Grete Kjelvik

# Human odor identification studied in healthy individuals, mild cognitive impairment and Alzheimer's disease

Thesis for the degree of Philosophiae Doctor

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Norwegian University of Science and Technology
Faculty of Medicine
Department of Circulation and Medical Imaging

NTNU – Trondheim
Norwegian University of
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**Evnen til å identifisere lukter studert hos friske individer, personer med mild kognitiv svikt og Alzheimers sykdom**

**Bakgrunn:** Luktidentifikasjon er evnen til å oppfatte og navngi en lukt riktig. Allerede i midten av 1970-årene ble de første studiene publisert som viste at evnen til å lukte er svekket ved nevrodegenerative sykdommer (Ansari og Johnson og Waldton). Majoriteten av pasienter med amnestisk mild kognitiv svikt (aMCI) og tidlig Alzheimers sykdom er vist å få redusert lukteevnen, særskilt evnen til å identifisere lukter. Siden områder i hjernens temporallapp er sentral både i luktprosessering, samtidig som entorhinal cortex er det område som trolig rammes tidligst ved Alzheimers sykdom, så er det av stor interesse å undersøke lukteevnen hos denne pasientgruppen. For å vurdere nytten av testing med lukt identifikasjon i klinikken, trenger vi en bedre forståelse av de nevronale prosessene som ligger til grunn for lukt identifikasjon i den menneskelige hjerne. I tillegg trenger vi standardiserte luktetester for bruk i Norge som er tilpasset norske forhold. Dette bør være tester som er enkle å administrere, som koster lite og tar kort tid å gjennomføre.

**Formål:** Denne avhandlingen har tre hovedmål. Det første målet var å undersøke nytten av kommersielle luktetester som "the Brief Smell Identification Test" (B-SIT), en modifisert versjon av B-SIT og "the Sniffin Sticks Identification Test" (SSIT) i norske populasjoner for å kunne skille pasienter med tidlig Alzheimers sykdom og aMCI fra friske kontroller. Det andre målet var å undersøke hvilke hjerneområder som aktiveres hos unge friske mennesker under vellykket identifisering av lukter. Det siste målet var å studere hvordan volumene av ulike strukturer i hjernen samvarierer med evnen til å identifisere lukter hos pasienter med mild grad av demens ved Alzheimers sykdom og friske sammenlignbare kontroller.

**Metoder:** Artiklene i avhandlingen baserer seg på fire eksperimentelle studier i fire ulike populasjoner. Det er gjennomført psykofysiske luktetester i alle de fire populasjonene, men det er studiene referert i artikkel I og artikkel II som i hovedsak beskriver luktetestens metodikk. I artikkel III har vi brukt funksjonell magnetisk

resonans bildedannelse (fMRI) for å studere aktiveringsmønsteret i hjernen ved luktidentifikasjon hos friske unge personer. Luktstimuleringen i skanneren ble gitt ved hjelp av et olfaktometer. I artikkel IV har vi brukt strukturell magnetisk resonans bildedannelse (strukturell MRI) for å studere assosiasjoner mellom volumer av ulike hjernestrukturer og evne til å identifisere lukter. Dette ble undersøkt hos pasienter med en aMCI og mild grad av demens ved Alzheimers sykdom og friske eldre personer.

**Hovedfunn:** Studie I demonstrerer at B-SIT er velegnet for bruk i Norge til å skille pasienter med Alzheimers sykdom (hvor noen av pasientene var i tidlig stadium) fra friske personer. Studie II viser at en modifisert versjon av testen B-SIT, er en like god test som den originale B-SIT, samtidig som den trolig kan være en bedre test til bruk i generelle populasjoner. Funnene fra Studie III indikerer at entorhinal cortex og hippocampus er sentrale områder i hjernen som aktiveres spesifikt når friske unge personer klarer å identifisere lukter. Studie IV demonstrerer at pasienter med aMCI eller tidlig Alzheimers sykdom som har relativt intakt luktefunksjon (ut fra både B-SIT og SSIT), har større volum av hippocampus enn de med redusert luktidentifiseringsevne.

**Konklusjon:** Våre funn viser at lukteskreening testene B-SIT og SSIT er godt tilpasset for bruk i Norge, og at en modifisert versjon av B-SIT vil være en like god test som den originale B-SIT. De nevronale prosessene som ligger til grunn for luktidentifikasjon i den menneskelige hjerne, ser ut til å inkludere et helt nettverk av strukturer, hvor særskilt entorhinal cortex og hippocampus er sentrale strukturer for at friske unge personer klarer å navngi lukter riktig. Luktetestene kan hjelpe til å skille ut de pasienter som er mer langtkommet i utviklingen av Alzheimers sykdom, fordi gruppen med redusert lukteidentifikasjonsevne hadde signifikant mer redusert hippocampus volum enn de med intakt lukteidentifikasjonsevne. Hva vi har funnet i studiene, har gitt økt kunnskap om nytten av bruk av luktetester i norske populasjoner, og ny kunnskap om de nevronale prosessene som ligger til grunn for luktidentifikasjon i den menneskelige hjerne.

**Navn kandidat:** Grete Kjelvik
**Institutt:** Institutt for Sirkulasjon og Bildediagnostikk
**Veildere:** Asta K. Håberg (hovedveileder), Linda R. White, Olav Sletvold og Knut A. Engedal.
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*Prøveforelesningen (oppgitt emne) finner sted torsdag 1. november kl 09: 15 i auditoriet, Medisinisk teknisk forskningssenter.*
*Disputas finner sted torsdag 1. November kl. 11:15 i auditoriet, Medisinsk teknisk forskningssenter.*

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**List of papers**

The thesis is based on the following publications, which are referred to in the text by Roman numerals: I-IV.

*I.* **Kjelvik G**, Sando S.B, Aasly J, Engedal K.A, White L.R. Use of the Brief Smell Identification Test for olfactory deficits in a Norwegian population with Alzheimer´s disease. *International Journal of Geriatric Psychiatry, Oct 22 (10): 1020-4, 2007.*

*II.* **Kjelvik G**, Bosnes B, Omli R, Skotnes L. H, Håberg A.K. and White L.R. Modification of the Brief Smell Identification Test by introduction of a placebo*. Neuroscience and Medicine, Volume 3, No. 2, 2012.*

*III.* **Kjelvik G**, Evensmoen H.R, Brezova V, Håberg A.K. The human brain representation of odor identification. *J Neurophysiol. 2012 Apr 25, In press, online.*

*IV.* **Kjelvik G**, Saltvedt I, White L.R, Stenumgård P, Sletvold O, Engedal, Skåtun K, Lyngvær A.K, Steffenach H.A. and Håberg A.K. Odor identification and brain structural MRI volume in MCI and early dementia in Alzheimer´s disease. *Submitted to Neurobiology of Aging, 2012.*

## V. Abbreviations

| | |
|---|---|
| OI | Odor Identification |
| AD | Alzheimer's Disease |
| MCI | Mild Cognitive Impairment |
| aMCI | Amnestic Mild Cognitive Impairment |
| fMRI | Functional Magnetic Resonance Imaging |
| MRI | Magnetic Resonance Imaging |
| PET | Positron Emission Tomography |
| UPSIT | University of Pennsylvaina Smell Identification Test |
| B-SIT | The Brief Smell Identification Test |
| SSIT | Sniffin Sticks Identification Test |
| SSDT | Sniffin Sticks Discrimination Test |
| SOIT | Scandinavian Odor Identification Test |
| BOLD | Blood Oxygen Level-Dependent |
| MMSE | Mini Mental Status Examination |
| MTL | Medial Temporal Lobe |
| SS | Sensitivity |
| SP | Specificity |
| oERP | Olfactory Event-Related Potentials |

# 1.0. Introduction

Loss of odor identification (OI) is often associated with neurodegenerative diseases such as Alzheimer's disease (AD). The utility of OI tests as clinical tools depends on a better understanding of the neuronal processes underlying OI in the human brain. However, the sense of smell is influenced by factors such as experience and culture, and feasible commercial olfactory screening tools need to be validated for use in the population that is to be tested.

## *1.1. The human olfactory system*

The human olfactory system is the route from the olfactory epithelium via the olfactory bulbs to the higher olfactory regions of the brain. Olfaction has immediate access to the olfactory cortex (only two synapses) without relay in the thalamus. Substances called odorants are capable of activating the olfactory system. An odor is defined as the sensation created by the olfactory organs. How the olfactory system decodes information from chemical compounds to produce odor perception is a complex process. Olfactory function is organized in both a parallel and hierarchical manner, depending on the character and complexity of the odor task. The hierarchical nature of olfactory processing is from a lower level of perception up to a higher level of perception, to produce the odor percept. Odor detection is the degree of presence of an odorant. This sensory process can be assessed by exposure to low odor concentrations, and determining the threshold at which the odor is detectable. The term higher olfactory function is used to describe brain functions that combine cognition and olfaction, and includes three main concepts. Firstly, odor recognition involves matching input with stored information. It is based on the ability to remember odors that have previously been presented. Secondly, odor discrimination is the ability to differentiate between two or more odorants. Thirdly, the most complex process is OI, the assignment of meaning and naming of an odor. Other aspects of the olfactory function often studied are intensity, pleasantness, quality, familiarity or edibility judgment.

### 1.1.1. The peripheral olfactory system

Odorants which consist of physiochemical molecules enter the nose through the nostrils into the upper part of the nasal cavity where the olfactory epithelium is located. The olfactory epithelium measures about one square centimetre on each side and lies in the roof of the nasal cavity. The olfactory epithelium consists of three distinct types of cells: olfactory receptor cells, supporting cells and basal cells. Unlike other neurons in the adult nervous system, the olfactory receptor neurons have the ability to regenerate and are unmyelinated. There are several million bipolar receptor cells, and these cells have cilia branching out into the layer of mucosa in the superficial layer of the epithelium. The odorants react with receptors, called odor-binding proteins, located on the cilia. Most odors are complex mixtures of many components. Each olfactory receptor cell processes only one type of odorant receptor (Buck and Axel, 1991), and each receptor is highly specialized and can detect a limited number of odorant substances (Duchamp-Viret et al., 1999). Thus each receptor may serve as one component of the code for many odorants and allow for the discrimination of a large number of different odorants (Kandel, 2000). Binding of odorants to these receptors causes activation of the enzyme adenylate cyclase, which converts adenosine triphosphate (ATP) to cyclic adenine monophosphate (cAMP), cAMP then causes sodium channels to open leading to depolarization of the cell membrane. If the activation is sufficient to cause an action potential, the information from the stimulus will be passed to the central nervous system (CNS).

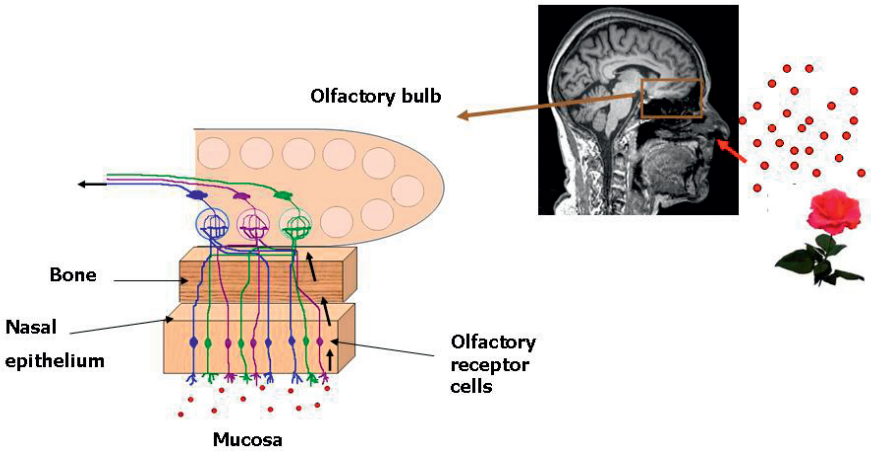


**Figure 1.** The peripheral part of the olfactory system (Figure adapted from Zelano 2005).

The olfactory cells of the epithelium are bipolar neurons which form the olfactory nerve, cranial nerve I. Once the axons leave the olfactory epithelium they collect into 20 or more bundles, and project ipsilaterally, and reach the olfactory bulbs. The olfactory bulbs, one in each hemisphere, are located under the ventral surface of the frontal lobes in the humans and contain around 50 000 mitral cells. Both inhibitory and excitatory processing takes place in the olfactory bulb. The granule cells are inhibitory interneurons, and periglomerular cells are involved in lateral inhibition while the excitation is from the mitral cells. The olfactory bulbs contain small structures called glomeruli where the axons from the olfactory neurons enter. The olfactory bulbs have about 2000 glomeruli each. The input from all neurons expressing the same receptor is collected by a single glomerulus. Axons from second-order neurons in the olfactory bulb form the olfactory tract, which projects directly to the primary olfactory structures in the brain (Hatt, 2004, Paysan and Breer, 2001).

### 1.1.2. The central olfactory system

The olfactory cortex is usually described as part of the allocortex, a cortex which is thinner and structurally less complex, with only three layers, compared to the six layers of the neocortex (Price, 1990). Our understanding of neural processing of olfactory stimuli is primarily based on animal studies (insects and mammals) (Carmichael et al., 1994, Haberly and Price, 1978, Insausti et al., 2002, Price, 1990).The areas receiving direct input from the olfactory bulb are called the primary olfactory cortex or areas (Price, 1990). The primary olfactory cortex encompasses five structures; the anterior olfactory nucleus, the olfactory tubercle (in humans this is an area perforated with blood vessels and is called SPA), the piriform cortex, parts of the amygdaloid complex (including periamygdaloid cortex and the anterior cortical nucleus of the amygdala), and the rostral part of entorhinal cortex. All of the structures mentioned above (except the olfactory tubercle) project back to the olfactory bulb. These primary olfactory cortical structures have several intra-cortical connections with each other (See Figure 2). The connections for piriform cortex, the amygdaloid complex and entorhinal cortex will be described below.

