RESEARCH ARTICLE

Corticalization of Motor Control in Humans Is a Consequence of Brain Scaling in Primate Evolution

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ABSTRACT

Control over spinal and brainstem somatomotor neurons is exerted by two sets of descending fibers, corticospinal/pyramidal and extrapyramidal. Although in nonhuman primates the effect of bilateral pyramidal lesions is mostly limited to an impairment of the independent use of digits in skilled manual actions, similar injuries in humans result in the locked-in syndrome, a state of mutism and quadriplegia in which communication can be established only by residual vertical eye movements. This behavioral contrast makes humans appear to be outliers compared with other primates because of our almost total dependence on the corticospinal/pyramidal system for the effectuation of movement. Here we propose, instead, that an increasing preponderance of the corticospinal/pyramidal system over motor control is an expected consequence of increasing brain size in primates because of the faster scaling of the number of neurons in the primary motor cortex over the brainstem and spinal cord motor neuron pools, explaining the apparent uniqueness of the corticalization of motor control in humans. J. Comp. Neurol. 000:000–000, 2015.

INDEXING TERMS: motor control; motor cortex; motor neurons; cortical expansion; number of neurons

Spinal and brainstem somatomotor neurons, the final neural effectors of movement, are controlled by two suprasegmental sets of descending fibers, corticospinal/pyramidal fibers originating directly from the motor cortices (as well as other cortical areas; Nudo and Masterton, 1988, 1990; Dunn and Strick, 1991; Galea and Darian-Smith, 1994; Lemon, 2008), descending in their vast majority through the medullary pyramids, and extrapyramidal fibers, originating indirectly from motor cortices and directly from discrete motor nuclei in the brainstem tegmentum, that descend dorsally to the pyramids (Sie, 1956; de Oliveira-Souza, 2012). Although both systems have been demonstrated in human and nonhuman primates (Nathan and Smith, 1955; Denny-Brown, 1966), the relative importance of one system over the other differs between humans and other primates, as evidenced by comparative anatomical studies (Nudo and Masterton, 1988) and the behavioral effects of lesions to each system. In small and medium-sized primates, bilateral injury to the medullary pyramid eliminates the independent use of digits in skilled manual actions while sparing the majority of motor control over the body (Lawrence and Kuypers 1968; Lawrence and Hopkins 1976; Porter, 1987; Lemon 1993; however, see Sasaki et al., 2004). In contrast, a similar injury in humans results in the locked-in syndrome, a state of mutism and quadriplegia in which communication can be established only by residual vertical eye movements (Fisher, 1977; Jagiella and Sung, 1989; Moon et al., 2002). The critical factors for the clinical picture are the completeness of the destruction of pyramidal tract fibers (Aguillar, 1969) and whether the pyramidal tract injury is bilateral (Fisher, 1992), with no influence of the height of pyramidal tract damage (internal capsule vs. ventral pons or medullary pyramid; for review see de Oliveira-Souza, 2012). Conversely, the interruption of

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all connections between the brainstem and the spinal cord in humans does not disrupt movements of the trunk and limbs, provided that the pyramidal tract is intact (Wiesendanger, 1973). These findings dispel objections that the locked-in syndrome might result from associated injuries to reticulospinal and tegmentospinal pathways and indicate that motor control in humans is exerted almost entirely through the corticospinal/pyramidal system. This heavy dependence on the cerebral cortex for motor control might make humans appear to be outliers compared with other primates in this respect (Fulton and Keller, 1932).

The scaling of brain and spinal cord volume, however, seems to contradict the behavioral evidence regarding the corticalization of motor control in humans. First, the mass of the cerebral cortex scales only proportionately with the mass of the spinal cord across nonhuman primate species (Burish et al., 2010). Furthermore, in a series of studies using horseradish peroxidase (HRP) tracer injections, Nudo and Masterton (1990) showed that the relative surface of the cerebral cortex (and supposedly also the cortical volume) containing neurons that project directly to the spinal cord is fairly constant across several primate species. These areas containing spinally projecting neurons include the primary motor cortex (M1) but are not limited to it, encompassing also premotor cortex (PM), supplementary motor cortex (SMA), and primary somatosensory cortex (S1; Nudo and Masterton, 1990). In humans, neurons projecting to the spinal cord through the corticospinal tract are also found in areas M1, PM, SMA, and S1 (Bubis and Landau, 1964; Seo and Jang, 2013). If the spinal cord and spinally projecting cortical areas scale in volume only proportionally to each other across primate species, then accounting for the predominance of cortical control over spinal motor neurons in humans apparently requires a major human-specific reorganization of the descending pathways involved in motor control.

