MEG-studies on Cognitive Disorders

Eero Pekkonen, Neurologist, MD, PhD

Key words: MEG, EEG, Alzheimer's disease, Parkinson's disease, Down syndrome, Mild cognitive impairment, Scopolamine

Abstract

Alzheimer's disease (AD) is a neurodegenerative disease characterized by memory impairment and progressive cognitive decline. Currently AD is the most common cause to dementia, and its prevalence may reach up to 25% among elderly subjects older than 80 years of age. In addition to damaged high level cognitive functions, electroencephalography studies have showed impairment of early brain processing in AD. Magnetoencephalography (MEG), which offers excellent spatial and milliseconds temporal resolution, is ideal tool to study noninvasively cortical activity. We have shown with MEG that parallel auditory processing between the hemispheres underlying stimulus detection is selectively delayed in Parkinson's disease, AD and that delayed auditory processing correlates with cognitive decline in AD. Results of pharmacological studies with scopolamine, which temporarily blocks cholinergic receptors in the brain, indicate that auditory processing and spontaneous activity are modulated by the cholinergic system. Sensitivity to cholinergic modulation appears to be age-related in the auditory system. MEG results also indicate damaged auditory processing in Down syndrome (DS), which is characterized by mental retardation, and cholinergic damage similar to AD. Slowing of spontaneous brain activity is a common finding in AD progression. Present MEG studies suggest altered oscillation activity in AD and in mild cognitive impairment (MCI), which often precedes dementia, compared with normal aging. Thus MEG might offer additional information to make a diagnosis between AD and MCI. Due to recent software development, MEG is now suitable to patients who have implanted deep brain stimulation (DBS) device. Our recent results tentatively suggest that DBS modulates somatosensory processing in PD. In conclusion, MEG appears to be a useful tool to study human brain activity in aging, neurodegenerative diseases, and even mental retardation.

Introduction

Anatomy of human brain can be accurately studied using magnetic resonance imaging (MRI) and computerized tomography (CT). Positron emission tomography (PET), functional MRI (fMRI), and single positron emission tomography (SPECT) offer a window to investigate human brain dynamics with a time resolution of several seconds to minutes. In contrast, electrical activity of the brain can be studied noninvasively with milliseconds time resolution using electroencephalography (EEG) and magnetoencephalography (MEG). EEG measures electrical currents, whereas MEG measures magnetic fields generated by electrical activity in the population of synchronously working neurons. Magnetic fields are not distorted by skull and scalp. MEG offers excellent spatial resolution to locate cortical sources, and current whole-head MEG systems allow one to investigate e.g. parallel cortical processing between the hemispheres and inter-hemispheric oscillations, the latter being the result of synchronously firing neurons.

I. Aging

Auditory stimuli elicit cortical responses termed P50 and N100. The latencies of these responses are about 50 and 100 ms respectively, and specifically N100 is regarded as an index of preattentive cortical processing underlying stimulus detection. Both responses are generated in or near the primary auditory cortex. Corresponding magnetic responses are P50m and N100m. Reite et al. (1981) showed with MEG that monaural stimuli elicited larger...
responses over the contralateral than over the ipsilateral hemisphere in healthy young subjects. They suggested that contralateral stimuli activated larger cortical area compared with ipsilateral stimuli. An MEG-study with healthy elderly subjects found no latency difference of P50m between the hemispheres, whereas the interhemispheric latency difference of the subsequent N100m response was delayed with aging (Pekkonen et al., 1995) suggesting to age-related impairment of preattentive auditory processing. Interestingly, the amplitude of the P50m response was increased with aging that suggests diminished inhibition of P50m generators in aging.

II. Alzheimer’s disease and mild cognitive impairment

Alzheimer’s disease (AD) is the most common cause of the dementia in western countries with age-related increase of prevalence. It is estimated that currently worldwide there are over 24 million people who have dementia. AD is characterized by progressive deterioration of memory and other higher cognitive functions. The pathological hallmarks are loss of neurons especially at the mesial temporal region, and accumulation of amyloid plaques and neurofibrillary tangles. Level of neurotransmitter acetylcholine is reduced. Currently, the cholinergic drugs can temporarily alleviate the symptoms, but not prevent the disease progression.

