From the Department of Neurobiology, Care Sciences and Society,
Karolinska Institutet, Stockholm, Sweden

LEXICAL AND ARTICULATORY ASPECTS OF SPEECH PRODUCTION IN COGNITIVE DECLINE

Per Östberg

Karolinska Institutet

Stockholm 2008

Published by Karolinska Institutet. Printed by Larserics Digital Print AB, Sundbyberg.

ISBN 978-91-7409-015-4

ABSTRACT

Background: Dementia may be defined as the attenuation of cognitive powers despite preserved basal consciousness. Its most common cause is Alzheimer's disease (AD). Pathoanatomical staging has made it clear that the disease passes through a protracted preclinical phase with slowly emerging symptoms. Such symptoms may include various forms of forgetfulness, such as forgetting the names of people, things, and places. Because word finding also wanes somewhat with normal aging, objective tests of word finding might help in separating benign word lapses from those reductions in lexical ability that may herald dementia. **Objectives:** The main aim of the thesis was to identify speech production tests of relevance to the diagnosis of AD and mild cognitive impairment (MCI). **Material and Methods:** The thesis is based on retrospective clinical data obtained from patients admitted to the memory clinic of the Department of Geriatrics, Karolinska University Hospital. All subjects had undergone an examine procedure for possible dementia. *Study I* explored the interrelationships of three word fluency tests and performance differences between the diagnostic categories. *Study II* investigated whether reductions in regional brain blood flow affected performance in a verb fluency task and a noun fluency task. *Study III* examined the production of an automatic word sequence in forward and reverse order as a diagnostic target. *Study IV* analyzed the capacity for rapid articulatory action in AD and related disorders. **Results:** Verb, noun, and letter-based fluency were found to be factorially distinct tests but with covariance between factors. Noun fluency was disproportionately impaired in AD. In MCI, however, verb fluency was more decreased than noun or letter-based fluency. Verb fluency performance was predicted by educational level and temporal lobe blood flow, while noun fluency was predicted by age and parietotemporal-occipital blood flow. Forward word sequence production was preserved across diagnostic categories. In contrast, backward word sequence production was impaired in MCI and devastated in AD. The diagnostic predictive power of backward word sequence production was approximately equivalent to that of the widely-used Mini-Mental State Examination. Sequential speech motion rate was modestly reduced in MCI and AD, but more markedly so in frontotemporal dementia and progressive nonfluent aphasia. In semantic dementia, articulatory capacity was at the level of participants without objective cognitive impairment and superior to the other categories. **Conclusion:** Lexical production tasks have application to the diagnosis of MCI and mild AD. The capacity for rapid articulatory action varies both between and within AD and related disorders. The potential neural correlates of this variation remain to be explored by future studies.

Sammanfattning

Bakgrund

Demens innebär att ens kognitiva förmågor avtagit till den grad att man inte längre klarar det dagliga livet fullt ut. Alzheimers sjukdom är den vanligaste orsaken till demens. Anatomiska undersökningar av hjärnförändringarna vid Alzheimer tyder på att sjukdomen utvecklas under lång tid innan symptomen sakta börjar märkas. Mycket forskning ägnas därför åt att kartlägga vad som kan vara tidiga tecken på demenssjukdom. Till de viktigaste symptomen hör olika sorters glömskhet som att tappa ord på personer, platser och saker. Många känner nog igen sig i sådana upplevelser, och en måttligt ökad ordglömska förknippas mycket riktigt med det normala åldrandet. Därför är det inte alls säkert att svårigheter att hitta ord beror på demensutveckling. Ett sätt att bedöma om ordglömskan är godartad eller mer djupgående är att använda särskilda test av förmågan att hitta ord. Sådana test kan innebära att man får säga vad mer eller mindre ovanliga saker heter eller att komma på ord så många ord som möjligt inom ett visst ämnesområde eller ord som börjar på en viss bokstav. De sistnämnda uppgifterna kallas ordflödestest. De utförs på begränsad tid, vanligen en minut, och är ganska krävande trots att man klarar av dem snabbt.

Syfte

Huvudsyftet med studien var att undersöka om test av förmågan att snabbt komma på ord och av artikulationssnabbhet kan vara relevanta för att diagnostisera lindriga grader av demens och en ännu lindrigare grad av kognitiv nedsättning, så kallad lindrig kognitiv störning.

Delstudie I

I denna studie undersöktes resultaten från tre olika ordflödestest hos 199 personer som genomgått en minnesutredning vid Geriatriska kliniken, Karolinska universitetssjukhuset. Det första testet, bokstavsstyrt ordflöde, gick ut på att komma på ord som börjar på en viss bokstav. Det andra testet, substantivflöde, innebar att man skulle räkna upp så många olika djurarter som möjligt, dvs. en kategori av substantiv. I det tredje, verbflöde, gällde det att komma på så många verb som möjligt som uttrycker aktiviteter som en människa kan utföra. Varje deltest genomfördes under en minut, och antalet korrekta ord per tiosekundersintervall noterades för att få en uppfattning om prestationen över tid. En explorativ faktoranalys enligt maximimetoden med oblik rotation av axlarna visade att de tre testen motsvaras av var sin bakomliggande faktor, och de tre faktorerna var i viss mån korrelerade

med varandra. Jämförelser mellan olika diagnoskategorier visade att substantivflöde (djur) var oproportionerligt nedsatt i gruppen Alzheimerdemens, medan däremot verbflöde var det jämförelsevis svåraste testet för gruppen lindrig kognitiv störning. Dessa två test framstod därför som mest intressanta i detta sammanhang och undersöktes närmare i delstudie II.

Delstudie II

Denna undersökning omfattade förutom verbflöde och substantivflöde även resultat från en röntgenundersökning av blodflödet i olika delar av hjärnan, s.k. enfotonemissionstomografi (SPECT). Syftet var att se om prestationen i ordproduktionstesten kunde kopplas till funktionsavvikelser i skilda delar av hjärnan. Data hämtades från 93 försökspersoner som genomgått minnesutredning vid Geriatriska kliniken, Karolinska universitetssjukhuset. Från SPECT analyserades 38 olika variabler genom principalfaktoranalys med varimaxrotation, vilket gav sju faktorer motsvarande större anatomiska regioner i hjärnan. Dessa användes sedan i multipla regressionsanalyser. Resultaten visade att prestationen i verbflöde predicerades av utbildningsnivå, dvs. ju högre utbildning desto högre resultat, och av blodflödet i temporalloben. Substantivflöde predicerades däremot av ålder – ju högre ålder, desto lägre resultat – och av blodflödet i parietotemporal-occipitalregionen. Prestationen på de två ordflödestesten ”förklarades” alltså i viss utsträckning av skilda bakomliggande faktorer, inklusive olika hjärnkorrelat.

Delstudie III

Den tredje studien inriktades på ordsekvensproduktion, en typ av ordproduktionsuppgifter som skiljer sig mycket från ordflödestesten. Ordsekvenser som månaderna tillägnas delvis genom en ”procedural” form av inlärning under barndomen och kvarstår som automatiserade listor i ordförrådet, vilkas ingående beståndsdelar ändå kan användas enskilt och flexibelt. Ändå finns en tydlig skillnad mellan att räkna upp t.ex. månaderna i den invanda ordningen och att göra det i omvänd ordning – framåt går snabbt och utan eftertanke, bakåt går långsammare och med viss tankemöda. I denna studie undersöktes om denna kontrast är av diagnostiskt värde vid lindriga grader av demens och lindrig kognitiv störning. Resultat från testet månader framåt-bakåt inhämtades från 234 personer som genomgått minnesutredning vid Geriatriska kliniken, Karolinska universitetssjukhuset. Den invanda, framåtriktade sekvensuppräkningen visade sig vara intakt vid demens. Förmågan att snabbt återge sekvensen i omvänd ordning var däremot tydligt nedsatt vid lindrig kognitiv störning och till stor del utslagen vid lindrig

Alzheimerdemens. Logistiska regressionsanalyser tydde på att en till två variabler från testet månader bakåt hade ungefär samma diagnostiska prediktionsförmåga som det mer tidskrävande Mini-Mental-testet.

Delstudie IV

I den sista delstudien undersöktes hur ett mått på talmotoriken, en basal men viktig delförmåga i språkanvändningen, varierar inom och mellan grupper med kognitiv nedsättning. I denna studie med totalt 236 försökspersoner ingick även 29 fall av frontotemporal lobär degeneration, en mindre vanlig demenssjukdom som ofta uppträder i 50-årsåldern. Den har tre huvudformer: frontotemporal demens, där förändringar i personlighet och beteende är mest framträdande, semantisk demens, som kännetecknas av bortfall i ordförråd och begreppsbildning samt progressiv ickeflytande afasi, där en typ av Broca-afasi är mest framträdande. Som mått på talmotorisk snabbhet användes sekventiellt artikulatoriskt rörelsetempo. Försökspersonerna fick repetera en stavelsesekvens med växlande artikulationsställe så snabbt och jämnt som möjligt under tio sekunder, varefter tempot beräknades som antalet korrekt repeterade stavelser per sekund. Rörelsetempot var måttligt nedsatt vid lindrig kognitiv störning och lindrig Alzheimerdemens; ungefär 10 % av fallen i dessa grupper hade påfallande lågt tempo. Mer tydligt nedsatt tempo sågs vid frontotemporal demens och i synnerhet vid progressiv ickeflytande afasi. Gruppen semantisk demens skilde sig inte från personer utan objektiv kognitiv störning, men hade signifikant högre rörelsetempo än övriga fyra diagnoskategorier inklusive lindrig kognitiv störning.

Slutsats

Ordproduktionstest har relevans för lindriga grader av kognitiv nedsättning, och av de undersökta testen gäller detta särskilt omvänd ordsekvensproduktion. Artikulationssnabbhet varierar både mellan och inom gruppen Alzheimerdemens och besläktade störningar. Korrelaten till denna variation behöver utforskas närmare.

LIST OF PUBLICATIONS

I. Östberg P, Fernaeus SE, Hellström Å, Bogdanović N & Wahlund LO. (2005). Impaired verb fluency: a sign of mild cognitive impairment. *Brain and Language, 95,* 273-279.

II. Östberg P, Crinelli RM, Danielsson R, Wahlund LO, Bogdanović N & Fernaeus SE. (2007). A temporal lobe factor in verb fluency. *Cortex, 43,* 607-615.

III. Östberg P, Fernaeus SE, Bogdanović N & Wahlund LO. (2008). *Logopedics Phoniatrics Vocology* (in press).

IV. Östberg P, Bogdanović N & Wahlund LO. (2008). Articulatory agility in cognitive decline. Submitted.

CONTENTS

LIST OF ABBREVIATIONS

AD	Alzheimer's disease
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
GDS	Global Deterioration Scale
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
PNFA	Progressive nonfluent aphasia
SCI	Subjective cognitive impairment
SD	Semantic dementia
SPECT	Single-photon emission computed tomography
TOT	Tip-of-the-tongue [state]

1 INTRODUCTION

1.1 GENERAL BACKGROUND

Human beings alone have the power to learn a language. So essential is this capacity that humanness has been typified as *zoon logon ekhon* in the Aristotelian tradition – a life form endowed with speech. Language indeed pervades our lives. From it stems many other abilities. It helps us acquire and disseminate factual knowledge, reflect on our past and future, disclose or conceal our feelings, ponder our situation, and plan a course of action. We readily carry out diverse speech acts such as asserting, requesting, questioning, promising, blaming, praising, and thanking.

Some plain empirical figures may illustrate human loquaciousness. Young men and women utter 16,000 words each day on average (Mehl *et al*., 2007), drawing on vocabularies of about 75,000 lexical items (Oldfield, 1963). The medium speaking rate for a turn in conversation is more than 200 words per minute, whereas articulation proceeds at a medium rate of around 5.3 syllables per second for an English utterance (Laver, 1994, p. 158).

The faculty of language subsumes an array of different constituent abilities. They include visual and auditory perceptual skills as well as motor skills necessary for speech and writing. Moreover, competent speakers of a language know, among other things, the correct pronunciation of words, how to combine them in sentences and to apply expressions with appropriate precision and style in a given context. Once acquired, these skills remain remarkably robust, given their regular and effortless use throughout adult life. Even eloquent readers will nonetheless testify that their exercise of language occasionally goes awry. Various slips of the tongue occur from time to time, involving the substitution of words related in meaning or in form, as well as substitutions or transpositions of speech sounds (Fromkin, 1973). Such slips are sometimes noticed by speakers themselves, sometimes only by listeners. One may also lose one's thread in conversation, so that an account or argument has to be discontinued, or one may be unable to bring a crucial term to mind, perhaps causing some embarrassment. The latter phenomenon is associated with what is referred to as the tip-of-the-tongue (TOT) states in psycholinguistics (Brown & McNeill, 1966; Brown, 1991). A person in the TOT state is momentarily unable to recall a word such as the name of a person or a common noun, but can usually rephrase its meaning. One may also be aware – frustratingly so – of the partial phonological form of the word, such as its first or last sound, the number of syllables, or its stress pattern (James, 1890, p. 252). Under experimental conditions, subjects may reliably indicate syntactic features such as gender or mass/count class of common nouns they cannot recall (Miozzo & Caramazza, 1997; Vigliocco *et al.*, 1999; Biedermann *et al.*, 2007).

Slips of the tongue and TOT states are a recurrent, although perhaps not very frequent, experience for many people. Word-finding trouble is commonly held to be part of getting old, but some persons fear they might be a sign of abnormal cognitive decline, that is, a symptom of dementia. Newspaper articles or medical brochures mention

word-finding trouble as an early symptom, and many people have observed the speech of friends or relatives afflicted by dementia. The question arises whether word-finding trouble in the worried well can be separated from the difficulties experienced by patients in early stages of abnormal cognitive decline, such as mild cognitive impairment and the mild dementia in Alzheimer's disease (AD). That is the main theme of this thesis.

1.2 WORD FINDING AND NORMAL AGING

1.2.1 Naturally occurring TOT states

Both physical and mental abilities wax and wane across the life span, so it would seem plausible that word finding could decline with advancing age. A few studies have addressed this question with regard to naturally occurring TOT states. Burke *et al.* (1991) had 130 participants record information about their TOT states in a diary during one month in addition to experimental data obtained in the laboratory. There was no age difference in the *expected* TOT state frequency estimated in advance by participants, indicating that the procedure was not age-biased. Old and mid-age participants recorded significantly more TOT states than young participants. The age difference in TOT state frequency was unrelated to sex, educational level, vocabulary score, and working memory span. More than half of the TOT states concerned proper names of persons and places or titles of books, films, and television shows, with some age-group differences across these word categories. Moreover, old participants gave less partial information (such as first or last letter) about TOT words and came up with fewer alternate words. Most TOT states resolved during the experimental period.