An alternative explanation, however, is that the linear scaling of mass across the motor cortex and spinal cord conceals a much different scaling of the number of neurons in the two structures. Indeed, we have found that 1) although the mass of the cerebral cortex as a whole scales almost linearly with its number of neurons across several primate species (Herculano-Houzel et al., 2007; Azevedo et al., 2009; Gabi et al., 2010; Herculano-Houzel, 2012), 2) the mass of the spinal cord increases very rapidly as it gains neurons (Burish et al., 2010). As a result, 3) the primate cerebral cortex gains neurons at a rate that is roughly the square of the gain in number of neurons in the spinal cord (Burish et al., 2010).

If cortical neurons were distributed equally across functional areas in primate evolution, then our previous data on the neuronal scaling rules that apply to the cerebral cortex and spinal cord would predict that the number of cortical motor neurons also scales with the square of the number of spinal motor neurons and thus provide a simple account for the corticalization of motor control in the human brain. Consistently with this proposition, the proportion of cortical neurons located in primary auditory and visual areas does not change systematically across primate species, but the total number of cortical neurons in these areas scales faster than subcortical neurons in the same functional systems (Wong et al., 2013; Collins et al., 2013). Likewise, the finding that spinally projecting neurons are found in similar proportions of the cortical surface across primate species (Nudo and Masterton, 1990) suggests strongly that the number of cortical motor neurons scales linearly with the total number of cortical neurons and hence with the square of the number of spinal motor neurons. We thus hypothesize that the corticalization of motor control in humans is a consequence of the faster scaling of the number of cortical motor neurons over the number of spinal motor neurons in primate evolution. The number of neurons in M1 of a number of primate species was recently determined (Young et al., 2013), so here test this hypothesis by examining how the number of neurons in M1 scales as the cerebral cortex and spinal cord gain neurons across primate species.

MATERIALS AND METHODS

We examined estimates of numbers of neurons and allometric scaling rules for 15 primate species, including humans. All estimates of numbers of neurons and the corresponding allometric scaling rules reported here and in the original studies were obtained by using the isotropic fractionator (Herculano-Houzel and Lent, 2005), which has been shown in two independent studies to yield estimates of numbers of neurons that are similar to those obtained by using stereology (Bahney and von Bartheld, 2014; Miller et al., 2014; Herculano-Houzel et al., 2015). The isotropic fractionator consists of dissolving the dissected and fixed tissue of interest into a suspension of free cell nuclei, which is performed with mechanical friction in a detergent solution. The total number of nuclei in suspension is determined by counting typically four DAPI-stained samples in a hemocytometer under a fluorescence microscope and multiplying the average density of cell nuclei in suspension by the total suspension volume. The percentage of cell nuclei belonging to neurons is then determined by immunocytochemistry to the universal neuronal nuclear

TABLE 1.

