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Residual Descending Motor Pathways Influence Spasticity after Spinal Cord Injury

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Abstract

Objective: Spasticity is one of the most common symptoms manifested in humans with spinal cord injury (SCI). The neural mechanisms contributing to its development are not yet understood. Using neurophysiological and imaging techniques, we examined the influence of residual descending motor pathways on spasticity in humans with SCI.

Methods: We measured spasticity in 33 individuals with motor complete SCI (determined by clinical examination) without preservation of voluntary motor output in the quadriceps femoris muscle. To examine residual descending motor pathways, we used magnetic and electrical stimulation over the leg motor cortex to elicit motor evoked potentials (MEPs) in the quadriceps femoris muscle and structural magnetic resonance imaging to measure spinal cord atrophy.

Results: We found that 60% of participants showed symptoms of spasticity, whereas the other 40% showed no spasticity, demonstrating the presence of 2 clear subgroups of humans with motor complete SCI. MEPs were only present in individuals who had spasticity, and MEP size correlated with the severity of spasticity. Spinal cord atrophy was greater in nonspastic compared with spastic subjects. Notably, the degree of spared tissue in the lateral regions of the spinal cord was positively correlated with the severity of spasticity, indicating preservation of white matter related to motor tracts when spasticity was present.

Interpretation: These results support the hypothesis that preservation of descending motor pathways influences spasticity in humans with motor complete SCI; this knowledge might help the rehabilitation and assessment of people with SCI.

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Author Contributions

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Potential Conflicts of Interest

Nothing to report.

Spasticity, commonly defined as a velocity-dependent increase in muscle tone due to the exaggeration of stretch reflexes,¹ manifests in >60% of people with spinal cord injury (SCI).²⁻⁵ Animal models of SCI showed that, after the injury, spinal motoneurons become highly excitable and sensitive to descending neurotransmitters.^{6,7} Animals with spinal cord transection showed more spasticity when residual spinal brainstem-derived monoamines were present.^{8,9} Lesions of descending motor tracts are also accompanied by increased afferent sprouting at the spinal cord level leading to symptoms of hyperreflexia.^{10,11} Although spasticity relates to an imbalance between inhibitory and excitatory supraspinal inputs controlling segmental networks,¹² the extent to which descending residual connections influence spasticity in humans with SCI remains poorly understood.

Self-reported questionnaires indicate that people with incomplete SCI have a higher prevalence of spasticity compared to people with complete SCI.²⁻⁵ However, the same studies also report higher spasticity in complete compared with incomplete SCI participants depending on the severity of the injury and symptoms tested. Clinical spasticity examinations revealed either similarities or discrepancies in the ability to elicit spasticity in people with complete and incomplete SCI depending on the severity of the injury and symptoms tested.^{2,4} A consistent observation across studies is that a number of individuals with SCI, including a diagnosis of clinically complete SCI, show spasticity.³⁻⁵ Another important observation is that postmortem analysis of spinal cords showed that ~60 to 70% of individuals with a diagnosis of clinically complete SCI showed evidence of some continuity of central nervous system (CNS) tissue across the injured segments.^{13,14} In agreement, neurophysiological studies showed that ~60 to 70% of individuals with a diagnosis of clinically complete SCI showed evidence of continuity of CNS tissue across the injured segments.¹⁵ Furthermore, in individuals with incomplete SCI, modulation of the excitability of descending motor pathways by either noninvasive brain stimulation^{16,17} or exercise training¹⁸ can change the degree of spasticity. Thus, we hypothesized that the presence of spasticity reflects the presence of descending motor pathway connectivity in humans with motor complete SCI.

To test our hypothesis, we examined spasticity using the Modified Ashworth Scale (MAS) and the pendulum test in individuals with chronic motor complete SCI. To examine residual descending pathways, we used magnetic and electrical stimulation over the leg motor cortex to elicit motor evoked potentials (MEPs) in the quadriceps femoris muscle and magnetic resonance imaging (MRI) to measure spinal cord atrophy. H-reflexes and maximal motor responses (M-max) in the quadriceps muscle were also measured in all participants.

Subjects and Methods

Subjects

Thirty-three individuals with SCI (mean age = 42.24 ± 14.65 years, 4 females; Table) and 27 age-matched controls (mean age = 41.93 ± 12.44 years, 6 females; $p = 0.75$) participated in the study. All participants gave informed consent to the experimental procedure, which was approved by the local ethics committee at the University of Miami. Participants with SCI had a chronic injury (> 1 year) and were classified using the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) examination as having a C2-

T12 SCI and by the American Spinal Injury Association Impairment Scale (AIS) as AIS A (n = 27) or AIS B (n = 6). Thirteen SCI individuals were under antispastic medication (baclofen and/or gabapentin and/or tizanidine; see Table). All subjects were asked to perform voluntary knee extension or hip flexion, but none of them was able to exert voluntary electromyographic (EMG) activity in the quadriceps femoris muscle. The degree of spasticity in the quadriceps femoris was examined in all SCI participants by using the MAS and the pendulum test.

