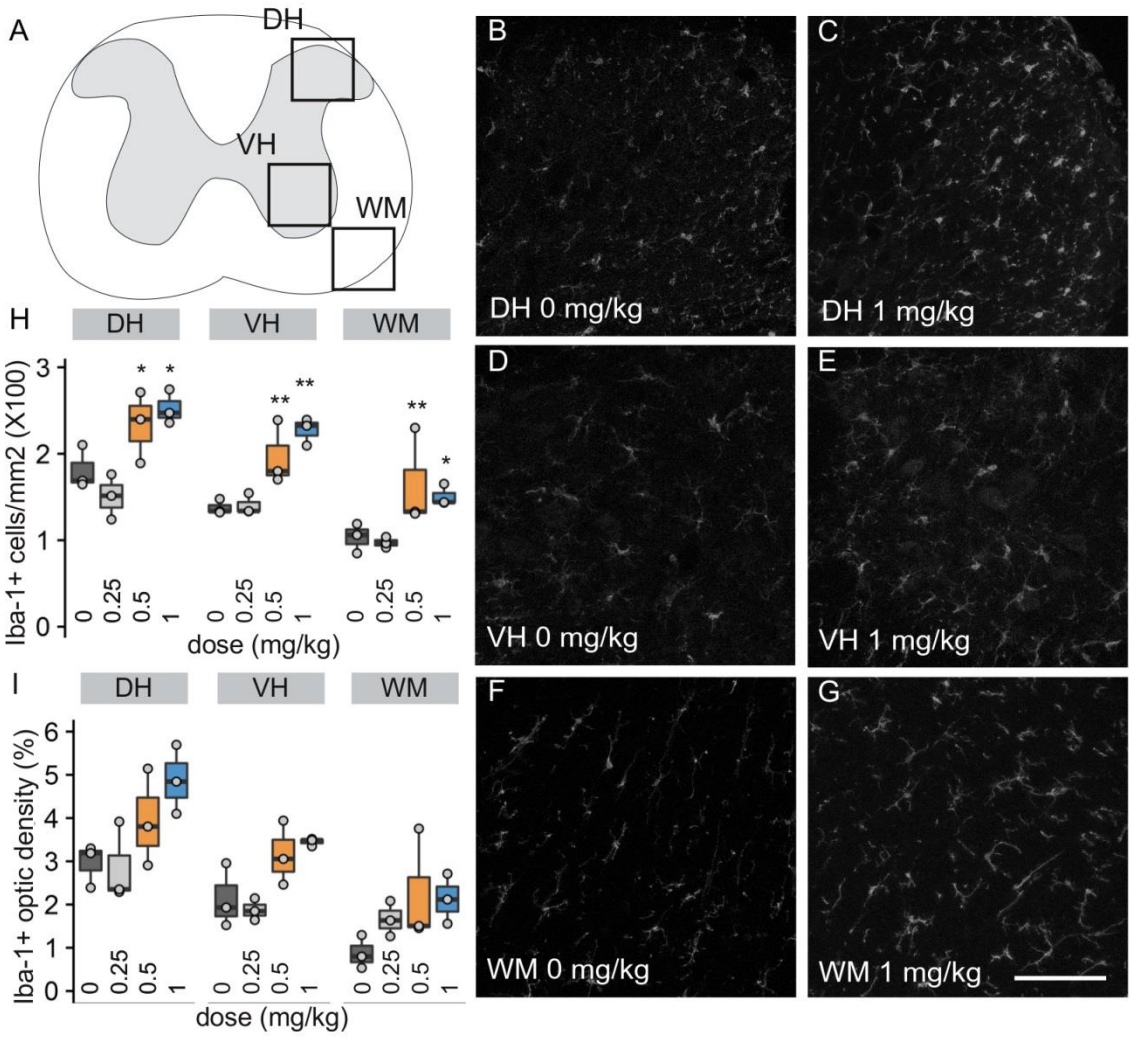
