Instant neural control of a movement signal

Hands-free operation of a cursor can be achieved by a few neurons in the motor cortex.

The activity of motor cortex (MI) neurons conveys movement intent sufficiently well to be used as a control signal to operate artificial devices[1–3], but until now this has called for extensive training or has been confined to a limited movement repertoire[2,3]. Here we show how activity from a few (7–30) MI neurons can be decoded into a signal that a monkey is able to use immediately to move a computer cursor to any new position in its workspace (14° × 14° visual angle). Our results, which are based on recordings made by an electrode array that is suitable for human use[4,5], indicate that neurally based control of movement may eventually be feasible in paralysed humans.

We recorded the activity of MI neurons in three *Macaca mulatta* monkeys that had been implanted with a Utah intracortical multi-electrode array[6]. Monkeys used one hand to move a manipulandum that controlled the position of a cursor displayed on a video monitor. Using this position-feedback signal, monkeys tracked a continuously moving visual target that began at an arbitrary location and followed a pseudo-random trajectory[7,8].

We then used a linear filter method to test whether we could reliably reconstruct the hand trajectory from neural activity obtained in subsequent trials. Our linear filter method can be considered as a weighted sum of neural firing (here grouped in 50-ms bins) that takes into account the previous 1 s of activity[7–9] (see supplementary information). Reconstruction accurately reflects hand trajectory, accounting for over 60% of the variance that was present in actual hand movements ($r^2 > 0.6$).

One of the monkeys then used neural control to move the feedback cursor to different targets (Fig. 1). For this closed-loop version of the experiment, reconstructions were computed continuously online in real time. An average of 1 min of continuous tracking and recording was used to construct preliminary linear filters. Once this model was constructed, the continuous task was switched to a new task that required the cursor to be moved to stationary targets (size, 0.6°), which were displayed one at a time at random locations on the monitor. During this time, hand control of the cursor position was substituted with neural control. For a period averaging 2 min, we constructed new decoding filters to relate firing to target position.

Task performance continued under two conditions: the feedback cursor could be controlled either by hand motion or by the neural signal in pseudo-randomly interleaved trials. The monkey immediately used the neural-activity-based signal to carry out the task without any further training (see movie in supplementary information). During this time, the monkey intermittently made arm movements, including, but not restricted to, target-directed hand motions (Fig. 1a). During some trials, however, the manipulandum was not moved; other muscle contractions may have occurred at this time, but these were not monitored (Fig. 1b).