In sum, and leaving aside interpretations pertaining to their "node structure theory", the study of Burke *et al.* (1990) thus confirms that word-finding trouble in everyday life becomes more frequent with age and transforms to some extent – personal names become more difficult and partial information about target words tends to become sparse. It should be added, however, that the number of TOT states in old participants averaged 6.56 in a month, so word-finding problems are not truly abundant in senescence.

1.2.2 Induced TOT states

1.2.2.1 Picture naming (nouns)

Investigators have also administered special tests to examine the effects of age on word finding. Such tests include naming in response to definitions and picture naming. In picture naming, famous persons, animals, inanimate objects or actions are presented pictorially, and subjects must provide an appropriate noun or verb for each item. A number of studies have used the Boston Naming Test, which is also widely utilized in clinical assessment of language function (Kaplan *et al.*, 1983). The standard version consists of 60 line drawings; they show plants, animals, one legendary creature, and miscellaneous inanimate objects. Subjects are to name them correctly and are provided with cues if unable to do so. Semantic cues are given if the depicted item is not recognized to begin with; this would be indicated by a verbal response whose denotatum resembles that of the target word visually but not conceptually, for example,

"snake" for pretzel. Otherwise phonemic cues (first sound of target word) are given to resolve a TOT state. Results may then be evaluated by the number of correctly named items, the amount of facilitation produced by semantic or phonemic cues, or the typological pattern of incorrect responses. The latter would include categories such as superordinates ("bird" for pelican), co-taxonyms ("flamingo" for pelican), or circumlocutions.

The question of whether an effect of aging *per se* on picture naming has been demonstrated is somewhat contentious. This is because performance is not always associated with age (LaBarge *et al*., 1986; Cruice *et al*., 2000; Shafto *et al*., 2007) or more or less complex interactions are obtained between age, education, living environment, and sex (Neils *et al*., 1995; Goulet *et al*., 1994; cf. Feyereisen, 1997). In a number of cross-sectional studies, performance on the Boston Naming Test declined with age, more clearly after age 70 (Nicholas *et al*., 1985; Albert *et al*., 1988). An age-related decline has also been observed in longitudinal follow-up studies (Au *et al.*, 1995; Connor *et al*., 2004), and it does not appear to be confounded by undetected dementia among older participants (MacKay *et al*., 2005).
Although the number of TOT states elicited for nouns by picture naming thus seems to increase with age, the facilitation provided by semantic and phonemic cues does not decrease (Nicholas *et al.*, 1985). However, old subjects tend to produce more off-target responses such as semantically related words, circumlocutions, or neologisms based on nominalization (e.g. "swinger" for pendulum, Albert *et al.,* 1988; Nicholas *et al.,* 1985; Au *et al.,* 1995).

1.2.2.2 Picture naming (verbs)

Other studies have addressed whether the ability to recall action verbs in response to pictures is similarly influenced by aging. Cross-sectional data using the experimental 55-item Action Naming Test indicate an age-related decline in naming actions with verbs that becomes more marked after age 70 (Nicholas *et al.,* 1985). Longitudinal data have supported these findings, with a significant decline for all age groups except the youngest (Ramsay *et al*., 1999). Again, there was an age-related increase in the number of errors, but no decrease in the benefit afforded by cues. The age-related decline in picture naming appears to be of similar magnitude for verbs and nouns when items from each lexical category are carefully matched (MacKay *et al.*, 2002).

The aforementioned studies did not report how fast responses were given for verbs and nouns. When response latency is taken into account, differences have been demonstrated between the two categories as well as a transitivity difference within the verb category. Noun items are thus named faster than verb items, and intransitive verb items are named faster than transitive verb items (Kauschke & von Frankenberg, 2008).

1.2.3 Brain correlates of TOT states

Until recently, the morphological brain correlates, if any, of age-related TOT states were wholly unknown. Shafto *et al.* (2007) used a set of 68 pictures of famous persons to elicit TOT states in 46 healthy adult participants, for which voxel-based

morphometric data had been derived from MRI scans. TOT states were found to be specifically associated with an age-dependent reduction of the left insular cortex, a mesocortical region which is densely interconnected with other brain areas (Augustine, 1996).

According to Shafto *et al.*, the insular-TOT association reinforces the notion "that phonological retrieval deficits underpin TOTs across the lifespan" (p. 2066). This hinges on the conception of the left insula as a motor speech area which, however, was recently challenged by Hillis *et al.* (2004). There is, moreover, no record of an increased frequency of phonological paraphasias or articulatory errors during picture naming in normal aging (see also Vousden & Maylor, 2006, who specifically investigated speech errors across the life span).

1.2.4 Word fluency

Word (verbal) fluency tests may be defined as continuous controlled word association tests (Cramer, 1968). They must thus not be confused with fluent, as opposed to hesitant, "real" speech. Subjects are given a broadly defined theme or set of words to be enumerated as exhaustively as possible in a limited time, usually one minute. The basic performance measure is the number of appropriate words uttered, but the distribution of words across time intervals or relations between the words (e.g. perseverations, size of subcategories) can also be analysed.

Word fluency involves partly different abilities than picture naming and may be considered more demanding than standard naming tests such as the Boston Naming Test. Whereas picture naming calls for more or less precise identification of objects and actions that are presented pictorially, word fluency requires a capacity for ratiocinative imagination, as speakers must bring words to mind in a fruitful way without external cues. This capacity is part of what cognitive neuroscientists call executive function. Persons who are deficient in this ability may thus name pictures with adequate precision and yet produce much fewer words than normal in a fluency task.

Three major types of word fluency tests need to be distinguished. In *letter-based fluency*, subjects enumerate words that begin with a given letter from any lexical category except numerals and, for unclear reasons, proper nouns. Letter-based fluency is also called phonemic, phonological, or lexical fluency. *Semantic fluency*, also named category fluency, targets a thing category, for example, a natural kind category such as animals or fruit, or nominal categories such as clothes or supermarket items. Because only common nouns are concerned, the semantic fluency tests could be designated more specifically as *noun fluency*. There is also a relatively novel *verb fluency* test, which involves the enumeration of things that people do (Piatt *et al.*, 1999b). Verb fluency is also referred to as action fluency. Although verb fluency is as semantic in character as the noun fluency tests, most authors do not label it so, restricting instead the term semantic fluency for tasks involving nouns.

Data on aging and word fluency are equivocal. Ravdin *et al*. (2003) assessed letter-based and noun fluency in 188 participants in ages 60-92. The results indicated a disproportionate decline in noun fluency with age, with a reversal to superior letter-based fluency performance in the oldest old, that is, above 80 years. In contrast, the presence of even mild depressive symptoms was associated with a relatively decreased performance on letter-based fluency. In a study of 165 healthy participants in ages 16-89, age emerged as a negative predictor of noun (animal) fluency (Tallberg *et al.*, 2008). In contrast, neither verb fluency nor letter-based fluency were significantly predicted by age. Similarly, in a study with 1,300 participants, age was found to influence noun fluency more negatively than letter-based fluency (Tombaugh *et al.*, 1999). Henry & Phillips (2006) suggested that the relative insensitivity of letter-based fluency to aging stems from its dependence on crystallized intelligence including vocabulary, which is retained in old age. Accordingly, letter-based fluency is predicted by educational level rather than age (Tombaugh *et al*., 1999; Tallberg *et al*., 2008). Likewise, verb fluency is positively correlated with educational level but not significantly associated with age (Piatt *et al.*, 1999b; Piatt *et al*., 2004; Woods *et al*., 2005b; Tallberg *et al*., 2008).

After this survey of how normal aging affects lexical performance, we may now turn to how abnormal cognitive decline affects speech and language abilities relevant to this thesis.

1.3 DEMENTIA AND SPEECH-LANGUAGE IMPAIRMENT

1.3.1 Historical remarks

Dementia may be defined as the attenuation of cognitive and cogitative powers despite retained intransitive consciousness. The clinical diagnosis of dementia is currently based on criteria in the International Statistical Classification of Diseases and Related Health Problems (ICD-10; World Health Organization, 1992) or the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000). The ICD-10 criteria require evidence for memory decline as well as a decline in other cognitive abilities supported, if feasible, by neuropsychological tests. The decline should have been present for at least six months for a confident diagnosis and delirium must be absent. The degree of memory and other cognitive decline must be enough to interfere with everyday activities. The DSM-IV-TR similarly requires multiple cognitive deficits for the diagnosis of dementia, including memory impairment and at least one of aphasia, apraxia, agnosia, or executive dysfunction. Again, these deficits must cause significant impairment in social or occupational functioning.

The ICD-10 and DSM-IV-TR criteria encapsulate the idea that memory impairment is primary in dementia and other deficits are secondary. This insight is not new. In his "Treatise on insanity and other disorders affecting the mind", the British physician and ethnologist James Cowles Prichard maintained that dementia develops in four stages distinguished by qualitatively different phenomena (Prichard, 1835, pp. 88-89). The first stage is forgetfulness or loss of memory, especially for recent events. The power of reasoning is preserved "within the sphere of distinct recollection," and judgment is still

sound “when the attention can be sufficiently roused” (p. 89). This stage resembles the contemporary concept of mild cognitive impairment. The second stage is irrationality or loss of reasoning powers. In the third stage, incomprehension, afflicted individuals become incapable of understanding the meaning of anything said to them. Finally, in the fourth stage, loss of instinct and volition deprives the individual “even of the animal instincts.” It should be mentioned that Prichard’s sample of dementia included presumed causes such as political excitement and suppression of hemorrhoids besides currently accepted etiologies (Prichard, 1835, p. 88).

A near half-century later, the French psychiatrist Jules Séglas published the monograph “Des troubles du langage chez les aliénés” (Séglas, 1892; reviewed by Kellogg, 1892; Obler & Albert, 1985; Berrios, 1995). It was based on lectures delivered at La Salpêtrière and dealt specifically with speech and language in psychiatric disorders. Séglas classified language disorders in the insane into disorders of speech, writing, and gesture. Speech and writing disorders were considered the result of intellectual disturbances (*dyslogies*), functional disturbances of the powers of expression (*dysphasies*), or disorders of utterance (*dyslalies*) or handwriting, respectively. Dyslogia included various changes in language content, including the release of “reflexive” or automatic speech and echolalia. Gestural disorders were held to be either independent of the mental disorders or resulting from them.

In the same year as the monograph by Séglas, the Austrian neurologist and psychiatrist Arnold Pick published a case report on the relations between aphasia and senile brain atrophy (Pick, 1892). In that article, Pick argued that aphasia syndromes held to arise only from focal brain lesions may in fact develop gradually with “diffuse” brain pathology, that is, senile brain atrophy. To prove his point, Pick described the case of a 71-year-old man who became forgetful and ill-tempered and gradually developed transcortical sensory aphasia, a language disorder characterized by preserved repetition abilities and fluent spontaneous speech but impaired comprehension and defective semantic content. The neuropathological examination showed a distinct atrophy of the left temporal lobe. This and other cases described by Pick were viewed as a “focalized” form of senile dementia, with implications for the relations between neurodegeneration and language abilities.

Pick’s first case has been considered an early example of primary progressive aphasia in current terminology. This is unconvincing, however, as the patient was markedly forgetful and had significant behavioural changes within two years after onset (Mesulam, 2001). Perhaps more noteworthy was the case of alleged “pure word deafness” of Sérieux (1893), the neuropathology of which was comprehensively studied by Dejerine & Sérieux (1897). Reassessment of Sérieux’ report casts doubt on the diagnosis of pure word deafness, indicating instead a semantic dementia, possibly combined with motor neuron disease (cf. Ceccaldi *et al.*, 1996, p. 50). This is consistent with the massive bilateral temporal lobe atrophy and severe neuronal loss in the upper cortical layers corroborated a century later (Mesulam, 2001, p. 426). As further neuropathological data accumulated (Liepmann, 1900; Stransky, 1903; Rosenfeld,

1909; Alzheimer, 1911), the view emerged that the atrophy resulted from a hereditary degenerative disorder (Richter, 1918). Although Altman (1923) drew attention to the systematic corticolaminar atrophy, the term Pick's disease was apparently not established until 1925 (*de ziekte van Pick*, Gans, 1925) and underpinned by pathoanatomical diagnostic criteria the following year (Onari & Spatz, 1926). The latter authors basically defined Pick's disease as circumscribed cerebrocortical atrophy ("umschriebene Großhirnrinden-Atrophie"). Atrophy of the outer cortical layers with regional accentuation, temporal or frontal, in the absence of neurofibrillary tangles was considered the essential feature.

Early students of Pick's disease distinguished between distinct clinical pictures at presentation. Schneider (1929) thus discerned "jocular-silly," akinetic, aphasic, and apraxic-asymbolic forms. Aphasia was investigated in detail by Lüers (1947, 1949). This author studied the gradual dissolution of language in two main forms of Pick's disease, the temporal lobe variant and the frontal lobe variant. The cases were drawn from the series described anatomically by von Bagh (1946). Because Lüers' study anticipated current concepts of language disorders in dementia and is rarely cited, it may be justified to comment on it in some detail.

Lüers basically found that the language disorders in the two forms are quite distinct. In the temporal lobe variant, the disorder starts with anomic aphasia. At this stage, word comprehension is only slightly compromised, whereas the anomia is quite marked. Later in the course, word comprehension deteriorates while repetition abilities are retained. This stage corresponds to a transcortical sensory aphasia. According to Lüers, this condition results from the disconnection of Wernicke's area from surrounding cortices by the atrophic process. She noted that one of the patients acquired a peculiar idiolect, referring to everything pleasant and positive as "all's paid" [*alles gezahlt*], whereas everything unpleasant and negative was referred to as "terribly sick" [*furchtbar kränklich*]. This is the "idiosyncratic word usage" reported later in semantic dementia (Snowden, Neary & Mann, 1996; Neary *et al.*, 1998). Moreover, some of the patients developed press of speech (logorrhea), which Lüers associated with the basal ganglia involvement known to occur in Pick's disease (von Braunmühl, 1930; von Bagh, 1946). A true Wernicke's (cortical sensory) aphasia can develop, but the final stage of language decline is a global (total) aphasia, and patients eventually become mute. Before that, however, fluent speech gradually becomes intermingled with speech automatisms ("stehende Redensarten"; cf. reflex language as a form of dyslogia, Séglas, 1892). They vary from complex combinations of phrases to strings of simple syllables with fixed metric patterns (Leischner, 1951). Lüers considered the severe end-stage aphasia in temporal Pick's disease as resulting either from contingent atrophy of Broca's area or from concomitant right-hemisphere atrophy. She concluded, "It is probably justified to speak of a specifically 'aphasic dementia'" ("Wahrscheinlich ist es berechtigt, von einer spezifischen 'aphasischen Demenz' zu sprechen"). Undoubtedly, then, Lüers' work heralded the current concept of primary progressive aphasia and semantic dementia in particular.