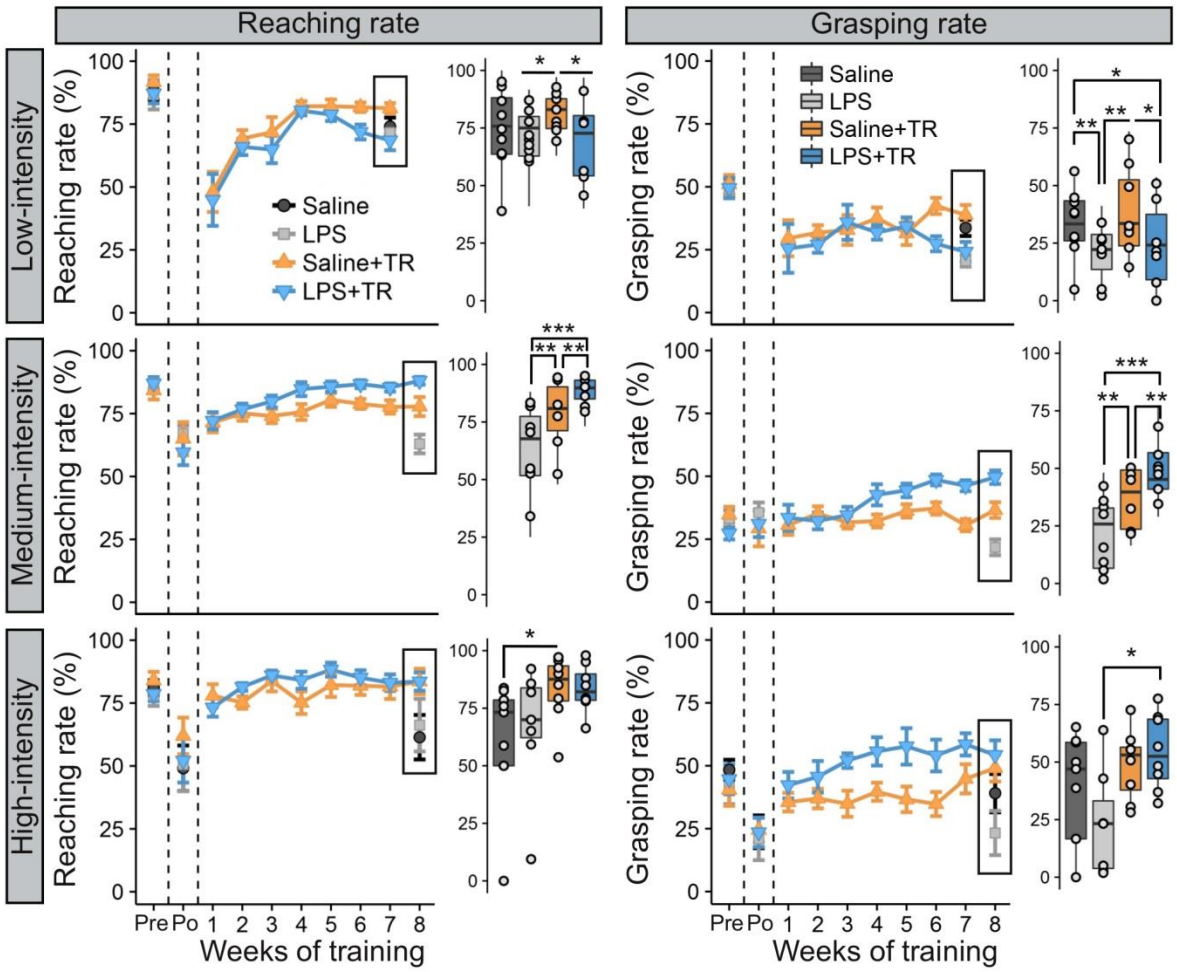


