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White matter hyperintensities alter functional organization of the motor system

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Abstract

Severe white matter hyperintensities (WMH) represent cerebral small vessel disease and predict functional decline in the elderly. We used fMRI to test if severe WMH impact on functional brain network organization even before clinical dysfunction. Thirty healthy right-handed/footed subjects (mean age, 67.8 ± 7.5 years) underwent clinical testing, structural MRI and fMRI at 3.0T involving repetitive right ankle and finger movements. Data were compared between individuals with absent or punctuate (n = 17) and early confluent or confluent (n = 13) WMH. Both groups did not differ in mobility or cognition data. On fMRI, subjects with severe WMH demonstrated excess activation in the pre-supplementary motor area (SMA), frontal, and occipital regions. Activation differences were noted with ankle movements only. Pre-SMA activation correlated with frontal WMH load for ankle but not finger movements. With simple ankle movements and no behavioral deficits, elderly subjects with severe WMH demonstrated pre-SMA activation, usually noted with complex tasks, as a function of frontal WMH load. This suggests compensatory activation related to disturbance of frontosubcortical circuits.

Keywords: White matter hyperintensities; Aging; Motor system; fMRI; SMA; Pre-SMA

1. Introduction

Some degree of age-related cerebral white matter hyperintensities (WMH) can be observed almost endemically on brain magnetic resonance imaging (MRI) scans in otherwise healthy elderly subjects. In particular more severe WMH (i.e., early confluent or confluent WMH according to the Fazekas scale (Fazekas et al., 1987) have been associated with small vessel disease. As they also demonstrate significant progression over time (Schmidt et al., 2003), WMH grades 2 and 3 are commonly considered as biologically more malignant (Schmidt et al., 2004).

In line with this notion, severe WMH have been associated with cognitive dysfunction, depression, disturbed micturition (Frisoni et al., 2007; Pantoni et al., 2005) and, most importantly, progression to disability (Inzitari et al., 2009) in the elderly. In the Leukoaraiosis and Disability (LADIS) study, the risk of transition to disability or death was more than 2-fold higher in the presence of severe WMH and 29.5% of individuals with severe WMH reached this end point after a mean follow-up of only 2.4 years. If and to what extent such transition is preceded by compensatory brain changes has not yet been investigated. Locomotor disability appears to represent an ideal focus of research in this context given both the correlation between increasing WMH severity and impaired walking and its impact on successful aging (Baezner et al., 2008).

Functional MRI (fMRI) greatly enhanced our understanding of central human motor control (Picard and Strick,

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2001). Using simple motor paradigms, it allows characterizing the distinct functional neuroanatomy of upper and lower limb movements (Enzinger et al., 2008; Luft et al., 2002; Rotte et al., 2002). Ankle movements as a key component of gait (Capaday, 2002) have been used recently to assess the functional effects of gait training using fMRI (Enzinger et al., 2009).

We hypothesized that more severe WMH might impact on functional network organization of the brain in yet clinically intact elderly individuals. We here therefore used such motor paradigms to test for preclinical functional changes in relation to WMH severity.

2. Methods

2.1. Subjects

An a priori defined sample of 30 individuals was randomly selected from the Austrian Stroke Prevention Study (ASPS; Schmidt et al., 2003) by a blinded study nurse on the basis of records on their degree of WMH on a previous structural MRI brain scan. The Austrian Stroke Prevention Study is a single-center prospective follow-up study on the cerebral effects of vascular and genetic risk factors in the normal elderly population of Graz, Austria. A history of neuropsychiatric disease (including stroke) is considered an exclusion criterion from this study. Once patients suffer from a stroke or any other of the exclusion criteria this is considered an endpoint for the study. Thus none of the participants invited for this study had suffered from a stroke. Also, participants were selected in that they did not have a clinically silent infarct or lacunae on MRI of the brain.

Subjects were then invited to undergo structural and functional MRI, as well as gait and cognitive testing on the same day. The local ethics committee approved the study. The study cohort consisted of 21 female and 9 male right-hand and right-foot dominant subjects (according to the Edinburgh Handedness Inventory) with a mean age of 67.8 ± 7.9 years (range, 48–84). They had normal or corrected to normal vision and a mean duration of education of 10.8 ± 2.4 years. On the new fluid attenuated inversion recovery (FLAIR) scans obtained at 3.0 T, the WMH grading according to the modified Fazekas scale (Fazekas et al., 1987; Inzitari et al., 2009) had to be reassigned in 2 individuals from grade 2 to a grade 1. We then dichotomized the group according to their WMH grade, as group A: grades 0 or 1, and group B: grades 2 or 3. Further characteristics are given in Table 1.

2.2. Magnetic resonance imaging

Imaging was performed on a 3.0 T Tim Trio system (Siemens Medical Systems, Erlangen, Germany) using a 12-element head array coil. Functional data were acquired using a single shot gradient echoplanar imaging (EPI) sequence (repetition time [TR] = 3000 ms, echo time [TE] = 30 ms, spin angle 90°, matrix size 64 × 64, pixel size 3 × 3 × 3 mm), with 210 volumes per functional run (scanning time 10.5 minutes).

Morphological imaging data were acquired using conventional turbo-spin-dual echo, FLAIR (TR = 9000 ms, TE = 70 ms, inversion time [TI] = 2500 ms, in plane resolution = 0.9 × 0.9 mm^2, slice thickness = 3 mm) and T1-weighted 3-dimensional magnetization prepared rapid gradient echo (MPRAGE) sequences (TR = 1900 ms, TE = 2.10 ms, TI = 900 ms, flip angle = 9°, resolution = 1 × 1 × 1 mm^3).

After rating and identification of WMH by a blinded experienced investigator (CE) on FLAIR-images, a trained technician (PL) segmented WMH. Global and frontal lobe lesion volumes were calculated by local thresholding and region growing using home-developed software, which was not feasible in 1 subject due to technical problems. Our semiautomatic lesion segmentation program limits user interaction to placing a seed point in each lesion. By region growing, i.e., stepwise inclusion of all neighbor pixels that fall within a predefined variation of the seed point, the borders of the lesion are found. To make this approach less sensitive for signal variations caused by noise and coil sensitivity, image preprocessing is needed which includes filtering and signal intensity normalization. Based on high resolution T1 scans, brain tissue volume was estimated using SIENAX as part of FSL (www.fmrib.ox.ac.uk/fsl).

2.3. The fMRI experiment

The paradigm involved unilateral active movements of the fingers II–V of the right hand in a wooden apparatus limiting the maximum degree of extension (Wegner et al., 2008). In a separate run, active right ankle movements to a maximum of 30° were performed in a purpose-built wooden apparatus as described previously (Enzinger et al., 2008, 2009). Blocks of active movement (30 seconds), visually paced at a fixed rate (1000 ms for dorsiflexion and plantarflexion, 1 Hz for finger movements), alternated with interspersed periods of absolute rest (21 seconds). The sequence of runs was pseudorandomized. Prior to entering the scanner, subjects practiced the paradigm using the same devices. In an attempt to reduce stimulus-correlated motion, subjects' heads were secured with Velcro straps in a foam-cushioned holder and their knees were flexed to approximately 135° using a soft roll placed beneath the knees.

2.4. Test of distal upper limb function - Purdue Pegboard Test

Visuopractical skills were evaluated using the Purdue's Pegboard Test, providing a score for motor function of the distal upper limb.

2.5. Test of lower limb function - gait and balance tests

Equilibrioception, gait, and motor proficiency were assessed with the Short Physical Performance Battery (SPPB) and 2 additional simple tests measuring the same construct (Baezner et al., 2008).