The piriform cortex is well defined in humans (Hummel et al., 2009, Zelano et al., 2005), and is part of the allocortex. The piriform cortex is the primary target of projections from the olfactory bulb (Kay and Freeman, 1998), and the anterior piriform cortex receives the majority of the direct projections from the olfactory bulbs. Piriform cortex also receives input from the orbitofrontal cortex, insula, basal forebrain, brainstem, thalamus and hypothalamus (Haberly and Price, 1978, Kowianski et al., 1999). The piriform cortex is a three-layered allocortical structure, where Layer I contains the dendrites from the pyramidal cells, and receives axonal endings from the lateral olfactory tract (Hawkes, 2009). Studies in rats indicate that Layer II contains tightly arranged pyramidal cell bodies, while Layer III contains more dispersed pyramidal cell bodies (Haberly and Price, 1978). Inhibitory interneurons are also found in Layer I and III. The piriform cortex is divided into a posterior (temporal) and anterior (frontal) part which have been found to have different specialized functions (Gottfried et al., 2006, Howard et al., 2009, Li et al.,

2006, Li et al., 2008). Further projections from the piriform cortex go to the secondary olfactory structures including hypothalamus, orbitofrontal cortex, insula, and the medial dorsal nucleus of the thalamus (Gottfried et al., 2006, Howard et al., 2009).

The amygdaloid complex lies rostral to the hippocampus, and contains three functional subdivisions. The anterior cortical nucleus of the amygdaloid complex, and the periamygdaloid cortex are part of the corticomedial nuclei and receive direct projections from the olfactory bulbs (Price, 1990). The periamygdaloid cortex and the anterior cortical nucleus project back to the piriform cortex, and also to secondary olfactory structures; insula, the basal ganglia, thalamus, hypothalamus and orbitofrontal cortex (Doty, 2003, Gottfried et al., 2002, Kowianski et al., 1999, Wyss, 1981).

The primary olfactory region in the rostral (anterior) entorhinal cortex receives direct projections from the olfactory bulbs (Amaral et al., 1987, Insausti et al., 2002, Price, 1990). Entorhinal cortex has intra-connections (whether these connections are reciprocal projections are unknown) with the other primary olfactory regions, including the amygdala, olfactory tubercle and anterior olfactory nucleus (Kowianski et al., 1999, Wyss, 1981). The olfactory information passes so to the anterior part of the hippocampus with direct projections from entorhinal cortex (Insausti et al., 2002).

The primary olfactory cortex projects to secondary olfactory structures, for example hippocampus, orbitofrontal cortex, insula and thalamus. A network of structures outside the core regions are often involved, determined by the nature of the olfactory task (Dade et al., 1998, Savic et al., 2000, Savic, 2002). Hippocampus is one of the secondary olfactory structures, and receives strong afferent input from the entorhinal cortex (Insausti et al., 2002). Both CA1 and the subiculum project back to the entorhinal cortex. Further details concerning the connections of the secondary olfactory structures are not described here, please see (Amaral et al.,

1987, Gottfried et al., 2006, Howard et al., 2009, Insausti et al., 2002, Insausti et al., 1987, Price, 1990).

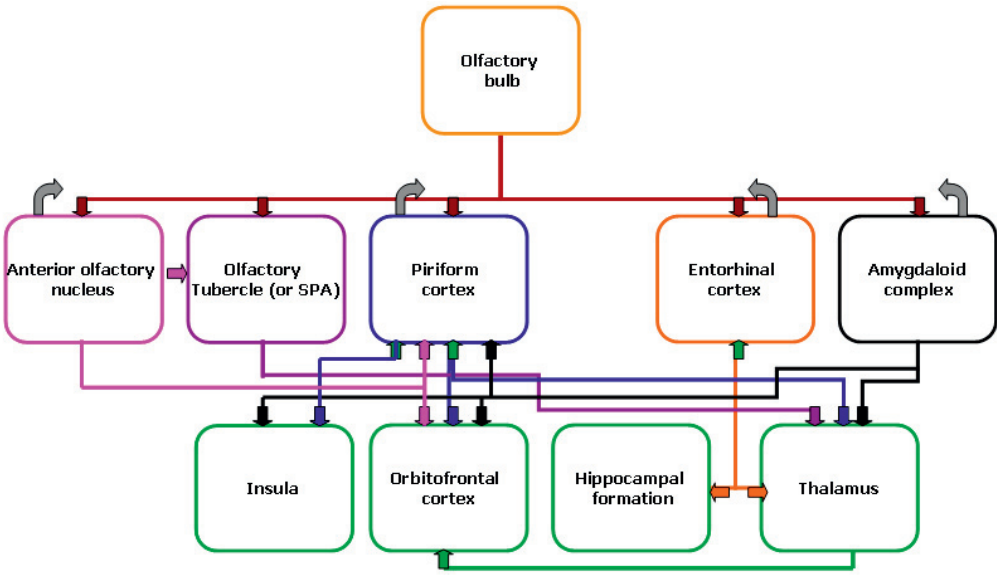


**Figure 2.** Central connections of the olfactory system (adapted from Zelano and Sobel 2005). The red arrows are projections from the olfactory bulb to the primary olfactory cortices, and the grey arrows are reciprocal connections to the olfactory bulb. Each primary olfactory cortical structure has a uniqe box and arrow color. The secondary olfactory structures are color-coded as green boxes. Green arrows indicate reciprocal connections from secondary to primary olfactory structures, or to other secondary structures.

### 1.1.3. Neuroimaging of olfactory function

Evidence from imaging studies has also elucidated the anatomy of human olfaction. Zatorre and colleagues were the first to demonstrate odorant-induced activity in the piriform cortex in humans, and in 1994 Koizuka and colleagues did the same with functional magnetic resonance imaging (fMRI) (Koizuka et al., 1994, Zatorre et al., 1992). Zatorre et al. (1992) investigated whole brain activation following odor

stimulation in 11 healthy subjects. The results from the PET-imaging were bilateral activation of piriform cortex, right orbitofrontal cortex, bilaterally insula and medial frontal cortices. Koizuka and colleagues obtained a significant increase in cerebral blood flow in the piriform cortex, orbitofrontal cortex, and inferior medial frontal lobe during odor stimulation (Koizuka et al., 1994). Since these pioneer studies, the olfactory structures have been mapped in humans with imaging methods, with more or less success.

The areas most often activated during passive smelling tasks are called the olfactory core regions (Savic, 2002). In general, activated areas observed with neuroimaging methods vary, perhaps caused by the use of different odors and odor tasks. Neuroimaging (fMRI and PET) of passive smelling of odors shows activation of the piriform cortex (Bengtsson et al., 2001, Gottfried et al., 2006, Howard et al., 2009, Savic et al., 2000, Zatorre et al., 1992, Zelano et al., 2005), amygdala (Royet et al., 2000, Savic et al., 2000, Zald and Pardo, 1997), orbitofrontal cortex (Bengtsson et al., 2001, Savic et al., 2000, Zald and Pardo, 1997, Zatorre et al., 1992), insular cortex (Bengtsson et al., 2001, Savic et al., 2000, Zatorre et al., 1992), and the anterior olfactory nucleus (Sobel et al., 1998).

Savic and colleagues reported further that odor induced brain activity depends on the nature of the specific odor task, whether or not a more widely distributed network of brain regions located outside the olfactory core regions also becomes engaged (Dade et al., 1998, Savic et al., 2000, Savic, 2002). Other brain-structures often activated during olfactory tasks are thalamus (Savic et al., 2000, Sobel et al., 2000), cingulate cortex (Savic et al., 2000; 2002), and cerebellum (Ferdon and Murphy, 2003, Savic, 2002). Imaging evidence describing the role of piriform cortex, entorhinal cortex and hippocampus in olfactory function will be outlined in the following section.

The anterior piriform cortex is considered to be involved in encoding of odorant structure (Gottfried et al., 2006). The posterior piriform cortex on the other hand, encodes the unique identity of an olfactory percept, and seems to have learning-induced neural plasticity (Gottfried et al., 2006, Howard et al., 2009). Humans are

exposed to odors continuously, but are able to select the odors that are most important and requring attention. Zelano and colleagues reported attention-dependent and attention-independent sub-regions (frontal and temporal part) in the piriform cortex (Zelano et al., 2005). Odorless sniffing has also been demonstrated to activate primary as well as secondary olfactory structures (Kareken et al., 2004, Simonyan et al., 2007, Sobel et al., 1998), and is often reported to lead to piriform cortical activity (Kareken et al., 2004, Koritnik et al., 2009, Sobel et al., 1998), but seldom in entorhinal cortex (Koritnik et al., 2009).

Relatively few of the olfactory neuroimaging studies have reported activation of the entorhinal cortex during olfactory tasks (Poellinger et al., 2001, Sobel et al., 1998, Suzuki et al., 2001, Wang et al., 2005, Zald and Pardo, 2000, Zatorre et al., 1992). In humans, olfactory input projects to the limited part of the anterior entorhinal cortex (Brewer, 2006), which may explain the weak or often lacking activation of entorhinal cortex in imaging studies.

The olfactory system is the sensory system with the most direct access to the hippocampus. Several studies of olfaction, using a wide variety of odorants and tasks have reported hippocampal activity, but lateralization and location along the anterior-posterior axis of the hippocampus varies (Bengtsson et al., 2001, Cerf-Ducastel and Murphy, 2001, Levy et al., 1997, Poellinger et al., 2001, Small et al., 1997, Tabert et al., 2007, Zald and Pardo, 2000, Zatorre et al., 2000). It is suggested that the hippocampus at the longitudinal axis (anterior to posterior) has functional differentiation (Small, 2002), the posterior part receiving the input from the visual cortex, while the olfactory input projects to the anterior part (Brewer, 2006, Small, 2002).

Neuroimaging evidence for OI more specifically, will be discussed in section 1.2.

## *1.2. Odor identification (OI)*

OI is a higher order odor function usually defined as the ability to name an odor. Johnson and colleagues suggested another definition of OI as the ability to identify the odor by any means, i.e. just to know what it is and not necessarily label it (Jonsson et al., 2005). OI involves both sensory and cognitive functions, and consists mainly of three processes. Firstly, OI requires a certain degree of olfactory sensitivity to detect the odor. Secondly, accurate recognition of the odorant is necessary (Doty, 2005), and lastly a search through semantic stores for the appropriate verbal label is required in order to name the odorant (Dempsey and Stevenson, 2002). Thus, at a conscious, perceptual level we perceive a holistic odor object based on the information from these combined processes (Wilson, 2006).

OI is categorized under semantic memory, but also rely on episodic memory. These are two types of declarative memory, supporting conscious recollection of the past and depend on the integrity of the medial temporal lobe (MTL) (Squire and Zola-Morgan, 1991). Episodic memory refers to memory for personally experienced events and experiences (Tulving, 1983), and semantic memory refers to the capacity for recollecting facts and our general knowledge about the world. OI relies on semantic memory, since the task depends on previously learned odor-name associations and successful retrieval of these associations (Murphy et al., 1997, Oberg et al., 2002). A more recently study also showed that semantic memory contributed significantly on OI performance in healthy individuals (Hedner et al., 2010). However, the semantic representation of odors is considered to depend not only on verbalization, but also on the context the odor occurred in, and here episodic memory comes in. In 1890 William James noted that "every perception is an acquired perception", and was referring to the odor object perception which is formed into a percept influenced by past experience, context, attention and expectation (Wilson, 2006). Thus odors are believed to be organized in an associative network in terms of the episodes that they relate to in an individual's past (Engen, 1987, Herz, 2003). In addition, behavioural studies indicate significant interactions between OI, semantic knowledge, odor

memory and verbalization (Larsson, 1997, Murphy et al., 1991, Perkins and Cook, 1990, Royet et al., 2004).

Humans are in general good at detecting odors and can discriminate between tens of thousands of odors (Doty, 1992). On the other hand, naming odors spontaneously is a very difficult task (Schab, 1991). In an un-cued OI task, a person with a normal sense of smell is seldom able to identify familiar odors in >50 % of the cases (Engen, 1987, Jonsson and Olsson, 2003). Often people are able to smell an odor and recognize it as familiar, but are still unable to produce a specific verbal label. This is described as the `tip of the nose phenomenon´ (Lawless and Engen, 1977). Typically, when given the name of the odor afterwords, the odor is recognized immediately (Lawless and Engen, 1977). Why humans perform so poorly in OI tasks could be caused by the way olfactory information is stored in the brain. It is thought that the odor percept is stored in the brain as a holistic percept, which seems to rely on several structures in the brain as well as the peripheral part of the olfactory system. Olfactory testing of the most famous patient in neuroscience, Henry Gustav Molaison or H.M., in the 1980s gives important information with regard to the brain structures supporting OI (Eichenbaum et al., 1983). Patient H.M. underwent bilateral resection of the anterior hippocampi, amygdalae, and entorhinal cortices due to intractable seizures, and became impaired in discriminating between different odor qualities as well as OI, while his ability to discriminate odor intensity remained intact (Eichenbaum et al., 1983).

Below, the role of amygdala, hippocampus and entorhinal cortex in OI will be highlighted based on evidence from studies in animals, neuroimaging and brain autopsies in humans.

Amygdala is often activated in olfactory tasks, and is one of the olfactory core regions receiving direct projections from the olfactory bulb. Studies report that the amygdala responds to odor intensity (Anderson et al., 2003) and valence (Zald and Pardo, 1997), as well as memory (components of smell). Furthermore, amygdala plays a role in the emotional processing of olfactory stimuli. A Positron Emission

Tomography (PET) study has shown that aversive odors activate the amygdala (Zald and Pardo, 2000). However, as far as we know, no evidence supports a specific role of amydala in OI.

