

Cortical excitability and age-related volumetric MRI changes

L.C. Silbert^{a,b,*}, C. Nelson^a, S. Holman^a, R. Eaton^a, B.S. Oken^a, J.S. Lou^a, J.A. Kaye^{a,b}

^a Department of Neurology, Layton Aging and Alzheimer's Disease Center, CR-131, Oregon Health and Science University, 3181 S.W. Sam Jackson Park Road, Portland, OR 97201, USA

^b Oregon Health and Science University and the Portland Veterans Affairs Medical Center, Portland, OR, USA

Accepted 4 February 2006

Abstract

Objective: Normative data on transcranial magnetic stimulation (TMS)-derived measures of cortical excitability in the elderly is sparse. Nevertheless, elderly subjects are included as controls in studies utilizing TMS to investigate disease states. Age-associated increased ventricular cerebrospinal fluid (vCSF) and white matter hyperintensity (WMH) MRI volumes have uncertain significance in non-demented elderly. Information regarding cortical excitability in neurologically intact elderly would augment our understanding of the pathophysiology of aging and assist in the interpretation of TMS studies involving elderly subjects.

Methods: Twenty-four healthy elderly subjects underwent TMS testing to determine outcomes of resting motor threshold (RMT) cortical silent period (cSP) and central motor conduction time for examination in relation to WMH, vCSF, and CNS volumes.

Results: Increased vCSF and WMH volumes were associated with decreased right and left hemisphere RMT. Smaller CNS volumes were associated with decreased right hemisphere RMT and shorted cSP.

Conclusions: Commonly observed age-associated MRI changes are associated with findings consistent with increased cortical excitability.

Significance: Age-related MRI findings likely reflect changes at a cellular level, and may influence cognitive and motor integrity in the elderly. Future TMS studies investigating cortical excitability may wish to consider neuroimaging markers of neurodegeneration prior to enrolling elderly subjects as controls.

© 2006 International Federation of Clinical Neurophysiology. Published by Elsevier Ireland Ltd. All rights reserved.

Keywords: Aging; TMS; White matter; Atrophy; Cortical excitability

Transcranial magnetic stimulation (TMS) is an emerging technique employed for use of treatment of certain neurologic and psychiatric conditions. In addition to its therapeutic potentials, TMS has helped to elucidate pathophysiologic mechanisms behind various neurodegenerative disease states, such as frontotemporal and vascular dementia, Alzheimer's and Parkinson's disease, and progressive supranuclear palsy, among others (Alagona et al., 2004; Lou et al., 2003; Nardone et al., 2005; Pierantozzi et al., 2004). Little information has been reported in regards to TMS-derived measures of cortical

excitability in the normal elderly, yet this population has been included as both patients and controls in studies investigating neurologic and psychiatric diseases. Poorer cognitive performance with advanced age has been well documented (Albert and Knoefel, 1994; Birren and Schaie, 1990). Furthermore, brain MRI findings of white matter hyperintensity (WMH) signal change and central atrophy, manifested as increase ventricular CSF (vCSF) volume, have been commonly observed in the elderly (Bryan et al., 1997; Longstreth et al., 1998) and may contribute to cognitive processing changes observed in this population (Cook et al., 2004; de Groot, 1998).

A significant effect of age on motor training-dependent cortical plasticity has been previously reported (Sawaki et al., 2003). Results from studies investigating the effects of age on TMS-derived measures of cortical excitability have been inconsistent (Kossev et al., 2002; Peinemann et al., 2001).

* Corresponding author. Address: Department of Neurology, Layton Aging and Alzheimer's Disease Center, CR-131, Oregon Health and Science University, 3181 S.W. Sam Jackson Park Road, Portland, OR 97201, USA. Tel.: +1 503 494 6976; fax: +1 503 494 7499.

E-mail address: silbertl@ohsu.edu (L.C. Silbert).

None have examined TMS measures of cortical excitability in relation to age-related MRI changes. The purpose of this study was to determine whether the commonly observed age-related MRI findings of WMH and atrophy are associated with altered cortical excitability, a possible reflection of diminished inhibitory tone and an indication that such common ‘non-specific’ observations may reflect a potentially deleterious functional change at the cellular level. Ultimately, this information may augment our understanding of cognitive changes that occur with increased age, as well as assist in interpretation of outcomes from future TMS studies in which elderly are included as participants.

