Cognitive and olfactory changes in aging

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Abbreviations

Aβ	Amyloid beta protein
AD	Alzheimer's disease
ApoE	Apolipoprotein E
APP	Amyloid precursor protein
BNT	Boston Naming Test
CCCRC	Connecticut Chemosensory Clinical Research Center
CHRNA4	Cholinergic receptor nicotinic alpha
COMT	Catechol O-methyltransferase
COWAT	Controlled Word Association Test
CVLT	California Verbal Learning Test
EMQ	Everyday Memory Questionnaire
fMRI	functional magnetic resonance imaging
FTD	Frontotemporal dementia
IQ	Intelligence quotient
LBD	Lewy body dementia
MCI	Mild cognitive impairment
aMCI	Amnestic mild cognitive impairment
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
PET	Positron emission tomography
SD	Standard deviation
SMC	Subjective memory complaints
SOIT	Scandinavian Odor Identification Test
UPSIT	University of Pennsylvania Smell Identification Test
VaD	Vascular dementia
WASI	Wechsler Abbreviated Scale of Intelligence

Abstract

Age is associated with decrease in several cognitive functions whereof some changes may indicate a beginning pathologic process resulting in a state of dementia. The papers included in the thesis addressed questions related to cognitive and olfactory changes in elderly individuals with an aim to gain knowledge on the influence of the Apolipoprotein E (ApoE) ε4 allele on cognition and to extend the understanding of the association between cognitive functioning and odor identification performance. The first paper investigated the impact of the ApoE ε4 allele on cognitive functioning in a sample of non demented elderly individuals recruited from a population with a high prevalence of this allele. Paper 2 addressed the question whether the Scandinavian Odor Identification Test (SOIT) and its cut-off scores for diagnosis (hyposmia and anosmia) is applicable and valid to be used in Norwegian samples of middle aged and older individuals. The occurrence of olfactory dysfunction was further investigated in the third paper. It was examined whether individuals who were unaware of an olfactory dysfunction performed lower on cognitive tasks compared to individuals with normal olfactory function. In paper 4, the interrelation between different odor identification tasks (familiarity, cued and free odor identification), their association with cognitive measures as well as age-related performance differences were investigated. The present thesis shows that deficits in cognitive performance, demonstrated in verbal learning and memory tasks, can be related to the ApoE ε4 allele. The papers on olfactory functioning revealed the applicability of the SOIT in the elderly segment of the Norwegian population. It was shown that olfactory dysfunction increases with age and that changes often remain unnoticed. Individuals unaware of their olfactory dysfunction performed lower on a number of cognitive measures. The ability to identify odors was associated with a varying number of cognitive measures depending on the demands of the task. In conclusion, this thesis strengthens the generality of previous findings demonstrating an association between ApoE ε4 and impaired performance on verbal learning and memory tasks. The findings indicate further that odor identification performance is associated with a number of cognitive measures, predominantly episodic memory functioning. Odor identification tasks may provide valuable information in the examination of elderly individuals at risk for pathological decline.

List of papers

I. Wehling, E., Lundervold, A.J., Standnes, B., Gjerstad, L., & Reinvang, I. (2007). ApoE status and its association to learning and memory performance in middle aged and older Norwegians seeking assessment for memory deficits, *Behavioral and Brain Functions, 3,* 57-66

II. Wehling, E., Espeseth, T., Reinvang, T., Lundervold, A.J., Bende, M., Brämerson, A., & Nordin, S. (submitted). Applicability of the Scandinavian Odor Identification Test for Norwegian use and age-related effects

III. Wehling, E., Nordin, S., Espeseth, T., Reinvang, I., & Lundervold, A.J. (submitted). Unawareness of olfactory dysfunction and its association with cognitive functioning in middle aged and older adults

IV. Wehling, E., Nordin, S., Espeseth, T., Reinvang, I., & Lundervold, A.J. (submitted). Familiarity, free and cued odor identification and their association with cognitive functioning in middle aged and older adults

It is the enormous disparities in degree of mental decline observed among those in late and middle life that constitute the most powerful challenge. On the one hand, there are those exemplified by Casals, Picasso, Bertrand Russell, Verdi and Michelangelo: creative, intellectually vigorous, active and committed with the fire and intensity of youth to the values and causes that had inspired them throughout their lives. At the other extreme is the substantial proportion of those already in an advanced state of dementia at 70 and some even in their 40s or 50s. It is the conviction that there must be causes definable by science underlying such disparities that inspires and sustains the efforts of those engaged in research in this field. Any success they achieve will contribute to freeing old age from the spectre of dying in a state of mental oblivion and so eliminate the worst scourge of the later years.

INTRODUCTION

Age is taking its toll on cognitive as well as sensory functions in human beings. Irrespective of whether these changes are due to the normal aging process or may indicate the beginning of a devastating neurodegenerative disease, they are of great importance in the individual's life and for the society at large. A considerable proportion of elderly individuals will be affected by sporadic late-onset Alzheimer's disease (AD), the most common form of dementia illnesses beyond the age of 65 years (Bachman et al., 1992). A definite diagnosis of AD can only be given at autopsy and the clinical diagnosis as well as the identification of the early changes relies so far heavily on alterations in neuropsychological test performance. In that the signs of early cognitive decline in patients with AD are heterogeneous and similar to what can be found in other types of neuropsychiatric disorders or may be attributed to be a part of the normal aging process, the collection of empirical evidence of possible markers for AD continues.

The ε4 allele of the Apolipoprotein E (ApoE) gene is a well-established risk factor for AD. There are, however, open issues with regard to its relation to normal cognitive aging in varying populations. The objective of the first paper was to examine the influence of the ε4 allele on cognitive performance in aging individuals coming from a population with a high frequency of the ε4 allele. Olfactory dysfunction occurs frequently in the elderly (Murphy et al., 2002). Lately, the clinical significance of an impairment to identify odors has increasingly been recognized as an important indicator for future cognitive decline and AD (Calhoun-Haney & Murphy, 2005; Swan & Carmelli, 2002). This induced papers 2-4, investigating the applicability of an olfactory test (paper 2), and furthermore the association between odor identification abilities and cognitive functioning (paper 3 and 4) in healthy middle aged and older individuals.

Cognitive aging

Cross-sectional behavioral research demonstrates a life long linear decline beyond the age of 20 in several cognitive domains including mental processing speed, working memory measures (visuospatial and verbal), and long-term memory measures (visuospatial and verbal) (Park & Minear, 2006; Park et al., 1996, 2002). Longitudinal studies support these findings although results show that reductions often do not occur before an age of 60 years and that

large inter-individual variability may be found (Christensen et al., 1999; Wilson, Beckett, Bennett, Albert & Evans, 1999; Wilson et al., 2002). Evidence indicates further that age-related decline is more pronounced in some cognitive domains including episodic and working memory function as well as perceptual speed, whereas minor changes have been found in semantic knowledge and vocabulary (Park et al., 2002). In further exploring age-related differences in memory functioning, Nyberg et al. (2003) demonstrated that elderly individuals exhibit a greater decline in measures of recall compared to recognition in an episodic memory task. Based on these findings and similar ones from other studies, it has been suggested that age differences may become particular apparent in tasks demanding self-initiated and effortful processing (Luo & Craik, 2008; Nyberg & Bäckman, 2004; Zacks & Hasher, 2006).

A variety of mechanisms have been proposed to be responsible for the deterioration of cognitive functioning. A well-known proposal refers to mental processing speed: Salthouse (1996) argued that the reduction in processing speed occurring with age leads to declines in several cognitive functions, including memory. He suggested that memory performance was only indirectly and weakly influenced by age when processing speed was controlled for. However, this suggestion has been criticized since not all tasks demonstrating age-related declines have a speed component (e.g. free recall) (Luo & Craik, 2008). Other approaches have suggested that a decline in working memory capacity (Craik & Bryd, 1982), or inhibitory processing or executive functioning (Hasher & Zacks, 1988) are of importance to explain age-related decline in cognitive functioning. Alternatively, Lindenberger and Baltes (1994) showed that sensory functioning was an important factor in mediating age-related declines in a variety of cognitive tasks. They argued that reduced sensory functioning not by itself, but as an indicator for overall neurological health, could result in poor performance.

Neuroimaging studies have contributed to better understanding of associate behavioral and structural changes in aging by showing a general shrinkage in gross volume with age and alterations occurring in both grey and white matters. It has been demonstrated that some brain areas, particularly in the prefrontal cortex, undergo the largest volumetric changes (Raz, 2004) and that these areas seem particularly affected by alterations of white matter density and neurotransmitter level (Bartzokis, Cummings, Sultzer, Nuechterlein & Mintz, 2003; Head et al., 2004; Volkow et al., 2000). Studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have repeatedly shown activation in areas of the

prefrontal cortex during episodic (encoding and retrieval) and working memory tasks (Cabeza & Nyberg, 2000), supporting a close relation between cognitive and structural changes. Other studies have shown that the hippocampus and the surrounding medial temporal cortex are important for episodic memory function (Nyberg, Cabeza & Tulving, 1996). However, it seems that the latter undergo only small age-related changes in normal aging individuals (Raz, 2004).

Thus, cognitive changes seen in normal aging individuals may often relate to changes occurring in the frontal areas of the brain. Luo and Craik (2008) suggested that multiple factors may account for age-related changes in cognitive function and that these factors may be interrelated. They suggest that differences in patterns of memory decline may provide important information to differentiate pathological (decline cause by a neurodegenerative disease such as AD) from normal aging.

Neuropsychological characteristics of preclinical Alzheimer's disease

An immense number of studies has demonstrated that individuals who develop AD experience deficits in verbal episodic learning and memory function (Albert, Moss, Tanzi & Jones, 2001; Bondi, Salmon, Galasko, Thomas & Thal, 1999; Grober & Kawas, 1997), and that impairment may occur 6-10 years before an AD diagnosis is given (Bäckman, Small & Fratiglioni, 2001; Grober et al., 2008; Tierney, Yao, Kiss & McDowell, 2005).

Although the progression of the neuropathological changes is not fully known, findings indicate that the decline in memory function parallels the neuropathological changes seen early in the AD disease process. Braak and Braak (1991) classified the development of intracellular changes into six stages. In stages I/II changes occur in the transentorhinal and entorhinal region of the temporal lobe, from where the pathologic process continues to the hippocampus and the temporal neocortex (stage III) and association areas of the adjoining neocortex (stage IV). The spreading then continues and covers finally the neocortex (stages V and VI).

Despite the convincing findings that impaired memory function is a core characteristic of incipient AD, there is also substantial evidence that deficits in other cognitive domains, including executive functioning, verbal ability, visuospatial functioning, attention and

perceptual speed, are present during the prodromal phase of AD (Bäckman, Jones, Berger, Laukka & Small, 2005; Storandt, Grant, Miller & Morris, 2006). In a recent review including studies of nondemented cognitively normal individuals, Twamley, Ropachi and Bondi (2006) found that early signs of AD may be found in a wide range of cognitive domains (either by showing early decline in these domains or revealing significant differences between a control group and individuals at risk for AD). Based on results most consistently registering impairments of attention, followed in frequency by deficits in verbal learning and memory, executive functioning, processing speed, and language, the authors concluded that although there has been a predominant focus on episodic memory function, other makers will occur with the development and use of experimental paradigms. Combined with their review of neuroimaging data indicating volume loss and metabolic changes in the temporal lobe, the authors proposed a model for a distinct course of decline in episodic memory function in preclinical AD. They suggested that after an initial drop in performance, the impairment remains stable for a number of years before another period of accelerated decline occurs one or two years before diagnosis (Figure 1) (Bäckman et al., 2001; Bunce, Fratiglioni, Small, Winblad & Bäckman, 2004; Smith et al., 2007; Twamley et al., 2006).

