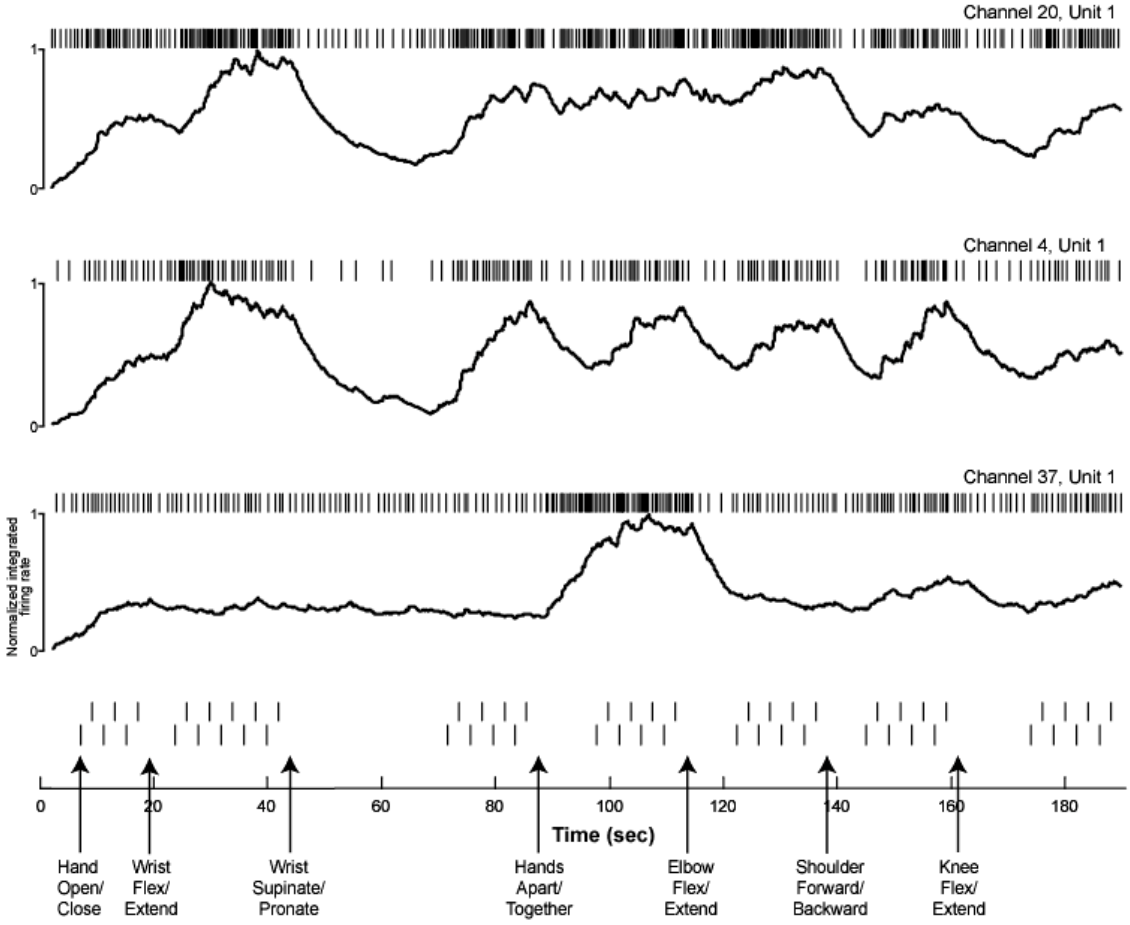
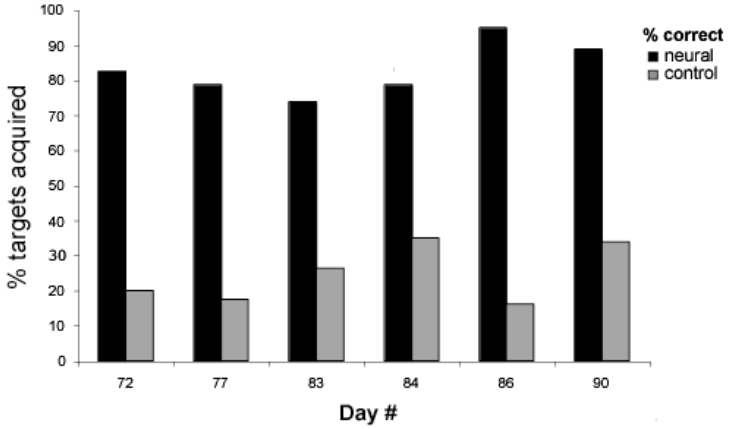
Supplementary Figures



