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Brain parenchymal fraction predicts motor improvement following intensive task-oriented motor rehabilitation for chronic stroke

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Abstract. *Background and purpose*: Infarct volume and location have a weak relationship with motor deficit in patients with chronic stroke. Recent research has focused on the relationship between spared or seemingly "healthy" neural tissue and motor function. In this study we examined MRI scans of patients with chronic stroke to determine if characteristics of seemingly normal parenchyma could predict either response to different forms of upper extremity physical rehabilitation or to pre-treatment motor status.
Methods: Individuals with chronic stroke (ages 60.6 ± 11.9 years) and mild/moderate upper extremity hemiparesis were administered either CI therapy ($n = 14$) or a comparison therapy ($n = 29$). The patients were assessed prior to and following therapy with MRI scans and the Wolf Motor Function Test (WMFT) Performance Time measure. Total voxels in combined grey matter (GM) and white matter (WM) segments (parenchymal volume) were divided by total voxels in GM, WM, and cerebrospinal fluid segments (intracranial volume) to obtain the brain parenchymal fraction (BPF).
Results: BPF correlated with treatment gains on the WMFT ($r(43) = –0.31$, $p = 0.04$). Significant correlations between pre-treatment motor function and BPF were not observed.
Conclusions: Individuals with greater BPFs after stroke show larger arm function gains after CI therapy, suggesting that reductions in volume of normal-appearing tissue may relate to ability to benefit from rehabilitation therapy in chronic stroke.

Keywords: Stroke, rehabilitation, parenchyma, neuroimaging, CI therapy, hemiparesis

1. Introduction

Infarct volume and location have a weak to moderate relationship with motor deficit in patients with acute stroke (Bayona et al., 2005; Mark et al., 2008). The relationship for infarct volume and motor deficit becomes diminished in chronic stroke patients (Mark et al., 2008) and for lesion location the relationship is weak except when the lesion is in the corticospinal tract as it passes through the centrum semiovale (Gauthier et al., 2009). Because stroke can be associated with structural changes beyond the area of infarction

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(e.g., white matter hyperintensities, enlarged periventricular spaces, global cerebral atrophy) (Mountz et al., 2003), it is possible that such structural changes may at least partly account for the limited ability of infarct size or location alone to explain the variation in clinical changes in chronic stroke. Global cerebral atrophy of grey and white matter structures presents a particularly promising target for investigation, because if global atrophy were found to predict clinical outcomes, this would suggest that a critical degree of parenchymal mass may be necessary for a particular level of post-stroke neurological performance or the ability to benefit from a rehabilitation therapy. This result in turn might be relevant to network models of purposive motor control.

Evidence of diffuse structural remodeling of the CNS, one kind of neuroplasticity, has been shown to occur in stroke patients to follow a form of intensive neurological rehabilitation termed Constraint-Induced Movement therapy (CI therapy). These changes involve increases in grey matter (GM) in sensorimotor cortex, more anterior motor areas and the hippocampus on both sides of the brain (Gauthier et al., 2008). CI therapy was founded on basic neuroscience research (Taub, 1980) and has proven efficacious in improving motor deficit following stroke (Taub et al., 1993; Wolf et al., 2006) and other types of neurological injury in adults (Shaw et al., 2005) and in children (Taub et al., 2004; 2007; 2011). Also, local atrophy in sensorimotor areas has been found to predict the magnitude of response to CI therapy (Gauthier et al., 2012). Accordingly, CI therapy can serve as an investigational "engine" with which to assess the intrinsic ability of the CNS to reorganize in response to prolonged alterations in the use of portions of the body (Nadeau and Wu, 2006).

Our laboratory has available the clinical and structural neuroimaging outcomes from a substantial group of adult hemiparetic chronic stroke patients who underwent either CI therapy or alternative motor rehabilitation. This resource allows investigating whether clinical outcomes may be related to specific CNS structural characteristics, and thus whether certain morphological properties may be specifically related to processes that can engender either profuse neuroplastic reorganization or positive response to rehabilitation therapy. In the present study, we used the brain parenchymal fraction (BPF) to index the extent of global cerebral atrophy in chronic stroke patients. The BPF is the parenchymal volume divided by the intracranial volume, which controls for variability in head size (Rudick et al., 1999). The parenchyma on structural MRI was used to represent the intracranial compartment that had residual neurological function, in contrast to the cerebrospinal fluid (CSF) space. We found that the amount of normal-appearing white and grey matter proportionate to intracranial space (as indexed by the BPF) predicted the amount of improvement due to CI therapy but not the pre-treatment motor status.

