Bionic hand transplantation: linking the cortex to the hand

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Adult brachial plexus injuries are rare but devastating, and their reconstruction is constrained by the difficulty of affecting nerve regeneration, the complex internal architecture of the plexus, and the pernicious effect of delay on recovery.[1] Conventional surgical reconstruction can make use of nerve grafts, nerve transfers, tendon transfers, and vascularised free functional muscle transfers. Some methods rely on the presence of viable proximal nerve stumps, which might not be present, particularly in injuries with root avulsion from the spinal cord. Restoration is always incomplete, with the distal-most motor units in the hand suffering the most delay in regeneration and the greatest losses of function.

As reconstructive techniques evolve, new treatment options arise. Spurred partly by military conflict, the reconstruction of limbs with no function has made rapid advances in the past decade. Vascularised composite allotransplantation and enhanced prostheses offer hope.

In *The Lancet*, Oskar Aszmann and colleagues[2] describe the use of established techniques to overcome some limitations of modern myoelectric prostheses. Their series consists of three patients who, having sustained brachial plexus injuries involving avulsion of C8 and T1 roots, underwent hand amputation followed by replacement with myoelectric prostheses. All patients had previously undergone primary brachial plexus reconstruction, 2–17 years previously, using a selection of methods including free-functioning muscle transfer, nerve grafts, and nerve transfers. All had preserved or recovered some shoulder and elbow function, and were able to generate at least two cognitively separate electromyographic signals in the forearm. For two patients, distal signals were established by means of free-functional muscle transfer, whereas one patient received nerve transfers to restore native muscle function (which, although inadequate to provide joint motion, was sufficient to produce a detectable electromyographic signal). Quality of life and functional outcomes (including Disabilities of the Arm, Shoulder and Hand score, Action Research Arm Test score, and Southampton Hand Assessment Procedure score) improved after surgery. Pain scores fell.

The CNS can dictate an almost infinite and highly nuanced repertoire of movement in the human arm and hand. Modern bionic prostheses, under the control of ever more sophisticated microprocessors and miniaturised motor units, are capable of reproducing an increasing array of these movements. However, between activator and effector there is a choke point where cortical signals must be channelled into the device. This constriction remains the limiting factor in control of bionic prostheses. At present, data transfer across this biological–mechanical interface is slow and of very low bandwidth. Diverse research to increase signal volumes continues, with interest ranging from development of cortical signalling through implantable cortical arrays,[3] to direct peripheral nerve signalling through implantable sensors sampling either the individual axon[4] or compound neural action potentials,[5,6] to permanently implanted sensors of muscle action potential.[7] However, almost every myoelectric prosthesis relies on transcutaneous muscle action potentials or surface electromyographic signals.[8] These low amplitude potentials require careful separation of signal from noise and are commonly limited to only two channels. Furthermore, for patients with either extensive muscle scarring or paralysis (as in brachial plexus injury), the signal must be derived from muscles not normally active during movement.

Aszmann and colleagues assume that device control is less intuitive and less readily learned than if the original activating neuromuscular pathways were available and employed for signalling.[2] They postulate that by redirecting the nerves that originally controlled movement into new areas of muscle from which the signal can be transduced, prosthesis control can be made more intuitive.[2] This process is known as targeted muscle reinnervation. For example, reinnervation of chest wall muscles such as the pectoralis major by the median nerve in one area and the radial nerve in another might allow surface electrodes from each of these areas of the muscle to control prosthesis finger flexion (median nerve area) and prosthesis finger extension (radial nerve area), with intuitive control since each nerve is signalling its original function when controlling the prosthesis.[9] This example requires electrodes remote from the

prosthesis and sacrifices some or all function in the muscle chosen for signalling.

Aszmann and colleagues,[2] rather than moving the nerve to another muscle, moved another muscle to the nerve in the form of a microvascular autotransplant of a redundant muscle. This free functional transplantation of muscle is common in reconstructive surgery with high reliability, and Aszmann and colleagues have now shown that, even where the transplanted muscle recovers too weakly to move the distal joints, its electromyographic signal can control a motorised prosthesis.[2] This is a very important finding for brachial plexus injury, in which distal nerve regeneration is often so delayed or impaired that motor function is not achieved.

After reconstruction, patients with severe brachial plexus injuries, avulsing the lower roots from the spinal cord, often achieve a stable and strong shoulder and elbow supporting an insensate and paralysed hand. Amputation and use of a functioning prosthesis is a treatment option, but until now most have used devices powered mechanically by the shoulders. To use a motorised prosthesis, discrete signals from muscle groups (preferably innervated by nerves that would normally serve the motor function being replicated by the prosthesis) are required, and using free functional muscle transfer to amplify the neural signal is rational. The present findings[2]—and others[10]—are encouraging, because this approach provides additional neural inputs into prosthetic systems that otherwise would not exist. However, the final verdict will depend on long-term outcomes, which should include assessment of in what circumstances and for what proportion of their day patients wear and use their prostheses. Compliance declines with time for all prostheses,[11] and motorised prostheses are heavy, need power, and are often noisy, as well as demanding skilled repair when damaged.

