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Relationship between excitability, plasticity and thickness of the motor cortex in older adults

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ABSTRACT

The relationship between brain structure, cortical physiology, and learning ability in older adults is of particular interest in understanding mechanisms of age-related cognitive decline. Only a few studies addressed this issue so far, yielding mixed results. Here, we used comprehensive multiple regression analyses to investigate associations between brain structure on the one hand, i.e., cortical thickness (CT), fractional anisotropy (FA) of the pyramidal tract and individual coil-to-cortex distance, and cortical physiology on the other hand, i.e. motor cortex excitability and long-term potentiation (LTP)-like cortical plasticity, in healthy older adults (mean age 64 years, 14 women). Additional exploratory analyses assessed correlations between cortical physiology and learning ability in the verbal domain. In the regression models, we found that cortical excitability could be best predicted by CT of the hand knob of the primary motor cortex (CT-M1$_{HAND}$) and individual coil-to-cortex distance, while LTP-like cortical plasticity was predicted by CT-M1$_{HAND}$ and FA of the pyramidal tract. Exploratory analyses revealed a significant inverse correlation between cortical excitability and learning ability. In conclusion, higher cortical excitability was associated with lower CT and lower learning ability in a cohort of healthy older adults, in line with previous reports of increased cortical excitability in patients with cortical atrophy and cognitive deficits due to Alzheimer's Disease. Cortical excitability may thus be a parameter to identify individuals at risk for cognitive decline and gray matter atrophy, a hypothesis to be explored in future longitudinal studies.

1. Introduction

The combined use of imaging techniques with high spatial resolution like magnetic resonance imaging (MRI), and non-invasive measurements of brain physiology like transcranial magnetic stimulation (TMS) has greatly advanced understanding of human brain function (Siebner et al., 2009). With regard to cognitive neuroscience of aging, use of these techniques offers great potential to investigate mechanisms of age-related structural and functional decline. However, most studies focused on young healthy individuals, or on patients with advanced neurodegeneration like Alzheimer's Disease (AD). So far, comprehensive evaluations in elderly individuals without overt dementia, most likely to yield information about compensatory mechanisms with regard to cognitive function, have not been conducted.

Different electrophysiological protocols have been used in exploring cortical neurophysiology. Resting motor threshold (rMT) is generally defined as the lowest stimulus intensity of a single pulse TMS that elicits a predefined, small motor response in the contralateral targeted muscle (Rossini et al., 1994). RMT is a measure of the excitability of corticocortical neuronal structures that are directly activated by TMS and project onto corticospinal output neurons (Ziemann, 2004). While being inter-individually highly variable, rMT is relatively stable and thus reproducible in a given individual (Wassermann, 2002). rMT is critically dependent on coil-to-cortex-distance (CCD) in a given subject (Stokes et al., 2005), but might be also influenced by other functional and anatomical parameters, particularly inter-individual structural variability of the motor cortex (Hübers et al., 2012) and age-related anatomical and physiological brain changes (Silbert et al., 2006). For example, a study in healthy young subjects indicated that deep white matter microstructure, as measured by fractional anisotropy (FA) in diffusion tensor imaging (DTI) may be an important contributor (Klöppel et al., 2008). However, a subsequent study could not confirm these results (Hübers et al., 2012), and thus the association between white matter

Abbreviations: TMS, transcranial magnetic stimulation; MEP, motor evoked potential; APB, abductor pollicis brevis muscle; rMT, resting motor threshold; CCD, coil-to-cortex distance; LTP, long term potentiation; PAS, paired associative stimulation; CT, cortical thickness; FA, fractional anisotropy; PT, pyramidal tract; M1, primary motor cortex; AD, Alzheimer's Dementia; VD, vascular dementia; MRI, magnetic resonance imaging; TR, repetition time; TE, echo time; FLAIR, fluid attenuation inversion recovery; DTI, diffusion tensor imaging; ROI, region of interest; WMH, white matter hyperintensities; GLM, general linear model; TMT, trail making test; AVLT, auditory verbal learning test; GABA, gamma amino butyric acid; NMDA, N-methyl-D-aspartate.

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microstructure and cortical excitability remains to be fully explored in healthy individuals. With regard to pathological conditions, rMT was decreased in patients with predominantly white matter damage as seen in vascular dementia (VAD) (Pennisi et al., 2011) or cortical atrophy due to AD (e.g. (Di Lazzaro et al., 2004; Ferreri et al., 2011). However, a potential association between cortical thickness (CT) and cortical excitability has not been investigated in healthy individuals or in patients so far.

Long-term potentiation (LTP) is assumed to be the basis of learning and memory (Rioult-Pedotti et al., 2000). In humans, LTP-like plasticity can be induced in the primary motor cortex (M1) by the paired associative stimulation (PAS) protocol (Stefan et al., 2000). Here, inter-individual variability was influenced by age (Fathi et al. 2010; Müller-Dahlhaus et al., 2008; Tecchio et al., 2008), cognitive decline (Battaglia et al., 2007), and white matter damage (List et al., 2013). Recently, associations between LTP-like cortical plasticity and cortical thickness (CT) in young healthy individuals have been reported (Conde et al., 2012). The association of LTP-like cortical plasticity and CT in older individuals has not been determined so far.

In the present study, we investigated associations between measures of brain structure and cortical physiology in a well-defined cohort of healthy older adults. We further asked in an exploratory approach if cortical excitability and LTP-like cortical plasticity were correlated with learning ability.