2. Methods

2.1. Participants

Chronic stroke patients who had participated in an earlier study (Gauthier et al., 2008) that examined the clinical efficacy of CI therapy with regard to structural neuroplastic changes on MRI were involved in the current study. Patients receiving full CI therapy ($n = 14$) had a mean age of 62.7 ± 9.3 years and a mean post-stroke chronicity of 2.3 ± 1.3 years; those receiving the comparison therapy ($n = 29$) had a mean age of 64.7 ± 12.7 years and a mean chronicity of 4.1 ± 4.0 years. Two patients in the comparison group dropped out prior to completion of therapy. Inclusion criteria included: mild/moderate to moderate upper extremity hemiparesis defined as ability to extend at least 10 degrees at the wrist and at each of the metacarpophalangeal joints of the thumb and at least two other fingers, and more than one year since stroke.

Table 1
Patient characteristics

	Age at injury ($y \pm$ SD)	Age at entry ($y \pm$ SD)	Years since infarct	Infarct volume (cm^3)	Right-hand Dom. (%)	Dominant limb affected (%)
CI therapy ($n = 14$)	60.4 ± 10.1	62.7 ± 9.3	2.3 ± 1.3	10.4 ± 24.4	85.7	42.8
Comparison ($n = 29$)	60.6 ± 12.9	64.7 ± 12.7	4.1 ± 4.0	15.0 ± 25.6	76.0	51.7
Total ($n = 43$)	60.6 ± 11.9	64.1 ± 11.7	3.5 ± 3.5	13.5 ± 25.0	79.1	48.0

Note. Values above in (mean $\pm$ SD) format.

Exclusion criteria included: current pharmacological treatments for motor impairment (e.g., anti-spasticity medications), previous CI therapy, serious medical conditions as judged by the project's Medical Director, claustrophobia, or aneurysm clips or any other metal in the body. Characteristics of patients in the two groups are summarized in Table 1. None of the differences between groups in the table were significant. This project was approved by the Institutional Review Board for human research at the University of Alabama at Birmingham.

2.2. Interventions

CI therapy consists of three main components: training of the more affected arm, a *transfer package,* and restraint of the less-impaired arm. Training of the more affected arm (by shaping) was done in the lab for approximately three hours each weekday for two consecutive weeks. The *transfer package* was administered to the experimental group, whereas the comparison group received the same therapy without the transfer package. It involves daily monitoring of real-world use of the affected arm, problem-solving with a therapist to overcome perceived barriers to use of the more-affected arm, and prescribed home practice of activities of daily living, among other procedures. Further details of the treatment have been described elsewhere (Morris and Taub, 2010; Taub et al., 2006a; 2006b). The transfer package requires 0.5 hours per day in addition to the three hours of daily training. The third component is restraint of the less-impaired arm for a target of 90% of waking hours over the duration of treatment. The comparison therapy consisted of the same treatment in the laboratory and the same amount of less-affected arm restraint as received by the CI therapy group but the transfer package component was not given.

2.3. Imaging

T1 MRI scans were obtained immediately prior to and immediately following the two weeks of motor therapy on a Philips 3.0 Tesla Intera machine. To correct for local field inhomogeneities, an N3 correction was applied to the images (Keihaninejad et al., 2010). Scans were then segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using SPM8 software. An image of the parenchyma was obtained by combining the GM and WM segments. GM, WM, and CSF segments were combined to obtain an image of the intracranial volume (Figure 1). Both processes were performed in MATLAB. The number of voxels in the parenchyma volume image was divided by number of voxels in the intracranial volume image to obtain the BPF. Only voxels that consisted of more than 50% of their designated matter compartment (GM, WM, or CSF) were included in the analysis. Individual voxel area was not relevant given that number of voxels was used as the metric for performing the BPF statistic.

2.4. Measures

The Wolf Motor Function Test (WMFT) was administered immediately prior to and following the therapy to evaluate treatment efficacy. The WMFT is a reliable and valid measure of motor ability of prompted movement in the laboratory (Morris et al., 2001; Wolf et al., 2006).

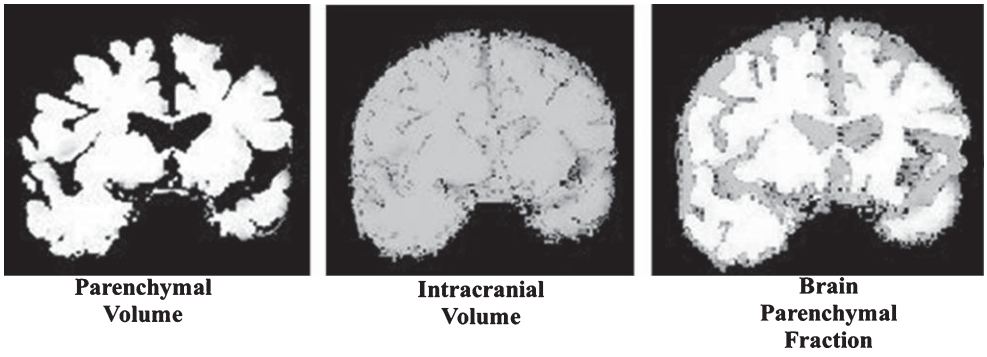

Fig. 1. Brain Parenchymal Fraction illustration.

