NAMING ABILITIES IN ADULTS WITH DOWN SYNDROME AND DEMENTIA

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Abstract

Accelerated Alzheimer-like neuropathological changes have consistently been documented in the fourth decade of life in individuals with Down syndrome (DS). Although the histopathological changes associated with the precocious aging process have been well documented, less is known about the clinical expression of Alzheimer's disease (AD) in this population. This has made it difficult to establish criteria for early-stage detection of dementia of the Alzheimer type (DAT). While naming difficulty is an early sign in the general population, it is unknown whether this is also a marker variable for individuals with Down syndrome, a genetic disorder that carries inherent speech impairments. The present study examined the naming abilities of 55 adults with Down syndrome between the ages of 26 and 66. The types of naming errors made on the Boston Naming Test (BNT) were evaluated for older DS individuals with a diagnosis of probable dementia (Group DAT, n = 18), unaffected older DS individuals (Group OND, n = 18), and unaffected younger DS individuals (Group YND, n = 19). As expected, significant differences in naming errors were not found amongst the participant groups. A verbal memory measure, the Fuld Object Memory Evaluation (FULD), was found to differentiate DS adults with and without a diagnosis of probable dementia. The results of the present study suggest that tests of confrontation naming may not be sensitive in detecting dementia-related decline in individuals with Down syndrome, and that the FULD is a useful measure in the assessment of early dementia in this population.

Dedication

To my beautiful angels Mikayla and Stefano – my reasons for everything I do.

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Early aging has been identified as a peculiar feature of Down syndrome (DS), a genetic disorder also known as Trisomy 21, in reference to the abnormality occurring on chromosome 21 which affects physical and cognitive development. While biological processes are not fully understood, interest in the effects of premature aging on individuals with Down syndrome has increased, as service providers recognize the untimely manifestations of age-related changes. Notable among these changes is the high rate of suspected dementia in Down syndrome individuals in middle age. Over a century ago, a relationship between Down syndrome and a "general decay" and "precipitated senility" was first noted (Fraser & Mitchell, 1876). More recently, post-mortem studies have consistently revealed that almost all individuals with Down syndrome have some structural abnormalities in their brains by age 40 (Ball & Nuttall, 1980; Jervis, 1948; Malamud, 1964; 1972; Ropper & Williams, 1980; Schweber, 1985). These structural features include neurofibrillary tangles, neuritic plaques, amyloid deposits, and general cell atrophy. These pathological changes are usually associated with Alzheimer's disease (AD) in non-developmentally delayed individuals (Brugge et al., 1994), yet the age of onset in the non-delayed population is often much later. Research has revealed the gene for beta-amyloid precursor protein (APP) is located on chromosome 21 (Robakis, Ramakrishna, Wolfe, & Wisniewski, 1987; St. Clair, 1987), suggesting a genetic link between the two disorders of AD and DS. Deposits of extracellular beta-amyloid in

neuritic plaques are associated with the onset of Alzheimer's related dementia. The triplication of chromosome 21 and the subsequent over-expression of the APP gene are linked to the increased risk of neuritic plaque formation in DS individuals (Royston et al., 1999). More recently is the discovery that a protein, produced by a gene that is located on chromosome 21, called Regulator of Calcineurin 1 (RCAN1), is implicated in neuron death in the hippocampus and cortex of people with Alzheimer's disease in the general population and in individuals with Down syndrome. With the identification of the culprit gene and protein comes the hope that therapies will be developed that interfere with the gene's ability to produce RCAN1 (Sun et al., 2011). A related discovery is that the toxic beta-amyloid protein that is responsible for Alzheimer's pathology in the brain also accumulates in the eyes of people with DS, and leads to distinctive cataracts. These cataracts are prevalent in DS and are sometimes seen at birth, yet until now it was unknown how they were related to the disorder. These same cataracts appear in individuals with advanced AD in the general population. An eye scanner is being developed to measure beta-amyloid in the lens to provide a method for early detection and monitoring of related brain pathology in both AD and DS (Moncaster et al., 2010).

Other research examining the relationship between dementia of the Alzheimer type and chromosome 21 has shown an increased prevalence of Down syndrome in the families of patients with Alzheimer's dementia (Heyman et al., 1984). It has also been noted that the mothers of individuals with Down syndrome have a specific vulnerability to developing Alzheimer's disease (Stanton & Coetzee, 2004). The presence of AD neuropathology in DS adults in middle age has prompted investigators to query whether

the majority of this group of adults is experiencing the early stages of Alzheimer's disease (Cutler, 1985).

Alzheimer's Disease

Alzheimer's disease is an acquired progressive degenerative brain disorder that eventually results in global deterioration of intellect and personality, referred to as dementia (Karlinsky, Hardy, & Rossor, 1993; Salmon & Bondi, 1997). The dementia state of Alzheimer's disease has been coined Dementia of the Alzheimer Type (DAT) (Ellis, McCulloch, & Corley, 1974). In Canada, it has been estimated that more than 5% of people over the age of 65 develop the Alzheimer's neuropathology, and this number increases to 25% for the population aged 85 and older. By the end of 2011 it is predicted that new cases of dementia will reach 111,560 per year, and by 2031 it is expected that over three-quarters of a million Canadians will have AD (Canadian Study of Health and Aging Working Group, 2000). Since there are no known explicit markers for the disease, AD can only be definitively diagnosed upon autopsy, by histopathological verification of the presence of characteristic brain abnormalities (National Institute for Health and Clinical Excellence, 2001). The neurological composition of the disease includes the presence of neurofibrillary tangles and senile plaques. The neurofibrillary tangles are bundles of fine fibers within the cell bodies of neurons that occur in clusters throughout the diseased brain; senile plaques are the by-products of neuronal degeneration that are found in the cerebral cortex in AD patients (Cummings, Vinters, Cole, & Khachaturian, 1998). These neuropathological changes are associated with the death of the neurons that

contain them (Wisniewski, Wisniewski, & Wen, 1985).

Although AD can only be definitively identified postmortem, MRI and PET imaging are providing some promising findings in the early detection of the disease. For instance, MRI allows for accurate volumetric measurements of medial temporal structures such as the hippocampus[1]. Since medial temporal neuronal loss has been identified as an important feature in AD, MRI can be used to some extent to corroborate the positive clinical diagnosis of probable AD (Scheltens, Fox, Barkhof, & Decarli, 2002). While structural MRI studies have primarily focused on hippocampal changes, functional PET imaging permits the measurement of brain glucose metabolism, which is thought to be involved in dementia severity (Vandenberghe & Tournoy, 2005). Most recently, a specialized type of PET scan has been used to detect the beta amyloid plaques (Aizenstein et al., 2008). The Pittsburgh Compound B (PiB) is a brain imaging agent used in PET scanning that may one day offer a definitive diagnosis of AD in living patients. PiB is injected into the vein prior to the scan and attaches to AD-related brain deposits. Early results have supported the use of the PiB PET scan in the evaluation of beta-amyloid deposits. Interestingly, the PiB method also detected protein deposits in the brains of adults without symptoms of AD who were categorized as having healthy brains, and researchers were cautious about offering an explanation for this result. Further research is needed to determine if PiB PET scans can be used to diagnose AD or help monitor a patient's response to drug treatment.

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[1] The temporal lobe is part of the cerebrum. The medial temporal lobes are areas lying on the inner side of the temporal lobe. This part of the brain includes several areas that are critical for memory functions, including the hippocampus. The hippocampus is considered to have an essential role in episodic and declarative memory functions.

In general, the difficulty with using MRI and PET technology is that they do not provide information about whether a person has a cognitive disorder. Cognitive deterioration remains a clinical question. Evidence suggests that neuroimaging techniques offer only modest benefits in detecting AD, and they are best used as adjunctive screening measures for undetected pathology (for a review of the contribution of neuroimaging in the diagnosis of AD, see Alzheimer's Association Neuroimaging Work Group Consensus Report, 2004; Twamley, Legendre, & Bondi, 2006).

Since a conclusive diagnosis can only be made post-mortem, the clinical diagnosis of the disease is typically qualified as "possible" or "probable" (McKhann et al., 1984; Nebes, 1992). Clinical diagnosis of probable AD requires the presence of an acquired and progressive episodic memory deficit in conjunction with impairment in at least one other cognitive domain, and associated with a significant impact on functional activities of daily living (Vandenberghe & Tournoy, 2005). The progressive dementia is typically confirmed by a battery of neuropsychological tests, in the absence of other brain diseases that could account for observed deficits (Karlinsky, Hardy, & Rossor, 1993). A detailed evaluation is conducted which includes a personal and family medical history, in addition to neurological, psychiatric, and clinical examinations. Clinical investigations indicate that the accuracy of diagnosis of AD varies from about 50% to 60% among general practitioners in community settings to approximately 80% to 90% among specialists in referral centers, when compared to post-mortem findings (Bowler, Munoz, Merskey, 1998; Corey-Bloom, Thal, & Galasko, 1995). Life expectancy following the first appearance of the disease generally ranges from 3 to 15 years, but survival up to 20

years has been reported (Lyon &Yaffe, 2003).

Alzheimer's Disease and Down Syndrome

The first scientific publication detailing the unusual premature aging and senility in individuals with Down syndrome was submitted over 120 years ago by Fraser and Mitchell (1876), who found that among a group of 62 adults with Down syndrome, a certain proportion died of an accelerated senility. The first observation of a relationship between the neuropathological features of AD and middle-aged individuals with DS was made while studying β-amyloid plaques, one of the key characteristics of Alzheimer's disease. As part of a series of autopsies, Struwe (1929) detailed the case of a 37-year-old person with DS who had numerous neuritic plaques. Jervais (1948) was the first to document a direct relationship between these neuropathological features of AD and DAT in adults with Down syndrome, following the results of autopsies on three adults with DS between the ages of 37 and 47. This account included a connection between the clinical signs of intellectual decline and the neuropathological changes in the brains of these individuals. Following the results of this study a relationship was suggested between Alzheimer's disease and Down syndrome.

A series of studies have examined the relationship between AD and DS (Burger & Vogel, 1973; Ellis, McCulloch, & Corley, 1974; Malamud, 1972; Ropper & Williams, 1980; Solitaire & Lamarche, 1966; Wegiel, Wisniewski, Dziewiatkowski, Popovitch, & Tarnawski, 1996) with results establishing that virtually all adults with DS over the age of 40 have developed the classically defined neuropathological features of AD, and that

the risk of such changes is specific to Down syndrome and not to individuals with developmental disabilities of other etiologies[2]. What is less certain, however, is whether or not these individuals are predisposed to the development of the dementia associated with the disease. Despite what might be expected from neuropathological observations, the cognitive-behavioural course of dementia does not become evident in all individuals with Down syndrome. It has been estimated that anywhere from 25% to 50% of the oldest adults with Down syndrome (those in their sixth decade of life), may continue to function at their lifelong capacity level, without any indications of developing Alzheimer's related dementia (Zigman, Silverman, & Wisniewski, 1996). One early hypothesis for the variable relationship between neuropathological and clinical indications is that the disease may be inhibited by "neuronal redundancy" (Crapper, Dalton, Skopitz, Scott, & Hachinski, 1975). According to this theory, it may be that certain basic functions are spared at the cost of certain higher order functions never developing. It has been suggested that there may be a substantial safety factor, or reserve, that is inherent in the neuronal circuitry of the brain (Teuber, 1974). The reserve of certain neurons may thus serve to protect the brain against insult and maintain regular functioning.

It may be that clinical dementia does not necessarily occur among aging DS adults, or if dementia does develop it may go unrecognized. While there is evidence of the neuropathological hallmarks of AD in DS, the clinical profile of dementia in this population is more difficult to delineate. The pre-existing cognitive deficits in

[2] For a review of the genetic aspects of the disease in Down syndrome see Schupf, 2002.

individuals with DS present a clinical challenge in the detection of early-stage dementia. When individuals with Down syndrome present to caregivers with a decline in cognitive, behavioural, occupational, and/or social functioning, these changes must be viewed against a background of pervasive cerebral maldevelopment. Other diagnostic challenges include language impairment, hearing and vision deficits, thyroid dysfunction, and the presence of mood disorders. The variance in baseline cognitive, language, psychosocial, and adaptive behaviour skills also make it more difficult to characterize the dementing process in people with DS in comparison to the non-delayed population (Dalton, Seltzer, Adlin, & Wisniewski, 1993; Devenny, Krinsky-McHale, Sersen, & Silverman, 2000; Lai, 1992; Lai & Williams, 1989). Currently, within the ICD-10 and DSM-IV classifications[3], there is no consensus on the diagnosis of dementia in people with intellectual impairment, including individuals with Down syndrome. While several recommendations have been made, there is no universally accepted standard for making a diagnosis of dementia in people with Down syndrome (Nieuwenhuis-Mark, 2009). A recent review of clinical practice in the United Kingdom found that the assessment of DS individuals for signs of dementia was highly inconsistent, with results indicating enormous variability in the test instruments and methodologies used (Auty & Scior, 2008).

Cognitive Characteristics of Down Syndrome

Down syndrome is the most prevalent chromosomal cause of cognitive

[3]See discussion below.

impairment (Dykens et al., 2000). The prevalence at birth of DS increases with maternal age, and ranges from 0.7/1000 for mothers aged 20 to 24 years, to 55/1000 births for those aged 45 to 49 years (Stanton & Coetzee, 2004). Unlike other genetic syndromes, the vast majority of individuals with DS in North America are correctly diagnosed in infancy (Dykens et al., 2000). Because of its long history (it was first described by H. Langdon Down in 1866) and high prevalence rate, there is a vast body of research on many aspects of Down syndrome. Despite the rich tradition of behavioural research, certain features of Down syndrome remain unclear, although interest in intellectual and adaptive abilities is growing.

While few studies have examined the cognitive profiles of individuals with Down syndrome, research evaluating basic intellectual strengths and weaknesses has been notably consistent. Cognitive deficits are a cardinal manifestation of Down syndrome. Developmental milestones such as sitting and walking generally show delay, and assessment with formal psychometric tests reveal intellectual delay, with the measured intelligence quotient (IQ) of Down syndrome individuals typically ranging from 35 to 55 (Epstein & Epstein, 1980). It is worthwhile to note that functional levels attained are not entirely organically determined. Individual abilities can be considerably influenced by the environment. Specifically, family, social, educational and/or vocational influences contribute to intellectual characteristics that can vary widely (Berg, 1993). While there is individual variation in certain skill attainment, the majority of DS individuals do present with cognitive impairments. These include deficits in language as compared to nonverbal functions (Bilovsky & Share, 1965; Greenwald & Leonard, 1979; Piper, Gosselin,

Gendron, & Mazer, 1986). DS children typically have difficulties in attending, discriminating, encoding, transforming, and transmitting complex or subtle stimuli, and they show lower levels of performance on tasks of sequential and simultaneous processing compared to mental-aged matched controls (Pueschel, 1988).

Individuals with Down syndrome typically perform better on visual-spatial tasks than on verbal or auditory tasks (Haxby, 1989; Rohr & Burr, 1978; Silverstein, Legutki, Friedman, & Takayama, 1982; Thase, Tigner, Smeltzer, & Liss, 1984). As shown by several investigators, (e.g., Hodapp et al., 1992; Powell, Houghton, & Douglas, 1997; Pueschel, Gallagher, Zartler, & Pezzullo, 1987) children with DS tend to show greater ability in repeating a series of hand movements presented visually by an examiner, as opposed to a series of verbally presented numbers. This ability has also been observed in infants and toddlers with DS, who show strengths in recall of hand movements and other visual gestures (Harris, Bellugi, Bates, Jones, & Rossen, 1997).

In general, research has shown that DS children demonstrate higher levels of adaptive behaviour (e.g., grooming, following rules, getting along with others) than of cognitive intelligence. In a comparison of performance on a test of adaptive behaviour, Cornwell and Birch (1969) found that throughout the childhood years, IQ's were generally lower than SQ's (social quotients), and that as the children grew older, the decline in IQ was more pronounced than in SQ, when compared to baseline measures.

Clinical Symptomatology of DAT

In the general population Alzheimer's disease does not always manifest a set of

homogenous signs, although there are characteristic features of decline. There are three commonly used published diagnostic criteria for AD in the general population. The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (APA, 1994) specifies the presence of multiple cognitive deficits, including memory impairment, in addition to deficits in social and occupational functioning. The DSM-IV guidelines are presented in Appendix A. The International Classification of Diseases (ICD-10) (WHO, 1994) considers severity and offers guidelines for mild, moderate, and severe stages of the disease. This diagnostic system places emphasis on the diagnosis of AD being one of exclusion. The ICD-10 criteria for AD are presented in Appendix B. The third diagnostic system was developed to refine clinical criteria, since it was found that 20% or more of cases with clinically assigned AD were found at autopsy to have other conditions and not AD (McKhann et al., 1984). In 1984, a work group for the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) issued a document establishing standardized criteria for Alzheimer's disease (McKhann, et al., 1984). The criteria were intended to provide a standard method for diagnosing AD in research, especially for assessing the natural history of the disease. The work group specified that the criteria are compatible with the definitions in the DSM and ICD. The NINCDS-ADRDA guidelines also offer criteria for the diagnosis of "probable", "possible", and "definite" Alzheimer's disease. A high diagnostic accuracy for AD has been reported when the NINCDS-ADRDA criteria have been used. Berg and Morris (1994) reported 96% accuracy, with AD confirmed in 102 out of 106 autopsies of

individuals with DAT. The NINCDS-ADRDA criteria are presented in Appendix C.

While a variety of symptoms may present in early onset, the most consistently observed deficit is the gradual deterioration in several aspects of psychological functioning, including deterioration in intellectual abilities, changes in emotional expression and overall personality, and failure of memory functions (Chui, 1989). Studies have shown that impairments in explicit memory are among the earliest manifestations of AD, with both the encoding of material to be remembered and the retrieval of information affected (e.g., Bondi, Salmon, Galasko, Thomas, & Thal, 1999; Le Moal et al., 1997; Masur, Fuld, Blau, Crystal, & Aronson, 1990). Memory has also been identified as the cognitive domain which shows the greatest decline in individuals in the early stages of dementia (Albert, Moss, & Milberg, 1989; Moss, Albert, Butters, & Payne, 1986; Welsh, Butters, Hughes, Mohs, & Heyman, 1991). Visuospatial dysfunction has also been identified as occurring in the early stages of the disease (Crystal, Horoupian, Katzman, & Jotkowitz, 1982; Teng, Chui, Schneider, & Metzger, 1987). Spatial disorientation is evidenced by getting lost in previously familiar places, or confusing basic directions. Observable impairments in memory may include the inability to learn new information or to recall previously learned information. Other cognitive deficits include disturbances in executive functioning such as planning, problem solving, organization, sequencing, judgement, and abstraction. There may be a loss of higher cortical functions such as losing the ability to dress or bathe oneself, despite having adequate motor strength to do so. Motor difficulties are rarely exhibited until the late stages of the disease, and sensory functions generally remain intact (Cummings, 1990).

Clinical expression of the disease thus often includes impairment in, and eventual loss of, adaptive skills necessary for successful personal, community, and occupational functioning.