Modified Ashworth Scale

This clinical scale measures resistance encountered during manual passive muscle stretching using a 6-point ordinal scale (0 = no increase in tone, 1/+1 = slight increase in tone with a catch and release or minimal resistance at the end or less than half of the range of movement, respectively, 2 = more marked increased tone through most of the range of movement but affected parts easily moved, 3 = considerable increase in tone and passive movement difficult, and 4 = affected part(s) rigid¹⁹). During testing, subjects were lying in a semisupine position with the trunk at an angle of 30° of flexion. This neutral position helps to avoid increases in spasticity related to the stretching of the rectus femoris or decreases in spasticity related to less stretched and more relaxed muscle.²⁰ The same rater performed all MAS assessments. Both legs were tested, and the leg with the higher MAS score was used for all measurements. Participants with a MAS score of 1 or +1 were grouped together as MAS 1. Participants were separated into spastic (MAS = 1, 2, 3, and 4, n = 20) and nonspastic (MAS = 0, n = 13) groups according to the MAS scores.

Pendulum Test

Knee angle was measured using a 3-dimensional (3D) motion system (Bonita 10; Vicon, Centennial, CO) with 3 reflecting external markers attached over the halfway point of the iliotibial band, the lateral knee epicondyle, and the lateral malleolus (Fig 1A). During testing, subjects were lying in the same semisupine position as for the MAS assessment and with the lower leg hanging over the edge of a bed. The examiner held the subject's heel and extended the leg to the horizontal position while the subject was told to relax. The heel was then released, which allowed the lower leg to swing/oscillate freely under the action of gravity until it came to rest. The pendulum test was repeated 10 times with a few minutes between trials. Kinematic data was collected at 100Hz, processed with Vicon software (Vicon Nexus), and exported to MATLAB (MathWorks, Natick, MA) for analysis. We measured the following parameters (see Fig 1A): (1) first swing angle (ie, the angle at which the natural backward swing stops its motion and which is below the resting angle) and (2) number of oscillations (ie, motions that cross over the resting angle and present a displacement of at least 3° toward extension^{21,22}). Participants were separated into spastic and nonspastic groups according to the MAS scores. Additionally, SCI participants were separated into more-spastic and less-spastic groups using the mean value for the first swing angle ($70.31 \pm 23.04^\circ$) and the number of oscillations (6.19 ± 3.61) measured in the SCI group. Here, if the first swing angle and the number of oscillation values were below the mean, individuals were categorized as morespastic (first swing angle = $55.22 \pm 14.54^\circ$, n = 20; number of oscillations = 3.07 ± 1.75 , n = 15). If values were above the mean, individuals were categorized as less-spastic (first swing angle = $93.54 \pm 10.77^\circ$, n = 13; number of

oscillations = 8.78 ± 2.50 , $n = 18$). Note that the majority of SCI participants identified by the MAS scores as spastic were also identified by the pendulum test as more-spastic (first swing angle = 17/20, number of oscillations = 13/15). Similarly, most SCI participants identified by the MAS scores as nonspastic were identified by the pendulum test as less-spastic (first swing angle = 10/13, number of oscillations = 11/18).

EMG Recordings

EMG was recorded from the quadriceps femoris muscle of the right side in control subjects and bilaterally in individuals with motor complete SCI through bipolar surface electrodes (Ag-AgCl, 10mm diameter, 1cm apart) secured on the skin. The signals were amplified, filtered (30–2,000Hz) and sampled at 5kHz for offline analysis (CED 1401 with Signal software; Cambridge Electronic Design, Cambridge, UK). Quadriceps femoris H-reflex, M-max, and MEPs were tested when subjects were seated in an armchair with the tested leg placed on a custom platform with the hip ($\sim 120^\circ$) and knee ($\sim 160^\circ$) flexed and the ankle restrained by straps in $\sim 110^\circ$ of plantarflexion.

Quadriceps Femoris H-Reflex and M-max

Percutaneous electrical stimulation of the femoral nerve was delivered (1 millisecond rectangular electrical stimulus, DS7AH; Digitimer, Hertfordshire, UK; see Fig 1B) through a cathode (10mm diameter Ag-AgCl electrode) placed in the femoral triangle and an anode (Ag-AgCl plaque) placed over the posterior aspect of the thigh. Stimulus intensities were increased in steps of 0.05mA, starting below H-reflex threshold and increasing to measure the H-max and M-max at rest (0.25Hz). The H-max and M-max were measured as peak-to-peak amplitude of the unrectified response in control subjects ($n = 21$) and both legs of individuals with ($n = 20$) and without ($n = 13$) spasticity as determined by the MAS.