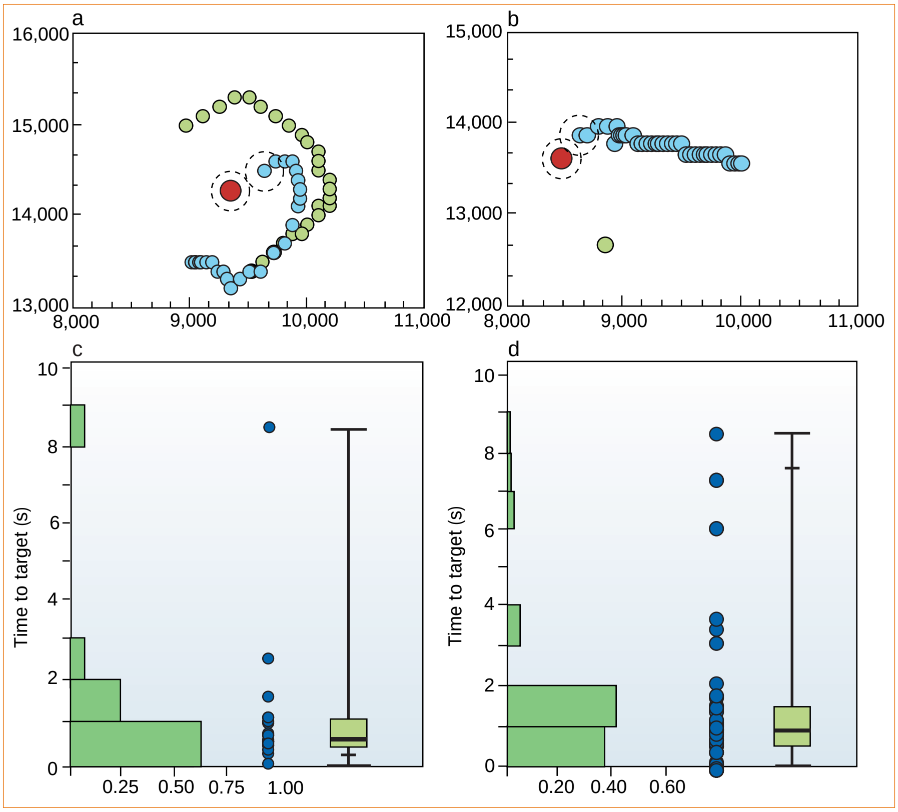

Figure 1 Performance of a target acquisition using hand or neural control. **a, b,** Trial examples showing the movement by hand (green) and by neural reconstruction (blue) of a cursor to a target (red). Dotted outlines represent the actual circumference of the target and cursor on the screen. In **a**, hand motion resembles the neurally controlled cursor path; in **b**, no manipulandum motion occurred, but the neurally controlled cursor reached the target. Each dot represents an estimate of position, updated at 50-ms intervals. Axes are in *x,y* screen coordinates (1,000 units corresponds to a visual angle of 3.5°); note that the two trials take place in different parts of the workspace. **c, d,** Comparable times are taken to reach the target under hand (**c**, $n = 20$) and neural (**d**, $n = 70$) control. Each panel shows three plots: data frequency distribution (histogram), trial times (spheres) and summary statistics (box and whiskers). The summary shows the median time taken to reach the target (horizontal line), the 25th and 75th percentiles (top and bottom of shaded box), and the range of the data (vertical lines).

Targets were considered to be acquired only if they were reached within 20 s of their appearance. We found that cursor control was nearly as good as direct hand-positional control. The time required to acquire targets using the neural signal was only slightly greater than that required for hand motions (Fig. 1c, d); this difference was not significant at $\alpha = 0.05$ by a two-sided Kolgorov–Smirnov test. By contrast, target acquisition was unsuccessful (> 1 min) if filters were randomly shuffled between cells or if a random number was added to the filter coefficients, indicating that properly constructed filters are necessary for neural control to operate. The marked, immediate success of the linear-regression method compared with other approaches may be related to the lack of strong assumptions about neuronal firing, to the power of the linear-regression method, or to the number and type of cells used for decoding.

Neuroprosthetic devices will comprise two learning systems: a mathematical algorithm and the subject's brain. A primary role of the algorithm is to transform neural activity into a control signal that operates in a functionally usable region of space. The utility of filters constructed during neural control suggests that visual and other feedback, coupled with a subject's dynamic learning, can compensate for inaccuracies in the model to provide an easily and voluntarily adjusted control signal. Our results demonstrate that a simple mathematical approach, coupled with a biological system, can provide effective decoding for brain–machine interfacing, which may eventually help to restore function to neurologically impaired humans.

Mijail D. Serruya, Nicholas G. Hatsopoulos*, Liam Paninski*, Matthew R. Fellows, John P. Donoghue

Department of Neuroscience, Box 1953, Brown University, Providence, Rhode Island 02912, USA
e-mail: mijail_serruya@brown.edu
**Present addresses: Department of Organismal Biology and Anatomy, University of Chicago, Chicago, Illinois 60637, USA (N.G.H.); Center for Neural Science, New York University, New York, New York 10003, USA (L.P.)*

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Sonography

Dizygotic twin survival in early pregnancy

It has been suggested that losses of twin conceptuses in very early pregnancy are high, and that for every liveborn twin pair there are a further 10–12 twin pregnancies that end up as a singleton birth[1]. Here we show that in a group of women who had double-ovulated and conceived, the probability of the second egg also becoming fertilized and developing is 20–30% — which is comparable to the probability of conception and survival of a single conceptus[2]. We conclude that the presence of one embryo does not affect the development of its twin.

So far, no direct measure has been available of the proportion of double ovulations that lead to twins. We have obtained this information by using ultrasound to identify pregnant women with two corpora lutea, and correlating these with the number who had one or two fetuses (dizygotic twins) in early pregnancy. The corpus luteum is an endocrine organ that develops in the ovary at the site at which the egg was released, and can therefore act as an indicator of the number of ovulation events.

