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Ludwig-Maximilians-Universität München  
Klinikum Großhadern  
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# What dementia can do to language processing: The special cases of diary writing and of proper name fluency



Dissertation  
zum Erwerb des Doktorgrades der Humanbiologie  
an der Medizinischen Fakultät der  
Ludwig-Maximilians-Universität zu München

vorgelegt  
von  
Nari Heitkamp  
aus München

2016

Mit Genehmigung der Medizinischen Fakultät  
der Universität München

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Tag der mündlichen Prüfung: 10.11.2016

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## ABSTRACT

The thesis at hand focuses on two main aspects: Firstly, the written text production in the preclinical phase of the semantic variant of primary progressive aphasia embedded in a longitudinal study; secondly, on the examination of Proper Names in patients suffering from Alzheimer's Disease in a fluency task setting. Both studies focus on aspects which have not been subject to scientific research so far.

The broad analysis of linguistics in written text production covered the levels of semantics, syntax and morphology and also included the examination of vocabulary and punctuation. The results showed an early onset of symptoms (approximately nine years before the clinical diagnose took place). Most surprising was the finding of an overwhelming amount of morphologic errors and an extreme usage of quotation marks. The results thus deepen the insight in the process of how the syndrome manifests itself in text production even before clinical diagnosis takes place.

The fluency tasks for Proper Names proved to be promising for future usage as a screening tool for dementia. It could be shown that Proper Name fluency must be distinguished from Common Name fluency and that performance is different in patients suffering from AD and healthy elderly. Also, performance differs depending on the Proper Name fluency task.

Die vorliegende Arbeit konzentriert sich auf zwei Schwerpunkte: Einerseits die schriftliche Textproduktion in der präklinischen Phase bei der semantischen Variante der Primär Progredienten Aphasie im Langzeitverlauf und andererseits die Untersuchung von Eigennamen bei Patienten mit Alzheimer Demenz in Form von fluency tasks. Beide Studien beleuchten Aspekte, zu denen bisher noch kaum wissenschaftliche Erkenntnisse vorliegen.

In der umfassenden Studie zur schriftlichen Textproduktion wurden Aspekte aus den Bereichen Semantik, Syntax und Morphologie, sowie Vokabular und Zeichensetzung untersucht. Die Ergebnisse zeigen vor allem einen frühen Onset von ersten Symptomen (ca. neun Jahre vor klinischer Diagnosestellung der Erkrankung). Es zeigte sich unerwarteterweise eine starke Häufung von morphologischen - im Vergleich zu semantischen - Auffälligkeiten und eine extreme hohe, wie auch falsche Verwendung von Anführungsstrichen. Die Ergebnisse erweitern also die bisher nur spärlich vorliegenden Erkenntnisse zum sprachlichen Abbauprozess in der schriftlichen Textproduktion im präklinischem Stadium.

Die fluency-Aufgaben für Eigennamen zeigten sich hinsichtlich einem späteren Einsatz als Screeningtool für Demenz als vielversprechend. In der Studie konnte folgendes gezeigt werden:

- 1) Die fluency für Eigennamen unterscheidet sich tatsächlich von der fluency für Appellativa.
- 2) Die Leistung der Versuchspersonen variiert in Abhängigkeit vom Eigennamen-fluency-task. Es ist also anzunehmen, dass die Aufgaben tatsächlich eigenständige Aufgaben darstellen und daher unterschiedlich verarbeitet werden.
- 3) Die Leistungsprofile in den Eigennamen-fluency-tasks von Gesunden und an Alzheimer Demenz Erkrankten unterschieden sich deutlich.

## 1 GENERAL INTRODUCTION



As a well known fact, our western society is growing older, thus the number of patients suffering from brain degeneration increases constantly. Not only its typical form - called Alzheimer's Disease (AD) - but also less known ones play a bigger role in the everyday life of clinical settings (e.g. in the form of dementia screening, and treatment approaches) and in nursing homes (e.g. in the form of stimulating interaction).

The modern research in the field of dementia began around the turn of the last century when the doctors Pick (1892), Serieux (1893) and Alzheimer (1907) reported about their first patients suffering from dementia. Publications by Warrington (1975), Mesulam (1982), Snowden et al. (1989) and Hodges et al. (1992) helped to further refine and outline the different variants of the syndrome. Since the publication of Gorno-Tempini et al. (2011), three subgroups in the field of language accented dementias, also labeled as primary progressive aphasia (PPA), are generally accepted: the semantic variant (svPPA), the agrammatic variant (avPPA) and the logopenic variant (lvPPA). The former term Semantic Dementia (SD, introduced by Neary, Snowden, & Mann, 2000) is now replaced by svPPA.

There are still a lot of open research questions in the quite well examined field of AD research as well as in the broad and relatively new area of the subgroups of PPA. This thesis will focus on two of these: written text production in svPPA and Proper Name fluency in AD patients. Therefore, a rough outline of the relevant background information on these two topics is provided in the following chapters 1.2 and 1.3.

## 1.1 MOTIVATION OF THIS THESIS

The focus of current research definitely lies on the more obvious study subject: spoken language production, mostly on the word level. Words examined are the so-called Common Names, thus words that label a certain category of things like dogs, flowers or cutlery. Proper Names however are nearly neglected, although they seem to be promising when applied in an early diagnostic intervention procedure for dementia (Adlam, Bozeat, Arnold, Watson, & Hodges, 2006; Mok, Lam, & Chiu, 2004; Palmer, Bäckman, Winblad, & Fratiglioni, 2003). Not only is the observation of language changes in demented persons overwhelmingly based on spoken language, it also neglects written language production, especially on the text level. But signs of the degradation of the language system can already be seen years before the clinical diagnose in written language production (P. Garrard, 2004; Snowden et al., 1996; van Velzen & Garrard, 2008) and might tell a different story than spoken language deterioration. With this thesis, the

author wants to shed light on those two aspects by analyzing written text production in the preclinical phase over a long time span and by trying to introduce Proper Name fluency as a possible screening tool for dementia.

## 1.2 LANGUAGE PRODUCTION IN DEMENTIA

Language production of patients suffering from dementia will be briefly introduced for the subgroup of svPPA-patients, where early language deterioration on the semantic level is the hallmark feature (comparable with the loss of memory in Alzheimer's Disease). The patient examined for the thesis at hand (described in chapter 2) also suffered from this syndrome. The chapter about written text production (see chapter 1.2.2) focuses on AD patients, simply because of a lack of evidence for other forms of dementia.

### 1.2.1 SPOKEN LANGUAGE PRODUCTION IN SVPPA

The language of patients suffering from svPPA is characterized as fluent but empty, including a lot of overlearned phrases and semantic paraphasias (Reilly, Rodriguez, Lamy, & Neils-Strunjas, 2010). While an untrained listener will not notice abnormalities in the beginning, degradation gets more accented over the course of time and errors become more obvious. The vocabulary gets less differentiated and semantic fine grained words get lost (Bozeat et al., 2003; Laisney et al., 2011). Syntax is said to be uninvolved in the degradation, with the exception of paragrammatic constructions due to difficulties in word finding (e.g. Gorno-Tempini, Hillis, et al., 2011; Leyton & Hodges, 2014; S. M. Wilson et al., 2010). Morphological errors can sometimes be found (Kave, Leonard, Cupit, & Rochon, 2007; Meteyard & Patterson, 2009). A core feature of svPPA diagnostics is an examination on the word level. There, impaired confrontation naming and impaired single word-comprehension are obligatory (Gorno-Tempini, Hillis, et al., 2011). However, as the diagnostic examination is being conducted on a single word level, potentially erroneous conclusions can be drawn about the patient's performance in connected text (Sajjadi et al., 2012).

### 1.2.2 WRITTEN TEXT PRODUCTION

On the text level, to the best of the author's knowledge, only three studies exist. Two of them used a computer-based analysis for novels of the renowned authors Iris Murdoch and Gerard Reve, who both were diagnosed with Alzheimer's Disease after finishing their last literary work piece. Garrard (2004) and van Velzen and Garrard (2008) compared pieces of work from the

early and middle state of the writing career of the authors with the last book they wrote. They found clear changes in the vocabulary: words used were of higher frequency and the vocabulary was less varied. The plot of both stories was considered as confusing and banal by literary reviewers.

The third study examining written text production in demented persons is called the “Nun-Study” (Snowden et al., 1996). Analysis of a single hand written page of novices showed a lower idea density per sentence (meaning the quantity of new propositions per sentence) and a lower degree of syntactic complexity if they were later affected by dementia from the Alzheimer’s type. The texts were already written 58 years (!) before the study took place.

On single word level surface agraphia (regularization of orthographically irregular words) and semantic paraphasia are typically regarded as markers of semantic loss corresponding to the features of the spoken language (e.g. Grossman & Ash, 2004; Gorno-Tempini et al., 2011).

When looking at the small number of data available, it seems like symptoms of dementia could already be found in written text examples years before a clinical diagnose can pinpoint the disease. Until now, there is no study conducted examining written text production in persons suffering from a language-accented form of dementia, such as svPPA or avPPA. It would be very interesting to ascertain how and when the disease manifests itself in those disease forms, to take a more detailed look at different linguistic levels and to describe its linguistic “fingerprint”. We had the chance to analyze the diary of a patient who wrote daily entries since his retirement and was diagnosed with svPPA twelve years later (patient HK). The study is described in detail in chapter 2 of this thesis.

## 1.3 PROPER NAMES

### 1.3.1 SCIENTIFIC FRAMEWORK

Proper Names are interesting for different fields of science, namely philosophy, linguistics and neurosciences. Those three will now be outlined briefly.

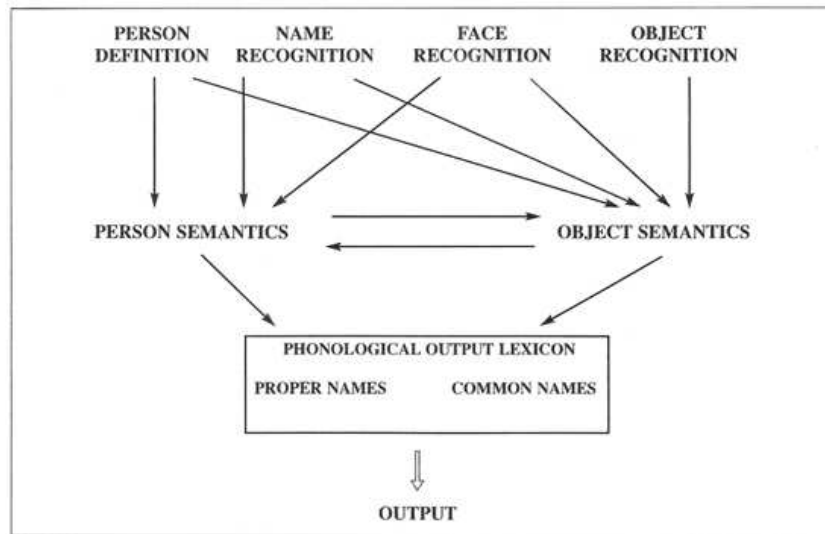
Proper Names have already been subject to philosophical considerations in the 19<sup>th</sup> century. Most famous are the classical works of the philosophers John Stuart Mill (1806-1873), Gottlob Frege (1848-1925) and Bertrand Russell (1872-1970). According to Mill, Proper Names can be defined as being individual (in contrast to general), non-connotative (in contrast to connotative)

and abstract (in contrast to concrete); names are more like symbols and do not have a content (Mill, 1843). Since Frege, we know about the famous example of the morning and evening star, which both identify the planet Venus. For him, names do not necessarily have a meaning, but a sense (Frege, 1892). For Russell, Proper Names were shortenings of descriptions. In a strict sense, the real proper names are only “this” and “that”. He puzzled with famous fictional sentences like “The king of France is bald” or “Unicorns have exactly one horn”, to clarify the meaning of Proper Names and their relationship to reality (Russell, 1905, 1910).

Also, linguistics is interested in better understanding the nature of Proper Names. Two main theories, the symmetrical and the asymmetrical-theory, dominate the discussion, where Proper Names are being examined in the context of nominal phrases. There are several advantages of the symmetrical theory, one of them being the statement that Proper Names are rigid, fixed designators that point like an arrow to the subject/object they name (following Kripke, 1980).

In modern neuroscience the distinction between Proper and Common Names is made by claiming that Common Names designate a category with items that share properties (like a dog, sharing the labels “animal”, “four legs”, “barks” with other members of the dog-category) and Proper Names refer to a single subject/object with a value worth of being individuated and its meaning consisting of a random combination of attributes (Carlo Semenza, 2006a), e.g. “Anna” as being a toddler’s favorite teddy bear with pink ears. It could be proved that Proper Names are harder to recall (James, 2004; McWeeny, Young, Hay, & Ellis, 1987; Pelamatti, Pascotto, & Semenza, 2003) and have different processing routes (Carlo Semenza, 2006b, see fig. 1).

Figure 1: Processing pathway for Proper and Common Names  
(Carlo Semenza, 2006b, p. 889)



### 1.3.2 PROPER NAMES AND DEMENTIA

Proper Names are special, that is what philosophy, linguistics and neurosciences were able to prove. But the question is as to what extent could this be interesting for patients suffering from dementia?

Current studies conducted with patient cohorts could show the following:

1. Patients in the state of mild cognitive impairment could name Proper Names of persons and buildings less proficiently than Common Names and are generally performing worse than control persons (Ahmed, Arnold, Thompson, Graham, & Hodges, 2008).
2. Patients in the state of mild cognitive impairment performed worse than others in a face recognition task (naming famous persons) if they later developed dementia (Estévez-González et al., 2004).
3. In patients suffering from Alzheimer Disease, not only semantic, but also post-semantic information seems to be damaged (Delazer, Semenza, Reiner, Hofer, & Benke, 2003).
4. Comparing patients suffering from AD and patients suffering from the semantic variant of PPA, the latter are more impaired when it comes to finding names than when it comes to recognizing faces, AD patients performed vice versa (J. S. Snowden, Thompson, & Neary, 2004).