Some authors have suggested that the period of poor but stable memory impairment may be of clinical importance (Smith et al., 2007). They suggest that compensatory mechanisms such as neurotransmitter up-regulation or activation of broad neural networks may be activated to maintain the former performance level. According to this view, the decline may be slowed down for some time. When the additional activated resources are compromised in the course of the disease, eventually through the continuous pathological changes, this might finally result in rapid memory decline at a second point in time. Other authors suggest that the onset of clinical symptoms may further be influenced by factors such as level of education, intelligence, leisure activities, commonly referred to as cognitive reserve (Fratiglioni & Wang, 2007).

The differential pattern of age-related changes in functioning (as described in the two previous sections) has induced the hypothesis that cognitive decline seen in aging individuals may be related to two distinguishable processes, one associated with normal cognitive aging, involving the prefrontal cortex, and one associated with pathological aging, related to alterations in medial temporal lobe functioning (Buckner, 2004; Hedden & Gabrieli, 2004). Thus, changes seen in normal aging associated with mild memory decline which can be

related to attention and executive functioning may be referred to changes in fronto-striatal systems. Changes due to neurodegenerative processes, i.e. AD, affect areas in the medial temporal lobe, starting in the entorhinal cortex, leading directly to memory impairment.
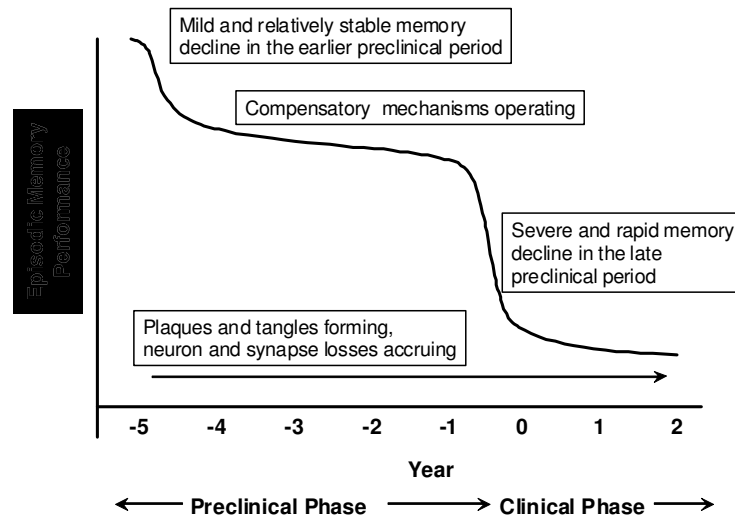
Figure 1: The figure, originally adapted from Twamley et al. (2006), shows the proposed nonlinear pattern of decline of episodic memory function during the preclinical phase of Alzheimer's disease.

Genetic factors in cognitive aging: the Apolipoprotein E

The urge to understand the molecular basis of pathological cognitive aging and AD was reinforced by genetic research identifying the ApoE as an important gene for understanding AD (Strittmatter et al., 1993). ApoE is a cholesterol-transporting protein coded on chromosome 19 by a polymorphic gene with three allele types: ε2, ε3, and ε4. As individuals inherit one allele from each parent, six ApoE genotypes are possible: ε2ε2, ε2ε3, ε3ε3, ε2ε4, ε3ε4, ε4ε4. It has been shown that the presence of one ε4 allele (heterozygote) increases the risk of developing AD and that the risk further increases in a dose-dependent manner, i.e. individuals who have inherited two copies of the ε4 alleles (homozygote) have a greater risk than those with only one copy (Corder et al., 1993). Results demonstrate further

that AD symptoms may occur earlier in patients carrying at least one ε4 allele (Blacker et al., 1997).

In a large meta-analysis, Farrer et al. (1997) found that the risk of AD increases up to 3 times in heterozygote carriers and up to 14 times in homozygote carriers compared to individuals carrying any of the other isoforms (all numbers reported here relate to studies including individuals of Caucasian origin, see below). In addition, the authors reported age and gender effects, indicating that the ε4 genotype was associated with an increased risk for AD between 40 and 70 years, thereafter diminishing. Gender effects were shown in that women were at higher risk for AD regardless of genotype and that the risk might further increase in women with the ε3/ε4 genotype. An important finding was that the association between ApoE ε4 and AD is apparently not uniform across all ethnic groups. That is, while the ε4 allele was found to be strongly related to the risk of AD in Caucasians, that association was inconsistent and weaker in Afro Americans and Hispanics. Other studies have corroborated these findings (Evans et al., 2003; Gureje et al., 2006; Maestre et al., 1995; Tang et al., 1998).

The ApoE ε3 allele is the most common form, found in approximately 78% of the general population, whereas ε2 (7%) and ε4 (15%) are less common (Roses, 1996). There is however, a noteworthy peculiarity in the distribution of ApoE frequencies, indicating a south-to-north gradient of the ε4 allele in Europe, with the proportion of ApoE ε4 carriers increasing from 10-15% in the south to 40-50% in the north (Figure 2; Gerdes, 2003). The functional consequences of this genetic variation have to be determined. So far, reviews have generally concluded that there is no geographic variation in the frequency of dementia (Hofman et al., 1991; Rocca et al., 1991). However, one study reported higher incidence rates in the northern compared to the southern countries (Fratiglioni et al., 2000). These findings emphasize the need to investigate the effect of genetic makers in general and of ApoE in particular in different countries and populations.

The neurobiological processes in the brain that account for the association of the ε4 allele and the risk for AD are still not understood, but a number of hypotheses exist (Bales, Dodart, DeMattos, Holtzman, & Paul, 2002; Mahley, Weisgraber, & Huang, 2006). Neurofibrillary tangles and amyloid plaques, consisting of tau and beta amyloid peptides (Aβ), respectively, are the hallmarks of AD. The "amyloid hypothesis" suggests that ApoE ε4 inhibits Aβ clearance and stimulates its extracellular deposition as well as enhances Aβ

production. Independent of Aβ, ApoE ε4 has been suggested to have an effect on the phosphorylation of the microtubule associated tau protein and thus contribute also to the formation of neurofibrillary tangle. These hypotheses are supported by post mortem studies of patients diagnosed with AD showing an increased density of neuritic plaques, amyloid deposition, and neurofibrillary tangles in ε4 carriers (Ghebremedhin et al., 2001; Polvikoski et al., 1995; Sparks et al., 1996).
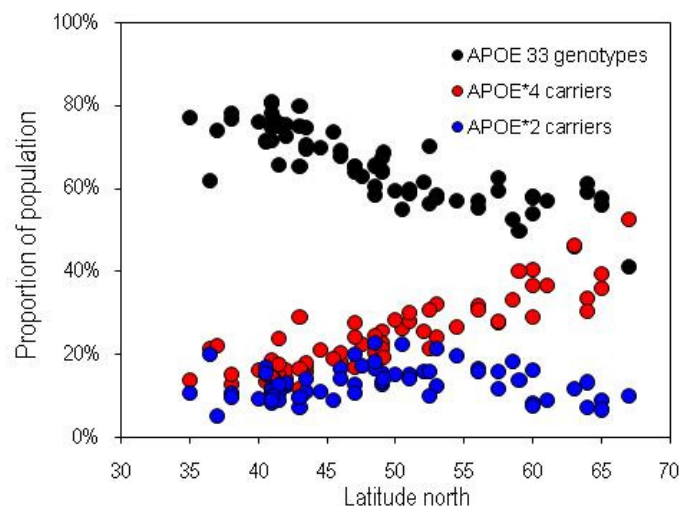
Figure 2: Proportion of individuals with the ApoE ε33 genotype and proportions of ApoE ε2 and ApoE ε4 carriers in various European populations, as functions of latitude north (with permission from Gerdes, 2003).

Another hypothesis links ApoE ε4 not explicitly to AD pathology, but to neuronal health in general. The "neuronal repair hypothesis" proposes that ApoE ε4 causes neurotoxicity, as its fragments are translocated into the cytosol were they interact with cytoskeletal elements (microtubules and microfilaments) or mitochondria. According to the neuronal repair hypothesis, ApoE ε4 may be related to neuronal health and brain function throughout lifetime and not only to pathological processes in older age. This hypothesis finds support in studies examining the influences of ApoE isoforms on normal cognition. Flory, Manuck, Ferrell, Ryan, and Muldoon (2000) found that in a middle aged sample, ε4 carriers performed significantly lower on learning and memory tasks than non carriers, and Greenwood,

Sunderland, Friz, and Parasuraman (2000) found that ε4 carriers exhibited deficits of shifting in tests of visual attention.

Despite the strong evidence of an association between ApoE ε4 and AD, it is important to note that it is possible to reach old age with normal cognition although being a carrier of the ε4 allele or conversely, to develop AD in the absence of the ε4 allele.

Apolipoprotein ε4 and cognition

Due to the findings in AD patients, efforts have been made to examine whether the ε4 allele confers a risk for cognitive impairment in non demented older individuals. While several studies have found that carriers of the ε4 allele perform lower on cognitive tests than non demented older individuals that do not carry the ε4 allele (Bartez-Faz et al., 1999; Bondi et al., 1995; Caselli et al., 1999, 2001; Dik et al., 2000; Flory et al., 2000; Helkala et al., 1996; Mayeux, Small, Tang, Tycko, & Stern, 2001; O'Hara et al., 1998), other studies have failed to find such a significant difference (Bennet et al., 2005; Bondi et al., 1999; Bunce et al., 2004; Small et al., 2000; Smith et al., 1998). A possible explanation for these conflicting results could be that the studies showing a significant difference between ε4 carriers and non carriers might have included individuals who were in a preclinical phase of AD during assessment. For example, in a study by Bondi et al. (1999) the ε4-related differences on a memory task were significantly reduced when those participants who developed AD at follow up were removed from the sample. Thus, since ApoE is involved in pathological processes due to AD and since cognitive deficits may be present several years before a clinical diagnosis of AD is given, it is difficult to separate preclinical AD from cognitive impairment unrelated to AD.

However, there may also be other reasons for the variability in results. Smith et al. (1998) found that ε4 carriers below the age of 80 years performed more poorly on delayed recall compared to non carriers whereas this pattern was reversed in individuals above the age of 80. Thus, the age-range included in studies seems to influence results. Other researchers have found that the type of cognitive tests applied may be of importance: Parasuraman, Greenwood, and Sunderland (2002) demonstrated that tests of spatial attention and working memory might be particularly sensitive to ε4 related impairments. Furthermore, sample characteristics such as the frequency of heterozygote and homozygote carriers or the sample size may contribute to results. In a meta-analysis, including cross-sectional studies on

cognitively intact older individuals, Small, Rosnick, Fratiglioni, and Bäckman (2004) concluded that the ε4 allele is associated with reduced global cognitive performance, episodic memory, and executive functioning, but that the ε4-related effect is rather modest. The authors argued further that the variability between findings seems to be a result of statistically significant but small differences between groups of ε4 carriers and non carriers, a specific impact of the ε4 genotype on certain cognitive domains as well as age- and zygosity-related factors.

Mild cognitive impairment

Recurring efforts have been made to define the boundary between cognitively normal aging and the prodromal phase of a clinically disclosed dementia (Collie & Marfuff, 2002; Tuokko & Hultsch, 2006). Among the concepts that have been proposed, mild cognitive impairment (MCI) has become one of the most frequently used in the past decade (Petersen et al., 1999). Originally, the concept was defined by subjective memory complaints (SMC), isolated memory impairment, otherwise normal cognitive function, intact activities of daily living, and the absence of a dementia (Petersen et al., 1999). In their study, the authors found that individuals classified as MCI demonstrated a significant higher annual conversion rate to AD (12%) compared to a control group (1-2%), leading to the suggestion that MCI is a significant risk factor for AD.