Historically, in the early 1900's Broca and Edinger traced direct connections of the olfactory tract into the hippocampus, though later this result was rejected (Brodal, 1947). However, the shortest pathway from a sensory organ to the hippocampus, measured in number of synapses, is found for olfaction. Imaging evidence suggests that the hippocampus is specifically involved in higher level processing of olfactory information (Staubli et al., 1984). Wilson and colleagues demonstrated that early OI deficits related to AD pathology are correlated with the number of tangles in entorhinal cortex and hippocampus (Wilson et al., 2007). However, no imaging studies of OI have reported activation in the entorhinal cortex yet. Evidence for the role of hippocampus in OI is also sparse. However, one study has reported increased activation in right hippocampus during OI in healthy elderly individuals (Suzuki et al., 2001), and another study reported activation in the subiculum, part of the hippocampal formation, in young healthy females during discrimination of odor quality (Savic et al., 2000). Murphy et al. 2003 demonstrated that left hippocampal volume loss was correlated with poorer OI ability in patients with AD (Figure 2) (Murphy et al., 2003), and they assumed a left hemispheric superiority for verbally mediated olfactory tasks (Murphy et al., 2003). However, a structural Magnetic Resonance Imaging (MRI) study showed a relationship between OI function in hippocampus bilaterally (Lojkowska et al., 2011). Lojkowska and colleagues showed in Mild Cognitive Impairment (MCI) patients (Figure 1) that there was a correlation between progressing deterioration in cognitive function, OI and decreased volume of the hippocampus (Lojkowska et al., 2011).

The hippocampus is well known to be particularly important for encoding, retrieving and associating information from all the senses. Some studies have reported that the hippocampal region is important for both episodic and semantic memory (Manns et al., 2003, Squire and Zola, 1998). However, the majority of studies report that it is mainly episodic memory which relies on the hippocampal region, and not semantic

memory (Nadel and Moscovitch, 1997, Reilly, 2001, Tulving and Markowitsch, 1998). Semantic processing is reported to be located in the posterior temporal lobe and ventrolateral prefrontal cortex (Badre et al., 2005, Binder et al., 2009, Bookheimer, 2002, Gough et al., 2005, Thompson-Schill et al., 1998, Wig et al., 2005), and Brocas area`s (Muller et al., 2003). Activation of areas relating to semantic processing is also found in OI imaging studies (Kareken et al., 2003).

## *Box 1: Dementia and Mild Cognitive Impairment (MCI)*

### Dementia

Dementia is an "umbrella" term for a set of symptoms including loss of memory, mood changes, and problems with communication and reasoning, caused by various diseases and conditions that results in damaged brain cells or connections between brain cells. When making a diagnosis of dementia, the DSM-IV or ICD-10 criteria are used [1]. To meet these criteria the cognitive impairment should be of such a degree that it leads to dysfunction in activities of daily living. Another criterion is that the person in question should have changed his/her behaviour.

AD is the most common cause of dementia and the most frequently occurring neurodegenerative disease. Estimates from 2006 report that 65 000 persons in Norway suffer from dementia and that about 10 000 new patients become demented every year [2]. If the number of elderly continues to increase, there is likely to be a doubling of the number of patients with dementia by the year 2040 [3].

### Mild Cognitive Impairment

The concept of mild cognitive impairment (MCI) has evolved to describe the transitional state between normal cognitive function and dementia [4], and the cognitive deficit is not severe enough to meet the criteria for dementia [5]. To use the term cognitive impairment should not lead to dysfunction in activities of daily living.

MCI has been distinguished into several subgroups, the most common being amnestic MCI (aMCI) characterized by memory deficits and complaints [6]. In 2011 a new concept was suggested, "MCI due to AD" to describe those symptomatic but non-demented individuals whose primary underlying pathophysiology is similar as in AD [7].

Having MCI is a risk for developing AD [8]. Persons with memory impairment, for instance subjects with aMCI, have an annual risk of progression to AD of 10-15 %, i.e. in five years about 50 % of all aMCI individuals have developed dementia [8,9].

In MCI patients the reduction in structural brain volume seems to be moderate compared to AD patients [10]. A reduction in overall volume in entorhinal cortex and hippocampus in MCI shows moderate to strong association with conversion to AD [11,12,13,14].

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## *Box 2: Alzheimer's Disease (AD)*

**Alzheimer`s Disease**

Alzheimer's disease (AD) is the most common neurodegenerative disorder in humans, and is the major cause of dementia in the elderly population. It is a progressive and degenerative illness that leads to death, and it is characterized clinically by a gradual onset and progression of memory loss.

Amyloid plaques, neurofibrillary tangles, neurodegeneration and inflammation are well-established hallmarks of AD. Neurofibrillary tangles are composed of paired helical filaments of hyperphosphorylated tau protein, whereas the main protein component of senile plaques is β–amyloid. Amyloid deposition occurs early, and is part of the earliest changes to take place in the development of AD [1].

According to NINCDS-ADRDA criteria of AD a pathological diagnosis is possible only at autopsy, and this are the criteria most frequently used for the diagnosis of AD [2].The NINCDS-ADRDA criteria classify AD based on degree of certainty and whether AD is associated with other disease processes. However, in 2011 the National Institute on Aging and the Alzheimer´s Association recommended new criteria to identify the disease also at a preclinical stages of AD [3]. To date, these criteria are only recommended for research purposes.

The pattern of neurodegeneration seen in early AD using structural MRI is similar to the progression of neurofibrillary pathology which usually begins and is ultimately most severe in MTL [1,4], particularly the anterior part of the entorhinal cortex and hippocampus [5,6]. Later (i.e. when subjects are in the clinical MCI phase), the disease spreads to the basal temporal lobe and paralimbic cortical areas such as the posterior cingulate gyrus and precuneus.

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## *1.3. Olfactory dysfunction*

Olfactory dysfunction can be caused by peripheral or central damage to the olfactory system. Anosmia is the total loss of olfactory function. This is a state with an inability to perceive odors, and can be either temporary or permanent. It is possible to be anosmic to one specific odor, this is called specific anosmia. Hyposmia, is a decreased ability to smell, on the other side is hyperosmia an increased ability to smell. Other technical terms to describe olfactory dysfunction exist, but we use the terms hyposmia and anosmia in the text. About 5 % of the general population is estimated to have no sense of smell (anosmia), and about 20 % of the general population has impaired olfactory function (hyposmia) (Bramerson et al., 2004, Landis et al., 2004, Murphy et al., 2002).

However, the majority of anosmia or hyposmia cases in the clinic are caused by upper respiratory infections (Jafek et al., 1990), head trauma (Doty et al., 1997b) nasal and sinus disease (Doty and Mishra, 2001), including nasal surgery, tumors in the nose and the most can be expected to reflect significant damage to the olfactory epithelium (Deems et al., 1991, Mott and Leopold, 1991).

Olfactory dysfunction can arise from a variety of reasons, and aging is the main risk factor for olfactory deficits. Further, olfactory deficits have been documented in psychiatric diseases like schizophrenia (Atanasova et al., 2008, Moberg et al., 1997b), anorexia and bullemia nervosa, alcoholic/drug addiction and major depression (Atanasova et al., 2008, Moberg et al., 1999, Zucco and Bollini, 2011). Olfactory deficits have also been reported for groups of patients with epilepsy (West and Doty, 1995), Autism Spectrum Disorders, Attention Deficit Hyperactivity Disorder, Obessive-compulsive disorders (Barnett et al., 1999, Segalas et al., 2011), multiple sclerosis (Doty et al., 1997a; 2003, Hawkes, 2003, Kovacs, 2004) and tumors in the brain and also vascular dementia (Gray et al., 2001). At last, olfactory dysfunction is common in neurodegenerative diseases, and will be discussed in section 1.3.2.

### 1.3.1. Olfactory dysfunction in aging

Aging is the most important factor affecting human olfactory function. After the age of 80 years above 60 % of individuals have marked dysfunction in olfactory abilities (Doty et al., 1984, Murphy et al., 2002, Zanni, 2005). Doty and colleagues suggested the decline starts at about 55 years of age, but a more recent study showed that a reduction starts as early as at 36 years of age (Doty et al., 1984, Hawkes, 2006). The reduced olfactory abilities can be found across several olfactory domains, including OI (Doty, 1984, Larsson et al., 2004). The aging effect is demonstrated in un-cued OI tests (Larsson and Backman, 1997), and in multiple choice tasks where possible odor names are available (Larsson et al., 1999).

Several reasons may cause the olfactory dysfunction seen in aging (Boyce and Shone, 2006, Seiberling and Conley, 2004), and effects of aging may occur at all levels of the olfactory system. Some of the main factors involved in age-related olfactory decline are described below. Firstly, the olfactory epithelium is damaged during life by environmental factors like toxins, viruses, bacteria and pollutants. Age-related deficits caused by such environmental factors have been seen in mice, and lead to decreased epithelial thickness, and decreased numbers of olfactory receptors and glomeruli (Hinds and McNelly, 1981, Rosli et al., 1999). Secondly, both the fibres in the olfactory bulb and the number of olfactory receptors decrease with age (Doty, 1984). And thirdly, age-related changes in the CNS may affect processing of olfactory input in primary and secondary olfactory regions. For instance, the histopathological characteristics of AD, neurofibrillarily tangles and amyloid plaques, can be expressed in cognitively normal elderly (Davis et al., 1999, Schmitt et al., 2000). Abnormal numbers of neurofibrillary tangles have been demonstrated particularly in the parahippocampal gyrus and hippocampus of healthy elderly people (Kovacs, 2004, Price, 1990). Wilson and colleagues showed that there is an association between OI ability and number of tangles in the entorhinal cortex and CA1/subiculum areas of the hippocampus in old age, but not in other cortical sites (Wilson et al., 2007). Neuroimaging studies show reduced activation in piriform and amygdalar region and orbitofrontal cortex in the elderly compared to younger adults (Cerf-Ducastel and

Murphy, 2003, Wang et al., 2005). Moreover, general brain atrophy, particularly in frontal and temporal lobe, is common in the elderly (Drachman, 2006), and will affect the function of these cortical regions.

### 1.3.2. Olfactory dysfunction in neurodegeneration

In the mid 1970s Ansari and Johnson, and Waldton, were the first to report that the ability to smell is compromised in neurodegenerative diseases (Ansari and Johnson, 1975, Waldton, 1974). Most neurodegenerative diseases appear to have some degree of olfactory dysfunction, though exactly which function is compromised varies according to which part of the olfactory system is affected. Moreover, the debut of the reduced olfactory ability varies.

The main neurodegenerative diseases where olfactory functions are affected are AD (Devanand et al., 2000, Koss et al., 1988, Murphy et al., 1990, Serby et al., 1991), Parkinson's disease (PD) (Haehner et al., 2011) and Huntington's disease (Moberg and Doty, 1997). Reduced olfactory function is also reported in patients with Down's syndrome (Nijjar and Murphy, 2002) and the Lewy Body variant of AD (Olichney et al., 2005). A study investigating PD patients showed that a motor-impairment in sniffing contributed to the early olfactory deficits in PD (Sobel et al., 2001). The results from a meta-analysis including 80 studies of AD and PD patients, reported that PD patients are more impaired on low-level perceptual olfactory tasks, whereas AD patients are more strongly impaired on higher-order olfactory tasks involving specific cognitive processes (Rahayel et al., 2012).

The patterns of neurodegeneration in AD and PD follow different trajectories and localizations, and it is not clear if the neuropathological abnormalities occur first in peripheral or in the central olfactory systems (Hawkes et al., 1999, Mesholam et al., 1998, Serby, 1987). According to Braak and colleagues, neurofibrillary tangles occur initially in the trans-entorhinal region between the hippocampus and the entorhinal cortex in AD (Braak and Braak, 1992). Other findings, though, suggest that the initial

pathology appears in peripheral olfactory structures (Kovacs et al., 2001, Price et al., 1991).

### 1.3.3. Olfactory dysfunction in MCI

Studies have shown that patients with MCI perform worse on OI tests and discrimination tests compared to healthy controls (Devanand et al., 2000, Eibenstein et al., 2005, Wang et al., 2002). Devanand and colleagues reported a significant difference in performance on the University of Pensylvannia Smell Identification Test (UP-SIT) between non-MCI and aMCI individuals (Devanand et al., 2010). This may indicate that the OI-test could have a predictive utility in separating persons with no MCI from those with MCI and AD (Devanand et al., 2010). However, other studies could not confirm the findings of Devanand et al. Westervelt and colleagues investigated OI abilities in different MCI subgroups, and found no differences in OI performance between the subgroups using the B-SIT (Westervelt et al., 2008). Two longitudinal studies have been conducted to evaluate the usefulness of OI tests as a predictor of conversion from MCI to dementia/AD. Devanand and colleagues found that OI in patients with MCI predicted AD at follow up (Devanand et al., 2000), but Bahar-Fuchs and colleagues failed to find such a statistically significant relationship (Bahar-Fuchs et al., 2010). A review by Sun and colleagues published in 2012 claimed the need for more longitudinal cohort studies to evaluate the usefulness of OI tests in predicting MCI to AD conversion (Sun et al., 2012).

Other studies have shown that by combining olfactory testing with neuropsychological tests and structural MRI (Devanand et al., 2008, Lojkowska et al., 2011), the prediction of conversion from MCI to dementia or AD can be improved. Lojkowska and colleagues showed that neuropsychological tests combined with OI tests improved the prediction of conversion from MCI to dementia (Lojkowska et al., 2011). They used a set of seven neuropsychological tests, and calculated a sum score, Cognitive Functions Index, for a general cognitive performance based on this. They also showed that by using the follow up data from two different time points, a

reduction in hippocampal volume, in addition to neuropsychological tests and OI tests, further increased prediction accuracy (Lojkowska et al., 2011). Devanand and colleagues reported that a combination of an OI test, hippocampal and entorhinal cortex volume, plus selective reminding test and questionnaire on functioning, predict conversion to AD, when patients were followed at six month intervals in a three year follow up study (Devanand et al., 2008).