Quadriceps Femoris MEPs

Transcranial magnetic stimulation (TMS) and transcranial electric stimulation (TES) were delivered over the leg representation of the primary motor cortex. TMS was delivered from a Magstim BiStim² and a Magstim 200² (Magstim Co, Whitland, UK) through a double-cone coil with a monophasic current waveform. The coil was positioned over the vertex and moved around this point to determine the optimal position for eliciting an MEP in the quadriceps femoris muscle (see Fig 1B). The right side was tested in control subjects ($n = 10$) and both legs in individuals with ($n = 14$) and without ($n = 10$) spasticity as determined by the MAS. In individuals in whom MEPs were not observed when using a single TMS pulse, pairs of TMS pulses at interstimulus intervals (ISIs) of 20 to 25 milliseconds were used. Pairs of TMS pulses at these ISIs increase the size of MEPs through a rise in cortical excitability induced by a conditioning stimulus.²³ Evidence showed that a Jendrassik maneuver also increases MEP size in lower limb muscles.^{24,25} Therefore, during stimulation of participants with motor complete SCI, to ensure maximum drive to spinal motoneurons, individuals were also asked at times to perform a Jendrassik maneuver, where they needed to clench their teeth and flex their fingers or arms bilaterally, into a hooklike form, with rest periods as needed. TMS stimuli were delivered at 4 second intervals (0.25Hz) at an intensity of 100% of the maximum stimulator output in SCI (single and paired pulse) and control (single pulse) subjects. In addition to using single and double TMS pulses to examine the

presence of descending connectivity, TES was used over the leg representation of the primary cortex in participants who consented to be tested (spastic SCI = 7, nonspastic SCI = 7). TES was delivered from a DS7AH (Digitimer) through an anode placed 5cm lateral and a cathode place 2cm anterior to the vertex. TES stimuli (200 millisecond rectangular electrical stimulus) were delivered at 4 second intervals (0.25Hz) at an intensity ranging from 50mA to the maximum intensity tolerated by the subject. We measured MEP peak-to-peak amplitude of unrectified responses.

Magnetic Resonance Imaging

The images were acquired on a TIM Trio 3T system using a 20-channel birdcage head/neck coil (Seimens, Erlangen, Germany). A T2-weighted turbo spin-echo sequence (repetition time = 3,060 milliseconds, echo time = 96 milliseconds, flip angle 135°, with transversal in-plane resolution of 0.6mm and 3mm slice thickness) was used, giving a good contrast between the spinal cord and the cerebrospinal fluid (CSF). To extract a segmented mask of the spinal cord cross section, we applied a semiautomatic method described earlier.²⁶ In short, a plane perpendicular to the spinal cord was defined from the superior edge of the C2 process and formed the midplane in an axial dataset with isometric resolution of 0.1mm³, and 5 slices were interpolated. Regions sampling the intensity of the CSF and the spinal cord were drawn manually, and a spinal cord mask was based on thresholding the image with the mean of the 2 regions. Anteroposterior width (APW) and left–right width (LRW) reflect the width in 2 orthogonal directions, whereas spinal cord area (SCA) reflects measure in all directions. Therefore, to assess the effect of atrophy in oblique directions, we measured the radius from the cord shape center of mass to its border, $R(\alpha)$, for angles α over the whole circle with an angular resolution of 6°. Mean measures of all 5 axial slices were used for statistical analysis to avoid random effects in single slices from nerve roots, noise, and other confounding effects. The same observer performed all manual steps blinded to the identity of the individual participants. Note that we tested MRI procedures in control subjects ($n = 13$) and individuals with ($n = 12$) and without ($n = 9$) spasticity as determined by the MAS. Some participants were not able to participate in the MRI session, because they had contraindication to MRI procedures (claustrophobia, metal implant, medical pump, or bullet within the spinal cord) or could not return for testing.

Data Analysis

Normal distribution was tested by the Shapiro–Wilk test and homogeneity of variances by the Levene test of equality and Mauchly test of sphericity. When sphericity could not be assumed, the Greenhouse–Geisser correction statistic was used. One-way analysis of variance (ANOVA) was performed to examine the effect of Group (controls, spastic SCI, nonspastic SCI) on the first swing angle and number of oscillations, H-max, M-max, H-max/M-max ratio, MEP, and MRI variables such as SCA, LRW, and APW. Holm–Sidak post hoc analysis was used to test for significant comparisons. Pearson correlation coefficient analysis was used as needed. The statistical analysis was conducted using SigmaPlot (Systat Software, San Jose, CA), and the significance was set at $p < 0.05$. Correlations between MAS scores and spinal cord atrophy measures were done using Pearson linear correlation coefficient with a script written in MATLAB. Group data are presented as mean $\pm$ standard deviation in the text.

Results

MAS and Pendulum Test

MAS scores showed that spasticity was present in 60.6% of individuals with motor complete SCI, whereas 39.4% did not show spasticity (Fig 2A). This demonstrates the presence of 2 strong subgroups of humans with motor complete SCI: individuals without (13/33) and with (20/33) spasticity. Within the spastic group, 85% of them exhibited marked spasticity (MAS = 2, 3, and 4; 17 participants) compared with a slight increase in muscle tone (MAS = 1; 3 participants; see Fig 2B).

Figure 3A illustrates kinematic traces during the pendulum test in a control subject and participants with SCI with (MAS = 3) and without (MAS = 0) spasticity. Note that the nonspastic participant exhibited similar first swing angle but a larger number of oscillations compared with the control subject. The spastic participant showed a reduced first swing angle and number of oscillations compared with the other participants. One-way ANOVA showed an effect of Group on the first swing angle ($F_{2, 45} = 14.60$, $p < 0.001$) and the number of oscillations ($F_{2, 45} = 14.09$, $p < 0.001$; see Fig 3B). We found that the first swing angle was reduced in spastic ($59.41 \pm 18.88^\circ$) compared with control ($84.45 \pm 10.48^\circ$, $p < 0.001$) and nonspastic ($87.10 \pm 18.65^\circ$, $p < 0.001$) participants. No differences were found between controls and nonspastic participants ($p = 0.68$). In addition, the number of oscillations was larger in nonspastic (8.98 ± 3.25) compared with spastic (4.37 ± 2.52 , $p < 0.001$) and control (5.04 ± 1.72 , $p < 0.001$) participants. No differences were found between spastic subjects and controls ($p = 0.44$).