In the frontal variant of Pick's disease, Lüers emphasized phonetic abnormalities such as slow, effortful, monotonous speech and abnormal stress patterns. A peculiar vocal diminuendo occurred during utterances. Phonological paraphasias were rare. Speech was gradually reduced, with shorter and shorter utterances, until mutism ensued. Repetition, automatic speech, naming, and comprehension were relatively spared. One case had echolalia. The clinical picture was apparently that of a transcortical motor aphasia. Speech automatisms or "stehende Redensarten" occurred. The language syndrome was interpreted as reflecting a general apathy ("Antriebsmangel"). She noted, however, that apathy could be restricted to speech production, as one case had speech impairment as the first sign of disease. In the final phase, the profoundly demented patients emitted mostly non-verbal sounds. Lüers' description of the language decline in frontal Pick's disease appears to fit Gustafson's (1987) description of frontal lobe degeneration of the non-Alzheimer type rather than that of progressive nonfluent aphasia (Neary *et al*., 1998), as anomia and phonological paraphasias were played down.

In contrast to the specific and diverse language symptoms in Pick's disease, the aphasia of Alzheimer's disease was described as a form of sensory aphasia occurring as part of a global dementia with disorientation, inattention, agnosia, and apraxia. Word-finding difficulties and impaired reading, writing, and calculation were considered typical; in advanced stages logoclonia occurred, a speech disorder characterized by rapid effortless syllable repetitions (e.g. Sjögren, 1952).

From the late 1970s onwards, interest in dementia research surged. A series of pioneering studies of dementia were carried out at Lund, Sweden, ranging from neuropathology to psychiatry and functional brain imaging. A regional cerebral blood flow study was aimed at investigating the relations between patterns of language impairment and cerebral blood flow patterns in presenile dementia (Gustafson *et al*., 1978). Regardless of the diagnosis – Pick or Alzheimer – predominantly receptive language disturbances were associated with reduced flow in postcentral regions, particularly in the temporoparietal region. Conversely, expressive language disturbances were linked to frontal and anterior temporal flow reductions, whereas certain mixed symptoms (logorrhea, jargonaphasia, and jargonagraphia) were seen in cases with both precentral and postcentral blood flow reduction.

During the 1980s and 1990s, large strides were taken in the understanding of the neuropathology and clinical presentations of dementia. New clinical concepts emerged, including primary progressive aphasia, frontotemporal dementia, and semantic dementia, and sophisticated experimental studies were conducted in the framework of cognitive neuroscience. Alzheimer's disease was brought into public awareness as the most common form of dementia. Because earlier stages of Alzheimer's have become diagnostic targets as part of secondary prevention, the attention has come to focus on the prodrome during which individuals become impaired but are not yet demented, that is, on MCI.

1.3.2 Mild cognitive impairment

As noted previously, the diagnostic criteria for dementia stipulate that impairment should be severe enough to interfere with activities of daily living or cause significant impairment in social or occupational functioning. However, whether such is the case is not always straightforward to determine. Reliable information about performance at work can be hard to obtain, and the interpretation of "significant" impairment may be difficult. It is furthermore clear that the underlying disease, in the case of Alzheimer's and related disorders, usually has a long oligosymptomatic phase with no apparent social or occupational impairment. Sooner or later, however, symptoms become conspicuous, and the impairment may be considered objective; this corresponds to Level 3 or mild cognitive decline of the Global Deterioration Scale (Reisberg *et al*., 1982). In current terminology, this level roughly equals mild cognitive impairment (MCI), a concept invoked to fill the diagnostic gap between benign age-associated forgetfulness and dementia, particularly Alzheimer's disease (AD).

Different definitions of MCI and closely related terms such as CIND ("cognitively impaired, not demented" or "cognitive impairment, no dementia") have been proposed (for review, see Davis & Rockwood, 2004; Winblad *et al.*, 2004; Gauthier *et al.*, 2006; Reisberg *et al.*, 2008). The definitions differ as to whether formal cognitive testing is required for the diagnosis, as to the distributional criterion for impairment (for example, 1.0, 1.5, or 2.0 standard deviation units below the mean), and as to which abilities are to be impaired. MCI may thus include amnestic MCI with isolated memory impairment, multi-domain MCI with memory and additional cognitive impairment, and non-amnestic MCI with intact memory but impairment in some other cognitive ability (Petersen *et al.*, 2001). Other data-driven subdivisions of MCI might emerge depending on the aim and direction of the test battery used, on the nature of the sample, and on the statistical procedures used to arrive at a classification of patients into subgroups. One aim in identifying subdivisions of MCI is to identify patterns that predict different forms of dementia in longitudinal studies (see e.g. Peters *et al.,* 2005).

Impaired declarative memory acquisition is considered the hallmark of MCI (Gauthier *et al.*, 2006). This may be documented by tests of delayed recall such as the Auditory-Verbal Learning Test of Rey (1964). However, there is also evidence for impairments in MCI that go beyond delayed recall. The decrements may be less marked but nevertheless significant. There is thus evidence for hyposmia in MCI (Devanand *et al*., 2000; Wang *et al*., 2002; Peters *et al*., 2003; Eibenstein *et al.*, 2005; Westervelt *et al*., 2007; Djordjevic *et al*., 2008), and impaired odour identification predicts the emergence of MCI in older adults (Wilson *et al.*, 2007). Moreover, MCI appears to be associated with certain language-related decrements, including decreased noun fluency (Hodges *et al.*, 2006; Fernaeus *et al.*, 2008), difficulties in the nominal mass/count domain (Taler & Jarema, 2004), picture naming (Duong *et al.*, 2006), and sentence comprehension (Nordlund *et al*., 2005). Divided attention is also impaired in MCI, suggesting that features of executive dysfunction emerge before the stage of dementia (Belleville *et al.,* 2007). At present, it is not clear what language tasks are suited to

detect MCI, although the language decrements listed above suggest that tests involving both lexical-semantic and executive abilities would be applicable.

1.3.3 Alzheimer's disease

1.3.3.1 Pathoanatomical considerations

AD is the most common cause of dementia (Huang *et al*., 2005). During the 1980s and 1990s, efforts were made to improve the diagnosis of the disease. Braak & Braak (1991) proposed a six-stage scheme for the pathoanatomical evolution of AD based on the topographical distribution of neurofibrillary changes in the cerebral cortex and other brain structures. They are commonly referred to as Braak stages I to VI. In stage I, a moderate number of neurofibrillary changes are found mainly in the transentorhinal region of the anteromedial temporal lobe. Their number increases during stage II but shows little increase outside the transentorhinal region; accordingly, these stages are referred to as transentorhinal stages. During stages III and IV, the neurofibrillary changes accrue within the transentorhinal and entorhinal regions, and the hippocampal formation becomes moderately involved. However, neocortical areas are still largely unaffected. These stages are thus called limbic stages. In stages V and VI, the neocortical association areas become severely involved. They are therefore referred to as isocortical or neocortical stages. Dementia does usually not become manifest before the neocortical stages (but cf. Braak & Braak, 1990).

According to Braak & Braak (1991, p. 256), the transentorhinal stages are likely to represent clinically silent periods of the disease, that is, its preclinical phase. In fact, the changes could even be overlooked on conventional neuropathological examination. The limbic stages, however, were considered potential correlates of clinically incipient AD. This is supported to some extent by neuropathological studies of MCI and related conditions. Morris *et al*. (2001) found that 84 % of cases with questionable or very mild dementia (Clinical Dementia Rating = 0.5) had AD pathology. Of the 15 cases of amnestic MCI studied by Petersen *et al*. (2006), all but the youngest one had some degree of AD pathology. However, seven cases also had argyrophilic grain disease (Braak & Braak, 1987), which appears to be commonly associated with amnestic MCI in older individuals who came to autopsy (Jicha *et al*., 2006b). Individuals who had amnestic MCI and went on to develop dementia had AD pathology in the majority of cases, although argyrophilic grain disease, Lewy body disease, and vascular disease were common in the sample (Jicha *et al*., 2006a).

1.3.3.2 TOT states and picture naming in AD

Early research efforts were aimed at aspects of language and communication in dementia such as naming and discourse (e.g. Bayles & Boone, 1982; Bayles & Tomoeda, 1983; Tomoeda & Bayles, 1993). Little information is available on the subjective frequency of word finding problems in AD. Presumably, most persons with dementia cannot estimate how often they experience TOT states in everyday life owing to their memory deficits. However, experimentally elicited TOT states have been studied in participants with Alzheimer's disease (Astell & Harley, 1996). Participants were given definitions and asked to supply the target word. The subjects with dementia

did experience TOT states in the experiment, but in contrast to controls they could not give any information about the target words. Moreover, the related words given by AD participants were usually semantically but not phonologically related to target words, again in contrast to controls. To Astell & Harley, these findings indicate insufficient activation of lemmas in AD; the lemma is a "level of representation" that links conceptual and phonological structure in the psycholinguistic theory of Levelt (1989).

Impaired naming is now generally considered a prominent deficit in AD, and many authors have investigated aspects of picture naming in the disorder (e.g. Cummings *et al.*, 1985; Shuttleworth & Huber, 1988). Impaired naming is paralleled by a deteriorating ability to adequately define the target words used in picture naming (Hodges *et al.*, 1996). Together with analyses of naming errors (Nicholas *et al.*, 1996), this suggests that semantic memory loss is a major factor behind the naming problems in AD. A recent study demonstrated that lexical variables derived from noun fluency data were associated with grey matter volumes in the mediotemporal limbic system, including the perirhinal and parahippocampal cortices (Venneri *et al*., 2008).

1.3.3.3 Word fluency in AD and related disorders

Objective measures of word finding ability such as word fluency are often used in the clinical assessment of dementia. However, there are a number of word fluency tests, the performance on which is differentially affected by normal aging. Moreover, the different word fluency tests may be more or less sensitive to diverse brain disorders. Letter-based fluency is thus disproportionately or selectively impaired in minor Broca's aphasia (Coslett *et al*., 1991), nonfluent progressive aphasia (Hodges and Patterson, 1996), and cerebellar pathology (Leggio *et al*., 2000). In contrast, noun fluency is not only disproportionately decreased in normal aging but even more so in AD (Henry *et al.,* 2004; Fernaeus *et al*., 2008), semantic dementia (Hodges & Patterson, 1996), Parkinson's disease (Henry and Crawford, 2004), schizophrenia (Henry & Crawford, 2005a; Kremen et al., 2003), and major depression (Fossati *et al*., 2003; but cf. Ravdin *et al*., 2003; Henry & Crawford, 2005b). Another difference is that performance on letter-based fluency, but not noun fluency, is facilitated by low doses of anticholinergic medication (Pompéia *et al.*, 2002). Finally, verb (action) fluency is thought to be particularly sensitive to disorders associated with striatal and perhaps cerebellar loop pathology, including Parkinson's disease (Piatt *et al.,* 1999a; Signorini & Volpato, 2006), HIV-1 infection (Woods *et al.*, 2005), schizophrenia (Woods *et al.*, 2007), and Friedreich's ataxia (De Nobréga *et al.,* 2007). So far, it appears that noun fluency is a better diagnostic predictor than letter-based fluency in AD. So far, however, the three major types of word fluency have not been comprehensively studied in a sample including the whole range of cognitive decline from mild subjective complaints to dementia.

Verb fluency provides an interesting addition to the previously used noun fluency tests, as the self-sustained recall of verbs may be contrasted with fluency tasks targeting various nominal categories. The double dissociation between verb and noun recall in aphasia was reported already in the 18th century (Vico, 1744; Linnaeus, 1745; for

discussion, see Denes & Dalla Barba, 1998, and Östberg, 2003). In modern aphasiology, deficits in recalling and using verbs grammatically have often been linked to frontal lobe lesions, whereas noun deficits (anomia) are usually associated with temporal lobe lesions. Even differential loci within the temporal lobe for nominal categories (persons, animals, tools) have been reported (Damasio *et al*., 1996), as have differential fMRI correlates of verb subcategories (Hauk *et al*., 2004).

1.3.3.4 Word sequence production

Every adult's vocabulary contains automatic word sequences, such as the names of the months, days of the week, seasons, numerals, and letters of the alphabet. By automatic is meant that the sequences are recalled almost without thinking in the normal (forward) direction, whereas reciting them backwards takes considerable effort unless one has rehearsed them in that order as well (Ebbinghaus, 1885/1971, p. 97). Automatic word sequences are often preserved as part of automatic or "non-propositional speech" in persons with aphasia, and may actually interfere with natural speech as speech automatisms (*Reihenreaktion*, Leischner, 1990). Automatic word sequences may thus be assumed to be spared in most forms of dementia (as may singing; Lüers, 1947; Gustafson *et al.*, 1978, p. 111). On the other hand, there is some evidence that automatic speech may be selectively impaired after right frontal lobe or right basal ganglia lesions (Speedie *et al.*, 1993; Ghacibeh & Heilman, 2003). This indicates a double dissociation of automatic and non-automatic speech. Although potentially relevant, the contrast between automatic versus non-automatic word sequence production has not been comprehensively studied in a sample with cognitive decline.

1.3.3.5 Motor speech function

The power of articulation is integral among human linguistic abilities. It depends on several brain structures, including the motor cortex, basal ganglia, and cerebellum, as well as on brain stem nuclei and motor cranial nerves involved in speech. The range of neurodegenerative diseases that cause motor speech disorders is wide, including Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, progressive supranuclear paralysis, multiple system atrophy, corticobasal degeneration, spinocerebellar atrophy, and Creutzfeldt-Jakob's disease (Duffy, 1995). Dysarthria is considered part of subcortical dementia syndromes (Cummings & Benson, 1992), whereas it is generally lacking in cortical dementias such as Alzheimer's disease. However, some patients with "atypical" AD have marked motor speech deficits (Croot *et al.,* 2000), as have patients with progressive nonfluent aphasia (Neary *et al*., 1998). However, motor speech function has rarely if ever been quantitatively evaluated in a memory clinic, so the prevalence of motor speech deficits and their correlates in different forms of primary degenerative dementia are actually unknown.

1.4 AIMS

As outlined above, there is evidence that some word fluency tests may be sensitive indicators of early-stage cognitive decline. However, the three major types of word fluency and their interrelationships have not been studied in a larger sample with cognitive decline. Nor has automatic versus non-automatic word sequence production

been investigated comprehensively in a memory clinic clientele. Likewise, the overall occurrence of motor speech impairment remains unexplored in cognitive decline.

Given this background, the present study was aimed at investigating lexical and articulatory aspects of speech production in the dementia of Alzheimer's disease and related disorders and, as to articulation, frontotemporal lobar degeneration. Specifically, the aims were:

(1) To study the factorial structure of verb, noun, and letter-based fluency and compare the performance on these tests in cognitive decline;

(2) To study the relations between regional cerebral blood flow patterns and verb and noun fluency in cognitive decline;

(3) To study automatic versus non-automatic word sequence production in cognitive decline, as well as the diagnostic predictive power of non-automatic word sequence production;

(4) To provide preliminary data on sequential speech motion rate in Alzheimer's disease, mild cognitive impairment, subjective cognitive impairment, and frontotemporal lobar degeneration.

