2017

Ci Therapy And Neuroplasticity After Brain Injury: Repurposing Brain Structures

Michelle Haddad
University of Alabama at Birmingham

CI THERAPY AND NEUROPLASTICITY AFTER BRAIN INJURY: REPURPOSING BRAIN STRUCTURES

by

MICHELLE M. HADDAD

EDWARD TAUB, COMMITTEE CHAIR
GITENDRA USWATTE
VICTOR W. MARK
MARK S. BOLDING
THOMAS A. NOVACK

A DISSERTATION

Submitted to the graduate faculty of the University of Alabama at Birmingham, in partial fulfillment of the requirements for the degree of Doctor of Philosophy

BIRMINGHAM, ALABAMA

2017

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MICHELLE M. HADDAD

MEDICAL-CLINICAL PSYCHOLOGY

ABSTRACT

Structural grey matter changes have previously been observed following treatment with Constraint-Induced Movement (CI) therapy in adults with stroke and multiple sclerosis, as well as children with cerebral palsy. The current study examined similarities and differences in patterns of neuroplastic change across these three patient populations after treatment with CI therapy. Longitudinal voxel-based morphometry (VBM) was used to quantify grey matter change. Widespread grey matter increases were detected in all three patient populations. These included consistent bilateral changes in primary and associated sensorimotor areas and hippocampus in the three different populations, despite the differing etiologies. Additionally, less consistent patterns of change were detected in each study population in cortical areas beyond those that typically play a role in sensorimotor ability. These patterns of grey matter increase were unique to patients treated with CI therapy and were not found in the corresponding control groups of each individual study. Taken together, these results suggest that CI therapy may enhance or induce neuroplasticity during the process of recovering real-world motor function after a period of chronic deficit. This process does not appear to occur in control groups of patients treated with comparison therapies.

Keywords: CI therapy, rehabilitation, neuroplasticity, grey matter, MRI brain

DEDICATION

This dissertation is dedicated to my parents, who have always accepted my dreams and supported me in running with them as far as possible.

ACKNOWLEDGEMENTS

I would like to thank all of my wonderful mentors for their wisdom, support, and time.

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INTRODUCTION

Neuroplasticity in the Adult Central Nervous System

Neuroplasticity in the brains of individuals who have experienced significant injury or disease has become an area of increasingly great interest over the last fifteen years. Previously, it was believed that the adult central nervous system (CNS) was hardwired and incapable of any sort of significant reorganization. A related belief held by practitioners in the field of neurorehabilitation was that in the chronic phase after CNS injury, no substantial recovery of function could take place, regardless of the intervention employed. However, these beliefs began to change in the latter part of the 20th century; beginning in the late 1980s, it was found that the nervous system was capable of significant neuroplastic change in response to environmental demand (Jenkins, Merzenich, Ochs, Allard, & Guic-Robles, 1990; Merzenich & Jenkins, 1993; Taub, Uswatte, & Mark, 2014). In addition it was found that Constraint-Induced Movement (CI) therapy could produce marked improvements in extremity function many years after brain damage (Taub et al., 1993).

Beginning in the mid-1980s, animal studies established that neuroplastic reorganization in the mature nervous system follows changes in the amount of use of a given modality (Kaas, Merzenich, & Killackey, 1983; Merzenich et al., 1984). Decreased input to the CNS has been shown to lead to the "invasion" of the cortical representation zone of an amputated or deafferented body part by other intact or more frequently used parts. This was initially demonstrated in nonhuman primates following the amputation of a digit (Merzenich et al., 1984) and somatosensory deafferentation of a forelimb (Pons et al.,

1991). The phenomenological converse of these processes has also been demonstrated. Sustained increase in the use of a body part leads to a corresponding increase in the brain's cortical representation of that modality (Jenkins et al., 1990), especially when the increased activity is behaviorally relevant. Although plasticity of cortical representation zones was once thought to be quite limited in scope (Merzenich et al., 1984), it has since been shown to affect a broader area over time (Pons et al., 1991).

Repurposing Brain Structures

Plasticity of cortical representation zones has also been demonstrated in humans after reduced input resulting from upper extremity amputation (e.g., Elbert et al., 1994; Flor et al., 1995; Ramachandran, Rogers-Ramachandran, & Stewart, 1992; Ramachandran, Stewart, & Rogers-Ramachandran, 1992) or stroke (Liepert, Bauder, Miltner, Taub, & Weiller, 2000), and increased use resulting from intense practice of a musical instrument (Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995), or the reading of Braille by blind individuals (Cohen et al., 1997; Sterr et al., 1998a, 1998b). The "re-purposing" of brain structures has often been studied in individuals who lack a sensory modality, such as those who are congenitally blind or deaf (Heimler, Weisz, & Collignon, 2014).

For example, considerable evidence suggests that the occipital cortex of congenitally blind individuals may be activated by non-visual inputs (e.g., Collignon, Voss, Lassonde, & Lepore, 2009; Heimler et al., 2014). It has further been observed that disruption of the occipital cortex in these individuals, either by damage or using Transcranial Magnetic Stimulation (TMS), impairs performance on non-visual tasks (Collignon et al.,

2009; Heimler et al., 2014). Collectively, these phenomena suggest that reorganization of the occipital cortex in early-blind individuals can be related to the performance of certain non-visual tasks, such as reading Braille, at both a functional and structural level (Roder et al., 1999; Sterr et al., 1998a). Similar evidence suggests functionally-relevant reorganization and enhancement in the non-auditory brain areas of deaf individuals. Multiple studies have shown that the recruitment of areas traditionally involved with auditory processing can innervate aspects of visual perception (e.g., visual motion, processing of sign language, peripheral visual stimulation) in early deaf individuals. However, there is less of a consensus on whether this type of plasticity is behaviorally adaptive (Heimler et al., 2014; Merabet & Pascual-Leone, 2010; Sharma, Campbell, & Cardon, 2014).

A related area of research has examined cortical reorganization during language recovery after left hemisphere stroke. Traditionally, the areas thought to innervate language comprise the frontotemporal left hemisphere, and the dominant view has been that transfer of language function to the right hemisphere following CNS injury is inefficient and may be associated with a poorer outcome when compared to restoration or modification of language functioning in the left hemisphere (Richter, Miltner, & Straube, 2008; Rosen et al., 2000; Szaflarski, Allendorfer, Banks, Vannest, & Holland, 2013). However, other evidence suggests that there is a role for recruitment of homologous areas of the right hemisphere during language recovery (Breier, Maher, Novak, & Papanicolaou, 2006; Breier, Maher, Schmadeke, Hasan, & Papanicolaou, 2007; Turkeltaub, Messing, Norise, & Hamilton, 2011). Right hemisphere plasticity does appear to be linked to the recovery of language functioning, as evidenced by several individuals who resumed language following a left-sided lesion, then experienced a second lesion to the right hemi-

sphere and subsequently showed a decline in language ability (Basso, Gardelli, Grassi, & Mariotti, 1989; Finger, Buckner, & Buckingham, 2003; Gainotti, 1993). This evidence suggests that areas in the right hemisphere had successfully assumed increased importance in the production and comprehension of speech after the first, left hemisphere stroke.

There has likewise been great interest in the role of neuroplasticity in motor recovery following stroke. Although initial emphasis was given to the sparing and reactivation of perilesional areas, it has since become clear that important changes occur not only in the surrounding sensorimotor cortices but in much more distant areas as well (Castro-Alamancos & Borrel, 1995; Nudo, 2007; Zeiler & Krakauer, 2013). Some studies have found evidence that modification and recruitment of the contralesional motor cortex (ipsilateral to the affected extremity) may be associated with poorer functional outcome, particularly in spontaneous recovery (Cramer, 2008a, 2008b; Cramer & Bastings, 2000). However, more recent evidence suggests that this far-reaching cortical reorganization is part of an ongoing process of enhanced plasticity (adaptive or maladaptive) following stroke, and may be harnessed by efficacious intervention strategies (summarized in Zeiler & Krakauer, 2013).

Implications for Rehabilitation

Cortical reorganization of brain structures due to congenital deficits or acquired CNS damage has often been conceptualized as a "double-edged sword" (Heimler et al., 2014; Merabet & Pascual-Leone, 2010; Merabet, Rizzo, Amedi, Somers, & Pascual-Leone, 2005). While such reorganization may be adaptive or allow for compensatory be-

havior, it may also be maladaptive for optimal recovery. In general, it appears that decreased input, leading to the shrinkage of cortical representation areas, is often linked to adverse consequences (e.g., phantom limb pain, Flor et al., 1995; Flor, Nikolajsen, & Staehelin Jensen, 2006, hemiparesis; Taub 2004). These adverse consequences may also prove a barrier to rehabilitation of the associated behavioral function if the intervention does not reverse this maladaptive plasticity. In rodent studies, training of the unaffected arm after simulated stroke was found to have detrimental effects on perilesional cortex, likely inhibiting functional recovery (Kim et al., 2015). A recent human study suggested that in order to be efficacious, therapies for motor rehabilitation must reach a certain threshold for overcoming shrinkage of cortical representation zones, after which point practice with a previously-impaired extremity becomes intrinsically reinforcing (Han, Arbib, & Schweighofer, 2008). In contrast to the effects of decreased use and shrinkage of cortical representation zones, increased cortical input, leading to expansion of the corresponding representation zone, often has adaptive consequences for the individual's behavior. This effect has been observed by Taub and coworkers in healthy individuals during specialized skill acquisition (e.g. musicians, Elbert et al., 1995), as well as during recovery from CNS damage as a result of CI therapy (e.g. stroke, Liepert et al., 2000; Kopp et al., 1999; Gauthier et al., 2008).

The implications of these findings for neurorehabilitation are twofold. First, patterns of cortical reorganization during spontaneous recovery from CNS damage may differ from those which occur as the result of efficacious behaviorally-based interventions. Second, in the absence of an efficacious intervention to increase use-dependent cortical input related to a given function, maladaptive neuroplasticity may occur, leading to ad-

verse outcomes for the individual. When an effective intervention is utilized, neuroplasticity may occur such that certain brain structures are "repurposed," making use of resources which have been spared from CNS damage. Thus it is important for the neurorehabilitation community to elucidate which interventions produce adaptive cortical reorganization and how these techniques may be harnessed to optimize behavioral recovery from CNS damage.

Constraint-Induced Movement Therapy

Development

CI therapy was first developed through basic neuroscience experiments in non-human primates (summarized in Taub, 1980). After deafferentation of a single forelimb, animals discontinued use of that extremity (Mott & Sherrington, 1895). Restoration of limb use could be achieved through intensive training (most effectively by behavioral shaping) of the deafferented arm and prolonged restraint of the intact arm (summarized in Taub, 1977, 1980). These same two techniques were applied successfully to humans after stroke (Taub et al., 1993) and follow-up research found the improved movement produced by CI therapy was associated with use-dependent neuroplastic changes in the brain (Gauthier et al., 2008; Kopp et al., 1999; Liepert et al., 2000; Liepert et al., 1998). Improved movement resulting from CI therapy has also been found to occur in cerebral palsy (Taub et al., 2007; Taub, Ramey, DeLuca, & Echols, 2004), traumatic brain injury (Shaw, Morris, Uswatte, McKay, & Taub, 2003) and chronic multiple sclerosis (Mark et al., 2008).

CI therapy has been shown to produce motor improvements in laboratory motor tests, where use of the more-impaired limb is requested, but the increase is greatest for spontaneous movement in the real-life situation (Taub, Uswatte, & Pidikiti, 1999). The efficacy of CI therapy has been demonstrated in multiple controlled trials (e.g., Taub et al., 1993; Taub et al., 2006) and this result has been replicated in numerous locations across the world (e.g., Bonifer, Anderson, & Arciniegas, 2005; Dettmers et al., 2005; Miltner, Bauder, Sommer, Dettmers, & Taub, 1999). In addition, a large, multi-site randomized clinical trial (EXCITE) found positive results in patients 3-12 months post-stroke (Wolf et al., 2006).

Treatment Protocol

CI therapy has four main components. The first is intensive training of the more-affected arm. The current standard in the CI therapy treatment administered at this university is 3 hr/day for 10 consecutive weekdays. Second, this training consists of the shaping of movements during repetitive task practice guided by a trained physical or occupational therapist. Patients are rewarded through verbal praise from the therapist for performing increasingly difficult "successive approximations" of a movement during practice. The third component of CI therapy is termed the "transfer package," which requires an additional half hour per day, resulting in an increase of daily therapy session length to 3.5 hours. The transfer package is a group of behavioral techniques designed to facilitate the transfer of therapeutic gains from the laboratory to the real-life situation. The transfer package consists of several behavioral techniques including a behavioral contract in which the patient agrees to wear a restraint on the less-impaired arm for a

specified amount of waking hours and use the more-impaired arm for specific activities agreed upon by the therapist and patient. Additionally, patients are assigned skill practice to be performed at home during each day of treatment. Compliance with carrying out these activities is then reviewed with the therapist on the following day, and real or perceived barriers to using the more-impaired arm in the life situation are addressed. Arm use in the life situation is monitored by daily administration of the Motor Activity Log, a scripted, structured interview concerning the amount and quality of 30 common and important activities of daily living carried out in the life situation. In addition, skill practice activities are assigned to individuals after the end of formal treatment. The transfer package is critically important for therapeutic outcomes and has been shown in adults to be associated with a greatly increased efficacy of the therapy (Taub et al., 2013). An additional component of CI therapy for an upper extremity is prolonged restraint of the less-affected upper extremity for a target of 90% of waking hours to encourage use of the more-affected arm. This has been found to be the least important of the components and can be dispersed with entirely without reducing outcome if the training conditions are arranged appropriately (Uswatte, Taub, Morris, Barman, & Crago, 2006).

Efficacy

CI therapy, including the transfer package, has been shown to promote use of a more-affected arm in the home environment nearly 2.4 times more than intensive practice alone (Gauthier et al., 2008; Taub et al., 2013). CI therapy produces large improvements in arm use for individuals who have very little functional use of their arm prior to therapy, and those who receive the therapy are often able to regain use of the formerly

hemiparetic arm for many daily activities, thereby increasing the functional independence of patients in the life situation (Taub et al., 1993; Taub et al., 2006; Wolf et al., 2006). Treatment gains in motor ability have been shown to persist for over two years post-treatment (Taub, 2004). CI therapy is considered to achieve its effects by at least two mechanisms: 1) overcoming learned nonuse and 2) plastic brain reorganization resulting from increased purposive movement of the more affected arm.

Overcoming Learned Nonuse

The learned nonuse formulation is based on the principle that hemiparesis following neurological insult is not entirely due to limited neurological capability but also has a behavioral component. Taub and colleagues first observed learned nonuse in experiments with deafferentated monkeys. Mott and Sherrington (1895) found that monkeys with a single deafferented forelimb never used that extremity. However, Taub and colleagues showed that they would use the affected extremity when induced to do so either by physical restraint of the intact forelimb or by the contingencies of reinforcement in a learning task. Thus, although the animals had the ability to use the deafferented forelimb after spontaneous recovery occurred over a period of months, they relied entirely on the intact arm to complete tasks unless the suppression of deafferented limb movement was targeted and counterconditioned (Taub, 1977, 1980).