While nonverbal functions appear to be affected to a greater extent than are verbal functions, it is the verbal deficits which are often more readily recognizable. Individuals with DAT tend to exhibit greater impairment on the linguistic features of speech, which describes the information content of spontaneous speech and confrontation naming (Powell, Cummings, Hill, & Benson, 1988). A common and prominent feature of language disturbance in DAT is word-finding difficulty, which is variously referred to in the literature as dysnomia, agnosia, or anomia[4]. It has been suggested that one of the earliest and most characteristic signs of AD in the general population is an inability to name to confrontation (Bayles, 1982; Campbell-Taylor, 1993). Individuals with DAT often lose the ability to name common objects. It may be a challenge for those with Alzheimer's disease to find the right words to express thoughts or even follow conversations. Certain studies have shown that the naming deficit is the earliest measurable language change associated with the disease (Appell, Kertesz, & Fisman, 1982; Martin & Fedio, 1983). The anomia in people with DAT is often disproportionally severe compared to other language deficits. In addition to it manifesting quite early in the course of the disease, anomia also advances with overall language degeneration (Appell et al., 1982; Kertesz, Appell, & Fisman, 1986). In an early study on the effect of dementia on speech, Critchley (1964) found that DAT patients presented with a "concrete

[4] In the present study, the term *anomia* will be used for consistency to refer to word-finding difficulty.

attitude" which was characterized by a marked difficulty in providing the names of items within a given category. Performance on naming tests was also examined by Stengel (1964) who found that when patients with dementia had difficulty producing names of objects, they often created new words and were unaware of their errors. Other studies have shown that when DAT patients were confronted with an inability to find a desired word, they would provide an adequate description or an appropriate synonym (Ajuriaguerra & Tissot, 1975; Martin & Fedio, 1983). Interestingly, although DAT patients have difficulty performing on tasks requiring the production of a specific referent, they do not differ from the general population on measures of word frequency in free speech (Howes, 1964; Miller & Hague, 1975), and their vocabulary remains relatively intact (Crookes, 1974; Martin & Fedio, 1983; Whitehead, 1973). The anomia in DAT has been described as quite specific. The majority of studies in the research literature have established that the naming difficulties are related to semantic functioning. The evidence supporting a semantically based naming deficit in DAT will be reviewed below.

Theoretical Model of Semantic Knowledge

Semantic memory is the component of long-term memory that contains the permanent representations of concept knowledge, words, and word meanings (Tulving, 1983). It represents an individual's general fund of knowledge and consists of over-learned facts that do not depend on contextual cues for their retrieval. Semantic memory is culturally shared, rather than based on personal experiences. Semantic memory stores

the information used to recognize an object, retrieve a label to name that object, and access the meaning of the label. In general, semantic memory is the mechanism by which knowledge of concepts is converted into words (Chertkow & Bub, 1990). An integral function of the semantic memory system is the ability to retrieve words upon visual presentation of an object. Changes in semantic memory have been cited as the first measurable changes in early DAT (Weingartner, Kawas, Rawlings, & Shapiro, 1993).

The general theoretical model for the organization of semantic knowledge is a complex network of concepts or representations that are related through serial and/or parallel associations (Lukatela, Lukatela, Carello, & Turvey, 1993; Rummelhart & McClelland, 1986). Concepts that share many attributes are more highly associated in this network than are those sharing fewer attributes (Collins & Loftus, 1975). The concepts that are strongly related are assumed to form conceptual categories that are comprised of exemplars that share many attributes. Concepts are grouped into categories based on their attributes. Within this model *peach* and *pear* are highly associated because they are both categorized as fruit. Similarly, since *dog* and *cat* share many features (e.g., four-legged animals, furry, pets), they are more highly linked in the model. The concepts *dog* and *chair* do not share obvious attributes and thus they are weakly associated in the network.

Neurobiological Basis of the Naming Deficit in Alzheimer's Disease

Neuropsychological theories of the cognitive deterioration that occurs in AD depend on a physiological basis for the representation of knowledge (Salmon, Butters, &

Chan, 1999). These theories rely on the early proposal by Hebb (1949) that the acquisition and preservation of knowledge occurs through anatomical changes in the association cortices that result from activating a specific group of cells in a circuit. Within this model anatomical changes occur at the level of the synapse, so any degeneration that causes synaptic loss presumably would interfere with the representation of knowledge. Hebb's model has been supported by research that has identified a strong relationship between cognitive degradation and synapse loss in the association cortices of AD patients (Terry, Masliah, Salmon, Butters, DeTeresa, Hill, Hansen, & Katzman, 1991).

The neurobiological course of AD has been identified as the spread of neuritic plaques and neurofibrillary tangles from the posterior toward the anterior part of the brain, particularly from the parietal and temporal regions to the frontal regions (Small & Leiter, 1998). Research using MRI scanning (Fama et al., 2000; Pihlajamaki et al., 2000) and SPECT indexing (Pasquier, Lebert, Grymonprez, & Petit, 1995), implicate the parietal and temporal regions as being central to the processes involved in semantic fluency. These areas tend to be most affected in the early stages of AD. Patients typically show difficulties with memory, organization of verbal material, recognition of familiar words, and spatial organization. In terms of naming, part of the deterioration that occurs has also been linked to the breakdown of semantic networks in the frontal lobes (Binetti et al., 1995; Flicker, Ferris, Crook, & Bartus, 1987), but this area is typically affected later in the disease process. Semantic information is presumably stored in a hierarchical manner in the association cortices (Marshall, 1988; McCarthy &

Warrington, 1990). Since naming requires access to the semantic network and its associations between pictures and words, damage to the network manifests as naming deficits. As neural deterioration spreads toward the frontal lobes, this naming impairment is observed as the inability for DAT patients to name upon confrontation.

Assessing Naming Deficits in Alzheimer's Disease

Since one of the earliest signs of the onset of dementia involves naming deficits (i.e., the inability to name upon visual presentation), the assessment of naming abilities has become an essential part of neuropsychological testing (Albert, 1981). Specifically, the study of naming errors has been important in AD research (Bayles & Tomoeda, 1983; Cox, Bayles, & Trosset, 1996; Goldstein, Green, Presley, & Green, 1992; Hodges, Salmon, & Butters, 1991; LaBarge, Balota, Storandt, & Smith, 1992; Nicholas, Obler, Au, & Albert, 1996). Anomia is typically assessed by visual confrontation naming, in which individuals are required to verbally identify familiar objects depicted in line drawings (Denckla & Rudel, 1976; Kaplan, Goodglass, & Weintraub, 1983; Temple, 1986). Research in which visual confrontation naming has been used suggests that anomia is likely due to disruptions which result in impaired lexical (name) retrieval, impaired semantic (meaning) access, or degraded semantic representation (Ashcraft, 1993; Blaxton & Bookheimer, 1993; Hanley, 1995; Henderson, Mack, Freed, Kempler, & Anderson, 1990; Marshall, Pound, White-Thompson, & Pring, 1990; Stimley & Noll, 1991). In other words, there may be problems with the neural pathways which allow the brain to retrieve the labels given to objects, or to access the stored meanings of words, or

there may be a breakdown in the way the meanings of existing words are stored in memory.

The research literature on naming abilities associated with normal aging and DAT suggests that, while naming deficits occur for individuals in both groups, the underlying processes may be quite different. In comparing normal aging and dementia, it is typically recognized that naming deficits related to DAT are far more pervasive and severe. Most models of confrontation naming (e.g., Melvold, Au, Obler, & Albert, 1994; Sandson, Obler, & Albert, 1987) distinguish at least three sequential stages in the process of naming: 1) the object is perceived and perceptually analyzed; 2) the lexical semantic representation is accessed; and 3) the phonological representation and motor articulatory sequences are activated for speech. A disruption at any one stage may result in impairment that manifests as anomia. Numerous studies have attempted to identify at which stage in the process is naming impairment produced, in both normal aging and in DAT. The findings of several studies support the hypothesis that in normal aging the lexicon remains intact, and naming difficulties are the result of access and retrieval problems (e.g., Burke, Worthley, & Martin, 1988; Nicholas, Obler, Albert, & Goodglass, 1985). In a study of naming that included the effects of priming, Bowles and Poon (1985) found that normal elderly participants could activate correct semantic representations, but they had difficulty retrieving the precise word from their lexicon. In contrast, in DAT patients, naming impairment is largely due to a *loss* of semantic information. While retrieval deficits may also play a role in the naming deficit in DAT, most studies (e.g., Hodges, Salmon, & Butters, 1991; Chan, Salmon, Nordin, Murphy, &

Razani, 1998; Henderson, Mack, Freed, Kempler, & Anderson, 1990; Salmon, Butters, & Chan, 1999; Tulving, 1983) point to a deterioration in the semantic organization of the lexicon, which could be the result of a more general degradation of the conceptual aspects of cognition. Furthermore, the disturbance to the integrity of the semantic network in DAT patients increases as the disease progresses.

Research supporting the hypothesis that semantic knowledge is primarily impaired in DAT has demonstrated that the meaning of words is somehow disturbed in the brains of those with dementia. On naming tests, AD patients tend to make errors which are semantically related to target words. For instance, an object may be called by the name of the category to which it belongs (e.g., *animal* instead of *horse*), or by the name of another member of the same semantic category (e.g., *cow* instead of *horse*) (Hodges, Salmon, & Butters, 1991; Martin & Fedio, 1983). The former type of semantic error in AD has been likened to the naming behaviour of young children (Ajuriaguerra & Tissot, 1975; Warrington, 1975), which is marked by the use of overextensions of specific labels to related referents (e.g., *dog* to refer to all four-legged animals). In children, only one to two features are used to characterize the meaning of a word, and as the child matures more features are learned and the meaning of a word is narrowed until it corresponds to a specific referent. It is proposed that in AD patients, the naming errors produced may represent a loss of specific attributes which results in a dedifferentiation of meaning (Clark, 1973). In effect, the narrowing down process which occurs in the developing child, is reversed in the DAT patient. This "bottom-up" degradation process (Hodges, Salmon, & Butters, 1992) has been described as an unravelling of linguistic

maturation (Martin & Fedio, 1983), resulting in a decrease in the specificity of accessible semantic information. Certain studies (e.g., Bayles, 1982; Huff, Corkin, & Growdon, 1986; Warrington, 1975) have examined the comprehension impairment for words and pictures and have proposed a central disturbance in the representation of object concepts. This means that people with DAT fail to categorize words and pictures because they can no longer retain a complete description of their meaning.

A case study of the genesis of misnaming pointed to the deterioration of the semantic distinction of words. Schwartz, Marin, and Saffran (1979) studied the degeneration of naming ability in a 62-year-old woman diagnosed with senile dementia. The patient was presented with 70 colour photographs of common household objects and she was asked to demonstrate the use of each item. While the patient consistently demonstrated object recognition through accurate gestures, she was unable to name any of the items except for "cup". In a subsequent task, the patient was asked to select the name of the stimulus item from five choices offered: two unrelated object names, a phonologically and orthographically similar name, the name of an item in the same semantic category, and the target name. The patient chose the semantic distractor 85% of the time. In other words, if a picture of a spoon were shown, a semantically related distractor item could be the word "fork", as spoon and fork both belong to the category of "cutlery". During a follow-up testing trial 21 months later, the patient chose the semantic distractor 61% of the time. The investigators concluded that the patient's lexical failure resulted from a progressive loss of semantic features. They reported that specific names no longer represented a unique referent, rather they symbolized a population of related

referents.

Use of the BNT in Identifying Naming Errors in DAT

One of the most common methods of formally assessing naming abilities is the administration of the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983), a 60-item test of line drawings of items that the patient is required to name upon presentation. The BNT has been identified as the most frequently administered test of confrontation naming (Barko-Collo, 2001; Williams, Mack, & Henderson, 1989), providing diagnostic information about naming deficits in a variety of degenerative disorders, including dementia. The BNT is widely used in the assessment of dementia as a sensitive indicator of both the presence and the degree of cognitive deterioration (Henderson, Mack, Freed, Kempler, & Anderson, 1990; Hodges, Salmon, & Butters, 1991; Lezak, 1995; Melvold, Au, Obler, & Albert, 1994; Miller, Rogers, Siddarth, & Small, 2005; Storandt, Botwinick, & Danziger, 1986; Storandt & Hill, 1989; Suribhatla et al., 2004; Vandenberghe & Tournoy, 2005). Even dementia patients with mild impairment tend to produce significantly lower scores on this measure than aphasic stroke patients (Margolin, Pate, Friedrich, & Elia, 1990). In clinical settings, the BNT is typically part of a neuropsychological test battery, and it is the most common stimulus for testing naming facility. It has been included in the CERAD[5] test battery as a reliable measure of naming impairment in Alzheimer's disease. Research using the CERAD

[5] The Consortium to Establish a Registry for Alzheimer's disease was established in 1986 by the National Institute on Aging in the United States to standardize procedures for the evaluation and diagnosis of patients with AD.

neuropsychological battery to compare performance between individuals with AD and elderly controls confirmed the utility of the BNT. Among the nonmemory tests on the CERAD (i.e., fluency, naming, and praxis), only confrontation naming aided in the discrimination between patients with early AD and elderly normal controls (Welsh, Butters, Hughes, Mohs, & Heyman, 1991). Knesevich, LaBarge, and Edwards (1986) demonstrated that the BNT was the best predictor, among a group of clinical measures, of the progression of DAT. Similarly, in a study examining tests of semantic memory, the BNT was found to be the only measure that could predict deterioration in AD patients (Beatty, Salmon, Troster, & Tivis, 2002).

The items depicted on the BNT range from highly common items at the beginning of the test (e.g., tree, pencil), to less common items toward the end of the test (e.g., sphinx, trellis). Results of various normative studies on the BNT suggest that naming abilities remain generally intact throughout advancing age in the unimpaired elderly (e.g., Van Gorp, Satz, Kiersch, & Henry, 1986), while severe difficulties in confrontation naming abilities are a common and prominent feature of DAT (e.g., Martin & Fedio, 1983). Several researchers have found the BNT is highly sensitive to very mild AD in the general population (LaBarge, Balota, Storandt, & Smith, 1992; Williams et al., 1989; Zec, Vicari, Kocis, & Reynolds, 1992), and it has also discriminated well between AD and vascular dementia (Barr, Benedict, Tune, & Brandt, 1992). In a study on word retrieval failure it was found that 80% of AD patients showed anomia on the BNT (Freedman, Snow, & Millikin, 1995). Another study found the BNT discriminated well between normal elderly subjects, individuals at risk for AD, and individuals already

diagnosed with AD (Cahn et al., 1995).

While the BNT is primarily employed to assess naming abilities, since the test requires individuals to label a picture on demand, it should be noted that visuoperceptual errors can also be made on this task. A visuoperceptual error is a response that shares visual characteristics with the target word. For example, for the target word *pretzel*, a visuoperceptual error could be *snake* or *knot*. To establish that the errors made by AD patients are indeed a result of impaired semantic knowledge, rather than a perceptual deficit, several investigations of the qualitative nature of naming errors have been conducted (e.g., Bayles & Tomoeda, 1983; Goldstein, Green, Presley, & Green, 1992; Hodges, Salmon, & Butters, 1991; Nebes, 1989). The results of these analyses indicate that the naming errors were overwhelmingly related semantically, rather than perceptually, to the target words presented. In their study of naming impairment in dementia, Bayles and Tomoeda (1983) concluded that since dementia patients are able to demonstrate through intricate gestures the recognition of objects they cannot name, it seems improbable that the patients misperceived the objects. These results have supported the hypothesis that the impairment identified using naming tasks in AD patients is one of semantic knowledge, not visual processing. DAT patients retain the ability to recognize objects and to use them appropriately beyond the time that they can name them accurately (Cummings & Benson, 1992).

In a more recent study, the *type* of semantic error produced by AD patients was examined in detail to better understand the particular deficits associated with semantic knowledge in AD (Lukatela, Malloy, Jenkins, & Cohen, 1998). Semantic errors were

studied independently and were classified into coordinate errors (e.g., saying *penguin* when shown a picture of a *pelican*), and superordinate errors (e.g., *bird* for *pelican*). In other words, coordinate errors are made when the individual substitutes the name of another member from the same category as the target word; superordinate errors are made when the general category name, to which the target word belongs, is identified. The BNT was employed as a sensitive test to detect these types of semantic errors. Consistent with the investigators' expectations, AD patients were found to make more overall naming errors compared to patients with vascular dementia and to a control group of unimpaired elderly subjects. Furthermore, qualitative differences between the groups were observed within the subtypes of semantic errors, in that AD patients demonstrated a greater propensity for naming a superordinate category instead of the target word. In other words, AD patients would provide the name of the larger category to which the required word belonged, (e.g., *animal* instead of *beaver*). It was noted that these results further supported earlier hypotheses that differentiation of within-category exemplars is impaired in AD patients, whereas knowledge of the category itself is preserved (Butters, Granholm, Salmon, Grant, & Wolfe, 1987; Chertkow & Bub, 1990; Johnson, Bonilla, & Herman, 1997; Martin & Fedio, 1983; Ober, Dronkers, Koss, Delis, & Friedland, 1986). In other words, the higher level concepts remain relatively intact (e.g., *fruit*), but the specific items belonging to each category are severely compromised (e.g., *peach, pear, plum*). The authors concluded that the tendency to make superordinate errors over any other type of semantic error in AD is specific to the disease. Similar results were found in a study examining the semantic impairment in DAT patients compared to those with

Huntington's disease, in that DAT patients had a greater tendency to produce general category labels on a fluency task (Troster, Salmon, McCullough, & Butters, 1989). The results indicated that DAT patients initially lose subordinate knowledge that includes the specific attributes of a semantic category, while the more general superordinate knowledge is preserved.

Down Syndrome and Dementia of the Alzheimer Type

Advances in medical, technological, and personal care have increased the life expectancy of individuals with Down syndrome over the last few decades. The average life expectancy for Down syndrome in 1929 was nine years (Penrose, 1949). By 1947 the life expectancy had risen to 15 years (Benda, 1969), and by 1961 the average age had increased to 18 years (Collmann & Stoller, 1963). By the beginning of the 1980's, individuals with Down syndrome had an average life span of 35 years (Holland, 2000), with many individuals living well into their seventies. The Down syndrome phenotype includes numerous anomalies, primarily physical and functional, with perhaps the most curious trait being premature aging. The characteristics of this early aging include changes in skin tone, early greying and/or loss of hair, hypogonadism, increased frequency of cataracts and hearing impairment, age-related increases in hypothyroidism, arthritis, seizures, degenerative vascular disease (Martin, 1978; Brown, 1985; Oliver & Holland, 1986), and early menopause in women (Schupf et al., 1997).

The substantial improvement in life expectancy has resulted in a growing population of middle-aged adults with Down syndrome. An outcome of this occurrence

is that as individuals with DS reach middle age they appear to be at high risk for developing features consistent with Alzheimer's disease observed in the general population. The neuronal changes observed in the brains of DS individuals at autopsy after age 40 are almost qualitatively and quantitatively indistinguishable from those seen in Alzheimer's disease in the general population (Solitaire & LaMarche, 1966; Wisniewski, Jervis, Moretz, & Wisniewski, 1979; Wisniewski, Wisniewski, & Wen, 1983). It has been noted that although structural imaging of the brain could be useful in evaluating neuropathological features in DS, it is scarcely ever diagnostic, especially since many people with DS have abnormal brain scans premorbidly (Stanton & Coetzee, 2004). Specific structural abnormalities have been detected with MRI in DS individuals with AD, which are changes that are also seen in non-intellectually disabled individuals with dementia, although these findings cannot be used to diagnose clinical AD with good accuracy in DS adults (Prasher et al., 2003). Currently, brain imaging has been useful in the differential diagnosis of various conditions in DS such as the presence of vascular lesions, and computed tomography (CT) scanning has shown cerebral atrophy in individuals with DS and suspected dementia (Stanton & Coetzee, 2004). Certain findings could potentially contribute to the diagnosis of AD in DS, such as CT scans showing a reduction in volume in the medial temporal lobe (Lawlor, McCarron, Wilson, & McLoughlin, 2001), which has also been shown in AD studies in the general population. Most recently, volumetric MRI has detected certain changes in brain anatomy in DS individuals with suspected AD (Beacher, et al., 2009), although further research is needed to determine if these changes may provide markers of clinical dementia.

