VERBAL LEARNING IN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE:

BEHAVIOURAL AND NEURAL APPROACHES

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This thesis is based on the following original publications:

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SWEDISH SUMMARY - SVENSK SAMMANFATTNING

Med åldern blir kognitiva symptom, såsom minnessvårigheter, allt vanligare. I en åldrad population blir den kognitiva prestationsnivån likaså en allt viktigare fråga med tanke på livskvaliteten. Det har även blivit allt viktigare att kunna skilja åt normalt åldrande från degenerativa hjärnsjukdomar som förorsakar demens, eftersom det nuförtiden finns effektiva mediciner tillgängliga för den vanligaste orsaken till demens, d.v.s. Alzheimers sjukdom. Dessa mediciner kan inte bota sjukdomen i sig, men de kan lindra symptomen för en viss period, vilket gör det viktigare att upptäcka sjukdomen i ett så tidigt skede så möjligt. Med tanke på den tidiga upptäckten av sjukdomen har diagnosen mild kognitiv svikt (Mild Cognitive Impairment, MCI) väckt allt mer intresse. Personer som lider av MCI har tydliga minnessvårigheter även om nedsättningen av minnesfunktionerna ännu inte väsentligt påverkar det dagliga livet. Ett flertal forskningsresultat tyder på att MCI-patienter har en förhöjd risk att insjukna i Alzheimers sjukdom. Med andra ord kan MCI ses som ett slags mellanstadium mellan normalt åldrande och lindrig Alzheimers sjukdom. För att få en djupare insikt i de neurokognitiva förändringar som demenssjukdomar och normalt åldrande för med sig, bör man kunna integrera psykologiska, psykofysiologiska och neurala aspekter. Detta är viktigt ur diagnostisk synvinkel och även med tanke på att på lång sikt kunna förbättra livskvaliteten för såväl demenspatienter som deras anhöriga.

Syftet med föreliggande avhandling var att med hjälp av både behaviorella undersökningsmetoder och funktionell hjärnavbildning (positronemissionstomografi, PET, syre-15-metoden) undersöka de underliggande neurokognitiva mekanismerna i episodiska och semantiska minnessystem vid verbal inlärning hos friska äldre personer, patienter med MCI och patienter med Alzheimers sjukdom. Dessutom undersöktes användbarheten av det kognitiva testbatteriet CERAD som kliniskt verktyg vid diagnostisering av MCI och tidig Alzheimers sjukdom.

I studie I undersöktes skillnader i testprestationer i CERAD mellan MCI-patienter och friska kontrollpersoner med fokus på uppgiften *inlärning av ordlista*. Därutöver utforskades sensitiviteten och specificiteten av CERAD som screeninginstrument vid MCI och Alzheimers sjukdom. Resultaten tydde på att MCI-patienter hade svårigheter med minnesinkodningen vid *inlärning av ordlista*, vilket dessutom var den enda uppgiften i vilken det upptäcktes skillnader mellan MCI-patienter och kontrollpersoner. I motsats till

inkodningen, upptäcktes inga svårigheter med att bevara den inlärda ordlistan i minnet hos MCI patienter, d.v.s. det fanns inga signifikanta skillnader i fördröjd minnesåterkallning mellan MCI-patienter och kontrollpersoner. Angående CERAD som screeninginstrument, tydde resultaten på att testbatteriet inte är tillräckligt sensitivt för att upptäcka MCI. Med andra ord finns det en risk för att personer med preklinisk Alzheimers sjukdom inte blir upptäckta ifall CERAD används som det enda screeninginstrumentet. Likaså tydde resultaten på att det kan finnas en risk för att en del kognitivt friska äldre personer kan få ett falskt positivt resultat. Dessa riskfaktorer borde beaktas med tanke på att CERAD blivit ett populärt screeninginstrument i Finland vid demensutredningar.

I studie II undersöktes verbal inlärning och glömska hos patienter med MCI och Alzheimers sjukdom samt hos friska äldre kontrollpersoner. Detta undersöktes med ett experimentellt ordinlärningsparadigm där försökspersonerna fick lära sig benämningar på föremål från äldre tider (d.v.s. sådana föremål som existerar på riktigt, men som försökspersonerna inte kände till) på så vis att hälften av föremålen och deras benämningar inövades med semantiskt stöd (semantiskt stöd = vad föremålet används till) och hälften inövades utan semantiskt stöd. Orsaken till att semantiskt stöd användes vid träningen, var tanken om att det kunde stöda ordinlärningen speciellt hos MCI-patienterna, vilkas semantiska minne är mera intakt än deras episodiska minne. Träningsfasen tog en vecka och utöver detta utfördes en uppföljningsundersökning en vecka, fyra veckor och åtta veckor efter träningsperioden. Vid uppföljningen undersöktes, förutom nivån på minnesåterkallningen av benämningarna på föremålen, även återkallningen av det semantiska stödet, igenkännandet av föremålen samt effekten av fonologiskt stöd vid återkallningen av benämningarna på föremålen. Resultaten från studie II indikerade att MCI-patienterna led av försämrad inkodningsförmåga jämfört med friska äldre kontrollpersoner, vilket framkom i MCI-patienternas försämrade förmåga att lära sig benämningarna på de nya föremålen. Patienterna med Alzheimers sjukdom lärde sig benämningarna på de nya föremålen ännu sämre än MCI-patienterna. Däremot fanns det under uppföljningen inga skillnader mellan de tre grupperna gällande glömskan av de nyligen inlärda benämningarna på föremålen. Med andra ord tydde resultaten på att en inlärningssvårighet var kännetecknande för både MCI och Alzheimers sjukdom, medan de inlärda benämningarna på föremålen bevarades i minnet på samma vis såväl i patientgrupperna som i kontrollgruppen. Därtill drog MCI-patienterna nytta av det

semantiska stödet vid återkallningen av ord vid sista uppföljningstillfället, vilket indikerade att patienternas bättre bevarade semantiska minnesfunktioner i viss mån kompenserade deras mera gravt försämrade episodiska minnesfunktioner. Resultaten för minnesåterkallningen av det semantiska stödet, liksom även igenkänningsuppgiften, uppvisade inga skillnader mellan MCI-patienterna och kontrollpersonerna, vilket antydde att dessa minnesområden var väl bevarade i MCI-gruppen.

I studie III och IV användes funktionell hjärnavbildning, PET, för att undersöka hjärnaktiveringsmönster vid benämning av nyligen inlärda, sällsynta föremål jämfört med bl.a. benämning av vanliga föremål hos friska äldre personer (studie III) och MCI-patienter (studie IV). Resultaten från studie III visade att benämning av nyligen inlärda, sällsynta föremål aktiverar ett nätverk av hjärnområden i vänstra hemisfären (frontotemporala områden och lillhjärnan) som är mera omfattande än det som aktiveras vid benämning av vanliga föremål. Detta i sin tur tyder på att benämning av nyligen inlärda, sällsynta föremål kräver en mera intensiv fonologisk och semantisk processering än benämning av vanliga föremål. I studie IV syntes en signifikant ökning av aktiveringen i främre delen av gyrus cinguli (anterior cingulate) hos MCI-patienter jämfört med kontrollpersoner vid benämningen av nyligen inlärda föremål som hade tränats utan semantiskt stöd. Resultaten indikerade att en högre grad av exekutiv uppmärksamhet krävdes hos MCI-patienterna än hos kontrollpersonerna.

ABSTRACT

The main focus of the present thesis was at verbal episodic memory processes that are particularly vulnerable to preclinical and clinical Alzheimer's disease (AD). Here these processes were studied by a word learning paradigm, cutting across the domains of memory and language learning studies. Moreover, the differentiation between normal aging, mild cognitive impairment (MCI) and AD was studied by the cognitive screening test CERAD.

In **study I**, the aim was to examine how patients with amnestic MCI differ from healthy controls in the different CERAD subtests. Also, the sensitivity and specificity of the CERAD screening test to MCI and AD was examined, as previous studies on the sensitivity and specificity of the CERAD have not included MCI patients. The results indicated that MCI is characterized by an encoding deficit, as shown by the overall worse performance on the CERAD Wordlist learning test compared with controls. As a screening test, CERAD was not very sensitive to MCI.

In **study II**, verbal learning and forgetting in amnestic MCI, AD and healthy elderly controls was investigated with an experimental word learning paradigm, where names of 40 unfamiliar objects (mainly archaic tools) were trained with or without semantic support. The object names were trained during a 4-day long period and a follow-up was conducted one week, 4 weeks and 8 weeks after the training period. Manipulation of semantic support was included in the paradigm because it was hypothesized that semantic support might have some beneficial effects in the present learning task especially for the MCI group, as semantic memory is quite well preserved in MCI in contrast to episodic memory. We found that word learning was significantly impaired in MCI and AD patients, whereas forgetting patterns were similar across groups. Semantic support showed a beneficial effect on object name retrieval in the MCI group 8 weeks after training, indicating that the MCI patients' preserved semantic memory abilities compensated for their impaired episodic memory. The MCI group performed equally well as the controls in the tasks tapping incidental learning and recognition memory, whereas the AD group showed impairment. Both the MCI and the AD group benefited less from phonological cueing than the controls. Our findings indicate that acquisition is compromised in both MCI and AD, whereas long-

term retention is not affected to the same extent. Incidental learning and recognition memory seem to be well preserved in MCI.

In **studies III and IV**, the neural correlates of naming newly learned objects were examined in healthy elderly subjects and in amnestic MCI patients by means of positron emission tomography (PET) right after the training period. The naming of newly learned objects by healthy elderly subjects recruited a left-lateralized network, including fronto-temporal regions and the cerebellum, which was more extensive than the one related to the naming of familiar objects (study III). Semantic support showed no effects on the PET results for the healthy subjects. The observed activation increases may reflect lexical-semantic and lexical-phonological retrieval, as well as more general associative memory mechanisms. In study IV, compared to the controls, the MCI patients showed increased anterior cingulate activation when naming newly learned objects that had been learned without semantic support. This suggests a recruitment of additional executive and attentional resources in the MCI group.

1. INTRODUCTION

The maintenance of cognitive capabilities is important for the quality of life as people get older. Cognitive problems become increasingly common with advancing age and their appearance often has a detrimental effect on subjective well-being and ability to lead an independent life. It has also become increasingly important to be able to differentiate normal aging from neurodegenerative disorders that cause dementia, as there is now effective medication that can slow down the progression of the most common cause of dementia, namely Alzheimer's disease (AD) (e.g. Ballard, 2000). Of special interest is the condition that has been coined as mild cognitive impairment (MCI), as it entails an increased risk of developing AD over the next few years (Petersen, 2004). To achieve a deeper understanding of the evolvement of dementia, both the cognitive and neural aspects of this process need to be studied and related to each other. This is important not only for the diagnostics but also for the treatment where the aim is to improve the quality of the patients' and their relatives' lives and to support the patients' cognition.

Memory impairment is the key cognitive deficit in preclinical and early Alzheimer's disease (e.g. Collie & Maruff, 2000). However, memory is a very broad and complex concept, including many different functions that can be selectively disrupted. Memory and learning has traditionally been investigated by asking the subjects to encode and retrieve familiar items such as words or objects. The topic of the present thesis, learning of new information, has received much less attention. A striking example of the immense learning capacity of the human brain is our ability to acquire, maintain and update a massive storage of words (usually tens of thousands of actively used words), which is functional throughout the life-span.

Among researchers there is still some disagreement about which subcomponents constitute the function we generally refer to as memory, and different models of memory overlap to a great extent. However, virtually all contemporary models distinguish between immediate and long-term memory. *Short-term memory (STM)* refers to temporary retention of a limited amount of information that may then be incorporated into a more stable, potentially more permanent memory store, i.e. into *long-term memory (LTM)* (Baddeley, 2000b; Jonides et al., 2008). Currently, the most influential theory about the structure and

function of the STM is the concept of *working memory (WM)* (Baddeley, 2000b). Working memory refers to a multicomponent system with limited capacity that provides temporary storage of information for the facilitation of complex cognitive activities, such as learning. One of the components is coined as the phonological loop that is thought to hold information that can be rehearsed verbally. The visuospatial sketchpad is suggested to hold visuospatial information. The central executive component is suggested to control the overall system. The episodic buffer (Baddeley, 2000a) that was added to the WM model afterwards is thought to integrate information from several sources.

Long-term memory can be divided into declarative and procedural memory, i.e., memory for facts and episodes vs. memory for skills and other cognitive operations, respectively (Squire, 1987). Declarative memory can further be divided into episodic and semantic memory, with episodic memory referring to memory for personally experienced and temporally specific events or episodes, whereas semantic memory refers to a store of knowledge including facts, concepts and word meanings (Tulving, 2002). Both lesion and neuroimaging studies have shown that the medial temporal lobes are crucial to episodic memory functioning (Gabrieli, 2001), whereas semantic memory seems to entail a broader network of cortical regions, including temporal and frontal areas (Martin, 2001).

Memory includes encoding, maintenance and retrieval, and is thus a highly active process that requires e*xecutive functions.* These functions refer to goal-directed, flexible use of cognitive abilities, e.g., sustaining, dividing and shifting attention according to task demands, inhibiting inappropriate responses, and solving problems. They seem to represent a cluster of closely related but partly separate cognitive processes that to a great extent rely on prefrontal brain regions (Miyake et al., 2000).

Learning can be either *intentional* or *incidental.* Whereas intentional learning denotes an active intent to learn something, incidental learning refers to passive learning that happens as a by-product of other information processing. For example, unknown words may be learned incidentally during normal reading (for review, see Swanborn & de Glopper, 1999).

The main focus of the present thesis is at verbal episodic memory processes that are particularly vulnerable to preclinical and clinical dementia. The tasks used for this purpose

involve word learning, thus cutting across traditional memory studies and the domain of language learning research. Moreover, the differentiation between normal aging, MCI and AD is studied by a current cognitive screening test.