Although Proper Name testing seems to be promising in the state of mild cognitive impairment and the early stage of dementia, the problem which has to be dealt with is the enormous effort to

test them. Until now, researchers had to build their own test material by collecting pictures of famous persons or family members of the patient. Even then, testing was highly dependent on external factors such as sight and visual processing abilities, and of course, personal interests of the patient: A person not interested in sports might have troubles in recognizing a famous tennis player from a picture which is not dependent on his ability to retrieve the Proper Name. But when interpreting the result one will not be able to differentiate what the underlying problem is. In order to get an easy-to-use tool to test Proper Name production, we combined the classic fluency tests with Proper Names and conducted a first approach on testing Proper Name fluency in healthy elderly and patients suffering from AD. The study is discussed in chapter 3 of this thesis.

## 2 FIRST STUDY:

### *LINGUISTIC ANALYSES OF WRITTEN TEXT PRODUCTION IN A CASE OF SVPPA*

## 2.1 ABSTRACT

We had the unique opportunity to analyze the diary of a man written over the twelve years before he was diagnosed with semantic variant of primary progressive aphasia (svPPA). Our hypotheses concerning the diary texts were based on findings in written texts in Alzheimer's disease and spoken language in svPPA. The results confirmed our predictions about the early finding of abnormalities, changed word use and svPPA-typical mistakes such as surface agraphia and semantic paraphasia. Unexpectedly, we also saw abnormalities in syntax and morphology and an explosive use of quotation marks. The earliest changes were found 9 years prior to clinical diagnosis and the greatest changes over time in these diary entries occurred 6, 3 and 1 year before. These written texts therefore showed different features to those associated with spoken language in svPPA and were sensitive to changes several years prior to diagnosis.

Own contribution remark: The research questions were put forward by Prof. Danek and myself, and discussed with PD de Langen. The patient HK was diagnosed and treated in Basel Memory Clinic, there, Rahel Schuhmacher realized the uniqueness of the patients diaries and the possibility to investigate them further. All the transcriptions were conducted by myself. PD de Langen supported with shaping the error categories, Stablab of the Ludwig-Maximilians-Universität in Munich helped with the statistical analysis. Dr. Croot read the manuscript intensively. The manuscript, including creation of figures, were written by myself. The chapter "Case Report HK" including table 1 (see chapter 2.3.1) was supported by Rahel Schumacher.

The article in a different variant has meanwhile been published online in the Journal of Neurolinguistics (N. Heitkamp et al. (2016), Journal of Neurolinguistics 39, p. 26-37).



## 2.2 INTRODUCTION

Despite the wide-ranging investigation of language impairment associated with dementia in the past thirty or so years (Appell, Kertesz, & Fisman, 1982; Mesulam, 1982; J. Snowden et al., 1989; Warrington, 1975), two aspects are still relatively neglected. First, there is a lack of knowledge about the development of symptoms and their order of occurrence in the preclinical phase of different types of dementia, and this is especially true of the less well-known syndromes. Second, written text production language presentations of dementia, including primary progressive aphasia (PPA) with its non-fluent, semantic and logopenic variants (nfPPA/svPPA/lvPPA), has barely been explored, in comparison with recent interest in spoken language production in these syndromes (Ash et al., 2006; Bird, Lambon Ralph, Patterson, & Hodges, 2000; Sajjadi, Patterson, Arnold, Watson, & Nestor, 2012; Sajjadi, Patterson, Tomek, et al., 2012; S. M. Wilson et al., 2010). In this study we had the opportunity to analyze the written texts of a man, HK, who was diagnosed with svPPA 12 years after he began to write daily diary entries. We studied the texts to identify the onset of linguistic abnormalities, and to document the “linguistic fingerprint” of the disease in this individual over time. We also considered whether HK’s written language would compare with changes reported in the written language of people with probable Alzheimer’s disease (AD) and the spoken language production of people with svPPA.

### *Longitudinal analysis of written language production in Alzheimer’s disease*

Garrard et al. (2005) conducted a computer-based analysis of the literary work of the renowned Irish author Iris Murdoch, who was diagnosed with AD 4 years before her death in 1999. Comparing three of her novels from different periods of her writing career, the authors found significant differences in lexical aspects. In particular, her last book, published in 1995, used higher frequency words and less varied vocabulary. Word length, use of different word classes, and the overall structure of the texts and syntactic composition did not differ between the three novels. Reviewers considered the plot of the last story to be shallow and banal.

A second computer-based study, carried out with texts from the Dutch writer Gerard Reve who also suffered from AD, showed similar results (van Velzen & Garrard, 2008): lower lexical diversity, trouble finishing the story (writer’s block), a shallow and confusing plot. The authors concluded that abnormalities of language use in written text production can be seen years before the clinical diagnosis of dementia.

The so-called Nun Study (Snowdon et al., 1996) is in accordance with this conclusion: there, the analyses of a single, hand written page, produced about 58 years before the study took place, enabled the researchers to identify the nuns later affected by AD. Their texts showed a lower rate of idea density (i.e. the quantity of propositions/ideas per sentence) and a lower degree of syntactic complexity. The future nuns were not professional writers, which might be why lower syntactic complexity was found very early on in their texts but not in Murdoch's and Reve's work.

The three studies cited above are to the best of our knowledge the only ones analyzing written texts of patients suffering from dementia. Other linguistic aspects (e.g. a detailed analysis of semantics) have not been analyzed yet. Although there are no longitudinal investigations of written texts in semantic dementia, the characteristics of spoken language have been investigated extensively, as described below.

#### *Characteristics of spoken language in semantic variant PPA*

Prominent abnormalities in semantic memory function are the hallmark feature of svPPA. When diagnosing the disease, impaired confrontation naming and impaired single word-comprehension are core and obligatory symptoms of svPPA (Gorno-Tempini, Cappa, et al., 2011), directly related to impaired object knowledge. Other indicators are surface dyslexia or dysgraphia, spared repetition and spared speech production. As Sajjadi et al. (2012) comment, the diagnostic examination is mostly conducted on single word level and potentially erroneous conclusions could be drawn about the patient's performance in connected text.

Typically, the spoken language of svPPA patients is described as fluent but empty, full of overlearned phrases and semantic paraphasias (Reilly et al., 2010). To a certain extent, the connected speech can thus sound "remarkably normal" (Sajjadi, Patterson, Tomek, et al., 2012, p. 860). Over time, patients tend to lose their differentiated vocabulary and use more general instead of semantically fine grained words (Bozeat et al., 2003; Laisney et al., 2011). Nouns are more affected by semantic paraphasias than other word classes (Bird et al., 2000), attributed to the overall lower frequency of nouns than verbs (see also Lambon Ralph, Graham, Ellis, & Hodges, 1998). Sajjadi et al. (2012) could not find a general increase in the use of closed-class words in their patients compared to controls during a semi-structured interview, but performance resembled that of mild AD patients in a picture description task.

In written language production in svPPA, surface agraphia (regularization of orthographically irregular words) and semantic paraphasia are frequently seen, and are typically regarded as markers of semantic loss corresponding to the features of the spoken language (e.g. Grossman & Ash, 2004; Gorno-Tempini, Cappa, et al., 2011).

People with svPPA patients are taken not to show any syntactic abnormalities except paragrammatic constructions resulting from word finding difficulties (e.g. Gorno-Tempini, Cappa, et al., 2011; Leyton & Hodges, 2014; S. M. Wilson et al., 2010). Agrammatic features such as short sentences and a so-called simplification or elision of grammatical markers (Tesak, 1990) are absent. The paragrammatic features that are seen include sentence inversions and repetitions of sentences or parts of sentences, mostly based on perseverations of words or ideas (e.g. Kleist, 1914; Schlenck, 1991).

Morphological errors (e.g. use of inflectional morphemes and function words) have occasionally been reported in spoken language production. Kavé, Heinik and Biran (2007) observed in their patient that considerations about morphological correctness was only impaired when semantics defined grammaticality. Also, judgment of irregularly inflected forms was impaired. They consider that some structural aspects of word knowledge depend on semantic information. Meteyard and Patterson (2009) report the substitution of closed class words or inflections, but they considered the abnormalities in their 8 patients as subtle. These authors explained the abnormalities by a semantic deficit which influences the encoding of the pre-verbal message, the lexical retrieval process and the early stages of grammatical encoding. That all levels of language production interact with semantic information and are therefore affected by the degradation of it is also supported by the findings of Benedet and colleagues (2006). They also found morphological and syntactic errors in their patient. He was impaired in the oral and written production of morphologically complex words, made errors with morphologic endings and inflectional forms, and was impaired when producing complex sentence constructions such as passive clauses. Error rate was higher for atypical, less familiar or infrequent constructions. Sajjadi et al. (2012) could not, however, replicate these findings.

Regarding the longitudinal development of language symptoms during the course of the disease, Czarnecki et al. (2008) report a patient who came to the hospital with memory complaints, before a diagnosis of svPPA with the routine test material was possible. Performance on neuropsychological and language testing was then only on the low range of average. Two years later, the patient's husband reported word substitutions, circumlocutory speech and semantic as well as spelling errors. In formal testing a deficit in word retrieval could be shown. Impairment

in the Boston Naming Test preceded abnormalities in semantic fluency. Warren and colleagues (2013) noted that the semantic deficit is often well compensated in the beginning of the disease and may only emerge on testing specialized knowledge. Other semantic modalities as well as other non-verbal domains, such as behavioral abnormalities, are only involved later.

### *The present study*

Our primary goals were to identify the onset of linguistic abnormalities in HK's diary entries, and to document the changes in written texts in this individual over time. We were then able to compare HK's diary entries with the features previously reported in written text production in AD and spoken language production in svPPA. To our knowledge, this is the first linguistic analysis of free written text production in svPPA. Our analyses included the level of semantics, syntax, morphology, vocabulary and punctuation.

Starting with the overall structure, on the basis of findings in the work of Iris Murdoch and Gerard Reve, we expected no change in the composition of the diary entries, but a decrease difference in the number of entries made, their length and a trivialization of their topics.

Surface agraphia and semantic paraphasia are regarded as the typical indices of semantic impairment in written text production in svPPA. We therefore expected to find these early, and to see them increasing over time. The semantic paraphasias should also have a progressively higher semantic distance from the target item over time, and occur earlier and more often in nouns than in other word classes (Bird et al., 2000; Gorno-Tempini, Cappa, et al., 2011).

The second main index of semantic impairment in svPPA is word-finding difficulty reflecting a loss of encyclopedic knowledge of the world. Therefore, as an indicator of increasingly restricted vocabulary, we predicted HK's diary entries would show a decreasing type-token-ratio (TTR) over the course of time. As a consequence of increasing word finding difficulties, we anticipated an increasing rate of high-frequency words and a decreasing rate of lower frequency words.

On the levels of syntax and morphology, we expected to find paragrammatic but no agrammatic errors. We drew information about the sentence structure by analyzing the patient's use of connectives. When classifying sentences into simple versus complex structures, we expected to find a high rate of simple constructions as found in the so called Nun-study (Snowdon et al., 1996). We did not expect gross morphological errors (Meteyard & Patterson, 2009). Appropriateness of punctuation as a way of structuring written text has not previously been

investigated in extended written texts in svPPA, however the only punctuation changes we predicted were those associated with any changes that emerged in overall sentence structure.

## 2.3 CASE REPORT

### 2.3.1 PATIENT HK

HK was a right-handed accountant of Swiss origin with 12 years of education. He presented in 2009, 12 years after his retirement at the age of 65, with word-finding difficulties that had been increasing for the three previous years, as reported by his partner. She had to repeat things several times and she noticed that he had difficulties in recalling his friends' names, and he had given up answering the phone and playing the organ. She had also started to support him in financial matters in order to prevent him from giving away large sums to strangers.

Detailed general medical, neurological, neuropsychological and neurolinguistic examinations were performed. Magnetic resonance imaging (see fig. 2) showed pronounced left temporal lobe atrophy.

Due to a subsequent diagnosis of cancer and ensuing hospital stays HK did not return to the Basel Memory Clinic. He died one year later. An autopsy was not performed.

Figure 2: MRI HK

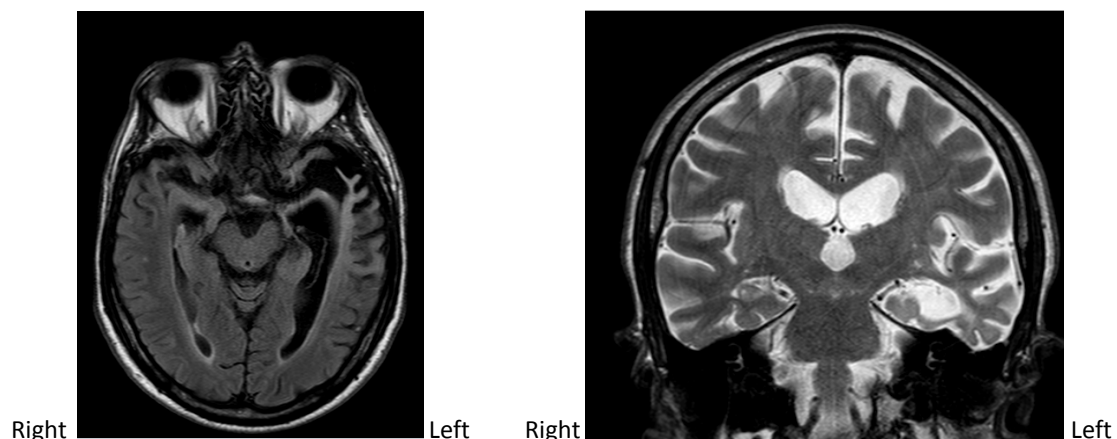


Figure 2: Transverse and frontal brain magnetic resonance images of patient HK taken at the age of 77 years (year 12 of the diary entries): There is asymmetric cerebral atrophy, predominantly affecting the left temporal lobe with so-called knife blade appearance of the temporal gyri.

