Magnetoencephalography of cognitive responses
A sensitive method for the detection of age-related changes

Magnetoencephalography (MEG) is a novel, state-of-the-art technique used in clinical neurophysiology, which promises better understanding of brain (dys)function. The "whole-head" MEG sensor-array enables a noninvasive visualization of the intracellular currents involved in transmission and processing of information in the working brain, on a millisecond timescale, taking into account all (superficial and deep) parts of the CNS simultaneously. 3D reconstruction algorithms are used to attribute sources to anatomically defined structures and cortical subdivisions. MEG recording during the performance of a simple decision-making task using a continuous Go-NoGo paradigm (=P300) enables the evaluation of the mechanisms of attentional and intellectual capabilities. Many psychiatric disorders are related to a state of confusion or disturbances of thought. This poster presents a brief report on fundamental and clinical research into cognitive decline during (normal) aging, carried out with our innovative MEG equipment.

In healthy subjects asked to discriminate high-pitched target tones among standard tones during an oddball detection task, when attention is correctly directed, a particular transient electrical potential is observed, called P300,[1] with maximal amplitudes around the vertex. The underlying generators are thought to be located in the medial temporal lobe regions. We recently demonstrated that MEG signals yield a more complete image of the complex neuronal interactions involved in this type of cognitive response, showing a large positive pole over the left precentral and frontal brain regions (Figure 1) *and a mirror-image pattern in the right hemisphere (not shown).[2] We are currently in the process of localizing the sources in a realistic head model.*

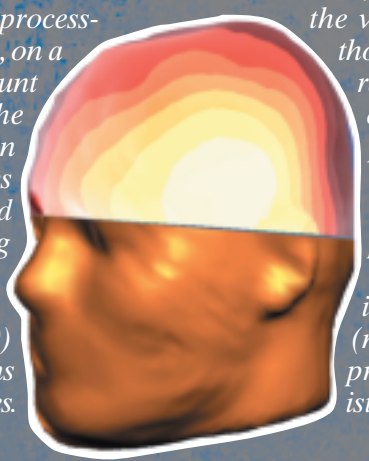

Figure 1. Top: 3D mapping of positive pole of MEG response to target tones. Bottom: averaged tracings in Broca's area for 2 age groups (young [<25 y] —; mid-age [34-47 y], ▬). Note the sustained positive wave >300 ms (horizontal scale 100 ms/division).

Intermezzo 1

In the aging brain, a general attenuation of the P300 response with a slowing of the time to reach the peak in drug-free volunteers (*Figures 1 and 2C, D*) is reported.[3] In young healthy volunteers, this response, characterized by its peak amplitude and peak latency, is known to be at least partly under cholinergic control[4,5] and can be enhanced by psychotropic drugs.[6] In the elderly, nootropic drugs are able to achieve a significant, restoration of P300.[7,8] The proven relationship between psychopharmacology, conscious attention, evoked (cognitive) responses and brain anatomy is a cornerstone concept in biological psychiatry research.

Researchers at our Institute are running programs to explore pathophysiological changes in schizophrenics, abstinent alcoholics, and Alzheimer patients, in comparison with normal aging in control subjects. This is achieved by plotting amplitude and latency parameters for individual subjects as a function of age (Figure 2). *Significant decline is found in subjects at the far ends of our age-range. Regression analysis shows a loss of signal of about 15% with a slowing of 10 to up to 20 ms with every decade of life. Preliminary findings indicate that MEG recordings are able to evidence age-related changes, as do electrical responses, and that these are already clearly visible before the age of 50 years. The slope of change in signal peak parameters is steeper than described in the literature for an even wider range of ages and pathophysiological situations.[9]*

