

Cognitive erosion and its implications in Alzheimer's disease

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Linköping University

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Interviewer: "Do you have problems with your memory?"

Patient: "Yes."

Interviewer: "In what way?"

Patient: "I don't remember."

Sometimes it seems, the more you know, the less you can conclude. /Selina Mårdh

Thank you,

To all of my participating patients, their spouses and to the control subjects who made this research possible. I hope that you and more after you can benefit from the results.

Thank you also to Thomas Karlsson, Jan Marcusson, Peter Berggren, Jan Andersson, Stefan Samuelsson and many others along the way.

I dedicate this thesis to Isak, Love, Silas and Valder.

Sincerely,

Selina Mårdh

Linköping, April, 2013

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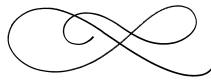
List of publications

The present thesis is based on the following original research articles:

- I Mårdh, S., Nägga, K., & Samuelsson, S. (2013). A longitudinal study of semantic memory impairment in patients with Alzheimer's disease. *Cortex*, 49(2), 528-533.
- II Mårdh, S., Karlsson, T., & Marcusson, J. (2013). Aspects of awareness in patients with Alzheimer's disease. *International Psychogeriatrics*, in press. Advance online publication. doi:10.1017/S1041610212002335
- III Mårdh, S. (2013). Weak central coherence in patients with Alzheimer's disease. *Neural Regeneration Research*, 8(8), 760-766.
- IV Karlsson, T., Mårdh, S., & Marcusson. (2013). Emotion and recollective experience in patients with Alzheimer's disease. *Submitted manuscript*.

Background and incentives

My interest in research started with a fascination for the mysteries of the human brain. The human brain still holds secrets to us, though mankind has been very persistent in her pursue to conquer and understand the brain in all its beauty. As vital and vibrant as the brain is when it is normal and in full function, as brutal and debilitating it is when it fails. This is a story of failure.



To understand the brain and its function, it is possible to study the brain in a straightforward manner – perform functional imaging and neuropsychological tests on normal individuals. Another approach is to study a dysfunctional brain, a brain where the localisation of the damage is known. An effective way of pinpointing function to area is to study the consequences of the damage in human behavior and performance and in that map behavior to biology (Shallice & Cooper, 2012). Two broad areas of brain research in the latter manner are traumatic head injuries (Maas et al., 2012) and the study of neurodegenerative cognitive disorders, such as Alzheimer’s disease. The present thesis focuses Alzheimer’s disease and involves research on behavior related to the damage on the brain, theories on degeneration patterns, and failing performance but also a story on the Alzheimer individual’s perspective and how to handle cognitive erosion in everyday life.

The word dementia originates from Latin and means “de=no” and “mens=mind”. Dementia is an umbrella concept, which includes several

neurodegenerative diagnosis, amongst them Alzheimer's disease. Clinically, there are numerous examples of individuals with an Alzheimer diagnosis to be treated as a person with no mind. An obvious example was the loving and caring couple who came for counselling to me and who had a later appointment with the doctor. At the doctor's office, they found out that the wife was diagnosed with Alzheimer's disease. They were asked to participate in a study, hence they came back to me for evaluation and to book a date for another visit. The hour that had passed since they last saw me had changed their lives forever. Unfortunately, the husband immediately turned to me as to an equal and ignored his wife. He went from being an empathetic, loving and worried husband to a man who was a caregiver. He portrayed this in a very obvious way by talking *about* his wife instead of *with* her. He no longer included her in the conversation though she was sitting next to him at the very same chair she was sitting on an hour earlier. This illustrates many peoples' perception of individuals with Alzheimer's disease. Individuals with Alzheimer's disease are people with no mind and are therefore not counted on or even included in their own social context.

Apart from studying the characteristics of the semantic decline in Alzheimer's disease, the present thesis aimed at gaining insight into the inner world and feelings of an individual suffering from Alzheimer's disease. The perspective of the Alzheimer patient is repeatedly neglected in research, literature and clinical practice. It is neglected in favour of the perspective of the spouse and significant others. In Sweden, the disease itself is often called "The disease of relatives" ("De anhörigas sjukdom").

Layout of the thesis

The present thesis comprises two major studies. The studies have been scientifically reported through four original research articles. The thesis as a whole comprises three major parts:

First introduced is the definition and etiology of Alzheimer's disease (AD) as well as a description of the concepts that are related to the research issues of the studies. The main concepts of the studies were memory, awareness, metacognition, central coherence and emotions. All concepts are explained in relation to AD, apart from the concept of central coherence, since the research of the present thesis is the first to relate central coherence to AD.

Second, the four research articles are summarized. In relation to each article, a statement of the "Contribution to theory" and "Contribution to the understanding of the Alzheimer individual" is made. The summaries of the articles are the highlights of the research. More details and results can be found in the full length articles at the end of the thesis.

Third, an overall discussion is undertaken. Methodological issues are addressed, an overall statement of the thesis contribution to theory and understanding of the AD individual is made as well as a statement of the clinical implications of the thesis.

At the end, all four of the research articles are included in full.

Alzheimer's disease

Alzheimer's disease is an irreversible, neurodegenerative age related disease and the most common of the dementias (for an overview, see Blennow, de Leon & Zetterberg, 2006; Ferri et al., 2005; The Lancet, editorial 2011). In Sweden, the incidence of AD is an estimation of 112 000 individuals (OmAlzheimer, 2013, April 17). Worldwide, the number is 24 million and increasing (The Lancet, editorial, 2011). Since Alois Alzheimer in 1907 (Alzheimer trans. Strassnig & Ganguli, 2005), first described what would later be called Alzheimer's disease, there has been a vast increase in knowledge on how the disease is manifested, both regarding clinical symptoms and the pathophysiological process underlying the disease (Jack Jr et al., 2011). The latest revision of the criteria for a clinical diagnosis of AD was made in 2009 on the initiative of the National Institute of Aging (NIA) and the Alzheimer's Association. The new criteria were published in 2011 (McKhann et al., 2011). The preceding criteria were established in 1984 and suggested that AD is a clinical-pathological entity in that subjects meeting the diagnostic criteria would also display an AD pathology in case of autopsy (NINCDS-ADR, 1984). The body of research in the last 28 years, though, allows for the conclusion that meeting the clinical criteria does not automatically mean having the underlying etiology and vice versa. The increase in knowledge makes it possible to distinguish between three different stages of the disease (Jack Jr. et al., 2011). The three stages include the preclinical stages of Alzheimer's disease (Sperling et al., 2011), the diagnosis of mild cognitive impairment due to Alzheimer's disease (Albert et al., 2011) and the diagnosis of dementia due to Alzheimer's disease (McKhann et al., 2011).

Clinical criteria and hallmark symptoms

Alzheimer's disease has a gradual onset over a long period of time. The most common presenting symptom is amnesia. The amnesia is usually manifested in problems to learn and recall new material, in forgetting of names and appointments and misplacement of belongings. Non-amnestic symptoms as impaired language skills (for example word finding), impaired visuospatial skills (for example face recognition and alexia) or executive dysfunction (for example impaired problem solving and impaired reasoning). More than one of these cognitive deficits should be present for the diagnosis of AD. Also, the cognitive decline should have been evident over a substantial period and have a history of worsening as observed by a clinician or reported by someone close to the possible AD individual (American Psychiatric Association, 1994; McKhann et al., 2011).