2 MATERIAL AND METHODS

2.1 SUBJECTS

2.1.1 Diagnostic assessment procedure

The subjects had been assessed for possible dementia at the Memory Clinic of the Department of Geriatrics, Karolinska University Hospital, Huddinge, Sweden. Referrals come from general practitioners, company doctors, and other specialists, for example, psychiatrists, occupational physicians, and neurologists. Patients may also come without referral. The memory clinic has a special commitment to Stockholm County residents under the age of 65.

The medical examination included general physical, neurological, and psychiatric evaluations. The global cognitive level was evaluated with the Mini-Mental State Examination (Folstein *et al*., 1975). Moreover, the level of subjective and objective cognitive impairment was rated on the Global Deterioration Scale (Reisberg *et al.*, 1982). Biochemical and cytological analyses of cerebrospinal fluid obtained by lumbar puncture were performed in addition to blood chemistry tests. Brain structure was examined using magnetic resonance imaging (MRI) or computed tomography (CT). Digital electroencephalography (EEG) and single-photon emission computed tomography (SPECT) were also conducted in many cases.

The subjects underwent a standardized neuropsychological examination. The test battery targeted attention and psychomotor speed, working memory, delayed recall, visuospatial skills, factual knowledge, and reasoning (for a detailed analysis with special reference to the Auditory-Verbal Learning Test of Rey, see Andersson *et al*., 2006). In addition, a neuromotor assessment was conducted by a physical therapist, and skills in activities of daily living were evaluated by an occupational therapist. The speech production data used in this thesis were drawn from speech-language assessments made by the author.

2.1.2 Diagnostic categories and criteria

2.1.2.1 Dementia in Alzheimer's disease

AD diagnoses were based on ICD-10 criteria in Study II-IV. Accordingly, the general criteria for dementia were fulfilled, with evidence for a decline in memory and other cognitive abilities sufficient to interfere with everyday activities. The medical history and assessments did not suggest any other cause of dementia. In Study I, subjects were classified as dementia of the Alzheimer's type (DAT) according to DSM-IV criteria. Neither ICD-10 nor DSM-IV diagnoses were further classified into early and late onset subtypes. The mean age for the category was highest in Study I (see Table 1).

2.1.2.2 Mild cognitive impairment

Mild cognitive impairment (MCI) was diagnosed according to modified Petersen criteria (Wahlund *et al.*, 2003). They require subjective memory complaints and objective signs of decline in any cognitive domain, with objective signs specified as test performance at least 1.5 standard deviation unit below the age-matched mean.

However, activities of daily living must be intact and patients not fulfil the DSM-IV/ICD-10 criteria for dementia. MCI was part all four studies of the present thesis (see Table 1).

2.1.2.3 Subjective cognitive impairment

Subjects in this category fulfilled neither the ICD-10 or DSM-IV criteria for dementia, nor the modified Petersen criteria for mild cognitive impairment delineated above. They were typically rated as Level 2 on the Global Deterioration Scale, corresponding to very mild (age-associated) cognitive decline with no objective evidence of any memory deficit on clinical interview, neuropsychological assessment, or in employment or social situations. Whenever in doubt, occupational impairment was ruled out by interviewing those in charge of the work. By definition, then, subjects in this category had objectively normal cognition. SCI subjects were included in Study I-IV as the objectively normal performance level (see Table 1).

2.1.2.4 Frontotemporal lobar degeneration

These subjects fulfilled the clinical diagnostic criteria for FTLD on an international consensus conference (Neary *et al*., 1998). More specifically, they were classified as frontotemporal dementia (FTD), progressive nonfluent aphasia (PNFA), or semantic dementia (SD). FTLD subjects were included in the sample used for factor analyses of word fluency performance in Study I and in group-level comparisons of articulatory agility in Study IV (see Table 1).

2.1.2.4.1 Frontotemporal dementia

Subjects with FTD had marked changes in comportment and insight. Complaints about insufficient performance and careless or peculiar behaviour were typically made at work or at home. When confronted with such complaints, patients flatly dismissed them or said they did not care. While erratic, forgetful, and inattentive in everyday life as well as in cognitive testing, subjects with FTD did not appear profoundly amnesic. In late stages, spontaneous speech was reduced concomitant with a general apathy. Echolalia and verbal perseverations were often observed. Two cases in this category showed signs of motor neuron disease late in the course and a third case had such signs, including a mild dysarthria, at the time of motor speech assessment in Study IV.

2.1.2.4.2 Progressive nonfluent aphasia

PNFA subjects had non-fluent spontaneous speech, impaired repetition, and anomia. However, the anomia was of the word-production type (Benson, 1979) rather than the semantic type seen in SD. Apraxia of speech was marked in some patients, with irregular articulatory breakdowns, phonetic paraphasias, and stuttering-like iterations. Their speech became unintelligible within a few years. Other patients, however, had sparse spontaneous speech with short but intelligible utterances. Single-word comprehension was preserved in early stages and in no case was prosopagnosia noted. A disproportionate deficit in reading and spelling pseudowords was sometimes observed, consistent with the pattern of phonological alexia and agraphia. One case developed signs of motor neuron disease.

2.1.2.4.3 Semantic dementia

Participants in this group had fluent spontaneous speech with normal articulation and prosody as well as prima facie normal sentence structure. Single-word repetition was preserved, whereas picture naming was severely impaired and not facilitated by prompting; moreover, patients could not reliable select the target word among distractors related in meaning, a pattern consistent with semantic anomia (Benson, 1979). Forced-choice semantic decision tasks typically resulted in chance-level performance and aliénation du mot, that is, lack of word recognition despite adequate repetition abilities. Some SD subjects developed odd idiolects involving overextension or, in one case, syntactic reduplication (Lindström, 1999). Pseudowords were appropriately spelled on dictation whereas real words with atypical orthography tended to be spelled according to a phonetic first-hand guess, a pattern consistent with surface agraphia. Conversely, words with atypical grapheme-phoneme relations were read aloud with regularization errors analogous to those in spelling while pseudowords were read appropriately, a profile matching surface alexia. Naming and recognition of famous faces was poor, indicating prosopagnosia, as was semantic categorization of pictured objects, consistent with associative agnosia. On case developed motor neuron disease several years after the onset of cognitive symptoms.

2.1.2.5 Other diagnoses

26 cases pertaining to other diagnostic categories formed part of the sample on the basis of which explorative factor analyses were conducted in Study I. They were not included in group-level comparisons owing to the small number of cases in each group. The categories included nine cases of anterograde amnesia diagnosed according to the R 41.1 code of the ICD-10, eight cases of unspecified dementia, six cases of vascular dementia, one case of dementia in Parkinson's disease, one case of traumatic aphasia, and one case of unspecified focal brain lesion.

Table 1. Number of subjects and mean age and MMSE score in the major diagnostic categories.

Category	**Study I**			**Study II**			**Study III**			**Study IV**		
	N	Age	MMSE	N	Age	MMSE	N	Age	MMSE	N	Age	MMSE
AD	57	72.0	22.8	33	64.8	23.4	69	66.3	23.5	58	66.0	23.5
MCI	60	66.7	27.1	30	60.5	27.6	99	61.2	27.7	89	61.2	27.6
SCI	40	61.7	28.8	30	56.9	29.3	66	58.0	29.2	60	57.6	29.1
FTLD	16	-	-	-	-	-	-	-	-	29	61.5	-

2.2 METHODS

2.2.1 Word fluency (Study I and II)

Study I involved three different word fluency tests: letter-based fluency, noun fluency, and verb fluency. In Study II, verb and noun fluency data were employed. Scores consisted of the number of appropriate words produced during each one-minute test, divided into six ten-second intervals to yield data on word production across time. The initial letters F, A, and S were used in letter-based fluency. Proper names, numerals, and inflections of previous words were not allowed. The category used for noun fluency was animals, and human activities ("things that people do") was used for verb fluency.

2.2.2 Word sequence production (Study III)

Subjects were instructed to produce the names of the months as quickly as possible in the forward direction. After that, they were instructed to recite the months backward as quickly as possible. The time for each task was taken with a chronograph and errors were noted. Subjects who initially felt that the backward task would be very difficult were encouraged to try their best.

2.2.3 Sequential speech motion rate (Study III and IV)

The "pataka" task was used to measure sequential speech motion rate in Study III and Study IV. It requires rapid alternation between three places of articulation: bilabial for [p], dental or alveolar for [t], and velar for [k]). Subjects were instructed to take a deep breath and repeat the syllable sequence [pataka] as quickly and evenly as possible for ten seconds. This relatively long measurement interval was used to potentially increase the sensitivity of the test. Additional demonstration and preparation were given as needed. Sequential speech motion rate was calculated as the number of correctly repeated syllables per second.

2.2.4 Single-photon emission computed tomography (Study II)

Subjects in Study II underwent a SPECT scan as part of their assessment for possible dementia. The scan was performed at the Department of Radiology, Karolinska University Hospital, Huddinge, usually within four days from verb and noun fluency testing. Subjects were injected with 1000 Mbq Tc-99m hexamethylpropylenamine oxime (Ceretec, Amersham Ltd). Data acquisition started 30 minutes after the injection, using a single-headed rotating gamma camera (Siemens Diacam) in 64 projections, evenly spread through 360°. The total acquisition time was 32 minutes. Tomographic slices were reconstructed using an iterative algorithm (Hosem, Nuclear Diagnostics AB, Sweden) with Chang attenuation correction. The attenuation coefficient was 0.12 cm^{-1}. The data were formatted as a three-dimensional data set with 64 × 64 × 64 cubic voxels with 3.5 mm sides. The resolution in a tomographic slice was 10.2 mm full width at half maximum. The data sets were post-filtered with a Butterworth filter, cutoff 1.0 cm^{-1}.

The BRASS software was used for image registration and quantification (Radau et al., 2001). The relative blood flow in selected brain regions was calculated as cerebellar

ratios (mean count per voxel of region/mean count per voxel of bilateral cerebellar cortex). The information obtained from the scans consisted of measurements of relative blood flow (cerebellar ratios) in 42 brain areas normalized to four cerebellar regions. The blood flow in the left and right lentiform nuclei and left and right anterior cingulate gyri was not reduced in any of the subjects. These four variables were therefore excluded from further analysis.

2.2.5 Statistical analysis

2.2.5.1 Study I

Factor analysis was used to explore the factorial structure of the word fluency data set. The word fluency data was first analysed using principal axis factoring with orthogonal (varimax) rotation, followed by maximum likelihood factoring with oblique (direct oblimin) rotation. Oblique rotation allows factors to be correlated. The maximum likelihood method yields a χ^2 goodness-of-fit test based on residuals. The resulting factor scores were used to compare performance in the three major diagnostic categories (SCI, MCI, DAT) on each word fluency factor. Moreover, multiple analysis of covariance was applied to the raw scores from word fluency intervals 1-6 for each test. Diagnostic category (SCI, MCI, DAT) was included as the independent variable, age and sex as covariates, and type of word fluency test (verb, noun, letter-based) as within-subject factor. Post hoc analyses were conducted using Scheffé's test or the LSD post hoc analysis in repeated measures. The SPSS and Statistica packages for Macintosh were used in the analyses.

2.2.5.2 Study II

Principal axis factoring with varimax rotation was conducted on the SPECT data to reduce the number of variables into a set suitable for multiple regression analysis. Factors with eigenvalues above one were retained following the Kaiser criterion. Verb and noun fluency data were likewise analyzed with principal axis factoring. Multiple regression analyses were conducted with scores from each word fluency factor (noun and verb) as the predicted variables, and SPECT factor scores together with age and education as predictor variables. Multiple analysis of variance (MANOVA) was applied to assess differences in hypoperfusion factor scores between the three diagnostic groups, diagnosis × fluency type interactions, and diagnosis × fluency interval interactions. The Fisher LSD test was used in post hoc analyses. All analyses were conducted using the Statistica package, version 4.1.

2.2.5.3 Study III

Group-level parametric significance testing was conducted with a 3 × 2 MANCOVA followed by Scheffé's post hoc analysis. Prediction of diagnostic category membership was based on binomial logistic regression analyses. Another binomial logistic regression analysis was conducted to assess the impacts of diagnostic category, age, and education on months backward response accuracy. A Kruskal-Wallis ANOVA was performed on the response accuracy data followed by Mann-Whitney U tests for pairwise diagnostic comparisons. The rejection level was set to 0.05 in all analyses. The Statistica package, version 7.1, was used.

2.2.5.4 Study IV

A 3 × 2 ANCOVA with age as a covariate was run to examine the effects of diagnostic category and sex on sequential speech motion rate. Post hoc analysis was conducted with Scheffé's test. Within-group variance was heterogeneous across the three major diagnostic categories, so differences obtained were corroborated with a Kruskal-Wallis ANOVA followed by multiple comparisons. Owing to the unequal group size situation, comparisons with frontotemporal lobar degeneration syndromes were conducted with the nonparametric Mann-Whitney U test. The Statistica package, version 7.1, was used as the computational tool, and the significance level was $\alpha = 0.05$ in all analyses.

3 RESULTS AND DISCUSSION

3.1 STUDY I: THREE TYPES OF WORD FLUENCY IN COGNITIVE DECLINE

This study compared verb, noun, and letter-based fluency performance in a sample with cognitive decline. Our basic approach was to explore the factorial structure of the data set. A principal factor analysis with orthogonal rotation resulted in a three-factor solution, roughly corresponding to the three types of fluency test. However, loadings were shared on the third factor, and the plot of loadings indicated a need for oblique rotation. Using maximum likelihood factoring with oblique rotation, a three-factor solution was arrived at, with factors corresponding approximately to each type of fluency test (see Table 2). Factor loadings ranged from fair to excellent (> 0.71, indicating 50 % overlapping variance). The factor correlation matrix showed that factor correlations were relatively large (letter-based and noun fluency, 0.72; letter-based and verb fluency, 0.61; verb and noun fluency, 0.55) and thus indicative of covariance between factors.

Table 2. Factor loadings based on maximum likelihood factoring with oblique rotation. Loadings > .30 are boldface.