Supplementary Figure 1 | Neuronal selectivity for imagined and performed movements. Over 190 seconds, MN was asked to imagine performing a series of limb movements: Open and closing his left hand, flexing and extending his left wrist, supinating and pronating his left wrist, bringing both hands together and apart, flexing and extending his left arm at the elbow, moving his left shoulder forward and backward, and flexing and extending his left knee. The time of movement instruction is indicated by an arrow; the "go" cues for each alternating movement, presented as text on the video monitor, are indicated by small vertical hash marks. The spiking activity of three simultaneously recorded units is displayed. Rasters indicate the time of each spike (thinned for visual clarity; every third spike is shown). Normalized, integrated firing rates appear beneath each raster, calculated as described in Figure 3. Both the top and middle unit display relatively non-selective increases in activity during the imagined performance of arm and hand movements. The middle unit (Channel 4) shows a particularly clear increase in activity associated with imagined performance, but not in the period between movement instruction (arrow) and go cue (hash mark). The bottom unit, similar to that shown in Figure 3, responds only during anticipation and imagined performance of performing the hands together/apart movement. Data from Channels 20, 4, and 37 on trial day 133.



Supplementary Figure 2 | Center-Out task performance with an alternate post-hoc control. As in Figure 6, target acquisition accuracy is presented by the dark bars for each of 6 dates (n=80 trials on each day). Though "control" targets were not present on the monitor during task performance, and the participant was not asked to avoid any locations on the monitor (which might have improved further improved cursor control; see Video 5), it is also of interest to know whether the cursor traversed the location of any of the other three (invisible) target locations before acquiring correct target (gray bars, control 24.8%; n=80, paired t-test, $p < 0.0001$).

Supplementary Methods and Results

Signal quality and variety. The signal (peak-to-peak) to noise (root mean square) ratio was 10.7 (n=3 sessions, 1 minute each session, all channels with units). Operator-sorted units were isolated during sessions on an average of 21.8 ± 11.2 electrodes. More than one unit could be discriminated from some electrodes (Fig. 2a). A total of 1536 units were recorded over the 57 sessions. These were neither a small number of consistent neurons recorded day to day, nor 1536 unique neurons, but most likely a varying set of neurons. The composition of the recorded ensemble appeared to change on a day-to-day basis. Twenty of 96 electrodes in MN never showed neural spikes.

MI activity during neural cursor control. To determine the number of neurons which changed their firing rate during neural cursor control, data collected during epochs in which no instruction was provided (i.e., "rest" periods) were compared to epochs that MN was actively performing the center-out task (i.e., "movement" periods).

Center-Out task description. For six sessions, after filter building was performed, the subject completed 80 trials of a 4-direction center out task: the participant was instructed to use his thoughts to move a circle (neural cursor) displayed on the screen to one of four peripheral targets, positioned at 0, 90, 180, and 270°, subtending at a visual angle of 4.8° (5 cm) from the center of the monitor; the distance from screen center to target center was 9.5 cm (9.12°). The circle was animated by the output values of the linear filter[45], regressing spiking activity onto 2-dimensional position on the screen. A trial began after the subject held the neural cursor in the center target for 500ms. At the start of a trial, one of four peripheral targets appeared on the screen. The participant was instructed to move the neural cursor to the target location and hold it at that location for 500ms. A trial expired after 7 seconds. Trials were considered successful if the target was acquired in 7 seconds or less; trials were considered failures if no target was acquired in 7 seconds. Regardless of whether or not the target was successfully acquired, because the neural cursor was under constant neural control, the participant needed to return the cursor to the center

target (and dwell there for 500 ms) before the next trial would begin. The neural cursor subtended a visual angle of 2.43° (2.5cm diameter). 20 trials were collected for each of the 4 peripheral targets.

As a control measurement, the same cursor kinematics were replayed, off-line, while both the correct target and one of the other three pseudorandomly selected "incorrect" targets were visible, representing a territory of the screen equivalent in size to that of the true target (which was the only one visible during task performance). If the neural cursor hit one of the post-hoc incorrect targets before hitting the correct target, this was marked as "control target acquired".

