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Oscillatory brain activity in memory disorders

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ACADEMIC DISSERTATION

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Abstract

Neuronal oscillations are thought to underlie interactions between distinct brain regions required for normal memory functioning. This study aimed at elucidating the neuronal basis of memory abnormalities in neurodegenerative disorders. Magnetoencephalography (MEG) was used to measure oscillatory brain signals in patients with Alzheimer's disease (AD), a neurodegenerative disease causing progressive cognitive decline, and mild cognitive impairment (MCI), a disorder characterized by mild but clinically significant complaints of memory loss without apparent impairment in other cognitive domains. Furthermore, to help interpret our AD/MCI results and to develop more powerful oscillatory MEG paradigms for clinical memory studies, oscillatory neuronal activity underlying declarative memory, the function which is afflicted first in both AD and MCI, was investigated in a group of healthy subjects. An increased temporal-lobe contribution coinciding with parieto-occipital deficits in oscillatory activity was observed in AD patients: sources in the 6–12.5 Hz range were significantly stronger in the parieto-occipital and significantly weaker in the right temporal region in AD patients, as compared to MCI patients and healthy elderly subjects. Further, the auditory steady-state response, thought to represent both evoked and induced activity, was enhanced in AD patients, as compared to controls, possibly reflecting decreased inhibition in auditory processing and deficits in adaptation to repetitive stimulation with low relevance. Finally, the methodological study revealed that successful declarative encoding and retrieval is associated with increases in occipital gamma and right hemisphere theta power in healthy unmedicated subjects. This result suggests that investigation of neuronal oscillations during cognitive performance could potentially be used to investigate declarative memory deficits in AD patients. Taken together, the present results provide an insight on the role of brain oscillatory activity in memory function and memory disorders.

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Contents

List of original publications

This thesis is based on the following publications:

I Osipova D., Ahveninen J., Jensen O., Ylikoski A., Pekkonen E. 2005. Altered generation of spontaneous oscillations in Alzheimer's disease. *Neuroimage* 27: 835–841.

II Osipova D., Rantanen K., Ahveninen J., Ylikoski R., Häppolä O., Strandberg T., Pekkonen E. 2006. Source estimation of spontaneous MEG oscillations in mild cognitive impairment. *Neuroscience Letters* 405: 57–61.

III Osipova D., Ahveninen J., Pekkonen E. 2006. Enhanced magnetic auditory steady-state response in early Alzheimer’s disease. *Clinical Neurophysiology* 117: 1990–1995.

IV Osipova D., Takashima A., Oostenveld R., Fernandez G., Maris E., Jensen O. 2006. Theta and gamma oscillations predict encoding and retrieval of declarative memory. *Journal of Neuroscience* 26: 7523–7531.

The publications are referred to in the text by their roman numerals.

Abbreviations

ACh	acetylcholine
AD	Alzheimers disease
ANOVA	analysis of variance
ASSR	auditory steady-state response
AVLT	Auditory-Verbal Learning Test
BA	Brodmann area
CVLT	California Verbal Learning Test
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
DICS	dynamic imaging of coherent sources
DSM-IV	Diagnostic And Statistical Manual of Mental Disorders, 4^{th} edition
ECD	equivalent current dipole
EEG	electroencephalogram, electroencephalography
ERP	event-related potential
ERF	event-related field
fMRI	functional magnetic resonance imaging
HVLT-R	Hopkins Verbal Learning Test- Revised
ISI	interstimulus interval
MCI	mild cognitive impairment
MEG	magnetoencephalogram,magnetoencephalography
MLR	middle-latency evoked field
MMSE	Mini Mental State Examination
MCE	minimum current estimate
MNE	minimum norm estimate
MRI	magnetic resonance imaging
MTL	medial temporal lobe
NINCDS	National Institute of Neurological and Communicative Disorders and
-ADRDA	Stroke/the Alzheimer's Disease and Related Disorders Association
PET	positron emission tomography
ROI	region of interest
SPECT	single photon emission computerized tomography
SQUID	superconductiong quantum interference device
TFR	time-frequency representation

1 Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline, behavioral disturbances and impairment in daily activities accompanied by appearance of neuritic plaques and neurofibrillary tangles in the brain (Whitehouse et al., 1982; Braak and Braak, 1996).

It is estimated that 1.53 % of the population over 65 years has AD (Preston, 1986), and the prevalence of AD increases with age reaching 30% or more between 80 and 85 years (Rocca et al., 1991). Thus AD is and will continue to be a substantial economic problem in Western countries. The most prominent clinical feature of AD is a progressive episodic memory decline combined with impairment in at least one other cognitive domain (such as e.g. language, motor or executive functions) (DSM-IV criteria, American Psychiatric Association, 1994). Often, normal aging and AD are seen as a cognitive continuum. In this continuum, the transitional stage between normal aging and degenerative disorders is referred to as mild cognitive impairment (MCI). Although there has been controversy regarding the precise definition of MCI, it is generally characterized by mild but clinically prominent memory complaints in elderly people with little impairment in other cognitive domains (Kluger et al., 2002). Reported yearly conversion rates from MCI to AD range between 1 and 25 % depending on the employed diagnostic criteria and the patient sample size (for a review, see Petersen, 2004). Notably, the distinction between normal aging and MCI or between MCI and AD can be quite subtle. Diagnostic accuracy can be improved by combining various measures, such as clinical observation, neuropsychological tests, biomarkers and neuroimaging. MEG oscillatory activity, which is thought to reflect the general mechanism of neuronal communication, could be useful in detecting functional brain abnormalities in AD. In the present study, MEG was used to investigate oscillatory abnormalities in degenerative disorders and in subjects with normal memory function.

2 Review of the literature

2.1 AD and MCI: cognitive, structural and fucntional defificts

2.1.1 Cognitive deficits in AD and MCI

AD is characterized by gradual progression of memory loss and other cognitive changes (Katzman, 1986; Lange et al., 2002). Already early in the course of the disease AD patients have difficulty with memory of recent events (anterograde amnesia) and deficits in learning, probably due to the inability to encode and store the acquired information (Knopman and Selnes, 2003). Indeed, in accordance with the notion that damage to medial temporal structures prevents the formation of new episodic memories but spares implicit and old explicit memories, medial temporal regions are the first ones to be affected in AD. However, as the disease progresses, affecting distant memories as well (retrograde amnesia), other cortical areas (such other temporal association and frontal) become involved and implicit memory also starts to suffer.

The working (or short-term) memory (Fig. 1), whose structural basis is represented by the parieto-frontal system for spatial locations and the inferior-temporal dorsolateral frontal system for objects, appears relatively preserved in early AD. AD patients perform adequately in working memory tasks for passive storage capacity (such as e.g. forward digit span) but they are impaired in active working memory capacity (tested in backward span tasks) (reviewed in Germano and Kinsella, 2005). This selective impairment is most likely due to the overall deficits in focused attention rather than reduced memory capacity per se.

The loss of newly learned verbal material is one of the major aspects of the memory impairment in AD (Kaltreider et al., 2000). These deficits can be measured with neuropsychological tests such as the Auditory-Verbal Learning Test (AVLT), California Verbal Learning Test (CVLT), and Hopkins Verbal Learning Test- Revised (HVLT-R) (Lezak, 1995). Validation studies of the neuropsychological battery used in The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) have also shown that delayed recall of a word list is the best to discriminate AD patients from controls (Welsh et al., 1992; Kaltreider et al., 2000) already at the early stages of the disease (Fox et al., 1998). AD patients are often able to recall only the last presented words on tasks of

verbal learning (the recency effect) (Lezak, 1995). Although the episodic memory deficit is initially the primary symptom, AD patients tend to make semantic errors in the memory retrival as well: they often tend to make false positive identifications, particularly of non-target words which are semantically related to the targets (Brandt and Benedict, 1998). Overall, in the language domain, AD patients demonstrate comprehension difficulties and their discourse is usually disturbed. Furthermore, as the disease progresses abstract thinking deteriorates as well.

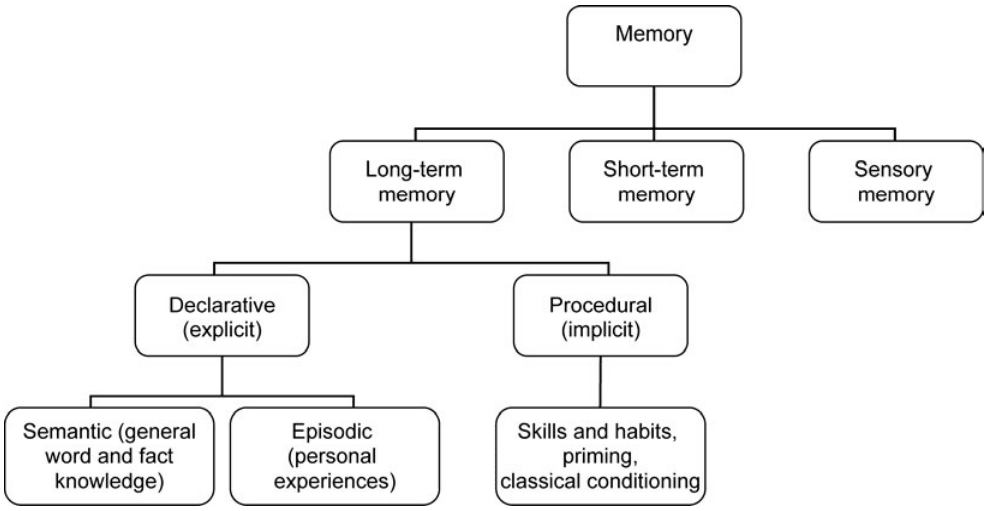

Figure 1 . Diagram of memory types. The concept of working memory is presently used as a synonym for the notion of short-term memory to emphasize the manipulation of information instead of passive storage.The main fundamental operations of memory processing are encoding (processing and combining of information), storage (creation of a permanent trace of the encoded information) and retrieval (calling back the stored information). Declarative (explicit) memory involves conscious recollections of previous experiences whereas implicit memory is an unconscious form of memory. Neural basis of explicit memory is constituted by the four limbic areas (the rhinal cortex, the amygdala, the hippocampus and the prefrontal cortex) which have reciprocal connections with the medial thalamus, the basal forebrain, and the neocortical sensory areas. The central element of the brain circuit for implicit memory is the basal ganglia that receive projections from the neocortex and send projections via the ventral thalamus and the globus pallidus to the premotor cortex.

Another early manifestation of AD is a prominent impairment in visuospatial skills (Crystal et al., 1982). AD patients experience problems with drawing, constructions and orientation in their surrounding (Smith et al., 2001; Mendez and Cummings, 2003) leading to impaired performance on such tests as Clock Drawing Test or Rey Complex Figure. Along with cognitive deficits, personality changes occur as well, however, usually later in the course of the disease. AD patients become indifferent and increasingly apathic without being aware of their impairment (Mendez and Cummings, 2003). Agitation, aggression and disinhibited behaviors may also appear as the disease progresses, with agitation being the most persistent symptom (Devanand, 1999; Mendez and Cummings, 2003). Delusions

occur in almost half of the AD patients (Wragg and Jeste, 1989), more frequently at the middle stage of AD, accompanied by progressive cognitive decline (Mendez and Cummings, 2003).

MCI diagnosis, in turn, is based on the objective memory deficit combined with usually preserved cognitive function, unimpaired activities of daily life, and no dementia. Longitudinal studies, which predict conversion from MCI to AD, have shown that episodic memory (such as delayed recall of word lists (de Jager et al., 2003) and paired-associates learning (Nestor et al., 2004), semantic memory (Nestor et al., 2003; DeCarli et al., 2004), attention processing (Amieva et al., 2004) and mental speed can consistently predict which patients will develop dementia of AD type. Similarly, in a retrospective study of patients with MCI who had developed AD, verbal and visual memory, associative learning, vocabulary, executive function and other verbal tests of general intelligence were impaired at baseline (Guarch et al., 2004).

2.1.2 Structural and functional brain changes in AD and MCI

AD is characterized by a progressive wide-spread neuronal loss in the brain. The earliest morphological changes in AD have been reported in the hippocampal and parahippocampal region (Hyman et al., 1984; for review, see Braak et al., 1993), potentially explaining why memory deficits are the major symptom of AD. Later in the course of the disease, distributed neocortical areas are affected giving rise to other cognitive dysfunctions. The results of the pathological reports of AD are confirmed by findings from structural magnetic resonance imaging (MRI) studies. Zakzanis et al. (2003), who conducted a meta-analysis of multiple MRI and computerized tomography (CT) studies of AD, concluded that the structures that best discriminate between AD patients and healthy subjects are the hippocampus and temporal and parietal cortices. The results of Pennanen et al. (2004) obtained in large groups of AD and MCI patients also suggest that the volumes of the hippocampus and the entorhinal cortex are significantly reduced in the following order: controls > MCI >AD. At the cellular level, the pathological diagnosis of AD is based on the large amounts of extracellular senile or neuritic plaques containing deposits of β-amyloid and intracellular neurofibrillary tangles with the greatest density in the temporal lobe (e.g. Ball et al., 1997). These neurodegenerative changes are associated with cholinergic denervation, specifically in the

basal forebrain (Mesulam and Geula, 1994; Inestrosa et al., 1996; Farlow, 2002). Both enzymes thought to hydrolytically disrupt acetylcholine in the brain, acetylcholinesterase and butyrylcholinesterase, have been shown to be linked to amyloid plagues (Mesulam and Geula, 1994; Inestrosa et al., 1996; Guillozet et al., 1997).

Functional imaging studies, such as positron emission tomography (PET) or single photon emission computerized tomography (SPECT) have demonstrated that already in very early AD blood flow and metabolism are reduced in the posterior cingulate gyrus and precuneus (Fox et al., 2001). This reduction can stem from a functional deafferentation caused by atrophy in the entorhinal cortex and the hippocampus, which are the first to be pathologically affected in AD. The subsequent areas to show flow or metabolic reduction are the medial temporal structures and parietotemporal association cortex (Matsuda, 2001). Consistent with the cognitive symptomatology of AD, neuroimaging studies have, further, shown reduced activation in the hippocampal formation and in the frontal and temporal cortex in AD patients during memory formation (Small et al., 1999; Schröder et al., 2001; Kato et al., 2001; Sperling et al., 2003). In retrieval tasks, AD patients have revealed wide-spread deficits (Kessler et al., 1991) or reduced activation in the hippocampus and parietal cortex (Bäckman et al., 1999).

