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COGNITIVE DECLINE AND ALZHEIMERS DISEASE IN PERSONS WITH DOWN SYNDROME

BY

Jane Alexander 

A Dissertation submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Special Education.

DEPARTMENT OF EDUCATIONAL PSYCHOLOGY

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FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommended to the Faculty of Graduate Studies and Research for acceptance, a Dissertation entitled Cognitive Decline and Alzheimers Disease in Down Syndrome submitted by Jane Alexander in partial fulfillment of the requirements for the degree of Doctor of Philosophy, in Special Education.

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DATE 25th November 1996

This Dissertation is dedicated to the memory of Laurie.

As researchers and practitioners, we must continue to question whenever we are told "what do you expect? they've got Down Syndrome". In the teachings of Brother Roger of the Taize Community and Jean Vanier, founder of the L'Arche communities, we need to work together for the good of the whole community.

Abstract

The prolonged life expectancy for persons with Down syndrome together with a suggested link between Alzheimer's Disease (DAT) and Down syndrome pose interesting problems for professionals working with this population and for their caregivers. Everyone who works with people with developmental disabilities, such as Down syndrome, would acknowledge the importance of independence and functioning in the general community. Yet the integrity and work placements of people with Down syndrome are threatened by a recognized cognitive decline in specific processes and a possible inevitable tendency to develop DAT.

In the general population DAT is diagnosed by the use of clinical rating scales. New imaging techniques in radiology hold the possibility of other methods of diagnosis. The use of neuropsychological tests of specific cognitive processes, clinical dementia rating scales and neuroradiological imaging all hold promise for diagnosis of dementia in people with Down syndrome. The specificity of the cognitive tests associated with the PASS theory of information processing may also differentiate between demented and non demented people with Down syndrome. Those non demented people with Down syndrome may exhibit particular cognitive deficits associated with the early aging peculiar to this syndrome, but which are amenable to remediation.

This study looked at cognitive functioning in a sample of people with Down syndrome between 25 and 61 years of age. Sensitive measures of planning and attention, the two cognitive processes found to be at risk of decline in this population, were taken. Data on these measures were compared over a period of five years. The Dementia Scale for Down Syndrome (DSDS)was administered. SPECT scans of a subset of the participants were performed. A pattern of decline in simultaneous processing is suggested, together with difficulty in completing the CAS tasks over age 50. SPECT scans on a subgroup of participants all indicated

abnormalities in rCP. The DSDS appeared to be a specific indicator for the presence of dementia in this population. Findings suggested that a low level of cognitive ability caused 100% of the participants to be identified as having a dementia on the Mattis Dementia Rating Scale. This finding was not supported by caregiver reports. It is hoped that this research gives further information on the nature of the link between Down syndrome and DAT, and on the specific nature of the cognitive decline exhibited by aging people with Down syndrome.

Acknowledgments

I would like to express my gratitude to several people and agencies who have supported this study. I am grateful to Dr. J.P. Das for his supervision and support, and to the other members of my supervisory committee, Dr. R. Mulcahy and Dr. R. Short, for their many helpful suggestions. I would like to thank the Scottish Rite Foundation of Canada for their faith in the research at the proposal stage and for the means to implement the study.

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Finally to Tim, Mark, Sarah, Rachel and Peter, thank you for your patience and understanding during the past three years as I have been working towards this personal goal.

TABLE OF CONTENTS

List of figures

List of Tables

CHAPTER ONE

The Problem

Down syndrome is "the most common cause of mental handicap in developed countries, accounting for around one third of all children with severe handicap. The prevalence of this syndrome is such that around 100 babies are born with Down syndrome each year and in the US it is much higher at about 7000 (Wishart, 1988).

In 1929 the average life span for a child born with Down syndrome was 9 years. By 1982 the average life span had increased to 35 years and 20% of the population of individuals with Down syndrome lived to over 50 years of age (Young & Kramer, 1991; Thase, 1982; Zigman, Schupf, Silverman & Sterling, 1989). Advances in medical science mean that people with Down syndrome now live longer and the effects of many of the health problems associated with this syndrome, such as congenital heart defects, can be overcome through medical intervention. Early intervention and individualized education programs have shown that this varied population are capable, intellectually, of more than was once thought.

The effects of early aging, a reported cognitive decline and a possible similarity with Alzheimer dementia, pose significant threats for the second half of the life span for people with Down syndrome. Premature aging and decline in social competence (Fenner, Hewitt & Torpy, 1987; Zigman, Schupf, Lubin & Silverman, 1987) bring increasing lethargy and difficulties in independent personal functioning. Early aging seems to be peculiar to Down syndrome and is not seen to such an extent in other groups of people with exceptionalities.

In people with Down Syndrome we see reduced cognitive performance with age, and dementia in up to 50% of people with Down syndrome over 35 to 40 years of age. Thase (1988) reported that the average life expectancy for individuals with Down syndrome was now exceeding 50 years of age and that with medical improvements applied early in life to those individuals now approaching mid life we can predict that life expectancy will

continue to rise. However, research has shown that people with Down syndrome eventually show neuropathological signs commonly associated with Alzheimer's dementia, (DAT), but that not all show the early clinical signs of dementia. We usually do not realize that people with Down syndrome have a type of dementia very similar to DAT until we see seizures in the individual. Cognitive decline is observed but at first, perhaps because they are functioning at a lower level than much of the general population, it goes unnoticed; but this is the time when intervention might have some effect. The literature shows that in time all people with Down Syndrome, at least neurophysiologically, will develop DAT. Schweber reported that from autopsy information of over 700 individuals with Down Syndrome all the individuals with Down syndrome over 35 displayed the typical neurological features of DAT. Schapiro (1988) reported that cognitive decline in older people with Down syndrome seems to occur in two stages separated by as much as twenty years;

First there is a decline in cognitive performance in processing skills and the formation of neuritic plaques. Miniszek (1983) proposed that cognitive changes might be the first behavioral pointers to the onset of premature senile dementia of the Alzheimer type for individuals with Down syndrome. This view has been supported in other research e.g. Hewitt, Carter and Jancar, 1986.

Second is a loss of overlearned behaviors, a deterioration in social, occupational and adaptive skills, dementia, neurofibrillary tangles, accelerated neuronal loss and brain atrophy. These will be discussed in more detail in the review of the literature in Chapter Two.

Importance of the study

Research at the Developmental Disabilities centre at the University of Alberta under J.P. Das has considered the cognitive decline of individuals with Down Syndrome. There is evidence that attentional and planning deficits are the early signs of dementia found exclusively in samples of the Down syndrome population (Das, Mishra, Davison &

Naglieri, 1995; Das, Davison, Hiscox, Mishra & Thapa, 1993). There has been a cross sectional study which reports these findings (Das, Divis, Alexander, Parrila & Naglieri, 1995).

Ultimately it may be possible to identify those individuals with Down syndrome who are at greatest risk of cognitive decline/early aging, and to attempt remediation. In this way independent functioning and living skills of these people could be improved to an extent that would enhance their quality of life. However, before this could happen various areas must be addressed and research findings confirmed. If the relationship between Down syndrome and Alzheimer's dementia is one which gives the same outcome i.e. presenile dementia leading to death, this should be clarified. In the medical field researchers are examining brain functioning in people with DAT through the use of Single Positron Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) imaging. Comparison of these findings with people with Down syndrome would be interesting. Similarly, 'cognitive decline' is a vast area. Could it be that cognitive decline starts with a specific process? Can this be identified and remediated in quite specific and targeted ways?

This study considers current research in two specific areas; cognitive psychology/information processing, and SPECT neuroradiological imaging (see Figure 1). It also considers the use of clinical rating scales in the assessment of dementia in exceptional populations. Current clinical instruments used to assess dementia may tend to over identify people with Down syndrome since these people's functioning and adaptive behaviors are generally lower than the general population. SPECT imaging has detected specific changes in regional cerebral perfusion (rCP) associated with DAT. Neuropsychological tests based on the PASS model have identified specific cognitive processes as being peculiarly at risk in the Down syndrome population. Is there a way to draw all these areas together in a way which will enhance our understanding of the pattern

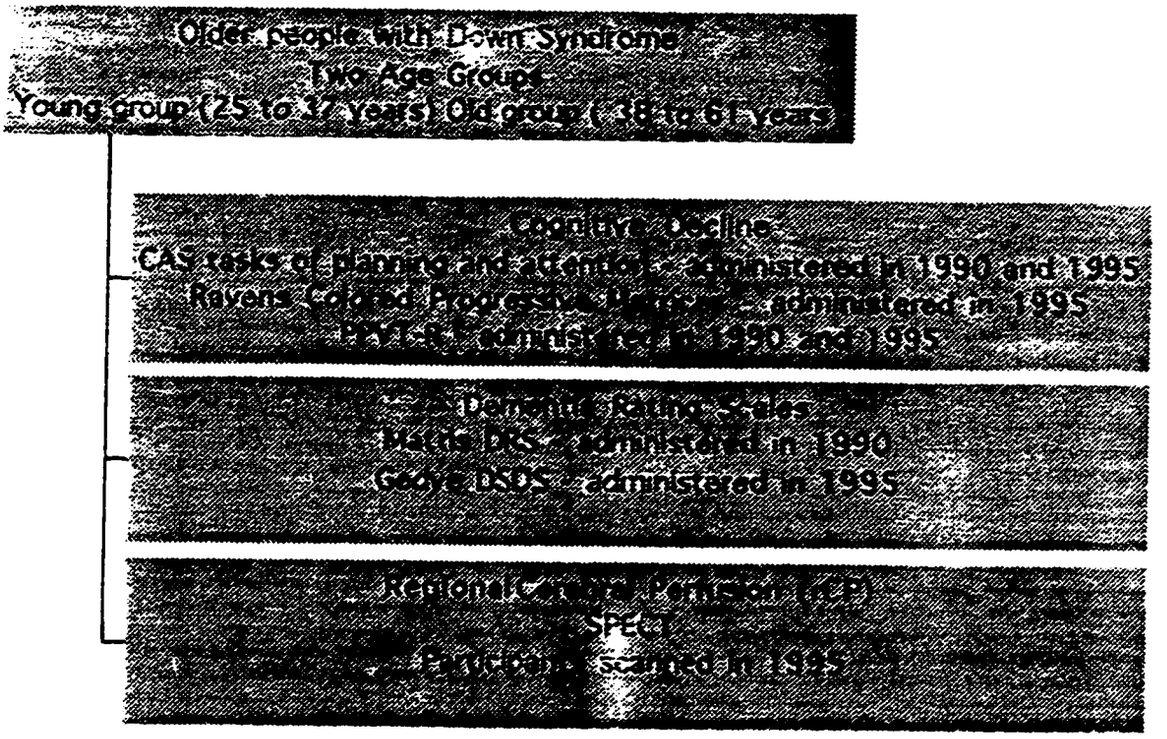
of cognitive decline observed in the Down syndrome population? It is possible that SPECT or neuropsychological tests, or both may be good discriminators of dementia in Down syndrome. The information from both of these methods of testing may agree or disagree with the dementia ratings given by more traditional clinical evaluations. Cognitive tests may be useful in differentiating between the demented and the non demented person with Down syndrome. Previous studies have shown that the tests associated with the PASS model can successfully discriminate between people with Down syndrome and persons with mental retardation of other etiologies.

SPECT imaging has detected specific changes in regional cerebral perfusion (rCP) associated with DAT. SPECT and PET imaging offer diagnostic promise for DAT in the general population. At the present time there is little research available which considers the use of this technology in the Down syndrome population. Such studies as do exist rely on small samples sizes. This population is believed to have an unusual tendency to develop a type of dementia very similar to DAT as diagnosed at autopsy.

SPECT may be a valuable diagnostic tool in that people with Down syndrome could be diagnosed with early stages of dementia and then receive intervention/remediation since in this particular population clinical signs of dementia are often not observed until the very late stages of the disease by which time it is too late to attempt an intervention.

I believe that it is important to explore the Down syndrome population in greater depth to see if there really are two distinct groups of older people with Down syndrome, the demented and the non demented. The assumption being that those people experiencing early cognitive decline rather than dementia may respond well to a remediation/intervention program. This study could help to validate neuropsychological testing's use as a measure of dementia by giving independent confirmation from the SPECT imaging.

Figure 1: Overview of the study



Rationale

People with Down syndrome are now living longer. In the last twenty years the field of special education has become increasingly concerned about the importance of early intervention. However, now we may need to intervene in later life with people with Down syndrome so that we can combat the effects of early aging. If the cognitive decline observed in individuals with Down syndrome is associated with the presence of DAT type changes in the brain this could be supported or even verified by using SPECT imaging on a sample of people with Down syndrome who have completed a series of cognitive function tests.

The importance of the study is twofold. There is always a need for research for the advancement of knowledge and science. In addition the implications of premature cognitive decline in terms of social and personal variables are severe. It may mean a loss of independent living and placement in a group home or larger institution, loss of a job, and the breakdown of relationships. Such people often turn in on themselves and become depressed and lethargic. Remediating this problem in a population such as Down syndrome is a new phenomenon as the life span is increasing beyond previous expectations. Therefore, the question of accurate diagnosis of DAT in persons with Down syndrome is key. The issue of quality of life must now be addressed and premature aging regarded in the same light as developmental delays in early life. Ultimately it may be found that it is impossible to reverse the cognitive effects of the early aging process at work here, but at the present time this is unknown.

It would be interesting to see whether those individuals with Down syndrome exhibiting poorest , or most reduced, rCP on SPECT exhibit the lowest measures of cognitive ability. It may be possible to look for trends in cognitive ability and the relationship of this to measurements of rCP taken during SPECT imaging. SPECT may be a valuable diagnostic tool in that people with Down syndrome could be diagnosed with early stages of dementia and then receive intervention/remediation. This is especially

important, since in this particular population, clinical signs of dementia are often not observed until the very late stages of the disease by which time it is too late to attempt an intervention.

It appears that there are two types of cognitive decline in Down syndrome. One is severe and is associated with the presence of a dementia, possibly Alzheimer's disease, as diagnosed by neurophysiological changes; the other is less severe with the people appearing non demented. However in both cases the cognitive decline is more rapid and severe than that seen in the normal aging population.

This study considered the decay of the specific cognitive processes associated with attention and planning in aging people with Down syndrome by looking at performance on specific cognitive tests over a period of five years. In this way data was examined to try and identify any sequence in the development of cognitive changes both structurally and functionally, and to see how these changes may relate to brain function measured through rCP by SPECT. A study such as this would build on the existing research of Schapiro, Haxby and Grady (1992), and Jernigen and Bellugi (1990).

The study considered neuropsychological tests which allow detection of smaller changes than the usual caregiver reports. It also considered the identification of neuropathological changes associated with dementia rather than aging by the use of SPECT. Both forms of assessment may offer a possibility of identification and remediation for people with Down syndrome in middle adulthood. If the results of this study support the view that there are two distinct groups of individuals with Down syndrome, demented and non demented, as detected by SPECT and cognitive testing this may be important for remediation. (Although additional research may prove that it is only possible to remediate the non demented population.) It would be hoped that these people would then be able to maintain independent personal functioning and integrity for an increased period of time.

Research Questions

The four research questions explored in this study were as follows:-

1) Is there a pattern of specific cognitive decline in persons with Down syndrome which is observable as they age?

2) Is there a pattern of both structural and functional neurological change in persons with Down syndrome?

3) Is it possible to differentiate between demented and non demented people with Down syndrome on the basis of information from neuropsychological tests and SPECT imaging?

4) Does the use of a caregiver report measure of DAT such as the DSDS appear to have diagnostic utility when compared with results from SPECT and neuropsychological tests?

Delimitations

This results of this study will only be generalizable to other persons with Down syndrome and not to other persons with developmental disabilities.

Limitations

This research study examined cognitive decline in a specific population. It did not propose that neuropsychological tests are to be used to diagnose dementia in other populations. However, the results suggest that the use of these tests could help to discriminate between cognitive decline due to the aging process and a cognitive decline due to a dementia of the Alzheimer type.

Summary

To date research on the cognitive decline of persons with Down syndrome has identified attention and planning as processes that may be at risk as people age. Research in three separate areas, cognitive psychology, radiology, and clinical medicine, appear to be providing exciting areas for further study. This study aims to link these three fields for a comparison of findings, i.e. are we producing mutually supportive research? Medical research has identified common characteristics in the SPECT scans of persons with DAT. It

seems logical to see if these findings extend to a group known to be at risk of developing DAT, a group who at post mortem show the neurophysiological changes associated with DAT but rarely show the clinical symptoms until they are in the late stages of the disease. To be able to diagnose the type of cognitive decline a person with Down syndrome exhibits as she/he ages and to be able to attempt remediation with those who are not demented, could mean an improvement in maintaining personal independence and integrity for a longer period of time.

In the next chapter a review of pertinent literature will be undertaken.

CHAPTER TWO

Review of the Literature

This review of the literature is organized around five main headings; 1) cognitive development - an overview and then specific studies on childhood and adulthood; 2) neurological development in Down syndrome; 3) cognitive decline and the relationship between Down syndrome and Alzheimer dementia; 4) newer methods of brain imaging and what they offer to the study of this subject and 5) diagnostic difficulties. The literature review presents an integrated review of the current literature and of the current state of research into these areas. Cognitive development will be taken to include studies of neurobiological and neurophysiological development; intelligence and achievement; cognitive tasks; cognitive style; concept formation; problem solving; hemispheric specialization and the development of perceptual, memory and motor skills. This review is necessarily selective, owing to the number of studies in this area and in the various subsets of interest. There are four questions which drive the review and which will be addressed in the summary of this chapter.

1) Is the premise that as people with Down syndrome age they show cognitive decline more than that normally associated with aging supported by the current research literature?

2) What do new medical imaging techniques have to offer in determining the similarity between the neurological changes seen in aging people with Down syndrome and those people with Alzheimer's Dementia?

3) Do people with Down syndrome exhibit specific cognitive deficits or are the deficits more global in nature?

4) What are the implications of premature cognitive decline in terms of social and personal functioning variables?

1: Cognitive development

The study of cognitive development by psychologists has burgeoned in recent years. This can be attributed to technological advances e.g. eye movement cameras, video recorders and computers, and also to the development of methods of study of infant cognition (see Flavell (1992) for a discussion of recent research). Imaging techniques such as magnetic resonance imaging (MRI) have improved our knowledge of, and ability to study, the brain and to consider brain-behavior relationships. These issues are discussed more fully in section 4 of this review of the literature.

"Cognitive development results from the interactions of individuals with their physical and social environments" (Ormrod, 1990; p.139). A great deal of information on cognitive development is available, not only cognitive development of children developing normally but also cognitive development of children exhibiting exceptionalities. Brown and Campione (1986) stated their belief that by being able to acquire a detailed description of the cognitive processes required for particular tasks it is possible to more precisely identify children's individual differences. Cognitive development is a rich, complex and multifaceted process (Flavell, 1992).

Conceptual model

What is meant by cognitive development? This question can be answered in different ways depending on the conceptual model one uses. For the purposes of this study the PASS information processing approach to cognition will be used. This approach stems from the work of Luria, Broadbent and Hunt. The model has both a neuropsychological and cognitive psychological base. The neuropsychological base allows comparisons to be drawn between the processes involved in cognitive functioning and what we know of brain functioning. Support for this model of information processing comes from many studies, specifically, Naglieri & Das (1987), Naglieri & Das (1988) and Das & Naglieri (1992).

Cognitive functions have been conceptualized as involving planning, coding and arousal by Luria (in Das, 1991). Luria first identified these functions and the regions of the brain responsible for these functions in the 1950s. In the past, measures of cognitive function have tended to be measures of intelligence which have been criticized as being static and too concerned with product rather than process. The cognitive functions identified by Das' PASS model of information processing are planning, attention and arousal, and successive and simultaneous processing. These five cognitive functions are proposed to underlie most of the developing child's behaviors. They are all required to function normally, however, different levels and combinations of deficits may present in the child as distinct learning problems. They influence short term memory (STM) and also retrieval and recall from long term memory (LTM). It is now assumed that in addition to certain regular stagelike specific increases in cognitive abilities as proposed by Piaget, there is also a general all pervasive cognitive development. "As the child's information processing capacity increases with increasing age, it makes possible new and more complex forms of cognition in all content domains, because the child can now hold in mind and think about more things at once" (Flavell, 1992; p.1000). A cognitive deficit may be specific or general, e.g. an inability to plan and organize skills, resources or information would reflect a pervasive and general cognitive deficit. The development of specific cognitive functions - planning, attention and arousal, successive and simultaneous processing, gives rise to the following:

a) growth of information processing capacity

b) development of a child's knowledge bases

c) the ability to apply strategies

d) abstract reasoning

(Das, 1991; Flavell, 1992)

The PASS system and its associated tests are useful for this study in that they take a person's knowledge base into account when measuring processes. The tasks used to assess

the functions are developed on a knowledge base that is so common to all people that prior/existing academic knowledge is not a factor. As a conceptual model the PASS theory could be criticized for its deliberate avoidance of an interpretation of memory. However this avoidance stems from a belief that it is more informative to look at memory in all four cognitive processes and in the knowledge base of the individual. The PASS model holds the premise that it is the nature of an individual's processing that affects their performance and that by assessing specific processes we can more usefully detect deficiencies or problems and attempt specific remediation. Since the proposed study will consider cognitive decline in persons with Down syndrome with a view to, at a later time, trying to develop a theory of cognitive development across the life span for persons with Down syndrome; it was felt that the PASS model was a good choice of conceptual model. It is a general theory of cognition not just of "intelligence" test performance. The PASS theory and its associated tests are useful for diagnosis and give greater perspective on individual functioning. The tests have been used in other research in this area (Das et al., 1993; Das and Mishra, 1995b).

