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Increased Brain Sensorimotor Network Activation after Incomplete Spinal Cord Injury

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Abstract

After complete spinal cord injury (SCI), activation during attempted movement of paralyzed limbs is sharply reduced, but after incomplete SCI—the more common form of human injury—it is unknown how attempts to move voluntarily are accompanied by activation of brain motor and sensory networks. Here, we assessed brain activation during ankle movement in subjects with incomplete SCI, among whom voluntary motor function is partially preserved. Adults with incomplete SCI ($n = 20$) and healthy controls ($n = 15$) underwent functional magnetic resonance imaging that alternated rest with 0.3-Hz right ankle dorsiflexion. In both subject groups, ankle movement was associated with bilateral activation of primary and secondary sensory and motor areas, with significantly ($p < 0.001$) greater activation in subjects with SCI within right hemisphere areas, including primary sensorimotor cortex and pre-motor cortex. This result was further evaluated using linear regression analysis with respect to core clinical variables. Poorer locomotor function correlated with larger activation within several right hemisphere areas, including pre- and post-central gyri, possibly reflecting increased movement complexity and effort, whereas longer time post-SCI was associated with larger activation in left post-central gyrus and bilateral supplementary motor area, which may reflect behaviorally useful adaptations. The results indicate that brain adaptations after incomplete SCI differ sharply from complete SCI, are related to functional behavioral status, and evolve with increasing time post-SCI. The results suggest measures that might be useful for understanding and treating incomplete SCI in human subjects.

Keywords: functional MRI; gait; motor cortex; sensory cortex; spinal cord injury

Introduction

Spinal cord injury (SCI) is a devastating neurological condition affecting over 1.2 million people in the United States, at a cost exceeding $40 billion annually.[1] SCI is associated with substantial motor and sensory loss below the injury site[2] attributed to interruption of ascending and descending tracts.[3,4] Because of the profound impact that SCI has, numerous restorative therapies focused on improved behavioral recovery are under study.[5–11] These developments underscore the need to better understand factors affecting behavioral recovery post-SCI.

One key set of questions related to behavioral recovery post-SCI focuses on changes in brain networks during attempted movement. The utility of restored connectivity across a spinal cord lesion may be limited by changes in brain function subsequent to SCI. Indeed, several reports have described reorganization of brain sensorimotor circuits post-SCI.[3,12–19] However, most of the human literature has focused on complete SCI, where studies generally report reduced activity of motor and sensory brain networks. Considerably less is known about how the brain adapts in the context of incomplete SCI, despite the fact that incomplete SCI is twice as prevalent as complete SCI.[1] Voluntary motor function is partially preserved after incomplete SCI, which suggests that adaptive changes in the function of brain sensorimotor networks would differ sharply from those described after complete SCI. There have been few studies examining these questions, however,[20,21] and thus knowledge concerning brain function during voluntary movement in subjects with incomplete SCI is scant.

To address these issues, we studied brain function in 20 subjects with incomplete SCI during voluntary ankle dorsiflexion movement, which plays a critical role in gait[22] and which has established validity for studying gait-related rehabilitative topics.[23,24] The goals of the present study were to 1) assess brain activation during voluntary movement in individuals with incomplete SCI as compared to age- and sex-matched healthy controls, 2) determine how changes in brain activation evolve with increasing time post-SCI,

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and 3) assess how brain activation varies in relation to two established measures of locomotor function post-SCI. We show that individuals with incomplete SCI exhibit increased brain sensorimotor activation during voluntary movement, that features of this activation vary in relation to key clinical variables (time post-SCI and locomotor status), and consider which adaptations reflect useful adaptations versus response to distress. The results clearly distinguish brain function after incomplete SCI from findings reported after complete SCI and emphasize the value that measures of brain function have for studying therapeutic interventions.

Methods

Subjects

Two cohorts of subjects were enrolled in this study: a group with incomplete SCI and a group of healthy nonimpaired, age-matched, sex-matched controls. The subjects were recruited from local hospitals and rehabilitation centers. Each subject provided informed consent in accord with institutional review boards at the University of California, Irvine (Irvine, CA) and the University of Cincinnati (Cincinnati, OH). Table 1 describes entry and exclusion criteria for individuals with SCI. Study criteria for nonimpaired individuals were age >18 years and no major neurological disease. Before magnetic resonance imaging (MRI) scanning, all subjects underwent a screening process and behavioral assessment, and then reviewed the functional MRI (fMRI) protocol.

