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LEXICO-SEMANTIC FEATURES IN EARLY STAGE ALZHEIMER'S DISEASE:

Influence of rivastigmine and comparison with elderly controls

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ABSTRACT

Alzheimer's disease is a devastating and disabling disease and will affect more and more people. Cholinesterase-inhibitors try to slow down this process, but its efficacy on language performance has barely been investigated. This study compares the lexico-semantic performances of 20 healthy elderly controls with 20 mild-to-moderate AD-patients on their spontaneous speech (1) and investigates the influence of 6-months rivastigmine intake these performances in AD-patients (2). Normal and AD-participants showed significant differences on Correct Information Units (CIU), Type-Token Ratio, Brunét's index and P-rate, with CIU as best discriminator (85%). After at least six months rivastigmine, AD-patients did not show significant differences.

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PREFACE

"Although my body may still be sputtering along, the day will come when I can no longer write a clear sentence and tell a coherent story. That day will be the actual time of death. The person in me who lives on until natural death occurs is only a shadow left by the deadly laugh of Alzheimer's."

(De Baggio, 2002, p. 117)

This truthful, but emotive quotation unlocks a part of one of the struggles that patients with Alzheimer's disease have to deal with. Different research groups all over the world endeavour to disclose the facts about the neuropathological mechanisms of this disease in order to develop a cause-directed medicine. In the meantime, language researchers do not sit back either and try to find that particular language measure that is able to differentiate early in the disease process and discriminate the patients from healthy older control groups. My working experience with persons dealing with Alzheimer's disease and their remarkable language pattern triggered me to do some research on this subject.

A master's thesis never is the accomplishment of one person only and I would like to take the opportunity to express my feelings of gratitude to some persons in particular. I'll start north and will come down to the south. In Utrecht, I would like to thank prof. Dejonckere for his quick and useful answers concerning all practical issues and prof. H. Quené for his welcome statistical help and lucid explanations on this matter. More to the south, in Rotterdam, I would like to thank Carina Paul for her splendid support in planning and following up on patients' testing and for her amazingly quick and usable e-mail answers. Last, but certainly not least I would like to thank my promotor, prof. dr. Evy Visch-Brink from Rotterdam, who let me be part of the Exelon-study and placed several participants' data at my disposal. Thank you for your well-considered remarks.

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Close to home, I thank my godfather for the help with Excel and my parents for their support, and even closer, I thank my loving and beloved Godfried, my help and haven, my soul mate! Thank you for your deep-rooted belief in my capabilities, for the challenging discussions, for putting things into perspective and for being there for me, even in the depths of the night.

Anne-Sophie Beeckman

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Germany. November 4, 1906. Alois Alzheimer gave a remarkable lecture in which he presented the case of a 51-year old woman, called Auguste D. (Figure 1) (Maurer, Volk & Gerbaldo, 1997). This woman showed a heterogeneous cluster of symptoms: progressive cognitive impairment, focal symptoms, hallucinations, delusions and psychosocial incompetence. Her disease would enter the world under the name 'Alzheimer's disease'.

Nowadays, 24.3 million people are estimated to have dementia, with one new case every seven seconds (Ferri et al., 2006). This amount is expected to double every twenty years. This will mean 42.3 million by 2020 and 81.1 million by 2040. Almost two-third of this population has Alzheimer's disease (O'Brien, 2008; Pariente et al., 2008). The increase rates are not uniform over the world: where developed countries are forecast to increase by 100% between 2001 and 2040, the increase for India, China and their South Asian and Western Pacific neighbours, is thought to increase by more than 300% (Ferri et al., 2006).

To people aged sixty years and older, dementia is one of the main causes of disability at an elder age (Mashta, 2007) and causes 1.2% of years lived with disability. This precedes stroke (9.5%), musculoskeletal disorders (8.9%), cardiovascular disease (5.0%) and all forms of cancer (2.4%) (Ferri et al., 2006).

1 INTRODUCTION

The Diagnostic and Statistical Manual of mental disorders (DSM-IV, 2000) defines dementia as multiple cognitive deficits that include memory and other cognitive deficits (agnosia, aphasia, apraxia or a disturbance in executive functioning), leading to impairment in social and occupational functioning.

Despite the characteristic clinical features of patients diagnosed with Alzheimer's disease, the confirmation of this disease can only be made post-mortem. Anatomopathological examination shows microscopic abnormalities, divided in three principal histopathological features: (1)

collections of intraneuronal cytoskeletal filaments called neurofibrillary tangles; (2) extracellular deposits of an abnormal protein in a matrix called amyloid in so-called senile plaques; and (3) a diffuse loss of neurons (Purves et al., 2004), approximately 32% of the original amount (Taler & Philips, 2007) (Figure 2), leading to neocortical cerebral atrophy. This neuron loss, due to cell dysfunction and cell death in nuclear groups of neurons, is responsible for deficits in the maintenance of specific neurotransmitters: serotonin, norepinephrine and acetylcholine (Cummings, 2004).

However, the link between the presence of neuropathological features and the prevalence of dementia in general and Alzheimer's disease in particular is not as static for all neuropathological features as would one expect. Recent post-mortem research (Savva et al., 2009) on brains of 456 participants with and without dementia shows a stronger association between the pathological features of Alzheimer's' disease and dementia in younger old persons than in older old persons. This is valid for neocortical neuritic plaques, but not for the neocortical cerebral atrophy: this atrophy is able to distinguish the cohort with dementia from those without. So, in older people (think age of 90), normal brains may resemble as Alzheimer's on particular neuropathological features, but it does not mean they do have Alzheimer's disease.

The mentioned neuropathological changes can be observed years before diagnosis and start in the entorhinal cortex, with a progressive extension in other brain areas (Schünke, Schulte, Schumacher, Voll & Wesker, 2007). Before dementia onset, hippocampal atrophy can be detected and progresses subsequently to clinically identifiable dementia (Taler & Philips, 2007).

Specific drugs called cholinesterase inhibitors (CI) are developed to enhance the cholinergic transmission, which is decreased in Alzheimer patients (Pariente et al., 2008). By degrading a specific enzyme, acetylcholinesterase, levels of acetylcholine will be increased. The three cholinesterase inhibitors (CI) are currently recommended as first-line drugs for symptomatic treatment of mild-to-moderate Alzheimer's disease: donepezil (Aricept®), rivastigmine (Exelon®) and galantamine (Reminyl®) (Cummings, 2004; Kaduszkiewicz, Zimmermann, Beck-Bornholdt & van den Bussche, 2005; Seow & Gauthier, 2007; Pariente et al., 2008). The fourth available CI, tacrine (Cognex®), is rarely used because of its hepatotoxic effects (Cummings, 2004).

Pariente et al. (2008) studied the prevalence of treatment in subjects with dementia among European countries in 2004 (Belgium, France, Germany, Italy, the Netherlands, Poland, Portugal, Spain & the United Kingdom). An overview of their results is given in Figure 3.

The efficacy of rivastigmine in 3- to 12-month placebo-controlled randomized clinical trials (RCTs) in mild-to-moderate stages of AD is demonstrated concerning global, cognitive (Kaduszkiewicz et al., 2005; Raina et al., 2008), functional and behavioural outcomes (Seow & Gauthier, 2007; Birks, Grimley Evans, Iakovidou & Tsolaki, 2000).