Cognitive Development in Down Syndrome

Research into the cognitive development of people with Down syndrome is interesting in that it has been carried out both in terms of its relationship to normal development and as a 'different' process. Individuals of a common etiology such as DS often display patterns of behavioral strengths and weaknesses unique to that group. Down syndrome is "invariably associated with trisomy of chromosome 21. In 95% of cases we see meiotic disjunction with triplication of the entire chromosome. In 4-6% we see translocation of part of chromosome 21 to another chromosome and in 1-4% the cells are a mosaic of normal and trisomic cells as the result of non disjunction in early embryonic development" (Kemper, 1988; p.21).Within the DS group certain developmental differences are observed. A study by Fishler & Koch (1991) found that children with mosaicism DS had higher IQs than those with non mosaicism DS. They also had better

verbal and visual perceptual skills. There is considerable variability in intellectual functioning in the DS population but for the purpose of this review some generalizations will be made.

Early deviations in development may cause problems for children later on. The development of children with Down syndrome may be charted from birth owing to the etiological homogeneity of the syndrome itself. It was once felt that there was nothing that set the child with Down syndrome apart from other children exhibiting intellectual challenges (Ellis & Cavaler, 1982; Fischer & Zeaman, 1970). The presence of Down syndrome gives rise to intellectual challenges of organic origin, i.e. a chromosomal abnormality. The view of some early researchers was that however such challenges came about, whether due to genetics, pathology, seizures etc. the maturational results should be the same. In the following sections research will be reported that specifically looks at the development of children with Down syndrome.

Results from a number of studies suggest that intellectual growth in Down Syndrome extends beyond the late teenage years over the twenties and early thirties. Fenner et al. (1987) reported an increase in MA in DS during the twenties and then a decline starting from the mid thirties. The increase was noted in 46% of their sample, however, the decline did not become significant until late in the fourth decade of life. This decline was noted much more in those individuals with DS aged over 45 (Fenner et al., 1987; Hewitt & Jancar, 1986; Dalton & Crapper, 1974).

This discussion will now consider more specific cognitive functions and development in Down syndrome.

Wishart (1988) reported that early development is hampered by a learning style which appears not to make the maximum use of learning situations. There is a lack of consolidation of early learning and a lack of ability to build on existing knowledge. There is a lack of ability to benefit from repeated opportunities to practice a task. In the early

months of life the mental retardation/delay associated with Down syndrome is compounded by poor muscle tone which is generally present.

In children with Down syndrome just as in others, affect and cognition are intimately related. The higher the level of cognitive functioning, the greater the differentiation of emotion (Cicchetti & Sroufe, 1976, 1978). Motti, Cicchetti and Sroufe (1983) found that affective motivational play style e.g. enthusiasm, positive affect, significantly correlated with level of cognitive development. Research studies on CA comparisons have suggested that children with Down syndrome are perceived as less intense in their expressions of affect than normally developing infants (Rothbart & Hanson, 1983). Cicchetti and Beeghly (1990) discuss some compelling evidence for the link between affect (emotional development) and cognition in children with Down syndrome. One noteworthy finding is that early laughter in babies with Down syndrome was a better predictor of later cognitive development than early level of cognitive development. Babies who had laughed before ten months had higher developmental quotients on the Bayley scales on infant development then those who laughed later. Cognitive development is continuous but slows progressively and results in a general decline of measured intelligence throughout infancy and early childhood. This apparent decline may reflect the fact that cognitive tests increasingly become more demanding in terms of adaptive behavior and problem solving. The tests also reflect a greater reliance on language based items.

Children with Down syndrome are believed to have delayed information processing, they seem less intense and interactive with their environment. More specifically, children with Down syndrome have been found to be delayed in their ability to process visual information, to develop complex voice features, cross modal referencing such as auditory-motor and visual-vocal processing (Pueschel, 1988), and developing recognition memory (Cicchetti & Ganiban, 1990). Beeghly and Cicchetti (1987) reported that children with Down syndrome have similar but delayed conceptions of self and other development. Varnhagen, Das and Varnhagen (1987) reported that children with Down

syndrome were particularly deficient in auditory sequential processing and auditory memory.(Marcell & Cohen, 1992), difficulties which manifest themselves in poor language comprehension and production and poor performance on tasks requiring verbal memory and verbal problem solving. These difficulties are felt to stem from a slow LTM access for lexical information (Varnhagen, Das and Varnhagen, 1987; p.404). As a group, children with DS have problems in attending, discriminating, encoding, transforming and transmitting complex or subtle stimuli. Children with Down syndrome perform less well in sequential and simultaneous processing than MA matched controls (Pueschel, 1988). Difficulties in successive processing have also been reported by Snart, O'Grady and Das (1982).Schapiro (1987) reported difficulties in visual-spatial ability, attention, memory and language function.

Language development is slower than in normally developing children, but not different (Steffens et al., 1992; Beeghly & Cicchetti, 1987; Pruess, Vadasy & Fewell, 1987). However language development tends to slow down with age in children with Down syndrome and few manage to use complex forms of language and abstract thinking. Young children with Down syndrome manifest substantial verbal language deficits in comparison to their level of cognitive development (Beeghly, Weiss-Perry & Cicchetti, 1990), but language skills can be modified with selective intervention (Fewell & Oelwein, 1991; Gunn & Berry, 1991; Gibson, 1989; Naganuma, 1987). However the language skills of children with Down syndrome are increasingly deviant relative to other cognitive skills with increasing chronological age (Young & Kramer, 1991; Miniszek, 1983; Wisniewski et al., 1978). Furthermore this deficit is in both anomia (the ability to name objects) and in comprehension.

To conclude, children with Down syndrome as a group have particular difficulty with language (Gibson, 1989), visual monitoring (Kopp, 1983), habituation memory (Barnet et al. 1971; Schafer & Peeke, 1982) and abstract reasoning. They have relative

strengths in visual motor integration (Gallagher, 1986) and social aspects of cognitive tasks e.g. the pragmatics of language (Beeghly & Cicchetti, 1987).

Academically, children with Down syndrome have a relative weakness in arithmetic (dyscalculia), and a relative strength in reading. Yet the deficits that this group as a whole experience and exhibit in attention and memory causes many problems for the child with Down syndrome. It has been suggested that they contribute to the formation of a learning style that is less than optimally suited to many regular classroom situations. The pervasive effects of deficits associated with this syndrome may lead to an underestimation of a child's existing abilities and of her/his potential. Research into the learning behaviors and processes of children with Down syndrome have included studies by Wishart (1991) Pueschel, Gallagher, Zartler & Pezzullo (1987).

Cognitive development in adulthood

After childhood and early adolescence cognitive development continues in the person with Down syndrome but then there is a surprising decline. It is surprising because it occurs earlier in the population of individuals with Down syndrome than in the general population and is an indicator of premature aging.

Some specific difficulties that have been reported in the literature include a loss of ability to manage the Block Design subtest of the WISC in aging individuals with Down syndrome Such a difficulty is also seen in Alzheimer prone subjects in the general population. The Block Design subtest requires fairly complex information processing skills (Gibson et al., 1988). With age there is an decrease in visual retention and short term memory (Schweber, 1985).In everyday situations, as people with Down syndrome age they tend to have growing difficulty in following verbal directions. Such a comprehension ability is critical in both independent and institutionalized living, and a deficit in this area could eventually lead to loss of job placement. Difficulties in language expression have also been reported by Chapman, Schwartz and Kay-Raining Bird (1989). Specific cognitive functions which distinguish the aging person with Down syndrome are involved in

information coding and articulation. The older person with Down syndrome may appear to be confused or incomprehensible due to articulation problems and this can lead to great frustration and misplacement of such people. Those persons with Down syndrome over 50 years of age are also significantly poor in number finding, in the Stroop test, speech rate, receptive attention and in planning (Das, et al., 1993). All people show an age related decline in attention and planning but it happens more quickly in persons with Down syndrome. Das et al. (1995a) found that people with Down syndrome over the age of 50 performed more poorly than younger persons with Down syndrome, particularly on tasks requiring planning and attention. In another study, (Das & Mishra, 1995b) people with Down syndrome over the age of 40 showed age-related decline on articulation related tasks. Once again when the age level was raised to 50 years, age-related decline in attention and planning was noted in a small group of people (n=4).

2: Neurological development in Down Syndrome

There is widespread disorganization of the brain in Down syndrome, Courchesne (1988) reported that in Down syndrome maldevelopment occurs throughout the cerebrum, cerebellum and portions of the limbic system. From a review of current literature (Coyle et al., 1986; Uecker et al., 1993; Kemper, 1988) it is possible to summarize the main neuroanatomical features of Down syndrome as follows.

The brain of a person with Down syndrome is typically smaller and lighter. There is a lack of surface complexity and abnormal shape. There is hypoplasia of the operculum and superior temporal gyrus. Poor frontal lobe development in Down syndrome gives rise to reductions in fine motor control of hands, fingers, lips, tongue and vocal cord. There is compression of the occipital lobes and decreased size of the cerebellum and brainstem. The cerebral volume of the brain of a person with Down syndrome is about 77% the size of young normal controls and cerebellar volume about 69% the size of normal controls (Jernigen & Bellugi, 1990).

There are irregularities in the layers which make up the cerebral cortex due to either dense neuronal packing or a lack of neuronal evidence. There is a reduced number of neurons in the visual cortex and also dendritic spine loss. The frontal cortex is important in the executive control of selective attention i.e. the ability to discriminate new and important information from old and insignificant information. Elliot, Weekes & Elliot (1987) suggest that like some children with learning disabilities and children with autism, people with Down syndrome have a different pattern of cerebral organization than that found in the general population. These authors suggest, for example, that speech reception is located in the right hemisphere in Down syndrome, rather than the left.

Hippocampal maldevelopment is also observed in persons with Down syndrome. This has effects on memory. Removal of the hippocampi in humans results in severe and sometimes permanent loss of memory (Gardner, 1975). There would also be an effect on spatial cognition as this part of the brain appears to be necessary in the formation of cognitive maps (O'Keefe & Nadel, 1978). Thus an individual with Down syndrome might manifest this in a difficulty in internally representing their external environment.

Recently, Frisk & Milner (1991) confirmed the view that function of the hippocampus is lateralized, with the left critical for processing verbal information and the right critical for processing spatial information (Uecker et al. 1993). In persons with Down syndrome the left hemisphere seems to be more damaged than the right.

In addition to structural abnormalities there are also significant differences in the timing of neural responses in the auditory sensory pathways at the brainstem level, and also in neural responses associated with cortical sensory-related ERPs in Down syndrome. Courchesne (1988) suggests that the cortical sensory related findings of Dustman and Callner (1979) may reflect structural and functional abnormalities in the granular cerebral cortex. Such abnormalities may be critical in the cerebellar processes associated with learning. The presence of neuritic plaques and tangles and Beta amyloid will be discussed in a later section of this review of the literature.

3: Cognitive decline and the relationship between Down Syndrome and DAT

The literature reflects no particular consensus on a particular cognitive deficiency as an indicator of dementia in Down syndrome, overall deterioration of short term and longer term visual memory and visual motor co ordination seem to be recurring features. Specific changes are documented here. Miniszek (1983) proposed that cognitive changes might indeed furnish the behavioral pointers to the onset of premature senile dementia of the Alzheimer type in individuals with Down syndrome. This view is supported in the work of Hewitt, Carter and Jancar, (1986).

Memory and related functions are useful markers for the onset of cognitive decline. Lott (1982) reported that memory for recent events and short term visual memory were among the first signs of intellectual decline for DS adults past the age of 35. Wisniewski, Wiesniewski & Wen(1985) reported visual memory loss and reduced learning capacity as behavioral indicators of dementia in DS individuals. Thase (1982, 1984) reported deficits in digit span, visual memory and object naming performance. Varnhagen, Das & Varnhagen(1987) indicated age-graded paucity of short term storage facility and limited capacity for processing auditory information. Schapiro (1987) reported deficits in language function, visuo spatial ability, attention and memory.

From the literature it would seem inevitable that all individuals with Down syndrome will develop dementia of the Alzheimer type on a neuropathological level (Miniszek, 1983; Gibson, 1988; Schweber, 1987). Schweber reported that from autopsy information on 700 individuals with Down syndrome, all of the individuals over age 36 displayed the typical neuropathological features of AD and that there is a possible genetic link between AD and Down syndrome evidenced by a possible linkage on chromosome 21 q 21 and 21 q 11. The study of elderly individuals with Down syndrome has major "importance in its potential contribution to an understanding of AD and the process of aging in general" (Miniszek, 1983, p.384).

Is cognitive decline inevitable? Perhaps it will be possible to stimulate an increase in brain capacity by the education of individuals with Down syndrome continuing into early adulthood and beyond. It will be interesting to see whether the increase in deinstitutionalised living and aging of people who have received early intervention programs makes a difference to the incidence or age of onset of AD in individuals with Down syndrome. Attempting remediation of cognitive deficiencies in adults with Down syndrome should take place in the middle adult years, if not before. If we wait to see the clinical signs of dementia then they will probably be in the latter stages of the disease and remediation will probably be too late. Crocker (1988) has placed the study of AD changes in Down syndrome among the five topical priorities for work related to cognitive ability.

"AD represents a major, if not the major, public health concern for the coming decades" (Thase, 1988; p.345). The clinical features of AD are:-

1) Impairment in STM and LTM

2) Impairment in abstract thinking and judgment

3) Disturbances of higher cortical functioning

4) Personality changes

5) Significant changes in work/leisure/relationships

These features are commonly observed in three stages over a period of five to ten years starting with memory loss and culminating in pronounced neurological signs, delusions and seizures.

The pathological features of DAT can only be confirmed at necroscopy whereas the clinical signs are usually observed during the early stages of the disease in the general population but not in the Down syndrome population.

There have been references to the occurrence of dementia in individuals with Down syndrome in the literature for over 100 years. The association between DAT and Down syndrome is supported by neuropathological studies (Godridge et al., 1987), which reveal cortical atrophy, neuronal loss, deficiencies in neurotransmitters (AChE and ChAT),

neuritic plaques, amyloid deposits and neurofibrillary tangles. Kesslak, Nagata, Lott and Nalcioglu (1993), report a number of studies which state that patients with Down syndrome over the age of 35 exhibit an increase of over 80% in the number of plaques and tangles, similar to changes seen in DAT (p.1039). Yet the clinical features of DAT are not seen in all older people with Down syndrome. An interesting finding of the research is that those individuals with Down syndrome who do present with clinical signs are later found to have more plaques and tangles than those who do not. The number of tangles has also been seen to correlate well with the index of dementia in DAT (Godridge et al., 1987). The risk of Down syndrome is increased by two and a half times in relatives of probands with DAT (Heston & Mastri, 1977; Heston, 1982; Heyman et al., 1983).

There exist many examples of single case gene mutations which are abiotropic, i.e. not obvious at birth, and which involve particular subsets of neurons. One such example is Huntingdon's Disease. The use of genetic science is the key to get at the fundamental mechanism of certain disorders. The probability of there being a genetic model for DAT is supported by the Down syndrome population incidence of an Alzheimer type of dementia.

The question is has Alzheimer's disease been shown to be caused by a single gene mutation or by more than one such mutation? Researchers have looked at five specific sources of information:

1) epidemiological studies;

2) concordance in identical twins;

3) pedigree analysis;

4) neuropathology of trisomy 21;

5) a possible phenotype in cultures of non neuronal somatic cells - although this literature is held by some people in the field to be rather suspect (Martin, 1993).

In the majority of individuals with Down syndrome we see reduced cognitive performance with age and dementia in up to 50% of individuals with Down syndrome over

35 to 40 years of age. In individuals with Down syndrome with dementia, vocabulary is usually a good indicator of premorbid level of function.

Thase (1988) reported the average life expectancy of people with Down syndrome to be now approaching 50 years of age. Could the documented link between Down syndrome and AD be an unexplained source of mortality in people with Down syndrome after age 30 relative to the general, and other mentally retarded, populations? Godridge's study (1987) reported that by middle age the brains of adults with Down syndrome in the study had undergone profound and currently irreversible neuronal degeneration involving three of the major neurotransmitter systems. These changes are very similar to DAT. An important difference in Alzheimer pathology in Down syndrome is that changes appear to occur over a period of thirty years. Schapiro (1988) reported that cognitive decline seen in older individuals with Down syndrome seems to occur in two stages separated by as much as twenty years:-

1) A decline in cognitive performance, in processing skills and the formation of neuritic plaques.

2) Loss of overlearned behaviors, a deterioration in social, occupational and adaptive skills; dementia, neurofibrillary tangles, accelerated neuronal cell loss and brain atrophy.

Schweber (1988) reported a marked and sudden brain weight loss in adults with Down syndrome diagnosed as demented compared to individuals with Down syndrome dying at the same age not diagnosed as demented. The implication is that the dementia of active DAT may be due to the onset of a pathological process, but if that is so then what is the triggering event?

Neuropathologists have been trying to establish general criteria for diagnosing DAT but at the moment their criteria do not correlate with cognitive decline. Some individuals who show a clinical diagnosis of DAT, i.e. cognitive decline, personality changes, neurological abnormalities, aphasia/apraxia; and have a pedigree of two or more

generations of affected subjects have still not been shown to have DAT. Other possible causes of dementia have been identified in some cases, for example, motor neuron disease plus dementia, also a prion protein disease similar to DAT. Interestingly, in Down syndrome the opposite is true, we often see neuropathological signs at post mortem when clinical signs have not presented. In normal aging of the brain it would be expected that abnormalities would occur. However in DAT neuropathological changes are specific and specialized. These changes suggest that DAT is a disease process and not an inevitable consequence of growing old (Schweber, 1988; p.67).

The neuropathological features of DAT are:

1) neurofibrillary tangles (usually as paired helical filaments)

2) Beta amyloid

3) Neuritic plaques

DAT causes massive degeneration in specific areas of the brain especially the hippocampus and cerebral cortex, areas associated with learning and memory. At the cellular level DAT is associated with neuronal degeneration, the loss of synaptic connections and the formation of plaques and neurofibrillary tangles. The plaques are extra cellular deposits consisting primarily of Beta-amyloid. Plaques cause neurons to become swollen and twisted the effects of which can be seen in circulatory dysfunction. Neurofibrillary tangles are neurons with abnormal fibrillar structures which cause cell degeneration. Beta amyloid has been shown to organize molecular cascades and initiates a process of neuronal degradation. Therefore, Beta amyloid cannot be seen, as was once thought, to be an inert deposit. The accumulation of beta amyloid initiates a process known as apoptosis. In apoptosis, the cell basically self destructs. Current research is examining the contribution of apoptosis to cognitive decline (Su et al., 1994; Cotman & Anderson, 1995). During apoptosis the external membrane of the cell begins to form blebs or extuberances. In these blebs are part of the cell's cytoplasm. In this way the cell degenerates without bursting.

The pathological features of DAT can only be confirmed at necroscopy whereas the clinical signs are usually observed during the early stages of the disease in the general population but not in Down syndrome. Is this just because the tools we use to detect clinical changes are not sensitive enough for this population? This question will be addressed in the section on diagnostic difficulties later in this review. In the United States DAT is reported to affect 8.1 - 12.5% of individuals over 65 years and approximately 47% of community dwelling elderly over 87 in the general population (Rapoport, 1991, p.298).

Recent Genetic Research

The fact that so many people with Down syndrome seem to develop an Alzheimer type of dementia in later life led many researchers to believe that there was a genetic link between the two conditions, and that this link would probably be found on chromosome 21. Early onset families in Martin's Seattle group study showed genetic linkage on chromosome 14. This linkage was supported by work by the Hislop group. Research with late onset families has indicated linkage on chromosome 19. A point mutation has been found on chromosome 21, although at a different place from that where the mutation was originally thought to occur.

The questions raised by this research mostly center around the amyloid protein. Beta amyloid is highly insoluble, directly neurotoxic and deposited extracellularly. Is it a result and/or cause of neuronal injury? Is it possible to get mutation amyloid? How specific would the neuronal injury have to be? The synthesis of an abnormal protein such as Beta amyloid could be directed either by abnormal genes or by abnormal modification. Is it possible that DAT is one result of a number of different causes? Amyloid and the protein precursor of amyloid, are very important in early neurological development. Martin (1993) has managed through cell culture work to express the protein precursor of amyloid aggregate from the C terminal domain. In blood cells it is 39 amino acids long, and in plaques it is 42 amino acids long. Marked with a string of 7 amino acids Martin has managed to make spontaneous amyloid in mice. However this amyloid is found in the

ileum and not in the brain, giving rise to the possibility that there is a suppresser in the brain degrading the amyloid under normal circumstances. It is then possible that the production of this suppresser is somehow changed in the face of a neuronal insult. DAT changes have not been successfully replicated in animal studies yet they always seem to happen in individuals with Down syndrome.