Similar results were observed when SCI participants were grouped into more-spastic and less-spastic groups based on the mean value measured in the SCI group (effect of Group on the first swing angle, $F_{2, 45} = 44.15$, $p < 0.001$; effect of Group on the number of oscillations, $F_{2, 45} = 33.03$, $p < 0.001$). Here, we found that the first swing angle was reduced in more-spastic ($55.22 \pm 14.54^\circ$) compared with control ($84.45 \pm 10.48^\circ$, $p < 0.001$) and less-spastic ($93.54 \pm 10.77^\circ$, $p < 0.001$) participants. No differences were found between control and less-spastic participants ($p = 0.07$). In addition, the number of oscillations was larger in less-spastic (8.78 ± 2.50) compared with more-spastic (3.07 ± 1.75 , $p < 0.001$) and control (5.04 ± 1.72 , $p < 0.001$) participants. A difference was also found between more-spastic subjects and controls ($p = 0.01$).

Quadriceps Femoris H-Reflex and M-max

Figure 4A illustrates raw H-reflex and M-max traces in a control subject and in participants with SCI with (MAS = 3) and without (MAS = 0) spasticity. Note that both SCI participants exhibited smaller M-max and similar H-max compared with the control subject. One-way ANOVA showed an effect of Group ($F_{2, 51} = 22.62$, $p < 0.001$; see Fig 4B) on the M-max. Post hoc tests showed that the M-max was reduced in spastic ($4.86 \pm 3.38\text{mV}$, $p < 0.001$) and nonspastic ($4.18 \pm 1.86\text{mV}$, $p < 0.001$) compared with control ($9.64 \pm 1.89\text{mV}$) participants. M-max values were similar between spastic and nonspastic individuals ($p = 0.59$). However, no effect of Group was observed on the H-max ($F_{2, 25} = 0.05$, $p = 0.95$; control = $1.96 \pm 1.33\text{mV}$, nonspastic SCI = $1.79 \pm 1.33\text{mV}$, spastic SCI = $1.98 \pm 1.39\text{mV}$).

suggesting that H-max size was similar across participants. In addition, one-way ANOVA showed an effect of Group ($F_{2, 25} = 4.60$, $p = 0.02$) on the H-max/M-max ratio. Post hoc tests showed that H-max/M-max ratio was larger in spastic (0.41 ± 0.07 , $p = 0.01$) and nonspastic (0.39 ± 0.23 , $p = 0.03$) participants compared with control subjects (0.22 ± 0.17). No differences were observed between nonspastic and spastic participants ($p = 0.79$).

Quadriceps Femoris MEPs

Figure 5A shows single MEP traces elicited by TMS in the quadriceps femoris muscle in SCI participants with and without spasticity. The graph on the right side shows in the x-axis data from individuals with (red dots) and without (green dots) spasticity, and the y-axis shows that MEP size normalized to the M-max. Participant number as listed in the Table is reported next to each individual data point. One-way ANOVA showed an effect of Group ($F_{2, 31} = 12.57$, $p < 0.001$) on the MEP size. Post hoc tests showed that MEP size was reduced in SCI participants with spasticity ($0.61 \pm 0.60\%$ of M-max) compared with controls ($9.40 \pm 8.88\%$ of M-max, $p < 0.001$; see Fig 5B). MEP latency was also delayed in SCI participants with spasticity (21.75 ± 2.89 milliseconds) compared with controls (18.84 ± 1.56 milliseconds, $p = 0.003$). MEPs were present in all SCI participants tested who had spasticity (14/14, ranging from 0.02 to 0.09mV) and controls (10/10, ranging from 0.11 to 2.77mV) but to a different extent. Notably, no MEPs were found in the nonspastic group in any of the participants tested ($0.01 \pm 0.01\%$ of M-max, $p < 0.001$). Similar to the results obtained with TMS, all spastic SCI participants tested with TES showed MEPs above the resting background EMG level ($0.82 \pm 0.60\%$ of M-max; 7/7), whereas the nonspastic SCI participants showed no presence of MEPs ($0.01 \pm 0.07\%$ of M-max; 7/7; $p = 0.001$).