On neuropsychological examination HK's collaboration was good. He sometimes behaved in a hasty manner, frequently checked the time on his watch and made unasked notes. HK was anosognostic for his deficits.

HK was fully oriented. In the Mini Mental State Examination (MMSE) (Aebi, 2002) he scored 21 out of 30 points (errors in recall, naming, reading, three-stage command, copying). In the Clock Drawing Test (Shulman, Gold, Cohen, & Zuccherro, 1993) he wrote down the time in words instead of numbers. His neuropsychological results are summarized in Table. 1. Overall, he showed more pronounced deficits in verbal than in non-verbal tasks. His deficits in verbal episodic memory were ascribed to his semantic impairment.

Table 1. Overview of HK's performance in neuropsychological tests

<b>Domain, Modality</b>	<b>Test</b>	<b>Score</b>	<b>D</b>	
Speed	TMT A	61 sec	∅	
	Stroop (color naming)	27 sec	↓↓↓	
Memory Span				
	Verbal	Digit span forward	3	↓↓↓
	Visual	Corsi Block	9	∅
Memory	Verbal	CERAD Encoding	11/30	↓↓↓
		CERAD Recall	3/10	↓
		CERAD Recognition	65%	↓↓↓
	Visual	CERAD Recall	0/11	↓↓↓
		Constructional praxis	CERAD Copy	10/11
Executive functions	Working memory	Digit span backward	2/12	↓↓↓
	Flexibility	TMT B	292	↓↓
	Category fluency	Animals	3	↓↓↓
	Letter fluency	S	7	∅
	Figural fluency	5-point test	22	∅
	Language	Naming	CERAD line drawings	5/15
Famous Faces			4/10	↓↓
Comprehension		PPTT	81%	↓

TMT: Trail Making Test, PPTT: Pyramid and Palm Trees Test

∅: no impairment (z-value > 1), ↓: mild impairment (-1.3 > z-value > -1.6), ↓↓: moderate impairment (-1.6 > z-value > -2.3), ↓↓↓: severe impairment (z-value < -2.3)

**Literature:** **TMT:** Army Individual Test Battery. Manual of directions and scoring. Washington, DC: War Department, Adjutant General's Office., 1944.; Reitan R. M. (1958). Validity of the Trail Making test as an indicator of organic brain damage. *Percept. Mot Skills*, 8, 271-276. **Stroop:** Stroop, J.R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, 18, 643-662; Regard, M. (1981). **COGNITIVE RIGIDITY AND FLEXIBILITY: A NEUROPSYCHOLOGICAL STUDY.** Unpublished Ph.D. Dissertation, University of Victoria.; O. Spreen, E. Strauss. A compendium of neuropsychological tests (2nd ed.) Oxford University Press, New York, NY (1998); **Memory Span:** Härting, C., Markowitsch, H.-J., Neufeld, H., Calabrese, P., Deisinger, K., & Kessler, J.(Hrsg.). (2000). Wechsler Gedächtnistest - Revidierte Fassung. Bern: Huber; **CERAD:** Morris, J. C., Heyman, A., Mohs, R. C., Hughes, J. P., van Belle, G., Fillenbaum, G., Mellits, E. D. & Clark, C. (1989). The consortium to establish a registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology*,39, 1159–1165; Aebi, C. Validierung der neuropsychologischen Testbatterie CERAD-NP: eine Multi-Center Studie. 2002, Doktorarbeit, Universität Basel.; **Category and Letter Fluency:** Aschenbrenner, S., Tucha, O., & Lange, K.W. (2000). Regensburger Wortflüssigkeits Test RWT. Göttingen: Hogrefe.; **5-point test:** Regard, M., Strauss, E., & Knapp, P. (1982). Children's production on verbal and non-verbal fluency tasks. *Perceptual and Motor Skills*, 55, 839-844; **Naming:** Kaplan, E.F. Goodglass, H., & Weintraub, S. (1978). The Boston Naming Test. Boston, MA: Veterans Administration Medical Center; **Famous Faces:** clinic internal material.; **PPTT:** Howard D, Patterson K (1992) The Pyramids and Palm Trees Test. A test of semantic access from words and pictures. Thames Valley Company, Bury St. Edmund

Spontaneous speech was fluent, yet profound word-finding difficulties with circumlocutions and semantic paraphasias as well as poor spoken-word comprehension (including test instructions) were noted. Naming of common objects as well as written word comprehension was severely impaired. A slight tendency towards confabulation and perseveration was noticed. HK was uncertain in matching semantic relations (he chose for example a light bulb instead of a candle to fit best with matches). Writing to dictation, word repetition and face recognition were not impaired. Furthermore, no signs of surface alexia were found. He failed in all of the 5 subtests of the BoSU (Bogenhausener Semantik-Untersuchung) (Glindemann, Klintwort, Ziegler, & Goldenberg, 2002) by scoring above or at cut-off (this test examines semantic performance non-verbally and verbally).

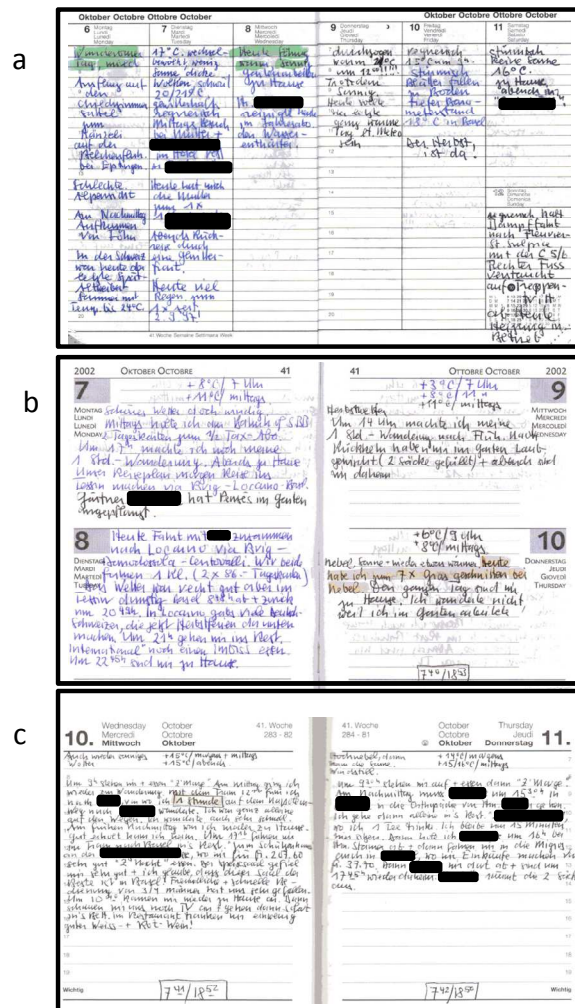
A diagnosis of svPPA was made on the basis of the neurological results in combination with the neuropsychological and neurolinguistic findings (Gorno-Tempini, Cappa, et al., 2011).

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### 2.3.2 DIARY

HK started his diary after retirement and kept on writing entries over 12 years, but changed the format over time. In year 1 to 2, he dedicated 2 pages to 1 week, in years 3 to 6, 4 days were described on 2 pages and 1 day per page was typical for years 7 to 12 (see fig. 3)

Figure 3: Example pages of the different almanac styles



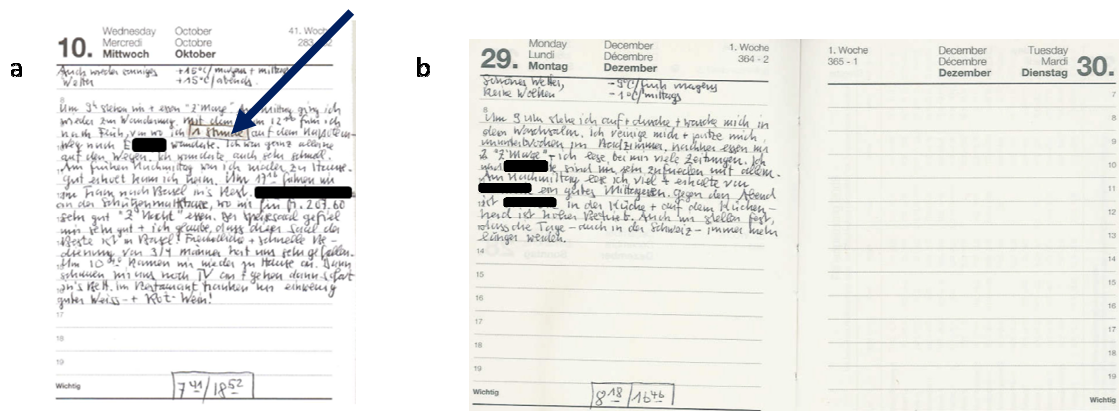
The first almanac style was used by HK in the first and second year of his diary writing (a). One double page contains a whole week. In years 3 to 6 HK used a different almanac format (b), namely one with 4 (Monday- Thursday) respectively 3 days (Friday – Sunday, and one section “notes”). From year 7 until year 12 one double page of the almanacs contained only two pages, thus 1 page per day (c). HK here developed what we call his typical composition of a diary entry.

The diary format clearly affected the length and composition of HK’s entries. HK developed a constant structure for his entries, starting out with a short comment about the weather, e.g. *Wolken + Sonne, leichter Nordwind* [Clouds + sun, smooth breeze from the north] (June, year 4), followed by the temperature. Up to 6 measurements per day are documented, e.g.: *+12°C / 7 Uhr*,



+20°C / 11 Uhr (June, year 6). Next, HK reported on the activities of the day and finally, he wrote down the time of sunrise and sunset. He additionally documented extreme weather conditions, e.g. *Hitzewelle* [heatwave] (June, year 9) and in the summer entries he mentions the number of blooming lilies and frogs in his pond. His writing style can be described as “objective” (Surd-Büchle, 2011): HK informs about events and activities of the day, often with details about time and costs (e.g. *Abends um 17.45h fahren wir zum Nachtessen nach A. ins Rest. 'A.C.B.', wo wir für 165,- sehr gut essen* [We drive to the restaurant ‘A.C.B.’ in A. at 5.45 p.m., where we have a really good dinner for 165,-] (June, year 8). Emotional states or thoughts are rarely included. For a few years HK goes on a daily walk for about an hour, which he describes in increasing detail over time. In most cases, he encircles the time he needed for his walk and marks it with color. He does the same with the number of flowers in his garden and of frogs in his pond, or with descriptions of extreme weather conditions. Regarding the colors used for marking, no system was detected. HK’s diary starts on January 1, 1997 and ends on December 29, 2008. A typical diary entry is exemplified by fig. 4a., his last entry can be seen in fig. 4b.

Figure 4: Typical diary entries of patient HK in years 11 and 12



The typical structure of a diary entry consists of a short comment on the weather condition in the upper left corner, the temperature notes (including the measurement-time) on the middle part on the top of the page, as well as the framed time of sunrise and sunset in the middle of the bottom of the page. Also, detailed information about prices and times of events are given. The entry of October 10<sup>th</sup>, year 11 (fig. 4a) shows a typical marking (framing and coloring) of the time HK needed for his daily walking tour (see arrow). Figure 4b shows HK last entry on December 29<sup>th</sup>, year 12. The barrier rituals (noting the weather condition, the temperature and time of sunrise and sunset) are still present. The content of the text is very shallow and topics are repeated several times. Proper names are blackened in both examples.

Original texts and translation:

a

Auch wieder sonniges Wetter

+15C/morgens + mittags

+15 C/abends

Um 9 h stehen wir + essen „Z'Morge“. Am Mittag ging ich wieder zur Wanderung. Mit dem Tram 12.16 fuhr ich nach F, von wo ich 1 Stunde auf dem Napoleonweg nach E wanderte. Ich war ganz alleine auf den Wegen. Ich wanderte auch sehr schnell. Am frühen Nachmittag war ich wieder zu Hause. Gut erholt kam ich heim. Um 17.16 fahren wir im Tram nach Basel in's Rest. „...“ an der Schützenmattstrasse, wo wir für Fr. 207,60 sehr gut „Z'Nacht“ essen. Der Speiseisaal gefiel mir sehr gut + ich glaube, dass dieser Saal der Beste ist in Basel. Freundliche + schnelle Bedienung von 3/4 Männern hat uns sehr gefallen. Um 10.40 kamen wir wieder zu Hause an. Dann schauen wir uns noch TV an + gehen dann sofort in's Bett. Im Restaurant tranken wir ein wenig guten Weiss- + Rot-Wein!

7.41/18.52

Also again sunny weather

+15C/in the morning + at noon

+15 C/in the evening

At 9 h we get + eat breakfast. At noon I went again on walking tour. With the tram 12.16 I drove to F, from where I walked 1 hour on the Napoleon road to E. I was totally alone on the roads. I walked also really fast. On the early afternoon I was at home again. Relaxed I got home. At 17.16 we went by tram to Basel to the restaurant „...“ on the Schützenmattstreet, where we had very good dinner for Fr. 207, 60. I liked the dining hall a lot + I think that this hall is the best one in Basel. Friendly + quick service of 3/4 men which we liked very much. At 10.40 we arrived at home again. Then we watched us TV + go then straight to bed. At the restaurant we had a bit of good white and red wine!