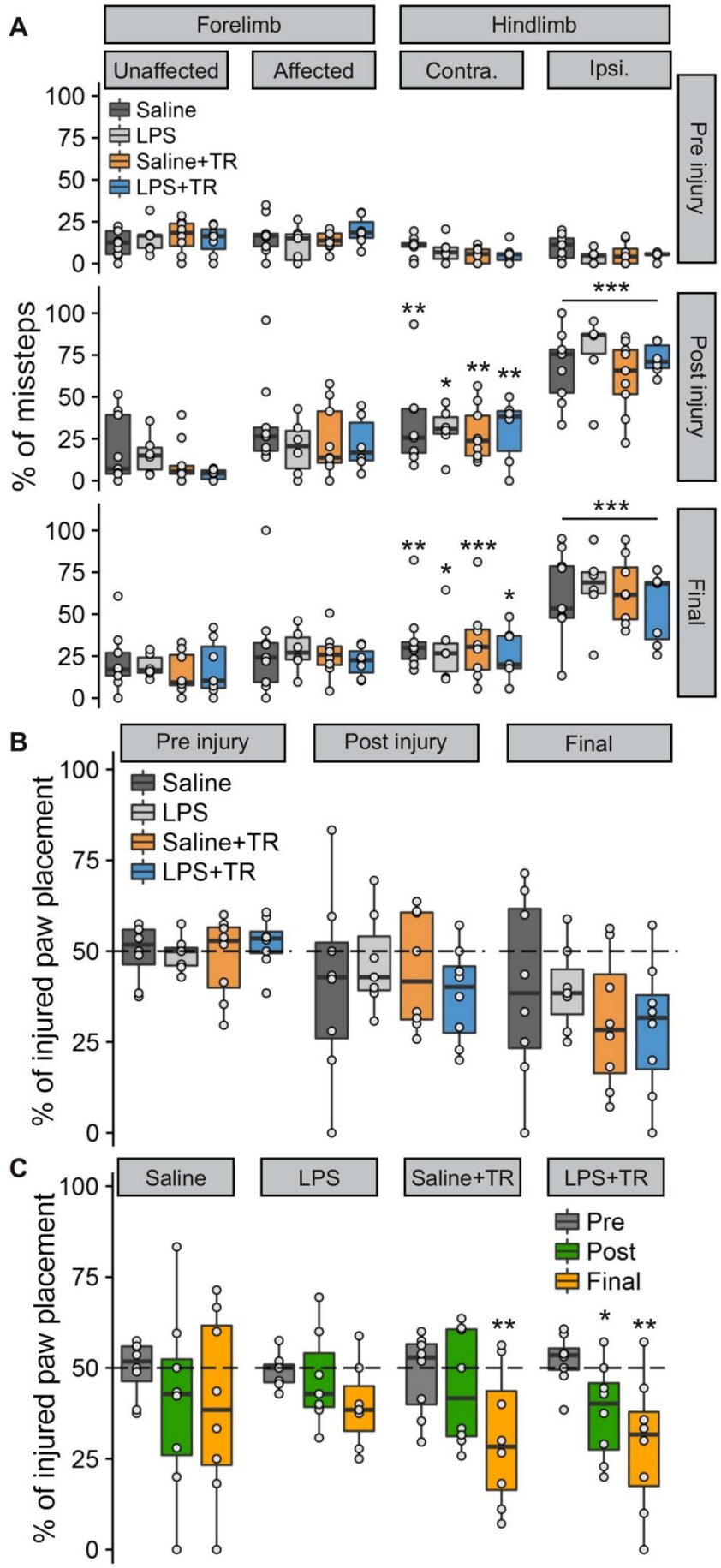
Supplementary Fig. 1. Systemic LPS administration induces a microglial response in the spinal cord. Seven days after systemic LPS (3 doses: 0.25, 0.5 and 1 mg/kg i.p.) or saline (0 mg/kg) injection, Iba-1 staining was conducted and analyzed in the dorsal horn (DH), ventral horn (VH) and white matter (WM) of the cervical spinal cord of intact animals (**A**). A representative picture of Iba-1 staining for saline injected animals is shown for the DH, VH and WM (**B**, **D** and **F** respectively). With the administration of LPS at 0.5 or 1mg/kg, an increase in the iba-1 staining is observed for DH, VH and WM (**C**, **E** and **G** respectively, only 1mg/kg is shown). Iba-1 positive cells were counted (**H**), showing a clear increase in the three measured areas (DH: $KWch_{(3)}$=8.07, p=0.044, VH: $KWch_{(3)}$=8.74, p=0.032, WM: $KWch_{(3)}$=8.58, p=0.036) in animals administered with 0.5 or 1 mg/kg in comparison to saline injected animals. This increase translated to an increase of the Iba-1+ density although