In a recent study, Calabria, Geroldi, Lussignoli, Sabbatini & Zanetti (2009) investigated the efficacy of rivastigmine and donepezil over a longer period of time in a 21-months follow up study. Functional and cognitive outcomes were evaluated in 427 patients with mild-to-moderate Alzheimer's disease. They found that first-time drug takers had a significant lower cognitive decline then patients who had already taken this type of drug (decline of respectively 1.2 and 3.8 MMSE points).

On the other hand, users of these cholinergic agents may suffer from a broad spectrum of adverse effects, with nausea, vomiting, diarrhoea and weight loss as the most common ones (Kaduszkiewicz et al., 2005). Additionally, the scientific basis to recommend these drugs is unstable. Kaduszkiewicz et al. (2005) assessed the scientific evidence for recommendation of these agents by systematically reviewing all published, double blind randomized clinical trials (RCT) examining efficacy on the basis of clinical outcomes from January 1989 till November 2004. Treatment with one of the CIs needed to be compared with placebo in patients with Alzheimer's disease. Nineteen of the 412 references met their inclusion criteria, augmented with three additional papers (after reviewing the bibliographies of the identified studies and of al available reviews for further studies). The number of original articles per CI was: 12 on donepezil, five on rivastigmine and five on galantamine. Two of these five rivastigmine trials did not show any significant benefit on primary endpoint measures, when the authors corrected for multiple comparisons. Two other studies showed significant dropout rates between placebo and treated group. They conclude that the "scientific basis for recommending donepezil, rivastigmine, or galantamine as preferred treatment for patients with Alzheimer's disease is questionable because minimal benefits were measured on rating scales and the methodological quality of the available trials was poor" (Kaduszkiewicz et al., 2005, p. 325). Moreover, initiating this treatment in severe stages is uncertain (Seow & Gauthier, 2007).

1.1 Language in normal aging

1.1.1 Lexical retrieval and vocabulary

In healthy older adults, word finding failures are rated as the most common, most affected by aging and most annoying problem with expressive language (as summarized in Burke & Shafto (2008)). This typical phenomenon is called tip-of-the-tongue (TOT) state and is defined as the temporary inability to produce a well-known word (Burke & Shafto, 2008). This is caused by the inability to map a well-defined idea or lexical concept to its phonological or orthographic form (Burke & Mackay, 1997) and may be explained by the transmission deficit theory implicating that TOTs happen when "connections between lexical and phonological representations in the language system are too weak to transmit adequate priming for phonological representations to reach threshold" (Burke & Shafto, 2008, p. 400). By activating the lexical presentations, one has the distinct feeling to know the word but the phonological code of the word is unavailable. These word-finding problems mostly affect proper names, general nouns and verbs (Obler & Pekkala, 2008) and are rather explained by phonological retrieval failures than by vocabulary problems, because of the insensitiveness of semantic cues (in favour of phonological cues) (Obler & Pekkala, 2008; Burke & Shafto, 2008).

As recorded in Bowles, Grimm & McArdle (2005), basic vocabulary shows a steeper decline than advanced vocabulary: basic vocabulary peaks at age thirty to decrease afterwards. Vocabulary decline in old age is generally accepted, although the exact decennium is still a discussion point, differing from age 70 (Lindenberger & Baltes, 1997) until age 90 (Singer et al., 2003). The transmission deficit hypothesis (James & MacKay, 2001) could provide some explanations. This model or hypothesis assumes that high frequency words, through their recent and frequent use, acquire a stronger connection in their representations, aiding their retrieval. On the other hand, the connections of low frequency words do not experience this strengthening effect, impairing their retrieval. In very old age, these connections may weaken or lead to eventual loss without reinstatement of low frequency words (Burke & Shafto, 2008).

1.1.2 Language comprehension

Language comprehension problems are not situated at single-word level but chiefly at sentence and text level (Burke & Shafto, 2008; Obler & Pekkala, 2008). Burke & Shafto (2008) describe a possible decline of semantic processing of sentences with climbing age and ascribe this to age-related slowing. From literature review, Burke & Shafto (2008) select a reduced retention of the heard or read sentences or texts and reduced performance on comprehension measures that depend on memory for the text. For text comprehension, older adults show a greater reliance on discourse structures such as situation models (Burke & Shafto, 2008). For Zwaan & Radvansky (1998), a situation model is a multidimensional representation of the topic of the text and includes information about space, time and causal relationships. Of course, working memory plays an important role because if functioning well, it will enhance the comprehension capacities as more information will be held on to. In listening, speeded or slowed language, an unfamiliar accent or complex syntax influences comprehension negatively. In reading texts, high-level inferencing does too (Obler & Pekkala, 2008).

1.1.3 Oral language production (spontaneous speech)

As in language comprehension, problems also are beyond single-word lexical retrieval level (Obler & Pekkala, 2008). Comparing to younger adults (mean age 19 years), older participants (mean age 72 years) present more speech errors, better auto-feedback and a different error pattern with more omissions and less "non-sequential substitution errors" (due to better self-monitoring) (McNamara, Obler, Au, Durso & Albert, 1992). Further, they demonstrate larger vocabulary and a greater Type-Token Ratio (Kemper & Sumner, 2001). Burke & Shafto (2008) summarize recent research on this issue and mention the decline of density of ideas with climbing age and the increase of off-topic verbosity (OTV). Finally, Burke & Mackay (1997) report the increase of pronouns and ambiguous references and more speech dysfluencies caused by more word repetitions and prolonged pauses (both filled and unfilled).

1.1.4 Written language

Older adults remain good at recognising correct spelling but fail at producing correct items (cf. lexical retrieval problems). Reading rates may be minimally slowed down because of perceptual problems (Obler & Pekkala, 2008).

1.2 Language and Alzheimer's disease

In general, language related problems are the second most frequent complaint at the initial visit (15% of AD patients), after memory complaints (73%). Alzheimer's disease may also start with language deficits (Prins, Prins & Visch-Brink, 2003) but according to Overman & Becker (2004), the primary presenting symptom of AD is the profound and progressive loss of memory.

1.2.1 Language symptoms

Very early in the disease course, AD patients often manifest deficits in language processing (Taler & Philips, 2007). Even long before symptoms of AD come apparent, retrospective studies showed the presence of subtle spontaneous language impoverishment (Forbes-McKay & Venneri, 2005).

The most prominent deficit is the word-finding problem or anomia (Appell, Kertesz & Fisman, 1982; Vuorinen, Laine & Rinne, 2000; (Obler & Pekkala, 2008; Balthazar, Cendes & Damasceno, 2008), leading to circumlocutions (Appell et al., 1982; Hier, Hagenlocker & Shindler, 1985; Smith, Chenery & Murdoch, 1989), paraphasias (Appell et al., 1982; Hier et al., 1985; Forbes, Venneri & Shanks, 2002) (semantic rather than phonemic paraphasias) (Appell et al., 1982), use of empty words (indefinite anaphora) (Hier et al., 1985), use of vague super ordinate or generic words instead of words with more precise meanings (Hier et al., 1985), impoverished vocabulary (Appell et al., 1982) and explanatory paraphrases (Hier et al., 1985). However, recent research on semantic error patters on the Boston Naming Test (BNT) in normal aging, amnestic Mild Cognitive Impairment and mild Alzheimer's disease showed similar patterns of spontaneous naming errors and subtypes of semantic errors in the three groups, with decreasing error frequency from coordinate (e.g. 'pear' for 'apple') to superordinate (e.g. 'fruit' for 'apple') to circumlocutory subtypes (e.g. 'a round thing to eat') (Balthazar et al., 2008), suggesting a complex underlying mechanism.

