one control-lesioned and two Nogo-treated animals exhibited functional recovery within 2 to 10 days of the lesion. This rapid post-lesion improvement suggests that recovery was mediated by spared rather than regenerating axons. Fourth, some statistical analyses seemed to have been conducted using pairwise comparisons of specific individuals in different groups, for reasons that are unclear. The inappropriate use of pairwise comparisons would lower the rigor for establishing statistical significance. Fifth, the anatomical data are primarily presented in camera lucida format, prohibiting the reader from assessing whether enhanced sprouting or regeneration in fact occurred, which can only be assessed from clear, high-quality images.

Finally, I do not understand the explanation for the peculiar triplicate figures published in the original online article, which the authors provided as "corrigendum." How could the same rostral half of a figure be attributed to three different animals while the corrected manuscript still uses the original drawing for one of the animals? If the original error occurred because a schematic was inserted as 'place holder' in the three different figures, the schematic should be replaced by the actual anatomy in all cases. Instead, the place holder is still there in one of the animals. The explanation of this anomaly requires further clarification.

Thus, the effects of Nogo antibodies in primates with spinal cord injury have not been established.

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1. Freund, P. *et al. Nat. Med.* **12**, 790–792 (2006).

To the editor:

We were surprised to read the title, abstract and conclusions of a recent article in *Nature Medicine* by Freund *et al.*: "Nogo-A specific antibody treatment enhances sprouting and functional recovery after cervical lesion in adult primates" (ref. 1), as no clear anatomical evidence of regeneration is provided in the paper.

The authors performed spinal cord lesions on monkeys, then quantified the "normalized cumulated axonal length" beyond the lesion in six monkeys, three treated with Nogo-A antibody and three with control. In the text, the authors report that the difference between the two groups "was not statistically significant ($P = 0.12$)," a conclusion that can be verified directly from the specific values reported in Supplementary Table 1 of ref. 1 (48.8 μm, 36.7 μm and 8 μm of regeneration for controls, compared to 59.3 μm, 46 μm and 79.9 μm in monkeys treated with Nogo-A antibody).

The authors do show a statistically significant increase in "the number of axonal swellings." However, this parameter was not validated as a measure of regeneration. Swellings are just as likely to be signs of incipient degeneration as they are of any anatomical improvement. Unless evidence is provided to the contrary, these data cannot be taken as evidence of enhanced repair.

Finally, the authors refer in the text to Supplementary Figure 1 as showing "sprouting for a total distance of 10–12 mm," but that figure does not in fact contain those data, nor could we find any data on the extent of sprouting in any of the other figures or tables, nor any indication of the statistical significance of this purported effect.

We were therefore surprised that the concluding paragraph states that "Neutralization of Nogo-A promotes regrowth of corticospinal (and possibly other) axons around the lesion and into the denervated spinal cord in macaque monkeys," as the data on regrowth (that is, regeneration) showed no statistically significant difference. We were equally surprised that the title and abstract claim that the Nogo-A antibody produces "enhanced sprouting," as sprouting was not documented.

Because the conclusions of the paper do not match the data that are presented, it would seem appropriate for the authors to revise their conclusions in an erratum.

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1. Freund, P. *et al. Nat. Med.* **12**, 790–792 (2006).

Freund *et al.* reply:

In an experimental injury situation, the key prerequisite for studying regeneration is the completeness of the transection of the studied fiber tract. In our paper, the crucial criterion for a complete lesion was not only the extent of the lesion as it appeared in reconstructed cross-sections for each monkey, but the full interruption of the corticospinal tract (CST) as assessed by anterograde transport of the tracer biotinylated dextran amine (BDA) from the hand area of the motor cortex.

As stated in our paper and on the basis of this criterion, 8 of 12 monkeys had a complete lesion of the CST in the dorsolateral funiculus (and not only 4 as claimed by our colleagues; see Supplementary Table 1 of ref. 1). Furthermore, among the animals that we considered for the tracing analysis of axonal arbors caudal to the lesion, only a single monkey—Mk-CP—had an incomplete CST lesion, as shown by the presence of a few BDA-labeled CST axons that were not transected at the level of the lesion.

Notably, manual dexterity using the Brinkman board test (Fig. 1 of ref. 1) was significantly ($P = 0.037$) different between the groups of anti–Nogo-A antibody–treated monkeys and of control antibody–treated monkeys. The conclusion of enhanced functional recovery in the monkeys treated with antibody to Nogo-A (anti–Nogo-A) is therefore justified.

Spinal cord injuries trigger a cascade of secondary tissue reactions as a result of bleeding, ischemia and inflammation, which lead to substantial variability within groups of animals. In this regard, the outcomes of the experimental injuries in our monkeys resemble the variability seen in human patients. In spite of the interindividual variability, however, the mean of the extent of the ventral column lesions in the control antibody–treated monkeys (28.5%) was almost identical to that in the anti–Nogo-A antibody–treated monkeys (28%; see Supplementary Table 1 of ref. 1). Note also that the only monkey in which both the dorsolateral and ventral funiculi were fully sectioned recovered better than any of the control monkeys, all of which had some portion of their ventral funiculi intact. The statement that there was slightly more ventral sparing in anti–Nogo-A antibody–treated monkeys is therefore inaccurate, and the assertion that the improved functional recovery of the anti–Nogo-A antibody–treated monkeys can be explained by the spared ventral funiculus is not supported by the data.