without being statistically significant (DH: $KWch_{(3)}$=6.17, p=0.103, VH: $KWch_{(3)}$=7.66, p=0.053, WM: $KWch_{(3)}$=6.17, p=0.103) (**i**). Scale bar: 100 µm. *p<0.05, **p<0.01 vs. 0 mg/kg group. In box-plots median (middle line), first and third quartile range (box) and interquartile range of 1.5 (whiskers) are represented.

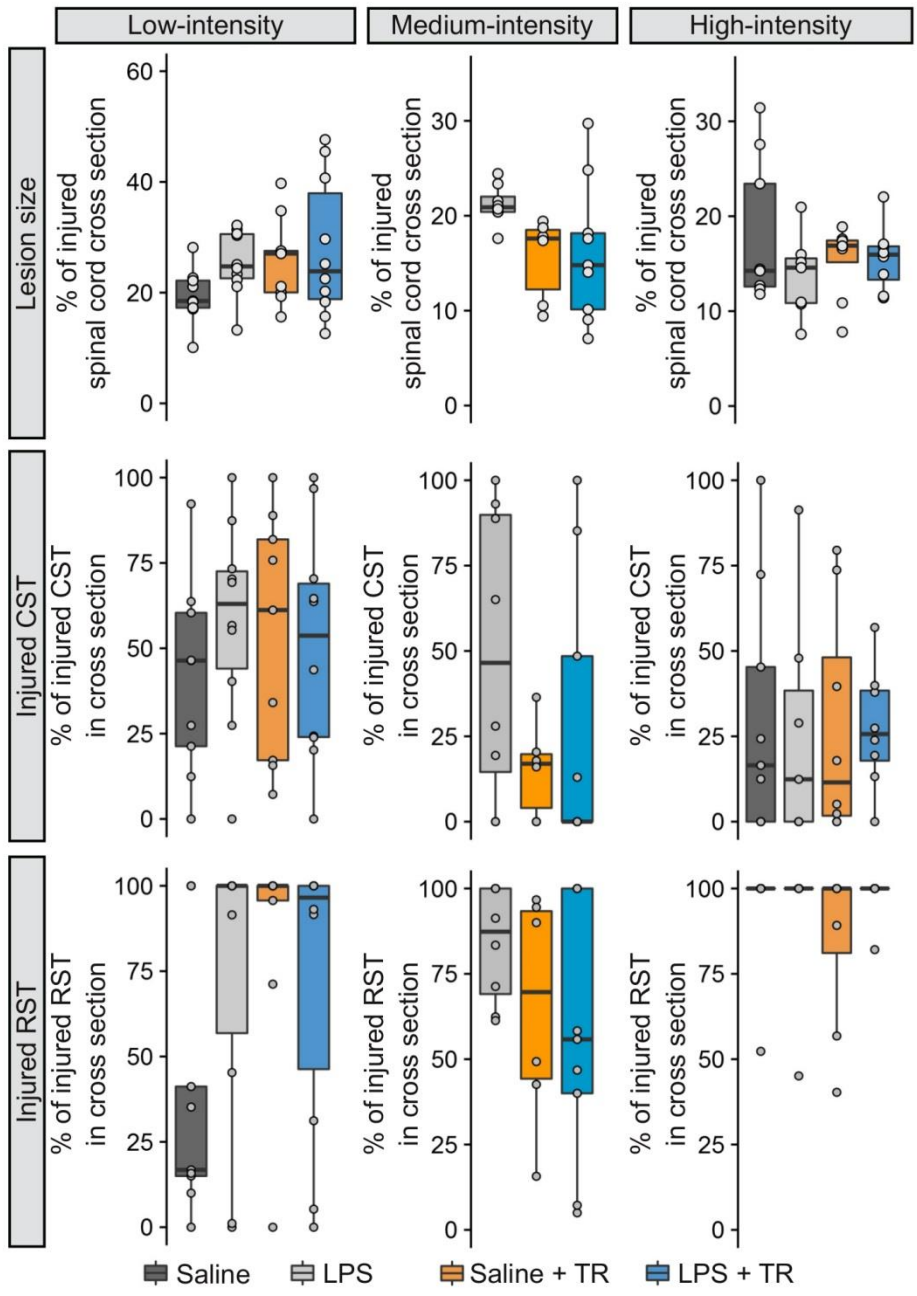


Supplementary Fig. 2. High- and medium- but not low-intensity training in combination with LPS enhance reaching and grasping after chronic spinal cord injury. In addition to success rate (Fig. 1), the SPG performance was measured by reaching rate (left column) and grasping rate (right column). No differences were observed in trained groups along the training period regarding reaching rate for any experiment (Low-intensity: $F_{(3,41)}$=0.64, p=0.59; Medium-intensity: $F_{(2,19.5)}$=0.89, p=0.42; High-intensity: $F_{(3,26.3)}$=1.31, p=0.29), although the interaction between weeks and treatment groups was significant for medium-intensity experiments ($F_{(11,462.3)}$=5.67, p<0.0001). At the end of the training period, differences in reaching were found in the low-intensity experiment ($KWch_{(3)}$=8.82, p=0.03), with differences between LPS+TR and Saline+TR groups (p=0.029). Contrary, following medium-intensity training ($KWch_{(2)}$=24.25, p<0.0001) the LPS+TR (p<0.0001) and