If amyloid is a result of neuronal damage how could this relate to Down syndrome? Neuronal damage is widespread in Down syndrome, including all of the cerebellum, cerebrum and dentate gyrus. From an epigenetic point of view Down syndrome brain development shows a sequence of developmental difficulties. Courchesne (1988) stated that "The mental retardation in DS is the product of an epigenetic process: Abnormal genetic programming creates abnormal internal structural configurations (too few inhibitory synapses, poorly functioning axospinous excitory synapses, functional axodendritic synapses, small synaptic sizes). These abnormal neural configurations produce abnormal neural activity... the end result is the sculpting of maladaptive microstructural configurations and functions throughout vast regions of the brain" (p.308). It is possible that the development of dementia in Down syndrome could involve genes in regions of chromosome 21 other than the critical DS region at 21 q 22.2 or 21 q 22.3. In 1990 Schapiro stated that "There is a locus of susceptibility to early-onset familial DAT on the proximal portion of the long arm of chromosome 21" (Schapiro et al., 1990; p.172). The current state of research on the genetic causes of DAT yields the following loci:-

1) 21 q 21 in about 3% of early onset DAT

2) 14 q 24.3 in about 95% of early onset DAT

3) 21 q 11 Possibly in early onset but not confirmed

4) 19 q 13 Occurs in late onset but it is not necessary or sufficient alone, perhaps it is a risk factor

5) Unknown In a select sample of DAT cases known collectively as the "Volga Germans" the gene is not 21, 19 or 14

Individuals with trisomic Down syndrome have three copies of chromosome 21 and may have increased levels of all products on this chromosome, including amyloid. It is possible that the DAT type changes seen in Down syndrome could be caused by an increased amyloid gene dosage effect or that the neuronal damage seen in Down syndrome results in increased amyloid production. The evidence would not seem to support a simple gene dosage effect in Down syndrome and there exists the possibility that the genetic mechanism of dementia may be different in Down syndrome than in DAT. In Down syndrome we see neuropathological changes and cognitive decline but not clear cut dementia.

Other recent genetic research has concerned one of the genes involved in the transportation of cholesterol, Apolipoprotein E (Apo E). Apo E has been identified as being associated with DAT in the general population, and is situated on chromosome 19. It exists in 3 forms, or alleles (Apo E 2, 3, 4). Inheritance of one or two Apo E alleles is associated with early onset DAT. An Apo E test has been developed, not to be diagnostic, but more as a predictive measure in that it considers a person's susceptibility to DAT.

4: Newer methods of brain imaging

Recently brain imaging techniques have become more readily available to researchers and clinicians - computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT). All of these imaging techniques are important as they allow study of the brain in living people; this is of particular note in the study of the dementias. Previously only studies at post mortem could diagnose specific dementias by which time diagnosis was rather academic. For a review of brain imaging in persons with mental retardation see Deb (1995).

Studies of DAT using CT have illustrated that DAT is accompanied by progressive cerebral atrophy, at the present time it is not known to what extent cortical atrophy occurs in Down syndrome and if there is a difference between demented and non demented people

with Down syndrome. Evidence from post mortem studies in Down syndrome (Wiesniewski, 1985; Schapiro, 1988), show that atrophy is seen to have occurred but at what age and how it is associated with dementia is unclear. It has been suggested (Schapiro, Haxby, and Grady, 1992) that cerebral atrophy does not occur in young adults with Down syndrome and that the cognitive deficits that are observed in these people are related to "inherent cerebral dysfunction and not to acquired cerebral atrophy" (p.728). Structural changes in the brains of individuals with DS detected using MRI include smaller frontal cortex and cerebellum and smaller hippocampal formations (Kesslak et al., 1993; Raz et al., 1995). The results of these and other such studies suggest that the gross neuroanatomy of DS differs from that of normal aging and that of DAT (Raz et al., 1995, p.363).

CT and MRI provide structural information about the brain whereas PET and SPECT provide functional information. These two procedures can be used to study cerebral metabolism (PET) and regional cerebral perfusion, rCP, (SPECT and PET). Early PET studies from the 1980s reported in Albert and Lafleche (1991) found a statistically significant decline in resting regional glucose metabolism and significant correlations between glucose utilization rates and cognitive performance. PET is unique in that it can non invasively offer diagnostic information on brain function, however, PET is currently not available in Edmonton. It is hoped that these imaging techniques will give improved criteria for the diagnosis of DAT Recent research into study of the dementias using SPECT imaging has found that "...patients with dementias had distinct brain image patterns consistent with the expected neuropathology' (O'Connell et al., 1991; p.306). SPECT and PET studies in Alzheimer's disease have demonstrated decreased rCP and metabolism particularly in the parietotemporal regions. There is a reported homogeneity of symptoms in SPECT studies of people with DAT (Albert and Lafleche, 1991) it would be interesting to see if there is such homogeneity in the population of people with Down syndrome, or

whether two distinct groups emerge - those with dementia and those with cognitive decline indicated by cortical atrophy.

SPECT imaging requires the injection of radiopharmaceuticals such as technetium 99 and Hexamethylpropylene Amineoxine (HMPAO). After a small amount of time (15 - 20 minutes) a series of images are taken over about a thirty minute period. These multi color images show regional differences in cerebral perfusion, and by inference, metabolism. Tc99mHMPAO SPECT has been shown to be appropriate for high resolution static imaging in relative or absolute flow units (Andersen, 1988). It provides a simple yet reliable technique that is practical in clinical use due to the relatively low cost of the radiopharmaceutical. At the present time a few small studies have reported that results of SPECT studies in young people with Down syndrome show abnormal rCP more typical of the usual pattern of rCP in Alzheimer's disease (Kao et al., 1993). Many of the available studies using SPECT with individuals with Down syndrome have a small subject pool, indeed some are just case studies. Two such case studies (Nakayasu et al. 1991; Rae-Grant et al., 1991) reported reduced rCP in bilateral parietal and temporal regions with Tc-99m HMPAO in two people with Down syndrome aged 52 and 46 respectively.

Radiological techniques such as SPECT, PET, MRI and CT can allow the study of the sequence of changes over time. Through such studies it is possible to state that in Down syndrome the neuropathological changes, which have been associated with Alzheimer's disease, begin in the hippocampus, amygdala and entorhinal cortex and only in later stages occur in the neocortex. In addition we now know that senile plaques are deposited first and then neurofibrillary tangles occur later. SPECT studies have shown that there is bilateral decreased rCP in the temporoparietal areas of the brain in DAT, plus frontocortical abnormalities in cases of severe dementia. This may correspond to the observations of Schapiro (1988), that cognitive decline in Down syndrome occurs in two stages separated by many years. Perhaps the use of the newer imaging techniques may shed light on the reason for this. These techniques have altered the generally held view of Alzheimer's

disease, which is now seen not as a global dementia, but as a progressive disease with specific localization of damage and loss of cognitive abilities (Rapoport, 1991).

In summary, the imaging techniques of SPECT and PET may well offer a way of being able to attempt a diagnosis of dementia in the mentally disabled population where other standardized tests and measures may be inappropriate. The early appearance of characteristic DAT type changes in rCP can be observed through SPECT and PET imaging before people develop clinical dementias (Deb, 1995). From the literature it would seem important to ascertain whether the exact location of the brain lesions seen in both Alzheimer's dementia and Down syndrome is important for a diagnosis of dementia and for specific cognitive functions. The present study considered the use of SPECT imaging with a small group of persons with Down syndrome. Given the cognitive difficulties reported in previous studies such as Das et al. (1995) it was anticipated that functional deficits would be observed on SPECT. We anticipated three possible groups, one 'normal', one showing perhaps functional deficits associated with aging in Down syndrome and a third group showing functional deficits associated with the presence of DAT non specific to persons with Down syndrome.

5: Diagnostic difficulties

The assessment of dementia of the Alzheimer type (DAT) in individuals with Down Syndrome has been the subject of much discussion in recent papers (Das et al., 1995b; Das et al., 1995a). The main difficulty highlighted in the literature concerns the use of appropriate instruments which discriminate between loss of functions related to DAT, and detection of pre existing difficulties. One issue raised by this discussion concerns the use of individual neuropsychological assessment and/or caregiver reports. The use of neuropsychological tests commonly used with the general population has been felt to be desirable if we wish to use individuals with Down Syndrome as a model for DAT. The Dementia Rating Scale (Mattis, 1988) has been used for this purpose. We need to discriminate between DAT and a general cognitive decline associated with aging. Are measures such as the Dementia Rating Scale, used with the general population, sensitive

enough to discriminate in this population, or do instruments such as the Dementia Scale for Down Syndrome (DSDS, Gedye, 1995) offer more promise?

Is Down syndrome a degenerative disorder with symptoms and neuropathological features in later life which mimic those of DAT? The absence of the symptoms of stages 1 and 2 of DAT may simply be due to a problem of detection. Individuals with Down syndrome function at a lower level (as measured by commonly accepted ability tests) from the general population, and so subtle changes in cortical functioning and memory may be harder to detect. Miniszek (1983) suggested that a difficulty in assessing regression with people with mental retardation whose individual levels of competence are low, may result in apparently non significant changes in memory and cognition in the population of individuals with Down syndrome. In practice a label of dementia is often not applied until late onset seizures have been observed. Changes that have been observed (Eisner, 1983) include decreases in grooming, inability to do simple chores, apathy, incontinence, and decline in language and motor activity. Yet the neuropathological changes observed in Down syndrome have little relation to the behavioral signs of dementia observed in elderly individuals with Down syndrome (Ropper & Williams, 1980).

In the general population the medical and rehabilitation professional use a variety of measures to diagnose a clinically significant dementia. An important point to come from all the research reviewed is that this is very difficult to do in the population of people with Down syndrome.

Summary

The answers to the questions driving the literature review will now be presented and the main points arising form the review will be summarized for the specific areas.

The current research would seem to confirm that as people with Down syndrome age, they show cognitive decline more than that normally associated with aging. In addition, within the population of people with Down syndrome at age 40 we see a

"universal cognitive deterioration compared to younger Down syndrome adults" (Schapiro, Haxby & Grady, 1992; p.724).

The new medical imaging techniques of SPECT and PET may well offer a way of being able to attempt a diagnosis of dementia in the mentally disabled population where other standardized tests and measures may be inappropriate. From the literature it would seem important to ascertain whether the exact location of the brain lesions seen in both Alzheimer's dementia and Down syndrome is important for a diagnosis of dementia and for specific cognitive functions. If attention and planning are most affected by early aging in Down syndrome then do those areas of the brain responsible for these cognitive processes contain more lesions in the older Down syndrome population? At the present time the pattern of cognitive changes seen in aging people with Down syndrome is analogous to that seen in people with early and moderate Alzheimer's disease. Schapiro, Haxby and Grady (1992) reported an inability to form new long term memories as being the most consistent and earliest deficit. Why is this so? What are the cognitive processes that underlie the formation of long term memories?

While it is difficult to generalize about such a heterogeneous group of individuals as those with Down syndrome, from the literature it is possible to draw some conclusions about the cognitive deficits most consistently observed. In childhood deficits are most common in language, visual monitoring, habituation memory and abstract reasoning. In later life deficits are noted in attention and planning, in following verbal directions and in language expression, in complex information processing skills, in visual retention and short term memory.

In the general population the medical and rehabilitation professional use a variety of measures to diagnose a clinically significant dementia. An important point to come from all the research reviewed is that this is very difficult to do in the population of people with Down syndrome.

In respect to the link between DAT and Down syndrome, it is hoped that this study will expand on existing research and support the theory that there exist two groups of older people with Down syndrome; the demented and the non demented. The importance of early identification of these groups perhaps in middle adulthood lies in the possibility of remediation of those people experiencing early cognitive decline. Although the remediation of such a group is outside the scope of the proposed study, the use of neuropsychological tests associated with the PASS model allows extremely specific processes to be identified for remediation. In addition, if tests based on the PASS model can differentiate between the demented and non demented person with Down syndrome then they may be valuable diagnostic tools.

CHAPTER THREE

Method

The study examined the cognitive functioning of older persons with Down syndrome. The study is built on previous work of the Developmental Disabilities Centre at the University of Alberta on intellectual decline and aging in Down syndrome. 30 of the participants has been involved in an earlier study at the University of Alberta (Das & Mishra, 1995b). In this earlier study the performance of persons with Down Syndrome and that of other persons with intellectual disabilities of other etiologies were compared. The results from these 30 participants provided the longitudinal comparison data from their testing in 1990. These 30 and the 6 new participants were seen in 1995 and data collected. The previous chapters have provided a rationale for the study. This chapter will address subject selection, study design, tests to be used, limitations of the study and finally a short discussion as to the usefulness and clinical application of the results.

Participants

The sample consisted of 36 adults with Down Syndrome. Participants were recruited from communities in and around Edmonton and lived either in the family home or in group homes. None of the participants resided in large institutional facilities. All had been diagnosed as having Down Syndrome in early childhood and many had received special educational services for most of their lives. Of the total sample 23 lived with their parents or another relative, and 13 lived in group homes. There were 12 women and 24 men in the sample and ages ranged from 25 years to 61 years. Of the 36 participants in this study one was married and the other 35 were single. There were equal numbers of people employed and unemployed. Parents were guardians for 20, other relatives for 10, the public guardian for 3 and another person - either a family friend or a lawyer for the remaining 3. The general health of the participants was good and is outlined in table one.

Insert table 1 about here

The high number of participants on medication for thyroid dysfunction (33.33%) is in accordance with results previously reported in the literature (Mani, 1988).

Participants were divided into two age groups, young and old. The mean age of the young group was 32.10 (SD 3.82, range 25 to 37 years) and the mean age of the older group was 47.59 (SD 8.87, range 38 to 61 years). The purpose of dividing the sample into these two groups was to consider differences in cognitive functioning and the presence of features of DAT developing over time. It was assumed from other similar studies that those participants in the younger group could be held to be free of DAT changes and symptoms, whereas in the older group one might expect to find a number of individuals at various stages of DAT (Zigman et al., 1987; Deb et al., 1992). Other studies in this area by Das and colleagues (Das et al., 1995a; Das & Mishra, 1995b; Das et al., 1995c) have considered changes in cognitive functioning related to age in persons with Down syndrome. In these studies, differences were found at 50 years of age, although sample sizes were small. Das & Mishra suggest "...that early signs of dementia may be detected by these tests that discriminate between individuals with DS and NonDS at age 40 and above" (Das & Mishra, 1995b, p.22). Two of the tests that discriminated at age 40, Number Finding and Expressive Attention, were included in the present study. Taking all this information into consideration it was decided that an age split at 38 was appropriate for this study. Furthermore, since the mean age of the older group in the study was nearly 48 years of age it was anticipated that any changes around age 50 would be detected.

Participants were all tested in their own homes. Permission was obtained from both the participants and their guardians. The testing sessions usually lasted for about one hour with the participant given a battery of tests described below, while the caregiver completed the DSDS through a structured interview with the researcher. When participants lived in group homes the DSDS was completed with both the primary caregiver in the group home and with the parent or guardian on a separate occasion. The only exceptions to this were cases where the parents of the person with Down syndrome had died and their nearest

Table 1: General health difficulties of participants

Health Problem	Absent	Present	Specifics
Heart attack	36	0	
Stroke	36	0	
Diabetes	35	1	
Head Injury	36	0	
Respiratory Problems	36	0	
Vascular Problems	35	1	Blood clot in leg
Severe allergies	30	6	Penicillin
Emotional trauma	34	2	Sexual abuse, depression
Thyroid Problems	24	12	
Cancer	35	1	Testicular

nearest "blood" relatives had not had much contact with the person with Down syndrome for a number of years. Each subject was paid an honorarium of $25 for participating in the project.

Eleven subjects with Down syndrome were involved in the imaging research. Subjects ranged in age from 33.33 to 61.42 years (mean age 48.03 years) with 7 males and 4 females in the group. All 36 subjects from the earlier phase of the study were approached and 15 volunteered for the imaging part of the study. Of these 15, the guardians of 3 of the subjects changed their minds just prior to scanning, 1 participant could not tolerate the idea of an injection at the last moment and became distressed so the procedure was discontinued and the remaining subject did not keep a number of appointments made for scanning.

Qualitative description of the participants

As a group there was enormous range in ability from almost independent living to a moderate care facility. There follow some short descriptions of certain participants and their families or caregivers to illustrate their levels of adaptive skills and independence. In order to ensure confidentiality the participants will be identified, somewhat impersonally, by their number in the study.

Participants

#16: This 30 year old woman does her own laundry, cooks, barbecues, plays golf and works part time at a local 'Smitty's" restaurant. She told me she did not want to have the SPECT scan thank you - a decision she made on her own. Her family have always encouraged her to extend her reading and writing skills everyday by following recipes and keeping her own recipe files. She rides her bike around the neighborhood and goes to exercise and aquasize classes offered to the *general* public at the local community center.

#21: A 27 year old man who works part time at MacDonalds, goes to build his literacy skills with a tutor (his choice) 2 days a week. He stays home on his own when his parents go away in the Winter. He shops, reads, takes the bus, goes to hockey games,

goes to a fitness club 2 or 3 times a week, and when he feels sick he takes himself to the Doctor's office.

#27 is a 33 year old man who is really the primary care giver in his family. He takes care of his father who has a chronic heart and respiratory condition. The young man cooks meals ranging from a simple pizza to a full roast dinner "with all the trimmings" by himself, he shops, does laundry and otherwise keeps house.

#18 is a delightful 59 year old gentleman. He is married, the only married participant, to another former resident of a large institution in Southern Alberta where he himself had lived for many years. He is now retired and keeps house while his wife works.

#22 is a 61 year old man who lives in a group home in Edmonton. He is retired and has been felt to have been deteriorating over the last few years. He seems to be losing appropriate social responses, for example he laughs out loud at singularly inopportune moments. He likes to imitate the group home staff and then snicker behind his hand. He gives away his prized possessions and then accuses others of stealing. He now needs verbal prompts to complete any simple activity such as vacuuming. His recognition of staff and long time friends has become almost random.

#19 is a 26 year old man who lives at home with his mother and step father. He is employed three days a week at a plant where he drives the lawn truck and washes large trucks with a power hose. He is very active with hockey and basketball. He goes to the gym twice a week and does weights.

#7 is a 50 year old woman who lives in her own apartment. She has a home worker who visits once a week to help with budgeting and any Doctor's appointments. This lady works full time in a hairdressing salon - an 'unsupported' placement which she enjoys. She has a history of sexual abuse for which she has received counseling. She is healthy and has many outside interests including Tai Kwondo, Karate, Bowling. She has many friends in the community including a boyfriend.

#6 had lived almost independently in an apartment for a number of years but in the Fall of last year he was moved back into group home in Stony Plain because of an increase in aggressive and depressed behavior. Since that time he appeared to become even more depressed and to have suffered more reductions in functioning as indicated by his caregiver in response to questions on the DSDS and in general conversation. On our first meeting #6 appeared to be very quiet and ill kempt. He was alone in his room with his lunch being taken up to him by staff. The skin on his hands was very rough and his nails were ragged and looked sore. His clothes were covered in paint - probably from his work at the vocational center that morning. Over the past years he has been through many changes of medication and there appears to have been some confusion between various doctors treating him as to what medications he should be on. In the Fall of 1995 he was on four different medications to try and control his depression and aggression. He was not reported to have thyroid dysfunction but this had not been formally assessed - even though it appears that many of his symptoms could be attributed to thyroid dysfunction as well as to a depression. He was reported as increasingly exhibiting forgetfulness in daily routines and showing a reduction in his speech and writing and reading skills. He was reported as previously enjoying hockey - both attending games and watching it on TV but now he is unwilling to attend games and appears to be totally disinterested- this has been observed over the past year. He was less able to occupy himself with appropriate activities reportedly as he was used to in the apartment setting and he is reported to spend a lot of time in his room sitting on his bed where he has started to self stimulate by rocking back and forth and by some hand flapping.

Since Christmas 1994 #6 was reported to have a longer 'lag' time between a verbal direction and carrying out the task. In addition he is reported to sometimes fail to recognize common objects or their function. Recently (in the last few months) his acts of aggression that were directed at objects, have been directed at people with some pushing - however, it was felt that this may be associated with changes in his medication. His movements are

becoming more slow and calculated. His caregiver gave an example of when he first met #6 (about 18 months ago) if they went to a store #6 would walk and reach out for the door and open in and walk through as one smooth and flowing set of movements. However, now #6 walks more slowly, will stop in front of the door as if he is thinking what to do next then open it, stop again and then walk through. In the past year #6 became increasingly difficult to get going in the morning with him wanting to stay in bed. When he was in the apartment it is reported that he got himself up and dressed and was ready to meet the bus for the vocational college in the mornings but that he would not be able to do this now and now even needs help in choosing appropriate clothing for the day. His facial affect was becoming flatter with less smiles and eye contact than before.

On our second visit he appeared to be extremely depressed. He attempted some of the tasks but then would give up within a few minutes and say he could not go on. He sat away from the table on a dining room chair and would not come closer to either of the researchers. He said he wanted to go up to his room. The group home workers said this was fairly typical of #6 and they did not seem to be concerned by the amount of time he spent alone. In addition #6's self stimulatory behaviors (e.g. rocking) seem to be increasing and are not confined to his bedroom. However, when I met with #6 in January 1996 it was like meeting a different person. His affect was no longer flat he was quite animated, talked a lot. We went for coffee and had a long conversation. He now has the case worker who used to work with him when he lived on his own. This lady said she had been shocked when she first saw #6 again after a period of some 18 months. He is reported to be improving almost daily, becoming more outgoing and taking more of a part in group home activities. His medication has been altered again and he is no longer on quite such a cocktail of drugs.

The last of the participants to be described in this section, participant #32, was a lady of 57 years who died in January of 1996. This lady lived at home with her sister and brother in law. She had deteriorated very quickly over the last year to the point where she

was unable to care for herself and seemed unaware of her surroundings. When I saw her at the close of 1995 she was unable to leave the house and spent most of her days crying and rocking. Her family were unable to arrange any home visits from their family physician or the local mental health team. Immediately following Christmas 1995 #32 seemed to lose all control over her behavior and physical state and was admitted to a locked unit in a local tertiary care home. She developed pneumonia and was hospitalized for two weeks after which she returned to the care facility and died in her sleep one week later.