Scaling Relationships Among M1, Cerebral Cortex, and Spinal Cord

Dependent variable	Independent variable	Best fit function	*P* value	95% CI for slope	Source
N_{M1}	N_{CX}	$N_{M1} = 291{,}626 \times 0.024\ N_{CX}$	0.0033	0.018–0.030	This study
N_{M1}	N_{SC}	$N_{M1} = 1.900 \times 10^{-10} \times N_{CX}^{2.495}$	<0.0001	1.921–3.069	This study
N_{CX}	M_{CX}	$N_{CX} = 36{,}561{,}963 \times M_{CX}^{0.955}$	<0.0001	0.799–1.111	Gabi et al., 2010
M_{SC}	N_{SC}	$M_{SC} = 4.285 \times 10^{-14} \times N_{SC}^{2.028}$	<0.0001	1.591–2.465	Burish et al., 2010
N_{SC}	M_{SC}	$N_{SC} = 3{,}956{,}712 \times M_{SC}^{0.471}$	<0.0001	0.387–0.555	Burish et al., 2010
M_{CX}	M_{SC}	$M_{CX} = 5.993 \times M_{SC}^{1.049}$	0.0002	0.728–1.371	Burish et al., 2010
N_{CX}	N_{SC}	$N_{CX} = 1.354 \times 10^{-5} \times N_{SC}^{2.003}$	0.0063	0.809–3.198	Burish et al., 2010
N_{ROB}	N_{SC}	$N_{ROB} = 5.694 \times N_{SC}^{1.018}$	0.0105	0.338–1.699	Burish et al., 2010
N_{SC}	M_{BD}	$N_{SC} = 4.26 \times 10^{6} \times M_{BD0.346}$	0.0015	0.291–0.427	Burish et al., 2010
N_{M1}	M_{BD}	$N_{M1} = 26{,}554 \times M_{BD}^{0.853}$	<0.0001	0.681–1.025	This study

[1]All mass units in grams. M_{CX}, mass of the entire cerebral cortex (both hemispheres); M_{SC}, mass of the spinal cord; M_{BD}, body mass; N_{M1}, number of neurons in M1; N_{CX}, number of neurons in the entire cerebral cortex (both hemispheres); N_{SC}, number of neurons in the spinal cord; N_{ROB}, number of neurons in the rest of the brain (ensemble of striatum, diencephalon, mesencephalon, pons, and medulla).

marker NeuN (Mullen et al., 1992; Millipore, Bedford, MA; catalog No. MAB377, RRID: AB_2298772).

The estimated total number of neurons in the cerebral cortex, rest of the brain (the ensemble of striatum, diencephalon, mesencephalon, pons, and medulla), and spinal cord; the mass of these structures; and several allometric rules reported here were originally published by Herculano-Houzel et al. (2007), Azevedo et al. (2009), Gabi et al. (2010), and Burish et al. (2010).

The number of neurons in M1 was determined by Young et al. (2013) by using anatomical landmarks to define the location of M1 and guide its dissection. The location of M1 in one of the species (galago) was additionally verified by functional mapping. Although the average total number of neurons in M1 in the different species was not reported by Young et al. (2013), here we retrieve these numbers by multiplying the reported surface area (in square millimeters) of M1 in each cortical hemisphere by the reported average surface density of neurons in M1 (in neurons per square millimeter). Because the average surface density had originally been calculated by dividing the direct estimate of numbers of neurons in M1 by its surface area, our calculation retrieves the original average counts of numbers of neurons in M1 obtained by Young et al. (2013). The numbers obtained were then multiplied by 2 to yield total numbers of M1 neurons in both cortical hemispheres for the sake of comparison with numbers of neurons in the entire cerebral cortex and spinal cord.

Numbers of neurons in M1, like numbers of neurons in the spinal cord and the rest of the brain, were not available for all 15 species. As indicated in Table 2, we used the reported average percentage of M1 neurons compared with the cerebral cortex as a whole to infer numbers of M1 neurons in the remaining species. Similarly, when data on structure mass of the spinal cord were available in the literature (MacLarnon, 1996), we used the published scaling rule relating numbers of neurons in the spinal cord to spinal cord mass to estimate the number of neurons in the structure of the missing species, as also indicated in Table 2. All scaling rules were calculated by fitting power functions to the data in JMP 9.0 (SAS, Cary, NC).

RESULTS

To examine how the number of neurons in M1 scales with the number of neurons in the spinal cord, we first compiled the data available on the number of neurons in M1 alone, in the cerebral cortex as a whole, and in the spinal cord from our previous studies. Because these data were not available for some species, we used known scaling relationships (listed in Table 1) to fill the gaps in the data set so that we could estimate how the number of neurons in M1 scales with the number of neurons in the spinal cord across all primate species that we have examined, including humans.

