Atrophy of Spared Gray Matter Tissue Predicts Poorer Motor Recovery and Rehabilitation Response in Chronic Stroke

Lynne V. Gauthier, PhD; Edward Taub, PhD; Victor W. Mark, MD; Ameen Barghi; Gitendra Uswatte, PhD

Background and Purpose—Although the motor deficit after stroke is clearly due to the structural brain damage that has been sustained, this relationship is attenuated from the acute to chronic phases. We investigated the possibility that motor impairment and response to constraint-induced movement therapy in patients with chronic stroke may relate more strongly to the structural integrity of brain structures remote from the lesion than to measures of overt tissue damage.

Methods—Voxel-based morphometry analysis was performed on MRI scans from 80 patients with chronic stroke to investigate whether variations in gray matter density were correlated with extent of residual motor impairment or with constraint-induced movement therapy-induced motor recovery.

Results—Decreased gray matter density in noninfarcted motor regions was significantly correlated with magnitude of residual motor deficit. In addition, reduced gray matter density in multiple remote brain regions predicted a lesser extent of motor improvement from constraint-induced movement therapy.

Conclusions—Atrophy in seemingly healthy parts of the brain that are distant from the infarct accounts for at least a portion of the sustained motor deficit in chronic stroke. (Stroke. 2012;43:453-457.)

Key Words: CI therapy ■ gray matter ■ lesion ■ morphometry ■ motor ■ rehabilitation ■ stroke

The deficit after stroke is clearly due to the brain damage that has been sustained as a result of ischemia or hemorrhage. However, there appears to be a decline in the influence of stroke lesion characteristics on severity of the motor deficit over the course of the first year poststroke.1 Although most studies in acute stroke report weak to moderate relationships between motor deficit and lesion volume,2–4 these relationships are largely absent in chronic stroke.5 To our knowledge, the only consistently replicated predictor of residual motor deficit in chronic stroke is lesion location at the intersection of the corona radiata and fibers from the corpus callosum.6,7 The extent to which lesions interfere with descending pyramidal fibers has also been shown to predict prolonged motor deficit,8,9 albeit with exceptions.10 Given that a substantial proportion of the variability in motor deficit cannot be accounted for by lesion factors alone, particularly among patients with chronic stroke with lesions outside the aforementioned region, we postulated that diminished structural integrity of brain structures remote from the lesion might contribute importantly to the sustained motor deficit.

There is some evidence to support this conjecture. Brain metabolism of intact regions is often decreased in chronic stroke and the extent of this decrement has been associated with poorer motor recovery.11–13 Furthermore, previous research has found that in chronic stroke, there may be significant bilateral diffuse structural loss in brain areas that are anatomically remote from the infarction.14–16 However, no study to date has systematically evaluated whether such changes may be correlated in chronic stroke with the amount of motor deficit or with changes in functional status. Accordingly, in this experiment, we evaluated whether chronic motor deficits in stroke are related to the amount of thinning in normal-appearing brain regions on MRI. We used voxel-based morphometry (VBM) to relate gray matter density (in brain areas without visible damage) to motor status of the paretic arm. In addition, we assessed the related question of whether regional gray matter thinning in patients with chronic stroke before treatment is related to the magnitude of improvement in motor status after constraint-induced movement (CI) therapy.17

Methods

Participants

Eighty-five patients with chronic stroke with mild to moderate motor deficit were enrolled in 1 of several studies examining their response to CI therapy or alternative motor interventions from 1997 to 2009.
Assessment of Pretreatment Motor Functioning

Motor functioning was assessed before and after treatment with the Motor Activity Log (MAL) and the Wolf Motor Function Test (WMFT), both of which have an established reliability and validity. The MAL quantifies how well and how often activities of daily living are carried out spontaneously by patients with their more-affected arm. In contrast, the WMFT measures how rapidly patients perform standardized tests with the more-affected arm on request in the laboratory.20,21 The WMFT measures how well patients perform standardized tests that they are required to carry out with the more-affected arm in the laboratory.20,21 The 2 measures thus assess different domains of motor ability; the MAL measures amount of spontaneous, real-world use of the more affected arm, whereas the WMFT measures capacity for carrying out standardized motor tasks with the more-affected arm on request in the laboratory. There is often a large difference between the 2 measures.22,23 Performance time on the WMFT was recorded as a log\(^2\) transformation of the mean time in seconds to more accurately portray patient progress.5