2. Methods

Participants were recruited via newspaper and internet advertisements and via the intranet of the Charité Hospital in Berlin, Germany. 30 subjects (63.9 ± 6.2 years, range 50–75 years, 14 females, 16.7 ± 2.7 years of education) were included in the study. None of the subjects reported use of psychoactive medication or recreational drugs, and none of them had a history of neurological or psychiatric disorders. The Mini Mental State Examination (MMSE; (Folstein et al., 1975), cut off ≤ 28); and Beck's depression inventory (BDI; (Hautzinger et al., 1994), cut off ≥ 12) were used for screening of cognitive deficits or depressive symptoms. All participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971).

The study was approved by the local ethics committee and conducted in accordance with the Helsinki Declaration on the use of human subjects in experiments. Written informed consent was obtained from all participants.

2.1. Magnetic resonance imaging

2.1.1. Image acquisition

Using a 3T system (Magnetom TIM Trio, Siemens, Erlangen, Germany) equipped with a 12-channel head coil, diffusion-weighted images (TR = 7500 ms, TE = 86 ms, 61 axial slices, voxel size of 2.3 × 2.3 × 2.3 mm^3; 64 directions with a b-value of 1000 s/mm^2 and one b0), high-resolution T1-weighted MPRAGE images (TR = 1900 ms, TE = 2.52 ms, 192 sagittal slices, voxel-size of 1.0 × 1.0 × 1.0 mm^3, flip angle = 9°), and fluid attenuation inversion recovery (FLAIR) images were acquired.

2.1.2. Coil-to-cortex distance (CCD)

CCD was determined on anatomic T1-weighted images. The location of the left hand knob was determined visually (Yousry et al., 1997), and the shortest distance between gray matter and the skull surface was defined as the CCD (according to Hübers et al., 2012). CCD_{left} denotes CCD on the left side.

2.1.3. Quantification of white matter hyperintensities

White matter hyperintensities (WMH) were identified on the FLAIR- and T2-weighted images, and severity was graded semiquantitatively on 4 levels using a modified version of the Fazekas scale (Pantoni et al., 2010): 0 = absence of WMH; 1 = punctuate foci below 10 mm, areas of grouped lesions must be smaller than 20 mm in diameter; 2 = single lesions between 10 and 20 mm, areas of "grouped" lesions more than 20 mm in any diameter; and 3 = large confluence of foci, single lesions of more than 20 mm in diameter.

2.1.4. Cortical thickness (CT) measurements

For CT measurements, we used FreeSurfer (Version 5.1.0), a set of automated tools for reconstruction of the brain cortical surface (Fischl et al., 1999), and is freely available for download online (http://surfer.nmr.mgh.harvard.edu). Technical details of these procedures are described in prior publications (Dale et al., 1999; Fischl et al., 1999, 2002; Han et al., 2006). The processing of T1-weighted images included removal of nonbrain tissue (Segonne et al., 2004), automated Talairach transformation and intensity normalization (Sled et al., 1998), as well as surface deformation to detect gray matter/white matter and gray matter/cerebrospinal fluid boundaries (Fischl et al., 2001; Segonne et al., 2007). The resulting representation of CT was then calculated as the distance between the above tissue boundaries (Fischl and Dale, 2000). The surface models of each subject were inspected visually for accuracy. For whole-brain cortical thickness analyses, we calculated cortical maps at the vertex-wise level by means of a general linear model (GLM) approach, which is implemented in QDEC from FreeSurfer. Individual CT maps were registered bilaterally to the standard template and smoothed with a Gaussian kernel of 25 mm FWHM.

2.1.5. Region of interest definition

A region of interest (ROI) comprising the hand area of left M1 (cortical area where rMT and LTP-like cortical plasticity were assessed, see section on "TMS measurements" below) was defined and subsequently drawn manually in the "knob-like" part of the precentral gyrus, which is further defined by the central sulcus and the superior frontal sulcus (Yousry et al., 1997). This hand drawn ROI had a size of 1775 vertices. The average thickness within this ROI in each subject was extracted for further multiple regression analyses.

2.1.6. Diffusion tensor imaging

2.1.6.1. Preprocessing of DTI data. We used FSL for preprocessing and fibertracking the left pyramidal tract (PT; tract containing the fibers originating from left M1), (http://www.fmrib.ox.ac.uk/fsl). A 3-dimensional rigid body registration was applied to correct for eddy currents and head motion, followed by brain extraction (Smith, 2002). Probability distributions were then calculated, allowing estimation of 2 dimensions per voxel (Behrens et al., 2006). Directional diffusivities were determined as lambda 1 > lambda 2 > lambda 3 and fractional anisotropy (FA) was calculated from those eigenvalues.

2.1.6.2. Probabilistic tractography of the pyramidal tract. In order to reconstruct the PT according to their cortical origins in $M1_{left}$, a ROI was drawn in the subcortical white matter on the individual FA maps in native space, as descried previously (Rüber et al., 2012). Further ROIs were placed in the posterior limb of the internal capsule and the basis pontis (Lindenberg et al., 2012). Using the brainstem ROI as the seed region and the ipsilateral internal capsule and subcortical ROIs as waypoint masks as well as a sagittal exclusion mask in the corpus callosum, we reconstructed the PT in the left hemisphere: fibers originating from M1, passing through the internal capsule and descending to the anterior pons. Probabilistic maps were generated by iterations of the streamline process. For every seed voxel in the brainstem ROIs, 5000 "particles" were propagated through the multi-tensor field. The resulting maps of streamline intensities were then constrained to voxels with more than 10% of the individual robust range in order to extract tract-specific FA values of the left PT ($FA\text{-}PT_{left}$) for regression analyses (see below).