We first sought to determine how the number of neurons in M1 scales with the total number of cortical neurons in primates. From data published on the number of neurons per square millimeter of M1 cortical surface, obtained using the isotropic fractionator and measurements of the flattened surface area of M1 (Young et al., 2013), the number of neurons in M1 of a single cortical hemisphere can be estimated at 148.5 million in the chimpanzee, 56–59 million in the baboon, 10–11 million in the owl monkey and squirrel monkey, and 4.7 million in the galago (Table 2). In comparing these numbers with estimates for the entire cerebral cortex obtained in the same way, we find that the number of neurons in M1 scales linearly with the total number of neurons in the cerebral cortex across six nonhuman primate species (linear fit, $r^2 = 0.961$, $P = 0.0033$, slope 0.024), varying around 2.4% of all cortical neurons in each

TABLE 2.

Numbers of Neurons in Primate Cerebral Cortex, Motor Cortex, and Spinal Cord[1]

Species	N_{CX}	N_{M1}	N_{SC}	N_{M1}/N_{SC}
Microcebus murinus	22.31×10^6 (1)	0.43×10^6 (pred[2])	1.68×10^6 (6)	0.26
Otolemur garnettii	226.09×10^6 (2)	9.4×10^6 (5)	5.73×10^6 (6)	1.64
Callithrix jacchus	244.72×10^6 (2)	5.87×10^6 (pred[2])	3.65×10^6 (6)	1.61
Aotus trivirgatus	441.90×10^6 (2)	22.18×10^6 (5)	5.82×10^6 (6)	3.81
Macaca fascicularis	800.96×10^6 (1)	19.22×10^6 (pred[2])	11.38×10^6 (6)	1.69
Cebus apella	1.14×10^9 (2)	27.36×10^6 (pred[2])		
Saimiri sciureus	1.34×10^9 (2)	20.52×10^6 (5)	4.69×10^6 (6)	4.78
Macaca radiata	1.66×10^9 (1)	39.84×10^6 (pred[2])	9.06×10^6 (6)	4.40
Macaca mulatta	1.71×10^9 (2)	41.04×10^6 (pred[2])	10.00×10^6 (6)	4.10
Papio cynocephalus	2.88×10^9 (1)	117.68×10^6 (5)	13.48×10^6 (pred[3])	8.73
Pan troglodytes	6.00×10^9 (pred[1])	0.30×10^9 (5)	15.16×10^6 (pred[4])	19.79
Pongo pygmaeus	9.00×10^9 (3)	0.22×10^9 (pred[2])		
Gorilla gorilla	9.00×10^9 (3)	0.22×10^9 (pred[2])		
Homo sapiens	16.34×10^9 (4)	0.39×10^9 (pred[2])	19.94×10^6 (pred[5])	19.56

[1]Numbers refer to both cortical hemispheres and M1 on both hemispheres. N_{CX}, number of neurons in the cerebral cortex of both hemispheres; N_{M1}, number of neurons in area M1 of both hemispheres; N_{SC}, total number of neurons in the spinal cord; N_{ROB}, total number of neurons in the rest of brain (ensemble of diencephalon, striatum, mesencephalon, pons, and medulla); N_{M1}/N_{SC}, ratio between numbers of neurons in M1 and spinal cord. (1) Values observed by Gabi et al. (2010); (2) values observed by Herculano-Houzel et al. (2007); (3) values predicted by Herculano-Houzel and Kaas (2011); (4) values observed by Azevedo et al. (2009); (5) values observed by Young et al. (2013); (6) values observed by Burish et al. (2010); (pred), values predicted as follows. pred[1], value predicted from the equation for $N_{CX} \times M_{CX}$ in Table 1 using M_{CX} of 252 g (Semendeferi and Damasio, 2000); pred[2], values predicted from N_{CX} in this table using the estimated 2.4% of cortical neurons in M1; pred[3], value predicted from the equation for $N_{SC} \times M_{SC}$ in Table 1 using M_{SC} of 13.231 g (MacLarnon, 1996); pred[4], value predicted from the equation for $N_{SC} \times M_{SC}$ in Table 1 using M_{SC} of 16.853 g (MacLarnon, 1996); pred[5], value predicted from the equation for $N_{SC} \times M_{SC}$ in Table 1 using M_{SC} of 29.700 g (MacLarnon, 1996).

hemisphere. If this percentage is extended to the human cortex, with an average of 16 billion neurons in both cortical hemispheres (Azevedo et al., 2009), we then estimate human M1 to contain ~192 million neurons in each cortical hemisphere.