1. Methods

1.1. Subject recruitment and entry criteria

Elderly men and women greater than 65 years of age currently enrolled in the Oregon Layton Aging and Alzheimer’s Disease Center studies on Aging were recruited to participate in this study. Entry inclusion criteria included a score of 24 or greater on the Mini-Mental State Examination (MMSE) (Folstein, 1975) a score of 12 or less on the Instrumental Activities of Daily Living Scale, a score of 10 or less on the Cornell Depression Scale (Alexopoulos et al., 1988), and a score of 0 on the Clinical Dementia Rating Scale (CDR) (Morris, 1993). All subjects had yearly neurologic assessment, and neuroimaging with MRI. At the time of entry into the TMS study, subjects must have been assessed within the last 6 months and determined to be non-demented (MMSE \geq 24, CDR = 0). Subjects with neurodegenerative diseases possibly associated with altered cortical excitability, such as Parkinson’s disease, multiple sclerosis, amyotrophic lateral sclerosis, and dystonia, were excluded from the study. Similarly, subjects on medications known to alter TMS-derived measurements of cortical excitability, such as sodium-channel blockers, GABAergic, and dopaminergic drugs were also excluded from this study. Subjects were excluded from the TMS study if they had a cortical infarct either clinically or on neuroimaging, or if they had ever had a seizure.

1.2. TMS recording methods

TMS experiments were performed using a figure-eight stimulating coil (external loop diameter 9 cm). The coil was powered by a Magstim 200 magnetic stimulator (Magstim, Dyfed, UK). An active surface electrode was placed over the belly of the first dorsal interosseus muscle (FDI) with a reference electrode placed distally at the muscle tendon insertion point. The motor evoked potential (MEP) signals were amplified using an A-M Systems Model 3000 AC/DC differential amplifier. MEPs were digitized and stored onto a PC using a National Instrument analog-to-digital board model PCI-MIO-16XE-10 (National Instruments, Austin,

TX). The bandpass filter was 100 Hz–10 kHz. The coil was held tangential to the scalp, oriented to induce electric current in the brain that flows in a posterior–anterior direction over the hand area of the motor cortex. The magnetic stimuli were delivered while the subjects were sitting comfortably in a reclining chair. Audio feedback was used to indicate muscle activity. All subjects were tested within the same time period between 9 a.m. and 1 p.m.

1.2.1. Resting motor threshold (RMT)

Cortical motor evoked potentials were obtained by stimulating the motor cortex over the contralateral hand motor strip by moving the coil 0.5 cm step sizes until the optimal site for generating a motor response was localized. RMT was taken as the lowest stimulus intensity capable of eliciting at least 5 MEP’s in the contralateral FDI muscle with an amplitude of 50 μ V or higher in 10 consecutive trials using an incremental step size intensity of 1% maximal stimulation output.

1.2.2. Central motor conduction time (CMCT)

A motor evoked potential response was obtained by supramaximal stimulation of the ulnar nerve by stimulating at the wrist using standard methods (Kimura, 2001). M-waves were recorded and latencies were measured. The minimum F-wave latency was determined from fifteen consecutive F-wave recordings of the ulnar nerve. MEP latency was taken from the average latency of 15 stimulations of the motor cortex during voluntary contraction of the contralateral FDI muscle. Central Motor Conduction Time (CMCT) was calculated using the formula: $CMCT = \text{cortical MEP latency} - [(F + M) - 1] / 2$ (Claus, 1990), where F, minimum F-wave latencies (ms); M, M-wave latency (ms); and 1, the delay time (ms) for antidromic activation of the alpha motor neuron.

1.2.3. Cortical silent period (cSP)

The motor cortex was stimulated while the contralateral FDI muscle was maximally contracted, inducing a period of electromyographic silence (silent period). TMS intensity was standardized at 40% above resting motor threshold. A minimum of 15 trials was given for each hemisphere. Between each stimulation a 2–3 s pause was given to prevent fatigue. EMG activity from the FDI was recorded for 600 ms, spanning from 310 ms before the stimulation to 290 ms after. This waveform was transformed using a short-time Fourier transform, which finds the total energy in the waveform at each time-point. A point was then selected from inside the post-MEP silent period, and the onset and offset of the SP were determined by searching in both directions for the first point that is equal to the mean value from a sample of the 310 ms preceding the stimulation. The SP duration was defined as the time elapsed between the beginning of the MEP and the SP offset (see Fig. 1).