	Factor loadings		
	Factor		
	1	2	3
FAS1	**.643**	.202	-.010
FAS2	**.807**	.032	.055
FAS3	**.778**	.057	.086
FAS4	**.840**	−.074	.051
FAS5	**.929**	−.061	−.023
FAS6	**.756**	.067	.095
VERB1	.052	.298	.046
VERB2	.139	.220	**.436**
VERB3	.212	.279	**.342**
VERB4	.073	.213	**.517**
VERB5	.054	.011	**.659**
VERB6	.097	−.052	**.660**
ANIM1	.223	**.766**	−.250
ANIM2	−.031	**.642**	.139
ANIM3	.021	**.471**	.313
ANIM4	−.084	**.674**	.085
ANIM5	.298	**.388**	.045
ANIM6	.059	**.543**	.003

Differences between the three major diagnostic categories are succinctly summarized on the basis of factor scores estimated for each case; these data were not presented in the

published article. The mean factor scores for SCI, MCI, and DAT are shown in Figure 1. It will be noticed that verb fluency performance was comparatively weak only in MCI, whereas DAT was characterized by a disproportionate noun fluency deficit. Verb fluency dropped distinctly during the later intervals in MCI. These intervals moreover generated the strongest loadings on the verb fluency factor (see Table 2), suggesting that performance during this part of the test is most relevant to MCI in this sample.

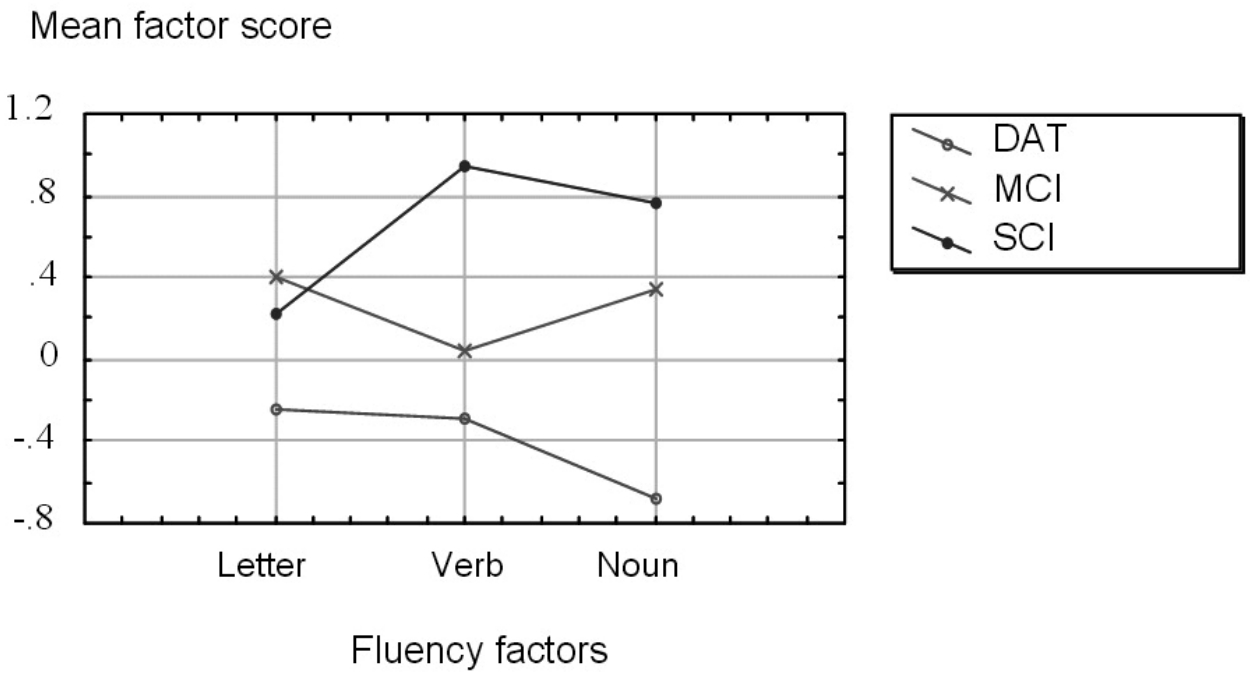

Figure 1. Mean factor scores for DAT, MCI, and SCI for each fluency factor.

Verb fluency deficits have so far been linked to disorders associated with striatal and cerebellar pathophysiology, including idiopathic Parkinson's disease (Piatt *et al*., 1999a; Signorini & Volpato, 2006), HIV-1 infection (Woods *et al*., 2005; Woods *et al.*, 2006), schizophrenia (Woods *et al*., 2007), and Friedreich's ataxia (de Nóbrega *et al.,* 2007). However, the MCI category in this study did not include cases known to have frontal lobe, extrapyramidal, or cerebellar disorders. It may therefore be asked why this group had a relatively weak verb fluency performance. One possibility is that verb and noun fluency depend on partly different brain structures that are also differently affected in MCI and DAT. The amnestic type of MCI is thus generally characterized by medial temporal lobe pathology, whereas the stage of dementia appears to be associated with the spread of pathology beyond this region to the higher cortical association fields (Braak & Braak, 1991; Petersen et al., 2006). However, because of the rich connections of the medial temporal lobe cortices, with an efferent trunk to the frontal region, it is possible that relatively circumscribed mediotemporal pathology might cause subtle impairments similar to those seen in frontostriatal disorders.

3.2 STUDY II: SPECT CORRELATES OF VERB AND NOUN FLUENCY

This study investigated whether verb and noun fluency have different brain correlates in patients with cognitive decline. Principal axis factoring of the SPECT variables resulted in seven hypoperfusion factors with eigenvalues above one. Based on the regions from which they received their substantial loadings, they were labelled Subcortical, Dorsofrontal-Central, Orbitofrontal, Temporal Lobe, Parietotemporal-Occipital, Brainstem, and Superoparietal-Central.

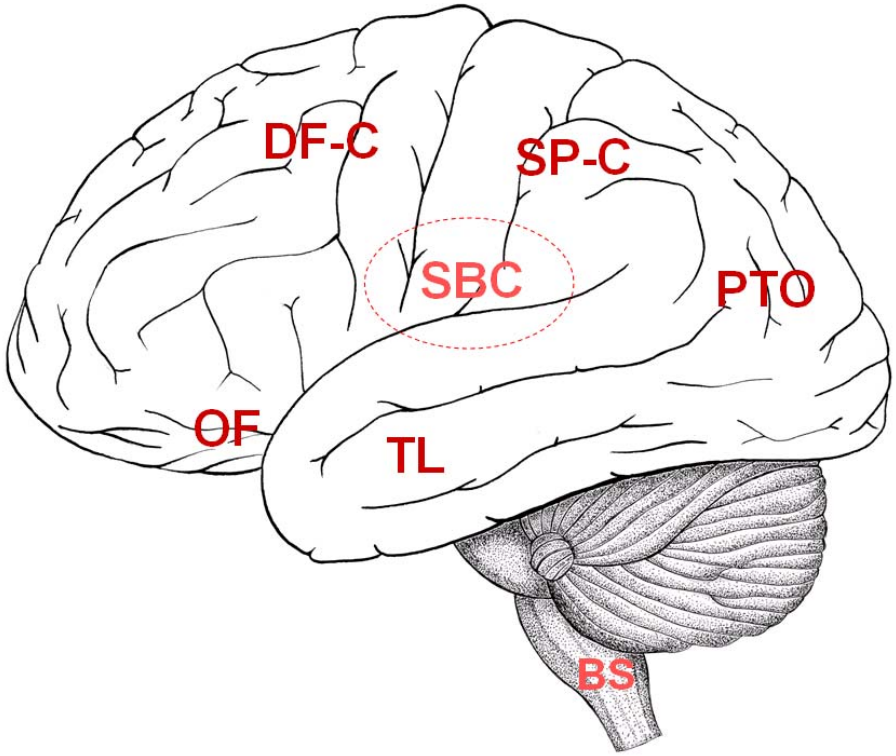

Figure 2. Localization of hypoperfusion factors. BS – brainstem; DF-C – dorsofrontal-central; OF – orbitofrontal; PTO – parietotemporal-occipital; SBC – subcortical; SP-C – superoparietal-central; TL – temporal lobe.

Principal axis factoring performed on the temporally-resolved word fluency data yielded one verb and one noun factor. SPECT factor scores were used as predictor variables in multiple regression analyses together with age and years of education to predict noun and verb fluency performance. Different predictor sets ensued for the two fluency types. Verb fluency was thus significantly predicted by years of education ($\beta = 0.42$, $p < 0.001$) and the Temporal Lobe factor ($\beta = -0.24$, $p < 0.01$), whereas noun fluency was significantly predicted by age ($\beta = -0.44$, $p < 0.001$) and the Parietotemporal-Occipital factor ($\beta = -0.21$, $p < 0.05$). Years of education thus emerged as a positive predictor for verb fluency, and age as a negative predictor for noun fluency. These results agree with those obtained for healthy controls by Tallberg *et al.* (2008). Two SPECT factors had significant beta weights in the negative direction, suggesting that decreased perfusion

parietotemporal-occipital region specifically impairs noun fluency performance, while decreased temporal perfusion specifically impairs verb fluency performance.

3.3 STUDY III: WORD SEQUENCE PRODUCTION IN COGNITIVE DECLINE

This study was concerned with forward versus backward word sequence production and its potential diagnostic relevance. The performance measures were the speech production time and correctness for each test. There were significant differences between all three diagnostic categories in backward speech production time, but not in forward production time (see Figure 3). On average, the MCI category needed twice the time of objectively unimpaired subjects to complete the backward task, and errors were more common. A few subjects with AD were unable to even initiate the backward test, and a majority performed it inaccurately. The average backward production time for AD was strongly increased.

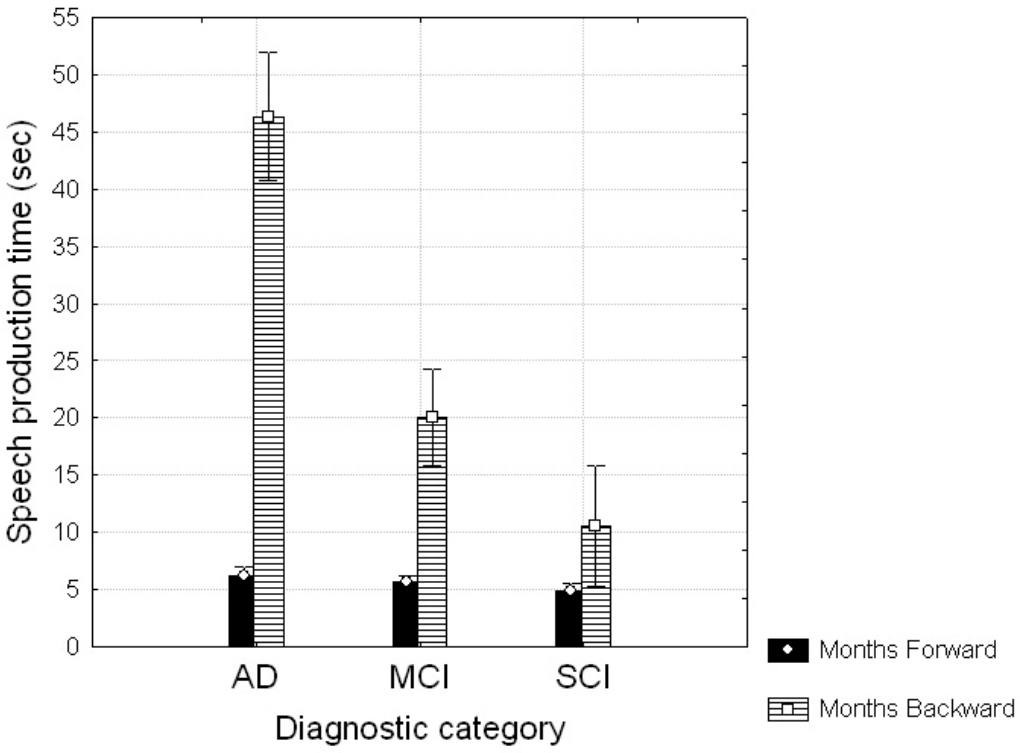

Figure 3. Interaction between diagnosis and direction (forward vs. backward) in word sequence production. Vertical bars denote 0.95 confidence intervals.

Based on these results, the diagnostic predictive power of the Months Backward test was calculated with binomial logistic regression analyses. The predictive power of the widely-used Mini-Mental State Examination (MMSE) was calculated for comparison. The diagnostic sensitivity and specificity was roughly equivalent that of the more time-consuming MMSE, but Months Backward had better specificity in the diagnosis of MCI versus SCI. That being so, Months Backward might prove useful in the detection of

early-stage dementia. The task arguable involves aspects of both declarative memory and executive abilities that are affected in the early stages of cognitive decline.

3.4 STUDY IV: ARTICULATORY AGILITY IN COGNITIVE DECLINE

In addition to the three large categories AD, MCI, and SCI, this study included all speech motor data from cases frontotemporal lobar degeneration syndromes available at the memory clinic (N = 29). Sequential speech motion rate differed significantly among the diagnostic categories (see Figure 4).

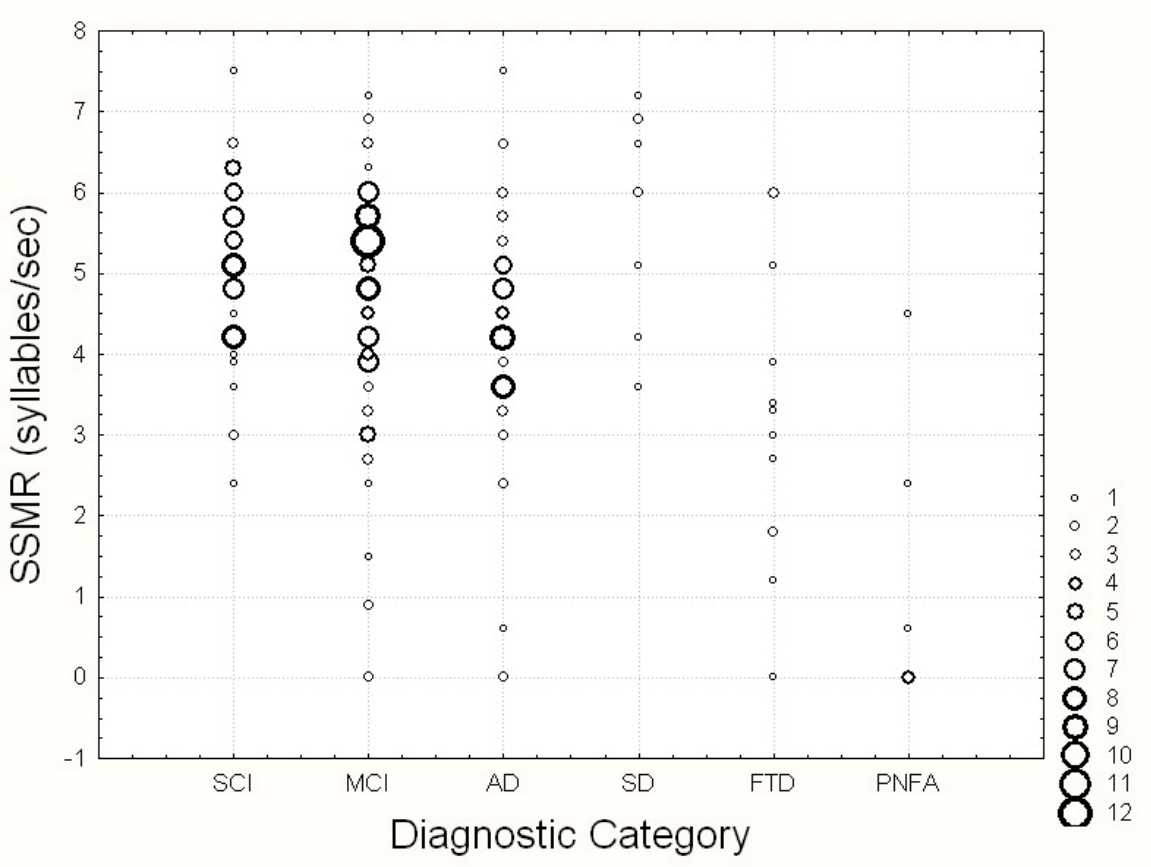

Figure 4. Frequency scatterplot of sequential speech motion rate (SSMR) across diagnostic categories.