Table 1. Inclusion and Exclusion Criteria for Individuals with SCI

Inclusion criteria:
1) Age ≥18 years
2) Incomplete SCI (ASIA grade C or D), experienced >1 month before enrollment
3) Motor grade 1–3 in the quads, hamstrings, and hip flexors and ability to ambulate with at least maximal assist
4) Normal range of motion (within functional limits for ambulation) in the lower extremities
5) As defined by the International Standards for Neurological Classification of SCI: Motor Incomplete. Motor function is preserved below the neurological level, and more than half of key muscle functions below the single neurological level of injury have a muscle grade less than 3 (grades 0–2) or at least half (half or more) of key muscle functions below the neurological level of injury have a muscle grade ≥3.
6) Able to ambulate at least 10 m with one-person assistance or assistive device or both
7) Medically stable
8) Stable dosage of any antispasticity medications expected for duration of study
9) English speaking

Exclusion criteria:
1) Excessive spasticity in the lower limbs (score ≥3 on modified Ashworth spasticity scale)
2) Excessive pain in lower limbs (score ≥8 during active exercise on Visual Analog Scale)
3) History of moderate-to-severe osteoporosis, heterotopic ossification, or recent lower-extremity fracture
4) Abnormalities of attention or cognitive function sufficient to interfere with study procedures
5) Enrolled in a current rehabilitation program
6) Contraindication to MRI
7) Current major depression

Table 1 provides a list of inclusion and exclusion criteria for subjects with spinal cord injury who were enrolled into this study.

SCI, spinal cord injury; ASIA, American Spinal Injury Association; MRI, magnetic resonance imaging.

Screening process

Screening focused on entry criteria and included review of medical history, completion of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition test for depression,[25] review of MRI exclusion/inclusion criteria, assessment of lower extremity range of motion, evaluation with the Visual Analog Scale for pain,[26] evaluation with the modified Ashworth spasticity scale, and evaluation with the American Spinal Injury Association (ASIA) Impairment Scale.[27]

Behavioral assessments

Subjects with SCI underwent motor, sensory, and functional testing before the fMRI. All assessments were administered by trained investigators during a single visit (day 1) approximately 1 week before the fMRI session, were standardized across the two study sites, and included medical history, handedness, footedness,[28] and degree of independence using the Spinal Cord Independence Measure (SCIM).[29] In addition, the following assessments were obtained.

International Standards for Neurological Classification of Spinal Cord Injury exam. Neurological assessment was performed consistent with the recommendation of the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI),[27] which assesses bilateral upper and lower extremities. Injury characteristics were classified according to neurological level of injury, ASIA motor score, ASIA sensory score, and overall ASIA Impairment Scale grade (A–D). All study team assessors were fully trained in accord with the ISNCSCI guidelines and had extensive clinical experience using the tool.

Performance Oriented Mobility Assessment. The Tinetti Performance Oriented Mobility Assessment (POMA) scoring scale is broken down into two parts: a gait portion (maximum score 12) consisting of initiation of gait, step length, step height, step symmetry, step continuity, path, trunk stability, and walking stance; and a balance portion (maximum score 16) consisting of sitting balance, rising, attempting to rise, immediate standing balance, nudging response, eyes closed balance, and turning 360 degrees while sitting down.[30,31] Higher POMA scores correspond to better motor function.

GAITRite analysis

Spatial and temporal parameters of gait were measured with the GAITRite mat (CIR Systems, Inc., Clifton, NJ) and used to determine self-selected gait velocity and cadence. The GAITRite mat is 460 cm long with an active sensor area 366 cm in length and 61 cm in width and samples at 80 Hz.[32] Each subject was instructed to walk at a self-selected gait for a total of two trials, after which data from these two trials were averaged. Individuals were allowed use durable medical equipment, if needed, to ambulate safely.

Magnetic resonance imaging acquisition

MRI data were acquired using a 3.0 Tesla (T) Phillips scanner at the University of California, Irvine, and a 4.0-T Varian Unity INOVA whole-body scanner at University of Cincinnati. During scanning, each subject wore bilateral padded MRI-compatible frictionless ankle splints[24] that restricted movement to 10 degrees of ankle dorsiflexion/plantarflexion, and that had a pedestal lifting foot/calf above the scanner bed, thereby preventing lateral leg rotation or postural compensation. Velcro straps were placed across the dorsal surface of each splint to hold the heel and forefoot in

place. Pillows were used to keep knees flexed at 15 degrees bilaterally. An observer confirmed that each subject correctly performed the task during each fMRI session.