Exclusion criteria are any involvement of vascular incidents such as stroke or infarcts, in relation to the onset of cognitive decline. Furthermore, there should not be any involvement of features from other dementias, for example behavioral frontotemporal dementia or dementia with Lewy bodies. The two final exclusion criteria involve evidence of other neurological diseases or treatment with medication that could alter cognitive performance (American Psychiatric Association, 1994; McKhann et al., 2011).

Pathophysiology

Prior to a clinical diagnosis of AD, the pathophysiological process in the brain has been going on for years and possibly decades (Braak & Braak, 1991; Morris, 2005). The pathology that is underlying the progressive cognitive decline is foremost a neurodegeneration and specifically loss of synapses (Terry

et al., 1991). Key incidences of the AD brain are the accumulation of intracellular neurofibrillary tangles and extracellular amyloid plaques (Braak & Braak, 1996). Neurofibrillary tangles are abnormal aggregates of the protein tau. Tau-protein occurs normally in the brain but in case of AD it is hyperphosphorylated (fully saturated) and loses its normal ability to stabilize the microtubules (axonal parts of the neuron) (for a review, see Martin et al., 2013; Shin, Iwaki, Kitamoto & Tateishi, 1991). This stabilizing ability is needed for axonal transport. Hence, Yoshiyama, Lee and Trojanowski (2012) suggest that the tau pathology can be reflecting the cognitive symptoms of AD. Amyloid plaques, also called senile plaques, consists of deposits of β -amyloid protein ($A\beta$) in the grey matter. Each of these key incidences, neurofibrillary tangles and amyloid plaques, occur in a well-defined order and affects the medial temporal lobe, lateral temporal and association parietal cortices, the prefrontal cortices, posterior association cortices and finally motor and sensory areas (Braak & Braak, 1996). Jacobs, Van Boxtel, Jolles, Verhey and Uylings (2012) propose a model where the chain of events leading to AD starts with myelin breakdown, which causes the amyloid accumulation and in turn, when reaching a threshold, cause a “cascade of events” to occur. These events include metabolism disruption, grey matter atrophy and cognitive alterations. Nath et al. (2012) have recently shown that intracellular $A\beta$ oligomers transfer by direct cellular connections, hence are probably responsible for driving the neurodegenerative disease progression.

At present, the most commonly utilized in vivo method of measuring pathology in AD is the use of neuroimaging for detection of brain atrophy (Thambisetty et al., 2011). As the research progresses, alternate methods are being explored. The most significant research progress in the last decades has been made in the field of biomarkers (Andreassen, 2000; Sperling et al., 2011).

A major reason for the big hunt on biomarkers in AD is the potential benefit of early diagnosis. Biomarkers of AD can be detected in vivo, using neuroimaging or cerebrospinal fluid (CSF). It is assumed that the earlier treatment can be started, the bigger the chance for treatment with a disease modifying effects (Cummings, Doody & Clark, 2007; Sperling et al., 2011). One of the more robust biomarker seems to be a significant increase in the level of cerebrospinal fluid tau protein (CSF-tau), although further research is needed since CSF-tau is also found in vascular dementia (Andreasen et al., 1998). Recent additions in this field are for example ocular biomarkers (Frost, Martins & Kanagasigam, 2010) and plasma biomarkers (Thambiseti et al., 2011).

Etiology

Despite the extensive research on the pathophysiology of AD, the etiology of AD still remains relatively unclear. It is not known what causes and starts the neurodegenerative process of the brain. However, several risk factors have been identified of which the most apparent is aging. Before 65 years of age, the disease is rare (about 1%) but after 85 years of age the prevalence is between 10-30% (depending on inclusion criteria used) (Mayeux, 2003). Other factors that are assumed to be more or less straightforwardly related to the origin of AD are cerebrovascular factors (such as hypertension, coronary heart disease, diabetes, obesity and smoking), genetics (Mayeux, 2003; Sperling et.al, 2011), and traumatic head injury (Jellinger, 2004). Additional indicative associations that have been suggested are low education, reduced brain size, low occupational attainment as well as reduced mental and physical activity in later life. Also, more women than men are affected by AD (Mayeux, 2003). None of the above mentioned risk factors have been firmly verified since it is very hard to disentangle the relations between cause and effect. For example,

lower than average mental ability scores has been found among children who later developed late onset AD (Whalley et.al., 2000). The lower mental ability could be interpreted as a risk factor but it could also be argued that the determinants of AD are established early in life, affecting both early mental abilities as well as the ability to assimilate higher education (Mayeux, 2003).

The genetic aspect of AD has been extensively studied. Denoted familial Alzheimer's disease (FAD), it typically displays an autosomal dominant mode of inheritance, i.e. the abnormal gene is only needed from one parent in order for FAD to be developed. This form of AD is rare (< 0.1%) and has an early onset. There is evidence of genes being involved in sporadic AD (non-FAD) as well. In these cases the genetic interference (presence of $\epsilon 4$ part of the apolipoprotein E, APOE), results in a three times increase in risk of developing AD and it also contributes to an earlier onset (Corder et.al., 1994).

Memory in Alzheimer's disease

As mentioned, a hallmark of AD is memory decline. Memory as such comprises several different types of memory systems that interact with each other. The most common classification of memory systems is a division according to type of storage in a temporal sense and according to memory content. Temporal aspects of storage are classified as long term storage or short term storage of information. Memory content can be classified as semantic, episodic or procedural (Shallice & Cooper, 2012). Semantic memory can be described as context-free knowledge about the world, objects and facts that are culturally shared. An example would be the fact that Sweden is a monarchy (Tulving, 1972). Episodic memories are memories that are unique to an individual in that they are related to a specific episode in a specific context, for

example, what you had for breakfast this morning. Procedural memories are memories connected to an act such as knowing how to drive a car or how to ride a bike. In AD, declining memory in general is the most obvious cognitive deficit (Adlam et al., 2006; Binetti et al., 1995; Hodges & Patterson, 1995). Spaan, Raaijmakers and Jonker (2005) have suggested that deficits in semantic memory in particular is an early indicator of AD (for review see Salmon, Butters & Chan, 1999) and virtually all AD patients show semantic memory deficits at later stages of the disease (Hodges & Patterson, 1995). Impairment in semantic memory is evident in for example problems with naming objects and pictures, problems in defining objects, and by poor comprehension of oral and written language. These deficiencies can be assessed by confrontation naming, categorical verbal fluency tests or word to picture matching (Bayles & Tomoeda, 1983; Henry et al., 2004; Lonie et al., 2009). Current research on semantics in AD focuses the nature of the semantic deficits both from a neuropsychological aspect as well as its biological correlates. It has been found that semantic memory impairment in early AD is associated with cortical atrophy in the anterior temporal lobe and also in the inferior prefrontal cortex. These are areas that are considered to be essential for semantic cognition (Joubert et al., 2010; Wierenga et al., 2011).