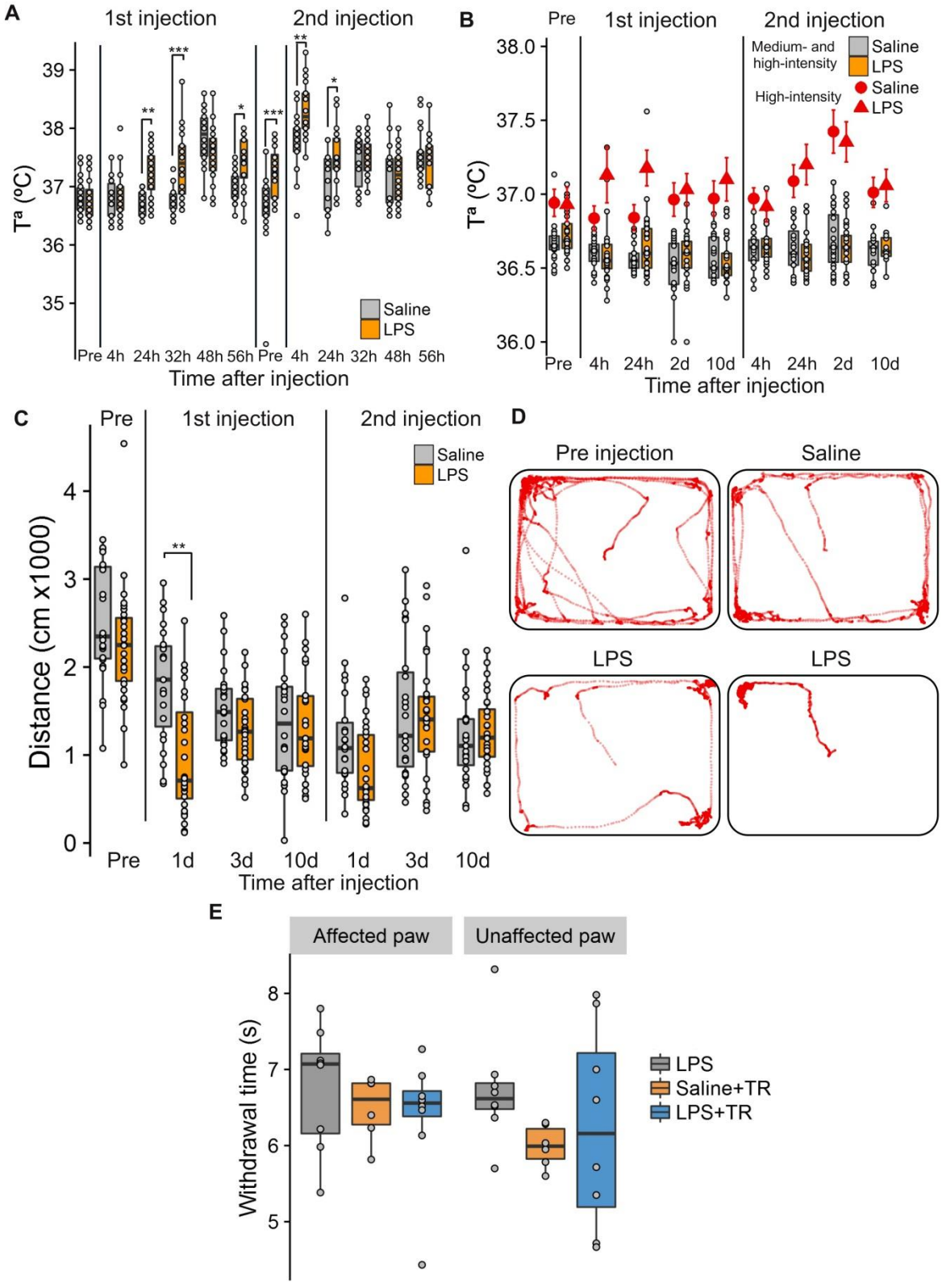
Saline+TR (p=0.0016) groups had significantly higher reaching rates than LPS animals. At the same time, LPS+TR group showed differences with Saline+TR group (p=0.0068). Considering high-intensity training ($KWch_{(3)}$=8.82, p=0.03), Saline+TR animals showed higher reaching rate than Saline group (p=0.038). Regarding the grasping rate, a significant interaction between treatment groups and weeks was observed at low-intensity ($F_{(9,401.2)}$=2.56, p=0.0069), medium-intensity ($F_{(11,462.8)}$=6.25, p<0.0001) and high-intensity training ($F_{(13,152.2)}$=2.01, p=0.022). At the end of the training period both LPS (p=0.002) and LPS+TR (p=0.024) animals showed a significant reduction in grasping rates compared to Saline+TR animals and compared to Saline group (vs. LPS p=0.004, vs. LPS+TR p=0.037) in low-intensity training ($KWch_{(3)}$=15.48, p=0.001). On the other hand, following medium-intensity training ($KWch_{(2)}$=26.87, p<0.0001) the LPS+TR animals showed better grasping rates than the LPS (p<0.0001) and Saline+TR (p=0.0023) groups. With high-intensity training ($F_{(3,28)}$=3.53, p=0.0275), LPS+TR animals showed higher grasping rates compared to LPS treated animals (p=0.025). Pre: pre-injury SPG assessment. Po: 1month post-injury SPG assessment. ***p<0.001. In line graphs mean and SEM are represented. In box-plots median (middle line), first and third quartile range (box) and interquartile range of 1.5 (whiskers) are represented.