Acquisition included a whole-brain, high-resolution T1-weighted volumetric scan (150 slices of 1-mm thickness with no gaps; repetition time [TR], 8.4 ms; echo time [TE], 3.9 ms; matrix, 256×200; and field of view [FOV], 256×204 mm) as well as three functional scans collected using a T2*-weighted gradient-echo sequence for blood-oxygenation-level–dependent contrast (TR = 2000 ms; TE = 30 ms; 26 slices with thickness 4 mm plus 1-mm interslice gap; FOV = 240×240 mm; and matrix, 96×95). Each of the three fMRI runs was 96 sec (48 brain volumes), during which subjects viewed a video that guided ankle movements. The video cued subjects to begin movement when the guide turned green and cued subjects to rest when the guide turned red. Each run consisted of 24-sec epochs that alternated rest with 0.3-Hz right ankle dorsiflexion. During the fMRI, a study team member observed the subject to assess compliance.

Statistical analysis

Behavioral assessments were compared between the two groups using Student's *t*-test and Fisher's exact test. Parametric statistical methods were used for measures for which the normality assumption was valid, using raw or transformed values; otherwise, nonparametric methods were used.

Functional MRI data were analyzed using SPM 8 (www.fil.ion.ucl.ac.uk/spm/) at one single site. The first two volumes from each run were discarded from all scans to allow for tissue equilibration. Pre-processing steps included realignment to the first image, co-registration to the mean echo echoplanar imaging (EPI) image, normalization to the standard Montreal Neurological Institute (MNI) EPI template, and spatial smoothing (full width at half maximum = 8 mm). Data were visually inspected for head movement after the realignment step. Images at rest were contrasted with images during right foot movement for each subject. For each subject, any fMRI run with excessive head motion in any of the three planes was excluded. We performed whole-brain analysis, examining voxels with threshold $p < 0.001$ without correction for multiple comparisons, assessing those clusters with significance of $p < 0.05$, uncorrected for multiple comparisons; if no activation was found using a threshold of $p < 0.001$ for these voxel-wise analyses, analysis was repeated using the exploratory threshold of $p < 0.01$. First, a one-sample *t*-test was used to characterize activation in each of the two subject groups. Next, a two-sample *t*-test examined differences between the two groups. Finally, correlations were calculated to delineate relationships between cortical activity and target assessments related to gait and ASIA scores. To understand whether having two sites affected results, fMRI analyses were repeated adding site as a covariate. In order to derive a between-group effect size, percent signal change was extracted from the left foot area of primary motor cortex (M1), at a threshold of $p < 0.001$.

Results

Clinical features of study enrollees are presented in Table 2. A total of 20 subjects with incomplete SCI and 15 healthy controls were enrolled. The subjects with SCI varied widely in time post-injury, averaging 7.8 years, ranging from 4 months to 31 years. In 15, the incomplete SCI was attributed to trauma, with varied causes in the other 5, including infection and inflammation. All subjects completed the three fMRI runs and executed isolated right foot movements as instructed. Data from 3 subjects with SCI were removed because of excess head movements.

Table 2. Subject Characteristics and Clinical Data

			Subjects with SCI, by site	
	Healthy controls (all subjects)	*Subjects with SCI (all subjects)*	*UC Irvine*	*U Cincinnati*
n	15	20	16	4
Age (years)	51 ± 19	52 ± 13	51.6 ± 13.8	53.3 ± 8.3
Sex (F/M)	3/12	4/16	14	2
Handedness (R = 2; L = –2)	1.9 ± 0.3	1.5 ± 0.9	1.6 ± 0.7	1.3 ± 1.5
Footedness (R = 2; L = –2)	1.4 ± 0.6	1.3 ± 0.9	1.3 ± 0.9	1.5 ± 1.0
Self-selected gait velocity (m/s)	1.35 ± 19.40	0.54 ± 0.35*	0.62 ± 0.33	0.22 ± 0.19†
Cadence (steps/min)	107 ± 11	63 ± 27*	71 ± 24	34 ± 16†
Time post-SCI (months)		93 ± 102	101 ± 110	55 ± 47
SCIM		78 ± 13	80 ± 13	72 ± 3
ISNCSCI				
ASIA (C)		3	2	1
ASIA (D)		17	14	3
ASIA Motor		80 ± 9	80 ± 10	78 ± 9
ASIA Light Touch		78 ± 18	77 ± 17	83 ± 20
ASIA Pin Prick		74 ± 19	71 ± 18	86 ± 17
POMA				
POMA balance		10 ± 5	10 ± 5	11 ± 4
POMA gait		6 ± 3	6 ± 3	5 ± 3
POMA total		16 ± 7	16 ± 7	16 ± 6

Table 2 lists characteristics of study enrollees. Values are mean ± standard deviation. Neurological level for subjects with SCI was C2 (in 2), C3 (3), C4 (1), C5 (1), C6 (4), C8 (2), T1 (2), T4 (3), T10 (1), and L2 (1). All subjects were right-footed except for 1 healthy control and 2 subjects with SCI who were ambipedal, and 1 subject with SCI who was left-footed.[28] POMA total score is the sum of balance and gait scores. Of the 15 healthy control subjects, 2 were studied at University of Cincinnati and 13 were studied at University of California, Irvine.