MCI participants had a modest reduction in overall rate as compared to SCI, but did not differ significantly from AD. FTD did not differ significantly from AD, but had significantly lower rates than MCI. Patients with SD did not differ significantly from SCI participants, but performed superior to all other groups including MCI. Around 10% of MCI and AD subjects had strikingly low sequential motion rates, with performances at least 2.2 standard deviation units below the mean for SCI. The factors behind this reduction are unknown. One possibility is that subcortical changes impair tracts or basal ganglia structures involved in speech motor structures, resulting in subtle articulatory decrements that show up more markedly during stringent testing. Subcortical white matter changes are common in AD, especially so in carriers of the ε 4 allele of apolipoprotein E (Bronge *et al.*, 1999). Non-specific white matter changes are also seen in MCI, but their clinical significance remains uncertain; at any rate, they have no effect

on the disease progression rate as measured by the MMSE (Bronge & Wahlund, 2003). Another possibility is that early predilection sites of the primary degenerative process interfere subtly with articulatory agility. Among such sites may be mentioned the anterior parahippocampal region, the noradrenergic locus coeruleus complex, and the cholinergic forebrain nuclei. Each may influence motor activity through its connections with other brain structures. The cholinergic nucleus subputaminalis of Ayala is of special interest. It may be specific to *Homo sapiens*, is bilaterally asymmetric (larger on the left), and projects to the posterior part of the inferior frontal gyrus (Šimić *et al*., 1999).

4 GENERAL DISCUSSION

4.1 SPEECH PRODUCTION TASKS

The present thesis was concerned with lexical and articulatory performance in samples drawn from a memory clinic clientele. The lexical tests included word fluency and word sequence production tests. These tests are different in character. Most word fluency tests target large or extremely large word sets (e.g. most words that begin with the letter F). Whereas the basic performance measure in word fluency is the number of appropriate words uttered, additional data can be derived from the output. For example, Pekkala *et al.* (2008) used semantic fluency tasks to elicit different types of perseveration (recurrent, continuous, and stuck-in-set) in subjects with different degrees of AD. In this study, scores were divided into six ten-second intervals following the procedure used by Fernaeus & Almkvist (1998) in their study of letter-based fluency. Word fluency typically follows a sloping curve, indicating that it becomes increasingly difficult to bring new words to mind during the test. In verb fluency, this tendency was accentuated in MCI (Study I). The last intervals of verb fluency also generated the strongest loadings on the verb fluency factor, and a diagnostic comparison based on mean factor scores indicated a relative decrement on verb fluency only in MCI. The apparent verb fluency deficit in MCI is paradoxical for two reasons. First, decreased verb fluency has so far been reported only in disorders thought to be associated with pathology of striatal (and possibly also cerebellar) loop components. Striatal or cerebellar pathology was not a feature of MCI in this sample. Secondly, as noun fluency is considered to be impaired relatively early in AD, one would expect this tendency in MCI too, given that incipient AD pathology is likely to be represented in the MCI group. Our subsequent study based on SPECT data explored whether performance in verb and noun fluency was associated with different patterns of reduced blood flow in the brain. Subjects in this study were somewhat younger than in Study I, perhaps reflecting a tendency for more extensive brain imaging assessment in younger patients. Differential prediction sets emerged for verb and noun fluency, with verbs predicted by temporal hypoperfusion and nouns predicted by parietotemporal-occipital hypoperfusion. According to these results, then, verb fluency decrease was not associated with frontostriatal pathology. Actually, however, studies that have attributed impaired verb fluency to frontostriatal disorders have so far not demonstrated a link between measures of frontal or striatal structures and verb fluency performance. The emergence of temporal lobe hypoperfusion as a significant predictor in a regression model suggests that pathophysiology in this region has at least some influence on verb fluency performance that goes beyond the effect of qualitatively different variables such as years of education, and also differs from the parietotemporal-occipital pathophysiology associated with impaired noun fluency performance. Data derived from structural brain imaging, such as ratings of subcortical white and grey matter changes or cortical volumetry, might disclose other and more detailed correlates of verb fluency in MCI and AD. For letter-based fluency it was shown that performance in the initial interval is specifically impeded by anterior white matter hyperintensities on MRI, in particular in the left frontal or lateral periventricular region (Fernaeus *et al*., 2001). A qualitative difference between initial and later intervals in semantic fluency tests is also likely to exist, in so far as initial production may rely on

associative lexical memory relatively resilient to cognitive decline (e.g. dog – cat), whereas production during later intervals would require an ability for ratiocinative imagination when such associative links have been exhausted (Fernaeus *et al.*, 2008).

It is an old observation that "automatic" language is often retained in aphasia and dementia and may then interfere with spontaneous speech as speech automatisms. Included in automatic speech are word sequences such as the numerals, days of the week, the names of the months, etc. Such sequences are part of every adult's vocabulary and are acquired largely through procedural learning during childhood. In contrast to word fluency tasks, the lexical content targeted in word sequence production is extremely limited. Interestingly, they can be said to typify the compositional character of declarative memory emphasized by Cohen *et al.* (1997): they are acquired and make sense as a complex whole, but the lexical items they consist of are also used individually and flexibly. The compositional quality of declarative memory thus allows one to think through for example the months backwards in retrospection or to use their names individually in discourse as when discussing past and future events. Clearly, however, a sequence such as the months can be very quickly recited in forward direction, whereas recitation in reverse order not only takes time but also requires some mental effort. This aspect of word sequence production becomes intensified in cognitive decline; few MCI and AD patients have any trouble recalling the months quickly, but they have marked to severe difficulties of reverse recall of the same sequence. One source of problems with reverse sequence recall may be that the compositional character of declarative memory becomes impaired in cognitive decline. Impaired individual may thus easily recall the sequence as a totality, but lose the ability to use its constituent items flexibly. A corollary of this interpretation is that AD patients would also have trouble answering questions such as "which is the ninth month of the year." Another source of problems with reverse recall would be difficulties in overcoming strong habitual responses, as with the usual sequential order. This problem would be part of what is referred to executive dysfunction. To be sure, some patients with cognitive decline are also more or less impaired in forward word sequence production, although they are a small minority in the sample studied. This decrement is possibly associated with distinct brain lesion patterns, striatal or cerebellar, and such data could increase the diagnostic value of word sequence production. In patients with more pronounced cognitive dysfunction, such as AD, a more detailed measure of the sequential response in addition to response time may be useful to avoid floor effects in the backward response mode. This might include the number of correct consecutive responses, number of omissions, transpositions, or repetitions, or a measure based on a combination of these variables.

The most basic speech production test in this study was the sequential speech motion rate or "pataka" task used in Study III as a covariate and subjected to detailed analysis with an expanded sample in Study IV. It is frequently used by speech-language pathologists and phoniatricians to assess articulatory agility in patients with dysarthria or apraxia of speech. In this study, a relatively long measurement interval (10 sec) was used. The rationale was that a longer measurement interval would be more demanding and therefore appropriate in a clientele with, usually, no obvious signs of motor speech

impairment. It must be conceded that the single measure employed in this study is very far from an exhaustive assessment of motor speech function. However, because the majority of subjects did not have any apparent motor speech disorders, an entire dysarthria battery would in all likelihood have yielded mostly ceiling results. Also, given the demands for clinical testing in a memory clinic, such a time-consuming battery could not have been performed in a large consecutive series of patients. On the other hand, more information may be derived from the sequential speech motion rate test than was used in this study. Recorded speech samples could be used for detailed acoustic-phonetic measurements. Such data could prove useful in conjunction with for example morphometric brain data or ratings of white matter changes. Given these provisos, the study provided some preliminary data of potential interest. For unknown reasons, sequential speech motion rate was clearly decreased in a subset of the MCI and AD samples, with no overall difference between these two groups. SD had superior rates to all other diagnostic categories and did not differ from objectively unimpaired controls.

4.2 SUBJECTS

As will be noticed in Table 1, subjects in this study were relatively young on average. This raises questions about whether the findings obtained can be generalized to other samples. This is admittedly doubtful for a number of reasons. The memory clinic in which the data were collected is a secondary or tertiary level clinic with a special commitment to relatively young patients in the Stockholm County. There is thus a bias towards young and "difficult" cases. This might affect the etiologies represented in the sample, since the prevalence of some dementias varies with age. FTLD is thus typically a disorder with presenile onset, whereas AD becomes more prevalent in old age. Argyrophilic grain disease is a frequent neuropathological finding, either in isolation or concomitant with other brain pathologies such as AD. Because clinical criteria are lacking at present, it is not widely known among clinicians and absent from clinical case series using standard diagnoses. However, almost half of the MCI cases reported by Petersen *et al*. (2006) had argyrophilic grain disease, and these patients were in their 80s or 90s when they died. Cerebrovascular changes also increase with age. When this study started, vascular dementia was an infrequent diagnosis at the Karolinska memory clinic (4 %; Wahlund *et al.,* 2003). In 2005, the proportion of vascular dementia had dwindled to 2 % (Andersson, 2007, p. 22). Similarly, Lewy body disease was conspicuous by its absence among the subjects in this study. It may be asked whether it was indeed lacking, or whether it was to some extent "hidden" among AD and MCI cases. Only long-term follow-up can give information on the prognosis and definitive diagnoses in the cases studied. What can be done in cross-sectional studies is to link specific signs and symptoms to neurobiological correlates, as was attempted to a limited extent in this thesis (Study II).

Another weakness was the absence of quantitative measures of depression that might have been utilized in multivariate analyses. At most, Cornell scale ratings were available for a third of the subjects in Study III. Such measures would have been of potential importance, as major depression is associated with word-finding difficulties even in patients on antidepressant treatment (Georgieff *et al*., 1998). Neither was there any

systematic check of medications used by the subjects that might have influenced performance on the speech production tests, such as anticholinergic drugs (note that low-dose antimuscarinic treatment may actually facilitate letter-based fluency in normal subjects; Pompéia *et al.*, 2002). At any rate, the AD patients were not on acetylcholine esterase inhibitors, as they as a rule went through their first examination for dementia at the memory clinic.

A limitation of the study was the use of subjects with subjective memory complaints (SCI) as the controls. A counterpoise is that the selection of SCI, MCI and AD as the main experimental groups brings the study closer to clinical reality, where the task is rarely that of comparing healthy asymptomatic individuals with those objectively impaired. Rather, the challenge is to separate benign forgetfulness from subtle but objective clinical signs. The use of SCI as a control group vis-à-vis MCI and mild AD is thus relevant from a clinical perspective. It should be recalled that the SCI group was objectively unimpaired by definition and had passed an extensive standard clinical assessment procedure under the same conditions as MCI and AD participants. This is seldom the case with healthy controls. The SCI category itself deserves further study from various aspects. However, this was considered to go beyond the scope of the present thesis.

Finally, subgroups of FTLD were used in comparison with MCI and AD in the study of articulary agility. Each of the FTLD subgroups was limited in number, reflecting the relatively low prevalence of FTLD even at a specialized memory clinic. Data collection for these groups therefore is a usually a long-term process which could be speeded up somewhat by multi-centre collaboration.

4.3 CONCLUSIONS AND FUTURE DIRECTIONS

- Verb fluency, noun (animal) fluency, and letter-based fluency can be regarded as distinct word production tests although covariant to some extent. In MCI, verb fluency is the most difficult test, with a decline in performance particularly during its later intervals. In AD, noun fluency is disproportionately impaired. Further research is needed to determine the neurobiological correlates of verb fluency performance in different disorders associated with cognitive decline.

- Verb fluency and noun fluency have different predictive sets. Verb fluency is predicted by educational level, whereas noun fluency is not. Conversely, noun fluency is negatively predicted by age, whereas verb fluency is not. In this regard, verb fluency agrees with letter-based fluency according to previous studies. For verb fluency, temporal lobe hypoperfusion was the only SPECT predictor. For noun fluency, parietotemporal-occipital hypoperfusion was the only SPECT predictor. The relation of verb fluency to striatal loop function proposed in recent publications should be addressed by detailed brain imaging studies.

- Forward word sequence production is relatively spared in cognitive decline. Backward word sequence production is clearly impaired in MCI and devastated in AD. Two variables from a backward word sequence production test (correct vs. incorrect and speech production time) have a diagnostic predictive power approximately equal to the MMSE. Subordinate abilities involved in this task, and their neural correlates, should be explored.

- Preliminary data on sequential speech motion rate in cognitive decline indicate that a subset of MCI and AD cases have markedly decreased rates. As a consequence, overall rates are modestly but significantly reduced in MCI and AD. More marked decrements are seen in FTD and in particular in PNFA. SD is set apart by rates superior to the other four categories. Subtle articulatory decrements and their relations to different brain changes remain to be investigated in primary degenerative dementia and related disorders.

5 ACKNOWLEDGEMENTS

This thesis sprang from many years of stimulating work at the memory clinic of the Department of Geriatrics, Karolinska University Hospital. It has been a privilege to participate in its multidisciplinary teams and to meet so many patients, and to perform research at the NVS Department at the Karolinska Institutet.

I am indebted to Professor *Lars-Olof Wahlund*, my main supervisor, in many ways. He was instrumental in my employment and suggested the main theme for this thesis. His wide scope of interests and gentle mentoring have repeatedly proved helpful through the years.

My co-supervisor, Dr. *Christina Hellman*, was my teacher of psycholinguistics and aroused my interest in that field. It definitely paid off when I entered the field of language and dementia. Her ready enthusiasm and backing have been greatly appreciated during the preparation of this thesis.

My co-authors, Dr. *Sven-Erik Fernaeus* and Associate Professor *Nenad Bogdanović*, have been staunch supporters. Their promptness in answering questions and untangling problems is admirable, as is their capacity for lateral thinking. Nenad Bogdanović also generously afforded me the opportunity to attend neuroscientific symposia organized by Fondation Ipsen in Paris in 2004 and 2005. Professor *Åke Hellström*, co-author, kindly devoted his time to discussion and advice on factor analysis and answered questions by e-mail.