7.41/18.52

b

Schönes Wetter, keine Wolken

-9C/früh morgens

-1C/mittags

Um 9 Uhr stehe ich auf + dusche + wasche mich in Waschsalon. Ich reinige mich + putze mich, ununterbrochen im Badezimmer. Nachher essen wir 2 „z'Morge“ + ich lese bei mir viele Zeitungen. Ich und C sind wir sehr zufrieden mit allem. Am Nachmittag lese ich viel + erhalte von C ein gutes Mittagessen. Gegen den Abend ist C in der Küche + auf dem Küchenherd ist hoher Betrieb. Auch wir stellen fest, dass die Tage – auch in der Schweiz – immer mehr länger werden. 8.18/16.46

Nice weather, no clouds

-9C/early in the morning

-1C/noon

I get up at 9 + take a shower + wash myself in the Laundromat. I clean + wipe myself, continuously in the bathroom. Afterwards, us 2 eat “breakfast” + I read at myself a lot of newspapers. I and C are very happy with everything. In the afternoon I read a lot + get a good lunch from C. Around the evening is C in the kitchen + on the kitchen stove is a lot going on. Also, we realize that the days – also in Switzerland – get even more longer. 8.18/16.46

8.18/16.46

## 2.4 MATERIALS AND METHODS

### 2.4.1 SAMPLING

The samples we drew for our analyses consisted of the last seven days of June and December for the 12 existing years. From the last year, we also analyzed one additional week per month from July until November, because of the increasing number of abnormalities. In order to have a complete set of 7 days we added single days from the previous or following week in November and December wherever HK left some days blank.

### 2.4.2 PROCEDURE OF ANALYSIS

The text of each sample was transcribed by the first author, N.H., and analyses were performed on the transcripts. In total, about 60 pages were analyzed by 2 raters (N.H., R.S.). One speaks Swiss German and was able to identify dialectal habits so that they were not counted as errors. Due to the fact that HK used a different format for his diary, which influenced his writing style, some analyses were only performed on the years 7-12, in order to obtain comparable data.

The type-token-ratio (TTR) as an indicator of the variability of the vocabulary was calculated by dividing the number of new words used (types) by the number of words used in total (tokens). The higher the result the more variation in vocabulary can be seen.

The basis for the analyses of word frequency was Baayen and Piepenbrock's CELEX database (1993). Before scanning the texts with CELEX, all punctuation marks and formatting were removed, and umlauts were rewritten. Additionally, all the orthographical mistakes were corrected and H.K.'s idiosyncratic abbreviations written in full (e.g. *Rest.* standing for "restaurant"). Some dialectal expressions, such as *Z'morge essen* [having breakfast], were substituted by standard German forms in order to allow the program to also analyze these words. The analysis was computer-based (Aichert, Marquardt, & Ziegler, unpublished) and the results were categorized into subclasses of high (frequency >10) and low frequency words (frequency ≤10).

For the analyses of the connectives we classified these as simple versus complex. The classification made is based on results about cognitive complexity respectively the age of connector usage in language acquisition (Veen, 2011 esp. p. 13-34; Reimann, 1996, 1998).

To test our assumptions about the "linguistic fingerprint" of svPPA in the texts, statistical analyses were performed whenever possible. We used a first-order autocorrelation of

considering the correlation between different points of time. A p-value below .05 indicated a significant change.

## 2.5 RESULTS

### 2.5.1 OVERALL STRUCTURE

#### 2.5.1.1 COMPOSITION OF ENTRIES AND ENTRIES MADE

The overall structure of the entries revealed that HK developed a consistent composition style for his daily texts over the years. In the first two years, his notes look like a memory back-up for appointments or events. Progressively, his entries got more prosaic, narrating about each day (see fig. 4a for an example page). Noting the temperature(s) can first be seen in year 2, time of sunrise/sunset in year 6. Towards the end of the last year a high number of missing entries were documented (n= 36, see fig. 5).

Figure 5: Number of unfinished and missing entries as of September of year 12

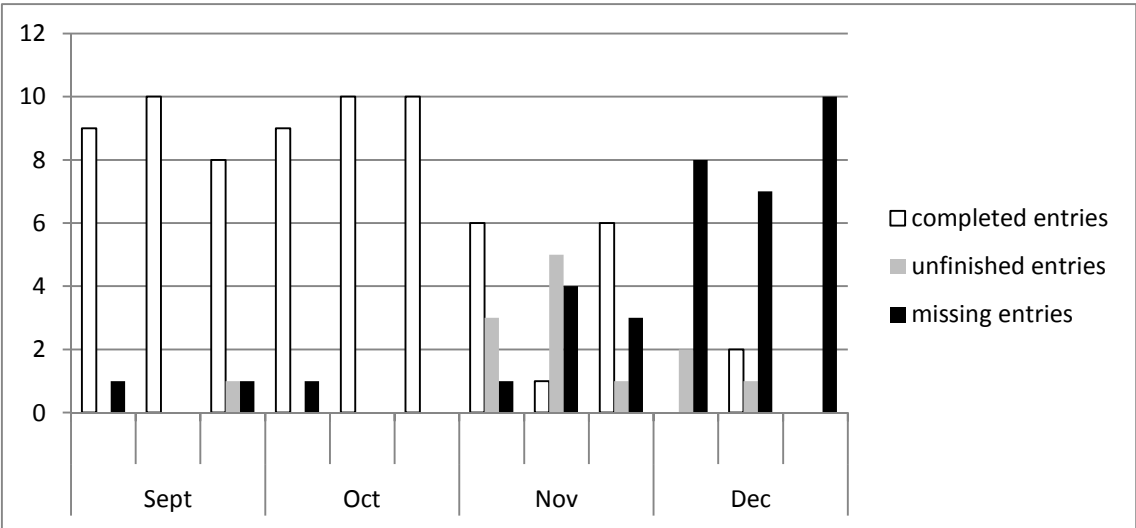
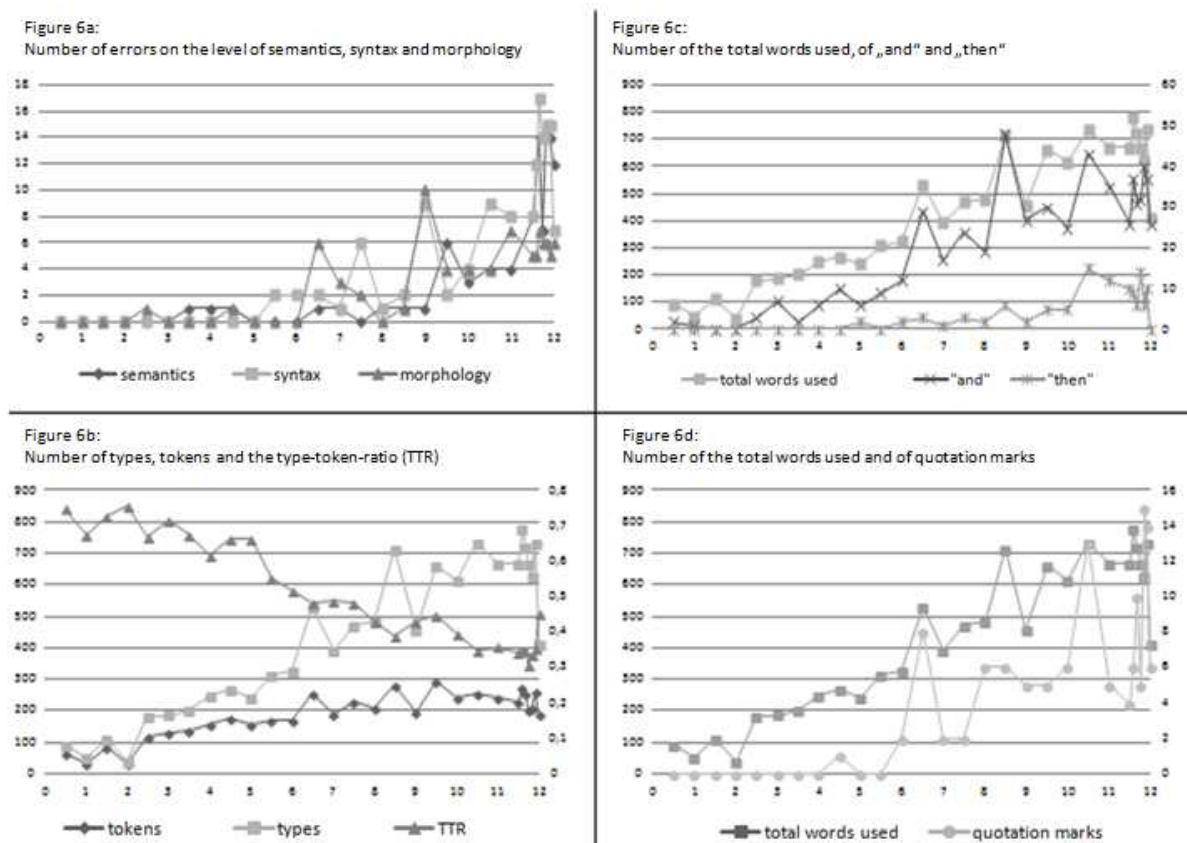


Figure 5 shows the increasing amount of diary entries unfinished by HK or days which he left totally blank in time spans of 10 days from September until December of year 12. Before, he had not missed a single day.

### 2.5.1.2 LENGTH OF ENTRIES

The analysis of the entry length (see fig. 6b) showed that the texts from the first two years were extremely short, due to HK's different entry format and writing style compared to the following years. The length then increases continuously and remains relatively constant from year 7 to 9 with an average of about 500 words per day<sup>1</sup>. Between year 10 and the summer of year 12 the amount sharply increases to about 700 words per entry. Subsequently (with the exception of November) it drops to 400 words in December. When analyzing the number of words statistically, we found that the change from year 7 to 12 is highly significant (p-value:  $p < 0.001$ ).

Figure 6: Overview figures over the 12-year time span



Figures 6a-d show the changes of different aspects of HK's language use in his diary entries spanning over 12 years. 6a shows the increasing amount of mistakes on the semantic, morphologic and syntactic level. 6b illustrates the number of words used in total per entry (types), the number of different words used (tokens) and their ratio, the so-called type-token-ratio (TTR). 6c shows the

<sup>1</sup> The summer of year 9 was excluded from this analysis: the patient had accompanied his partner on a treatment at a health resort, where he produced an unusually high volume of written material.

total number of words (types) in comparison to the amount of the words *und* [and] as well as *dann* [then]. Gd indicates again the total number of words used (types) in comparison with the increasing amount of quotation marks HK used.

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### 2.5.1.3 TOPICS REPORTED

Over the time span of 12 years, we observed a change of topics in the texts of HK. Initially, he mostly notes distinctive and extraordinary events, such as *Heute zum 1x Besuch des neu eröffneten ACV in O* [Today the first visit to the newly opened ACV<sup>2</sup> in O] (June, year 4). Subsequently, he describes his daily walks and the weekly grocery shopping in more and more detail, which can be exemplified by the following entries: *Kommissionen in R + O gemacht* [Went shopping in R + O] (June, year 3). *Nachher gehe ich schnell meinen Kaffee im nebenstehenden Coop trinken, bleibe nur 3 Minuten sitzen + hole dann C im Studio ab. Mit C fahre ich dann wieder in den Coop zurück, wo wir Fr. 63,35 Einkäufe machen. Um 16.44 verlassen wir den Coop.* [Afterwards I go to the Coop next door for a quick coffee, stay only 3 minutes + then pick up C at the studio. Together with C I drive back to Coop where we shop groceries for 63,35 Francs. We leave Coop at 4.44 pm.] (June, year 11). The first time he mentions the topic of breakfast is in year 7, later on he does so on a daily basis. HK then also describes other daily routines in more detail, such as dinner, going to bed and *Lichterlöschen* [turning off the lights].

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### 2.5.2 ERRORS ASSOCIATED WITH SEMANTIC MEMORY IMPAIRMENT

Frequency of occurrence of surface agraphia and semantic paraphasia were analyzed. The statistic analysis showed a significant increase of both error types over time (p-value 0.0002).

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#### 2.5.2.1 SURFACE AGRAPHIA

The results of the analysis show that HK produced overall 12 errors matching the definition of surface agraphia. The frequency of occurrence shows a clear increase towards the end of his entries: 1 in year 8 (*Blanschbecken* instead of *Planschbecken*), 1 in year 9 (*The* instead of *Tee*), 2 in year 10 (*The* instead of *Tee*, *began* instead of *begann*) then 8 in year 12 (e.g. *nam* instead of *nahm*, *Cüffeur* instead of *Coiffeur*).

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#### 2.5.2.2 SEMANTIC PARAPHRASIA

In total 20 semantic paraphasias were detected. Analysis of their temporal distribution showed an increase towards the end of the 12-year time span. The first two semantic paraphasias

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<sup>2</sup> ACV stands for „Automobil Club Verkehr“, the Swiss automobile association

occurred in year 4, another one in years 5 and 7. In years 8 to 11, HK produced 3 semantic paraphrasias per year, then in year 12 the number increased to 4 to 8 semantic paraphrasias per week.

The analyses further showed that the relation between the semantic paraphrasia and target item becomes more distant over time. First, substitutions are easily understandable, e.g. *Das Essen hat uns sehr gefallen* [The meal pleased us very much] (December, year 10). In the last months of year 12 it becomes more difficult to understand the sense of his texts and to uncover the target item behind his paraphrasias. For example, HK writes: *C hat sich dann auch gut angelegt* [sic.] [C then also attached well] (November, year 8).

Comparing the frequency of semantic paraphrasias with regard to the word class, the analyses showed no tendency for one special class: 6 nouns, 7 verbs and 7 adjectives/adverbs were affected.

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### 2.5.3 VOCABULARY

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#### 2.5.3.1 TYPE-TOKEN-RATIO

Given the different text styles over the 12 year time span, the analysis of the TTR becomes interesting from year 7 on, where HK writes longer texts. The analysis showed that the TTR lies constantly at about 0.5 from year 7 to the summer of year 8. Afterwards it fluctuates around 0.45 until the summer of year 10, and then falls to 0.35 until the summer of year 11. This number stays relatively constant until the end, with exception of the last month of year 12 (see fig. 6b). The statistical analyses showed a significant change over time (p-value: 0.00).

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#### 2.5.3.2 FREQUENCIES

Analysis of word frequencies for years 6 to 12 revealed a significant rise in the number of high-frequency words (p-value 0.0161) that was accompanied by a significant decline in low-frequency words (p-value 0.0161).