Table: Pretreatment Patient Characteristics (n=80)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean±SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.9±12.3</td>
<td>38</td>
<td>87</td>
</tr>
<tr>
<td>Chronicity, y</td>
<td>4.3±4.0</td>
<td>0.8</td>
<td>20</td>
</tr>
<tr>
<td>Infarction volume, cm(^3)</td>
<td>14.4±29.5*</td>
<td>0.02</td>
<td>157.1</td>
</tr>
<tr>
<td>Motor Activity Log</td>
<td>1.0±0.7</td>
<td>0.0</td>
<td>2.6</td>
</tr>
<tr>
<td>Quality of Movement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>scale (0–5 points)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wolf Motor Function</td>
<td>1.3±1.0</td>
<td>0.1</td>
<td>3.8</td>
</tr>
<tr>
<td>Test log(^2) performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of purely</td>
<td>51.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>subcortical infarcts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage with right</td>
<td>48.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hemiparesis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage right-handed</td>
<td>88.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>before stroke</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Table SD indicates standard deviation.
*Positively skewed distribution, 34 patients had infarcts that were <3 cm\(^3\).

Interventions

Forty-four of 80 patients were randomly assigned to receive CI therapy, a motor rehabilitation therapy with proven efficacy for treating hemiparesis in chronic stroke.17,24,25 The other 36 patients received comparison interventions or attenuated forms of CI therapy. Only those patients assigned to CI therapy (n=44), the most effective intervention, were retained for the analysis examining gray matter predictors of therapy outcome. The demographics of those receiving CI therapy were similar to those of the entire sample. Patients receiving CI therapy had a mean age of 62.1±12.2 years and mean stroke chronicity of 4.3±3.9 years; 23 were women, 22 exhibited right hemiparesis, and 41 were right-handed before stroke.

MRI Analysis

Noisier scans, largely those obtained on the older scanners, were initially processed through a modified version of the noise reduction approach devised by Placidi and colleagues.26 A modified version of the Contourlet Hidden Markov Tree toolbox (Version 1.0) by Minh Do (http://www.ifp.uiuc.edu/~minhdo/software/) was modified in Matlab 7.5 for this purpose. Scans were then corrected for radiofrequency inhomogeneity using the Statistical Parametric Mapping toolbox (SPM5, Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm). Skull-stripping was performed using an in-house program to prevent extrabrain voxels from being classified as gray matter. Images were equated for deficit side by flipping left to right the brains of patients with right arm hemiparesis. Magnetic artifacts and focal structural change (eg, infarcts, peri-infarcts) were masked through manual tracing using MRIcro/MRicon software and refined using a semi-automated intensity thresholding technique. These tracings served as exclusion masks during (1) segmentation and normalization of the brain to prevent damaged tissue from affecting the algorithm; and (2) statistical analysis such that only remaining brain that was visibly spared from ischemia was analyzed.

VBM involves voxelwise comparisons of local gray matter density or volume.27 Each patient’s pretreatment brain scan underwent a procedure of joint normalization (to standard space) and segmentation (into gray matter, white matter, and cerebrospinal fluid) using SPM5 software. Brains were normalized to custom older adult templates28 that were rendered symmetrical by averaging the original templates with their mirror image. Tracings of damaged tissue were then normalized using an identical transformation to create normalized masks of abnormal tissue. These regions of abnormal tissue were removed from each patient’s gray matter image before smoothing. Finally, images were smoothed using a 10-mm Gaussian kernel to suppress noise and effects due to residual differences in gyral anatomy. The VBM processing steps are depicted in Supplemental Figure I (http://stroke.ahajournals.org).

Statistical Analysis

To determine whether a patient’s motor status at pretreatment was related to the extent of atrophy, separate voxelwise multiple regressions were performed correlating gray matter density with MAL and WMFT scores, respectively (n=80). Confounding factors that could relate to gray matter density (scanner strength, age, peri-infarct volume, chronicity, and cortical versus subcortical lesion classification) were covaried out of the model. Voxelwise multiple regression analyses were similarly conducted to examine whether gray matter density predicts treatment outcome from CI therapy (n=44). Beta coefficient t statistics for motor status/outcome were initially thresholded at \(t_{uncorrected}=0.05\) (t=±1.99 and \(t=±2.02\), respectively). SPM5 software was used to perform 2-tailed clusterwise statistics, corrected for familywise error (FWE), on each cluster of voxels exceeding this threshold.29