While there are unequivocal neuropathological findings typical of AD, there is limited neuropsychological evidence of Alzheimer's related dementia in people with Down syndrome. Diagnosing dementia in DS individuals is problematic in that it depends upon recognizing changes in several domains of cognitive ability that may already be impaired due to pre-existing intellectual disability, but which may be deteriorating further due to aging and/or dementia. The difficulty of making a diagnosis of AD in individuals with DS is owed, in part, to methodological problems in detecting the disease, and also to a host of medical and psychological conditions associated with the syndrome which may mimic or mask the presence of AD. These are problematic especially since many general practice physicians who may treat the entire family, including the DS individual, may not be aware of these special conditions that are commonly found in Down syndrome, and they may go undetected. By the time the symptoms manifest, they may automatically be assumed to be related to AD, even when they are in fact caused by another physical or psychological condition.

Differential Diagnosis: Masking Disorders in Down Syndrome

Behavioural changes are almost invariably noted in supporting a probable diagnosis of dementia. Caution is warranted, though, in that behavioural changes may be indistinct in their origin. Functional decline in individuals with Down syndrome is not always indicative of Alzheimer's disease. Several other conditions, including some reversible ones, occur in persons with Down syndrome which mimic the symptoms of dementia. As such, there is a high risk of misdiagnosis, especially since the performance

of individuals with masking disorders on cognitive measures will be similar to that of persons undergoing dementia-related decline. Often the most observable symptoms in individuals with DS and clinically-assigned probable AD are vague and unassuming. In their review of eight articles with case reports describing the clinical changes in 14 individuals with DS and Alzheimer's neuropathology, Oliver and Holland (1986) found that 9 of the patients had as observable symptoms, "apathy", "depression", "lethargy", "withdrawn", and "lost interest". Similarly, Evenhuis (1990) described the clinical course of 14 patients with DS and early-stage dementia and found that 13 patients showed apathy and withdrawal, 9 patients had loss of self-help skills, and 7 patients had daytime sleepiness. These types of behavioural changes can accompany a number of other conditions in individuals with Down syndrome. For instance, leukemia occurs more often in children and adults with DS than in the general population (Odell, 1988; Rajantie & Siimes, 2000). The initial visible symptoms of this blood cell cancer are tiredness, weight loss, and an overall decline in functioning.

The differential diagnosis of functional decline requires a detailed medical, familial, and social history, and a thorough physical examination. While individuals with Down syndrome need the usual health care screening procedures which are recommended for the general population, there are also certain congenital anomalies and medical problems that occur at a much higher frequency in Down syndrome and which need to be evaluated.

Thyroid Disease. Thyroid disease is common among individuals with Down syndrome. In one study of 55 DS patients ranging in age from 27 to 67 years, 50% had

clinical features associated with hypothyroidism, and 22% had a formal diagnosis of the disease. Those patients who had hypothyroidism were all over the age of 39 (Mani, 1988). Dinani and Carpenter (1991) found that of 106 adults with DS, 41% had abnormal thyroid function, and of these individuals, more than 60% were over the age of 35. Specific symptoms of hypothyroidism include reduction in energy, motivation, and enthusiasm, and a general decline in cognitive functioning, including memory and attention. Since the signs of hypothyroidism may be subtle in Down syndrome and may be attributed to the syndrome itself or to dementia, yearly thyroid screening and close monitoring is essential. In its most severe state, hypothyroidism can cause an individual to appear as if they are suffering from dementia (Galley, 2005). Hypothyroidism is one of the most frequent causes of reversible dementia. Symptoms of dementia will disappear once hormone therapy is administered.

Sleep Disorder. A decline in functioning in persons with DS can also be the result of sleep apnea. This condition is characterized by a temporary cessation of breathing during sleep, which often results in excessive daytime sleepiness, lethargy, and irritability (Silverman, 1988). In addition, the cumulative effect of insufficient and/or poor quality sleep can produce a decline in mental alertness and concentration, and can diminish an individual's overall cognitive production. Sleep apnea may produce behavioural changes such as irritability, depression, or paranoia (Galley, 2005). Obstructive sleep apnea occurs in approximately 50% of DS individuals (Stebbens, Dennis, Samuels, Croft, & Southall, 1991). Obesity, underdeveloped facial features, and smaller airways in people with DS are contributing factors to this condition (Kanamori,

Witter, Brown, & Williams-Smith, 2000).

Depression. The major differential diagnosis is between DAT and depressive disorder. Depression has been cited as one of the most frequently diagnosed psychiatric disorders in individuals with DS (Collacott, Cooper, McGrother, 1992; Myers & Pueschel, 1991; Szymanski, 1988). The reported significantly high prevalence of depression in adults with DS is frequently found to be related to the elevated rate of hypothyroidism common in the syndrome. In a study of 61 adults with DS and 43 adults with developmental disability of other etiology, it was found that only those adults with DS showed depression and decline in functioning (Sovner & Hurley, 1983). Depression can mimic symptoms of dementia and it can coexist with the disease. As in the general population, there is considerable overlap between the symptoms of depression and dementia in adults with DS. Typical signs of depression in the general population include an overall sad and irritable mood, disturbances in appetite, sleep, and energy, in addition to decreased interest in previously enjoyed activities. In individuals with DS presenting symptoms are likely to involve skill and memory losses, tearfulness, irritability, significant reduction in activity level, loss of adaptive living skills, hallucinatory-like self-talk, and even extreme withdrawal with psychotic features (Burt, Loveland, & Lewis, 1992; Lazarus, Jaffe, & Dubin, 1990; Warren, Holroyd, & Folstein, 1989). One feature of major depression specific to individuals with developmental disability is the loss of activity of daily living skills. For example, the onset of urinary incontinence is often associated with depression amongst those with DS, and this symptom can also be seen in DS individuals presenting with features of dementia (Pary,

1992).

Self-Talk. Self-talk is common and generally developmentally appropriate, in considering the mental age of most individuals with DS. As is the case in young children in the general population, self-talk plays an essential role in the cognitive development of individuals with Down syndrome (Cohen, 1999). It helps them to coordinate thoughts and actions. In non-delayed children the use of self-talk is progressively internalized with age and increased intellectual abilities. The developing child begins to privately think, rather than say aloud directions for his/her behaviour. In DS adults, intellectual and speech impairments may contribute to their audible self-talk. They may think out loud in order to process daily life events. When self-talk develops quite suddenly in an adult with Down syndrome, caregivers may be concerned that it is symptomatic of a problem, and may liken it to the rehearsing which is sometimes seen in individuals in the general population when confronted with memory lags as a result of the onset of dementia. Social and environmental factors should first be considered, in that an individual with DS who develops self-talk during middle age may use it as a coping strategy for changes in their environment, such as a residential move, the loss of a family member or friend, or a change in routine.

Impaired Hearing and Vision. Adults with Down syndrome are at an increased risk for both auditory and visual impairment. It has been estimated that 40% to 77% of adults with DS experience hearing loss, either sensorineural or conductive or both, and 46% develop cataracts (Keiser, Montague, Wold, Maune, & Pattison, 1981). Impairment in hearing and vision may manifest in notable changes in behaviour, including

withdrawal, apathy, and reduced interest in social activities (Jozsvai, 1999).

Vitamin B12 Deficiency. In addition to preventing pernicious anemia, vitamin B12 is required for the maintenance of myelin, which is a component of the central nervous system. Inadequate synthesis of myelin leads to neurological damage. In the general population a vitamin B12 deficiency can cause forgetfulness, irritability, decreased appetite, withdrawal, a general functional decline, and dementia. The symptoms of this vitamin deficiency disappear following intramuscular injection of vitamin B12. It has been suggested that individuals with Down syndrome may have a lowered ability to absorb vitamin B12. A study of biochemical disturbances in institutionalized patients with DS found that vitamin B12 was moderately lower when compared to controls (Hestnes et al., 1991). Cartlidge and Curnock (1986) described a 3-year-old girl with DS who presented as lethargic, irritable, and had decreased appetite with weight loss, and withdrawal. The patient was found to have malabsorption of vitamin B12, and all of her symptoms disappeared following medical therapy. Vitamin B12 deficiency is recognized as a reversible cause of behavioural change or cognitive decline in individuals with DS (Galley, 2005).

Other conditions that can produce cognitive and behavioural changes include bereavement, general physical illness or pain, secondary effects of medication, and changes in routine or social environment (Johansson & Terenius, 2002). These conditions may lead to withdrawal, general apathy, decline in self-care skills, incontinence, and irritability. These changes may be mistaken for the early onset of dementia of the Alzheimer's type.

Clinical Detection of DAT in Down Syndrome

Since the diagnosis of DAT is based on signs and symptoms and not on pathological data, there is risk of misdiagnosis. Within clinical settings, making a diagnosis of dementia typically requires the presence of a decline in memory and other cognitive functions, such as speech, for at least six months. Progressive impairment in explicit memory is typically recognized as an early indication of dementia in the DS population, as it is among individuals in the general population (Brugge et al., 1994; Devenny et al., 2000; Krinsky-McHale, Devenny, & Silverman, 2002; Stanton & Coetzee, 2004; Thase, Liss, Smeltzer, & Maloon, 1982). The deterioration of general cognitive functioning is usually coupled with changes in personality, mood, and behaviour. Application of these criteria to diagnose Alzheimer's disease in Down syndrome is difficult, given the various physical conditions that can diminish cognitive and behavioural functioning, and mimic dementia.

Clinical diagnosis of dementia in Down syndrome largely relies on measurable differences in performance on various neuropsychological tests. Ideally, performance is compared to prior results from baseline testing. If premorbid testing is not available, individuals suspected of having dementia are tested, and follow-up evaluation occurs at six-month and twelve-month intervals to note changes in performance.

It has been noted that in the general population there is no specific test or procedure to detect the features of AD before the onset of its manifestations, nor is there a clinical instrument available to monitor the entire range of deficits produced by the disease (Crapper-McLachlan, Dalton, Galin, Schlotterer, & Daicar, 1984). The majority

of cognitive test batteries used invariably include intelligence tests. Similar to individuals in the general population, people with DS suspected of having DAT are evaluated by examining changes in performance on these measures (Dalton, Seltzer, Adlin, & Wisniewski, 1993). Performance scores on these tests may be of limited value, though, since individuals with DS often score very poorly on many items, making comparisons uninformative (Dalton & Wisniewski, 1990; Dalton 1992). Assessing DS individuals can be particularly restricted by test floor effects on measures usually administered to detect DAT (Vicari, Nocentini, & Caltagirone, 1994). When performance on a test is not much above zero or above the level of test error, subsequent testing will not be able to identify a decline. Another limitation is that most psychometric tests cannot be used with individuals with severe cognitive impairment. Additionally, cognitive measures tend to be more sensitive to global cognitive deterioration rather than to deficits of single cortical functions, and it is the loss of single cognitive abilities that is the initial marker of decline in DAT in the general population (Vicari, Nocentini, & Caltagirone, 1994).

One of the most challenging aspects of assessment with the DS population involves the lack of reliable and sensitive instruments. Few psychological assessment measures have been normed on DS individuals in general, and there are no tests currently agreed upon for use in detecting dementia-related declines in this population. Typically, when testing DS adults, adult versions of neuropsychological tests that are used in the general population are modified, or children's versions are administered (Deb, 2003). For instance, the Mini-Mental State Examination (MMSE) (Folstein, Folstein, &

McHugh, 1975) has been amended to offer multiple choice answers for orientation questions (Wisniewski & Hill, 1985). The McCarthy Verbal Fluency test (McCarthy, 1972) is an example of a measure designed for children of normal cognitive functioning which is also used with intellectually impaired adults. The Boston Naming Test is administered as a test of language even though norms have not been developed for individuals with developmental disabilities. These tests are all used to test abilities in people with intellectual impairments, but their validity is questionable, given they have been specifically designed for use with the general population (Deb, 2003). In terms of using existing tests for dementia screening, since individuals with intellectual impairment present with a range of cognitive abilities, it is difficult to determine cut-off scores. Deb and Braganza (1999) compared clinicians' diagnoses of dementia with various dementia rating scales, including the MMSE, among DS adults with and without dementia. They found it possible to administer the MMSE to just over half of their subjects (34 of 62 adults) because of varying degrees of severity of cognitive impairment. Thirty of these 34 subjects scored below 24, which is the cut-off score for individuals in the general population for possible dementia, yet 23 of these subjects had no diagnosis of dementia according to the clinicians' clinical diagnoses or to the other rating scales administered.

An added problem in detecting developing impairments in DS individuals stems from environmental factors. It has been suggested that most individuals with DS typically lead "sheltered" lives and rely on caregivers to assist them with daily living needs and, as a result, they have few intellectual demands placed upon them (Crayton & Oliver, 1993; Miniszek, 1983). As such, the initial symptoms of DAT, including memory

loss and general confusion, are less likely to be detected from simple observation of daily functioning. If inconsistencies in performance are noted, they may be dismissed as due to the pre-existing cognitive impairment instead of to the onset of dementia. This may be contrasted with those who develop DAT in the general population, who are detected at an early stage since substantial demands in social and occupational domains more readily reveal a decline in performance. The tendency to attribute changes in behaviour or ability to intellectual disability is referred to as "diagnostic overshadowing" (Reiss, Levitan, & Szyszko, 1982). In considering cognitive and behavioural changes in people with DS, diagnostic overshadowing can result in delayed referrals to specialist services or no medical attention at all.

Another potential difficulty that arises during assessment involves the personality characteristics of people with Down syndrome. DS individuals have been described as being generally happy and easy-going (Gilmore, Campbell & Cuskelly, 2003; Wisniewski, Hill, & Wisniewski, 1992). A certain personality stereotype exists with DS individuals frequently being described as having charming personalities (Rodgers, 1987; Wishart & Johnston, 1990), and as being "nice", "lovable", "cheerful", "generous", and as "getting on well with other people" (Carr, 1995). Consideration is needed during assessment in that DS individuals may be overly agreeable and suggestible, and they may produce answers to queries about mood and behaviours according to what they think is expected.

Perhaps one of the most prominent contributing factors to the difficulties in identifying early signs of clinical dementia in persons with DS is that any changes in

functioning are superimposed on a background of especially limited verbal and communication skills (Dalton et al., 1993).

Linguistic Features in Down Syndrome

To date, most clinical investigations have attempted to map the changes which occur in DAT in the non-developmentally delayed population onto the life experiences of individuals with Down syndrome. One of the earliest signs of DAT in the non-delayed population is subtle loss of language functions (Bayles & Boone, 1982). This clinical symptom has also been indiscriminately applied to the diagnosis of DAT in DS. However, what is often overlooked is that the language of DS individuals is already limited *before* a decline in functioning can even be identified. Language development is already compromised by the syndrome.

Of the many manifestations of the syndrome, the cognitive developmental impairment appears to be the most detrimental to speech and language acquisition and usage (Jung, 1989). Previous studies have concluded that language abilities are relatively more impaired than other areas of cognition in the DS population (Clibbens, 2001; Fowler, Gelman, & Gleitman, 1994; Miller, 1996). Language has been referred to as a "major area of deficit" in DS (Sigman & Ruskin, 1999), and expressive language difficulties have been particularly noted (Chapman, 2006; Miller & Leddy, 1999). Research on language development in DS children has consistently demonstrated that there is a large discrepancy between measured language skill and expectations of language acquisition based on assessment of mental age (Cicchetti & Beeghly, 1990). In

other words, language production among children with Down syndrome lags behind expected performance based on mental age. Children with DS show deficits in expressive language skills which are above and beyond the cognitive limitations associated with the syndrome (Dodd, 1975; Rohr & Burr, 1978). Observed language deficits are also disproportionate to nonverbal abilities, according to motor, intellectual, and social indices. Studies of the syndrome's effect on speech have documented that infants with Down syndrome demonstrate preverbal vocalizations commensurate with non-delayed children, but the onset and development of meaningful speech lags behind by approximately seven months (Stoel-Gammon, 1981). Areas of language delay also include morphology, syntax, semantics, and comprehension. Size of vocabulary has also been found to be smaller in children with Down syndrome, relative to their mental age and in comparison to non-delayed children matched on chronological age. Fowler (1990) concluded that based on the findings of the majority of studies, the generalization has emerged that Down syndrome exerts a considerable deleterious influence on the ultimate language level an individual will attain. While it is recognized that some DS individuals will reach the language level of a 5-year-old and will have limited reading and writing skills, the majority of DS children will not exceed the level of simple phrase structure grammar which is comparable to that of a non-delayed child under the age of 3 (Fowler, 1990).

The profile of weaknesses in expressive language skills in children with Down syndrome also shows changes over time. Miller (1992) found that as children with DS become older and as their mental age (MA) increases, a greater percentage of them show

expressive language deficits. While 54% to 61% of children with DS having MA's less than 24 months exhibited expressive deficits, 83% to 100% showed expressive language deficits when MA's were 24 months or higher.

A variety of hypotheses have been offered to explain the discrepancy between measured mental age and final language attainment in DS individuals. Common explanatory proposals include a maturational account, which posits that all language development in DS children occurs before the chronological age (CA) of seven. Since there is a discrepancy between the DS child's chronological age and mental age, a child between CA four and six years is typically at MA two to three years. Thus, if language development caps at this level, the DS child will have attained the language abilities of a 3-year-old non-delayed child (Fowler, 1990). A second explanation for the specific language deficit proposes that neurological structures underlying language are impaired in DS children. There is considerable evidence of anatomical, physiological, and neurochemical abnormalities in the brains of DS children (Ross, Galaburda, & Kemper, 1984), which may be related to the specific deficits in language function. Functional neuroimaging PET data have shown significant reductions in cerebral glucose metabolism in the primary language areas of young adults with DS when compared to non-delayed age- and sex-matched controls, which may point to an underlying pathological basis for the specific language deficits in DS (Azari et al., 1994).

The literature cites two competing theories of language development among children with Down syndrome. The first view, originally led by Lenneberg (1967), contends that early language development in DS is "slow but normal". In other words,

language acquisition in DS follows the same course as that of normally developing children, but at a considerably slower pace. Lenneberg also states that children with Down syndrome show a "cumulative deficit" in language, in that their performance most approximates normal development early in life, and then becomes increasingly delayed with time. Studies supporting this view have demonstrated that the development of prelinguistic vocalizations in DS infants is similar to that of normally developing infants, while onset of meaningful speech and of syntax is delayed (for review see Stoel-Gammon, 1990). A critical period of development is proposed, during which language is acquired, and it is limited to the first 12 years of life, irrespective of the stage of development reached at the chronological age of 12. Consistent with the "cumulative deficit" account, are findings that the difference between DS and other developmentally delayed groups increases with age, with individuals with Down syndrome falling further behind with time.

Competing with the maturational account of language development is a second view that proposes a unique language deficit in DS individuals. Contrary to the notion that language in DS children simply proceeds at a slower rate, other research (Miller, 1987) has shown that children with Down syndrome show a *specific deficit* in language learning when equated on mental age with children who have developmental disabilities of other etiologies, and with normally developing children. In other words, the language of children with DS is not just a delayed version of normal language development; rather it is qualitatively different and quite specific to the syndrome. This view proposes that children with Down syndrome are particularly at risk for deficits in language learning. A

longitudinal investigation of young DS children examined the relationship between comprehension and production in 43 participants, aged 11 to 58 months (Miller, Rosin, Pierce, Miolo, & Sedey, 1989, as cited in Stoel-Gammon, 1990). Results showed that language production lagged behind comprehension and mental age, suggesting the presence of a specific language deficit that adversely affects production of speech in Down syndrome, but not general comprehension.