### 1.3.4. Olfactory dysfunction in AD

In 1987 Rezek described olfactory deficits as a neurological sign in AD (Rezek, 1987), and since then many studies have shown that olfactory impairment is very common in AD, and that AD patients perform worse at olfactory tests than both healthy controls and MCI patients (Murphy et al., 2003, Steinbach et al., 2010, Westervelt et al., 2008). The olfactory dysfunction in AD is reported to affect the detection threshold, discrimination, olfactory memory and OI (Arnold et al., 1998, Serby et al., 1991, Wilson et al., 2007, Wilson et al., 2009). In particular, dysfunction in OI seems to occur at a very early stage, and many studies indicate that the first observed odor deficit is indeed related to OI, and not the ability to detect odors (Christen-Zaech et al., 2003, Hedner et al., 2010, Larsson et al., 2000, Nordin et al., 1997, Rahayel et al., 2012, Serby et al., 1991). The deficits in olfactory function may occur prior to the advent of typical cognitive deficits and behavioural disturbances in AD (Bacon et al., 1998, Devanand et al., 2000, Graves et al., 1999).

It has been widely debated whether the earliest pathological changes in AD related to olfactory dysfunction occur in the olfactory epithelium, bulb, or more central MTL and/or other higher order structures in the brain. The two major theories that attempt to explain the olfactory loss in AD are the olfactory vector theory, and the degenerative theory. The olfactory vector theory is based on environmental agents, which are considered to enter the brain via the olfactory mucosa, and subsequently cause damage to the neuronal cells (Doty, 2008). Based on this theory the damaging toxins do not mainly cause damage to the epithelium, but also use this route to

reach the brain (Youngentob et al., 2001). The olfactory system has the shortest pathway from a sensory organ (in this case epithelium) to the MTL, measured in the number of synapses. However, in general the olfactory vector theory lacks evidence and support.

The degenerative theory of olfactory dysfunction in AD is based on the earliest pathological changes being found in the MTL (Braak and Braak, 1992, Devanand et al., 2012). Early neurodegeneration in entorhinal cortex and hippocampus will lead to specific impairment of functions relying heavily on these structures. Testing of such functions will hence be particularly sensitive indicators of the earliest stages of the disease. According to this theory, olfactory tasks with greater cognitive components should challenge the system most effectively, and thus have greatest sensitivity for detection of AD (Iqbal, 2001).

Abnormal changes have been observed in the olfactory epithelium in patients with probable AD (Tabaton et al., 1991, Talamo et al., 1989). Amyloid-beta and paired helical filament -tau occur early and severely in brain regions sub serving olfaction, and also in the olfactory epithelium (Arnold et al., 2010). Amyloid and neurofibrillary tangles are also found in the olfactory bulbs in AD (Kovacs et al., 2001). In addition, neurofibrillary tangles are observed in the anterior olfactory nucleus of some AD patients even before neurodegenerative changes can be seen in entorhinal cortex (Kovacs et al. 2001). Thomann et al. 2009 carried out MRI studies, and showed a reduction in size of the olfactory bulb and tract in the early stages of AD (Thomann et al., 2009a, Thomann et al., 2009b). Olfactory bulbs are reduced in size in persons with olfactory loss compared to healthy people (Haehner et al., 2008). This is also seen in elderly compared to younger people who do not complain of any loss of olfactory sense (Yousem et al., 1998), as well as in patients with AD (Thomann et al., 2009b).

Few studies have investigated the olfactory deficits in patients with AD using imaging methods. However, recent new studies using functional magnetic resonance imaging (fMRI), PET and structural MRI have been published (Bahar-Fuchs et al., 2010,

Forster et al., 2010, Kareken et al., 2001, Murphy et al., 2003, Wang et al., 2010). One study demonstrated fMRI to be sensitive to changes in olfactory function due to AD. Blood oxygen level-dependent (BOLD) signals in the primary olfactory cortex, hippocampus, and insula regions were markedly reduced in AD patients compared to healthy control subjects of similar age (Wang et al., 2010). A PET study reported a positive association between OI scores and odor-induced activity in the right piriform cortex, though this was in a combined group of AD patients and healthy controls, and the sample size was small (8 patients and 8 controls) (Kareken et al., 2001). In a Fludeoxyglucose, 18F (FDG) PET study of different olfactory domains (OI, odor discrimination and threshold) performed in patients with early AD, the OI scores correlated with the normalized FDG uptake in clusters with peaks in the right superior parietal lobe, fusiform gyrus, inferior frontal gyrus and preuncus (Forster et al., 2010). Another study used Pittsburg Compound B (PIB) PET-scanning, and an OI task in 24 persons with aMCI, 20 AD patients and 19 controls. The OI scores and PiB binding differentiated aMCI and controls clearly, but no differences in OI scores between aMCI patients who where PIB-positive and those who where PiB-negative were found (Bahar-Fuchs et al., 2010).

The role of olfactory event-related potentials (oERPs) is considered useful in the diagnosis of AD (Morgan and Murphy, 2002). However the results from research studies using oERPs generated in the medial temporal cortex is contradictory (Kettenmann et al., 1997). In one study about half of the patients with AD or MCI had a normal response to olfactory stimulation (Peters et al., 2003), whereas in another study, changes in oERPs latency measures resulted in a 100 % correct classification of AD (Morgan and Murphy, 2002).

## 2.0. Methods

Methods used to investigate the aims of the thesis were new advanced MRI-based techniques; fMRI (Paper III) and structural MRI (Paper IV), in combination with psychophysical tests (Paper I, II, and IV).

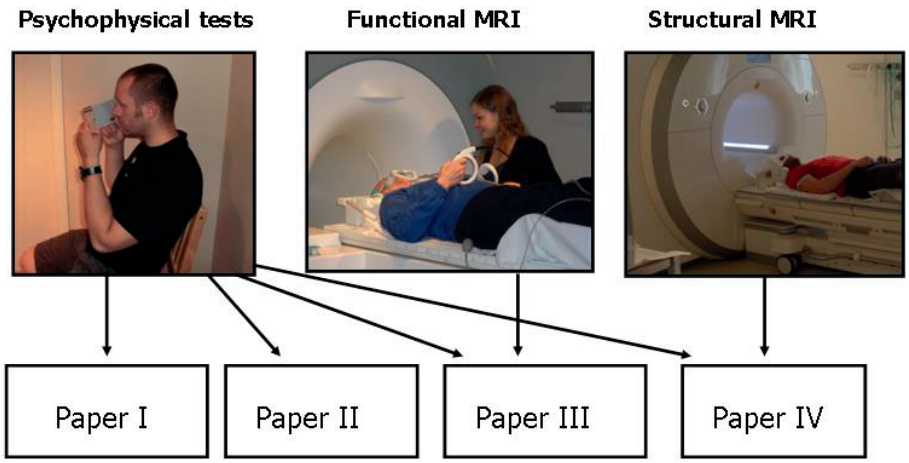


**Figure 3.** A schematic representation of the methods used in the thesis.

### *2.1. Psychophysical tests*

Psychophysical tests are standardized methods to assess olfactory function in patients with olfactory loss, and may help us obtain objective evaluation of the olfactory performance. Various types of test have been developed for use in different cultural regions to assess domains of olfactory function (Eibenstein et al., 2005).

OI tests can be divided into three groups based on how they are organized: 1) spontaneous or un-cued OI tests, 2) yes/no identification tests and 3) multiple choice tests (Hawkes, 2009). In naming tests no alternatives are given, while for the yes/no identification tests the subjects are asked questions like "does this smell like a

banana?". The multiple choice tests are the most common, and consist of a number of commonly known odors that the participants are instructed to name after being presented with alternatives to choose between (i.e. forced multiple choice; usually with four odors). The multiple choice tests are often based on "scratch and sniff" techniques. The University of Pennsylvania Smell Identification Test (UPSIT) is one of the most widely used smell tests in the world and is produced in the USA by Sensonic Inc. (Doty et al., 1984). The UPSIT consists of 40 "scratch and sniff" odorants. B-SIT (also known as CC-SIT) is a short validated version of the UPSIT, originally made for self-evaluation of olfactory function (Doty et al., 1996, Sensonic Inc., Haddon Heights, USA). B-SIT is a 12-item, four choice, "scratch and sniff" test, and the odorants are placed on strips embedded in 10-50 µm ureaformaldehyde polymer microcapsules, and released when the strips are scratched with a special pencil. The odorants included in the test are cinnamon, turpentine, lemon, smoke, chocolate, rose, paint thinner, banana, pineapple, gasoline, soap and onion. Each correctly identified odor receives one point, thus giving a possible score of 0-12 points with the B-SIT.

Sniffin Sticks Test is a European product by the Burghart Company, and is a battery including the Sniffin Sticks Odor Identification Test (SSIT), Threshold test and the Sniffin Sticks Discrimination Test (SSDT) (Hummel et al., 1997, Kobal et al., 1996). Also a 12-item screening version has been developed (SSSIT) (Hummel et al., 2001). Sniffin Sticks are felt-tip pens filled with an odorant, where removal of the caps releases the odors. The pen is held approximately two centimetres in front of the nostrils. SSIT contains 16 single sticks and a multiple choice task, where a list of four descriptors is presented. The sticks contain familiar odors such as orange, leather, cinnamon, peppermint, banana, lemon, liquorice, garlic, coffee, apple, clove, pineapple, rose, aniseed and fish. For the SSIT part of the test, subjects need to select one of the four items presented both in writing and orally, which best describe the odor. The SSDT consists of 16 triplets, where two pens have the same smell, while one of the three pens contains a different odor. The subjects are asked to identify the pen with the different odor, and are blindfolded during the task because the pens are color-coded. In SSIT and SSDT, correctly-identified odors receive one

point, giving a possible score range of 0-16 for both SSIT and SSDT. The B-SIT and SSIT are commercial olfactory screening tools developed for use in different countries (Doty et al., 1996, Hummel et al., 1997, Kobal et al., 1996), but are not successfully validated cross-culturally (Kobal et al., 1996, Hummel et al., 1997, Hummel et al., 2007). Therefore many local variants have been developed. The B-SIT test has been translated into various languages (Swedish, Danish, Dutch, English, German, Greek, Chinese and Turkish), and in some cases odor-changed because they vary across cultures (Sensonics.com). For the SSIT, many local variants have been developed (England, Australia, Greece, Italy, Holland, Sri Lanka, Brazil and Taiwan) (Konstantinidis et al., 2008, Neumann et al., 2012, Shu and Yuan, 2008, Yuan et al., 2010). The local variants produced have been modified in a manner which includes translation, and in some cases the odor-items changed and/or different distractors included. A ten-item version of the B-SIT was developed, specially design to evaluate AD patients, called B-SIT A (Tabert et al., 2005). Furthermore, "Taste strips" from the Burghart Company (Burghart Messetechnik GmbH, Wedel, Germany) constitute a validated taste test (Landis et al., 2009), where subjects have to identify one taste at a time from a list of five descriptors, i.e. sweet, sour, salty, bitter and "nothing to taste" (multiple five-choice).

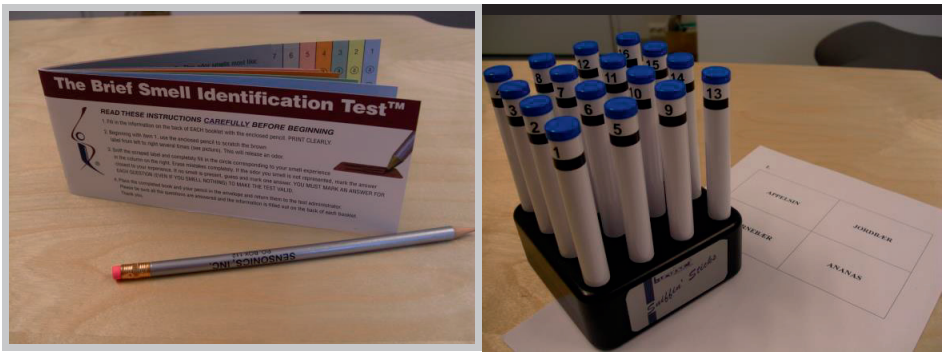


**Figure 4.** The psychophysical tests for measuring OI used in this thesis were SSIT (right side) in study III and IV and B-SIT (left side) in study I, II, III and IV.

## *2.2. Magnetic Resonance Imaging (MRI)*

MRI is often divided into structural MRI and fMRI. MRI uses strong magnetic fields and radio waves to create images of biological tissue. The static magnetic field created by an MRI scanner is expressed in units of Tesla. The magnetic field inside the scanner affects the properties of nuclei of certain atoms with uneven mass number, and a significant magnetic moment. MRI is based on signals from hydrogen nuclei which are abundant in fat and water in the human body. Nerve cells, for example, are relatively rich in water, whereas the fatty coating around the nerve fibers and cells, called myelin, has less.

A hydrogen nucleus consists of a single proton that spins around its own axis. The spinning inducing a magnetic field with a certain direction and size, called the magnetic moment, which induces the type of signal that is detected by MRI scanners. When a person is inside the powerful magnetic field of the scanner, the average magnetic moment of many protons becomes aligned parallel with the direction of the field (Bo), in order to maintain a low energy state, or equilibrium. During image acquisition, a radiofrequency (RF) pulse is turned on, the energy of the RF pulse is absorbed by the hydrogen nuclei, and the total amount of magnetic moment is flipped into the transverse plane. When the RF pulse is turned off, the spins of the protons return to their low energy state or equilibrium, and the magnetization becomes re-aligned with static magnetic field. Several relaxation processes occur (e.g. T1 recovery, T2 decay) and at different rates in different types of tissue, and this RF signal can be measured with receiver coils in the MRI-scanner and constitutes the basis of the different types of MR contrasts.

### 2.2.1. Structural MRI

Measuring atrophy in AD with structural MRI is a powerful biomarker (Vemuri and Jack, 2010), and structural MRI was used to obtain volumetric measurements of

brain structures in Paper IV. Whole brain structural MRI scans were acquired on a Siemens 3.0 Tesla Trio MRI-scanner and a 12 channel head coil at St.Olavs Hospital. A T1-weighted 3D-scan was obtained with sagittal acquisition and repetition time (TR) =2300 ms and echo time (TE) =2.94 ms and 256 scans. The structural volume data were analyzed using NeuroQuant (CorTechs Labs Inc., CA, USA) which performs an anatomical segmentation and volumetric measurement of brain structures (http://www.cortechs.net/index.php) (Brewer, 2009). Several structures were estimated, but in the present context only the brain structures most relevant for AD, and considered to be involved in olfaction were included; total volume of hemispheric white matter, cortical grey matter, thalamus, hippocampus, amygdala, and the ventricular space. The volume of each structure was calculated as a percentage of the overall intracranial volume.