Results

Extent of Atrophy Correlates With Amount of Motor Deficit Pretreatment

Lower scores on the MAL were associated with reduced gray matter density in motor and motor-associated areas contralateral and ipsilateral to the motor deficit (cluster sizes=54 373 voxels and 49 939 voxels, respectively, \(P_{\text{FWEcorrected}}<0.0001\))
and in the insula/temporal lobe ipsilateral to the motor deficit (cluster size=22,350 voxels, $P_{\text{FWEcorrected}}=0.012$). Longer performance times on the WMFT (ie, greater impairment) were correlated with reduced gray matter density in motor areas contralateral to the motor deficit (cluster size=93,428 voxels, $P_{\text{FWEcorrected}}<0.0001$), to a lesser extent in ipsilateral motor areas, and in the thalamus, hippocampus, and insula ipsilateral to the more-affected arm (cluster size=45,316 voxels, $P_{\text{FWEcorrected}}<0.0001$). The Figure A–B displays spatial maps of suprathreshold clusters for the MAL and WMFT.

To ensure that the subjects who received CI therapy were representative of the total sample, statistical analyses were repeated on this subsample of patients ($n=44$). Nearly identical correlations were found between gray matter density and both MAL and WMFT pretreatment scores with only 1 major difference: the spatial extent of the MAL findings was diminished for the premotor and supplementary motor areas in the less affected hemisphere, likely due to reduced power to detect an effect.

**Extent of Atrophy Correlates With Motor Gains After CI Therapy**

Reduced gray matter density in the primary motor cortex contralateral to the more-affected extremity (cluster size=17,531 voxels, $P_{\text{FWEcorrected}}=0.037$) and greater gray matter density in posterior temporal–lateral occipital cortex contralateral to the deficit (cluster size=31,896 voxels, $P_{\text{FWEcorrected}}=0.001$) predicted less improvement on the MAL after CI therapy (Figure C). Less improvement on the WMFT after CI therapy (ie, greater time scores) was predicted by reduced gray matter density in several brain regions, including (1) bilateral cerebral peduncles, pons, medulla, and cerebellum contralateral to the more-affected arm, contralateral anterior temporal lobe (cluster size=73,292 voxels, $P_{\text{FWEcorrected}}<0.0001$; (2) contralateral supplementary motor cortex and premotor cortex (cluster size=16,577 voxels, $P_{\text{FWEcorrected}}=0.05$); and (3) temporal–occipital region (motion processing area) of the hemisphere ipsilateral to the motor deficit (cluster size=17,572 voxels, $P_{\text{FWEcorrected}}=0.041$; Figure D).

**Discussion**

Decreased density of noninfarcted tissue that is seemingly healthy is correlated with poorer pretreatment motor status and reduced response to an efficacious rehabilitation therapy. This finding provides evidence that at least part of the origin of the motor deficit in patients with chronic stroke is the extent to which gray matter density in motor areas remote from an infarct is affected. Thus, the structural integrity of apparently healthy gray matter tissue in chronic stroke is fundamentally important to motor control and real-world spontaneous use of the paretic arm.

The topography of this relationship differs somewhat between outcome measures and assessment occasion (ie, pretreatment deficit in motor ability [WMFT scores], pretreatment amount of spontaneous use of the more affected arm in the life situation [MAL scores], and amount of improvement produced by CI therapy in both WMFT and MAL scores). However, a consistent finding across measures is that residual reduced motor functioning and reduced motor response to CI therapy are correlated with decreased gray matter density in contralateral sensorimotor cortical areas. In the ipsilateral hemisphere, decreased gray matter density in sensorimotor areas also predicted less real-world more-affected arm use at pretreatment (MAL score). Of note, these are the same brain regions in which gray matter increases correlated with improvements in real-world arm use from CI therapy.30 Gray matter density in bilateral cerebral peduncles, pons, medulla, cerebellum, anterior motor areas (prefrontal and supplementary motor areas) and regions of the temporal
lobes was positively correlated with CI therapy-induced improvement on a laboratory-based measure of motor function (WMFT). These areas represent a network of brain regions involved in motor function, visual motion processing, and cognitive function. In summary, the structural integrity of widely distributed brain structures in both hemispheres is associated with better spontaneous motor recovery and rehabilitation response. The topography of these findings is consistent with functional alterations and suggests a distributed neural network of motor recovery in chronic stroke.

