Asymmetrical activation of trunk muscles following unpredictable loading of an outstretched arm

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When an individual moves an arm, trunk muscles are activated to oppose the reactive forces from the movement and stabilise the trunk. When the movement is predictable, there is a specific pattern of activation in the trunk muscles, with some trunk muscles being activated prior to the movement of the arm. However, when the movement of the arm is unpredictable there is a different pattern of activation of specific trunk muscles. In addition, the corticospinal drive to the erector spinae muscles on one side of the back is increased when the opposite arm is abducted (Davey et al. 2002) and there is evidence to suggest that the corticospinal drive to trunk muscles is asymmetric (Strutton et al. 2004; Kuppuswamy et al. 2005). Here we examine whether there is asymmetry in responses of trunk muscles to an unpredictable loading of an abducted arm. Eighteen healthy right-handed human subjects were recruited. Bilateral surface electromyographic (EMG) recordings were made from the deltoid, erector spinae at T12 and L4 vertebral levels and the rectus abdominis muscles. A modified bucket with a microswitch in the handle was used for the weight drop protocol. Subjects were blindfolded and stood upright with their right arm abducted to 90 deg holding a tube connected to the bucket handle by a length of string. The bucket was dropped, either loaded with a 1.25 kg weight or empty (randomly selected to prevent a learning effect), at intervals of at least 5 s. Subjects were instructed to hold their arm stable to arrest the fall of the bucket. The microswitch was triggered when the bucket was dropped and this triggered the data acquisition system to record EMG activity. The protocol was then repeated with the left arm abducted. After a brief rest period, the entire protocol was repeated again. The amplitudes and latencies of the responses (to the weighted bucket drop) in each of the trunk muscles opposite the abducted arm were examined for differences. The sizes of the responses were significantly larger (P < 0.001; one way ANOVA with Holm-Sidak test) in ES T12 than ES L4 and RA in both right and left arm abduction scenarios (L ES T12 0.10±0.02 mV; L ES L4 0.04±0.01 mV; L RA 0.03±0.01 mV; R ES T12 0.07±0.01 mV; R ES L4 0.03±0.004 mV, R RA 0.03±0.01 mV).

When the right arm was abducted the latencies of the responses were significantly (P < 0.001; one way ANOVA with Holm-Sidak test) shorter in the left ES muscles at T12 (62.93±2.14 ms) than at L4 (73.74±3.68 ms). However, when the left arm was abducted the differences between the muscles on the right were not significant (ES T12; 64.05±2.81 vs ES L4 74.17±3.55 ms). Interestingly the latencies were significantly different between contralateral ES at T12 and the RA in both scenarios. The preferential use of the right arm may lead to asymmetry in the activation of the trunk muscles as postural stabilisers and this has implications for the development of low back pain. Furthermore, it remains to be established if left-handed individuals exhibit similar asymmetry.


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Opioids non-selectively suppress the transmission in non-nociceptive and nociceptive short-latency spinal FRA, but in addition the transmission in the long-latency FRA pathways and the generation of spinal locomotor activity. (For references on FRA see Schomburg, 1990 and 1997).
The aspect of an engagement of the spinal FRA system in the development of RLS would allow for an experimental testing of the therapeutic effectiveness of different compounds for RLS.

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Motor commands can produce sensations of displacement of the hand in the absence of peripheral feedback
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The role of ‘inflow’ and ‘outflow’ signals in judgments of limb position has been debated for over a century. A previous study suggested that illusions of movement do not accompany the motor commands used in attempts to move a paralysed limb (McCloskey & Torda, 1975; for review see Gandevia, 1987). We used ischaemic paralysis of the arm to generate a phantom hand and found that its perceived position changed with attempted contractions.
Six naïve human subjects were used. Subjects had their right hand held, fingers extended, in a frame which could rotate about the wrist. Subjects used their left hand to signal with a pointer the perceived position of the right wrist. The wrist was passively moved to different positions and the subject matched its position while subjects exerted moderate flexion or extension efforts at a given angle. The mean change from the passively matched position was small, 2.4 ± 2.0 deg in the direction of extension with extension contractions and 5.4 ± 7.0 deg in the direction of extension with extension contractions (flexion vs extension, paired t test, P=0.06). During paralysis, all subjects experienced a phantom hand with the extended fingers perceived as flexed. Then, when attempting to flex or extend at any wrist position subjects showed large illusions of displacement, in the direction of flexion for flexion efforts (by 21.1 ± 12.7 deg) and in extension for extension efforts (30.5 ± 12.6 deg, P=0.002).

This result establishes a definitive role for ‘outflow’ signals in position sense and sheds new light on the sensory processes underlying the generation of phantom limbs.