### 2.2.2. Functional MRI

fMRI is a non-invasive method for indirectly observing neural activity, based on hemodynamic responses to neural activity. The principle of fMRI imaging is to take a series of images of the brain in quick succession and statistically analyze the images for differences among them. Ogawa and his colleagues demonstrated that gradient echo (i.e.T2*-weighted) MRI signals are sensitive to the level of blood oxygenation in the brain, and this phenomena was called blood oxygen level-dependent (BOLD) contrast (Ogawa et al., 1990).

The physiological basis of the method depends on the relationship between neuronal and vascular processing. The activated neuronal cells need energy (in the form of ATP), from oxidative metabolism, which requires oxygen provided by oxygenated hemoglobin in the red blood cells in the surrounding capillaries. The hemoglobin has varying magnetic susceptibility depending on the presence of the oxygen. Without attached oxygen, the resulting deoxygenated hemoglobin is paramagnetic, while oxygenated hemoglobin is diamagnetic (See figure 5, A) (Ogawa et al., 1990).

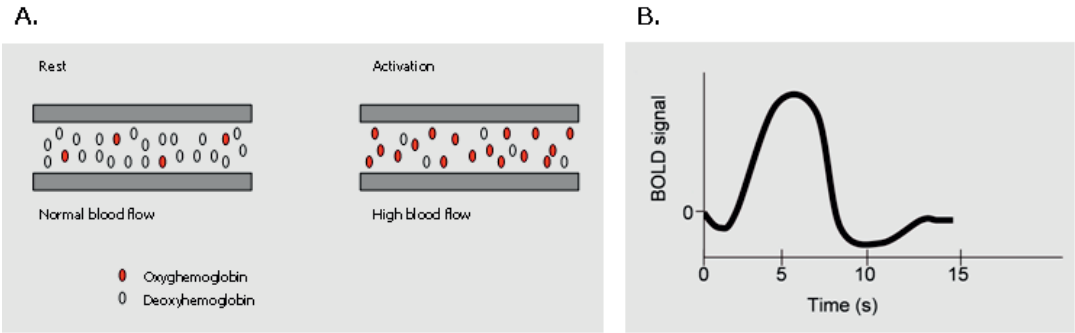


**Figure 5.** A. Illustration of the difference in concentration of deoxygenated hemoglobin (grey) and oxygenated hemoglobin (red) in a resting and activated state. B. The Hemodynamic Response Function (HRF).

When neural activity increases, the blood flow will also increase within 1-2 seconds after the beginning of activity, and reaches its maximum amplitude after about 4-6 seconds. BOLD fMRI thus measures a correlate of neural activity, the hemodynamic response, HRF, see Figure 5, B. The HRF is the change in MRI signal on T2* images following local neuronal activity. The hemodynamic response results from a decrease in the amount of deoxygenated hemoglobin present within a voxel (Huettel, 2004). After the HRF, a poststimulus undershoot occurs where the BOLD signal is below the baseline (see Figure 5, B). The cause of this undershoot is still a matter of debate (Buxton, 2012), but may be a result of a reduced arteriolar and capillary blood flow, and increased venous blood volume (Huettel, 2004). The exact relationship between the hemodynamic responses and the underlying neural activity remains to be elucidated (Attwell and Iadecola, 2002). However, it has been shown that the BOLD signal reflects neural activity and in particular local synaptic processing (Logothetis et al., 2001, Viswanathan and Freeman, 2007).

In order to capture changes in the BOLD signal, fast imaging sequences like Echo Plannar Imaging (EPI) are necessary (Poustchi-Amin et al., 2001). However, the use of EPI has certain costs. Its main limitation is the magnetic field inhomogeneity in regions of the brain close to bone and air-filled sinuses, i.e. susceptibility artefact (Gorno-Tempini et al., 2002, Ojemann et al., 1997). In particular, this is a problem

for imaging the MTL and the areas involved in olfactory function, and signal loss may appear for these regions. In addition, the BOLD signal from the MTL and other deep brain structures is lower due to coil effects (Kaza et al., 2011).

### 2.2.3. Olfactometer

fMRI provides a way of observing the active brain while participants solve different cognitive tasks or are exposed to specific stimuli (Krause et al., 2006). MRI can be used to produce activation maps showing which parts of the brain are involved in a particular mental process. For olfactory functional studies, MRI-compatible systems to deliver odors to the subjects are required. For this project two olfactometers were built, one manually-controlled olfactometer used in Paper III, and one automatically-controlled olfactometer used in an fMRI experiment not included in this thesis.

The manually-controlled olfactometer consisted of three glass chambers, one filled with water and two with odorants, and a mechanical switch box to regulate airflow through the individual chambers. The olfactometer was built by the Medical Technical Department at St. Olav's Hospital. The design allowed administration of multiple odors by replacing the glass chambers filled with odorants. This was possible due to the long odor-free breaks in the fMRI-paradigm. Medical air flowing at a rate of 15 l/min was passed through the olfactometer, allowing the odors to be released from the liquids. From the chambers odors were conveyed via Teflon tubing to a nasal mask (Respironics, ScanMed AS, Norway). Task instructions with regard to odor presentation, duration and switching were coordinated by E-Prime (Psychology Software Tools, Pennsylvanina, USA), and displayed to the experimenter on an LCD screen in the scanner room.

The MR-compatible automatically-controlled olfactometer was designed by an engineer at the Norwegian University of Science and Technology (NTNU). Background information from other studies and laboratories for building inexpensive MR-compatible olfactometers was compiled by members of the fMRI group and a

sketch of the olfactometer served as a basis for the engineer's design. This olfactometer consisted of 14 glass chambers for liquids, and from these chambers odors were conveyed via Teflon tubing to a nasal mask (Respironics, ScanMed, AS, Norway). The odor presentation sequence, i.e. timing, duration and order of presentation was programmed with the olfactometer. The olfactometer is started by the experimenter using a remote control exactly at the time of initation of task instructions and fMRI scanning.

In order to remove odors and also ensure the movement of air past the subject's nostrils, a hole at the superior end of the mask was made and connected to the hospital`s gas evacuation system. All tubings were made of very low absorbent material (Teflon Fluorinated Ethylene Propylene), to avoid absorption of odor molecules into the tubes (Vigouroux et al., 2005). Task instructions concerning the operation of the automatically-controlled olfactometer by the experimenter were used in E-Prime (Psychology Software Tools, Pennsylvanina, USA). The experimenter viewed the task instructions on the computer-screen in the scanner room. Responses from volunteers were recorded using response buttons (NordicNeuroLab AS, Bergen, Norway). Both button use and reaction times were logged in E-prime. The subjects were told not to sniff, but to breathe regularly throughout the entire experiment, and to let the air pass over and into the nose. Each odorant was presented for 10.4 seconds to ensure that at least one breathing cycle was completed within the stimulus duration. A behavioural experiment was carried out to measure respiration rate and depth of respiration during presentation of identified and non-identified odors. Respiration rate and depth were measured with a respiration-belt connected to Powerlab (AD Instruments Pty Ltd. Unit 13, 22 Lexington Drive, Bella Vista, NSW 2153, Australia).

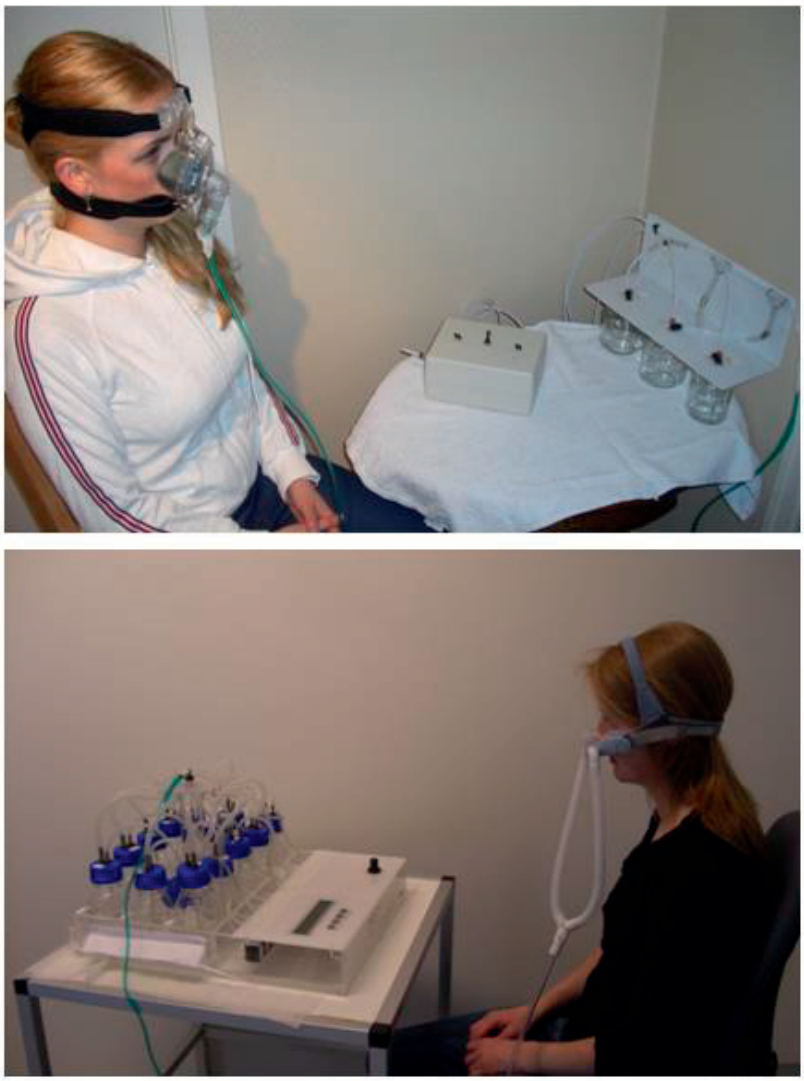

**Figure 6.** Images of the two olfactometers produced for this project. The manually-controlled olfactometer used in study III is shown in the upper image. The automatically-controlled olfactometer is shown in the lower image and was used in an fMRI experiment not included in this thesis.

## 3.0. Aims

This thesis had three main aims. The first aim was to investigate the feasibility of using commercially available olfactory screening tools in Norwegian cohorts (B-SIT, as well as a modified version of B-SIT, and SSIT). The second aim was to explore the neuronal correlates of OI in the healthy human brain. The third aim was to identify the anatomical brain substrates underlying OI abilities in patients with aMCI and early dementia in AD.

Four studies were performed, each targeting different aspects of the aims.

1. Are B-SIT and SSIT suitable tests for separating patients with AD, early dementia in AD, and aMCI from healthy controls in Norwegian cohorts, and could a modified version of B-SIT by introduction of a placebo be a more appropriate approach to study OI, in particular in a general population? (Study I, II and IV)

2. Which human brain structures engender successful OI? (Study III and IV)

3. How are the OI abilities in patients with aMCI and early dementia in AD related to volumes of brain structures, and performance on cognitive tests? (Study IV)

# 4.0. Summary of papers

## *4.1. Paper I*

*Use of the Brief Smell Identification Test for olfactory deficits in a Norwegian population with Alzheimer's disease*.

The purpose of this paper was to further our knowledge of the the validity of the B-SIT in distinguishing patients with AD from healthy controls in a Norwegian cohort.

The study included 39 patients with a diagnosis of AD according to the NINCDS-ADRDA criteria, and 52 gender and age-matched controls, healthy relative to their age. The ability to identify odors was tested with B-SIT and a non-standardized OI-task (freshly ground coffee).

The results from the study showed a highly significant difference in OI measured by B-SIT between patients with AD diagnosis and controls. The results showed an optimal cut-off point of ≥8 of B-SIT score for the AD patients group, with sensitivity of 79 % and specificity of 92 % for distinguishing between AD and healthy controls. Turpentine was the odor with the lowest score for any of the items in the test, correctly identified by only 21.2 % of the controls and 23.1 % of the AD patients (chance level).

To conclude, the B-SIT test appears to be well-suited for use in a Norwegian cohort. This study showed that the B-SIT test could detect deficits in OI among patients with AD and healthy controls, in a Norwegian setting.

## *4.2. Paper II*

*Modification of the Brief Smell Identification Test by introduction of a placebo.*

As awareness increases among the population that reductions in olfaction are associated with neurodegenerative diseases, it may be necessary to introduce an odourless placebo test, so the subjects do not actually know whether they cannot smell, or whether there is nothing to smell. Previous studies showed turpentine to be an odor not generally recognized in Norway, were only 21 % of the healthy controls (Paper I), and 37.5 % of the healthy young subjects (Paper III) identified turpentine.

Seventy-one elderly individuals, healthy for their age, were recruited from a sub-study of the third Nord-Trøndelag Health Study (HUNT3). Participants were warned that there might be nothing to smell prior to olfactory testing. They were blindfolded before being given the modified B-SIT where one item (turpentine) had been replaced with a placebo, and one odor alternative answer to three other items was replaced by the alternative "none/other" (actual odor unchanged).

The replacement of the item "turpentine" with a placebo resulted in a significantly improved score for the item (53.5 %) compared to a previous study ($p<0.0005$) (Paper I). There was no overall difference in the median or mean score achieved by the cohort compared to results obtained previously using the conventional B-SIT.

To conclude, it is possible to introduce the concept that there may be "nothing to smell" to the B-SIT without compromising the test for healthy control individuals. Introduction of a placebo and the alternatives "none/other" seem to be a more appropriate approach for olfactory testing in healthy subjects and patients with neurodegenerative diseases.

## *4.3. Paper III*

*The human brain representation of odor identification.*

The utility of OI tests as a clinical tool depends on a better understanding of the neuronal processes underlying OI. The main aim of the present study was to directly compare the neuronal correlates to identified odors versus non-identified odors in the human brain to understand the neurobiology of OI, as this is increasingly being used as a sensitive marker for neurodegenerative diseases such as AD.