1.1. WORD LEARNING

Several alternative models for word learning have been put forward, and their methodological and empirical background varies considerably. The cognitive mechanisms underlying word learning have also been much debated (Baddeley, Gathercole, & Papagno, 1998; Gupta & MacWhinney, 1997; Markson & Bloom, 1997; Martin & Gupta, 2004: Waxman & Booth, 2000). At question is to which degree language learning is either domain specific or non-specific and which memory and learning mechanisms are involved in vocabulary acquisition. While some researchers argue strongly that working memory (Baddeley et al., 1998) or short-term memory (Martin & Gupta, 2004) is essential in word learning, others stress the importance of declarative memory processes (Ullman, 2004) and incidental learning (Saffran, Newport, Aslin, Tunick, & Barrueco, 1997).

1.1.1. Memory mechanisms underlying word learning

According to Baddeley (2000a, 2000b), a crucial functional element in word learning is the verbal WM (phonological loop) that consists of two components, the phonological store and the subvocal articulatory rehearsal process. The acoustic or phonological memory trace is held in the phonological store, and is assumed to decay within a few seconds unless it is maintained by the rehearsal process. In word learning, the verbal WM enables the temporary storage of unfamiliar sound patterns of words until long-term representations are established. It should be mentioned, though, that although verbal WM is important for the learning of phonological forms of words, it does not account for the buildup of visual and semantic representations. In fact, Duyck, Szmalez, Kemps, and Vandierendonck (2003) have suggested that the learning of word associations can rely on other resources, such as the visuospatial sketchpad. An integrative model on word learning by Gupta and MacWhinney (1997) assumes that verbal STM and word learning involve common underlying cognitive mechanisms. Firstly, they are related because they depend on the same core phonological processing mechanisms. Secondly, they are

related because of their use of rehearsal and chunking. This would also explain the correlation found between performances in these two cognitive domains. In other words, the model views verbal STM and word learning as involving common underlying mechanisms, without any implication that they are causally related. Furthermore, Ullman (2004) has proposed an influential model, called the declarative/procedural model, of how memory circuits contribute to language, including word learning. More specifically, it claims that word learning relies heavily on declarative memory subserved by temporal lobe structures, whereas mental grammar underlies procedural memory that is subserved by a network of brain structures, including frontal/basal ganglia circuits, with a probable role for parts of the parietal cortex, superior temporal cortex and the cerebellum. The lexical/declarative and the grammatical/procedural memory are thought to interact in several ways and similar types of knowledge may be acquired by both systems. An impairment of the declarative system is expected to lead to altered processing by the procedural system, and vice versa. Finally, Saffran et al. (1997) have stressed the incidental memory mechanisms in word learning, as both children and adult language learners are remarkably skillful at automatically absorbing detailed linguistic information from language input. More specifically, Saffran et al. (1997) showed that children and adults can extract words from a speech stream by exploiting the sequential probabilities of syllable sequences. This statistical learning mechanism may support not only word segmentation but also the acquisition of other aspects of language.

To summarize, the abovementioned models have aimed at identifying the explicit and implicit memory mechanisms involved in word learning. It has even been suggested that one of these mechanisms, verbal WM, has evolved primarily in order to serve vocabulary development (Baddeley et al., 1998). This is supported by the significant correlations between nonword repetition performance (a verbal WM measure) and vocabulary development across a wide range of ages. It should also be noted that the models shortly presented above show considerable overlap. For example, the model by Gupta and McWhinney (1997) can be seen as an extension of the WM model by Baddeley (2000a, 2000b). Certain aspects of WM are also brought up in relation to the declarative/procedural model by Ullman (2004). At a more general level, word learning can be seen as an associative learning task. For example, to learn a novel concrete noun, one

needs to associate an object, a name (phonological representation) and a concept with each other.

1.1.2. Neural correlates of word learning

With regard to the neural basis of the proposed cognitive mechanisms underlying word learning (see above), the verbal WM has been associated with frontal and parietal brain activation. More specifically, it has been suggested that the phonological store is associated with left parietal activation, while the rehearsal process is associated with left posterior-inferior frontal activation (Broca's area). Also cerebellar activations are often found in verbal working memory tasks (for review, see Cabeza & Nyberg, 2000). The declarative/procedural model by Ullman (2004) strongly emphasizes the role of the medial temporal lobe structures in word learning. However, also other areas, such as the ventrolateral prefrontal cortex, have been suggested to be involved in the encoding of new memories and the selection or retrieval of declarative knowledge (for review, see Buckner & Wheeler, 2001), i.e., the same brain areas that are also consistently found to be activated in WM tasks (for review, see Smith & Jonides, 1999). Ventral prefrontal cortex activation has also been related to associative learning that can be linked to word learning, where one should learn and associate three components (word, concept, and external referent) with each other. In general terms, the ventral prefrontal cortex is seen as a part of a system where associations are made between visual cues and the choices that they represent (for review, see Passingham, Toni, & Rushworth, 2000).

Thus far, the neural mechanisms of word learning (more specifically the retrieval of newly acquired words) have received scant attention in the functional neuroimaging literature. Neuroimaging experiments on word learning conducted on healthy subjects have suggested predominantly left hemisphere mechanisms (Breitenstein et al., 2005; James & Gauthier, 2004; Raboyeau et al., 2004). With regard to acquisition of lexical-semantic knowledge (object meaning), the most prominent brain correlates that have been put forward are the left inferior frontal cortex (James & Gauthier, 2004) and the left temporal lobe, more specifically posterior superior temporal sulcus and middle temporal cortex (Raboyeau et al., 2004), and left medial temporal structures (Breitenstein et al., 2005). Acquisition of lexical-phonological knowledge (object name) has been related to inferior

parietal lobe (Breitenstein et al., 2005, Cornelissen et al., 2004) and left temporal cortex function (Hulten, Vihla, Laine, & Salmelin, 2009). In addition, anterior cingulate activation has been found in association with lexical learning, interpreted to reflect attentional processes needed to access recently learned words (Raboyeau et al., 2004). The abovementioned results partly overlap with those found in functional neuroimaging studies on naming familiar objects, but differences are also found (Bookheimer, Zeffiro, Blaxton, Gaillard, & Theodore, 1995; Martin, Wiggs, Ungerleider, & Haxby, 1996; Murtha, Chertkow, Beaugard, & Evans, 1999; Zelkowicz, Herbster, Nebes, Mintun, & Becker, 1998). For instance, inferior frontal activation is found in retrieval of both familiar and recently learned new words, but the temporal activation in retrieving familiar names has been found in posterior inferior areas (fusiform gyrus), and have thus differed from that found in studies on word learning, which report activation increases in left medial temporal structures, as well as superior and posterior middle temporal cortex. Also, the inferior parietal lobe activation observed in some studies on naming of newly learned objects has not been characteristic for naming of familiar objects.

1.2. MILD COGNITIVE IMPAIRMENT (MCI) AND ALZHEIMER'S DISEASE (AD)

Mild cognitive impairment (MCI) has become an important research topic, as patients with this condition have been shown to be at risk of developing Alzheimer's disease (AD) or other neurodegenerative diseases (Collie & Maruff, 2000; Petersen, 2004; Petersen et al., 2001). There is heterogeneity concerning the MCI criteria, but generally MCI refers to persons who do not fulfil the criteria for AD or dementia, but who show some form of cognitive decline (for review, see Palmer, Fratiglioni, & Winbland, 2003). Of particular interest is amnestic MCI that refers to subjects with isolated episodic memory impairment (Collie & Maruff, 2000; Petersen et al., 1999; Petersen et al., 2001; Petersen, 2004). Amnestic MCI is the form that most often leads to AD, the turnover rate being approximately 12% per year (Petersen & Morris, 2003).

1.2.1. Cognitive changes in MCI and AD

Although particularly amnestic MCI has attracted considerable research interest, the nature of the memory impairment in this condition is still fairly little studied. Recent studies have shown that the episodic memory impairment in MCI is characterized by a decreased learning efficacy (Moulin, James, Freeman, & Jones, 2004; Ribeiro, Guerreiro, & Mendonca, 2007) and impaired delayed recall (Fernandez-Ballesteros, Zamarrón, & Tàrraga, 2005; Moulin et al., 2004; Petersen & Morris, 2003). Verbal memory tasks appear to cause somewhat more problems than nonverbal ones (for review, see Collie & Maruff, 2000). The episodic memory impairment in amnestic MCI may not be totally isolated, as it has recently been argued that other domains of cognition may be affected as well (see e.g. Bäckman, Jones, Berger, Laukka, & Small, 2004). Subtle preclinical deficits in amnestic MCI, i.e. impairments that cannot be found in standard neuropsychological tests, have been found in cognitive domains such as executive functioning (Collie, Maruff, & Currie, 2002; Davie et al., 2004).

When the disease progression leads to the diagnosis of AD, the neuropsychological deficits are widespread and marked (for reviews, see Collie & Maruff, 2000; Spaan, Raaijmakers, & Jonker, 2003). Alzheimer's disease is characterized by impairments of episodic and semantic memory, attention, executive function and visuospatial ability, with episodic memory problems appearing first (cf. amnestic MCI) and visuospatial impairments appearing at a later stage (Belleville, Peretz, & Malefant, 1996; Binetti et al., 1998; Colette, Van der Linden, Bechet, & Salmon, 1999; De Jager, Hogervorst, Combrinck, & Budge, 2003; Dudas, Clague, Thompson, Graham, & Hodges, 2005; Greene, Baddeley, & Hodges, 1996; Hodges, Salmon, & Butters, 1992; Laatu, Portin, Revonsuo, Tuisku, & Rinne, 1997; Nebes & Brady, 1991; Perry, Watson, & Hodges, 2000).

Acquisition of new words has not previously been studied in MCI. In AD, lexical acquisition has been investigated by studying new verb learning through incidental learning (Grossman et al., 2007; Grossman, Mickanin, Onishi, Robinson, & D'Esposito, 1997). These studies showed that the AD patients were impaired at acquiring the new word's meaning compared with controls, reflecting the AD patients' semantic memory difficulties. However, the AD patients did acquire grammatical knowledge associated with a new word

inci, indicating that AD patients can learn about a new verb and maintain the newly acquired knowledge over a week following incidental learning.

1.2.2. Neural changes in MCI and AD

Regarding the biological basis of the cognitive deficits in MCI, structural magnetic resonance imaging (MRI) studies have indicated gray matter reduction in medial temporal areas (De Toledo-Morell et al., 2004, Dickerson et al., 2001; Karas et al., 2004; Pennanen et al., 2005). Functional imaging imaging has revealed alterations in regional glucose metabolism and blood flow in temporoparietal areas (for review, see Wolf et al., 2003). There are also PET studies that have aimed at identifying characteristic patterns of glucose metabolism in MCI patients that have converted to AD or whose cognitive abilities have deteriorated significantly over time. The changes predicting cognitive decline included reduced glucose metabolism in temporoparietal and posterior cingulate cortex, as well as frontal cortical areas (Chetelat et al., 2005; Drzezga et al., 2003; Mosconi et al., 2004). In other words, although changes in medial temporal areas have been heavily emphasized in MCI because of their well-known link to episodic memory, other brain areas may be affected at the preclinical phase of AD as well (see also Bäckman et al., 2004). In AD, the cognitive decline is related to progressive temporoparietal brain atrophy, especially in the entorhinal cortex and hippocampus, as shown by structural imaging studies (for review, see Nestor, Scheltens, & Hodges, 2004) and neuropathological findings (Braak & Braak, 1991). In addition, a recent structural neuroimaging study by Thomann et al. (2008) found significantly larger cerebellar atrophy in AD patients compared with controls. Furthermore, the temporoparietal distribution (extending further to different frontal areas) of these neural changes has been verified by resting-state metabolic studies of brain function in AD (for review, see Salmon, Lekeu, Bastin, Garraux, & Collette, 2008; Silverman, 2004). In sum, the structural and functional brain changes are more widespread in AD compared with MCI (De Santi et al., 2001) which is in line with the more severe and global cognitive deficits in AD compared with MCI.

There are fewer cognitive neuroimaging studies on MCI than on AD. The few relevant studies in MCI have mostly focused on task-related activation patterns in medial temporal structures and the posterior cingulate, and they have found decreased activation in MCI

patients compared with healthy controls during encoding (Johnson et al., 2006; Machulda et al., 2003) and recognition tasks (Johnson et al., 2006; Ries et al., 2006). However, Saykin et al. (2004) reported reduced activation in frontoparietal areas during a working memory task in MCI patients relative to controls. Recently, Dannhauser et al. (2008) found that verbal encoding related to decreased activation in the left ventrolateral prefrontal cortex in MCI compared with controls. In contrast, Yetkin, Rosenberg, Weiner, Purdy, and Cullum (2006) found increased activation in the MCI group compared with the control group during a working memory task in frontal and temporal areas, as well as the anterior cingulate. Dickerson et al. (2004) studied medial temporal lobe function by fMRI in MCI patients and found that the right parahippocampal gyrus was recruited to a larger extent during memory encoding in MCI patients showing greater clinical impairment. Furthermore, Bokde et al. (2006) studied functional connectivity of the right middle fusiform gyrus in MCI during a face-matching task. They found that MCI affected functional connectivity from the fusiform gyrus to visual areas and medial frontal areas, including anterior cingulate. Finally, a recent PET study by Moulin et al. (2007) on word-pair learning suggested different activation patterns in MCI patients vs. elderly controls. In the MCI group, incremental learning failed to elicit changes in frontal activations but instead showed increased occipital activation. During retrieval, the MCI patients only showed a left frontal activation increase and no right frontal or left temporal activation increases as the controls did.

Although cognitive neuroimaging studies in MCI are scarce, the corresponding literature in AD is more extensive (for review, see Almqvist, 2000; Wermke, Sorg, Wohlschläger, & Drzezga, 2008). The findings of these studies have been quite variable: they have showed loss of activated regions, emergence of newly activated regions (compensatory activation), reduced activation, or no change at all. There are also cognitive activation studies with fMRI conducted with people at genetic risk for AD (=carriers of the APOE ϵ4 allele) that have found differences in the activation patterns between the risk group and the healthy controls (Bookheimer et al., 2000; Smith et al., 2002).

In sum, the existing cognitive neuroimaging studies on both MCI and AD have revealed differences in brain activation patterns when compared to controls, but the observed

changes have been quite variable. A number of factors may explain the heterogeneity of the results, including differences in tasks, experimental designs and patient samples.