A similar phenomenon is seen in chronic stroke patients. Many patients possess the potential to use their more-impaired arm in the chronic phase, but still use only the less-affected arm in most tasks (Andrews & Stewart, 1979; Taub, 1980). This phenome-

non has been termed learned nonuse and is explained as a conditioned suppression of movement (Taub, 1977, 1980; Taub, Uswatte, Mark, & Morris, 2006). Immediately after CNS damage, patients confront a real inability to use their affected arm, possibly due to post-injury reduction in excitability. Due to the consequent lack of use, the cortical representation zone of the more-affected limb decreases in size, which may make movement of this limb more demanding and effortful, potentially having a punishing effect on attempts to use the arm (summarized in Han et al., 2008; also Taub, 1980; Taub et al., 2006). Although CNS excitability and intrinsic motor ability begins to improve spontaneously after recovery from the initial effects of CNS injury, patients retain the learned pattern of behavior and continue their reduced use or nonuse of the affected arm. Therefore, there is a gap in patients' capacity to use the more affected arm and their actual use of the arm. CI therapy can overcome learned nonuse with a combination of positive reinforcement, motivation, and physical restraint of the less-affected arm which induces the patient to use their more-impaired arm for an extended period of time (Taub, 1980; Taub et al., 2006).

CI Therapy and Neuroplasticity

CI therapy reduces the prior shrinkage of cortical representation zones after stroke by targeting learned nonuse and increasing use of the more-affected extremity (Taub, 1980; Taub et al., 2006). Brain mapping and functional imaging methods have found that CIMT produces neurophysiological changes within the brain; however studies do not agree upon the exact location of those changes (Kopp et al., 1999; Liepert et al., 2000; Schaechter et al., 2002; Taub et al., 1999; Wittenberg et al., 2003). Research from this

laboratory has thus far indicated that CI therapy increases grey matter of the sensorimotor cortex, more anterior motor areas, and hippocampi in adult chronic stroke patients, persons with chronic MS, and children with CP following treatment with CI therapy. Exploratory whole-brain analyses in all three studies have further suggested that significant grey matter increases may occur in bilateral temporal and parietal lobes. Increase in deep-brain grey matter including the basal ganglia also seemed likely, though that had not yet been demonstrated prior to the current study.

The current study comprised systematic analysis of grey matter changes between patient populations to further elucidate the pattern of grey matter increases produced by an efficacious therapy. Thus far, a systematic analysis of regions of interest beyond the areas primarily involved in innervating movement had not been conducted, nor had there been a formal comparison of patterns of cortical and subcortical reorganization between the three patient populations. The proposed study sought to conduct such a combined analysis, utilizing brain scans acquired by this laboratory's CI therapy studies over the past two decades.

Specific Aims and Hypotheses

The Specific Aims were:

*Specific Aim 1***:** Evaluate and compare traditional voxel-based morphometry (VBM) techniques, which employ unified segmentation/normalization and lesion masking, with new-

er methods utilizing DARTEL (diffeomorphic anatomic registration via exponentiated lie algebra algorithm) normalization and no lesion masking for identifying changes in grey matter in the brain after CI therapy in persons with stroke, CP, and MS.

*Hypothesis 1***:** Both methods will show similar patterns of grey matter change within each patient group.

*Specific Aim 2***:** Identify where changes in grey matter take place in persons with stroke, CP, and MS after CI therapy. Although gross whole-brain analyses have been used to generally identify grey matter changes in the vicinity of the sensorimotor cortices, this aim is new in that it seeks to objectively localize all areas of significant grey matter change in each group. This type of systematic analysis utilizing a probabilistic anatomical atlas has not previously been performed by this laboratory. This will also be the first time subcortical change is examined in areas beyond the hippocampus.

Hypothesis 2a: There will be similar patterns of grey matter increase in bilateral sensorimotor cortices and hippocampi among the three groups, because the more-affected arm was be treated in all three.

Hypothesis 2b: Location of more diffuse changes outside of sensorimotor areas will differ because of differences in the populations studied (e.g. etiology of brain damage, age).

Specific Aim 3: Evaluate whether there is a correlation between change in real-world use of the more-affected arm and structural brain changes in adults with stroke and MS, and children with CP after CI therapy. Correlations have previously been examined for the

sensorimotor cortices and hippocampus, but not elsewhere in the brain. This study additionally utilizes a new technique to examine possible correlations *only* at the location of significant clusters of *t* values, rather than in a gross anatomically defined ROI.

Hypothesis 3: Change in real-world use of the more-affected arm will be strongly correlated with grey matter change in at least one ROI for each study group.

RESEARCH DESIGN AND METHODS

Participants

Inclusion Criteria

The following inclusion criteria were common to participants in all three studies: 1) chronic mild to moderate upper extremity hemiparesis, 2) substantial nonuse of the hemiparetic arm in daily life, as assessed by the Motor Activity Log (MAL) or Pediatric Motor Activity Log Revised (PMAL-R) in children, see Clinical Outcome Measures below, and active range of motion measurement, 2) ability to pick up and release a small object such as a ball with the more-affected hand, 3) no more than mild to moderate pain during movement, 4) absence of other structural CNS disorder, and 5) absence of other severe disorder that could substantially limit arm movement (e.g., arthritis). Adults (stroke and MS samples) were also required to have a MiniMental State Exam score >23/30. Participants were excluded if they had 1) previous CI therapy exposure or were currently receiving other pharmacological or behavioral treatments for their motor deficit, 2) severe vision or hearing problems, 3) uncontrolled seizures, or fixed contractures in the upper extremities that would limit participation in CI therapy, or 4) ferromagnetic metals in the body, claustrophobia, or other medical conditions that would prohibit safely

undergoing MRI. Participant characteristics specific to each study are discussed in the following sections.

Stroke. Sixteen patients (6 male), with chronic stroke and mild to moderate upper extremity hemiparesis, were randomized to the CI therapy condition in the initial study (Taub et al., 2008; Taub et al., 2013; Gauthier et al., 2008). There were twenty patients enrolled in a comparison control group. Participants were aged 38 years to 87 years (mean 63.3 years ± 8.6 years). On average, mean time since stroke onset was 2.3 ± 1.1 years. Three of these patients had right hemiparesis (Gauthier et al., 2008; Uswatte et al., 2006; Wolf et al., 2006). Unfortunately, due to prior data loss resulting from technical failure, only eleven of the original sixteen participants had scans available for processing in the present study. Participant characteristics are presented in Table 1.

Table 1. Stroke Study Participant Characteristics

SID	Gender	Age (Years)	Chronicity (Years)	Dominant Side	Deficit Side
1	F	73.67	2.50	R	L
2	F	65.25	2.30	R	R
3	F	45.42	4.50	R	R
4	M	60.00	2.25	R	L
5	M	59.33	3.91	R	R
6	M	66.42	1.33	R	L
7	F	61.01	3.59	R	L
8	M	72.16	1.83	L	L
9	M	75.58	1.50	L	L
10	M	58.00	1.00	R	L
11	F	60.92	1.00	R	L

Multiple Sclerosis. Ten adults (1 male) with a history of chronic MS and predominantly unilateral arm paresis were randomized to the CI therapy condition in the initial study; ten patients were randomized to a comparison control group. Mean age was 46.7 years ± 7.6 years, and mean time since first MS onset was 15.4 ± 8.8 years. Two participants had predominantly right-sided motor deficit. Participants enrolled in the MS study were additionally required to have a relapse-free period of at least 3 months. Patients were allowed to continue their typical medications (Mark et al., 2008). One participant

was not able to provide valid MRI due to spasticity in the scanner. Scans from nine subjects were analyzed. Participant characteristics are presented in Table 2.

Table 2. MS Study Participant Characteristics

SID	Gender	Age (Years)	Chronicity (Years)	Dominant Side	Deficit Side
1	F	60.00	25.10	R	L
2	F	46.80	18.20	R	L
3	F	40.50	4.10	R	R
4	F	46.80	2.80	R	L
5	M	53.20	26.80	R	L
6	F	36.40	12.20	R	L
7	F	55.40	4.50	R	L
8	F	47.80	16.80	R	R
9	F	48.10	21.00	L	R

Cerebral Palsy. Ten consecutive children (6 male) with cerebral palsy received CI therapy in the initial study. Participants were aged 24 months to 90 months (mean 39 months ± 18 months). Eight of these participants had right hemiparesis (Sterling et al., 2013). Participant characteristics are presented in Table 3.

Table 3. CP Study Participant Characteristics

SID	Gender	Age (Years)	Deficit Side
1	F	2.17	R
2	M	2.75	R
3	F	7.50	R
4	M	2.50	R
5	F	3.16	L
6	M	2.08	L
7	M	3.33	R
8	M	3.33	R
9	F	3.17	R
10	M	2.25	R

The stroke and MS studies were performed at the University of Alabama at Birmingham, while the CP study took place through the Pediatric CI Therapy Program at Children's Hospital of Alabama. All adult participants provided informed consent. For the CP study, informed consent was obtained from each child's parent. All procedures were approved by the Institutional Review Board at the University of Alabama at Birmingham.

Clinical Outcome Measures

Stroke and Multiple Sclerosis

Motor Activity Log (MAL). This is a structured, scripted interview of how well and how often patients use their impaired arm for 30 frequently performed activities of daily living (e.g., brushing teeth, dressing) (Taub et al., 1993). The patient responds on an 11-step Likert scale anchored by definitions at 6 points on how successful the weaker arm was for performing each activity during a specified period of time (lower numbers indicate less use). This laboratory has made a video depicting stroke patients carrying out 8 of the MAL items at each of the rating steps to aid participants in making accurate judgments about their own quality of movement. This video was shown prior to the administration of the MAL at both pre-treatment and post-treatment. The MAL is a reliable and valid measure of real-world arm use (Uswatte et al., 2006; Uswatte, Taub, Morris, Light, & Thompson, 2006 van der Lee, Beckerman, Knol, de Vet, & Bouter, 2004) and correlates well with objective measures of arm use in the life situation (Uswatte, Taub, Morris, Vignolo, & McCulloch, 2005; Uswatte, Foo, et al., 2005; Uswatte, Taub, Morris, Light, et al., 2006). To further ensure the accuracy of this self-report measure, the MAL was administered to a caregiver or family member, whenever possible, to assess whether there was corroboration of the patient's report, yielding high correlations (Uswatte, Taub, et al., 2005). The full MAL was administered before and immediately after treatment and on Mondays of the second and third (if there was one) treatment weeks. The first and last

halves of the MAL were given alternately on the other treatment weekdays so that during each week of treatment, three full MALs were administered.

Wolf Motor Function Test (WMFT). This test (Taub et al., 1993; Wolf et al., 1989) is a valid and reliable objective measure of in-laboratory motor ability involving movements made on request as rapidly and well as the patient can perform them (Morris, Uswatte, Crago, Cook, & Taub, 2001; Wolf et al., 2001). The test items consist of 15 timed movements, which range from gross movements of the whole arm to detailed fine movements. The WMFT was administered before and after treatment. Mean performance rate on the WMFT was used as part of the assessment of clinical outcomes in the stroke and MS studies. This metric is calculated by dividing a sixty second time interval by the participant's actual task completion time, and is considered to be the preferred scoring method for assessing hemiparesis in patients with stroke (Hodics et al., 2012).

Cerebral Palsy

Pediatric Motor Activity Log Revised (PMAL-R). This test is a structured, scripted interview, based on the adult MAL. Parents were asked to rate the quality (How Well scale) and amount (How Often scale) of more-affected arm use by the child on 22 upper-extremity activities in the life setting over a specified period (the previous day or week). As on the MAL, the scales are anchored by definitions at 6 points. Internal consistency and test-retest reliability is high. Convergent validity of this measure has been supported by a strong correlation with behavioral observation of the amount of spontane-

ous more-affected arm use during structured play in the laboratory setting (Uswatte et al., 2012). Support for the validity and reliability of the original version of the PMAL has been confirmed (Uswatte et al., 2012). The revised version used in the CP study departed from the original by (1) replacing upper-extremity tasks that are not performed commonly in daily life or are performed in a highly variable manner with those that are not and (2) including a procedure to verify the responses given by participants (Uswatte et al., 2012). The full PMAL-R was administered before and immediately after treatment and on Mondays of the second and third treatment weeks. The first and last halves of the PMAL-R were given alternately on the other treatment weekdays so that during each week of treatment, three full PMAL-Rs were administered (Uswatte et al., 2012).

Neuroimaging

MRI Acquisition

Stroke. T1 scans were obtained on a 1.5 Tesla Phillips Intera MRI scanner and a 3 Tesla GE Signa scanner. Scans encompassed the whole brain and were 160 slices of 1-mm thickness, set parallel to the orbital-meatal line, containing no gaps between slices. Imaging protocol for 1.5 Tesla scanner: SENSE head coil, T1 Turbo-field Echo (TFE), TR (repetition time) = 30 ms, TE (echo time)= 6 ms, matrix size = 256x256, voxel size = 1.04x1.05x1.00 mm^3, field of view (FOV) = 230, and flip angle = 45°. Imaging protocol for the 3 Tesla scanner: SENSE head coil, T1 Turbo-field Echo (TFE), TR (repetition time) = 9.85 ms, TE (echo time)= 4.59 ms, matrix size = 240x240, voxel size = 1.04x1.05x1.00 mm^3, field of view (FOV) = 240, and flip angle = 8°

Multiple Sclerosis. All participants underwent volumetric T1-weighted MPRAGE 3 Tesla brain MRI on a Siemens Magnetom Allegra scanner. Images were obtained with the following scanning parameters: 176 slices of 1mm thickness containing no gaps, SENSE head coil, T1 Turbo-field Echo (TFE), TR (repetition time) = 2080 ms, TE (echo time) = 3.93 ms, matrix size = 256x256, voxel size = 1.04 x 1.05 x 1.00 mm3, field of view (FOV) = 250, and flip angle = 8. The slices of the scan were set parallel to the anterior commissure—posterior commissure line. FLAIR images were also obtained from each patient to aid in identifying brain pathology and peri-infarct tissue.

Cerebral Palsy. T1 MRI scans were obtained on a 1.5 Tesla Phillips Intera MRI scanner at Children's of Alabama. The T1 images were collected with the following parameters: ~130 slices of 1mm thickness containing no gaps, SENSE head coil, T1 TFE (turbo-field echo), TR (repetition time) = shortest, TE (echo time) = 4.60ms, matrix size = 240 x 240 and reconstructed = 256 x 256, voxel size = 1.04 x 1.05 x 1mm^3, field of view = 250 and flip angle = 8.

Images from all three populations were stored in uncompressed Digital Imaging and Communications in Medicine (DICOM) format on the UAB Clinical Image Management System (CIMS) archive developed by the Computer-Assisted Neurosurgery Facility at UAB and converted to Analyze format for analysis.