Magnetic Resonance Imaging

Figure 6A shows 2 axial slices obtained from the C2 level in individuals with (MAS = 4) and without (MAS = 0) spasticity. SCA (green), LRW and APW (yellow), and CSF (blue) are outlined. One-way ANOVA showed an effect of Group ($F_{2, 31} = 13.80$, $p < 0.001$) on SCA. Post hoc analysis revealed that SCA was reduced in spastic ($64.53 \pm 9.34\text{mm}^2$, $p = 0.01$) and nonspastic ($53.21 \pm 9.33\text{mm}^2$, $p < 0.001$) participants compared with controls ($74.35 \pm 9.25\text{mm}^2$). Importantly, SCA was further reduced in nonspastic compared with spastic participants ($p = 0.02$). One-way ANOVA showed an effect of Group ($F_{2, 31} = 6.95$, $p = 0.003$) on LRW. Post hoc analysis revealed that LRW was reduced in nonspastic ($10.83 \pm 1.01\text{mm}$) compared with spastic ($12.11 \pm 0.87\text{mm}$, $p = 0.006$) and control ($12.06 \pm 0.74\text{mm}$, $p = 0.005$) participants. However, no differences were observed between control and spastic individuals ($p = 0.89$). We also found an effect of Group ($F_{2, 31} = 7.14$, $p = 0.003$) on APW. Post hoc analysis revealed that APW was significantly reduced in spastic ($6.85 \pm 0.93\text{mm}$; $p = 0.03$) and nonspastic ($6.32 \pm 0.86\text{mm}$; $p = 0.003$) participants compared with controls ($7.76 \pm 0.93\text{mm}$), but no difference was observed between spastic and nonspastic groups ($p = 0.20$; see Fig 6B).

Figure 7 shows a polar plot illustrating the correlation coefficient between R(α) and MAS scores. Correlation coefficients between spinal cord atrophy and the MAS score are shown for all angles (black dashed line) and highlighted in directions with significant correlations ($p < 0.05$, red lines). We found that MAS scores correlated with radii in 2 sectors in the left

and right lateral regions of the spinal cord (see red lines and light orange shaded regions) but not with any other regions of the spinal cord.

Correlation Analysis

A negative correlation was found between MAS scores and the first swing angle during the pendulum test ($r = -0.64$, $p < 0.001$), showing that individuals with severe spasticity exhibited smaller first swing angle. No correlation was found between MAS scores and the H-max ($r = 0.09$, $p = 0.72$), M-max ($r = 0.15$, $p = 0.40$), and H-max/M-max ratio ($r = 0.24$, $p = 0.36$). H-max values did not correlate with MEP size ($r = 0.17$, $p = 0.72$). Notably, a positive correlation was found between MAS scores and MEP size ($r = 0.55$, $p = 0.006$; see Fig 5B) and between MAS scores and SCA ($r = 0.57$, $p = 0.01$) and LRW ($r = 0.60$, $p = 0.006$) but not between MAS and APW ($r = 0.39$, $p = 0.10$). SCA was not correlated with the level of injury in nonspastic ($r = 0.50$, $p = 0.17$) or spastic ($r = 0.16$, $p = 0.64$) participants. No correlation was found between physiological and kinematic outcomes and the time postinjury (first swing angle, $r = -0.16$, $p = 0.36$; H-max, $r = -0.18$, $p = 0.49$; M-max, $r = -0.09$, $p = 0.63$; H-max/M-max ratio, $r = -0.20$, $p = 0.43$; MEP size, $r = -0.21$, $p = 0.48$) or medication intake (first swing angle, $r = 0.11$, $p = 0.54$; H-max, $r = -0.001$, $p = 0.99$; M-max, $r = 0.04$, $p = 0.81$; H-max/M-max ratio, $r = 0.28$, $p = 0.27$; MEP size, $r = 0.19$, $p = 0.51$).

Discussion

Our novel findings demonstrate that preservation of descending motor pathways influences spasticity in humans with motor complete SCI. Note that the inclusion of participants with motor complete SCI allowed us to examine the involvement of residual descending connections on spasticity. First, we found that MEPs in the quadriceps femoris muscle were present in individuals with but not in those participants without symptoms of spasticity. MEP size correlated with the severity of spasticity. Second, we found that spinal cord atrophy was greater in nonspastic compared with spastic subjects and the degree of spared tissue in the lateral columns of the spinal cord correlated positively with the severity of spasticity, showing preservation of white matter tracts when spasticity was present. We propose that the presence of residual descending motor pathway connectivity with spinal motoneurons plays a role in the development of spasticity in humans with motor complete SCI.

Spasticity after SCI

Several definitions have been proposed for spasticity,²⁷ with the most common being that spasticity is a velocity-dependent increase in muscle tone due to the exaggeration of stretch reflexes.¹ This definition has been broadened and challenged over the years, opening the consideration of other symptoms of upper motor neuron lesion when referring to spasticity.²⁸ Here, we measured spasticity using the MAS and the pendulum test, which are examinations widely used in clinical settings. We found that 60% of individuals with motor complete SCI showed some degree of spasticity as detected by both clinical examinations. This is consistent with previous findings showing that a large proportion of humans with complete SCI develop spasticity.²⁻⁵ This is also consistent with evidence showing that the

MAS is sensitive for assessing limb spasticity after chronic complete SCI.²⁹ Limitations have been highlighted in the inter-rater reliability³⁰ and validity³¹ of the MAS. Therefore, the pendulum test offers a controlled alternative to detect the severity of spasticity in the quadriceps femoris muscle.^{21,22} We found that the first swing angle of the knee joint was a better indicator of spasticity compared with the number of oscillations, consistent with previous results.²¹ In our study, MAS and pendulum test scores were negatively correlated, supporting the view that the pendulum test has good predictive value for detecting the presence of extensor spasticity detected by the MAS.³² These clinical findings together support the existence of 2 subgroups among participants with motor complete SCI: those without spasticity and those with marked spasticity. The lack of a relationship between the degree of spasticity and time postinjury, level of injury, and intake of spasticity medication suggests that other factors contributed to our results.