1.2.3. Cognitive screening for MCI and AD

Cognitive screening tests are used to detect cognitive impairment, and to assess the need for more detailed neuropsychological assessment and medical examination, which could then lead to a diagnosis. Efforts have been made to develop short, easily and quickly administered cognitive tests that would be sensitive and specific for AD. Until the mid-90's the Mini-Mental State Examination (MMSE) was the most used screening test for dementia. When it comes to specificity, the MMSE has been shown to be excellent, but its sensitivity to clinically diagnosed probable AD has been found to be relatively low (~.65) (Gallassi, Morreale, Di Sarro, & Lorusso, 2002; Tangalos et al., 1996; Wind et al., 1997). Its sensitivity to preclinical AD has been shown to be even lower (Tang-Wai et al., 2003; Tierney, Szalai, Dunn, Geslani, & McDowell, 2000). The CERAD test battery (The Consortium to Establish a Registry for Alzheimer´s Disease) (Welsh et al., 1994) encompasses measures in the cognitive domains where impairments associated with AD first occur, and it has been found to have high re-test reliability, inter-rater agreement and longitudinal validity (Welsh-Bohmer & Mohs, 1997). Delayed recall and savings scores (i.e. delayed recall adjusted for acquisition) on the CERAD Wordlist learning test are well preserved in normal aging but impaired early on in dementia, which is important for the detection of early impairment in cognitive function (Welsh et al., 1994). The CERAD test battery has been recommended as a screening instrument for memory problems in persons aged >55 years in Finland (Hänninen et al., 1999). If individuals perform below the cut-off score in the memory tests or in several of the non-memory tests, subsequent neurological and neuropsychological assessments are recommended. If the performances on one or two non-memory tests fall below the cut-off scores, a follow-up testing (6-12 months) is recommended, as well as an evaluation of possible mood-related reasons for the cognitive decline.

2. AIMS OF THE PRESENT THESIS

The primary aim of the present thesis was to explore verbal learning in amnestic MCI, AD and healthy elderly. Study I was directly related to clinical practice, whereas studies II-IV were experimental with a specific word learning paradigm, including both behavioural as well as neural measures.

In **study I**, the aim was to examine how patients with amnestic MCI differ from healthy controls in the different CERAD subtests. Of particular interest were the performances on the Wordlist learning test that was expected to be a sensitive measure here. Also the sensitivity and specificity of the CERAD screening test to MCI and AD was studied. One should note that previous studies on the sensitivity and specificity of the CERAD have not included MCI patients.

In **study II**, verbal learning and forgetting in amnestic MCI, AD and healthy elderly controls were investigated with an experimental word learning paradigm, where the names of unfamiliar objects were trained with or without semantic support. Verbal memory in MCI and AD has traditionally been investigated by tasks where patients are asked to encode and retrieve familiar items, e.g., words and objects. To date, the learning of new names of objects has not been studied in MCI and AD. Manipulation of semantic support was expected to have some beneficial effects in the present learning task especially for the MCI group, as semantic memory is quite well preserved in MCI in contrast to episodic memory.

In **studies III and IV**, the neural correlates of naming newly learned objects were examined by means of positron emission tomography (PET). The former study addressed only healthy elderly subjects and the latter examined whether amnestic MCI would induce changes in the brain activation patterns related to naming of newly learned objects, compared with healthy elderly controls. In both studies, it was also explored whether provision of semantic information would show an effect on naming of newly learned objects at the neural level. Studies on novel word learning in healthy subjects are scant in the functional neuroimaging literature, and the neurocognitive mechanisms of word learning in MCI patients have not been examined before.

3. PARTICIPANTS AND METHODS

3.1. PARTICIPANTS

Subject characteristics are shown in Table 1. Neuropsychological assessments (studies I-IV), CERAD tests (study I) and the experimental word learning paradigm (studies II-IV) were conducted at the Department of Psychology at the Åbo Akademi University, Finland. The PET scans (study III-IV) were carried out at the Turku PET Centre, Finland. All the healthy elderly subjects were recruited from various community sources. They all volunteered in the study and were native speakers of Finnish. None of the control subjects reported subjective cognitive impairments, linguistic dysfunctions, neurological illnesses or psychiatric problems. Neither did the controls show any cognitive deficits in the neuropsychological assessments as compared with age-appropriate norms.

The MCI and AD patients were referred to the studies by a neurologist. Neurological findings for the MCI patients did not meet the NINCDS-ADRDA (McKhann et al., 1984) criteria for probable AD, and there were no other neurological or psychiatric disorders explaining the subjective memory complaint in these patients. Based on neurological examination and a neuropsychological assessment they all met the criteria for amnestic MCI (Petersen et al., 2001). These criteria are as follows: (1) memory complaint preferably corroborated by an informant, (2) impaired memory function for age and education, (3) preserved general cognitive function, (4) intact activities of daily living, and (5) not demented. The patients with probable AD met the NINCDS-ADRDA criteria (McKhann et al., 1984). The specific criteria are as follows: (1) dementia established by clinical examination and documented by MMSE or some similar examination and confirmed by neuropsychological tests, (2) deficits in two or more areas of cognition, (3) progressive worsening of memory and other cognitive functions, (4) no disturbance of consciousness, (5) onset between ages 40-90 (most often after the age 65), and (6) absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition. A signed informed consent in keeping with the Declaration of Helsinki was received from all subjects before participation. All study protocols were approved by the local ethical committee.

3.1.1. Study I

Fifteen healthy elderly, 15 amnestic MCI patients and 15 patients with probable AD participated in study I. Five of the patients with probable AD also participated in study II. All subjects underwent a neuropsychological assessment, including the Finnish versions of the following tests: Wechsler Memory Scale-Revised (Wechsler, 1996), four subtests from the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1992) (Digit Span, Similarities, Block Design, Digit Symbol), the Benton Visual Retention Test-C, Trail Making A+B and Boston Naming Test (Laine, Koivuselkä-Sallinen, Hänninen, & Niemi, 1997). There were no significant differences between the three groups in age or years of education (means and standard deviations shown in Table 1).

3.1.2. Studies II-IV

Altogether 34 subjects participated in studies II-IV (Table 1). All were native speakers of Finnish. Twelve of the participants in study II were healthy elderly, 13 were amnestic MCI patients and 9 were mild AD patients. Ten of the healthy elderly subjects in study II participated in the PET experiment (studies III and IV), and 10 of the MCI patients served as subjects in study IV. All 34 subjects were neuropsychologically assessed by the Finnish versions of the following tests: the CERAD (Welsh et al., 1994; Pulliainen, Hokkanen, Salo, & Hänninen, 1999), the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1992) (Digit Span, Block Design, Digit Symbol, Similarities), the Wechsler Memory Scale-Revised (Wechsler, 1996), the Benton Visual Retention Test-C, the Trail Making A+B, the Stroop test, the Boston Naming Test (Laine et al., 1997) and the Word Fluency test (semantic and phonological). In addition to the standard neuropsychological assessment, three tests were administered to all subjects, namely a non-verbal semantic test (Category-specific odd-one-out test; Laine, Schmied, & Trefzer, 1998), a word span/non-word span test, and a synonym judgement task (with both the auditory and written synonym judgements performed orally) derived from the experimental Finnish translation of the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA; Kay, Lesser, & Coltheart, 1992). The subject groups were matched by age and years of education (controls/MCI/AD in study II and controls/MCI in study IV) (means and standard deviations are shown in Table 1). All subjects participating in the PET experiments (studies

III-IV) were right-handed. In studies III and IV, a structural T1-weighted MRI image of the brain was taken from each subject.

Hereafter, the amnestic MCI patients in the present thesis will be referred to as MCI patients.

Table 1. Subject characteristics in the four studies.

	Subjects	**N**	**♂/♀**	**Age years**	**Education years**	**MMSE**
				Mean (SD)	**Mean (SD)**	
Study I	Healthy elderly	15	11/4	68.1 (3.9)	9.8 (4.0)	27.4 (1.7)
	MCI	15	9/6	67.5 (9.2)	8.2 (2.1)	26.5 (2.3)
	AD	15	11/4	71.9 (5.8)	8.9 (3.3)	22.8 (3.4)
Study II	Healthy elderly	12	9/3	66.0 (7.3)	11.6 (3.7)	29.1 (0.7)
	MCI	13	7/6	69.5 (8.2)	10.3 (3.3)	27.5 (1.5)
	AD	9	6/3	73.8 (4.5)	11.9 (3.4)	25.3 (3.2)
Study III & IV	Healthy elderly	10	7/3	65.5 (6.9)	11.3 (3.9)	29.0 (0.7)
Study IV	MCI	10	4/6	68.6 (8.6)	11.2 (3.3)	27.3 (1.5)

3.2. METHODS

3.2.1. CERAD (study I)

In study I the Finnish CERAD (Pulliainen et al., 1999) was administered to all subjects. The test battery consists of 9 subtests that are described in Table 2. Note that the CERAD also includes another screening instrument, namely the Mini-Mental State Examination (MMSE).

Table 2. CERAD subtests.

Subtest	**Description**	**Max. score**	**Cut-off score**
1. Verbal fluency	Generating animal names (60 seconds)	-	<15
2. Naming	Visual confrontation naming of 15 pictures	15	<11
3. MMSE	Thirty questions and tasks (orientation in time and space, memory, cognitive control)	30	<25
4. Wordlist learning	List of 10 words shown to the patient 3 times, free recall after each presentation	30	-
5. Constructional praxis	Copy of 4 line drawings	11	-
6 a. Wordlist learning (del)	Delayed recall of 10 words	10	-
6 b. Wordlist learning (savings)	Delayed recall adjusted for acquisition (Delayed recall/Immediate recall x 100)	100%	<80%
7. Wordlist recognition	Recognition (yes/no) of the 10 stimulus words amongst 10 distractors	100%	<80%
8 a. Constructional praxis (del)	Delayed recall of 4 line drawings	11	-
8 b. Constructional praxis (savings)	Delayed recall adjusted for acquisition (Delayed recall/Immediate recall x 100)	100%	<60%
9. Clock drawing	Draw a clock showing the time ten past eleven	6	<5

3.2.2. Experimental word learning paradigm (studies II-IV)

The experimental design is depicted in Figure 1. In studies II-IV, each subject received training during 4 sessions, and underwent a naming test on a 5th session (in most cases one day after the last training session). Sessions 1-5 took place on separate days within a time period of maximally 2 weeks. Furthermore, a follow-up (reported only in study II) was conducted one week, 4 weeks and 8 weeks after the 5th session.

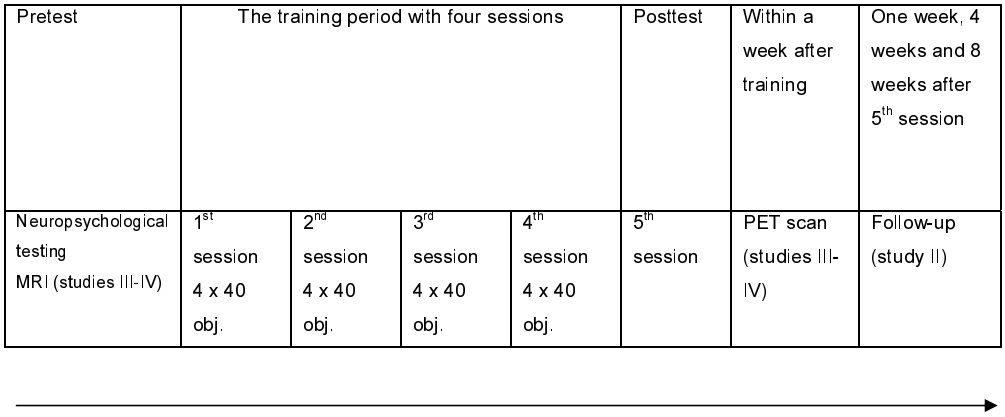

Figure 1. Experimental design (studies II-IV).

3.2.2.1. Stimuli

The stimuli used in the training paradigm were black-and-white outline drawings of non-living objects, selected from the pool of unfamiliar objects employed by Cornelissen et al. (2004). The objects mainly represented archaic domestic tools unknown to modern-day people. The stimulus categories were as follows (studies II-IV): unfamiliar but real objects for which both the name and the definition was given during training (SemPhon; n=20) and unfamiliar but real objects for which only the name was given (Phon; n=20) during training. In the PET experiment (studies III and IV), three additional stimulus categories were used: unfamiliar but real objects for which no information was given (UnFam; n=20), real familiar

non-living objects (Fam; n=20), and visual noise patterns (VNP; n=20). The names of the SemPhon and Phon objects were matched on several linguistic features (word length, number of syllables, number of vowels, number of consonants). Visual complexity between the four groups of objects (SemPhon, Phon, UnFam, Fam) as well as associative potential (only for SemPhon, Phon, UnFam objects) were also checked for.

3.2.2.2. Training

To ensure that the SemPhon and Phon objects were originally unfamiliar to the subjects, they were presented for naming at the first session prior to any training. Maximally 2 out of the 40 object names were allowed to be familiar to a subject. During each training session, all 40 objects were shown four times in a pseudorandomized order. The objects were shown as a PowerPoint slide show, one picture at a time for a period of 10 seconds. The subjects were asked to read aloud the name printed below the object. If the object's definition was also given, they were to read that aloud as well. However, the subjects were instructed to learn only the object names provided. The experimenter was present during the whole training procedure.

Training sessions 2-4 were preceded by a *naming test* where the objects were presented on the computer screen, thus yielding 3 measurements during the training and one after the training (the 5th session). In the naming test, the subjects were instructed to name the object as soon as possible. They were given 10 seconds to name each object, and the correct answer was not provided. Furthermore, each training session (sessions 1-4) was followed by a *pointing-and-naming test*, where all the objects were presented on a paper sheet and the examiner pointed at the objects one at a time in a pseudorandomized order and asked the subjects to name each one. If the subjects were not able to name the object in 10 seconds, the correct answer was given to them, and thus even the pointing-and-naming test included some training.