Procedures: Clinical

Stroke and MS

Participants randomized to CI therapy received intensive in-laboratory training of the more-impaired arm on functional tasks. Positive reinforcement and shaping were used to gradually increase performance and use of the more-affected arm during in-laboratory tasks. The tasks involved a variety of activities; many were designed to simulate movement in the life situation. Specific tasks used for each patient depended on the individual nature of the motor deficit and patient preferences among tasks of similar effect. During in-laboratory sessions, rest periods were provided as-needed to prevent excessive fatigue. The less-affected arm was constrained in a padded safety mitt for a target of 90% of waking hours to reduce use of the hand. However, patients were told not to use the mitt when any safety concerns were present or during sleep (Gauthier et al., 2008).

Transfer Package procedures designed to transfer gains achieved in the laboratory to the activities of daily living in the life situation included: behavioral contracting, home practice assignments, keeping an activity diary, and administration of the MAL as part of a daily 30 minute review and problem-solving discussion with the therapist to overcome perceived barriers to affected limb use. Patients received 35 hours of direct therapist contact over 10 consecutive weekdays, 3.5 hours/day. All participants underwent MRI in the week before training and the week following training (Gauthier et al., 2008). The MAL and Wolf Motor Function Test (WMFT; see below) were also administered at pre- and post-treatment to assess clinical status.

Cerebral Palsy

CI therapy in the pediatric population utilizes the same basic procedures as the adult treatment protocol, but there are a few notable differences. Pediatric CI therapy is similar to the adult therapy protocol in that intensive motor training and shaping are used during the in-laboratory sessions. However, rather than a removable mitt, the child's less-affected arm is continuously restrained in a long arm cast. On the last two days of treatment, the cast is removed and motor training is then focused on bilateral activities. Additionally, the transfer package techniques are carried out with the child's caregivers rather than the patient directly. The pediatric transfer package, just as in the adult case, includes a behavioral contract, steps to induce continuation of use of the more-affected arm in the life situation, and guidance to overcome perceived barriers to using the more-affected arm in everyday life. Children in the CP study received in-laboratory treatment for 3.5 hours/day over a 15 weekday period, making their total treatment time somewhat higher than the two adult groups at 52.5 hours total direct therapist contact.

Children received MRI scans 3 weeks prior to receiving CI therapy (baseline), immediately before treatment (pre-treatment), and immediately after the 3-week treatment period (post-treatment). Baseline and pre-treatment scans were used to control for the possibility of brain change due to brain development by assessing whether statistically significant grey matter changes occurred between the two scans. At each of the three testing occasions, the PMAL-R was administered (Sterling et al., 2013).

Data Processing

Voxel-Based Morphometry

Longitudinal voxel-based morphometry (VBM) was used to analyze the T1 MRI scans. VBM is an automated, unbiased procedure used to evaluate changes in the brain at each voxel (Ashburner & Friston, 2000). It involves the realignment of MRIs, segmentation/normalization of the brain, and smoothing of the grey matter portions (Good et al., 2001).

Spatial normalization is a critical step for longitudinal MRI analyses. Its function is to warp all scans into identical stereotactic space, so that any individual or group differences may then be attributed to treatment effect, rather than extraneous variables (e.g. total brain volume, slight variations in head positioning within the scanner). Spatial normalization becomes complex when it has to deal with populations containing large brain lesions, because these scans often have greater individual differences than do healthy brains. Although multiple normalization algorithms have been developed to handle this challenge, there is no clear consensus on the optimal method for the analysis of brain scans containing large lesions such as those seen in stroke or CP. Two different methods were utilized by the present study to complete the analysis, allowing a comparison of different approaches to longitudinal analysis of brain scans containing significant pathology.

Unified Segmentation. The first, more traditional approach, is based on the method described by (Good et al., 2001) and has been used by this laboratory in past neuroim-

aging studies. It utilizes the Unified Segmentation algorithm in the SPM8 extension of MatlabR2014(b), which combines skull stripping, segmentation of grey matter, white matter, and cerebrospinal fluid (CSF) compartments, bias correction, and spatial normalization under the same iterative model using probabalistic tissue maps as priors. Cost-function masking was employed with this protocol to exclude lesioned tissue in an effort to improve the accuracy of the analysis. This method has frequently been used by other groups in the analysis of brains with focal pathology (Crinion et al., 2007).

First, images were equated for deficit side by flipping right/left the brains of subjects with left arm hemiparesis. Post-treatment scans were realigned to the pre-treatment scan using a rigid body spatial transformation. Particular voxel values for the post-scan were determined using 7th degree B-spline interpolation. This step improves accuracy of longitudinal comparisons by correcting for any differences in orientation between pre- and post-treatment scans before both scans are warped into standard space for additional analysis.

Lesion masks were created for each scan in MRICron to eliminate these regions from the normalization process and the subsequent statistical analysis (FLAIR images were used to assist in the identification of brain pathology in addition to the T1 scans). The masked area was then excluded from both pre- and post-treatment scans in all subsequent steps of the analysis, thus aiming to reduce distortion caused by the lesion. Pre- and post-treatment scans were skull-stripped and segmented into grey matter, white matter and CSF and normalized to Montreal Neurological Institute (MNI) stereotactic space, utilizing the SPM8 Unified Segmentation algorithm as described above. Identical normalization parameters were applied to both pre- and post-treatment scans. Remaining voxels

mistakenly identified as grey matter ($\leq$ 5% grey matter in the voxel) were manually removed from the analysis by setting them to the background value of zero. The grey matter portion was then smoothed using a 10mm Gaussian kernel, which is standard practice by this laboratory and in general VBM analysis (Gauthier et al., 2008; Gauthier, Taub, Mark, Perkins, & Uswatte, 2009). Finally, the segmented and normalized pre-treatment grey matter partition was subtracted from the equivalent post-treatment partition, creating a difference image which allowed for quantification of longitudinal grey matter changes. The Unified Segmentation image processing pipeline is illustrated in Figure 1.

Figure 1. Unified Segmentation Processing Pipeline

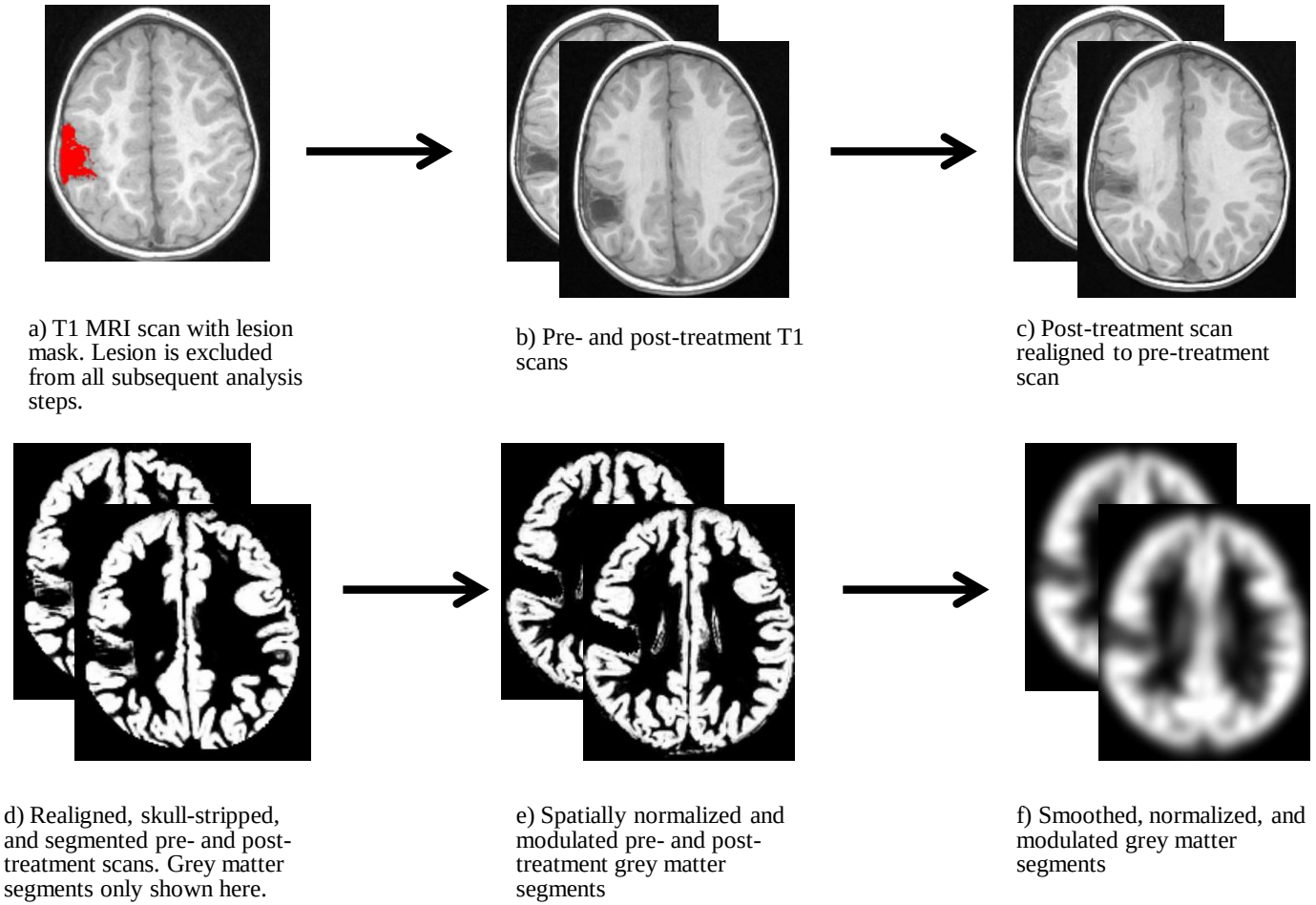


Figure 1. Stepwise illustration of the Unified Segmentation processing pipeline.

DARTEL. DARTEL (diffeomorphic anatomic registration via exponentiated lie algebra algorithm) is a normalization procedure which has not previously been utilized by this laboratory. Compared with Unified Segmentation, DARTEL uses more parameters to estimate the warping needed during the normalization process, creating an average template of the grey matter and white matter tissue maps from all scans. Each grey matter segment is then warped into alignment with this average template, allowing better alignment of each scan before additional analyses are conducted. DARTEL is newer than Unified Segmentation and is viewed with increasing favor by the structural neuroimaging field, at least for the analysis of scans from healthy individuals (Ripolles et al., 2012). Adapting DARTEL procedures, which are typically used for cross-sectional analysis, to a longitudinal format involved the creation of two different average templates, one from the pre- and post-treatment scans of each individual subject, and a second group-level template. Subject scans were warped to both individual and group-level templates in this analysis to account for the longitudinal nature of the data, whereas traditional cross-sectional analyses typically only warp scans to one average template created for the entire group. This procedure was based on the methods of Asami et al. (2012), a prior study which adapted cross-sectional DARTEL techniques for longitudinal analysis.

First, MRI scans were once again equated for deficit side by flipping right/left the brains of subjects with left arm hemiparesis. Post-treatment scans were realigned to the pre-treatment scan using a rigid body spatial transformation with 7th degree B-spline interpolation in a procedure identical to that used in the Unified Segmentation processing pipeline. Scans were then skull-stripped and segmented to grey matter, white matter, and

CSF partitions, utilizing the standard SPM12 preprocessing algorithms. An additional tissue prior equivalent to the average intensity of white matter and CSF was used during segmentation to accommodate for T1 signal hypointensity due to CNS damage, as recommended by several prior studies (Crinion et al., 2007; Ripolles et al., 2012; Seghier, Ramlackhansingh, Crinion, Leff, & Price, 2008).

Once preprocessing was complete, a subject-specific longitudinal DARTEL template was created for each individual pair of pre- and post-treatment grey and white matter segments. Grey matter segments from both time points were warped to the template space and modulated by the Jacobian determinant of the transformation, a procedure used to preserve individual differences in the amount of grey matter while standardizing other aspects of the scan. Next, a group template was created using all of the subject-specific templates created in the previous step. The previously warped and modulated pre- and post-treatment grey matter segments were then warped to the group template space, again modulating them by the Jacobian determinant of the group-level transformation. Finally, the twice-warped, twice-modulated grey matter segments were linearly transformed into MNI space, using the standard DARTEL toolbox script, and smoothed using a 10mm Gaussian kernel. Pre- and post-treatment smoothed, modulated, and normalized grey matter segments were utilized in the final longitudinal analysis. The DARTEL processing pipeline is illustrated in Figure 2.

Figure 2. DARTEL Processing Pipeline

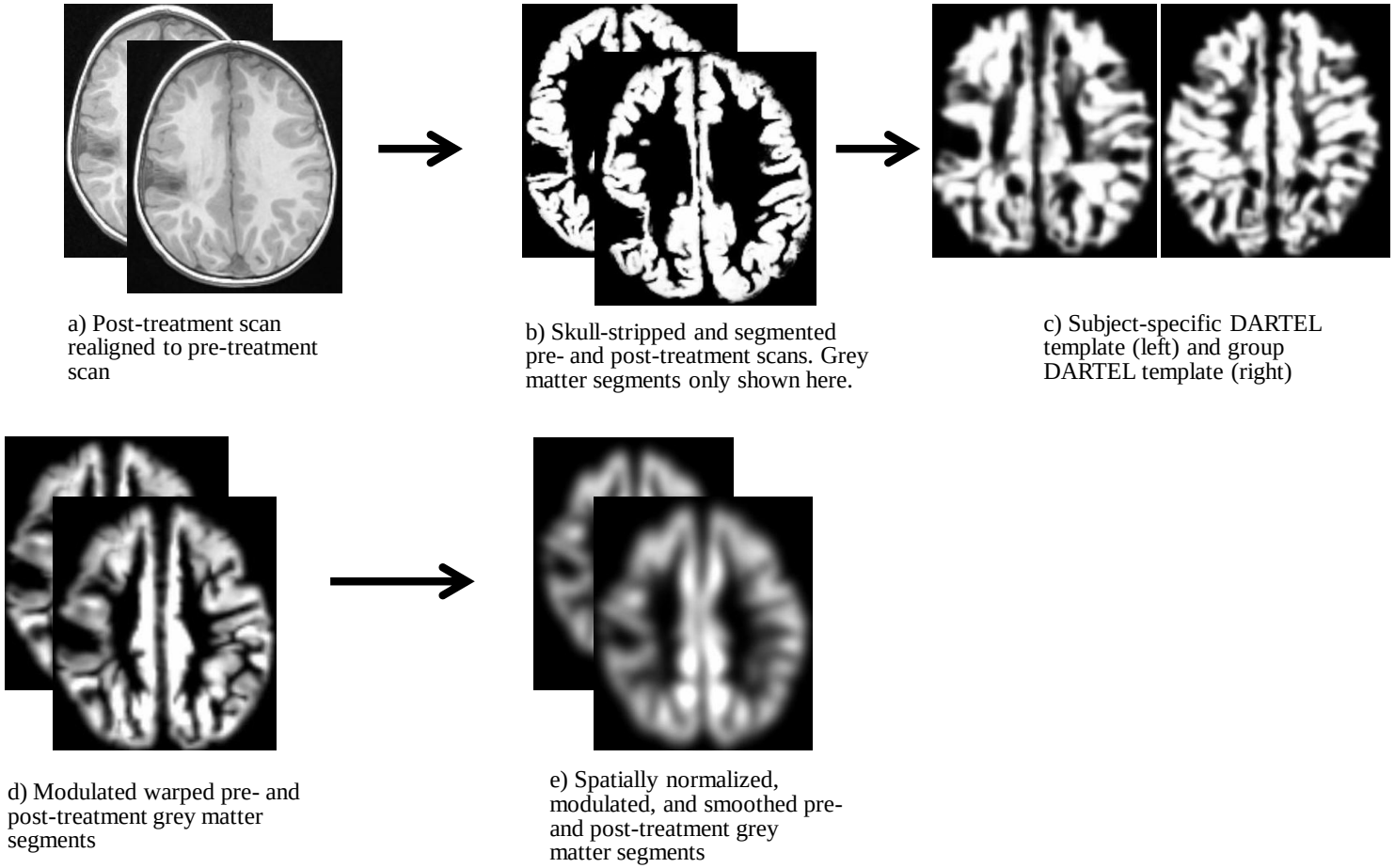


Figure 2. Stepwise illustration of the DARTEL processing pipeline.