The visual instructions were displayed on a computer monitor in front of the human subject (59 cm away from eye to center of monitor), subtended at a visual angle of 18.72° (20cm) degrees. The subject was seated in his wheelchair for all sessions, with his arms positioned on the arm rests of the chair.

Grid task description. The grid task clinical trial endpoint tests for the ability to move the neural cursor to a random target on successively finer grid squares displayed on the screen and to dwell on that target for a predetermined amount of time. For this task, the screen was divided into between 16 to 64 square targets. The color of one randomly selected square was changed to indicate the target for each trial. The participant was required to maintain the neural cursor within the borders of the target square for 220, 250, or and 500ms before credit was given for a successful target acquisition; so long as the cursor dwelled over the target for the required time, the target was successfully acquired. This did not require a deliberate "hold", but sufficient control to keep the cursor at the target location for the defined time period. A new target was presented as soon as the correct target was acquired. The participant had 5 seconds to acquire the target, or the trial was marked as incorrect and a new target was presented. The control consisted of an equivalent time of running the 16 target grid task while the computer monitor was turned away from the participant and he was instructed to rest.

MN successfully selected from among 16 targets with 57.8 ± 25.9% accuracy (control = 5.56 ± 7.26%; 500 ms hold time, paired t-Test, $n=9$, $p<0.0001$, see Supplemental Methods) and was able to direct the cursor to a desired location on a 64 square grid task, although performance was considerably degraded (16.7 ± 13.2% average success rate) when each target covered only 1/64th of the screen. It is noteworthy that success was highly affected by dwell time. Shortening the dwell from 500 to 250 or 220 ms increased target acquisition success at all tested grid tasks (up to 64) ($n=12$, paired t-test, one-tailed, $\alpha=0.05$, $p<0.0003$). Thus, shorter dwell requirements helped to demonstrate that the neural cursor could be moved to a location and that spatial accuracy was masked by temporal constraints. Systematic evaluation of spatial and temporal control parameters continues as part of the ongoing clinical trial.

Direct control of prosthetic devices: For the robotic limb, neural output was used to drive a multi-joint robotic arm with a two-finger gripper hand. A filter was constructed so that "shoulder" rotation, "elbow" flexion and extension, and gripper opening/closing could be independently controlled (via separate servo motors) by moving the neural cursor to each of 5 screen targets. MN successfully controlled the robot within ~10 minutes and was able to grasp a piece of candy and deliver it to the hand of the technician at another location.

Supplementary Discussion

Summary of neurophysiologic findings: We report at least three novel neurophysiologic findings. First, we have demonstrated with at least one human participant that neuronal spiking related to imagined or intended arm movements persists years after SCI within a grossly identifiable anatomic landmark in human precentral cortex. Within the small patch of MI, neurons have a diverse set of properties: they may be activated by proximal or distal intended actions, they can be specific or related to multiple actions, and they can be related to actual as well as imagined actions (Figs. 3, S1). Such heterogeneity within the arm area is consistent with that observed in monkey MI.[46] Second, human MI activity, at least in SCI, appears to be profoundly influenced by internally generated signals and requires neither normal somatic sensory input nor limb movement to show movement-related properties. These findings also confirm that imagined movements modulate MI neuronal spiking activity, as suggested by functional imaging studies.[47-50] Third, human MI neurons in SCI have directional tuning and timing features qualitatively similar to those found in intact non-human primates.[5,20]