2.5. Statistical analysis

Independent samples *t* tests were used to examine differences in pre-treatment characteristics, including BPF, between the CI therapy and comparison therapy groups. Pearson correlation coefficients were calculated to examine the association between BPF and pre-treatment motor performance, as well as the relationship between BPF and change in motor performance due to the treatments. Mixed-model repeated measures ANOVAs were used to examine within group changes due to treatment and between groups differences in treatment change on the WMFT.

3. Results

The groups improved on the WMFT performance time score measure ($F(1,41) = 6.59$; $p = 0.01$); no interaction effect was observed, indicating that there was no difference between groups following motor therapy on this measure. The groups were therefore combined for this analysis (Table 2). Amount of improvement in the groups was similar to that in past studies (Gauthier et al., 2008).

There was a moderate relationship in the entire sample between BPF and treatment change on the WMFT ($r(43) = –0.31$, $p = 0.04$) (Fig. 2). Longer time scores reflect worse performance; a negative correlation indicates that a negative change (improvement) in performance time was related to a larger BPF (i.e., roughly more parenchyma). At pretreatment there was no relationship between BPF and the WMFT ($r(43) = 0.15, p = 0.33$). Additionally, there was no relationship between overall infarct volume and treatment change on the WMFT ($r(43) = 0.17$, $p = 0.29$).

Pre-therapy BPF was not different between the groups ($t(41) = 0.34, p = 0.74$), being 0.768 ± 0.057 for

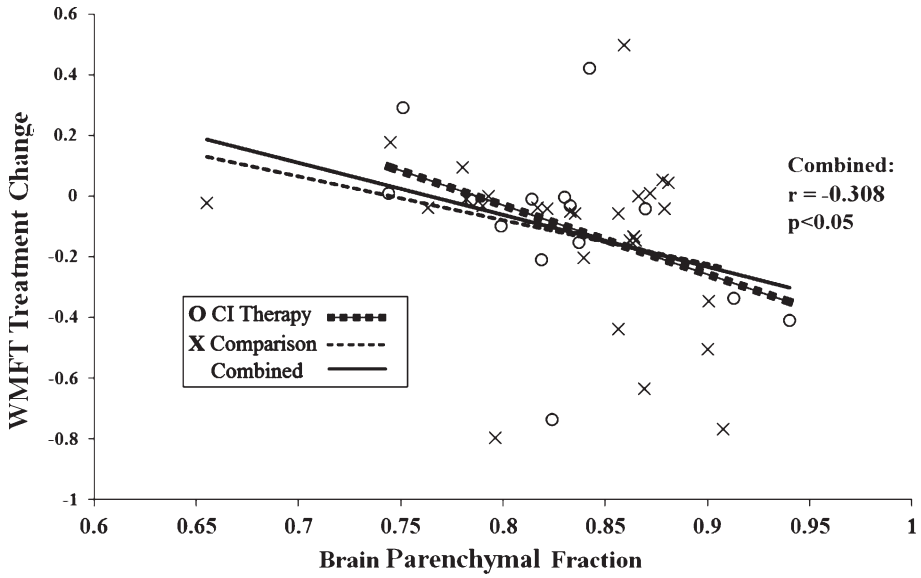

Fig. 2. Correlations between Brain Parenchymal Fraction and treatment change on the Wolf Motor Function Test. Lines of best fit are given for the CI therapy group, the comparison group, and the groups combined. On the Wolf Motor Function Test, a decrease in performance time represents an improvement.

Table 2

Log^2 mean (±SD) Wolf motor function test performance time outcome for CI therapy, comparison therapy, and their combined total

	Pre-treatment	Post-treatment	Treatment change	d′ *
CI therapy[a]	0.86 ± 1.02	0.77 ± 1.04	$–0.10 \pm 0.28$	0.36
Comparison therapy[b]	1.13 ± 1.15	0.92 ± 1.03	$–0.12 \pm 0.28$	0.43
Total[c]	1.05 ± 1.09	0.87 ± 1.02	$–0.12 \pm 0.28^{\dagger}$	0.43

Note. A decrease in performance time represents an improvement. *Cohen's d′ is a within-subjects measure of effect size. It is the mean change divided by the SD of the change. A value of 0.36 is considered moderate in the meta-analysis literature. $^{\dagger}p = 0.01$; $^{a}n = 14$, $^{b}n = 29$, $^{c}n = 43$.

the CI therapy group and 0.762 ± 0.058 for the comparison group. Additionally, there was no change in BPF due to therapy in either the CI therapy ($t_{(13)} = 0.82$, $p = 0.43$) or comparison group ($t_{(28)} = -0.01$, $p = 0.99$).