We next considered how the brain and cerebral cortex scale together with the spinal cord. We found previously that brain mass and spinal cord mass are linearly correlated across nonhuman primate species (Burish et al., 2010), such that the spinal cord mass represents on average 11.2% ± 3.8% of total CNS mass across species, a value that does not vary in concert with with body or CNS mass (Spearman correlation, $P = 0.7773$ and 0.4229, respectively). The cerebral cortex, in particular, gains mass across nonhuman primates as a power function of spinal cord mass of exponent 1.049, that is, proportionately to the spinal cord (Burish et al., 2010). With regard to structure mass, then, larger primates seem to have larger spinal cords with an only proportionally larger brain and cerebral cortex.

However, the number of neurons in the primate cerebral cortex scales much faster than the number of neurons in the spinal cord. Across eight nonhuman primate species, we previously found that the mass of the spinal cord increases very rapidly as the spinal cord gains neurons, with the latter raised to an exponent of 2.028 (Burish et al., 2010). This happens both with an increase in the average size of spinal neurons (including their axon and dendrites) and with the addition of disproportionately larger numbers of nonneuronal cells, which account for the vast majority of cells in the primate spinal cord (Burish et al., 2010).

The apparently coordinated increase in mass of cerebral cortex and spinal cord conceals a much faster increase in the number of neurons in the cerebral cortex than in the spinal cord: the former scales with the latter raised to an exponent of 2.003 ($P = 0.0063$). In contrast, the number of neurons in the ensemble of brainstem, diencephalon, and striatum (the "rest of brain") increases only linearly with the number of neurons in the spinal cord, with an exponent of 1.018 (Table 1).

Thus, as the spinal cord gains neurons, the rest of the brain gains neurons proportionally, but the cerebral cortex gains neurons much faster, with the square of the number of neurons in the spinal cord (Burish et al., 2010). If M1 represents a constant percentage of the total number of neurons in the cerebral cortex, as shown above, then the number of neurons in M1 should also scale with the square of the number of neurons in the spinal cord across primate species, leading to an increasing preponderance of cortical motor neurons over spinal neurons with increasing brain size.

We tested this hypothesis directly by calculating the number of neurons in M1 and in the spinal cord, and the ratio between them in the different species for which these values have either been estimated directly or could be predicted from values in the literature using the scaling relationships listed in Table 1. As shown in

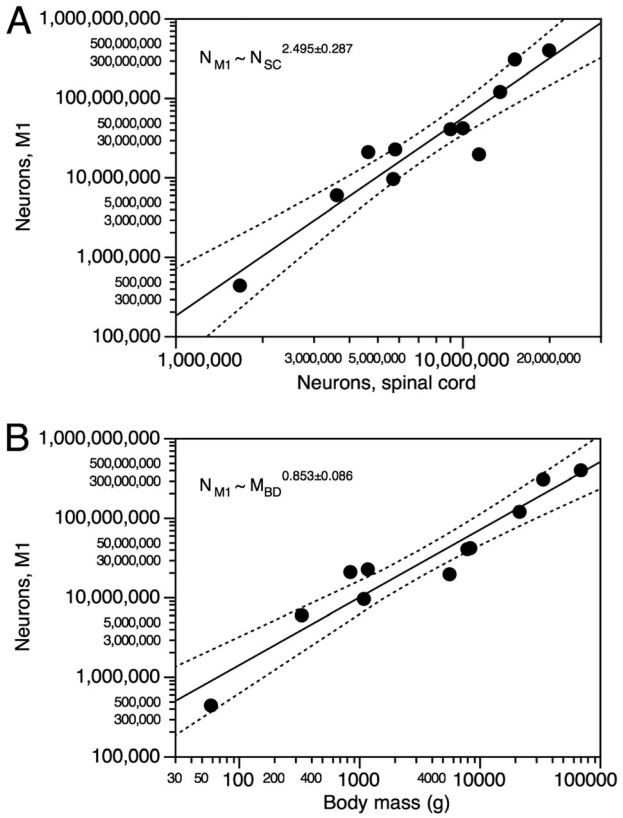

Figure 1. Number of neurons in cortical area M1 scales faster than the number of neurons in the spinal cord (**A**) but more slowly than body mass (**B**). Graphs show the number of neurons in M1 in both cortical hemispheres (neurons, M1) plotted as a function of the total number of neurons in the spinal cord (A) or of body mass (B). Each circle represents one species. Human is the circle at the farthest right. Data for body mass are from Burish et al. (2010) or Gabi et al. (2010); data on numbers of neurons were obtained as described in Table 2.