The delay versus deviance debate has been viewed by some as conceptually ill-founded. Rondal (1988) asserts that both circumstances exist, in that slow development in DS is the result of neurological delay, visual and auditory deficits, and motor impairments, but that qualitative deviances also exist. These deviances include memory impairments, the use of more stereotyped expressions, more gestures, and less sophisticated syntax as compared to normally developing children of corresponding mental age. Deviance in language development is also noted in the poor use of personal pronouns, and the use of intonation rather than inverted word order when asking a question (Campbell-Taylor, 1993). Whether language in DS is quantitatively or qualitatively different, convincing evidence has emerged from both literatures that demonstrates that aspects of language development and communicative competence are affected in ways that are peculiar to the syndrome.

Research on language in older adults with Down syndrome has shown that while receptive language diminishes somewhat with age, expressive language is not significantly affected (Carter Young, & Kramer, 1991; Cooper & Collacott, 1995). Cross-sectional analyses of language in young DS adults and older DS adults have shown

no age-related differences (Haxby, 1989; Rasmussen & Sobsey, 1994). Little or no change in nonverbal reasoning and expressive language has been noted until the age of 60 in DS adults (Das, Divis, Alexander, Parrila, & Naglieri, 1995). While there is some cognitive decline associated with aging in DS, such as slight declines in long-term memory and visuospatial construction, expressive language seems to be preserved (Stanton & Coetzee, 2004).

Naming in Individuals with Down Syndrome

One of the most striking linguistic features in individuals with Down syndrome is impairment in expressive language abilities (Chapman, Seung, Schwartz, & Bird, 1998; Sabsay & Kernan, 1993). Although there are few published studies that document it, word-finding difficulty is one component of a language production impairment that contributes to the deficit evident in expressive language in DS individuals. It has been demonstrated in the research literature involving language abilities that individuals of all ages with DS demonstrate a considerable impairment in confrontation naming. An early study examining the nature of language impairment in Down syndrome individuals demonstrated word-finding difficulty in their expressive language behaviour (Cornwell, 1974). Children and adolescents with Down syndrome were given the following verbal and conceptual tasks: (a) name objects (e.g., a fork was shown and the subject was asked, "What do you call this?"), (b) describe the function of objects (e.g., a shoe was shown and the subject was asked, "What do we use this for?"), (c) recognize objects (e.g., pictures of six objects were shown and the subject was asked, "Show me the cup."), and

(d) recognize object by function (e.g., pictures of six objects were shown and the subject was asked, "Show me which one we buy candy with."). Results indicated that performance on the expressive tasks was poorer than performance on recognition tasks. For instance, verbalizing the label *car* was more difficult than pointing to a picture of a car. This outcome suggests that labels for common objects were actually in the lexicon of the participants, yet they had difficulty producing them on demand. Cornwell also observed that while there was evidence of comprehension of the function of an object, the inadequate language skills of the DS children resulted in a failure to express the information verbally. The DS children often used gestures, mimicry, and peripheral verbalizing to signify the function of an object. In another early study on language, Lyle (1960) tested verbal aspects of Down syndrome subjects including proficiency for word naming, and found that DS individuals developed at a slower pace and placed at a lower achievement level compared to subjects with developmental delay of other etiologies. Moreover, these findings were maintained across home, institutional, and experimental environments, and they were not noticeably related to IQ level. More recently, a study of speech production errors found that DS adults had significant difficulties vocalizing words represented by a picture when compared to adults with other developmental delays (Bunn, Simon, Welsh, Watson, & Elliott, 2002). The investigators concluded that DS adults are at a disadvantage when required to formulate speech from pictures. An investigation of language abilities in adults over age 35 found that naming production is an area of weakness in Down syndrome (Vicari, Nocentini, & Caltagirone, 1994).

In an attempt to explain the pattern of increasing linguistic deficit in relation to

nonverbal cognitive status with increasing chronological age in DS children, the characteristics of the linguistic environment have also been examined. It has been suggested that this pattern may be the result of a failure of the environment to support language learning through a protracted developmental period, and that differences may exist in expectations for performance (Miller, 1987). In other words, parents of DS children may have lower expectations of their children's language abilities and may expend less effort reinforcing language acquisition commensurate with their non-delayed peers. Greenwald and Leonard (1979) found that children with Down syndrome used more gestures than verbal means in expressing imperatives and declaratives, compared to non-delayed cognitively-matched children. It has been suggested that when communication is demanded, DS children use more gestures over words (Miller, 1987). This behaviour may not be corrected by caregivers, and a preference for gestural expression over verbal expression may be established, thus making it more difficult for DS individuals to perform verbally when under communicative pressure.

Other early studies have advanced that DS children exhibit significant deficits in referential looking behaviour, which is characterized as the ability to establish joint reference to objects (Gray, 1978; Gunn, Berry, & Andrews, 1982; Ryan, 1974; Schaffer, Collis, & Parsons, 1977). In other words, referential looking occurs when the child looks at the object the caregiver is looking at. Essentially, it is "looking where someone else is looking." In one study, it was found that DS subjects, aged 8 to 22 months developmentally, engaged in less than one-half of the referential looking behaviour of the matched non-delayed controls (Jones, 1980). Similarly, Jenkins and Ramruttun (1998)

found that DS children aged 21 to 53 months engaged in referential looking significantly less compared to non-delayed children. Referential looking, and subsequently establishing joint reference to objects, is essential for vocabulary learning and overall language development. It may be that there is a difference in the visual behaviour essential for referential language development in DS children which contributes to naming deficits.

Down syndrome is linked to a variety of physical and cognitive conditions which make speech and language problems more likely to occur. These include repeated middle ear infections due in part to narrow ear canals, low muscle tone in the mouth, an oral cavity that is relatively small in relation to tongue size, and hearing loss (Kumin, 1994). Hearing and oral structure abnormalities have been identified as contributing to language impairments in Down syndrome (Dykens et al., 2000). It has been estimated that between 60% and 80% of DS children have inner-ear involvement (Pueschel, 1990). In the developing child, hearing problems often result in missed opportunities to receive spoken language. Hearing problems may be related to the finding that DS children show strengths in visual tasks as opposed to those tasks requiring auditory processing.

Semantic Errors in Individuals with Down Syndrome

In reviewing the research literature on Down syndrome, it is worthwhile to note that no systematic studies have been conducted on semantic factors on naming tasks in DS. Although it has been documented that confrontation naming is impaired in DS individuals in general, the specific types of errors made have not been investigated. Only

one unpublished study funded by the National Down's Syndrome Association has commented on semantic errors in children (Buckley, 1996). The developmental progress of 15 DS children between two to four years of age was followed in terms of their reading abilities, and exceptional results were achieved. One notable case was of a female DS child who learned 30 words in one month at two years and six months of age. Although it was not the intention of the investigator to study errors, it was reported that when the children were reading single words, a consistent type of error was observed, namely the semantic error. The DS children were saying words that had the same meaning as the one they were looking at but had no visual similarity. For instance, if the printed word was "shut", the child would say "closed". The investigator concluded that the DS children were decoding the print for meaning, but it was unclear as to why they produced this consistent error type. The results of this study suggest that a specific semantic impairment may be present in Down syndrome. To date, no studies have examined semantic error patterns in picture naming in Down syndrome.

Naming in Individuals with DS-DAT

To date, research on the language of DS individuals with a probable diagnosis of dementia is remarkably limited. Most investigators have described loss of communicative functions in aging DS people in general and vague terms, and often methodological procedures are described in an abbreviated and cursory manner. Limited information is available for establishing DS-DAT diagnostic criteria related to language functions. Dalton and Crapper-McLachlan (1986) reviewed research studies of the

clinical manifestations of DAT in DS adults and found little information concerning language dysfunctions.

Too often comparisons of the language functions of DS adults with DS-DAT adults are limited to case studies or small participant samples. In a longitudinal case study of a DS adult with a diagnosis of DAT, picture naming ability was tracked over a period of 20 months (Klendaras, McIlvane, & Mackay, 1989). Naming performance and error patterns were found to be progressive, continuous, and consistent with those expected in individuals with DAT in the general population. Based on the results of their single case, the authors concluded that naming tests are likely useful in documenting the progression of DAT in DS adults. In another study four individuals with DS and with confirmed Alzheimer's pathology at postmortem showed declines in communication skills (Rasmussen & Sobsey, 1994). The results were based on caregiver descriptions, and no information was provided about whether the decline was in receptive or expressive abilities. In another investigation, the cognitive-linguistic abilities of DS adults with and without dementia were compared on a standardized battery to the performance of individuals with mild and moderate DAT in the general population (Moss, Tomoeda, & Bayles, 2000). The performance of non-DAT DS subjects was found to be poorer on several linguistic measures compared with DAT individuals in the general population. This finding highlights the effect of pre-existing cognitive impairments in DS adults. While marked reductions were observed across all cognitive-linguistic domains in DS-DAT, only two individuals were in this group.

Despite considerable discussion in the research literature concerning the

discrepancy between neuropathology and the clinical expression of DAT in the DS population, and an equally active discussion identifying anomia as an early sign of DAT in the general population, to date no studies have systematically investigated whether there is a difference in naming and error patterns in individuals with suspected DS-DAT compared to unaffected DS adults.

Purpose

Although it has been well documented that neuropathological indications in individuals with Down syndrome in middle age resemble those found in Alzheimer's disease in the general population, the clinical manifestation of dementia does not affect all DS adults. There is a clear discrepancy between the pathology and the clinical syndrome. Furthermore, research examining the clinical course of the premature aging process in individuals with Down syndrome has shown little consensus that any pattern of cognitive impairment emerges which reliably predicts early-stage dementia. Although commonly agreed upon tests are used in various combinations in neuropsychological batteries in clinical settings, to date there is no standard or widely accepted diagnostic protocol for identifying Alzheimer's dementia in adults with Down syndrome. Moreover, the assessment instruments that are commonly used have not been normed on an adult DS population. Currently, most clinical test batteries for detecting dementia in Down syndrome employ measures that are used to diagnose the disease in the general population. These test batteries typically examine orientation, memory functions, perceptual disturbances, and daily living skills. Since studies of DAT in the general population provide overwhelmingly consistent evidence for a genuine semantic memory disturbance, and since anomia in DAT patients is often disproportionately severe in relation to other language deficits, a test of confrontation naming is invariably included in

most batteries. One of the most widely used nonmemory verbal measures, the Boston Naming Test, has not been normed on DS adults yet it is often included in clinical and research settings when assessing dementia in this population. While performance on one test, such as the BNT, is not used independently to produce a definitive diagnosis of dementia, it is relied upon extensively to provide information about language impairment, specifically anomia. In this regard, it is important to evaluate whether the BNT is a useful measure of dementia-related language decline in Down syndrome, and whether the construct being measured is even a suitable indicator of dementia in this population. In other words, while anomia is recognized as an early sign of DAT in the general population, perhaps it is not a risk factor for individuals in which confrontation naming ability is already impaired. Since nonmemory verbal performance is premorbidly compromised in DS individuals, nonmemory language tests such as the BNT may not be appropriate for detecting dementia in this population.

The purpose of the present study was to evaluate the performance of DS adults with a diagnosis of probable dementia on a measure used in detecting dementia-related anomia in individuals with Alzheimer's disease in the general population. Specifically, the aim of the present research was to evaluate whether the Boston Naming Test is an appropriate measure to be included in a neuropsychological test battery for detecting dementia in the Down syndrome population. The research design was patterned after an earlier study of naming errors in Alzheimer's and vascular dementia in the general population (Lukatela, Malloy, Jenkins, & Cohen, 1998) that examined semantic errors in detail. For that investigation the errors made on the BNT were analysed to evaluate the

quality of semantic errors, in order to understand the deficits associated with semantic knowledge in Alzheimer's disease. The results showed that the naming deficit in AD in the general population is a deterioration of semantic processes involved in naming. The findings supported the suggestion that in AD differentiation within semantic categories is impaired, and knowledge of broader semantic categories is maintained. The researchers concluded that the results served as evidence that the pattern of semantic naming errors in AD is syndrome specific. This finding was tested in the present study with DS adults with and without a diagnosis of probable DAT, to determine whether similar patterns regarding naming facility exist that could assist in the clinical diagnosis of the disease in this population.

Since the three major published diagnostic criteria (DSM-IV, ICD-10, NINCDS-ADRDA) specify that the diagnosis of probable AD requires the presence of an acquired and progressive episodic memory deficit, and since a memory evaluation is typically included as part of a neuropsychological assessment of DAT, the present study will also examine performance on a memory measure. In the general population, loss of episodic memory is recognized as a core feature of dementia (Albert, 2002; Backman, Small, & Fratiglioni, 2001; Small, Fratiglioni, Viitanen, Winblad, & Backman, 2000). Verbal memory impairment is one of the earliest changes associated with DAT, and measures of memory have been shown to be among the most sensitive to the early stages of decline (Linn et al., 1995). Similarly, it has been reported that declines in memory are an early indication of dementia in the DS population (Devenny et al., 2000; Sano, Aisen, Dalton, Andrews, Tsai, et al., 2005; Stanton & Coetzee, 2004). In a study examining changes in

explicit memory associated with dementia in DS adults (Krinsky-McHale et al., 2002), participants with early-stage DAT showed severely diminished long-term storage and retrieval processing abilities. The investigators stated that the results of their study clearly confirmed that memory processes are affected during early dementia in DS adults, as measured by a modified version of the Selective Reminding Test (SRT; Buschke, 1973). The SRT is a test of verbal memory performed by reading to participants a series of words to be remembered, and then asking for recall of these words across multiple learning trials. Following each trial, participants are reminded only of those items not recalled.

Since previous studies have supported that a decline in memory is evident in DS individuals in the early stages of probable DAT, the present study included a verbal memory measure, the Fuld Object Memory Evaluation (FULD; Fuld, 1977). The FULD is a test of memory and learning, and it was developed based on the selective reminding procedures of the SRT. One limitation of using the SRT with the DS population is that success on the test requires a greater command of the English language, compared to the FULD. A study examining the two tests reported lower sensitivity for a sum-of-recall score on the SRT when compared to the FULD (Masur et al., 1990). The FULD appears to be more suitable for DS individuals as it accommodates visual and/or auditory difficulties, since the stimulus objects to be recalled require multiple processing through all major modalities (Fuld, 1980).

Sano and colleagues (2005) used a modified version of the FULD with a DS sample and reported that it was a good test of verbal memory, and it was sensitive to the

presence of the initial stages of dementia. The test was modified by the researchers to permit a shortened testing session. The study, however, presented with methodological limitations in that it relied on a retrospective review of data from seven different sites, and dementia status was based on the best estimate made from chart reviews. In the present investigation the original version of the FULD will be used with the expectation that it will be similarly useful as a measure in the assessment of early dementia. Although it is not the primary aim of the present study to specifically evaluate memory processes in the DS population, it is anticipated that this measure will help to differentiate DS participants with and without DAT, and to characterize part of the cognitive decline associated with early dementia in DS adults.

Rationale

The rationale for the present investigation is highlighted by the paucity of current research on language-based changes in suspected DS-DAT individuals. To date, an association between naming facility in DS and Alzheimer type dementia has not been well characterized, nor have sensitive markers detecting early-stage clinical dementia been identified. By including naming tests such as the BNT in neuropsychological test batteries to detect DAT in DS individuals, an attempt is being made to identify loss of cognitive-linguistic functioning in a population whose typical cognitive-linguistic capabilities are already impaired and not fully understood. Rather than rely upon diagnostic information borrowed from the general population, it is important to evaluate whether a test of word-finding is appropriate for inclusion in a test battery to detect

dementia in the Down syndrome population. While reports in the current literature of anecdotal observations and case studies are informative, such results are of limited value in generalizing to the larger DS population. The present investigation included a larger participant sample than that typically encountered in the research literature to date. It was anticipated that the present investigation would provide information on the linguistic features of speech in suspected DS-DAT individuals that will aid in the future development of sensitive neuropsychological tests for the detection of dementia in Down syndrome. Additionally, given that memory decline is one of the earliest symptoms of DAT in the general population and also in the DS population, the FULD was included as a memory measure, and it is anticipated that it will be an effective measure to include in a neuropsychological test battery to detect DAT in DS adults.

Hypotheses

Based on the current literature available on the characteristics of language in Down syndrome, specifically the presence of impaired verbal abilities, it is predicted that differences will not be found in naming facility and error types between DS and DS-DAT individuals. In other words, the pattern of semantic errors found to be specific to individuals with probable Alzheimer's dementia in the general population is not expected to be observed as a linguistic feature in individuals with Down syndrome with a diagnosis of probable Alzheimer's dementia. Since individuals with DS seem to experience difficulties with confrontation naming in general, differences in performance on the Boston Naming Test between DS individuals with (group DAT) and without (group OND

and group YND) a diagnosis of probable dementia are not expected. With regard to the utility of the FULD as a test to be included in a neuropsychological battery, it is expected that this measure will be effective in characterizing the decline in memory that has been demonstrated in the general population and in the DS population. The hypotheses of the present investigation are as follows:

1. Frequency of naming errors on the BNT will not vary amongst the three groups. That is, differences in performance on the BNT will not be found between the DAT group and the two non-affected groups (OND and YND), which in turn will not differ. It is predicted that a test of confrontation naming is not a sensitive indicator of early-stage dementia-related decline in DS, since it has been demonstrated in the research literature to date that impairment in confrontation naming is characteristic of the premorbid language profile in DS.

2. Frequency of semantic errors on the BNT will not vary amongst the three groups. Again, this hypothesis is based on the premise that impairment in verbal abilities, specifically confrontation naming, may be inherent to DS. Therefore difficulties with the specific components of naming, such as semantic naming ability, are not expected in the early stages of dementia.

3. The *types* of semantic errors on the BNT will not vary amongst the three groups. DS adults with and without a diagnosis of probable dementia will not

vary in their semantic error patterns. It is expected that the specific pattern of impairment of within-category exemplars that is found in AD patients in the general population will not be found amongst the DS-DAT group. This hypothesis is again based on the premise that confrontation naming is impaired in DS individuals. The effect of semantic factors on naming ability has not been systematically evaluated in DS individuals, but the results of one study on early reading ability in DS children (Buckley, 1996) suggest that some difficulties with semantic errors exist premorbidly.

4. The DS-DAT group will demonstrate poorer performance on the FULD compared to the two non-affected groups. Previous studies have noted that a decline in memory is evident in early-stage DS-DAT that is likely similar to the impairment found in dementia patients in the general population. It is expected that the FULD will be an effective measure in differentiating DS adults with and without a diagnosis of probable dementia. Differences in performance on the FULD on not expected between the two unaffected groups (OND and YND).