The implementation of the original criteria has varied across studies, resulting in large inconsistencies with regard to prevalence rates, rates of conversion from MCI to AD, and stability of the diagnosis over time (Tuokko & McDowell, 2006). Likewise, it has been reported that a substantial number of elderly individuals in addition to a predominant memory impairment, or even in the lack of such an impairment, show subtle cognitive impairment in other cognitive domains, e.g. language, executive functions, and attention (Larrieu et al., 2002; Lopez et al., 2003; Ritchie, Artero, & Touchon, 2001). Other studies revealed that MCI could be confused with depression based on similar neuropsychological profiles (Chen, Ganguli, Mulsant, & DeKosky, 1999; Yaffe et al., 1999). Thus, the term MCI refers to a condition of heterogeneous clinical presentation, etiology, and outcome.

Recently, the original criteria were modified (Petersen, 2004), introducing a broader classification system which includes distinguished clinical subtypes of MCI and suggestions

about underlying distinct etiologies (Figure 3). The original concept, renamed amnestic MCI (aMCI), is thought to represent the majority of individuals who will progress to a diagnosis of AD over time. It is also recognized that these kind of symptoms may be related to a psychiatric diagnosis of depression. The other non amnestic categories include single and multiple cognitive domains which are considered to represent the transitional phase between normal aging and other forms of dementias (e.g. frontotemporal dementia (FTD), vascular dementia (VaD), Lewy body dementia (LBD)). The robustness of these clinically recognizable subtypes and the etiological linkages remain to be shown, in particular with regard to findings indicating no direct association between MCI subtypes and ultimate dementia diagnosis (Fischer et al., 2007). Moreover, the implementation and operationalization of the individual criteria leading to any kind of MCI classification still remain open, and the ongoing debate about the clinical significance and outcome of MCI will surely continue (Ames, Petersen, Knopman, & Gauthier, 2006).

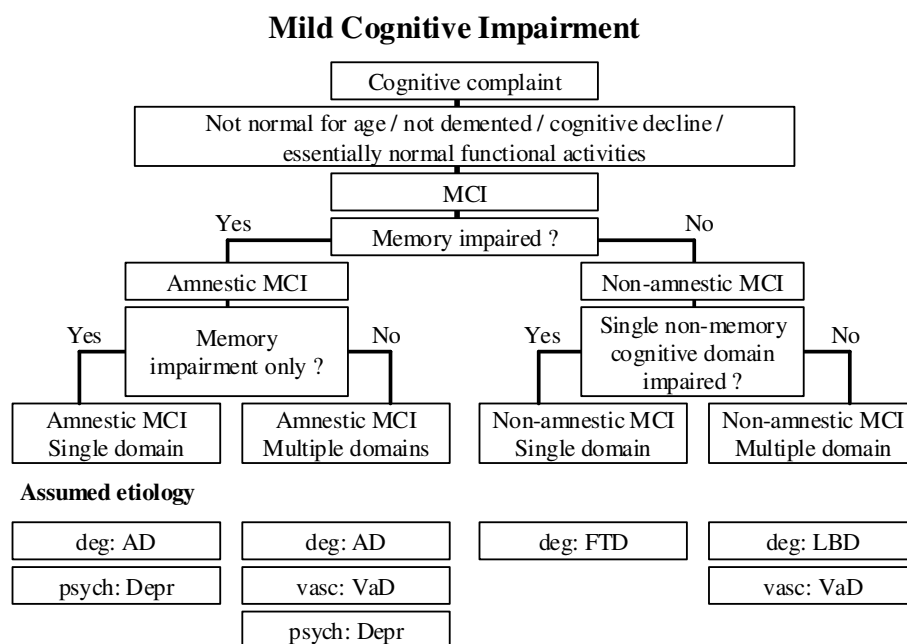**Mild Cognitive Impairment**

Figure 3: The figure, adapted from Petersen (2004), shows the classification process of subtypes of mild cognitive impairment and the presumed underlying etiologies (bottom rows). (deg = degenerative; psych = psychiatric, vasc = vascular; AD = Alzheimer's disease; Depr = Depression; VaD = Vascular Dementia; FTD = Frontotemporal Dementia; LBD = Lewy Body Dementia)

Defining cognitive impairment

Despite the convincing findings of early indicators for pathologic cognitive decline, the definition of "objective impairment" remains a matter of discussion.

When Petersen et al. (1999) proposed the concept of MCI, they defined impairment as performance scores ≥ 1.5 standard deviations (SDs) below age-matched normative material on the assessed memory test. Nevertheless, the literature reveals the use of various cutoff scores to define impairment, ranging from 1 SD (e.g. Busse, Hensel, Guhne, Angermeyer, & Riedel-Heller, 2006; Crowell, Luis, Vanderploeg, Schinka, & Mellan, 2002; Palmer, Bäckman, Small, & Fratiglioni, 2006) to 1.96 SD (Bickel, Mösch, Seigerschmidt, Siemen, & Förstl, 2006), and varying cutoffs have been used for different MCI subtypes (Zanetti et al., 2006). One rational behind the choice of low cutoffs is that an overly stringent cutoff score might limit the likelihood of detecting early stages of impairment (Crowell et al., 2002). On the other hand, a lower cutoff may result in a higher rate of individuals falsely identified as impaired. Busse et al. (2006) examined the consequences of varying cutoffs and concluded that a lower cutoff (1 SD below the mean of age- and education-specific norms) should be applied when high sensitivity is requested, while a more stringent cutoff (1.5 SD below the mean of age- and education-specific norms) should be applied when high specificity and high positive predictive power is required.

The use of cutoff scores has been disputed repeatedly and it has been pointed out that psychometric cutoff scores should not be crucial for the classification as MCI, but that the classification should be based on clinical judgment based on an overall impression from several assessment sources (Petersen, 2004; Winblad et al., 2004). However, some authors have expressed concern about this suggestion, as they see a risk that this might prevent the work to specify precise criteria (Tuokko & McDowell, 2006). They argue that clinical judgment comprises multiple factors, e.g. patient and rater characteristics as well as measurement issues which individually may influence the reliability of the evaluation of cognitive impairment.

In addition to the arbitrary use of cutoff scores, there is a considerable number of factors which may influence performance results and in turn a definition of impairment. This includes factors inherent to the measures themselves (e.g. reliability, validity, test demands),

the assessment environment (e.g. participants anxiety, fatigue), and the frequency of assessment procedures.

Olfaction

The human sense of smell has often been described as poor and inferior in comparison to the other senses (Köster, 2002). However, besides its well known importance for survival and reproduction (Doty, 2003), an increasing body of research has contributed to the understanding by identifying the neuronal bases and the organization of olfaction (Savic, Gulyas, Larsson, & Rolland, 2000; Zelano & Sobel, 2005;), its relevance for quality of life (Blomqvist, Brämerson, Strjärne, & Nordin, 2004; Hummel & Nordin, 2005) as well as its clinical importance (Holbrook & Leopold, 2006).

Olfactory changes in aging

Impaired olfactory functioning (hyposmia) appears in about 20% of the general population, whereas a lack of smell functioning (anosmia) is estimated to be present in about 5% of the population (Brämerson, Johansson, Ek, Nordin, & Bende, 2004; Landis, Konnerth, & Hummel, 2004; Murphy et al., 2002). These numbers increase significantly with age and beyond the age of 70 years more than 50% of all individuals may be affected (Doty et al., 1984; Murphy et al., 2002). Thus, a significant number of elderly individuals will experience age-related olfactory dysfunction that may impair health and well-being, self-sufficiency, and quality of life (Hummel & Nordin, 2005). But despite the far-reaching consequences, olfactory dysfunction often remains unrecognized, and few elderly individuals report impairment to their physicians either because they fail to notice the gradual decline or they attribute it to normal changes associated with aging (Murphy et al., 2002; Nordin, Monsch, & Murphy, 1995).

A decline in olfactory function most commonly starts in the 5th and 6th decade of life with a considerable drop in the 7th decade (Doty et al., 1984; Brämerson et al., 2004). The age-related impairment of olfactory functioning can be observed across several olfactory domains, including basal functions such as detection sensitivity (the ability to detect the presence of an odor) (Stevens & Cain, 1987) and discrimination (the evaluation whether the

presented odors are identical or differ from each other) (Schiffman & Pasternak, 1979), and in tasks involving cognitive processes such as odor identification (the ability to identify and find the appropriate verbal label for an odor) (Doty et al., 1984; Larsson, Nilsson, Olofsson, & Nordin, 2004), and odor recognition (Larsson & Bäckman, 1997).

Besides age, gender differences in olfactory functioning suggesting a female advantage are commonly reported (Doty et al., 1984; Brämerson et al., 2004; Murphy et al., 2002). While studies have not consistently found a better female performance on sensitivity tests (Öberg et al., 2002), results are more consistent for olfactory tasks requiring cognitive processing such as odor identification tests. Using an odor identification task in a community-based study, Doty et al. (1984) found higher performance scores in women than men at all ages. In a population-based study including participants above the age of 50 years, Murphy and colleagues (2002) found a higher prevalence of olfactory dysfunction in men (aged 50-97 years) and an interaction effect between gender and age. However, an interaction effect was not corroborated by results from two separate population-based studies (Brämerson et al., 2004; Larsson et al., 2004). The reasons for a female advantage remain still not well understood. Based on results from studies assessing odor memory, some authors have suggested that a female advantage in verbal processing may contribute to the differences (Öberg, Larsson, & Bäckman, 2002).

The olfactory dysfunction associated with increasing age may be caused by several factors, including age-related histological changes (e.g. neurogenesis of olfactory cells), somatic or health-related variables (e.g. trauma, diabetes, surgery, medication), environmental factors (e.g. exposure to toxins) (for an overview see for example Seiberling & Conley, 2004), and cognitive functioning (Larsson, Finkel, & Pedersen, 2000; Larsson et al., 2004; Larsson, Öberg, & Bäckman, 2005).

Odor identification

Odor identification refers to the ability to retrieve the correct name of an odor. This process requires that the individual has formerly experienced an odor and that an odor-name association has been established. Thus, odor identification relies on semantic memory function, the system where an individual's knowledge is stored (Gazzaniga, Ivry, & Mangun, 2002). In practice, the identification of odors without cues has shown to be difficult, and

performance on odor identification tasks has hardly shown to exceed 50% (Engen, 1987). Several suggestions have been made to explain the poor performance. Based on experiments demonstrating that initial free identification performance improved significantly over trials when feedback was provided and that label quality improved over consecutive trials (e.g. from far miss to veridical), Cain (1979) suggested that poor identification performance could be referred to a poor linkage/association between odors and names, a failure to retrieve the odor-name association (implicating that knowledge is existent but that it needs support to be utilized), or a failure in perception, that is a misperception leading to difficulties in identification. Based on findings showing that individuals had more difficulties to generate information about an odor's name than to describe the qualitative feature of an odor, Engen (1987) suggested that an inherently weak association between odors and names is responsible for poor identification. Other authors have suggested that a lack of formalized learning procedures may account for naming difficulties (de Wijk, Schab, & Cain, 1995). They argue that odors are learned gradually and in reference to the objects that release them or to a specific context. Thus, smell perceptions may be interpreted and stored in accordance to the available information. Besides the verbal-semantic factors it has been suggested that impairment in sensory-perceptual functioning may lead to failures in odor identification (Cain, 1979). Obviously, a certain degree of sensitivity is required to be able to discriminate and identify odors. However, findings indicate that deficits seen in odor identification performance in older individuals cannot exclusively be related to sensory deficits but seem to be related to cognitive limitations (Larsson & Bäckman, 1997; Murphy, Cain, Gilmore, & Skinner, 1991).