Role of Descending Motor Pathways in Spasticity

Most studies agree that loss of supraspinal input is a landmark of spasticity, but only a few of them have examined the contribution of descending motor pathways to spasticity in humans with SCI. On one side, self-reported questionnaires and clinical examinations suggest that individuals with incomplete SCI, which means a higher degree of descending connectivity, had a higher prevalence of spasticity compared with people with complete SCI.²⁻⁵ However, the same studies also report opposite findings depending on the severity of the injury and the symptoms used to test spasticity. A consistent observation across studies is that a large number of individuals with a diagnosis of SCI, including clinically complete SCI, show spasticity.³⁻⁵ Lack of voluntary control in humans with clinically complete SCI does not necessarily imply that spinal motoneurons caudal to the lesion are completely deprived of descending innervation. Postmortem analysis of spinal cords^{13,14} and physiological studies¹⁵ showed that ~60 to 70% of individuals with a diagnosis of clinically complete SCI showed evidence of continuity of CNS tissue across the injured segments. Although we cannot make a direct comparison, we note that in our study 60% of the participants presented spasticity, which is consistent with the proportion of humans with discomplete injuries.

Spasticity has been related to an imbalance between inhibitory and excitatory supraspinal inputs controlling segmental networks.¹² Multiple descending motor pathways modulate the activity of spinal networks.^{33,34} Therefore, it is likely that multiple descending motor pathways contribute to spasticity. Of particular interest is the influence of the corticospinal tract. In animals, lesions of the corticospinal tract are accompanied by increased afferent sprouting at the spinal cord level leading to symptoms of hyperreflexia.^{10,11} We found that MEPs by TMS were present in the quadriceps femoris muscle only in participants who presented spasticity. The latency of these MEPs was consistent with activation of corticospinal responses in humans with SCI.³⁵ To further examine the presence of descending connectivity, we quantified MEPs elicited by electrical stimulation over the leg representation of the primary motor cortex, which likely reflect activation of corticospinal axons directly.^{36,37} Consistent with our results using single and double TMS pulses, we found that MEPs elicited by electrical stimulation were present in all spastic but not in nonspastic participants. Although MEPs elicited by TMS stimulation over the motor cortex

provide an index of corticospinal excitability, subcortical influences can also contribute to changes in MEP size.³⁸ To address this possibility, we tested H-reflexes, because their size is influenced by presynaptic mechanisms and by the excitability of spinal motoneurons.³⁴ We found similar H-reflex sizes in SCI participants with and without MEPs, suggesting that it is less likely that changes at this level contributed to our results. Our results also showed that H-max/M-max ratios were higher in SCI compared with control subjects but similar between spastic and nonspastic participants. Note that M-max values were smaller in SCI participants compared with control subjects and H-max values were similar across groups. Motoneurons contributing to the generation of the H-reflex are recruited in an orderly sequence from the smallest to the largest, whereas the M-max provides an estimate of the response of the entire motoneuron pool.³⁴ Thus, it is possible that in SCI participants the smaller M-max is mainly due to the loss of larger motor units, which are less likely to be recruited into the H-max. This is consistent with evidence showing the loss of larger myelinated motoneurons in ventral roots at or near the lesion epicenter following SCI.³⁹ Another possibility is that the primary afferent input is overall stronger after SCI. Presynaptic inhibition at the terminal of Ia afferents is reduced⁴⁰ and polysynaptic facilitation Ia afferents to motoneurons is increased⁴¹ in humans with SCI. Both could contribute to explain the similar H-reflex size across groups regarding the changes in the M-max. These results also agree with evidence showing that in individuals with SCI, spasticity is less likely to be associated with increased excitability of connections between Ia afferents and spinal motoneurons,^{41,42} highlighting the complex and imperfect relationship between the H-max/M-max ratio and spasticity.⁴³ Importantly, the presence of similar H-reflexes in both groups suggests that spinal motoneurons, in the group of participants without MEPs, are sensitive in response to Ia afferent stimulus and therefore should also be sensitive in response to descending volleys if these volleys are present.

A critical question is why we did not find MEPs in nonspastic participants. We favor the possibility that the presence of spinal cord atrophy contributed to our findings. Cortical white and gray matter atrophy is present at high cervical segments after chronic complete SCI.^{44,45} We found greater spinal cord atrophy in nonspastic compared with spastic participants. Note that the LRW was reduced in nonspastic compared with spastic participants, suggesting the loss of descending pathways in the nonspastic group. The more detailed assessment of the whole shape of the spinal cord in Figure 7 show that the correlations to atrophy captured by LRW were isolated to lateral regions of the cord. This is consistent with evidence showing that the main portion of the corticospinal tract is located in the dorsal aspect of the lateral columns⁴⁶ and that LRW atrophy correlates with motor scores and MEP amplitudes in individuals with SCI.²⁶ This is also supported by our results showing that the degree of spared tissue in the lateral region correlated positively with the severity of spasticity. The lack of differences in the APW in spastic and nonspastic individuals suggests that trophic changes in the spinal cord were more specific to descending motor tracts.^{26,47,48} More severe injuries might result in larger loss of descending connections and therefore large atrophy at distant segments. In animals, retrograde degeneration of the corticospinal tract correlates to the severity of injury.⁴⁹⁻⁵¹ In humans, also a greater loss in SCA at a distance from the injury correlates with the magnitude of atrophy in the sensorimotor cortex.^{44,45,52} Because no differences were found in the time