In summary, the primary focus of the present study was to examine the diagnostic utility of a test of confrontation naming in the early diagnosis of DAT in DS. DS and DS-DAT individuals will be compared on their performance on the Boston Naming Test to determine whether they differ in the frequency and quality of their naming errors. Specifically, the frequency of overall naming errors and semantic naming errors will be

examined. The present study will also examine whether differences exist between DS and DS-DAT individuals in terms of the contribution of omissions, visuoperceptual, and phonological factors on naming errors. Gender will also be evaluated to determine whether differences in naming errors exist for DS adults. Gender differences on the BNT have been demonstrated in the general population, with women performing significantly worse than men among early-stage AD patients. Multiple explanations for this finding have been reported including the suggestion that the difference reflects greater severity of language impairment in female AD patients (Ripich, Petrill, Whitehouse, & Ziol, 1995), and certain items on the BNT may be more salient for men, and thus easier for them to name (Randolph, Lansing, Ivnik, Cullum, & Hermann, 1999). Gender differences have not been found for dementia rates in the DS population (Coppus et al., 2006; Tyrrell et al., 2001). In terms of expressive language abilities in DS, although there is little research examining the role of gender, it has been documented that amongst DS adolescents there are no gender differences (Buckley, 1995; Laws & Bishop, 2003).

Additionally, performance on the FULD for DS and DS-DAT adults will be compared. This measure was included because it is believed that, similar to those individuals in the initial stages of DAT in the general population, early-stage DS-DAT individuals will show a decline in verbal memory. As such, it is expected that the FULD will be shown to be effective in detecting dementia-related decline in DS individuals.

Method

Data Selection and Screening

The data used in the present investigation were selected from the Neuropsychological Baseline Assessment Service database compiled in a nonresidential treatment centre (Surrey Place Centre, Toronto), for individuals with a developmental disability. Testing for the clinical records that were used from the database took place during a 6-year period within the context of the regular baseline and diagnostic assessment service. The present investigator was among the group of clinicians who tested individuals and collected the data for the baseline service.

All individuals had a physical examination by their family physicians within six months prior to baseline testing, which included laboratory blood tests to identify thyroid dysfunction, folate, and Vitamin B12 deficiency. At the time of testing, none of the participants had active major medical disorders, seizure disorder, or uncorrected thyroid problems. None of the participants had a diagnosis of depressive disorder, nor were symptoms of depression reported directly by the participants, their caregivers, or their family physician. All participants had a hearing test prior to the assessment. Written consent for using clinical data was obtained from each client or legal guardian at the time of testing. Approval for the use of data from the baseline database for the purposes of the present investigation was granted by the Director of Clinical Programs at Surrey Place Centre, Dr. Terri Hewitt, and the Surrey Place Centre Research and Ethics Review Board. Confidentiality was maintained by removing client names prior to entering clinical data into a research database.

Research Participants

The clinical records of 55 adults with Down syndrome, between the ages of 26 and 66 years, were employed from the Neuropsychological Baseline Assessment Service database. Participants were assigned to one of three groups based on their clinical diagnosis and age. Group DAT (dementia of the Alzheimer type; n = 18) participants are those individuals already diagnosed by a clinical psychologist with probable early-stage dementia according to the NINCDS-ADRDA criteria, and criterion cut-off scores on the Dementia Scale for Down Syndrome (DSDS; Geyde, 1995). The DSDS is a caregiver-rated scale that was specifically developed to assess dementia related functional declines in DS adults. Group OND (older, no dementia; n = 18) are adults age 40 and older. Participants in Group OND had DSDS scores below cut-off criterion for dementia. Group YND (young, no dementia; n = 19) are adults 39 years old and younger. The cut-off age of 40 that differentiates the younger group from the older group is based on the research literature. As previously stated, it has been established that neuropathological changes are expected in some form in DS adults around the age of 40.

None of the participants in the DAT group were taking medications related to their dementia diagnosis.

The intellectual functioning of the individuals in the present study was within the estimated mild or moderate level of intellectual disability, as determined by performance on the Peabody Picture Vocabulary Test (PPVT-R; Dunn & Dunn, 1981, or PPVT-III; Dunn & Dunn, 1997). The PPVT is a test of word knowledge that requires the participant to select from four drawings the one that best depicts the meaning of a spoken

word. Since visual processing is also necessary to interpret the drawing, this test has been identified as a test of intelligence, and it has been used in previous research as a measure of overall intelligence (Haxby, 1989). The PPVT is highly correlated with the WAIS full-scale IQ score (Carvajal, Shafer, & Weaver, 1989). In a comparison of the PPVT-III and the WAIS-III, it was found that the PPVT-III is an accurate instrument for predicting the intellectual functioning of adults, and it can provide an estimate of general intellectual abilities for screening purposes (Bell, Kerry, Lassiter, Matthews, & Hutchinson, 2001). The PPVT has also been shown to be a useful estimate of premorbid IQ in older adults with cognitive impairment (Snitz, Bieliauska, Crossland, Basso, & Roper, 2000). Previous research has used the PPVT to assess overall cognitive ability in DS adults (e.g., Teipel et al., 2003). DS individuals functioning within the severe and profound ranges were excluded because neuropsychological tests, such as the BNT, cannot be administered due to limited comprehension and verbal abilities. With regard to the relationship between level of intellectual functioning and early onset of dementia, the current literature presents variable results (see Bush and Beail, 2004 for a review). A number of investigators, though, have indicated that severity of intellectual impairment may not have a significant effect on the onset and duration of dementia (e.g., Holland, Hon, Huppert, Stevens, & Watson, 1998; Prasher, 1997).

Measures

All participants were administered a battery of neuropsychological tests by a clinical psychologist or psychometrist. Included in the test battery were the Boston

Naming Test (BNT), and the Fuld Object Memory Evaluation (FULD). The BNT and the FULD are commonly included in neuropsychological test batteries used to detect DAT in the general population (e.g., Jin et al., 1989; Langa et al., 2005; Loewenstein et al., 2004; Loewenstein et al., 2001; Mast, MacNeil, & Lichtenberg, 1999; Pekkonen et al., 1999; Pohjasvaara et al., 2001; Ylikoski et al., 1999).

Boston Naming Test. The BNT was administered according to the recommendation made in the published test manual in regards to achieving test basal with individuals who may be expected to have failures early in the examination. In following these recommendations, all participants were given items starting from the beginning of the test, and the basal rule is eight consecutive pictures correctly named. After six consecutive failures, administration was discontinued. The score on this measure is the number of items correctly identified, with higher scores representing better performance. The psychometric properties of the BNT are presented in Appendix D.

Fuld Object Memory Evaluation. The FULD was developed to evaluate different component abilities of memory functioning. It provides scores for long-term storage, retrieval, consistency of retrieval, and failure to recall items even after reminding. The participant is not told that this is a memory test. Ten common items (e.g., ball, cup, key) are placed in a black bag and the participant is asked to identify each item by touch. In instances where tactile identification is not successful, the participant is asked to visually identify the item. If the participant is unable to name an object by touch or visual

inspection, the name is provided by the examiner. Each item is removed from the bag as it is identified. After all of the items have been identified, they are returned to the bag. The participant is presented with a 60-second verbal fluency distractor task, to prevent rehearsal, before being asked to recall the original ten objects. If the exact name of the object is not used, a word conveying the meaning or use of the object (e.g., "drinking" for the cup), or a gesture indicating the use of the object is accepted. Verbal reminders of any unrecalled items are provided by the examiner. The participant is offered four more chances to learn and recall the items, with a 30-second distractor task in between each trial. There are a total of five learning trials. After 15 minutes, during which other tests are administered, the participant is asked to recall the original ten items in a delayed recall trial. According to Fuld (1977), since each trial is preceded by a verbal distractor, recall is assumed to be from long-term storage. Several indices have been derived from this protocol and provide information about the storage and retrieval of new information. There are five component scores commonly evaluated, although several additional memory scores have been used in screening for dementia. *Total Recall* is the sum of items correctly named across all five trials. *Storage* efficiency is defined as the number of different items recalled at least once across the five learning trials. *Repeated retrieval* is the total number of items recalled on successive trials without reminding. *Ineffective reminding* measures the failure to modify recall behaviour in response to selective reminding. A *delayed recall* trial provides additional information about long-term storage and retrieval.

The FULD has been shown to differentiate dementia from normal aging memory

changes (La Rue, D'Elia, Clark, Spar, & Jarvik, 1986; Tuokko, Vernon-Wilkinson, Weir, & Beattie, 1991). It has also been found to differentiate primary degenerative dementia from depression or other organic disorders (La Rue, 1989), and to detect memory impairment in elderly who later became demented (Fuld, Masur, Blau, Crystal, & Aronson, 1990; Masur, Sliwinski, Lipton, Blau, & Crystal, 1994). The FULD has been identified as a useful measure for evaluating suspected dementia in elderly of differing demographics (Summers, Lichtenberg, & Vangel, 1995; Wall, Deshpande, MacNeill, & Lichtenberg, 1998), and it is minimally affected by differences in education or cultural background (Fuld, Masur, Crystal, & Aronson, 1988; Jacobs et al., 1997; La Rue, Romero, Ortiz, Liang, & Linderman, 1999; Loewenstein, Duara, Arguelles, & Arguelles, 1995; Mast, Fitzgerald, Steinberg, MacNeill, & Lichtenberg, 2001). In a study of individuals in the general population aged 75 to 85 who were considered cognitively intact when tested, investigators found a high correlation (-.83) between performance on the FULD and the number of primitive senile plaques later observed in the participants' brains post-mortem (Fuld, Dickinson, Crystal, & Aronson, 1987). The investigators suggested that this finding supported the use of the FULD in possibly detecting dementia during the early course of the disease.

In comparing the FULD with the Mini Mental Status Exam (MMSE; Folstein, Folstein, & McHugh, 1975), which is commonly used as a screening measure for AD, the FULD was found to be a more accurate instrument for detecting AD (Mast et al., 2001). Since the test optimizes processing of information by including tactile discrimination, visual confrontation, in addition to verbal and auditory identification, this test is well

suited for low-functioning or cognitively impaired individuals, and for individuals with a particular sensory deficit. Another advantage is that common objects are used which are salient and familiar to even the most uneducated individuals (Loewenstein & Rubert, 1992), and this also reduces the problem of inattention during testing. The psychometric properties of the FULD are presented in Appendix E.

Procedure

BNT.

The BNT protocols for each participant were used to assess error patterns. All errors produced by subjects were recorded during testing as per the procedure outlined in the test manual. The errors were classified according to the following categories developed for the present investigation, that are based on the picture naming studies in aphasia (Kohn & Goodglass, 1985) and in Alzheimer's and vascular dementia (Hodges, Salmon, & Butters, 1991; Lukatela, Malloy, Jenkins, & Cohen, 1998).

Error Classification

General Error Categories

1. *Omissions*: includes "don't know" and nonresponses.

2. *Visuoperceptual Errors*: responses visually similar to the target word, (e.g., "snake" instead of "pretzel".)

3. *Semantic Errors*: responses that have similar meaning as the target word, (e.g., "globe" instead of "map".)

4. *Phonemic Errors*: responses that share at least two phonemes or rhyme with the target word, (e.g., "iglow" instead of "igloo".)

The error responses often meet criteria for more than one error category. For instance, semantically related errors may also share visual characteristics with the target word (e.g., escalator and stairs). For this reason, the present investigation followed the suggestion of Lukatela and colleagues (1998) and made the general error categories mutually nonexclusive.

The semantic errors were further classified into three mutually exclusive categories, to analyze semantic errors in detail and the deficits associated with semantic knowledge in AD. This classification of semantic errors was used by Lukatela and colleagues to investigate whether semantic errors represent difficulties in differentiating between closely related exemplars of a given general semantic category. The investigators found that, in the general population, differentiation of within-category exemplars is impaired in AD, and the AD patients made greater superordinate type naming errors, rather than coordinate type errors. The same premise was tested in the present study in the DS population using the following semantic error classification:

Semantic Error Categories

1. *Coordinate Errors*: responses that belong to the same semantic category as the target word, (e.g., "penguin" instead of "pelican".)

2. *Superordinate Errors*: responses that belong to a broader semantic category than the target word, (e.g., "bird" instead of "pelican").

3. *Functional-circumlocutory Errors*: responses that functionally describe the target word, (e.g., target word is "compass" and response is "to make circles").

Due to the nature of the BNT administration protocol, specifically the guidelines

regarding test discontinuation, the total number of responses given by participants varies. To document differences amongst the three groups in their naming abilities, the analysis followed that of Lukatela and colleagues in using error scores calculated as the proportion (percentage) of the total number of responses. To compare the three groups on the types of errors made, the error scores were calculated as the proportion of total number of errors, (e.g., the visuoperceptual errors as the proportion of total number of errors made). The semantic categories were analysed in similar fashion, with semantic error subtype scores being calculated as a proportion of total semantic errors.

FULD.

Several types of memory scores from the FULD have been used to evaluate episodic memory in DAT patients in the general population. The present study will compare the three groups on three memory scores that have been shown in previous studies (Loewenstein et al., 1995; Loewenstein et al., 2000; Marcopulos, Gripshover, Broshek, McLain, & Brashear, 1999; Marcopulos & McLain, 2003; Mast et al., 2001; Plehn, Marcopulos, & McLain, 2004; Sano et al., 2005; Summers et al., 1995) to be highly sensitive in differentiating normal functioning elderly from those with early-stage dementia. Two of the component scores from the original validation study (Fuld, 1977) will be used. *Total Recall* (TR) scores range from 0 to 50. *Delayed Recall* (DR) ranges from 0 to 10 items. In addition, *Immediate Memory* (IM) is the total recall score for trial 1, with scores ranging from 0 to 10. Fuld and colleagues (1990) demonstrated that the first trial of recall is capable of discriminating very early dementia from normal

functioning in the general population, with a sensitivity of .86 and a specificity of .82.

Results

The results will be presented in the following manner. First, the demographic characteristics of the participants will be reported. Second, a description of the preliminary analysis will be provided. Third, the descriptive statistics for all of the naming error categories from the BNT and the three memory scores from the FULD will be presented. Next, the analyses for each of the hypotheses will be reported. All of the statistical analyses in the present study were conducted with an alpha level of .05, unless otherwise specified.

Demographic Characteristics

BNT and FULD protocols were included in the analyses for a total of 55 participants. The demographic information regarding age, gender, and intellectual level for the three groups is presented in Table 1. The mean age for Group YND (n = 19) was 33.6, the mean age for Group OND (n = 18) was 47.7, and the mean age for Group DAT (n = 18) was 51.5. An ANOVA was conducted on the variable of age for the three groups to evaluate whether their means were different. Results of the ANOVA indicated that there was a significant difference in relation to age, F (2, 52) = 58.10, $p < .001$. As expected, Tukey HSD post hoc comparisons revealed that group YND was significantly younger than group OND ($p < .001$) and group DAT ($p < .001$), and no significant

difference in age was found between group OND and group DAT.

There were a total of 36 males and 19 females across the three groups. All three groups were very similar based on gender and range of intellectual functioning. The ratio of males to females was approximately equal in each group, with more males (over 60%) compared to females. A chi-square test was performed to determine whether the three groups differed with respect to gender. There was no statistically significant difference amongst the three groups, χ^2 (2, N = 55) = .23, $p > .05$. With regard to level of intellectual functioning, Group DAT and Group OND both had 3 individuals functioning within the mild range of developmental disability, and 15 individuals functioning within the moderate range. Group YND was comparable to Group DAT and Group OND, with 5 individuals in the mild range and 14 individuals in the moderate range. The three groups did not differ significantly with respect to level of intellectual functioning, χ^2 (2, N = 55) = .72, $p > .05$.

Table 1.

Demographic Characteristics for All Participants

	Group DAT (n = 18)	Group OND (n = 18)	Group YND (n = 19)
Age (years)			
Range	42 – 59	40 – 66	26 – 39
M	51.5	47.7	33.6
SD	5.22	6.75	3.63
Gender			
Male	12	11	13
Female	6	7	6
Intellectual Level			
Mild	3	3	5
Moderate	15	15	14

Preliminary Analyses

Prior to statistical analyses all variables were examined through SPSS 12.0 for Windows for accuracy of data entry, outliers, and all assumptions necessary for analysis of variance (ANOVA). Tabachnick and Fidell (1996) recommend that univariate outliers be identified as observations with z-scores greater than 3.29, $p < .001$. Using this criterion no univariate outliers were identified. Tests of normality were performed for all variables. Skewness (the symmetry of the distribution), and kurtosis (the peakedness of the distribution), were examined. When a distribution is normal, the values of skewness and kurtosis are zero. It has been suggested that values between +1 and –1 for skewness, and between +3 and –3 for kurtosis represent acceptable ranges (Tabachnick & Fidell, 1996). All of the values for skewness and kurtosis in the present study were within the acceptable ranges. Results of the preliminary analyses showed that all variables met the assumptions of ANOVA.

Descriptive Statistics

The means and standard deviations for the performance on the BNT, including the general error categories, for the three groups are presented in Table 2. The same pattern was demonstrated for all three groups in terms of the type of errors produced. As displayed in Figure 1, the most frequently made error type for each of the three groups was the semantic error. This was followed by visuoperceptual errors and omissions. Across the three groups the least frequently made error type was the phonemic error.

Table 2.

Means and Standard Deviations for General Error Type on the BNT for Each Group

	Group DAT	Group OND	Group YND	$F(2, 52)$	p	partial η^2
Total Number of Responses	37.28 (11.84)	39.94 (8.94)	40.68 (9.56)	.56	.57	.02
Total Number Correct	19.56 (9.35)	23.39 (9.59)	26.32 (7.99)	2.62	.08	.09
Total Number of Errors	17.72 (5.24)	16.72 (5.21)	14.37 (4.79)	2.13	.13	.08
Error Score[a] (%)	50.31 (14.51)	43.39 (14.00)	35.91 (10.97)	5.49*	.01	.17
Types of Error Scores[b]						
Omissions (%)	16.46 (21.19)	17.48 (14.41)	21.30 (15.68)	.40	.67	.02
Visuoperceptual (%)	22.14 (12.70)	22.28 (13.75)	23.66 (10.16)	.09	.92	.00
Phonemic (%)	7.82 (7.20)	5.39 (6.27)	6.45 (7.15)	.56	.57	.02
Semantic (%)	41.62 (17.42)	36.42 (11.82)	38.25 (13.96)	.59	.56	.02

Note. Standard deviations are presented in brackets.
[a]calculated as the proportion of total numbers of responses
[b]calculated as the proportion of total number of errors

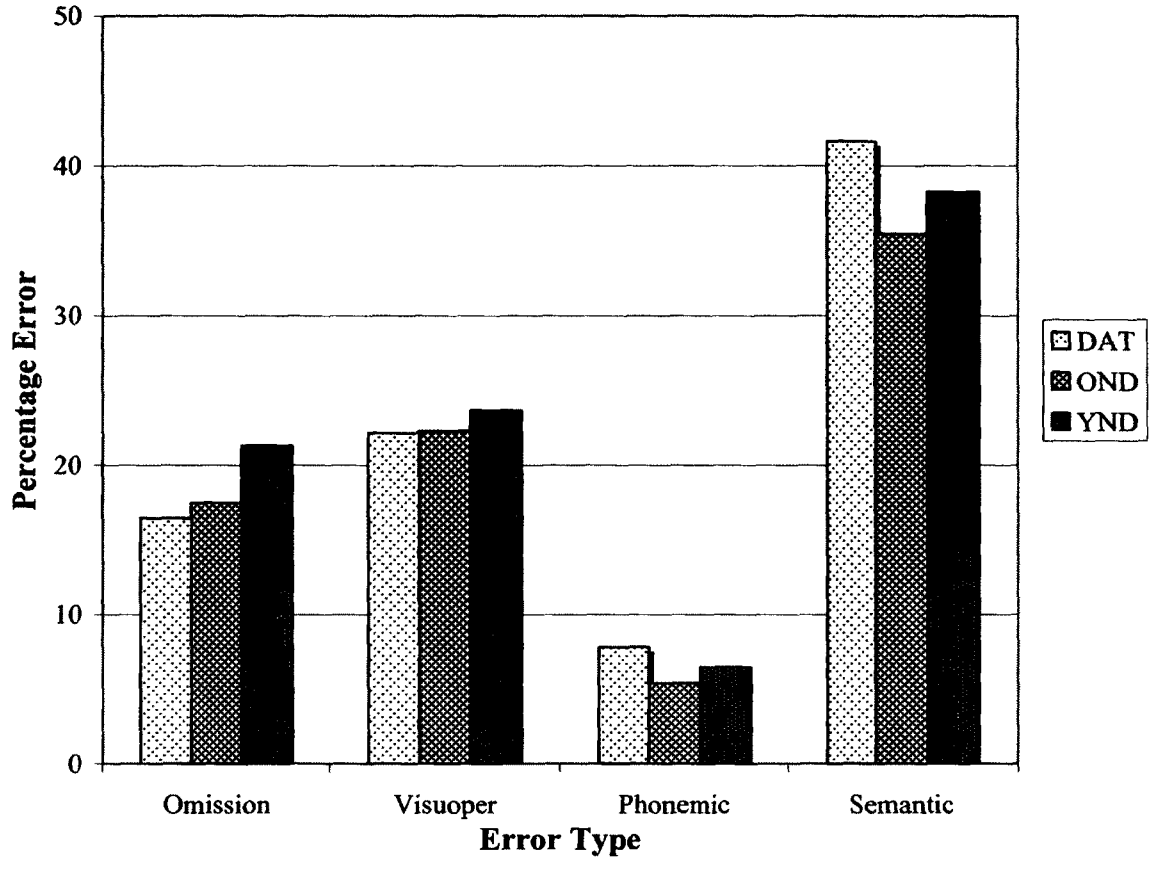

Figure 1. Groups by general error types on the BNT (based on percentage error from total errors).