*$p < 0.0001$, all healthy controls versus all subjects with SCI. None of the measures differed according to enrollment site when examining all subjects.

†$p < 0.05$ when comparing only subjects with SCI across enrollment sites.

F, female; M, male; R, right; L, left; SCI, spinal cord injury; SCIM, Spinal Cord Independence Measure; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; ASIA, American Spinal Injury Association; POMA, Performance Oriented Mobility Assessment; UC, University of California; U, University.

During right ankle movements, healthy control subjects showed activation in a network that included pre-central gyrus, post-central gyrus, dorsal premotor cortex, supplementary motor area (SMA), and inferior parietal lobule bilaterally ($p < 0.001$; Fig. 1A), with the total volume of significant activation across the brain being 162 cc. In subjects with SCI, the pattern of activation was very similar to that present in healthy controls; however, the total volume of significant activation across the brain (232 cc) was notably larger ($p < 0.001$; Fig. 1B). A two-sample *t*-test revealed significant ($p < 0.001$) differences in activation between the two subject groups, with subjects with SCI exhibiting larger activation than controls, particularly in right precentral gyrus, post-central gyrus, dorsal pre-motor cortex, and SMA bilaterally (Fig. 1C). In several of these brain regions, greater activation was found with increased time post-injury ($p < 0.001$; Table 3; Fig. 2A). Note that no brain area showed greater activation with less time post-injury, and there were no areas where control subjects showed significantly greater activation compared to subjects with SCI, at $p < 0.001$ or at the exploratory threshold of $p < 0.01$. Findings for the magnitude of activation (percent signal change in the left M1 foot area) showed a trend in the same direction as the whole-brain analyses, with SCI showing a task-related signal increase of $1.05 \pm 0.47\%$ as compared