Data Analysis

Identical statistical procedures were used on the final images from both image processing pipelines. Diffuse changes in grey matter volume were mapped using clusterwise statistics. This method identifies increases in grey matter over a significant number of adjacent voxels by examining the probability of these voxels exceeding a particular statistical threshold (in this case, $\alpha = .05$). Nonparametric Monte-Carlo procedures in SnPM13 were used to correct for familywise error. Following identification of voxels with significant grey matter changes, the voxelwise *t* value maps were superimposed on a standard template brain (MNI average 152 T1 scan). The Harvard-Oxford Structural Atlas (http://www.cma.mgh.harvard.edu/) toolbox in FSLView (http://fsl.fmrib.ox.ac.uk/fsl/fslview/), a freely available analysis software, was then utilized to identify the anatomical regions of interest (ROIs) where significant changes had been detected. Template masks representing areas of overlap between an anatomically defined area and a significant cluster of *t* values were created and used to quantify specific amount of grey matter change in each custom ROI. Pearson correlations were then calculated between amount of grey matter change in these clusters of statistically significant change and clinical improvement from pre- to post-treatment.

RESULTS

Comparison of DARTEL and Unified Segmentation Pipelines

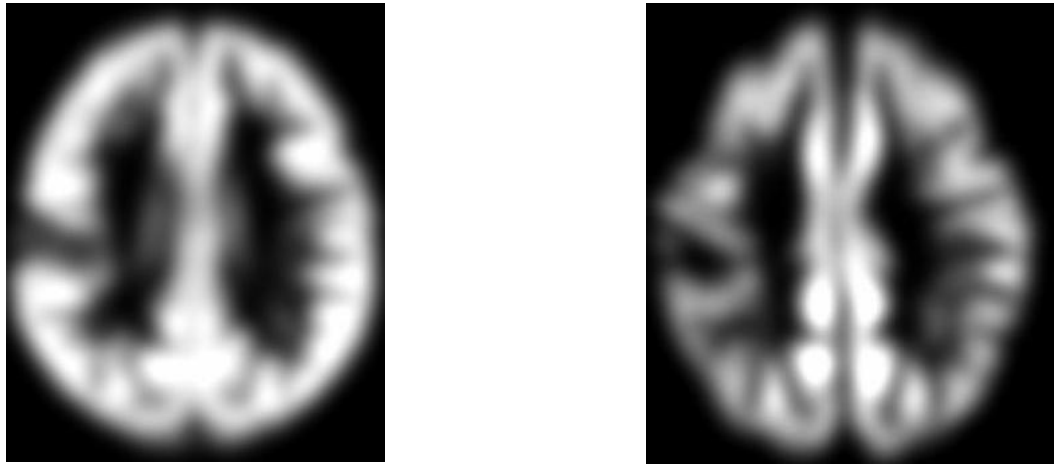
Results from the original Unified Segmentation analyses of the MS and CP study data were successfully replicated and confirmed using this laboratory's standard imaging pipeline (Unified Segmentation), as expected. Because scans from only two thirds of the original stroke sample were available for re-analysis in the current study, it was not possible to exactly replicate the results from the original 2008 study (Gauthier et al., 2008). However, the scans that were available were re-analyzed for as close a replication as could be obtained. Specific results of these analyses are presented below.

There were no significant neuroplastic changes identified by the DARTEL analysis pipeline. Due to this unexpected finding, significant troubleshooting of the DARTEL procedure was undertaken, including visual and quantitative (where possible) comparison of intermediate processing steps to those obtained using this laboratory's older and more standard Unified Segmentation pipeline. First, difference images were produced to compare spatially normalized grey matter segments obtained from SPM8 Unified Segmentation and SPM12's preprocessing segmentation algorithm. These revealed that the grey matter segments preserved by SPM12 were smaller in volume and intensity than those obtained from SPM8. In the CP study sample, these differences in grey matter segments between the two protocols reached statistical significance ($t_{FWE} = 5.48$, $p < .05$). Additionally, on visual inspection, the subject-specific and population DARTEL templates appeared distorted, likely due to brain pathology in our study populations. This distortion appeared to be carried forward in the analysis, affecting the final spatial normalization and smoothing step as well, which is expected since parameters from the DARTEL tem-

plates are utilized to spatially transform the individual subject scans. Comparison of normalized grey matter segments from DARTEL and Unified Segmentation analyses are presented in Figure 3.

Due to the lack of significant results from the DARTEL processing pipeline, only the results obtained from the Unified Segmentation analyses were carried forward to address Aims 2 and 3. From this point forward, all results refer to those obtained from the SPM8 Unified Segmentation processing pipeline.

Figure 3. Comparison of Unified Segmentation and DARTEL Normalized Images



a) Normalized modulated grey matter segment from Unified Segmentation pipeline

b) Normalized modulated grey matter segment from DARTEL pipeline

Figure 3. Comparison of the final product from Unified Segmentation (left) and DARTEL (right) image processing pipelines. Images shown are from the same subject, at identical anatomical coordinates.

Clusterwise Analysis of Neuroplasticity Following CI Therapy

Stroke

Due to aforementioned data loss, only 11 of the original 16 subjects from this population had scans available for re-analysis. Analysis of the data available did not reach statistical significance in a clusterwise analysis. However, in the interest of obtaining as much information as possible from the data available, an uncorrected cortically-rendered map of *t* values was produced from the 11 subjects with scans remaining. A threshold of 2.2-6.7 was applied to this *t* map on the basis of the statistics obtained from the original clusterwise analysis of all 16 participants. While the *t* values in this partial sample did not reach statistical significance when corrected for familywise error, the uncorrected values had the same general configuration as the earlier, larger sample where the *t* values were significant when corrected for familywise error. The thresholded but uncorrected *t* map produced by the current analysis was used in subsequent ROI analyses, although results must be interpreted with caution.

Multiple Sclerosis

Clusterwise analysis revealed an increase in grey matter volume following CI therapy in the bilateral sensorimotor cortices, $p_{FWE} = 0.022$. Additional areas of significant change are discussed in the ROI analysis below. There was no change observed in subjects given a control therapy.

Cerebral Palsy

Clusterwise analysis revealed an increase after CI therapy in grey matter volume in bilateral sensorimotor cortices, $p_{FWE} = .04$. Additional areas of significant change are discussed in the following section.

There was no significant *decrease* of grey matter volume detected in any of the three study populations.

Surface-rendered *t* maps from each population are presented in Figures 4-9.

Maps showing the maximal extent of significant grey matter change are presented in figure 10.

Figure 4. Surface Rendered Cortical Map of Significant Grey Matter Increase (Stroke)

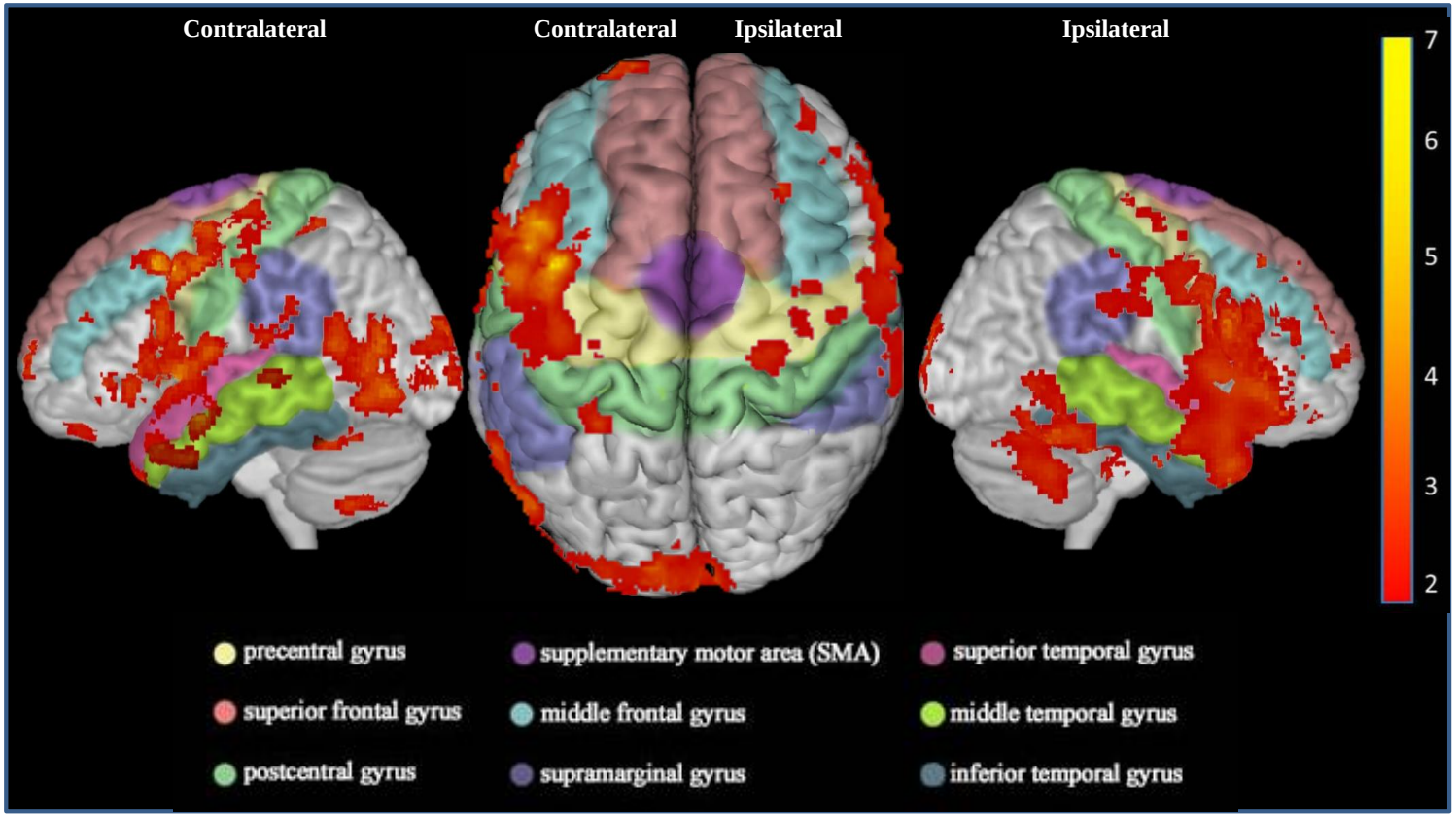


Figure 4. Cortical surface–rendered image of grey matter change after CI therapy in stroke. Grey matter increases are displayed as red-based areas on a standard brain. Surface rendering was performed with a depth of 24 mm. Color bar values indicate *t* statistics ranging from 2.2 to 6.7. **Note: This figure displays uncorrected t values.*

Background color coding indicates the approximate locations of major cortical regions of interest as determined by the Harvard-Oxford Structural Atlas probability maps.

Figure 5. Approximate Brodmann Locations of Significant Grey Matter Increase (Stroke)

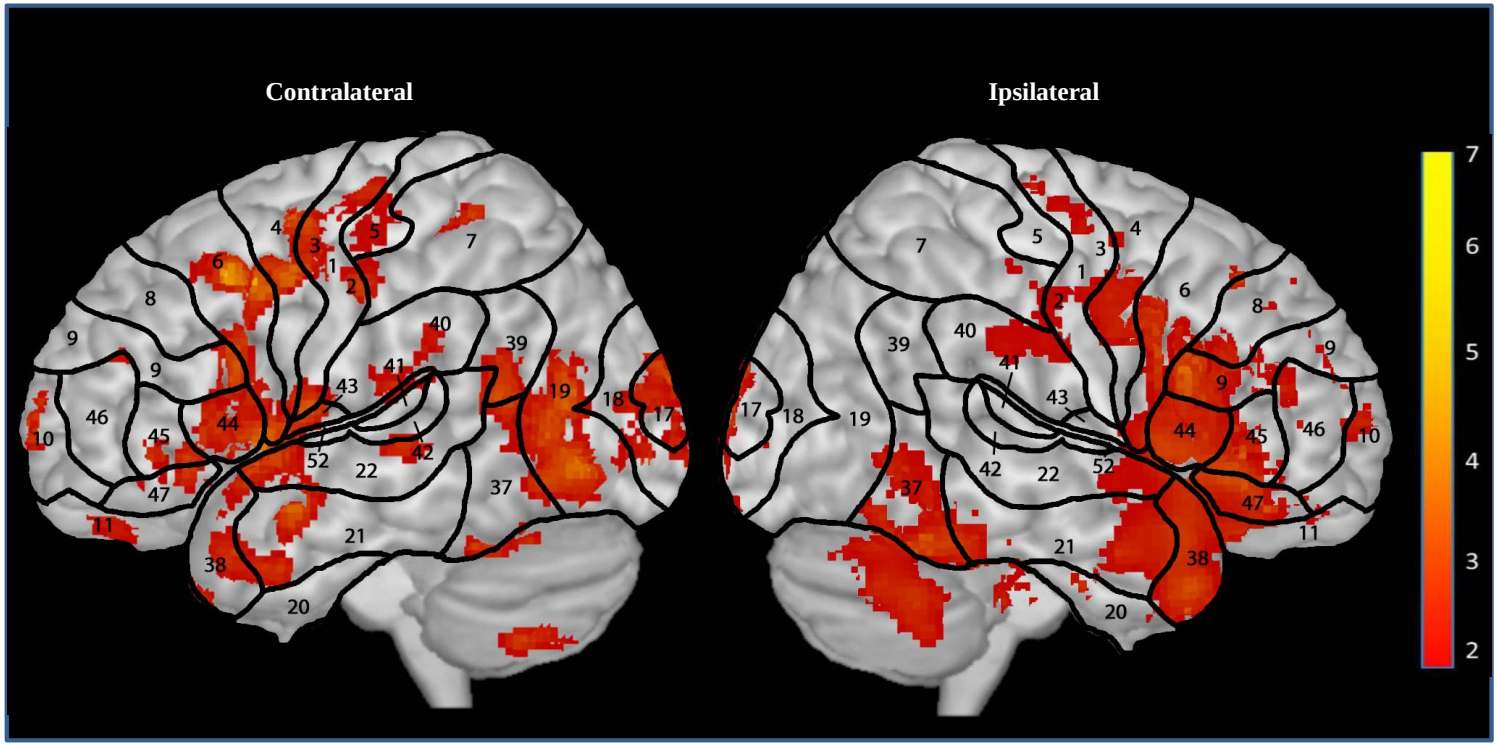


Figure 5. Cortical surface–rendered image of grey matter change after CI therapy in stroke. Grey matter increases are displayed on a standard brain. Surface rendering was performed with a depth of 24 mm. Color bar values indicate *t* statistics ranging from 2.2 to 6.7. Numbered overlay illustrates approximate correspondence of Brodmann areas to location of grey matter changes **Note: This figure displays uncorrected t values.*