The means and standard deviations for the semantic error subtypes for the three groups are presented in Table 3. A trend was also noted within the semantic error classification, in that all three groups made coordinate errors most frequently. The frequency of semantically related error types for the three groups is shown in Figure 2.

Examples for each of the types of errors produced on the BNT are presented in Appendix F.

Table 3.

Means and Standard Deviations for Semantic Error Subtypes[a] on the BNT for Each Group

	Group DAT	Group OND	Group YND	$F(2, 52)$	p	partial η^2
Coordinate (%)	43.13 (15.21)	47.23 (18.47)	52.83 (21.09)	1.29	.28	.05
Superordinate (%)	26.19 (19.49)	20.33 (15.28)	20.81 (18.76)	.59	.56	.02
Functional-Circumlocutory (%)	25.13 (16.64)	32.45 (22.74)	26.36 (18.63)	.73	.49	.03

Note. Standard deviations are presented in brackets.
[a]semantic error subtype scores were calculated as a proportion of total semantic errors

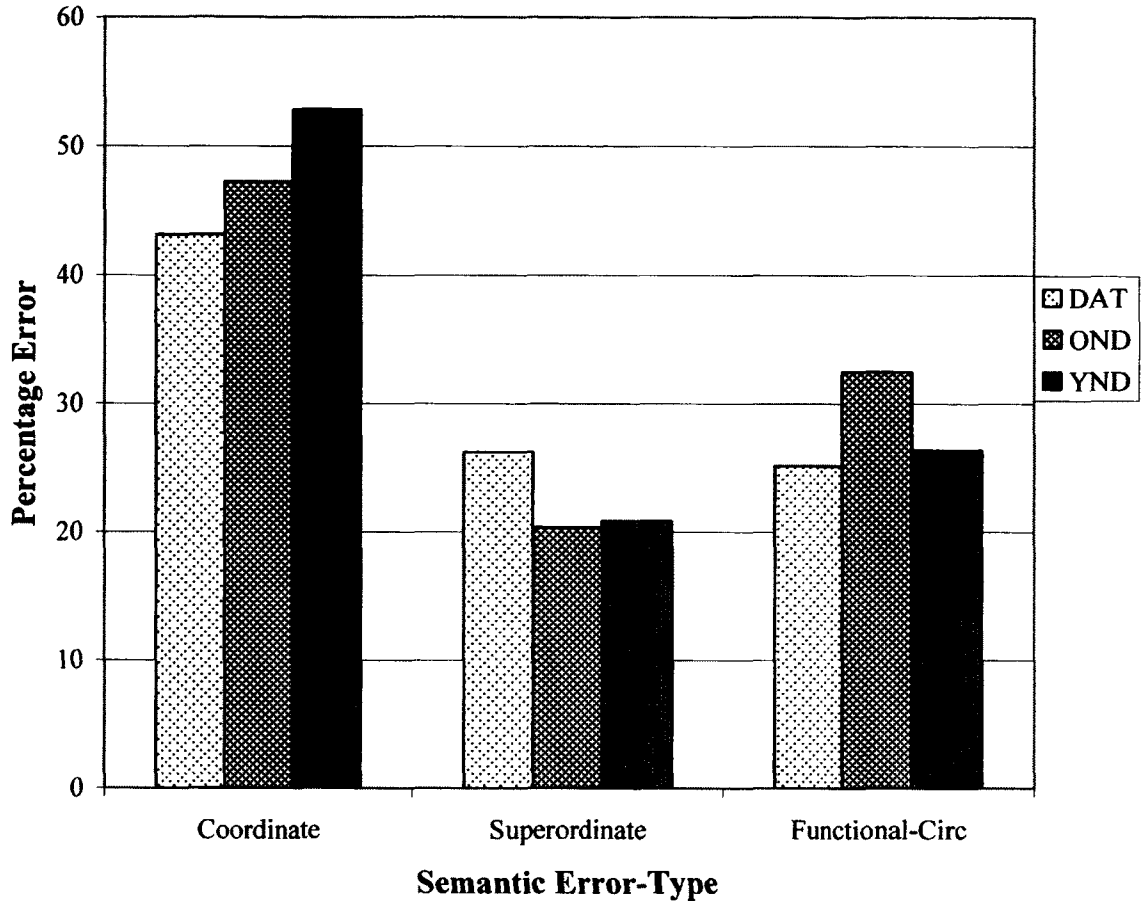

Figure 2. Groups by semantic error subtypes on the BNT (based on percentage error of total semantic errors).

The means and standard deviations for the performance on the FULD for the three groups are presented in Table 4. On the IM trial, the DAT group produced an average of 20% of the items, while both the OND and YND groups demonstrated approximately a 50% recall rate. Across the five trials (TR) and on the delayed recall (DR) task the DAT group demonstrated poor performance with about an 18% recall rate for both measures.

The OND and YND groups' recall rate was over 60% across the five trials, and over 70% for delayed recall.

Table 4.

Means and Standard Deviations for Memory Scores on the FULD for Each Group

	Group DAT	Group OND	Group YND	$F(2, 52)$	Pairwise Comparisons	Effect Size (d)
Immediate Recall (IM)	2.06	5.28	5.00	32.46*	DAT < OND*	2.24
(score out of 10)	(1.51)	(1.45)	(1.00)		DAT < YND*	2.37
Total Recall (TR)	9.22	32.17	33.21	108.87*	DAT < OND*	3.83
(score out of 50)	(6.47)	(5.84)	(4.12)		DAT < YND*	4.58
Delayed Recall (DR)	1.83	7.17	7.32	96.94*	DAT < OND*	3.80
(score out of 10)	(1.62)	(1.25)	(1.16)		DAT < YND*	4.03

Note. Standard deviations are presented in brackets.
* $p < .001$.

Testing the Hypotheses

Hypothesis 1. It was predicted that performance on the BNT would not be affected by dementia status, specifically in terms of naming errors. In other words the DAT group would not significantly differ from the two non-affected groups, OND and YND, which in turn would not differ. An ANOVA was conducted to evaluate the relationship between dementia status and two measures of overall performance on the BNT: total number of responses and error score. Given that two ANOVA tests were performed, the alpha level was adjusted to $p = .025$ using the Bonferroni correction to control for Type I error (incorrectly rejecting the null hypothesis when it is true). While there was an observed trend toward fewer overall responses on the BNT for individuals with a diagnosis of probable dementia, a significant difference was not found amongst the three groups on this measure. An unexpected result was noted in that a significant difference was indicated for the error score, F (2, 52) = 5.49, $p = .01$, partial $\eta^2 = .17$. Tukey HSD post hoc contrasts indicated only one difference existed, between the YND group and the DAT group, ($p = .01$). There were no significant differences between the YND and the OND groups, ($p = .28$), or the OND and DAT groups, ($p = .37$). To further explore this finding, the relationship between age and error scores was examined by plotting these variables on a graph. The correlation between age and error score was then examined for the three groups. There was no significant correlation found for the DAT group ($r = .02$, $p = .93$) or for the OND group ($r = -.00$, $p = .99$) with respect to age, but there was a significant positive correlation for the YND group ($r = .49$, $p = .03$), suggesting that age was influencing error scores for the YND group, but not for the two

older groups. A preliminary analysis evaluating the homogeneity-of-slopes assumption indicated that the relationship between age and error score did not differ significantly as a function of the group. Using group as the between subjects factor and age as the covariate, a test of between subjects effects for the error score showed no interaction between age and group F (2, 49) = 1.19, p = .31. Based on this finding, an ANCOVA was conducted. The results of this analysis showed that, once age was controlled for, there was no significant difference among the groups in terms of the error scores produced, F (2, 51) = 1.12, p = .33. The adjusted means for the error score are presented in Table 5.

Table 5.

Adjusted Means for the Error Score on the BNT for Each Group

	Group DAT	Group OND	Group YND	$F(2, 52)$	p	partial η^2
Error Score	48.44	42.47	38.56	1.12	.33	.04

Hypothesis 2. It was predicted that in comparing semantic naming ability on the BNT, differences would not be found between the dementia affected and non-affected groups. An ANOVA was performed to compare the performance of the three groups in terms of overall semantic errors. As expected, significant differences were not found amongst the group means, $F(2, 52) = .59, p = .56$, partial $\eta^2 = .02$.

With regard to the remaining types of error scores, an ANOVA was conducted using the Bonferroni correction with an adjusted alpha level ($p = .017$). There were no significant differences found amongst the three groups for frequency of visuoperceptual errors, phonemic errors, or omissions. The results of these comparisons are presented in Table 2.

Hypothesis 3. The three groups were compared on the subtypes of semantically related errors produced. It was predicted that semantic error patterns would not differ amongst the groups. In other words, differences were not expected based on dementia status in terms of the types of semantic errors made. An ANOVA was performed on the three semantic error subtypes – coordinate, superordinate, and functional-circumlocutory – using the Bonferroni correction with an adjusted alpha, $p = .017$. As predicted, significant differences were not found amongst the three groups for any of the semantic error subtypes. The results of the ANOVA for the semantically related errors are presented in Table 3.

Additional Analyses for the BNT

In addition to the formal hypotheses put forward regarding the relationship between naming performance on the BNT and dementia status, it was of interest to further examine a trend that emerged from the above analyses. Having examined the means for the general error types and semantic error subtypes, it was found that a pattern was demonstrated across the three groups. Each of the three groups tended to make semantic errors most frequently compared to other general errors (see Table 2). Based on these findings, it was of interest to examine whether individuals with Down syndrome, as a group, make certain types of naming errors significantly more frequently than other types of errors. A repeated ANOVA was conducted for the general error types for the entire sample (N = 55). The results of the repeated ANOVA across the three groups for general error types revealed a significant difference F (3, 162) = 44.95, $p < .001$, partial $\eta^2 = .45$. Pairwise comparisons were performed using the Bonferroni adjustment for multiple comparisons, ($p = .0083$). Significant differences were found for each of the pairs of naming errors except for the difference between the mean for visuoperceptual errors and the mean for omissions. These results suggest that, irrespective of age and dementia status, individuals with DS made semantic errors more frequently than any other type of error on the BNT. The results of these analyses are presented in Table 6. The means for the four general error types are depicted in Figure 3.

Table 6.

Pairwise Comparisons for General Error Types on the BNT Across All Groups

	M	*SD*	Mean Difference	*P*
Pair 1				
Visuoperceptual	22.71	12.05		
Phonemic	6.55	6.84	16.16*	< .001
Pair 2				
Visuoperceptual	22.71	12.05		
Omission	18.47	17.13	4.25	.17
Pair 3				
Visuoperceptual	22.71	12.05		
Semantic	38.76	14.46	-16.04*	< .001
Pair 4				
Phonemic	6.55	6.84		
Omission	18.47	17.13	-11.92*	< .001
Pair 5				
Phonemic	6.55	6.84		
Semantic	38.76	14.46	-32.21*	< .001
Pair 6				
Omission	18.47	17.13		
Semantic	38.76	14.46	-20.29*	< .001

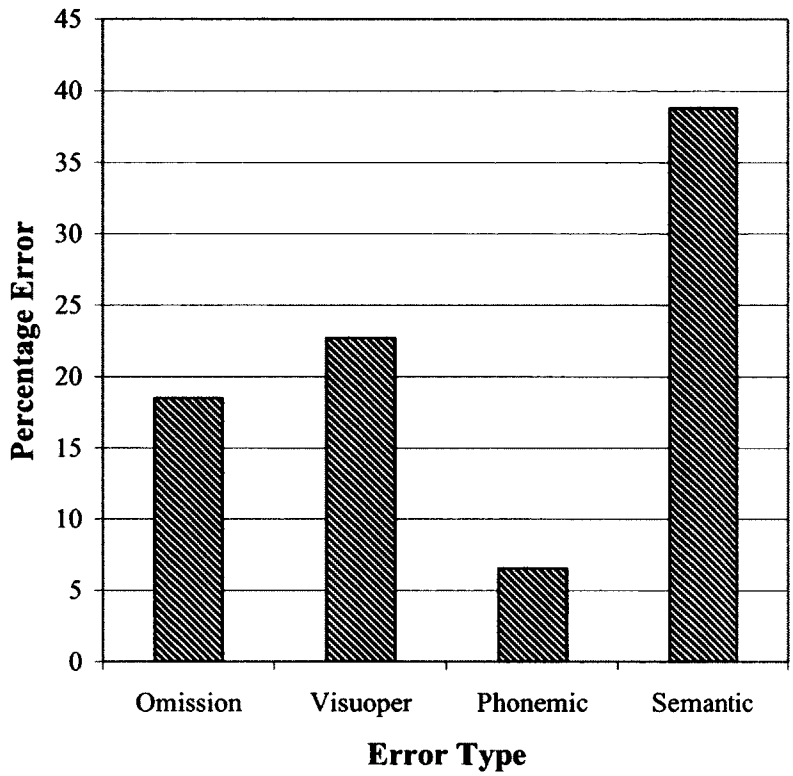

Figure 3. General error types on the BNT (based on percentage error from total errors) across all groups, N = 55.

In evaluating the semantically-related errors, each of the three groups tended to make coordinate errors most frequently (see Table 3). A repeated ANOVA was conducted for the semantic error subtypes for the entire sample (N = 55). The results of the repeated ANOVA across the three groups for semantic error subtypes revealed a significant difference F (2, 108) = 20.08, $p < .001$, partial $\eta^2 = .27$. Pairwise comparisons were performed using the Bonferroni adjustment for multiple comparisons, (p = .017). The difference between the mean for superordinate errors and the mean for functional-

circumlocutory errors was not significant, although significant differences were found for the remaining two semantic pairs. These results indicate that, irrespective of age and dementia status, individuals with DS made coordinate errors more frequently than any other type of semantic error on the BNT. The results of the pairwise comparisons for semantic error subtypes are presented in Table 7. The means for the three semantic error subtypes are depicted in Figure 4.

Table 7.

Pairwise Comparisons for Semantic Error Subtypes on the BNT Across All Groups

	M	*SD*	Mean Difference	*P*
Pair 1				
Coordinate	47.82	18.57		
Superordinate	22.41	17.82	25.41*	< .001
Pair 2				
Coordinate	47.82	18.57		
Functional-Circ	27.95	19.39	19.87*	< .001
Pair 3				
Superordinate	22.41	17.82		
Functional-Circ	27.95	19.39	-5.54	.62

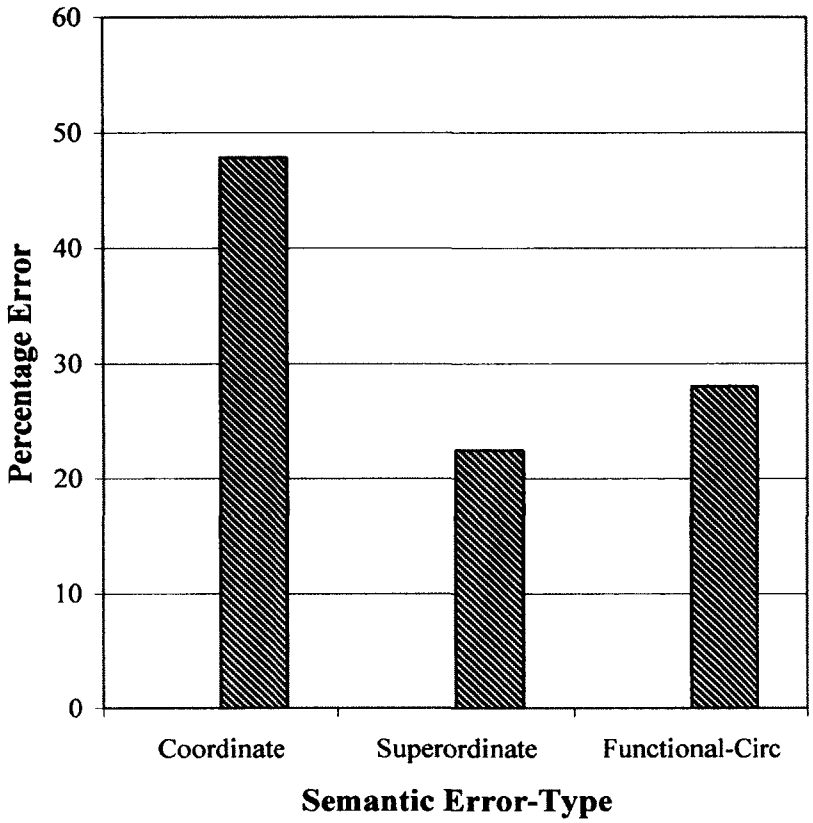

Figure 4. Semantic error subtypes on the BNT (based on percentage error of total semantic errors) across all groups, N = 55.

Hypothesis 4. It was predicted that individuals in the DAT group would demonstrate poorer performance on the FULD compared to the two non-affected groups (OND and YND), which in turn would not differ. An ANOVA was performed for each of the three memory scores using Bonferroni adjusted alpha levels of $p = .017$ (see Table 4).

In regards to IM, results showed a significant difference in performance amongst the three groups, F (2, 52) = 32.46, $p < .001$. Pairwise comparisons revealed that group DAT performed significantly more poorly than group OND ($p < .001$), and group YND ($p < .001$). There was no significant difference between group OND and group YND. Concerning TR, a significant difference in performance amongst the three groups was also found, F (2, 52) = 108.87, $p < .001$. Pairwise comparisons mirrored the patterns shown for IM in that group DAT performed significantly more poorly than group OND ($p < .001$), and group YND ($p < .001$). No difference was found between group OND and group YND. Similar results were also shown for the final performance measure, DR. A significant difference was revealed amongst the three groups, F (2, 52) = 96.94, $p < .001$. Pairwise comparisons showed that group DAT performed significantly more poorly compared to group OND ($p < .001$), and also compared to group YND ($p < .001$). Again, no significant difference between group OND and group YND was detected. The effect sizes ranged from 2.18 to 4.58, which are regarded as large effect sizes (Cohen, 1988).

