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Deciphering neural drive

Decoding the firing of individual spinal motor neurons enables the offline control of prosthetic limbs.

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Efforts to restore the functionality of a lost limb via an artificial replacement are slowly moving from conventional technologies such as suspending the prosthetic limb from the stump using compressing sockets to fixating it directly into the skeleton by osseointegration[1] (Fig. 1). Restoration of sensory feedback is progressing from sensory substitution[2] to appropriate sensory perception elicited by long-term interfaces implanted in the brain[3] or in the peripheral nervous system[4,5]. Patients can now intuitively control more than one robotic joint, owing to myoelectric pattern recognition[6] (MPR) and surgical techniques such as targeted muscle reinnervation[7] (TMR) and free muscle transfer[8]. Each of these technologies has its caveats, from the need for surgical interventions to the long-term instability of non-invasive and highly invasive neural interfaces[9]. Although these technologies are not mutually exclusive and can be combined[5,10], a near-perfect solution is yet to be clinically implemented. Therefore, efforts continue to be directed towards achieving natural control of the prosthetic limb.

Muscle contraction is the ultimate physiological response to natural motor volition. Harvesting information from the neural drive of distally available muscles would thus result in an intuitive neural control interface. Reporting in *Nature Biomedical Engineering*, Farina and colleagues now show that this is possible: they measured the firing of individual spinal motor neurons, and used their discharge timings to control prosthetic upper limbs offline[11].

Clinically used robotic prostheses measure the global activity of a muscle, or group of muscles, to activate one prosthetic function — for example, in a transhumeral amputee an electrode over the biceps brachii muscle activates the closing of the prosthetic hand, whereas another electrode over the antagonistic muscle (the triceps brachii) commands its opening. The combined activity of motor units as recorded by one electrode is often used as a proportional control signal (contraction strength being proportional to the speed of actuation of the prosthesis). Farina and colleagues used instead an array consisting of more than 50 smaller and closely spaced electrodes to reconstruct the propagation of individual motor action potentials (as opposed to only their summation; Fig. 2a). Once individual motor units were identified by deconvolution[12], their discharge timings were mapped into offline prosthetic commands.

Such direct control requires independently controlled muscles, which are scarce in higher amputations at the upper-arm level or above. TMR increases the number of independent myoelectric sources by surgically deinnervating a non-joint-actuating muscle (or a segment of it), and then hyper-reinnervating it with nerves that carry more valuable information so as to enable intuitive control of lost distal joints. TMR effectively transforms functionally useless muscles into biological amplifiers of neural commands that are intended for the missing limb (Fig. 2b). Direct control can then be used to allow the subject to independently actuate different prosthetic joints proportionally and simultaneously. However, a limiting factor in the use of global myoelectric activity is the crosstalk interference from neighbouring muscles, which can even be present after TMR owing to the proximity of myoelectric sites. MPR has been previously found to be beneficial after TMR[13], as it can incorporate crosstalk as part of the aimed movement. Overall patterns of muscular activation recorded by all electrodes are used in MPR to determine motor volition, rather than single one-to-one relationships as in direct control. MPR was initially developed as an enhancement over direct control in non-TMR subjects with more distal amputations (for example, transradial),