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Figure 6. Surface Rendered Cortical Map of Significant Grey Matter Increase (MS)

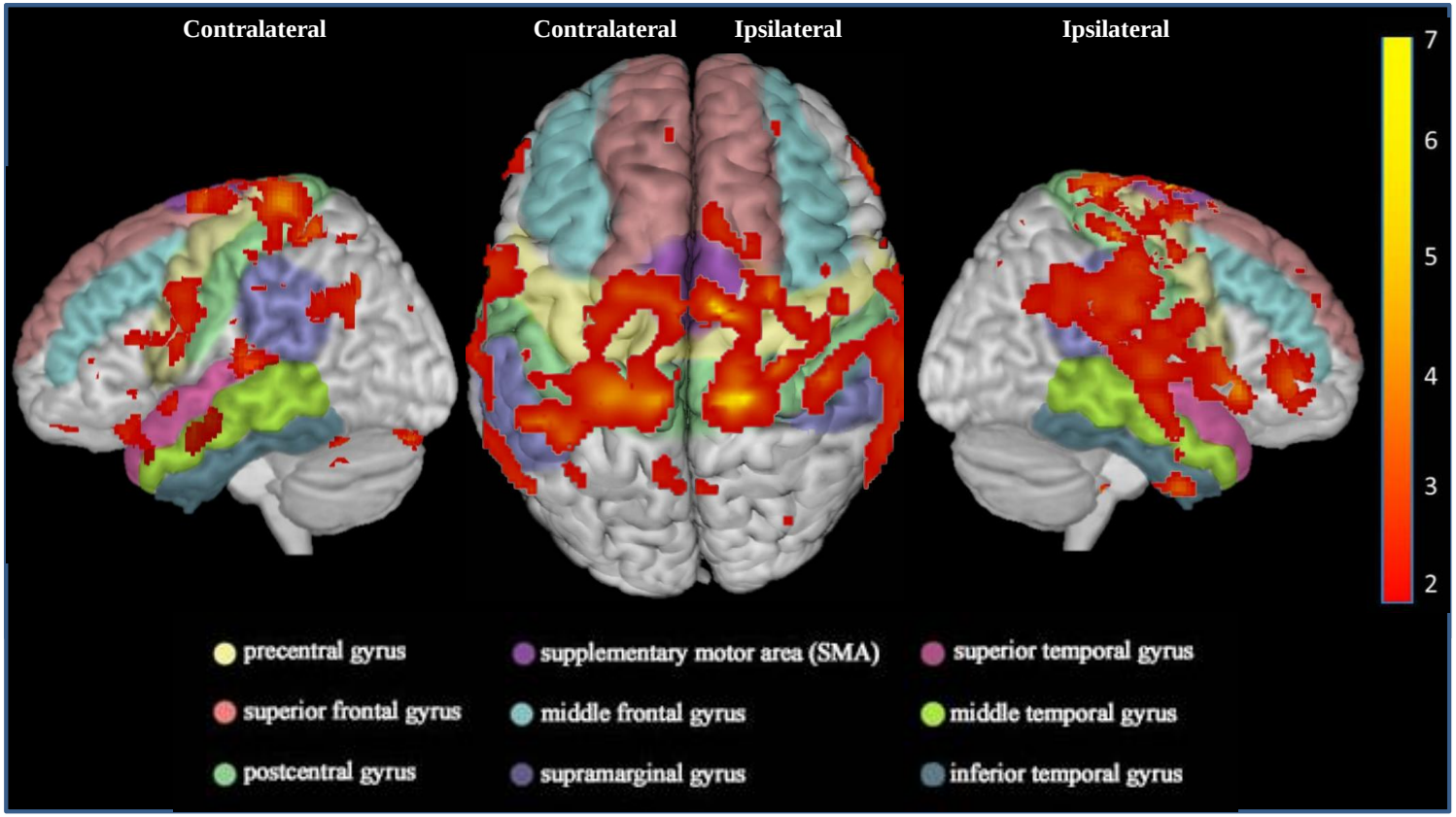

Figure 6. Cortical surface–rendered image of grey matter change after CI therapy in MS. Grey matter increases are displayed as red-based areas on a standard brain. Surface rendering was performed with a depth of 24 mm. Color bar values indicate *t* statistics ranging from 2.2 to 6.7, corrected for familywise error.

Background color coding indicates the approximate locations of major cortical regions of interest as determined by the Harvard-Oxford Structural Atlas probability maps.

Figure 7. Approximate Brodmann Locations of Significant Grey Matter Increase (MS)

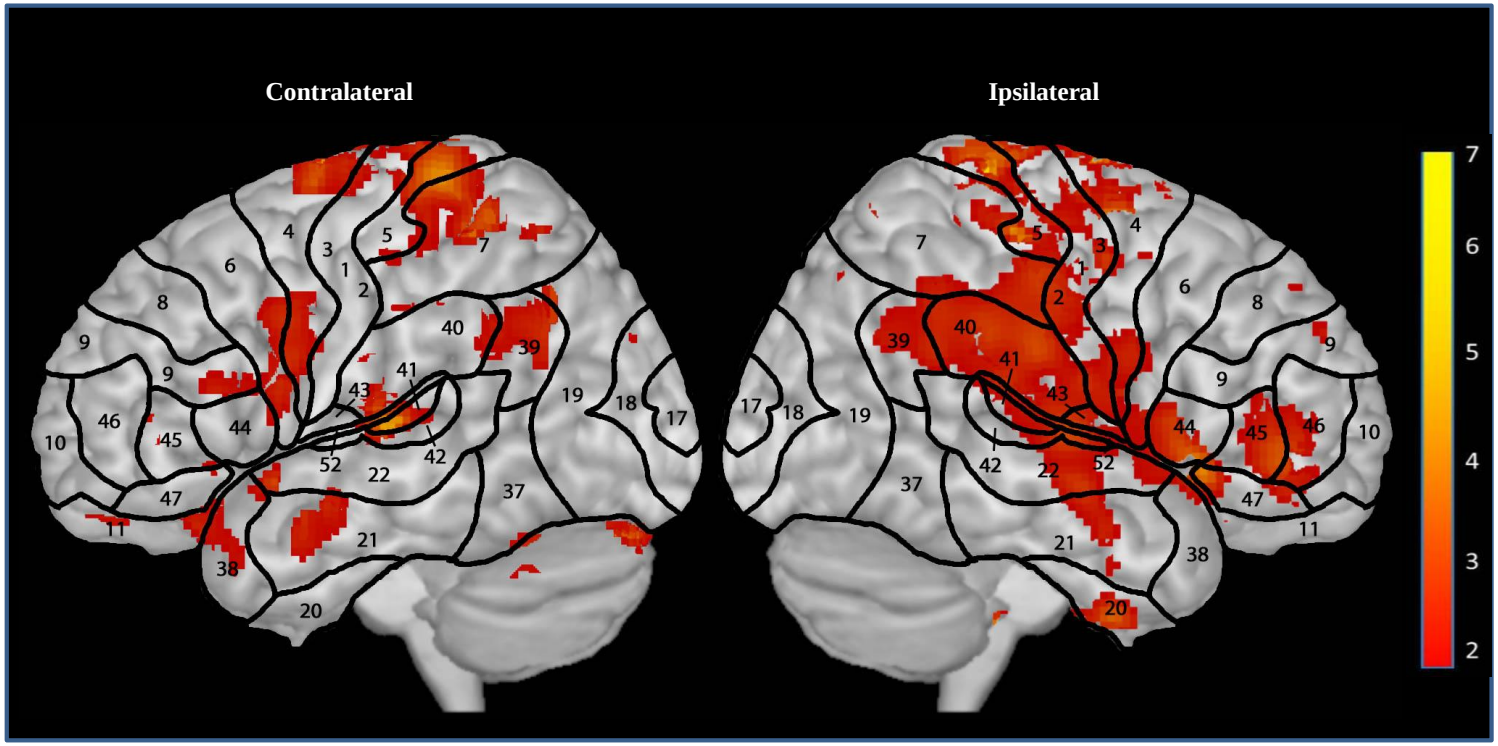

Figure 7. Cortical surface–rendered image of grey matter change after CI therapy in MS. Grey matter increases are displayed on a standard brain. Surface rendering was performed with a depth of 24 mm. Color bar values indicate *t* statistics ranging from 2.2 to 6.7, corrected for familywise error. Numbered overlay illustrates approximate correspondence of Brodmann areas to location of grey matter changes

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Figure 8. Surface Rendered Cortical Map of Significant Grey Matter Increase (CP)

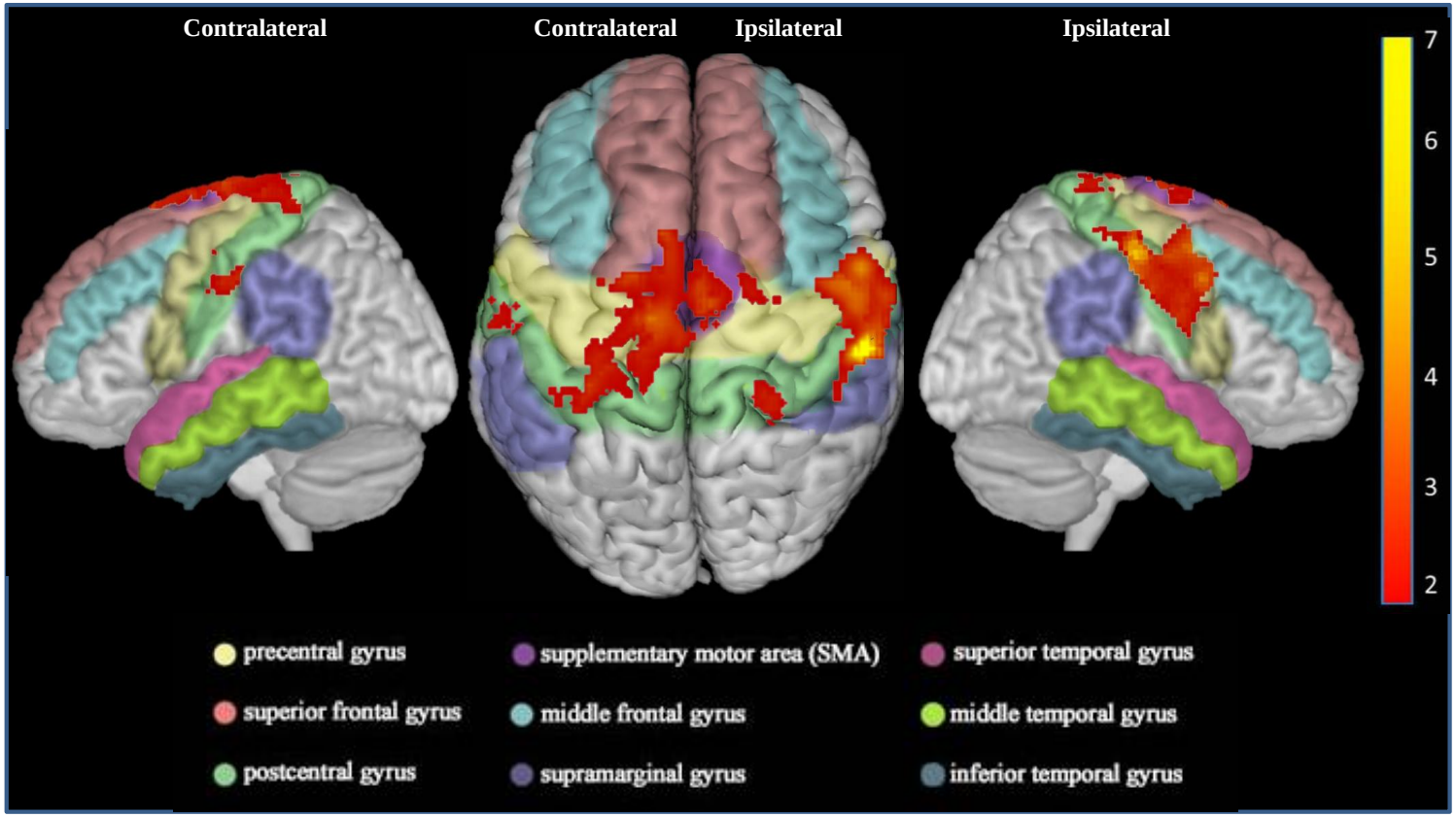

Figure 8. Cortical surface–rendered image of grey matter change after CI therapy in CP. Grey matter increases are displayed as red-based areas on a standard brain. Surface rendering was performed with a depth of 24 mm. Color bar values indicate *t* statistics ranging from 2.2 to 6.7, corrected for familywise error.

Color coding indicates the approximate locations of major cortical regions of interest as determined by the Harvard-Oxford Structural Atlas probability maps.