Some comparison might be made with patients being considered for hand transplantation following limb loss. When the amputation is below the elbow, similar targeted muscle reinnervation and free functioning muscle transfer might enable intuitive signals to control a below-elbow prosthesis with signals transduced proximally. Here, the issues of compliance and utility are more complex because hand transplantation offers a silent, cosmetic, always-on, self-repairing, intuitive, and sensate

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replacement, albeit with the ongoing risks and costs of immunomodulation (which might be less troublesome in healthy patients than previously believed).[12,13] There is no doubt that targeted muscle reinnervation and free functioning muscle transfer will be assessed in both brachial plexus injury and arm loss, and lessons will be learned in both cases, mutually informing practice. It is also hard to escape the conclusion that the two enormous repertoires of the human motor cortex and the human hand will never be adequately connected through a choke point of a few sensing channels, and innovation will call for a broadband connection, by whatever means.

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Attention deficit hyperactivity disorder and premature death

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In *The Lancet*, Søren Dalsgaard and colleagues[1] provide strong evidence that attention deficit hyperactivity disorder (ADHD) is a risk factor for premature death. Although no single study can be definitive, this one comes close. The data come from the medical registers of Denmark, where diagnoses of ADHD are conservative. The sample was large—1·92 million people, of whom 32 061 had ADHD—and the follow-up was long, with little missing data. Most importantly, the authors adjusted for potential confounders. The result is a simple, albeit worrying, conclusion—that during the 32 year follow-up period, people diagnosed with ADHD were about twice as likely to die than were people without ADHD (adjusted mortality rate ratio [MRR] 2·07, 95% CI 1·70–2·50).

What mechanistic pathways link ADHD and premature death (figure)? One pathway follows ADHD's well known risks for oppositional defiant disorder or conduct disorder. In patients with ADHD, these antisocial disorders increase the risk for substance use disorders.[2,3] In the Danish study,[1] the effects of antisocial and substance use disorders were cumulative. People with ADHD and all these disorders had an eightfold increase in mortality (adjusted MRR 8·29, 95% CI 4·85–13·09). Since antisocial and substance use disorders lead to aggression, violence, and crime, their link with premature death is not surprising.

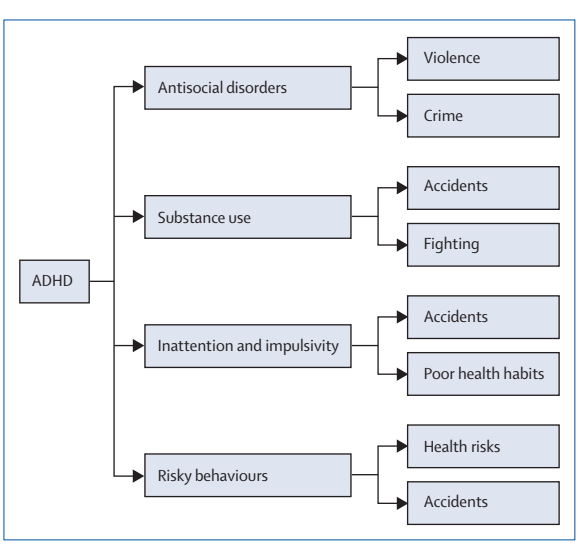

Figure: **Pathways to premature death**
ADHD=attention deficit hyperactivity disorder.

The antisocial pathway is not the only route to premature death, and Dalsgaard and colleagues' data[1] show a clear independent contribution of ADHD. ADHD increased the risk for premature death both in people without antisocial and substance use disorders and those with these disorders. This result suggests the existence of an ADHD-specific pathway to premature death. But what is this pathway? One clue is the fact that most of the premature deaths of people with ADHD (42 deaths among 79 people for whom the cause of death was known) were caused by accidents. Meta-analyses have shown that adults with ADHD are at a small but significantly increased risk for accidents while driving.[4] A study of insurance claim databases reported that people with ADHD were more likely to have had accident claims of any type compared with controls. Meta-analyses have also suggested a link between ADHD and mild traumatic brain injury.[5]

Why are people with ADHD at increased risk for accidents? The cause is not known for sure but several findings are notable. Two of the core symptoms of ADHD, inattention and impulsivity, would seem to be risk factors for accidents, and medications that reduce these symptoms improve performance in a driving