At the NVS Department, Professor *Bengt Winblad* must be mentioned for invaluable support. Co-author and fellow PhD student *Raffaella Crinelli* provided, with her indomitable vigour, a shot in the arm during lulls and tendered useful advice in academic matters. *Olof Lindberg*, Associate Professor *Jeffrey Looi*, and *Bram Zandbelt* gave research-related diversion from the thesis through their morphometric studies of frontotemporal lobar degeneration. Dr. *Christin Andersson* made useful suggestions during the preparation of the final draft. *Anette Eidehall*, *Kristina De Sinegube Lund*, and *Inga Volkmann* helped out in administrative matters.

At the Clintec Department of Karolinska Institutet, I would like to thank Professor *Britta Hammarberg*, whose knowledge and commitment to speech-language pathology inspired me already during my basic training, and who has since supported me in many ways. A cornucopia of clinical information and puns, Associate Professor *Per-Åke Lindestad* provided an early impetus towards the neurology of communication. Dr. *Ellika Schalling* discussed aspects of neurogenic communication disorders and gave helpful advice on many occasions. *Ulla Föhrer* and *Barbara Wall* were eminent clinical instructors, who stimulated me to pursue further studies relating to both developmental and acquired language disorders. *Erik Arvidsson* collected word sequence production data in healthy controls as part of his Master's thesis.

Many persons at the Karolinska University Hospital facilitated work with this thesis in different ways. At the Department of Geriatrics, I would like to thank *Sinikka Svensson*, head of department, and Associate Professor *Johan Lökk*, head of the Section for Neurogeriatrics. Dr. *Christian Andersen* assisted at many times during the preparation of this thesis. *Lars Hovell* gave indispensable help in computer matters. I am moreover obliged to the staff of the Memory Clinic, all included, for excellent cooperation through the years.

At the Department of Speech and Language Therapy, I wish to thank *Christina Blom*, head of department, and Dr. *Ing-Mari Tallberg*, section coordinator, for facilitating the progress of my work, and for keeping an open eye on the relevance of clinical research. I am also grateful to Ing-Mari Tallberg for many interesting discussions about language and dementia and for inviting to me to lecture at the courses arranged by her at the Karolinska Institutet.

Barbara Wall, mentioned above, and Associate Professor *Graham Budd* improved my English. My gratitude is furthermore extended to Graham Budd for sharing his lucid erudition and for procuring precious article reprints.

Finally, financial support from The Swedish Alzheimer Foundation, Aina Börjeson's foundation for speech-language pathology research and treatment, and The Gun and Bertil Stohne Foundation is gratefully acknowledged. Study I and II are reprinted by permission from Elsevier, and Study III by permission from Taylor & Francis.

6 REFERENCES

Albert MS, Heller HS & Milberg W. (1988). Changes in naming ability with age. *Psychology of Aging, 3,* 173-178.

Altman E. (1923). Über die umschriebene Gehirnatrophie des späteren Alters. *Zeitschrift für die gesamte Neurologie und Psychiatrie, 83***,** 610-643.

Alzheimer A. (1911). Über eigenartige Krankheitsfälle des späteren Alters. *Zeitschrift für die gesamte Neurologie und Psychiatrie, 4***,** 356-385.

Andersson C, Lindau M, Almkvist O, Engfeldt P, Johansson SE & Jönhagen ME. (2006). Identifying patients at high and low risk of cognitive decline using Rey Auditory Verbal Learning Test among middle-aged memory clinic outpatients. *Dementia and Geriatric Cognitive Disorders, 21,* 251-259.

Andersson C. (2007). *Predictors of cognitive decline in memory clinic patients.* Thesis for doctoral degree. Stockholm: Karolinska Institutet.

Astell AJ & Harley TA. (1996). Tip-of-the-tongue states and lexical access in dementia. *Brain and Language, 54,* 196-215.

Au R, Joung P, Nicholas M, Obler LK, Kass R & Albert ML. (1995). Naming ability across the adult life span. *Aging and Cognition, 2,* 300-311.

Augustine JR. (1996). Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Research, 22,* 229-244.

von Bagh K. (1946). *Klinische und pathologisch-anatomische Studien an 30 Fällen systematischer umschriebener Atrophie der Grosshirnrinde (Pickscher Krankheit).* Annales Academiae Scientiarum Fennicae, Series A. V. Medica – Anthropologica. Helsinki: Suomalaisen Tideakatemia.

Bayles KA & Boone DR. (1982). The potential of language tasks for identifying senile dementia. *Journal of Speech and Hearing Disorders, 47,* 210-217.

Bayles KA & Tomoeda CK. (1983). Confrontation naming impairment in dementia. *Brain and Language, 19,* 98-114.

Belleville S, Chertkow H & Gauthier S. (2007). Working memory and control of attention in persons with Alzheimer's disease and mild cognitive impairment. *Neuropsychology, 21,* 458-469.

Benson DF (1979). *Aphasia, alexia, and agraphia.* New York: Churchill Livingstone.

Berrios G. (1995). Disorders of thought and language in psychiatry: a conceptual history. In: Sims A (ed), *Speech and language disorders in psychiatry*, pp. 15-30. London: Gaskell.

Biedermann B, Ruh N, Nickels L & Coltheart M. (2008). Information retrieval in tip of the tongue states: new data and methodological advances. *Journal of Psycholinguistic Research, 37,* 171-198.

Braak H & Braak E. (1987). Argyrophilic grains: characteristic pathology of cerebral cortex in cases of adult onset dementia without Alzheimer changes. *Neuroscience Letters, 76,* 124-127.

Braak H & Braak E. (1991) Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica, 82,* 239-259.

von Braunmühl A. (1930). Picksche Krankheit. In Bumke O (ed), *Handbuch der Geisteskrankheiten,* vol. 11, part VII, p. 673-715. Berlin: Springer.

Bronge L, Fernaeus SE, Blomberg M, Ingelson M, Lannfelt L, Isberg B & Wahlund LO. (1999). White matter lesions in Alzheimer patients are influenced by apolipoprotein E genotype. *Dementia and Geriatric Cognitive Disorders, 10,* 89-96.

Bronge L & Wahlund LO. (2003). Prognostic significance of white matter changes in a memory clinic population. Psychiatry Research, 122, 199-206.

Brown AS. (1991). The tip of the tongue experience: a review and evaluation. *Psychological Bulletin, 109,* 204-222.

Brown R & McNeill D. (1966). The “tip-of-the tongue”phenomenon. Journal of Verbal *Learning and Verbal Behavior, 5,* 325-337.

Burke DM, MacKay DG, Worthley JS & Wade E. (1991). On the tip of the tongue: what causes word finding failures in young and older adults? *Journal of Memory and Language, 30,* 542-579.

Ceccaldi M, Soubrouillard C, Poncet M & Lecours AR. (1996). A case reported by Sérieux: the first description of a “primary progressive word deafness”? In Code C, Wallesch CW, Joanette Y & Lecours AR (eds), *Classic cases in neuropsychology*, pp. 45-52. Hove: Psychology Press.

Cohen NJ, Poldrack RA & Eichenbaum H. (1997). Memory for items and memory for relations in the procedural/declarative memory framework. *Memory, 5,* 131-178.

Connor LT, Spiro A, Obler LK & Albert ML. (2004). Change in object naming ability during adulthood. *Journal of Gerontology: Psychological Sciences, 59,* 203–209.

Coslett HB, Bowers D, Verfaellie M & Heilman KM. (1991). Frontal verbal amnesia. Phonological amnesia. *Archives of Neurology, 48,* 949-955.

Croot K, Hodges JR, Xuereb J & Patterson K. (2000). Phonological and articulatory impairment in Alzheimer's disease: a case series. *Brain and Language, 75,* 277-309.

Cruice M, Worrall L & Hickson L. (2000). Boston Naming Test results for healthy older Australians: a longitudinal and cross-sectional study. *Aphasiology, 14,* 143-155.

Davis HS & Rockwood K. (2004). Conceptualization of mild cognitive impairment: a review. *International Journal of Geriatric Psychiatry, 19,* 313-319.

Fernaeus SE & Almkvist O. (1998). Word production: dissociation of two retrieval modes of semantic memory across time. *Journal of Clinical and Experimental Neuropsychology, 20,* 137-143.

Cummings JL & Benson DF. (1992). *Dementia: a clinical approach*. 2nd ed. Boston: Butterworths.

Cummings JL, Benson F, Hill MA & Read S. (1985). Aphasia in dementia of the Alzheimer type. *Neurology, 35,* 394-397.

Damasio H, Grabowski TJ, Tranel D, Hichwa RD & Damasio AR. (1996). A neural basis for lexical retrieval. *Nature, 380,* 499–505.

Dejerine J & Sérieux P. (1897). Un cas de surdité verbale pure terminée par aphasie sensorielle, suivi d'autopsie. *Comptes Rendus des Séances de la Societe de Biologie (Paris), 49*, 1074-1077.

Denes G & Dalla Barba G. (1998). G.B. Vico, precursor of cognitive neuropsychology? The first reported case of noun-verb dissociation following brain damage. *Brain and Language, 62,* 29–33.

De Nóbrega E, Nieto A, Barroso J & Montón F. (2007). Differential impairment in semantic, phonemic, and action fluency performance in Friedreich's ataxia: possible evidence of prefrontal dysfunction. *Journal of the International Neuropsychological Society, 13*, 944-952.

Devanand DP, Michaels-Marston KS, Liu X, Pelton GH, Padilla M, Marder K, Bell K, Stern Y & Mayeux R. (2000). Olfactory deficits in patients with mild cognitive impairment predict Alzheimer's disease at follow-up. *American Journal of Psychiatry, 157,* 1399-1405.

Djordjevic J, Jones-Gotman M, De Sousa K & Chertkow H. (2008). Olfaction in patients with mild cognitive impairment and Alzheimer's disease. *Neurobiology of Aging, 29,* 693-706.

Duffy JR. (1995). *Motor speech disorders: substrates, differential diagnosis, and management.* Boston: Mosby.

Duong A, Whitehead V, Hanratty K & Chertkow H. (2006). The nature of lexico-semantic processing deficits in mild cognitive impairment. *Neuropsychologia, 44,* 1928-1935.

Ebbinghaus H. (1885/1971). *Über das Gedächtnis. Untersuchungen zur experimentellen Psychologie.* Darmstadt: Wissenschaftliche Buchgesellschaft.

Eibenstein A, Fioretti AB, Simaskou MN, Sucapane P, Mearelli S, Mina C, Amabile G & Fusetti M. (2005). Olfactory screening test in mild cognitive impairment. *Neurological Sciences, 26,* 156-160.

Fernaeus SE & Almkvist O. (1998). Word production: dissociation of two retrieval modes of semantic memory across time. *Journal of Clinical and Experimental Neuropsychology, 20,* 137-143.

Fernaeus SE, Almkvist O, Bronge L, Östberg P, Hellström Å, Winblad B & Wahlund LO. (2001). White matter lesions impair initiation of FAS flow. *Dementia and Geriatric Cognitive Disorders, 12,* 52-56.

Fernaeus SE, Östberg P, Hellström Å & Wahlund LO. (2008). Cut the coda: early fluency intervals predict diagnoses. *Cortex, 44,* 161-169.

Feyereisen P (1997). A meta-analytic procedure shows an age-related decline in picture naming: comments on Goulet, Ska, and Kahn (1994). *Journal of Speech, Language & Hearing Research, 40,* 1328-1333.

Folstein MF, Folstein SE & McHugh PR. (1975). 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12,* 189-198.

Fossati P, Guillaume, Ergis AM & Allilaire JF. (2003). Qualitative analysis of verbal fluency in depression. *Psychiatry Research, 25,* 17-24.

Fromkin VA. (1973). *Speech errors as linguistic evidence*. The Hague: Mouton.

Gans A. (1925). De ziekten van Pick en van Alzheimer. *Nederlandsch Tijdschrift voor Geneeskunde, 2,* 1953.

James W. (1890). *The principles of psychology.* Vol. 1. New York: Henry Holt.

Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, Belleville S, Brodaty H, Bennett D, Chertkow H, Cummings JL, de Leon M, Feldman H, Ganguli M, Hampel H, Scheltens P, Tierney MC, Whitehouse P & Winblad B; International Psychogeriatric Association Expert Conference on mild cognitive impairment. (2006). Mild cognitive impairment. *Lancet, 367,* 1262-1270.

Georgieff N, Dominey PF, Michel F, Marie-Cardine M & Dalery J. (1998). Anomia in major depressive state. *Psychiatry Research, 77,* 197-208.

Ghacibeh GA & Heilman KM. (2003). Progressive affective aprosodia and prosoplegia. *Neurology, 60,* 1192-1194.

Goulet P, Ska B & Kahn HJ. (1994). Is there a decline in picture naming with advancing age? *Journal of Speech & Hearing Research, 37,* 629-644.

Gustafson L. (1987). Frontal lobe degeneration of non-Alzheimer type. II. Clinical picture and differential diagnosis. *Archives of Gerontology and Geriatrics, 6,* 209-223.

Gustafson L, Hagberg B & Ingvar DH. (1978). Speech disturbances in presenile dementia related to local cerebral blood flow abnormalities in the dominant hemisphere. *Brain and Language, 5,* 103-118.

Hauk O, Johnsrude I & Pulvermüller F. (2004). Somatotopic representation of action words in human motor and premotor cortex. *Neuron, 41,* 301-307.

Henry JD & Crawford JR. (2004). Verbal fluency deficits in Parkinson's disease: a meta-analysis. *Journal of the International Neuropsychological Society, 10,* 608-622.

Henry JD & Crawford JR. (2005a). A meta-analytic review of verbal fluency deficits in schizophrenia relative to other neurocognitive deficits. *Cognitive Neuropsychiatry, 10,* 1-33.

Henry JD & Crawford JR. (2005b). A meta-analytic review of verbal fluency deficits in depression. *Journal of Clinical and Experimental Neuropsychology, 27,* 78-101.

Henry JD, Crawford JR & Phillips LH. (2004). Verbal fluency performance in dementia of the Alzheimer's type: a meta-analysis. *Neuropsychologia, 42,* 1212-1222.

Henry JD & Phillips LH. (2006). Covariates of production and perseveration on tests of phonemic, semantic and alternating fluency in normal aging. *Neuropsychology, Development and Cognition. Section B, Aging, Neuropsychology and Cognition, 13,* 529-551.

Hillis AE, Work M, Barker PB, Jacobs MA, Breese EL & Maurer K. (2004). Re-examining the brain regions crucial for orchestrating speech articulation. *Brain, 127,* 1479-1487.