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### 2.5.4 SYNTAX

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#### 2.5.4.1 SYMPTOMS OF PARAGRAMMATISM AND AGRAMMATISM

In total, errors of sentence composition (sentence inversion or repetition of (parts of) sentences)) occurred 85 times, 64 of which involved perseveration. A clear increase starts in the summer of year 8 (see fig. 6a). We also found two characteristic syntactic errors: *heim nach*



*Hause* [instead of either of the two *heim* or *nach Hause*, both meaning home] and *wir schauen uns den TV an* [instead of *wir schauen TV*, we watch TV], which HK produced from the summer of year 7 onwards. HK here returns to the standard construction of “gehen nach x” [going to x] and “wir sehen uns x an” [we look at x] and ignores the special construction rule in the context of “going home” and “watching TV”. The “home-construction” appears 29 times in total, the “TV-construction” 22 times. Summing up the number of these two constructions together with sentence inversions, repetitions and word elisions, would make a total amount of 136 mistakes on the syntactic level in HK’s texts (see fig. 6a).

Word omissions, typically regarded as a symptom of agrammatism, began with one missing word in the summer of year 6, two in the winter of the same year and again one in the summer of year 7. Missing words occurred again in October and November of year 12 (in total here: 3, e.g. *Um 11 Uhr fahren wir [sic.] unserem Auto nach R.* [At 11 o’clock we drive our car to R.] (October, year 12).

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#### 2.5.4.2 CONNECTIVES

The syntactic structure was examined indirectly on the basis of HK’s use of subordinate clauses, by analyzing his use of connectives (“connectives” refers to sentence-linking words here). Since these do not form a syntactically homogeneous class, but are defined by their function, the connectives analyzed are a selection of the ones used by HK, and hence no claim for completeness is made.

As can be seen in fig. 7, *und* [and] (n=589) and *dann* [then] (n=115) clearly outnumber the other connectives (in total: 46). Their occurrence (compared to the total number of words used) also rises markedly over time (and: from 0.031 in year 1 to 0.059 in year 12; then: from 0 to 0.145, fig. 6c). HK also uses *aber* [but] (n=16) and *wegen* [because of] (n=16) relatively often. *Weil* [since/because] is used 6 times, *trotz* [in spite of] 3 times and *trotzdem* [nonetheless] twice. *Obwohl* [although] was found once, as were *deswegen* [hence] and *danach* [afterwards].

Using a more simple syntactic structure (parataxe built with *and* or *then*) thus shows a highly significant increase over the years (p-value 0.000).



Figure 7: Patient HK's use of connectives

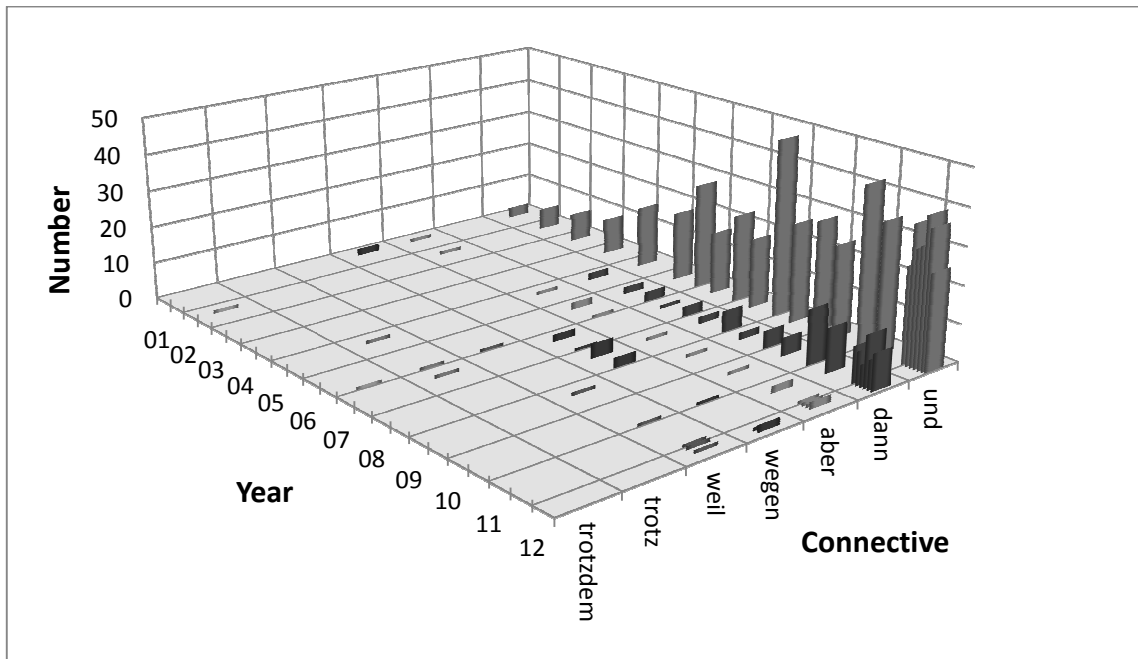


Figure 7 shows HK's use of connectives in his diary entries. On the x-axis the time span of 12 years, on the y-axis the number of used connectives can be seen. 7 different connectives are represented in the figure: in spite of (*trotz*, *trotzdem*), because (*weil*, *wegen*), but (*aber*), then (*dann*), and (*und*). Over the years an increase especially of the coordinating conjunction *und* as well as *dann* can be seen.

## 2.5.5 MORPHOLOGY

On the level of morphology we observed abnormalities of HK's use of inflectional morphemes to indicate number, gender or case and unusual usage of function words such as prepositions and articles. In total we found 83 mistakes of this kind (fig. 6a), beginning from year 5 on. The increase of errors is highly significant (p-value 0.0001).

### 2.5.5.1 INFLECTIONAL MORPHEMES

To characterize HK's use of inflectional morphemes we analyzed markers for time, gender, case and number. The first errors can be seen in year 5, followed by 4 instances in year 7, 2 in year 9, 1 in year 11, and 7 in year 12. In total we found 15 incorrect inflectional morphemes. For example HK wrote *anschliessend trinken wir im Rest. unsere [sic.] Kaffee* [afterwards we had our coffee in the restaurant] (June, year 7). Two of the erroneous inflectional morphemes concerned

time whereas one was formed by the regularization of the strong verb “laufen” [go]: *laufte* instead of *lief* [went] (August, year 12).

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#### 2.5.5.2 FUNCTION WORDS

In total we detected 60 instances of an incorrect function word. The first error was found in the summer of year 5; from the summer of year 7 on their number constantly increases. Examples are: *Wir alle erschrecken am* [sic.] *Donner-Lärm* [We all get frightened on thunder noise] (June, year 9) or *Wir haben mit Hrn. K. einen nächsten Termin um* [sic.] *30. September [...]* *abgemacht* [We’ve fixed our next appointment with Mr. K. at September 30<sup>th</sup>] (July, year 12).

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#### 2.5.5.3 PUNCTUATION MARKS

HK sometimes duplicates punctuation marks, e.g. *Hagel!!!* [hail!!!] (June, year 2); this is considered as being appropriate in context. However, there is an increasing and abnormal use of quotation marks (see fig. 6d). Their usage appears successively more obsessive and inadequate. They barely occur at the beginning of the diary entries but over the course of time, dialect words like *Z’Morge* [breakfast] or *Z’Nacht* [dinner] as well as common words appear more often with quotation marks. The analysis showed that the first abnormal use of quotation marks begins in year 5 with *Hoch* [high] (June) regarding the weather, in year 6 *Vesper* [vespers] (December) and *Laden* [shop] (December) follow. Other ordinary words like *Brot* [bread] (December, year 10), *Post* [post office] (October, year 12) were put between quotation marks, too. Overall, the frequency of abnormally used quotation marks rises from 0 in years 1 -4 to 15 per week in year 12 (see fig. 6d). It is only in the last month that the number of quotation marks decreases. Statistical analyses yielded a significant increase of HK’s usage of punctuation marks in HK’s diaries (p-value 0.0000). The correct usage of quotation marks, e.g. while citing, was of course not included to this analysis.

## 2.6 DISCUSSION

We had the privilege of analyzing the diaries of a person diagnosed with svPPA 12 years after he had started writing them, allowing a unique opportunity to gain insight about written language production in the preclinical and early-to-mid phases of svPPA. We discovered the first abnormalities in HK’s diary entries (semantic paraphasias, word omissions, wrong inflectional morphemes and function words) around year 4, but from the end of year 6 to year 7 we saw a clear increase, steadily rising for the following years (despite some oscillation). Years 7, 9 and 11

have increasing spikes of incorrect language use but they seem to be compensated a little later again until in year 12 they became so severe that HK abandoned writing his diary.

We investigated the overall structure of his diary entries, the topics reported, the vocabulary (type-token-ratio and word frequencies), the symptoms of surface agraphia and semantic paraphasia, the syntax (symptoms of agrammatism/paragrammatism, use of connectives and punctuation marks), and morphologic aspects. We tested several hypotheses derived from changes detected in written texts by people with probable AD dementia and in spoken language in svPPA.

We expected no change in the composition of the diary entries, but less entries made, decreased entry length and a trivialization of their topics. The text composition stayed stable as expected; also HK made less entries in the end and reported more often in more details about trivial day-to-day routines. Concerning the entry length, we first found an increasing phase (year 1-6), then a stable phase (year 7-9), then a sharp increase (year 10 – summer of year 12) followed by a sharp decline in the end of year 12.

We expected to find signs of surface agraphia and semantic paraphasia early and increasing over time; in total we did find them but they were not dominant – compared to other linguistic abnormalities – and only occurred from the last third of the whole time span. The prominent word-finding difficulties in spoken language in svPPA led us to expect a decreasing TTR, with higher frequency words being increasingly used over time, which could be confirmed. We predicted paragrammatic but no agrammatic errors and few if any morphological errors or changes in punctuation. Surprisingly, we found more errors on the level of syntax and morphology than on the semantics and a high amount of abnormal use of quotation marks.

Our two overall aims were to identify the earliest indicators of cognitive change in HK's diary entries and to track the important changes in these diary entries over time. The earliest changes concerned the occurrence of semantic paraphasias, word omissions, wrong inflectional morphemes and function words. The main changes observed over time were the increase of the use of high-frequency words, errors in morphology and syntax as well as the content of the reported topics and an erroneous use of quotation marks, beginning from year 4 on and increasing steadily with spikes in the years 7, 9 and 11.

### *Comparison of findings in written text production in AD and the present study*

Problems with the writing process itself and writer's blocks are reported about the authors Iris Murdoch and Gerard Reve (Peter Garrard et al., 2005; van Velzen & Garrard, 2008). In a non-professional writer, we see incomplete entries or simply blank pages as an indicator of such a blockage. In the diary of HK, in year 12 an increasing amount of entries remain unfinished, is completed by the partner, or pages are simply left blank (see fig. 5). By analyzing the overall structure of the entries we found some rigid routines (e.g. noting the daily weather condition). These elements can be seen as habits that constitute a so called "barrier ritual" (Surd-Büchele, 2011), i.e. a ritual supporting the diving in and out of the writing situation. The barrier ritual enlarges over time and can be seen as a first indicator of a strategy to deal with the progressively demanding writing process.

Regarding the content, in the preclinical phase of AD, both the celebrated writers Murdoch and Reve produced stories that were shallower and more banal, and some slightly chaotic and illogically-composed passages (Heumakers, 1998; Kakutani, 1996). Of course there is considerable difference between composing a fictional story and telling about one's daily life: the topics of a diary are heavily influenced by the daily routines of the writer. Nevertheless, the analysis of the reported issues in HK's diary showed the same pattern: HK's reports get more mundane over the course of time. The underlying change of lifestyle in HK's case (more restricted, routine activities) is also typical of the majority of people suffering from dementia (Shany-Ur & Rankin, 2011).

In order to analyze the vocabulary HK used, TTR and word frequency were calculated. The TTR, which gives information about the variability of the vocabulary, changed notably over time with a remarkable drop in year 10 (see fig. 6b). The decrease in the early years can be explained by the nature of the diary entries, which become increasingly prosaic. The more prose-like writing style automatically triggers a higher number of repetitions in the vocabulary, e.g. caused by pronouns. The high result in December of year 12 can again be explained by the form of the entries itself, since the length of the texts drops from around 700 words to 400. It should be noted that the TTR dropped over the course of time as expected, but the decrease took place between the summer of year 10 and the summer of year 11, thus 2 to 3 years before the clinical diagnosis of svPPA. Also in line with previous findings of written text production in AD (Peter Garrard et al., 2005; van Velzen & Garrard, 2008), low-frequency word usage decreased and high-frequency word usage increased in HK's diaries.

Concerning syntactic composition/sentence construction, our expectation was to find an increasing rate of simple connections (parataxis) expressed with “and” or “then” in combination with a decline of syntactically (and mentally) more demanding connectives such as “despite” or “hence” (hypotaxis). The number of “ands” and “thens” indeed fully outnumbered all other connectives used (115 vs. 46), and HK’s use of these two connectives also rose significantly during the whole time span.

#### *Comparison to spoken language production in svPPA*

The tendency of svPPA patients to talk fluently with less semantic content in the beginning (Warren et al., 2013) would be mirrored by an initial increase in content/length of entries. This is the exact pattern we found. The subsequent decrease of entry length is in line with the more pronounced difficulties in language processing overall.

Surface agraphia and semantic paraphasia are the most well-known abnormalities in written text production of patients suffering from svPPA (Gorno-Tempini, Cappa, et al., 2011). Therefore we expected both error types to occur often in the diaries. In total, we only found 12 mistakes with the characteristics of surface agraphia. Among these, 4 occurred in the years 8 to 10, and 8 in the year 12. The hypothesis of an increasing number of errors of this type, especially in the last year, can thus be confirmed, although we were surprised with the overall low number and perhaps at how late they appeared in the texts. However, if these errors reflect a loss of “semantic glue” associated with deteriorating semantic memory (Patterson, Graham, & Hodges, 1994), they would be expected to follow, rather than anticipate semantic memory decline. Our expectation regarding an increase of semantic paraphasias towards the end of the 12-year time span could also be confirmed (in total: 20). Up to year 8 only one semantic paraphasia was observed, followed by 3-5 per year up to year 11. In the last year, 4-8 semantic paraphasias per week (!) could be detected. In addition, there was an increasing semantic distance between target and paraphasia. However, the semantic paraphasias were equally spread over nouns, verbs and adjectives/adverbs, so the results of Bird et al. (2000) were not replicated.