Awareness in Alzheimer's disease

In relation to the study of memory decline in particular and cognitive decline in general it is of interest to understand the level of awareness in AD individuals. Awareness is a normal and ubiquitous phenomenon in humans. It has been described as the essence of our mental lives. Conscious awareness is thought to be a part of the explanation of many of our complex cognitive

functions, such as problem solving, perception, attention, imagination and more (Paller, Voss & Westerberg, 2009). Awareness in relation to AD is not a straightforward concept and has been defined and studied in many ways with somewhat conflicting results (for a review of the history of the topic, see Ecklund-Johnson & Torres, 2005; Hardy, Oyebode & Clare, 2006, McGlynn & Schacter, 1989; Morris & Hannesdottir, 2004). Awareness in AD has been reported, including awareness of cognitive impairment, disease awareness and awareness of problems in social interaction and handling of everyday situations (Correa, Graves & Costa, 1996; DeBettignies, Mahurin & Pirozzolo, 1990; Maki et al., 2012; Verhey, Rozendaal, Ponds & Jolles, 1993).

Unawareness of problems, in the case of AD, a cognitive inability to conceptualize the patient's own cognitive problems is often referred to as anosognosia (first introduced by Babinski in 1914; Heilman, 1991; McGlynn & Schacter, 1989). Anosognosia is derived from the words “nosos” (disease) and “gnosis” (knowledge) (for a review on anosognosia and AD, see Lorenzo & Conway, 2008). Anosognosia represents consequences of a lesion to the brain and a break with the normal monitoring of a change in an individual's mental and/or physical health (Ecklund-Johnson & Torres, 2005). Starkstein et al. (1997) concluded that anosognosia is common, although not mandatory in AD (Orfei et al., 2010). Yet other investigators consider anosognosia to be a general part of AD that increase with progression of the disease (Barrett, Eslinger, Ballentine, & Heilman, 2004; Kashiwa et al, 2005; Starkstein, et al., 2006). It has been found that anosognosia is not related to degree of cognitive deterioration in a straightforward manner, but in part to ‘frontal’ dysfunction (Dalla Barba, et al., 1995; Hanyu et al., 2008) and to procedural skills. Hanyu et al. (2008) compared regional perfusion deficits between AD patients who were unaware of memory impairment and those who were aware of memory impairment. Their main

finding was a significant decrease in perfusion in the lateral and medial frontal lobes in the unaware group, suggesting a frontal involvement in level of awareness. Anosognosia may be a heterogeneous phenomenon, in that unawareness of cognitive deficits may be independent from unawareness of behavioral changes (Starkstein, Sabe, Chemerinski, Jason & Leiguarda, 1996). Also, anosognosia is considered to vary in degree from lack of concern of to an explicit denial of disorder (Bisiach, Vallar, Perani, Papagno & Berti, 1986).

Differences in the result of level of awareness in AD can in part be explained by methodological differences between different studies. In general, there are four different approaches to the study of awareness in patients suffering from neurological illness (Clare, 2004; Morris & Hannesdottir, 2004). These approaches regard 1) clinician's ratings of patients (Correa, Graves & Costa, 1996); 2) discrepancies between patients' ratings and ratings conducted by relatives (Debettignies, et al., 1990); 3) discrepancies between patient's self-ratings and performance on cognitive tasks (Dalla Barba, Parlato, Iavarone, & Boller, 1995); and 4) combinations of these approaches. None of the above mentioned methodologies can give a full account of awareness in AD. For example, Clare (2004) argues that the method of discrepancies between patient and spouse ratings rests on the presumption that the spouse holds the truth about the patients' awareness, hence giving the spouse the privilege of interpretation. This method is questionable, not least since it has been established that there is great disagreement between patient and caregiver in ratings of memory capacity and self-care (Vasterling, Seltzer, Foss & Vanderbrook, 1995).

Metacognition in Alzheimer's disease

An aspect of awareness could be the knowledge and monitoring of cognitive functioning (or "cognition on cognition"; "thinking of one's own

thinking”), which is commonly referred to as metacognition. Metacognition is regarded as a fundamental component of the cognitive architecture (Flavell, 1979; Perfect, 2002). Hence metacognition is involved in several cognitive functions, such as memory, problem solving, listening, and reading comprehension (Flavell, 1979). Metacognition requires a conscious monitoring of one’s own thinking and performance. This is evident in the kind of tests commonly used to measure metacognition, i.e., asking an individual to predict how many words they think they would remember from a list of words presented to them (Galeone, Pappalardo, Chieff, Lavarone & Carlomagno, 2011; Hager & Hasselhorn, 1992). A variation of this prediction task is to ask individuals to postdict their performance. Oyeboade, Telling, Hardy and Austin (2007) have concluded that patients with AD overestimated predictions of memory performance while Moulin (2002) found that postdictions appeared relatively spared in AD. These conflicting results suggest that predictions and postdictions tap different aspects of metacognitive memory functioning. Differences in test used could also account for differences in results ranging from spared (Bäckman & Lipinska 1993; Souchay, Isingrini, Pillon & Gil, 2003) to impaired metacognition in AD (Correa, Graves & Costa, 1996; see Moulin, 2002, for a review on metacognition in dementia).

Central coherence

Prior to the present thesis, the possibility of describing the information processing of AD in terms of central coherence has not been recognized. The concept of central coherence was first developed by Frith (1989). She used the term to describe an important aspect of normal information processing, namely, being able to construct meaning in a context by inferring details of a stimulus

into a whole. Frith and Happé (1994) later suggested that central coherence is a cognitive style of information processing, representing a continuum of normal information processing where individuals' performance ranges from weak to strong. The concept weak central coherence is described as not being able to see the whole, the context, but only the separate details of a stimulus. Strong central coherence would be the opposite; seeing the big picture without being able to distinguish the details. Information processing in a normal, healthy individual is characterized by an unconscious drive to find meaning and context in stimuli and in the surrounding world (Happé, 2011). To date, central coherence in general and weak central coherence in particular has been studied in autistic individuals (Best, 2008; Frith & Happé, 1994; Happé & Briskman, 2001;), in individuals with Asperger's syndrome (Joliffe & Baron-Cohen, 2001; Le Sourn-Bissaoui, Caillies & Gierski, 2011) and in the research on eating disorders (Lopez et al., 2008; Lopez, Tchanturia, Stahl & Treasure, 2008; Lopez, Tchanturia, Stahl & Treasure, 2009). It has been suggested that individuals with the diagnosis mentioned above has an information processing that is characterized by weak central coherence. Lately, though, there are examples of researchers who suggest that weak central coherence is not as predominant in autism as it has been described in the literature so far (Bills Ashcraft, 2010). To establish central coherence in autistic individuals, researcher have used for example the Hooper Visual Organization test (Hooper, 1958), the Object Integration test (Joliffe & Baron-Cohen, 2001) and Scenic test (Joliffe & Baron-Cohen, 2001) and the Block design test (Shah & Frith, 1993). Currently within the domain of central coherence researchers are concerned with finding out what cognitive capacities are associated with the concept of central coherence. There has been evidence that the visuospatial construction aspect of central coherence is associated to executive control

(Pellicano, Maybery & Durkin, 2005). So far, there is no empirical data on the neural bases of weak central coherence.