Families

Parental concerns ranged from "what will happen to x when I'm gone?" to concerns over some participants drinking alcohol - should the be "allowed" to?, or smoking. Parents/caregivers ranged from actively encouraging independence to seemingly actively discouraging it by, for example, shaving a 40 year old son who has the skills to do this himself especially if he is given an electric razor.

The mother of participant #19 reported that she had insisted on moving her son out of a 'special school' in the city and moving him into the mainstream. She said she raised him with expectations. She expects him to have his own space and to run it how he wants. Mom said "in this environment he's treated normally, not 'Downs'." Mom encourages him to push his limits by setting challenges for him and then celebrating his successes as a family. This lady has always been a strong advocate for her son. When the family lived in Duncan, B.C., she started a program with Health Units there to put out pamphlets to families with children with disabilities to help them understand what was happening and how to access resources. Of society's attitudes and of the opportunities available for her son she said "We've broken down doors."

The widowed mother of #8 is very protective of her 40 year old son. She does not allow him to help in the house as it is not "man's work" and does not let him use the kettle or the stove "in case he burns himself". She makes sure he is in bed by 9 o'clock every week night. She shaves him. He does not leave the yard except to go to work at one of the

local agencies. Participant #8 is a very cheerful man, he is very talkative and speaks both English and German very well.

The mother of #10, a 30 year old man reported her bad experiences from when he was young and how they still hurt her and affect her interactions with "professionals". For example, she reported seeing "mongoloid idiot" written on his medical file when he was a little boy and said that the pediatrician would be rude about her son in front of her other children. She also reported that she was told after her son's birth that she should give him up and put him in an institution, when she refused she reported being told that her decision would ruin the lives of her other children.

Another redoubtable lady was the 81 year old widowed mother of subjects 1 and 2. These two men are two of a group of three triplets born in 1954. The two men are both affected by Down syndrome but appear to be non identical. The third triplet was reported to be a normal functioning male. He was killed in a motor accident a few years ago. In all their mother had 14 children and has 9 still living. The triplets were born a little premature but as far as mom was concerned the pregnancy seemed normal. After the boys birth she had to leave them in the hospital as they were small and sickly. She reported that on one particular occasion she went to visit them and they seemed close to death. She felt that the hospital were not feeding or looking after the boys appropriately and so she took them home and looked after them with her husband. She almost lost them to ill health on many occasions but this remarkable older lady stressed her belief in doing her best for them and treating them as normally as possible while shielding them from infections as far as she was able when they were little. This lady was unaware for many years that her two sons had Down syndrome, she said she thought they were "just retarded" however she felt that the 'boys' should be encouraged to do as much for themselves as they possibly could. To that end she has continued to work on self help skills at home even into their 40th years. Mrs. X commented on the attitudes of some other members of the family towards her two sons. One focus for her were the comments made to her by other family members on what

was to happen when she passed away. She feels the family are pressuring her to give up the boys to another family member now but in her words "they might as well dig my plot now". She comments that living with the boys keeps her going.

Another older lady, the 74 year old mother of participant #7 talked about raising her daughter and about her conviction that early work on social and self help skills had helped her become as self sufficient as she is today. Participant number 7 lives in her own apartment quite independently with visits once a week from a case worker to give her help with budgeting and some correspondence.

Her mother is anxious at times about #7 going to bars sometimes in the evening and occasionally drinking there. The worry was more with her seeming difficulty in deciding on appropriate behavior and people, rather than with her actually taking a drink. Her mother proudly showed me photographs of #7 in her karate uniform at a local tournament when she had been breaking blocks of wood!

There is a certain tragic element to #7's story. She had in the past been treated for some emotional disorders associated with sexual abuse by a close family member in recent years but is felt to be recovering well and dealing with the issues well through counseling. The sexual abuse took the form of coerced oral sex and inappropriate exploitation of #7 through certain photographs being taken. Her mother reported her feelings of anger and sadness over the fact that she had not been aware of the presence of the abuse until her daughter asked her if she really had to do it any more and graphically described what she had been coerced into doing. The mother also spoke of her sorrow over the fact that she and her daughter had decided not to prosecute the family member because of possible retribution or social difficulties with children in the family. There is now some friction in the family as certain family members are of the opinion that the whole thing was made up and did not in fact take place. Mom commented that she had kept certain photographs in case she ever decided to bring matters to a head. This was obviously a very sensitive subject for this old lady and an area that has not been resolved in any final way.

The last family in this section are the two sisters of #32. These two ladies had shared the care of their younger sister following their mother's death in 1985. On our first meeting in Fall 1995 these ladies were extremely tearful and described themselves as being just "at the end". They said they did not know what to do for their sister anymore and could not find anyone to help them. They described various medical practitioners involved with their family as being unwilling to come to the house to see their sister even though they could not get her to the surgery because of her extreme agoraphobia. Their Doctor was continuing to prescribe medication for #32 and to try her on new medication without seeing her. The sisters described how they felt that this was wrong but that he must know best because he is the doctor. They had also been told "what do you expect she's got Down syndrome, she's retarded". This was the most difficult meeting in the study because of all the emotions involved. The sister were sure there was something else they should be doing but did not know who to turn to. When the eldest sister telephoned me the day after #32 died she was very sad and finding it hard to accept that 57 was considered old age for someone with Down syndrome. At the time of writing she reported still feeling that there was more she should have done, been more insistent, and to have expected the same level of medical care for her sister with Down syndrome as her sister with cancer had received.

Design

The study is of a quasi experimental static group design. Random selection of subjects was not possible due to the small size of the population of persons with Down syndrome and to the stringent medical requirements for the imaging part of the study.

Tests and procedures

The study had a multi modal approach in that it combined neuropsycholological testing with clinical assessment of dementia and SPECT neuroradiological imaging. Sensitive tests of cognitive functioning based on the PASS model together with a more general test of cognitive ability were used. Two different dementia rating scales were

administered one in 1990 and another in 1995. Functional neuroradiological imaging through SPECT with Tcm99 HMPAO was carried out on a small subgroup of the sample.

Dementia Rating Scales:

Mattis Dementia Rating Scale (DRS)

The DRS (Mattis, 1988) provides an easily administered and objectively scored measure of general cognitive ability for individuals suffering from brain dysfunction. The DRS has been described as an omnibus measure of cognitive function which weights verbal functions more heavily than non verbal functions (Haxby et al., 1993, p.579). The split half reliability and test-retest reliability has been reported to be .90 and .97 respectively, for the total test. Five specific abilities are measured by the subtests; Attention, Initiation/Perseveration, Construction, Conceptualization and Memory. There is a total of 36 tasks in this test. The different subtests provide acceptable concurrent and predictive validity measures (r's in the range of .71 to .86) as mentioned in the manual. Each subtest has several items. One total score for each subtest was used. The DRS had been administered during data collection in 1990, for a discussion of findings see Das et al. (1995c).

Dementia Scale for Down Syndrome (DSDS)

The DSDS (Gedye, 1995) has been developed in Canada and standardized on adults with DS in British Columbia who have been studied longitudinally since 1987. The concurrent validity co efficient is reported as .81 and the inter rater reliability co efficient as .91. Data is collected from caregivers and does not rely on direct performance from the individual with DS. The scale addresses a most important consideration when dealing with this population. Namely, the need to separate the features that are typical of the person from features that indicate a loss of functioning. The DSDS identifies whether the individual has features of early, middle or late dementia. It comprises 60 items, 20 per stage and a screening interview. Items on the DSDS reflect cognitive losses in memory, language,

comprehension, temporal and spatial recall. Items also consider reductions in interests and initiatives and some specific physical changes. Features are described and are then marked as being either present, absent, not applicable or typical of adults self. When a feature is present the onset of the feature is recorded by month/season and year. Specific examples of behavior associated with the feature are solicited and recorded in the protocol. Additional questions concerning later stages of dementia are asked dependent on the number of items present in earlier stages. In this study absence of dementia was recorded with a numerical value of 0, early stage by 1, mid stage by 2, and late stage by a value of 3. The DSDS was administered during the second round of data collection in 1995.

Cognitive Functioning

The subjects were given a broad spectrum battery which included the Peabody Picture Vocabulary test - Revised (PPVT (R)), the Ravens Coloured Progressive Matrices, and measures taken from the Cognitive Assessment System (CAS).

Peabody Picture Vocabulary Test-Revised -PPVT-R (Dunn, 1981)

This is a verbal test but one which does not specifically require phonological coding or articulation which may have a detrimental effect on performance of this particular population. Also, the pictures are simple line drawings free of fine detail and figure-ground confusion which may impede performance of people with visual-perceptual impairments (Umberger, 1985). The test is a measure of receptive language rather than a comprehensive measure of mental ability but it is a well established and well regarded research tool. Reviewers of the PPVT(R) have found it to satisfy criteria for reliability and validity (Umberger, 1985; McCallum, 1985; Wiig, 1985). The mean reliability coefficients established for the PPVT(R) for internal consistency are in the range .61 to .86 for form M and retest alternate forms of reliability is in the range .73 to .91 (Umberger, 1985). This test was administered in both 1990 and 1995.

Ravens (1965) Coloured Progressive Matrices

Raven's Coloured progressive Matrices were used as a general measure of non verbal intelligence. The matrices were designed for use with young children and old people, including people with intellectual disabilities. The test requires the participant to choose 1 of 6 figures to best complete images of increasing difficulty. The test involves perceptual abilities and visuo spatial reasoning. Test retest reliability over the whole range of ages is reported as .90. It has widespread research use including studies involving people with DAT (Measso et al., 1993; Heidrich & Denny, 1994; Gainotti et al., 1991).

Based on what is already known about the cognitive functioning of older people with Down syndrome the neuropsychological tests used in this study were chosen specifically. Many of the tests were taken from the Cognitive Assessment System of Das and Naglieri as it is compatible with the conceptual model of cognition driving the study and with the proposed objectives of the research (see Das, Naglieri & Kirby, 1994, for a review of the CAS tests). The Cognitive Assessment System (CAS) was developed by Das and Naglieri and is currently being standardized. However, it has had research use, including use with the Down syndrome population. The rationale for using the PASS measures of the CAS battery is based on prior research (Das et al., 1995a; Das et al., 1993; Das, 1992; Das and Naglieri, 1992) which has found that the tests are discriminative between the four processes of planning, attention simultaneous and successive processing.

Planning and attention are the specific cognitive processes of interest in this study. These two cognitive processes were selected on the basis of prior studies with the Down syndrome population (Das, et al., 1995a; Das et al., 1993; Das et al., 1995c). These studies considered what, if any, intellectual changes take place in persons with Down syndrome. The processes of planning and attention were identified as being particularly at risk for decline in people with Down syndrome, particularly in those persons aged above 50.

The use of the young age CAS tasks might be assumed to be appropriate. We used 5-7 year old tests and certain 8-18 year old tasks. In using the 5-7 year old items it was anticipated that "floor" effects due to existing cognitive deficits would be avoided.

Planning Tasks

Planned Search. This test, in its standard version (Visual Search), was used by Teuber, Battersby, and Bender (1949) to identify visual search deficits after cerebral lesion. Planned Search requires the individual to develop an efficient scanning strategy to find a particular stimulus on a search field. The version used in this study consisted of 16 items; 4 automatic search items and 12 controlled search items. Each item consists of two search fields per page. At the center of each field is an encircled target pattern which appears only once in the field of many distracting patterns surrounding the target. In the controlled search items the target and the distracting patterns belong to the same category (e.g., a picture among pictures), whereas in the automatic search items the target and the distracting patterns belong to different categories (e.g., a picture among numbers, or a number among letters). The subject was instructed to take note of the target pattern and to find an identical pattern among those in the distracting field. Each search performance was timed from the point the page was exposed to the moment the second target was found. The maximum time was 90 seconds per item. The time scores of the first 4 items were totaled to form the automatic search score (PS-A), and the time scores from the last 12 items were totaled to form the controlled search score (PS-C).

Matching Numbers. This task was developed to measure planning by virtue of a need for an efficient system of determining which of the two numbers match (Das, Naglieri, & Kirby, 1994). The task requires the subject to find and circle as quickly as possible the two numbers which are the same in each of four rows on a page. There are six numbers of the same length in each row. The numbers increase in length from two to seven digits over the three pages of items. The time limit per page is 90 seconds. The subject's score is the total number of correctly circled numbers.

Attention Tasks

Number Finding. This test is a self-paced vigilance task. The subject is given a printed sheet of single digits varying from 1 to 9 that are arranged randomly in rows, 9 digits per row. The subject is required to locate and underline three particular digits (1, 2, and 3) on a page which contains both target and distracter digits. The version used in this study consisted of two pages of digits and the subject's score was the total number of correct responses. This test had been shown to differentiate between people with and without Down Syndrome (Das & Mishra, 1995), the question now is whether or not it can differentiate between older and younger people with Down syndrome, or between those who are demented and those who are not.

Expressive Attention : This task requires the subject to identify, as quickly as possible, whether pictures on a given page depict large or small animals, regardless of the size of the picture. For example, a mouse would be a small animal and an elephant would be a big animal even when the pictures might be inversely proportional to the actual size of these animals. The version used in this study consisted of three pages of stimulus pictures. In page 1, all the pictures are of the same size, in page 2 the size of the pictures is relative to the actual size of the animals, and in page 3 the picture size is the opposite of the actual size. The subject's score in this task was the performance time in page 3 divided by the number of correct responses. Maximum time allowed to complete page 3 was 180 seconds.

Receptive Attention. This task was developed by Naglieri and Das (1987) based on the original work of Posner and Boies (1971). The task is composed of four stimulus pages, each containing 10 rows of picture pairs, five in each row. In the first two pages subjects are required to underline, row by row, all the pairs of pictures that are the same, for example, two identical pictures of dogs or cats. In the last two pages the subjects are required to underline all the pictures that have the same name but which may have a

different appearance, for example, two dogs that are not identical. The subject's score is the time it takes to finish all four pages divided by the number of correct responses.

Imaging procedures

Regional cerebral metabolic rates for glucose were measured in the resting state using SPECT and 99mTc HMPAO. 99mTc HMPAO is a lipophilic agent that crosses the blood-brain barrier with rapid uptake. Uptake in the brain is about 5% of the injected activity with no significant late redistribution. Activity of 99mTc HMPAO is highest in grey matter and is proportional to rCP. Activity is symmetric. Dementia is considered a clear clinical indication for functional brain imaging, for example, DAT can be differentiated form other dementias by characteristic decrease in rCP in the parietotemporal cortex but not in sensory-motor cortex, basal ganglia, visual cortex or cerebellum.

99mTc HMPAO was introduced into clinical trials in Europe in 1984, and received a license by the Food and Drug Directory, National Health, Ottawa, in November 1986. No side effects were anticipated due to 99mTc HMPAO and none have been reported in the literature. The radiation dose for the subjects undergoing SPECT scans were significantly less than those delivered by a CT scan and were judged by the medical agency involved as being comparable with doses given in other studies.

Procedure

The SPECT procedure necessitated the participant attending the Cross Cancer Institute, where the scanner is housed, for approximately two hours. Each participant was injected with between 750 - 1000 MBQ (routine dose), 99mTc-HMPAO through a line inserted in the antecubital fossa. During injection each participant completed the planned search task (automatic) from the Das-Naglieri Cognitive Assessment System (CAS). Following injection a rapid sequence of images was obtained on a gamma camera/computer system to assess arrival of the radiopharmaceutical. The participant lay quietly on an imaging coach while the gamma camera was rotated through 360 degrees around the participant's head. This took around 45 minutes. On completion of imaging the

participant was free to leave, there being no residual side effects of the procedure. Three rapid sequence SPECTs, each with 64 frames were collected. The SPECTs were then added together if there was no patient movement. Three SPECTs per patient were acquired at an acquisition time of 10 seconds per frame thus making it a total of 30 seconds per frame and at least 100K for the total acquisition.

Projection images were acquired with a Picker PRISM2000 dual headed camera. SPECTs were then analyzed using a Metz reconstruction filter. All studies were displayed in sagittal, transverse and coronal sections for qualitative analysis. Each set of images was reported "blind" by an experienced radiologist. The results of the SPECT scans were presented in a written report. Areas of decreased or poor rCP were identified, and an indication given of whether this was compatible with a diagnosis of DAT.

Following this qualitative analysis, regions of interest were identified and counts were measured and compared with normal ranges using additional "brain fitting analysis". There were 14 regions of interest consisting of left or right superior frontal, inferior frontal, parietal, occipital, temporal, midbrain, and cerebellum. The three dimensional regions of interest (ROI) model used in this study is fully described in Hooper et al. (1990).

Written informed consent for all testing was obtained from both the participant and her/his guardian following ethics approval from the appropriate departments of the University of Alberta. Consent for SPECT imaging was obtained separately from other testing and the procedure was reviewed in detail with participants prior to the scanning appointment.

Summary

In summary, neuropsychological testing was carried out on a group of older people with Down syndrome to examine planning and attention processes. A measure of dementia was taken using the DSDS and a SPECT scan performed. It is hypothesized that any cognitive deficits seen in the non demented group of people with Down syndrome reflect changes in mental status that are related to aging rather than dementia. The deficits observed

in the demented group, as measured by neuropsychological tests, may be useful in determining the early signs and patterns of dementia in Down syndrome. Decline in attention and planning process if they are detected as anticipated, has implications for everyday living for these people. Lack of attention and an associated low state of arousal can lead to people not turning up for work, not preparing meals etc. Similarly poor planning can lead to reduced performance at work and in reduced safety in the community. If through this research it is possible to identify specific processes in decline and also the presence of dementia then careworkers with this population may have a better understanding of the types of remediation possible with their clients. Families may also better understand a person's seemingly 'strange' behavior if it can be diagnosed as being a result of a dementia. These and other areas will be discussed in relation to the results of the study and existing research in Chapter 5.

CHAPTER FOUR

Results

The results from this study are presented both quantitatively and qualitatively with the quantitative results given first. It is hoped that this treatment of the data, together with the description of the population in chapter 3, will show the heterogeneity of the group of participants. Results will be presented from longitudinal comparisons and cross sectional comparisons. The longitudinal data reflects changes between the 1990 and 1995, Cross sectional comparisons consider the relative performances of the young and old groups. In addition, performance of the young and old groups will be considered over time.

Statistical Analysis

Statistical calculations were performed with SPSS for Windows (release 6.1). Both parametric and nonparametric statistical methods were employed. Table 2 presents the descriptive statistics for the sample as a whole and for the two age groups for the DRS (1990), Ravens (1995), PPVT-R (1990 & 1995), and the DSDS (1995).

Insert table 2 about here

PPVT-R

Paired t-tests for the 30 subjects for whom longitudinal data was available revealed a significant difference at the .05 level on performance on the PPVT-R, indicating that performance on this measure had changed as people aged, when the sample was considered as one group ($t=2.45$, $df,29$, $p = .021$).

The cross-sectional analysis was based on the mean level of performance of the two different age groups. As described in Chapter 3, subjects were divided into two age

Table 2: Means and Standard Deviations in Dementia Rating Scale (DRS), Peabody Picture Vocabulary Test-Revised (PPVT-R), Ravens Progressive Colored Matrices, and Dementia Scale for Down Syndrome (DSDS).

	Whole group n=36	DS Young (25-37) n=19	DS Old (>38) n=17
Test	Mean (SD)	Mean (SD)	Mean (SD)
DRS	86.68 (27.59)	91.22 (28.45)	80.39 (26.12)
PPVT-R 1990	70.83 (28.20)	73.65 (24.74)	67.15 (32.87)
Mental Age	6.46 (2.61)	6.55 (2.04)	6.33 (3.30)
PPVT-R 1995	65.83 (32.89)	71.95 (24.55)	58.56 (40.31)
Mental Age	6.19 (3.16)	6.44 (2.16)	5.9 (4.10)
DSDS	.33 (.89)	.158 (6.88)	.53 (1.07)
RAVENS	12.62 (6.72)	14.74 (5.57)	9.93 (7.25)

groups. The younger group were aged between 25 and 37 years and the older group were aged between 38 and 61 years. The mean age of the young group was 32.10 (SD 3.82), and the mean age of the older group was 47.59 (SD 8.87).

A two way analysis of variance with repeated measures on the PPVT-R scores revealed no significant difference by age group over time ($F(28,1) = 3.81$, $p=.06$). There was a high level of correlation, as might have been expected, between the PPVT-R scores 1990 to 1995 in both the young and old groups. In the young group .937 at $p<.00$ and in the old group .928 at $p<.00$.

Dementia Rating Scales

It may appear to be difficult to compare the results of the Mattis DRS and the Gedye DSDS since they are based on such widely divergent conceptual models. However, each test purports to identify individuals with dementia. Dementia can be viewed as a condition which, once present, does not subside. Therefore we can compare the numbers of people meeting the criteria for a diagnosis of dementia on the DRS in 1990 with performance on the DSDS in 1995. The research question under consideration is the clinical utility of dementia rating scales with the population of people with Down syndrome. In this study we examined the number of people as a whole, and by age group, identified as having dementia on each measure. The results on the DRS indicated that all participants met the criteria for dementia. When these results were considered cross-sectionally no significant difference was found between age groups on the Mattis DRS ($F(29, 1) = 1.17$, $p=.29$). The mean of the older group on the DRS was lower than the younger group, 80.39 (SD 26.12) and 91.22 (SD 28.45) respectively. Both means were well below the critical cut off score of 137 recommended by Mattis (1988) and the cut off score of 129 recommended by Monsch et al. (1995).