Moderate correlations were observed between BPF and age at injury or entry into therapy ($r(43) = -0.30$, $p = 0.05$; $r(43) = -0.38$, $p = 0.01$, respectively). The relationship between BPF and number of years since infarct was not significant ($r(43) = -0.22$, $p = 0.16$).

4. Discussion

These results indicate that the more intact brain tissue that individuals have in the chronic stroke phase, the greater their arm function gains after either CI therapy or an attenuated form of motor therapy on a measure of the maximum motor ability that a stroke patient is capable of when this is requested in the laboratory, as is the case on the WMFT. There was no difference in BPF between the groups before treatment. BPF itself did not change as a result of treatment.

The findings suggest that one of the factors that is important for the magnitude of the response to an efficacious rehabilitation therapy in chronic stroke is the amount of neural resources (e.g., total amount of parenchyma) remaining available after the injury. There does not appear to be a strong relationship between the volume of infarcted tissue and either the amount of motor deficit or improvement due to therapy in individuals in the chronic phase of stroke (Mark et al., 2008). Location of the lesion in chronic stroke is also not important, with the exception of lesions that are located in the centrum semiovale, where the corticospinal tract takes input from the ipsilateral hemisphere in the area that is adjacent to the corpus callosum (Gauthier et al., 2009; Lo et al., 2010; Sterr et al., 2010). Therefore, a factor important for the potential to recover motor function following rehabilitation would appear to be related to the characteristics of remaining, non-infarcted tissue. This laboratory has previously found that CI therapy outcome is correlated not only with regional grey matter increase in sensorimotor areas of the brain bilaterally (Gauthier et al., 2008) but with diffuse grey matter thinning at locations distant from the infarct (Gauthier et al., 2012). The results from this experiment are consistent with the latter result and show that it can be picked up on a whole brain basis.

Smith et al., (2008) found that BPF correlates negatively with deterioration of cognitive abilities and progression from mild cognitive impairment to Alzheimer's dementia. In patients with multiple sclerosis (MS), BPF also correlates with cognitive impairment (Hildebrandt et al., 2006), predicting cognitive difficulty better than does lesion burden, and it has been used to track disease progression in patients with MS (Benedict et al., 2004). A number of studies have also investigated BPF after stroke, though not in relation to rehabilitation. For example, MRIs performed earlier than six months post-stroke showed that lower BPF was associated with reduced recovery (Lee et al., 2010). However, in that study, MRIs were performed in the acute/subacute phase of stroke when infarcted tissue had yet to cavitate (which would increase the CSF space and therefore decrease the BPF). Stroke is also associated with increased rates of cerebral atrophy (DeCarli et al., 2005; Kraemer et al., 2004), and thus the BPF following stroke likely continually decreases over time.

The finding that greater BPF (roughly, increased parenchyma) correlates with greater improvement in motor function in response to motor rehabilitation may be analogous to *cognitive reserve*, a concept formulated in part on the basis of the frequent observation that there is no direct relationship between the degree of anatomic pathology and the degree of clinical impairment (Stern, 2002). The amount of recovery then would be based not on the amount of neural tissue directly destroyed by an insult (e.g., the infarct), but on the amount of tissue remaining after the focal injury and whatever additional damage [e.g., atrophy at remote locations (Gauthier et al., 2012)] had taken place. The "reserve" in the present experiment would be the potential to improve, and not the spontaneous recovery of the ability independent of therapy.

In this study tissue classification was based on an approach in which a voxel is characterized as being parenchyma if more than 50% of its volume is occupied by either WM or GM, or a combination of the two. This is an arbitrary cutoff or threshold. However, this problem is inherent to any BPF study that uses a thresholding approach similar to that employed here (Keihaninejad et al., 2010). Additional research would be of interest to determine the applicability of the BPF/motor improvement relationship in other populations who have neurological disease that is either static (e.g., traumatic brain injury) or progressive (e.g., MS).

The results from this study demonstrate that individuals with higher proportions of parenchymal volume relative to their intracranial space after stroke show larger arm function gains after administration of two components of CI therapy: training of the more affected arm, and restraint of the less-impaired arm. This suggests that the remaining parenchyma may be a form of reserve capacity providing a basis for improvement if an efficacious therapy is administered.

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