Emotions in Alzheimer's disease

The last concept related to AD in the present thesis is emotions. There are conflicting theories as to how emotions are affected in AD. The areas of the brain that are considered to be involved in emotional reactions, the amygdala and hippocampus, are prone to a substantial atrophy during course of AD (Chan, et al., 2001; Hamann, 2001). However, based on clinical examples, there are testimonies of AD individuals seeming to remember emotionally valenced situations or happenings. A classic example is the Kobe earthquake in Japan 1995, which was studied in relation to remembering in AD by Ikeda et al. (1998). Many aspects of emotion have been studied in numerous ways in relation to different phenomenon within AD. It seems that in some aspects there is an emotion related sparing in AD and in other aspects there is not. For example, AD patients have been shown to be able to correctly identify emotions (pleasant or unpleasant figures) although the emotional stimuli did not improve their memory performance (Schultz, deCastro & Bertolucci, 2009). Facial emotion recognition has been studied extensively, in part due to hopes on being able to use this knowledge in clinical practice (Luzzi, Piccirilli & Provinciali, 2007). Although Luzzi, Piccirilli and Provinciali found preserved ability in identifying facial emotions in 70% of their AD sample, others have found a general impairment in facial emotion recognition in AD as well as in individuals with mild cognitive impairment (MCI). The latter results suggest that emotion based processing in the brain is an early deficit in the course of illness (Drapeau, Gosselin, Gagnon, Peretz & Lorrain, 2009; Spoletini et al.,

2008). Henry et al. (2008) found the facial expression “disgust” to be selectively spared in AD as compared to the other expressions that they found were severely impaired; anger, happiness, sadness, surprise and fear. Other areas of emotion research involve memory for emotion words (Phan, Wager, Taylor & Liberzon, 2002), memory for stories with negative emotional content (Kazui, et al., 2000). Through neuroimaging it has been shown that different aspects of emotions tap different domains of the brain (Phan, Wager, Taylor & Liberzon, 2002). This could account for some of the disparate results as to the status of emotion response in AD. Another confounding for different results could be the wide variety of different methodologies and tests used between different research studies.

Aim and Design approach

The aim of the present thesis was twofold:

First, to describe the pattern of semantic memory deterioration during the course of illness in AD by means of a longitudinal study.

Second, to create a multifaceted picture of the individual with AD, originating in the individual's own perspective of her disease. The concepts in focus were memory, awareness, metacognition, central coherence and emotions.

The present thesis used a mixed methods design approach, hence including both quantitative and qualitative methods (Howe, 1988; Onwuegbuzie & Leech, 2005). In the research area of cognitive neuropsychology, the quantitative method approach is prevailing. Rigorous statistical methods and laboratory based methods are often applied. With the ambition of the present thesis, it would be futile to try to reach the aim through quantitative methods alone. To meet the aim of the thesis, an eclectic choice of methods was made. The thesis comprises two separate studies, which are described in the chapter "Summary of the studies".

Summary of the studies

First study

The first study was a longitudinal study with a quantitative neuropsychological approach. The general purpose of the study was to monitor a group of AD patients on semantic impairment through disease development to see how the disease was manifested and how AD individuals differed from individuals in a normal aging process. Each participant of the study (both patients and control subjects) was seen at three different occasions, each occasion one year apart (± 1 month). The interval was chosen from the rationale that one year would give a noticeable deterioration in cognition (in general 3-5 points less in Mini Mental State Examination, MMSE, per year) but it was still feasible to assume that many patients would manage to perform all of the tests at all three occasions. This study resulted in one paper described below as article I.

Article I, A longitudinal study of semantic memory impairment in patients with Alzheimer's disease
(Mårdh, Nägga & Samuelsson, 2013)

Semantic impairment is an early hallmark of AD (Spaan et al., 2005) and there has been conflicting theories on what happens with the patients' semantic knowledge as the disease develops. There are two major prevailing theories; either the theory on loss of semantic knowledge where semantic knowledge is considered to be declining as disease progresses (Chertkow & Bub, 1990), or the theory on problems with access to semantic knowledge, i.e., difficulties in retrieving information from semantic long-term storage (Nebes, Martin, &

Horn, 1984). The purpose of the present study was twofold; first, to see how AD patients differ in semantic impairment over time as compared to a matched control group; second to try to clarify whether AD patients display a loss of semantic knowledge (i.e., the degraded store view) or if it is a matter of problems in accessing the semantic knowledge (i.e., the degraded access view) (Shallice, 1988; Warrington & Shallice, 1984).

Twenty-five AD patients and 25 healthy elderly control subjects were tested on three occasions with one year apart (\pm 1 month). At the final occasion, twelve patients and twenty control subjects followed through with all the tests. The AD patients were diagnosed according to DSM-IV (American Psychological Association, 1994) and also, diagnosis were based on neuroradiological (e.g., CT scan), neurological, neuropsychological and medical evaluations at the University hospital in Linköping and at Vrinnevi Hospital in Norrköping. None of the patients evidenced any vascular incidents. The control subjects were matched on age, education, and gender, see Table 1.

Table 1. Demographic characteristics of the participants in article I, first occasion (standard deviations in parenthesis).

	AD	Controls	P
Age	77 (5.5)	73 (4.7)	n.s.
Female/Male	18/7	16/9	n.s.
Years of education	8.2 (2.1)	9.7 (3.5)	n.s.
MMSE; Mini Mental State Examination	20.8 (4.9)	27.6 (1.5)	<0.01

The study was quantitative and the test battery comprised three tests; word reading ability, reading comprehension and a semantic attribute judgment task. The reading ability test consisted of 32 nouns. The same words were used in the comprehension task and in the attribute task.

The first purpose, to see how AD patients differ from controls in semantic impairment over time, was met by comparing the two involved groups on all tests and all occasions. There was no difference between the two groups in the word reading ability test at the first two occasions, though a significant difference was found at the third occasion when the patients made a total of 12 errors (12/384) while the control subjects made no errors. Overall the AD patients were impaired on the two semantic tasks (reading comprehension and attribute judgment task) as compared to the control subjects. The difference between the groups was evident already at the first occasion. See table 2.

Table 2. Means and standard deviations on the MMSE and semantic tests across test occasions

Type of test	Alzheimer			Control		
	1 st occasion	2 nd occasion	3 rd occasion	1 st occasion	2 nd occasion	3 rd occasion
MMSE (max 30)	20.8(4.9)	18.2(5.4)	15.7(6.2)	27.6(1.5)	27.9(1.8)	28.2(1.7)
Proportions of words comprehended	.86(.1)	.84(.1)	.78(.1)	.95(.4)	.96(.04)	.96(.03)
Proportions of attributes chosen	.82(.1)	.74(.2)	.73(.2)	.97(.02)	.97(.02)	.97(.2)

To meet the second purpose, to distinguish between the hypothesis on loss or access, the nature of the semantic impairment was analyzed. All the words (n=32) from the word reading test were tracked across tests and over time. In the comprehension test, the pattern that emerged revealed that there was error consistency in the patients test results, that is, the errors made at the first occasion were made at the second and third occasion as well. This supports the theory on loss of semantic memory. Hence there was no random access to the comprehension of words, which would have indicated random problems in accessing the semantic storage. Both for words comprehended and for the semantic attribute judgment task, the same pattern held true. It was also evident from the results of the semantic attribute judgment task that semantic concepts lost their specificity during the course of illness in favor for more general knowledge of the concepts. The AD patients identified fewer semantic attributes in total to a concept as disease progressed. It was also evident that the proportion of essential attributes were lower as disease progressed than the proportion of less essential attributes, see table 3.