Comprehension declines with the progression of the disease (Hier et al., 1985). According to the pragmatic level, there is "a lack of questions, commands, second-persons pronouns, reference to the speaker as an ego, and loss of terms" (Appell et al., 1982, p. 76).

Phonemic and syntactic processes are relatively preserved in the early phase of AD (Appell et al., 1982; Hier et al., 1985; Blanken, Dittmann, Haas & Wallesch, 1987), though syntax might be less complex (Hier et al., 1985). Comprehension of simple sentences tends to be preserved, in contrast to the comprehension of more complex sentences (Appell et al., 1982).

According to Glosser (1991), patients with Alzheimer's dementia showed impairments on the so-called "macro-level processing" and more specific on thematic coherence measures. Chapman and colleagues (2002) recapitulated the documented discourse disruptions in early AD: reduced embedding of ideas, interrupted flow of information during verbal expression and impaired gist-level processing. Briefly, gist-level processing transforms explicit content to generalized semantic meaning, through cognitive-linguistic processes. So, verbal or visual information is 'upgraded' to a higher, more generalized level of semantic meaning (Chapman et al., 2002). To evaluate gist-level processing, participants were told a story and were asked to summarize it, to give the main idea and to draw its moral.

1.2.2 Structural language assessments

Assessment of language skills can be done in different ways. First of all, there are specific tests, divided by Taler (2007) in standardized versus non-standardized tests. Because of several negative aspects of testing such as e.g. the lack of ecological validity, these structural language assessments are not always favoured. First, standardized and non-standardized language tests will be discussed. Spontaneous speech will be discussed in 1.2.3).

Standardized language tests may be test batteries such as Aachener Aphasie Test (AAT) (Huber, Poeck, Weniger & Willmes, 1983), Boston Diagnostic Aphasia test (BDAE) (Goodglass, Kaplan, Barresi, Weintraub & Segal, 2001), Western Aphasia Battery (WAB) (Kertesz & Raven, 1982) or Comprehensive Aphasia Test (CAT) (Swinburn, Porter & Howard, 2004). These tests were originally designed for diagnostic purposes in aphasia patients. Examples of tests developed for Alzheimer patients are Arizona Battery for Communication Disorders of Dementia (ABCD) (Bayles & Tomoeda, 1993) and Addenbrooke's Cognitive Examination Revised (ACE-R) (Mioshi, Dawson, Mitchell, Arnold & Hodges, 2006).

Next to the test batteries are the more specific tests, concerning naming and semantic, phonological and syntactic processing. Examples of (confrontation) naming tests are the Boston Naming Test (BNT) (Goodglass, Kaplan, Weintraub & Segal, 2001), Graded Naming Test (GNT) (McKenna & Warrington, 1983) and Palpa task 52 (Kay, Lesser & Coltheart, 1992). Verbal fluency (category) and Semantic Association Test (SAT) (Visch-Brink, Stronks & Denes, 2005) are examples of semantic processing. Palpa task 15 and 16 (Kay et al., 1992) and phonemic fluency are examples of phonological tests. Syntactic processing tests are less common, but could comprehend the Token Test or the Test for the Reception of Grammar (TROG) or Verb and Sentence test (VAST) (Bastiaanse, Maas & Rispens, 2000).

Non-standardized language tests could include single-word identification, lexical-semantic processing and sentence and discourse level (receptive level) and production of definitions, spontaneous speech and writing parts for the productive section (productive level).

Linguistic disorders are mostly assessed by structured tasks, but these tests are not sensitive enough to detect subtle changes in communication behaviour, as frequently reported by the families of sufferers (Bucks, Singh, Cuerden & Wilcock, 2000). The usage of spontaneous speech samples could solve this problem.

1.2.3 Spontaneous speech

In aphasia literature, spontaneous speech is used in different ways. Prins and Bastiaanse (2004) make a distinction among: (1) semi-spontaneous speech, as elicited by situational pictures or by role-playing and (2) spontaneous speech in a conversation or dialogue or elicited by an interview with open questions.

1.2.3.1 (Dis)advantages

Using spontaneous speech has many advantages: besides its clinical value (Prins & Bastiaanse, 2004), it is more natural (Orange & Kertesz, 2000), it resembles the natural communication exchange, it is the easiest possible testing procedure that can be applied immediately, it provides information about level & type of language impairment, abstracting from any test design (Rossi, 2007), it might be useful to discriminate mild AD patients from cognitively normal older persons (Visch-Brink et al., 2009), it could reveal more than smaller units of language (Chapman et al., 2002) and it is an ecologically valid method of monitoring change in Alzheimer's disease (Arkin & Mahendra, 2001).

On the other hand, this research domain being relatively unexplored territory (Prins & Bastiaanse, 2004), it requires in-depth knowledge of linguistics (del Toro et al., 2008) and received less attention because of its very time-consuming character (Prins & Bastiaanse, 2004; Visch-Brink et al., 2009) and because of the lack of knowledge about which parameters should be used (Visch-Brink et al., 2009).

1.2.3.2 Spontaneous speech in previous research

Pure, spontaneous speech in AD in order to investigate semantic aspects of language is rarely investigated, because many of the studies investigated semi-spontaneous speech (picture description). Only five studies were found which used spontaneous speech in interview situation.

1. Blanken et al. (1987) compared the performance of patients suffering from moderate senile dementia of the Alzheimer type DAT (n=10), Wernicke's aphasic (n=5) and normal controls (n=5) using a semi-standardized interview. After transcription, following measures were investigated: average sentence length (divided into simple and complex sentences), numbers of words in each class (nouns, verbs, adjectives and adverbs), Type-Token Ratio (TTR, see 2.7.2) and instances of word-finding difficulties. Grammatically, DAT patients produced significantly shorter simple sentences than the elderly controls but there was no reliable evidence for even a mild systematic paragrammatism. Concerning the word classes, DAT participants produced significantly more adverbs and less nouns and verbs than the elderly controls. DAT participants also showed a significant lower lexical richness on nouns and verbs (respectively TTR nouns and TTR verbs). Although DAT participants showed a small higher frequency of word finding difficulties, their performances did not differ significantly from the elderly controls. Analysis of the responding behaviour revealed drastic handicaps on the level of pragmatics of discourse. Only a quantitative description was given and showed, comparing with the Wernicke's patients, that DAT participants used more non-fulfilling responding behaviour (confabulated, non-related and 'I don't know' responses) and the so-called 'other' category (nil-reactions, echolalic and check-backs). The responding behaviour of elderly controls was not mapped.

The difference of recorded speech length for each group and the relative short-length interviews could, according to Bucks et al. (2000), compromise the results. Education level was not taken into account and another shortcoming was the very small sample size of the groups.