Figure 9. Approximate Brodmann Locations of Significant Grey Matter Increase (CP)

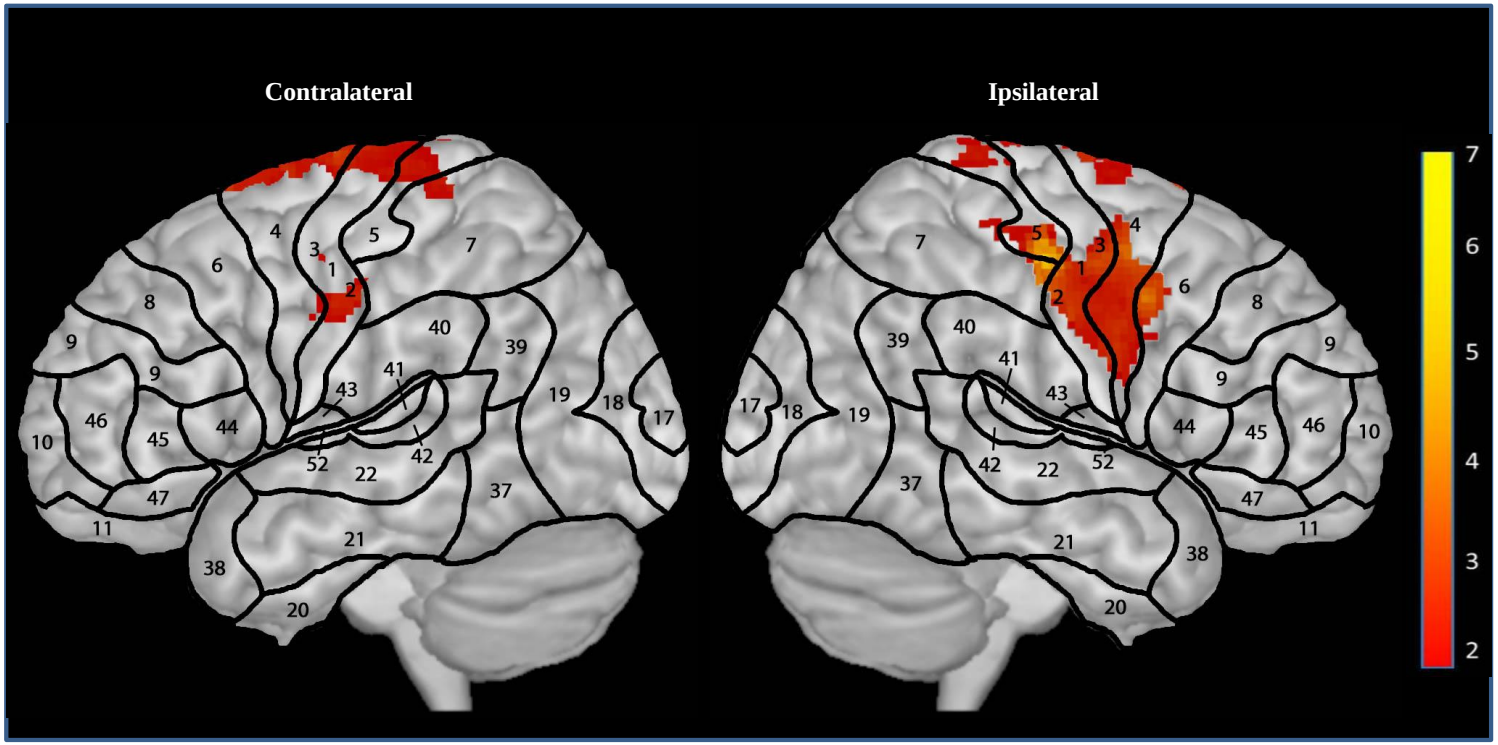

Figure 9. Cortical surface–rendered image of grey matter change after CI therapy in CP. Grey matter increases are displayed on a standard brain. Surface rendering was performed with a depth of 24 mm. Color bar values indicate *t* statistics ranging from 2.2 to 6.7, corrected for familywise error. Numbered overlay illustrates approximate correspondence of Brodmann areas to location of grey matter changes

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Figure 10. Maximum Extent of Grey Matter Change

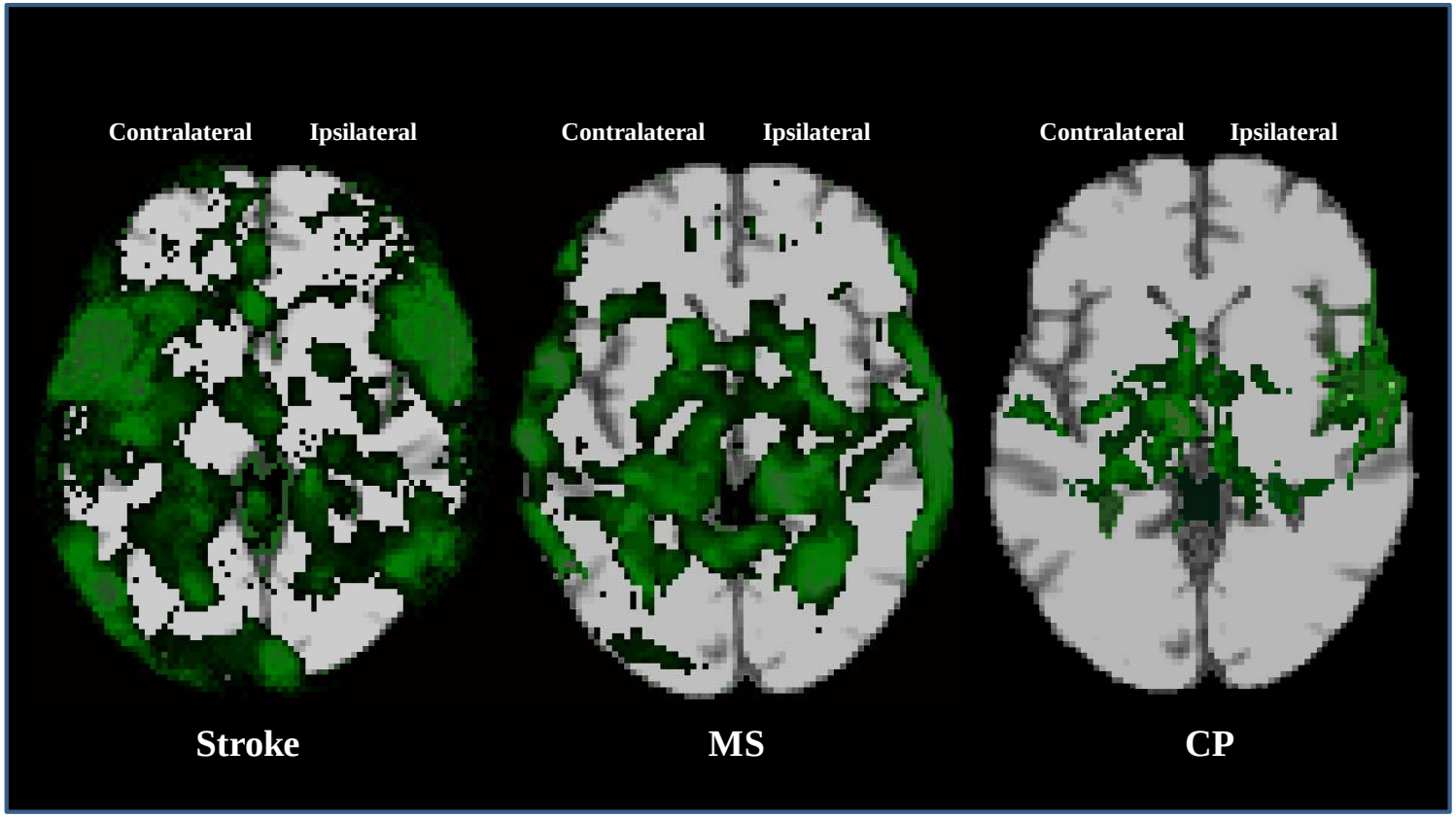

Figure 10. Maximum extent of significant grey matter change in each study population. Lighter green indicates more contiguous slices with significant grey matter change, while darker green indicates fewer contiguous slices.

ROI Analysis

Analysis utilizing the Harvard-Oxford Structural Atlas revealed significant grey matter change in multiple ROIs in each study population (although it should be noted that in the partial stroke sample, these results were uncorrected for familywise error and are assumed to represent statistical significance on the basis of the previous analysis containing the full study sample). These included areas traditionally subserving sensorimotor function (e.g., precentral gyrus, postcentral gyrus, hippocampus) as well as more distal areas (e.g., temporal and occipital lobes). Of note, these results are specific to the groups treated with CI therapy, and were not present in the control groups in each respective study. Additionally, percent magnitude of change was calculated in the area of significant clusters in the precentral gyrus, postcentral gyrus, and supramarginal gyrus in each group, because these were the regions where the largest and most robust clusters of significant grey matter change were localized by *t* map. In the stroke sample, change was approximately 4% (contralateral to the more-affected arm) and 6.5% (ipsilateral) in the precentral gyrus, 4% (contralateral) and 6% (ipsilateral) in the postcentral gyrus, and 3% (contralateral) in the supramarginal gyrus. There were no significant clusters in the ipsilateral supramarginal gyrus for the stroke sample. In the MS sample, change was approximately 4% (contralateral) and 3.5% (ipsilateral) in the precentral gyrus, 4% (contralateral) and 4% (ipsilateral) in the postcentral gyrus, and 4% (contralateral) and 3.5% (ipsilateral) in the supramarginal gyrus. In the CP sample, change was approximately 5.5% (contralateral) and 2.4% (ipsilateral) for the precentral gyrus, 5% (contralateral) and 2% (ipsilateral) for the postcentral gyrus, and 2% (ipsilateral) for the supramarginal gyrus. There were no significant clusters in the contralateral supramarginal gyrus. Final-

ly, in each study population, there were some significant clusters of grey matter change identified in the cerebellum. However, detailed analysis of cerebellar grey matter was not the focus of the present study. Additional results of the cortical ROI analysis are presented in Table 4. Subcortical ROI results are presented in Table 5.

Table 4. Cortical ROI Analysis

	MS		CP		Stroke	
	contra	**ipsi**	**contra**	**ipsi**	**contra**	**ipsi**
superior frontal gyrus	X	X	X	X	X	X
middle frontal gyrus	X	X		X	X	X
pars triangularis	X	X			X	X**
pars opercularis	X	X			X	X*
precentral gyrus	X	X	X	X	X	X
temporal pole	X	X			X	X
superior temporal gyrus (anterior)	X	X			X	X
superior temporal gyrus (posterior)	X	X			X	
middle temporal gyrus (anterior)	X	X				
middle temporal gyrus (posterior)	X	X			X	X
middle temporal gyrus (temporal occipital)					X	X
inferior temporal gyrus (anterior)	X	X			X	X
inferior temporal gyrus (posterior)	X	X			X	X
inferior temporal gyrus (temporal occipital)	X	X			X	X
postcentral gyrus	X	X	X	X	X	X
superior parietal lobule	X	X			X*	
supramarginal gyrus (anterior	X	X		X	X	
supramarginal gyrus (posterior)	X	X		X	X	
angular gyrus	X	X			X	
lateral occipital cortex (superior)	X	X			X	X
lateral occipital cortex (inferior)	X	X			X	X
frontal medial cortex					X	
intracalcarine cortex	X	X			X	X
supplementary motor area	X	X	X	X		X
subcallosal cortex					X	X
insular cortex					X	
paracingulate gyrus					X	

Note: X's denote the presence of statistically significant grey matter increase in the ROI. Asterisks denote significant correlations between grey matter change and MAL change.
* $p < .05$; ** $p < .01$

Table 4 (continued). Cortical ROI Analysis

	MS		CP		Stroke	
	contra	**ipsi**	**contra**	**ipsi**	**contra**	**ipsi**
cingulate gyrus (anterior)					X	X
cingulate gyrus (posterior)			X	X*	X	X
precuneus cortex	X	X	X	X*	X	X
cuneal cortex					X	X
frontal orbital cortex	X	X			X	X*
parahippocampal gyrus (anterior)			X			X
parahippocampal gyrus (posterior)	X	X			X	X
lingual gyrus	X	X			X	X
temporal fusiform cortex (anterior)			X			
temporal fusiform cortex (posterior	X	X	X		X	X
occipital fusiform cortex	X	X			X	X
occipital fusiform gyrus	X	X				X
central opercular cortex		X			X	X*
parietal operculum cortex	X	X			X	
frontal operculum cortex					X	
planum polare		X			X	X
Heschl's gyrus	X				X	
planum temporal	X	X			X	X*
supracalcarine cortex					X	
occipital pole					X	X

Note: X's denote the presence of statistically significant grey matter increase in the ROI. Asterisks denote significant correlations between grey matter change and MAL change. * $p < .05$; ** $p < .01$

Table 5. Subcortical ROI Analysis

	MS		CP		Stroke	
	contra	**ipsi**	**contra**	**ipsi**	**contra**	**ipsi**
thalamus	X	X			X	
caudate		X				
putamen	X	X				X
pallidum		X				
hippocampus	X	X	X		X	X
amygdala		X				X
accumbens						

Note: X's denote the presence of statistically significant grey matter incease in the ROI.

Correlation of Neuroplastic Changes and Clinical Outcomes

Few significant correlations were revealed between grey matter increase and change on clinical outcome measures. These results are displayed in Tables 2 and 3. None of these significant correlations were in areas traditionally subserving motor function, and none overlapped between study populations. These correlations are in effect a post-hoc analysis which utilizes the clusterwise *t* statistics to perform planned comparisons. It is possible that the significant correlations obtained from the ROI analysis simply represent false positives from performing a large number of comparisons. Overall, the lack of significant correlations likely represents a lack of statistical power due to small sample size.

DISCUSSION

Methodological Considerations

The lack of significant findings from the DARTEL image processing pipeline is somewhat unexpected due to the fact that this technique is generally regarded by the field as more advanced and sensitive than the Unified Segmentation procedure (Klein et al., 2009; Tahmasebi, Abolmaesumi, Zheng, Munhall, & Johnsrude, 2009; Yassa & Stark, 2009). However, a closer examination of the literature suggests that the inconsistent findings resulting from the current study may in fact reflect a larger problem in the structural neuroimaging field, namely the relative lack of standardized procedures for the analysis of images in populations with significant brain pathology. Longitudinal VBM analyses are less common than their cross-sectional counterparts, and few groups are currently performing any structural voxel-based studies on patient populations with large lesions.

Relatively little is known regarding best practices for segmentation and normalization of the lesioned brain, and there is a lack of standardization in the literature. Both of these steps are crucial to the VBM analysis procedure, and both are challenged by the presence of pathology in the brain (Ripolles et al., 2012). Automated methods of segmentation and normalization, including those used in both processing pipelines in this study, function by minimizing the difference between a subject's brain and one or more template maps, based on parameters such as overall size and position of the brain as well as signal type and intensity typically generated by a given tissue class (e.g., grey matter, white matter, CSF). However, these templates are designed for use with healthy brains. Attributes including size, position, and even signal attenuation from tissue in the damaged brain are likely to differ from the estimates used by these algorithms, and may vary greatly even between individuals with the same etiology (e.g., very different lesion characteristics from cerebrovascular etiology; Crinion et al., 2007).

Several past studies have examined the best way to handle focal lesions in VBM analysis, although there is no clear consensus on the outcome (Andersen, Rapcsak, & Beeson, 2010; Crinion et al., 2007; Malone et al., 2015; Seghier et al., 2008). The use of cost-function masking to exclude lesioned areas from the analysis when utilizing a Unified Segmentation approach is the most traditional, and perhaps still the most popular. Some studies have challenged the need for the use of masking, substituting custom tissue priors (i.e. creating a "template" for lesioned tissue in addition to those automatically provided for grey matter, white matter, and CSF) in the segmentation step to accommodate for signal hypointensity in the lesioned area (e.g., Crinion 2007), while others have found this to be less accurate overall (e.g., Andersen et al., 2010). An additional recent

study compared ten different normalization methods on lesioned brains, finding good performance for both Unified Segmentation and DARTEL, although neither worked perfectly (Ripolles et al., 2012). Notably, all of these review studies have focused on the processing of brains with focal lesions *in the infarcted area*, treating the rest of the brain as if it is healthy. In reality, this type of isolated pathology is not representative of the patients treated with CI therapy in our studies. In patients with chronic cerebrovascular conditions, such as stroke, other abnormalities have been noted, including diffuse atrophy not limited to the infarcted/perilesional area (Gauthier, Taub, Mark, Barghi, & Uswatte, 2011). In a disease like MS pathology, including diffuse demyelination, white matter abnormalities, and widespread atrophy, is quite different throughout the brain when compared to the sort of artificial focal lesion approach that has been used in these past studies to examine the performance of segmentation and normalization algorithms. It is likely, then, that these widespread abnormalities introduce additional sources of error variability during the VBM process, which have not been well-examined in the literature to date.