Thus, as expected, the performance of Group DAT on the FULD was significantly worse compared to the two non-affected groups (OND and YND), which did not differ.

That is, group DAT produced significantly fewer items on immediate recall, across the five trials, and in the delayed recall task than did group OND and group YND.

Discussion

Virtually all individuals with DS over the age of 40 show some degree of neuropathological abnormality postmortem that is nearly indistinguishable from that seen in individuals with Alzheimer's disease in the general population. In spite of the ubiquitous presence of AD neuropathology, not all individuals with DS develop clinical dementia. The clinical diagnosis of dementia in DS adults is difficult to make since it requires distinguishing a decline in abilities related to an adult-onset pathological condition from deficits that are typical of long-standing performance, which is in the intellectual disability range. It has been well established that the clinical course of Alzheimer-related dementia is not the same in DS individuals as is observed in the general population, in that the neuropathology is not necessarily followed by behavioural manifestations in DS. Although the clinical prognosis differs, the diagnostic protocol is typically based on criteria used for diagnosis in the general population. Currently, there is no agreed upon neuropsychological test battery for the detection of early-stage dementia in DS individuals. Test administration has typically been patterned after that observed in assessing individuals in the general population, even though most of these tests have not been normed on individuals with DS. The present study primarily examined the sensitivity of one such instrument, the Boston Naming Test, a measure that is typically used in clinical and research settings to evaluate language based patterns of decline.

Specifically, the BNT is often used to assess anomia, which is one of the earliest signs of DAT in the general population. Research has indicated that the language impairment in early DAT in the general population involves semantic functioning, and the error patterns exhibited on the BNT have been used to identify this characteristic naming dysfunction. Furthermore, research has shown that for individuals in the early stages of DAT, categorical information remains available whereas information about specific attributes becomes less accessible. While research has documented this specific anomia in DAT in the general population, the same theory has not been tested in the DS population. While there may be similarities in the histopathological profiles for DAT individuals in both the general and DS populations, the pre-existing cognitive impairments and the language deficits in DS make it difficult to draw parallels in their clinical presentation. The aim of the present study was to evaluate whether a test of confrontation naming is a sensitive measure in detecting early-stage clinical DAT in individuals with DS. Additionally, the original version of the Fuld Object Memory Evaluation was examined to determine whether it is a useful measure in assessing early DS-DAT, as has been found for a modified version of the test that was examined in a previous research study (Sano, 2005).

Confrontation Naming in DS and DS-DAT

In the present investigation, in comparing performance on the BNT between DS individuals with and without a diagnosis of probable dementia it was predicted that the frequency of naming errors would not vary amongst the groups. Specifically, it was of

interest to examine whether the number of naming errors produced by DS individuals within the same age range varied according to their dementia status. While individuals with DAT showed a slight tendency toward poorer performance in picture naming, they did not significantly differ from non-affected individuals within the same age range. This is quite different from findings in the general population between AD patients and normal elderly controls where differences in overall errors are quite pronounced, with the affected group showing declines in performance. There are several possible explanations for the findings of the present study. First, while loss of language function is one of the earliest clinical signs of AD in the general population, language is premorbidly limited in DS individuals. People with DS show difficulties with confrontation naming from a young age. A test of confrontation naming may not be a sensitive measure of the early onset of dementia in a population for which this language ability is already impaired. Subtle differences may exist based on dementia status, however, the effect is not as substantial, nor as diagnostically useful, as it is for contributing to clinical decisions about the presence of dementia in the general population. It is possible that DS individuals in the early stage of dementia may experience subtle naming declines, but unlike what is observed in the general population, a test of confrontation naming does not differentiate between affected and non-affected groups. The findings of the present study may represent the low sensitivity of a test standardized for use in non-delayed populations. Quite simply, picture naming tests such as the BNT may not be sufficiently sensitive in detecting variations in abilities among individuals with DS and suspected dementia.

A second possible explanation for the present findings is that the clinical progression of dementia in DS may differ from the typical course of the disease found in the general population. While anomia has been identified as a clinical sign in the early stages of the disease in the general population, it may be that for individuals with DS significant declines in confrontation naming ability do not occur until the *later* stages of AD. Early anomia is readily detected in the general population since it represents a dramatic change in the affected individuals' typical language abilities. For persons with DS, a decline in naming ability may not be as readily detected, since naming errors mark their expressive language abilities over the course of their lifetime. Early degenerative effects on limited language skills may be difficult to recognize. By the time severe impairment occurs to this language feature, the disease may be quite advanced and neuropsychological testing may not be possible because of the severity of symptoms. Thus, for persons with DS it may be that different thresholds exist for the presentation of the clinical symptoms of AD, and anomia may not be a clinical feature of the early stages of the disease in this population. This explanation is somewhat supported by the suggestion made by certain investigators that the early DAT exhibited in DS more closely resembles frontal lobe dementia, rather than the temporal lobe dementia typically experienced in the general population (Ball, Holland, Treppner, Watson, & Huppert, 2008; Deb, 2003; Holland, Hon, Huppert, Stevens, 2000). In typical AD, temporal lobe dysfunctions tend to occur during the early stages of the disease, including memory disturbance. Frontal lobe signs, including changes in behaviour and personality, typically occur during the later stages of AD. It has been noted that in the DS population the

reverse may occur, with certain frontal lobe signs marking the early development of the disease. Research has shown that DS individuals tend to have structurally abnormal and likely underdeveloped frontal lobes (Deb, 1997). This may predispose DS-DAT adults to show frontal signs early in the disease such as apathy, general slowness, and loss of inhibition. Temporal signs - such as impaired organization and categorization of verbal material, in addition to disturbance of language comprehension - may not occur until the later stages of the disease. Results of a longitudinal study of personality and behaviour changes provide support for the hypothesis that frontal lobe impairment likely marks the preclinical stage of AD in DS (Ball et al., 2006). These early changes were followed by an increase in frontal lobe associated executive dysfunction. An examination of caregiver reports of early signs of DS-DAT described several frontal lobe related symptoms that are usually observed later in the course of dementia among individuals in the general population. These symptoms included slowness in activities and speech, loss of interest and withdrawal from activities, and emotional and behavioural problems (Deb, Hare, & Prior, 2007). To account for the early onset of frontal lobe signs in DS, as compared to the general population, Holland and colleagues (1998) extended the notion of the *reserve capacity model*, originally proposed by Mortimer (1988). In the model, the reserve capacity is a hypothetical concept defined as the amount of remaining functional brain tissue. Since the frontal lobe regions are underdeveloped in DS, it is hypothesized that the reserve capacity of this brain region is relatively low. Changes associated with frontal lobe impairment, such as behaviour changes, occur earliest in DS-DAT because only a small amount of neuropathology would be required to compromise functioning.

While the theory is still somewhat incomplete because it does not account for certain temporal-related signs occurring during the early stages of probable dementia in DS, such as episodic memory impairment, it does recognize the unusual presentation of clinical symptoms of AD. Thus, on the basis of these findings regarding the early frontal symptoms, it is possible that a different clinical subtype of Alzheimer's disease may exist in Down syndrome.

Finally, a third possibility that offers explanation for the present results is that anomia may not be a clinical feature of DAT in DS. The progressive naming difficulty that is characteristic of AD in the general population may not be an underlying functional deficit for DS persons with probable dementia. It may be that naming impairment should not be considered a requisite deficit in the diagnosis of DS-DAT.

Semantic Errors in DS and DS-DAT

In addition to examining whether the frequency of overall errors on a task of picture naming differentiated between affected and non-affected DS individuals, the quality of errors was also evaluated to determine whether certain patterns of errors occurred based on dementia status. In examining the relative contributions of different factors on naming errors made by AD patients in the general population, previous research has shown that AD patients make disproportionally more semantic errors compared to other types of errors. Furthermore, in examining the semantic error subtypes, differentiation of within-category exemplars is impaired in AD. This means that AD patients tend to make more naming errors of a superordinate nature. Thus, in

addition to the severity of naming problems experienced by AD patients, the pattern of semantic errors is specific in the early course of the disease. As predicted, this distinctive pattern was not shown to exist for individuals with DS-DAT in the present study. The frequency of semantic errors did not differentiate between dementia affected and non-affected DS individuals. An interesting finding of the current study is that, across age and dementia status, DS individuals as one group exhibited significantly more semantic errors over any other type of error. Thus, while the frequency of semantic errors did not indicate the presence of dementia or age-related declines, the results suggest the possibility of a syndrome-specific effect for semantic impairment in DS. This finding somewhat supports the outcome of the unpublished investigation cited in the literature review (Buckley, 1996) of reading abilities in DS children, in which it was reported that, of the reading errors made by children, the most consistent type was semantic in nature. It may be that a specific semantic naming impairment is characteristic of the language profile in DS that warrants further investigation.

Another unique naming feature was noted across all three groups, and this one was with respect to the subtypes of semantically related errors. Evaluating semantic error subtypes did not contribute to group discrimination. However, an interesting finding was that, irrespective of age and dementia status, the DS participants in the present study tended to make significantly more coordinate errors, compared to superordinate and functional-circumlocutory errors. A possible explanation for this finding can be drawn from research on early language learning in DS (Miller, 1987). It may be that expectations for language acquisition are lower for DS children compared to non-delayed

children, and caregivers are not as inclined to correct inaccuracies in language usage. It is suggested here that the learning environment for DS children may support the development of within-category semantic naming errors. In a supposed scenario a DS child, in pointing to an ink pen, states "I want pencil". If caregivers believe that sufficient meaning has been conveyed and a mutual understanding is reached at this level of communication, they may be satisfied in not correcting the naming error. If the label 'peanut' is used to describe all varieties of nuts, and this is understood by everyone in the DS person's environment, it may seem unnecessary to insist that 'almond', 'walnut', or 'filbert' be appropriately applied. Similarly, it may be deemed sufficient that in seeing a picture of a rhinoceros, the term hippopotamus is used. These are three hypothetical examples presented to demonstrate that it is quite possible that a certain lower level of language attainment may be expected and, in turn, reinforced in DS children, and that this could contribute to a lifelong pattern of semantic naming errors of a coordinate nature. The practical implications of this finding are in addressing the early language learning needs of DS children. In the classroom and in the home environment special attention and specific teaching techniques could be applied to assist DS children in developing within-category differentiation.

Age-Related Findings in Naming in DS

The primary focus of the present investigation was to compare the naming performance of DS individuals with and without a diagnosis of dementia, and it was found that naming errors do not differentiate the two groups. In order to address a

possible argument that individuals in the non-affected older group may, in fact, already be in the early stages of dementia but have not been diagnosed yet, a younger non-affected group was included in the present study. The consensus in the current literature is that cortical changes are noted in DS persons after the age of 40. Presumably, these changes do not significantly affect those under the age of 40. If one were to argue that individuals in the non-affected older group (Group OND) in the present study performed similarly to those in the dementia group (DAT) because they are perhaps already afflicted with the early onset of dementia, it would be expected, as previously mentioned, that significant differences in performance on the BNT would be noted between Group OND and the younger group (YND). That was not the case in the present investigation. Significant differences between the two unaffected groups were not found in overall frequency of errors, general error types, or semantic error subtypes. The results of this study indicate that there are no substantial differences in performance on a task of picture naming that can differentiate DS groups based on age or dementia status. As previously discussed, it could be that anomia is just more difficult to assess in DS individuals, in which case sensitive clinical tests need to be developed to detect this naming dysfunction. This explanation implies that a test of confrontation naming, such as the BNT, is not a sensitive measure of early onset dementia. An alternate explanation is that DS individuals already have difficulty with confrontation naming premorbidly, and therefore a nonmemory verbal test may not be clinically relevant in evaluating dementia-related changes.

The finding in the present investigation that there were no age-dependent

differences in naming performance is supported by the research literature on the effects of aging on language in DS adults. Overall, these studies have shown that expressive language abilities remain largely stable with advancing age.

Verbal Memory in DS and DS-DAT

In the present study DS individuals with and without probable dementia were compared to determine whether episodic memory processes are compromised during early-stage DAT. Previous studies have demonstrated that performance scores on the FULD can differentiate dementia from memory impairments associated with normal aging in the general population. Additionally, one study found that a modified version of the FULD was sensitive to the initial stages of dementia in DS adults. In the present study, in comparing performance on the original version of the FULD between DS individuals with and without probable dementia, it was proposed that the dementia-affected group would demonstrate overall poorer performance on this measure of verbal memory. As predicted, significant differences were shown between the dementia-affected and non-affected groups on each of the three memory scores. On the Immediate Recall (IM) trial, the DAT group recalled fewer items than the OND and YND groups, suggesting that the initial level of recall was affected by the presence of probable dementia. In addition to retrieval difficulties, this finding may be related to impaired ability amongst DS adults with DAT to incorporate multiple pieces of new information into their long-term storage, and this is consistent with previous findings of memory deficits associated with early-stage DAT in the general population. It is unlikely that this

finding is a result of the DAT group not recognizing or not paying attention to the original presentation of the items. Since multiple sensory modalities are used during this task (i.e., visual, tactile, audio, verbal), after the original 10 items are initially presented, each participant must indicate in some way that he/she is familiar with them. Thus, failure to recall items during the first trial cannot be attributed to inattentiveness or unfamiliarity with the test materials (Fuld, 1980).

A significant difference was also found for the Total Recall (TR) score, with the DAT group recalling fewer items across all five trials compared to the OND and to the YND groups. In addition to the ability to recall information, the TR score reflects whether learning and storage has occurred with the aid of verbal reminders following each trial. Thus, even with reminders of items missed during each recall, the DAT group demonstrated difficulty recalling additional items during subsequent trials. This result is consistent with the original validation study which revealed that reminding cognitively impaired participants of items missed did not tend to improve their performance when compared to cognitively intact elderly participants (Fuld, 1980).

For the Delayed Recall (DR) trial, significant differences were again found, with the DAT group recalling fewer objects compared to both the OND and the YND groups, and this is consistent with prior research in the general population. There are at least two possible explanations for this result. Poorer scores for the DAT group may be related to impaired ability to store new information, which in turn limits the amount of information available for subsequent retrieval. In other words, reduced retrieval may be a result of a storage deficit. In their study of explicit memory associated with early dementia, Krinsky

and colleagues (2002) found that in early-stage DAT, in addition to impaired ability to store new information, the ability to retrieve items that were stored was significantly impaired. Thus, a second explanation to account for these results is that both storage and retrieval are compromised in DS adults with early-stage DAT.

The FULD was not found to be sensitive to the effects of age in the present study, in that significant differences were not found between the two non-affected groups (OND and YND). This is consistent with results found for the general population. It has been reported that performance on the FULD is not influenced by age or educational level (Chung & Ho, 2009; La Rue, 1989).

The present study supports the use of the original version of the FULD as an effective measure to be included as a clinical tool in a dementia test battery to detect cognitive decline associated with early-stage DAT in DS adults functioning within the mild and moderate ranges. The FULD offers several advantages over other explicit memory measures that are typically based on recall of verbal lists. First, the FULD uses common and familiar objects as the presentation stimuli and the administration procedure ensures that participants have indicated recognition of each object prior to the commencement of the recall trials. This minimizes the chances of inattention or unfamiliarity with test stimuli compromising recall. This advantage is particularly salient for DS adults who often show difficulty with other memory measures such as orientation questions, since these types of tasks request information that the DS individual may not have learned (e.g., the year of their birth; how to tell time), or they are related to current affairs of which the DS individual is not aware. A second advantage of the FULD is that

it employs multiple sensory modalities for encoding information (visual, audio, verbal, haptic), which increase the chances of participants actually processing the stimuli to be remembered. Another advantage is that synonyms, descriptions, and gestures are accepted if exact names of objects are not provided. For example, in place of the word "cup", acceptable responses include "glass", "for drinking", or a demonstration of holding a cup and drinking from it. This allows the participant to demonstrate that his/her memory is intact even if language problems exist. A final advantage of the original FULD is that it is a task for learning and recall that is not highly dependent on processing speed and it allows for multiple learning and recall opportunities. Five chances to store a limited amount of new information are provided, and the participant can demonstrate evidence of this storage by retrieving the information after distraction tasks (Fuld 1980).

Overall, the present results support earlier findings (based on a modified version of the FULD) that verbal explicit memory is affected during early-stage DAT in DS adults. DS adults with probable DAT show clear deficits in their ability to encode and/or retrieve new information from long-term storage, compared to non-affected DS adults.

Applied Implications of this Research

The findings of this study have practical implications for both research and clinical domains. One of the contributions made to the research literature is in documenting that one of the earliest changes observed in DAT in the general population may not be a sign of early DAT in the DS population. Improving early diagnosis of DAT

is a primary goal of much of the current research on the DS adult population. In research, earlier and accurate diagnosis improves recruitment for clinical trials to test new preventative and treatment medications. On the basis of the current findings, future research is directed to identifying the unique language profiles of DS individuals, in general, and of DS adults in the early stages of DAT. Although there is consistent evidence of anatomical, physiological, and neurochemical abnormalities in the brains of DS individuals, such anomalies have not yet been specifically related to observed language functions. The present study also provided additional support to previous findings of the presence of memory impairment in the early stages of DAT in DS. The results suggest that the FULD is a sensitive measure to be included in a neuropsychological test battery for detecting clinical dementia. The present results indicate that, similar to what has been found in the general population, memory impairment characterizes the cognitive decline associated with early-stage dementia in the DS population.

Determining whether commonly used assessment methods are effective in documenting the progressive cognitive decline associated with AD among DS adults is also clinically important. In the present study it was found that the Boston Naming Test was not a sensitive measure to be employed in a test battery for early-stage dementia in DS. Since the performance of DS adults with and without dementia was similar on several aspects of this test, it appears to have little diagnostic or practical value for detecting dementia in this population. The challenge of distinguishing the onset of a pathological condition from pre-existing cognitive impairment has been repeatedly

demonstrated in the research literature, and again was shown in the present study. Most certainly, the development of sensitive measures to detect clinical dementia in DS is needed. The major applications of neuropsychological assessment to the clinical diagnosis of DAT in DS include 1) early detection; 2) differential diagnosis; and 3) staging, or measuring severity and progression. Each of these clinical applications demands sensitive and reliable measures. Neuropsychological tests are clinically useful only if they can be used to accurately classify a high percentage of individuals belonging to the various diagnostic groups, (e.g., AD versus depression). Thus, the clinical significance of specific tests depends on the size of the difference, or magnitude of effects, between groups (Zec, 1993). Clearly this task is difficult in the DS population, since levels of premorbid functioning vary considerably. The challenge now is to establish sensitive and reliable indices of the clinical aspects of the disease and its progression that capture all of the unique phenotypic characteristics of DS, including language abilities.

Early detection of dementia is important in order to learn about the potential contribution of different risk factors for the DS population. Appropriate estimates of the earliest cognitive changes that might be attributed to DAT are necessary in order to evaluate the effect of pharmacological and psychosocial interventions on the course of the disease. Several medications have been licensed for use in mild and moderate DAT in the general population (e.g., acetylcholinesterase inhibitors and memantine), and research has shown these drugs to be effective in slowing the decline of functional ability in AD (Stanton & Coetzee, 2004). Research on the use of anti-dementia drugs in the DS

population is very limited (for a review see Prasher 2004). The accurate and early diagnosis of DAT in DS would help in developing clinical trials in DS individuals for these same pharmacological treatments, since it is still unknown whether similar gains in treatment could be made in this population. It would be unfortunate if the benefits of such treatments were not experienced by DS individuals with dementia. It is clear that early diagnosis directly affects patients and their caregivers, and it informs appropriate care and quality of life.