2. Sevush, Leve & Brickman (1993) evaluated spontaneous speech (fluency, syntax and paraphasias) of a group of DAT-patients (n=150), next to other language measures (comprehension, repetition, oral reading, writing and naming) and digit call, orientation, praxis and other measures (right-left discrimination, calculation, word fluency and abstract thinking) in order to investigate the influence of disease onset on these performances. Factor analysis of the cognitive scores provided two factors. Factor one consists of spontaneous speech, repetition, comprehension, reading, writing, digit span and left/right discrimination while factor two includes long-term memory, orientation, object naming and abstraction. Regression analysis showed that this first factor was lower in early-onset patients, supporting a greater language decline in DAT patients with an early versus a later disease onset.

3. Romero & Kurz (1996) rated spontaneous speech of 63 mild or moderate DAT patients on six scales from the section on spontaneous speech of the Aachener Aphasie Test (AAT) (Huber et al., 1983) evaluating communication (COMM), articulation and prosodics (ART), automatic speech (AUTOM), semantic structure (SEMAN), phonematic structure (PHONE) and syntactic structure (SYNT). This longitudinal study measured the rate of spontaneous decline in patients with Alzheimer's disease at 1-year follow-up. First of all, at follow-up, spontaneous speech showed to be significantly more impaired for all measures, except for phonematic structure. Secondly, they found that a higher rate of language decline was positively correlated with less severe initial language impairment and the presence of positive family history for Alzheimer's disease. They also investigated the presence of the typical pattern of impairment of spontaneous speech. This 'typical pattern' could be found in "which phonetic impairment is not stronger than impairment of automatic speech, which is not stronger than impairment of semantic structure, which in turn is not stronger than impairment of global communicative ability (COMM ≤ SEMAN ≤ AUTOM ≤ PHONE profile)" (Romero & Kurz, 1996, p. 37). They found this pattern in 86% of their cases at baseline or at follow-up and, this way, found evidence for a "considerable intrafunctional homogeneity of clinical phenotype in AD" (Romero & Kurz, 1996, p. 38). This means that groups of patients may exhibit similar profiles of impairment within the same psychological function (e.g. language or memory). Nevertheless, Bucks et al. (2000) argued that the sensitivity of the measures in this study and in the study of Levush, Leve & Brickman (1993) might be limited by the use of qualitative rating scores.

4. Bucks et al. (2000) compared the spontaneous speech of participants with probable dementia of Alzheimer type (suffering with mild to moderate-severe cognitive impairment) (n=8) and healthy older controls (n=16), using a semi-structured interview (lasted between 20 and 45 minutes), striving to collect at least 1000 words of conversation from each participant. Eight linguistic measures were used: noun rate (N-rate), pronoun rate (P-rate), verb rate (V-rate), adjective rate (A-rate), clause-like semantic unit (CSU) rate (all per 100 words), Type-Token Ratio (TTR), Brunét's Index (W) and Honoré's statistic (R) (See 2.7 for a more detailed description). The most important measures for discriminating between normal and DAT participants were N-rate, P-rate and Brunét's index. They concluded "significant, objectively measurable lexical differences in the spontaneous, conversational speech of individuals with a diagnosis of probable dementia of Alzheimer type and healthy older participants" (Bucks et al., 2000, p. 83). The authors carefully suggest using these measures as a basis for developing new tests of language functions.

5. Visch-Brink et al. (2009) conducted a pilot-study and compared (1) the spontaneous speech of AD patients (n=9) with the spontaneous speech of persons with normal cognition (n=8) and (2) the spontaneous speech of the same group of AD patients before and after treatment with rivastigmine. They found (1) a 100% discrimination between the spontaneous speech of AD patients and healthy volunteers on the linguistic parameters empty words and compound sentences. Only empty words improved (2) after treatment with rivastigmine on AD patients, while the ADAS-cog scores decreases.

At initial visit, language related problems are, with 15%, the second most frequent complaint. These language symptoms could comprehend word-finding problems, leading to circumlocutions, paraphasias, use of empty or vague words, impoverished vocabulary and explanatory paraphrases. Initially, the semantic aspect of language is affected the most with phonemic and syntactic processes relatively preserved in the early phase of Alzheimer dementia (AD) (Appell et al., 1982; Hier et al., 1985; Blanken, Dittmann, Haas & Wallesch, 1987).

To objectify the reported language issues, several tests are at the disposal of the speech and language pathologist (SLT), both standardized e.g. Arizona Battery for Communication Disorders of Dementia (ABCD) (Bayles & Tomoeda, 1993) and non-standardized tests (e.g. test on single-word identification). Although linguistic disorders are mostly assessed by these type of tests, they lack sensitivity to objectify the subtle communication changes as reported by the family. Analysis of spontaneous speech could solve this problem because it is immediately applicable, it is more natural (Orange & Kertesz, 2000) by resembling the natural communication exchange, it could reveal more than smaller units of language (Chapman et al., 2002) and it is an ecologically valid method (Arkin & Mahendra, 2001). Although the advantages of language assessment through spontaneous speech are clear and although early stage Alzheimer patients clearly show abnormalities in spontaneous speech (Visch-Brink et al., 2009), research is scarce. Only five studies were found where, among other things, lexico-semantic aspects of language in DAT participants were investigated. The influence of rivastigmine on spontaneous speech is studied even less. Only Visch-Brink et al. (2009) performed a pilot study to investigate this. With this study, we want to (1) compare the performance on lexico-semantic measures of healthy older controls (HOC) with early stage patients with

Alzheimer's disease (AD) and we want to look for measures that are able to discriminate well between those two groups. Next (2), we want to compare the lexico-semantic performances of patients with Alzheimer's disease before and after at least six months rivastigmine intake.

2 METHODS

2.1 Participants

There were 40 participants: 20 individuals with a diagnosis of probable dementia of Alzheimer type (DAT) and 20 healthy older controls (HO). The **DAT group** (8 males, 12 females) comprised individuals suffering with early stage probable AD as measured by the Mini-Mental State Examination (MMSE: Folstein, Folstein & McHugh, 1975). Dementia diagnosis was based on the DSM-IV criteria (DSM-IV, 2000) and supported by neuropsychological testing. All patients underwent a comprehensive geriatric assessment and were recruited from the Erasmus MC Memory Clinic. Patients with other forms of dementia, previous brain haemorrhage or ischemic infarct, psychiatric disorders, stuttering, developmental language disorders or contra-indications for rivastigmine (e.g. hypersensitivity for one of the active substance, severe AD, severe liver function disorders) were excluded. Half of this group (n=10) started with an oral intake of rivastigmine, the other half used a transdermal patch. The **control group** (8 males, 12 females) consisted of normal cognitive older people without depression, history of cerebrovascular accident, psychiatric disease and memory or language complaints. Both groups were matched with the control group for age, sex and education. They all lived in the same geographical area and were all native Dutch speakers. Table 1 shows the mean age and education level for DAT and control participants, with MMSE and ADAS-cog (Alzheimer's Disease Assesment scale-cognitive subscale) (Rosen, Mohs & Davis, 1984) at time one for DAT participants. ADAS-cog is a psychometric multi-item test battery evaluating selected aspects of attention, memory, orientation, language, reasoning and carrying out instructions. The scores range from 0 (no impairment) to 70 (very severe impairment). A *t* test for independent samples was carried out on the data to look for differences in the distribution of mean age and education and showed no significance at the 5% level for neither age (t_{38}=0.269, p=0.789) nor education (t_{38}=1.752, p=0.088). Concerning ADAS-cog on time 1 and time 2, Wilcoxon signed ranks test showed that DAT participants did not score significantly different (Z=-0.223, p=0.824).