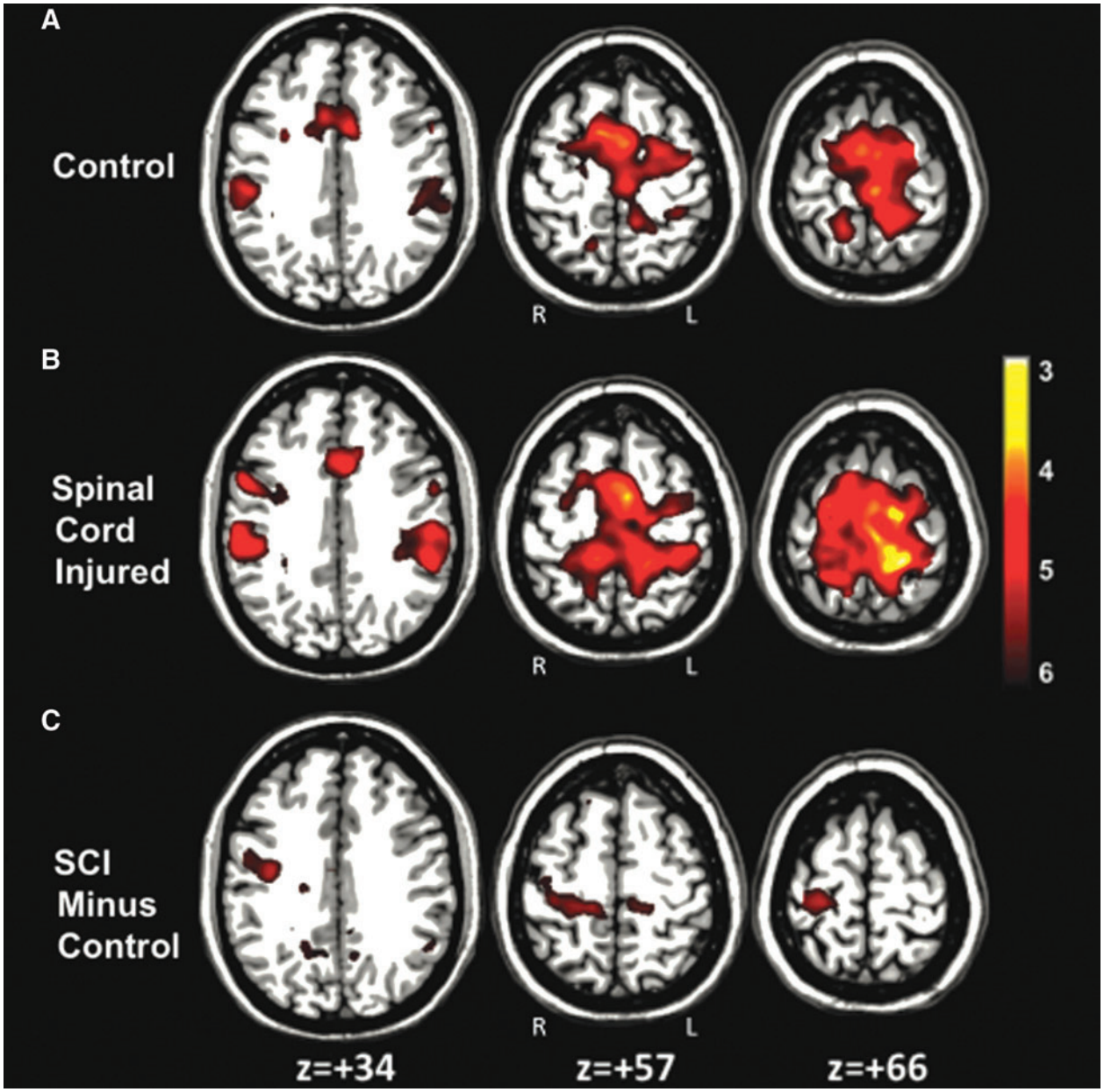

FIG. 1. Areas of significant ($p < 0.001$) activation during 0.3-Hz right foot dorsiflexion are depicted in (**A**) healthy control subjects and in (**B**) subjects with incomplete SCI. Although the pattern of activation was generally similar overall across the two groups of subjects, the volume of significant activation was larger in subjects with SCI (232 vs. 162 cc). In (**C**), specific areas are presented in which brain activation was significantly larger among subjects with SCI as compared to healthy control subjects. R = right; L = left. z values are the axial slice level within Montreal Neurological Institute (MNI) standard stereotaxic space. Color bar indicates the z score for the contrast of interest. SCI, spinal cord injury.

Table 3. Clinical Characteristics That Correlated with Larger Brain Activation

Clinical characteristic	*Activation volume (cc)*	*Activation coordinates*	*Activation site*
Greater time post-injury			
(see Fig. 2A)	2.4	−52, −30, 44	Left post-central gyrus and inferior parietal lobule
	1.4	12, −6, 62	Left and right supplementary motor area
Higher gait velocity			
(see Fig. 2B)	2.9	−36, 42, 34	Left dorsolateral pre-frontal cortex
	2.8	−58, −24, 40	Left post-central gyrus and inferior parietal lobule
	2.7	42, 30, 36	Right dorsolateral pre-frontal cortex
Higher POMA gait score			
	2.4	44, 42, 24	Right dorsolateral pre-frontal cortex
Lower POMA gait score			
(see Fig. 2C)	11.2	12, −44, −2	Right parahippocampal gyrus
	10.3	34, −6, −2	Right posterior putamen
	7.8	8, −22, 50	Right pre- and post-central gyri

Table 3 presents features whereby increased brain activation during right ankle movement correlated with target clinical characteristics. Activation was assessed at $p < 0.001$ for time post-injury and $p < 0.01$ for the gait measures. Higher gait velocity and POMA gait scores indicate better motor function. Location coordinates (x, y, z) correspond to activation peak in Montreal Neurological Institute (MNI) standard stereotaxic space. See also Figure 2B, C.
POMA, Performance Oriented Mobility Assessment.

to that found in healthy controls (0.80 ± 0.32; $p = 0.09$); this describes a medium effect size, of 0.60. We evaluated site of MRI acquisition as a covariate, and results were not affected.

Regression analyses of subjects with SCI revealed that activation varied in relation to some, but not all, target assessments. Higher gait velocity was associated with greater activation ($p < 0.01$) within left post-central gyrus, left inferior parietal lobule, and dorsolateral pre-frontal cortex bilaterally (Table 3; Fig. 2B); no area showed greater activation with lower gait velocity. For the POMA gait assessment ($p < 0.01$), higher scores correlated with greater activation within right dorsolateral pre-frontal cortex and with lesser activation within several areas in the right hemisphere, including right pre- and post-central gyri (Table 3; Fig. 2C); POMA gait scores were partly related to gait velocity ($r^2 = 0.36$; $p = 0.01$). ASIA motor score, ASIA total sensory score, and SCI neurological injury level did not show either a positive or negative correlation with degree of activation in any brain area, at $p < 0.001$ or at $p < 0.01$.