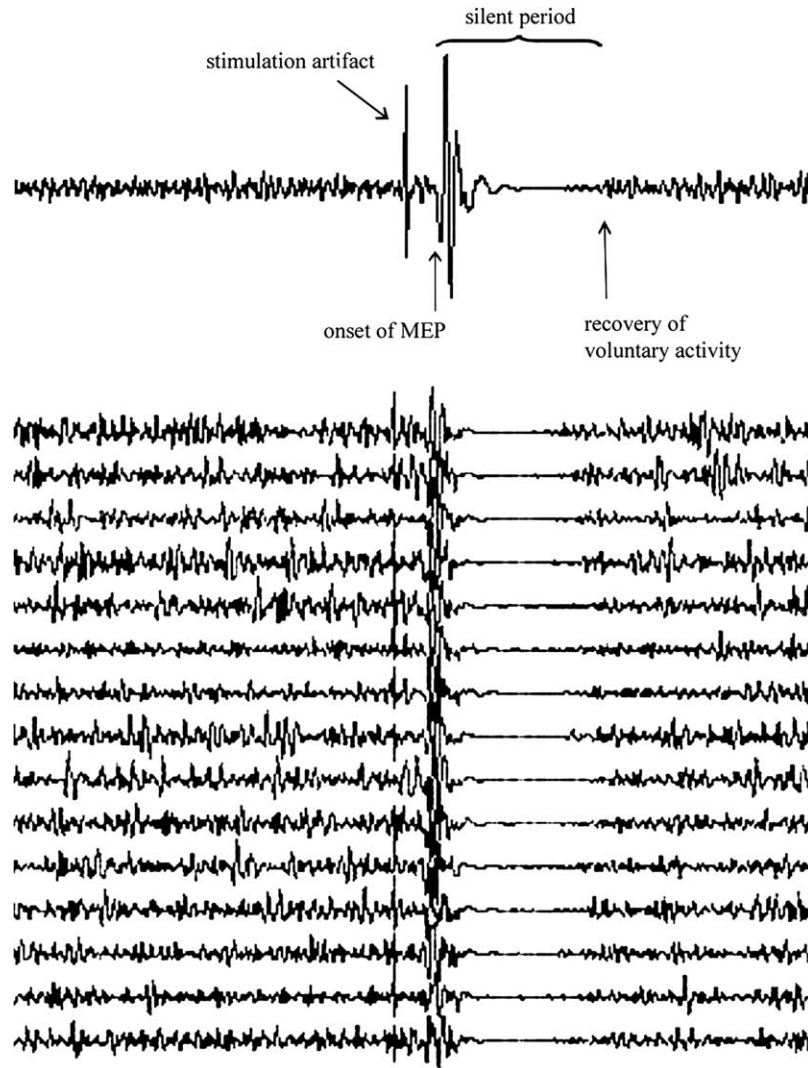


Fig. 1. Example of cortical silent period measurement taken from an average of 15 stimulations of the motor cortex at 140% resting motor threshold from one subject with high %CNS volume.

1.3. MRI procedures

The general procedures have been described previously (Mueller et al., 1998). Briefly, MRI scans were performed with a 1.5 Tesla magnet. The protocol consists of: slice thickness of 4 mm (no gap), 24 cm field of view with a 256×256 matrix (0.86 mm \times 0.86 mm pixel size) and 0.5 repetitions per sequence. The brain was visualized in two planes using the following pulse sequences: (1) T_1 -weighted sagittal images centered in the midsagittal plane with the pituitary profile (including the infundibulum) and cerebellar vermis clearly delineated: TR = 600 ms, TE = 20 ms—images; (2) T_2 -weighted coronal images perpendicular to the sagittal plane; multi-echo sequence, TR = 2800 ms, TE = 30/80 ms. Coronal plane is determined by a line drawn from the lowest point of the splenium to the lowest point of the genu of the corpus callosum on the midsagittal image.

1.3.1. Image analysis

Images were evaluated blind to the age and other demographic characteristics of the subject. Image analysis software, REGION is used to quantitatively assess regional brain volumes of interest (Kaye et al., 1997). Regions of interest (ROI) assessed were: total deep and periventricular WMH volume, cerebral volume, and total ventricular CSF volume, volumes were calculated by multiplying the brain area by the slice thickness for all slices in which the brain appears. Volumetric data was analyzed corrected by total intracranial volume (ICV), giving % brain volume values. The intraclass correlation coefficient as a measure of reliability of volume determination was >0.9 for all regions.

1.4. Quantification of WMH using REGION

Using REGION's sampling tools, the analyst selects representative, unambiguous pixels of WMH (as well as

Table 1
Subject characteristics

	Mean \pm SD	Range
Age	88.7 \pm 6.3	69.9–94.5
MMSE	28.5 \pm 1.35	25–30
% Right handed	100	
SES (Hollingsworth scale)	47.5 \pm 11.5	25–63
Education (years)	14.5 \pm 3.2	8–20
Time from MRI to TMS (mo.)	4.8 \pm 4.1	0–16.8
Time from MMSE to TMS (mo)	3.1 \pm 3.0	0–13.2
% vCSF volume (ccCSF/ccICV \times 100)	4.31 \pm 1.44	1.91–6.98
%WMH volume (ccWMH/ccICV \times 100)	1.41 \pm 1.39	0.22–6.52
% CNS volume (ccCNS/ccICV \times 100)	73.67 \pm 5.13	65.55–84.69
Time from MRI to TMS (mo.)	4.8 \pm 4.1	0–16.8

brain tissue, fluid, and bone) from the multi-echo sequence display. A regression model then uses the proton density and T2 intensities and location of each pixel to differentiate tissue types. WMH is distinguished from brain tissue and fluid based on higher signal on both the proton density and T2 images. Areas of high signal, which immediately about ventricular fluid, as visualized on the coronal image are considered periventricular. WMH bounded by brain tissue on all sides is considered deep high signal.