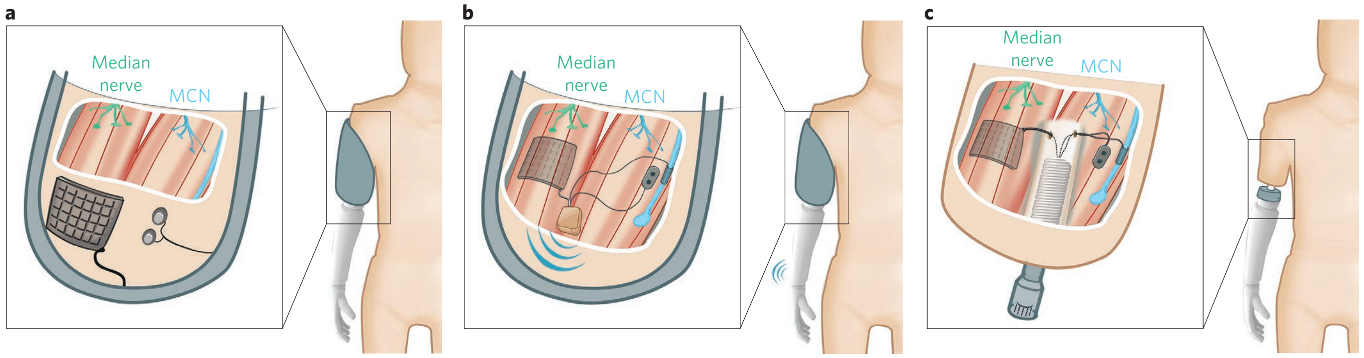

Figure 1 | Interfacing technologies for prosthetic control with targeted muscle reinnervation (for instance, long head of the biceps brachii muscle reinnervated by the median nerve). **a**–**c**, Prosthetic mechanical attachment by socket suspension (**a**,**b**) or direct skeletal fixation (**c**). Non-invasive surface (**a**) and implanted (**b**,**c**) electrodes accessed by wireless (**b**) or wired (**c**) electrode–prosthesis communication. Neural drive can be directly accessed by implanted neural electrodes, or decoded using high-density muscular electrode arrays. Direct neural sensory feedback can be delivered using implanted neural electrodes (**b**,**c**). MCN, musculocutaneous nerve. Figure courtesy of Jason Millenaar.

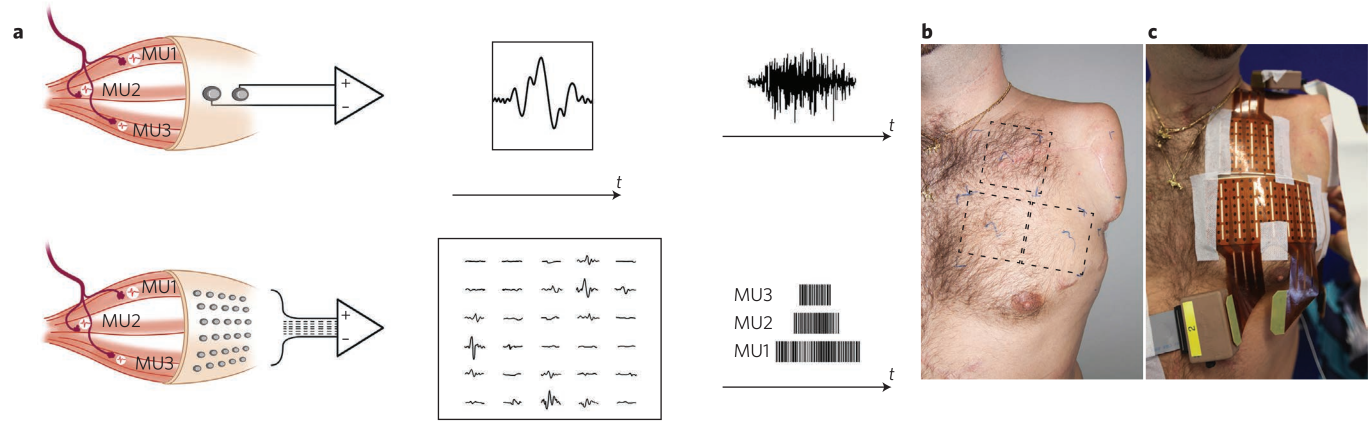

Figure 2 | Surface-electromyography technologies. **a**, Top: conventional differential recording of electromyographic signals using two electrodes that capture the combined activation of active motor units (MU) over time to approximate muscular contraction. Bottom: instead, high-density electromyography allows for deconvolution algorithms to identify single motor units and their firing rate to extract neural drive. **b**,**c**, Decoding of neural drive in a glenohumeral amputee with targeted muscle reinnervation (**b**; dotted squares indicate the position of rerouted nerves) using high-density electromyography. Three electrode arrays provide the raw electromyographic signals needed for decomposition of individual spinal motor neurons (**c**). Panel **a** courtesy of Jason Millenaar and panels **b**,**c** courtesy of Ivan Vujaklija.

where available musculature allows MPR to deliver intuitive, proportional and simultaneous prosthetic control[14]. Similarly to conventional direct control, global features of the combined activity of motor units have been used in MPR.