Discussion

A number of therapeutic developments highlight the need to better understand the effects that SCI has on the processes underlying voluntary movement. Given that most survivors of SCI live for decades post-injury, the effect of time on behavioral outcomes is also important. To date, few studies examining brain adaptation to SCI have focused on incomplete SCI despite this being twice as common as complete SCI,[1] and available reports are small and inconsistent. The present study examined brain function during voluntary ankle dorsiflexion in subjects with incomplete SCI and found that movement was associated with recruitment of the same brain networks as healthy controls, but to a larger extent. Several brain sites showed increased activation, and none showed decreased activation, with greater time post-SCI. Brain activation was greatest in those with faster gait, suggesting that these changes represent favorable adaptations. Together, results indicate that brain adaptations after incomplete SCI differ sharply from complete SCI,[14,15] are behaviorally relevant, and evolve over time.

Subjects with incomplete SCI showed brain activation that was similar in pattern, but larger in extent, as compared to healthy controls. When healthy subjects performed right ankle dorsiflexion, significant sensorimotor network activation was present bilaterally. This is consistent with past studies of unilateral ankle movement, which have reported bilateral activation in sensorimotor areas.[24,33–35] When subjects with incomplete SCI made the same movements, activation was in a similar pattern, but 43% larger, especially within right hemisphere sensorimotor regions (pre-central gyrus, post-central gyrus, and dorsal pre-motor cortex) as well as SMA bilaterally. This pattern of activation among subjects with incomplete SCI—recruitment of brain sensorimotor areas ipsilateral to limb movement plus SMA—may reflect increased movement complexity and effort[36–38] and has been described as a compensatory response in other forms of incomplete central nervous system (CNS) motor system injury, such as stroke,[39,40] multiple sclerosis (MS),[41,42] and early amyotrophic lateral sclerosis.[43,44] The current findings are concordant with the limited data available regarding brain activation during voluntary movement of infralesional muscles after incomplete SCI. We previously studied 7 patients with incomplete SCI during finger tapping[20] and found increased fMRI activation within sensorimotor and pre-motor areas, although these subjects had inflammatory rather than traumatic SCI. Lundell and colleagues[21] reported fMRI findings from 17 subjects with incomplete SCI during ankle movement and found that overall activation was more diffuse as compared to healthy controls; image analysis was limited in this study; however, because only descriptive group comparisons were provided, without formal statistical analysis. Other studies have combined complete and incomplete SCI.[3,45] In sharp contrast with past studies of subjects with complete SCI, which describe decreased brain activation during attempted voluntary movement,[14,15] current findings emphasize a distinct pattern of increased brain activation after incomplete SCI.

Gait is a core clinical measure in the context of SCI,[46] and in addition to activation differences compared to healthy individuals, current results suggest differences in brain organization in relation to level of locomotor function after incomplete SCI. A majority of subjects with incomplete SCI regain some degree of ambulatory function; however, gait-related abnormalities are common and thus locomotor training is a key therapeutic target.[46,47] Gait velocity in healthy controls was faster than subjects with incomplete SCI (Table 2). Among subjects with SCI, the fastest walkers had the greatest activation within several brain regions, including left postcentral gyrus and bilateral dorsolateral prefrontal cortex (Table 3), suggesting that increased activity in these regions