In considering the DSDS scores which appear to be so much lower than all the others (see table 2), it should be remembered that the DSDS scores are category scores where 0 indicates absence of a dementia, 1 indicates early stage, 2 mid stage, and 3 late

stage dementia. Five of the participants were identified as having dementia using the DSDS. However, for one participant aged 33 a differential diagnosis of depression was indicated. This person was followed up at three and six monthly intervals and was seen to be improving in terms of his social behaviors and group home staff reported that he was "...much more like his old self". The remaining four participants with dementia were all over 50 years of age and were also on thyroid medication.

Ravens Colored Progressive Matrices

The Ravens Colored Progressive Matrices were administered in 1995 and results considered cross-sectionally. There was a significant difference by age. Analysis of variance revealed a significant difference by group on the Ravens ($F(32, 1) = 4.78$, $p = .036$) with poorer performance in the older group. Mean scores on the Ravens were 14.74 (SD 5.57) young group; 9.93 (SD 7.25) old group (see table 2). Scores that have been reported for the general population (Measso et al., 1993) would be 30.3 (SD 4.9) and 27.7 (SD 5.3) for young and old groups respectively. So the scores for the participants with Down syndrome are much lower than the normal population - as might have been predicted by their lower mental functioning. However, the mean scores are more similar to DAT data reported by Bottini et al. (1992). Bottini reported scores of 13.1 (SD 6.15) for a group of patients with DAT, mean age 70.6 (SD 7.17). The Ravens scores of 14.74 of the younger group in the present study is in the normal range for 6 year old children at about the 50th percentile of scores reported by Raven (1965). This would be in keeping with the mental age of this group indicated by the PPVT-R. The older group's score of 9.73 would place them below the 25th percentile for 5 and a half year old children reported by Raven (1965).

CAS tasks

To examine the distribution of the scores on the various tests administered in the study, the Lilliefors test was applied. On this test ps>.200 indicates normal distribution. Nearly all the test scores were found to be normally distributed (ps>.200) the exceptions

being the time score for expressive attention in 1995 (p = .0017), the number of items correct on Expressive attention in both 1990 (p = .1109) and in 1995 (p = .0835). The number of correct scores for Receptive attention in 1990 were not normally distributed (p = .0798). Scores on the Matching Numbers task in 1995 just failed to reach significance (p = .1844). However, since the scores in 1990 were normally distributed it was felt that parametric statistical tests would be robust enough for this violation in normal distribution.

Planned Search - Automatic

Longitudinal analysis with the Wilcoxon Matched pairs signed-ranks test revealed that as a whole performance was lower in 1990 than in 1995. Cross sectional analysis using Analysis of variance with repeated measures on Planned Search-automatic, showed a significant difference by group over time ($F(25,1) = 5.4$, $p = .029$).

Planned Search - Controlled

Cross sectional analysis of variance with repeated measures on Planned Search-controlled, showed a significant difference by group over time ($F(24, 1) = 5.78$, $p = .024$).

Expressive Attention

As the scores for Expressive Attention were not normally distributed (Lilliefors test, p = .0117) for number of items correct in 1995, or for time scores in 1990 and 1995 (p = .1109 and .0835 respectively) non parametric statistics were used. Kruskal-Wallis analysis of variance showed no significant difference by group in 1990 or 1995 on number of items correct, or on time taken to do the task.

Receptive Attention

Analysis of variance with repeated measures on receptive attention - number correct, showed a significant difference over time ($F(16, 1) = 5.61$, $p = .031$), but not by group ($F(16, 1) = 1.20$, $p = .289$).

No other significant differences on the CAS tasks, either longitudinal or cross-sectional, were detected.

As a previous study (Das et al. 1995), had shown that many participants had found certain of the CAS tasks too difficult note was taken of the participants' ability to attempt the tasks. The majority of people were able to attempt all the tasks. However, the most difficult task appears to have been the Expressive attention task where 9 people were unable to comprehend/attempt this task in 1995. The easiest task for the group as a whole was the planned search task which only 5 participants were unable to comprehend/attempt in 1995. There was a general increase in the number of people having difficulties with the tasks from 1990 to 1995 mostly made up of people in the older group. It was hypothesized that this inability to attempt some of the CAS tasks by a large proportion of the older group may be significant. This was explored by the use of Chi square comparisons on the ability of subjects to attempt the CAS tasks by group. None of the Chi square analyses proved to be significant.

Given that the sample size in this study was small, the tests of statistical significance were supplemented by calculating effect sizes. The tests looked at the size of the effect without regard to sample size (Smith & Glass, 1987). Effect sizes are reported in Table 3. At $p = .05$ only the Ravens effect size of .74 was significant. There were moderate effect sizes for receptive attention, matching numbers and planned search-automatic. This could suggest that with a larger sample we might have found more significant differences in performance between young and old people with Down syndrome.

Insert table 3 about here

Mattis DRS and CAS tasks

The relationships between the DRS (1990) and performance on the CAS tests in 1990 and 1995 were examined and data is presented in Table 4. The results indicated that a

very low score on the DRS, <80, resulted in significantly different performance in 1990 on all CAS tasks and the PPVT-R, but not on planned search-automatic. However, in 1995 those who had historically scored <80 on the DRS in 1990 only differed in performance from the >80 group on PPVT-R, planned search-controlled and receptive attention (see Table 4). Therefore, the groups >80 DRS and <80 DRS had changed over the five years and become more similar in their performance on a number of tests.

Insert table 4 about here

Relationships within dimensions of the PASS model

Mean scores on the CAS tests were considered by group. Correlations above $r = .5$ are reported in Tables 5 and 6. In Table 5 we can see that in the younger group correlations for planned search-controlled (.91), number finding (.72) and receptive attention (.64), were relatively strong between 1990 and 1995. However, scores on the other tasks were not, indicating that performance may have changed over time. In the older group, as we can see in Table 6, scores on Planned Search-automatic (.80), Planned Search-controlled (.76) and Receptive Attention (.94) were strongly correlated. This implies performance had not changed much over time. However, Matching Numbers, Number Finding and Expressive Attention scores were not well correlated. The correlations in both groups raise questions as to the reliability of some of the CAS tasks over time with people with Down syndrome. Alternatively, the correlations may raise questions as to the restriction of range in scores in this group of people.

Table 3: Effect sizes, Means, (SD) and t scores by measure - CAS tasks 1995

Measure	Group1 Mean (SD) n	Group 2 Mean (SD) n	t	d
PPVT 95	71.95 (24.55) n=19	58.56 (40.31) n=16	1.21	.40
PPVT 90	73.647 (24.741) n=17	67.154 (32.868) n=13	.62	.22
Ravens	14.74 (5.57) n=19	9.93 (7.26) n=15	2.19*	.74
DRS	91.222 (28.445) n=18	80.385 (26.12) n=13	1.08	.40
DSDS	0.158 (.688) n=19	00.529 (1.07) n=17	-1.25	.41
Planned Search Auto.	5.61 (3.36) n=18	9.27 (7.81) n=13	-1.086	.61
Planned Search Cont.	22.58 (17.16) n=17	27.93 (19.15) n=13	- .80	.29
Matching Numbers #Correct	12.67 (3.35) n=15	10.23 (4.69) n=13	1.60	.60
Number Finding #Correct	48.31 (25.25) n=16	41.58 (26.23) n=12	.69	.26
Expressive Attention Time #s 1,2,3	265.4 (195.04) n=15	224.13 (97.66) n=8	.56	.27
Expressive Attention #Correct #s 1,2,3	107.67 (12.77) n=15	102.25 (15.00) n=8	.91	.39
Receptive Attention #Correct	41.75 (5.9) n=12	37.33 (7.16) n=9	1.55	.67

Table 4: Significant findings on relationship between low score on DRS and CAS tests

Test	DRS>= 80 Mean (SD) n	DRS< 80 Mean (SD) n	t value	p
Ravens	15.83 (4.08) 18	8.42 (6.57) 12	3.49	.003
Expressive attention (1990): Number of correct responses	109.28 (12.15) 18	80.42 (36.86) 12	2.52	.022
Expressive attention (1990): Time taken	185.39 (55.63) 18	345.92 (144.81) 12	-3.66	.003
Matching Numbers (1990): Number of correct responses	12.94 (3.13) 17	7.64 (5.71) 11	2.82	.014
Number Finding (1990): Number of correct responses	41.72 (22.65) 18	16.75 (15.27) 12	3.61	.001
PPVT (1990)	86.67 (20.86) 18	47.08 (19.97) 12	5.18	.000
Planned search (1990): Controlled	18.92 (7.87) 18	35.94 (21.08) 12	-2.68	.019
Receptive attention (1990): Number of correct responses	38.35 (6.96) 17	18 (9.26) 10	6.49	.000
Planned search (1995): Controlled	17.42 (7.58) 18	35.54 (23.94) 9	-2.22	.055
Receptive attention (1995): Number of correct responses	41.82 (5.57) 17	30.00 (3.46) 3	3.51	.002
PPVT (1995)	85.58 (20.49) 19	37.67 (18.32) 12	6.32	.000

(1990 and 1995 are the years of test administration)

In considering the relationships between the measures of Planning and Attention, we see different patterns between the young and old groups. Correlations were examined in each group between the two planning tasks (Planned Search and Matching Numbers) and the three attention tasks (Number Finding, Expressive Attention and Receptive Attention). In the young group the correlations between the planning tasks were strong. The young group's performance on the attention tasks correlated quite well but some longitudinal changes were evident. In 1995 performance on the expressive attention task was no longer significantly correlated with performance on the other two attention tasks. In 1990 all three attention tasks had been strongly correlated in the young group.

Insert Tables 5 and 6

In the old group in both 1990 and 1995, Planned Search-controlled and Matching Numbers correlated well, but Matching numbers did not correlate strongly with Planned Search-automatic. On the attention tasks in 1990 scores for the old group were strongly correlated for Receptive attention and Number Finding, but performance on the Expressive attention task did not correlate well with the other two attention tasks. In 1995 performance on the three attention tasks was not strongly correlated for this group. It has already been pointed out that the Expressive Attention task appeared to be the one which the group as a whole found to be the most difficult.

Table 5: Significant Correlations (p.05) between CAS measures above r=.5 for Group One (Young).

	PSA	PSC	FPSA	FPSC	FMNC	MNC	NFC	FNFC	RAC	FRAC	EAC	FEAC
PSA 1995		.55 (.02)	.56 (.02)				.53 (.04)					
PSC 1995				.91 (.00)	-.80 (.00)	.57 (.03)	-.63 (.01)					-.87 (.00)
FPSA 1990				.60 (.01)	-.60 (.01)	-.62 (.01)	-.64 (.01)			-.67 (.00)		-.61 (.01)
FPSC 1990					-.84 (.00)	-.69 (.01)	-.51 (.04)			-.61 (.01)		-.90 (.00)
FMNC 1990						.64 (.01)	.56 (.03)			.53 (.04)		.76 (.00)
MNC 1995										.57 (.04)	.67 (.01)	.57 (.03)
NFC 1995								.72 (.00)	.76 (.00)	.71 (.00)		.53 (.04)
FNFC 1990										.76 (.00)		.54 (.02)
RAC 1995										.64 (.03)		.61 (.04)
FRAC 1990												.71 (.00)
EAC 1995												.75 (.00)

Table 6 : Significant correlations (p<.05) between CAS measures above r=.5 for Group Two (old).

	PSA	PSC	FPSA	FPSC	FMNC	MNC	NFC	FNFC	RAC	FRAC	EAC	FEAC
PSA 1995		.84 (.00)	.80 (.01)	.62 (.05)								
PSC 1995				.76 (.01)	-.72 (.03)	-.65 (.02)	-.58 (.05)					
FPSA 1990				.66 (.02)							-.78 (.04)	-.71 (.01)
FPSC 1990					-.62 (.04)							-.77 (.00)
FMNC 1990								.87 (.00)		.78 (.01)		
MNC 1995												.63 (.05)
NFC 1995												
FNFC 1990										.66 (.04)		
RAC 1995										.94 (.01)		
FRAC 1990												
EAC 1995												

It was anticipated that certain of the CAS tasks would be better explored by looking at the individual subtests which make up the CAS task. For example, when looking at the Receptive attention task, two of the subtests rely on the subject performing a physical match and the second two tests consider a name match. Consequently we examined these subtests both longitudinally and cross sectionally (Table 7).

Insert 7 about here

Cross sectional results which examined the relationship between the two age groups across time on the individual subtests by analysis of variance, revealed only one significant difference. This was on the second of the Expressive attention tasks, the older group had fewer correct responses (F (21, 1) = 4.90, p.038). However, no such difference was noted on the time taken to complete this task (F (21,1) = 3.36, p.081).

The longitudinal data shown in table 7 revealed some significant differences in performance on the subtests. The group as a whole scored significantly higher in 1995 on the second of the number finding tasks (t = -2.85, df 24, p =.009). Performance on number finding task 1 was significantly slower in 1995 (t = -12.41, df 25, p = .000). As a whole group, participants scored better in 1995 on the first receptive attention task, which required a physical match, (t =-2.47, df 24, p = .021). Performance was also better in 1995 for receptive attention task 3, which required a name match, (t = -2.27, df 19, p = .035). The remaining significant finding was on the time taken to complete the second matching numbers task where performance was better for the group as a whole in 1995 (t =3.84, df 23, p =.001).

Table 7: T Tests for Paired Samples on Subtests of CAS: 1990 compared with 1995

Subtest		Whole Sample		Young Group		Old Group	
		t-value	p	t-value	p	t-value	p
Number finding number correct	task 1	-1.63	.116	-2.12	.051**	-0.21	.836
	task 2	-2.85	.009*	-2.58	.021*	-1.23	.254
Number finding false detections	task 1	-1.73	.096	-0.85	.409	-1.61	.141
	task 2	-1.19	.245	-0.91	.375	-0.73	.488
Number finding time taken	task 1	-12.41	.000*	-7.48	.000*	-19.61	.000*
	task 2	-0.59	.561	0.07	.947	-11.42	.000*
Expressive attention number correct	task 1	-1.32	.201	-0.15	.885	-2.42	.042*
	task 2	-0.65	.520	0.73	.475	-2.20	.064
	task 3	0.05	.964	0.77	.454	-2.65	.038*
Expressive attention time taken	task 1	1.56	.131	1.18	.256	2.31	.050*
	task 2	1.84	.080	0.56	.582	2.11	.073
	task 3	-0.47	.646	-0.35	.732	-0.29	.779
Receptive attention number correct	task 1	-2.47	.021*	-2.23	.042*	-1.05	.325
	task 2	-1.01	.323	-0.80	.438	-0.60	.563
	task 3	-2.27	.035*	-2.20	.047*	-0.71	.507
	task 4	-0.65	.523	-0.94	.365	0.22	.833
Receptive attention false detections	task 1	0.71	.484	1.09	.293	-0.37	.719
	task 2	0.79	.436	1.69	.113	-1.28	.237
	task 3	0.00	1.0	1.05	.314	-1.08	.328
	task 4	0.00	1.0	-0.32	.754	0.54	.611
Receptive attention time taken	task 1	0.43	.672	1.15	.270	-0.84	.424
	task 2	1.32	.199	1.67	.117	0.16	.877
	task 3	-1.46	.160	-1.04	.318	-0.98	.371
	task 4	-0.21	.836	0.67	.520	-0.84	.441
Matching numbers time taken	task 1	0.57	.573	1.17	.262	-0.59	.571
	task 2	3.84	.001*	1.92	.076	5.16	.001*
Matching numbers number correct	task 1	0.38	.709	1.47	.164	-0.20	.847
	task 2	0.56	.582	-0.67	.517	2.67	.029*

When the longitudinal changes were considered by old and young groups other significant differences were observed. In the young group better performance in 1995 was noted on the following tasks: Number Finding task 1 more items correct in 1995 (t =-2.12, df 15, p = .051); Number Finding task 2 more items correct in 1995 (t = -2.58, df 15, p = .021); Receptive Attention task 1 - physical match more items correct in 1995 (t = -2.23, df 15, p = .042); and Receptive attention task 3 - name match, more items correct in 1995 (t = -2.20, df 13, p = .047). It was also noted that better performance in 1995 on Number Finding task 1 was associated with longer time taken to complete this task (t = -7.48, df 15, p = .000).

Upon examination it was observed that performance in the older group also had some significant changes over time. Three of the tasks took significantly longer in 1995 these were; Number Finding task 1 (t = -19.61, df 9, p = .000), Number Finding task 2 (t = -11.42, df 8, p = .000), and Expressive Attention task 1 (t = 2.31, df 8. p =.05). Performance appeared to have deteriorated significantly on three tests with scores being lower in 1995 than in 1990; Expressive Attention task 1 (t = -2.42, df 8 p = .042), Expressive Attention task 3 (t = -2.65, df 6, p = .038), and Matching Numbers task 2 (t = 2.67, df 8, p = .029). On only one task had performance significantly improved in either time taken or score obtained, this was on the second Matching Numbers task where performance was slower in 1990 (t = 5.16, df 8, p = .001).

Considering the group findings it appears that performance in the young group tended to have improved over the five year time period while performance in the older group seemed to be deteriorating.

As a post hoc analysis we considered splitting the participants at age 50 as in earlier studies Das (1995c, 1995c) had observed changes in the scores of people with Down syndrome over the age of 50. When the sample was divided at age 50 a group of 28 people was formed in the young group (under 50) and 8 people made up the old group (50 and

over). The very uneven ns and small group sizes limited the statistical tests available. There were further complications in that although there were 8 people in the older group, the number of participants who had actually managed to complete the CAS tasks was very low and varied from test to test. Use of the Chi square statistic was considered to look at differences in ability to perform the CAS tasks between the young and old groups. The statistic used was Fisher's exact test of probability. Fisher's test was applied and significant differences were found between the old and young groups' ability to attempt each of the CAS tasks in 1995; Planned Search ($p = .0028$), Matching Numbers ($p = .0164$), Expressive Attention ($p = .05$), and Receptive Attention ($p = .0164$).

Behavioral observations and strategies used on CAS tasks

In terms of behavior on the CAS tasks the following points were noted. Many had difficulties keeping along the lines when the number of lines and choices increased. The task that caused the most difficulty was the Expressive Attention Task where subjects had to discriminate between large and small animals. Many insisted on naming the animal in this task , for example, elephant - big and mouse - small. Others went into great conversations for example "Oh a mouse, like Mickey mouse, I've seen him. Have you been to Disneyland?, this mouse is small." Once a conversation had started in this way it became quite difficult to redirect and no sense of urgency for the task could be established. In the second level of this task those who could read found no problems on the Expressive attention tasks difficult. This suggests something of a dilemma. The early items intended for younger children should be conceptually easier for these people than the later items. However this was obviously not the case.

In the Visual Selective Attention task many people continued to try and match numbers as they had had to in an earlier task. In Receptive attention, problems came with trying to assign categories to pictures when pairs of pictures were no longer identical. The responses of the participants to the Receptive attention task was to have been expected. A

physical match would be expected to be faster than a name match. In the first part of the Receptive attention task participants underline identical pictures, whereas in the second part of the task the pictures can be different if the category is the same. For example an apple and a pear are both fruit and so can be underlined. To perform a name match is to perform a higher level task requiring more complex cognitive coding than the perceptual encoding required for a physical match.

The most common strategy observed for Planned Search was to keep a finger on the stimulus picture. The examiners also saw lots of self talk and think aloud strategies. In addition metacognitive strategies were observed in the receptive attention task for example "the same? no" etc.

In tasks where matching numbers was required many seemed to continue to try and match the first number on a row with one of the others even when it became apparent that there was not another one in the row, people seemed to assume that they must have missed it rather than it was not one of the pair of numbers they were looking for. Other people kept their hand on the beginning of the line to keep their place in the task. Pages with lots of numbers met with comments such as "Oh boy this one's hard" even before they were told what to do.

The idea of working as quickly as you can was obviously difficult for some people to grasp as is shown by the following example. In the Visual selective task where speed is really important subject #8 had long discussions with himself as he worked "Where's the 3, come on down baby" and lots of joking around. Also on this task some people tried to find all the 1s then all the 2s and 3s and were very stubborn when we tried to redirect them to work along the lines and look for the 1 2 and 3s at the same time.

The idea of pairs in receptive attention was very difficult for some people and frustration soon set in on this one - the fact that there were some "pears" in the task did not help at all! Occasionally people would come out with really strange but appropriate

comments, for example on this task subject #20 "Oh boy I like twins" when he saw two faces next to each other.

Use of strategies

When subjects were asked about the strategies they had used they often claimed they did not know. We saw many people following along a line with their finger and some strange interpretation of the rules. For example subject #19 would only accept numbers 1 2 and 3 when they were next to each other on the Visual Selective Task.

Some of the timed tasks were affected by speech impediments. Even when the tasks did not require a verbal response some people felt that they had to give one and would not be redirected. Tasks were also affected by the amount of self talk certain individuals used to guide them through the tasks. We also encountered some very stubborn thinking on the animal task - where for example #30 insisted that some of the animals were medium and proceeded to tell us so as he went through the task. Subject number 30 could also not be dissuaded from telling the examiner the various sounds the animals made and what they ate.

A reasonable number of the subjects tried to go through tasks by columns rather than by lines. Many vision problems were noted with people working very close up to the page or showing confusion over smaller figures were noted.

Results from neuroradiological imaging with SPECT

Eleven subjects with Down syndrome were involved in the imaging research. Subjects ranged in age from 33.33 to 61.42 years (mean age 48.03 years) with 7 males and 4 females in the group. Scans were read 'blind', a qualitative report issued and then quantitative analysis was performed. The quantitative analysis of regions of interest was performed using Neurofit analysis software (Version 3.25). Comparisons were made against Cross Cancer Institute PAO Autofit normal ranges.