A
Forelimb
Hindlimb
Unaffected
Affected
Contra.
Ipsi.
Saline
LPS
Saline+TR
LPS+TR
Pre injury
Post injury
Final
% of missteps
B
Pre injury
Post injury
Final
% of injured paw placement
C
Saline
LPS
Saline+TR
LPS+TR
Pre
Post
Final
% of injured paw placement

Supplementary Fig. 3. The improvement in SPG induced by combining SPG training with LPS did not translate to untrained tasks. In addition to analyzing the performance in the trained task (SPG), animals with high-intensity training were tested in two untrained tasks: grid walk test (**a**) and cylinder test (**b** and **c**). These two tasks were evaluated before the injury (Pre-injury), 1 month after injury (Post-injury) and at the end of the training period (Final). In the grid walk test the number of missteps (see methods) relative to the total number of steps for each paw was quantified as a percentage. No differences between groups ($F_{(3,28.5)}$=0.916, p=0.445) were found at any time (group x time interaction: $F_{(6,297.3)}$=0.47, p=0.827) or for any analyzed paw (group x paw interaction: $F_{(9,288.9)}$=0.25, p=0.98). A main effect of time ($F_{(2,298)}$=89.29, p<0.0001) and its interaction with paw ($F_{(6,288.9)}$=28.3, p<0.0001) were found significant. Comparing pre-injury with post-injury and final time points per paw and group showed significant differences in both contralateral (contra.) and ipsilateral (ipsi.) hindlimbs. For the cylinder test, the number of times the affected paw was placed on the cylinder wall relative to the total number of forepaw placements was calculated as a percentage (see methods). No differences between groups were observed at any time point ($F_{(3,25.5)}$=0.278, p=0.84). A main effect of time was found ($F_{(2,51.6)}$=10.29, p=0.0001). Longitudinal comparisons within groups (**c**) revealed a significant decay in the wall placements of the affected paw over time in Saline+TR and LPS+TR groups. ***p<0.001, **p<0.01, *p<0.05 comparing pre-injury vs. post-injury and Final time points within groups. In box-plots median (middle line), first and third quartile range (box) and interquartile range of 1.5 (whiskers) are represented.