Concerning syntax, it is said that only signs of paragrammatism (like sentence inversions or duplications and substitutions on the morphological level) can be detected in the speech of svPPA patients (Gorno-Tempini, Cappa, et al., 2011). Results showed the expected, paragrammatic phenomena like sentence inversions (in total 85), but also the typical agrammatic feature of word elision (in total 7). However, Klann (2001) also defines an excessive

use of the connectives “and” and “then”, prominent in HK’s diary entries and already discussed above, as a typical feature of agrammatism.

Two syntactically remarkable constructions should be discussed in more detail: *heim nach Hause* [home to home] and *wir sehen uns (den) TV an* [we watch us (the) TV], where HK ignores the necessary construction rules. It is quite interesting to see, that these two syntactic building rules exclusively got lost. We do not know about studies that reported or examined this aspect in svPPA before.

We did not find typical overlearned phrases as reported by Reilly and colleagues (2010), but what did increase in HK’s texts were the barrier rituals, which mostly consist of recurring standard constructions. Also, HK reports about more mundane and thus more rigid standard routines of his daily life which result in similar constructions. We can thus summarize that HK doesn’t produce standard overlearned phrases but idiosyncratic sentences.

#### *Unexpected findings of the present study*

Regarding the use of punctuation marks, we did not expect any change. This could be confirmed, except for the use of quotation marks. Whereas HK uses them adequately in the first years, he totally overuses them later (the drop in the last month should be seen as a consequence of the shorter entries there). In our view, the most plausible explanation for this finding lies in the feeling of oddness that HK presumably developed for more and more words. We may speculate that his decreasing knowledge about word meanings, which is characteristic for svPPA (Gorno-Tempini, Cappa, et al., 2011), left HK with a strange feeling about the remaining word hulls. Therefore, he marked them by putting them between quotation marks, as if they were foreign, exotic words he is no longer familiar with. This may be consistent with the finding of svPPA patients who report a lack of feelings of familiarity for famous people (J. S. Snowden, Thompson, & Neary, 2004).

Another unexpected result were the numerous morphological errors (incorrect use of inflectional morphemes and function words), which have not been previously reported to this extent. It is difficult to determine whether word-finding difficulties formed the basis for syntactic and morphological abnormalities in HK’s diary entries, as proposed for morphological difficulties in spoken language (e.g. Gorno-Tempini, Cappa, et al., 2011). Search movements are only documented indirectly in written texts by corrections or unfinished words/phrases. The writer is not under time pressure and his product, the text, is therefore not as elusive as spoken

language: he can take the time to think about the proper word or phrase; he can correct a wrong word or circumscribe a missing one. We did not find many corrections in HK's texts and it is therefore difficult to point to specific instances of word-finding difficulties. In our view, problems of monitoring the language production process and working memory seem to be a more plausible cause. HK was impaired in the corresponding neuropsychological tests, consistent with monitoring difficulties.

A second possible reason for the large number of morphologic errors in HK's texts was formulated by Kavé, Heinig and Biran (2007). They concluded that some structural information is influenced by semantics. Considering the lemma-lexeme structure in the mental lexicon as described by Levelt (1995), it seems also possible that not only the semantic part of the lemma-information (consisting of meaning and syntax) can be damaged by the degradation caused by dementia, but also retrieval of the corresponding morpho-phonological form, in this case especially morphology. Our data do not, however, allow us to determine whether the morphologic information itself or the pointer function from the lemma to the morpho-phonological form is affected.

We conclude that it will be important in future to better investigate language monitoring and working memory in svPPA patients, and to further investigate aspects of semantic and morphosyntactic retrieval during language production to better understand language changes in the preclinical phase of svPPA. In our study, monitoring and working memory seem to have a greater influence on written text production than semantic degradation.

#### *Changes in written text in the preclinical phase of svPPA*

First changes could be seen in year 4, whereas language difficulties get more pronounced from year 7 on. In year 12 the patient abandoned his diary writing. We know that HK consulted his general practitioner in year 10, where he reported some memory problems. That summer, he started to take the medication "Symfona", capsules made from ginkgo extract. This is an indicator about his own (or his partner's) estimation of his condition. We therefore saw the onset of pronounced language difficulties fully 3 years before the first consultancy of a general practitioner and 6 years before the clinical diagnosis.

### *Summary*

To sum up the results of the study, we found changes in the number of entries made, their length and the topics reported. The vocabulary showed less variation and words of higher frequency were used more often. Symptoms of surface agraphia and semantic paraphasias, as well as paragrammatic and agrammatic errors did occur. The sentence structure became progressively simpler and incorrect inflectional morphemes and function words were used. Quotation marks were surprisingly overused, which we tentatively suggest may have been due to a feeling of increasing oddness about the world. In conclusion, our analysis of the diary entries revealed the onset of clear abnormalities in the texts about 6 years before the clinical diagnosis took place and showed a higher degree of syntactic and morphologic than semantic problems, which we attribute to problems in monitoring and/or difficulties during the text production process during morphologic encoding. In this study, the characteristic semantic problems reported in svPPA patients emerged later in the course of disease and were less dominant in HK's written language than were other features.



*3 SECOND STUDY:*

*4 DIFFERENT TYPES OF FLUENCY FOR PROPER NAMES IN AD PATIENTS AND HEALTHY ELDERLY CONTROLS*

### 3.1 ABSTRACT

Introduction: Sensitive and easy-to-perform tests to detect early Alzheimer’s dementia (AD) are needed for everyday work in clinics. By combining two promising approaches, verbal fluency and proper names (PNs, here only first names) for the first time, we want to examine PN fluency as a possible screening tool for AD. The aims of this study thus were 1, to describe the performance of healthy controls, 2, to characterize the performance of patients suffering from AD and 3, to investigate the role of the PN fluency type on the output.

Methods: Patients and matched controls were tested with 4 different types of PN fluency: first names beginning with the letter “a” (formal PN fluency – PN-FF), of women/men (minimal semantic PN fluency – PN-minSF) and of persons personally known by the patient (semantic PN fluency – PN-SF).

Results: We could find a clear difference in the amount of reactions between controls and the AD cohort in all tasks. Patients produced significantly less items in general and showed an overall stable performance in all 4 tasks. Controls’ performance however did differ in dependence of the fluency task; they always had the fewest reactions in the PN-FF.

Conclusions: This study could show that PN fluency seems to be a sensitive tool to discriminate healthy controls easily and significantly from AD patients. Further research on larger cohorts, including patients with mild cognitive impairment, would be of additional value.

Own contribution remark: The research questions were put forward by Prof. Danek and myself, and discussed with Prof. Semenza. The idea to combine Proper Names and fluency tasks came from me. All the cohort persons were tested by myself, in the patient group, former Bachelor Students (Stefanie Dandolo, Julia Glaser, Barbara Heß, Kathleen Langkow and Hannah Mentz) helped collecting the data. Statistical analysis was supported by Stablab of the Ludwig-Maximilians-Universität, Munich. The manuscript, including creation of figures, was written by myself.

### 3.2 INTRODUCTION

Due to reported findings about the sensitivity of both verbal fluency (VF) and proper name (PN) retrieval in patients in the state of mild cognitive impairment (MCI) or suffering from Alzheimer's Dementia (AD), we were driven by the question if a combination of those two tests would add up to a sensitive and easy-to-use tool to screen for AD.

Verbal fluency tests (VFT) are used to examine the ability of divergent thinking during a problem solving process (Aschenbrenner, Tucha, & Lange, 2000). Divergent thinking is characterized by the goal of producing as many solutions as possible with an undefined approach to them. In the English speaking countries the *Controlled Oral Word Association Test* (COWA - Lezak, Howieson, & Loring, 2004) is probably the most common test, in German, the *Regensburger Wortflüssigkeitstest* (RWT - Aschenbrenner et al., 2000) is the only standardized test for VF. The tests consist mostly of three different types of tasks: semantic fluency for a certain category (like clothing or groceries), formal (also: letter) fluency for words beginning with a certain letter (mostly F, A or S) and a task that requires switching between two categories (like animals – flowers) or two different initial letters (like P – M). There is mostly a time limit of 1 minute for producing as many items as possible of the required type. Not only the capacity to selectively search for the correct words, also monitoring and continuously updating the words already used, mental set shifting strategies for a strategic search as well as following the given rules are necessary to fulfill the task properly (Elfgren & Risberg, 1998; Rende, Ramsberger, & Miyake, 2002; Shimamura, 2002).

According to some studies (Adlam et al., 2006; Mok et al., 2004; Murphy, Rich, & Troyer, 2006; Palmer et al., 2003) VFTs are an appropriate tool to screen for AD in the early (pre-clinical) phase. Sailor's, Zimmerman's and Sander's (2011) results show that the difference between AD patients and healthy controls is larger in semantic fluency tasks than in formal ones. Other studies (e.g. Monsch et al., 1997) and a meta-analysis of 153 studies (Henry, Crawford, & Phillips, 2004) showed that AD patients were more impaired in semantic fluency tasks than in formal ones and that this impairment also was more significant than measures of verbal intelligence or psychomotor speed. According to Laws et al. (2010), semantic fluency, on the one hand, seems to be affected early in AD and stays relatively stable in the course of the disease, formal fluency, on the other hand, is less impaired at the beginning but declines steeper over time.

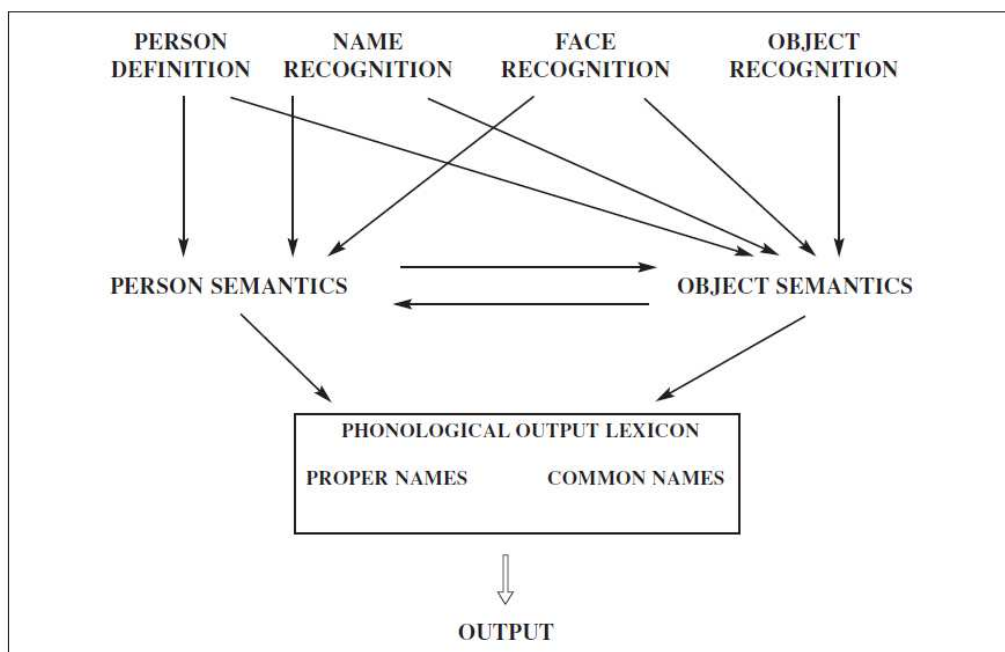
The influence of education (Amieva et al., 2005; Fritsch, McClendon, Smyth, & Ogrocki, 2002; R. S. Wilson et al., 2004), sex (Laws, Adlington, Gale, Moreno-Martínez, & Sartori, 2007; Laws et al., 2010; Moreno-Martínez, Laws, & Schulz, 2008; Tombaugh, Kozak, & Rees, 1999; Wallentin,

2009) and the nature of the asked categories (Azuma et al., 1997; Diaz, Sailor, Cheung, & Kuslansky, 2004) (e.g. the presence of sub-categories or clusters within a category which may facilitate the retrieval of items) on VFT is still on debate.

The combination of the fluency tasks with the retrieval of PNs seems promising. PNs and common nouns (CNs) fulfill different functions: PNs are used for individuation, CNs for categorization. Therefore names are stored differently and have a different semantic content. There is no obvious hierarchy between names, thus we cannot talk of a hierarchal structured network as it is the case in CNs (e.g. *living thing – animal – mammal – cow*), a basic level (a level where items show the largest accordance of sensations and where items are processed the fastest) doesn't exist either. Regarding the semantic content, CNs are defined by the membership of their corresponding category with its special properties (e.g. an *apple* belonging to the category *fruit –being healthy, natural, juicy,...*), PNs are not (e.g. *Tony* doesn't necessarily belong to the category *male* and *human*, *Tony* could e.g. also be a certain cuddle toy). If we know a person/animal/thing with a certain name, the semantic properties define the named subject. Or in other words the semantic content of a PN is a random combination of properties. Thus, PNs are arbitrary and unique labels of persons/animals/things given by someone. This makes them so hard to remember and easy to forget (James, 2004; Pelamatti et al., 2003; Carlo Semenza, 2006b). The retrieval of a PN normally follows the pathway from face/name recognition/person definition to the semantic content of the person and then to its phonological representation (see fig. 8).

We know that the processing pathways for PNs and CNs follow different routes (Carlo Semenza, 2006b), but the location of PNs in the brain is not totally clear yet. Often involved in PN anomias as well as in PN sparing is the left temporal lobe, but also the opposite pattern, an intact temporal lobe and damage in the basal ganglia, the thalamus and the occipital lobe were observed (Carlo Semenza, 2006b). The review of Yasuda et al. (2000) states that in PN processing a complex network - mainly located in the left hemisphere - is involved. But because of its specialization on aspects of personal relevance the right hemisphere might contribute to the recognition of PNs as well (Ohnesorge & Van Lancker, 2001; Carlo Semenza, 2006a).