postinjury between spastic and nonspastic participants, it is less likely that this factor contributed to our results. A cervical lesion affects the structural integrity of a higher number of axons and neurons compared with a thoracic lesion.^{52,53} However, consistent with previous results,⁴⁴ we observed more atrophy in our spastic participants regardless of the level of injury, suggesting that it is less likely that this factor affected our results.

Conclusions

Our electrophysiological and neuroimaging findings demonstrate for the first time that the presence of descending connectivity in humans with motor complete SCI influences spasticity. Nonspastic participants showed no evidence for corticospinal responses and larger lateral spinal cord atrophy, and spastic participants showed corticospinal responses and lesser atrophy. The ability to determine the presence of descending connectivity by examining spasticity might open avenues for the rehabilitation and assessment of humans with SCI.

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FIGURE 1:

Experimental setup. (A) Schematics showing the leg and kinematic recordings during the pendulum test using a 3-dimensional motion system with 3 reflecting external markers (shown as *dark dots*). The following parameters were measured: first swing angle (*green arrow*), and the number of oscillations (*gray arrows*). The number of oscillations was measured until the leg stop moving (resting angle, dotted line). (B) Transcranial magnetic stimulation (TMS) was applied over the leg representation of the primary motor cortex to activate corticospinal neurons (red dark) projecting directly or indirectly to quadriceps femoris motoneurons (red) located around the third and fourth lumbar segment (L3-L4) to elicit a motor evoked potential. Electrical stimulation (Elect. Stim.) was applied over the femoral nerve to evoked an H-reflex in the quadriceps femoris muscle through activation of Ia afferent projections (blue) and motoneurons (red) and a motor response (M-wave) through direct activation of spinal motoneurons' axons.

FIGURE 2:

Modified Ashworth Scale (MAS) score distribution. (A) MAS score distribution showed that spasticity was present in 60.6% of individuals with motor complete spinal cord injury (SCI; $n = 20$), whereas 39.4% did not show spasticity ($n = 13$). (B) Individual MAS scores showed that within the spastic group, the majority of participants exhibited marked spasticity (MAS = 2, 3, and 4) compared with a slight increase in muscle tone (MAS = 1). This demonstrates the presence of 2 strong subgroups of humans with motor complete SCI: individuals without (MAS = 0) and with marked (MAS = 2, 3, and 4) spasticity.

FIGURE 3:

Pendulum test. (A) Kinematic traces recorded during the pendulum test in a control subject and participants with spinal cord injury (SCI) with (Modified Ashworth Scale [MAS] = 3) and without (MAS = 0) spasticity. Waveforms represent the average of 10 trials. Note that the nonspastic individual exhibited similar first swing angle but a larger number of oscillations compared with the control subject. The spastic individual showed a reduced first swing angle and number of oscillations compared with the other participants. (B) Boxplot charts show the group data (controls = 15, nonspastic SCI = 13, spastic SCI = 20). The abscissa shows the groups tested (controls = blue bar, nonspastic SCI = green bar, spastic SCI = red bar), and the ordinate shows the first swing angle (in degrees, upper graph) and the number of oscillations (lower graph). The top and bottom lines of the boxes correspond to the 95% confidence interval, and the lines in the boxes correspond to the median. The 2 bars extend from the maximum to the minimum value. *** $p < 0.001$.

FIGURE 4:

H-reflex and maximal motor response (M-max). (A) Raw H-reflex and M-max traces in a control subject and in participants with spinal cord injury (SCI) with (Modified Ashworth Scale [MAS] = 3) and without (MAS = 0) spasticity. Waveforms represent the average of 5 trials. Note that both SCI participants exhibited smaller M-max and similar H-max compared with the control subject. (B) Boxplot charts show the group data (controls = 21, nonspastic SCI = 13, spastic SCI = 20). The abscissa shows the groups tested (controls = blue bar, nonspastic SCI = green bar, spastic SCI = red bar). The ordinate shows the H-max (in millivolts, upper graph), the M-max (in millivolts, middle graph), and the H-max/M-max ratio (lower graph). The top and bottom lines of the boxes correspond to the 95% confidence interval and the lines in the boxes correspond to the median. The 2 bars extend from the maximum to the minimum value. * $p < 0.05$, *** $p < 0.001$.