3.2.2.3. Follow-up (study II)

The naming test described above was accompanied by a cueing procedure during the follow-up (sessions 5-8). If the subjects could not name the object in 10 seconds, a phonological cue (the first syllable of the object name) was given, and the subjects were thereafter given 10 additional seconds to name the object. In sessions 5-8, a recognition test and a semantic test were also performed. The recognition test preceded the naming test. It consisted of the 40 trained objects and 40 similar but untrained objects that were shown to the subjects for 5 seconds on the computer screen in a pseudorandomized order. The subjects were to decide whether or not the object had been among the 40 trained ones. A semantic test was performed after the naming test. The subjects were shown the 40 trained objects in a pseudorandomized order and asked to decide whether or not the object was presented with a definition during training. If yes, the subjects were asked to report the definition as fully as possible. The definitions given at this task were scored by two raters. The inter-rater reliability was high.

3.2.3. PET imaging (studies III-IV)

Positron emission tomography (PET) as a functional neuroimaging method relies on the positive correlation between the level of neural function and regional cerebral blood flow (rCBF) increases that support the activity. By contrasting rCBF patterns during the task of interest with those in a reference condition, one can reveal brain regions that are participating in the task of interest. While the non-invasive functional magnetic resonance imaging (fMRI) method is nowadays more common in cognitive neuroimaging, the PET method suited well for the present purposes as overt verbal responses were collected from the subjects during scanning. The silence of the PET scanner as well as its somewhat lower sensitivity to small head movements that can be elicited by articulation were positive features for the present studies (for review, see Buckner & Logan, 2001; Rugg, 2000).

PET imaging was conducted within a week after training. Each subject underwent 12 PET scans with ^{15}O-water, including a rest condition (eyes open, blank screen) and 5 experimental conditions (SemPhon, Phon, UnFam, Fam, VNP). All the conditions were presented twice, yielding two separate blocks with 6 conditions in a pseudorandomized

order, so that no condition was immediately repeated. The presentation order of the two blocks was counterbalanced across participants.

3.2.3.1. Experimental conditions in the PET session

(1) SemPhon condition. The subjects were shown 20 trained SemPhon objects. The subjects were instructed to name each object aloud. If they could not retrieve the name of the object, they were instructed to stay silent and concentrate on the next object. In this and the four following conditions each object was shown twice within a scan, with no objects being immediately repeated. *(2) Phon* condition. The subjects were shown 20 trained Phon objects and were instructed to name the objects aloud. *(3) UnFam* condition. The subjects were shown 20 untrained UnFam objects. The subjects had seen them only once before the PET-scanning, on the 5th session as a part of a recognition test. The subjects' task was to say "picture" every time an UnFam object appeared on the screen, *(4) Fam* condition. The subjects were shown 20 familiar objects and the instruction was to name each of them. The subjects had seen and named them once before the PET scanning (on the 5th session), *(5) VNP* condition. The subjects were shown 20 black and white visual noise patterns and the task was to say "picture" every time a new random pattern appeared.

3.2.3.2. PET data acquisition and processing

In order to register relative changes in the regional cerebral blood flow (rCBF) between the experimental conditions, 12 emission PET scans were obtained for each subject using a GE Advance PET scanner (General Electric Medical Systems, Milwaukee, WI, USA), providing 35 transverse slices covering the entire brain and spaced 4.25 mm apart (centre to centre). The task block that lasted approximately 3 minutes and was initiated 15 s prior to the intravenous bolus (10 ml in 10-15 s) administration of 300 MBq ^{15}O-water. Emission data were acquired in 3D mode for 90 s starting when the true coincidence rate exceeded 15 kcps. Scans were separated by approximately 10 minutes. The images were reconstructed using a filtered back-projection algorithm into a series of 35 slices including 128 x 128 voxels each, yielding an in-plane pixel dimension of 2.34 x 2.34 mm.

The PET image preprocessing and statistical analysis was performed using the Statistical Parametric Mapping software (Friston 2004; Friston et al., 1995). The SPM99 was used in study III and the SPM2 in study IV, implemented in Matlab version 6.1 (Mathworks Inc., USA). In order to compensate for inter-scan head motion, a two-step image realignment procedure was performed. Each reconstructed PET image was realigned to the first image in the series and a mean of the realignment images was created. Then all images were realigned to the mean one. After this the realigned images were spatially normalized into a coordinate space defined by the Montreal Neurological Institute (MNI) PET brain template that approximates the standard stereotactic space of the Talairach and Tournoux brain atlas (Talairach & Tournoux, 1988). An isotropic Gaussian filter of 16 mm full width at half maximum was applied to smooth each normalized image to compensate for residual inter-individual differences in brain shape and to suppress high frequency noise in the images. An inter-scan difference in global signal was removed by proportional scaling of gray matter voxel values to their mean value.

3.2.4. Statistical analyses

In **study I**, MANOVA was used to study overall differences between the three groups on the combined CERAD measure. Subsequent one-way ANOVAs were conducted to further study the differences between the three groups in the following CERAD subtests: Verbal Fluency, Naming, MMSE, Wordlist learning (sum of 3 trials), Wordlist delayed recall, Wordlist savings, Wordlist recognition, Constructional praxis, Constructional praxis (delayed recall), Constructional praxis (savings) and Clock drawing. The Tukey post hoc test was used to analyze pairwise group differences. Because several statistical comparisons were performed, a Bonferroni-corrected alpha level was used both in the ANOVAs and in the post hoc tests. A repeated measures ANOVA was used to analyse the learning of the wordlist (trial 1, 2 and 3) in the three groups. Sensitivity [=correct positives/(correct positives+false negatives)] and specificity [correct negatives/(correct negatives+false positives)] were calculated for the following subtests using the current cut-off scores based on Finnish normative data (Pulliainen et al., 1999): Verbal fluency, Naming, MMSE, Wordlist savings, Wordlist recognition, Constructional praxis savings and Clock drawing. The sensitivity and specificity of the Wordlist recognition test were also explored in the cut-off range 81-95, and the optimal cut-off scores were reported. In the

Finnish CERAD no cut-off scores have been put forth for the Wordlist learning and delayed recall tests, and thus the sensitivity and specificity of these subtests were explored using different cut-off scores (16-20 for the Wordlist learning test and 5-8 for the Wordlist delayed recall test). The optimal cut-off scores for these subtests were reported.

In **study II**, a three-way mixed model ANOVA was conducted to study the naming performance of the newly learned objects in the three subject groups, separately for the training period (sessions 2-5) and for the follow-up (sessions 5-8). Statistically significant interactions were analyzed further by subsequent two-way mixed model ANOVAs (training period) and by subsequent paired-samples t-tests (follow-up). Cued recall (phonological cueing), recall of the semantic definitions (both quantitative and qualitative performance), and recognition memory in the three groups were analyzed by two-way mixed model ANOVAs. As the sample sizes were somewhat different and the assumption of homogeneity of variance as shown by Levene's test was not always met, the Games-Howell post hoc test was used in all the analyses when examining the pairwise group differences. For within-subject factors with more than two levels, corrected probabilities (the Huynh-Feldt procedure) were reported.

In study III, the results from the verbal training were analyzed by a repeated measures ANOVA. The PET results were analyzed with a fixed-effect model to estimate the effects of conditions. The conditions were compared to each other as linear contrasts using *t*-statistics and the following threshold criteria: height threshold T=4.67 corresponding to $p<.05$, corrected for multiple non-independent comparisons (Worsley et al., 1996) along with the cluster extent threshold of 50 contiguous voxels. Anatomical location of the activated foci were found by directly transferring the MNI coordinates of the rCBF peaks into the atlas of Talairach and Tournoux (1988).

In study IV, the behavioural results were analyzed by a three-way mixed model ANOVA. The statistical analysis of the PET results was done in the following steps. At the first step, each individual PET data were fit to a single-subject model and subject-specific inter-condition contrasts were calculated. At the next step, in order to make inferences at the population level, a second level analysis treating subjects as random effects was done by creating a separate model for each inter-condition contrast and entering one contrast file

per subject into the random effects (RFX) model. Due to the relatively small sample size (10 subjects per group), a non-parametric permutation-based method [Statistical non-parametric mapping (SnPM); Nichols & Holmes, 2002)] was chosen. More specifically, the SnPM3b software run under SPM2 with 1024 permutations and 16 mm variance smoothing was used for both within- and between-group analyses.

Previous research indicates that the left inferior frontal cortex and the left temporal cortex are particularly important in verbal episodic recall (Cabeza et al., 2003; James & Gauthier, 2004; Lundström, Ingvar, & Petersson, 2005; Nyberg et al., 2003; Raboyeau et al., 2004). Additionally, the anterior cingulate is thought to participate in more general modulation of executive and attentional control processes in particularly demanding tasks (for review, see Bush, Luu, & Posner, 2000). Therefore, the activation patterns between the MCI patients and the controls were compared when they named newly learned objects vs. saw unfamiliar objects (and said “picture”) by performing volume of interest (VOI) analyses for three selected brain regions. Binary masks for the VOIs were generated with the MARINA software, version 0.6.1 (Walter et al., 2003). The VOI masks covered the following brain structures: the anterior cingulate VOI that included bilateral anterior cingulate cortex, the left frontal (BA 45, 47) VOI that included the triangular (BA 45) and orbital (BA 47) parts of the left inferior frontal gyrus, and the left temporal VOI (BA 21, 22, 38, 20, 37) that included the superior, middle, and inferior gyri of the left temporal lobe. The results of the RFX SnPM analyses were assessed with pseudo-t-statistics and thresholded at a voxel-level family-wise error (FWE) chance probability $p<.05$ corrected either for the whole brain volume (in the within-group comparisons) or for a volume of interest (in the VOI-based between-group comparisons). Anatomical location of the activated foci were found by directly transferring the MNI coordinates of the rCBF peaks into the coordinate space of the Talairach and Tournoux atlas (1988).

Additionally, correlations between naming success in the SemPhon and Phon conditions and brain activation were explored separately for the control and the MCI group at the second level in a series of SnPM analyses. For each of the contrasts SemPhon vs. UnFam and Phon vs. UnFam, the corresponding contrast files (one per subject) were entered into a non-parametric permutation test along with the regression vector representing the naming score. In addition to RFX SnPM analyses for the whole-brain volume, such

analyses were repeated separately for each VOI. The threshold of significance was set as $p<.05$, FWE-corrected for the analysed volume.

4. RESULTS

4.1. PERFORMANCE ON THE CERAD IN MCI AND AD (study I)

Significant overall group differences on the combined CERAD variable including 14 subtest measures were observed. At the subtest level, a significant main effect of group was found on the following CERAD variables: Verbal fluency, Naming, MMSE, Wordlist learning (sum of 3 trials), Wordlist learning (delayed recall), Wordlist savings, Wordlist recognition, Constructional praxis (delayed recall) and Constructional praxis (savings). Post hoc tests showed significant differences between the control group and the AD group in all the abovementioned tests, with the AD patients performing significantly worse. In MMSE, Wordlist learning (delayed recall), Wordlist learning (savings) and Wordlist learning (recognition) the MCI group outperformed the AD group. No statistically significant pair-wise differences were found between the controls and the MCI patients on these measures.

The analysis of the Wordlist learning trials showed that the number of remembered items increased across subject groups during the three trials, albeit the amount of items learned differed between the three groups. Post hoc analyses revealed significant differences between the controls and the AD group, as well as between the controls and the MCI group, but not between the MCI and AD group, indicating that the Wordlist learning of the MCI patients was almost as poor as that of the AD group (Table 3). The interaction term was non-significant, indicating that the relative degree of learning over trials was similar in all three groups.

Table 3. Means and standard deviations of the three groups on the CERAD Wordlist learning test. Tukey's post hoc revealed significant differences between the control group and the AD group, as well as between the control group and the MCI group.

	Control	**MCI**	**AD**
	Mean (SD)	Mean (SD)	Mean (SD)
Wordlist learning (trial 1)	5.9 (1.2)	3.9 (1.2)	3.4 (1.9)
Wordlist learning (trial 2)	7.8 (1.2)	6.2 (1.5)	5.3 (1.7)
Wordlist learning (trial 3)	7.9 (1.4)	6.9 (1.5)	5.5 (1.8)

For those subtests that have cut-off scores based on Finnish norms, the sensitivity and specificity were calculated (Table 4). The subtests Verbal fluency, Naming and MMSE had high specificity, but the sensitivity to MCI was poor. The Wordlist learning (savings) had a high sensitivity to AD, but the sensitivity to MCI and the specificity was low. In Wordlist learning (recognition) the specificity was perfect, and the sensitivity to AD mediocre, but almost no MCI patients were identified. Cut-off scores of 86% and 92% provided a higher sensitivity and only a slightly reduced specificity (Table 4). Since the Wordlist learning test was the only discriminator between the controls and the MCI group, the sensitivity and specificity of cut-off scores 16-20 were calculated. A cut-off score of 16 yielded a specificity of 0.93. The sensitivity to MCI was 0.33 and over half of the mild AD patients were identified as correct positives. Increasing the cut-off score reduced the specificity. Previous studies have found the delayed recall of wordlist to be very sensitive to AD and thus the sensitivity and specificity of this measure using the cut-off scores 5-8 were calculated. The optimal cut-off score was found to be 6: it yielded no false positives and 80% of the mild AD patients performed below this level. However, the sensitivity to MCI was fairly low (0.26) (Table 4).

Table 4. Sensitivity and specificity of the CERAD tests (cut-off scores in parentheses, WLL= wordlist learning).

