
5	1	3	2	6	1	6	(1-2) 3
C1							
1	1	5	1	4	2	8	(1-2) 3
2	2	5	2	5	2	9	(3-2) 5
3	1	5	2	3	1	8	(2-1) 3
4	1	4	1	5	2	7	(3-1) 4
5	1	4	1	6	2	6	(2-3) 5
C2							
1	1	3	1	2	2	6	(3-2) 5
2	1	2	1	3	1	7	(3-3) 6
3	1	2	2	3	1	7	(1-3) 4
4	1	4	1	4	1	6	(3-2) 5
5	1	4	1	2	1	5	(3-3) 6

Note. Ts - test sessions; Tt - test trials to criterion during successful test session; Pr - memory probe

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