The relationship between odor identification performance and cognitive functions is not well characterized. It has been shown that performance is dependent on the cognitive demands of the odor identification task: the availability of response alternatives increases identification performance significantly (Doty et al., 1984). Thus, by bypassing the difficulties of name generation/retrieval of a name from semantic memory the cognitive demands will decrease. However, performance has not shown to be perfect despite of available cues. Another factor influencing performance has shown to be the distinctiveness of response alternatives. Engen (1987) found that performance increased significantly (on average 93% correct) when response alternatives were highly distinctive compared to approximately 50% correct answers when response alternatives were similar to the target that had to be identified. Studies investigating the associations between cognitive measures and

cued odor identification performance have demonstrated that general semantic knowledge (Larsson et al., 2000, 2004), processing speed (Larsson et al., 2004), and episodic memory (Economou, 2003) were positively related to successful odor identification performance. A study examining the association between free odor identification and cognitive measures revealed significant correlations between olfactory performance and measures of processing speed and verbal fluency (Larsson et al., 2005).

A factor that has attracted little attention in relation to odor identification performance is education. In that the number of years spent in the educational system may correlate with cognitive abilities, it may influence odor identification performance through the influence on semantic memory function. Studies so far have been inconsistent with regard to the influence of education. Larsson et al. (2004) and Olofsson et al. (in press) found that education was positively correlated with odor identification performance, but this influence was not reliably confirmed in other studies (Larsson et al., 2000, 2005).

Despite the difficulties of verbal identification, the sensation of an odor often elicits a feeling of familiarity. Cain (1980) used the term "preverbal identification" referring to the condition where the generation of a verbal label is impossible although the individual is able to indicate that an odor is familiar. Lawless and Engen (1977) introduced the "tip of the nose" phenomenon where the individual experiences a strong feeling of familiarity, possibly able to specify an odor's source and access information about its quality, but not to retrieve the name. Köster (2002) pointed out that the feeling of familiarity may be of greater importance in real life when an odor is detected or recognized in order to behave adequately. According to Larsson (2002), different degrees of familiarity may be distinguishable, indicating the "implicit level of odor knowledge" (Larsson, 2002, p.236). Thus, low familiarity may be generated by a vague perception that cannot be associated with semantic information, while a high degree of familiarity may reflect access to more detailed information or possibly even access to a name. Schab (1991) proposed that knowledge on the complex process of odor identification could be increased if response accuracy admitted more than a single verbal label. He suggested to conceptualize odor identification as continuum with different levels of informational specificity: reaching from a basic feeling of familiarity, through a level of wide ranging identification including broad descriptions and some kind of specific knowledge, to a final level of identification where the individual is able to identify an odorant by a specific

name. So far, few studies have investigated the interrelation of different levels of odor identification and their association with cognitive functions. Cain (1979) reported that familiarity has an impact on identification: when responses were divided in categories labeled as "veridical", "near miss", and "far miss", he found that odors evaluated as highly familiar often received a verdical label. However, results also demonstrated that odors rated as highly familiar could receive labels belonging to the category "far miss". Other studies indicate that high familiarity increases odor recognition performance (Larsson & Bäckman, 1997; Rabin & Cain, 1984).

Tests of odor identification

Different tests of odor identification have been developed for different cultural regions and clinical settings, e.g. the University of Pennsylvania Smell Identification Test (UPSIT; Doty, Shaman & Dann, 1984) and the Connecticut Chemosensory Clinical Research Center Identification Test (Cain, 1989) have been developed in the USA, and the Sniffin' Sticks in Central Europe (Kobal et al., 1996). The reason for having developed several tests of this kind is due to cultural aspects of the test odors. Thus, correct identification is possible only if the individual has had previous experience with the odor quality. The Scandinavian Odor Identification Test (SOIT, Nordin et al., 1998) was developed in Sweden to provide a test valid for the Scandinavian population. It contains 16 odorous items as natural oils that are kept in glass bottles. So far, its applicability has also been demonstrated for Finish populations (Nordin, Nygroos, Maunuksela, Niskanen, & Tuorila, 2002).

Olfactory dysfunction in Alzheimer's disease and individuals at risk for Alzheimer's disease

A large body of evidence has demonstrated olfactory impairment in AD (Kovács, 2004; Mesholam, Moberg, Mahr, & Doty, 1998; Murphy, 1999). Results from earlier studies demonstrated significant correlations between odor identification scores and the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), supporting the usefulness of olfactory tasks in detecting olfactory dysfunction occurring together with the cognitive deficits in AD (Koss, Weiffenbach, Haxby, & Friedland, 1988; Serby, Larson, & Kalkstein,

1991). Studies using olfactory threshold tests have been less consistent in showing impairment in AD. While some authors have reported impairment (Knupfer & Spiegel, 1986), others have not (Koss, Weiffenbach, Haxby, & Friedland, 1987). Furthermore, odor detection levels have not always shown significant correlations with performance score on the MMSE (Larsson et al., 1999; but see also Murphy, Gilmore, Seery, Salmon, & Lasker, 1990), and impaired odor identification performance has been found despite normal detection levels (Koss et al., 1988; Serby et al., 1991). Morgan, Nordin, and Murphy (1995) suggested that detection impairment in AD may contribute to the observed deficit in identification performance, although additional cognitive components seem to contribute to the impairment. In a meta-analysis, Mesholam et al. (1998) concluded that odor detection, discrimination and identification were likely to be equally impaired in AD, and that divergent results concerning threshold tests could be due to assessment difficulties.

The apparent olfactory deficits seen in AD are suggested to correspond to the pathological changes in AD taking place in temporal lobe structures. Early pathological changes have been demonstrated in the entorhinal cortex (Braak & Braak, 1991), an area of high importance in olfactory processing: it receives input from the olfactory bulb through the lateral olfactory tract, the frontal cortex and the amygdala and projects to the hippocampus and orbitofrontal cortex (Cleland and Linster, 2003; Savic et al., 2000; Sobel, Johnson, Mainland, & Yousem, 2003). Other studies have reported that earliest pathological changes in AD involve the olfactory bulb (Hyman, Arrigada, & Van Hoesen, 1991; Kovács, Clairns, & Lantos, 2001). Thus, areas that are important for the processing of olfactory information are among the first affected by neuropathological changes in AD.

The findings of olfactory deficits in AD has motivated researchers to investigate olfactory functioning in individuals at risk of AD, e.g. individuals carrying the ε4 allele and individuals classified as MCI. Bacon, Bondi, Salmon, and Murphy (1998) found higher threshold levels in ε4 carriers the year prior to an AD diagnosis compared to the threshold in those individuals who did not progress to AD. Other studies have demonstrated lower odor identification performance scores in ε4 carriers compared to scores in a control group (Murphy, Bacon, Bondi, & Salmon, 1998; Suzuki et al., 2004; Wang et al., 2002). A more recent study failed to replicate those findings (Handley, Morrison, Miles, & Bayer, 2006). However, results revealed the greatest impairment in odor identification in ε4 carriers with a positive family history compared to non carriers with a positive family history of AD and ε4

carries in the control group. The authors concluded that odor identification deficits may not solely be caused by the possession of the ε4 allele. Two longitudinal studies reported significant differences in odor identification performance between ε4 carriers and non carriers (Calhoun-Haney & Murphy, 2005; Olofsson et al. in press). Calhoun-Haney and Murphy (2005) found that elderly ε4 carriers showed a larger decline in odor identification performance than non carriers. Olofsson et al. (in press) reported a significant difference in odor identification performance between ε4 carriers and non carriers in a group of 75-80 year olds. In the latter study, both genotype groups demonstrated decline in global cognitive functioning (MMSE) and odor identification performance, and the ε4 allele was shown to be associated with progression to dementia. However, a significant effect of genotype remained when preclinical and diagnostic cases of dementia were controlled for.

Studies investigating patients classified as MCI indicate that these patients may perform lower on odor identification tasks than normal individuals (Devanand et al., 2000; Djordjevic, Jones-Gotman, DeSousa, & Chetkow, 2008; Westervelt, Bruce, Coon, & Tremont, 2008). Westervelt et al. (2008) found that odor identification performance was impaired in MCI patients compared to normal controls but better than in patients with AD. Notably, the results did not show significant differences in clinical subtypes of MCI.

In a longitudinal study examining MCI patients, Devanand et al. (2000) reported that olfactory impairment was predictive for progression to AD. In addition, the authors pointed out that unawareness of olfactory dysfunction could be of particular interest. Their analyses revealed that low olfactory performance did not predict time to develop AD when demographic and clinical variables were controlled for. However, it was possible to predict time to development of AD when the status of unawareness of olfactory deficit in addition to impaired olfactory performance was included in the analyses. Thus, the authors suggested a unique contribution of the status of unawareness to the prediction of time to develop AD.

It has also been debated whether olfactory impairment in non demented elderly may be associated with decline in general cognitive ability (Graves et al., 1999; Swan & Carmelli, 2002). Longitudinal studies in healthy elderly individuals have demonstrated that cognitive decline, predominantly in episodic memory functioning and perceptual speed, can be predicted by performance on odor identification tasks (Swan & Carmelli, 2002; Wilson, Arnold, Tang & Bennett, 2006). It is, however, important to note that these studies differ in their strictness of excluding individuals with cognitive impairment at follow up examination,

and thus eventually might have included individuals in an early phase of AD. Another study reported an accumulation of amyloid plaques and neurofibrillary tangles in the entorhinal cortex and hippocampus of community-dwelling elderly individuals accounting for 12% of the variance in an odor identification task that had been administered on average 2.2 years before death (Wilson, Arnold, Schneider, Tang & Bennett, 2007). The authors reported further, that controlling for AD did not mediate the relationship between odor identification performance and neuropathology in the olfactory processing areas. This could imply that neuropathological changes that impair olfactory functioning are also present in individuals free from dementia.

In sum, findings demonstrate that olfactory impairment, particular in odor identification performance may occur at a very early stage of AD, prior to the onset of typical cognitive and behavioural disturbances. This prompted the suggestion that olfactory assessment could be a useful adjunct in the neuropsychological assessment to detect early AD (Graves et al., 1999; Morgan et al., 1995).

SUMMARY OF STUDIES

Research questions

This thesis has focused on the age period in life where cognitive and sensory changes often commence and consecutively may become more distinct. A series of cross-sectional was carried out to investigate the following issues:

1) The research aim in paper 1 was to investigate patterns of cognitive performance in a Norwegian sample of ApoE ε4 carriers and to evaluate if these were similar to those shown in earlier samples from other populations, e.g. Bondi et al., (1995; 1999). This question was motivated by findings indicating differences between varying ethnic groups with regard to an ApoE ε4 - AD association and by the finding showing that individuals from Nordic countries more frequently are carriers of the ε4 allele.

2) Paper 2 addressed the question whether the SOIT and its cut-off scores for diagnosis is applicable and valid to be used in Norwegian samples (middle aged and older individuals). Would results reveal performance differences between Norwegian and

Swedish individuals and would frequencies of diagnosis of olfactory dysfunction differ?

3) Two research questions motivated paper 3. The first referred to whether the number of individuals unaware of their olfactory deficit would increase significantly with age. The second question referred to whether cognitive function in individuals unaware of their olfactory dysfunction, and to whether this group showed different performance on cognitive tasks compared to individuals who showed normal olfactory functioning.