	Sensitivity		Specificity
	MCI vs. controls	**AD vs. controls**	**Controls vs. MCI and AD**
CERAD tests where cut-off scores based on Finnish norms are available (in parenthesis)			
Verbal fluency (15)	0.26	0.53	1
Naming (11)	0.13	0.4	1
MMSE (25)	0.13	0.73	0.93
WLL (savings) (80)	0.33	0.8	0.66
WLL (recognition) (80)	0.07	0.6	1
Constr.praxis (savings) (60)	0.33	0.8	0.66
Clock drawing (5)	0.06	0.33	0.86
CERAD tests where optimal cut-off scores are presented (in parenthesis)			
WLL sum score of 3 trials (16)	0.33	0.6	0.93
WLL sum score of 3 trials (18)	0.33	0.8	0.86
WLL sum score of 3 trials (20)	0.73	0.86	0.8
WLL delayed recall (6)	0.26	0.86	1
WLL recognition (86)	0.33	0.73	1
WLL recognition (92)	0.46	0.8	0.93

4.2. VERBAL LEARNING IN MCI AND AD (study II)

For the training period, significant overall group differences were found (see Table 5), with controls expectedly showing the best performance and AD patients showing the lowest overall performance. Post hoc analyses showed significant differences between all three groups. The overall naming performance of the newly learned objects increased significantly during training. Also, a significant interaction between test session and group was found, i.e. the learning curves of the 3 groups differed from each other. Subsequent analyses showed that all learning curves differed significantly from each other (controls vs. MCI group, MCI vs. AD group and control vs. AD group), with controls learning the fastest and the AD patients the slowest while the MCI patients were situated in between. Regarding semantic support, the only significant finding was the stimulus type and group interaction, and subsequent analyses showed that the stimulus type and group interaction failed to reach statistical significance between the control vs. AD group or between the MCI vs. AD group, but it was statistically significant between the control vs. MCI group. This was due to the fact that the control subjects learned more names of Phon than SemPhon objects, whereas the MCI patients learned an approximately equal amount of SemPhon and Phon objects.

For the follow-up (see Table 5), significant overall group differences were found again, with the controls showing the best performance and the AD patients showing the worst performance. Post hoc analyses showed significant differences between all three groups. Also, the overall forgetting of the newly learned object names increased significantly during follow-up. In contrast to the training period, the test session and group interaction was non-significant, reflecting similar forgetting curves in the three groups. Concerning semantic support, the only significant finding was the interaction of test session and stimulus type. Subsequent analyses showed that during session 8 (i.e., 8 weeks after training) more SemPhon object names than Phon object names were recalled. Even though the three-way interaction of test session, stimulus type and group failed to reach statistical significance, further analyses were conducted, based on the hypothesis concerning the beneficial effects of semantic support in MCI patients. This effect would be due to the relatively well preserved semantic memory in MCI that could compensate for a deficit in episodic memory. Consequently, if semantic support would show a benefit at recall, its

possible effects should be best visible at the last test session. In line with this hypothesis, the results showed that the MCI group was the only subject group that did benefit from semantic support at the last test session.

Table 5. Means and standard deviations of the number of correctly named objects (SemPhon, max. 20/Phon, max. 20) in the three groups, shown separately for the training period (sessions 2-5) and follow-up (sessions 5-8).

	Session 2	**Session 3**	**Session 4**	**Session 5**
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Naming test - Training period				
Control	4.9 (3.4)/5.7 (3.5)	11.3 (4.0)/12.3 (4.5)	15.4 (2.8)/15.8 (3.4)	18.3 (1.6)/19.3 (0.9)
MCI	1.9 (1.4)/1.6 (1.0)	5.1 (4.0)/4.3 (2.8)	8.4 (4.0)/8.1 (3.7)	10.9 (3.2)/10.8 (4.0)
AD	0.1 (0.3)/0.3 (0.7)	1.2 (1.9)/1.9 (2.8)	2.2 (2.9)/3.3 (4.4)	4.0 (4.3)/4.1 (4.7)
	Session 5	**Session 6**	**Session 7**	**Session 8**
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Naming test - Follow-up				
Control	18.3 (1.6)/19.3 (0.9)	18.3 (2.0)/18.0 (2.4)	17.1 (2.2)/16.7 (3.0)	16.3 (3.0)/16.0 (3.0)
MCI	10.9 (3.2)/10.8 (4.0)	10.4 (3.4)/9.6 (4.6)	8.5 (4.6)/7.5 (4.0)	8.3 (4.9)/6.9 (4.3)
AD	4.0 (4.3)/4.1 (4.7)	3.0 (3.4)/4.4 (4.6)	2.4 (2.2)/2.7 (3.3)	1.8 (2.3)/1.2 (1.8)

As to the phonological cueing (see Table 6), 5 of the control subjects were able to name all the objects correctly at one or more test sessions and were therefore not given phonological cues. Thus, only 7 controls were included in the statistical analysis. To investigate the effect of phonological cueing on naming, the cueing benefit was computed in percent, i.e., the number of correctly named items after cue divided with the total amount of phonological cues given. The analysis revealed a significant main effect of group. Post hoc analyses further showed a significant difference between the control and the MCI group and the control and the AD group, reflecting the fact that the control group benefited significantly more from the phonological cues than the MCI and AD group. The

difference between the MCI and AD group was just at the level of significance. The main effect of test session was also significant, reflecting the fact that the overall benefit of cueing decreased somewhat from session 5 to 7.

In addition to name recall, possible group differences in the number of objects correctly recognized as having a definition were analyzed (see Table 6). A significant main effect of group was found, and post hoc tests further showed differences between the control group and the AD group as well as between the MCI group and the AD group, with the controls recognizing the most definitions and the AD patients the least. No difference was found between the control group and the MCI group. The overall amount of correct recognitions diminished significantly during the follow-up period. The interaction of test session and group was also significant. Whereas the controls performance remained roughly at the same level during the follow-up, the amount of correct recognitions diminished in both patient groups. This was confirmed by further analyses where the interaction of test session and group was significant between the control and the MCI group as well as between the control and the AD group, but not between the MCI and the AD group.

When analyzing the quality of the recalled definitions (see Table 6), a significant main effect of group was found. Post hoc analyses showed that the control group and the MCI group did not differ from each other significantly, whereas the controls and the AD patients showed a significant difference, as did the MCI and AD patients, with controls performing best and AD patients performing worst. The overall quality of the recalled definitions deteriorated significantly during the follow-up.

In the recognition memory task (see Table 6), a significant main effect of group was found. As shown by post hoc tests, the performance of the control group differed significantly from the performance of the AD group, as did the performance of the MCI group and AD group, with controls performing best and AD patients performing worst across test sessions. No statistically significant difference was found between the control and the MCI group. The overall performance level deteriorated significantly during the follow-up. The interaction of test session and group was significant, reflecting the fact that compared with the controls' non-deteriorated performance, the MCI patients' performance deteriorated somewhat and the AD group's performance deteriorated even more during follow-up. This

was confirmed by subsequent analyses showing significant differences for the interaction of test session and group between all three groups (control vs. MCI group, MCI vs. AD group, and control vs. AD group).

Table 6. Means and standard deviations of the benefit of phonological cues in percent (naming test), of the amount of correct recognitions of definitions (n=20) (semantic test), of the quality of the recalled definitions (semantic test) and of the percentage of correct discriminations (recognition test) during follow-up, i.e. sessions 5-8 in the three groups studied.

	Session 5	**Session 6**	**Session 7**	**Session 8**
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Naming test				
Benefit of phonological cueing (%)				
Control	75.0 (33.7)	89.2 (12.2)	67.2 (22.5)	77.8 (13.3)
MCI	63.0 (18.3)	54.8 (18.4)	54.4 (16.5)	51.5 (20.0)
AD	44.9 (18.2)	35.3 (16.3)	35.4 (20.6)	31.6 (19.6)
Semantic test				
Correct recognitions of objects with definition (max. 20)				
Control	17.0 (2.5)	17.4 (2.0)	17.4 (2.5)	16.8 (2.6)
MCI	18.1 (1.9)	17.1 (2.2)	15.7 (3.4)	15.9 (3.7)
AD	13.9 (4.4)	11.9 (3.8)	11.0 (3.8)	10.9 (6.2)
Semantic test				
Quality of definitions (scale: 0-2)				
Control	1.3 (0.2)	1.2 (0.2)	1.2 (0.3)	1.1 (0.2)
MCI	1.2 (0.2)	1.0 (0.2)	0.9 (0.2)	0.9 (0.2)
AD	0.6 (0.4)	0.5 (0.3)	0.4 (0.3)	0.4 (0.3)
Recognition test				
Correct discriminations (%)				
Control	100.0 (0.0)	100.0 (0.0)	99.8 (0.5)	99.8 (0.5)
MCI	100.0 (0.0)	99.7 (0.5)	99.0 (1.3)	98.2 (2.3)
AD	96.4 (4.1)	94.7 (6.0)	92.1 (7.2)	90.7 (7.2)

4.3. NEURAL CORRELATES (PET) OF VERBAL LEARNING IN HEALTHY ELDERLY (study III)

All subjects learned the names of the objects effectively before the PET session; mean percentage of correctly named objects on the 5th session was 94%. During the PET scanning, the mean percentage of correctly named trained items was 88%. A repeated measures analysis of variance (ANOVA) indicated that the subjects learned the names of the Phon objects better than those of the SemPhon items, yielding a significant main effect of stimulus type. As expected, the main effect of test session was also statistically significant, reflecting successful learning of the new names during the training period.

As the brain activation pattern in the SemPhon condition did not differ significantly from that of the Phon condition (even when the cluster extent threshold was set to 0) in terms of rCBF patterns, these two conditions were pooled together forming the "Trained" condition. These pooled imaging results showed rCBF increases in the left superior temporal cortex (junction of BA 22 and 38), frontal regions (Broca's area, BA 44), and in the cerebellum when trained objects were contrasted with familiar objects (Figure 2a). When the Trained objects were contrasted with unfamiliar non-trained objects, rCBF increases were found in the left prefrontal (BA 9, 46/10, BA 47) and precentral (BA 44/6) cortices, as well as in the anterior superior temporal gyrus (BA 22). On the right hemisphere, rCBF increases were found in the anterior part of the superior temporal cortex (BA 22 and BA 38) and in the superior temporal sulcus. Furthermore, activation was found in the cerebellum (Figure 2b). Familiar objects, when compared with the visual noise patterns, elicited bilateral occipital activation in the ventrolateral occipito-temporal cortex. The peaks were located in the left middle occipital gyrus (BA 18) and the right fusiform gyrus (BA19). When compared with rest, the familiar objects elicited bilateral increases in the posterior temporal cortex (peaking in the left BA 22 and right BA 21), the cerebellum, in the right premotor (BA 6) and occipital (BA 18) regions, as well as in the left anterior temporal cortex (BA 22).

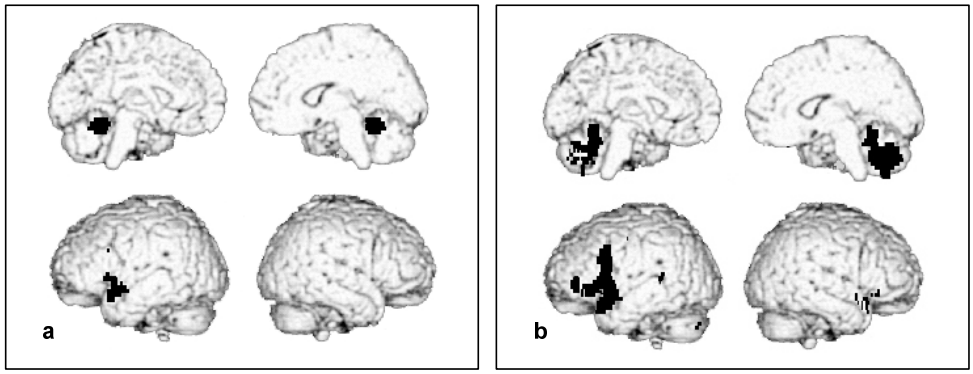

Figure 2. Areas of relative rCBF increase (p<.05 corrected, k>50 voxels) in the a) trained objects vs. familiar objects contrast and the b) trained objects vs. unfamiliar objects contrast projected onto the reconstructed lateral and medial surfaces of the anatomical MRI/SPM99 brain template.

4.4. NEURAL CORRELATES (PET) OF VERBAL LEARNING IN MCI (study IV)

The MCI patients learned 56% of the object names before the PET session. During the PET scanning, the mean percentage of correctly named trained items was 53%. The MCI patients' overall performance was significantly lower than that of the controls, even though both groups showed a learning effect during the training period. As in study II, the significant interaction of test session and group showed that the learning curves of the two groups differed significantly from each other. The interaction of stimulus type and group reached significance, too. This was due to the fact that the control subjects learned more names of Phon than SemPhon objects, whereas the MCI patients learned an approximately equal amount of SemPhon and Phon object names.

The between-group PET results (VOI analysis) revealed that when newly learned objects that had been learned without semantic support (Phon) were contrasted with unfamiliar non-trained objects, a significantly higher increase in rCBF for the MCI patients than for the controls was found in the anterior cingulate VOI, with maxima in BA 32 (Figure 3a). When newly learned objects that had been learned with semantic support (SemPhon) were contrasted with unfamiliar non-trained objects, no significant differences were found

in the anterior cingulate. Albeit only approaching statistical significance in the left frontal VOI (left BA 45, 47), an activation peak in the SemPhon vs. UnFam contrast was found when the MCI patients were compared with the controls (Figure 3b). The Phon vs. UnFam contrast did not yield any significant effects in the frontal VOI. In the left temporal VOI (BA 21, 22, 38, 20, 37) (Figure 3c), no group differences were found for either contrast. The control subjects did not demonstrate any activation increases in any of the VOIs in either contrast when compared with the MCI group. Furthermore, the whole-brain correlation analyses showed a significant positive correlation between naming performance and cerebellar activity for the Phon condition in the MCI group in the cerebellum. The VOI-related results in the left frontal area (peak in BA 47/11) showed a negative correlation for the Phon condition in the MCI group. No significant correlations were found in the control group.