Comparison to prior work: It is useful to compare the published methods and results from prior efforts which recorded intracerebral signals for external device control by persons with physical disability. Of Kennedy et al.'s first three patients, only the stroke patient[35] was reported to achieve cursor control using action potential-based signals. In comparing that report to our current effort, the sensor, signals, interface and control were substantially different. Unlike the sensor used in the current study, which employed an array of extracellular electrodes to record many single neurons, Kennedy et al. used an implant of 1-2 glass cone electrodes that record from cellular processes induced to grow into the cone over weeks. Based on the published data it is difficult to compare these signals to the neuronal spiking patterns we observed in MN. By contrast, activity in MN is directly comparable to movement-related activity observed in MI of intact monkeys (Fig. 4). Further, cone electrodes have not provided ensemble spiking, which forms the basis of MN's control signal. Decoding also differed in that, in the cone electrode report, only increases in averaged firing rate (not decreases or other changes in periodicity) were used as a signal source, rather than the population spiking patterns reported here, which would seem to more closely capture signals related to desired hand movement.[51] The control interface also differed significantly in the two studies. Unlike MN, signals used for neural control with the cone electrode were initially generated during purposeful and still-intact movement of various face parts (eye, eyebrow, mouth, tongue); through learning, cortical activity was later dissociated from facial movement. In contrast, MN's neuronal ensemble activity was immediately linked to imagined arm actions (Fig 3; Supp Fig 1). This difference may suggest different placement or selectivity of the recording electrodes, amounts of plasticity in the two forms of central nervous system damage, or other mechanisms. Finally, MN achieved two-dimensional cursor control using decoded neuronal ensemble output that enabled real-time video game performance and basic robotic arm control, while the reported cone-electrode patient used still-intact neck, brow, or toe EMG activity to control unidirectional (downward) cursor excursion and neural activity to achieve unidirectional (rightward) control in a serial spelling task. While it is difficult to compare these measures of control directly, the present NMP appears to offer a more rapidly acquired and higher dimensional control system.

Supplementary Video Legends:

Videos are selected for visual clarity, and do not necessarily represent consistently recorded data.

Video 1: Center-Out task. The goal of this task is to move the neural cursor to the location of the target ("money bag", the target preferred by MN). The cursor must be held over the target for 500ms in order to register a success. Trial day 86. This was the best recorded day of Center-Out performance (see Fig. 6) (QuickTime 3.7 MB).

Video 2: Video showing use of a computer interface with the neural cursor. Opening and closing simulated email using the neural cursor, while reading aloud, and drawing a circle with a neural cursor-enabled "Paint" program. The neural cursor first is used to open two simulated email messages. Selection is made only by passing the cursor over the icon. This is followed by three attempts to paint a circle with the neural cursor. The email and initial two circle drawing attempts are continuous video. Approximately 8 minutes later, after several other tasks were performed, the third circle drawing attempt was performed. Trial day 98. Mail icon selection was typical of his performance over the several days this task was provided. He was able to complete a loop on each day, from the first day requested; the third circle shown here was the most symmetric drawn (QuickTime 1.6 MB).

Video 3: Neurally-controlled television. MN uses the neural cursor to operate a television remote control via a computer interface; commands are sent to the television via an infrared system (Spitfire, Innotech Systems, Port Jefferson, NY). This is the first day that MN was shown this TV controller. Trial day 86 (QuickTime 1.6 MB).

Video 4: Neural "Pong". Continuous control of the 1 dimensional "neural paddle" is shown. Trial day 70. This was the first day that he was shown the Pong task (QuickTime 2.9 MB).

Video 5: Neural "HeMan" game. The object is to capture the treasure chests while avoiding the square obstacles. Trial day 90. This was the third day that MN played the HeMan game (QuickTime 2.8 MB).

Video 6: Direct neural control of a prosthetic hand. MN was initially instructed to move a neural cursor "up" to open the hand, and "down" to close the hand. While at first he looked at both the video monitor and prosthetic hand, he disregarded the monitor after a few trials and regarded only the hand while manipulating it in real time. He is describing aloud what he intends the hand to do. Trial day 114. This was the first day that MN was shown the prosthetic hand (QuickTime 2.3 MB).

Video 7: Transport of an object from one location to another via direct neural control of a multi-articulated robot arm. MN was asked to grab a piece of candy with the robotic arm, then to place it into the hand of an operator. Neural control of the robot arm is achieved by directing the neural cursor over targets on the screen. Each target directs the activity of one of three independent motors which actuate 1) rotation about the "shoulder" joint; 2) flexion/extension about the "elbow" joint, and 3) opening and closing the "hand". A piece of candy is placed between the grippers, and MN then closes the hand. The robot arm is then rotated about the shoulder, extended toward the destination, and the candy is released into the operator's hand. Trial day 209. This was the first and only day that robot arm control was attempted (QuickTime 1.7 MB).

Video 8: Trial Participant #2 performing Center-Out task. The goal of this task is to move the neural cursor to the location of the target ("money bag"). The cursor must dwell over the target for 500ms in order to register a success. Trial day 190. This appeared to be among the best recorded Center-Out performances for this participant (QuickTime, 7.4 MB).

Supplementary References:

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