Farina and co-authors evaluated their decoding paradigm in six subjects following TMR. In three glenohumeral TMR subjects, motor-neuron discharge timings were compared to those from conventional global myoelectric features as discriminants of 7, 9 and 11 movements using MPR. The number of motor units was found to be relatively constant between reinnervation sites (23.1 ± 11.2), and their discharge timings showed higher offline accuracy than conventional myoelectric features (97% and 85%, respectively). The authors argued that improved accuracy resulted from the identification of highly interfering signals, which can be hard to discern by using global myoelectric features. Patterns provided by single electrodes that average myoelectric activity might be too close to each other to be discriminated; an electrode grid instead provides individual motor-neuron firings and the location of their innervated muscle fibres.

In a complementary experiment, three transhumeral TMR subjects were asked to ramp contractions of a single muscle to the maximum and slowly go back to relaxation while myoelectric recordings were performed through the electrode grids. Motor-neuron identification allowed Farina and co-authors to observe the two physiological mechanisms that are responsible for the increase in muscular activation: recruitment of additional motor neurons and increased discharge firing rate. The pooled motor-neuron discharge timings were found to be a closer estimate of contraction intensity than global myoelectric activity, notably reducing the effect of spurious envelope fluctuations due to stochastic amplification of concurrent motor action potentials. A closer approximation of muscular contraction force increases the precision of proportional actuation of the prosthesis. Moreover, the authors mapped the decoded motor spike trains into kinematics in one of the transhumeral TMR subjects by using signal- and model-based approaches (respectively dimensionality reduction without labelling and forward biomechanical estimation of joint moments). Decoding up to three degrees of freedom produced an average coefficient of determination (R^2) of 0.73 for the simultaneous activation of all three degrees of freedom.

There is a well-known gap between clinical reality and research achievements in controlled environments[15]. Reliability is fundamental for prosthetic users to trust and accept their artificial devices, and this might be compromised by increasing the complexity of the employed man/machine interface. In general, the larger the number of electrodes required, the more likely it is that problems will arise. The proposed approach requires considerably more electrodes with a smaller surface area in contact with the skin, which can more easily result in motion artefacts saturating the bioelectric amplifiers. Surface electromyography is plagued with such practical problems, particularly when employing dry electrodes, as required in clinical practice. Farina and co-authors used adhesive wet electrodes (Fig. 2c); however, it is difficult to use these daily and for prolonged periods of time. In principle, the authors' technique could also be used with multichannel implanted electrodes, in which case the practical problems are transferred to the development of long-term stable high-density connectors, leads and transcutaneous communication interfaces. In any case, the increased number of electrodes requires a more sophisticated analogue front-end and acquisition electronics, along with additional computational demands posed by the processing algorithms, which must be computed in real time and in an embedded portable processing unit.

Farina and colleagues propose one of the most physiologically based decoding neural interfaces tested to date in humans. They demonstrated its feasibility in three offline experiments in ideal conditions, one of which evaluated proportional and simultaneous control in one subject. Further real-time and real-life evaluations integrating proportional and simultaneous control are necessary to determine the practical feasibility of the proposed technology in prosthetic limb control. From a scientific viewpoint, the non-invasive decoding of motor-neuron activity is a fantastic tool for scientists to study the progression of muscle reinnervation and the variables that can affect its success. By allowing physicians to monitor the gradual appearance of motor-neuron connections to muscle fibres, this technology could also be used as a diagnostic or prognostic tool beyond the rehabilitation of amputees. ❐

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