Anatomical and functional brain changes, much weaker but somewhat similar to AD and different from normal aging, have been demonstrated in neuroimaging studies in MCI (Pietrini et al., 1993; Berent et al., 1999; Pennanen et al., 2004). Computed tomography and MRI have revealed atrophy of, respectively, the left (Wolf et al., 1998) and the right (Pennanen et al., 2005) medial lobe in MCI patients. Furthermore, a longitudinal MRI study reported that the rate of conversion from MCI to AD was greater in MCI patients who had smaller hippocampi at baseline (Jack et al., 2000). A recent post-mortem study compared the brains of five MCI patients and seven age-matched controls and found that the nucleus basalis, which plays an important role in cholinergic innervation of the neocortex, contained significantly more tangles and pre-tangles in MCI patients than controls (Mesulam et al., 2004). This finding suggests that cholinergic depletion takes place already at the preclinical stage of the dementia. SPECT studies have shown low parietal-temporal perfusion and left/right parietal-temporal asymmetry in MCI (Celsis et al., 1997). The observed hypoperfusion was intermediate between that found in healthy subjects and in patients with AD. Another study reported that reduced temporoparietal blood flow as assessed with SPECT predicts development of AD in 80% of subjects who

progressed from the point of questionable dementia (Johnson et al., 1998).

The role of electroencephalogram/magnetoencephalogram (EEG/MEG respectively) in diagnosis of degenerative disorders will be discussed in chapter 2.3.

2.1.3 Cholinergic hypothesis of AD

Although AD is associated with deficits in several neurotransmitter systems, including noradrenergic (Mann, 1983; Marcyniuk et al., 1986) and serotonergic (Palmer et al., 1987), dysfunction of the cholinergic system seems be a major neurochemical phenomenon underlying cognitive and functional changes associated with AD (Davies and Maloney, 1976; Rylett et al., 1983; Arendt et al., 1984; Reinikainen et al., 1988) (Whitehouse et al., 1982). The brain cholinergic system is involved in modulation of various cognitive functions, including arousal, attention, learning and memory (Mesulam, 1987; Goto et al., 1990), and in regulation of cortical and thalamic electrical activity (Shute and Lewis, 1967; McCormick, 1992). As a transmitter substance, it employs acetylcholine (ACh) which is terminated by hydrolysis accelerated by one or more of the cholinesterase enzymes (acetylcholinesterase or butyrylcholinesterase). The action of ACh is mediated by two major classes of receptors: nicotinic and muscarinic. Although nicotinic receptors also play a role in role in mediating cognitive performance, muscarinic receptors are thought to be the main type of cholinergic receptors in the central nervous system (for review, see Caulfield, 1993). For a review on the 8 major cholinergic cell groups in the CNS, see Mesulam (1988).

Histopathological studies reported the wide-spread reduction of cholinergic markers in AD patients. The most severely affected structures are nucleus basalis and medial septum in the basal forebrain which project to the hippocampus, amygdala and cortex (Whitehouse et al., 1982). The amount of choline acetyltransferase is also reduced in the cortex and hippocampus of AD patients (Perry et al., 1977). The reduction of cholinergic markers has been shown to correlate with the degree of cognitive decline (Bartus et al., 1982) and EEG/MEG slowing in AD (Coben et al., 1983; Penttilä et al., 1985; Berendse et al., 2000). The involvement of the cholinergic system in the AD pathology is further confirmed by the observation that in healthy subjects cholinergic antagonists, such as e.g. scopolamine, can produce transient cognitive deficits (Sunderland et al., 1986; Broks et al., 1988) and EEG/MEG changes (Sannita et al., 1987; Neufeld et al., 1994; Osipova et

al., 2003) similar to those observed in AD. In the light of cholinergic deficits in AD, cholinesterase inhibitors are the most frequently used type of medication, especially for patients with mild to moderate symptoms (for review, see Ellis, 2005). The ones currently used in clinical practice are donepezil hydrochloride, galantamine hydrobromide, and rivastigmine tartrate. Neuropharmacologically, cholinesterase inhibitors prevent cholinesterase-induced hydrolysis of ACh, resulting in the subsequent increase in ACh concentration in central synapses and the enhancement of cholinergic function.

Current theories suggest that the ACh system may regulate the flow of activity between different brain regions during memory formation (reviewed in Hasselmo, 1999), for example, by coordinating the hippocampus in acquiring recent memories and the cortex in storing remote memories. More specifically, a two-stage model of memory consolidation (for a review, see Buzsaki, 1989) suggests that the initial memory formation occurs during active waking and deeper consolidation occurs via the formation of additional memory traces during quiet waking or slow-wave sleep. High levels of ACh during active wakefulness set the appropriate hippocampal dynamics for inflow of information by suppressing feedback connections, both within the hippocampus and between the hippocampus and the association cortex. This facilitates the encoding and prevents interference from already existing representations. At a low level of cholinergic activation, such as during slow-wave sleep, there is a release of cholinergic suppression. This permits outflow of activity, both within the hippocampus and to the cortex. Interestingly, low doses of cholinergic antagonist scopolamine impair encoding of new information, but have little effect on the retrieval of information encoded prior to scopolamine administration (Ghoneim and Mewaldt, 1975; Hasselmo and Wyble, 1997). This evidence supports the notion that reduced cholinergic modulation interferes with the feedforward sensory input hindering the encoding of new information.

Notably, cellular-level studies suggest that the cholinergic system modulates brain oscillatory activity in the regions crucial for normal memory functions. High levels of ACh are associated with the presence of theta oscillations in the hippocampus (Winson, 1974), whereas low cholinergic activity is linked to the presence of the hippocampal sharp waves. During a theta stage, the model predicts formation of new long-term memory representations in the hippocampus, with little interference from and disruption to remote memories in the cortex. During a sharp-wave stage, strong repetition and spread of recently acquired traces become consolidated and integrated with permanent

representations in the cortex. Rhythms in similar frequency bands can be also measured from the neocortex with EEG/MEG but it is unclear whether they reflect same cognitive processes.

2.2 Measurement of brain electromagnetic activity

The clinical prediction of conversion from normal aging to MCI and finally to AD requires combined measures from neuropsychological testing, clinical observation and neuroimaging. Structural and functional brain data can thus provide useful information about memory disorders. Although the accuracy of clinical diagnosis using NINCDS criteria is about 80–90 % (Rossor, 2001), it may often be problematic to identify AD, especially at early stage of the disease. Brain electromagnetic activity reflects neuronal synchronization, which is partly modulated by cholinergic system. Given abnormalities in ACh transmission in AD (and possibly MCI), characterization of electromagnetic activity and its sources is likely to provide insights on impaired brain dynamics in neurodegenerative disorders in terms of oscillation frequencies and loci of generation. This information could add accuracy to early AD diagnosis.

MEG and EEG are non-invasive brain-imaging techniques with millisecond temporal resolution. While EEG measures electric potential differences on the scalp, MEG records extracranial magnetic fields generated by the neuronal currents (see Figure 2). It is measured with superconducting quantum interference devices (SQUIDs), which are sensitive detectors of magnetic flux. A sensory stimulus evokes synchronous neuronal activity in a small part of the cortex causing the movement of ions as a result of their concentration gradients. Measured signals are thought to originate both from the currents in the dendrites of neurons during synaptic transmission and the return current in the extra-cellular medium. A magnetic field produced by action potentials is thought to be invisible to MEG because these currents flow in opposite directions and the magnetic fields, therefore, cancel out. Since neuronal currents should have similar orientations to generate detectable magnetic fields, MEG signals are believed to originate in the pyramidal cells in the cortex, which are generally aligned perpendicularly to its surface. Hence MEG measures predominantly activity from the sulci where neurons are oriented parallel to the surface of the head.

2.2.1 Sensor-level measurements

MEG allows noninvasive measurement of both spontaneous rhythms and magnetic event-related fields (ERFs). EEG/MEG rhythms are defined as regularly recurring waveforms of similar shape and duration (Steriade, 1993). The frequency bands of the rhythms are historically termed delta (0–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–40 Hz), and gamma (40–100 Hz). Different EEG rhythms are associated with distinct behavioral states. Delta waves prevail during the deep stage of normal sleep, whereas its presence during wakefulness in adults is generally regarded as a sign of pathological process in the brain. Normal theta activity is associated with memory processes (e.g. Klimesch et al., 1996; Klimesch et al., 1997). Alpha rhythm is reported mainly during relaxed wakefulness, although it has been observed in memory tasks as well (Jensen et al., 2002; Sauseng et al., 2005). Idling alpha rhythm is the strongest over the occipital regions and is dampened by opening the eyes. Fast beta waves occur during epochs of increased alertness (Steriade et al., 1990b) and gamma activity associated with attention and information processing (Tallon-Baudry and Bertrand, 1999; Gruber et al., 1999; Tallon-Baudry et al., 2005). Other patterns of synchronized spindle oscillations in cortical EEG can be observed during the early stages of sleep or low arousal and vigilance (Steriade et al., 1990b; Riekkinen et al., 1991).

ERFs, in turn, are averaged segments of MEG time-locked to the presentation of an external stimulus. Averaging MEG signals increases signal-to-noise ratio of the time-locked brain activity. Like their electric counterparts, event-related potentials (ERPs), ERFs consist of different components which are mostly named according to their polarity and order (or average latency). The present work will address exlusively auditory ERFs. Auditory ERFs are though to reflect different stages of auditory processing depending on their origin. Auditory ERFs are classified as brain-stem (1–10 ms post stimulus onset), middle-latency (10–70 ms post stimulus onset) and long-latency (50–800 ms post stimulus onset) components. Middle-latency responses (MLRs) are the earliest cortical responses, most distinct components of which peak at approximately 25 and 30 ms post stimulus (termed Na and Pa respectively). Both intracranial (Liégeois-Chauvel et al., 1994) and MEG (e.g. Mäkelä et al., 1994) measurements showed that middle-latency ERFs are generated near the primary auditory cortex.

With certain stimulation parameters, when presentation occurs periodically at a fast rate, an ERF starts to oscillate at the frequency of the stimulus and its harmonics. In this

case, the ERF is termed steady-state response (as opposed to transient ERFs). The amplitude of the auditory steady-state response (ASSR) reaches its maximum at stimulation rates around 40 Hz (Hari, 2005).

In the ongoing discussion about the nature of ASSR, they are either classified as evoked responses, induced activity or as a separate third class. Originally, it has been thought that AASR is produced by the summation of MLR (Galambos et al., 1981). However, some experimental evidence does not support this notion failing to explain an ASSR by superposition of MLR (Santarelli and Conti, 1999; Ross et al., 2002). Ross et al. (2005) conclude that ASSR is likely to be induced activity, "facilitated by the rhythmic stimulation with frequencies close to the best responding frequency of the underlying neural network." Their result supports the hypothesis of ASSR being a separate neural oscillation, in addition to ongoing brain activity (Ross et al., 2005). In general, induced gamma oscillations have been proposed to play an important role in sensory information processing, such as e.g. temporal binding in auditory perception (Joliot et al., 1994).

2.2.2 MEG source estimation

The second main task of MEG is determination of the origin of the signals. This can be applied to both ERFs and spontaneous activity. Although source localization procedure is easier with MEG due to its selective sensitivity to predominantly tangential currents, the interpretation of the MEG data is complicated due to the so called "inverse problem", i.e. estimation of the neuronal sources corresponding to a certain distribution of magnetic fields on the scalp. The inverse problem is ill-posted since it has no unique solution: infinite number of current distributions can produce the same magnetic field measured outside the brain. Therefore, *a priori* constraints are employed to determine the source distributions.

Equivalent current dipole (ECD) is a popular source model in MEG research (for review, see Hämäläinen et al., 1993). It approximates the flow of electrical current in a small area caused by synchronous activity of tens of thousands of neurons. The ECD is calculated by fitting the predicted and measured magnetic field patterns in the least-squares sense. However, the estimation of ECD models is only meaningful if the scalp field has a focal character and there are strong assumptions about the number of activated

areas. Other analysis methods, which have the advantage of not making as strong *a priori* assumptions of the number of sources, include the minimum-norm estimates (MNE) (Hämäläinen and Ilmoniemi, 1994). MNE gives the most reliable results when constraints based on the known brain anatomy and physiology are applied. Jensen and Vanni (2002) have developed a method which calculates minimum-current estimates (MCE, Uutela et al., 1999) in the frequency domain. The algorithm first Fourier-transforms consecutive time segments, then calculates source estimates for the real and the imaginary parts and averages them. Such estimate of the source currents explains most of the data while minimizing the absolute sum of the currents with respect to the L_1-norm. This approach favors a solution with a few distinct source locations. Another source localization technique, dynamic imaging of coherent sources (DICS), uses a spatial filter in the frequency domain (Gross et al., 2001). Spatial filters are designed to pass activity from a certain spatial location, while suppressing activity or noise originating from other locations. In order to localize oscillatory activity, power is calculated at each point of the three-dimensional grid that covers the entire brain. These source localization techniques are compared in Liljeström et al.(2005).

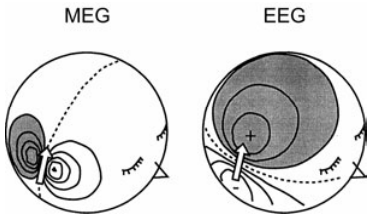

Figure 2. Schematic illustration of orthogonal with respect to each other magnetic field and electric potential patterns produced by a tangential dipole (white arrow). Since MEG is sensitive mainly to tangential dipoles, it measures predominantly cortical activity from the fissures where current is oriented parallel to the cortical surface. (Reprinted figure with permission from Hämäläinen M., Hari R.., Ilmoniemi R.., Knuutila J. and Lounasmaa O.V. Reviews of Modern Physics 65: pp. 413–497. 1993. Copyright (1993) by the American Physical Society).