Figure 8: Retrieval pathway of a Proper Name (Carlo Semenza, 2006b, p. 889)



The retrieval of a name always passes, first, the person semantics and then the phonological output form, independent of the input modality.

Studies on proper name retrieval report increasing troubles to access PNs in picture naming tasks in healthy elderly persons (Evrard, 2002), impaired recall of PNs as well as profound problems in naming faces in MCI (Ahmed et al., 2008; Estévez-González et al., 2004) and AD (Delazer et al., 2003; Greene & Hodges, 1996; C Semenza, Borgo, Mondini, Pasini, & Sgaramella, 2000; C Semenza, Mondini, Borgo, Pasini, & Sgaramella, 2003a; Werheid & Clare, 2007). Delazer et al. (2003) examined the PN retrieval in AD and found a post-semantic access problem (shown by many experienced tip-of-the-tongue-phenomena), problems in accessing the phonological representations and a degradation of the representation itself (expressed by less sensitivity to phonological cueing). It could be shown that PN retrieval was more sensitive to early AD than other tests, and Semenza and colleagues (2003a) suggested including PN testing into the screening routines in the early phases of AD. However, in most cases, the PN studies are conducted via picture naming tasks. But because naming famous persons via pictures has some negative aspects (1, visual and face recognition abilities are needed and clearly influence the results 2, knowledge about famous people is highly dependent on personal interests, age, culture, social status etc. and 3, requires huge efforts with regard to arranging and updating the test material) it would be of advantage to test PNs differently: less dependent on external factors, easier to carry out and with easy-to-collect norm data.

We therefore developed a PN fluency test based on the existing ones for CNs (thus including formal and semantic aspects) and studied healthy controls and AD patients with it. To the best of our knowledge no study has reported on different kinds of PN fluency in any type of test persons. Our aims thus were 1, to describe the performance of healthy elderly controls, 2, to describe the performance of AD patients and 3, to describe differences in the amount of produced reactions in respect to the fluency task. We expected to find clearly different performance patterns in patients and healthy controls. If that is possible, we hope to suggest PN fluency as a useful, quick and easy-to-perform test to include with screenings for AD. Reactions in the minimal semantic condition (naming female/male names) should be the same because of their parallel design (details on the test composition are described under Materials and Methods). Regarding the findings in common fluency testing, the semantic task (naming familiar persons) should be easier than the formal condition (naming first names beginning with “a”). The non-hierarchical organization of PNs and the flood of semantic information they contain, however, point to more difficult processing. So we hypothesized that the performance in naming familiar persons of healthy controls is significantly better than the performance of patients. Performance in the minimal semantic task should oscillate somewhere between results of the formal and semantic condition.

### 3.3 MATERIALS AND METHODS

#### 3.3.1 TEST MATERIAL

On the basis of existing VFT (compare e.g. Aschenbrenner et al., 2000; Lezak et al., 2004) we developed a fluency test for proper first name fluency (PNF). In accordance with formal fluency tests on CNs we decided to choose A as the first letter, also in order avoid difficulties with hearing impaired elderly individuals. Based on an internet-search for first names used in Germany we found that first names beginning with the letter A are relatively frequent, consequently it was also made sure that there is a pool of names big enough (n = 6097) to choose from (“Baby-Vornamen.de - Beliebte Vornamen aus aller Welt - Babynamen und Kindernamen für Jungen und Mädchen,” n.d.). In accordance with the existing VFT, we named this task the PN formal fluency task (PN-FF).

Because of the special character of first names, we decided not only to differentiate between formal and semantic fluency, but also to test a minimal semantic task (PN -minSF). This type of fluency task asks the patient to produce as many female/male first names as possible. The

minimal semantic information about the sex of the name bearer is here the only limiting factor for the reactions. We did not include a test of an “inbetween” level of semantics, which is more demanding than female/male and has less semantic content than a person personally known (e.g. PNs of a certain semantic category like *politicians* or *actors*), because these would again be highly dependent on the personal interests of the patient. Also, we did not include a task where a shift between categories was asked, because we wanted to avoid effects of nuisance in the control group and effects of excessive demands in the AD group.

Lastly, we asked to produce as many first names of persons know personally, e.g. family members, friends, colleagues, neighbors etc. as possible. Surely, there is some they have left semantic information connected to their first name, although of a different amount (compare a life-long partner for 30 years to the new neighbor). But this fact can also be considered in CNs (compare your semantic information of a *dog* and a *gnu*). This task was named the PN semantic fluency task (PN-SF). To check if the persons named by the patient were really familiar, we asked the patient to tell us about the person “behind” each name after the test session.

We decided to have a time frame of 90 seconds for each fluency task in order to give the patients enough time and to avoid ceiling effects in the control group.

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### 3.3.2 PROCEDURE

Before each of the four tasks, patients and controls were instructed to produce as many words of the required category as possible within 90 seconds. Because both groups had already done fluency tasks before, we were sure that they understood the instruction and did no special exercise beforehand. Patients and controls were first asked to produce as many first names beginning with the letter “a” as possible, then first names of girls/women, then of boys/men and at least first names of people they know personally, such as family members, friends, neighbors or colleagues. In between, we presented other tasks as distractors: MOCA (Nasreddine et al., 2005) and the test for handedness (Oldfield, 1971) only for the control group, Repeat and Point Test (Hodges, Martinos, Woollams, Patterson, & Adlam, 2008, german version: Heitkamp, Ebert, Danek, not published) for both groups, and two subtests of the Semantic Battery (Joubert et al., 2010, german version: Knels and Heitkamp, not published) only for the patient group. Reactions were noted with marks after 30 seconds and 60 seconds and the number of produced items was calculated. The production of a name was counted once, even if it was produced more often. Wrong answers in reference to the demanded category were not counted. In the end, we interviewed the patients about the persons named in the PN-SF task. Also, a small pedigree was drawn together with the interviewer in order to exclude test persons with less than 5 living

relatives, which could have had an effect on the last fluency task. None of the tested persons fulfilled this exclusion criterion.

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### 3.3.3 PATIENTS

We examined 12 patients suffering from AD in a mild to moderate state of the disease. The group consisted of 8 women and 4 men. They were included in the study in the order of their appearance at the following institutions: Neurologische Poliklinik of Ludwig-Maximilians-Universität München, Klinik Nürnberg Nord and the Alzheimer-Therapie-Zentrum in Bad Aibling. Detailed information about the distribution of age and years of education can be found in table 2.

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### 3.3.4 CONTROLS

The control group consisted of 12 healthy persons, matched for age and sex with the patient group. In order to exclude persons with so far undetected mental impairments the control group had to pass the MOCA (Nasreddine et al., 2005) with a score of  $\geq 27/30$ . A detailed characterization of the group can be found in table 2. All control group persons were retired and lived on their own.

**Table 2: Demographic data of patients and controls**

	N= total (female/male)	age (mean)	age (deviation)	education in years (mean)
patients	12 (8/4)	77,58	60-91	12,2 <sup>3</sup>
controls	12 (8/4)	76,00	69-89	15,4

## 3.4 RESULTS

Firstly, we compared our data from the PN fluency with the only available German norm data for fluency from the RWT (subtests are first names, CN fluency for words starting with the letter “m” and items belonging to the category “animals”; Aschenbrenner, Tucha, & Lange, 2000) in order to see if we were really testing something different with fluency for PNs or if data is comparable to CN fluency. A different time frame for reactions (1-2 minutes instead of 90 seconds) in the

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<sup>3</sup> We have not been able to get proven information about education for one patient, the mean years of education are thus calculated from n=11.



RWT and results only given as percentile ranks made this somewhat difficult. Therefore, only the numbers of reactions given within the first minute of our PN testing were compared. Table 3 shows the number of corrects reactions of our control group as well as the percentile ranks of the RWT's subtest.

Table 3: Overview of the performance of healthy controls (n=12) after 1 minute and norm data available from the RWT

	PN-FF "a"	PN- minSF "women"	PN-minSF "men"	PN-SF "familiar persons"	First names	Formal fluency "m"	Semantic fluency "animals"
<b>Control group</b> Mean (range)	11,33 (6-17)	20,33 (15-29)	19,92 (14-27)	19,66 (15-25)	-	-	-
<b>RWT group</b> > 65 years (±PR 25 - ± PR75)	-	-	-	-	17 (12-22)	9,5 (7-12)	15 (12-18)
<b>RWT group</b> > 12 years education + age > 65 years (±PR 25 - ± PR75)	-	-	-	-	19 (15-23)	14 (12-16)	17 (15-19)

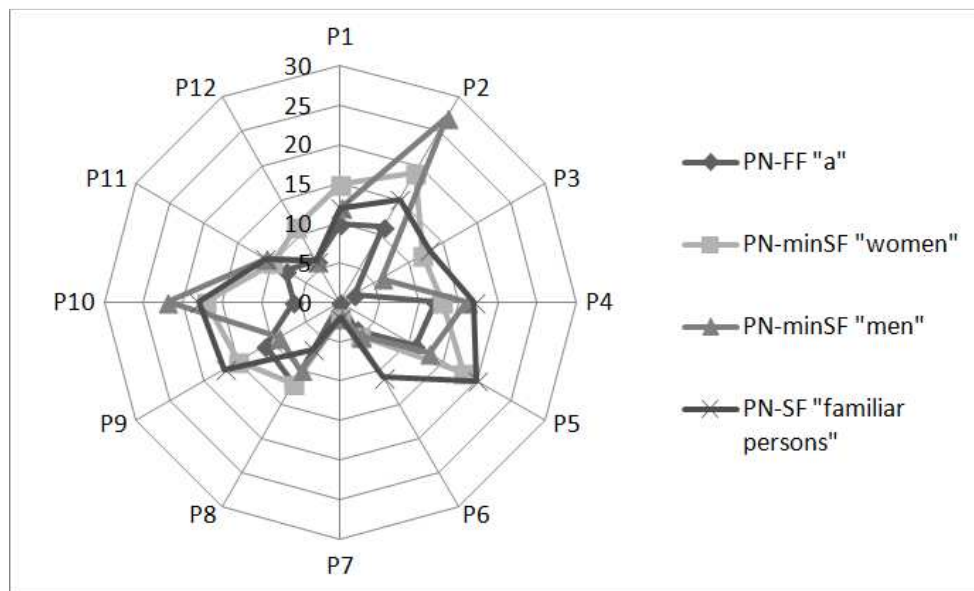
The comparison of the RWT data with our PN fluency results shows that PN fluency testing has to be considered as a different fluency task than fluency for CNs, even when asking for the category of "first names".

The comparison shows that no PN fluency result of our test cohort can be equalized with a fluency task for CNs. Formal fluency seems to be much more demanding for PN (mean 11,33) than for CNs (mean 17 respectively 19). The semantic tasks for PN failed to differ after 1 minute from the minimal semantic tasks in healthy controls, but the difference was significant after 90 seconds. The formal PN fluency seems to correlate least with the general "first name" fluency task of the RWT. "First names" as a semantic category in the RWT correlates more with the standard semantic fluency category "animals" and with the minimal semantic tasks of our PN fluency test. According to the results, semantic fluency for PNs (mean 19,66) cannot be compared to CNs (mean 15 respectively 17).

### 3.4.1 COMPARISON OF PATIENTS AND HEALTHY CONTROLS

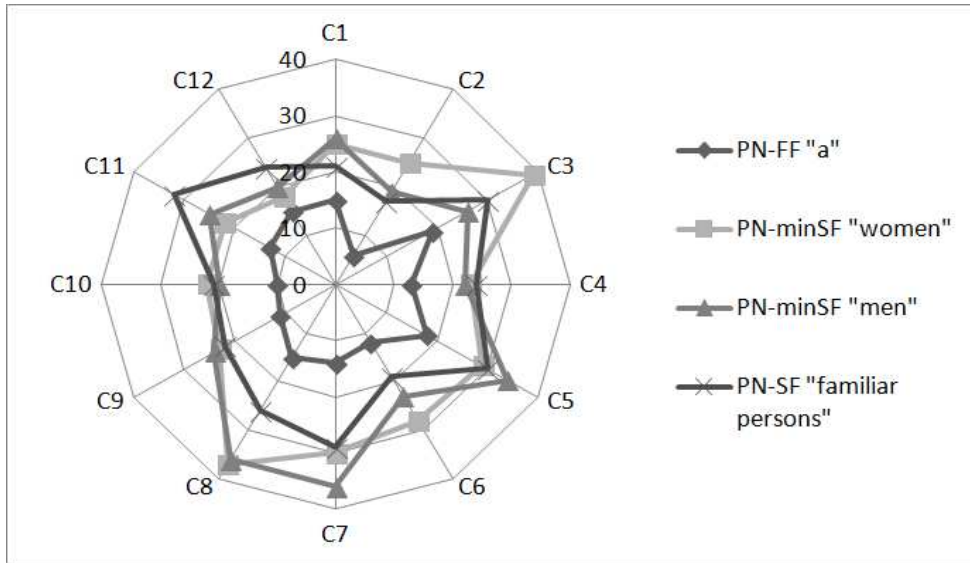
The comparison of the results from the patient (see fig. 9) and the control group (see fig. 10) showed that patients produced in general a smaller amount of reactions. The calculation of the Walch two sample t-test showed that the performance of patients compared to controls significantly differed in all tasks (p-value PN-FF: .001517, p-value PN -minSF "women":  $3.833 \times 10^{-6}$ , p-value PN -minSF "men":  $3.24 \times 10^{-5}$ , p-value PN-SF:  $7.877 \times 10^{-6}$ ), but was smallest in the formal task (see also fig. 11).

Figure 9: Results patients



The patients codes are noted on the outside of the chart, the rings show the number of produced items. The different proper name fluency tasks can be read off the different lines. It can be clearly seen that performance of the patients does not differ much among the 4 different sub tasks but that, nevertheless, it was most difficult to produce first names beginning with the letter "a", thus the formal PN fluency, compared to the rest of the tasks.