Hodges JR, Erzinçlioğlu S & Patterson K. (2006). Evolution of cognitive deficits and conversion to dementia in patients with mild cognitive impairment: a very-long-term follow-up study. *Dementia and Geriatric Cognitive Disorders, 21,* 380-391.

Hodges JR & Patterson K. (1996). Nonfluent progressive aphasia and semantic dementia: a comparative neuropsychological study. *Journal of the International Neuropsychological Society, 2,* 511-524.

Hodges JR, Patterson K, Graham N & Dawson K. (1996). Naming and knowing in dementia of Alzheimer's type. *Brain and Language, 54,* 302-325.

Huang J, Meyer JS, Zhang Z, Wei J, Hong X, Wang J, Wen H, Wu W, Wu J & Chowdhury MH. (2005). Progression of mild cognitive impairment to Alzheimer's or vascular dementia versus normative aging among elderly Chinese. *Current Alzheimer Research, 2,* 571-578.

Jicha GA, Parisi JE, Dickson DW, Johnson K, Cha R, Ivnik RJ, Tangalos EG, Boeve BF, Knopman DS, Braak H & Petersen RC. (2006a). Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. *Archives of Neurology, 63,* 674-681.

Jicha GA, Petersen RC, Knopman DS, Boeve BF, Smith GE, Geda YE, Johnson KA, Cha R, Delucia MW, Braak H, Dickson DW & Parisi JE. (2006b). Argyrophilic grain disease in demented subjects presenting initially with amnestic mild cognitive impairment. *Journal of Neuropathology and Experimental Neurology, 65,* 602-609.

Kaplan E, Goodglass H & Weintraub S. (1983). *The Boston Naming Test.* 2nd ed. Philadelphia: Lea & Febiger.

Kauschke C & von Frankenberg J. (2008). The differential influence of lexical parameters on naming latencies in German. A study on noun and verb picture naming. Journal of Psycholinguistic Research (in press).

Kellogg TH. (1892). [Review of:] Des troubles du langage chez les aliénés. *American Journal of Insanity, 49,* 103-105.

Kremen WS, Seidman LJ, Faraone SV & Tsuang MT. (2003). Is there disproportionate impairment in semantic or phonemic fluency in schizophrenia? *Journal of the International Neuropsychological Society, 9,* 79-88.

LaBarge E, Edwards D & Knesevich JW. (1986). Performance of normal elderly on the Boston Naming Test. *Brain and Language, 27,* 380-384.

Laver J. (1994). *Principles of phonetics.* Cambridge: Cambridge University Press.

Leggio MG, Silveri MC, Petrosini L & Molinari M. (2000). Phonological grouping is specifically affected in cerebellar patients: a verbal fluency study. *Journal of Neurology, Neurosurgery, and Psychiatry, 69,* 102-106.

Leischner, A. 1951. Über den Verfall der menschlichen Sprache. *Archiv für Psychiatrie und Zeitschrift Neurologie, 187,* 250-267.

Leischner A. (1990). Die Reihenreaktion bei Aphasikern. *Fortschritte der Neurologie und Psychiatrie, 58,* 252-261.

Levelt WJM. (1989). *Speaking. From intention to articulation*. Cambridge, MA: MIT Press.

Liepmann H. (1900). Ein Fall von Echolalie. *Neurologisches Centralblatt*, *19*, 389-399.

Lindström J. (1999). *Vackert, vackert! Syntaktisk reduplikation i svenskan* [Beautiful, beautiful. Syntactic reduplication in Swedish.] Studier i nordisk filologi 77. Helsinki: Svenska litteratursällskapet i Finland. (Doctoral Dissertation.)

Linnaeus C. (1745). Glömska af alla Substantiva och i synnerhet namn. *Kungliga Svenska Vetenskaps-Akademiens Handlingar, 6,* 116–117.

Lüers T. (1947). Über den Verfall der Sprache bei der Pickschen Krankheit. *Zeitschrift für die gesamte Neurologie und Psychiatrie, 179,* 94-131.

Lüers, T. (1949). Die Atrophie der „Sprachregion". In Urban HJ (ed), *Festschrift zum 70. Geburtstag von Prof. Dr. Otto Pötzl,* p. 325-334. Innsbruck: Universitätsverlag Wagner.

Mackay AI, Connor LT, Albert ML & Obler LK. (2002). Noun and verb retrieval in healthy aging. *Journal of the International Neuropsychological Society, 8,* 764-770.

MacKay A, Connor LT & Storandt M. (2005). Dementia does not explain correlation between age and scores on Boston Naming Test. *Archives of Clinical Neuropsychology, 20,* 129–133.

Mehl MR, Vazire S, Ramírez-Esparza N, Slatcher RB & Pennebaker JW. (2007). Are women really more talkative than men? *Science, 317,* 82.

Mesulam MM. (2001). Primary progressive aphasia. *Neurology*, *49*, 425-432.

Miozzo M & Caramazza A. (1997). Retrieval of lexical-syntactic features in tip-of-the-tongue states. *Journal of Experimental Psychology: Learning, Memory, and Cognition,* 23, 1410-1423.

Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings J & Benson DF. (1998). Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology, 51,* 1546-1554.

Neils J., Baris JM, Carter C, Dell'aira AL, Nordloh SJ, Weiler EM & Weisiger B. (1995). Effects of age, education, and living environment on Boston Naming Test performance. *Journal of Speech & Hearing Research, 38,* 1143-1149.

Nicholas M, Obler L, Albert M & Goodglass H. (1985). Lexical retrieval in healthy aging. *Cortex, 21,* 595-606.

Nicholas M, Obler LK, Au R & Albert ML. (1996). On the nature of naming errors in aging and dementia: a study of semantic relatedness. *Brain and Language, 54,* 184-195.

Nordlund A, Rolstad S, Hellström P, Sjögren M, Hansen S & Wallin A. (2005). The Goteborg MCI study: mild cognitive impairment is a heterogeneous condition. *Journal of Neurology, Neurosurgery, and Psychiatry, 76, 1485*-1490.

Obler LK & Albert ML. (1985). Historical note: Jules Séglas on language in dementia. *Brain and Language, 24,* 314-325.

Oldfield RC. (1963). Individual vocabulary and semantic currency: a preliminary study. *British Journal of Social and Clinical Psychology, 2,* 122-130.

Onari K & Spatz H. (1926). Anatomische Beiträge zur Lehre von der Pickschen umschriebenen Großhirnrinden-Atrophie („Picksche Krankheit"). *Zeitschrift für die gesamte Neurologie und Psychiatrie*, 101, 470-511.

Östberg P. (2003). 18th century cases of noun-verb dissociation: the contribution of Carl Linnaeus. *Brain and Language, 84,* 448-450.

Pekkala S, Albert ML, Spiro A III & Erkinjuntti T. (2008). Perseveration in Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders, 25,* 109-114.

Peters JM, Hummel T, Kratzsch T, Lötsch J, Skarke C & Frölich L. (2003). Olfactory function in mild cognitive impairment and Alzheimer's disease: an investigation using psychophysical and electrophysiological techniques. *American Journal of Psychiatry, 160*, 1995-2002.

Peters KR, Graf P, Hayden S & Feldman H. (2005). Neuropsychological subgroups of cognitively-impaired-not-demented (CIND) individuals: delineation, reliability, and predictive validity. *Journal of Clinical and Experimental Neuropsychology, 27,* 164-188.

Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L & Winblad B. (2001). Current concepts in mild cognitive impairment. *Archives of Neurology, 58,* 1985-1992.

Petersen RC, Parisi JE, Dickson DW, Johnson KA, Knopman DS, Boeve BF, Jicha GA, Ivnik RJ, Smith GE, Tangalos EG, Braak H & Kokmen E. (2006). Neuropathologic features of amnestic mild cognitive impairment. *Archives of Neurology, 63,* 665-672.

Piatt AL, Fields JA, Paolo AM, Koller WC & Tröster AI. (1999a). Lexical, semantic, and action verbal fluency in Parkinson's disease with and without dementia. *Journal of Clinical and Experimental Neuropsychology, 21,* 435-443.

Piatt AL, Fields JA, Paolo AM & Tröster AI. (1999b). Action (verb naming) fluency as an executive function measure: convergent and divergent evidence of validity. *Neuropsychologia, 37,* 1499-1503.

Pick A. (1892). Über die Beziehungen der senilen Hirnatrophie zur Aphasie. *Prager Medicinische Wochenschrift*, *17*, 165-167.

Pompéia S, Rusted JM & Curran HV. (2002). Verbal fluency facilitated by the cholinergic blocker, scopolamine. *Human Psychopharmacology, 17,* 51-59.

Prichard JC. (1835). *A treatise on insanity and other disorders affecting the mind.* London: Sherwood, Gilbert, and Piper.

Ramsay CB, Nicholas M, Au R, Obler LK & Albert ML. (1999). *Applied Neuropsychology, 6,* 57-67.

Ravdin LD, Katzen HL, Agrawal P & Relkin NR. (2003). Letter and semantic fluency in older adults: effects of mild depressive symptoms and age-stratified normative data. *The Clinical Neuropsychologist, 17,* 195-202.

Reisberg B, Ferris SH, Kluger A, Franssen E, Wegiel J & de Leon MJ. (2008). Mild cognitive impairment (MCI): a historical perspective. *International Psychogeriatrics, 20,* 18-31.

Richter H. (1918). Eine besondere Art von Stirnhirnschwund mit Verblödung. *Zeitschrift für die gesamte Neurologie und Psychiatrie*, *38*, 127-160.

Rosenfeld M. (1909). Die partielle Großhirnatrophie. *Journal für Psychologie und Neurologie, 14,* 115-130.

Schneider C. (1929). Weitere Beiträge zur Lehre von der Pickschen Krankheit. *Zeitschrift für die gesamte Neurologie und Psychiatrie*, 120, 340-384.

Séglas J. (1892). *Des troubles du langage chez les aliénés.* Paris: Rueff Editeurs.

Sérieux P. (1893). Sur un cas de surdité verbale pure. *Revue de Médecine, 13,* 733-750.

Shafto MA, Burke DM, Stamatakis E, Tam P & Tyler L. (2007). On the tip-of-the-tongue: neural correlates of increased word-finding failures in normal aging. *Journal of Cognitive Neuroscience, 19,* 2060-2070.

Shuttleworth EC & Huber SJ. (1988). The naming disorder of dementia of Alzheimer type. *Brain and Language, 34,* 222-234.

Signorini M & Volpato C. (2006). Action fluency in Parkinson's disease: a follow-up study. *Movement Disorders, 21,* 467-472.

Šimić G, Mrzljak L, Fučić A, Winblad B, Lovrić H & Kostović I. (1999). Nucleus subputaminalis (Ayala): the still disregarded magnocellular component of the basal forebrain may be human specific and connected with the cortical speech area. *Neuroscience, 89,* 73-89.

Sjögren H. (1952). Clinical analysis of morbus Alzheimer and morbus Pick. *Acta Psychiatrica Scandinavica, 27, Suppl 82,* 67-115.

Snowden JS, Neary D & Mann DMA. (1996). *Fronto-temporal lobar degeneration: fronto-temporal dementia, progressive aphasia, semantic dementia.* New York: Churchill Livingstone.

Speedie LJ, Wertman E, Ta'ir J & Heilman KM. (1993). Disruption of automatic speech following a right basal ganglia lesion. *Neurology, 43,* 1768-1774.

Stransky E. (1903). Zur Lehre von den aphasischen, asymbolischen und katatonen Störungen bei Atrophie des Gehirns. *Monatsschrift für Psychiatrie*, *13***,** 464-486.

Taler V & Jarema G. (2004). Processing of mass/count information in Alzheimer's disease and mild cognitive impairment. *Brain and Language, 90,* 262-275.

Tallberg IM, Ivachova E, Tinghag KJ & Östberg, P. (2008). Swedish norms for word fluency tests: FAS, Animals and Verbs. *Scandinavian Journal of Psychology* (in press).

Tombaugh TN, Kozak J & Rees L. (1999). Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Archives of Clinical Neuropsychology, 14,* 167-177.

Tomoeda CK & Bayles KA. (1993). Longitudinal effects of Alzheimer disease on discourse production. *Alzheimer Disease and Associated Disorders, 7*, 223-236.

Venneri A, McGeown WJ, Hietanen HM, Guerrini C, Ellis AW & Shanks MF. (2008). The anatomical bases of semantic retrieval deficits in early Alzheimer's disease. *Neuropsychologia, 46,* 497-510.

Vico GB. (1744). *Principi di scienza nuova.* Terza impressione. Naples: Stamperia Muziana.

Vigliocco G, Vinson DP, Martin RC & Garrett MF. (1999). Is "count" and "mass" information available when the noun is not? An investigation of tip of the tongue states and anomia. *Journal of Memory and Language, 40,* 534–558.

Vousden JI & Maylor EA. (2006). Speech errors across the lifespan. *Language and Cognitive Processes, 21,* 48-77.

Wahlund LO, Pihlstrand E & Jönhagen ME. (2003). Mild cognitive impairment: Experience from a memory clinic. *Acta Neurologica Scandinavica, 107,* Supplement 179, 21-24.

Wang QS, Tian L, Huang YL, Qin S, He LQ & Zhou JN. (2002). Olfactory identification and apolipoprotein E epsilon 4 allele in mild cognitive impairment. *Brain Research, 951,* 77-81.

Westervelt HJ, Bruce JM, Coon WG & Tremont G. (2007). Odor identification in mild cognitive impairment subtypes. *Journal of Clinical and Experimental Neuropsychology, 8,* 1-6.

Wilson RS, Schneider JA, Arnold SE, Tang Y, Boyle PA & Bennett DA. (2007). Olfactory identification and incidence of mild cognitive impairment in older age. *Archives of General Psychiatry, 64,* 802-808.

Winblad B, Palmer K, Kivipelto M, Jelić V, Fratiglioni L, Wahlund LO, Nordberg A, Bäckman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, de Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van Duijn C, Visser P & Petersen RC. (2004). Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine, 256,* 240-246.

Woods SP, Carey CL, Tröster AI, Grant I & The HNRC Group. (2005a).

Action (verb) generation in HIV-1 infection. *Neuropsychologia, 43*, 1144-1151.

Woods SP, Scott JC, Sires DA, Grant I, Heaton RK, Tröster AI & The HNRC Group. (2005b). Action (verb) fluency: Test-retest reliability, normative standards, and construct validity. *Journal of the International Neuropsychological Society, 11,* 408-415.

Woods SP, Morgan EE, Dawson M, Scott JC, Grant I & The HNRC Group. (2006). Action (verb) fluency predicts dependence in instrumental activities of daily living in persons infected with HIV-1. *Journal of Clinical and Experimental Neuropsychology, 28,* 1030-1042.

Woods SP, Weinborn M, Posada C & O'Grady J. (2007). Preliminary evidence for impaired rapid verb generation in schizophrenia. *Brain and Language, 102,* 46–51.