We included 17 females with normal olfactory function in the study. All participants underwent an fMRI experiment with post-scanning assessment of spontaneous un-cued OI. Post scan assessment also included testing with B-SIT and SSIT. Analysis was done to compare spontaneously identified versus non-identified odors at a whole brain level, as well as in ROIs (anatomical and functional) in the medial temporal lobe. Parameter estimate values and BOLD signal curves were obtained from the functional ROI`s in central olfactory structures. The number of activated voxels and maximum parameter estimate values were obtained from anatomical ROIs in the hippocampus and the entorhinal cortex.

At the whole brain level, correct OI gave rise to increased activity in left entorhinal cortex, and secondary olfactory structures including orbitofrontal cortex. In entorhinal cortex and hippocampus, the BOLD signal increased specifically in response to identified odors and decreased for non-identified odors. Episodic as well as semantic memory systems appeared to support OI.

The study demonstrated clearly that brain activity in relation to spontaneous OI is distinct from non-identified odors, and also differs from activity during passive smelling. The results support a specific role for entorhinal cortex and hippocampus in OI.

## *4.4. Paper IV*

*Odor identification and brain structural MRI volume in MCI and early dementia in Alzheimer's disease.*

In Paper I we found that a minority of the patients with AD still had a relatively intact OI function, although the majority of these patients had reduced OI function. A prospective follow-up study of patients with a diagnosis of aMCI or early dementia in AD was designed, with the aim to understand the anatomical substrates underlying deficits in OI performance. Other aims were to explore the relationship between OI function and volumetric and cognitive measures in healthy elderly individuals, compared to patients with aMCI and early dementia in AD with intact and reduced OI abilities.

12 patients with a diagnosis of aMCI, and six with early dementia in AD were included from the Memory Clinic at St. Olavs Hospital. In addition, 30 controls were included from the Trondheim area. All participants were evaluated with three psychophysical tests; B-SIT, SSIT and SSDT. In addition, a taste test was used as well as cognitive tests. Brain structural volume data was recorded from all participants and blood samples were collected for ApoE-genotyping. The overall group of patients was divided into two subgroups based on their OI abilities, according to the performance on B-SIT and SSIT.

The baseline B-SIT score did not differentiate patients with MCI from those with early AD at baseline ($p>0.4$), but prospectively a significant difference in B-SIT scores at baseline was found between patients with stable MCI 6-8 months later, and those that had progressed to an early stage of dementia in AD (t-test, $p = 0.037$). Hippocampal volume was significantly reduced in the impaired OI group compared to the intact OI group, when subgroups were divided based on both OI-tests used in this study. To conclude, the results suggest that patients with aMCI and early dementia in AD can be subgrouped into "intact" and "impaired" OI groups based on simple olfactory tests, and that sub divisions help distinguish those with a more advanced development of AD.

# 5.0. Discussion

The overall aim of this doctoral thesis was to investigate the feasibility of using commercial olfactory screening tools in Norwegian cohorts, and to explore the neuronal correlates and anatomical brain substrates of OI in healthy young and older adults, and patients with aMCI and early dementia in AD.

## *5.1. The use of olfactory screening tools in Norway*

In the clinic OI tests are increasingly used in addition to neuropsychological testing, for the diagnosis of neurodegenerative diseases like AD and PD (Wolfenberger, 1999). The present work (Study I, II and IV) shows that B-SIT and SSIT both demonstrated a highly significant difference in olfactory performance between patients with an AD diagnosis and controls, early dementia in AD and controls, and aMCI compared to controls. Furthermore, both B-SIT and SSIT had high sensitivity (SS) and specificity (SP) for use in Norwegian cohorts (Paper I, II and IV). B-SIT showed even greater discrimination between AD patients and controls than a previous study (Suzuki et al., 2004). SSIT showed a moderate sensitivity compared to another study using the same cut-off (cut-off ≤8, SS 96.4 %, SP 78.1 %) (Miyamoto et al., 2010), however the SS and SP are more or less similar to what others report for SSIT in other cohorts (Boesveldt et al., 2008, Konstantinidis et al., 2008, Shu and Yuan, 2008, Yuan et al., 2010). This verifies that there is comparable SS and SP for both B-SIT and SSIT in Norway, as found in other countries worldwide.

Norms have been developed both for B-SIT (Doty, 2001) and SSIT (Hummel et al., 2007), for distinguishing between subjects with normal and abnormal OI function. Still, there is no consensus for a specific cut-off value that distinguishes AD patients with impaired OI function from healthy age and sex-matched subjects. Therefore, we used cut-off scores based on results from previous studies in AD and healthy elderly people, with B-SIT (Westervelt et al., 2007) and SSIT (Boesveldt et al., 2008) (Paper IV). In paper IV, using a cut-off of 7, B-SIT showed SS of 86 % and SP of 82 %,

while SSIT, using a cut-off of 8, also showed high SS and SP (83 % and 82 %, respectively). Since a cut-off for B-SIT of 7 was used (7 items of total 12, is 58 %), the cut off for SSIT should perhaps have been 9 (9 items of total 16, giving 56 %) for the cut-offs to be similar. In fact the accuracy of SSIT scarcely changed when the cut-off was raised to 9 of 16 items, giving an SS of 83 % and SP of 82 %. Results from the present work show that there are weak effects on SS and SP depending on where the cut-off is set.

The combined group of patients with aMCI and early dementia in AD showed a mean OI score of 6.6 points for B-SIT (Paper IV), while the AD patients showed a mean score of 6 points (Paper I). This latter result is in line with the B-SIT score for AD patients in another study (Westervelt et al., 2008), but a higher score than reported in a Japanese population (Suzuki et al., 2004). There was no large age difference between the patients with AD in our study I compared to Suzuki et al., but the mean score on MMSE (19.6) was lower in Suzuki et al. compared to the AD patients in Study I (mean score on MMSE 23). More severely affected cognitive abilities may have been a contributing factor leading to lower B-SIT scores.

Compared to previous studies of MCI patients (Tabert et al., 2005, Westervelt et al., 2008, Wang et al., 2002), the B-SIT score in Paper IV was rather low. In a study based on 10 odors, a mean score 9.6 was found in a group of MCI patients (Tabert et al., 2005). The MCI patients in this study had a mean score on MMSE of 27.3, compared to a mean score of 25.5 on MMSE in our study IV, which may explain the better performance on B-SIT for the patients in Tabert et al. Since both aMCI patients and patients with an early stage of dementia in AD were included, the mean performance in Paper IV may be lower than in an exclusive MCI group as used in the other studies (Tabert et al., 2005, Wang et al., 2002, Westervelt et al., 2008). Many of the patients in Study IV converted to AD within the 6-18 months follow up. However, when separating patients with aMCI at baseline (n=12), from the patients with early dementia in AD (Study IV), the mean score on B-SIT was 6.9 in the pure aMCI group, which is in line with previous studies (Wang et al., 2002, Westervelt et al., 2008).

In Paper IV we subdivided the patients according to B-SIT and SSIT scores into "intact" or "impaired" OI function. More patients were considered "intact" by SSIT than by B-SIT (Paper IV). However, everyone considered "intact" by B-SIT was also considered so according to SSIT scores. There was a strong positive correlation between B-SIT and SSIT scores, both in patients with early AD and aMCI, and in the control group (Paper IV). Another study comparing B-SIT, Sniffin Sticks (including the SSIT) and the European Test of Olfactory Capabilities (ETOC), found a correspondence between all the tests. All the tests separated subjects with normal and abnormal olfactory function significantly (Koskinen et al., 2004). However, when olfactory function was categorized by Sniffin Sticks (entire test), 36 out of 48 categorized as anosmic, hyposmic or without loss of smell based on B-SIT, where similar to those achieved by Sniffin Sticks (Koskinen et al., 2004). This may be caused by some patients being on the border between what can be considered "intact" and "impaired" OI according to a given test in both studies.

OI tests were found to have comparable ability to distinguish between healthy controls and patients with aMCI or AD in Norway as in other countries, and therefore seem to be well adapted for use here. Yet some restrictions were found both for SSIT and B-SIT. Correct identification is possible only if the individuals have had previous experience of the odor presented, and using relevant tests adapted to the culture of the study population is important. Neumann and colleagues reported a lack of familiarity in the British cohort for the item turpentine (Neumann et al., 2012). This is in line with our findings, for SSIT in study IV, and B-SIT in all of our studies. Turpentine was the odor-item most seldom identified in controls in all our studies using B-SIT, (21.2 %, 37.5 %, 25 % correctly identified in Paper I, Paper III and Paper IV, respectively). In paper I and IV the patients were older, which may explain the slightly better performance in the young subjects in Paper III, compared to the older groups in Papers I and IV.

In Paper II we replaced turpentine with a placebo, which resulted in a significantly improved score for the item (53.3%) compared to previous study, Paper I

($p<0.0005$). In the development of the B-SIT version (or CC-SIT), the most familiar odors in several countries were selected from UP-SIT (Doty et al., 1996). In a Swedish population (n= 96), a study item analysis on the difficulty of the UP-SIT items was performed (Doty et al., 1996, Sandmark et al., 1989). In Sweden most of the UP-SIT items were correctly identified by 90 % or more of the population, including the item turpentine, which was correctly identified by 88.68 %. The recognition pf turpentine in Sweden was thus much better than in our Norwegian cohorts. Turpentine seems not to be a common everyday odor among Norwegians. Despite the modification of item two (Study II), it was still the item with the lowest number of correct answers. However, we believe this may caused by the faint odor that is carried by the paper in new B-SIT booklets.

Turpentine is also an odor item in SSIT, but in this test turpentine was correctly identified by 67.4 % of the healthy controls (Paper IV). The distractors of turpentine in SSIT were mustard (0%), rubber (13 %) and menthol (19.6 % answered this). The distractors for turpentine in B-SIT were soap, dog and black pepper. The other differences observed between B-SIT and SSIT were based on how the odors are presented. The odor presentation in B-SIT may depend on how the experimenter scratches the booklet, while in SSIT the odors are released when removing the cap of the pen, and the latter presentation is thus similar each time. Olfactory performance may therefore be affected by the alternatives in a given test, odor familiarity, and how the odors are released in the test.

OI tests appear to have several benefits as a screening tool in patients with AD. Firstly, the administration of the tests is simple and easy to perform. Secondly, OI tests take only a few minutes. The latter is especially important for patients with AD who have a reduced time window of short-term memory. The alternatives in OI tests for each odor were given orally twice; before smelling the odor and afterwords, for both patients and controls. However, the AD or MCI patients reduced memory function could have affected their choice, and they may have more often chosen from the two last alternatives. However, the results from Paper I demonstrated that patients with AD did not choose from the last two test alternatives more often than

the first two. Thirdly, OI tests are inexpensive, and this is important because of cost-constraints in clinical practice. Another important aspect is that the use of standardized tests e.g. SSIT and BSIT, gives the opportunity of comparing results with previous research across countries. We are in collaboration with the company producing B-SIT (Sensonics Company) to develop a Norwegian version based on the present work (work in progress). The B-SIT was claimed to be a self-administrative test by the company when first produced (Doty et al., 1996). However, in my opinion this is not an optimal way for testing patients with neurodegenerative diseases such as AD. On the other hand, I believe that OI tests are well-suited for use both by general practitioners and in specialized clinics.

### 5.1.1. Ethical considerations regarding the use of OI tests as screening tools for neurodegenerative disease

Paper II highlights the ethical challenges connected with the use of olfactory testing for screening in a general population. Since olfactory impairments are common in the elderly, and might predict cognitive decline and AD, such information might potentially spread uneasiness in the elderly population and their relatives. Individuals who believe that they or their loved ones have a poor sense of smell may equate this with insipient dementia. In Paper II, we investigated a modified B-SIT version by introduction of a placebo to see if this could be a more appropriate approach for testing olfaction in large samples.

Introducing the alternative "none/other" to an odorless placebo has several benefits. Firstly, this modification allows the experimenter to introduce the concept that there might be nothing to smell to the test-subject. Secondly, such a modification reduces expectation that every odor task will be a true odor. Thirdly, this allowed us to remove the item turpentine identified by very few Norwegians in study I. We believe that a psychophysical test like B-SIT should ideally provide information and answers for the tester rather than for the test subject, and an olfactory test where the subjects have no particular expectation of odors would hence be preferable.

An increasing number of healthy controls will probably be included in OI research in coming years due to the focus on olfaction and AD. The volunteers in study II were not participating in a research study involving an increased risk or presence of a neurodegenerative disease. Rather, they wanted to contribute to a sub-study of HUNT3. In addition, there are no treatment options for MCI/AD, and early detection is not associated with better prognosis at present. Based on our findings the modified version in Paper II may be a more acceptable approach to olfactory testing.

## *5.2. Approaches to successful OI*

Previous findings claim that neuronal correlates of odor processing are task-dependent (Dade et al., 1998, Savic et al., 2000, Savic, 2002). The analysis of whole brain activation during passive smelling, showed bilateral activation in piriform cortex and amygdala in healthy young subjects (Study III). Activation was also observed in orbitofrontal cortex and thalamus bilaterally, and right cingulate gyrus and left insula. Many of these structures are reported to be olfactory core regions (Dade et al., 1998, Savic, 2002, Savic et al., 2000). In addition, smaller clusters were reported in for example cerebellum, superior frontal gyrus, precentral gyrus, paracingulate gyrus and right putamen. In the present work, the OI analysis reported activation in some of the same structures as in passive smelling, including both primary and secondary olfactory areas, as well as in a number of other cortical regions. However the precise localization of the activity within these regions varied. Significantly increased activity was found bilaterally in orbitofrontal cortex, thalamus, insula, putamen, visual cortex (VA BA17), premotor cortex, secondary somatosensory cortex and cerebellum. Right cingulate gyrus and right pallidum were also more active for identified odors. In addition, many different structures were activated in the left hemisphere, see Paper III. The finding that OI activated unique regions as well as regions found in passive smelling, supports the hypothesis that olfactory information is processed by a network of brain regions, and that the nature of the olfactory task determines which additional brain regions are recruited (Dade et al., 1998, Savic et al., 2000, Savic, 2002).