Figure 10: Results controls



The codes of the healthy controls are noted on the outside of the chart, the rings show the number of produced items. The different proper name fluency tasks can be read off the different lines. The results clearly show that, as expected, the 4 different tasks of proper name fluency differ from each other. Furthermore, it can be seen that the formal fluency task, producing first names beginning with the letter "a", was the most challenging one for the patient and the two equally difficult tasks of minimal semantic requirement, producing as many first names of girls/women respectively of boys/men, also show equal results. Finally, the semantic PN task, to produce as many first names of familiar persons, oscillates around the two minimal semantic tasks.

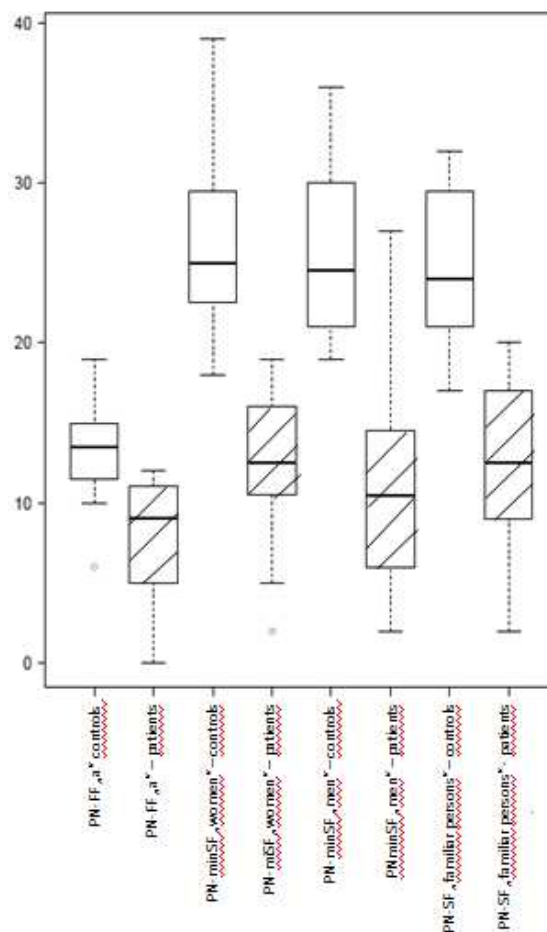
### 3.4.2 COMPARISON OF FLUENCY TYPES

The results show that the first task (PN –FF) was the most demanding one for healthy controls; here they produced fewer items than in the other tasks (mean 13,42). As expected, the reactions on the two PN-minSF tasks - which were designed as tasks of equal complexity - did not differ (mean for women’s names: 26,75; for men’s names: 25,92). The number of correct responses on the PN-SF oscillates between the formal and the two minimal semantic tasks (n = 17-32, mean 24,58). Only one control person (HJK) produced the maximum number of reactions in the semantic task (n=32).

It was shown that patients produced, overall, a very balanced amount of answers (mean PN-FF: 7,75; PN-minSF women: 12,52; PN-minSF men: 11,58; PN-SF: 12,42), but the formal task was here, too, the one with fewest reactions.

We conducted a Kruskal-Wallis rank sum test in order to check on the significance of the variation between the reactions of the different types of fluency. The p-value in the patient group was .07861, thus not significant, in the control group  $1.062 \times 10^{-5}$ , thus clearly significant (see also fig.11).

Figure 11: Performance of patients and controls in all 4 proper name fluency tasks



Overview of the performance of healthy controls and patients (striped boxplots) on all of the 4 PN fluency tasks.

### 3.5 DISCUSSION

In our study we combined two aspects which are well known to differentiate (early) AD from healthy controls in order to see if their combination yields brings a test which is easy and quick to perform and helps discriminating between AD patients and healthy elderly: verbal fluency and proper name retrieval. On the basis of existing VFTs, patients and matched controls were examined with the PN fluency test, consisting of 4 subtests: formal fluency (PN-FF, first names beginning with the letter A), two minimal semantic tasks (PN-minSF, first names of women/men) and a semantic task (PN-SF, first names of persons personally known). To the best of our knowledge a differentiated fluency test on PN has not been conducted yet in any sort of test person cohort. We therefore wanted to describe the performance of healthy controls. Our hypothesis was, on the one hand, that patients and controls should perform significantly different and that, on the other hand, there should be differences in the amount of produced reactions, depending on the fluency sub task.

When comparing the norm data from the RWT (Aschenbrenner et al., 2000) with our data in order to see if PN fluency really is something different than fluency for CNs, we found a clear distinction of the two tasks types. Especially the RWT task “producing as many first names as possible” made clear that there is a clear difference in results in dependence of the task: PN fluency is not asking for the semantic category of “first names” but examining items within this category. It would be interesting now to see which results can be achieved in larger test cohorts and investigate if different search strategies are used and in which way PN fluency challenges cognitive processes differently than CNs or the category of “first names”. Regarding the time frame, it seems to be important to give healthy controls a time frame of 90 seconds so that their reactions are not capped by the interviewer.

Analysis of the PN fluency itself showed a clear difference between the performance of patients and controls in all tasks. Patients produced in general fewer items and had an overall stable performance, independent of the subtask. Least discrepancy between controls and patients was found in the formal task (PN-FF), the most demanding one for healthy controls. We explain this finding with the unusual request - finding first names beginning with a certain letter - which has probably never been asked of a test person before. But producing less formal than semantic answers also reflects a common pattern in healthy elderly (Laws et al., 2010) and could also be shown in our AD group. It would now be interesting to investigate if the different reaction pattern of patients suffering from AD is already apparent in the MCI phase. If so, a future development of AD could easily and quickly be predicted. Advantages of PN fluency testing are

obvious: no influence from external factors such as visual abilities or personal interest of the patient and no effort in arranging the test material. Semenza et al.'s claim to include PN retrieval in AD screening could then easily be realized (C Semenza, Mondini, Borgo, Pasini, & Sgaramella, 2003b).

The analyses of the two minimal semantic tasks (PN-minSF) showed that all tested persons performed similar, which is what we expected because they were designed as tasks of equal difficulty. Controls had a wider range in producing female first names, patients, however, in producing male first names.

The semantic PN fluency task, producing as many first names of persons personally known as possible was slightly more easily compared to the PN-minSF for patients than for controls. We speculate that this finding might result from a ceiling effect in controls: they produced much more female and male names within 90 seconds. In this task, all of the controls "climbed" along the alphabet from a certain point onwards, whereas patients lacked this strategy, so their production was slower. Probably controls also performed at ceiling (compare Moreno-Martínez et al., 2008) in the category familiar persons, so that the smaller pool of familiar persons compared to the definitely larger pool of female/male names contributed to this finding. Patients thus performed slightly better in producing familiar persons than female/male names, though not significantly better.

In patients, however, we failed to find a significant difference between the different PN fluency tasks. One possible explanation could be a floor effect in the patient group, but it could also be possible that this finding is "normal", meaning that AD patients in a mild and moderate phase of the disease do show a balanced performance in all the PN fluency tasks. As mentioned, they do not profit from the search strategy "alphabet" in the two minSF tasks, formal fluency seems to be quite demanding, whereas "familiar persons" seems to be the easiest category. Further research in larger cohorts with mild AD or MCI patients could help clarify this. In severe dementia, however, Morena-Martínez et al. (2008) already proved floor effects for VFT. Because there was no significant change of the data after 30/60 seconds compared to the data after 90 seconds (analyses conducted for 9 out of 12 patients, see fig. 12) a time frame of 60 seconds would be sufficient for the patient group although a better comparison to performance of healthy controls is shown after 90 seconds.

Figure 12: Patients` data after 30, 60 and 90 seconds

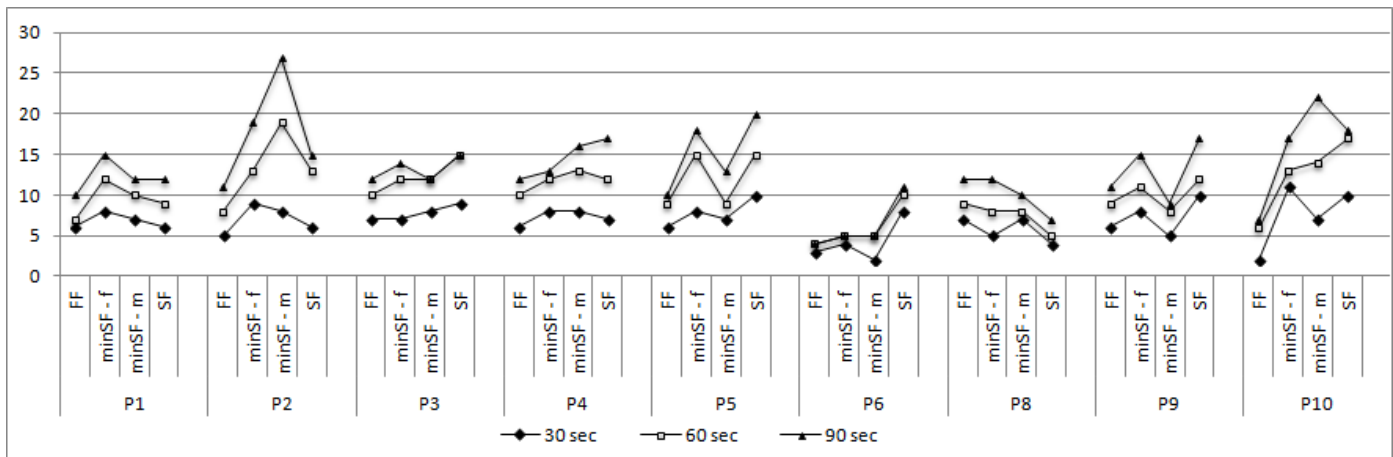


Figure 12 shows the reaction patterns of all four PN fluency tasks of 9 patients after 30, 60 and 90 seconds. It can be seen that patterns do not differ significantly and that the amount of reactions between 60 and 90 seconds, in most cases, does not change the reaction pattern.

Due to obvious limitations in this study in terms of sample size, lack of CN fluency data from the patients and variation of patient cohort further research is needed and seems to be promising. When having norm data for healthy elderly, PN fluency testing could prove to be an easy-to-perform and sensitive test tool to screen for AD maybe already in the MCI state. Resulting from our findings, a reduction of the test battery to PN-FF and PN-SF, as well as a time frame of only 60 seconds should be sufficient.

It would also be very interesting if a comparison with results of patients suffering from early primary progressive aphasia (PPA) or its semantic variant (svPPA) showed different patterns of PN fluency production than controls and AD patients. A qualitative analysis taking into consideration the time factor of the named persons (thus in the formal task – old-fashioned vs. modern names, and in the semantic task familiar persons who met during childhood vs. more recent acquaintances) would be interesting, too (compare Delazer et al., 2003; Fine, Delis, Paul, & Filoteo, 2010).

## 4 GENERAL DISCUSSION



#### 4.1 LINGUISTIC ANALYSIS OF WRITTEN TEXT PRODUCTION IN A CASE OF SVPPA

Chapter 2 of this thesis reported about the study based on the diary of patient HK, diagnosed with the semantic variant of PPA, twelve years after he began to write daily entries. The examination included a broad analysis of different linguistic levels, thus covering aspects of vocabulary, syntax, semantics and morphology.

Changes could already be found nine years before the clinical diagnosis took place. Surprisingly, the majority of errors was found on the morphologic and not on the semantic level. It seems thus to be of clinical interest to establish if morphologic abnormalities are common in svPPA-patients in the preclinical phase and always precede semantic errors or if this is only the case in written text production, or only in our patient. Also, the study indicates that written text production might be used as a documentation tool for very early changes in language use or patients of high education not applicable for the average test materials.

If there were enough time and staff capacity it would, of course, have been interesting to analyze more of the available data to get a more detailed insight into the course of linguistic decline visible through the errors in the texts of HK. Hopefully, more of those analyses will be conducted in the future to get a comprehensive view of the disease, which might influence some speech therapy strategies and will help to clarify what the brain deterioration does to the language system.

#### 4.2 4 DIFFERENT TYPES OF PROPER NAME FLUENCY IN AD PATIENTS AND HEALTHY ELDERLY CONTROLS

In part 3 of the thesis the author reported on a study that tested, for the first time, Proper Name fluency in a cohort of patients suffering from AD and healthy elderly controls. Proper Name fluency was split in 4 different tasks: Producing as many first names as possible beginning with the letter “a”, as many female/male first names and as many first names of personally known persons within a time span of 90 sec.

Even though the study had its limitations, it could show that working with Proper Name fluency in patients suffering from AD seems promising. The test aimed at a different target than normal fluency tasks conducted with Common Names, control persons and patients performed differently and Proper Name fluency tasks also differed from each other (with the exception of female/male ones which were also initially designed as a parallel task).

One of the next steps in future research should definitely be trying to apply the test to a large cohort, including patients suffering from different variants of dementia, especially language-accented ones, and patients in the state of mild cognitive impairment (MCI). If those results show different patterns of production rates it would further be very interesting to do a follow-up study in the MCI-cohort to check if Proper Name fluency is a sensitive tool to easily detect persons with a higher risk of suffering from dementia in the course of time. Also a qualitative analysis of the produced items would be an interesting subject. Results could help to clarify the possible storage modalities of Proper Names.

#### 4.3 CONCLUSION

The motivation of the thesis at hand was to shed light on two aspects of language deterioration in the course of dementia which have not been subject to scientific studies before: the longitudinal analysis of written text production in the preclinical phase of svPPA and Proper Name production in patients suffering from Alzheimer's Disease and healthy elderly in the form of a newly developed fluency task. Both studies revealed interesting and promising aspects, worth to be investigated in more detail. The author hopes that the work conducted here will be refined by future research to deepen the insights gained - for the benefit of the patients.

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Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Thema

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Nari Heitkamp