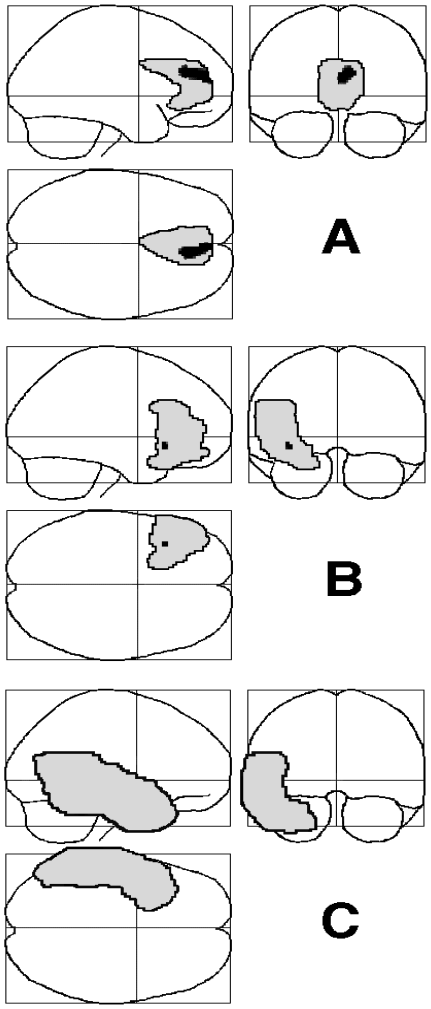

Figure 3. Group differences in activations obtained in the VOI-based analyses. The VOIs and activation clusters are shown as three orthogonal projections to the right, posterior and superior views in the MNI template space. The VOIs are shown as black contours filled with gray. Activation differences between the groups are shown in black inside of the VOIs. a) The anterior cingulate VOI includes an area that is activated more by the MCI patients than by the control group in the Phon vs. UnFam contrast ($p<.05$, FWE corrected for the VOI). b) The left frontal (BA 47 and 45) VOI shows an area that is activated more by the MCI group than the control group in the SemPhon vs. UnFam contrast ($p=.054$ FWE corrected for the VOI; the cluster shown at $p<.06$ VOI-corrected voxel threshold). c) The left temporal VOI showed no significant group differences.

5. DISCUSSION

There has been an increasing research interest in memory and aging. As deficits in learning and memory are often the first symptoms of the most common form of dementia, AD, it would be very important to be able to differentiate these symptoms from more benign age-related changes in memory. The first study addressed the sensitivity and specificity of a cognitive screening battery CERAD in the differential diagnostics of MCI and AD. A special emphasis was put on a wordlist learning subtest expected to be sensitive to memory disorders in these two patient groups. The other three studies focused at the ability to learn new words by healthy elderly, MCI patients, and AD patients. In this regard, it was somewhat surprising to find out that relatively few studies have focused on the learning capacity of patients suffering from preclinical and early AD. Nevertheless, it is common for geriatric patients to complain not only about difficulties in remembering names, but also about learning new words or a new language. The present thesis presents new results on the ability of healthy elderly, MCI patients and AD patients to learn new words. Word learning was investigated by an experimental word learning paradigm and by employing both behavioural and neural measures.

5.1. SCREENING FOR MCI AND AD WITH THE FINNISH CERAD (study I)

In **study I,** the only CERAD subtest that showed significant differences between healthy controls and MCI patients was the Wordlist learning test, with the MCI patients showing a worse overall learning performance than the controls. The AD patients' performance was significantly worse than that of the controls on almost all CERAD subtests. The results indicate that encoding of material to episodic memory is compromised in MCI, which is in line with findings from previous studies on MCI and preclinical AD (Collie & Maruff, 2000; Grober & Kawas, 1997; Morris et al., 1991; Petersen, Smith, Ivnik, Kokmen, & Tangalos, 1994; Petersen et al., 1999; Wang & Zhou, 2002). As regards the CERAD, also Moulin et al. (2004) reported an overall difference between MCI patients and controls in the CERAD Wordlist learning test. However, Moulin et al. (2004) also found that the learning curves of MCI patients and controls differed from each other, with MCI patients showing a less steep curve. No group differences in the learning curves were found in study I, and one reason for this discrepancy could be that the present patient sample was smaller than that of

Moulin et al. (2004). An alternative explanation is that the MCI patients in the Moulin et al. (2004) study were cognitively slightly more impaired the patients in study I: the average MMSE score in their MCI group was 25.7 compared with 26.5 in study I. In any case, the present results give further support for the view that MCI is characterized by an encoding impairment, which can impede learning of new information, as seen in early AD patients (for review, see Germano & Kinsella, 2005). Furthermore, no cut-off score has been assigned to the Wordlist learning test in the Finnish CERAD. This hampers the clinical use of the test, as previous studies have shown that verbal episodic learning problems are amongst the earliest signs of preclinical AD (e.g., Collie & Maruff, 2000; Morris et al., 1991; Linn et al., 1995; Petersen et al., 1994). Accordingly, the sensitivity and specificity of the sum score of the three trials of the Wordlist learning test was explored using a range of cut-off scores. A cut-off score of 16 yielded a sensitivity of 0.33 to MCI and 0.6 to AD with a specificity of 0.93. The sensitivity of the test was raised when the cut-off score was raised, but the number of false positives also increased. Interestingly, a recent Finnish normative study on CERAD (Pulliainen et al., 2007) including 321 cognitively healthy persons between the ages 63-79 found similar results to ours. Although the study by Pulliainen et al. (2007) did not address the sensitivity and specificity of CERAD to MCI and AD, their results showed that 90% of the healthy elderly learned more than 15 words in the Wordlist learning test, i.e., a score of 15 or less was seen as significantly deviant.

It is somewhat surprising that the controls and the MCI patients did not show significant differences in the delayed recall of the Wordlist learning test either in absolute terms or in the delayed recall adjusted for acquisition (Savings score). Previous findings have shown that MCI patients are impaired especially on delayed recall in verbal episodic memory tasks (Petersen et al., 1999). One reason for this discrepancy might be that the delays in the CERAD memory tests are too short (usually approximately 5 minutes) to fully tap the episodic memory consolidation problems in MCI. For example, the delayed recall on the WMS-R Logical memory test, where the delay is usually 30 minutes, has been found to be a good predictor of patients who will later convert to AD (Elias et al., 2000; Marquis et al., 2002). The findings from study I may also indicate that retention is not impaired to the same extent as acquisition in MCI, in line with e.g. Grober and Kawas (1997). Also for the recall performance in the Wordlist learning test, a cut-off score is lacking in the Finnish CERAD, although this test has been shown to be the best discriminator between normal

aging and early AD (Welch-Bohmer & Mohs, 1997). Calculations on the present data showed that a cut-off score of 6 seemed to be very specific and sensitive to clinically diagnosed AD, but only 26% of the MCI patients were identified using this cut-off. Furthermore, the Savings scores in both Wordlist learning and Constructional praxis were found to be relatively unspecific, i.e., several healthy controls were identified as false positives using this measure, which was quite unexpected. This suggests that the current cut-off scores (80 and 60, respectively) in the Finnish CERAD Savings scores might be too high. Results from the recent CERAD study by Pulliainen et al. (2007) with healthy elderly subjects also indicated that the current cut-off scores may be rather high, but the authors argued that a false positive result may not be as detrimental as a negative one.

Previous studies have shown results close to ceiling for healthy elderly people in the Wordlist recognition test (Karrasch & Laine, 2003), suggesting that the current cut-off score (80%) in the Finnish CERAD might be fairly low. A cut-off score of 86% for Wordlist recognition in the present study yielded a moderate sensitivity for MCI and relatively good sensitivity for AD, with a perfect specificity. This finding suggests that the cut-off in this subtest might be adjusted to increase sensitivity without losing specificity. Likewise, normative results from healthy elderly subjects have indicated that the cut-off score for Wordlist recognition may be too high (Pulliainen et al., 2007). There were no significant differences in the MMSE scores between the MCI patients and the controls. This finding is in line with previous studies showing a low sensitivity of the measure in preclinical AD (Grober, Hall, Lipton, & Teresi, 2007; Tang-Wai et al., 2003; Tierney et al., 2000), and also clearly shows how important it is to develop new screening tools for the detection of milder and earlier phases of AD. When comparing normal elderly controls and clinically diagnosed probable AD patients, the results in study I clearly show that almost all CERAD tests are sensitive enough to reveal significant differences. This reflects the fact that in order to fulfil the diagnostic criteria of probable AD, the cognitive decline has to affect other cognitive domains than just memory.

In sum, the results from study I suggest that MCI patients suffer from an encoding impairment when trying to learn a wordlist. Interestingly, neither the delayed recall performance nor the Savings score of the Wordlist learning test showed significant differences between controls and MCI patients, indicating intact memory retention for the

MCI group in this subtest. In fact, no CERAD subtests, except Wordlist learning, showed significant differences between controls and MCI patients. Furthermore, part of the individuals with preclinical AD might not be detected, when using the CERAD test battery as the sole screening instrument. There is also a risk that some cognitively healthy elderly people might receive a false positive result. These risk factors should be considered, especially as CERAD is becoming an increasingly popular instrument in Finland for detecting people at risk for dementia or already showing signs of dementia.

5.2. VERBAL LEARNING IN MCI AND AD (STUDY II)

In **study II,** the aim was to explore how subjects with mild cognitive impairment (MCI), subjects with early Alzheimer's disease (AD) and age-matched controls learned and maintained the names of previously unfamiliar rare objects that were trained with or without semantic support (object definitions). Word learning in MCI has not previously been studied. This is somewhat surprising, as word learning is such an important part of our everyday life - we develop and modify our mental lexicon throughout life. The study of word learning abilities of MCI patients and AD patients could also shed light on cognitive plasticity in MCI and AD. The present paradigm also enabled a comparison between semantic memory and episodic memory functions. It was hypothesized that semantic support might have some beneficial effects in the present learning task especially in the MCI group, as semantic memory functions are relatively well preserved in MCI compared to episodic memory. In the follow-up, the effects of phonological cueing on the naming of newly learned objects and retrieval of the object definitions, as well as recognition of the objects were also studied.

The MCI patients learned the names of the unfamiliar objects more poorly than the controls, and the AD patients' performance was inferior to that of the MCI group. The results are in line with recent studies that have showed a decreased learning efficacy in MCI (Moulin et al., 2004; Ribeiro et al., 2007). There is also increasing evidence that early AD patients suffer from an encoding impairment that impedes the acquisition of new information (for review, see Germano & Kinsella, 2005). One should bear in mind, though, that previous studies have used paradigms that are very different from the one used in the present study, measuring learning over much shorter time periods. Moreover, episodic

verbal learning tests are usually based on previously familiar materials. In fact, the results from the word learning paradigm used in the present study probably reflect at least partly also semantic memory functions and not merely episodic memory processes (see also the discussion in 5.3. concerning the PET findings). It should also be noted that the MCI patients could nevertheless retrieve 54% of the object names at the end of the training, and even the AD group could retrieve 20% of the object names. In other words, repeated exposure and training did in fact result in learning in both patient groups, showing that their verbal learning abilities were impaired but by no means lost.

One explanation for the difference between the learning performances of the controls and both patient groups might be the difference in their ability to use memory strategies. When asked after training, the controls reported plenty of self-generated strategies. For example, they often associated the name of the object either to a familiar name that phonologically resembled it or to some well-known object in order to use that as a memory cue. This is in line with previous studies that have shown that healthy individuals usually call upon prior knowledge when encoding and retrieving new information (for review, see Brown & Craik, 2000). However, the MCI patients and AD patients reported hardly any self-generated strategies. It has been shown that AD patients are impaired in manipulating, integrating and organizing relevant features of new information in order to facilitate acquisition (for review, see Germano & Kinsella, 2005), and considering MCI as a prodromal stage of AD, this type of impairment might be reflected in the MCI patients' results as well.

With regard to forgetting during the follow-up, all three groups showed similar forgetting curves despite the fact that their overall performance differed. As mentioned above, there is some controversy as to which aspects of verbal episodic memory are predominantly affected in MCI and AD: acquisition (e.g. Greene et al., 1996; Grober & Kawas, 1997), consolidation (e.g. Hart, Kwentus, Harkins, & Taylor, 1988), or both (Moulin et al., 2004). The present findings indicate that, also when learning is measured over a longer time period, acquisition seems to be the key deficit in MCI and AD. According to the standard model of memory consolidation (for review, see Moscovitch et al., 2005), the hippocampal formation is necessary for the acquisition and retrieval of recent memories, but is no longer needed when long-term consolidation is complete and permanent memory storage has taken place in the neocortical networks. Subsequently, as hippocampal regions are first

affected in MCI and AD, the present findings would be in line with the idea that impaired acquisition of the names of the unfamiliar objects in the MCI and AD group was at least partly due to hippocampal damage. However, those names that had been successfully acquired despite hippocampal dysfunction were consolidated and stored in less affected brain areas and therefore accessible during follow-up. When interpreting the present results, one should also note that the follow-up consisted of several test trials that may boost learning (for review, see Brown & Craik, 2000). In other words, the test trials *per se* might have influenced the follow-up performance to some extent. Nevertheless, the possible beneficial effect from the test trials should have been similar in all three groups.

It should also be noted that the AD patients in the present study were quite well-performing when looking at their mean MMSE score (25.3). For example, Greene et al. (1996) considered AD patients with a MMSE score of 24 or above to have a "minimal" deficit.

Semantic support did not enhance verbal learning during training in MCI and AD. In contrast, the control group learned more names of the Phon objects than the SemPhon objects during training. Similar results on healthy subjects were found in a study by Whiting, Chenery, Chalk, Darnell, and Copland (2007), who studied the effects of dexamphetamine on new word learning with a paradigm similar to the present study. However, in contrast to the present study, the learning of the semantic support was encouraged in their study, which might have led to learning of the descriptions at the expense of the names. In studies by Cornelissen et al. (2004) and Hulten et al. (2009) who also used a similar paradigm, the object names with and without semantic support were learned equally fast. In sum, although there is some variation in whether semantic support decreases the learning performance of new names or not in healthy individuals, none of the abovementioned studies, including the present one, have neither found a beneficial effect of semantic support on learning. This is somewhat surprising when considering studies that show that "deep" processing enhances learning (e.g. Craik & Tulving, 1975). On the one hand, given the difficulty of the task, it is plausible that the subjects used any means they had in order to learn the names, such as self-generated associations, regardless of semantic support. It has even been suggested, based on behavioural evidence, that sometimes indirectly available information may be learned more effectively than observable object features (Bloom, 2000). In the present task, the lack of additional

verbal information (the definition) might even have enabled a better exploration of the Phon objects and their names in healthy subjects.