Table 2, although the number of neurons in the spinal cord varies only 11.9-fold between mouse lemur and human, the number of neurons in M1 varies 907-fold between the two species, that is, by nearly the square of the increase in spinal neurons, as predicted. As a result, the ratio of numbers of neurons in M1 to those in the spinal cord increases 75-fold between mouse lemur and man; although we estimate the mouse lemur to have roughly four times more neurons in the entire spinal cord (1.7 million neurons) than in M1 (0.4 million neurons), human M1 is estimated to contain 390 million neurons, nearly 20 times more neurons than the roughly 20 million neurons estimated for the spinal cord (Table 2).

Using the data in Table 2, we calculate that the number of neurons in primate M1 scales with the number of neurons in the spinal cord raised to a large exponent of 2.495 ± 0.287 ($r^2 = 0.893$, $P < 0.0001$; Fig. 1A). This is in stark contrast to the approximately linear scaling of numbers of neurons in the rest of the brain with numbers of neurons in the spinal cord, resulting in a fairly constant ratio between the rest of brain neurons and spinal neurons across species (Burish et al., 2010). Interestingly, the number of neurons in M1 still scales slightly below linearity as body mass increases across primates, as a power function of body mass with exponent 0.853 ± 0.086 ($r^2 = 0.916$, $P < 0.0001$; Fig. 1B) but much faster than the scaling of numbers of neurons in the spinal cord with body mass (exponent 0.346; Table 2).

DISCUSSION

Here we show that the number of neurons in the primate M1 scales roughly with the number of neurons in the spinal cord squared, such that the ratio of the number of neurons in M1 to those in the spinal cord increases rapidly as the latter gains neurons across species, reaching values of nearly 20:1 in human and chimpanzee, in contrast to ratios below 2:1 in smaller primates. In contrast, the number of neurons in the rest of the brain scales only linearly with the number of neurons in the spinal cord (Burish et al., 2010). Given that M1 is a major source of direct corticospinal/pyramidal input onto motor neurons and that only a small fraction of neurons in some structures of the rest of brain is a source of direct extrapyramidal input onto spinal motor neurons, the increasing numerical preponderance of cortical motor neurons over the rest of the brain and spinal neurons with increasing body size in primates is indicative of a corticalization of motor control that is a simple, direct consequence of the faster scaling of numbers of cortical neurons as a whole over numbers of neurons in the rest of the brain and spinal cord (Burish et al., 2010).

Although both direct (corticospinal) and indirect (reticulospinal, bulbospinal) pathways ultimately originate from motor cortices, the efficacy or strength of the indirect pathways of motor control is still limited by the number of neurons in the brainstem, which we show here to scale much more slowly than the number of neurons in M1. Indeed, growing anatomical evidence has shown that the reticulospinal pathway in humans is composed of collections of only a few axons scattered throughout the anterior and lateral columns that do not assemble in well-defined tracts (Nathan et al., 1996).

Note that the corticalization of motor control that is evident in numbers of neurons is not apparent at the level of structure mass, given that the different neuronal scaling rules that apply to primate cerebral cortex and spinal cord result in seemingly proportional scaling of the two structures (Burish et al., 2010), with motor cortex representing a seemingly constant fraction of