Table 3. Means and standard deviations for the proportions of semantic attributes indicated for compre-hended and not comprehended words in the AD group on all three occasions.

	Comprehended	
	Yes	No
<i>First occasion</i>		
Attributes, tot	.84(.19)	.77(.18)
Attributes, essential	.86(.22)	.80(.24)
Attributes, less essential	.82(.26)	.74(.27)
<i>Second occasion</i>		
Attributes, tot	.77(.25)	.65(.28)
Attributes, essential	.80(.27)	.68(.32)
Attributes, less essential	.73(.32)	.62(.34)
<i>Third occasion</i>		
Attributes, tot	.77 (.27)	.62 (.31)
Attributes, essential	.79 (.29)	.66 (.35)
Attributes, less essential	.75 (.32)	.57 (.38)

Contribution to theory

We found that the nature of the semantic deficiency in AD is most likely to be due to loss of semantic knowledge. This is in concordance with Chertkow

and Bub (1990) and in contrast to the degraded access view proposed by Nebes et al. (1984) and others. In addition to a contribution to the theoretical debate on loss of semantic knowledge versus problems in accessing semantic knowledge in AD, we have taken a rare methodological approach in the study of these concepts. The uniqueness of our study was the longitudinal approach examining item-by-item consistency across time in the same AD individuals. The pattern of error consistency was thus confirmed both across time and in the same individuals. It is important to examine the same individuals across time since the progression of disease is relentless, which makes it crucial to be able to disregard individual differences and just look to the “true” pattern of the deterioration as such. Applying the longitudinal approach also enabled us to study the nature of semantic concept representation. We could conclude that only the general information of a semantic concept remains and that the more specific information of the same concept is lost.

Contribution to the understanding of the Alzheimer individual

The results of the first study contribute to the picture of the semantic breakdown in the progression of AD. The error pattern reveals that it is most likely that semantic concepts the AD patient cannot describe or explain, are lost rather than hard to retrieve. It could also be concluded that AD patients lose specific attributes of a concept before more general attributes. This pattern of the semantic breakdown reveals that the surrounding world of an AD patient is less nuanced than the surrounding world of a person who is experiencing a normal ageing process. Emerging from data it can be assumed that an individual with AD in a forest would know she was surrounded by trees but wouldn't be able to distinguish between for example birch trees and oak trees.

The specific attributes that reveal a tree's specific sort/kind would be lost in favor for the more general knowledge that it is merely a tree.

Second study

In pursue of understanding the patient's perspective of their disease, a second study on awareness, central coherence and emotions was undertaken. The study resulted in three articles, described as article II, article III, and article IV in the following text. To fully explore the patient's perspective, a mixed methods design approach was applied, comprising both qualitative interviews and quantitative neuropsychological testing. Concerning awareness, the patients' spouses were interviewed and for all the neuropsychological testing of the second study, a control group was recruited matched on age, education and gender. Diagnosis of AD was made according to the criteria of NINCDS-ADRDA (McKhann et al., 1984) and DSM-III-R criteria (American Psychological Association, 1987). None of the included AD individuals suffered from depression or had any vascular components in their diagnosis. All subjects were recruited from the University hospital in Linköping.

Article II; Aspects of awareness in patients with Alzheimer's disease (Mårdh, Karlsson & Marcusson, 2013)

The focus of article II was the AD patient and her perception of the disease. It is of clinical interest to understand how AD patients are aware of their disease, how they think of their own thinking and how well they are calibrated with their spouse in disease related issues. Different aspects of awareness have been studied before, (see the above section on "Awareness in Alzheimer's disease") but as described, there are some methodological issues that need to be addressed in this area of research. Article II addresses some of

these by employing a mixed methods design approach. In this approach we have addressed the relevant aspects from both a qualitative and a quantitative perspective.

In line with the main purpose of the present article, three main questions were explored, namely:

- 1) How do AD individuals express disease awareness?
- 2) How do AD individuals describe management of cognitive deficits in everyday life?
- 3) How well do the thoughts and judgments of one spouse (AD) agree with the beliefs of the other spouse, i.e., spouse calibration?

Three test groups were recruited for the study, namely, AD patients, their spouses and a matched control group. For demographics, see table 4.

Table 4. Demographic characteristics of the participants in article II (standard deviations in parenthesis).

	AD	Controls	p
Age	76.2 (5.9)	75.7 (4.7)	n.s.
Female/Male	11/4	10/5	n.s.
Years of education	8.1 (2.8)	8.8 (4.6)	n.s.
MMSE; Mini Mental State Examination	18.0 (6.3)	27.9 (1.8)	<0.001
ADAS psych	0.5 (1.2)	0.2 (0.6)	n.s.
ADAS cog	25.0 (10.7)	6.3 (2.4)	<0.001

The patients and the matched control group went through a neuropsychological examination comprising MMSE (Folstein, Folstein, &

McHugh, 1975), ADAScog (Alzheimer's Disease Assessment Scale; Rosen, Mohs, & Davis, 1984), ADASpsych (Rosen, Mohs, & Davis, 1984) and a metacognition assessment; memory prediction task. In addition to this, the patients and their spouses were interviewed separately. They were asked the same set of questions on disease awareness, metacognition and coping strategies, see table 5. The answers from the patients and their spouses were compared in order to understand if they were well calibrated in their perception of disease awareness, metacognitive status, and coping strategies. The interviews were transcribed and analyzed according to the qualitative method of continuous comparisons of similarities in grounded theory (Strauss, 1987).

Table 5. The interview questions employed in the study.

	Interview questions
Disease awareness	Do you have problems with your memory? Can you tell me your diagnosis? Can you describe the implications of the disease? Have you noticed that relatives or friends have changed their behavior towards you?
Metacognition	Can you describe your memory change? Can you describe errors occurring in speech and action? Can you describe what you usually think about?
Description of management of cognitive deficits in everyday life	Do you have any tricks or strategies to manage difficult situations that occur in everyday life?

1) How do AD individuals express disease awareness? The analysis of the interviews revealed that all patients admitted to having memory problems and that almost half of the patients (7/15) were aware of diagnosis. 9/15 patients could give an adequate description of the implications of disease. Also 7/15 patients noticed that relatives and friends had changed their behavior towards them since they received their diagnosis. They gave examples of being neglected and excluded from their own social context. These experiences were associated with negative feelings. These results led us to conclude that the patients in our sample were aware of their disease. This is contradictory to some other research on awareness in dementia (Moulin, James, Perfect, Timothy &

Jones, 2003; Souchay, Isingrini, Pillon, & Gil, 2003). Furthermore, we found no evidence of anosognosia in our sample.