The results from Paper III demonstrated an increased activity in left entorhinal cortex in the within-subject whole brain analysis. In addition, significant differences in the parameter estimate values between identified and non-identified odors in the functional entorhinal ROI, as well as the very high number of activated voxels and maximum parameter estimate value in the anatomical entorhinal region of interest (ROI) were found. This is the first imaging study of OI to report increased activation in entorhinal cortex (Kareken et al., 2003, Savic et al., 2000, Suzuki et al., 2001). This may be due to the use of very different olfactory tasks and odors in previous studies. However, some studies support the role of entorhinal cortex in OI (Eichenbaum et al., 1983, Wilson et al., 2007). Based on our findings, the entorhinal cortex is specifically involved in OI, and hence damage to this structure will affect OI performance directly as well as also compromise input to the hippocampus, another structure important for both OI and in MCI and AD.

Hippocampal pathology has also been connected with OI deficits (Lojkowska et al., 2011), and the present work supports the hypothesis that the hippcampus is specifically involved in higher level processing of olfactory information (Staubli et al., 1984). The larger number of activated voxels and mean maximum parameter estimate values in the anatomical hippocampal ROI, combined with a positive BOLD signal for identified odors, and a negative BOLD signal for non-identified odors in the functional ROI, further substantiate this claim. Previous research has also reported activation in the right hippocampus during OI tasks (Murphy et al., 2003, Suzuki et al., 2001), and during odor recognition memory (Jones-Gotman and Zatorre, 1993, Zatorre et al., 2000). The role of hippocampus in OI may be related to its role in odor memory function.

MTL is important for both episodic and semantic memory (Manns et al., 2003, Squire and Zola, 1998), but the majority of studies report that episodic memory mainly relies on the hippocampal formation (Nadel and Moscovitch, 1997, Reilly, 2001, Tulving and Markowitsch, 1998). We believe that the hippocampal activation seen in our experiment stems from its role in episodic and semantic memory (discussed in

section 5.2.1.). Episodic memory is involved in OI because odors are strongly connected to the episodes when the odor encoding took place. Recently, an episodic odor memory test (three versions exist) was developed by Professor Maria Larsson and colleagues at Karolinska Institutt, Sweden. This is a modified version of the SSIT. The test includes an encoding phase, and then the odor is presented, intermixed with a number of new odors that were not presented earlier. The test is used in the Swedish National Study on Aging and Care (SNAC), but no study using this test has been published yet. Based on our findings, we believe such a test could be used to elucidate the role of hippocampus in OI. However, such a test may be too difficult to perform for the patients with early AD.

### 5.2.1. OI and semantic memory

OI is typically categorized under semantic memory, since the task depends on previously learned odor-name associations, and successful retrieval of these associations (Murphy et al., 1997, Oberg et al., 2002). In the total group of patients and controls, there was a significant correlation for both B-SIT and SSIT with the stereognosis test, verbal memory (Ten Word Test, total recall and delayed recall) and MMSE (Paper IV). All this tests have a semantic component, supporting the theory that OI relies on semantic memory (Murphy et al., 1997, Oberg et al., 2002) and that better semantic and verbal memory abilities are associated with better OI abilities (Economou, 2003, Larsson et al., 2000).

Reduced OI may sometimes arise from a problem with selecting the correct label from a number of related alternatives. Based on our findings it is clear that test methodology employed for B-SIT and SSIT may affect performance. Unpublished data from Paper IV, investigated the OI mistakes in the SSIT. In healthy controls the most common odors mistaken were lemon (35.5 %), turpentine (32.4%), apple (32.4%) and pineapple (35.5 %) (Unpublished data, Paper IV). These results are very similar to a study from a British population, where lemon, turpentine, apple and cloves were the odors most commonly mistaken (Neumann et al., 2012). These

authors suggested that when the distracter odor names given in the multiple choice task are too similar, then OI becomes more difficult (Doty, 2003). This is nicely exemplified by the odor apple, where the distracters are orange, peach and lemon. The odor in SSIT with the highest OI score on the other hand is fish, correctly identified by 96.7 %, which has the distracters bread, cheese and ham. The use of similar or more distinct distracters has also previously been shown to affect the performance of olfactory tests (Engen, 1987), and another study with more contrasted distracters improved the test results (Gudziol and Hummel, 2009). On the other hand, the difficulty of cued OI increases with the number of verbal cues presented (Negoias et al., 2010), again pointing to how OI performance is influenced by the actual task the participant is performing.

However, B-SIT frequently uses the alternative "fruit", which is a very general term. For example for item 12 (odor onion) the alternatives are chocolate, banana and fruit. Since banana is a fruit, giving an alternative in this manner may be misleading for the person tested. In Paper II we decided to replace all the "fruit" alternatives occurring in B-SIT (three items). These changes did not improve the overall scores on the test, or even the scores on the specific test alternative. Thus there was actually no advantage with the distractor "fruit", except that it was a convenient distractor to replace with "none/other". In my opinion the distracters used in the B-SIT items are in general more different than for SSIT. One example is pineapple; in B-SIT (item 9), the distracters are smoke, whiskey and onion, whereas in SSIT (item 13), the distractors are pear, plum and peach. I believe this is a benefit of the B-SIT test compared to the SSIT.

## *5.3. The role of OI in AD*

Based on the present work, the OI deficit in aMCI and early dementia in AD appears to be of central origin and not due to deficits in odor perception per se. We did not find significant differences between persons with aMCI or early dementia in AD and controls, in the performance of SSDT. However, we did not investigate odor detection abilities, but we observed that "intact" and "impaired OI" groups performed

equally well on the SSDT (paper IV), and this indicates no sensory deficit in these patients. This is in line with previous studies of OI where deficits have been shown to occur in the early stage of the diseases, whereas the ability to detect odors is affected later (Christen-Zaech et al., 2003, Hedner et al., 2010, Larsson et al., 2000, Nordin et al., 1997, Rahayel et al., 2012, Serby et al., 1991). A possible explanation for the relatively intact discrimination abilities seen in our study could be that the patients in study IV were still in an early stage of AD.

It is widely debated whether the earliest pathological changes in AD are related to damage in the peripheral part of the olfactory system, or more central structures of the brain. Many studies have reported significant histological changes in peripheral olfactory structures (Buschhuter et al., 2008, Kovacs et al., 2001, Tabaton et al., 1991, Talamo et al., 1989) in patients with OI dysfunction in AD. However, we did not measure the olfactory bulb volume, but studied the more central structures of the brain. In Study IV, OI performance (based on SSIT and B-SIT) was associated with a significantly reduced volume of hippocampus in patients with aMCI and early dementia in AD. Hippocampal volumes have also been found to correlate significantly with OI performance in previous studies (Lojkowska et al., 2011, Murphy et al., 2003, Smitka et al., 2011), and support a specific role of hippocampus in OI. Thus it may be reasonable to suggest that OI deficits in patient groups result from early MTL changes. Unpublished data support these findings. To investigate the neuronal correlates to OI in neurodegeneration, we conducted a similar fMRI study to that reported in paper III, with the participants in paper IV (18 patients and 29 controls had completed the fMRI experiment). In this study, an automatically-controlled olfactometer was used, and responses were logged according to identified odors or non-identified odors in the fMRI-experiment. Significance was tested at the voxel level $z= 2.3$, and the cluster thresholding at $p<0.05$ (contrast identified odors> non-identified odors). In both patients and controls, the unpublished results show bilateral activation in insula, cingulate gyrus and cerebellum. In addition activation in left amygdala was seen in both patients and controls. Interestingly, no activation was observed in hippocampus or entorhinal cortex during OI in aMCI or AD patients. In healthy elderly individuals, activation was seen in the left entorhinal cortex.

Furthermore, we used a whole brain analysis using voxel based statistics, z=2.3 and p<0.05, uncorrected (contrast identified>non-odors in controls>patients). Activation was seen bilaterally in entorhinal cortex and hippocampus in the healthy elderly (z between 1.7 and 1.9). These findings support that changes in the brain in AD patients can be observed in relation to olfactory function, as shown in other imaging studies (Bahar-Fuchs et al., 2010, Forster et al., 2010, , Kareken et al., 2001, Murphy et al., 2003, Wang et al., 2010). It also supports the changes in MTL in early AD causing OI deficits.

Results from earlier work have demonstrated that the deficits in olfactory function in MCI and AD may occur prior to the advent of typical cognitive dysfunction and behavioral disturbances (Bacon et al., 1998, Devanand et al., 2000, Graves et al., 1999). In the total group of patients and controls in Study IV there was a correlation between general cognition (measured with MMSE), verbal memory (Ten Word Test; total recall and delayed recall) and hippocampal volume, as described in section 5.2.1. No correlation was found between the rey-test (figure copying) and hippocampus. But in the subgroups of patients with "intact" or "impaired" OI, there was no difference in performance on the neuropschychological tests, but a significant difference was seen for the hippocampal volume. Based on this, we concluded that OI ability is a better predictor of hippocampal volume loss in patients with aMCI or early dementia in AD, than the neuropsychological tests used in this study. It is possible that the olfactory modality is more sensitive to changes in hippocampal volumes than input from other modalities, since olfactory input is just a few synapses away from the peripheral sensory organ. Alternatively, the fact that OI draws on both episodic and semantic memory may render it more dependent on the hippocampus. However, these theories are speculations. Unfortunately, we do not have measures for entorhinal cortex, which would have been particular interesting to explore, especially the association between entorhinal thickness/volume and hippocampal volume.

In paper III we reported increased activation during OI in the cortical regions sub serving sensory systems other than olfaction, e.g. primary visual and auditory

cortices, and higher order somatosensory regions. Such activation may represent cortical reinstatement, i.e. activation of cortical regions involved in encoding of specific sensory details during previous experiences with the identified odors (Eldridge et al., 2000, Gottfried et al., 2004, Johnson and Rugg, 2007, Vaidya et al., 2002). Because OI is a complex process, it requires a network of structures in the brain which support specific memories, semantic knowledge, sensory details, earlier experience, feelings, and thoughts about the presented odor. Dependence on such a distributed network of brain regions may render OI particularly vulnerable to neurodegenerative changes. This may imply that OI tests may be tests of disconnection, and not only MTL dysfunction. One method suited to study white matter connections in the brain is Diffusion Tensor Imaging (DTI). In a recent study, significant DTI differences between stable MCI versus progressive MCI subjects were observed. Fractional anisotropy (FA) was significantly higher in controls compared to MCI in networks involving the corpus callosum, right temporal, and frontal pathways (Haller et al., 2010). In our unpublished fMRI data, the BOLD-responses were generally much weaker, and limited to smaller regions in the patients compared to the healthy individuals, as shown in a recent study (Wang et al., 2010). Our findings reflect how OI is dependent on MTL, though an entire network of structures is involved, and damage to this system in AD may cause the OI deficits.

### 5.3.1. The predictive role of OI in AD

In the current setting, the success of an OI test as a screening tool depends on its ability to predict the development of neurodegenerative diseases such as AD. In paper IV we described that the B-SIT score did not differentiate between patients with aMCI and those with early dementia in AD at baseline ($p > 0.4$). However, prospectively after the 6-18 months follow up, a significant difference in B-SIT score was found between patients that progressed to AD compared to those who remained stable in their cognitive functions. These results indicate that a low B-SIT score could be a predictor for more rapid development of AD, detectable even in a small sample. However, similar results were not obtained with SSIT, and this may be caused by the

differences between B-SIT and SSIT discussed in section 5.1. This discrepancy between two OI tests may explain the reported contradictory evidence for the OI tests as predictors for developing AD, where mainly two longitudinal studies have demonstrated OI tests as predictors of conversion from MCI to dementia/AD (Devanand et al., 2000, Lojkowska et al., 2011). These studies used the UP-SIT test, and the SSIT (with presentation of four figures for each smell). Many cross-sectional studies of OI in AD/MCI have been performed, but more longitudinal studies are required to evaluate the value of OI testing as a predictor of conversion to AD.

Earlier studies have suggested a possible clinical relevance of unawareness related to olfactory dysfunction. In paper IV we reported that the study patients had poor insight regarding their OI (k=0.21), which is in agreement with data reported by Nordin et al. and Doty et al. (Doty and Ferguson-Segall, 1987, Nordin et al., 1995), which found unawareness of reduced olfactory function in MCI, early AD and AD patients. In Study IV, no correlation between the diagnosis at 6-18 months follow up, or subjective report of olfactory function in the patients was found, in agreement with previous studies (Bahar-Fuchs et al., 2011, Djordjevic et al., 2008). Conversely, some researchers have claimed that patients with low olfactory scores and reduced awareness of their own OI dysfunction were more likely to develop AD (Devanand et al., 2000, Tabert et al., 2002).

As suggested earlier, olfactory testing together with neuropsychological tests may help to more accurately predict whether or not a patient with MCI will convert to dementia/AD (Devanand et al., 2000, Lojkowska et al., 2011). Our group of patients was too small to use more sophisticated statistical methods to determine the contribution of various OI and neuropsychological tests to predict AD development. However, our findings suggested that OI ability is related more to hippocampal volume loss than the neuropsychological tests used in our study. Since hippocampal volume is a sensitive marker for the risk of developing AD, replication of our findings in larger populations would verify whether OI is a more sensitive marker of hippocampal volume than neuropsychological tests. If so, OI may be a potential

inexpensive and accessible biomarker for hippocampal volume even without MRI measurements.

## *5.4. Methodological considerations*

We used three different types of test to investigate olfactory function; psychophysical tests (Paper I-IV), fMRI (Paper III) and structural MRI (in combination with psychophysical tests) (Paper IV). Methodological issues and challenges with these types of methods are discussed below.

The studies included in this thesis are cross-sectional studies. However, study IV had longitudinal aspects, though the sample size was restricted. For future research, both longitudinal studies and larger samples of patients are required to obtain more knowledge about the olfactory hypotheses in AD.