Of the eleven subjects with Down syndrome none of the SPECT scans were reported as "normal", nor were they interpreted as having changes associated with normal aging. The results from this study are in accordance with Nakayasu et al. (1991) cited in Schapiro (1993), and Rae-Grant et al., (1991) which reported reduced rCP in bilateral parietal and temporal regions with Tc-99m HMPAO in people with Down syndrome. Reduced temporal lobe perfusion was observed on all 11 scans. The qualitative results for all subjects are shown in Table 8.

Insert Table 8 about here

Summary results for comparisons with PAO normal ranges are given in Table 9. It can be seen that deficits were observed in regions of particular interest in DAT, namely parietal and temporal, in 7 participants. Where the number in the table is positive it reflects an increase in rCP in some areas which corresponds to rCP in other areas being reduced. Only one participant, KE, had normal SPECT rCP patterns. The remaining 10 were abnormal when compared to the normal PAO range data.

Two of the participants, DST and SF, appeared to have had small strokes, or cerebro-vascular-accidents (CVAs) at some time in the past. This is indicated by large focal deficits.

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insert tables 9 and 10 here

Summary results for asymmetry are given in Table 10. The asymmetry data is important as asymmetry is the best descriptor of DAT in the early stages. In early DAT we would expect to see asymmetry in temporal and parietal rCP. Later in DAT this asymmetry is not seen as by this time perfusion deficits have become bilateral and more widespread.

Table 8: Data and results of 99Tcm-HMPAO brain SPECT of 11 subjects with Down syndrome - Qualitative Analysis

Subject Number	Sex	Age (Years)	SPECT Perfusion deficts
1	Male	41.33	Bilateral temporal~
3	Female	48.75	Temporoparietal~
6	Male	33.33	Bilateral Temporal~
7	Female	50.83	Bilateral temporal, Right parietal~
8	Male	40.50	Bilateral Temporoparietal*
18	Male	59.17	Temporal
22	Male	61.42	Diffuse cortical atrophy
25	Female	43.83	Bilateral Temporparietal & frontal*
26	Female	51.50	Bilateral temporoparietal*
28	Male	58.00	Bilateral temporoparietal & frontal*
34	Male	39.67	Temporal~

* analogous to a diagnosis of DAT
~ analogous to deficits observed in either very early DAT or typical of individuals attending the memory clinic

Table 9: Summary table for SPECT scans for 11 participants with Down Syndrome as compared to PAO normals

Region	Participant											
	KB	KE	SF	PH	OK	CM	WN	DST	MS	BT	EK	# Subjects with abnormalities
Superior Frontal			-3.8	2.8		2.3			1.5	2.4		5
Inferior Frontal	2.8		4.3		-2.2						1.9	4
Total Frontal				2.2		1.8				2.2	1.8	4
Parietal			-4.1			1.6		-2.3				3
Occipital	2.2			-1.9	1.5	-1.8		-4.5		-3.0		6
Temporal	-2.1			3.4	-3.5		1.8				-1.7	5
Midbrain				-2.4			2.2			-2.0	2.9	4
Cerebellum	-2.6				1.6	-1.7			-2.1			4
Total Hemisphere			-2.3					-3.8				2

Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Where the space is blank, the number is within 1.5 SD of the mean.

Table 10: Summary table for asymmetry in SPECT scans for 11 participants with Down Syndrome as compared to PAO normals.

Region	Participant										
	KB	KE	SF	PH	OK	CM	WN	DST	MS	BT	EK
Superior Frontal			-3.8	2.8		2.3			1.5	2.4	
Inferior Frontal	2.8		4.3		-2.2						1.9
Parietal			-4.1			1.6		-2.3			
Occipital	2.8			-1.9	1.5	-1.8		-4.5		-3.0	
Temporal	-2.1			3.4	-3.5		1.8				-1.7
Midbrain				-2.4			2.2			-2.0	2.9
Cerebellum	-2.6				1.6	-1.7			-2.1		
Total Hemisphere			-2.3					-3.5			

Values are asymmetry expressed as standard deviations from the normal database mean. Values > 1.5 standard deviations are considered clinically significant. Asymmetry = 100* (left- right) / (right - left). Where the space is blamk, the number is within 1.5SD of the mean.

(Individual data for all 11 participants can be found in Appendix A)

Imaging data is presented in Appendices A to D for four participants. Appendix A contains the 3D image composites and tomography slices for subject WN. This 51 year old lady has a history of declining cognitive and behavioral functioning. The SPECT images clearly show bilateral temporal and parietal deficits in keeping with DAT. Four months after this scan was taken her functioning had deteriorated to such an extent that she had been placed in an Alzheimer care facility in the Edmonton area.

In Appendix B we can see a similar pattern of deficits for a 43 year old lady. In this case there is some involvement of the frontal lobes together with bilateral temporal and parietal atrophy. This specific pattern of cerebral atrophy can be compared with Appendix C which shows the tomography slices of a 61 year old man with Down syndrome with widespread cortical atrophy which is not typical in persons presenting with DAT. Appendix D shows the tomography slices for the youngest person in the group, 33 years old. The SPECT scans for this subject revealed temporal cerebral atrophy. Such a picture could indicate early memory impairment or very early DAT. The history of this subject gave a picture of changes in behavior, adaptive and cognitive functioning. It is proposed that this subject be followed over time to consider the presence of DAT or of a progressive cognitive decline due to accelerated aging.

CAS tasks and SPECT

How did the performance of the 11 participants who received SPECT scans differ on the CAS tasks when compared with the rest of the sample? We found that there were no significant differences based on performance in 1990. However, by 1995, the second round of data collection, some deterioration in functioning had occurred. In the planned search task the scanned group took longer than the rest on automatic search (t = -2.31, p =.046) and controlled search (t = -2.68, p = .012). The scanned group also obtained fewer correct responses on the Expressive Attention task (t = 2.39, p = .026), the Receptive attention task (t = 2.31, p = .032) and the Matching Numbers task (t = 2.88, p = .008).

As a post hoc investigation, the participants who had received SPECT scans were given further tests of successive and simultaneous processing from the CAS battery. It was anticipated that the perfusion deficits observed on SPECT in temporal and parietal regions would be reflected in poor processing on these tasks. Only 9 of the 11 participants were able to be tested. Of the two people not included, one refused to be tested and the other had deteriorated greatly and had been placed in an Alzheimer care facility. This participant had deteriorated to such an extent that she was reported to be in an almost constant vegetative state. The results from the 9 remaining participants reflected great difficulty in most of the tasks.

The nine participants were administered two simultaneous processing tasks, Simultaneous Verbal and Figure Memory. In the Simultaneous Verbal task the subject was read aloud a question answered by one of six different pictures on a page. The subject had to point to the correct picture to answer the question. There were 29 items on the test and the subject's score was the total number of correct responses. The scores obtained ranged from 1 to 15 with a mean score of 5.22. Figure Memory requires a geometric design to be reproduced by the participant. The participant is shown the design for five seconds and then the stimulus is removed and the subject has to trace the stimulus figure within a more complex design. The task consists of 20 designs and the subject's score in this task is the number of designs correctly reproduced. The participants found this to be a difficult task with three of them becoming quite upset and confused. Scores ranged from 0 to 4 with a mean score of 1.22 correct responses.

Two tasks of successive processing were given Word Series and Speech Rate. The Speech Rate task required the subject to say a series of words 10 times as fast as possible. Only 1 participant could manage to complete this task with a mean response time of 19.25 seconds, of the others 1 managed to give responses to 2 items, and the rest were unable to get even the first item correct seeming to be unable to hold three words in memory. When we considered the data from SPECT there were no distinguishing features between the one

who could do this task and the rest who could not. The final task, Word Series appeared to be equally difficult for the participants. This task requires the subject to repeat a series of single syllable words in the same order in which they were presented. There were nine familiar words given in groups from two to nine words. The task had a maximum score of 30 points. Scores for the 9 participants ranged from 0 to 5 with a mean score of 1.77.

What conclusions are we able to draw? On the face of it, people with Down syndrome who had abnormalities on SPECT involving the temporal and parietal regions, also had great difficulties in cognitive tests involving successive and simultaneous processing. The tests came from a model of information processing that suggests that these processes relate to temporal, parietal and occipital regions of the brain. Does SPECT have a predictive power for identifying people who have difficulties in successive and simultaneous processing? Do the CAS tasks indicate temporal and parietal abnormalities? The answer to both questions is that this is possible but by no means certain. Such questions are outside the bounds of this study and require further investigation with a significantly larger sample.

The results will be discussed in the following chapter. Implications for practice and suggestions for future research will be considered.

CHAPTER FIVE

Discussion

The results of the study will be discussed in such a way as to specifically answer the research questions posed in Chapter 1. To recapitulate, this study sought to link current research in two specific areas; cognitive psychology/information processing, and SPECT neuroradiological imaging. It also considered the use of clinical rating scales in the assessment of possible dementia in people with Down syndrome. Reviews of the literature indicated that current clinical instruments used to assess dementia tend to over identify people with Down syndrome since these people's functioning and adaptive behaviors are usually lower than the general population. SPECT imaging has detected specific changes in regional cerebral blood perfusion (rCP) associated with DAT. Neuropsychological tests based on the PASS model have identified specific cognitive processes as being particularly at risk in the Down syndrome population. Is there a way to draw all these areas together so that it will enhance our understanding of the pattern of cognitive decline that has been observed in the Down syndrome population? It is possible that SPECT or neuropsychological tests, or both, may be good discriminators of dementia in Down syndrome. Previous studies have shown that the tests associated with the PASS model can successfully discriminate between people with Down syndrome and persons with mental retardation of other etiologies (Das, Divis, Alexander, Parrila & Naglieri, 1995a; Das, Davison, Hiscox, Mishra & Thapa, 1993; Das & Mishra, 1995b; Das, Mishra, Davison & Naglieri, 1995c). The next step was to see whether these same tests could differentiate between people with Down syndrome with and without DAT, given that sudden decline may indicate the presence of dementia.

1: Is there a pattern of specific cognitive decline in persons with Down syndrome which is observable as they age?

Traditional testing methods for detecting cognitive decline have been proven to be inadequate with the Down syndrome population, due in part to floor effects (Wisniewski &

Rabe, 1986; Oliver & Holland, 1986). The tasks used in the study were those associated with planning and attention as these had been implicated in earlier work and it was anticipated that these tests may have a certain predictive power in detecting DAT in this population. However, this was clearly not the case. The tests of the CAS indicated severe decline in a number of cases - but not in all the old group. The question of homogeneity of groups could be partly responsible. The functioning of individuals with Down syndrome varies so widely that it is very difficult to get homogeneity in any age group. This is a problem often noted in studies in this area many of which also suffer from small sample sizes which serves to compound the difficulties of heterogeneity of subjects.

Das' earlier findings in this area have suggested that planning and attention appear to be the two areas of cognitive functioning that differentiate people with Down syndrome from other people with developmental disabilities. However, they did not differentiate between the young and old groups in this study as we had hoped. This finding could well be related to the low functioning of the participants. If this is the case then this study supports earlier findings (Das & Mishra, 1995; Das et al., 1995a) that at low levels of general intellectual functioning planning and attention cannot be separated in individual components. Although the cognitive functions of the PASS model are interactive, there is a hierarchical nature to the PASS model. Attention is the "root" process. Without attention, or with low ability to attend, a subject's performance on tasks requiring the higher level process of planning would be adversely affected. It could be, that to detect subtle changes over time which relate to cognitive decline and possible DAT in Down syndrome, we need to retrace our steps. This study did not specifically look at simultaneous and successive processing, perhaps these processes may change more with age and remain more discrete. The Ravens Coloured Progressive Matrices, which are a measure of simultaneous processing, did discriminate between young and old groups. It may be important to look more closely at the issue of simultaneous processing. Indeed, in an earlier study (Das et al., 1995) a group of older persons with Down syndrome performed significantly more poorly

on a task requiring simultaneous processing than both a group of younger persons with Down syndrome and another non Down syndrome group of people with intellectual disabilities.

It is a possibility that the CAS tasks were not measuring the same cognitive functions in the expected way in this group of people. For example, in the Stroop type test (Expressive Attention) the easier items were treated as a decision making task by many of the subjects. This made it a very different task from one which looked at speed of output from semantic memory.

We used the 5-7 year old tasks from the CAS in this study. The use of the 5 -7 year old tasks appears, at first sight, to have been appropriate for this population. For example, in the case of the Matching numbers task only 2 of the participants - both in the young group - managed to attempt the tasks for 8 to 18 year olds. However, an important question is raised by the quality of performance of the subjects as a whole. Could the low levels of performance exhibited by the subjects with Down syndrome on the 5 to 7 year old tasks of the CAS be attributed not to poor cognitive processing but to different processing? This seems to have been the case in terms of the Expressive attention task discussed earlier. It is apparent that in order for the 5 to 7 year old tasks to be appropriate for use with older adults with Down syndrome, certain conditions must be met. The task must measure the same thing, in this case specific cognitive processes, in both populations. In the PASS model cognitive processes are performed in the context of an individual's knowledge base. The knowledge base is built from the individual's interactions with the environment and general accumulation of life experiences. Therefore the formation of the knowledge base is a dynamic process. The role of a knowledge base is also central to both Piagetian and Neopiagetian views of human development. Case et al. (1996) comment on the interaction between intellectual processes and specific content, context and cultural factors.

We can generalize about types of processing but to generalize about levels of processing when we use a task designed for a young child and use it with older adults with

Down syndrome without considering the influence of the knowledge base on performance, is to make a grave error. If we anticipate that an individual of 5 -7 years of age can perform a certain task, should we assume that the individual with an intellectual disability will be able to perform the same task? Or rather more to the point, that the person with an intellectual disability will perform/complete that task in the same way. Even taking into account equality in Mental Age (MA) between the participants in this study and children aged between 5 to 7 years of age, the life experiences and therefore the knowledge bases of the two groups are widely different. Perhaps the performance of the subjects with Down syndrome on the Expressive Attention task, and the way in which it seemed to become a decision making task, can be partly explained in terms of the influence of the knowledge base?

The large standard deviations on many of the measures used indicate that there was considerable variability in performance within each of the two age groups. The poorest performers in the younger group having similar scores of people in the older group. A larger sample which permits the sectioning of subjects into 10 or even 5 year, age groups with testing every year may yield more useful results.

It might have been expected that decline in language related skills would be a part of a pattern of cognitive decline in adults with Down syndrome. The lack change in the PPVT-R scores over time by the whole group indicate that this might be so. Impairment of verbal skills has been reported in the literature as preceding the development of dementia in Down syndrome, occurring during childhood years (Brugge, Nichols, Salmon, Hill, Delis, Aaron & Trauner, 1994).The lack of significant differences on the PPVT-R by age groups over time may be due to the very low functioning of a number of the subjects on the PPVT-R, floor effects of this test could make it insensitive in detecting subtle changes. This is a difficulty noted by other researchers (Brugge et al., 1994; Caltagirone, 1990). The results of this study are in keeping with those of similar studies such as Haxby (1989) who found no significant difference between old and young groups of people with DS on tests of

language function and would seem to confirm that the PPVT-R is not suitable for detecting age related decline in adults with Down syndrome. A future study could consider possible decline in expressive, rather than receptive, language skills.

What if we had taken a higher age threshold for the older group. Das' earlier studies had indicated that age 50 may be a "watershed" age for people with Down syndrome. As described in Chapter Four, the performance of the people aged 50 and over was considered as a post hoc analysis. Significant differences in ability to attempt the CAS tasks were found between individuals aged 50 and those aged below 50. It is possible that inability to do the CAS tasks in someone who could previously manage them, could indicate a significant decline and possible dementia. Indeed, the people in the present study who were aged over 50 and who were unable to do the CAS tasks were also identified as having dementia on the DSDS. In addition, the five people in the over 50 group who received a SPECT scan were identified as having abnormal rCP. A future, and much larger, study could consider the relationship between the findings and try to replicate them. However, the obvious difficulty seems to be that just as low cognitive functioning may lead to a false positive on the DRS, low cognitive functioning may also lead to an inability to perform the CAS tasks. Diagnostically we need to be able to differentiate between low cognitive functioning and dementia.

In answer to the research question, a pattern of decline in simultaneous processing is implicated by the findings of this study.

2: Is there a pattern of both structural and functional neurological change in persons with Down syndrome?

The SPECT clearly showed that temporal and parietal regions of the brain were predominantly associated with cerebral atrophy. Given this finding it is hypothesized that tasks of simultaneous and successive processing which according to Luria and Das are associated with these areas, would be better screening tests than tasks of planning and attention. Indeed the Ravens, which is a test that involves simultaneous processing,

showed significant differences between the young and old groups. These findings give suggestions for future research in this area.

SPECT and PET studies in Alzheimer's disease have demonstrated decreased rCP and metabolism particularly in the parietotemporal regions. The results would seem to indicate two groups (although numbers are small). One group who appear to be homogeneous, symptomatically, with results reported in other studies of persons with DAT, and another group with more diffuse deficits in rCP. This could be an expression of the degenerative nature of Down syndrome. Further study is needed to examine the hypothesis of degeneration and to follow a group of such subjects over time to rule out later development of DAT.

The apparent universality of deficits in rCP, or abnormal SPECT scans, in all 11 of the participants scanned gives rise to another research question. Namely, could SPECT be used to monitor changes in the temporal/parietal lobes and to distinguish between a cognitive decline which could be the expression of aging in Down syndrome, and DAT. The utility of such a tool would be to help in planning and placement options for individuals and their families. Many family members in the study described behavioral changes in their child or sibling where the person was becoming more stubborn and rigid in their behavior. Understanding the cause of behavioral changes may make them easier to deal with, and to plan for, by the family.

Unfortunately it was not possible to scan all participants from the earlier part of the study. More research is needed to explore fully the relationship between performance on the CAS tasks of planning and attention and the presence of rCP abnormalities on SPECT. The small number of subjects, in what must be regarded as a pilot study, precluded the use of statistical analyses of any power to be able to make statements about the discriminative power of SPECT as a diagnostic tool for DAT with this population. However, the results do replicate findings by other researchers (Kao et al., 1993; Rae-Grant et al., 1991;) and clearly indicate the need for larger scale studies and the potential worthwhile nature of

SPECT as a diagnostic tool in this "difficult" population. Difficult, in the sense that floor effects found on the more normally used neuropsychological assessments for DAT in the general population, make them questionable instruments for use with people with developmental disabilities, such as Down syndrome.

The group of 11 people who received the SPECT scans, although they were randomly selected - in that all subjects were invited for the SPECT scan, 15 agreed, but these 11 were the only ones to successfully complete the SPECT procedure- differed in their performance on various CAS tasks. As a group these eleven people took longer to complete the planned search tasks and obtained fewer correct responses on the expressive attention, matching numbers and receptive attention tasks in 1995. When the data were explored and all subjects were ranked according to their performance on the CAS tasks, these eleven people were not the poorest performers. It could be hypothesized that if we had been able to scan all the poorest people on each measure we may have observed abnormalities in rCP, at least in the temporal region for each person. Whether this would have led to a diagnosis of DAT or memory impairment/cognitive decline cannot be ascertained.

If the cognitive decline observed in individuals with Down syndrome is associated with the presence of DAT type changes in the brain it was expected that this would be supported, or even verified, by using SPECT imaging on a sample of people with Down syndrome who completed a series of cognitive function tests based on the PASS model. Patterns of performance on CAS tasks, Ravens, PPVT-R and results from SPECT were not as intimately related as we had hoped.

3: Is it possible to differentiate between demented and non demented people with Down syndrome on the basis of information from neuropsychological tests and SPECT imaging?

It was expected that those individuals with Down syndrome exhibiting most deficits in rCP on SPECT would exhibit the lowest measures of cognitive ability. In other words,

we might have expected results from the DRS, CAS tasks and SPECT scans to be related in their ability to differentiate between demented and non demented people with Down syndrome.

The DRS is targeted to detect the presence of dementia and to differentiate among levels or stages of dementia. In this study it could be interpreted as having failed to both detect dementia and differentiate levels, unless we are to believe that all the individuals in the study are in the latter stages of a dementia such as DAT. This argument would not seem to be supported by evidence from the other measures. The DRS provides an overall measure of cognitive function although verbal functions are more highly weighted than non verbal. As the results of the PPVT-R show this group of people are low functioning in this area and could therefore be expected to score in a lower range than the general population on the DRS. The use of a test the majority of which is beyond a persons capabilities, even before any cognitive decline is taken into account raises the question of floor effects. The floor effects with the use of the DRS and this particular sample of people with Down syndrome may have resulted in a lack of sensitivity and questionable reliability in the DRS' ability to determine the possible presence of dementia (which is the purpose of this test) as opposed to the presence of low cognitive functioning.

Another difficulty with the use of the DRS in this population concerns the use of cut off scores to determine dementia. The DRS uses a cut off of 137 (Mattis, 1988) to indicate cognitive dysfunction. Possible scores range from 0 -144. Studies have shown a steady decline and wider ranges of scores on the DRS with advancing age and decreasing educational level (Schmidt et al., 1994). Monsch et al. (1995) reported the optimal DRS cut off score for DAT to be 129. Both the score suggested by Mattis and that suggested by Monsch would seem still to be too high if we are to obtain reliable and valid results using the DRS with adults with Down syndrome. "Too high" in that a person with Down syndrome who is not demented would be unlikely to reach the DRS cut off score for DAT.