The results obtained by the current study appear to suggest that Unified Segmentation with cost-function masking performs more consistently in brains with chronic diffuse pathology than DARTEL. First, this laboratory's past results with the Unified Segmentation pipeline have been consistent across three separate studies of patients treated with CI therapy. Additionally, these results are specific to the experimental groups, with no significant grey matter changes detected in the corresponding control groups. The scans from these control groups were analyzed using the same Unified Segmentation processing pipeline and did not differ, at pre-treatment, from the experimental groups in disease etiology or general anatomical characteristics (e.g., total grey matter volume). If the

significant grey matter changes detected by the Unified Segmentation protocol were simply false positives resulting from noise, one would expect to see the same sort of changes in the control groups. Second, only significant grey matter *increases* were detected by the Unified Segmentation pipeline. Once again, if false positives were being detected, one would expect to see grey matter increases and decreases detected in roughly equal amounts. Finally, upon visual inspection of the intermediate results at each processing step of the DARTEL pipeline, abnormalities were noted that suggested segmentation and normalization were not functioning optimally.

Overall, questions remain regarding best practices for analyzing images with chronic diffuse pathology. Future work should be undertaken to continue optimizing the VBM process in these populations. This might include comparison of these techniques over a larger sample size than the one available in the present study, or synthetic alterations to create a dataset that simulates known pathology of a more diffuse nature. The results from the methodological comparison in this study highlight the importance of continuing to work toward standardization of practices in structural voxel-based analyses, since two image processing pipelines designed to assess the same thing can have such disparate results.

Location of Neuroplastic Changes Following CI Therapy

The second major aim of this study was to anatomically localize the neuroplastic changes following treatment with CI therapy, and compare them across study populations. As expected, bilateral cortical grey matter increases were detected in sensorimotor areas (i.e., superior frontal gyrus, precentral gyrus, postcentral gyrus) in all three popula-

tions. Although the clusters of voxels where significant change was detected did not exactly overlap, they fell within the same anatomically-defined ROIs for all three CI therapy groups. Additional areas where significant grey matter increase (i.e., supramarginal gyrus, precuneus cortex, middle frontal gyrus) was detected in all three study populations were those which also fit within the expected functional context of the CI therapy intervention. The supramarginal gyrus, an ROI where increases were bilateral for the MS group and unilateral for the CP and stroke groups, has a role in somatosensory association. Precuneus cortex, the site of bilateral grey matter increase across all three groups, contributes to motor coordination and visual attention to spatial targets (Cavanna & Trimble, 2006). The middle frontal gyrus is an area that has been linked to executive functions such as attention and concentration, which may additionally be increased through general participation in the CI therapy treatment protocol (Talati & Hirsch, 2005). Given that most tasks in the CI therapy treatment protocol (e.g., stacking cones) require both visual attention and a high degree of eye-hand coordination, it is perhaps not surprising to find grey matter changes in these ROIs outside primary sensorimotor areas. Magnitude of change in the most robust areas of grey matter increase was also substantial at 4-6%, a specific metric not previously examined by this laboratory.

While it may at first glance appear notable that there were fewer areas of significant grey matter increase identified in the CP participants, this is most likely an artifact caused by the large lesions in this population. Because masking large lesions results in the exclusion of many voxels from subsequent analysis in order to improve accuracy of the analysis, it is possible (perhaps even likely) that areas of significant grey matter increase may have been missed in the CP sample.

In addition to the areas where grey matter increase was detected in all three groups, more diffuse changes occurred in areas that are not typically associated with sensorimotor function, including parts of the temporal and occipital lobes. Although the pattern and location of these changes differed between study populations, all three populations showed evidence of widespread neuroplasticity. Of important note is the fact that these widespread neuroplastic changes occurred only in the groups of participants treated with CI therapy and were not present in the corresponding control groups.

Subcortically, all three groups had grey matter increases detected in the hippocampus, an area associated with spatial navigation, exercise, learning and memory (Maguire et al., 2000). The MS and stroke groups additionally had grey matter increases detected in subcortical areas traditionally associated with the regulation of voluntary motor control, including the thalamus, caudate, and putamen. Although this laboratory has previously demonstrated evidence of grey matter increases in multiple cortical areas and the hippocampus, widespread subcortical change has not previously been systematically analyzed. The findings of grey matter change in the basal ganglia and thalamus are a first for this laboratory and therefore particularly important results.

General Considerations

Overall, these findings support the possibility of enhanced neuroplasticity in the injured CNS (Zeiler & Krakauer, 2013; Caleo, 2015). They may further suggest that CI therapy activates or augments this process in patients with chronic motor deficits while comparison therapies do not. Although this area of investigation is relatively new in the human literature, the concept of "neurorestoration," or designing interventions to harness

natural processes of neuroplasticity in order to make full use of existing brain structures during recovery is becoming an increasingly hot topic in the rehabilitation field (Corbett, Nguemeni, & Gomez-Smith, 2014; Di Pino et al., 2014). A recent rodent model of CI therapy found histological evidence for enhanced neuroplasticity and possible neurogenesis following the treatment (Zhao, Zhao, Xiao, Jolkkonen, & Zhao, 2013). A continuation of this line of work found additional evidence for the rodent model of CI therapy promoting neurogenesis and inhibiting the apoptotic pathway even in aged rats, a closer approximation of the typical human stroke population (Qu et al., 2015). While not a direct model of CI therapy, another recent rodent study found histological evidence of neuroplastic processes in functionally relevant areas in rats that underwent a limb rehabilitation protocol, but not in those that were left to spontaneously recover (Wang, Conner, Nagahara, & Tuszynski, 2016).

Functional imaging studies examining stroke recovery in humans additionally support the existence of widespread neuroplasticity beyond perilesional areas or those that traditionally innervate sensorimotor functioning. Multiple studies have found widespread bilateral activation accompanying movements of the paretic hand in patients who have experienced stroke (summarized in Di Pino et al., 2014). TMS utilized to disrupt activation resulted in corresponding degradation of paretic hand movement, suggesting that the observed widespread activation directly corresponded to paretic hand use. Alternatively, a previous functional imaging study specifically examining CI therapy patients found that movement of the paretic hand was associated with widespread cortical activation which *decreased* as rehabilitation progressed and movements became less effortful. Concurrently, the motor map size increased in the affected hemisphere motor cortex in CI

therapy patients (Wittenberg et al., 2003). These findings, taken together with those from the present structural imaging study, may indicate that underlying neuroplastic processes allowed less effortful, more functional movement of the paretic limb after treatment with CI therapy.

While there is robust evidence for the existence of considerable neuroplastic reorganization during recovery from CNS injury, the exact nature of this process remains unknown (Di Pino et al., 2014; Prosperini, Piattella, Gianni, & Pantano, 2015; Reid, Rose, & Boyd, 2015). One model, referred to as "vicariation," posits that activation of spared brain areas substitutes for those that have been damaged. A similar view has been expressed by this laboratory, on the basis of both past CI therapy studies and a synthesis of the use-dependent neuroplasticity literature, suggesting that the damaged CNS possesses significant capacity to make use of spared neural resources, particularly in the context of efficacious rehabilitation therapy (Taub et al., 2014). A second theory is that widespread neuroplasticity in the damaged brain is the result of an imbalance in activation between affected and unaffected hemispheres. This "interhemispheric competition" model suggests that in the healthy brain, there is a balance of mutual inhibition between the two hemispheres. Unilateral damage disrupts this balance, resulting in increased inhibition of the affected hemisphere by the unaffected, decreasing excitation and further impairing function. Neuroplastic reorganization during rehabilitation and recovery might then reflect attempts by the nervous system to restore the balance of inhibition. A recent synthesis of functional imaging literature suggests that there is evidence for both models of neuroplastic reorganization during recovery from CNS injury, depending on the degree of damage in a given brain (Di Pino et al., 2014). The current findings of widespread grey

matter plasticity following treatment with CI therapy may reflect either or both types of neuroplastic reorganization occurring during the course of treatment.

Understanding of the mechanisms underlying neuroplastic reorganization during functional recovery from CNS injury is an area that continues to evolve rapidly in the literature. Increasing focus is being placed on creating interventions that promote or enhance natural processes of neuroplasticity while meeting patients' needs for recovery of real-world motor function in activities of personal value (Winstein & Kay, 2015). At the same time, there is increasing need for multimodal imaging techniques which can further elucidate the mechanisms at work in these processes (Auriat, Neva, Peters, Ferris, & Boyd, 2015). The current study comprises a first, exploratory analysis of neuroplasticity across multiple etiology populations treated with CI therapy. Although the obtained results suggest widespread neuroplasticity in both traditional sensorimotor areas and beyond, interpretation of this data is ultimately limited by the small sample size and single imaging modality.

When considering the results of the current study in the context of the wider neurorestoration and neuroimaging literature, it is important to remember that "recovery" and "neuroplasticity" are not necessarily synonymous. While other studies have found some evidence that alternate interventions may produce a neuroplastic response, CI therapy has advantages as an efficacious motor therapy which should not be overlooked when focusing on neuroimaging results. In terms of recovery of real-world motor function, CI therapy produces large improvements over and above those obtained using comparison therapies. This result is independent of the imaging findings regarding neuroplastic responses which may accompany the clinical treatment change. While there

is a popular assumption that neuroplasticity is associated with clinical recovery, in reality we are only beginning to elucidate the nature of this relationship. Additionally, while other studies provide context for the existence of widespread neuroplastic changes during recovery from CNS injury, it is not possible to make a direct comparison between these therapies and CI therapy, except concerning the UAB study control groups, for the following reasons.

First, many of the studies supporting widespread neuroplasticity following CNS injury are examining metabolic cascade in the acute phase of injury. Others, which perform histology on subjects through the chronic phase of recovery, and do indicate actual structural changes including neurogenesis, are rodent models of CI therapy or similar forced-use interventions. While these latter results, of course, are not completely comparable to human results, they seem to show favorable support for CI therapy as an intervention which promotes neuroplasticity. Second, to our knowledge, there are no other studies assessing *structural* neuroplastic change in participants receiving an efficacious motor therapy. Many of the claims of "neuroplasticity" during recovery from CNS injury base this finding on functional imaging changes. It is assumed that because patterns of activation change, there is a corresponding underlying structural change. Several of these studies make the further assumption that increased magnitude of activation during functional imaging is a positive sign for recovery. However, this may or may not be the case. The exact nature of functional, structural, and clinical changes is not known at this time.

In contrast, the current study provides direct evidence for widespread structural neuroplastic change following CI therapy, specifically grey matter increase in sensorimotor cortices, as well as more distal regions. The magnitude of these changes was relatively

large, with a 4-6% increase in grey matter in the most robust areas of change. Additionally, these changes were specific to the CI therapy groups and were not observed in the UAB comparison control groups. While it is possible that other interventions might produce some neuroplastic response during the course of treatment, that was not observed to follow the comparison therapies used in these specific studies. Finally, treatment with CI therapy has clear advantages in terms of real-world motor outcome, regardless of specific imaging findings.

Future work should be undertaken to further our understanding of the neuroplastic processes specific to CI therapy, as well as its ability to enhance or trigger endogenous capacity for CNS reorganization in the chronic phase of motor deficit. White matter changes have already been quantified in subjects with MS who have undergone CI therapy. A current study in this laboratory is combining fMRI with the standard structural analyses in participants undergoing CI therapy for motor deficit following traumatic brain injury. This type of functional imaging study could help to determine the extent to which the widespread grey matter increases typically observed following CI therapy correspond to a pattern of activation in both perilesional cortex and more distal brain areas during motor tasks. Ultimately, these results will help enhance our understanding of the way the damaged brain may generate new neurons or "repurpose" remaining structures to make optimal use of its resources during functional recovery from CNS damage.

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APPENDIX A

INSTITUTIONAL REVIEW BOARD APPROVAL

UAB CKW **Project Revision/Amendment Form** irb

Form version: June 26, 2012

In MS Word, click in the white boxes and type your text; double-click checkboxes to check/uncheck.

- Federal regulations require IRB approval before implementing proposed changes. See Section 14 of the IRB Guidebook for Investigators for additional information.
- Change means any change, in content or form, to the protocol, consent form, or any supportive materials (such as the Investigator's Brochure, questionnaires, surveys, advertisements, etc.). See Item 4 for more examples.

1. Today's Date	1/9/15	9756

2. Principal Investigator (PI)

Name (with degree)	Victor W. Mark, MD	Blazer ID	vwmark
Department	Physical Medicine & Rehabilitation	Division (if applicable)	
Office Address	SRC 190	Office Phone	934-3499
E-mail	vwmark@uab.edu	Fax Number	975-5952

Contact person who should receive copies of IRB correspondence (Optional)

Name	Sherricka Embery	E-Mail	sembery@uab.edu
Phone	996-5014	Fax Number	975-9754
Office Address (if different from PI)			

3. UAB IRB Protocol Identification

3.a. Protocol Number: X090415004

3.b. Protocol Title: Brain Responses to Rehabilitation in Progressive MS (Exploring the Effects of Rehabilitation on Brain Remodeling in Progressive MS)

3.c. Current Status of Protocol—Check ONE box at left; provide numbers and dates where applicable

- ☐ Study has not yet begun — No participants, data, or specimens have been entered.
- ☐ In progress, open to accrual — Number of participants, data, or specimens entered:
- ☐ Enrollment temporarily suspended by sponsor
- ☒ Closed to accrual, but procedures continue as defined in the protocol (therapy, intervention, follow-up visits, etc.)
  - Date closed: 4/1/2014
  - Number of participants receiving interventions: 0
  - Number of participants in long-term follow-up only: 28
- ☐ Closed to accrual, and only data analysis continues
  - Date closed:
  - Total number of participants entered:

4. Types of Change

Check all types of change that apply, and describe the changes in Item 5.c. or 5.d. as applicable. To help avoid delay in IRB review, please ensure that you provide the required materials and/or information for each type of change checked.

- ☐ **Protocol revision (change in the IRB-approved protocol)**
  In Item 5.c., if applicable, provide sponsor's protocol version number, amendment number, update number, etc.
- ☐ **Protocol amendment (addition to the IRB-approved protocol)**
  In Item 5.c., if applicable, provide funding application document from sponsor, as well as sponsor's protocol version number, amendment number, update number, etc.
- ☒ **Add or remove personnel**
  In Item 5.c., include name, title/degree, department/division, institutional affiliation, and role(s) in research, and address whether new personnel have any conflict of interest. See "Change in Principal Investigator" in the IRB Guidebook if the principal investigator is being changed.
  - ☒ **Add graduate student(s) or postdoctoral fellow(s) working toward thesis, dissertation, or publication**
    In Item 5.c., (a) identify these individuals by name; (b) provide the working title of the thesis, dissertation, or publication; and (c) indicate whether or not the student's analysis differs in any way from the purpose of the research described in the IRB-approved HSP (e.g., a secondary analysis of data obtained under this HSP).
- ☐ **Change in source of funding; change or add funding**
  In Item 5.c., describe the change or addition in detail, include the applicable OSP proposal number(s), and provide a copy of the application as funded (or as submitted to the sponsor if pending). Note that some changes in funding may require a new IRB application.