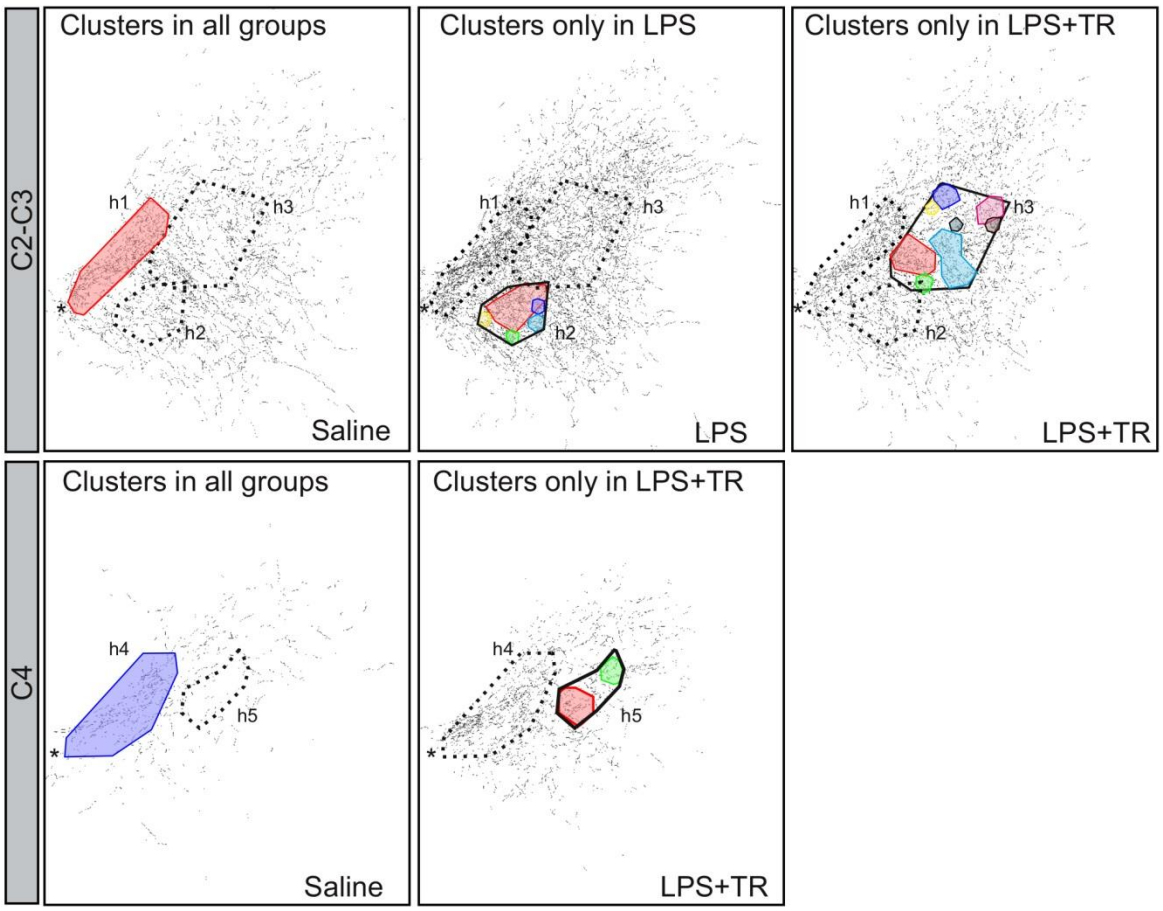


Supplementary Fig. 4. Lesion size. Lesion size comparisons are shown for the high-, medium- and low-intensity rehabilitative training. The cross-sectional distribution of injured spinal cord was mapped and the amount of injured spinal cord, corticospinal tract and rubrospinal tract were calculated as a percentage of their respective total cross-sectional areas (see methods). No statistical differences were found in any of the measures for the three experiments. Mean and SEM are represented. In box-plots median (middle line), first and third quartile range (box) and interquartile range of 1.5 (whiskers) are represented.



Supplementary Fig. 5. Systemic LPS did not affect the well-being of the animals beyond three day after injection. Temperature and general activity were measured at different time