Fitz and Teri (1994) suggested that global measures of cognitive functioning are not good predictors of functional status at mild levels of cognitive impairment because decline in one area can be masked by strengths in another. The DRS was administered in 1990. Scores across the two age groups were low at this time as has been shown. It would be reasonable given the literature to suppose that performance would have declined over the five years to 1995. On the basis of the DRS scores it had been expected that we would find more people meeting the criteria for dementia on the DSDS. This was not the case.

If this study was successful in using neuropsychological tests which allow detection of smaller changes than the usual caregiver reports, and in the identification of neuropathological changes associated with dementia rather than aging, by the use of SPECT then this may offer a possibility of identification and remediation for people with Down syndrome in middle adulthood. (If the results of this study support the view that there are two distinct groups of individuals with Down syndrome, demented and non demented, as detected by SPECT and cognitive testing this may be important for remediation. (Although additional research may prove that it is only possible to remediate the non demented population.) It would be hoped that these people would then be able to maintain independent personal functioning and integrity for an increased period of time.

4: Does the use of caregiver report measures of DAT type changes have diagnostic utility when compared with SPECT and neuropsychological data?

The DSDS is completed by a psychologist interviewing familiar caregivers. It considers behavioral changes over time and provides for certain behaviors being typical of a person with DD. The presence or absence of these same behaviors makes it difficult for tests of global cognitive and behavioral functioning such as the DRS, to detect subtle changes of functioning in these populations. Requiring people to perform tasks beyond their level of ability can result in "floor" effects with a resulting lack of sensitivity in the assessment. Evidence of this "floor" effect was apparent in our study when all subjects were identified with possible dementia by the DRS and only 6 by the DSDS. Of the six

subjects identified as having possible dementia on the DSDS, 3 were new to the study in 1995 and therefore DRS scores from 1990 were only available for 3 subjects. The scores of these three on the DRS were 45, 69 and 75, some of the lowest scores obtained. If we wish to use assessment devices designed for the general population with persons with developmental disabilities, large scale studies are needed to explore appropriate cut off scores for this population. These scores may well be lower than those we would expect in a higher functioning group.

Research has shown the difficulties inherent in diagnosing Alzheimer Type Dementia (DAT) where levels of education and intellectual functioning are an issue (Schmidt, et al., 1994; Kittner et al., 1986). The prevalence of DAT in such populations is held to be just as great as in the general population and in the case of persons with Down syndrome, to be increased and to occur at an earlier age (Hewitt et al., 1986; Evanhuis, 1992). Early detection of DAT in individuals with Down syndrome is as pertinent an issue as it is in the general population. There is a need for objective and reliable assessment materials for individuals with DD who have pre existing cognitive impairment. The onset of dementia is a gradual process and the use of a longitudinal assessment tool such as the DSDS allows for examiners to follow the speed of deterioration of skills and also any possible resumption of skills where a reversible dementia is present.

Neuropathologists have been trying to establish general criteria for diagnosing DAT but at the moment their criteria do not correlate with cognitive decline. Some individuals who show a clinical diagnosis of DAT, i.e. cognitive decline, personality changes, neurological abnormalities, aphasia/apraxia; and have a pedigree of two or more generations of affected subjects have still not been shown to have DAT. Other possible causes of dementia have been identified in some cases, for example, motor neuron disease plus dementia, also a prion protein disease similar to DAT. Interestingly, in Down syndrome the opposite is true, we often see neuropathological signs at post mortem when clinical signs have not presented. In normal aging of the brain it would be expected that

abnormalities would occur. However, in DAT, neuropathological changes are specific and specialized. These changes suggest that DAT is a disease process and not an inevitable consequence of growing old (Schweber, 1988; p.67). At the present time we most often diagnose DAT by excluding other possibilities.

The results of the SPECT scans were, in this instance, considered to be the 'gold standard' against which we judged the accuracy of the other scales. Small sample size precluded the use of statistical analyses, however, sensitivity and specificity calculations were made to evaluate the accuracy of the DSDS (Lilienford & Lilienford, 1980). As expected, the DRS over identified the number of persons with DAT. The DSDS resulted in 57% sensitivity and 100% specificity. It can be seen that the use of this test may miss a number of cases. However, the slow progressive nature of DAT and the use of the DSDS as an ongoing assessment process with interviews being repeated at yearly, or even 6 monthly visits, would result in these false negatives being picked up in an acceptable time period. However the 'cost' of a large number of false positives from the use of the DRS would be greater in terms of family trauma and coping.

One subject, #6, met the differential diagnosis for medication induced cognitive decline and also depression on the DSDS. Although the DSDS indicated DAT the researcher felt that the differential diagnosis was warranted. This was supported by a 6 month follow up assessment which indicated that the participant's behaviors had improved markedly and some cognitive gains had been made. However the SPECT scan gave clear indications of early memory impairment or early DAT - type deficits in rCP. Appendix E gives the tomography slices for this subject which indicate cerebral atrophy present in the temporal region. These results were surprising given the subject's age of 33 years.

The results point to the importance of caregiver report to be used in the assessment of DAT in the Down syndrome population. The caregiver reports obtained through the clinical use of the DSDS provided close links to the information obtained in the SPECT scans for the 11 people in that portion of the study.

Conclusions

People with Down syndrome are now living longer. Life expectancy has been reported to now exceed 50 years of age (Thase, 1982; Baird & Sadovnick, 1987; Eyman et al., 1991). Holland and Oliver (1995) cite studies by Fryers (1986) and McGrother & Marshall (1990) which indicate figures of around 15% of males and 20% of females in the population of people with Down syndrome as being over 55 years of age. In the last twenty years the field of special education has become increasingly concerned about the importance of early intervention. We may need to intervene in later life with people with Down syndrome so that we can combat the effects of early aging.

In this study, neuropsychological testing was carried out on a group of older people with Down syndrome to examine planning and attention processes. A measure of dementia was taken using the DSDS and SPECT scans performed on a small sub group of participants. It was hypothesized that any cognitive deficits seen in the non demented group of people with Down syndrome would reflect changes in mental status related to aging rather than dementia. It was further hypothesized that any deficits observed in the demented group, as measured by neuropsychological tests, may be useful in determining the early signs and patterns of dementia in Down syndrome. The results of the study showed that the DSDS identifies fewer people as having dementia than the DRS. The SPECT scans indicated abnormalities in all 11 of the participants scanned. Finally, although clear decline was seen in some cases there was not an age effect such as was expected on the CAS tasks. This may have been due to general low functioning in the group which made discrete measurement of separate cognitive processes problematical, or to floor effects.

In respect to the link between DAT and Down syndrome, it is hoped that this study can expand on existing research, and support the theory that there exist two groups of older people with Down syndrome; the demented and the non demented. In this study the DSDS gave clear indications of the presence of dementia in a small number of participants. The

importance of early identification of these groups, perhaps in middle adulthood, lies in the possibility of remediation of those people experiencing early cognitive decline. Although the remediation of such a group is outside the scope of current studies at the Developmental Disabilities Center at the University of Alberta, the use of neuropsychological tests associated with the PASS model allows extremely specific processes to be identified for remediation. The potential cognitive changes associated with DAT in Down syndrome are not well characterized and research continues to look for sensitive measures to detect early dementia. Planning and attention are processes which seem to differentiate people with Down syndrome from people with intellectual disabilities of other etiologies. However, successive and simultaneous processing may be the processes which illustrate cognitive decline due to aging or possible dementia, within the Down syndrome group.

Implications for practice

In order to recognize and maximize individual potential in spite of biological differences we must develop and expand our knowledge of assessment devices best suited to this population. By developing skills of community based health teams to work with these individuals and their families we develop stronger and healthier links between community resources and families themselves. Involvement in longitudinal assessment which considers behavioral changes means families can develop and maintain skills for facing new challenges in a healthy way. By educating families in the progressive nature of DAT, families can plan ahead and avoid dealing with care crises. The importance of such planning has been stressed in a number of studies (Seltzer, Krauss & Heller, 1991; Smith, Tobin & Fullmer, 1995). Home visitors will be able to use the DSDS to screen for other conditions known to be risk conditions for individuals with DD. Such conditions include hypothyroidism, arthritic changes, hearing or vision changes and depression. Identifying such conditions in a screening assessment can help identify new or developing problems that need referral to the appropriate medical specialist.

The use of a measure such as the DSDS would seem to fulfill the first requirement of detecting a progressive dementia (a deterioration of cognitive, physical and adaptive skills) as recommended by the AAMR-IASSID workgroup on Epidemiology and Alzheimer Disease (Zigman et al., 1995, p.1). The second recommended requirement is a characteristic pattern of neuropathology. In this study we considered this issue in relation to the use of Single-photon emission computerized tomography (SPECT) with individuals with Down syndrome.

It appears that there are two types of cognitive decline in Down syndrome. One is severe and is associated with the presence of dementia, possibly DAT, as diagnosed by neurophysiological changes; the other is less severe with the people appearing non demented. However in both cases cognitive decline is more rapid and severe than that seen in the general population. The SPECT results indicate the presence of progressive brain atrophy,. However, this alone is not enough evidence to confirm or diagnose the presence of DAT. Cognitive decline in the non demented group of individuals in this study is felt to be associated with the degenerative nature of Down syndrome.

Cognitive decline in persons with DS and DAT is reported to be global in nature (Haxby, 1989), however, apart from the Ravens, measures of cognitive functioning used in this study have proved to be insensitive in detecting change in this population. The use of SPECT imaging procedures allows comparison with normal aging adults and people with DAT. Future studies may provide us with a comparison group of people with DS at various ages. The results of this study suggest that decline may be attributed to atrophy in the temporal lobes of the brain and that this atrophy is found at young ages. The other group is the group which develops DAT. This occurs at earlier ages than in the general population but on SPECT scans presents with the same pattern of symptoms. Karlinsky et al. (1993) reported that "NINCDS - ADRDA criteria emphasize that individuals suspected of having [DAT] must undergo a detailed medical evaluation that should encompass a medical history, neurological, psychiatric and clinical examinations, neuropsychological

tests and laboratory tests" (p.9). Based on the results obtained in this study, it is suggested that the diagnostic schedule for persons with Down syndrome suspected of severe cognitive decline, query DAT, should start with a medical examination to rule out hypothyroidism, and other pseudo dementias such as that caused by depression, and then continue with a screening instrument such as the DSDS which allows for the individual to be considered not only in the light of changes associated with DAT but also in relation to their present and previous level of functioning. Those subjects meeting the criteria for a diagnosis of DAT on the DSDS could then proceed to SPECT scan to act as the "gold standard" for diagnosis. The use of SPECT may well allow clinicians to detect a characteristic pattern of neuropathology in individuals with Down syndrome. This is the second of two recommended requirements by Zigman and colleagues (1995) from the AAMR-IASSID workgroup on epidemiology and Alzheimer Disease. Further research with this group of individuals should involve the use of SPECT as part of a regular screening process. The group as a whole tolerated the procedure quite well. Given that baseline information is now available, the use of SPECT to study progressive changes and decline/possible DAT should be explored.

Haxby (1989) suggested that behavioral changes occur earlier than onset of dementia and therefore caregiver reports and clinical neurological examinations may be insensitive for diagnostic use in DAT. In the DSDS we appear to have a caregiver report measure based on significant behavioral changes associated with DAT in persons with DS.

In conclusion, it is becoming more frequently the case that older parents of children with Down syndrome are being survived by their offspring. Education of parents and other family members regarding the aging process in Down syndrome and possible diagnosis of DAT is necessary to help plan residential and vocational placements. Several researchers have looked at the need for such planning (Smith, Tobin & Fullmer, 1995; Janicki & Wisniewski, 1985; Seltzer, Krauss & Heller, 1991). The early detection of DAT in

individuals with DS is as pertinent an issue as in the general population and is worthy of further study.

There is a need for reliable and objective assessment materials for detecting DAT in the population of individuals with developmental disabilities including individuals with Down syndrome. Such instruments must be valid in the presence of pre existing cognitive impairment. Although there is no treatment for the person with DAT that will prevent the disease running its course, a diagnosis can still be helpful. A diagnosis provides a starting point for acceptance and understanding of behavioral changes. It can provide a focus for future planning, residential or vocational. Selective screening of individuals with Down syndrome for the presence of DAT should become an accepted part of their health care given the high risk of developing this disease.

We should explore further specific tests of cognitive functions associated with the temporal and parietal lobes. Perhaps the tests of the CAS could be extended for greater sensitivity for people who are lower functioning. The use of such measures as the DSDS and SPECT imaging shows promise for reliable screening/diagnosis of DAT in individuals with Down syndrome. In such a way the requirements of the AAMR-IASSID workgroup on epidemiology and Alzheimer disease can be met in this population. That is to say, we can identify progressive dementia through deterioration in cognitive, physical and adaptive skills monitored over time with a longitudinal assessment instrument such as the DSDS. In addition we can identify specific and characteristic patterns of neuropathology and functioning deficits through the use of SPECT imaging.

There is a caveat to the findings of this study. Reliable and objective assessment of people with Down syndrome, or with intellectual/developmental disabilities in general, raises a question of validity. The issue of using a dementia rating scale such as the DRS with this population when it was normed for the general population has already been discussed around the idea that it was perhaps measuring cognitive level but not dementia.

The question of who we take as our comparison group applies to each area of testing in this study. In considering the SPECT data, the scans of the participants were compared with those from a "normal" data base. The question we were seeking to answer was; Can we see evidence of the perfusion deficits normally associated with DAT? The answer we have is that yes we see the perfusion deficits but we cannot be sure that they are attributable to DAT in this particular instance. Earlier studies such as those by Kao et al. (1993) have indicated that perfusion deficits normally seen in DAT are evident in persons with Down syndrome even at an early age. Therefore when we look for deficits are we looking for the same decrease in perfusion in temporal and parietal regions or should we be looking for say 200% greater deficits because of the 'normal' picture in Down syndrome? This question cannot be answered at the present time because we do not have a data base of what is 'normal' in Down syndrome to use for comparative purposes. Therefore in this instance was the SPECT data valid as a measure of dementia given that we do not have a clear picture of what is normal in this population? The scans were definitely abnormal in that they differed from the norm but we need find that norm for Down syndrome.

Finally, in terms of cognitive tests if we wish to make them applicable to this population we need norm data. It has been shown that we cannot compare the performance of this group of people to the norm in any meaningful way. We know that they differ from the general population but what should we look for to detect a significant change in this specific group? If we wish to detect the presence of DAT as opposed to aging what specific features are we looking for? earlier studies (Das et al., 1995a; Das & Mishra, 1995b; Das et al., 1993) have suggested that we look at attention and planning. The results of this study suggest we also consider successive processing. In order to consider these cognitive processes as indicators of age associated cognitive decline or early DAT in this population, we must first extend the levels of our tests to exclude the floor effects evident in the present study. Secondly, we need to collect enough data to have norms for this population at various ages.

The closing argument of this dissertation begs more questions than it answers, but it is this: What if everything reported here illustrates the expression of aging in Down syndrome and not development of DAT? It is perhaps part of our nature to try and make things fit with what we already know, i.e. if something looks like DAT it must be DAT. The cognitive and neuropsychological tests in this study seemed to have given unexpected results with this population. The argument I have put forward was that people with Down syndrome may solve problems in a qualitatively and quantitatively different way from the "normal" population. This means that assuming a 40 year old with Down syndrome with a mental age of 6 will solve tasks designed for 5 year old children in the same way as a child, is an erroneous assumption. Similarly, we know that the gene responsible for the production of beta amyloid is situated on chromosome 21, a chromosome duplicated in people with Down syndrome. Therefore, it is highly probable that in this population more amyloid is deposited in the brain in the form of plaques and tangles. In such a case we might expect the results seen in our SPECT data. Where deposits are found in parietal and temporal regions we see a DAT type pattern which may result in a clinical expression of dementia. In other cases deficits in rCP were observed in other areas, frontal and occipital, and in a few cases deficits were diffuse and involved nearly all areas of the brain. It is also possible that some people with Down syndrome will develop a 'true' DAT by inheriting the Alzheimer gene as in the general population. Is it also possible that some people with Down syndrome appear to have DAT on SPECT by the chance accumulation of plaques and tangles in the appropriate regions of the brain. In other words is there support here for the argument that Down syndrome is a degenerative disorder characterized by diffuse cortical atrophy in later life; the results of which may mimic a number of conditions, including DAT, and result in an accelerated cognitive decline? I believe that this is so.

The discrepancy between DAT neuropathology at post mortem, SPECT findings and diagnosis of clinical dementia reported in the literature must be further explored. The

time appears to be right for a longitudinal study which incorporates all these aspects following cohorts of individuals with Down syndrome from age 20 up. If centers could combine techniques and methodologies so that normal ranges for rCP in Down syndrome could be established, then we might be able to make more definitive statements about the link between DAT and Down syndrome.

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Appendix A: SPECT Data

Comparison with CCI PAO Autofit Normal Ranges for WN

Region	% of total counts/volume
Right superior frontal	1.7
Left Superior frontal	ok
Right Inferior frontal	-1.7
Left inferior frontal	ok
Right parietal	ok
Left parietal	ok
Right occipital	ok
Left occipital	ok
Right temporal	ok
Left temporal	ok
Right midbrain	ok
Left Midbrain	-1.9
Right cerebellum	2.2
Left cerebellum	2.1
Right subtotal	ok
Left subtotal	ok
Right frontal	ok
Left frontal	ok
Total superior frontal	2.2
Total Inferior frontal	-2.2
Total frontal	ok
Total parietal	-1.8
Total occipital	ok
Total temporal	ok
Total midbrain	-2.1
Total cerebellum	3.1
Overall total	na

Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Ok - number is within 1.5 SD of the mean. Na - normal range has not been defined for this measurement.

Comparison with CCI PAO Autofit Normal Ranges for DST

Region	% of total counts/volume
Right superior frontal	ok
Left Superior frontal	ok
Right Inferior frontal	ok
Left inferior frontal	ok
Right parietal	ok
Left parietal	ok
Right occipital	-3.1
Left occipital	ok
Right temporal	1.5
Left temporal	2.4
Right midbrain	ok
Left Midbrain	ok
Right cerebellum	ok
Left cerebellum	ok
Right subtotal	-2.7
Left subtotal	2.7
Right frontal	ok
Left frontal	ok
Total superior frontal	ok
Total Inferior frontal	ok
Total frontal	ok
Total parietal	ok
Total occipital	-2.4
Total temporal	3.2
Total midbrain	ok
Total cerebellum	ok
Overall total	na

Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Ok - number is within 1.5 SD of the mean. Na - normal range has not been defined for this measurement.

Comparison with CCI PAO Autofit Normal Ranges for MS

Region	% of total counts/volume
Right superior frontal	ok
Left Superior frontal	ok
Right Inferior frontal	ok
Left inferior frontal	ok
Right parietal	ok
Left parietal	ok
Right occipital	ok
Left occipital	ok
Right temporal	ok
Left temporal	1.9
Right midbrain	ok
Left Midbrain	ok
Right cerebellum	ok
Left cerebellum	ok
Right subtotal	ok
Left subtotal	ok
Right frontal	ok
Left frontal	ok
Total superior frontal	ok
Total Inferior frontal	-1.6
Total frontal	-1.7
Total parietal	ok
Total occipital	ok
Total temporal	2.7
Total midbrain	-1.7
Total cerebellum	ok
Overall total	na

Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Ok - number is within 1.5 SD of the mean. Na - normal range has not been defined for this measurement.

Comparison with CCI PAO Autofit Normal Ranges for BT

Region	% of total counts/volume
Right superior frontal	ok
Left Superior frontal	ok
Right Inferior frontal	ok
Left inferior frontal	ok
Right parietal	ok
Left parietal	ok
Right occipital	-2.1
Left occipital	ok
Right temporal	2.1
Left temporal	1.9
Right midbrain	ok
Left Midbrain	ok
Right cerebellum	ok
Left cerebellum	ok
Right subtotal	ok
Left subtotal	ok
Right frontal	ok
Left frontal	ok
Total superior frontal	ok
Total Inferior frontal	ok
Total frontal	ok
Total parietal	ok
Total occipital	-1.6
Total temporal	3.3
Total midbrain	ok
Total cerebellum	ok
Overall total	na

Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Ok - number is within 1.5 SD of the mean. Na - normal range has not been defined for this measurement.

Comparison with CCI PAO Autofit Normal Ranges for CM

Region	% of total counts/volume
Right superior frontal	ok
Left Superior frontal	ok
Right Inferior frontal	ok
Left inferior frontal	ok
Right parietal	2.2
Left parietal	ok
Right occipital	ok
Left occipital	1.6
Right temporal	ok
Left temporal	ok
Right midbrain	ok
Left Midbrain	ok
Right cerebellum	-2.2
Left cerebellum	-1.6
Right subtotal	ok
Left subtotal	ok
Right frontal	ok
Left frontal	ok
Total superior frontal	ok
Total Inferior frontal	ok
Total frontal	ok
Total parietal	2.6
Total occipital	ok
Total temporal	ok
Total midbrain	ok
Total cerebellum	-2.8
Overall total	na

Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Ok - number is within 1.5 SD of the mean. Na - normal range has not been defined for this measurement.

Comparison with CCI PAO Autofit Normal Ranges for OK

Region	% of total counts/volume
Right superior frontal	ok
Left Superior frontal	-1.5
Right Inferior frontal	ok
Left inferior frontal	ok
Right parietal	ok
Left parietal	ok
Right occipital	ok
Left occipital	-1.6
Right temporal	ok
Left temporal	2.1
Right midbrain	ok
Left Midbrain	ok
Right cerebellum	ok
Left cerebellum	ok
Right subtotal	ok
Left subtotal	ok
Right frontal	ok
Left frontal	ok
Total superior frontal	-2.4
Total Inferior frontal	ok
Total frontal	-1.5
Total parietal	ok
Total occipital	-1.8
Total temporal	ok
Total midbrain	ok
Total cerebellum	ok
Overall total	na

Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Ok - number is within 1.5 SD of the mean. Na - normal range has not been defined for this measurement.