Because of the reported relationship between RMT and distance from the coil to the underlying cortex (McConnell et al., 2001), the left and right coil-to-cortex distance was approximated for each subject. Scalp-cortex measurements were made on 5 separate coronal slices for each subject. The initial slice was chosen as the coronal image with the most distinct superior colliculus, as this image provided the best view of the precentral gyrus that could be consistently obtained across subjects; measurements were made on this slice, the two slices immediately anterior to it, and the two slices immediately posterior. For each slice, the precentral gyrus was located (Jackson and Duncan, 1996). The two points on the surface of the cortex which were closest to and furthest from the scalp, respectively, were visually determined, and then measured using NIH Image v. 1.63. If there was no visually obvious fluctuation in scalp-cortex distance across the gyrus, only one point was measured, and this distance was recorded as both the longest and shortest distance. The 10 measurements for each subject were then averaged.

Table 2
TMS outcomes for right and left hemispheres

	Right hemisphere		Left hemisphere		Paired <i>t</i> -test
	Mean \pm SD	Range	Mean \pm SD	Range	<i>P</i> -value
RMT (% max output)	45.3 \pm 13.8	23.0–81.0	49.4 \pm 12.5	30.0–88.0	0.008
SP (ms)	187.2 \pm 52.8	102.2–264.5	188.9 \pm 32.8	112.4–253.2	0.699
CMCT (ms)	7.7 \pm 1.8	3.6–10.9	8.3 \pm 1.5	5.3–12.3	0.465
MEP amp (μ V)	1.6 \pm .72	0.57–2.88	1.7 \pm 1.0	0.3–4.7	0.876
MEP/MAP (%)	27.5 \pm 17.1	6.2–60.0	24.2 \pm 17.6	4.6–67.1	0.058

1.5. Statistical analysis

The statistical program JMP (SAS Institute, Cary, NC) was used for statistical analysis. MRI regions of interest were examined as continuous variables. Data were analyzed for relationships between TMS-derived measures of cortical excitability and MRI regions of interest using a multivariate regression analysis, adjusting for age at TMS visit. The relationship between age and TMS outcomes of RMT, cSP, and CMCT, were examined using simple regressions. Interhemispheric differences were explored using paired *t* tests. A secondary analysis of the data was performed in which %WMH, %CNS, and %vCSF volumes were all entered into a mixed stepwise regression analysis with potential confounders of age at TMS testing, and for RMT, coil-cortex distance for TMS outcomes of right RMT, left RMT and cSP. Statistical significance was taken as $P < 0.05$.

One subject had a left and right hemisphere RMT greater than 2.5 standard deviations from the mean of the group. Therefore, all analyses in which RMT was examined in relation to MRI volumes were performed without data from this subject included. One subject had a %WMH volume greater than 2.5 standard deviations from the mean on the group. Therefore, multiple regression analyses in which %WMH volume was used as a continuous variable were performed without data from this subject included.

2. Results

Twenty-four right-handed, non-demented subjects (9 men and 15 women) underwent TMS testing. Subject characteristics are outlined in Table 1 (See Table 1). There was a negative association between right hemisphere RMT and age ($R^2 = 0.23$, $P = 0.0219$). There was no relationship between age and left hemisphere RMT, CMCT, or cSP ($P > 0.05$). There was no difference between left and right hemisphere total white matter hyperintensity volume (paired *t*-test, $P > 0.05$). A significant difference existed between right and left hemisphere RMT (paired *t*-test, $P = 0.008$) so analyses for each hemisphere were performed separately (See Table 2).

2.1. Resting motor threshold

Right and left RMT was obtained for all subjects. After adjusting for age, there was a relationship between lower right hemisphere RMT and increased %WMH ($P=0.0368$) and %vCSF ($P=0.0005$) volumes (See Fig. 2). There was a marginal association between lower right hemisphere RMT and decreased %CNS volume ($P=0.0676$).

After adjusting for age, lower left hemisphere RMT was related to increased %vCSF ($P=0.0189$) volume (See Fig. 2). There was a marginal association between lower left hemisphere RMT and increased %WMH ($P=0.0795$) and decreased %CNS ($P=0.0965$) volumes.