Another advantage of MEG over EEG with respect to source modeling stems from the fact that magnetic fields are not distorted by the skull and surrounding tissues. Therefore, the head model used in MEG source localization can be constructed from the brain only, whereas accurate EEG head model requires information about conductivities and shapes of the skull, cerebrospinal fluid and scalp.

2.3 MEG/EEG activity in AD and MCI

2.3.1 Spontaneous rhythms in AD and MCI

AD is a predominantly cortical dementia which makes functional brain abnormalities more detectable with EEG/MEG. The most prominent functional deficit, slowing of spontaneous EEG/MEG rhythms, has been reported in multiple studies of AD (Coben et al., 1983; Penttilä et al., 1985; Schreiter-Gasser et al., 1993; Berendse et al., 2000; Huang et al., 2000). In other words, similarly to the effects of scopolamine, delta (2–4 Hz) and theta (4–7 Hz) power are enhanced and alpha (7–12 Hz) and beta (12–30 Hz) power are decreased. Furthermore, EEG deficits have been found to correlate with the degree of cognitive impairment (e.g. Soininen et al., 1982; Erkinjuntti et al., 1988; Brenner et al., 1988). As discussed in detail in Chapter 2.3.4, since ACh and ascending cholinergic pathways are involved in generation of desynchronized EEG/MEG activity, the reason for the EEG/MEG slowing in AD is likely to be the loss of cholinergic innervation of the neocortex, to the greatest extent in the nucleus basalis.

However, the handful of EEG studies investigating spontaneous oscillations in MCI has produced less clear results. Huang et al. (2000) and Jelic et al. (2000) found no power differences between MCI and controls in any frequency bands. There is evidence of reduced beta-band synchronization in MCI (Stam et al., 2003), which is however contradicted by more recent studies (Stockholm subject cohort in Koenig et al. (2005)). EEG/MEG studies of synchronization in AD have, in turn, revealed decreased alpha and beta band coherence suggesting functional disconnections among various regions (e.g. Leuchter et al., 1987; Besthorn et al., 1994; Locatelli et al., 1998). The reason for the reduced long-range coherence can be both anatomical disconnection manifesting in the atrophy of the long cortico-cortical fibers and synaptic changes.

2.3.2 Sources of spontaneous activity in AD

Although the power of various frequency bands has been investigated in multiple studies, fewer authors have attempted to investigate the distribution of sources of spontaneous brain rhythms in AD. However, an interesting question remains whether it is the frequency of existing sources that gradually shifts to lower frequencies (the so-called

"slowing"), or the oscillators in other frequency bands take over. EEG studies of oscillatory sources in AD have reported an anterior shift of alpha and beta generators in AD patients (Dierks et al., 1993; Huang et al., 2000). However, these attempts were based on equivalent current dipole (ECD) models, thought to represent the "center of gravity" of neuronal activation possibly reflecting a larger area of activation. Recent studies have therefore tried to investigate the spontaneous rhythm generation by using distributed source analysis that allows modeling of multiple generators. For example, in their EEG study, Babiloni et al. (2004) reported changes in the configuration of alpha sources, found to be more profoundly attenuated in the posterior rather than anterior brain regions. However, the EEG source modeling approach utilized in this study did not reveal specific source locations, since the analysis rather concentrated on the activation in entire brain regions. The only EEG study in MCI did not show changes in the distribution of oscillatory sources (Huang et al., 2000).

2.3.3 Auditory ERPs/ERFs in AD and MCI

Certain components of event-related potentials (ERPs) and their magnetic counterparts, event-related fields (ERFs) have been shown to be altered in AD (Green et al., 1992; Pekkonen et al., 1994; Pekkonen et al., 1999). Whereas the late auditory ERP components (such as N1m) appear to decrease in AD (Pekkonen et al., 1999), there is also evidence suggesting that earlier auditory ERP components might be increased in amplitude in subjects at risk for AD (Boutros et al., 1995). Sensory gating measured by the P50 response also seems to be impaired in AD (Cancelli et al., 2006). In MCI, such middle-latency component as P50, seems to be increased (Golob et al., 2002; Irimajiri et al., 2005).

2.3.4 Cholinergic modulation of EEG/MEG activity

As discussed above, the brain cholinergic system plays a central role in synchronizing large-scale brain oscillations across various brain regions (Kanai and Szerb, 1965; Celesia and Jasper, 1966). This modulation is presumably carried out via both local and long-distance oscillatory networks, whose dynamics can be successfully studied with

EEG/MEG. Well-documented cholinergic deficits in AD (e.g. Mesulam and Geula, 1994; Inestrosa et al., 1996) and MCI (Mesulam et al., 2004) can thus underlie EEG/MEG abnormailities observed in these disorders.

During the waking stage, EEG/MEG is represented mostly by desynchronization. It has been demonstrated that release of ACh from the cortex is high during the periods of EEG desynchronization, and reduced when EEG is synchronized (Kanai and Szerb, 1965; Celesia and Jasper, 1966). Pathological changes in the cholinergic system and pharmacological interventions, such as administration of ACh antagonists, affect neocortical EEG/MEG activity, blocking desynchronization and producing high amplitude slow wave activity (Longo, 1966; Vanderwolf and Robinson, 1981). In human EEG studies with scopolamine these changes of spontaneous activity manifest themselves in decreased alpha (Sannita et al., 1987; Ebert et al., 1998) and beta (Sloan et al., 1992) power and increased theta (Sannita et al., 1987) and delta (Sannita et al., 1987; Neufeld et al., 1994; Ebert et al., 1998) power. This synchronization is thought to originate from the summation of hyperpolarizing outward currents from cortical pyramidal cells (e.g. Amzica and Steriade, 1998).

There is evidence that both the cholinergic pathway arising in the brain stem and projecting to the thalamus and the cholinergic pathway of the basal forebrain projecting to the neocortex play a role in EEG modulation, since networks of both thalamic and cortical oscillators are thought to modulate cortical oscillations (Lopes da Silva et al., 1973; Lopes da Silva et al., 1980). In the thalamus, ACh depolarizes relay neurons in brain slices (McCormick, 1989). This notion is important since depolarization of the membrane of the thalamic neurons is associated with desynchrony and hyperpolarization is associated with synchrony of the EEG (e.g. Curro Dossi et al., 1991). However, the role of basal forebrain cholinergic neurons in regulation of neocortical EEG may be greater than that of the brainstem cholinergic pathway, since the major cholinergic projections to the cortex originate in the basal forebrain and lesions to the basal forebrain produce greater EEG deficits (Stewart et al., 1984) than lesions to the brainstem mesopontine tegmentum (Webster and Jones, 1988). The major effect of ACh on cholinoceptive cortical neurons is a relatively prolonged reduction of potassium conductance that makes cortical cholinoceptive neurons more susceptible to other excitatory inputs (Steriade et al., 1990b). In addition, ACh increases the frequency of intracellular membrane oscillations and reduces inhibitory after-hyperpolarization after discharge (McCormick and Prince, 1986;

Metherate et al., 1992). However, the effect of ACh on cortical neurons can also be inhibitory, either directly or through the mediation of GABAergic interneurons (Kimura and Baughman, 1997).

Cholinergic system is thought to play an important role in plasticity of the auditory cortex (McKenna et al., 1988; Hars et al., 1993; Bakin and Weinberger, 1996), modulating responses to temporal and sequential stimuli. Synaptic potentiation in the auditory cortex was shown to be attenuated by cholinergic antagonists (e.g. atropine) and restored by cholinergic agonists (Seki et al., 2001; Kudoh et al., 2004). Long-term pairing of basal forebrain and sound stimulation leads to substantial changes in the area of cortex responsive to the paired acoustic stimulus (Kilgard and Merzenich, 1998; Mercado et al., 2001).

Data obtained in rats indicates that ACh may facilitate auditory signal perception through a mechanism of parallel synaptic modulation in the thalamus (Mooney et al., 2004). In the primary sensory (lemniscal) pathway, ACh enhances synaptic signal relay in a global fashion. In the nonlemniscal pathway, cholinergic modulation adapts to the context of local neuronal activities suppressing synaptic transmission in more depolarized neurons and preventing thus “irrelevant” acoustic stimuli from overloading the limbic system. In more hyperpolarized cells and in the presence of synchronized cortico-thalamic and sensory afferents, ACh prompts burst firing. Such event-triggered synaptic bursting may facilitate the induction of long-term synaptic potentiation or recurrent excitation in the lateral amygdala (Clugnet and Ledoux, 1990) and/or cortical networks (Beierlein et al., 2002), which cannot be fulfilled by random, single spike discharge (Lisman, 1997).

Many components of auditory magnetic evoked responses in healthy subjects appear to be modulated by cholinergic transmission (Jääskeläinen et al., 1999; Ahveninen et al., 1999; Pekkonen et al., 2001; Ahveninen et al., 2002). The enhanced amplitude of earliest cortically-generated components of the auditory ERF, has been reported in MEG studies after the administration of scopolamine, the antagonist of the muscarinic ACh receptors, in young (Jääskeläinen et al., 1999; Pekkonen et al., 2001) and elderly (Ahveninen et al., 2002) subjects.

2.4 Electrophysiological studies of declarative memory in non-demented subjects: methodology for predicting AD?

Impairment of declarative (primarily, episodic) memory is a major symptom of AD. The insight on neural basis of episodic memory in healthy subjects is essential for understanding memory deficits observed in AD.

A widely used paradigm to study declarative memory formation is to compare brain activity during encoding of items which subsequently were retrieved versus those which were forgotten ("subsequent memory effect") (e.g. Sanquist et al., 1980; Paller et al., 1987; Rugg, 1990). Declarative memory retrieval is often investigated by comparing the brain activity recorded during correctly recognized old versus correctly identified new items (the "old/new effect") (reviewed in Rugg, 1995). Previous fMRI and PET studies have shown an increased activation in the medial temporal lobe and inferior prefrontal areas associated with memory formation (Wagner et al., 1998; Brewer et al., 1998; Kirchhoff et al., 2000; Otten et al., 2001; Davachi and Wagner, 2002; Strange et al., 2002; Weis et al., 2004), whereas anterior prefrontal cortex, parietal cortex, and medial-frontal areas were activated during the old/new effect (Henson et al., 1999; Konishi et al., 2000; Donaldson et al., 2001; reviewed in Rugg and Henson, 2002; Weis et al., 2004; Wagner et al., 2005). To investigate the brain dynamics on a faster time scale, EEG and MEG have been applied to characterize respectively ERPs and ERFs (Rugg, 1995; Tendolkar et al., 2000; Friedman and Johnson, 2000; Takashima et al., 2006). These studies have shown that the differential effects with respect to encoding and retrieval start relatively late (~0.3 s) after stimulus onset. Unfortunately, given that these ERP/ERF effects are spatially very distributed, reliable localization of the involved sources has been problematic.

Relatively late oscillatory responses (>0.2 s) which are induced by, but not phase-locked to the stimulus like ERPs/ERFs, can reflect important cognitive processing as well (Tallon-Baudry and Bertrand, 1999). Strong arguments support the case that oscillatory neuronal synchronization plays an essential role in neuronal processing in general (reviewed in Singer, 1999; Salinas and Sejnowski, 2001). Indeed, successful declarative encoding of words was first shown to be associated with changes in EEG theta (4–8 Hz) power (Klimesch et al., 1996) and coherence (Weiss et al., 2000); however, the sources of the theta activity in these studies were not identified. A study employing intracranial EEG recordings in epileptic patients reported an increase in the frontal and right temporal theta activity and widely distributed gamma (30–100 Hz) activity (Sederberg et al., 2003)

associated with successful encoding of words. Using depth-electrode recordings in epileptic patients, Fell et al. (2001) demonstrated an increase in rhinal-hippocampal gamma-band synchronization during word encoding. This increase was subsequently shown to correlate with theta coherence over subjects (Fell et al., 2003).

These intracranial studies suggest that theta and gamma oscillations play an important role in memory formation. However, the electrode locations were defined by the surgical requirements and some of the findings might be related to the pathology *per se* or to the administered drugs. Due to its good temporal and spatial resolution, MEG allows us to monitor the temporal dynamics of oscillatory activity in various frequency bands and to identify the involved sources. The role of oscillations in memory encoding and retrieval is an essential question for research on AD, the disorder known to be associated with theta-rhythm abnormalities probably due to the deficits in cholinergic transmission.

3 Aims

Given the role of oscillatory activity in cognitive processing, our major goal was to study oscillatory abnormalities in degenerative disorders and in subjects with normal memory function.

(a) MEG was used to examine abnormalities in the distribution of focal oscillatory sources in AD patients and healthy elderly controls

(b) Given that MCI and AD represent a continuum of cognitive impairment, in continuation to Study I, MEG was employed to investigate abnormalities in oscillatory sources in MCI and elderly controls, and compare the obtained data with that from Study II

(c) Since auditory steady-state response is thought to represent both evoked and induced activity at the 40 Hz range reflecting the entrainment in the underlying neural networks, MEG was used to investigate differences between AD patients and healthy age-matched subjects in responses to the fast-rate stimulation

(d) MEG was used to investigate oscillatory activity involved in memory encoding and retrieval in young healthy subjects, aiming at developing a paradigm suitable for clinical memory studies.

4 Methods

4.1 Subjects

All studies were approved either by the Ethics Committee of the Helsinki University Central Hospital or Commissie Mensgebonden Onderzoek – Regio Arnhem Nijmegen (Title: "Imaging Human Cognition", # CMO 2001/095). A written informed consent was obtained from all the subjects and patients or their closest relatives after a detailed explanation of the procedures. Control subjects and the subjects of study IV had no history of neurological, psychiatric, or other severe diseases. Patients had no history of stroke, head trauma, or any other neurological diseases except gradual decline of cognitive functions and memory. Neither patients, nor control subjects reported using drugs affecting the central nervous system. The patients took various antihypertensive drugs, statins, and antiplatelet agents, but none of them had diabetes or thyroid disease. Demographic data and the number of subjects for each study are presented in Table 1.