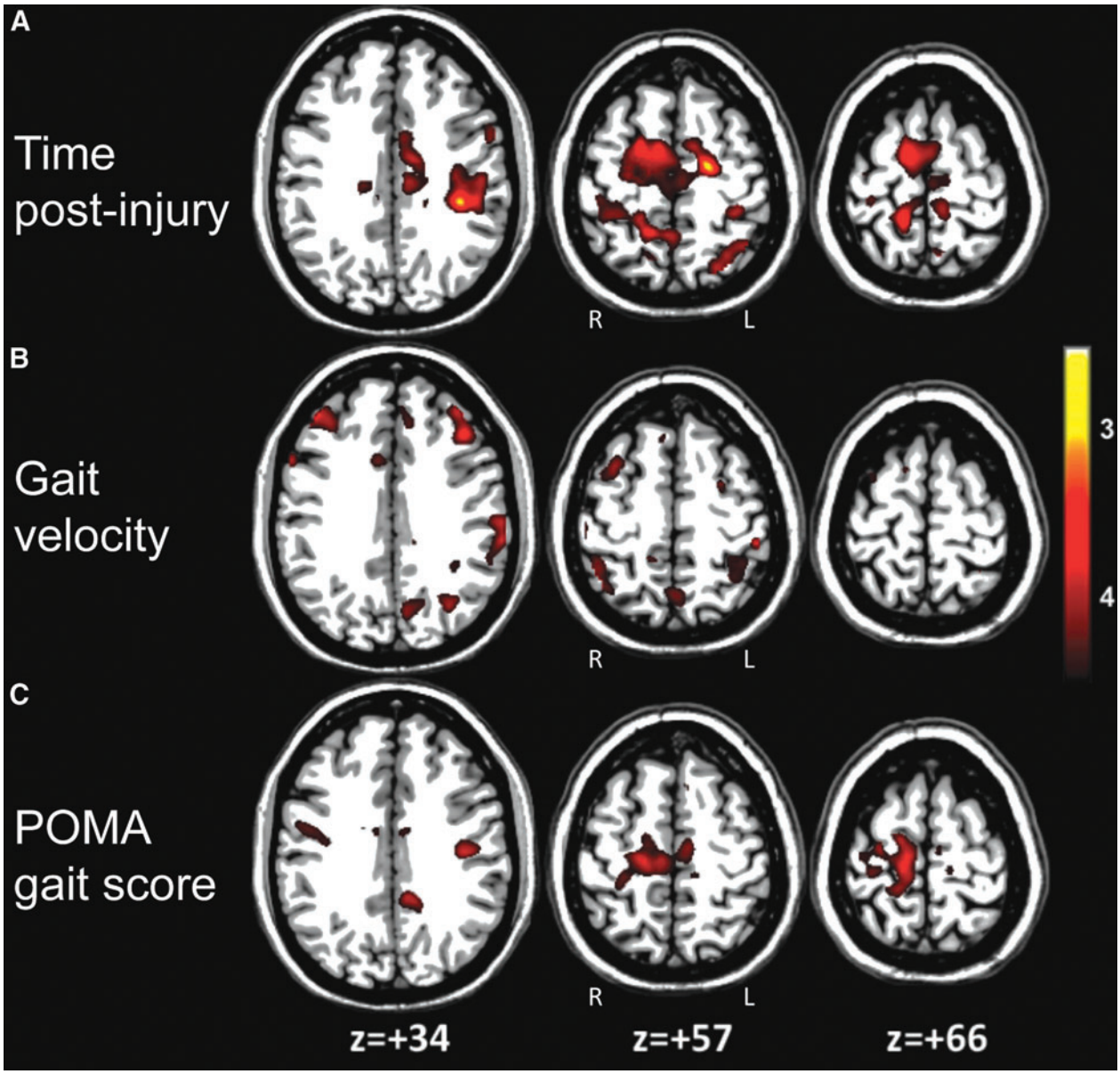

FIG. 2. Among subjects with incomplete SCI, brain activation during right ankle movement correlated with several key clinical measures. (**A**) Brain activation was increased in parallel with greater time post-injury within supplementary motor area plus left frontoparietal regions. (**B**) Faster self-selected gait velocity was associated with greater activation within left parietal areas, including postcentral gyrus, plus dorsolateral pre-frontal cortex bilaterally. The data therefore indicate that brain activation in these areas during right ankle movement corresponds with success in executing movement. (**C**) Poorer gait function (lower POMA gait score) correlated with increased activation within several right hemisphere regions, including pre- and post-central gyri. R = right; L = left. z values are the axial slice level within Montreal Neurological Institute (MNI) standard stereotaxic space. Color bar indicates the z score for the contrast of interest. POMA, Performance Oriented Mobility Assessment; SCI, spinal cord injury.