4) Paper 4 addressed the question how different components of the odor identification process (i.e. tasks assessing familiarity, cued and free identification) interrelate, how they relate to various cognitive measures and whether age-related performance differences could be found in the three olfactory tasks.

METHODS

Participants

The samples included in the studies presented were recruited from two different projects on cognitive aging. The first study included a sample of 70 individuals aged 50-75 years who were referred to clinical assessment in a research project through their primary physician. These individuals sought help for memory deficits and subjective memory complaints that had lasted for at least 6 month which was an inclusion criterion in addition to an estimated IQ score > 80 and an MMSE score ≥24. Participants had to be free from dementia based on results from the study protocol.

The remaining three studies in this thesis included community-dwelling samples of middle aged and older individuals (45-80 years), recruited through advertisement in local newspapers in Bergen and Oslo. For the detailed exclusion criteria, see individual papers. The varying sample sizes in the different papers relate to either specific exclusion criteria and/or the availability of data.

Neuropsychological assessment

In the present thesis, the following neuropsychological tests assigned to cognitive domains have been used:

General intellectual abilities were assessed using the Norwegian translation (Ørbeck, & Sundet, 2007) of subtests from the Wechsler's Abbreviated Scales of Intelligence (WASI; Wechsler, 1999). The subtest Matrices was used to assess nonverbal fluid reasoning and the Vocabulary subtest yields a measure of general verbal ability. Based on these two subtests, a total IQ score was estimated according to the available norms. To obtain measures of *memory function*, the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 2000; Norwegian translation: Sundet & Lundervold, 2004), the Rey-Osterrieth Complex Figure Test (Osterrieth, 1944; translation: Corwin & Bylsma, 1993), and the Verbal Paired Associates Test (Andersen, 1976) were included. Different aspects of *executive functioning* were assessed using the Trail Making Test B (Reitan & Davidson, 1974) and the Color-Word Interference Test (Delis, Kaplan, & Kramer, 2001)/Stroop Color Word Test (Jensen & Rohwer, 1966). The Controlled Word Association Test (COWAT; Benton & Hamsher, 1989) and the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983) were used to obtain measures of *verbal function*. The Digit Symbol Test (Wechsler, 1981) and the Trail Making Test A (Reitan & Davidson, 1974) yielded measures of attention and psychomotor speed. In paper 3, the revised version of the Everyday Memory Questionnaire (EMQ; Baddeley, 1997; Sunderland, Harris, & Gleave, 1984) was included to asses subjective evaluation of memory functioning.

Olfactory assessment

Olfactory assessment included a questionnaire on self-reported factors potentially influencing olfactory functioning (adapted from the Multi-Clinic Smell and Taste Questionnaire; Nordin, Brämerson, Murphy, & Bende (2003)) and questions about the self-reported status of the sense of smell. Time restrictions implicated that detection sensitivity was assessed by using a simplified version of the CCCRC Threshold Test (Cain, 1989) to describe the participants in terms of normosmia, hyposmia or anosmia with respect to detection sensitivity. Detection of 55 ppm butanol was categorized as normosmia, detection of 4444 ppm but not 55 ppm as hyposmia, and no detection of 4444 ppm as anosmia. Scores on the ability to identify odors were obtained by using the SOIT (Nordin et al., 1998). In addition to the standard procedure, participants were asked to make judgments of familiarity on individual items and freely identify a presented odor before cues for

identification were provided. Since the odor identification task will continuously be used, a disclosure of the response alternatives here is not possible.

SUMMARY OF RESULTS

Paper 1: ApoE status and its association to learning and memory performance in middle aged and older Norwegians seeking assessment for memory deficits

This study examined whether deficits in learning, memory and other cognitive functions were more prominent in carriers of the ε4 allele compared to non carriers, recruited from a population with a high prevalence of the ε4 allele. The sample comprised 70 consecutively referred patients aged 50-75 seeking assessment due to subjective memory complaints. Participants included in the study were classified as non demented based on clinical evaluation and results on cognitive tests. Fifty-six percent of the individuals in the sample were carriers of the ε4 allele. These individuals showed poorer performance than non-carriers on the MMSE, on a number of measures of verbal memory function from the CVLT, and on visual recall. In 46% of the participants, psychometric criteria for aMCI were met, based a performance score $\geq$ 1.5 SDs below the age and gender adjusted norm on the delayed free recall measure from the CVLT. The findings may partly be explained by a significant number of participants being in a preclinical phase of AD. However, the observed deficits in learning performance and the lack of significant age modulation of the genetic association suggest a more general genetic effect. The findings are consistent with known neurobiological function of ApoE ε4, including both increased risk of neurodegenerative disease and reduced synaptic integrity in older age.

Paper 2: Applicability of the Scandinavian Odor Identification Test for Norwegian use and age-related effects

The objective of this study was to evaluate the applicability of the SOIT for Norwegian use since it was developed and validated on Swedish participants. Other objectives were to study at what age performance in odor identification most clearly declines and whether diagnosis of olfactory dysfunction was comparable in Norwegian and Swedish samples. SOIT results of 256 Norwegian participants were compared with the results of 667

Swedish participants. The participants were divided into three age groups: 45-54 (young middle-aged), 55-64 (old middle-aged) and 65-75 (old) years. Results revealed that the Norwegian participants did not differ from the Swedes in their performance on the SOIT or in diagnostic distribution based on cut-off scores of the test. Gender- and age-related effects on identification performance in the Norwegians imply prognostic validity of the SOIT. The age-related effect-size was larger when comparing old middle-aged with the old, than when comparing the young middle-aged with the old middle-aged. The findings suggest that the SOIT is valid for use in Norwegian samples, and that the ability to identify odorous items is fairly well preserved at middle age, declining predominantly at old age.

Paper 3: Unawareness of olfactory dysfunction and its association with cognitive functioning in middle aged and older adults

One aim of this study was to investigate the accordance of subjectively (self-reported) and objectively (test of odor identification) assessed olfactory functioning. A second aim was to compare those individuals unaware of their olfactory dysfunction with those with normal olfactory function with respect to performance on cognitive tests. In total 253 participants, constituting a group of middle aged and a group of old, were evaluated with the SOIT, a question of self-evaluated olfactory function, neuropsychological tests of cognitive function, and the EMQ. Among those with an olfactory dysfunction, the proportion being unaware of the olfactory dysfunction was high in both middle aged (83%) and old (70%) participants. Performance on neuropsychological tests showed that persons unaware of their olfactory dysfunction performed poorer on cognitive tests of verbal learning and memory function, attention and executive functioning than participants with normal olfactory function. In the middle aged group, the results also revealed that the participants unaware of their olfactory dysfunction reported more memory difficulties. Our findings strongly suggest that self-reports and objective assessment of olfactory function has clinical relevance in the evaluation of aging individuals.

Paper 4: Familiarity, cued and free odor identification and their association with cognitive functioning in middle aged and older adults

The aim of the study was to examine the association between familiarity, cued and free odor identification performance and cognitive and demographic variables in healthy middle aged and older adults. It was hypothesized that the three olfactory tasks would be associated with different measures of cognitive functioning and that age would affect performance differently. Based on the argument that a decline will be most apparent on tasks demanding effortful processing, we expected that the age-related decline would be most pronounced in the free identification task. A third aim was to investigate the role of familiarity in explaining performance on free identification. One-hundred and thirty six participants (aged 45-79 years) with normal olfactory sensitivity were assessed with the SOIT and standardized tests of cognitive function. Results revealed that familiarity ratings did not correlate with any of the cognitive measures, while cued odor identification was related to a larger number and free odor identification with the largest number of cognitive variables. For both identification tasks, the strongest correlations were found for scores on processing speed and verbal memory. In this sample, only free odor identification showed a marginal significant decline with age. The results suggest that the different olfactory tasks involve different levels of cognitive processing.

DISCUSSION

The papers included in the thesis addressed questions related to cognitive and olfactory changes in elderly individuals with an aim to gain knowledge on the influence of the ApoE ε4 genotype on cognition and to extend the understanding of the association between cognitive functioning and odor identification performance. The first paper demonstrated that the ApoE ε4 genotype is associated with poorer cognitive performance on measures of verbal learning and memory function in a sample recruited from a population with a high frequency of the ε4 allele. In a series of studies on olfactory functioning, the applicability of the SOIT in a Norwegian sample was shown and it was demonstrated that olfactory dysfunction is present in a considerable number of elderly individuals. The findings suggest further that unawareness of olfactory dysfunction is associated with lower performance on measures of verbal learning and memory function in elderly individuals and that the process of odor identification is correlated with different measures of cognitive functioning.

ApoE ε4 and cognitive performance

The first paper contributes to the debate on whether the ApoE ε4 allele affects cognitive performance, in particular episodic memory function, in non demented individuals. Earlier findings were replicated in a sample recruited from a population with a high frequency of the ε4 allele. Thus, our findings are congruent with other studies discussed in the introduction (e.g. Bondi et al., 1995; 1999) and strengthen the generality of previous findings. The possibility that individuals in a preclinical stage of AD were included in the sample was discussed. The findings stress the importance of longitudinal studies investigating genetic influences in different populations with different frequencies of a specific genotype. In a study from the Betula project, a population-based longitudinal study in Sweden, where also elevated frequencies of the ApoE ε4 allele have been reported (Eggertsen, Tegelman, Ericsson, Angelin, & Berglund, 1993), Nilsson et al. (2006) observed ε4-related deficits in particular for recall measures of episodic memory. The authors explicitly discussed the risk of the inclusion of preclinical cases of AD and excluded individuals who had developed AD within the final testing point. They concluded that despite the possibility of further preclinical cases of AD in their sample, the dose effect shown in their data supported a differential effect of the ApoE ε4.

An explanation for the south-to-north gradient remains unknown. Gerdes (2003) speculated that ApoE ε4 may be an important factor for survival as it may protect against vitamin D deficiency which occurs in areas with periods of shortened/no sunlight. He further suggests that ApoE ε4 may either be related to a better re-absorption of the vitamin or increase its production. This remains a topic of further research.

The ApoE gene is regarded as one of the most important genes influencing cognitive aging and risk for AD. Although several other genes have been suggested to be related to AD, these associations seem weak and not always replicable (Bertram & Tanzi, 2004). In studies focusing on non pathological changes in aging other genetic factors have been shown to exert influences on cognition. For example, de Frias et al. (2004; 2005) found that polymorphisms of the catechol O-methyltransferases (COMT) gene are related to decline in executive functioning in elderly adults. Furthermore, Espeseth et al. (2006) showed that interactive effects of genes (ApoE and a nicotinic receptor subunit gene (CHRNA4)) may be responsible for differences in behavioral data. In a review concerning genetic influences on normal cognitive aging, Deary et al. (2004) concluded that the impact of genes on cognition emerges

from a life-long general factor and age-specific factors. The authors suggested, that the effects of individual genes seem to be rather small and that cognitive functions are likely to be influenced by a combination of effects from several genes (polygenic effects). They argued that also genetic influences seen in normal aging may be due to an accumulation of several late-onset disease-related polygenic effects which indirectly might exert an influence on cognition.