Mild cognitive impairment (MCI) is regarded as a transitional stage between normal aging and dementia. MCI patients have mild memory impairment, which does not, at least significantly, affect the activity of daily living (ADL). MCI patients have generally preservation of other cognitive functions. Head MRI scans are usually normal. MCI patients have increased risk of getting dementia.

EEG-studies have shown abnormalities of P50 response in AD (Green et al., 1992). First MEG-studies showed ipsilaterally delayed N100m response (Pekkonen et al., 1996). A subsequent study with larger patient sample indicated that there was a damaged preattentive auditory processing in the left hemisphere as indexed by delayed N100m (Pekkonen et al., 1999). Further, impaired language functions in AD group significantly correlated with delayed N100m, suggesting that loss of neurons is contributing to both the damaged preattentive and subsequent higher cortical functions.

There is decreased alpha-, beta-, and gamma-band synchronization in AD (Stam et al., 2002). Further, mean resting frequency is declined in AD compared with normal aging (Fernandez et al., 2002). Osipova et al. (2005) showed, in addition, that sources of oscillation activity are altered in AD. Further, sources of oscillation appear be different in AD, MCI, and healthy subjects. Hence MEG might offer additional information about transition of MCI to AD.

III. Down syndrome

Down syndrome (DS) is usually caused by an extra chromosome 21. The incidence is about 1:700 births. Major symptom is mental retardation, and life expectancy is around 50-60 years. Interestingly, the brain pathology is quite similar than that in AD. EEG studies have found shortened latencies of brainstem responses, whereas subsequent N100 was delayed (Vieregge et al., 1992; Diaz and Zuron, 1995). We measured ten DS patients with MEG, and results showed delayed P50m and N100m responses (Pekkonen et al., 2007). Further, the N100m was attenuated, unlike in AD. Thus, degeneration of the cholinergic system might contribute to the damaged auditory processing.

IV. Parkinson’s disease

Parkinson’s disease (PD) is a progressive neurodegenerative disease that is characterized by muscle rigidity, bradykinesia, and resting tremor. The symptoms are caused by gradual loss of neurotransmitter dopamine in the basal ganglia. Our MEG-study found increased interhemispheric latency difference of the P50m and N100m in non-demented PD-patients compared with healthy subjects (Pekkonen et al., 1998). The delayed auditory processing, however, did not correlate with the lateralization of the extrapyramidal symptoms. Our preliminary MEG-results with PD-patients, who have deep brain
stimulation (DBS), suggest that DBS modulates somatosensory processing (data on file).

V. Scopolamine and cortical processing

Loss of cholinergic neuron and decline of choline acetyltransferase (ChAT) are typical findings in DS and especially in AD. To confirm whether cholinergic system modulates auditory processing, we performed a series of studies with scopolamine, which temporarily block muscarinic receptors in the brain. The results showed that scopolamine increased the P50m amplitude, and delayed N100m latency in young healthy subjects (Pekkonen et al., 2001). A subsequent combined EEG/MEG-study with elderly healthy subjects showed scopolamine induced delay of N100m, but not significant amplitude changes (Pekkonen et al., 2005). Interestingly, electrical P50 and N100 responses were delayed by scopolamine. Hence scopolamine appears to have age-related sensitivity to modulate auditory processing. Present results suggest also that scopolamine increased theta activity and decreased interhemispheric coherence in the theta band (Osipova et al., 2005).

VI. Discussion

MEG is suitable to investigate brain dynamics in neurodegenerative diseases. Preattentive auditory processing preceding higher cortical processing appears to be delayed already in normal aging, but especially in AD, PD and DS. Further, spontaneous brain activity and sources of oscillations are abnormal in AD and MCI. That auditory processing and brain oscillations are modulated by the cholinergic system, MEG appears to be a useful tool to monitor cholinergic cortical activity in neurodegenerative diseases. Due to recent software development, patients with metal objects implanted in the brain are now suitable for MEG recordings. However, further studies are needed to confirm whether MEG can be used in clinical settings to improve the early diagnosis of AD and MCI.

References