		Age	Number (females)	MMSE
Study I	*AD*	72.1 ± 7.5	11(6)	20.8 ± 4.0
	Controls	71.2 ± 5.8	12(5)	29.3 ± 1.0
Study II	*MCI*	79.0 ± 3.0	9(0)	28.1 ± 1.2
	AD	68.0 ± 5.5	5(0)	24.4 ± 1.7
	Controls	72.0 ± 4.8	10(0)	29.5 ± 0.7
Study III	*AD*	72.5 ± 7.7	10(5)	21.5 ± 3.5
	Controls	71.1 ± 5.7	12(5)	29.3 ± 1.0
Study IV	*Controls*	25.0 ± 4.8	13(9)	–

Table 1. Age, gender and MMSE scores for all participants.

AD diagnosis was established following the National Institute of Neurological and Communicative Disorders and Stroke/the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984). MCI diagnosis was based on the presence of a new subjective memory complaint, objective evidence of impairment in one or more memory tests applied in the patients' clinical evaluation according to age-norms, normal general cognitive functions and activities of daily living in the absence of dementia (Petersen, 2003). In addition to clinical neurological evaluation, patients underwent a head MRI or computer tomography CT scan (all but one subject) to

exclude other underlying neurological pathology.

The cognitive assessment included the Mini Mental State Examination (MMSE) (Studies I-III) and the five subtests of Consortium to Establish a Registry for Alzheimer's Disease (CERAD): Word List Memory; Constructional Praxis; Word List Recall; Word List Recognition; Constructional Praxis Recall (Studies I and III). Only controls with an MMSE score exceeding 25/30 were included in the study (Folstein et al., 1975). The results of neuropsychological tests are presented in Table 2.

	Study I	Study III
Wordlist Learning (10)	4.0±1.7	4.0±1.8
Copy of Figures (11)	8.1 ±1.9	8.5±1.4
Wordlist Recall (100%)	37.3±36.0	36.0±38.0
Wordlist recognition (100%)	63.5±27.6	63.3±29.3
Recall of drawings (100%)	47.7±39.3	51.2±35.7

Table 2. The results of the neuropsychological assessment of AD patients (CERAD, Studies I and III). The number in parenthesis indicates a maximal possible score.

4.2 Measurements of brain function

4.2.1 General methodology

Measurements for Studies I–III were carried out at the Biomag laboratory, Helsinki University Central Hospital using 306-channel Neuromag Vectorview system (Elekta-Neuromag, Helsinki, Finland). Measurements for Study IV were conducted at the F.C. Donders Center for Cognitive Neuroimaging, Nijmegen (the Netherlands) using a whole-head MEG with 151 axial gradiometers (VSM/CTF Systems, Port Coquitlam, Canada). The pass band and sampling rate were 0.1–190 Hz and 600 Hz (Studies I–III), respectively. In Study IV low pass filtering was performed at 150 Hz with a sampling rate of 600 Hz.

Subjects were seated comfortably in a magnetically shielded room with the head inside the helmet. Vigilance of the subjects was observed by on-line video monitoring during the recordings. For Studies I-III respective locations of marker coils to cardinal points of the head (nasion, left and right preauricular points) were determined with an Isotrak 3D-

digitizer (Polhemus, Colchester, VT). The magnetic fields produced by the coils were used in determining the position of the subject's head in relation to the MEG sensor array. A set of additional physiological landmarks was digitized for the individual characterization of a spherical conductor model used in Study I and II. All source modeling conducted was based on the coordinate system, in which the *x* axis points from the left to the right preauricular point, y axis is perpendicular to the *x* axis and passes through the nasion, and *z* axis is orthogonal to *x* and *y*. In Study IV head localization was done before and after the experiment using marker coils placed at the cardinal points of the head (nasion, left and right ear canal). In all studies, electrooculogram was recorded for the subsequent artifact rejection. Artifact rejection was performed off-line, and all epochs containing eye blinks or with amplitude exceeding 3000 fT/cm were rejected (Studies I-III). The artifact rejection algorithm employed in Study IV is described below.

The frequency bands investigated in Studies I and II were based on definitions commonly used in clinical practice (Niedermeyer, 2005). In studies I and II, relative power was calculated by dividing the mean delta (2–4 Hz), theta (4–7), alpha (7–12), and beta (12–30) power by the total power at 2–30 Hz. The mean power spectra were obtained for five brain regions by averaging activity from 22 frontal, 32 central, 32 occipital, and 38 left and 38 right temporal planar gradiometers (Fig. 3).

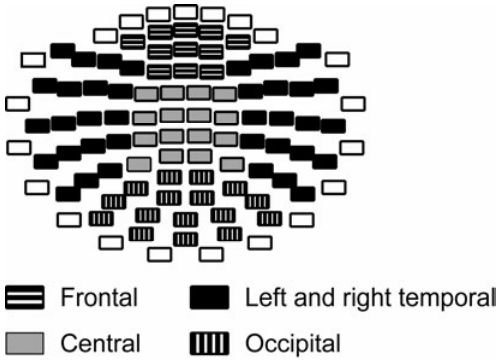

Figure 3. Gradiometers assigned to the each of the five brain regions. The outer gradiometers were excluded from the analysis due to the low signal-to-noise ratio. (Reprinted from Neuroscience Letters 405: Osipova D., Rantanen K., Ahveninen J., Ylikoski R., Happola O., Strandberg T., Pekkonen E. Source estimation of spontaneous MEG oscillations in mild cognitive impairment. pp: 57–61. Copyright (2006), with permission from Elsevier).

MCE source modeling performed in Studies I and II is the most reliable in case a significant peak is present in a power spectrum (Jensen and Vanni, 2002). Alpha rhythm is known to be the strongest over the posterior regions (Salmelin and Hari, 1994; Ciulla et al., 1999) resulting in a good signal-to-noise ratio. Therefore, peak frequencies were

determined from the mean spectra of the posterior (bilateral temporal and occipital) channels. In case of bimodal peaks, the peak of greater magnitude was chosen. MCEs were then calculated from Fourier-transformed consecutive data segments with respect to the individual peak frequency (6–12.5 Hz in Study I) or (6–10.3 Hz in Study II). The current estimates for all data segments were averaged (Jensen and Vanni, 2002), resulting in a distributed current estimation for a specific frequency. The lattice constant was 10 mm, and points closer than 30 mm to the sphere origin were excluded from the current estimates. A spherical conductor model was applied with the origin individually determined for every subject.

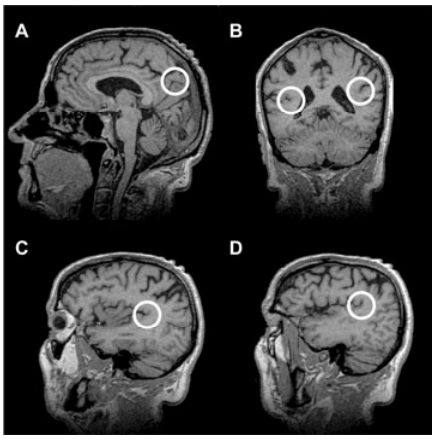

Figure 4. Sagittal view of the parieto-occipital (A), and coronal (B) view of left temporal, and right temporal regions of interests (ROIs) in one subject. Sagittal view of the temporal ROIs in the left (C) and right (D) hemispheres. (Reprinted from Neuroimage 27. Osipova D., Ahveninen J., Jensen O., Ylikoski A., Pekkonen E. Altered generation of spontaneous oscillations in Alzheimer's disease. pp: 835–841. Copyright (2005), with permission from Elsevier).

Three regions of interest (ROIs) of identical size were placed individually for each subject in the parieto-occipital and right and left temporal areas. The ROIs were selected after visual inspection based on the loci of the strongest activation in single subjects. Single subject data strongly resembled the GA distribution. ROIs were positioned with respect to the individually digitized head coordinate system (Fig. 4). The center of the parieto-occipital ROI (mean coordinates across subjects in Study I: x = 0 ±0.3 mm; y = -31 ±6.7; z = 82.8 ±9.2; in Study II: x = 0 ±0.3 mm; y = -35.5 ±7.2; z = 82.3 ±8.5) was placed at the midline of the head, and the temporal ROIs (In Study I, left: x = -42.8 ±3.7; y = 0.4 ±4.2; z = 61.5 ±8.3; right: x = 44.7 ±3.1; y = -0.3 ±4.7; z = 62.7 ±7.0; in Study II, left: x = -44.3 ± 4.8; y = 1.6 ±6.2; z = 58.9 ± 7; right: x = 46.4 ±4; y = 0.8 ±5.5; z = 60.5

±7) were located above the line connecting preauricular points. The uniform-sized ROIs were selected to standardize the magnitude of activation within an ROI between the subjects. Activities in ROIs were calculated using a Gaussian kernel with a radius of 15 mm (60% activation defined the radius). The absolute value of the total current at the frequency of interest was used to normalize the activation within the ROI, thus reducing the variance between the subjects.

4.2.2 Sources of oscillatory brain activity in AD (Study I)

Spontaneous activity was recorded for 2 min with eyes closed. On the average, 60 epochs (minimum 35) 3.4 s each underwent Fast Fourier Transform (2048 points, Hanning window with 50% overlap).

4.2.3 Source of oscillatory brain activity in AD, MCI and normal aging (Study II)

The measurement was conducted for 2 minutes with the subjects being awake with the eyes closed. 67 ±5 epochs each 3.4 s long underwent Fast Fourier Transform (2048 points, sliding Hanning window shifted with 50% overlap). One MCI patient was excluded from the ROI analysis due to insufficient source estimates.

4.2.4 Auditory steady-state response in AD (Study III)

The subjects were presented with 40-Hz trains of 5-ms bursts of pure tones (700 Hz) to the left ear at 60 dB above subjective hearing threshold that was individually measured before the recording. There were no significant differences between the two groups in the threshold values *per se* ($p > 0.6$). The subjects were instructed to ignore the stimulation and to concentrate on a silent video movie.

The ASSRs were averaged online. At least 500 averages were obtained for each subject. The analysis period was 750 ms (including a 150-ms prestimulus baseline). The responses were band-pass filtered at 10–48 Hz. Dipole models representing an estimate of the “center of gravity” of the cortical activation were calculated with the center of

symmetry at {*x*, *y*, *z*} {0, 0, 45 mm}. Equivalent current dipole (ECD) was modeled at one ASSR peak for each subject, separately in each hemisphere, based on a subset of gradiometers over the right and left temporal lobes. The ECD fitting procedure was guided by the total-field power in the respective channel subset to select a peak consistent across this subset. One ECD per hemisphere was then entered into a time-varying multidipole model to explain the measured whole-head MEG data in the least-squares sense (Hämäläinen et al., 1993). The absolute values of dipole amplitudes were averaged between 0–500 ms post stimulus onset, and subjected to statistical analysis. Additionally, a frequency domain analysis (Fast Fourier Transform, sliding Hanning window of 4096 points with 50% overlap) was conducted to compare 40 Hz power between the two groups in both hemispheres. The power values were averaged across the left and right temporal channels. The channel selections were identical to those used in source analysis. On average, 105±44 epochs underwent frequency analysis. Since the aim of the frequency domain analysis was simply to verify the time domain findings, we did not perform source analysis in the frequency domain.

4.2.5 The role of theta and gamma oscillations in declarative memory (Study IV)

Ongoing brain activity was recorded in two sessions. 480 real-life photographs of either buildings or landscapes (240 in each category) were used as stimuli. Pictures were obtained from websites and had resolutions exceeding 480 x 640 pixels. Pictures of well-known buildings and landscapes were avoided. Each subject participated in an encoding session followed by a retrieval session.

In the encoding session, 120 images of buildings were presented randomly intermixed with 120 images of landscapes. Stimuli were projected onto a screen with a visual angle of approximately 8.5 degrees vertically and 10.8 degrees horizontally. Each trial started with a fixation cross displayed with a random duration of 1.2–1.8 s (mean 1.5 s) followed by the actual stimulus presented for 1 s (Fig. 5). A question mark was displayed for 1 s after the stimulus offset, followed by the next fixation cross. During the presentation of the question mark, the subjects were instructed to make a building/landscape decision by a button press with the left or right index finger respectively. Note that no motor responses were given during the presentation of pictures. The response time of the subject had no

influence on the duration of each trial. The subjects were instructed to memorize the images for the subsequent memory test in the retrieval session.

The retrieval session followed approximately 5–10 minutes after the encoding session (Fig. 5). The 240 stimuli from the encoding session were randomly intermixed with 240 new pictures. The timing of the retrieval session was similar to the encoding session. Subjects were instructed to respond with a left index finger button press when they were highly confident that the presented picture had been previously shown in the encoding session. When subjects were highly confident that the picture was new, they were instructed to give a right index finger button press. To avoid guesses, subjects were asked not to respond when they were uncertain. The stimuli in the encoding session were counterbalanced across subjects such that the set of old pictures for one subject corresponded to the set of new pictures for another subject. All investigations were carried out between 9 a.m. and 6 p.m.

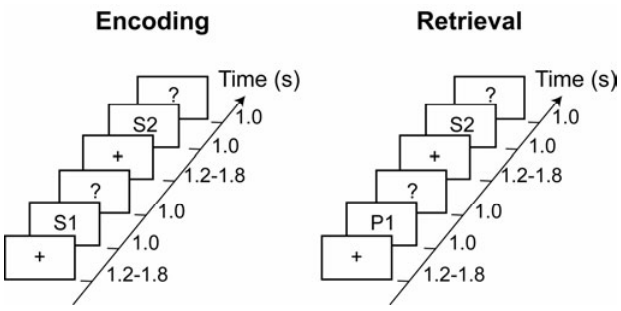

Figure 5. The experimental design used in the study. In the encoding session subjects were shown photographs (e.g. S1, S2) and instructed to make a building/landscape decision by a button press. In the retrieval session, participants were shown pictures from the encoding session (e.g. S2) intermixed with the new stimuli (e.g. P1). They were instructed to respond to whether the picture had been shown in the previous session. Based on the answers trials in the encoding session were classified as later remembered and later forgotten. Trials in the retrieval session were labeled as correctly recognized (HITs), correctly rejected, and forgotten old items (MISSes).(Reprinted with permission from: Osipova D., Takashima A., Oostenveld R., Fernandez G., Maris E., Jensen O. Theta and gamma oscillations predict encoding and retrieval of declarative memory. Journal of Neuroscience. 2006; 26 pp.:7523–7531. Copyright 2006 by the Society for Neuroscience).