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Modulation of the H-reflex within naturally occurring sway during quiet standing
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Previous research has observed a decrease in reflex excitability as subjects move from lying or sitting to a standing position. This decrease is thought to be due to increased presynaptic inhibition at the Ia synapse (Katz et al. 1988; Koeja et al. 1993). It is not known whether these same reflexes are modulated in a similar fashion within naturally occurring postural sway during quiet standing. H-reflex and M-wave recruitment curves were obtained in the right soleus (SOL) and medial gastrocnemius (MG) muscles while human subjects (n=7) were in a standing position. Electrical stimuli (1 ms duration pulse between 0.5 to 14 mA) were delivered to the tibial nerve when the body was naturally swaying forward (centre of pressure (COP) at 1.6 standard deviations (SD) anterior to the mean baseline COP) or backward (COP at 1.6 SD posterior to the mean baseline COP). The two sway conditions were characterized by a difference of 0.5 deg, 1.1 cm, and 0.8 cm in the mean ankle angle, position of the centre of pressure, and position of the centre of mass, respectively. Compared to when swaying backward, forward sway resulted in a significant increase in Hmax for the SOL and MG muscles by 11.2 ± 8.6% and 19.7 ± 13.1% (mean ± SD), respectively. No differences were found in the Mmax for SOL and MG between sway conditions. The greater Hmax for the two muscles during forward sway may have been due to the concomitant increase in motoneurone excitability, as reflected by the significant increase in background electromyographic (EMG) activity of the SOL and MG (19% and 12%, respectively). While the increase in the SOL Hmax during forward sway was comparable to the increase in background SOL EMG activity, the increases in MG Hmax and MG EMG activity were disproportional. This was verified by a significant reduction (42%) in the MG Hmax:EMG activity ratio during forward sway. An explanation for the less than expected growth in MG Hmax during forward sway may be an increase in presynaptic inhibition, thereby reducing the efficacy of the Ia synapse. Such an increase of inhibition may be a result of increased inhibitory activity from primary afferent depolarization interneurones, or lie within the synapse itself due to increased Ia-afferent input through muscle lengthening (Wood et al. 1996; Pinniger et al. 2001). We conclude that reflex excitability is differentially modulated for the SOL and MG muscles.

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within the natural sway parameters of upright stance and that the observed differences between these muscles imply a functional divergence during quiet standing.


This study was supported by the Swedish Research Council.

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**Limb muscle responses to vestibular stimulation during treadmill walking in man**

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Bipolar binaural galvanic vestibular stimulation (GVS) induces medium latency (ML) responses in leg and trunk muscles and sway towards the anode side in standing subjects. During walking, GVS applied early in stance induces ML responses in ankle muscles of the stance limb (Iles et al. 2004) and path deviation towards the anode (Bent et al. 2004). Mean ML emg increases seen during walking were 75% and 73% in soleus and tibialis anterior, respectively, but with considerable inter-subject variability (soleus range 14-182%, coefficient of variation 74%, n=12; tibialis anterior range 0-248%, coefficient of variation 102%, n=11). Walking subjects with their eyes shut made left hand contact with a front platform so that they could maintain their position on the treadmill. We reasoned that variation in hand contact area and pressure might cause variation in response to GVS because hand contact reduces leg muscle ML responses during standing and replaces them with arm muscle responses (Britton et al. 1993). We have studied ML response amplitude in 12 control subjects.

In three subjects we measured stance leg ML response amplitude (in a window 120-250 ms after GVS onset) with eyes shut and light fingertip contact with the platform. This was compared with eyes shut and firm grasp of one or both side-rails parallel to the treadmill belt. In a fourth subject we compared eyes open and no hand contact with eyes open and firm grasp. In all four cases firm grasp abolished the GVS induced excitatory ML responses in both soleus and tibialis anterior. To examine the relative importance of vision and touch we studied all the permutations of vision and contact in each of two subjects, analysing the data with ANOVA and the Bonferroni multiple comparisons post test. Grasping the side-rails produced a large and significant diminution compared to light touch or no hand contact. ML responses (at 140 ms) were recorded in the upper limbs during firm grasp of both hands with eyes closed. With the GVS anode on the left, the right triceps brachii was excited and the left inhibited. Excitatory responses could be elicited at all times during the stride. The effects of providing support through the arms during walking are similar to those seen during standing: responses in the legs are reduced and ML responses appear in arm muscles. This may be related to reports of reduced body sway resulting from hand contact during treadmill walking (Dickstein & Laufer, 2004).


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**Body sway responses evoked by audio frequency vibration of the mastoid process in standing humans**

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Audio frequency mastoid vibration is known to activate vestibular afferents in humans and experimental animals (1,2). However, balance responses evoked by mastoid vibration have not been reported thus far. In the present study we measured whole body responses evoked by mastoid vibration and endeavoured to determine their origin.

Ten healthy subjects were studied while standing upright upon a force platform, with their feet together and eyes shut. 500 Hz bone-conducted tones of 127 dB FL (force level) and 2 s duration were delivered over the mastoid process using a B71 clinical bone vibrator. The 3-D movement of a marker attached to the C7 spinous process was measured at 200 Hz using a motion capture system (CODA mpx 30). Ground reaction forces were measured using a force platform (Kistler). In a baseline study, right mastoid, left mastoid or null stimuli were delivered randomly to subjects facing forwards. Subjects were then studied with their heads rotated by 45 and 90 deg to the left and the right sides. Because low frequency vibration applied directly to neck muscles may produce body sway (3) we compared the response to mastoid stimulation with that evoked by stimulation directly above the external acoustic meatus or along the length of the sternocleidomastoid (SCM) muscle.

Mastoid vibration evoked a force response that commenced at ~200 ms and peaked at ~450 ms. The medio-lateral (ML) components were oppositely directed for left and right sided stimulation while antero-posterior (AP) components had a similar direction. This resulted in oblique sway away from the stimulated ear and forwards. Peak force amplitudes (mean±SEM) of 0.86±0.19 N (ML) and 0.59±0.23 N (AP), and C7 marker displacements of 12.55±3.5 mm (ML) and 5.77±1.7 mm (AP) were significantly different from the null stimulation condition (repeated measures ANOVA; respectively, p<0.001; p=0.015; p=0.009; p=0.041). The direction of body sway measured as the angle between the point of maximum displacement and the baseline position was significantly correlated with head yaw angle (r=0.74, p<0.05). Vibration along the length of the SCM evoked lateral displacement of the body, which decreased significantly...
as the stimulus moved distally, away from the mastoid. Vibration over the temporal fossa directly above the external acoustic meatus evoked oblique sway similar to mastoid vibration. 

Unilateral mastoid vibration evokes oblique anterolateral sway similar to that observed in response to monopolar galvanic vestibular stimulation. Its dependence on head position and stimulation site suggests a vestibular origin for this response.


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C7

Visuo-vestibular influences involved in the 'broken escalator phenomenon' gait after-effect (GAE)

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The 'broken escalator phenomenon', the odd balance sensation experienced when walking onto an escalator which is stationary, is an after-effect of gait adaptation (1). This gait after-effect (GAE) demonstrates dissociation between knowledge and action as it occurs despite full awareness that the escalator will not move. This study investigates visuo-vestibular influences on this GAE. The experiments involved three sequential conditions: (1) walking onto the stationary sled (BEFORE); (2) walking 15 times onto a moving sled (MOVING) at 1.3m/s; and (3) a second set of stationary trials (AFTER) with clear warning that the platform will NOT move. In experiment 1 we tested 9 labyrinthine-defective subjects (LDS) and 13 age-matched normal controls. In experiment 2, 5 LDS and 5 age-matched controls repeated the experiment but, in the AFTER trials, subjects first walked blindfolded and then with full vision (eye re-opening). Gait velocity, trunk position, foot contact and leg EMG were measured. (i) The LDS were, as expected, significantly more unsteady during MOVING trials. During AFTER trials, both patients and controls experienced an after-effect, shown as increased gait velocity and a forward trunk overshoot, with eyes open or closed. (ii) No significant group differences in the after-effect were present. (iii) However, re-opening the eyes in experiment 2 induced a significantly larger after-effect (trunk overshoot) in the LDS. In conclusion, (i) confirms the prominent role of the vestibular system during external postural perturbations (as in the MOVING trials). (ii) When the perturbation is internally generated, as in the AFTER trials, the CNS relies less on sensory feedback and more on feed-forward mechanisms to maintain balance. (iii) Re-emergence of the after-effect on eye re-opening reveals the existence of a high order 'visual context' component in locomotor learning, which is enhanced in the absence of vestibular function.


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Age-related changes in muscle response times and magnitudes in time-critical obstacle avoidance

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In daily life, independent and safe locomotion requires the ability to continuously adjust the locomotor pattern in response to environmental demands, like obstacles in the travel path. Adjustments of leg trajectories in response to an obstacle or target displacement can be as fast as 120 ms in young subjects (Weerdesteyn et al. 2004; Reynolds & Day, 2005). In obstacle avoidance under time pressure, elderly have been reported to be less successful (Chen et al. 1994). At the neuromuscular control level, however, it is not clear whether this is due to delayed onset latencies, reduced amplitudes, or both.

In the present study, obstacle avoidance under time pressure was studied in 10 young (24.4 ± 2.8 years; mean ± SD) and 9 older adults (70.8 ± 4.9 years). The participants walked on a treadmill at a speed of 3 km/h. An obstacle was dropped 30 times in front of the left foot in late stance, early swing, and mid-swing (low, medium and high time-pressure, respectively). Muscle activity in response to the obstacle was measured by surface electromyography (EMG) from the left biceps femoris (BF), rectus femoris (RF), tibialis anterior (TA), and medial head of gastrocnemius (GM). Initial response latencies were determined, as well as response magnitudes over the first 50 ms of the response (normalized with respect to muscle activity in the corresponding phase of the step cycle during unperturbed walking).

In both young and older adults, a large (14.1±10.3 (mean ± SD) times control activity) initial response was consistently observed in BF. There was a significant main effect of both time-pressure and age on BF onset latency (ANOVA, p=0.011 and p=0.007, respectively), but no significant age x time-pressure interaction (p=0.57). BF onset latencies were on average 105±9 ms in the young and 119±10 ms (means ± SD) in the older adults. Onset latencies decreased with increasing time-pressure. Response magnitudes of the 4 muscles over the first 50 ms were larger in young than in older adults (increase of 78% in BF, 152% in RF, 65% in TA, and 25% in GM; MANOVA, p=0.04).

The results of the present study indicate that in obstacle avoidance under time pressure, both increased central processing time, as indicated by delayed onset latencies, and reduced muscle activation rates are likely to contribute to the reported higher failure rates in the elderly (Chen et al. 1994). Similar results have been obtained in stumbling experiments (Schillings et al. 2005). These findings could help to explain the large numbers of obstacle-related falls in the elderly.


Aerobic and anaerobic training have different effects on central fatigue
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The effect of central fatigue on the non-exercising arm following fatigue of the contralateral arm has previously been investigated using transcranial magnetic stimulation (TMS) (Humphry et al. 2004). The aim of this study was to examine whether central fatigue and recovery from it is different in aerobic and anaerobic trained subjects compared with sedentary controls. Twenty-four healthy human volunteers in 3 equal groups of 8 age-matched subjects (control, aerobic and anaerobic athletes) took part in two separate sessions. Both sets of trained athletes routinely performed over 8 h exercise per week on average, specific to either aerobic or anaerobic sports. Both groups also averaged over 8 years of training. Control subjects averaged less than 1 h of physical activity per week.

In session 1, a 4.5 kg weight was attached to the non-dominant forearm and subjects performed bicep curls until exhausted. In session 2, the dominant arm was exhausted first, followed by the non-dominant arm. The central limit of endurance (CLOE) was calculated as the percentage difference between the time taken by the non-dominant arm to fatigue in session 1 and 2. Digital dexterity and maximum voluntary contraction (MVC) were also measured before and after exhaustion. TMS was applied using a MagStim 200 connected to a 9 cm circular coil centred over the vertex and the change of motor-evoked potentials (MEPs) in biceps brachii and thenar muscles was monitored bilaterally during both sessions and for a recovery period of 30 min.

All three groups showed significant reductions in MEPs for the non-exercising biceps after exhaustive exercise of the opposite biceps (P<0.05, repeated measure ANOVA). MEP size recovered 20 min post-exhaustion in aerobic athletes, 30 min in controls but was not recovered in anaerobically trained athletes at 30 min (P<0.05, post hoc Holm-Sidak). The CLOE (±SEM) was significantly different between groups (aerobic athletes 106.8±7.1%; anaerobic athletes 69.4±6.4%; controls 83.9±5.7%, repeated measures ANOVA on ranks, P=0.002). There was no central fatigue evident for thenar MEPs and no effect on digital dexterity or MVC after exhaustive exercise for any group.

Thus, in comparison to control and anaerobic subjects, aerobically trained athletes demonstrate reduced central fatigue and faster recovery from it, whereas anaerobic athletes more closely resemble control individuals. We propose that long-term aerobic training results in attenuation of the normal central fatigue response to exercise.


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Activity of callosal neurons in primate SMA during a bimanual precision grip task

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The supplementary motor area (SMA) is important in bimanual motor control; although dense callosal connections serve to link SMA in each hemisphere, little is known about the firing patterns of these cells. We here report recordings from antidromically identified corpus callosum (CC) neurons in the hand representation of SMA, in two m. mulatta monkeys trained to perform a bimanual precision grip task for food reward.

The monkeys initiated the task by placing both hands on home pads. Audiovisual cues indicated whether right hand, left hand or both were to be used, and following an instructed delay, the monkeys reached out and performed a precision grip (1s hold period). After training was complete, the monkeys were implanted (under full general anaesthesia: 1.5–2.5% isoflurane inhalation in 50:50 N2O:O2 and aseptic conditions) with a stainless steel headpiece to allow atraumatic head fixation and a recording chamber sited above a craniotomy exposing SMA. Single units were recorded in daily microelectrode penetrations whilst the animals performed the trained task.

CC neurons were identified antidromically by stimulation through chronically implanted electrodes in the corpus callosum close to the midline. Thirty-five CC units were encountered, and 13 units were recorded long enough to permit firing rate analysis (≥10 trials per task type). The mean antidromic latency was 1.8ms (22/35 had latencies < 1.8ms; 4/35 had latencies > 3ms). CC neurons had low mean firing rates during the trial for all three movement types, at 3.7±5.2Hz, 3.1±3.6Hz and 3.5±4.6Hz for ipsilateral, contralateral and bilateral trials, respectively (mean±SD). The corresponding mean peak modulations (difference between minimum and maximum rate) from trial start to the end of the hold period were 12.9±14.8Hz, 15.1±21Hz and 17.7±23.9Hz. However, some cells showed a much higher rate just after the hold phase, when the monkey reached out for its reward. Aligning analysis to the peak lever release velocity often revealed a substantial modulation, in units that otherwise showed little task-related activity (see Fig. 1). Across all 13 units, the mean firing rates for the 2s period centred on the peak lever velocity were 13±9.5Hz and 18.3±18.2Hz for reaches with the ipsilateral and contralateral hand; corresponding mean peak modulations were 12.3±8.9Hz and 17.5±17.9Hz. The overall low mean and peak firing rates of most CC neurons suggest against a role for interhemispheric communication of detailed movement parameters, such as force or velocity. Alternatively, CC neurons may be signalling the timing of behavioural events, and a low ‘baseline’ firing rate would provide a better signal-to-noise ratio.
mg/kg/h alfentanil, and aseptic conditions) with EMG electrodes, a headpiece to allow head fixation, and a recording chamber over the central sulcus. Daily recordings were made from cortical areas 4 (M1), 3a or 2 using glass insulated platinum electrodes or tetrodes. LFP (bandpass 1-100 Hz; referenced to the headpiece) and contralateral EMG from 10 hand and forearm muscles were recorded during task performance.

LFP from M1 and area 3a showed significant coherence with EMG in the 20-30 Hz range; coherence with area 2 was weak, and failed to reach significance (P>0.05) when averaged over all 10 available EMG recordings (Figs 1 and 2, left column). Cortico-muscular coherence could be caused by descending pathways from the cortex (e.g. the corticospinal tract), or by ascending inputs carrying sensory feedback from muscle (e.g. the dorsal columns). We investigated these possibilities by calculating directed coherence (DC; Kaminski & Blinowska, 1991), which assesses the extent to which the past history of one signal can predict another. We introduced a novel normalisation for DC:

\[ DC_i \leftarrow j(f) = |H_{ij}(f)|^2 \frac{S_{jj}(f)}{S_{ii}(f)} \]

where \( H_{ij}(f) \) is the transfer function, and \( S_{ii}(f) \) and \( S_{jj}(f) \) are the power spectra of the two signals. This normalisation makes DC independent of the signal scale. We verified by numerical simulation that the calculation of significance limits (P<0.05; see Evans & Baker, 2003) normally used for standard coherence is also valid for DC with this normalisation.

DC in the LFP \( \rightarrow \) EMG direction was significant for all three areas in the 20-30 Hz band. For somatosensory areas, this might be produced by several pathways, including reciprocal cortico-cortical connections with M1. By contrast, although significant DC in the EMG \( \rightarrow \) LFP direction was seen for all areas, it was especially strong for M1 (Figs 1 and 2, right column). We conclude that 20-30 Hz oscillations in areas 3a & 2, as well as M1, can synchronise with muscle activity.

\[ \text{Figure } 1. \text{ Coherence (left) and DC (right) between LFP and contralateral flexor digitorum profundus (FDP) EMG. Dotted line marks significance level (P<0.05).} \]

\[ \text{Figure 2. Averaged coherence (left) and DC (right) between LFP and 10 contralateral EMGs.} \]


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Time-specific activation of transcallosal projections between the left dorsal premotor and the right motor cortex during selection of movement in humans

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The dorsal premotor cortex (PMd) has a role in selection of movements through a densely interconnected network linking the premotor areas and the motor cortex (MCx) of the two hemispheres. Mochizuki et al. (2004) recently described a method using paired pulse transcranial magnetic stimulation to explore the transcallosal projections connecting the PMd with the contralateral primary MCx. They found that the amplitude of EMG responses evoked by a standard TMS pulse to the left MCx could be modulated by applying a conditioning stimulus (CS) to the right PMd some 8-10 ms beforehand. Inhibition occurred if the intensity of the CS was 110% rest motor threshold (RMT). In another study facilitation was induced at a similar interstimulus interval (8 ms) using low intensity CS to the left PMd (CS=80% RMT) (T. Bäumer, F. Bock, G. Koch, R. Lange, J.C. Rothwell, H.R. Siebner & A. Münchau, unpublished observations). We tested how the excitability of these connections changed in the reaction interval of an acoustic choice reaction time (CRT) task in 10 healthy subjects.

\[ \text{Figure 1. Coherence (left) and DC (right) between LFP and contralateral flexor digitorum profundus (FDP) EMG. Dotted line marks significance level (P<0.05).} \]
Is muscle afferent contribution to the soleus muscle activity decreased during human spastic walking?

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The aim of this study was to investigate the contribution of proprioceptive feedback to the activation of the soleus muscle during the stance phase of walking in spastic patients. Twelve hemiparetic spastic patients (cerebral stroke) and 12 age-matched able-bodied controls participated in the study. Antispastic medication was interrupted 24 hr before the test and the spasticity level was evaluated with the Ashworth score. All subjects walked on a treadmill at a comfortable speed (~ 1 km/h) with the left leg attached to a robotic actuator that can dorsiflex and plantarflex the ankle.

Fast plantar flexion perturbations (6 deg, 500 deg/s) were applied in the mid-stance phase to investigate the contribution of feedback from ankle plantar flexors to the soleus EMG. To investigate the afferent-mediated modulation of the soleus EMG, the ankle dorsiflexion during the stance phase was slightly enhanced or reduced mimicking variations in the ankle kinematics during normal walking. Four levels of ankle dorsiflexion enhancements and reductions (± 2 deg/± 6 deg/s; ± 4 deg/± 10 deg/s) were applied 250 ms after heel contact (300 ms duration). A control step was recorded before each perturbed step (25 each). MANOVA tests were used to compare responses between the groups and regression analysis was used to test the relationship between the velocity of the ankle dorsiflexion and the soleus EMG.

The amplitude of the short latency stretch reflex response was significantly increased in the patients compared with the controls (p=0.02). The fast plantar flexion perturbations produced a drop in the soleus EMG that was significantly larger in the healthy volunteers than the patients (p=0.03). The slow-velocity dorsiflexion enhancements and reductions generated in the control subjects’ increments and decrements, respectively, in the soleus EMG. However, in the spastic patients these responses were decreased. Moreover, there was an inverse relationship between the Ashworth scale and the amplitude of the responses to the slow perturbations (slope of the regression lines). There was no relationship between walking speed and the slope of the regression lines.

These results confirm that afferent feedback contributes to the soleus activity during the stance phase of human walking, and that afferent feedback enhances and modulates this activity according to the ankle kinematics. While the short latency soleus stretch reflex was hyper-excited in the patients, the afferent feedback contribution to the soleus activity during spastic walking was depressed. We speculate that part of the walking impairment in spastic patients is caused by either reduced afferent feedback or impaired integration of the afferent feedback within CNS.

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Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.

Suppression of voluntarily activated single motor units with TMS

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Subthreshold transcranial magnetic stimulation (TMS) applied to the human motor cortex suppresses voluntarily generated EMG activity (Davey et al. 1994; Petersen et al. 2001). The onset latency of the suppression of the EMG activity is about 10 ms later than the short latency excitation produced by TMS at intensities above motor threshold. This difference in latency can suggest that TMS may be activating either inhibitory pathways with several synaptic connections or slowly conducting axons acting on the cortical cells which are responsible for the EMG activity, or secondly, that the voluntary EMG may be generated via slowly conducting descending pathways.

Here we applied subthreshold TMS to the motor cortex in awake human subjects and investigated the effect on the firing probability of single motor units activated by volition. Single pulses of TMS were delivered at stimulus intervals of 1-3 s. Post stimulus time histograms were generated for each single motor unit (24 units from biceps brachii and 13 units...
from first dorsal interosseus, FDI) using 113-405 TMS pulses per unit.

A clear suppression of 5 biceps units was seen at a mean latency of 18.1 ms with subthreshold magnetic stimulation of the motor cortex. At higher stimulus intensities a short-latency excitation occurred at a mean latency of 14.1 ms. Thus, the mean latency difference between excitation and suppression was 4.0 ms for the biceps units and 2.9 ms for the FDI units. The firing probability of the motor units was reduced by approximately 40% in both muscles during the suppression of activity.

Subthreshold stimulation depressed single motor unit activity a few milliseconds after the short-latency excitation that is seen at higher intensities of stimulation. This suggests that pathways with fast conduction velocity are part of the voluntary activation of single motor units and that the suppression by TMS occurs via inhibitory circuits within a few synapses of the cortical output cells.


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Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.

Motor cortical activity is synchronous with 10 Hz discontinuities during slow finger movements in monkey

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During slow finger tracking movements, discontinuities can be seen in finger acceleration at ~10 Hz (Vallbo & Wessberg, 1993); whether the motor cortex (M1) contributes to this activity is uncertain. We recorded right finger acceleration and contralateral sensorimotor EEG (differential recording, electrodes 20 mm anterior and posterior and 30 mm lateral to vertex) from 8 normal human subjects performing slow index finger flexion-extension tracking movements. Coherence was calculated between EEG and acceleration during flexion. Significant coherence at 8-10 Hz was only found in 3/8 subjects (Fig. 1A). The mean coherence (Fig. 2A), averaged over all 8 subjects, showed a significant peak at 9.8 Hz, although this was weak (coherence = 0.018).

We compared this result with data from a macaque monkey, trained to perform a similar slow finger flexion task for food reward. Following training, the animal was implanted (under general anaesthesia, 3.0-5.0% sevoflurane inhalation with 0.025 mg/kg/h alfentanil, and aseptic conditions) with a headpiece for head fixation, and a recording chamber. Daily experimental sessions made up to 10 simultaneous microelectrode penetrations into M1, recording local field potential (LFP; bandpass 1-100 Hz, referenced to the headpiece) whilst the animal performed the task. In contrast to the human data, LFP-accelerometer coherence often showed robust ~10 Hz peaks (Fig. 1B). The average coherence spectrum over 10 simultaneously recorded sites had a peak of 0.16 at 9.8 Hz (Fig. 2B). Out of 113 recording sites, 91 showed at least one significant bin in the 8-10 Hz band.