Mild cognitive impairment in patients seeking help for memory impairment

Besides the findings concerning ApoE and cognitive performance, the first paper highlights some of the challenges associated with the concept of MCI, and two aspects should be addressed here. Our definition of aMCI was based on criteria proposed by Petersen et al. (1999) and required an objective cognitive impairment ($\geq$ 1.5 SDs below peer norms) on one particular measure (delayed free recall from the CVLT) at a single point of time. In the context of our study this definition seemed reasonable as measures of episodic memory function have shown to be particularly sensitive to effects of the ε4 allele and to be good predictors of decline to AD. Thus, our objective was primarily to examine how many individuals defined as aMCI were carriers of the ε4 allele. However, with regard to the initially cited literature it seems reasonable to discuss whether the combination of cognitive measures would have added important information. It would be of interest to examine how many of the individuals classified as aMCI were impaired on tests of other cognitive domains e.g. executive functioning. These kinds of analyses could contribute to the discussion on subtypes of MCI and on the utilization and availability of compensatory resources. Thus, the combination of measures seems indicated to improve the knowledge about patterns of cognitive changes. Furthermore, the finding that 45% of the sample was classified as aMCI whereas a large proportion remained "unlabled" or considered "unimpaired" seems to deserve some comment. Having in mind that the participants in the study were recruited in a clinical setting, a higher occurrence of individuals with cognitive impairment was expected. A different definition of impairment (e.g. 1 SD below norms on the same measure) would have classified 63% as aMCI, while only 30% would have been in that group if we had chosen to base our definition on results (1.5 SDs below norms) from the Verbal Paired Associates Test. Furthermore, it is not possible to exclude the fact that the individuals performing in a "normal" range did not actually experience a decline: they might have had a high former level

of cognitive functioning, making them aware and worried about an age-related decline. In sum, this demonstrates that varying cutoffs and tests engender different groups of individuals and yield different types of information. Accordingly, rates of conversion from MCI to dementia may vary substantially. This highlights some of the concerns associated with the concept of MCI. The question is whether we should, based on the above discussed findings, label an individual with a term that means that someone does not have AD, or has it, or might get it. One suggestion could be to omit assumptions about the underlying pathological causes but rather use MCI descriptively (Tuokko & Hultsch, 2006). This may be enough to make MCI useful in a clinical setting where the clinician recognizes that a patient has cognitive deficits and decides to follow him/her up carefully, refer him/her to special assessment/examination, and suggest community support to maintain quality of life.

Applicability of the SOIT

The second paper established a basis for the application of the SOIT. Despite an eventual intuitive assumption that there are few cultural differences between Norwegian and Swedish individuals, we found it reasonable to investigate the applicability of the SOIT in Norwegian participants before using it on extended research questions. Our results introduce and qualify the SOIT as a standardized method to assess odor identification performance in Norwegian samples. One general concern with regard to our study may be the format of its presentation. We used the standardized version of the SOIT, including response alternatives that may be considered rather distinct, based on the argumentation that its applicability had to be confirmed to be able to further use this version in clinical as well as in research settings. Our results revealed a distribution that was slightly negatively skewed, so that caution seems appropriate when using the SOIT in well functioning samples of adults. However, since no differences were found between Norwegian and Swedish data, the latter collected from a population-based study; this seems sufficient evidence for our conclusions. The results enable further studies in clinical samples with regard to sensitivity and specificity. Other studies have demonstrated that specific item analyses could be of further interest: Ashendorff, Constantinou, Duff, and McCaffrey (2005) analyzed the individual items of the UPSIT (Doty et al., 1984) in community dwelling adults. Based on the results revealing that a number of items were generally poorly identified by elderly individuals, the authors suggested that deficits in the remaining items (which were not generally poorly identified) could signal

atypical olfactory deficits which could be of interest for clinicians. Another study revealed that item-specific pleasantness influenced overall identification performance, i.e. unpleasant odors were more consistently identified while identification of pleasant odors showed more age-related variance (Konstantinidis, Hummel, & Larsson, 2006). In sum, item analyses may further increase knowledge on the age-related changes seen in odor identification performance.

Unawareness of olfactory dysfunction

Paper 3 investigated age-related changes in unawareness of olfactory dysfunction based on performance on the SOIT. On the one hand, these findings have practical relevance as unawareness may be linked to risks in everyday life, such as detection of smoke, gas leaks, or spoiled food. Thus, persons working with elderly individuals should be made aware of the risk of olfactory deficits and possible implications. On the other hand, the results animate a number of questions by showing an association between the status of unawareness and diminished cognitive performance. Also earlier studies have reported an age-related increase in unawareness of olfactory dysfunction (Murphy et al., 2002; Nordin et al., 1995), although few have investigated further implications. Devanand et al. (2000) suggested that unawareness of olfactory dysfunction in MCI patients could possibly serve uniquely in the prediction of time to develop AD. Our results do not allow such far reaching suggestions but may be considered as a starting point for further questions and research. The request to estimate ones own sense of smell requires the individuals' access to information of his/her current olfactory status. This process of determining one's own abilities and disabilities is a part of meta-cognition, the part of mental function responsible for monitoring and regulating behavior. Meta-cognition is a multidimensional construct, and research concerning meta-cognition and age has mostly focused on memory functioning (Hertzog & Hultsch, 2000). One prominent example is the issue of cognitive complaints, in particular subjective memory complaints (SMC). So far, neither cross-sectional (Jonker, Launer, Hooijer, & Lindenboom, 1996; Jungwirth et al., 2004; Podewils, McLay, Rebook & Lyketsos, 2003) nor longitudinal studies (Dufoil, Fuhrer, & Alperovitch, 2005; Martin & Zimprich, 2003; Frerichs & Tuokko, 2006) have provided conclusive results on whether SMCs have predictive validity for objective memory impairment or future development of AD. However, in a review, Jonker, Geerlings, and Schmand (2000) concluded that individual characteristics and the context in

which complaints are expressed may be decisive. That is, complaints in a clinical setting might have a different validity than responses to a questionnaire in population-based studies. More recently, Fisk and Rockwood (2005) suggested that there could be a graded risk associated with subjective and objective impairment. That is, individuals with neither subjective nor objective impairment may have the lowest risk of progression to dementia, followed by a higher risk if objective impairment but no subjective complaint is present, and the highest risk where both subjective and objective impairment exist. Additionally, it has been shown that awareness of cognitive deficits in MCI patients may range from clear insight and even overestimation (Clément, Belleville, & Gauthier, 2008; Kalbe et al., 2005) to a level of severe unawareness comparable to the one seen in patients with AD (Vogel et al., 2004). These studies strengthen the view that aspects of meta-cognition may contain important information with regard to changes in functioning.

Our findings raise the question why some elderly individuals fail to update their meta-cognitive knowledge on olfactory function. At this point it has to remain speculative, but one hypothesis could be that some individuals receive little feedback on olfactory functioning in everyday life. Then, unawareness would be rather normal. However, this could also generate the question on how feedback on olfactory functioning is integrated in meta-cognition. Would individuals have given the same estimation about their function if they had been asked after completion of the task? Another concern may be the way of assessment: The question in study 3, "How do you estimate your sense of smell?" is rather global and the individuals did not obtain any detailed information on the tasks besides that their smell function would be assessed. Nordin et al. (1995) used a similar procedure to assess odor detection sensitivity. Thus, the question used here may not have mapped directly into odor identification ability but was possibly rather associated with the ability to detect odors. It is therefore important to replicate the findings with specific questions regarding awareness of detection sensitivity and identification ability. In sum, these arguments show that if unawareness of functional deficits such as olfaction is proposed as representing a unique measure to predict cognitive decline, more general information on these aspects of meta-cognition in normal aging individuals is needed to be able to evaluate their contribution to detect normal and eventually pathological processes in aging.

The process of odor identification and its association with cognitive measures

Paper 4 examined the odor identification process and its association with measures of cognitive function. Even though the data collected are not extensive enough to address the general difficulties associated with odor identification, they may provide some usable information. Results demonstrated that familiarity, cued and free identification are closely related to each other. Furthermore, the finding that the individual tasks correlated with a varying number of cognitive measures strengthens a common notion that free odor identification is the most difficult task, if difficulty is equated with the number of cognitive functions involved. A more speculative hypothesis would be that free odor identification, by showing to be associated with the largest number of cognitive functions, includes the most elaborated network of cognitive functioning. Results from neuroimaging studies support the idea of varying networks being involved in olfactory processing (Royet et al., 1999; 2001; Savic et al., 2000). These studies demonstrate different patterns of activation depending on the demands of the tasks, and Savic et al. suggested that olfactory processing seems to be organized in both a parallel and hierarchical fashion.

The finding that both cued and free identification were strongest related to a measure of episodic memory is in agreement with earlier studies (Swan & Carmelli, 2002; Wilson et al., 2006). Even though it remains speculative, it seems reasonable that based on this close connection, odor identification is sensitive to changes in episodic memory function. This could further support the notion of some authors that odor identification performance could be a valuable adjunct in the assessment of elderly individuals in the risk of AD. However, longitudinal studies with strict inclusion criteria are necessary to investigate trajectories of performance in different olfactory tasks to be able to further understand the interrelation of sensory and cognitive variables. The results are insofar noteworthy as odor identification has been described as relying on semantic knowledge (de Wijk et al., 1995). Based on findings demonstrating that odor identification/naming often contains individual information, Herz and Eich (1995) argued that odors are retained in "personal meaning-associative networks" and may therefore also be of episodic and not only semantic nature.

In this study, the amount of variance unaccounted for is notable. This suggests that other factors are likely to be important for odor identification performance. Larsson et al. (2005) found that sensory factors, in particular quality discrimination but also odor sensitivity, explained a large amount of age-related variance in identification ability. Thus, a more

extensive assessment of olfactory functioning could possibly have added important information. This concern is further strengthened by two recent studies showing that olfactory tests supplement each other and increase the reliability of olfactory diagnosis in early stages of olfactory dysfunction (Lötsch, Reichman, & Hummel, 2008; Djodjevic et al., 2008).

General considerations

A general concern to a more extensive assessment of olfactory functioning is the assessment of other causes for olfactory dysfunction. We used a self-report questionnaire to outline potential factors influencing olfactory functioning. However, based on these data it is not possible to definitely exclude other causes for an olfactory deficit. To be able to use olfactory performance as predictors for cognitive functioning or decline, a careful examination of the upper respiratory system and an individual's medical history should be taken into account to obtain clinically reliable results.

Another concern is that all papers included in this thesis are cross-sectional. It is known that results from this kind of studies may be confounded by cohort differences such as level of education, socioeconomic status, or cultural factors (Hofer & Sliwinski, 2001). Thus, age-related differences may be overestimated. On the contrary, longitudinal studies may underestimate age-related changes due to practice effects and attrition. However, the results presented in paper 1, 3, and 4 stress the advantage of longitudinal designs to follow-up impaired individuals (paper 1) or to be able to further examine olfactory and cognitive changes (paper 3 and 4). Furthermore, recruitment methods may have influenced our results. In paper 2-4, samples were drawn from a larger project on cognitive aging where the participants were self-recruited. This might have caused an overrepresentation of high performing adults. It must also be acknowledged that even though the focus in this thesis has been directed towards olfactory dysfunction and the early detection of AD, other neurodegenerative diseases are accompanied by olfactory dysfunction, e.g. Parkinson's disease (Haehner et al., 2007) or dementia of vascular type (Gray et al., 2001). Finally, the association of ApoE ε4 and olfactory dysfunction was addressed in the introduction but no results concerning this issue were reported in any of the studies. This was due to the fact that no significant results were found when running the analyses.

Concluding remarks

In sum, this thesis strengthens the contribution of neuropsychological assessment in elderly individuals in combination with other risk factors for AD, i.e. ApoE ε4, to describe individual differences of cognitive impairment. The findings on olfactory functioning assessed by means of an odor identification tasks emphasizes the contribution of this method in the neuropsychological assessment of aging individuals.