All data analysis was performed using the FieldTrip toolbox developed at the F.C. Donders Centre for Cognitive Neuroimaging (http://www.ru.nl/fcdonders/fieldtrip) using Matlab 7.0.4 (The MathWorks, Inc). The trials from the first session were divided into two categories: later remembered and later forgotten, depending on the response given in the recognition session. Trials in the recognition session were classified as correctly identified previously seen pictures (HIT), correctly rejected new stimuli, not recognized old pictures

(MISS), and new pictures incorrectly identified as old, i.e. false alarms. The number of trials with false alarms was too low for the analysis. The performance rates are presented at Table 1. The chance level in this task was 50%.

In this study partial artifact rejection was performed by rejecting segments of the trials containing eye-blinks, muscle and SQUID artifacts. By this procedure smaller segments of a trial, rather than a whole trial, can be rejected. This is advantageous when calculating time-frequency representations based on sliding time windows since fewer full trials have to be rejected (in the subsequent averaging the number of segments applied is of course taken into account). In order to ensure that segments were sufficiently long for the subsequent analysis, segments shorter than 0.6 s were discarded as well. On the average, the fraction of data segments rejected due to artifacts were 16.4±9.2 % (later remembered), 16.8±10% (later forgotten), 21.9±13.1% (HIT), 20.0±10.9% (correctly rejected), 19.9±10.4% (MISS). For the sensor level analysis, an estimate of the planar gradient was calculated for each sensor using the signals from the neighboring sensors. The horizontal and vertical components of the planar gradients approximate the signal measured by MEG systems with planar gradiometers. The planar field gradient simplifies the interpretation of the sensor-level data since the maximal signal is located above the source (Hämäläinen et al., 1993).

Time-frequency representations (TFRs) of power were calculated for each trial using a FFT (multi)taper approach applied to short sliding time windows (Percival and Walden, 1993). The data in each time window were multiplied with a set of orthogonal Slepian tapers. The Fourier transforms of the tapered time windows were then calculated and the resulting power estimates were averaged across tapers. The power values were calculated for the horizontal and vertical component of the estimated planar gradient and then summed. The planar gradient power estimates were subsequently averaged over multiple trials for a given condition. For the frequencies 5–34 Hz, an adaptive time window of 3 cycles for each frequency ($\Delta T = 3/f$) and an adaptive smoothing of $\Delta f = 1/\Delta T$ was applied. This resulted in one taper being applied to the data from the sliding time window. In the higher frequency bands (35–180 Hz), a fixed time window of $\Delta T = 0.2$ s and a frequency smoothing of $\Delta f = 10$ Hz was used which resulted in three tapers being applied to the sliding time window. The change in power was calculated with respect to a baseline period -0.5 to -0.3 s prior to the presentation of the stimulus.

A frequency-domain beamforming approach (Dynamic Imaging of Coherent Sources,

DICS) was used to identify sources of oscillatory activity. Note, that for source reconstruction the data from the true axial sensors and not the planar gradient estimate was used. The DICSs technique uses adaptive spatial filters to localize power in the entire brain (Gross et al., 2001; Liljeström et al., 2005). The filter employs the cross-spectral density matrix which is calculated separately in the pre- and post-stimulus periods of the individual trials and averaged. The data length of the segmented trials for the theta sources was no less than 0.5 s and for the gamma sources no less than 0.2 s. Multisphere forward models were fitted to individual head-shapes identified from the individual MRIs (Huang and Mosher, 1997) obtained for 12 out of 13 subjects. The brain volume of each individual subject was discretized to a grid with a 0.5 cm resolution. Using the cross-spectral density matrices and the forward models, a spatial filter was constructed for each grid point and the power was estimated for each condition in each subject. The individual subjects' source estimates were overlaid on the corresponding anatomical MRI, and the anatomical and functional data were subsequently spatially normalized using SPM2 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm) to the International Consortium for Brain Mapping template (Montreal Neurological Institute, Montreal, Canada, http://www.bic.mni.mcgill.ca/brainweb). After spatial normalization, the beamformer source reconstructions were averaged across subjects.

4.3 Statistical analysis

In Study I, a three-way repeated measures ANOVA (group by frequency by region) with contrasts was carried out to compare power values between the groups. The activations within the ROIs, as well as the peak frequencies, were compared using *t*-tests. The distribution of the results of neuropsychological testing and the activation in ROIs were tested for normality and compared using two-tailed Pearson correlation coefficient.

In Study II spectral power at the five brain regions and four frequency bands was compared between the MCI patients and controls using a three-way repeated measures ANOVA (with group as a between-subject factor, and frequency and brain region as within-subject factors) with age as a covariate. To investigate more specifically which regions and frequency bands differ between the groups in case of significant main effect, a set of univariate ANOVAs with contrasts and age as a covariate was employed. Disease-related changes in the ROI activity, in turn, were analyzed using two-way repeated

measures ANOVA (group as a between-subject factor and ROI as within-subject factor) with contrasts and age as a covariate, and those in the peak frequency with a one-way ANOVA, with age as a covariate. Greenhouse-Geisser correction was used in all repeated-measures analyses.

In Study III a two-way repeated measures ANOVA (group by hemisphere) with contrasts was carried out to compare ASSR dipole locations and amplitudes between AD patients and controls. A two-way repeated measures ANOVA (group by hemisphere) was employed to test the log-transformed 40-Hz power differences between AD patients and controls.

In Study IV the significance of the difference between the two trial types in the encoding session (later remembered and later forgotten), and the three trial types in the retrieval session (HIT, correct rejection, MISS) was established using a randomization test (Maris E. and Oostenveld R., unpublished work). This test effectively controls the Type-I error rate in a situation involving multiple comparisons (such as 151 sensors) by clustering neighboring sensor pairs that exhibit the same effect. Time points were averaged within the 0.3–1 s interval, which is in agreement with the time course of memory effects indicated in ERP studies. This window of analysis also avoids interference of early visual evoked responses. Data points were also averaged within frequency bands. The frequency boundaries of theta, alpha, and beta bands were based on those widely accepted in EEG/MEG literature (Niedermeyer, 2005). The frequency boundaries of the gamma band were based on visual inspection of the TFRs for the averaged conditions. The randomization method identified sensors whose t-statistics exceeded a critical value when comparing two conditions sensor by sensor ($p < 0.05$, two-sided). To correct for multiple comparisons, the sensors which were neighboring in space were grouped as clusters. The cluster-level test statistic was defined as the sum of the t-statistics of the sensors pairs constituting a cluster. The Type-I error rate for the complete set of 151 sensors was controlled by evaluating the cluster-level test statistic under the randomization null distribution of the maximum cluster-level test statistic. This was obtained by randomizing the data between the two conditions across multiple subjects. By creating a reference distribution from 3000 random draws, the *p*-value was estimated according to the proportion of the randomization null distribution exceeding the observed maximum cluster-level test statistic.

5 Results

5.1 Sources of oscillatory brain activity in AD (Study I)

The three-way ANOVA revealed a significant group effect (F (1,21) = 11.2, $p < 0.01$), and a significant group by frequency band interaction (F (3,63) = 5.0, $p < 0.01$), indicating increased slower and reduced faster activity in AD patients. Contrasts revealed an increase in delta power in the frontal (F (1,21) = 7.3, $p < 0.05$) and occipital (F (1,21) = 5.7, $p < 0.05$) regions; overall increase in theta power (frontal: F (1,21) = 6.3, $p < 0.05$; central: F (1,21) = 6.2, $p < 0.05$; left temporal: F (1,21) = 8.7, $p < 0.01$; right temporal: F (1,21) = 7.3, $p < 0.05$; occipital: F (1,21) = 6.9, $p < 0.05$); and decrease in beta power in the frontal region (F (1,21) = 7.1, $p < 0.05$) in AD group (Fig. 6).

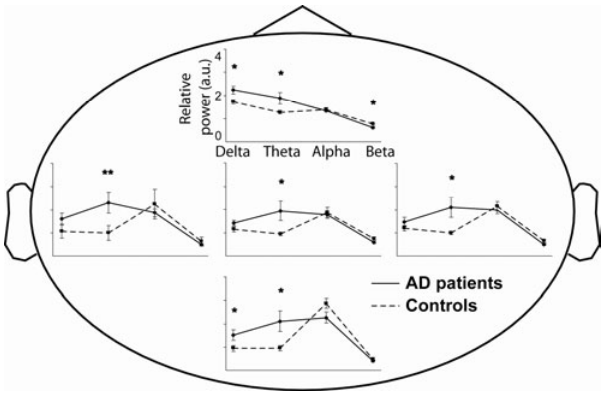

Figure 6. Mean relative power and standard errors in delta, theta, alpha and beta bands in AD and control groups in the frontal, left temporal, central, right temporal and occipital regions. * p < 0.05; ** p < 0.01. (Reprinted from Neuroimage 27: Osipova D., Ahveninen J., Jensen O., Ylikoski A., Pekkonen E. Altered generation of spontaneous oscillations in Alzheimer's disease. pp: 835–841. Copyright (2005), with permission from Elsevier).

Activation in the parieto-occipital ROI was significantly weaker in AD patients ($p < 0.01$) whereas activation in the right temporal ROI was enhanced ($p < 0.05$) (Fig. 7). In addition, there was a statistically insignificant trend toward the increase in the left temporal ROI in the AD. The neuropsychological test scores, presented in Table 2, were correlated against the ROI activations. The results indicated that only one out of eighteen correlations was found to be significant. The scores of the constructional praxis (figure copying) subtest inversely correlated with the activation in the right ROI in AD patients ($r = –0.73$, $p < 0.05$).

The peak frequency for the AD group was 8.5 Hz (±1.36) and 9.5 Hz (±1.25) for the controls. The peak frequency showed a trend for decrease in the AD group but the result was not significant ($p < 0.07$). However, in the AD group, peak frequency inversely correlated with the activation in the right ROI ($r = –0.8$, $p < 0.01$).

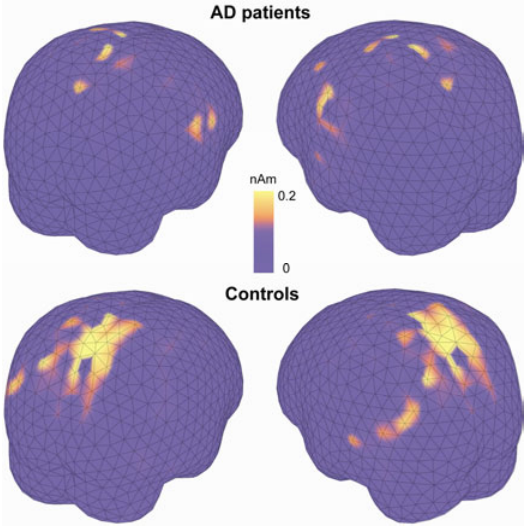

Figure 7. Grand averages of MCEs in AD and control groups. Parieto-occipital activation in AD patients is decreased whereas temporal activation is enhanced (Reprinted from Neuroimage 27: Osipova D., Ahveninen J., Jensen O., Ylikoski A., Pekkonen E. Altered generation of spontaneous oscillations in Alzheimer's disease. pp: 835–841. Copyright (2005), with permission from Elsevier).

5.2 Sources of oscillatory brain activity in MCI (Study II)

The three-way ANOVA revealed a significant group effect ($F(2, 20) = 3.7$, $p < 0.05$), and a significant group by frequency band by region interaction ($F(3,63) = 5.0$, $p < 0.01$). According to contrasts, a significant group effect was found in the theta band in the central ($F(2, 20) = 6.5$, $p < 0.01$), left temporal ($F(2, 20) = 6.2$, $p < 0.01$), right temporal ($F(2, 20) = 3.9$, $p < 0.05$) and occipital ($F(2, 20) = 5.6$, $p < 0.05$) regions (Fig. 8). Specifically, the theta spectral power was lower in the controls and MCI patients than that in the AD patients in the central (controls versus AD patients: contrast estimate −1.0, 95% confidence interval (CI) [−1.5−0.4], $p < 0.01$; MCI versus AD patients: contrast estimate −1.0, 95% CI [−1.8−0.3], $p < 0.05$), left temporal (controls versus AD patients: contrast estimate −1.1, 95% CI [−1.7−0.4], $p < 0.01$; MCI versus AD patients: contrast estimate −0.9, 95% CI [−1.8−0.1], $p < 0.05$) and occipital (controls versus AD patients: contrast

estimate −1.3, 95% CI [−2.2−0.5], $p < 0.01$; MCI versus AD patients: contrast estimate −1.3, 95% CI [−2.4−0.2], $p < 0.05$) regions. Theta band power in controls was lower than that in AD patients in the right temporal region (contrast estimate −1.0, 95% CI [−1.7−0.2], $p < 0.05$). There were no significant differences in power between MCI patients and controls.

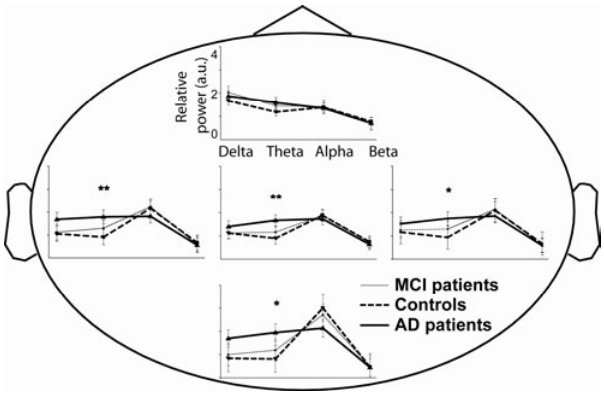

Figure 8. Mean relative power and standard errors in delta, theta, alpha and beta bands in MCI, AD and control groups in the frontal, left temporal, central, right temporal and occipital regions. * $p < 0.05$; ** $p < 0.01$.