2.2. Cortical silent period (cSP)

Fifteen subjects underwent TMS testing for both left and right hemisphere cortical silent period. There was no difference between left and right hemisphere post-MEP cSP duration (paired t -test, $P>0.05$). Therefore, the following cSP results are presented as an average of both the left and right hemisphere. After adjusting for age, there was a relationship between shortened cSP duration and decreased %CNS ($P=0.029$) volumes (See Fig. 2). No association existed between cSP duration and either %WMH or %vCSF volumes ($P>0.05$).

2.3. Central motor conduction time (CMCT)

CMCT originating from both the right and left hemispheres were calculated for 13 subjects. Because there was no hemispheric difference in CMCT (paired t -test, $P>0.05$), an average is presented here. There was no association between CMCT and %vCSF, %CNS, or %WMH volumes (Regression, $P>0.05$).

2.4. F-wave amplitude

Right and left arm ulnar nerve F-wave amplitudes were obtained on 23 and 13 subjects, respectively. There was no difference between left and right arm ulnar F-wave amplitudes (paired t -test). There was no difference in left or right arm ulnar nerve F-wave amplitude between subjects in the high and low %WMH, %CNS, or %vCSF volume groups (t -test, $P>0.05$).

2.5. Secondary analyses

There was no difference between approximated left and right hemisphere scalp–cortex distance (paired t -test, $P>0.05$). Right hemisphere scalp–cortex distance was positively related to right hemisphere RMT ($R^2=0.20$, $P=0.0297$, regression). The relationship between left

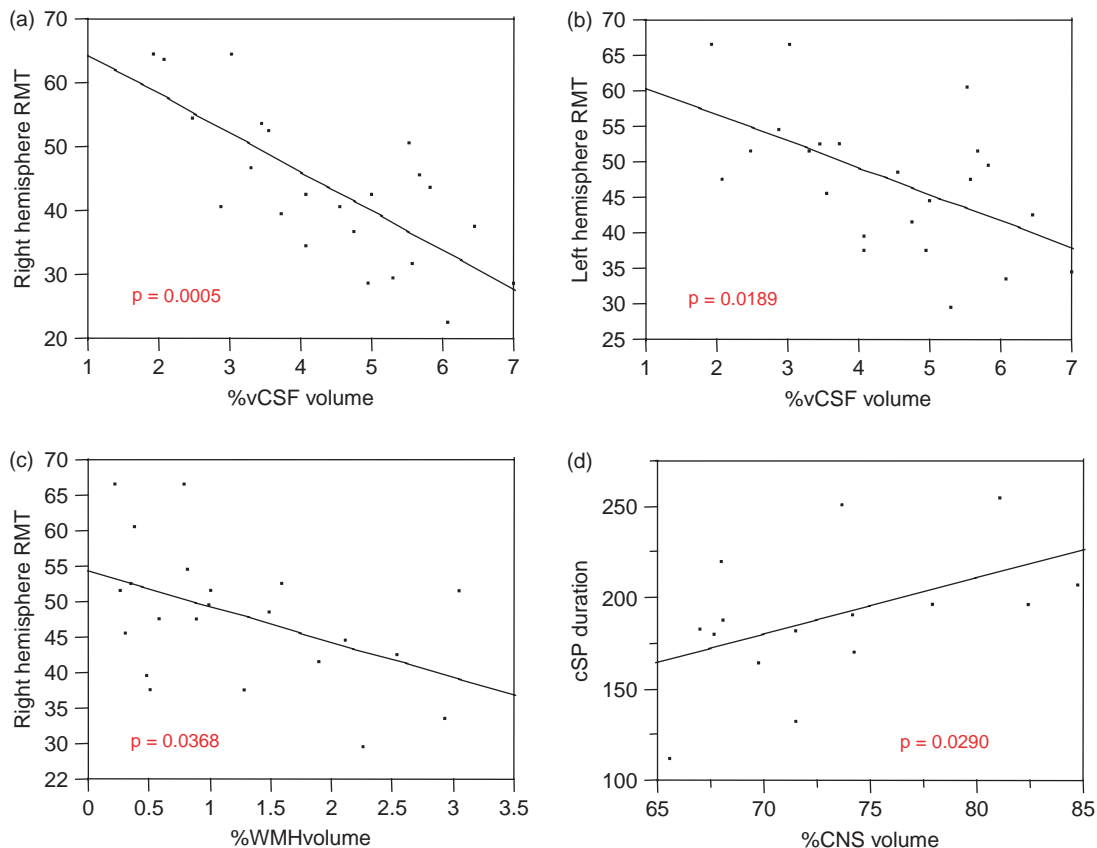


Fig. 2. Scatterplots of relationships between (a) right hemisphere RMT and vCSF volume, (b) left hemisphere RMT and %vCSF volume, (c) right hemisphere RMT and %WMH volume, and (d) cSP and %CNS volume.