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Doctoral Theses at The Faculty of Psychology, University of Bergen

1980	Allen, H.M., Dr. philos.	Parent-offspring interactions in willow grouse (Lagopus L. Lagopus).
1981	Myhrer, T., Dr. philos.	Behavioral Studies after selective disruption of hippocampal inputs in albino rats.
1982	Svebak, S., Dr. philos.	The significance of motivation for task-induced tonic physiological changes.
1983	Myhre, G., Dr. philos.	The Biopsychology of behavior in captive Willow ptarmigan.
	Eide, R., Dr. philos.	PSYCHOSOCIAL FACTORS AND INDICES OF HEALTH RISKS. The relationship of psychosocial conditions to subjective complaints, arterial blood pressure, serum cholesterol, serum triglycerides and urinary catecholamines in middle aged populations in Western Norway.
	Værnes, R.J., Dr. philos.	Neuropsychological effects of diving.
1984	Kolstad, A., Dr. philos.	Til diskusjonen om sammenhengen mellom sosiale forhold og psykiske strukturer. En epidemiologisk undersøkelse blant barn og unge.
	Løberg, T., Dr. philos.	Neuropsychological assessment in alcohol dependence.
1985	Hellesnes, T., Dr. philos.	Læring og problemløsning. En studie av den perseptuelle analysens betydning for verbal læring.
	Håland, W., Dr. philos.	Psykoterapi: relasjon, utviklingsprosess og effekt.
1986	Hagtvet, K.A., Dr. philos.	The construct of test anxiety: Conceptual and methodological issues.
	Jellestad, F.K., Dr. philos.	Effects of neuron specific amygdala lesions on fear-motivated behavior in rats.
1987	Aarø, L.E., Dr. philos.	Health behaviour and sosioeconomic Status. A survey among the adult population in Norway.
	Underlid, K., Dr. philos.	Arbeidsløyse i psykososialt perspektiv.
	Laberg, J.C., Dr. philos.	Expectancy and classical conditioning in alcoholics' craving.
	Vollmer, F.C., Dr. philos.	Essays on explanation in psychology.
	Ellertsen, B., Dr. philos.	Migraine and tension headache: Psychophysiology, personality and therapy.
1988	Kaufmann, A., Dr. philos.	Antisosial atferd hos ungdom. En studie av psykologiske determinanter.

	Mykletun, R.J., Dr. philos.	Teacher stress: personality, work-load and health.
	Havik, O.E., Dr. philos.	After the myocardial infarction: A medical and psychological study with special emphasis on perceived illness.
1989	Bråten, S., Dr. philos.	Menneskedyaden. En teoretisk tese om sinnets dialogiske natur med informasjons- og utviklingspsykologiske implikasjoner sammenholdt med utvalgte spedbarnsstudier.
	Wold, B., Dr. psychol.	Lifestyles and physical activity. A theoretical and empirical analysis of socialization among children and adolescents.
1990	Flaten, M.A., Dr. psychol.	The role of habituation and learning in reflex modification.
1991	Alsaker, F.D., Dr. philos.	Global negative self-evaluations in early adolescence.
	Kraft, P., Dr. philos.	AIDS prevention in Norway. Empirical studies on diffusion of knowledge, public opinion, and sexual behaviour.
	Endresen, I.M., Dr. philos.	Psychoimmuniological stress markers in working life.
	Faleide, A.O., Dr. philos.	Asthma and allergy in childhood. Psychosocial and psychotherapeutic problems.
1992	Dalen, K., Dr. philos.	Hemispheric asymmetry and the Dual-Task Paradigm: An experimental approach.
	Bø, I.B., Dr. philos.	Ungdoms sosiale økologi. En undersøkelse av 14-16 åringers sosiale nettverk.
	Nivison, M.E., Dr. philos.	The relationship between noise as an experimental and environmental stressor, physiological changes and psychological factors.
	Torgersen, A.M., Dr. philos.	Genetic and environmental influence on temperamental behaviour. A longitudinal study of twins from infancy to adolescence.
1993	Larsen, S., Dr. philos.	Cultural background and problem drinking.
	Nordhus, I.H., Dr. philos.	Family caregiving. A community psychological study with special emphasis on clinical interventions.
	Thuen, F., Dr. psychol.	Accident-related behaviour among children and young adolescents: Prediction and prevention.
	Solheim, R., Dr. philos.	Spesifikke lærevansker. Diskrepanskriteriet anvendt i seleksjonsmetodikk.
	Johnsen, B.H., Dr. psychol.	Brain assymetry and facial emotional expressions: Conditioning experiments.
1994	Tønnessen, F.E., Dr. philos.	The etiology of Dyslexia.
	Kvale, G., Dr. psychol.	Psychological factors in anticipatory nausea and vomiting in cancer chemotherapy.
	Asbjørnsen, A.E., Dr. psychol.	Structural and dynamic factors in dichotic listening: An interactional model.

	Bru, E., Dr. philos.	The role of psychological factors in neck, shoulder and low back pain among female hospitale staff.
	Braathen, E.T., Dr. psychol.	Prediction of exellence and discontinuation in different types of sport: The significance of motivation and EMG.
	Johannessen, B.F., Dr. philos.	Det flytende kjønnet. Om lederskap, politikk og identitet.
1995	Sam, D.L., Dr. psychol.	Acculturation of young immigrants in Norway: A psychological and socio-cultural adaptation.
	Bjaalid, I.-K., Dr. philos	Component processes in word recognition.
	Martinsen, Ø., Dr. philos.	Cognitive style and insight.
	Nordby, H., Dr. philos.	Processing of auditory deviant events: Mismatch negativity of event-related brain potentials.
	Raaheim, A., Dr. philos.	Health perception and health behaviour, theoretical considerations, empirical studies, and practical implications.
	Seltzer, W.J., Dr.philos.	Studies of Psychocultural Approach to Families in Therapy.
	Brun, W., Dr.philos.	Subjective conceptions of uncertainty and risk.
	Aas, H.N., Dr. psychol.	Alcohol expectancies and socialization: Adolescents learning to drink.
	Bjørkly, S., Dr. psychol.	Diagnosis and prediction of intra-institutional aggressive behaviour in psychotic patients
1996	Anderssen, N., Dr. psychol.	Physical activity of young people in a health perspective: Stability, change and social influences.
	Sandal, Gro Mjeldheim, Dr. psychol.	Coping in extreme environments: The role of personality.
	Strumse, Einar, Dr. philos.	The psychology of aesthetics: explaining visual preferences for agrarian landscapes in Western Norway.
	Hestad, Knut, Dr. philos.	Neuropsychological deficits in HIV-1 infection.
	Lugoe, L.Wycliffe, Dr. philos.	Prediction of Tanzanian students' HIV risk and preventive behaviours
	Sandvik, B. Gunnhild, Dr. philos.	Fra distriktsjordmor til institusjonsjordmor. Fremveksten av en profesjon og en profesjonsutdanning
	Lie, Gro Therese, Dr. psychol.	The disease that dares not speak its name: Studies on factors of importance for coping with HIV/AIDS in Northern Tanzania
	Øygard, Lisbet, Dr. philos.	Health behaviors among young adults. A psychological and sociological approach
	Stormark, Kjell Morten, Dr. psychol.	Emotional modulation of selective attention: Experimental and clinical evidence.
	Einarsen, Ståle, Dr. psychol.	Bullying and harassment at work: epidemiological and psychosocial aspects.

1997	Knivsberg, Ann-Mari, Dr. philos.	Behavioural abnormalities and childhood psychopathology: Urinary peptide patterns as a potential tool in diagnosis and remediation.
	Eide, Arne H., Dr. philos.	Adolescent drug use in Zimbabwe. Cultural orientation in a global-local perspective and use of psychoactive substances among secondary school students.
	Sørensen, Marit, Dr. philos.	The psychology of initiating and maintaining exercise and diet behaviour.
	Skjæveland, Oddvar, Dr. psychol.	Relationships between spatial-physical neighborhood attributes and social relations among neighbors.
	Zewdie, Teka, Dr. philos.	Mother-child relational patterns in Ethiopia. Issues of developmental theories and intervention programs.
	Wilhelmsen, Britt Unni, Dr. philos.	Development and evaluation of two educational programmes designed to prevent alcohol use among adolescents.
	Manger, Terje, Dr. philos.	Gender differences in mathematical achievement among Norwegian elementary school students.
1998		
V	Lindstrøm, Torill Christine, Dr. philos.	«Good Grief»: Adapting to Bereavement.
	Skogstad, Anders, Dr. philos.	Effects of leadership behaviour on job satisfaction, health and efficiency.
	Haldorsen, Ellen M. Håland, Dr. psychol.	Return to work in low back pain patients.
	Besemer, Susan P., Dr. philos.	Creative Product Analysis: The Search for a Valid Model for Understanding Creativity in Products.
H	Winje, Dagfinn, Dr. psychol.	Psychological adjustment after severe trauma. A longitudinal study of adults' and children's posttraumatic reactions and coping after the bus accident in Måbødalen, Norway 1988.
	Vosburg, Suzanne K., Dr. philos.	The effects of mood on creative problem solving.
	Eriksen, Hege R., Dr. philos.	Stress and coping: Does it really matter for subjective health complaints?
	Jakobsen, Reidar, Dr. psychol.	Empiriske studier av kunnskap og holdninger om hiv/aids og den normative seksuelle utvikling i ungdomsårene.
1999		
V	Mikkelsen, Aslaug, Dr. philos.	Effects of learning opportunities and learning climate on occupational health.
	Samdal, Oddrun, Dr. philos.	The school environment as a risk or resource for students' health-related behaviours and subjective well-being.
	Friestad, Christine, Dr. philos.	Social psychological approaches to smoking.
	Ekeland, Tor-Johan, Dr. philos.	Meining som medisin. Ein analyse av placebofenomenet og implikasjoner for terapi og terapeutiske teoriar.

H	Saban, Sara, Dr. psychol.	Brain Asymmetry and Attention: Classical Conditioning Experiments.
	Carlsten, Carl Thomas, Dr. philos.	God lesing – God læring. En aksjonsrettet studie av undervisning i fagtekstlesing.
	Dundas, Ingrid, Dr. psychol.	Functional and dysfunctional closeness. Family interaction and children's adjustment.
	Engen, Liv, Dr. philos.	Kartlegging av leseferdighet på småskoletrinnet og vurdering av faktorer som kan være av betydning for optimal leseutvikling.

2000

V	Hovland, Ole Johan, Dr. philos.	Transforming a self-preserving "alarm" reaction into a self-defeating emotional response: Toward an integrative approach to anxiety as a human phenomenon.
	Lillejord, Sølvi, Dr. philos.	Handlingsrasjonalitet og spesialundervisning. En analyse av aktørperspektiver.
	Sandell, Ove, Dr. philos.	Den varme kunnskapen.
	Oftedal, Marit Petersen, Dr. philos.	Diagnostisering av ordavkodingsvansker: En prosessanalytisk tilnærmingsmåte.

H	Sandbak, Tone, Dr. psychol.	Alcohol consumption and preference in the rat: The significance of individual differences and relationships to stress pathology
	Eid, Jarle, Dr. psychol.	Early predictors of PTSD symptom reporting; The significance of contextual and individual factors.

2001

V	Skinstad, Anne Helene, Dr. philos.	Substance dependence and borderline personality disorders.
	Binder, Per-Einar, Dr. psychol.	Individet og den meningsbærende andre. En teoretisk undersøkelse av de mellommenneskelige forutsetningene for psykisk liv og utvikling med utgangspunkt i Donald Winnicotts teori.
	Roald, Ingvild K., Dr. philos.	Building of concepts. A study of Physics concepts of Norwegian deaf students.