points after each LPS injection. All animals that received LPS showed sickness behavior (i.e., stayed inactive in a corner of their home-cage, piloerection, eyes semi-closed) within the first day after injection followed by a complete recovery on the second day. For low-intensity, rectal temperature was measured before and at 4, 24, 32, 48 and 56h after LPS administration (**A**). A group effect ($F_{(1,36)}$=15.4, p=0.0003) and its interaction with time ($F_{(11,396)}$=5.9, p<0.0001) were found significantly different. An LPS induced increase in rectal temperature was found 24, 32 and 56, but not at 48h after the first injection. Following the second injection rectal temperatures were higher in animals with LPS at 4 and 24h after injection. For medium- and high-intensity training (**B**), although an increase of skin (bar graph, pooled data from the medium- and high-intensity groups) and rectal (red graph, only the high-intensity group was evaluated) temperature were observed 24h after injection these differences were not statistically significant for group effect (skin: $F_{(1,106.3)}$=1.65, p=0.201; rectal: $F_{(1,30.9)}$=2.01, p=0.165) nor its interaction with time (skin: $F_{(8,380.8)}$=1.15, p=0.32; rectal: $F_{(8,217.3)}$=0.79, p=0.6). The general activity was studied in medium- and high-intensity training before and at 1, 3 and 10 days after injection by measuring the running distance in an open field for 5min (**C**). A main group effect ($F_{(1,48.9)}$=5.85, p=0.019) and its interaction with time ($F_{(6,292.5)}$=4.08, p=0.0005) were found significant. Only at 1 day after injection did LPS animals show a reduced walking distance in respect to Saline animals (after injection 1: p<0.0001; after injection 2: p=0.036). An example of the distance the animal locomoted 1 after the first LPS injection is shown in **D**. Moreover, the sensitivity to heat stimuli was also determined at the end of the medium-intensity training experiment (**E**) showing no differences between groups in the affected ($F_{(2,19)}$=0.57, p=0.57) or unaffected ($F_{(2,19)}$=1.17, p=0.33) forepaw. ***p<0.001, **p<0.01, *p<0.05. In box-plots median (middle line), first and third quartile range (box) and interquartile range of 1.5 (whiskers) are represented.



Supplementary Fig. 6. DBSCAN cluster analysis of the BDA+ pixels in the grey matter rostral to the injury. Hotspots of high-density BDA+ pixelated areas (see Fig. 4) were detected by applying a DBSCAN algorithm (see methods). Hotspot h1 was formed exclusively by overlapping the clusters found in all the groups proximal to the central canal (*; top left panel) localized medially along the vertical axis of the edge between the gray and the white matter. Hotspot h2 was formed by the 5 exclusive clusters found in the LPS group in the C2-C3 block (top middle panel), situated more laterally and ventrally to h1. Hotspot h3, situated more laterally and dorsally to h2, was created by unifying the 8 clusters found only in the LPS+TR group in C2-C3 block (top right panel). Similar to h1, hotspot h4 was formed by overlapping the proximal cluster to the central canal found in all the groups in block C4 (bottom left panel) and was found to be a highly dense axonal area with a pixel

density above 50%. Finally, hotspot h5, situated more laterally than hotspot h4, was created by the 2 clusters exclusively found in the LPS+TR group with respect to the other groups in block C4. No unique clusters were found for the Saline+TR group in either the C2-C3 or C4 blocks.

Supplementary Fig. 7. Split channels of merged panels in Fig. 5 and Fig. 6

Fig. 5:

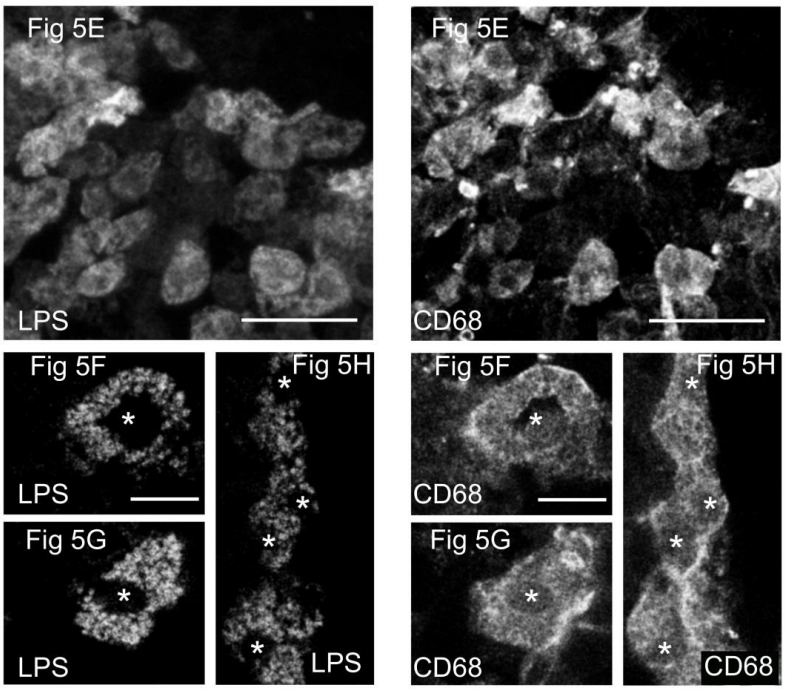


Fig. 6: