LETTER TO THE EDITOR

No dawn yet of a new age in spinal cord rehabilitation

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Sir,

Recently Angeli et al. (2014) reported that tonic epidural electrical stimulation of lumbar spinal cord in four near completely motor paralysed subjects with spinal cord injury revealed some limited voluntary movements in lower limbs. The idea is put forward that electrical stimulation evokes neuronal activities which sum with intention-related spinal locomotor programs to become supra-threshold. Are these the first steps on the way to a ‘spinal neuroprosthesis’ or even a training device to relearn walking as the authors enthusiastically envisage (Harkema et al., 2011; Angeli et al., 2014)? The present comment is a critical view on the achievements and the projected perspectives in light of previous findings.

What is so significantly new to allow these goals to be claimed at all? Not really much indeed when expecting new mechanisms: enhancement or ‘appearance’ of residual voluntary activity, here achieved under tonic electrical stimulation of the spinal cord, can also be obtained by other ‘unspecific’ means: mechanical stimulation (e.g. bare-foot walking and pinching) and electrical stimulation of the skin, reduction of body weight support (Harkema et al., 2011), enhanced excitability of the spinal cord (spasticity; reduction in antispastic medication) and others. In particular ‘Jendrassik manoeuvres’ (see examples for vivid application in Angeli et al.’s Supplementary Video 3 and moderate action in Supplementary Video 4) not only acutely and time-locked elevate residual voluntary muscle activity (Supplementary Videos 1 and 2 in Harkema et al., 2011), but can ‘willingly’ evoke seemingly all-or-nothing multi-joint flexion ‘mass’ movements in near completely motor-paralysed limbs (Dimitrijevic et al. 1984). In 6/6 lower limbs (in five subjects) that showed this feature, intensive locomotor training led to well-controlled even independent overground stepping (see Table 1 in Wernig and Müller, 1992; Wernig et al., 1995). It appears that Patient A45 in Supplementary Video 3 (Angeli et al., 2014), while under electrical stimulation, purposely produces similar multi-joint mass flexion movements under considerable Jendrassik-type activity: with intensive ‘pressing’, ‘stabilizing’ the rib cage, isometric contractions of neck, rump, arm muscles etc. hip flexion initially develops slowly to turn into a fast, almost all-or-nothing multi-joint flexion (time sequence not readily detectable as such from the disjointed and somewhat diluted sequences in Supplementary Videos 3 and 4). A feature of the injured spinal cord often ignored and not well understood, is the preference to react with multi-joint flexion or extension patterns even when a single joint only is intended to be moved (Maegele et al., 2002); vice versa, muscles are activated in the context of flexion/extension patterns that cannot be activated singularly in resting positions. Possibly, these patterns represent phylogenetic old ‘reflexes’ that are detectable early in ontogeny (see infant stepping) and can reappear with injury.

The initial missing of multi-joint flexion movements in the present patients (Harkema et al., 2011; Angeli et al., 2014) and their appearance under electrical stimulation could have technical reasons (too low effort applied by the patient e.g. shorter time allowed for activation as indicated in Fig. 6 in Harkema et al., 2011) or injury-related differences in recruiting of spinal (motor) programs. However, Angeli et al. (2014) also report on significant effects of ‘training-related learning’: with daily (home) training of limb flexion under electrical stimulation over many weeks, the amount of ‘mind-controlled’ muscle activity can increase and electrical stimulation stimulus threshold decrease. Also the indication of graded muscle response...
culminating in vision and auditory-guided motor fine adjustments (Figs 6 and 7) are bound to be due to activity-related functional or structural plasticity in spinal connectivity. The amount of grading of intention-induced force (and EMG signals) is demonstrated in Fig. 6; evaluation reveals the suggested over-all trend, but manifests also considerable variability among the four patients: there is poor discrimination between low and medium-sized intention to produce muscle contractions in all four patients and good reactions to high intention in two patients only (Patient B13, Fig. 6B). In this context it would be helpful to have an independent measure for the amount of ‘Jendrassik-type activity’ to dissociate from ‘mind-driven’ activity mediated via the regular corticospinal tracts. Could EMG signals from non-paralysed muscles proximal to the lesion segments, e.g. intercostal muscles serve as such? It seems that the already reported recordings (Harkema et al 2011; Angeli et al., 2014) can be interpreted this way.

As mentioned above, the authors also observed rather distinct ‘learning effects’ in connection with stimulation intensity, but their demonstration—particularly in Fig. 7A—needs further explanation. Stimulus strength actually has to be increased with time in Patients A53 and A45 and muscle strength in Patients A45 and B13 are highest at the very first recording, only in Patient B07 the claimed changes are obvious.

Can the present findings be reconciled with our previous results (see below)? The demand and effects of locomotor training on the treadmill or overground are more elaborate, as they already aim at up-right walking. Accordingly, specific training focuses on proper limb settings and loading (summarized as ‘rules of spinal locomotion’, Wernig and Muller, 1992; Wernig et al., 1995, 1998, 1999) during upright walking. It was shown before that body-weight carrying upright locomotion creates proprioceptive signals from load and length receptors in muscles, which in turn facilitate spinal locomotor programs and—after weeks of training—often enable severely paralysed subjects with spinal cord injury some independent walking over ground (Wernig and Muller, 1992; Wernig et al 1995, 1999; Behrman and Harkema, 2000). It was suggested that these skills become manifest in the course of ‘activity-related learning’, as was previously observed in spinal cats (Lovely et al., 1986; Barbeau and Rossignol, 1987). These new locomotor skills are maintained and thus fulfil criteria of a ‘carry over’ effect (Wernig et al., 1998). It is but consequential for Angeli et al. (2014) therefore, to combine a context-related training protocol (upright walking) with epidural stimulation. Firstly, results with electrical stimulation indeed indicate that during periods of ‘intention to walk’ on the treadmill, motor output is enhanced over purely passive stepping (Fig. 8). It will be interesting to see more of this kind and also find direct evidence for facilitated locomotion. The answer will decide whether epidural stimulation possibly can serve as a ‘neuroprosthesis’ effective only while the stimulator is on, or can eventually develop into a learning device.

A source of uncertainty is the actual structure(s) stimulated by the mounted electrode. There is evidence for activation of dorsal and ventral roots from transcutaneous spinal cord stimulation (Minassian et al., 2007), which would amount at least to a partial ‘direct’ stimulation of motor neurons (and afferents). Also the multipolar electrode used by the group allows preferential (direct) stimulation of different motor pools, apparently depending on intensity and precise position of the active electrode (Sayenko et al., 2014). However, the present authors do not report muscle activities anyhow synchronized to stimulus frequency, which one would expect at least for frequencies below fusion frequency for the respective muscles; this renders predominant direct stimulation as less likely.

In conclusion, it is obvious that epidural stimulation is effective in enhancing/evoking voluntary movements in near completely motor-paralysed spinal cord injury patients; the also applied Jendrassik manoeuvres have similar effects but have not been separately monitored. Thus, the amount of truly active flexion movement so far is rather unclear, while extension movements appear to happen mostly passive. The claim of standing carrying full body-weight is not sufficiently documented. Also the evidence for the claimed carry-over effect is not conclusive. It will be interesting to see effects of electrical epidural stimulation applied during locomotor training on the treadmill when proper limb setting and stepping, even aided by therapists, produce gait facilitating propioceptive signals to the spinal cord.

References


Sayenko DG, Angeli C, Harkema SJ, Edgerton VR, Gerasimenko YP. Neuromodulation of evoked muscle potentials induced by epidural...