The difference between LFP and EEG is intriguing, as they yield similar results for corticomuscular coherence at ~20 Hz during steady contractions. One possibility is that EEG sums spatially over a larger population than LFP, producing cancellation. We simulated this in the monkey by averaging together all LFPs simultaneously recorded in one session (maximum inter-electrode distance at the surface 2.1 mm), and then calculating coherence between averaged LFP and acceleration (Fig. 2C, for the same session as Figs 1B and 2B). The average of this spectrum over 15 sessions (3-10 LFPs/session, mean 7.5) showed considerable coherence at ~10 Hz (Fig. 2D).

We conclude that M1 activity does contribute to 10 Hz discontinuities during slow finger movement.

Figure 1. Cortical coherence with finger acceleration. A, using sensorimotor EEG in 5 human subjects. B, using LFP from 5 different M1 sites in a single monkey.

Figure 2. Average coherence spectra with finger acceleration. A, using EEG in the human (n=8 subjects); B, using LFP in monkey (n=10 sites). C, coherence spectrum between finger acceleration and the average of 10 simultaneously recorded LFPs. D, average of 15 spectra calculated as in (C) from different recording sessions.


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Enhancing cortical excitability and motor behaviour in chronic stroke with theta burst stimulation

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Recovery of human hand function after stroke depends on reorganisation of the motor system around the area of the lesion. Recent functional imaging studies have suggested that as patients recover hand movements they show increased activation of perilesional cortex on the stroke hemisphere and reduced activation of the non-stroke hemisphere. Experiments with repetitive transcranial magnetic stimulation (rTMS) in healthy subjects have shown that it is possible to induce changes in the excitability of motor areas of cortex that outlast the stimulation by 30-60 min. The question we ask here is whether we can use these methods to induce optimal patterns of reorganisation after stroke. The present experiments represent a proof of principle study that tests the effectiveness of a single session of rTMS, given using a theta burst protocol (TBS), on physiological and behavioural measures of hand function.

Six patients with a first ever supratentorial motor stroke and incomplete recovery of the hand, were studied at least 1 year after the ictus. All patients were tested under 3 conditions: inhibitory TBS over the non-stroke side (continuous pattern, 80% aMT, 300 pulses); facilitatory TBS over the stroke side (intermittent pattern, 80% aMT, 600 pulses); and sham stimulation. Changes in corticospinal excitability were assessed by single pulse TMS both on the stroke (MEP amplitude during rest and contraction, input-output curves at rest) and the non-stroke side (MEP amplitude at rest). The effect on motor behaviour of the hand was tested using two different reaction time protocols (simple and choice reaction times to a somatosensory stimulus applied to the left or right hand). Changes in reaction times were sought at 10, 20 and 30 min after the stimulation.

After facilitation (iTBS) of the stroke hemisphere the amplitude of active MEPs on the affected side increased in all patients by up to 50% (P<0.001). Input-output curves were also increased in the majority of the subjects. When compared to the sham condition, the affected hands were slightly but significantly faster in the simple reaction task throughout the testing period (P=0.033), while there was no difference in the choice reaction times. In contrast, inhibition (cTBS) of the non-stroke side had no consistent effect on either the reaction times or the electromyography of the affected side even though it suppressed the MEPs evoked in the unaffected hand. There were no adverse events.

A single session of facilitatory TBS (iTBS) over the stroke side in chronic patients increased corticospinal excitability and improved simple reaction times in the affected hand for 40 min. In the future we hope to give patients physical therapy during this time window of increased excitability. This may improve or speed up the long term effects of conventional treatment.


Improvements in locomotor function in subjects with incomplete spinal cord injury are associated with changes in inter-muscular coherence

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Treadmill training with partial body-weight support improves locomotor function in humans with incomplete spinal cord injuries (iSCI). A recent study has shown that subjects who improve their locomotor ability also demonstrate increases in corticospinal tract function as assessed by transcranial magnetic stimulation (TMS) (Thomas & Gorassini, 2005). In the present study we examined if increases in inter-muscular coherence recorded during walking, especially in the 24-40 Hz band which may indicate common cortical drive (Mima & Hallet, 1999), were also associated with locomotor improvement. Coherence was measured between the hamstrings and quadriceps muscles during the stance phase of walking.

Coherence was measured before and after 3-5 months of intensive treadmill training in 12 subjects with iSCI. In subjects who demonstrated functional improvements in walking (termed responders), there was also an increase in the level of coherence in the 24-40 Hz frequency band (p<0.05, paired t test, Fig. 1). In subjects who did not improve in their locomotor ability (non-responders), coherence in the 24-40 Hz frequency band was low and did not change after training. There were no significant changes in coherence values in the range of frequencies from 5-18 Hz (spinal band) in both groups.

Increased coherence in the 24-40 Hz band after training may represent increased corticospinal drive to the musculature during walking. Interestingly, in 8 subjects who also participated in TMS experiments, the amount of increase in 24-40 Hz coherence was significantly related to the amount of increase in evoked muscle responses to TMS. We propose that measures of inter-muscular coherence can provide information concerning the contribution of spared corticospinal pathways in mediating motor recovery following rehabilitation.