Comparison with CCI PAO Autofit Normal Ranges for PH

Region	% of total counts/volume
Right superior frontal	2
Left Superior frontal	ok
Right Inferior frontal	ok
Left inferior frontal	ok
Right parietal	ok
Left parietal	ok
Right occipital	ok
Left occipital	ok
Right temporal	ok
Left temporal	-2.8
Right midbrain	1.8
Left Midbrain	3.2
Right cerebellum	ok
Left cerebellum	ok
Right subtotal	ok
Left subtotal	ok
Right frontal	ok
Left frontal	ok
Total superior frontal	1.5
Total Inferior frontal	-1.9
Total frontal	ok
Total parietal	ok
Total occipital	ok
Total temporal	-2.8
Total midbrain	3.8
Total cerebellum	ok
Overall total	na

Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Ok - number is within 1.5 SD of the mean. Na - normal range has not been defined for this measurement.

Comparison with CCI PAO Autofit Normal Ranges for SF

Region	% of total counts/volume
Right superior frontal	-3.2
Left Superior frontal	ok
Right Inferior frontal	1.9
Left inferior frontal	ok
Right parietal	ok
Left parietal	4.1
Right occipital	ok
Left occipital	ok
Right temporal	ok
Left temporal	ok
Right midbrain	-3.2
Left Midbrain	-2.6
Right cerebellum	ok
Left cerebellum	ok
Right subtotal	-1.7
Left subtotal	1.7
Right frontal	ok
Left frontal	ok
Total superior frontal	-3.3
Total Inferior frontal	ok
Total frontal	-1.7
Total parietal	4.2
Total occipital	ok
Total temporal	ok
Total midbrain	-4.5
Total cerebellum	ok
Overall total	na

Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Ok - number is within 1.5 SD of the mean. Na - normal range has not been defined for this measurement.

Comparison with CCI PAO Autofit Normal Ranges for KE

Region	% of total counts/volume
Right superior frontal	ok
Left Superior frontal	-2.1
Right Inferior frontal	ok
Left inferior frontal	ok
Right parietal	ok
Left parietal	ok
Right occipital	ok
Left occipital	ok
Right temporal	2.2
Left temporal	2.3
Right midbrain	ok
Left Midbrain	ok
Right cerebellum	ok
Left cerebellum	ok
Right subtotal	ok
Left subtotal	ok
Right frontal	ok
Left frontal	ok
Total superior frontal	-2.8
Total Inferior frontal	ok
Total frontal	-1.8
Total parietal	ok
Total occipital	-2
Total temporal	3.7
Total midbrain	ok
Total cerebellum	ok
Overall total	na

Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Ok - number is within 1.5 SD of the mean. Na - normal range has not been defined for this measurement.

Comparison with CCI PAO Autofit Normal Ranges for KB

Region	% of total counts/volume
Right superior frontal	ok
Left Superior frontal	ok
Right Inferior frontal	ok
Left inferior frontal	ok
Right parietal	ok
Left parietal	ok
Right occipital	ok
Left occipital	ok
Right temporal	ok
Left temporal	ok
Right midbrain	ok
Left Midbrain	ok
Right cerebellum	ok
Left cerebellum	ok
Right subtotal	ok
Left subtotal	ok
Right frontal	ok
Left frontal	ok
Total superior frontal	ok
Total Inferior frontal	ok
Total frontal	1.5
Total parietal	ok
Total occipital	ok
Total temporal	ok
Total midbrain	ok
Total cerebellum	ok
Overall total	na

Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Ok - number is within 1.5 SD of the mean. Na - normal range has not been defined for this measurement.

Right/Left asymmetry Measured comparison with asymmetry PAO normal for BT

Region		
Superior frontal	6.49	2.4
Inferior frontal	3.33	ok
Total frontal	4.82	2.2
Parietal	1.03	ok
Occipital	-5.19	-3
Temporal	0.83	ok
Midbrain	-2.75	-2
Cerebellum	-1.6	ok
Total Hemisphere	-0.1	ok

Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Ok- number is within 1.5 SD of the mean

Right/Left asymmetry Measured comparison with asymmetry PAO normal for MST

Region		
Superior frontal	4.54	1.5
Inferior frontal	1.93	ok
Total frontal	3.23	ok
Parietal	0.07	ok
Occipital	-0.19	ok
Temporal	-0.34	ok
Midbrain	1.43	ok
Cerebellum	-4.56	-2.1
Total Hemisphere	-0.04	ok

Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Ok- number is within 1.5 SD of the mean

Right/Left asymmetry Measured comparison with asymmetry PAO normal for DS

Region		
Superior frontal	4.35	ok
Inferior frontal	1.77	ok
Total frontal	3.04	ok
Parietal	-2.39	-2.3
Occipital	-7.64	-4.5
Temporal	-0.95	ok
Midbrain	0.12	ok
Cerebellum	-2.35	ok
Total Hemisphere	-1.91	-3.8

Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Ok- number is within 1.5 SD of the mean

Right/Left asymmetry Measured comparison with asymmetry PAO normal for CM

Region		
Superior frontal	6.42	2.3
Inferior frontal	1.94	ok
Total frontal	4.2	1.8
Parietal	2.33	1.6
Occipital	-3.13	-1.8
Temporal	0.38	ok
Midbrain	-0.55	ok
Cerebellum	-3.79	-1.7
Total Hemisphere	0.27	ok

Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Ok- number is within 1.5 SD of the mean

Right/Left asymmetry Measured comparison with asymmetry PAO normal for OK

Region		
Superior frontal	1.74	ok
Inferior frontal	-3.16	-2.2
Total frontal	-0.89	ok
Parietal	1.24	ok
Occipital	2.44	1.5
Temporal	-4.08	-3.5
Midbrain	-0.72	ok
Cerebellum	1.94	1.6
Total Hemisphere	-0.05	ok

Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Ok- number is within 1.5 SD of the mean

Right/Left asymmetry Measured comparison with asymmetry PAO normal for PH

Region		
Superior frontal	7.44	2.8
Inferior frontal	1.86	ok
Total frontal	4.79	2.2
Parietal	-0.35	ok
Occipital	-3.35	-1.9
Temporal	4.71	3.4
Midbrain	-3.27	-2.4
Cerebellum	-0.07	ok
Total Hemisphere	0.8	ok

Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Ok- number is within 1.5 SD of the mean

Right/Left asymmetry Measured comparison with asymmetry PAO normal for SF

Region		
Superior frontal	-7.7	-3.8
Inferior frontal	8.72	4.3
Total frontal	1.38	ok
Parietal	-4.48	-4.1
Occipital	0.4	ok
Temporal	0.25	ok
Midbrain	-1.94	ok
Cerebellum	-2.41	ok
Total Hemisphere	-1.09	-2.3

Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Ok- number is within 1.5 SD of the mean

Right/Left asymmetry Measured comparison with asymmetry PAO normal for KE

Region		
Superior frontal	3.83	ok
Inferior frontal	-0.94	ok
Total frontal	1.25	ok
Parietal	0.42	ok
Occipital	-0.73	ok
Temporal	0.16	ok
Midbrain	-1.42	ok
Cerebellum	-0.6	ok
Total Hemisphere	0.04	ok

Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Ok- number is within 1.5 SD of the mean

Right/Left asymmetry Measured comparison with asymmetry PAO normal for KB

Region		
Superior frontal	-1.79	ok
Inferior frontal	5.91	2.8
Total frontal	2.07	ok
Parietal	0.41	ok
Occipital	3.6	2.2
Temporal	-2.24	-2.1
Midbrain	0.25	ok
Cerebellum	-5.45	-2.6
Total Hemisphere	0.12	ok

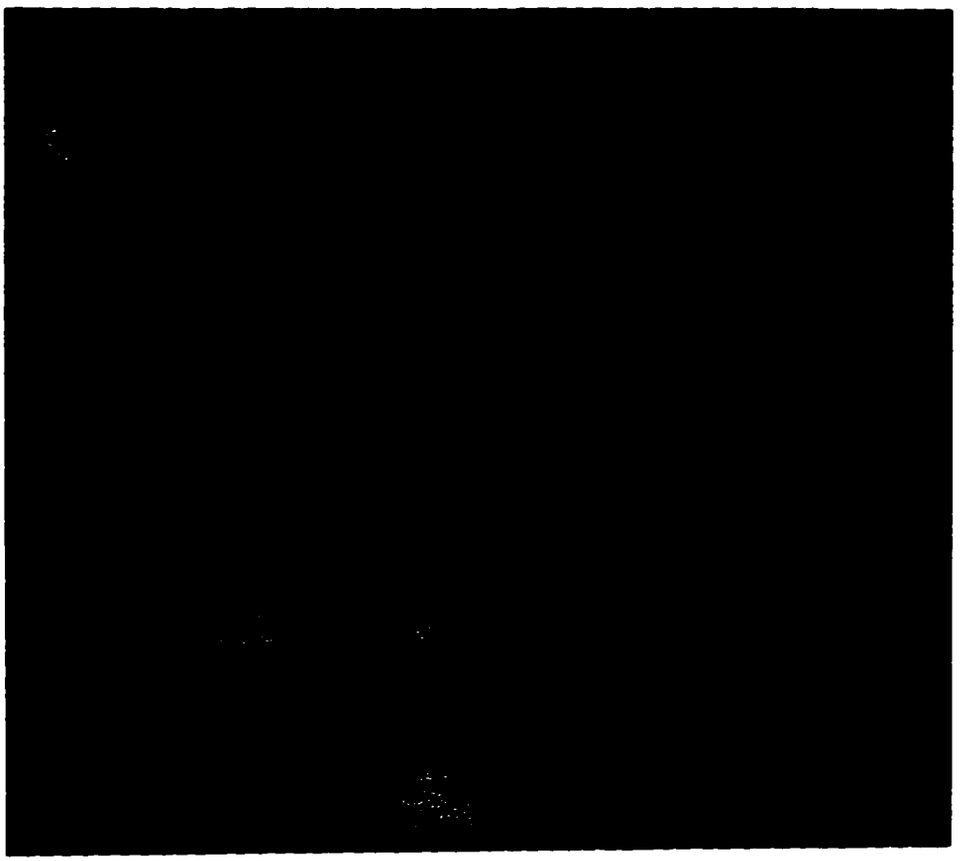
Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Ok- number is within 1.5 SD of the mean

Right/Left asymmetry Measured comparison with asymmetry PAO normal for WN

Region		
Superior frontal	2.82	ok
Inferior frontal	-1.38	ok
Total frontal	0.86	o
Parietal	-0.79	ok
Occipital	1.27	ok
Temporal	2.73	1.8
Midbrain	3.03	2.2
Cerebellum	-0.54	ok
Total Hemisphere	0.89	ok

Numbers indicate the number of standard deviations a value is above or below (negative) the predefined mean for a particular region. Ok- number is within 1.5 SD of the mean

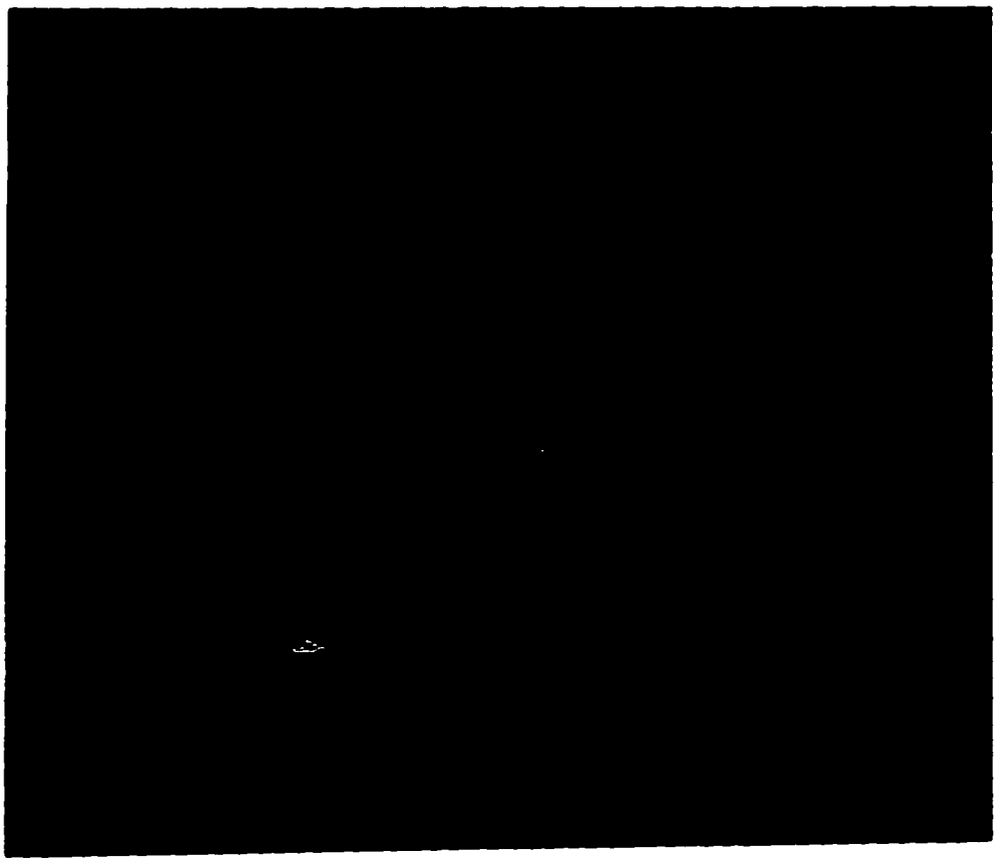
Appendix B: SPECT Images for WN



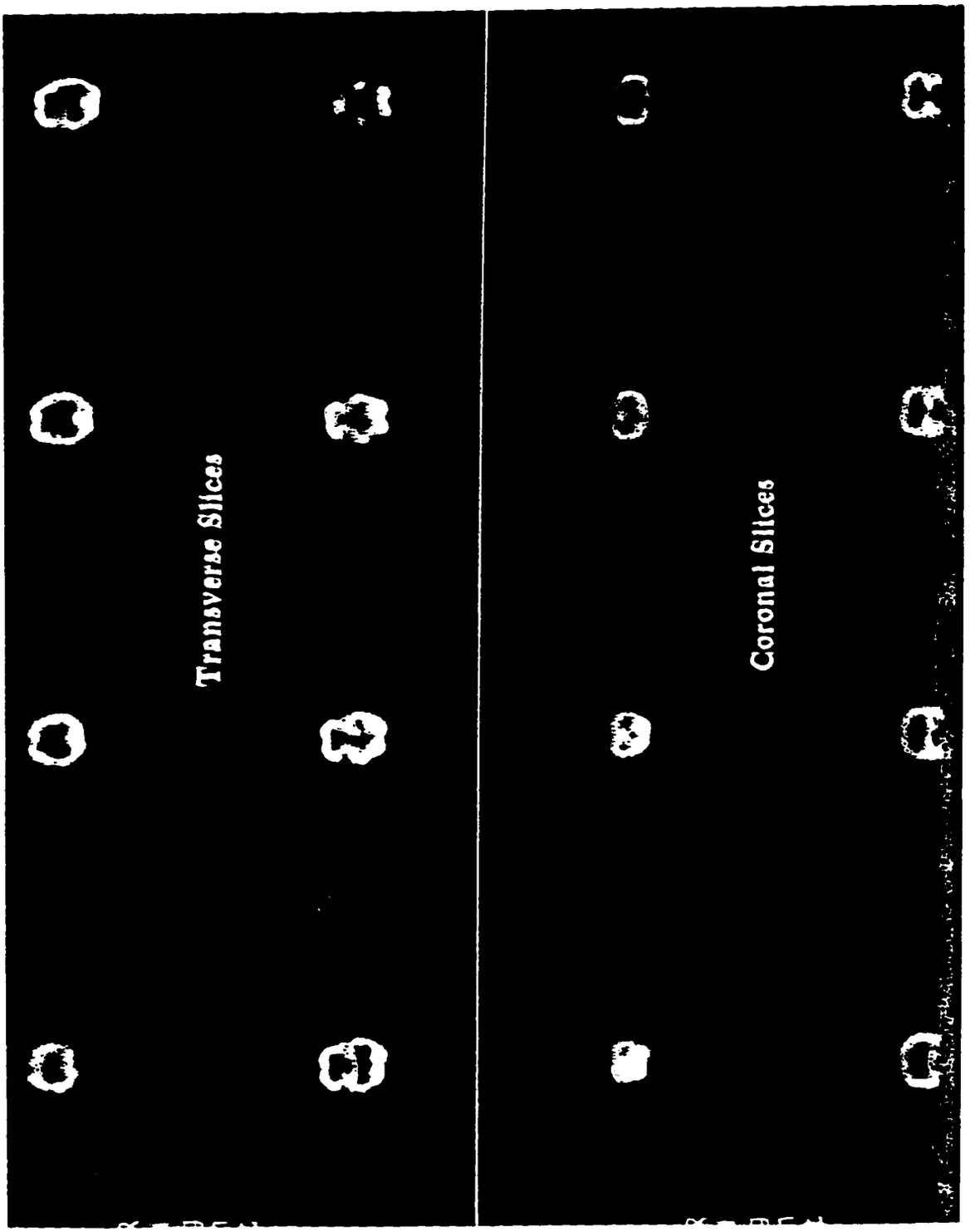
Transverse Slices
Coronal Slices

Appendix C: SPECT Images for OK

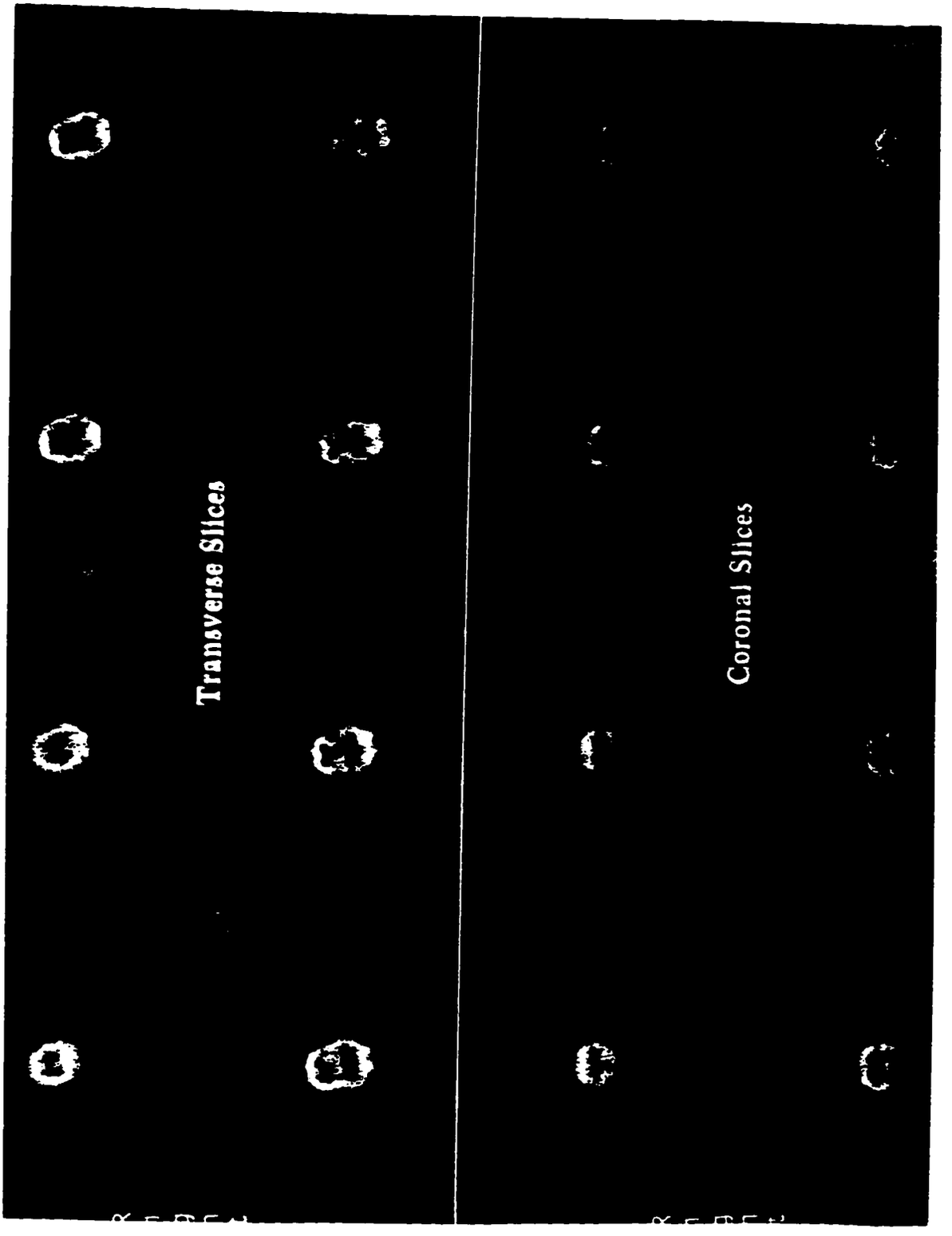
Transverse Slices
Coronal Slices



Appendix D: SPECT Images for KB


Transverse Slices
Coronal Slices

Appendix E: SPECT Images for CM


Transverse Slices
Coronal Slices