As shown by the grand-average minimum-current estimates (Fig. 9), the source distributions at individual alpha peak frequency suggested significant abnormality of alpha generation in AD patients, while there was no difference between the MCI patients and controls in the parieto-occipital alpha activations. The ROI analysis showed a significant source amplitude difference between the AD versus MCI patients and controls (contrast estimate −0.012, 95% CI [−0.023−0.001], $p < 0.05$), while there was no significant difference between the MCI patients and controls in the parieto-occipital or temporal regions. However, the main effect of the repeated-measures ANOVA remained non-significant ($p = 0.07$).

According to the ANOVA with age as a covariate, the group difference in alpha peak frequency, being lower in MCI (8.2±0.7 Hz) and AD (8.5±1.5 Hz) patients than the controls (9.2±0.7 Hz), was non-significant ($p = 0.09$).

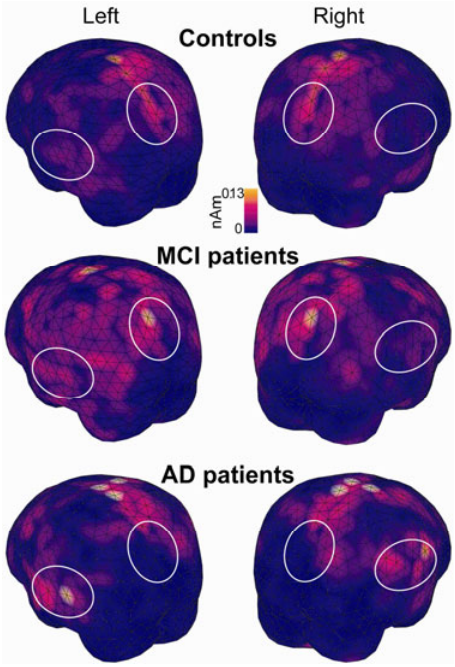

Figure 9. Grand average MEG source estimates in the controls, MCI and AD patients. Source estimates for each subject were calculated for the individual peak frequency in the spectrum (range 6–10.3 Hz). Controls and MCI patients have a similar pattern of strong parieto-occipital activation, whereas in AD patients parieto-occipital activation is decreased and temporal sources are enhanced. (The loci of temporal and parieto-occipital activation, determined individually with the ROI approach, have been encircled). (Reprinted from Neuroscience Letters 405: Osipova D., Rantanen K., Ahveninen J., Ylikoski R., Happola O., Strandberg T., Pekkonen E. Source estimation of spontaneous MEG oscillations in mild cognitive impairment. pp: 57–61. Copyright (2006), with permission from Elsevier).

5.3 Auditory steady-state response in AD (Study III).

The main effect of ANOVA (group by hemisphere) indicated a significant increase of ASSR dipole amplitude in AD patients (F (1,20) = 5.4, $p < 0.05$). Contrasts revealed a significant increase in ASSR dipole amplitude in the right (F (1,20) = 5.0, $p < 0.05$) and a trend in the left hemisphere in AD patients ($p = 0.057$). The difference in the left (ipsilateral) hemisphere was not significant probably due to the reduced signal-to-noise ratio and increased variance. In the right hemisphere, mean dipole amplitude was 3.4±1.3 nAm in the AD group, and 2.3±0.9 nAm in the control group. In the left hemisphere, mean dipole amplitude was 2.7±1.7 nAm for AD patients and 1.5±0.8 nAm for controls. Grand averaged dipole amplitudes for both groups and both hemispheres are presented in Figure 10A.

There were no significant differences in the source locations (Table 3) or orientations. A given extracranial magnetic field can be modeled by an indefinite number of solutions,

for example, by a weaker superficial or a stronger deep source. The lack of significant differences in dipole locations thus suggests that the source amplitude differences between the groups did not result from group differences in the source depth. The dipole coordinates for both groups were averaged in the head coordinate system and then co-registered to the International Consortium for Brain Mapping template (Montreal Neurological Institute, Montreal, Canada; http://www.bic.mni.mcgill.ca/brainweb/) (Fig. 10B).

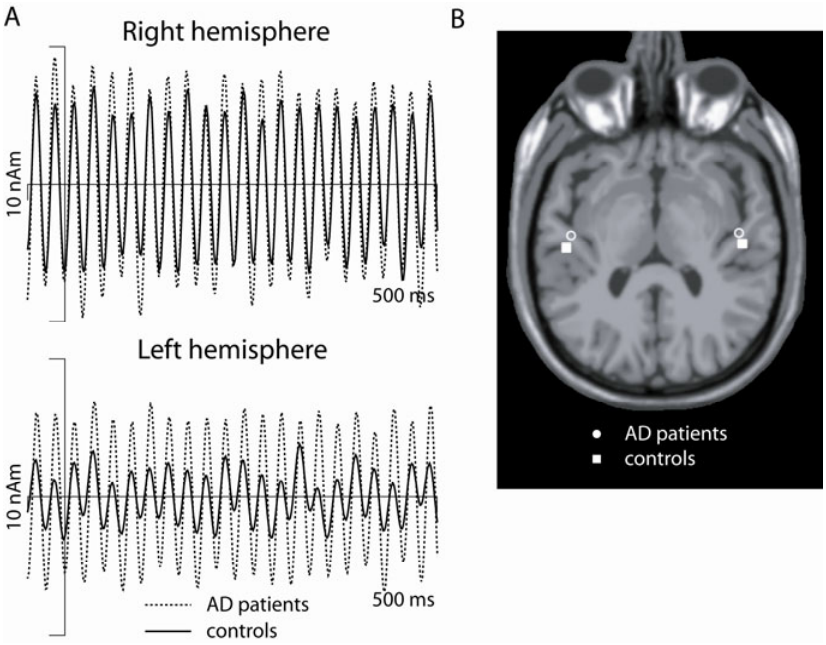

Figure 10. A. Grand averaged dipole amplitudes in the right and left hemisphere in AD and controls groups. Dipole amplitudes of the AD patients were significantly increased in the contralateral (right) hemisphere and showed a strong trend for increase in the ipsilateral (left) hemisphere. B. Mean locations of ASSR dipoles in both groups overlaid on the standard brain (Montreal Neurological Institute, Montreal, Canada). The horizontal view is tilted along the Sylvian fissure. (Reprinted from Clinical Neurophysiology 117: Osipova D., Ahveninen J., Pekkonen E. Enhanced magnetic auditory steady-state response in early Alzheimer's disease, pp.1990–1995, 2006, with permission from The International Federation of Clinical Neurophysiology).

Consistent with the ECD modeling results, the frequency domain analysis indicated significantly increased 40 Hz power in AD patients as compared to controls (F (1,20) = 10.3, $p < 0.01$). The means and standard deviations of the log-transformed power values are presented in Table 3. The fact that no source analysis has been performed in the frequency domain is unlikely to confound the results, given the similarity between the time and frequency domain findings. Finally, the difference between ipsi- and contralateral hemispheres was significant ($p < 0.01$) in controls but in not in AD patients ($p > 0.1$).

	Right hemisphere (mm)			Left hemisphere (mm)		
	x	***y***	***z***	***x***	***y***	***z***
AD patients	47.3 ±9.6	19.4 ±12.7	56.9 ±7.3	-48.6 ±5.6	20.5 ±10. 9	60.4 ±7.0
Controls	48.8 ±5.8	15.3 ±12.0	62.1 ±4.6	-51.3 ±7.6	12.2 ±9.7	61.4 ±12.6

Table 3. Mean coordinates and standard deviations of ASSR dipole locations in both hemispheres in AD and control groups. Dipole locations did not differ significantly between the groups.

5.4 The role of theta and gamma oscillations in declarative memory (Study IV).

Behavioral performance

In the encoding session, the building/landscape decision was performed with a mean accuracy of 96.5± 2.8% demonstrating that subjects were attending to the stimuli. Incorrect (2.7±1.8%) and no response (0.6±1.0%) trials were excluded from the analysis. Notably, the d-prime values were higher for buildings than landscapes. Recognition memory performance for buildings and landscapes separately is presented in Table 1. Accuracy of recognition was calculated as a difference in probabilities of a correct old judgment (HIT) and an incorrect old judgment for a new item (false alarm; FA) (*Pr*= probability HIT – probability FA). Due to the low number of FA trials, the recognition performance substantially exceeded chance level (mean *Pr* = 0.44 (SD 0.12), t12 = 12.48; $p < 0.001$).

Encoding session

The time-frequency representations (TFRs) of power for the combined planar gradients were calculated for different conditions. In the gamma band (60–90 Hz), strong activity was identified over posterior areas for both later remembered and forgotten items (Fig. 11). The TFRs revealed that the gamma activity was stronger for later remembered compared to later forgotten items during the 0.3–1 s time interval of the item presentations (Fig 11B,C). This reflects the subsequent memory effect. Randomization analysis identified two clusters of occipital sensors corresponding to a significant difference in the gamma band between the two conditions ($p < 0.01$ and $p < 0.05$) (Fig 11A). Further, sources of gamma activity were identified with the beamformer analysis (Gross et al., 2001; Liljeström et al., 2005). As shown in Figure 11D gamma sources in both conditions

were located bilaterally in Brodmann areas (BA) 18 and 19. Comparison of source strength for the later remembered and later forgotten trials revealed that the source difference between the conditions was in the same areas. The location of these sources is consistent with the topographies of power in Fig. 11A.

In the theta band (4.5–8.5 Hz), a systematic difference in theta power was observed when comparing the encoding period for later remembered to forgotten trials (Fig. 12). This difference was most pronounced over the right temporal areas (Fig. 12A). The TFRs over right temporal sensors showed that the difference was the strongest during the 0.3–1 s period of the presentation interval (Fig 12B,C). In the theta band, statistics was done for 6.0±2.2 Hz, where the ±2.2 Hz smoothing was determined by our spectral estimation approach. The randomization approach identified a cluster of sensors over the right temporal cortex with a significant difference in the theta band ($p < 0.05$) (Fig 12A). The sources of the effect in the theta band could not be successfully identified, most likely due to an insufficient signal-to-noise ratio. A prerequisite for a good signal-to-noise ratio in the Beamformer analysis is a reliable estimate of power which is based on a sufficiently high number of cycles. In the theta band, that requires epochs of much longer duration as compared to higher frequencies (since each cycle in the theta band is longer than that e.g. in the gamma band). The insuffiently low number or trials results in inaccurate estimation of the covariance matrix employed in the Beamformer analysis. The source estimates in the theta band were discarded based on the lack of consistency between subjects and between source and sensor data.

There were no significant effects in either alpha (8–13 Hz) or beta (13–25 Hz) frequency bands during encoding.

Retrieval session

Old/new effects were identified by comparing hits to correct rejections. Strong gamma band activity was observed over the posterior brain regions during retrieval. The frequency range was 60–90 Hz, similarly to that observed during the encoding session. This gamma activity increased in the last part of the retrieval interval (0.3–1 s) over the occipital region for hits compared to correct rejections, reflecting the old/new effect. The increase was weak but statistically significant ($p < 0.05$). The primary sources of the gamma activity were localized in BA18 and 19, similarly to the ones in the encoding session. The difference in source strength involved parietal and occipital sources. However, due to the

relatively low signal-to-noise ratio, the spatial distribution of this source power difference outside BA18/19 should be interpreted with caution.

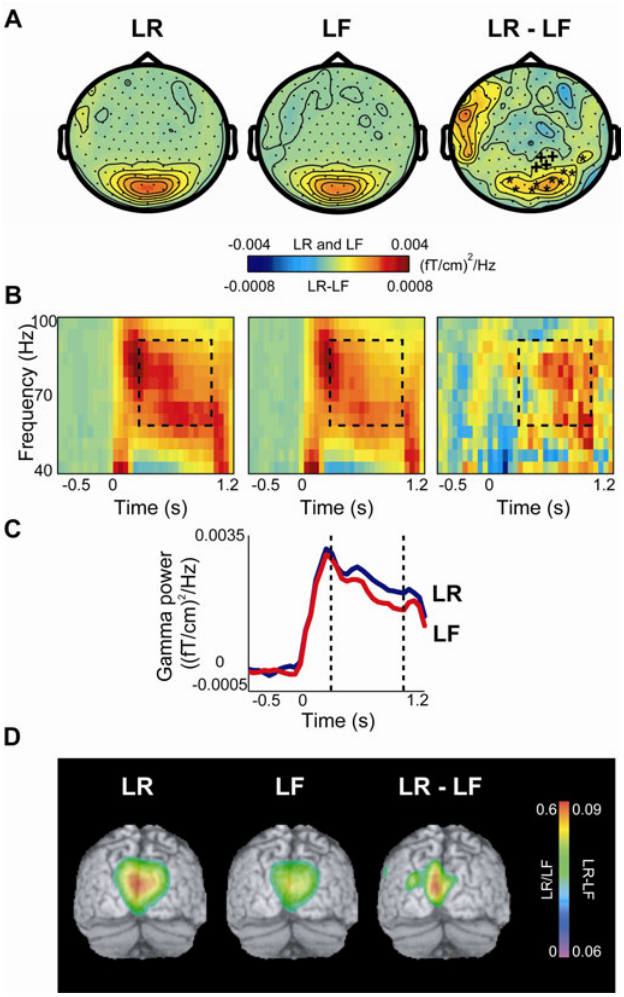

Figure 11. Gamma activity during the encoding session: the subsequent memory effect. (A) The grand average of the topography of gamma power for the later remembered (LR), later forgotten (LF) trials and their subtraction (LR-LF). Two adjacent clusters of occipital sensors showed significant increase in gamma power ($p < 0.01$, marked with *; $p < 0.05$, marked with +). (B) Grand-averaged time-frequency representations of power from one significant sensor showing the time course of gamma oscillations during LR, LF and their difference. (C) Grand-averaged gamma power averaged between 60–90 Hz for both conditions for the same sensor as in (B). (D) Source reconstruction of gamma activity, averaged over subjects, and overlaid on the MNI standard brain. The sources for LR and LF conditions were located bilaterally in BA18/19. The difference in power (LR-LF) revealed sources in BA18/19 as well. The power of the source representations was thresholded at half maximum. (Reprinted with permission from Osipova D., Takashima A., Oostenveld R., Fernandez G., Maris E., Jensen O. Theta and gamma oscillations predict encoding and retrieval of declarative memory. Journal of Neuroscience. 2006; 26 pp.:7523–7531. Copyright 2006 by the Society for Neuroscience).