2.2 Design

Design 1: control group versus AD

The first design wants to compare the performance of healthy controls and Alzheimer's patients on lexical-semantic measures. The null hypothesis (H_0) claims that there is no difference between controls and Alzheimer's patients on these measures. According to the alternative hypothesis (H_a), these two groups do differ. The independent variable is the presence of Alzheimer's disease or not. The semantic measures are dependent between-subject variables.

Design 2: Alzheimer's patients before and after rivastigmine

The second design compares the performance of Alzheimer patients before (time 1) and minimal six months after (time 2) rivastigmine intake. Time is the independent variable. The semantic measures (See 2.7) are independent variables. The average time between time 1 and 2 was 8.3 months (SD: 3.4, range: 6-15).

2.3 Power

Design 1

Research by Bucks et al. (2000) revealed that healthy individuals produced a mean Type-Token Ratio of 0.32 and standard deviation 0.02, while for DAT patients these values are 0.26 and 0.04, respectively. According to Lenth (2006), with 20 healthy individuals and 20 DAT patients and the significance level of 2.5% (Bonferroni correction), the power equals 1.

Design 2

According to (Bucks et al., 2000), DAT patients produced a mean Type-Token Ratio of 0.26 with a standard deviation of 0.04. To become half as good as the healthy individuals, they should obtain a difference of 0.03 on the mean (with SD of 0.04), which equals an effect size of 0.75. This gives an acceptable power of 0.75 (Lenth, 2006).

2.4 Recruitment and participation's agreement

These patients are part of a current study on the influence of rivastigmine on spontaneous speech of patients with Alzheimer's disease, from the project group leaded by Evy Visch-Brink, Carina Paul and Tischa van der Cammen. All the patients were recruited from Erasmus MC Memory Clinic. Participants or their main representatives signed a written informed consent.

2.5 Speech sample

Participant and examiner would typically sit in front of each other in a quiet setting. The participants were tested individually in a quiet room. Spontaneous speech was elicited by means of a semi-structured interview with the spontaneous speech section of Aachener Aphasie Test (AAT) (Huber et al., 1983). The interviewer did not correct the responses and no stimulus or interruption was provided unless the participant was clearly becoming distressed by his/her inability to respond. Clear interview guidelines were followed. Questions were asked slowly and repeated or reworded as necessary. Emotional topics such as death of loved ones were avoided as much as possible e.g. by switching to a new question. Interviews were recorded with a tape recorder and a small microphone.

2.6 Transcription

The responses of test persons and participants were audio-recorded and transcribed verbatim or orthographically, including repetitions, incomplete words, interjections, paraphasias and mispronunciations. Both the questions and the comments of the examiner, as well as the answers of the participants, were transcribed, with a new paragraph denoting every conversational turn. The first fifty words were not counted. The next three hundred words were analyzed according to a protocol with fixed parameters. Three hundred words are considered to be reliable for linguistic analysis (Prins & Bastiaanse, 2004). Furthermore, with fixed number, absolute numbers can be used instead of percentages. Afterwards, semantic measures were counted. The following words were not counted: 'yes', 'no' and 'ehm'. To be accepted as a correct word, at least fifty percent of the target word needed to be pronounced.

2.7 Linguistic measures

Vocabulary diversity measures are common in linguistic research. They are used in linguistic studies including child language development, language impairment, foreign and second language learning, the development of literacy, authorship studies, forensic linguistics, stylistics, studies of schizophrenia and many other areas (McKee, Malvern & Richards, 2000). As mentioned earlier (cf. supra), the effects of AD on spontaneous speech and Alzheimer's disease has received little attention to in earlier research. Therefore, in this research, semantic measures may be based on e.g. aphasia research too.

2.7.1 Word classes (per 100 words)

A first approach, described in Bucks et al. (2000) is the analysis of spontaneous speech according to word classes. In this approach, only nouns, pronouns and adjectives are counted. Nouns and adjectives are considered as open classes (quasi unlimited possibilities) and pronouns as closed classes (limited number of possibilities).

First of all, the noun rate (N-rate) tells more about the ability to use nouns, which is an important issue in AD patients because they commonly experience word-finding difficulties. It would be sensitive to monitor word-finding difficulties (Bucks et al., 2000). Secondly, the pronoun rate (P-rate) contrasts well with the N-rate and quantifies the use of indirect referencing (Bucks et al., 2000). And finally, the adjective rate (A-rate) seemed to be important to characterize the colour or quality of the speaker (Bucks et al., 2000). The reference works Smedts & Van Belle (2003) and Coppen, Haeseryn & de Vriend (2007) provide a detailed description on the classification. In case of conflict between the applicable documents, EV decides.

2.7.2 Measures of richness of vocabulary/lexical richness

1. Type-token ratio (TTR)

According to Gordon (2008), Type-Token Ratios (TTR) are the second commonly used semantic measures to analyze the informational value of single words. It is used in all types of linguistic research: from schizophrenia research (He, 2006), over bilingual research (Daller, van Hout & Treffers-Daller, 2003) to Alzheimer's disease (Bucks et al., 2000). This simple measure of vocabulary size is measured as the ratio of the type (a lemma) to the tokens (total different forms of lemmas) (Boxum & Zwaga, 2007):

$$TTR = \frac{type}{token}$$

where higher values are associated with a broader vocabulary. This measure is generally found to correlate positively with the length of text sampled (Bucks et al., 2000; Thomas, Keselj, Cercone, Rockwood & Asp, 2005). However, this lexical measure is disadvantaged by its sensitivity to text length (McKee et al., 2000; Daller, van Hout & Treffers-Daller, 2003). Samples with a larger token number will have a lower TTR value and vice versa (McKee et al., 2000). Because our samples have a fixed number of words, the length problem will be avoided.

2. Brunét's index (W)

Brunét's index also quantifies lexical richness, but without being sensitive to text length (Brunét, 1978). It is calculated as:

$$W = N^{V^{(-.165)}}$$

with N being the total text length and V representing the total vocabulary used by the participant. This measure generally varies between 10 and 20 (Singh, 2001). The lower the value, the more elaborate the speech.

3. Honoré's statistic (R)

Honoré's Statistic (Honoré, 1979) is also insensitive to length and is calculated as:

$$R = \frac{100 \log N}{1 - \frac{V_1}{V}}$$

where V_1 is the number of words in the vocabulary spoken once (hapax legomona), V the total vocabulary used and N the total text length. Higher values of R indicate a richer vocabulary (Honoré, 1979). V_1 and V have shown to be linearly associated. Honoré's statistic generates a lexical richness measure that establishes the number of words used only once by the participant as a proportion of the total number of words used (Bucks et al., 2000). In most cases, values lie between 1000 and 2000 (Singh, 2001).

Singh (1997, p. 831) had chosen these previous measures "from a large number of linguistic features after careful experimentation".

2.7.3 Anomia index

According to Wepman, Bock, Jones & van Pelt (1956), anomia leads to an increased usage of pronouns, at the expense of nouns. They defined the anomia index as the ratio

$$1 - \left(\frac{nouns}{nouns + pronouns} \right).$$

A larger anomia index will indicate an increasing anomia degree (Hier et al., 1985).