As only two small ultrasound studies have identified the corpus luteum in early pregnancy[3,4], we confirmed these findings in a larger series at our centre, where the ovaries of all pregnant women are routinely examined. We scan mainly low-risk pregnancies, as well as women who had assistance in conceiving. In scans of 504 women where both ovaries were seen in early pregnancy (5–9 weeks gestation), the corpus luteum could be identified in 94.6% of cases. Its mean diameter was 19.6 mm (± 5.28 standard deviation). Single ovulations were distributed equally between the two ovaries, occurring on the left in 49.3% of cases.

Table 1 Distribution of double-ovulation events

	Both left	One in each	Both right
Spontaneous	7	14	6
Iatrogenic	2	6	7
Unknown	3	3	0
Total	12	23	13

Forty-eight cases of double ovulation were identified by ultrasound scans of 504 women during early pregnancy. Of these cases, 27 were spontaneous, resulting in 9 sets of twins and 18 singletons; and 15 were induced, resulting in 3 twin pairs.

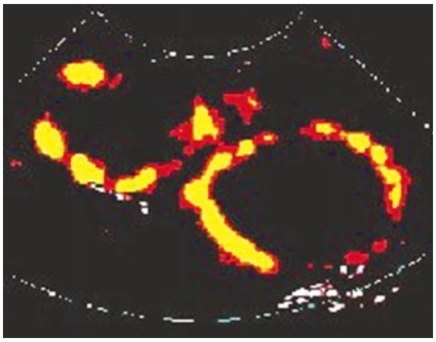

Figure 1 Doppler ultrasound of two corpora lutea in one ovary (signifying dual ovulation). The corpus luteum typically appears as an echo-filled cyst with a ring of peripheral vascularity. Colours reflect variations in blood flow, with yellow as the fastest.

There were 48 cases of double ovulation identified by these ultrasound scans (Fig. 1). Of these (Table 1), 27 were spontaneous, with 9 among this group conceiving twin pairs (30%) and the remainder singletons. Fifteen double ovulations were induced by clomiphene citrate, and among these there were three sets of twins (20%). We were unable to determine whether the dual ovulation was spontaneous or induced in the remaining six cases, of which three were twin pregnancies. Maternal age among those who had double-ovulated (32.5 years) was not significantly different from those who had had a single ovulation (30.7 years; $P = 0.07$, t-test). All sets of twins were of dichorionic and diamniotic placentation on ultrasound examination, which is consistent with dizygotic twinning.

We conclude that the presumption of huge losses of dizygotic twins in early pregnancy[1] is unfounded, as we would then have seen many more double ovulations with a singleton-pregnancy outcome (signifying an aborted twin). The probability of the second egg also becoming fertilized seems to be similar to that of one egg becoming fertilized in a singleton pregnancy[2]. The presence of one embryo therefore does not impede the development of its twin.

Our study does not, of course, eliminate the possibility that both twins might be lost at a higher rate than singletons. However, we do not believe that this would fit with our finding that the second egg has the same chance of developing as a singleton pregnancy once the first egg is fertilized.

The distribution of spontaneous double ovulations is consistent with a random spread of ovulation between left and right ovaries (Table 1). This suggests that the mechanism responsible for dual ovulation involves signalling from outside the ovary, rather than local intra-ovarian control[5], as we would then have seen more double ovulations from the same ovary.

We have confirmed that the corpus luteum can be readily identified in an early-pregnancy scan, enabling us to characterize a significant number of double ovulations in the human. To our knowledge the last attempt to do this was in 1794, when William Hunter observed after 400 dissections of pregnant uteri: "When there is one child, there is only one corpus luteum; and two in the case of twins. …In some of these cases, there were two distinct corpus lutea in one ovarium."[6].

Stephen Tong*, Simon Meagher†, Beverley Vollenhoven*†

**Department of Obstetrics and Gynaecology, Monash University, Monash Medical Centre, Clayton, Victoria 3168, Australia*
e-mail: stephen.tong@med.monash.edu.au
†Monash Ultrasound for Women, Monash IVF, Epworth Hospital, Richmond, Victoria 3121, Australia

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