Furthermore, it is somewhat surprising that semantic support did not facilitate word learning during training to a greater extent in the MCI group, as semantic memory is better preserved than episodic memory in MCI. However, it is possible that the semantic support would have shown effects with a larger subject sample and with a longer training period. It is also possible that the ability to use any kind of support or memory strategies is limited in MCI. The results may also have been different had the patients explicitly been asked to use the semantic support when encoding the names. It could also be that the definitions that were employed in the present paradigm were not salient enough to support word learning. Another issue that needs to be taken into account is the possibility that the MCI patients had already slight subclinical problems in semantic memory functions. As for the AD patients, the task was very difficult and an easier task with fewer object names to learn might have given different results for this group.

However, during follow-up, the MCI group did benefit from semantic support at the last test session, i.e., 8 weeks after training. Hence, even though the MCI patients did not show an effect of semantic support during training, they showed an effect at the stage where forgetting of the names had started to take place. This result might indicate that with the aid of their relatively well-preserved semantic memory, the MCI patients had created richer associations for the SemPhon object names than for the Phon object names in the long-term memory store. The fact that the controls did not benefit from semantic support at the end of the follow-up is not unexpected, as they reported of self-generated meanings and form-related associations for both SemPhon and Phon object names. In other words, regardless of stimulus type, the controls seemed to spontaneously incorporate the SemPhon and Phon object names in pre-existing semantic and lexical-phonological networks. The fact that the AD patients did not significantly benefit from semantic support at the end of the follow-up is probably due to the fact that their semantic memory functions were already compromised and therefore they could not benefit from this type of support anymore. Finally, it is possible that both MCI and AD patients would have shown larger benefits from semantic support both during training and retrieval, if the semantic definitions would have been given as cues during the naming tests. It has namely been found that AD

patients are able to benefit from semantic retrieval cues when encoding has been combined with support at retrieval (Almkvist, Fratiglioni, Agüero-Torres, Viitanen, & Bäckman, 1999).

Phonological cueing benefited the controls' naming performance to a significantly greater extent than it did for the MCI and the AD group. The present results are not in line with previous findings, showing that phonemic cueing can benefit AD patients and controls to the same extent (Hodges, Salmon & Butters, 1993). However, Hodges et al. (1993) studied phonemic cueing in relation to naming of famous faces, and their study is thus not directly comparable with the present one. The results from study II suggest that both the MCI and AD group might be impaired in accessing the phonological representations of the object names when compared with healthy controls, although overall, both patient groups in the present study did benefit from the phonological cues to a certain extent.

To study maintenance in semantic memory, *recall of the semantic support* that half of the objects had been trained with was also checked for. Note that this can be considered as an incidental learning task, as the subjects had been told to remember only the name. Both with respect to the number of objects correctly recognized as having a definition as well as the quality of the retrieved definitions, no differences were found between the MCI patients and the controls. These findings speak for well-preserved incidental learning ability in MCI. Studies on incidental learning in MCI are scant. A recent fMRI study by Mandzia, Pat McAndrews, Grady, Graham & Black (in press) showed that MCI patients performed significantly worse than normal controls on an incidental memory task. However, they used a recognition task while our task required free recall, which makes a comparison difficult. The MCI patients' ability to learn the definitions to the same degree as the controls did is probably related to the nature of the task. The definitions already had some kind of representation in semantic memory and the learning process was probably less dependent on episodic memory functions that are first affected in MCI. In this context, it is of interest to consider a study by Holdstock, Mayes, Isaac, Gong, & Roberts (2002) where two patients with damage in the hippocampus vs anterolateral temporal cortex were examined. Their findings suggested that whereas rapid acquisition of episodic and semantic information is critically dependent on the hippocampus, the hippocampal processing is less important for the gradual acquisition of semantic information through

repeated exposure. In other words, in their view, consolidation of semantic memories can occur without hippocampal processing. The AD patients recognized significantly fewer definitions than the other subject groups. The definitions given by the AD group were also less precise than those of the MCI group and the control group. This was not unexpected, since previous studies have shown that tests on incidental learning are sensitive to AD (Demakis, Sawyer, Fritz, & Sweet, 2001; Lindeboom, Schmand, Tulner, Walstra, & Jonker, 2002). During the follow-up, the retention of the number of recognized definitions in both patient groups was inferior to that of the controls.

Recognition memory was probed by a test that consisted of the 40 trained objects and 40 similar but untrained objects that were shown to the subjects on the computer screen and the subjects were to decide whether or not the object had been among the 40 trained ones. The performance of the MCI group did not differ significantly from that of the controls, showing cognitive plasticity in MCI in this task. Recent studies on recognition memory based on face and object recognition (Dudas et al., 2005; Wolk, Signoff, & DeKosky, 2008) have shown impaired item recognition in MCI. The present findings are, again, difficult to compare with previous studies, as recognition was measured after extensive training. In other words, it is possible that the MCI patients' recollection would have been impaired compared with controls, if the recognition test had been performed in the beginning of the training period. Also, in comparison to traditional recognition memory tasks that tap episodic memory functions, the presently used might have reflected rather semantic memory functions, as the objects and their features probably at least partly were incorporated to pre-existing semantic networks. It is also interesting to note that findings from animal studies have shown that the medial temporal lobes are less important in more difficult object discrimination tasks that are learned gradually than in simple quickly learned object discrimination tasks. In addition, similar object discrimination tasks in human amnesic patients have suggested that the first few trials of each testing day are especially sensitive to memory deficits (for review, see Zola & Squire, 2000). It is thus possible that the recognition memory task in the present paradigm, where the objects are repeated several times, was less dependent on the medial temporal lobes, i.e. the brain areas first affected in MCI. At a more general level, recognizing objects is easier than retrieving the names for them, and requires less self-initiated processes. One may also speculate, to what extent the memory traces for the physical features of the objects are different from

those of the object names (cf. *dual coding* hypothesis that proposes modality-specific semantic stores; for review, see Brown & Craik, 2000). The AD patients in study II performed more poorly than both the controls and the MCI patients in the recognition task. This is not unexpected, as the AD patients probably already suffered from more widespread brain pathology. However, the AD patients still managed to discriminate on the average 93% of the objects correctly during follow-up, which can be regarded as a rather good performance. Finally, although the MCI patients' overall recognition performance did not differ from that of the controls', it did deteriorate somewhat during the follow-up, whereas the controls' did not, suggesting problems in long-term retention in MCI in this type of task. The AD group showed even more deterioration over time.

To summarize, the results from study II show that new word learning is possible in MCI and even to some extent in AD, although (as expected) learning is not as efficient as for healthy controls. Forgetting of the newly learned names was similar across groups, pointing to a word learning deficit instead of a retention deficit in MCI and early AD. In addition, the MCI patients were able to benefit from semantic support when naming the newly learned words at the last test session, suggesting that they can indeed benefit from their better preserved semantic memory functions to compensate for their more impaired episodic memory abilities. Likewise, the results concerning the retrieval of the definitions and recognition memory, suggest that these memory functions are well preserved in MCI. These well-preserved domains of memory may thus be potentially useful when planning behavioural treatment attempts.

5.3. NEURAL CORRELATES OF VERBAL LEARNING IN HEALTHY ELDERLY AND MCI (STUDIES III-IV)

In **study III**, the aim was to investigate the naming-related brain activity when healthy elderly subjects retrieved the names of successfully learned unfamiliar objects, which they had trained with or without semantic support. As in study II, the healthy elderly subjects in study III could recall somewhat better the names of the Phon than the SemPhon objects. Even though semantic support did not have a facilitating effect on learning at the behavioural level in these healthy elderly subjects, it was of interest to explore whether it would have an impact on brain activation patterns.

The naming-related activation patterns for the SemPhon and Phon objects did not differ significantly from each other. In a previous study, James and Gauthier (2004) found activation in the inferior frontal cortex in relation to matching objects that had been learned with a name and semantic features, as compared with objects that had been trained with a name only. The discrepancy between their results and the present findings, are probably explained by differences in the research paradigms. Firstly, all novel objects in their study were highly similar and did not resemble any well-known objects. Secondly, their subjects performed a matching task (they indicated by a button press if two objects were the same or different), whereas the subjects in study III performed a language production task, i.e. retrieved the names of the objects. Training was also conducted in a different manner, and the results of the two subject groups employed by James and Gauthier (2004) indicate that even slight differences in the training protocol and stimuli can yield partly different brain activation patterns. The lack of difference in brain activation patterns between the SemPhon and Phon objects in the present study might be due to the fact that the healthy subjects often used self-generated semantic and phonological associations in both the SemPhon and the Phon condition. Given the difficulty of the task, it seems plausible that the subjects used any means they had to learn the objects and their names, including self-generated associations. Finally, the results from study III replicate those of Cornelissen et al. (2004) and Hulten et al. (2009) who employed a similar paradigm and failed to find differences in the learning of SemPhon and Phon item names either at the behavioural or at the neural level as measured by magnetoencephalography (MEG).

The SemPhon and Phon objects were thus pooled together to form a category coined as Trained objects. The naming of the Trained objects activated Broca's area, left anterior temporal areas, and the cerebellum, when compared with the naming of familiar objects. When the naming of the newly learned objects was contrasted with unfamiliar control objects, a more extensive bilateral activation pattern was observed than in the Trained vs. familiar objects contrast. This was expected, since the contrast is less specific in the way that the unfamiliar objects do not match with any lexical-semantic representations. As the subjects merely produced a generic response ("picture") to the unfamiliar objects, the naming of Trained objects required more phonological processing and more complex articulations. Therefore, it seems natural to find a more extensive left fronto-temporal

activation, with emphasis on prefrontal areas as well as additional cerebellar activation, than in the Trained vs. familiar objects contrast. This probably reflects involvement of both semantic and phonological processes that were not seen to such an extent in the Trained vs. familiar objects contrast, in which both conditions required retrieval of unique lexical entities. The fact that right temporal activation was also found might reflect recruitment of more general resources for memory retrieval.

Broca's area and nearby regions have been found to be activated in a number of neuroimaging studies on object naming (for review, see Martin, 2001), suggested to reflect both semantic and phonological processes (Poldrack et al., 1999; Woodward et al., 2006). The activation of Broca's area that was found when naming Trained objects can reflect one or both of the abovementioned processes. The subjects reported of self-generated meaning and form-related associations, which suggests that they had incorporated the Trained objects and their names in pre-existing semantic and lexical-phonological networks by the time of the PET scanning. Furthermore, one could assume that the semantic retrieval associated with naming of the familiar objects is different from that of the Trained objects, as the familiar objects have been learned early on in childhood. The same argument can be made for retrieval of phonological output representations. It is thus plausible that the retrieval of the phonological representations of the newly learned Trained items required enhanced phonological retrieval.

The temporal lobe activation found in the Trained vs. familiar contrast was anterior. Temporal activation, although occasionally found in anterior temporal regions (Murtha et al., 1999; Etard et al., 1999), tends to be posterior-inferior (fusiform gyrus) when naming familiar objects (Bookheimer et al., 1995; Martin et al., 1996; Murtha et al., 1999; Zelkowicz et al., 1998). However, the present task was different in that brain activation patterns for naming of newly learned objects was studied. Which processes might then underlie the anterior temporal activation that was found in the present study? Based on case studies, Holdstock et al. (2002) have shown that the anterolateral temporal cortex underlies the slow acquisition of semantic information through repeated exposure, whereas the initial encoding of information depends on the hippocampus. Furthermore, based on single case reports and PET studies, Markowitsch (1995) has argued for a memory retrieval system that encompasses both the anterolateral temporal and the

ventrolateral frontal regions. In short, the frontal part would be related to effortful initiation of retrieval while the temporal component would serve as an important interface to more posterior areas responsible for long-term memory storage. Markowitsch (1995) argues that this system is left-lateralized for retrieval of semantic knowledge. The left anterior temporal activation that was observed during naming of Trained objects could thus reflect enhanced functioning of such a retrieval system. The Trained items would thus have become at least partly integrated with the existing lexical-semantic networks in the brain, rather than being represented as episodic memory traces. In other words, the retrieval of newly learned names of objects would be slowly approaching the naming of familiar objects. This fits with the findings of McCandliss, Posner, and Givon (1997), who found a shift in processing artificial language stimuli in the direction of English stimuli after 20 hours of training, as measured by ERPs. Nevertheless, it is plausible that the naming of newly learned objects requires much more retrieval effort than naming familiar objects. Enhanced retrieval effort can incorporate semantic and phonological processes discussed above, as well as associative memory processes related to the ventral prefrontal cortex (for review, see Passingham et al., 2000), and to the cerebellum (for review, see Baillieux, DeSmet, Paquier, De Deyn, & Mariën, 2008; Desmond & Fiez, 1998), i.e. areas that showed increased activation during naming of the Trained objects in the present study.

The cerebellar activation that was found in study III might also reflect the search of lexical items via procedural memory processes, as proposed in the declarative/procedural (DP) model by Ullman (2004). Also, Broca's area is another critical component of Ullman's procedural memory system, where it is seen as an important area when selecting declarative knowledge, i.e. the role of this region is to recall and maintain information that is actually stored in temporal and temporo-parietal regions. The present results fit nicely with this thought, as well. However, in contrast to Ullman's model, activation in the parietal cortex, thought to play an important role in procedural memory, especially in phonological processing, was not found in the present study. It is possible that the present paradigm might have enhanced semantic processing to a larger extent than phonological processing [cf. also discussion below concerning the discrepancy between the present results and those of Cornelissen et al. (2004)]. Based on neuroimaging and lesion studies, the cerebellum has also been related to verbal working memory functions (for review, see

Baillieux et al., 2008). In other words, the cerebellar activation that was found may also reflect enhanced phonological processing for the newly learned objects.

In cognitive neuroimaging studies on episodic memory, a commonly observed pattern of left frontal activity during encoding and right frontal activity during retrieval is captured by the hemispheric encoding/retrieval asymmetry (HERA) model (for review, see Habib, Nyberg, & Tulving, 2003). There may be several reasons for the fact that the HERA pattern was not observed in the present study. First, the participants performed a naming task and the naming of the newly learned objects may have involved semantic memory to a significant degree. Second, encoding and retrieval was studied over a much longer time period in the present study. Third, the experimental stimuli used in the present study were novel.