2.7.4 Correct Information Unit (CIU) analysis

Nicholas & Brookshire (1993) were the first to publish a standardized rule-based system for quantifying the informativeness of connected speech, called Correct Information Unit (CIU) analysis. Accurate, relevant and informative words (both content and function words), regardless the grammatical form, are defined as CIUs. Therefore, CIUs are scored per word.

Adults without brain damage (n=20) and aphasic patients (n=20) were given a variety of ten stimuli and connected speech was analysed by using CIU. The calculated measures (words per minute, percent CIUs and CIUs per minute) appeared to be more sensible to distinguish between aphasic and non-brain-damaged speakers than the counted measures (number of words and number of CIUs). Given the high interjudge reliability and the session-to-session stability of performance, this analysis became one of the most commonly used measures of the informativeness of single words (Gordon, 2008). In aphasic patients, CIU were found to reflect aphasia severity in connected speech (Gordon, 2008).

Until today, no publications were found where this measure was used in Alzheimer patients. Rules for scoring and counting words and correct information units will be followed as pointed out in Appendix B in Nicholas & Brookshire (1993).

2.8 Statistical analysis

The data will be analysed on a personal computer using the Statistical Package for Social Science for Mac (SPSS version 16.0) software.

Design 1

In order to discriminate between healthy and AD patients, a discriminant analysis was carried out. This examines the predictive power of the measures (Bucks et al., 2000): it determines whether groups differ regarding the mean of a variable and then use that variable to predict group membership of e.g. new cases ("Discriminant function analysis," 2008). Correlations of participants' characteristics with lexico-semantic measures were investigated with Pearson's correlation coefficients. Differences on performances between healthy older participants and Alzheimer participants were tested with independent samples *t* tests.

Design 2

Paired (two-tailed) *t* tests were applied to search for differences between the performances of Alzheimer patients at time 1 (before rivastigmine intake) and time 2 (after at least 6 months of rivastigmine intake). For all statistical tests, an alpha of 0.05 was selected.

3 RESULTS

3.1 Normal participants versus DAT participants

3.1.1 Correlations among variables

First of all, the correlation of participants' characteristics to lexico-semantic measures i.e. performance was investigated (See Table 2). For **healthy older participants**, age did not correlate significantly with any of the linguistic measures. Highest education level at the other hand did for hapax legomena, Brunét's index & anomia index. A correlation value *r* between 0.50 to 0.80 (absolute values) suggests a moderate correlation. *R*-values between -0.50 and 0.50 are considered to indicate a weak relationship (Devore & Peck, 2001). In this case, there is a tendency that a higher education level will lead to a lower anomia-index ($p<0.01$) and P-rate ($p<0.05$). Other correlations are lower and are showing a weak relationship. For **DAT participants**, age and MMSE score did not correlate significantly with any of the linguistic measures. ADAS-cog score however did for total vocabulary, TTR, Brunét's index, A-rate, N-rate, P-rate and anomia index. Education level only correlated significantly for A-rate ($p<0.05$). Despite the significance, only A-rate showed a quite high coefficient (0.69) and may suggest that a higher education level provides the use of more adjectives. Other correlation values were smaller than the absolute value of 0.50 and are considered to express a weak relationship (Devore & Peck, 2001).

3.1.2 Descriptive statistics and *t* test for independent samples

Means, standard deviations, minima and maxima of the used linguistic measures are shown in Table 3. A *t* test for independent samples was carried out on the data and showed significant differences at the 1% level for CIU and at 5% level for V, TTR, Brunét's W and P-rate. Showing higher lexical richness (higher TTR and lower Brunét's W), more CIUs and a lower P-rate for normal participants. The other linguistic measures showed differences (with worse performances for AD participants), albeit not significant.

3.1.3 Discriminant analysis

In order to identify which variables discriminate the best between the two groups and how well they predict participant group membership, discriminant analysis was carried out (Sharma, 1996).

Univariate ANOVA for each independent variable showed significant differences for the two groups concerning the TTR, Brunét's index, pronoun-rate and CIU. All p-values were lower than 0.05 and for CIU the p-value was even below 0.001. Comparing to the Alzheimer participants, normal participants score higher on TTR and CIU and lower on Brunét's index and Pronoun-rate.

Box's test of equality showed that the covariance matrices of the two groups did not differ significantly ($p=0.982$, F approx$=0.001$, $df_1=1$, $df_2=4332$). Almost 59% ($eigenvalue^2=0.766^2=0.587$) of the variation between these two groups can be explained by the discriminant function. This is quite good.

Stepwise statistics ($p_{in}=0.05$, $p_{out}=0.10$) resulted in a discriminant function equal to CIU. If only CIU was used as discriminating variable, 85% of the respondents could be classified in the right group (controls or the AD patients) (Wilks' lambda: 0.566, chi-square: 21.321, df=1, $p<0.001$). For the remaining 15% that was not correctly classified, noun-rate was the best parameter to discriminate, but its contribution will be small anyway because of low remaining percentage.

When CIU was removed from the discriminant analysis, the best discriminator between the two groups on spontaneous speech was TTR with a 70% discrimination (Wilks' lambda: 0.872, chi-square: 5.117, df=1, $p=0.024$), but with a clearly less significant p-value.

Thus, given the data, we can conclude that CIU scores clearly distinct between control and AD patients. Moreover, CIU seems to have a high discriminating power such that other indicators become unnecessary.

3.2 Influence of rivastigmine on spontaneous speech in DAT participants

The overview of means, standard deviations, minima and maxima for each of the used linguistic measures with the Alzheimer participants at time 1 (before rivastigmine intake) and time 2 (after at least 6 months of rivastigmine intake) did not show large differences (See Table 4). A paired-samples *t* test was performed for each linguistic measure in order to determine if patients' performance changed significantly from time 1 to time 2. As expected from looking at the describing values, none of the linguistic measures showed significant differences at the 5% level (See Table 4). So, none of the linguistic measures changed significantly, in positive or negative way, after at least six months of rivastigmine intake. There was also no difference in performance on the ADAS-cog scores (t_{19}=0.443, p=0.663 (two-tailed)).

Searching for answers, we took a closer look on our populations. We investigated the influence of gender on the performances of our participants at time one and time two and found no significant difference on time one for gender. On time two, gender influenced the participants' performances: women scored significantly lower than men, with lower scores for female DAT participants for hapax legomena (V1), TTR total, TTR verb and TTR content and higher scores for Brunét's index (See Table 5). Differences in age or education level could not explain these differences because no significant differences were found for age (t=0.315, df=18, 2-tailed p=0.756) or education level (t=1.660, df=18, 2-tailed p =0.114).

4 DISCUSSION

4.1 Normal participants versus DAT participants

With a 85% correct classification performance Correct Information Units (CIUs) have shown to be the best measure to discriminate between normal and DAT participants and by this way, to be the most sensitive measure to detect lexical-semantical differences between normal and DAT participants. DAT participants presented lower CIU-scores, indicating that hey produce less accurate, relevant and informative words than our control group. CIUs have not been used before in DAT participants although they showed promising results in people with aphasia and although this analysis is considered as one of the most commonly used measures of informativeness of single words (Gordon, 2008).