2) *How do AD individuals describe management of cognitive deficits in everyday life?* Thirteen out of 15 patients could describe their memory change and they did it in terms of cognitive aspects of change (“...now it is harder to think and follow a dialogue.”), action related aspects of change (“....can’t find things that I put away the last hour.”), and social aspects of memory change (for example finding it hard to interact with friends). Two thirds of the patients admitted to having errors occur in speech and action but only one third could describe these errors. Half of the patients could describe what they usually thought about during the days. See article II for more detailed examples and quotes (Mårdh, Karlsson & Marcusson, 2013). Only six out of 15 patients claimed they had any strategies or tricks to manage difficult situations that arose in their everyday life. The six patients reported on both cognitive and practical strategies. Amongst the spouses there were also six individuals (not within the same couple) who reported on compensatory strategies, though the spouses only reported on practical strategies. Furthermore, the patients in our sample were not able to accurately predict their memory performance in the metacognitive memory task, but overestimated their memory capacity. Taken together, the results on awareness and metacognition imply that although the patients were aware of their disease and 60% could describe the implications of disease, they were not able to monitor their cognitive abilities on an online basis. Their ability to think of their own thinking (metacognition) was reduced. Another implication of this reduction in metacognition was that they could not translate their cognitive impairment into possible problems in handling everyday situations.

3) *How well do the thoughts and judgments of one spouse (AD) agree with the beliefs of the other spouse, i.e., spouse calibration?* We found that patient and spouse were not calibrated concerning the studied issues. Out of the three aspects of metacognition in the interviews (i.e., describe memory change, describe errors occurring in speech and action, describe what you usually think about) there was only one (describe memory change) where the patients and spouses were calibrated. For example, although disease awareness, was as frequent in spouses as in AD patients on a group level, there was no agreement within couples.

Contribution to theory

In preceding studies of awareness in AD there have been important methodological concerns. The present study was an attempt to meet some of these concerns. In using a mixed methods design, I feel we have made a more fair assessment of the studied concepts since the concept of awareness and the concept of metacognition as well as spouse calibration would seem to have qualitative as well as quantitative features.

Traditionally, AD patients' statements are not assigned importance. In this material we can conclude that even though we don't know what is true and what is not, they put forward a story on being neglected and tell us the negative feelings associated with that. Furthermore, although we concluded that the patients in our sample had disease awareness, the patients were not able to understand the practical consequences of their cognitive deterioration. An important finding in this article was that as many as half of the patients had noticed that either their relatives and/or their friends had changed their behavior towards them since diagnosis. They could also describe in what way the change was evident. These are aspects that are not commonly illuminated in the

research on AD. Furthermore, patients and spouses were not well calibrated as to consequences of illness and thoughts on disease. The one aspect that they agreed on was what kind of memory problems that generally comes with an Alzheimer disease. Despite disease awareness and ability to describe disease implications, the patients report on few, if any, compensatory strategies. These findings are important, not only as a contribution in theory but as a cue for reflection in the everyday care of AD individuals.

Contribution to the understanding of the Alzheimer individual

According to the results of this study, having AD means not being able to translate cognitive shortcomings into practical reality, despite having awareness of the shortcomings that are associated with the disease. It is possible to assume that this discrepancy could lead to frustration in everyday life. The lack of insight of the shortcoming may lead to repeated incidents of failure, which in turn would lead to frustration and feelings of inadequacy. This could be evident in normal everyday activities as getting dressed or turning on the TV.

The poor calibration between spouses that was evident in the present study makes it reasonable to assume that spouses do not interpret the AD individual or their thoughts in the right way. That is, the AD spouse does not have the same perception of how the disease is manifested or how aware the AD individual is of this. This would imply that it is hard for the AD individual to get their message through even to their lifelong partner. In concordance to the general picture of the individual with “no mind”, it seems, the spouses just assume that their close one does not have a story to tell. It could be assumed that this finding is not unique to AD. Employing a study focusing on the calibration between patient and spouse may reveal similar problems in other chronic diseases.

Article III; Weak central coherence in patients with Alzheimer's disease

(Mårdh, 2013)

The general purpose of the third article of this thesis was to explore central coherence in AD patients. The concept of central coherence was developed to describe normal information processing as being able to interpret details of information in the surrounding into a whole (Frith, 1989). Thorough clinical examples it was assumed that AD individuals suffer weak central coherence, hence not being able to interpret details into a whole. For instance, the AD individual who asked whose drawer it was over there, referring to a drawer in her own kitchen interior. Hence she was not able to infer the separate parts of the kitchen interior into a whole, understanding that it belonged together.

In order to test central coherence in our sample of AD patients and control subjects, a black and white drawing of a fire was used. The participants' task was to describe the picture.

Two hypotheses were proposed to cover the purpose of this study:

- 1) Alzheimer patients are on the weak end of central coherence, as compared to matched control subjects.
- 2) Alzheimer patients differ from control subjects in what constitutes their stories.

Nine Alzheimer patients diagnosed according to the criteria of NINCDS-ADRDA (McKhann et al., 1984) and ten control subjects, matched on age, education and gender were included in the study, see table 6. The reason for not

including all of the patients and controls that were included as a total in study II, was the extensive analysis of data required for the test included in this part of the study.

Table 6. Demographic characteristics of the participants in article III (range in parenthesis).

	AD	Controls	P
Age	76.2 (62-84)	75.6 (66-84)	n.s.
Female/Male	7/2	7/3	n.s
Years of education	7.3 (6-11)	8.3 (6-20)	n.s
MMSE, Mini Mental State Examination	15.9 (8-24)	28.0 (26-30)	<0.01
BDS	5.9 (1-14)	14.5 (12-19)	<0.01
ADAScog	27.6 (13-44)	5.9 (2-11)	<0.01

Both of the hypotheses were verified.

1) AD patients suffer from weak central coherence as compared to the control group. This was apparent in their reporting of the picture of the fire. None of the AD patients mentioned the context of the fire but merely described the picture in a fragmented way by listing the separate objects the picture comprised of. This was in contrast to the control group where all but two participants mentioned the context of the fire.

2) The two groups described the picture using the same amount of time and the same amount of words. The structure of the stories, though, differed between groups. For example, the AD group used fewer concrete nouns but more pronouns than the controls, see table 7. For more details, see article III.

Table 7. Amount words generated (mean), separated into grammatical categories.

Grammatical category	Amount words generated		
	Control subjects (n=10)	Alzheimer patients (n=9)	p
Verbs	43.8	42.6	n.s.
Adjectives	4.5	5.3	n.s.
Concrete nouns	35.4	16.9	<0,01
Abstract nouns	5.1	3.7	n.s.
Pronoun	45.9	49.9	<0,05
Total amount of words generated	245.5	221.6	n.s.

Contribution to theory

The concept of weak central coherence has mainly been used in the literature on the research of alterations of mind in autistic individuals. This is, so far, the first study to relate the concept to Alzheimer's disease. It was concluded that AD patients suffer from weak central coherence, hence adding a new aspect of the multifaceted clinical picture of AD. AD is a neurodegenerative disease and it can be assumed that AD individuals have had a normal coherence prior to disease onset and that they are sliding down the continuum of central coherence as the disease progresses. In relating central coherence to AD, a tool for understanding the AD patient's perception of the world has been created. The notion of central coherence is understandable and very graphic when related to the AD individual. In addition, applying the

concept to AD, opens up for the study of central coherence in other diseases and psychiatric conditions.

Contribution to the understanding of the Alzheimer individual

It can be assumed that an AD individual can see the different objects around her but is not able to merge them into an understandable whole. The “clues” of laying out clothes on the bed would not be very helpful since the individual wouldn’t be able to draw the conclusion that those items imply that it is time to get dressed. Having AD would mean a constant struggle to make sense of the surrounding world. It would be essential to be surrounded by thoughtful and attentive people who take care in creating a safe, meaningful and explicit environment.

Article IV; Emotion and recollective experience in patients with Alzheimer’s disease

(Karlsson, Mårdh & Marcusson, submitted manuscript)

As previously mentioned, there are conflicting theories of how emotions are affected in AD. Several different aspects of emotion have been studied, like, memory with emotional content (Schultz, deCastro & Bertolucci, 2009), emotional recognition from voice, face and music (Drapeau, Gosselin, Gagnin, Peretz & Lorrain, 2009) and facial emotion recognition (Spoletini et.al., 2008). In the present study, we focused emotionally valenced words and their possible effect on explicit and implicit memory.

Eighteen AD patients and 15 matched control subjects were included in the study. All the patients were recruited from the Department of Geriatrics at Linköping University. The patients were diagnosed according to the NINCDS-ADRDA (McKhann et al., 1984) and DSM-III R criteria (American

Psychological Association, 1987). For the tests of this article an additional three patients as compared to article II of study II, were recruited. These three patients were available but had no spouse as was required for inclusion in the tests of article II. For demographics of the two groups included in this article, see table 8.

Table 8. Demographic characteristics of the participants in article IV (standard deviations in parenthesis).

	AD	Controls	p
Age	76.2 (5.3)	75.7 (4.7)	n.s.
Female/Male	12/6	10/5	n.s.
Years of education	8.2 (2.6)	8.8 (4.6)	n.s.
MMSE; Mini Mental State Examination	18.5 (6.0)	27.9 (1.8)	<0.001
BDS; Behavioral Dyscontrol Scale	7.1 (4.9)	14.5 (2.4)	<0.001
ADAS psych	0.5 (1.2)	0.2 (0.6)	n.s.

The emotionally valenced words were collected from Ali and Cimino (1997) and translated to Swedish. In total, the material comprised sixteen positively valenced words (e.g. kiss, baby), 16 negatively valenced words (e.g. grave, anxiety) and 16 neutral words (e.g. butter, engine). Half of the words were used in an implicit memory task (word-fragment completion) and half the words were used in an explicit memory task where the participant also was asked to indicate the recollective status of the words they recognized.

The three main results emerging from this study were 1) AD patients displayed significant deficits as to recollective experience, 2) negative words produced a stronger sense of recollection than did positive and neutral words (see table 9), 3) the magnitude of recollection for the three kinds of valenced

words were similar in AD and in controls. Also it was concluded that the AD individuals had relatively spared implicit memory and that valence did not influence performance in the implicit task (word fragment completion), see table 10. These are the main findings, for more results and further details, see article IV.

Table 9. Estimates of recognition memory performance, expressed in d prime, for healthy controls and Alzheimer's disease patients. The numbers depict means and SE.

Valence	Type of Recollective Experience	Group	
		Controls	Alzheimer
Neutral	Remember	.94 .29	-.02 .27
	Know	1.33 .29	.51 .27
	Guess	.29 .21	.27 .19
Positive	Remember	.88 .27	.09 .24
	Know	.53 .27	.15 .25
	Guess	.33 .19	.27 .18
Negative	Remember	1.35 .25	.47 .22
	Know	.69 .26	.76 .24
	Guess	.06 .14	.12 .13

Table 10. Performance in the word-fragment completion task with respect to healthy controls and Alzheimer's disease patients. The numbers depict the level of fragmentation at which successful identification took place and SE.

Valence	Previous Study	Group	
		Controls	Alzheimer
Neutral	No Previous Study	.46	.27
		.04	.03
	Previous Study	.53	.38
Positive	No Previous Study	.44	.25
		.04	.03
	Previous Study	.53	.36
Negative	No Previous Study	.51	.31
		.03	.03
	Previous Study	.53	.36
		.03	.03

Contribution to theory

The theory building in the area of emotion in general and in emotion related to AD in particular, is very divergent. Through our results on emotionally valenced words in AD, we suggest that the neural processing of different emotions reflect separate and dissociable networks. This conclusion was drawn since we have obtained different results as to recollection between differently valenced words (neutral, positive and negative). The results on impaired conscious recall of emotion words is in line with others (Ochsner, 2000) as is the results on spared implicit memory (Heindel, Salmon, Fennema-Notestine & Chan, 1998).

Contribution to the understanding of the Alzheimer individual

The AD individuals were concluded to have profound difficulties regarding recollection of new material, while non-recollective sources to recognition memory performance (*i.e.*, ‘knowing’ about the previous appearance of an event) were less affected. Also, emotional valence affected explicit recognition memory in similar ways in AD individuals and controls. In the AD individual’s world, this means forgetting about all kinds of neutral and positive events but still being able to respond to negative events at a significant level, based upon non-recollective memory processes. Hence, in everyday life it can be assumed that the things that will stand out are negatively valenced.

Overall discussion

Methodological issues

In the study of AD it is common to have small sample sizes, as do the present thesis. There were two major reasons for this, namely; the inclusion criteria applied and the extensive data analysis performed. As mentioned, the AD individuals included had a diagnosis of AD free from vascular incidents. Also, we did not include AD individuals who suffered from major depression or any other disorder of mood. Depression in this context is an important issue since it is not uncommon in chronic or lethal maladies, including AD. Since depression also may be complicated by concomitant cognitive problems, it is possible that depression could contribute to alterations of awareness. Nakaaki et al. (2008) found alterations in estimation of memory ability, metacognition, in Alzheimer patients with depression as compared to Alzheimer patients without depression. However, we did not address this issue in that we used depression as an exclusion criterion. Our findings, thus, apply to Alzheimer patients free from manifest mood disorder (or psychiatric disorders, other than AD). The strict inclusion criteria concerning diagnosis, coupled with the fact that the AD individuals included had to be mild to moderate to manage the test situation, resulted in a limited number of possible participants at the time for inclusion. The data analysis of grounded theory (for interview data) and the analysis of the central coherence test is very extensive and time consuming, hence further limiting the feasible amount of participants.

Contribution to theory

The present thesis has made important contributions to theory foremost by taking a mixed methods design approach to a neurodegenerative disease. The result of this comprehensive design approach is a multifaceted and well-represented picture of the patient with Alzheimer's disease regarding the studied concepts. In the following, the present thesis contribution to theory will be discussed in relation to the concepts that were outlined in the introductory section, namely; memory, awareness, central coherence and emotions.

Memory in Alzheimer's disease

The first theoretical contribution to the concept of AD was a position in the long-running theoretical debate on the nature of the degeneration of the semantic memory impairment in AD. Through our longitudinal study, we could conclude that semantic knowledge that cannot be recalled by an AD patient is lost. This outcome challenges the notion of semantic preservation in AD and supports models stating that unaccessible information is unavailable by loss. Also, support was found for the fact that semantic concepts gradually lose their specific features in a progressive AD decline. This is a finding that could hold implications for other cognitive domains as well. The AD individual may possess a less fine-grained knowledge about the world, also in terms of past events, the individual's own behavior, or emotions.