the cerebral cortex (Nudo et al., 1990). It must be kept in mind that only a (so far unknown) fraction of M1 neurons is projection neurons controlling spinal motor neurons directly, just as not all spinal cord neurons are motor neurons. Similarly, only a very small proportion of rest of brain neurons is expected to be the origin of extrapyramidal projections to spinal motor neurons, those located in structures such as some sectors of the reticular formation and the vestibular nuclei (Nathan et al., 1996). Still, the faster scaling of the number of total M1 neurons over neurons in the rest of the brain and in the spinal cord indicates that pyramidal inputs scale disproportionally rapidly in comparison with extrapyramidal inputs onto spinal motor neurons in man, even though cortical neurons are ultimately at the origin of both projections. It also remains possible that, in humans, corticobulbar branches of pyramidal tract neurons could more profoundly influence reticulospinal neurons than in smaller primates. However, there is anatomical evidence that in humans many projections of the premotor cortex descend in the pyramidal tracts directly to the spinal cord without terminating significantly in reticulospinal tegmental nuclei (Minckler et al., 1944; Kuypers, 1958), so this possibility seems an unlikely explanation for the corticalization of motor control in the human species.

Although M1 is not the sole source of cortical control over spinal motor neurons (Nudo and Masterton, 1990), the fact that the amount of cortical surface with spinally projecting neurons is relatively constant across primate species suggests that the total number of cortical neurons that control spinal motor neurons (including M1, but not limited to it) scales linearly with the total number of cortical neurons, and thus with roughly the square of the total number of neurons in the spinal cord. Our results thus indicate a cortical takeover of spinal motor control with increasing brain size in primates. Such corticalization of motor control offers a simple explanation for the finding that, although pyramidal lesions impose little damage to movement control in small primates and other small animals, bilateral lesions of the medullary pyramid in human patients cause quadriplegic mutism (Fisher, 1977; Jagiella and Sung, 1989; Moon et al., 2002).

Competition and activity-dependent axon elimination play a role in the shaping of cortical projections onto spinal motor neurons (Martin, 2005), so it is likely that descending pyramidal and extrapyramidal axons also compete over spinal motor neurons for the establishment of functional connectivity and control of muscle units on the basis of activity and relative numbers, as occurs in the development of sensory systems (Hubel and Wiesel, 1965; Tanaka, 1991; Kaas and Catania, 2002). We predict that the large numerical preponderance of cortical over noncortical direct inputs to spinal motor neurons in humans translates into a similar majority of motor units controlled by pyramidal inputs from M1 rather than by extrapyramidal fibers. If the 20:1 ratio of M1 neurons to spinal cord neurons translates into a 20:1 ratio of pyramidal over nonpyramidal fibers, then ~95% of all motor units in the spinal motor neuron-innervated body are subject to cortical control in humans. Such a large percentage would explain the devastating effects of bilateral pyramidal lesions for motor control in humans, in contrast to the much more modest effects in smaller primates.

It appears remarkable that fine motor control over the body is achieved with very small numbers of spinal neurons in primates: between 1 and 20 million neurons (not all of which are motor neurons). Similarly, motor control in the adult mouse is achieved with a total of only 2 million neurons in the spinal cord (Fu et al., 2013) and 1 million neurons in cortical motor areas (Herculano-Houzel et al., 2013). Moreover, increases in body mass, which translate into roughly equivalent increases in muscle mass, are apparently not followed by proportional increases in numbers of motor neurons. As shown by Burish et al. (2010), increases in body mass are accompanied by only slightly increased numbers of neurons in the primate spinal cord, only some of which are motor neurons, as a power function of exponent 0.346. Similarly, the number of motor neurons in the facial nucleus (the functional equivalent of spinal motor neurons for the control of the facial musculature) has been found to scale with body mass raised to an exponent of only 0.184 in marsupials (Watson et al., 2012) and 0.127 in primates (Sherwood, 2005). This scaling of numbers of motor neurons with increasing body mass well below linearity implies that the average size of motor units (that is, the number of muscle fibers controlled by individual motor neurons) increases with body mass, thus possibly making movement control coarser in larger animals (Watson et al., 2012), even with the corticalization of control over these motor neurons indicated by our present data. It will be interesting to determine whether the faster scaling of numbers of neurons in motor cortex over spinal motor neurons entails a disproportional increase in numbers of those neurons controlling hand movements, thus possibly compensating for any increases in average motor unit size and preserving manual dexterity with increasing body size.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ROLE OF AUTHORS

RdO-S proposed the problem; SH-H compiled and analyzed the data; SH-H, JHK, and RdO-S wrote the manuscript.

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