H	Fekadu, Zelalem W., Dr. philos.	Pridicting contraceptive use and intention among a sample of adolescent girls. An application of the theory of planned behaviour in Ethiopian context.
	Melesse, Fantu, Dr. philos.	The more intelligent and sensitive child (MISC) mediational intervention in an Ethiopian context: An evaluation study.
	Råheim, Målfrid, Dr. philos.	Kvinners kroppserfaring og livssammenheng. En fenomenologisk – hermeneutisk studie av friske kvinner og kvinner med kroniske muskelsmerter.
	Engelsen, Birthe Kari, Dr. psychol.	Measurement of the eating problem construct.
	Lau, Bjørn, Dr. philos.	Weight and eating concerns in adolescence.

2002

V	Ihlebæk, Camilla, Dr. philos.	Epidemiological studies of subjective health complaints.

	Rosén, Gunnar O. R., Dr. philos.	The phantom limb experience. Models for understanding and treatment of pain with hypnosis.
	Høines, Marit Johnsen, Dr. philos.	Fleksible språkrom. Matematikklæring som tekstutvikling.
	Anthun, Roald Andor, Dr. philos.	School psychology service quality. Consumer appraisal, quality dimensions, and collaborative improvement potential
	Pallesen, Ståle, Dr. psychol.	Insomnia in the elderly. Epidemiology, psychological characteristics and treatment.
	Midthassel, Unni Vere, Dr. philos.	Teacher involvement in school development activity. A study of teachers in Norwegian compulsory schools
	Kallestad, Jan Helge, Dr. philos.	Teachers, schools and implementation of the Olweus Bullying Prevention Program.
H	Ofte, Sonja Helgesen, Dr. psychol.	Right-left discrimination in adults and children.
	Netland, Marit, Dr. psychol.	Exposure to political violence. The need to estimate our estimations.
	Diseth, Åge, Dr. psychol.	Approaches to learning: Validity and prediction of academic performance.
	Bjuland, Raymond, Dr. philos.	Problem solving in geometry. Reasoning processes of student teachers working in small groups: A dialogical approach.

2003

V	Arefjord, Kjersti, Dr. psychol.	After the myocardial infarction – the wives' view. Short- and long-term adjustment in wives of myocardial infarction patients.
	Ingjaldsson, Jón Þorvaldur, Dr. psychol.	Unconscious Processes and Vagal Activity in Alcohol Dependency.
	Holden, Børge, Dr. philos.	Følger av atferdsanalytiske forklaringer for atferdsanalysens tilnærming til utforming av behandling.
	Holsen, Ingrid, Dr. philos.	Depressed mood from adolescence to 'emerging adulthood'. Course and longitudinal influences of body image and parent-adolescent relationship.
	Hammar, Åsa Karin, Dr. psychol.	Major depression and cognitive dysfunction- An experimental study of the cognitive effort hypothesis.
	Sprugevica, Ieva, Dr. philos.	The impact of enabling skills on early reading acquisition.
	Gabrielsen, Egil, Dr. philos.	LESE FOR LIVET. Lesekompetansen i den norske voksenbefolkningen sett i lys av visjonen om en enhetsskole.
H	Hansen, Anita Lill, Dr. psychol.	The influence of heart rate variability in the regulation of attentional and memory processes.
	Dyregrov, Kari, Dr. philos.	The loss of child by suicide, SIDS, and accidents: Consequences, needs and provisions of help.

2004

V

	Torsheim, Torbjørn, Dr. psychol.	Student role strain and subjective health complaints: Individual, contextual, and longitudinal perspectives.
	Haugland, Bente Storm Mowatt Dr. psychol.	Parental alcohol abuse. Family functioning and child adjustment.
	Milde, Anne Marita, Dr. psychol.	Ulcerative colitis and the role of stress. Animal studies of psychobiological factors in relationship to experimentally induced colitis.
	Stornes, Tor, Dr. philos.	Socio-moral behaviour in sport. An investigation of perceptions of sportspersonship in handball related to important factors of socio-moral influence.
	Mæhle, Magne, Dr. philos.	Re-inventing the child in family therapy: An investigation of the relevance and applicability of theory and research in child development for family therapy involving children.
	Kobbeltvedt, Therese, Dr. psychol.	Risk and feelings: A field approach.

2004 H

	Thomsen, Tormod, Dr. psychol.	Localization of attention in the brain.
	Løberg, Else-Marie, Dr. psychol.	Functional laterality and attention modulation in schizophrenia: Effects of clinical variables.
	Kyrkjebø, Jane Mikkelsen, Dr. philos.	Learning to improve: Integrating continuous quality improvement learning into nursing education.
	Laumann, Karin, Dr. psychol.	Restorative and stress-reducing effects of natural environments: Experiencal, behavioural and cardiovascular indices.
	Holgersen, Helge, PhD	Mellom oss - Essay i relasjonell psykoanalyse.

2005

V

	Hetland, Hilde, Dr. psychol.	Leading to the extraordinary? Antecedents and outcomes of transformational leadership.
	Iversen, Anette Christine, Dr. philos.	Social differences in health behaviour: the motivational role of perceived control and coping.

2005 H

	Mathisen, Gro Ellen, PhD	Climates for creativity and innovation: Definitions, measurement, predictors and consequences.
	Sævi, Tone, Dr. philos.	Seeing disability pedagogically – The lived experience of disability in the pedagogical encounter.
	Wiium, Nora, PhD	Intrapersonal factors, family and school norms: combined and interactive influence on adolescent smoking behaviour.
	Kanagaratnam, Pushpa, PhD	Subjective and objective correlates of Posttraumatic Stress in immigrants/refugees exposed to political violence.
	Larsen, Torill M. B. , PhD	Evaluating principals` and teachers` implementation of Second Step. A case study of four Norwegian primary schools.

	Bancila, Delia, PhD	Psychosocial stress and distress among Romanian adolescents and adults.

2006
V

	Hillestad, Torgeir Martin, Dr. philos.	Normalitet og avvik. Forutsetninger for et objektivt psykopatologisk avviksbegrep. En psykologisk, sosial, erkjennelsesteoretisk og teorihistorisk framstilling.
	Nordanger, Dag Øystein, Dr. psychol.	Psychosocial discourses and responses to political violence in post-war Tigray, Ethiopia.
	Rimol, Lars Morten, PhD	Behavioral and fMRI studies of auditory laterality and speech sound processing.
	Krumsvik, Rune Johan, Dr. philos.	ICT in the school. ICT-initiated school development in lower secondary school.
	Norman, Elisabeth, Dr. psychol.	Gut feelings and unconscious thought: An exploration of fringe consiousness in implicit cognition.
	Israel, K Pravin, Dr. psychol.	Parent involvement in the mental health care of children and adolescents. Emperical studies from clinical care setting.
	Glasø, Lars, PhD	Affects and emotional regulation in leader-subordinate relationships.
	Knutsen, Ketil, Dr. philos.	HISTORIER UNGDOM LEVER – En studie av hvordan ungdommer bruker historie for å gjøre livet meningsfullt.
	Matthiesen, Stig Berge, PhD	Bullying at work. Antecedents and outcomes.

2006
H

	Gramstad, Arne, PhD	Neuropsychological assessment of cognitive and emotional functioning in patients with epilepsy.
	Bendixen, Mons, PhD	Antisocial behaviour in early adolescence: Methodological and substantive issues.
	Mrumbi, Khalifa Maulid, PhD	Parental illness and loss to HIV/AIDS as experienced by AIDS orphans aged between 12-17 years from Temeke District, Dar es Salaam, Tanzania: A study of the children's psychosocial health and coping responses.
	Hetland, Jørn, Dr. psychol.	The nature of subjective health complaints in adolescence: Dimensionality, stability, and psychosocial predictors
	Kakoko, Deodatus Conatus Vitalis, PhD	Voluntary HIV counselling and testing service uptake among primary school teachers in Mwanza, Tanzania: assessment of socio-demographic, psychosocial and socio-cognitive aspects
	Mykletun, Arnstein, Dr. psychol.	Mortality and work-related disability as long-term consequences of anxiety and depression: Historical cohort designs based on the HUNT-2 study
	Sivertsen, Børge, PhD	Insomnia in older adults. Consequences, assessment and treatment.

2007
V

	Singhammer, John, Dr. philos.	Social conditions from before birth to early adulthood – the influence on health and health behaviour

	Janvin, Carmen Ani Cristea, PhD	Cognitive impairment in patients with Parkinson's disease: profiles and implications for prognosis
	Braarud, Hanne Cecilie, Dr.psychol.	Infant regulation of distress: A longitudinal study of transactions between mothers and infants
	Tveito, Torill Helene, PhD	Sick Leave and Subjective Health Complaints
	Magnussen, Liv Heide, PhD	Returning disability pensioners with back pain to work
	Thuen, Elin Marie, Dr.philos.	Learning environment, students' coping styles and emotional and behavioural problems. A study of Norwegian secondary school students.
	Solberg, Ole Asbjørn, PhD	Peacekeeping warriors – A longitudinal study of Norwegian peacekeepers in Kosovo
2007 H	Søreide, Gunn Elisabeth, Dr.philos.	Narrative construction of teacher identity
	Svensen, Erling, PhD	WORK & HEALTH. Cognitive Activation Theory of Stress applied in an organisational setting.
	Øverland, Simon Nygaard, PhD	Mental health and impairment in disability benefits. Studies applying linkages between health surveys and administrative registries.
	Eichele, Tom, PhD	Electrophysiological and Hemodynamic Correlates of Expectancy in Target Processing
	Børhaug, Kjetil, Dr.philos.	Oppseding til demokrati. Ein studie av politisk oppseding i norsk skule.
	Eikeland, Thorleif, Dr.philos.	Om å vokse opp på barnehjem og på sykehus. En undersøkelse av barnehjemsbarns opplevelser på barnehjem sammenholdt med sanatoriebarns beskrivelse av langvarige sykehusopphold – og et forsøk på forklaring.
	Wadel, Carl Cato, Dr.philos.	Medarbeidersamhandling og medarbeiderledelse i en lagbasert organisasjon
	Vinje, Hege Forbech, PhD	Thriving despite adversity: Job engagement and self-care among community nurses
	Noort, Maurits van den, PhD	Working memory capacity and foreign language acquisition
2008 V	Breivik, Kyrre, Dr.psychol.	The Adjustment of Children and Adolescents in Different Post-Divorce Family Structures. A Norwegian Study of Risks and Mechanisms.
	Johnsen, Grethe E., PhD	Memory impairment in patients with posttraumatic stress disorder
	Sætrevik, Bjørn, PhD	Cognitive Control in Auditory Processing
	Carvalhosa, Susana Fonseca, PhD	Prevention of bullying in schools: an ecological model

2008 H	Brønnick, Kolbjørn Selvåg	Attentional dysfunction in dementia associated with Parkinson's disease.
	Posserud, Maj-Britt Rocio	Epidemiology of autism spectrum disorders
	Haug, Ellen	Multilevel correlates of physical activity in the school setting
	Skjerve, Arvid	Assessing mild dementia – a study of brief cognitive tests.
	Kjønniksen, Lise	The association between adolescent experiences in physical activity and leisure time physical activity in adulthood: a ten year longitudinal study
	Gundersern, Hilde	The effects of alcohol and expectancy on brain function
	Omvik, Siri	Insomnia – a night and day problem
2009 V	Molde, Helge	Pathological gambling: prevalence, mechanisms and treatment outcome.
	Foss, Else	Den omsorgsfulle væremåte. En studie av voksnes væremåte i forhold til barn i barnehagen.
	Westrheim, Kariane	Education in a Political Context: A study of Konwledge Processes and Learning Sites in the PKK.

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