CIU analysis is a robust measure that is frequently used in patients with vascular accidents. It was designed by Nicholas and Brookshire (1993) to quantify the informativeness and efficiency of the connected speech of adults with aphasia. Spontaneous speech was elicited with ten stimuli: four single pictures, two picture sequences and two requests for personal information. In Alzheimer's disease, this measure is not used before, so this study is the first to implement CIU in spontaneous speech in patients with Alzheimer's disease, with very promising results. CIU analysis is easy to use but one has to carefully read the rules (Appendix in Nicholas & Brookshire, 1993). After your first CIU analysis, ask an expert in this matter to check for possible mistakes, as we did.

The next best discriminator, with a 70% correct classification performance was Type-Token Ratio of all words (TTR) with a lower TTR for DAT participants indicating that DAT participants use a less broad vocabulary. Another proof of smaller lexical richness in DAT participants came from the significant differences in Brunét's index, where DAT participants scored higher, again indicative of less elaborate speech. It is surprising that no more or better discriminators were found because therapists familiar with Alzheimer's disease are able to discriminate language of healthy elderly from Alzheimer's patients.

Both groups also differed on use of pronouns with DAT participants producing significantly more. These results are confirmed in literature (Nicholas, Obler, Albert & Helm-Estabrooks, 1985; Hier, Hagenlocker & Shindler, 1985; Almor, Kempler, MacDonald, Andersen & Tyler, 1999). Almor et al. (1999) attributed this to the working memory impairment hypothesis because they found that pronoun use increases with decreasing working memory.

Because of the multiple comparisons, a Bonferroni correction may be carried out. We decided not to, because of the small number of groups and because of the conservativeness of this correction. When this correction should be applied, our main findings concerning TTR and CIU would stay ahead, contrary to Brunèt's index and pronoun-rate.

In contrast with Bucks et al. (2000), we did not find any significant differences between individuals with DAT and HO participants on N-rate, A-rate, Honoré's R and total TTR, although our sample sizes were bigger (Bucks et al. (2000): 16 normal participants, 8 participants with DAT). We suggest various explanations for these differences. First of all, let us consider the characteristics of the participants. Our participants were much older: the average age of our HO participants and DAT participants was respectively 14.3 and 9.2 years higher. Maybe we should have looked for participants younger than age 70 because of the documented decline of e.g. vocabulary in this age group (Lindenberger & Baltes, 1997). Comparing the years of education is difficult because in our study, we used education levels instead of years, but in contrast to Bucks et al. (2000), our study groups did not show significant difference on this topic.

Secondly, a big difference on DAT severity was observed. We chose for early stage patients whereas Bucks et al. had mild to moderate-severe cognitive impaired DAT participants (cf. our MMSE-scores (M=24.9, SD=3.8, range=14-30) versus theirs (M=15, SD=6.8, range=3-24)). As generally known, lower MMSE-scores indicate higher DAT severity (Folstein et al., 1975). Another difference was the number of words. Bucks et al. (2000) used 1000 words per speech sample (compared to our 300 words). However, according to Prins and Bastiaanse (2004) three hundred words is considered as reliable for linguistic analysis.

A complete comparison with the study of Visch-Brink et al. (2009) is difficult because our study concentrated on lexico-semantic measures only and their study included other language and speech aspects such as 'speech rate', 'syntactical correct sentences' and 'self-corrections'. None of our variables as present in their study (TTR content words, TTR nouns or

TTR verbs) were able to discriminate well between normal and AD participants. Because of their good results of empty words (and compound sentences) in the discrimination between AD patients and healthy volunteers, empty words have shown to be a promising measure and needs to be further investigated.

In summary, this study is the first to use CIU analysis in spontaneous speech in patients with Alzheimer's disease, with very promising results. For clinical purposes, CIUs may be a useful measure to differentiate between early DAT-patients and healthy older adults, but more research is necessary to confirm this hypothesis in larger samples of both healthy older and DAT participants. In addition, more normative data from a large sample of healthy older adults is required.

4.2 Influence of rivastigmine on spontaneous speech in DAT participants

In our study, none of the linguistic measures showed a significant difference after at least six months (average: 8.3 months) rivastigmine intake. Neither did the scores on ADAS-cog. Searching for answers, we took a closer look on our populations and found different sex-related performances on time two, but not at time one. On time two, women scored significantly lower than men, with lower scores for female DAT participants for hapax legomena (V1), TTR total, TTR verb and TTR content and higher scores for Brunét's index

Gender differences in DAT-patients have been found in cross-sectional studies with larger language impairment for women. Hebert et al. (2000) summarizes reported gender differences on naming, word recognition and verbal fluency. A recent study of Moreno-Martinez, Laws & Schulz (2008) confirms smaller word fluency in female Alzheimer patients for both living (insects, trees, animals) and non-living fluency (vehicles, tools, musical instruments). Language differences are not held back in longitudinal studies. Hebert et al. (2000) followed 410 patients with Alzheimer's disease for an annual control (four median controls) and examined the rate of decline in language and other cognitive functions. Male and female DAT participants showed similar rates of decline language and in other cognitive functions. Large number of patients, the low number of dropouts and the annual controls, strengthen this finding.

Contrary to our results, other studies support the usefulness of speech analysis in the follow-up of treated AD patients (Bucks et al., 2000; Chapman et al., 2002; Visch et al., 2009).

Of course, it is difficult to estimate the amount of decline when these patients would not have taken rivastigmine. Therefore it would be useful and interesting to compare these results to e.g. dropouts, patients who bear the medicine badly and have to stop it. Additionally, it would be interesting to compare the results of the DAT participants with the normal participants after a comparable time in order to see if results of DAT participants remain stable whereas results of normal participants decline. Other studies with larger sample sizes and other linguistic measures are necessary in order to find measures that are able to discriminate from healthy older adults, early in the disease process.

5 CONCLUSION

In summary, this study is part of a larger study investigating the influence of rivastigmine on all language domains in spontaneous speech in patients with dementia of Alzheimer type (DAT) and comparing performances of DAT patients with healthy elderly controls.

In this part, we wanted to investigate which lexico-semantic measures are able to discriminate well between healthy older participants and participants with dementia of Alzheimer type. Our study was the first to use Correct Information Unit (CIU) analysis in participants with dementia of Alzheimer type. CIU showed to be the strongest discriminator between those two groups and may held a promising future in early detection of Alzheimer's disease. To confirm our results, further investigations and bigger sample sizes are required to confirm these findings. Future studies could investigate the minimum of words needed to discriminate reliably between healthy and DAT participants, the discriminative power of CIUs in e.g. picture description or could set up norms on CIUs and other lexico-semantic measures.

Regarding the influence of rivastigmine intake on our lexico-semantic measures, no significant differences were found for our DAT participants after at least six months rivastigmine intake. Maybe our measures are not sensitive enough to detect differences and influences on other linguistic domains need to be studied such as syntax (see Visch-Brink et al., 2009), discourse (Chapman 2002) or cohesion (del Toro et al., 2008).