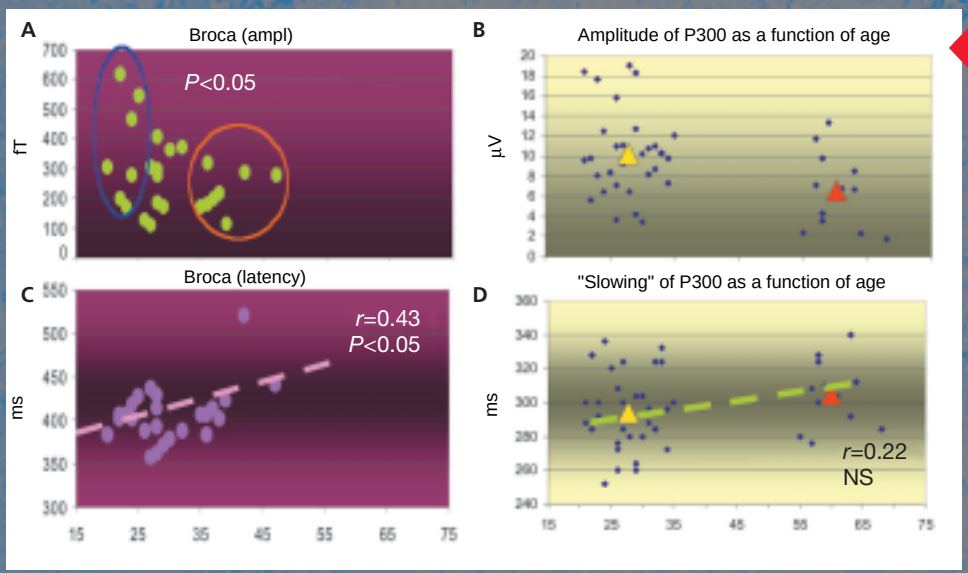

Figure 2. A. Scattergram of amplitude (ampl) for target-specific MEG response in Broca's area; **B.** Mean amplitude of electrical response (P300, Cz electrode) in young (▲) and aged (▲) healthy subjects; **C.** Scattergram of MEG response latency; **D.** mean latency for P300.

In conclusion:

MEG imaging provides a novel means of studying the neuronal events involved in the recruitment of attentional resources, and could herald new discoveries in the field of integrative brain functions.

Intermezzo 2

One of the advantages of MEG as applied to sensory physiology is that straightforward activation maps (eg, auditory response, *see Figure 3*) can be recorded. Source localization through MEG has yielded revolutionary results for the evaluation of impaired hearing, stroke, or epilepsy,[11] and is even able to demonstrate disturbed patterns in schizophrenic patients.[12]

Figure 3. A. Auditory MEG response; **B.** Topographic mapping; **C.** Source localization (red arrow) using a spherical model.

Perspectives: *The sensitivity of MEG in identifying modifications in normal adults makes it a promising diagnostic tool in the early identification of various forms of dementia.[10] Studies are currently being carried out in patients with dementia and related mood disorders, in collaboration with the World Health Organization (WHO), in order to validate the technique.*

REFERENCES

1. Pfefferbaum A, Roth WT, Ford JM. Event-related potentials in the study of psychiatric disorders. *Arch Gen Psychiatry.* 1995;52:559-563. **2.** Boeijinga PH, Soufflet L, d'Ardhuy XL, Toussaint M, Macher JP. P300 and M300; response changes with probability of infrequent stimuli. *Brain Topogr.* 1998;11:75-76. **3.** Polich J. EEG and ERP assessment of normal aging. *Electroencephalogr Clin Neurophysiol..*1997;104:244-256. **4.** Liogier X, Boeijinga PH, Renault B, et al. Effects of serotonin-selective and classical antidepressants on the auditory P300 cognitive potential. *Neuropsychobiol*. 1999;40:207-213. **5.** Perry E, Walker M, Grace J, Perry R. Acetylcholine in mind: a neurotransmitter correlate of consciousness? *Trends Neurosci.* 1999;22:273-280. **6.** Dierks T, Frölich L, Ihl R, Maurer K. Event-related potentials and psychopharmacology. Cholinergic modulation of P300. *Pharmacopsychiatry*. 1994;27:72-74. **7.** Saletu B, Semlitsch HV, Anderer P, Resch F, Presslich O, Schuster P. The investigation of antihypoxidotic/nootropic drugs (tenilsetam and codergocrine-mesylate) in elderlies with the Viennese Psychophysiological Test System (VPTS). *Methods Find Expt Clin Pharmacol.* 1989;11:43-55. **8.** Semlitsch HV, Anderer P, Saletu B, Binder GA, Decker KA. Cognitive psychophysiology in nootropic drug research: effects of *Ginkgo biloba* on event-related potentials (P300) in age-associated memory impairment. *Pharmacopsychiatry*. 1995;28:134-142. **9.** Polich J. P300 clinical utility and control of variability. *J Clin Neurophysiol.* 1998;15:14-33. **10.** Kugler CF, Taghavy A, Platt D. The event-related P300 potential analysis of cognitive human brain aging: a review. *Gerontology*. 1993;39:280-303. **11.** Stefan H, Schüler P, Abraham-Fuchs P, et al. Magnetic source localization and morphological changes in temporal lobe epilepsy: comparison of MEG/EEG, EcoG and volumetric MRI in presurgical evaluation of operated patients. *Acta Neurol Scand Suppl.* 1994;152:133-134. **12.** Reite M, Teale P, Sheeder J, Rojas D, Simon J. Neuropsychiatric applications of MEG. In: Hashimoto I, Okada YC, Ogawa S, eds. *Visualization of Information Processing in the Human Brain: Recent Advances in MEG and Functional MRI.* EEG suppl 47. 1996

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