hemisphere scalp–cortex distance and left hemisphere RMT did not reach statistical significance ($P=0.1316$, simple regression). Age at TMS testing, %WMH, %CNS, %vCSF, and for RMT outcomes, coil–cortex distance, were all entered into a mixed stepwise regression analysis for TMS outcomes of left RMT, right RMT, and cSP. In all analyses in which RMT was the outcome, coil–cortex distance did not remain in the model, and MRI volumes accounted for most of the variance. For the outcome of right RMT; %vCSF: $P=0.0002$. for outcome of left RMT; %vCSF: $P=0.0187$. For the stepwise analysis in which cSP was the TMS outcome, %CNS volume accounted for most of the variance in the model, but did not reach statistical significance ($P=0.1729$). The variable age did not remain in the model for any of the above analyses.

3. Discussion

We have shown that the common age-related MRI findings of increased WMH change and increased ventricular CSF volume observed with normal aging are significantly associated with decreased right and left hemisphere resting motor threshold. Similarly, age-associated decreased CNS volume was associated with decreased right hemisphere RMT and decreased SP duration. No such relationships between MRI regions of interest and F-wave amplitudes were found, supporting a cortical origin to observed differences in TMS measures of cortical–spinal excitability between MRI volume groups.

Within the age-range of the population participating in this study, older age, in and of itself, was not consistently associated with changes in measures of cortical–spinal excitability. The association between RMT and age-related MRI volume changes may partially explain discrepant findings among prior studies investigating the effects of age on TMS-derived measures of cortical excitability in which MRI data was not obtained, as the degree of cortical excitation may differ relative to MRI-measured volume loss associated with age. Results from this study show significant hemispheric differences in resting motor threshold, with lower resting motor threshold of the right hemisphere compared with the left. Evidence from other studies has suggested a predilection towards increased cortical excitability in the dominant cerebral hemisphere of young and middle-aged right-handed individuals (Ilic et al., 2004; Triggs et al., 1994). Two prior studies investigating cortical excitability in the elderly have found no hemispheric difference in resting motor threshold (Matsunaga et al., 1998; Rossini et al., 1992). Importantly, subjects in these studies were relatively younger (range, 51–86 years of age) than in our study where the mean age of the subjects was 88.7 years. Accordingly, differences among studies may represent the fact that each is capturing a different cross-section of a continuum of age-related changes

in cortical excitability, a possible reflection of well described cognitive processing changes observed with advanced age.

There was a stronger statistical relationship between lower right hemisphere RMT and enhanced age-related volumetric change (i.e. increased ventricular CSF volume, increased WMH signal, and decreased CNS volume) compared with left hemisphere RMT and volumetric outcomes of interest. The etiology of this differential relationship between hemisphere threshold and age-related volumetric outcomes remains open to interpretation. One theory of aging proposes that right hemispheric function declines to a greater degree than the left hemisphere (Brown and Jaffe, 1975; Goldstein and Shelly, 1981; Orbelo et al., 2005; Weller and Latimer-Sayer, 1985). Findings from this study provide electrophysiological support for the presence of a differential sensitivity of the right hemisphere to a potentially more diffuse degenerative process.

In this study, decreased RMT was strongly associated with increased ventricular CSF volume on brain MRI. Increased ventricular CSF volumes may be indicative of degenerative changes occurring in the white matter. Alternatively, because of constraints of volumetric MRI analysis pertaining to volume average effects, ventricular CSF MRI volumes may be a more precise measurement associated with cortical volume loss, indicating a sub-clinical pathological process of cortical neuronal degeneration. It is well known that many neurodegenerative diseases, including Alzheimer's disease, are associated with a lower motor threshold compared with age-matched controls (de Carvalho et al., 1997; Di Lazzaro et al., 2004; Liepert et al., 2001). Clinical and pathological follow-up of our current subject cohort will be helpful in clarifying the central process driving the association between CSF volume and cortical excitability observed in this study.

A limitation of this study is the somewhat narrow range of age represented by subjects. Further studies investigating cortical excitability that include a wider range of elderly participants will be helpful in further elucidating the contribution of age itself on the relationship between cortical excitability and MRI changes that may contribute to functional decline.