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FIGURES

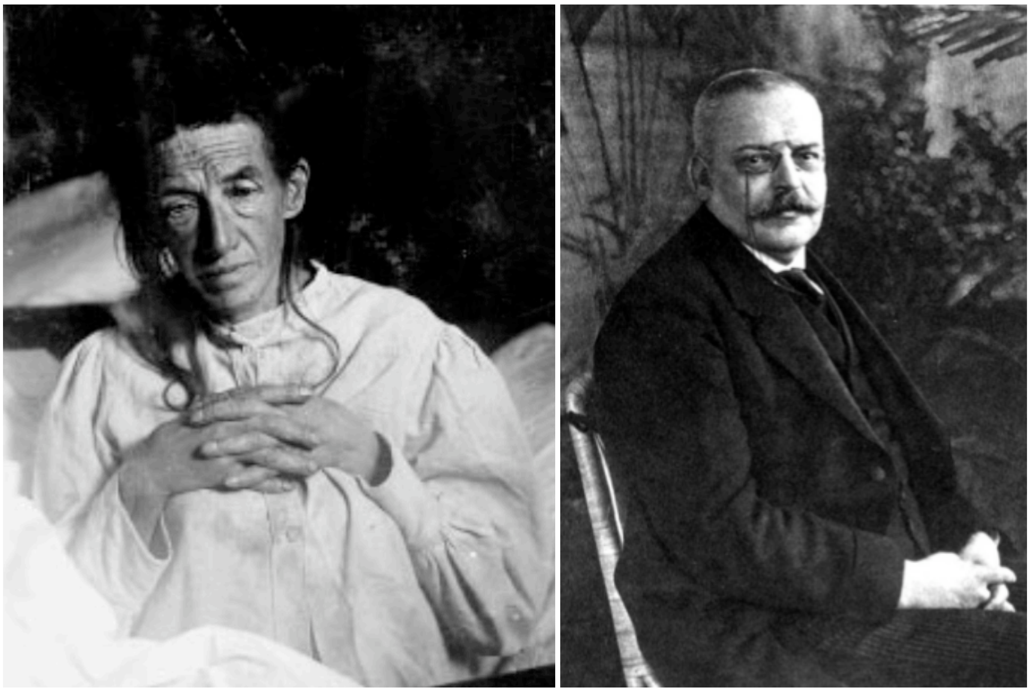

Figure 1: (left) Auguste D. (Maurer et al., 1997), (right) A. Alzheimer (Jucker, Beyreuther, Haass, Nitsch & Christen, 2006)

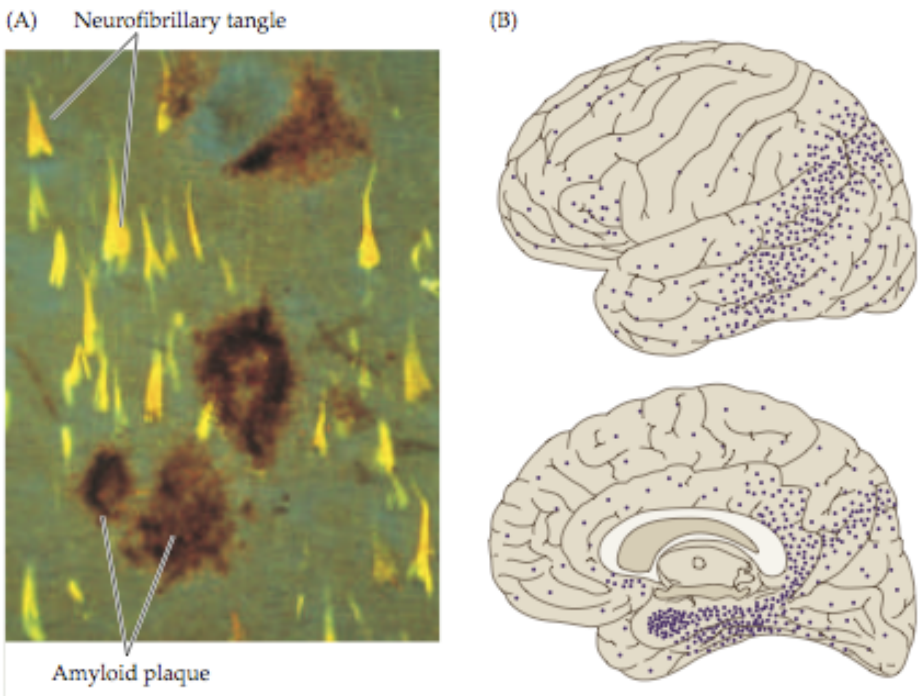

Figure 2: A) Histological section of the cerebral cortex from a patient with Alzheimer's disease, showing characteristic amyloid plaques and neurofibrillary tangles. (B) Distribution of pathologic changes in Alzheimer's disease. Dot density indicates severity of pathology. (Purves et al., 2004, p. 750)

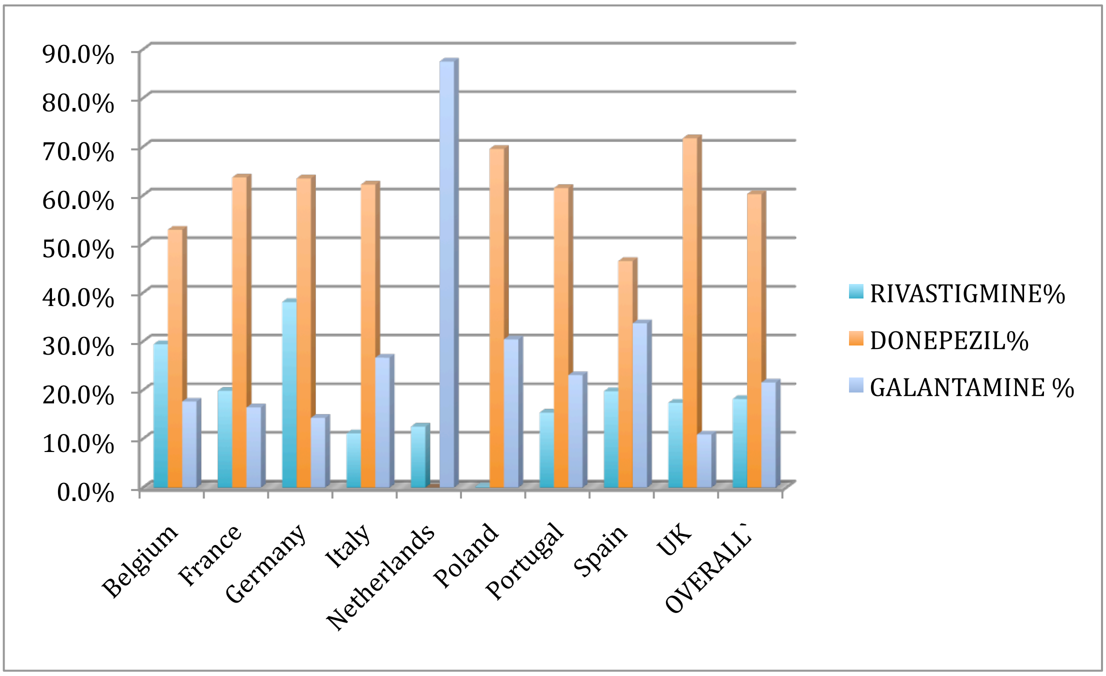

Figure 3: Prevalence of treatment for cholinesterase inhibitors in nine European countries on 1 January 2005 (after Pariente et al. (2008))