New insight in the Alzheimer's disease progression revealed by a combination of functional and structural information

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INTRODUCTION: Combining structural and functional information of the human brain provides detailed information of the neurodegenerative diseases and the influence of the disease on cortical brain areas. In this study, the structural information is assessed by cortical thickness analysis based on anatomical MR images whereas the functional information is provided by transcranial magnetic stimulation (TMS) study of motor cortex excitability. In order to examine the relationship between structure and function of the brain we studied the correlation of cortical thickness and TMS parameters in patients with Alzheimer's disease (AD) or mild cognitive impairment (MCI) as well as age-matched healthy controls.

MATERIALS: Patients with AD (n=18, 7 males, age: 73.6±7.3 years, MMSE:19.2±4.3) and patients with MCI (n=22, 12 males, age: 71.6±7.4 years, MMSE:24.0±2.9) were recruited in this study from population-based databases along with age-matched healthy controls (n=25, 11 males, age: 73.0±6.1 years, MMSE:28.5±1.3). AD patients were diagnosed using the NINCDS-ADRDA criteria, and MCI patients using the original criteria of the Mayo Clinic Alzheimer's Disease Research Center. Controls showed no impairment after detailed neuropsychological evaluation. Informed written consent was obtained from all participants according to the Declaration of Helsinki and the study was approved by the local Ethics Committee.

METHODS: Cortical thickness analysis was performed on T1-weighted MR images acquired with a 1.5 T MR scanner (MAGNETOM Avanto, Siemens AG, Erlangen, Germany) with the 3D-MPRAGE (magnetization-prepared rapid acquisition gradient echo) sequence. Cortical thickness was computed using the pipelining method developed at the McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal Canada [1]. The method provides a thickness map for each subject both in standard ICBM152 space and subject's native space thus enabling statistical analysis on cortical thickness. TMS setup consisted of eXimia navigation system combined with a magnetic stimulator and a biphasic figure-of-eight TMS coil with mean wing radius of 50 mm (eXimia NBS System and TMS Stimulator, Nexstim Ltd., Helsinki, Finland). The navigation system was used to control online the TMS stimulation parameters on the basis of individual T1-weighted images. The optimal stimulation site for the right thenar (abductor pollicis previs) muscle was located using the anatomical information provided by individual MR images and the corresponding EMG signal (ME 6000, Mega Electronics Ltd., Kuopio, Finland). The motor threshold (MT; i.e. the minimum TMS intensity able to elicit motor evoked potentials (MEPs) in 50% of the trials) was determined for each participant and the corresponding electric field (EF) value at the surface between WM and GM was fed into statistical analysis. Correlation analysis between EF and cortical thickness was performed on the left hemisphere within all groups using an ANCOVA model with age, gender and scalp-to-cortex distance at the motor area as nuisance variables. Negative correlation means that the thinner the cortex, the stronger the stimulation intensity required to produce MEPs. The areas with significant negative correlation ($p<0.05$, FDR-corrected) were further entered into an ROI-analysis in which the mean cortical thickness in each ROI was calculated for each subject. These mean values were further correlated with the EF value within each group and ROI, thus providing more detailed information about specific ROI in the different subject groups.

RESULTS: Whole brain correlation analysis was performed for all subjects together. EF values correlated negatively with cortical thickness in the pre- and post-central gyrus (ROI 1), in the cuneus (ROI 2) and in the precuneus (ROI 3). The correlation map is presented in Fig.1. ROI analyses were performed for each subject group separately. In all ROIs, the cortex was thinnest in the AD group, whereas cortical thickness varied most within the MCI group. In ROI 1, only MCI patients had significantly negative correlation between EF value and cortical thickness ($p=0.002$). In ROI 2, the most significant correlation was in the AD group ($p=0.031$) and controls showed barely significant correlation ($p=0.047$). In ROI 3, AD subjects had the most significant correlation ($p=0.004$) and MCIs showed significant correlation as well ($p=0.014$).

DISCUSSION AND CONCLUSIONS: By increasing the TMS intensity and the EF value, both the maximum of the induced electric field and the size of the brain volume that is directly influenced increase. Therefore, two mechanisms contribute to brain excitation: either the maximum EF is strong enough to activate neurons with higher threshold or more neurons are activated in larger area so that the net excitation is delivered through white matter axons. Healthy controls have only weak or no correlation between cortical thickness and EF value. It may be that healthy brain has its own individual threshold at which it reacts, independent of the cortical thickness and amount of gray matter cells.

In dementia, gray matter is atrophic, i.e. consisted of fewer neurons. Thus, based on the findings of negative correlation between EF and cortical thickness, one would expect that the EF required to elicit a MEP would be highest in the AD group. This was not the case in our study as there was no correlation in motor area in AD group. It has been previously shown that motor cortex excitability is increased in AD patients as compared to controls, i.e. lower stimulation intensity is required to generate MEPs [2]. Perhaps this hyperexcitability counterbalances the neuronal loss in the motor cortex occurring in AD, thus providing support for the reasonably good motor functions even at late phase of the disease. Furthermore, it has been shown that motor areas are the last areas undergoing degeneration in AD, whereas cuneus and precuneus are affected at a rather early stage of the disease [3]. According to our data, in these areas similar compensatory hyperexcitability as in the motor cortex is not shown, since the mean cortical thickness of both cuneus and precuneus does correlate negatively with the EF value showing the most significant correlation in AD group. In MCI subjects, the motor cortex excitability has not yet increased although the cellular loss has already begun, as indicated by the strong negative correlation between cortical thickness and EF value especially on the motor cortex. Based on our results, it seems that the cuneus is still reasonably intact whereas some changes might already have happened in the precuneus.

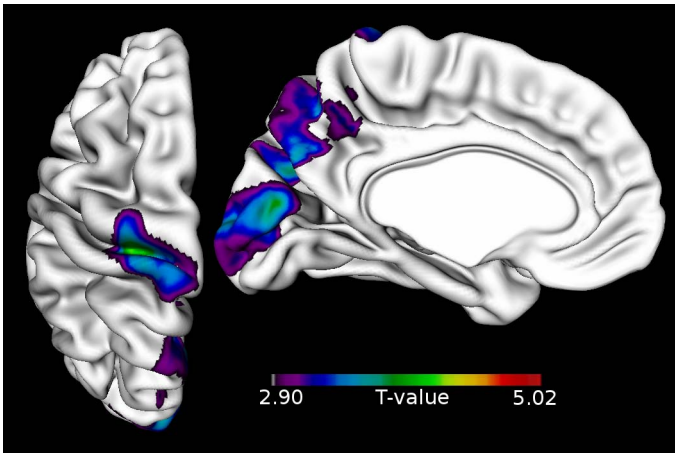

Figure 1 The areas with significant negative correlation between cortical thickness and EF value ($p<0.05$, FDR-corr.), all subjects.

To conclude, our results show that the evolution of the disease proceeds with different dynamics in the structure and function of neuronal circuits from normal conditions via MCI to AD.

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