provided additional cortical resource toward sensory processing and cognitive/attentional aspects of voluntary movement.[48,49] The POMA gait assessment considers numerous gait-related behaviors, such as initiation, symmetry, and stance, and so is a more-complex reflection of gait function as compared to gait velocity alone. Better POMA gait scores correlated with increased activation in right dorsolateral pre-frontal cortex, similar to gait velocity findings, as well as with decreased activation within several right hemisphere regions, including precentral and postcentral gyri (Table 3; Fig. 2C). Increased recruitment of sensorimotor cortex ipsilateral to limb movement may reflect greater movement complexity/effort and likely reflects a common compensatory response to CNS injury, as has been described in relation to locomotor function specifically.[50–52] In the current cohort, the fact that subjects with the best POMA gait scores had the least reliance on right sensorimotor cortex activity during right foot movement further supports the idea that these features of brain activation may be more a sign of distress than a sign of useful compensatory adaptation. On average participants were strongly right-handed and right-footed, so the increased right sensorimotor recruitment associated with SCI state (and which was larger among SCI in relation to POMA gait) is the nondominant hemisphere. Increased recruitment of nondominant

sensorimotor areas during dominant limb movement is observed post-CNS injury (MS, stroke, and SCI) and in controls with increasing movement speed and complexity.[39–41,53] Whereas several features of brain activation correlated with gait measures (velocity, POMA gait score), none correlated with impairment measures (injury level, ASIA motor score, and ASIA sensory score), which are simple tabulations of total deficit. This constellation of findings lends further credence to ankle dorsiflexion paradigm as a valid probe of locomotor function.[15,23,24,34,54,55]

Time is also a major covariate for understanding the effects of SCI on the CNS,[56] but to date few studies have examined its impact on activation of brain motor networks during attempts to move voluntarily. Time post-injury is a key distinguishing factor in relation to locomotor function after incomplete SCI,[47,57] which likely reflects many of the changes that evolve during the years post-SCI, such as altered cardiac function, bone density, muscle changes, and changes in autonomic nervous system function.[58–60] In the current study, increased time after incomplete SCI was associated with increased activation in brain regions, including post-central gyrus and SMA (Table 3). These results indicate that with longer time after incomplete SCI, greater cerebral resource is needed to generate voluntary movement. The finding that brain activation evolves over time post-SCI echoes the findings of Jurkiewicz and colleagues,[61] who performed serial fMRI scans in 6 quadriparetic subjects with wide-ranging deficits during the first year post-SCI and found that over time activation tended to increase in primary motor cortex and decrease in other sensorimotor cortices. Other studies have focused on supralesional (unaffected) limbs and also found changes with time post-SCI. Sabre and colleagues found that the extent of motor cortex activation during hand movement increased with time post-SCI in a population containing subjects with either complete or incomplete SCI.[45] Lotze and colleagues also studied a population containing subjects with either complete or incomplete SCI and described shifts in somatotopic map organization of precentral gyrus that became more exaggerated with time.[62] Rao and colleagues reported similar findings in the post-central gyrus of rhesus monkeys.[63] Although these metrics and populations differ from the current study, they do support that the functional anatomy in the brain for generating voluntary movement evolves with time post-SCI, a finding that underscores the potential importance of continued rehabilitative training for maintaining neural networks over the years post-SCI.

Improving locomotor function is a key therapeutic target for subjects with SCI,[46,47] a goal aided by the direct correspondence between preclinical locomotor endpoints[64–68] and clinical gait-related endpoints. The current study examined brain activity during ankle dorsiflexion, which plays a critical role at several points in the gait cycle,[22] and which has established validity for investigating gait-related rehabilitative strategies.[23,24] Subjects with incomplete SCI showed supranormal activation that increased with time. Features of brain activation in this group, such as extent of left post-central gyrus activity, may represent favorable adaptations, whereas other features, such as right sensorimotor activity, may reflect distress. Strengths of the current study include focusing on individuals with incomplete SCI, who have received limited study despite representing 66% of the SCI community,[1] and a focus on infralesional muscles, a major therapeutic target. Other strengths include attention to key covariates, such as time post-SCI and gait velocity. One limitation of the study is that, despite restricting enrollment to individuals with ASIA C or D (motor/sensory incomplete) SCI, motor abilities nevertheless spanned a wide range (Table 2). A second limitation is that some exploratory analyses used a more-liberal threshold to define significance. The choice of statistical threshold in fMRI data analysis is a complex decision influenced by many factors. Use of lower thresholds improves sensitivity,[69] but can come at a price, such as spatial specificity, and so when a study has very high power, there may be advantages to incorporating additional analyses, such as voxel-wise correction methods.[70] However, use of unnecessarily high thresholds reduces sensitivity and can lead to unacceptably high rates of false-negative results.[71] A third limitation for this study is potential issues related to the focus on traumatic SCI, and not addressing injury to the spinal cord attributed to other etiologies, such as inflammation or infection. In stroke and other forms of acute CNS injury, measures of brain function show increasing promise to inform therapeutic approaches and clinical trial methodology,[72,73] for example, to serve as biomarkers or to stratify patients. The current study supports extension of this approach to the setting of incomplete SCI.

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