Limitations of this Research

The present investigation addressed some of the limitations of previous research that have been cited in the literature (e.g., Slomka & Berkey, 1997). The majority of studies comparing abilities between DS adults and DS-DAT adults have involved very small sample sizes, which makes it difficult to generalize findings beyond the specific group used in the investigation. Additionally, in many previous studies DS individuals within an institutional setting were predominantly used, whereas the present research employed data from a community-based sample. Also, in the present investigation all of the participants were screened for conditions that could be expressed as pseudodementia, and this is an important step that is often overlooked in research on dementia in DS adults.

While the above stated considerations were made in the present research, there are certain limitations in the design of this study that warrant discussion. One of the limitations of the present methodology is a shared concern in many investigations,

namely the participants included DS individuals within the mild and moderate levels of intellectual functioning only. Individuals with severe and profound cognitive impairment were excluded from the present study because the BNT and the FULD cannot be administered to individuals functioning within these intellectual ranges. This is a limitation typically encountered in the research literature, since DS individuals with severe and profound cognitive delay demonstrate the greatest communication impairments and also the lowest baseline abilities, and they typically cannot participate in most neuropsychological tests. Therefore, the results of the present study apply only to a subpopulation of DS. Unfortunately, to date, there is no single assessment battery that can be administered to individuals of all intellectual ability ranges. Future research could include participants with severe and profound delay by examining evidence of skill-loss, even when skills are limited (e.g., the ability to feed oneself). Practical assessment methods for lower functioning individuals involve caregiver reports and direct observation of changes in abilities.

While the present investigation included a larger sample size than is typically encountered in the research literature, a further increase in the number of participants would be favourable. The number of participants in the present investigation was constrained by the availability of individuals who presented to the Neuropsychological Baseline Assessment Service. Although many clinical studies are confronted with this difficulty, it must be acknowledged that it is possible that less strong effects may be missed with a smaller sample size. Future research would perhaps benefit from conducting a priori power analysis to provide an estimate of the ideal sample size.

Another possible limitation is that this investigation employed a cross-sectional design. That is, individuals of different age ranges and dementia status were compared at one point in time. The disadvantage of this design is that it does not permit the assessment of individual changes that may occur over time. It may be that a longitudinal approach, where a fixed group of individuals is evaluated at selected intervals over an extended period of time, would be important, particularly since the diagnosis of dementia implies deterioration from a previous level of functioning. The repeated administration of tests offers an opportunity to compare performances on multiple baseline measures over time. It is noted, though, that a longitudinal approach also presents with direct disadvantages for this particular study. An important methodological limitation of a longitudinal design is participant attrition. Participants may not be available for long-term follow-up due to loss of interest, geographic relocation, declining health, or death. While some of the participants in the present study have received follow-up testing for various reasons, it is only a small percentage of the original group and thus longitudinal data is not available for comparison. Another difficulty that is introduced with a longitudinal design is that those participants who are retested may be more cognitively intact than those who drop out of the study (Zec, Markwell, Burkett, & Larsen, 2005). Practice effects are also a consideration with longitudinal research involving repeated testing. The FULD has only one alternate test form, while the BNT does not have an alternate version. Another disadvantage of using a longitudinal design is that many of the potential masking conditions that were screened for in the present study (e.g., depression, thyroid dysfunction, hearing problems), may develop between testing periods and

subsequently influence assessment outcomes.

Although the present investigation employed a community-based design, rather than an institutional sample, it should be acknowledged that the DS individuals used in the present study represented those that presented to the clinic. Therefore, they may not be representative of the wider population of DS individuals who may not have received clinical services.

Future Directions

A review of the literature on dementia in the DS population indicates that the present investigation was the first to evaluate confrontation naming abilities in DS individuals with AD. The findings of the present research raise additional questions about the effect of AD on language functions in DS that warrant future consideration. It would be of interest to examine whether there are specific language functions that are either affected or spared by AD, and whether certain language functions are more severely affected than others. Before such questions can be examined, though, the baseline language functions of DS individuals need to be determined. As previously mentioned, it has been demonstrated in the research literature that DS individuals present with a unique pattern of language abilities, although little is known about the underlying physiological and cognitive mechanisms. A somewhat promising area of research has developed within the last 20 years involving the examination of cerebral specialization. It is widely accepted that for individuals in the general population the left hemisphere is

where language is located, whereas the right hemisphere is important for spatial ability, interpreting senses, and emotions. For DS individuals there is a theory that the brain hemispheres represent opposite functions. Certain investigators (e.g. Elliot, Weeks, & Chua, 1994; Hartley, 1981; Pipe, 1983), believe that in Down syndrome language is located in the right hemisphere, and hence DS individuals possess right hemisphere language dominance. The significance of this model of reversed cerebral specialization, in terms of phenotypic expression, has yet to be established. This model, however, does suggest that genetically mediated characteristics that are associated with DS are directly related to a syndrome-specific pattern of brain organization, and by extension, language function. Whether the selective linguistic weaknesses observed in DS are associated with abnormalities in the cerebral representation of language is undetermined. Further investigation of the anomalous pattern of brain organization and language structure may aid in directing research into whether language is affected by the disease process of AD. If there is a language impairment in DS-DAT, it would be important to also examine whether its progression parallels the progressive impairment of other cognitive functions. Future examination of these issues will contribute to the development of diagnostic criteria that are unique to the DS population, and also to establish which features of the disease are shared with individuals with DAT in the general population. This highlights the necessity of establishing both normative information for the DS population, and baseline data for DS individuals so that optimal levels of performance can later be compared when declines in ability are suspected.

Additionally, in the present study it was found that DS individuals, irrespective of

age and dementia status, made semantic errors most frequently on the BNT and these semantic errors were typically of a coordinate type, suggesting perhaps a syndrome-specific effect on language. Further investigation of this semantic impairment across several age groups will contribute to an understanding of the unique language functions of DS individuals.

Among DS adults it is especially difficult to differentiate the presence of early-stage dementia from declines related to aging or masking disorders and from lifelong intellectual deficits. In the present study, while the FULD was found to be useful for the early identification of DS-DAT, and it seems to hold promise as a diagnostic tool as part of a larger battery, further research is needed on the use of this measure with DS adults. In order to describe the cognitive progression of decline with greater precision, normative data on the FULD for the DS population need to be established.

Conclusions

While AD in the general population is quite uniform with regard to the progression of the disease and the relationship between neuropathological indications and behavioural manifestations, the same is not true for the disease in Down syndrome. Alzheimer's dementia in this population is neither uniform in its progression, nor is there any decided relationship between the neurological and clinical presentations of the disease. The presence of cortical changes is not sufficient to predict the onset of dementia, nor are these changes reliable clinical indices of the dementia pattern in DS. It

has been proposed that since the cortical distribution of AD neuropathology in DS is not adequate to result in clinical manifestations as in the general population, other aspects of the neuropathology may also differ. Deb (2003) suggests that the confirmed plaques and tangles in the brains of DS adults may signal neither the beginning nor the end of the disease, and that their presence does not necessarily verify that AD has developed.

The results of the present study contribute to the overwhelming evidence in the research literature that the clinical diagnosis of AD in DS is difficult, owing to a host of factors including pre-existing cognitive impairment, comorbid conditions, and lack of sensitive neuropsychological test instruments. It may also be that DS adults exhibit signs and symptoms atypically and perhaps it may be most reasonable to reconceptualize AD in this population as a disease that is distinct from that occurring in the general population. Holland, Karlinsky, and Berg (1993) suggested that while DS and AD probably share a common causal process, it is possible that a clinical profile of AD in DS will emerge that is different from that of AD in the general population. They added that this clinical profile may benefit from less emphasis on cognitive changes as a defining feature. The results of the current study lend support to the idea that the clinical course of dementia is, in many ways, quite unique for individuals with DS. It has been suggested that due to their pre-existing intellectual delay, DS individuals may never have developed the exact skills that are diagnostic for the development of early DAT in non-delayed individuals (Zigman, Silverman, Wisniewski, 1996). It has also been proposed that abnormal brain development in DS may interact with AD pathology, somehow modifying the clinical presentation of the disease (Holland et al., 1998). It is important to consider

that even though DS adults have vastly different life experiences than do individuals without cognitive impairment, there is no alternative diagnostic definition for Alzheimer's dementia than that used for the general population. The findings of the present investigation contribute to the research evidence that indicates that DS-DAT is likely a clinical disorder separate from DAT in the general population. This suggests the need for an operational redefinition. It may be that the neuropathological features of AD represent a single disease that has several etiologies and various clinical expressions that represent unique populations. Rather than try to map the clinical signs found in DAT in the non-delayed population onto the experiences of DS adults, it may be most suitable to develop diagnostic criteria specifically for this population. Equally important is the development of psychometric tests specifically designed for, and normed on, DS individuals. For instance, the present study highlighted that, for DS individuals in the early stages of DAT, the exact pattern of language functioning needs to be specified, and sensitive measures need to be developed to address the unique language abilities in this population. This would also involve identifying cognitive profiles through baseline testing and frequent retesting of abilities throughout the DS person's lifetime.

In summary, the results of the current study add to the growing evidence that DAT in the Down syndrome population may represent a distinct disease process. Perhaps reframing is needed so as not to continually apply the DAT symptomatology of AD patients in the general population to the DS population. It should follow that neuropsychological measures be developed based on the unique needs and development of DS individuals. It may be that a clinical disorder that is independent from classical

dementia be established, or an operational definition be developed, to better characterize what is observed to be specific to the clinical presentation of DAT in DS. Rather than view changes through the lens of typical development, the phenotypic expression of Alzheimer's disease in Down syndrome may best be captured through a lens unique to this population.

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Appendix A

DSM-IV Diagnostic Criteria for Dementia of the Alzheimer's Type*

A. The development of multiple cognitive deficits manifested by both

(1) memory impairment

(2) one or more of the following cognitive disturbances:

(a) aphasia (b) apraxia

(c) agnosia (d) disturbance in executive functioning

B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The course is characterized by gradual onset and continuing cognitive decline.

D. The cognitive deficits in criteria A1 and A2 are not due to any of the following:

(1) other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., Parkinson's disease, Huntington's disease, brain tumour)

(2) systemic conditions that are known to cause dementia (e.g., hypothyroidism, niacin deficiency, HIV infection)

(3) substance-induced conditions

E. The deficits do not occur exclusively during the course of a delirium.

F. The disturbance is not better accounted for by another Axis I disorder (e.g., Major Depressive Disorder, Schizophrenia).

* Adapted from the DSM-IV (APA, 1994)

Appendix B

ICD-10 Diagnostic Criteria for Dementia of the Alzheimer's Type*

Dementia is a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation. The following features are essential for diagnosis:

(1) Decline in memory, thinking, and reasoning capacities which is sufficient to impair personal activities of daily living. The memory impairment affects registration, storage, and retrieval of new information, and it may affect previously learned material.

(2) The symptoms and impairments should be evident for at least six months.

(3) The onset is insidious with slow deterioration.

(4) There is an absence of other systemic or brain disease which can induce a dementia state; there is an absence of a sudden onset or of neurological signs of focal damage.

(A) Early onset : before the age of 65, with a relatively rapid deteriorating course and with marked multiple disorders of the higher cortical functions.

(B) Late onset: after the age of 65, usually in the late 70s or thereafter, with a slow progression, and with memory impairment as the principal feature.

* Adapted from the ICD-10 (WHO, 1994)

Appendix C

NINCDS-ADRDA Diagnostic Criteria for Dementia of the Alzheimer's Type*

1. Criteria for the clinical diagnosis of PROBABLE AD include:

    (a) dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests

    (b) deficits in two or more areas of cognition

    (c) progressive worsening of memory and other cognitive functions

    (d) no disturbance of consciousness

    (e) onset between ages 40 and 90, most often after age 65

    (f) absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition

The diagnosis of PROBABLE AD is supported by:

    (g) progressive deterioration of specific cognitive functions such as language, motor skills, and perception

    (h) impaired activities of daily living

    (i) family history of similar disorders

    (j) laboratory results

The diagnosis of PROBABLE AD is unlikely if:

    (a) the onset is sudden

    (b) there are focal neurologic findings

    (c) there are seizures or gait disturbances at the onset or very early in the course of

the illness

2. Criteria for the clinical diagnosis of POSSIBLE AD:

   (a) may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course

   (b) may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia

   (c) should be used in research studies where a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause

3. Criteria for the clinical diagnosis of DEFINITE AD:

   The clinical criteria for probable Alzheimer's disease and the histopathologic evidence obtained from a biopsy or autopsy.

* Adapted from McKhann, Drachman, Folstein, Katzman, Price, & Stadlan (1984).

Appendix D

Psychometric Properties of the Boston Naming Test

The published 60-item version of the BNT was accompanied by two sets of adult norms that were described by the authors as provisional (Kaplan, Goodglass, & Weintraub, 1983). One of the sets is based on years of formal schooling (under 12 and over 12 years), and the second set includes five age groups, with the highest one being 50 to 59 years of age. The means and standard deviations for BNT total score vary little across these groups. For instance, the means of the schooling groups are 55.73 (under 12 years) and 55.71 (over 12 years). For the second normative set, the mean and standard deviation for the 50 to 59 year old group is 55.82 (2.63), and it varies little from a younger group aged 20 to 29 years with a mean and standard deviation of 55.86 (2.86). Based on these norms, it seems that at least until age 50 to 59, advancing age does not affect performance on the BNT. Several studies support the finding that naming ability remains relatively stable until individuals reach the age of about 70 (Albert, Heller, & Milberg, 1988; LaBarge, Edwards, & Knesevich, 1986; Nicholas, Obler, Albert, & Goodglass, 1985; Van Gorp, Satz, Kiersch, & Henry, 1986). Selected studies have reported BNT normative data for healthy older adults (Farmer, 1990; Nicholas, Brookshire, MacLennan, Schumacher, & Porrazzo, 1989; Van Gorp, Satz, Kiersch, & Henry, 1986).

The BNT is designed to measure deficits in naming ability or severity of aphasia, but it is not a good measure of skill level or proficiency within the normal range (Mitrushina, Boone, Razani, & D'Elia, 2005). In other words, although it is a sensitive

test for naming impairment in the general population, it does not discriminate between average, above average, and superior naming ability.

The BNT manual does not include information on test-retest reliability, although several clinical studies have reported their findings. High test-retest reliability on the BNT (r = .91) was documented over a one-to-two week interval for a sample of 31 healthy older adults (aged 50 to 76 years) (Flanagan & Jackson, 1997). Another study that employed a mixed normal sample (aged 15 to 83 years) reported test-retest reliability of .92 over an 11-month period (Dikmen, Heaton, Grant, & Temkin, 1999). The validity of the BNT was also assessed as part of an educational program on 136 independently living older Australian adults (Worrall, Yiu, Hickson, & Barnett, 1995). Standard scoring and an analysis of errors were conducted. High interrater reliability was reported for the total score (94.89%) and for error scoring (98.17%).

With regard to a dementia population, good test-retest reliability was demonstrated in a study examining cognitive test performance in detecting dementia related decline (Locascio, Growdon, & Corkin, 1995). Patients with and without AD were tested every 6 to 24 months over a period of 5.5 years. Correlations across sessions were .84 to .88 for the AD group, and .77 for the normal control group.

A moderately high correlation was reported between BNT performance and verbal fluency (for animal names) with r = .50 for AD patients and r = .52 for a normal control group ($p < .001$ for both correlations) (Locascio et al., 1995). The BNT was also found to be highly correlated with reading vocabulary (r = .81, $p < .001$) (Hawkins et al., 1993). High correlations were also reported between the BNT and the Wechsler Adult

Intelligence Scale – Revised Verbal IQ (r = .74, p < .001), and Vocabulary subtest (r = .79, p < .001), in a clinical sample of heterogeneous neurological conditions (Thompson & Heaton, 1989)

An early study comparing BNT performance with measures of different aspects of memory, such as immediate and delayed recall, suggested that BNT scores and Wechsler Memory Scale scores are unrelated (Albert et al., 1988). The investigators concluded that although their results cannot prove the absence of an effect, (since memory ability is important in the retrieval of information), their findings do suggest that naming ability and memory function are weakly related in healthy older adults. While the BNT does not significantly correlate with basic episodic memory performance in unaffected older adults, correlations have been noted between the BNT and memory for a very mildly demented group. LaBarge and colleagues (1992) reported a correlation between BNT scores and memory performance as measured by the Wechsler Memory Scale subtests of Associate Learning (r = .52, p < .01), and Logical Memory (r = -.40, p < .05). Moderately strong correlations were also noted between total errors on the BNT and basic intelligence, as measured by the Wechsler Adult Intelligence Scale subtests of Information (r = -.69), Comprehension (r = .63), and Block Design (r = .56). The investigators concluded that these results indicated that poor BNT performance is only one of many symptoms of a more generalized cognitive deficit in very mild dementia.

Appendix E

Psychometric Properties of the Fuld Object Memory Evaluation

The FULD was first validated (Fuld, 1980) by demonstrating that it differentiated mentally impaired from mentally intact aged nursing home residents whose dementia status was determined by their scores on Blessed, Tomlinson and Roth's (1968) mental status test. It was reported that the Blessed et al. test was selected because error scores on this test have been shown to correlate significantly with the number of senile plaques seen in the cerebral cortex of elderly patients upon postmortem examination. Twenty-one mentally intact and 21 moderately impaired elderly individuals participated in the validation study. Results showed that impaired individuals recalled significantly fewer items on the FULD compared to mentally intact individuals ($F(1, 40) = 18.67, p < .005$). Normative data were provided for community-residing and institutionalized 70- to 79-year-olds and 80- to 89-year-olds.

The discriminative validity of the FULD test was determined by the test's ability to distinguish normal from dementing individuals at the time of diagnosis (Fuld et al., 1990). Recall on the first trial demonstrated a sensitivity of .86, and a specificity of .82. The investigators concluded that one trial of recall on the FULD is capable of discriminating between normal functioning and very early dementia. The clinical utility of the FULD was examined in another study using logistic regression in a sample of geriatric patients to determine the test's ability to differentiate demented patients from those who were not demented (Mast et al., 2001). Results supported the use of the FULD as an accurate screening measure for AD. The following four estimates of clinical utility

were determined: sensitivity (the percent of dementia cases correctly identified as demented) was 93.2%; specificity (the percent of non-demented cases correctly identified as non-demented) was 63.5%; positive predictive power (the percent of cases scoring below a cut-off score who were actually demented) was 81.2%; and negative predictive power (the percent of cases scoring above a cut-off score who were non-demented) was 84.6%. Performance on the FULD was not significantly correlated with education, age, or gender. A significant correlation ($r = .65$, $p < .001$) was found between performance on the FULD and dementia status (as determined by a geriatrician examination in accordance with NINCDS-ADRDA criteria).

Appendix F

Examples of Errors on the Boston Naming Test

Type of Error	Examples
Visuoperceptual	mask = face pretzel = snake pretzel = knot seahorse = giraffe stilts = sticks dominoes = blocks rhinoceros = hippo
Phonemic	igloo = iglow unicorn = hornicon stilts = sticks
Semantic	
Coordinate	pelican = penguin helicopter = plane octopus = fish beaver = chipmunk canoe = kayak, sailboat rhinoceros = hippo
Superordinate	pelican = bird camel = animal beaver = animal canoe = boat acorn = nut rhinoceros = animal
Functional-Circumlocutory	racquet = play tennis toothbrush = brushing teeth wreath = Christmas bed = sleeping