During retrieval, a modulation in theta (4.5–8.5 Hz) band was found when comparing hits to correct rejections. The difference in theta band activity when comparing hits to correct rejections was lateralized over right posterior regions; this effect was statistically significant in the time window 0.3–1 s ($p < 0.05$). Similarly to the first session, source analysis for the theta band did not produce any convincing results, again, probably due to an insufficient signal-to-noise ratio. Recognition effects were identified by comparing hits to misses. No significant effects were observed in the theta band; however, the gamma band modulations were highly robust. The difference in the gamma activity was also significant between hits and misses (two adjacent clusters of $p < 0.01$ and $p < 0.05$). The sources of the gamma activity were located bilaterally in BA18 and 19; the difference in source strength was also confined to the same areas.

Beta power was bilaterally significantly decreased for the hits as compared to correct rejections ($p < 0.01$; data not shown). For hits vs. misses, beta power was also decreased bilaterally over wide areas ($p < 0.03$; data not shown). However, since hits responses were consistently given with the left index finger, and correct rejections and miss responses with the right index finger, the lateralized effects in the beta band are most likely explained by motor preparation (e.g. Pfurtscheller et al., 1998). No effects were found in the alpha band in the retrieval session.

Figures illustrating the findings from the retrieval session are shown in the appendix (Study IV).

Induced vs. evoked activity

The EEG/MEG literature distinguishes between evoked and induced oscillatory activity. Evoked activity is phase-locked to the stimuli and is thus also present in the ERPs/ERFs. Induced activity is not strictly phase-locked to the stimuli and is not present in the ERPs/ERFs (see Tallon-Baudry and Bertrand, 1999). In order to clarify whether the changes we observed are due to modulations in evoked activity, we calculated the TFRs for the ERFs. Only one cluster of six fronto-temporal sensors in the gamma band was significant for HITs compared to CRs ($p < 0.05$). However, the location of this significant cluster was clearly different from the posterior cluster showing the increase in induced gamma activity (Fig. 4). No other significant memory related changes in evoked activity were observed (data not shown). Notably, Takashima et al. (2006) found memory effects in the ERFs during the encoding session using the same paradigm. These ERF effects had

very slow time courses and were sustained over several hundred milliseconds. Therefore, they would be present only in the low frequency ranges (<2 Hz) and cannot be considered oscillatory phenomena. We conclude that the memory-related effects in the gamma and theta band are explained by induced oscillatory activity rather than the difference in the ERFs.

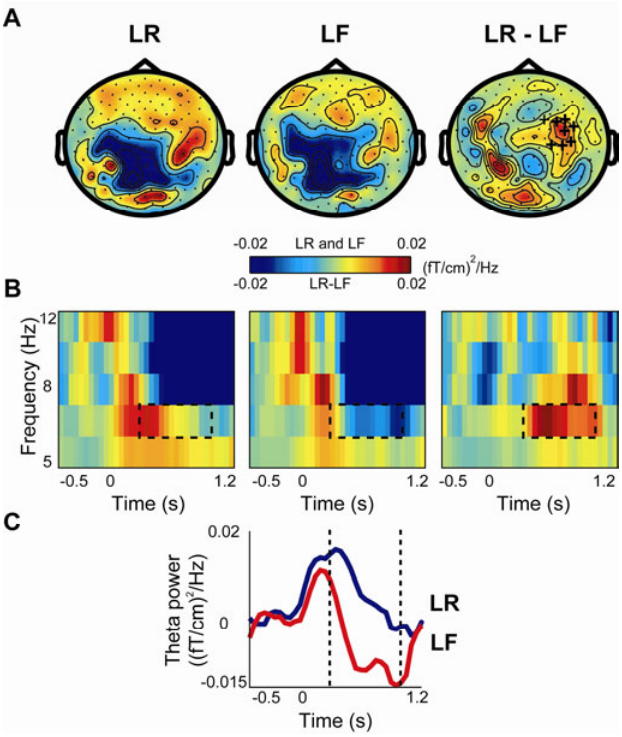

Figure 12. Theta activity during the encoding session: the subsequent memory effect. (A) The grand average of topography of theta power for the later remembered (LR), later forgotten (LF) trials and their difference (LR-LF). The cluster of right temporal sensors which showed significantly increased power in the LR as compared to the LF condition is indicated by the crosses ($p < 0.05$). (B) Grand-averaged time-frequency representations of power from a significant representative sensor showing the time course of theta oscillations during LF, LR and their difference. (C) Grand-average of theta power (4.5–8.5 Hz) for both conditions for the same sensor as in (B). (Reprinted with permission from Osipova D., Takashima A., Oostenveld R., Fernandez G., Maris E., Jensen O. Theta and gamma oscillations predict encoding and retrieval of declarative memory. Journal of Neuroscience. 2006; 26. pp.:7523–7531. Copyright 2006 by the Society for Neuroscience).

6 Discussion

Oscillations are thought to be one of the mechanisms of communication between brain regions required for cognitive processing, including memory tasks. In this study, abnormalities of oscillatory brain signals were investigated in order to elucidate the neuronal basis of degenerative abnormalities in memory function. First, power and sources of oscillatory activity were investigated in patients with memory disorders and healthy aged subjects. The results revealed abnormalities in spontaneous MEG activity in AD but not in MCI and normal aging, manifesting, mostly, in increased theta power and enhanced temporal and reduced occipito-parietal oscillatory sources in 6–12.5 Hz frequency range. Further, the amplitude of ASSR to auditory stimulation was significantly increased in AD patients as compared to healthy subjects. Finally, in the attempt to develop an optimal paradigm suitable for the analysis of brain rhythms involved in memory processing directly, it was found that increase in theta and gamma oscillations can predict successful memory encoding and retrieval. This approach could be potentially used to investigate declarative memory deficits in AD patients.

6.1 Abnormalities in oscillatory activity in AD and MCI

The distribution of sources of spontaneous activity in the 6–12.5 Hz frequency band was studied in AD, MCI and healthy aged subjects by applying MCE (Uutela et al., 1999), which allows simultaneous mapping of several oscillatory sources in the brain (Jensen and Vanni, 2002). In the control subjects, similarly to MCI patients, sources of spontaneous alpha-band activity were concentrated, as expected (Williamson and Kaufman, 1989; Hari and Salmelin, 1997; Ciulla et al., 1999), in or near the parieto-occipital sulcus. AD patients, on the other hand, had reduced parieto-occipital activation, accompanied by enhanced sources in the temporal regions. Theta band power was increased in AD patients but not in MCI patients or controls. Our findings thus suggest that changes in electromagnetic activity in AD are mostly due to an increase in activation of temporal generators oscillating in the frequency of 6–12.5 Hz, rather than to slowing of existing sources. Functionally, these generators might represent either upper theta or lower alpha band activity.

One possible interpretation is that the temporal sources represent the so-called

temporal “tau” rhythm, and the observed activity might reflect increased relative contribution of the 6–10 Hz sources in the temporal cortex, which have been suggested to coincide or replace occipital alpha when the subject is drowsy (Hari, 2005). However, given that the duration of the measurement did not exceed two minutes and the data was subsequently checked for the presence of sleep spindles, and no increase was found at 12–15 Hz (Zygierewicz et al., 1999), there is no direct evidence suggesting that our AD patients were drowsier than MCI patients or controls. Also, in terms of clinical diagnosis, these patients were at an early stage of the disease with no fundamental problems in understanding, or following the task instructions during the 2-minute recording. The second possible interpretation is related to the theta rhythm. The peak frequencies for which source localization was performed varied from 6 to 10.2 Hz in the AD group but due to blurred definitions of frequency bands in neurodegenerative diseases it is problematic to strictly differentiate alpha and theta bands in AD. Furthermore, as pointed out by Niedermeyer (1997), the midtemporal alpha-band rhythm may partially overlap with the upper theta. Thus one could interpret the temporal activation in AD as an increase in upper theta power, also supported by the results of power analysis. This explanation is particularly interesting, because theta activity is thought to be engaged in memory operations (Klimesch et al., 1996; Jensen and Tesche, 2002; Sederberg et al., 2003; Fell et al., 2003), which is the first cognitive domain to be impaired in both AD and MCI. The role of theta activity in memory performance has been addressed in Study IV. However, it remains to be determined whether focal task-related theta rhythm and the resting-state theta which manifests in the diffuse pathological enhancement in AD patients are based on a common neurophysiological mechanism.

Even though not statistically significantly, the peak frequencies showed a strong trend for being lower in AD as compared to the control subjects. Moreover, the peak frequency in AD patients inversely correlated with the activation in the right ROI, indicating the possible involvement of the upper theta band (up to 8.5 Hz) in patients with specifically pronounced temporal activation. These results are in line with the data of Fernandez et al. (2002), who reported increased dipole density of slow activity (up to 8 Hz) in the temporo-parietal regions of AD patients, and PET studies, which demonstrated correlation between the increased slow rhythms and reduced oxygen metabolism in temporo-parietal regions in AD (Buchan et al., 1997). In MCI patients, the posterior alpha peak frequency, on average, was also lower than in control subjects. Although this difference was non-significant, it is

interesting to note that this tendency resembles the EEG abnormalities reported in other studies on MCI (Fernandez et al., 2006) and AD (Penttilä et al., 1985; Schreiter-Gasser et al., 1993).

The enhanced temporal-lobe contribution associated with parieto-occipital deactivation, suggest that the “anterior shift” in sources identified with ECD modeling in AD shown in EEG studies of Dierks et al. (1993) and Huang et al. (2000) can be interpreted as a relative change in posterior/temporal generators. This pattern of generator changes is partly in agreement with the interpretations of Babiloni et al. (2004) who found that suppression of alpha sources in AD is specifically pronounced in the posterior brain regions as compared with their central counterparts. The study of Babiloni et al. (2004), on the other hand, revealed no enhancement of sources in the temporal regions in AD patients. Fernandez et al. (2002), however, reported increased temporoparietal sources of slow activity, which is consistent with our results. The reasons for the discrepancy between our results, as well as the results of Fernandez et al. (2002), and the data of Babiloni et al. (2004) are unclear at present. Once reason could be that the EEG/LORETA approach used by Babiloni and his collaborators (2004) produced quite diffuse sources for the spontaneous rhythms, although other source modeling methods, such as ECD, MCE and Dynamic imaging of coherent sources (DICS), seem to point to fairly focal generators of oscillatory sources (Liljeström et al., 2005). Our MCE models of MEG activity, with relatively narrow point-spread function, indicated a clear pattern of focal loci of activity at the individual level, robust in most controls but mainly abnormal in AD patients. In MCI, however, our result is principally consistent with earlier EEG observations (Huang et al., 2000) although only few MEG source estimation studies on alpha activity have been published to date.

Notably, differences in the temporal ROI activation between the AD and control groups were statistically significant only in the right hemisphere and inversely correlated with the results of a constructional praxis subtest. It is noteworthy that this change in the right hemisphere MEG source pattern correlated with performance in a neuropsychological tests that are generally believed to measure predominantly right hemispheric functions (Lezak, 1995). Although this result requires further empirical corroboration, it suggests that our MCE estimates measure clinically relevant functional changes in the brains of AD patients. The lateralization of this correlation result also supports the interpretation that the observed changes are not due to reduced vigilance in

AD patients.

Animal studies suggest that alpha rhythm is likely to be generated by networks of both thalamic and cortical oscillators (Lopes da Silva et al., 1973; Lopes da Silva et al., 1980). Thalamic pathology has been observed in both AD and MCI, by using functional (Callen et al., 2002; Nestor et al., 2003) and anatomical (Karas et al., 2004; Pennanen et al., 2005) neuroimaging methods. However, the temporoparietal cortex seems more spared in MCI than in AD patients (Nestor et al., 2003; Karas et al., 2004). One might thus speculate that the tendency toward a reduction of the alpha peak frequency in MCI reflects thalamic pathology, whereas the temporoparietal changes, potentially explaining the "anterior shift" of alpha sources in AD (Huang et al., 2000), might only be associated with clinically evident AD. To test this hypothesis, follow-up studies in MCI patients with a much larger number of subjects are needed.

Furthermore, alpha rhythm generators are thought be modulated by brainstem cholinergic neurons (Steriade et al., 1990a). Given that deficits in the brain cholinergic transmission are suggested to be the major neurochemical phenomenon underlying cognitive and functional changes associated with AD (Davies and Maloney, 1976; Rylett et al., 1983; Arendt et al., 1984; Reinikainen et al., 1988), it is possible that the present abnormalities in MEG oscillatory sources and power spectra could reflect pathological changes in the cholinergic system . Interestingly, the increased delta and theta power, and the trend toward the peak-frequency reduction of alpha, resemble the pattern of spontaneous EEG changes observed after administration of scopolamine, a centrally acting antagonist of muscarinic ACh receptors (e.g. Osipova et al., 2003). Further, the administration of scopolamine was shown to impair delayed memory performance (Ahveninen et al., 2002) suggesting the involvement of cholinergic system in mnemonic operations.

Taken together, mapping of oscillatory sources with MCE revealed the decreased power of alpha sources within the parieto-occipital region often accompanied by the enhanced activation in the temporal lobes in AD patients, as opposed to MCI patients and controls. Thus resting brain activity in MCI patients seems to differ from observations in early AD. The conclusiveness of this negative result is supported by the fact that the MCI patients were, on average, slightly older than the controls (and the non-medicated, recently diagnosed AD patients), which decreases the probability that there was an undetected abnormality in the control sample. However, the tendency toward the slowing of

spontaneous alpha activity in MCI suggests that some of the MCI patients might develop more profound oscillatory abnormalities inherent for AD.