Concerning memory in AD we were also able to confirm the results of others concerning impaired recollection in general in AD and concerning spared implicit memory in AD. It seems that memory in AD is not a straightforward phenomenon but different aspects of memory are affected in different ways, ranging from severely impaired recollection to relatively preserved priming.

Awareness in Alzheimer's disease

A second major contribution in the theoretical approach of AD in the present thesis is that I have made a point of assigning importance to the patient's perspective and her own story. This perspective is often neglected in favor of the perspective of significant others. There is no telling whether or not the reports from individuals with a declining cognition are absolutely true in an objective manner. The important aspect of this approach is that they do report on thoughts and feelings that are true to the individual in the reporting moment. They are able to report on thoughts and feelings in relation to their disease and the change that has come with it. This is worth taking into consideration in interacting and caring for the AD individual as well as in planning future research studies or new medical trials. They are not individuals with no mind.

Central coherence in Alzheimer's disease

In the further understanding of the AD individual, a third contribution to theory was made in the present thesis by introducing a new concept in relation to AD. The concept of central coherence. Invoking this concept as a feature of AD and in the clinical picture of the disease, offers a unique way of clarifying the AD individual's perception of her surrounding world. It was concluded that AD individuals have weak central coherence, hence not being able to infer details into a whole. The understanding this brings to the experience of living with the disease has huge implications for every day care. Furthermore, it is possible to assume that it would be equally fruitful to apply the concept of central coherence to other neurological, psychiatric, or chronic medical disorders as well.

Emotions in Alzheimer's disease

Emotionally valenced words have so far been under-researched in favor for other aspects of emotion in AD. This was the fourth major theoretical contribution of this thesis. It could be concluded that negative emotion words had a stronger sense of recollection in AD than did neutral or positive emotion words. This finding was similar in AD individuals and normal controls. Since the AD group also evidence marked deficits regarding recollection, it is likely that negative words still can influence performance through non-recollective memory states—such as ‘knowing’ about the past.

Contribution to the understanding of the Alzheimer individual – linking the pieces together

Taken together, the pieces give us a picture of a group of individuals who gradually lose the nuances and details of their surroundings. The knowledge they cannot recall is lost. They are aware of their shortcomings but they cannot estimate their performance or foretell the problems their shortcomings create in their everyday life. They notice that their loved ones change their behavior towards them and they feel they are not counted on anymore. Furthermore, they perceive their world in a fragmented way, seeing the objects but are not able to link them together into a meaningful whole. Although they suffer severe deficits in recollective memory, they respond to negatively valenced words in the same way as normally ageing individuals.

Clinical implications

The findings of the studies of the present thesis give valuable information on how to understand and relate to an individual with Alzheimer's disease. This

can have direct implications for the managing of patients in care-giving as well as in the relation between a patient and her significant other in individual households. The knowledge would be valuable and have impact in at least four major areas, as described below.

The first area is to have knowledge of how the cognitive decline of AD is manifested. It would, for example, be no use trying to explicitly retrieve semantic knowledge that seems forgotten since it is most probably lost. It would be more fruitful to focus on abilities that are still working. Another aspect of the cognitive decline is that semantic concepts lose their specificity. This is important not least in the everyday communication. Knowing that the AD individuals' surrounding world is less nuanced than your own would enhance understanding when the AD individual is unable to define a zebra by its stripes.

A second area of importance is to be aware of your spouse's or patient's level of awareness in relation to diagnosis and memory deficit. This is of clinical interest also since it has been found that caregivers' perceived burden could be affected by the patients' level of awareness (DeBettignies et al., 1990). Apart from that, it would enhance understanding between individuals and the communication would probably have a different character if both parties felt there was consensus regarding thoughts on disease. Also, the realization that the AD individual has metacognitive abilities but that there is a gap between what they can understand about their own cognition and how they handle that in their everyday life. For the AD individual, it can be assumed that this repeatedly leads to frustrating situations and incidents of failure. This could be apparent in daily chores, for example in trying to make coffee or getting dressed. Knowledge of this in caregivers and spouse could enhance understanding in daily situations. In part, unmanageable situations could be avoided in favor for

situations where the AD individual still is in control, hence avoiding frustration and possible catastrophic reactions.

Three, to understand that your AD spouse or patient sees the different objects of her surrounding but cannot infer them into context. This impairment makes coffee brewing difficult even if the coffee is right next to the coffee machine. Insight in this could help the caregiver to have a different approach in relation to everyday chores, leading the AD individual in every step of the coffee making instead of just hinting and giving clues.

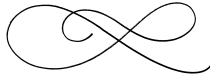
Four, to be aware of the fact that the emotion words that have the strongest sense of recollection by an AD individual are the negative ones. This should make it even more important to create a positive atmosphere and fill life with positive experiences. Even if the AD patient cannot explicitly recall the memory affiliated with the negative emotion, it is possible that the negative feeling is present.

In addition to the four major areas described above, the findings of this thesis can be applied to many everyday life situations and also have an effect on different approaches to caregiving. It has been concluded time and again that the environment and relations to others are crucial factors for the well-being of demented individuals (Burgio, 1996; Lawlor, 1996; Lazarus, Cohler, & Lesser, 1996). An unpleasant environment could have a negative impact on behavior as well as a pleasant environment can have a positive, mood improving impact of behavior. In the light of the findings from the present thesis, other aspects emerge. It is not just important to create a positive atmosphere but it is crucial to create context and give AD individuals means as to understand their social environment. Failing to help AD individuals in understanding their environment could trigger depression, agitated behavior or catastrophic reactions. This is evident in numerous clinical examples ranging from agitated behavior in

relation to managing the personal hygiene to frustrating situations at the dinner table. It is not hard to empathize with the individual who does not understand why somebody who they don't recognize, all of a sudden gets you undressed and dragged into the shower. In interacting with an AD individual, it is not enough to bring soap and a towel and assume they automatically understand that it is time for a shower. They can see the objects but cannot infer them into a meaningful whole. Depending on the relation between the caregiver and the AD individual, the outcome could be feelings of provocation and frustration (Lawlor, 1996). It has been concluded that triggers of aggressive or catastrophic reactions include for example the encounter of new environment, reduced communicative ability, realization of own illness and forgetfulness and/or a difficult relationship to spouse in the past. Other triggers could be moving to an unfamiliar place, unidentified noise, insufficient lighting or contradictory patient management style (Haupt, 1996). Applying the new knowledge from this thesis to the examples just mentioned highlights the need for creating safe environments but also to help AD individuals to get their message through to spouse and caregivers and to make spouse and caregivers aware of the thoughts and feelings of the AD individual. Also, to understand where possible frustration and anger comes from will give caregivers more patience and understanding in everyday situations. Enhanced knowledge leads to enhanced understanding, which would give enhanced calm, patience and confidence in the care. Apart from improving the patient-spouse relationship, it would be valuable for management of care corporations as well as the staff to work through their routines in accordance to the new knowledge on Alzheimer individuals.

The end

So far, man has failed to solve the enigma of the eroding brain. The impairment that comes with a dementia of Alzheimer type overshadows every attempt of memory training, coping strategies and medication. The research, though, will continue with flawless effort. I hope that it will be a story of success.



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