This study investigates TMS measures of cortical excitability in relation to age-related MRI findings in the non-demented elderly. Findings from this study suggest that age-related MRI findings of increased WMH signal and atrophy are associated with electrophysiological observations of increased cortical excitability. Prior TMS studies have demonstrated changes in cortical excitability remote from the lesion in stroke subjects, with a tendency towards increased excitatory activity in the non-affected hemisphere (Butefisch et al., 2003; Shimizu et al., 2002). Furthermore, it has been shown that the intact ipsilateral hemisphere can functionally compensate for focal contralateral cortical motor dysfunction (Strens et al., 2003), supporting a

compensatory role of changes in cortical excitability observed in the non-affected hemisphere of stroke subjects. A recent study, however, has demonstrated that improved motor performance can be achieved by decreasing the excitability of the contralesional motor cortex in stroke subjects (Takeuchi et al., 2005), suggesting, as others have, that increased contralesional cortical excitability impairs motor performance in some stroke patients (Murase et al., 2004). Subjects participating in this study did not have neurologic signs or a history of motor stroke. Nevertheless, it is possible that observed changes in cortical excitability corresponding to evidence of cortical and subcortical neurodegeneration on MRI is the result of a similar but bi-hemispheric and chronic process. Whether these changes contribute to age-related decline in cerebral processing or are part of a compensatory response to maintain corticospinal output remains uncertain.

This study is the first to demonstrate findings of increased cortical excitability in subjects with neurodegenerative MRI changes in non-demented elderly. These results provide evidence that such commonly observed age-related imaging findings reflect functional changes at a cellular level that may affect cognitive and motor integrity in a population at risk for declining cognition and mobility. Future studies may wish to consider neuroimaging markers of neurodegeneration prior to enrolling elderly subjects as controls in TMS studies in which cortical excitability is the outcome of interest.

Acknowledgements

This study was supported in part by grants from the Department of Veterans Affairs and National Institutes of Health (P30 AG 08017, M01 RR000334, and K23 AG 24826-01), Paul B. Beeson Career Development Award in Aging, and American Academy of Neurology Foundation Clinical Research Training Fellowship.

References

- Alagona G, Bella R, Ferri R, Pennisi G, Carnemolla A, Maci T, Domina E, Maertens de Noordhout A. Motor cortex excitability in Alzheimer's disease and in subcortical ischemic vascular dementia. *Neurosci Lett* 2004;362(2):95–8.
- Albert ML, Knoefel JE. *Clinical neurology of aging*. 2nd ed. New York: Oxford University Press; 1994.
- Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell scale for depression in dementia. *Biol Psychiatry* 1988;23(3):271–84.
- Birren JE, Schaie KW. *Handbook of the psychology of aging*. The handbooks of aging, vol. 2. 3rd ed. San Diego, CA: Academic Press; 1990.
- Brown JW, Jaffe J. Hypothesis on cerebral dominance. *Neuropsychologia* 1975;13(1):107–10.
- Bryan RN, Wells SW, Miller TJ, Elster A, Jungreis C, Poirier V, Lind B, Manolio TA. Infarctlike lesions in the brain: prevalence and anatomic characteristics at MR imaging of the elderly—data from the Cardiovascular Health Study. *Radiology* 1997;202(1):47–54.
- Butefisch CM, Netz J, WeBling M, Seitz RJ, Homberg V. Remote changes in cortical excitability after stroke. *Brain* 2003;126:470–81.
- Claus D. Central motor conduction: method and normal results. *Muscle Nerve* 1990;13:1125–32.
- Cook IA, Leuchter AF, Morgan ML, Dunkin JJ, Witte E, David S, Mickes L, O'Hara R, Simon S, Lufkin R, Abrams M, Rosenberg S. Longitudinal progression of subclinical structural brain disease in normal aging. *Am J Geriatr Psychiatry* 2004;12(2):190–200.
- de Carvalho M, de Mendonca A, Miranda PC, Garcia C, Luis ML. Magnetic stimulation in Alzheimer's disease. *J Neurol* 1997;244(5):304–7.
- de Groot JC. Cognitive correlates of cerebral white matter changes. *J Neural Transm Suppl* 1998;53:41–67.
- Di Lazzaro V, Oliviero A, Pilato R, Saturno E, Dileone M, Marra C, Daniele A, Ghirlanda S, Gainotti G, Tonali PA. Motor cortex hyperexcitability to transcranial magnetic stimulation in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2004;74:555–9.
- Folstein MF. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12(3):189–98.
- Goldstein G, Shelly C. Does the right hemisphere age more rapidly than the left? *J Clin Neuropsychol* 1981;3(1):65–78.
- Ilic TV, Jung P, Ziemann U. Subtle hemispheric asymmetry of motor cortical inhibitory tone. *Clin Neurophysiol* 2004;115(2):330–40.
- Jackson JD, Duncan JS. *MRI neuroanatomy: a new angle on the brain*. New York, NY: Churchill Livingstone; 1996.
- Kaye JA, Swihart T, Howieson D, Dame A, Moore MM, Karnos T, Camicioli R, Ball M, Oken B, Sexton G. Volume loss of the hippocampus and temporal lobe in healthy elderly persons destined to develop dementia. *Neurology* 1997;48(5):1297–304.
- Kimura J. *Electrodiagnosis in diseases of nerve and muscle: principles and practice*. 3rd ed. New York: Oxford Press; 2001.
- Kossev AR, Schrader C, Dauper J, Dengler R, Rollnik JD. Increased intracortical inhibition in middle-aged humans; a study using paired-pulse transcranial magnetic stimulation. *Neurosci Lett* 2002;333(2):83–6.
- Liepert J, Bar KJ, Meske U, Weiller C. Motor cortex disinhibition in Alzheimer's disease. *Clin Neurophysiol* 2001;112(8):1436–41.
- Longstreth Jr WT, Bernick C, Manolio TA, Bryan N, Jungreis CA, Price TR. Lacunar infarcts defined by magnetic resonance imaging of 3660 elderly people: the Cardiovascular Health Study. *Arch Neurol* 1998;55(9):1217–25.
- Lou JS, Benice T, Kearns G, Sexton G, Nutt J. Levodopa normalizes exercise related cortico-motoneuron excitability abnormalities in Parkinson's disease. *Clin Neurophysiol* 2003;114(5):930–7.
- Matsunaga K, Uozumi T, Tsuji S, Murai Y. Age-dependent changes in physiological threshold asymmetries for the motor evoked potential and silent period following transcranial magnetic stimulation. *Electroencephalogr Clin Neurophysiol* 1998;109(6):502–7.
- McConnell KA, Hahas Z, Shastri A, Lorberbaum JP, Kozel FA, Bohning DE, George MS. The transcranial magnetic stimulation motor threshold depends on the distance from coil to underlying cortex: a replication in healthy adults comparing two methods of assessing the distance to cortex. *Biol Psychiatry* 2001;49(5):454–9.
- Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 1993;43(11):2412–4.
- Mueller EA, Moore MM, Kerr DC, Sexton G, Camicioli RM, Howieson DB, Quinn JF, Kaye JA. Brain volume preserved in healthy elderly through the eleventh decade. *Neurology* 1998;51(6):1555–62.
- Murase N, Duque J, Mazzocchio R, Cohen G. Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol* 2004;55:400–9.