6.2 A lack of inhibition in AD? Auditory steady-state response in AD (Study III)

Another important finding of the present study is that the amplitude of the ASSR, most likely reflecting both induced and evoked activity, was significantly increased in AD as compared to healthy subjects. One possible interpretation of this result is an impaired adaptation of auditory neurons. ASSR experiments in healthy subjects have demonstrated a differential pattern of refractoriness for transient and steady-state responses: in case a short gap is present in a sequence of stimuli ASSR can quickly return to its initial amplitude, whereas the transient response (such as e.g. P50) has an inverse pattern of remaining refractory for the short gaps (Gutschalk et al., 2004). The present result thus suggests that ASSR evoked by continuous fast-rate stimulation is a sensitive measure of inhibition, which seems to be impaired in AD as compared to healthy subjects.

Middle latency components, the superposition of which is often thought to result in ASSR (Galambos et al., 1981), have been investigated in several EEG studies on AD. While the later P50 component was reported to be decreased (Buchwald et al., 1991; O'Mahony et al., 1994) or absent (Green et al., 1992) in mild-moderate AD, there is evidence that earlier MLR components could be unchanged (Buchwald et al., 1991; O'Mahony et al., 1994). However, the present findings of increased ASSR amplitudes in AD patients resemble the findings in subjects at risk for AD (Boutros et al., 1995) and in patients with MCI (Golob et al., 2002), showing an increased P50 amplitude as compared to healthy controls. The lack of inhibition in a double-click paradigm has also been reported in non-medicated AD patients (Cancelli et al., 2006). Further, the administration of the muscarinic antagonist scopolamine, often used as a pharmacological model of AD, has resulted in enhanced amplitudes of early auditory ERF components (Jääskeläinen et al., 1999; Pekkonen et al., 2001; Ahveninen et al., 2002). Our results thus resemble those obtained in high-risk groups which subsequently develop into clinically prominent AD. Notably, patients in our study have been only recently diagnosed with AD. This may explain the similarity of the present results to those reported in MCI and subjects at risk for AD.

However, some experimental evidence fails to explain an ASSR by superposition of MLR (Santarelli and Conti, 1999; Ross et al., 2002). This implies that ASSR can be viewed as induced activity. The results of Ross et al.(2005) support the hypothesis of ASSR being a separate neural oscillation overlapping with the ongoing brain activity. To our knowledge, at present no studies on induced gamma activity in AD have been conducted, although changes in synchronization of spontaneous gamma activity in AD have been reported (Stam et al., 2002; Koenig et al., 2005). In general, induced gamma oscillations have been proposed to play an important role in sensory information processing, such as e.g. temporal binding in auditory perception (Joliot et al., 1994), but the actual relationship between the steady-state gamma and binding is largely unknown (Tallon-Baudry and Bertrand, 1999).

In our study, ASSR sources were most likely localized in the primary auditory cortex, which is supported by the previous human (Mäkelä and Hari, 1987; Hari et al., 1989; Pantev et al., 1993) and animal (Franowicz and Barth, 1995; Eggermont, 1997) studies. It is thought that cortical neurodegeneration in AD starts from the medial temporal regions, and then progresses to the higher order areas of the neocortex (for a review, see Braak et al., 1999). At the same time, the cortical degeneration is accompanied by the progressive changes in the basal forebrain ACh system that innervates the neocortex, including auditory cortices. It is possible that the present effects reflect changes in such diffuse projection systems, regulating the function of the auditory cortex (reviewed in Hu, 2003). The conclusion that the cholinergic system may be involved in the modulation of auditory cortex can also be supported by the fact that ASSR was increased, not decreased, in AD patients, resembling earlier findings obtained by a blockage of cholinergic muscarinic receptors in both elderly (Ahveninen et al., 2002) and young subjects (Jääskeläinen et al., 1999; Ahveninen et al., 1999; Pekkonen et al., 2001).

Several theories of cognitive aging (e.g. Hasher and Zacks, 1988) have suggested that aging is associated with deficits in inhibitory function, leading to inadequate filtering of relevant information. This notion is consistent with our results. Moreover, our results support the idea that such deficient gating may affect stimulus processing already at an early cortical stage. Interestingly, previous studies suggest that abnormal adaptation of auditory neurons may be associated with cholinergic abnormalities; genetic linkage studies suggest that abnormal P50 suppression to paired click stimuli in schizophrenia may stem from an impairment in a specific nicotinic receptor gene (Freedman et al., 1997). This is

especially interesting given the crucial role of the cholinergic system in the modulation of higher cognitive functions and its reported abnormalities in AD. Although it has been shown that application of ACh in cell studies produces mainly excitatory effects in the auditory cortex (Cox et al., 1994; Aramakis et al., 1999), it has also been shown that muscarinic receptors, in turn, have both excitatory and inhibitory subtypes (Durieux, 1996), and that the ACh effects depend on the type of postsynaptic neuron (Pirch, 1995). It is possible that the cholinergic modulation might suppress weak and enhance strong input activation functioning analogously to the noise filter. In AD this mechanism might be impaired, leading to the lack of inhibition in cortical auditory processing.

The results of Study III suggest an enhancement of the ASSR in AD patients with mild to moderate cognitive deterioration, as compared to healthy elderly subjects. This possibly reflects decreased inhibition in auditory processing and deficits in adaptation to repetitive stimulation with low relevance, probably due to abnormalities in cholinergic modulation.

6.3 Optimal paradigm to investigate oscillatory abnormalities in AD?

Despite providing some insight on neurophysiological deficits in AD, recording MEG during a mnemonic task can be more sensitive that resting-state measurements. Therefore, this study aimed at developing an MEG paradigm suitable for investigating the neural basis of memory abnormalities in memory disorders, such as AD. A declarative memory task was specifically chosen since deterioriation of declarative (or more specifically, episodic) memory is one of the earliest and major symptoms of AD. Our results showed that declarative memory encoding and retrieval are associated with modulations of oscillatory activity in the gamma and theta bands. Successful memory trace formation, the subsequent memory effect, was accompanied by a large magnitude of gamma power produced in occipital areas (BA18/19). This gamma power was significantly stronger for the later remember than for the later forgotten items. The effects in the gamma band occurred in the 0.3–1 s interval with respect to stimulus onset. Further, theta power was increased over the right temporal areas with respect to subsequent memory but the sources could not be identified. In the retrieval session the old/new effect was expressed as gamma power being significantly greater for hits compared to correct rejections. The old/new effect was also associated with a significant increase in the theta power over right

parietotemporal regions. The recognition effect was expressed as high power in the gamma band when comparing hits to misses. The gamma sources for both effects were identical to those in the encoding session. To the best of our knowledge, this is the first study demonstrating induced gamma activity in the occipital areas associated with declarative memory encoding and retrieval.

Present results are consistent with previous EEG studies which have demonstrated an increase in theta power for the subsequent memory effect (Klimesch et al., 1996) and old/new effect (Klimesch et al., 2000). These studies applied words, whereas in the present study pictorial stimuli were utilized. In addition, our results show that the effects in the theta band most likely originate in the right temporal lobe. The effects in the theta band over right temporal cortex are consistent with findings from intracranial EEG recordings (Sederberg et al., 2003). In addition to these results, increased power in the gamma band was identified in the occipital cortex. Understandably, the locations of electrodes in intracranial EEG depend on the type of pathology or on the requirements of presurgical mapping, which often leave the occipital region uncovered. Moreover, it is difficult to differentiate pathology- or medication-related high frequency activity from regular gamma oscillations, whereas in the present study unmedicated young healthy subjects were measured.

Further, given important differences in evoked and induced activity, we can conclude that our findings do not stem from changes in evoked fields but rather from induced activity in the theta and gamma bands. Overall, these findings support previous intracranial EEG data suggesting a role for both theta and gamma oscillations in declarative encoding.

6.3.1 Physiological role of theta and gamma oscillations during declarative memory encoding

Synchronization in the gamma bands in the visual system has been related to feature binding and selective attention in cats (Eckhorn et al., 1988; Gray and Singer, 1989) and monkeys (Kreiter and Singer, 1996; Gail et al., 2000; Fries et al., 2001). Several MEG studies have likewise shown a relationship between the gamma-band activity and visual perception (Kaiser et al., 2004; Adjamian et al., 2004; Hoogenboom et al., 2006). Thus, the increase in gamma band power during declarative memory encoding and retrieval most

likely reflects enhanced neuronal synchronization. Experimental and theoretical work shows that a neuron receiving multiple inputs is more likely to fire if these inputs are synchronized (see Salinas and Sejnowski, 2001 for a review). Thus, the increase in synchronized activity in BA18/19 is likely to lead to a stronger drive to downstream areas directly involved in memory encoding and retrieval.

Theta oscillations could play a role in synaptic plasticity. It has been shown both in *in vitro* and *in vivo* recordings that long-term potentiation in the rat hippocampus can be induced by pairing of the inducing stimulus with the peak of the hippocampal theta rhythm (Huerta and Lisman, 1993; Hölscher et al., 1997). It is possible that the right temporal theta activity reflects neuronal dynamics that is optimal for synaptic plasticity which facilitates memory encoding. Notably, a flow of information between different brain regions during memory formation is modulated by ACh (reviewed in Hasselmo, 1999). In animals, high levels of ACh are accompanied by the hippocampal theta oscillations (Winson, 1974) coinciding with the encoding of new representations. Memory formation in humans also seems associated with an increase in the neocortical theta activity (Sederberg et al., 2003). Low doses of cholinergic antagonist scopolamine impair encoding of new information, but have little effect on the retrieval of information encoded prior to scopolamine administration (Ghoneim and Mewaldt, 1975; Hasselmo and Wyble, 1997) which supports the notion that reduced cholinergic modulation interferes with the feedforward sensory input, disrupting the encoding of new information.

In AD, cholinergic markers are decreased (Davies and Maloney, 1976; Whitehouse et al., 1982; Arendt et al., 1984), whereas theta activity is significantly increased in rest (e.g Coben et al., 1983; Penttilä et al., 1985; Schreiter-Gasser et al., 1993). Therefore, it seems that the relationship between ACh and pathologically enhanced diffuse theta activity in AD differs from that between ACh and memory-related theta oscillations. It is unlikely but possible that the increase in theta power in the right temporal region observed in Study IV represents hippocampal activation, whereas wide-spread theta in Studies I and II is mainly of neocortical origin. If it is not the case, and theta activity observed in all of these studies originates in the neocortex, increase in the theta power in AD can either represent the overcompensation of theta activity without the involvement of the cholinergic system or reflect an independent phenomenon. Thus, it would be interesting to investigate how the loci and other properties of memory-related theta oscillations are modulated by the overall theta during a successful memory formation in progression of AD.

6.3.2 Working memory needed for declarative memory formation

It has been proposed that there are strong connections between working memory and processes involved in declarative encoding and retrieval (Baddeley, 2000). Both theta and gamma activity has been reported during maintenance of working memory representations in monkeys (Pesaran et al., 2002; Lee et al., 2005) and humans (Gevins et al., 1997; Sarnthein et al., 1998; Tallon-Baudry et al., 2001; Raghavachari et al., 2001; Jensen and Tesche, 2002; Howard et al., 2003; Kaiser and Lutzenberger, 2005). Additionally, a physiologically realistic computational model which accounts for the functional interaction between these two rhythms during working memory maintenance was proposed by Lisman and Idiart (1995). Predictions from the model has been tested in several studies (reviewed in Jensen, 2006). The model was later extended to account for the encoding of long-term memory representations. In particular it was argued that synaptically dependent hippocampal encoding requires working memory maintenance (Jensen and Lisman, 2005). These ideas are consistent with a recent study by Mormann et al. (2005) who observed that declarative memory operations were modulating the theta and gamma band activity recorded from the medial temporal lobe (MTL) in epileptic patients. Recent neuroimaging studies support that working memory plays a role for declarative encoding (Davachi and Wagner, 2002; Ranganath et al., 2005). This leaves open the possibility that the theta and gamma activity observed during encoding and retrieval in our study is related to working memory operations required for declarative memory operations. From that perspective the gamma activity in visual areas might reflect representations being reinforced by top-down activity from areas directly engaged in encoding and retrieval (see e.g. Fig. 6 in Ranganath et al., 2004). This reinforcement might be related to working memory operations supporting successful memory performances.

A handful of studies, which employed a memory task while recording MEG from AD patients, to our knowledge, has investigated only working memory. They reported decreased alpha (Hogan et al., 2003; Pijnenburg et al., 2004) and beta (Pijnenburg et al., 2004) synchronization, along with reduced amplitude of long-latency ERFs (Maestu et al., 2004) in AD patients. However, if occipital gamma activity in our study indeed reflects activation of visual representations required for working memory performance during declarative memory formation, it would be interesting to see whether there are abnormalities in the gamma band power in AD.

In conclusion, successful declarative encoding and retrieval seem to be associated with

increases in occipital gamma and right hemisphere theta power in healthy young unmedicated subjects. This paradigm may be sensitive to investigate declarative memory operations whose impairment constitutes the major cognitive deficit of AD.

7 General conclusions

This study demonstrated abnormalities in oscillatory and evoked brain activity in AD. (i) The power of oscillatory sources in the 6–12.5 Hz band was decreased in the parieto-occipital and enhanced in the temporal regions in AD patients, as opposed to MCI patients and healthy elderly subjects. Thus MCI and early AD appear to have different impact on resting brain activity. However, the tendency toward the slowing of spontaneous alpha activity in MCI suggests that some of the MCI patients might develop more profound oscillatory abnormalities inherent for AD. (ii) ASSR was enhanced in AD patients, as compared to healthy elderly subjects, possibly reflecting decreased inhibition in auditory processing and deficits in adaptation to repetitive stimulation with low relevance. (iii) A paradigm sensitive to neurophysiological correlates of declarative memory, which is one of the major cognitive deficits in AD, was developed. This paradigm revealed that both successful declarative encoding and retrieval are associated with increases in occipital gamma and right hemisphere theta power in healthy young unmedicated subjects. This approach may be potentially useful to investigate declarative memory deficits in memory disorders, such as AD and MCI. Since oscillations are thought to be one of the mechanisms of communication between different brain regions, our work provides an insight on neuronal abnormalities in aging and memory disorders.

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