☐ **Add or remove performance sites**
In Item 5.c., identify the site and location, and describe the research-related procedures performed there. If adding site(s), attach notification of permission or IRB approval to perform research there. Also include copy of subcontract, if applicable. If this protocol includes acting as the Coordinating Center for a study, attach IRB approval from any non-UAB site added.

☐ **Add or change a genetic component or storage of samples and/or data component—this could include data submissions for Genome-Wide Association Studies (GWAS)**
To assist you in revising or preparing your submission, please see the IRB Guidebook for Investigators or call the IRB office at 934-3789.

☐ **Suspend, re-open, or permanently close protocol to accrual of individuals, data, or samples (IRB approval to remain active)**
In Item 5.c., indicate the action, provide applicable dates and reasons for action; attach supporting documentation.

☐ **Report being forwarded to IRB (e.g., DSMB, sponsor or other monitor)**
In Item 5.c., include date and source of report, summarize findings, and indicate any recommendations.

☐ **Revise or amend consent, assent form(s)**
Complete Item 5.d.

☐ **Addendum (new) consent form**
Complete Item 5.d.

☐ **Add or revise recruitment materials**
Complete Item 5.d.

☐ **Other (e.g., investigator brochure)**
Indicate the type of change in the space below, and provide details in Item 5.c. or 5.d. as applicable.
Include a copy of all affected documents, with revisions highlighted as applicable.

▶

5. Description and Rationale

In Item 5.a. and 5.b, check Yes or No and see instructions for Yes responses.
In Item 5.c. and 5.d, describe—and explain the reason for—the change(s) noted in Item 4.

☒ Yes ☐ No **5.a. Are any of the participants enrolled as normal, healthy controls?**
If yes, describe in detail in Item 5.c. how this change will affect those participants.

☐ Yes ☒ No **5.b. Does the change affect subject participation, such as procedures, risks, costs, location of services, etc.?**
If yes, FAP-designated units complete a FAP submission and send to fap@uab.edu. Identify the FAP-designated unit in Item 5.c.
For more details on the UAB FAP, see www.uab.edu/cto.

5.c. Protocol Changes: In the space below, briefly describe—and explain the reason for—all change(s) to the protocol. ✓ Added in SIRB.

▶ We request the following change in personnel: We would like to add Michelle Haddad, MA, Graduate Research Assistant - Psychology Department, as a co-Principal Investigator.

5.d. Consent and Recruitment Changes: In the space below,
(a) describe all changes to IRB-approved forms or recruitment materials and the reasons for them;
(b) describe the reasons for the addition of any materials (e.g., addendum consent, recruitment); and
(c) indicate either how and when you will reconsent enrolled participants or why reconsenting is not necessary (not applicable for recruitment materials).

Also, indicate the number of forms changed or added. For new forms, provide 1 copy. For revised documents, provide 3 copies:
- **a copy of the currently approved document (showing the IRB approval stamp, if applicable)**
- **a revised copy highlighting all proposed changes with "tracked" changes**
- **a revised copy for the IRB approval stamp.**

▶

Signature of Principal Investigator Victor W. Mark MD Date 1/12/15

FOR IRB USE ONLY

☐ Received & Noted ☑ Approved Expedited* ☐ To Convened IRB

Marilyn Dass 1-21-15

Signature (Chair, Vice-Chair, Designee) Date

DOLA 11-25-14

Change to Expedited Category Y / N / NA

*No change to IRB's previous determination of approval criteria at 45 CFR 46.111 or 21 CFR 56.111

UAB CCW

Project Revision/Amendment Form

Form version: June 26, 2012

RECEIVED JAN 15 2015 OFFICE OF INSTITUTIONAL REVIEW BOARD

In MS Word, click in the white boxes and type your text; double-click checkboxes to check/uncheck.

- Federal regulations require IRB approval before implementing proposed changes. See Section 14 of the IRB Guidebook for Investigators for additional information.
- Change means any change, in content or form, to the protocol, consent form, or any supportive materials (such as the Investigator's Brochure, questionnaires, surveys, advertisements, etc.). See Item 4 for more examples.

1. Today's Date	1/12/2015	9757

2. Principal Investigator (PI)

Name (with degree)	Edward Taub, PhD	Blazer ID	etaub
Department	Psychology	Division (if applicable)	
Office Address	CPM 714	Office Phone	205-934-2471
E-mail	etaub@uab.edu	Fax Number	205-975-6140

Contact person who should receive copies of IRB correspondence (Optional)

Name	Gitendra Uswatte, PhD	E-Mail	guswatte@uab.edu
Phone	205-975-5089	Fax Number	205-975-6140
Office Address (if different from PI)			

3. UAB IRB Protocol Identification

3.a. Protocol Number: X080724013

3.b. Protocol Title: Structural Neuroplasticity Induced by Different Motor Therapies After Stroke

3.c. Current Status of Protocol—Check ONE box at left; provide numbers and dates where applicable

- ☐ Study has not yet begun — No participants, data, or specimens have been entered.
- ☐ In progress, open to accrual — Number of participants, data, or specimens entered:
- ☐ Enrollment temporarily suspended by sponsor
- ☐ Closed to accrual, but procedures continue as defined in the protocol (therapy, intervention, follow-up visits, etc.)
  - Date closed:
  - Number of participants receiving interventions:
  - Number of participants in long-term follow-up only:
- ☒ Closed to accrual, and only data analysis continues
  - Date closed: 2/1/10
  - Total number of participants entered: 90

4. Types of Change

Check all types of change that apply, and describe the changes in Item 5.c. or 5.d. as applicable. To help avoid delay in IRB review, please ensure that you provide the required materials and/or information for each type of change checked.

- ☐ **Protocol revision (change in the IRB-approved protocol)**
  In Item 5.c., if applicable, provide sponsor's protocol version number, amendment number, update number, etc.
- ☐ **Protocol amendment (addition to the IRB-approved protocol)**
  In Item 5.c., if applicable, provide funding application document from sponsor, as well as sponsor's protocol version number, amendment number, update number, etc.
- ☒ **Add or remove personnel**
  In Item 5.c., include name, title/degree, department/division, institutional affiliation, and role(s) in research, and address whether new personnel have any conflict of interest. See "Change in Principal Investigator" in the IRB Guidebook if the principal investigator is being changed.
  - ☒ **Add graduate student(s) or postdoctoral fellow(s) working toward thesis, dissertation, or publication**
    In Item 5.c., (a) identify these individuals by name, (b) provide the working title of the thesis, dissertation, or publication, and (c) indicate whether or not the student's analysis differs in any way from the purpose of the research described in the IRB-approved HSP (e.g., a secondary analysis of data obtained under this HSP).
- ☐ **Change in source of funding; change or add funding**
  In Item 5.c., describe the change or addition in detail, include the applicable OSP proposal number(s), and provide a copy of the application as funded (or as submitted to the sponsor if pending). Note that some changes in funding may require a new IRB application.
- ☐ **Add or remove performance sites**
  In Item 5.c., identify the site and location, and describe the research-related procedures performed there. If adding site(s), attach notification of permission or IRB approval to perform research there. Also include copy of subcontract, if applicable. If this protocol includes acting as the Coordinating Center for a study, attach IRB approval from any non-UAB site added.

☐ **Add or change a genetic component or storage of samples and/or data component—this could include data submissions for Genome-Wide Association Studies (GWAS)**
To assist you in revising or preparing your submission, please see the IRB Guidebook for Investigators or call the IRB office at 934-3789

☐ **Suspend, re-open, or permanently close protocol to accrual of individuals, data, or samples (IRB approval to remain active)**
In Item 5.c., indicate the action, provide applicable dates and reasons for action; attach supporting documentation.

☐ **Report being forwarded to IRB (e.g., DSMB, sponsor or other monitor)**
In Item 5.c., include date and source of report, summarize findings, and indicate any recommendations.

☐ **Revise or amend consent, assent form(s)**
Complete Item 5.d.

☐ **Addendum (new) consent form**
Complete Item 5.d.

☐ **Add or revise recruitment materials**
Complete Item 5.d.

☐ **Other (e.g., investigator brochure)**
Indicate the type of change in the space below, and provide details in Item 5.c. or 5.d. as applicable.
Include a copy of all affected documents, with revisions highlighted as applicable.

▶

5. Description and Rationale

In Item 5.a. and 5.b, check Yes or No and see instructions for Yes responses.
In Item 5.c. and 5.d, describe—and explain the reason for—the change(s) noted in Item 4.

☐Yes ☒No **5.a. Are any of the participants enrolled as normal, healthy controls?**
If yes, describe in detail in Item 5.c. how this change will affect those participants

☐Yes ☒No **5.b. Does the change affect subject participation, such as procedures, risks, costs, location of services, etc.?**
If yes, FAP-designated units complete a FAP submission and send to fap@uab.edu. Identify the FAP-designated unit in Item 5.c.
For more details on the UAB FAP, see www.uab.edu/cto

5.c. Protocol Changes: In the space below, briefly describe—and explain the reason for—all change(s) to the protocol.

✓ Added in SIRB. EKW

▶ We request the following change in personnel: We would like to add Michelle Haddad, MA, Graduate Research Assistant - Psychology Department, as a co-Principal Investigator.

5.d. Consent and Recruitment Changes: In the space below,
(a) describe all changes to IRB-approved forms or recruitment materials and the reasons for them;
(b) describe the reasons for the addition of any materials (e.g., addendum consent, recruitment); and
(c) indicate either how and when you will reconsent enrolled participants or why reconsenting is not necessary (not applicable for recruitment materials).

Also, indicate the number of forms changed or added. For new forms, provide 1 copy. For revised documents, provide 3 copies:
- **a copy of the currently approved document (showing the IRB approval stamp, if applicable)**
- **a revised copy highlighting all proposed changes with "tracked" changes**
- **a revised copy for the IRB approval stamp.**

▶

Signature of Principal Investigator Edward Taub Date 1/14/15

FOR IRB USE ONLY

☐ Received & Noted ☑ Approved Expedited* ☐ To Convened IRB

Marilyn Dass 1-21-15

Signature (Chair, Vice-Chair, Designee) Date

DOLA 8-22-14

Change to Expedited Category Y / N / NA

*No change to IRB's previous determination of approval criteria at 45 CFR 46.111 or 21 CFR 56.111

UAB

Project Revision/Amendment Form

Form version: June 26, 2012

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1. Today's Date	1/12/2015	9758

2. Principal Investigator (PI)

Name (with degree)	Edward Taub, PhD	Blazer ID	etaub
Department	Psychology	Division (if applicable)	
Office Address	CPM 714	Office Phone	205-934-2471
E-mail	etaub@uab.edu	Fax Number	205-975-6140

Contact person who should receive copies of IRB correspondence (Optional)

Name	Gitendra Uswatte, PhD	E-Mail	guswatte@uab.edu
Phone	205-975-5089	Fax Number	205-975-6140
Office Address (if different from PI)			

3. UAB IRB Protocol Identification

3.a. Protocol Number: X101119006

3.b. Protocol Title: Structural Brain Changes in Children with Cerebral Palsy Following CI Therapy

3.c. Current Status of Protocol—Check ONE box at left; provide numbers and dates where applicable

- ☐ Study has not yet begun — No participants, data, or specimens have been entered.
- ☐ In progress, open to accrual — Number of participants, data, or specimens entered:
- ☐ Enrollment temporarily suspended by sponsor
- ☐ Closed to accrual, but procedures continue as defined in the protocol (therapy, intervention, follow-up visits, etc.)
  - Date closed: — Number of participants receiving interventions: — Number of participants in long-term follow-up only:
- ☒ Closed to accrual, and only data analysis continues
  - Date closed: 11/1/11 — Total number of participants entered: 10

4. Types of Change

Check all types of change that apply, and describe the changes in Item 5.c. or 5.d. as applicable. To help avoid delay in IRB review, please ensure that you provide the required materials and/or information for each type of change checked.

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- ☒ **Add or remove personnel**
  In Item 5.c., include name, title/degree, department/division, institutional affiliation, and role(s) in research, and address whether new personnel have any conflict of interest. See "Change in Principal Investigator" in the IRB Guidebook if the principal investigator is being changed.
  - ☒ **Add graduate student(s) or postdoctoral fellow(s) working toward thesis, dissertation, or publication**
    In Item 5.c. (a) identify these individuals by name; (b) provide the working title of the thesis, dissertation, or publication; and (c) indicate whether or not the student's analysis differs in any way from the purpose of the research described in the IRB-approved HSP (e.g., a secondary analysis of data obtained under this HSP).
- ☐ **Change in source of funding; change or add funding**
  In Item 5.c., describe the change or addition in detail, include the applicable OSP proposal number(s), and provide a copy of the application as funded (or as submitted to the sponsor if pending). Note that some changes in funding may require a new IRB application.

☐ **Add or remove performance sites**
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☐ **Report being forwarded to IRB (e.g., DSMB, sponsor or other monitor)**
In Item 5.c., include date and source of report, summarize findings, and indicate any recommendations.

☐ **Revise or amend consent, assent form(s)**
Complete Item 5.d.

☐ **Addendum (new) consent form**
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☐ **Other (e.g., investigator brochure)**
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▶

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☐ Yes ☒ No **5.b. Does the change affect subject participation, such as procedures, risks, costs, location of services, etc.?**
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For more details on the UAB FAP, see www.uab.edu/clo.

5.c. Protocol Changes: In the space below, briefly describe—and explain the reason for—all change(s) to the protocol. ✓ Added in SIRB. ekw

▶ We request the following change in personnel: We would like to add Michelle Haddad, MA, Graduate Research Assistant - Psychology Department, as a co-Principal Investigator.

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(a) describe all changes to IRB-approved forms or recruitment materials and the reasons for them;
(b) describe the reasons for the addition of any materials (e.g., addendum consent, recruitment); and
(c) indicate either how and when you will reconsent enrolled participants or why reconsenting is not necessary (not applicable for recruitment materials).

Also, indicate the number of forms changed or added. For new forms, provide 1 copy. For revised documents, provide 3 copies:
- **a copy of the currently approved document (showing the IRB approval stamp, if applicable)**
- **a revised copy highlighting all proposed changes with "tracked" changes**
- **a revised copy for the IRB approval stamp.**

▶

Signature of Principal Investigator Edward Taub Date 1/14/15

FOR IRB USE ONLY

☐ Received & Noted ☑ Approved Expedited* ☐ To Convened IRB

Marilyn Das 1-21-15

Signature (Chair, Vice-Chair, Designee) Date

DOLA 9-19-14

Change to Expedited Category Y / N / NA

*No change to IRB's previous determination of approval criteria at 45 CFR 46.111 or 21 CFR 56.111