- Nardone R, Florio I, Lochner P, Tezzon F. Cholinergic cortical circuits in Parkinson's disease and in progressive supranuclear palsy: a transcranial magnetic stimulation study. *Exp Brain Res* 2005;163(1):128–31.
- Orbelo DM, Grim MA, Talbott RE, Ross ED. Impaired comprehension of affective prosody in elderly subjects is not predicted by age-related hearing loss or age-related cognitive decline. *J Geriatr Psychiatry Neurol* 2005;18(1):25–32.
- Peinemann A, Lehner C, Conrad B, Siebner HR. Age-related decrease in paired-pulse intracortical inhibition in the human primary motor cortex. *Neurosci Lett* 2001;313(1–2):33–6.
- Pierantozzi M, Manella M, Palmieri MG, Koch G, Giordano A, Marciani MG, Bernardi G, Stanzione P, Stefani A. Different TMS patterns of intracortical inhibition in early onset Alzheimer dementia and frontotemporal dementia. *Clin Neurophysiol* 2004;115(10):2410–8.
- Rossini OM, Desiato MT, Caramia MD. Age-related changes of motor evoked potentials in healthy humans: non-invasive evaluation of central and peripheral motor tracts excitability and conductivity. *Brain Res* 1992;593(1):14–19.
- Sawaki L, Yaseen Z, Kopylev L, Cohen LG. Age-dependent changes in the ability to encode a novel elementary motor memory. *Ann Neurol* 2003;53(4):521–4.
- Shimizu T, Hosaki A, Hino T, Sato M, Komori T, Hirai S, Rossini PM. Motor cortical disinhibition in the unaffected hemisphere after unilateral cortical stroke. *Brain* 2002;125:1896–907.
- Strens LHA, Fogelson N, Shanahan P, Rothwell JC, Brown P. The ipsilateral human motor cortex can functionally compensate for acute contralateral motor cortex dysfunction. *Curr Biol* 2003;13:1201–5.
- Takeuchi N, Chuma T, Matsuo Y, Watanabe I, Ikoma K. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. *Stroke* 2005;36:2681–6.
- Triggs WJ, Calvanio R, Macdonell RA, Cros D, Chiappa KH. Physiological motor asymmetry in human handedness: evidence from transcranial magnetic stimulation. *Brain Res* 1994;636(2):270–6.
- Weller MP, Latimer-Sayer DT. Increasing right hand dominance with age on a motor skill task. *Psychol Med* 1985;15(4):867–72.