At least 2 potential processes may explain the correlation between gray matter density and motor function in chronic stroke: (1) greater gray matter atrophy in subjects with greater motor impairment; and (2) greater neuroplastic compensation in subjects exhibiting greater motor recovery. There is stronger support for the first mechanism. Longitudinal and large cross-sectional studies of the topographical structural changes after stroke in humans have indicated that widespread cortical atrophy occurs.14–16 A longitudinal study in animals also showed bilateral thinning of gray matter after simulated stroke in the same brain areas in which we observed a correlation between gray matter density and motor performance.32 Furthermore, gross losses of gray matter are visible to the naked eye in scans from many cases in our data set (see Supplemental Figure II). Such structural changes may reflect the consequences of transsynaptic physiological alterations in these areas.11,13 Evidence for a generally atrophic process does not preclude the possibility of selective increases in amount of gray matter after stroke that may mitigate postischemic atrophy and support motor recovery.30,34,35 For example, increased functional activity has been observed in compensatory brain regions after chronic stroke36,37 and may be linked with increased cortical thickness in these areas.36 Thus, selective neuroplastic compensation, possibly mediated by the amount of use of the impaired arm,30 may counteract widespread atrophy and contribute to partial restoration of motor function in chronic stroke.

Our finding that greater spontaneous recovery of motor function and enhanced rehabilitation response are associated with gray matter density in areas distant from the infarct suggests that therapies aimed at preserving or improving the integrity of remaining tissue are critical for optimal motor recovery. Longitudinal studies should trace the trajectories of widespread atrophy and selective growth in brain tissue and their contribution to motor status from acute to chronic stroke. Improved understanding of factors that attenuate the observed atrophy will identify additional targets for therapeutic intervention.

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Disclosures
None.

References
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**Figure 1:** VBM processing steps for one participant. From left to right: original image, skull-stripped and corrected for inhomogeneity, native space grey matter, normalized grey matter, smoothed normalized grey matter with damaged tissue removed. Arrows point to the infarct.
**Figure 2:** Pronounced atrophy remote from the infarct is readily visible in a large proportion of patients in our sample. To demonstrate this phenomenon, brains of stroke patients from this study (left column) are compared with age- and sex-matched healthy subjects from the OASIS dataset (right column). From top to bottom (neuro-radiological orientation): extensive atrophy of the thalamus and insula following a left (L) cortical lesion to Brodmann’s areas (BA) 4 & 6 in a 44 year old (yo) male (M); atrophy of the motor cortex and insula following an infarct to the L corona radiata in a 51 yo M; pronounced atrophy to bilateral motor cortices in a 61 yo female (F) after right (R) superior temporal and corona radiata infarct; motor cortex atrophy in a 59 yo M following L multifocal infarct to lateral BA 4 and BAs 39 & 40; atrophy in the L insular region following a large R hemisphere lesion (shown) in a 54 yo M.
脳卒中を免れた灰白質組織の萎縮は慢性期脳卒中における不良な運動回復およびリハビリテーション効果を予測する

Atrophy of Spared Gray Matter Tissue Predicts Poorer Motor Recovery and Rehabilitation Response in Chronic Stroke

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背景および目的: 脳卒中後の運動障害は持続した構造的脳損傷に起因することは明らかであるが、急性期から慢性期にかけてこの関係は弱くなる。我々は、慢性期脳卒中患者における運動障害および強制誘導運動療法に対する反応が、明らかな組織損傷の程度よりも、病変から離れた脳構造の構造的健全性とより強く関連している可能性を検討した。

方法: 慢性期脳卒中患者80例のMRIスキャンを対象とし、ボクセル単位の形態解析を行い、灰白質の密度の変動が残存する運動障害の程度または強制誘導運動療法により誘導される運動回復と相関しているかどうかを調べた。

結果: 非梗塞性運動領域の灰白質密度の低下は、残存する運動障害の大きさと有意に相関していた。さらに、複数の離れた脳領域の灰白質密度の低下は、強制誘導運動療法による運動改善の程度が低いことを予測した。

結論: 梗塞から離れていて外見的に健常な脳部位の萎縮は、慢性期脳卒中における持続的運動障害の少なくとも一部の原因となる。

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(A) 治療前のMALスコアと灰白質密度。 (B) 治療前のWMFTパフォーマンス（時間スコアが大きいほどパフォーマンスは悪く）と灰白質密度。 (C) 灰白質密度とMALを指標とする治療転帰。および(D) 灰白質密度とWMFTを指標とする治療転帰のそれぞれの相関を示すβ係数値の陰上クラスターのサーフェスレンダリング。カラーバーは個々のボクセル相関統計値の大きさを示す。「左」半球が影響が大きかった半球である。MAL：自発運動の記録、WMFT：Wolf運動機能検査。