In Study I, patients with AD diagnosis according to the NINCDS-ADRDA criteria were included (McKhann et al., 1984). In Study IV, patients fulfilling the accepted diagnostic criteria for aMCI (McKhann et al., 1984, Petersen et al., 1999, Winblad et al., 2004) were included. The overall group of patients (both aMCI and early dementia in AD) was divided into two subgroups for further analysis based on their OI abilities according to performance on B-SIT and SSIT (Study IV). In the clinic, it is not easy to clearly differentiate aMCI from early dementia in AD, which is one of the reasons the Dubois research criteria consider aMCI an early expression of AD (Dubois et al., 2007). Neither was there a significant difference in OI performance between the aMCI patients and the patients with early dementia in AD. Therefore, we decided to group the aMCI and early dementia in AD patients together as they probably all represent patients in an early stage of AD and because the sample size was small. However, we can not be sure that all aMCI patients would progress to AD.

In Papers I and II, psychophysical tests were used to measure olfactory function. Olfactory screening tests are developed to be brief and easy. The B-SIT may be

administered in less than 5-6 minutes, but has a lower reliability compared to the UP-SIT (Doty et al., 1996). It is necessary to state that Studies I and II are not a validation of the B-SIT. Study II is rather an example of how a modification of the test can fit the Norwegian population better for research purposes, and possibly for patients with neurodegenerative diseases. Validation of the tests requires studies in larger populations of individuals performing the OI tests.

In Paper III we used fMRI and a home-built olfactometer to measure activity in the brain during OI. There are several challenges to studying olfaction with fMRI. Firstly, odors are not quantifiable, and it is therefore impossible to know whether the subjects were presented with exactly the same amount of perceived stimulus. Also each individual's experiences with an odor may vary based on previous encounters with the odors. Moreover, there is a connection between breathing, sniffing and smelling (Johnson et al., 2006, Mainland and Sobel, 2006).The use of a high-sensitivity measure of nasal airflow (for example pneomatotachograph) could have been used to record sniffing in the fMRI experiment, because sniffing modulates and drives activity through the olfactory system. Furthermore, there was a lack of synchronization between odor onset and respiratory cycle in study III. Inclusion of continuous breathing monitoring and odor presentation at the time of inspiration would have improved the study. However, this was not possible to implement properly with the olfactometer, since the air with the odor was delivered via tubes, and not directly into the nose as in olfactory event-related potentials (oERPs), and there was no feedback connecting respiration and odor delivery.

The benefit of an olfactory fMRI-method is its non-invasive nature, and the opportunity to study neuronal correlates to different types of olfactory tasks in both healthy participants and patient groups. Major challenges in the literature of olfactory studies include large differences in experimental design, including odor selection and number, odor presentation intervals, analysis methods, and scan protocols. Also cultural differences with regard to odor repertoire may play a role. These differences make it difficult to directly compare the results across studies. Another issue in our fMRI results is the use of liberal statistics. It is well known that there are significant

between region differences in the amplitude of the BOLD signal (see e.g. Aguirre et al., 1998, Birn et al., 2001, Handwerker et al., 2004, Miezin et al., 2000), and that BOLD signals from the MTL, and in particular the entorhinal cortex, have lower Z values than for instance in the cortex (Ojemann et al., 1997, Tabert et al., 2007). The reason for this is a complex combination of MRI technical and local anatomical-physiological properties of the entorhinal cortex, and perhaps also related specifically to olfactory stimuli. MR technical issues affecting the BOLD signal in entorhinal activity are linked to a susceptibility artefact (Gorno-Tempini et al., 2002, Ojemann et al., 1997) and coil effects (Kaza et al., 2011).

In paper IV, we used the Software NeuroQuant to perform automatic segmentation of brain structural volumes. Fully automatic segmentation of brain structures has several advantages; it is fast and requires very little manual input (Brewer, 2009). However, such a method may have several weaknesses. Automatic segmentation without manual intervention could lead to more mis-segmentation, and thus inaccurate volume calculation. However, Neuroquant has been compared with expert manual computer-aided segmentation, and the structural volumes from each method were found to correlate significantly with each other (Brewer, 2009). The same study also validated the program´s ability to differentiate between healthy controls and the atrophy of brain structures affected early in AD patients, thus supporting the validity of the volumetric measures in this study. Several studies have used automated segmentation with satisfactory results (Colliot et al., 2008, Chupin et al., 2009). In addition, no measurements of the volume of entorhinal cortex were done, and should be included in further studies of OI.

# 6.0. Conclusions

In this thesis, olfactory function was investigated with imaging methods and neuropsychological tests in Norwegian cohorts.
The main results of the thesis are as follows:

1) Both B-SIT and SSIT are well-suited for use in Norwegian cohorts. Both tests showed a highly significant difference in olfactory performance in OI between patients with AD, patients with aMCI, and patients with early dementia in AD, compared to healthy elderly. Both tests are inexpensive, rapid, and easy to administer in the clinic.

2) Introduction of a placebo and the alternatives "none/other" seem to be a more appropriate approach for olfactory testing in healthy subjects and patients with neurodegenerative diseases. The replacement of the item "turpentine" with a placebo resulted in an improved score for the item in a Norwegian setting.

3) During an OI task activation is seen in a network of structures in the brain, and hippocampus and entorhinal cortex appear to be important for the processing of successful OI in healthy young subjects.

4) aMCI and early dementia in AD patients with impaired OI function have significantly more reduced hippocampal volumes than patients with relatively intact OI function. OI-tests may help distinguish those patients who are more advanced in the development of early AD.

## *6.1. What the future may bring*

When the mechanism of olfactory dysfunction is well-understood and well-established, olfactory deficits can become a useful biomarker to include in a test battery for AD. I believe we need to perform more longitudinal studies, with standardized methods and neuroimaging in a large group of patients with MCI and relatively intact OI function. I believe this is important in understanding why the disease particularly affects olfactory function, and will provide answers to the olfactory hypothesis of OI in AD. I believe that a psychophysical OI test, in addition to structural MRI, will be a promising investigative combination providing useful information about OI deficits in the early phase of the disease.

## 7.0. References


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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

**2000**

158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.

162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

**2001**

178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT

192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

**2002**

201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

**2003**

216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.

217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

**2004**

235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA

244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

**2005**

248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

**2006**

269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT

272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION
279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS
280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
282. Idar Kirkeby-Garstad: CLINICAL PHYSIOLOGY OF EARLY MOBILIZATION AFTER CARDIAC SURGERY
283. Linn Getz: SUSTAINABLE AND RESPONSIBLE PREVENTIVE MEDICINE. CONCEPTUALISING ETHICAL DILEMMAS ARISING FROM CLINICAL IMPLEMENTATION OF ADVANCING MEDICAL TECHNOLOGY
284. Eva Tegnander: DETECTION OF CONGENITAL HEART DEFECTS IN A NON-SELECTED POPULATION OF 42,381 FETUSES
285. Kristin Gabestad Nørsett: GENE EXPRESSION STUDIES IN GASTROINTESTINAL PATHOPHYSIOLOGY AND NEOPLASIA
286. Per Magnus Haram: GENETIC VS. AQUIRED FITNESS: METABOLIC, VASCULAR AND CARDIOMYOCYTE ADAPTATIONS
287. Agneta Johansson: GENERAL RISK FACTORS FOR GAMBLING PROBLEMS AND THE PREVALENCE OF PATHOLOGICAL GAMBLING IN NORWAY
288. Svein Artur Jensen: THE PREVALENCE OF SYMPTOMATIC ARTERIAL DISEASE OF THE LOWER LIMB
289. Charlotte Björk Ingul: QUANITIFICATION OF REGIONAL MYOCARDIAL FUNCTION BY STRAIN RATE AND STRAIN FOR EVALUATION OF CORONARY ARTERY DISEASE. AUTOMATED VERSUS MANUAL ANALYSIS DURING ACUTE MYOCARDIAL INFARCTION AND DOBUTAMINE STRESS ECHOCARDIOGRAPHY
290. Jakob Nakling: RESULTS AND CONSEQUENCES OF ROUTINE ULTRASOUND SCREENING IN PREGNANCY – A GEOGRAPHIC BASED POPULATION STUDY
291. Anne Engum: DEPRESSION AND ANXIETY – THEIR RELATIONS TO THYROID DYSFUNCTION AND DIABETES IN A LARGE EPIDEMIOLOGICAL STUDY
292. Ottar Bjerkeset: ANXIETY AND DEPRESSION IN THE GENERAL POPULATION: RISK FACTORS, INTERVENTION AND OUTCOME – THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
293. Jon Olav Drogset: RESULTS AFTER SURGICAL TREATMENT OF ANTERIOR CRUCIATE LIGAMENT INJURIES – A CLINICAL STUDY
294. Lars Fosse: MECHANICAL BEHAVIOUR OF COMPACTED MORSELLISED BONE – AN EXPERIMENTAL IN VITRO STUDY
295. Gunilla Klensmeden Fosse: MENTAL HEALTH OF PSYCHIATRIC OUTPATIENTS BULLIED IN CHILDHOOD
296. Paul Jarle Mork: MUSCLE ACTIVITY IN WORK AND LEISURE AND ITS ASSOCIATION TO MUSCULOSKELETAL PAIN

297. Björn Stenström: LESSONS FROM RODENTS: I: MECHANISMS OF OBESITY SURGERY – ROLE OF STOMACH. II: CARCINOGENIC EFFECTS OF *HELICOBACTER PYLORI* AND SNUS IN THE STOMACH

**2007**

298. Haakon R. Skogseth: INVASIVE PROPERTIES OF CANCER – A TREATMENT TARGET ? IN VITRO STUDIES IN HUMAN PROSTATE CANCER CELL LINES
299. Janniche Hammer: GLUTAMATE METABOLISM AND CYCLING IN MESIAL TEMPORAL LOBE EPILEPSY
300. May Britt Drugli: YOUNG CHILDREN TREATED BECAUSE OF ODD/CD: CONDUCT PROBLEMS AND SOCIAL COMPETENCIES IN DAY-CARE AND SCHOOL SETTINGS
301. Arne Skjold: MAGNETIC RESONANCE KINETICS OF MANGANESE DIPYRIDOXYL DIPHOSPHATE (MnDPDP) IN HUMAN MYOCARDIUM. STUDIES IN HEALTHY VOLUNTEERS AND IN PATIENTS WITH RECENT MYOCARDIAL INFARCTION
302. Siri Malm: LEFT VENTRICULAR SYSTOLIC FUNCTION AND MYOCARDIAL PERFUSION ASSESSED BY CONTRAST ECHOCARDIOGRAPHY
303. Valentina Maria do Rosario Cabral Iversen: MENTAL HEALTH AND PSYCHOLOGICAL ADAPTATION OF CLINICAL AND NON-CLINICAL MIGRANT GROUPS
304. Lasse Løvstakken: SIGNAL PROCESSING IN DIAGNOSTIC ULTRASOUND: ALGORITHMS FOR REAL-TIME ESTIMATION AND VISUALIZATION OF BLOOD FLOW VELOCITY
305. Elisabeth Olstad: GLUTAMATE AND GABA: MAJOR PLAYERS IN NEURONAL METABOLISM
306. Lilian Leistad: THE ROLE OF CYTOKINES AND PHOSPHOLIPASE $A_2$S IN ARTICULAR CARTILAGE CHONDROCYTES IN RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS
307. Arne Vaaler: EFFECTS OF PSYCHIATRIC INTENSIVE CARE UNIT IN AN ACUTE PSYCIATHRIC WARD
308. Mathias Toft: GENETIC STUDIES OF LRRK2 AND PINK1 IN PARKINSON'S DISEASE
309. Ingrid Løvold Mostad: IMPACT OF DIETARY FAT QUANTITY AND QUALITY IN TYPE 2 DIABETES WITH EMPHASIS ON MARINE N-3 FATTY ACIDS
310. Torill Eidhammer Sjøbakk: MR DETERMINED BRAIN METABOLIC PATTERN IN PATIENTS WITH BRAIN METASTASES AND ADOLESCENTS WITH LOW BIRTH WEIGHT
311. Vidar Beisvåg: PHYSIOLOGICAL GENOMICS OF HEART FAILURE: FROM TECHNOLOGY TO PHYSIOLOGY
312. Olav Magnus Søndenå Fredheim: HEALTH RELATED QUALITY OF LIFE ASSESSMENT AND ASPECTS OF THE CLINICAL PHARMACOLOGY OF METHADONE IN PATIENTS WITH CHRONIC NON-MALIGNANT PAIN
313. Anne Brantberg: FETAL AND PERINATAL IMPLICATIONS OF ANOMALIES IN THE GASTROINTESTINAL TRACT AND THE ABDOMINAL WALL
314. Erik Solligård: GUT LUMINAL MICRODIALYSIS
315. Elin Tollefsen: RESPIRATORY SYMPTOMS IN A COMPREHENSIVE POPULATION BASED STUDY AMONG ADOLESCENTS 13-19 YEARS. YOUNG-HUNT 1995-97 AND 2000-01; THE NORD-TRØNDELAG HEALTH STUDIES (HUNT)
316. Anne-Tove Brenne: GROWTH REGULATION OF MYELOMA CELLS
317. Heidi Knobel: FATIGUE IN CANCER TREATMENT – ASSESSMENT, COURSE AND ETIOLOGY
318. Torbjørn Dahl: CAROTID ARTERY STENOSIS. DIAGNOSTIC AND THERAPEUTIC ASPECTS
319. Inge-Andre Rasmussen jr.: FUNCTIONAL AND DIFFUSION TENSOR MAGNETIC RESONANCE IMAGING IN NEUROSURGICAL PATIENTS
320. Grete Helen Bratberg: PUBERTAL TIMING – ANTECEDENT TO RISK OR RESILIENCE ? EPIDEMIOLOGICAL STUDIES ON GROWTH, MATURATION AND HEALTH RISK BEHAVIOURS; THE YOUNG HUNT STUDY, NORD-TRØNDELAG, NORWAY
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