The few previous studies on neural correlates of word learning have, in line with the results in the present study, also found predominantly left-lateralized activation in spite of having used different paradigms (Breitenstein et al., 2005, Cornelissen et al., 2004; Hulten et al., 2009; James & Gauthier, 2004; McCandliss et al., 1997; Raboyeau, 2004). The MEG studies by Cornelissen et al. (2004) and Hulten et al. (2009) had a similar paradigm to the present study, but differed in that they employed a delayed naming paradigm that might have enhanced the role of the phonological storage component in the naming task. This, in turn, might account for the fact that the naming-related activation in the Cornelissen et al. (2004) study was found in the inferior parietal cortex, suggested to reflect phonological storage (Awh et al., 1996). The study by Hulten et al. (2009) further differed from the present one and the Cornelissen et al. (2004) study in that they asked the subjects to learn both the names and the definitions of the objects, thus encouraging a broader learning experience. This might have enhanced semantic processing, as they found a strong left temporal effect in relation to naming newly learned objects. Breitenstein et al. (2006) found modulations of activation in the left hippocampus in relation to vocabulary acquisition. Given their research paradigm, the results seem to reflect novel, implicit language learning, whereas the present results tap slower, more explicit acquisition processes in word learning. This interpretation would also be in line with the findings of Holdstock et al. (2002).

When familiar objects were contrasted with both visual noise patterns and a rest condition, they elicited activation increases in bilateral occipital areas and the fusiform gyrus. The findings are in line with previous neuroimaging studies on naming familiar objects (Bookheimer et al., 1995; Martin et al., 1996; Murtha et al., 1999; Zelkowicz et al., 1998). These results give further support to the claim that the retrieval of newly learned names recruits specific brain areas.

At a more general level, the findings from study III showed that the naming of newly learned objects recruits a distributed neural network. This network encompasses Broca's area that is typically activated in language-related tasks. Both the frontal and temporal activation that was observed in the present study was left-lateralized, suggesting a domain-specific verbal mechanism, although not necessarily specific to word learning/retrieval only. On the other hand, the present study found activations that are usually not observed in relation to naming familiar objects and that may reflect more general memory mechanisms. First, the temporal activation we found was anterior, as opposed to posterior temporal activation that is typical during naming of familiar objects. Second, activation increases were found in the cerebellum, an area that has traditionally not been regarded as important for linguistic processing, although recent studies have shown that it may have a larger contribution in language processing than previously thought (for review, see Baillieux et al., 2008). In sum, the results from study III indicated that the naming of newly learned unfamiliar objects entails neural processes that are partly different from the naming of familiar objects. This, in turn, prompted us to extend the experiment to MCI patients (study IV).

In **study IV**, the naming of newly learned objects in subjects with MCI compared with healthy elderly controls by means of PET was studied. Although an effect of semantic support was not found in healthy elderly either at the behavioural or the neural level in study III, it was hypothesized that semantic support might have an effect in the MCI group, as semantic memory functions are relatively well preserved in MCI in contrast to episodic memory. As in study II, the behavioural results of study IV study showed a decreased learning efficacy in the MCI group. Semantic support did not facilitate the learning performance in either subject group (for a discussion on this issue, see section 5.2).

The MCI patients showed increased activation in the anterior cingulate compared with the controls when naming newly learned objects that had been learned without semantic support (Phon) vs. seeing unfamiliar control objects (and saying "picture") (UnFam). Increased activity in the anterior cingulate has been related to executive and attentional control processes in tasks requiring substantial cognitive effort (for review, see Bush et al., 2000), and it has also been argued that the anterior cingulate interacts with e.g. prefrontal cortical regions (Bush et al., 2000; Markela-Lerenc et al., 2004). The fact that the MCI patients showed greater activation than the controls is reasonable, as the task was cognitively more demanding for the MCI patients than for the controls, as shown by their decreased naming performance. Task difficulty has also been found to be positively correlated with activity in the anterior cingulate (Barch et al., 1997). Anterior cingulate activations have been found in studies targeting similarities in regionally specific activations across different kinds of cognitive tasks (Cabeza et al., 2003; Nyberg et al., 2003), including working memory, episodic memory and semantic memory tasks. Accordingly, it is plausible that the present findings reflect executive and attentional demands, required to a greater extent for the patients, rather than task-specific processes. It is also of interest to note that Yetkin et al. (2006) found increased anterior cingulate activation for MCI patients compared with controls in a working memory task. A possible explanation for the larger difference between the MCI patients and the controls in the Phon vs. UnFam than in the SemPhon vs. UnFam contrast could be related to the fact that the controls learned the names of Phon objects more efficiently than those of the SemPhon objects. Thus one could argue that the retrieval of the Phon object names was easier and less effort-demanding (i.e. posing less executive and attention demands) than the retrieval of the SemPhon object names for the controls than for the MCI patients.

In addition to the anterior cingulate activation, a nonsignificant trend of increased activation in the left prefrontal cortex was found in the MCI group compared with the controls in the SemPhon vs. UnFam contrast. The prefrontal cortex has been found to be activated in a number of tasks (for review, see e.g. Cabeza & Nyberg, 2000), and it is possible that the activation trend found in the present study may also reflect enhanced executive, attentional and/or other control processes in the MCI group. Along the same lines, as the left mid-ventrolateral prefrontal cortex has been found to be activated in episodic, semantic and working memory tasks (Nyberg et al., 2003), it is possible that the activation reflects

working-memory processes that contribute to long-term memory tasks by updating and maintaining information. Furthermore, the left prefrontal cortex has been shown to be involved in semantic processing (Fiez, 1997; Fletcher & Henson, 2001; Gabrieli, Poldrack, & Desmond, 1998; Hagoort, 2005) and in such executive processes as response selection, memory search, effortful initiation of retrieval, and maintenance of information on-line (Gabrieli et al., 1998; Hagoort, 2005; Markowitsch, 1995). There is also evidence for more task-specific left prefrontal activation, as the results of Cabeza et al. (2003) have suggested. They found that activity in the left prefrontal cortex and frontopolar regions was greater for episodic retrieval than for visual attention, thus reflecting greater verbal/semantic demands in the episodic retrieval task. Therefore it is possible that the activation that was found in the present study may reflect task-specific semantic processes that are recruited to a greater extent in the MCI group as a compensatory mechanism [cf. also Moulin et al. (2007) who proposed that the different activation patterns in MCI patients vs. controls in an episodic memory task would reflect the patients' higher reliance on compensatory semantic processing]. This could also explain why the Phon vs. UnFam contrast did not show a significant group difference, as one would expect more semantic processing for the SemPhon objects, especially regarding the patients who apparently did not use self-made strategies for the Phon objects.

The correlational analyses between brain activation and task performance showed significant results for the MCI group only: the better the performance in naming Phon objects was, the more activation in the cerebellum was found. This might reflect associative memory processes (for a review, see Desmond & Fiez, 1998), or, verbal working memory processes (for review, see Baillieux et al., 2008). Another possible reason that needs to be taken into account is that the increased cerebellar activity for better naming performance might reflect enhanced search of lexical items, as proposed by the declarative/procedural model by Ullman (2004). Furthermore, the better the naming of Phon objects was, the less activity was seen in the left frontal area. This correlation might reflect intense but unsuccessful attempts, requiring additional executive efforts, to retrieve the name of a recently learned object.

5.4. METHODOLOGICAL CONSIDERATIONS AND FUTURE DIRECTIONS

The number of subjects in all four studies was small, which limits the generalizability of the results. Larger samples should be studied in order to validate the findings, as all significant group differences might not be detected due to limitations in statistical power. The small group sizes are of special concern in study I, as it was a clinical study that was concerned with the application of cut-off scores of CERAD to MCI and AD. The results from study I can thus be regarded only as preliminary results. In study III, the number of participants was not considered sufficient for a random-effect statistical analysis of the PET data, and therefore a fixed-effect model was used to estimate effects of conditions. In study IV, the PET data was analyzed by a non-parametric permutation-based method that is suitable for small sample sizes. The group sizes were also somewhat different in study II, which was controlled for by using the Games-Howell post hoc test. In addition, the distribution of gender was uneven in all studies, and should be better balanced in future studies. Another important factor that should be taken into consideration, especially in relation to study I, is the role of educational background. As educational background has been shown to affect CERAD performances (Karrasch & Laine, 2003), its role in the CERAD test scores of MCI and AD patients would be worth studying (the subjects in study I were matched on the group level for age and level of education). Furthermore, although all the MCI patients in the present thesis met the criteria for amnestic MCI, the group is probably heterogeneous. While some subjects may progress to AD, others may remain stable or develop other dementing disorders.

As with all new paradigms, the present word learning task has its strengths and its weaknesses. Creating a paradigm that would not be too easy for healthy subjects and not too difficult for the patients, especially the AD patients is a challenging task. In hindsight the learning of the object names proved to be very difficult for the AD patients and put them under great strain, and was thus not a very motivating and comfortable task to perform. On the other hand, if the task had been modified for each group individually, it would not have been possible to directly compare the groups with each other. This also led to the situation that in the PET study (study IV), the naming performance of the MCI group was worse than that of the control group. One could thus claim that the PET results of the

MCI patients might be less reliable. However, a very strict criterion was used, and all answers that were even slightly wrong or had a longer latency were excluded. It is possible that the MCI group would have performed somewhat better if they had been given more time. Furthermore, it was evident that the MCI patients were trying hard to retrieve the names of the newly learned objects during PET scanning, instead of behaving randomly.

PET as a method has its limitations. It has poor temporal resolution and allows only for blocked designs, as opposed to event-related designs that are possible to conduct with fMRI. Blocked designs used in PET activation studies have their limitations in that they make it difficult to assess which effects are stimulus-related. Blocked designs do not allow post hoc analyses of e.g. correct and false answers that could be analyzed separately. In addition, the number of scans per subject is limited when using PET, which restricts the number of blocks that can be employed. This also leads to the fact that it is usually necessary to pool data across subjects to gain sufficient statistical power to detect effects. This, in turn, requires that each subject's images are spatially normalized into a standard space and smoothed to compensate for inter-individual differences. This has two consequences. Firstly, the spatial resolution of data across subjects is lower than the resolution of the PET method. Secondly, there is no possibility to study individual differences in brain activation patterns. It would also have been ideal to be able to collect PET data before, during and after training, but this was not possible due to several reasons. Despite its limitations, PET as a method does have advantages compared with e.g. fMRI, one of them being that PET detects activity in all brain regions with roughly equal sensitivity. With regard to this, it is interesting to note that fMRI is less sensitive to e.g. activation changes in the anterior temporal lobes (for review, see Buckner & Logan, 2001), an area that was found to be important when naming newly learned objects. Also, PET is less sensitive to head movements, which is an important aspect when the experimental design requires overt speech, as the present paradigm did.

In the present paradigm, definitions of the objects were used in order to study whether the MCI group could benefit from their relatively well preserved semantic memory in the word learning task. Some of the definitions used in the present paradigm were quite detailed and should be made more salient if used in the future. Also, the semantic support could have shown a larger effect on naming performance, had the definitions been given as cues

to the subjects at the naming tests. It would also be interesting to study whether encouraging the patients to come up with self-generated definitions and associations to the objects would affect the learning of the object names. This might have helped the patients to store the names in long-term memory even more effectively than the semantic support provided in the present paradigm. Furthermore, it would also be interesting to see if some form of enhanced phonological processing in relation to learning object names would benefit MCI and AD patients, as phonological processing is thought to be relatively intact in both MCI and AD. Another interesting idea comes from studies where subjects are verbally instructed to perform actions (e.g. “roll the ball”) according to verbal instructions. The typical result in such studies is that memory for enacted action phrases is superior compared to events encoded without enactment (for review, see Nilsson, 2000). This type of multimodal processing could be interesting to apply to new word learning as well. It would also be of interest (although probably difficult to implement) to use real objects instead of pictures. Finally, it is also important to note that the present results might have been somewhat different, if living objects had been used instead of nonliving objects, as lesion and neuroimaging studies have indicated object category specific deficits and category specific brain activations, respectively (for review, see Martin, 2001).

Concerning the recognition memory task in study II, the recognition of the newly learned objects was investigated, but it would also have been interesting to study the recognition performance of the objects with their corresponding names between groups. How that could be implemented without influencing later naming performance is a more difficult question.

Finally, the present results showed that naming of newly learned objects recruited specific brain areas. In the light of previous studies, the results of each activated brain area have been interpreted separately, as the data does not provide information about the possible interactions of the different brain areas. Future studies are needed to shed light on the question how these different aspects of areas of brain activation are functionally tied together, and also how the different aspects of memory, word learning and executive functions work in concert.

6. CONCLUSIONS

Studies I and II indicated that MCI is characterized by an encoding deficit, as shown by the overall worse performance on the CERAD Wordlist learning test compared with controls, as well as a decreased learning efficacy in learning new object names. As a screening test, CERAD was not very sensitive to MCI. Based on the present data, the CERAD subtests Wordlist learning, Wordlist delayed recall and Wordlist recognition could, however, show a higher sensitivity to MCI if cut-off scores are modified.

The experimental word learning paradigm showed, as expected, that the learning ability of the mild AD patients was more compromised than that of the MCI patients. Nevertheless, forgetting of the object names showed a similar pattern in all subject groups, indicating that when learning is measured over a longer time period, acquisition seems to be the key deficit both in MCI and early AD. Semantic support did not have an effect on learning during training. It nevertheless showed a beneficial effect on long-term retention of the object names in the MCI group, but not in the AD group, suggesting that MCI patients can compensate for their episodic memory impairment by better preserved semantic memory functions. Incidental learning seemed to be well preserved in the MCI patients, as their performance did not differ from that of the controls when retrieving the incidentally learned object definitions. Also their object recognition memory did not differ significantly from that of the controls. These well-preserved domains of memory are potentially useful when planning behavioural treatment attempts.

At the neural level, naming of newly learned objects by healthy elderly subjects recruited a left-lateralized network, including fronto-temporal regions and the cerebellum, which was more extensive than the one related to the naming of familiar objects. Semantic support showed no effects on the PET results for the healthy subjects. The observed activation increases may reflect lexical-semantic and lexical-phonological retrieval, as well as more general associative memory mechanisms. Compared to the controls, the MCI patients showed increased anterior cingulate activation when naming newly learned objects that had been learned without semantic support. This suggests a recruitment of additional executive and attentional resources in the MCI group.

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