FIGURE 5:

Motor evoked potentials (MEPs). (A) Single MEP traces elicited by transcranial magnetic stimulation in the quadriceps femoris muscle in spinal cord injury (SCI) individuals with and without spasticity (left panel). Waveforms show 5 individual traces for each participant. The graph on the right side shows individual data. The abscissa shows SCI participants tested (with spasticity = *red dots*, without spasticity = *green dots*). Participant number as listed in the Table is reported next to each individual data point. The ordinate shows the MEP-max (as a percentage of the maximal motor response [M-max]). (B) Graphs show group data (controls = 10, nonspastic SCI = 10, spastic SCI = 14). The abscissa shows the groups tested (controls = blue bar, nonspastic SCI = green bar, spastic SCI = red bar). The ordinate shows

the MEP-max (as a percentage of the M-max, left graph) and the MEP-max with a different scale (as a percentage of the M-max, middle graph). A positive correlation was found between Modified Ashworth Scale (MAS) scores and MEP size (right graph). Error bars indicate standard error of the mean. *** $p < 0.001$.

FIGURE 6:

Cervical spinal cord structural magnetic resonance imaging. (A) Two axial slices obtained from the C2 level in individuals with (Modified Ashworth Scale [MAS] = 4) and without (MAS = 0) spasticity. Images show the spinal cord area (SCA, green), left to right width (LRW, yellow), anterior to posterior width (APW, yellow), and cerebrospinal fluid (CSF, blue). (B) Boxplot charts show the group data (controls, n = 13; nonspastic spinal cord injury [SCI], n = 9; spastic SCI, n = 12). The abscissa shows the groups tested (controls = blue bar, nonspastic SCI = green bar, spastic SCI = red bar). The ordinate shows the SCA (in square millimeters, upper graph), LRW (in millimeters, middle graph), and APW (in millimeters, lower graph). The top and bottom lines of the boxes correspond to the 95% confidence interval and the lines in the boxes correspond to the median. The 2 bars extend from the maximum to the minimum value. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. A = anterior; I = inferior; L = left; P = posterior; R = right; S = superior.

FIGURE 7:

Directional magnetic resonance imaging correlations between spinal cord radius and Modified Ashworth Scale scores. Correlations are plotted for all directions (dashed black lines) with sectors of high significance highlighted ($p < 0.05$, red lines, light orange shaded regions). The radial axis shows the correlation coefficient, and the spinal cord drawing illustrates the main directions in the plot. A = anterior; L = left; P = posterior; R = right.

TABLE.

Spinal Cord Injury Participants

Participant	Age, yr	Gender	AIS	Level	Etiology	Time Postinjury, yr	MAS Score	Medication(s)	H-M	Pendulum	MEPs	MRI
1	75	M	A	T2	T	22.9	0	None	x	x	x	
2	29	M	A	T2	T	5.8	0	BAC	x	x		
3	66	M	A	C5	NT	6.3	0	BAC, GBP	x	x		x
4	46	F	A	T11	T	26	0	None	x	x	x	x
5	21	M	A	C4	T	4	0	BAC	x	x	x	x
6	42	M	A	C4	T	6.8	0	None	x	x	x	
7	23	M	A	T6	T	1.6	0	None	x	x	x	
8	33	F	A	T2	T	3.7	0	None	x	x	x	x
9	33	F	B	C4	T	14.8	0	None	x	x	x	x
10	50	M	A	C4	T	33.4	0	None	x	x	x	x
11	58	M	A	T4	T	2.2	0	BAC	x	x	x	x
12	52	F	A	C2	T	12.8	0	None	x	x	x	x
13	57	M	A	T6	T	18	0	None	x	x		x
14	66	M	A	C6	T	11.2	1	BAC, GBP	x	x		
15	27	M	A	C5	T	1.8	1	None	x	x		
16	28	M	A	T2	T	10	1	BAC, TIZ	x	x		
17	43	M	A	T4	T	22.6	2	BAC	x	x	x	
18	29	M	A	C5	T	10.6	2	None	x	x	x	x
19	56	M	B	T6	T	30.9	2	None	x	x	x	x
20	30	M	B	T11	T	3	2	None	x	x	x	x
21	62	M	A	T5	T	35	3	None	x	x		
22	52	M	A	C5	T	3.3	3	BAC, GBP	x	x	x	x
23	39	M	A	T8	T	12.1	3	BAC	x	x		
24	49	M	A	T10	T	17	3	None	x	x	x	x
25	26	M	A	T7	T	2	3	None	x	x	x	x
26	28	M	A	T12	T	1	3	GBP	x	x	x	x
27	20	M	B	C4	T	1.9	3	None	x	x		x
28	25	M	A	C6	T	2.2	4	BAC	x	x	x	x

Participant	Age, yr	Gender	AIS	Level	Etiology	Time Postinjury, yr	MAS Score	Medication(s)	H-M	Pendulum	MEPs	MRI
29	47	M	A	T9	T	2.3	4	BAC, GBP	x	x	x	
30	45	M	A	T5	T	16.7	4	None	x	x	x	x
31	42	M	B	C6	T	23.5	4	GBP	x	x	x	
32	51	M	A	T5	T	9.5	4	None	x	x	x	x
33	44	M	B	T3	T	25	4	None	x	x	x	x

Individuals tested for H-M, pendulum, MEPs, and MRI are identified with an x.

AIS = American Spinal Injury Association Impairment Scale; BAC = baclofen; F = female; GBP = gabapentin; H-M = H-max and M-max; MAS = Modified Ashworth Scale; MEP = motor evoked potential; MRI = magnetic resonance imaging; NT = nontraumatic; T = traumatic; TZ = tizanidine.