Virtual agency, embodiment and analgesia in phantom limb pain

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Phantom limb pain (PLP) in man may result from loss of sensory input and central plasticity (see Flor et al. 2001), though Ramachandran, following use of a mirror box, suggested that it may result from motor intention unrestrained by and mismatched with sensory return (Ramachandran & Rogers-Ramachandran, 1996).

We have developed a virtual arm seen on a screen, or in VR-spec-tacles, which moves in real-time relation to movement of the amputee’s stump recorded using a magnetic motion sensor. The arm moves to a table and grasps an apple as the subject guides his stump or shoulder forward and medially. Six patients with severe PLP (aged 32 - 87 and with forequarter to mid-humerus amputations 2 months to 15 years previously) have tried this for several hours over 1-2 days. Four learnt to move the virtual arm and felt their phantom arms move and grasp. With virtual agency and re-embodiment their pain reduced, in three from 7–9 to 2-4 on a visual analog scale and in one from 4 to 0; (t=3.88, n=4, significant at the 2.5% level, compared with a 30% fall as considered due to distraction, Flor, 2002). Patients commented on the difference between just seeing the avatar move and intending its movement, in terms of both the perceived effort involved and the subsequent perception. ‘It is much heavier and needs more effort to move the virtual arm than just to move the avatar from the shoulder alone.’ Pain relief required active movement and mental concentration. No effect was seen in two; one had poor motor control of the stump following root avulsion, whilst both had had paralysis of their phantoms (and arms) for years before the trial. This absence of an effect suggests decay in the mechanisms of intention with time, described by Ramachandran (1994) as ‘learned paralysis.’ These results show that the sense of virtual agency can develop quite rapidly, within 30 min, and be associated with perception in the phantom of both predicted movement and touch. The mechanisms of this effect are unclear but suggest a close relation between agency, sensation and integrity of the body image (see Tsakiris & Haggard, 2005); pain may occur when these break down and be reduced during their temporary, virtual restoration.


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Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.

C20

A cerebellar deficit in dyslexics? Evidence from peg-moving

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Developmental dyslexia is diagnosed when literacy skills are not commensurate with a person’s general cognitive ability and education. While the most common difficulty found in dyslexia is poor phonological processing, many dyslexics are remarkably clumsy; they have poor balance and atrocious handwriting, suggesting that they may also have motor deficits. These have been ascribed to cerebellar abnormalities. To establish whether the motor difficulties described in dyslexic children persist into adulthood, we tested 18 dyslexic adults and 22 control good readers matched for age and general IQ on Annett’s peg-moving task. The dyslectic participants performed significantly more slowly than control adults on the peg-moving task with their dominant hands (p = 0.004). Furthermore, the response times of both dyslexics and controls carrying out orthographic and phonological reading tasks (that did not involve hand movements) correlated with their dominant hand peg-moving ability (orthographic r = 0.45, p = 0.005; phonological r = 0.38, p = 0.025). These results suggest that the motor speed deficit in dyslexia may not be simply a sign of developmental delay, but their cerebellar deficit may persist into adulthood. Furthermore, motor speed may be related to the speed at which literacy information is processed. These results add to the mounting evidence that cerebellar abnormalities are involved in dyslexia.

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Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.
Cortico-cortical interactions in motor and premotor cortex of macaque monkeys investigated with chronically implanted microarrays: effects of ICMS and transient inactivation with muscimol

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One of the distinguishing features of the ventral premotor cortex (area F5) is that low-threshold repetitive intracortical microstimulation (rICMS) evokes digit movements. We investigated whether these motor effects result from a direct influence upon the spinal networks controlling digit movements or upon cortico-cortical connections with the primary motor cortex (M1). We evoked digit movements from F5 or M1 using small arrays of low impedance chronically implanted microwires and then tested whether these motor responses were affected by local microinjections of the GABA_A agonist muscimol into the hand area of M1. Two macaque monkeys were used. The hand area in both F5 and M1 were first localised using structural MRI and subsequent mapping of both areas using rICMS at low threshold (< 10 μA in M1 and < 20 μA in F5). During mapping, monkeys were lightly sedated using ketamine/medetomidine (6.4 mg kg^-1/80 μg kg^-1, respectively).

After mapping was complete, chronic microwires were implanted under deep anesthesia (intubation with isoflurane at 2-2.5% in a 1:1 O_2-N_2O mixture) at the centres of the hand/digit representations of M1 and F5. The length, arrangement and implantation angle of each array was based upon the ICMS mapping results, and targeted the rostral bank of the central sulcus (M1) and inferior limb of the arcuate sulcus (F5). Each 5-electrode array carried a guide tube that could carry the needle of a microsyringe for muscimol delivery.

After implantation, rICMS was delivered to arrays so as to evoke stable EMG responses recorded from digit muscles. The effects of rICMS delivered to F5 while M1 was inactivated were investigated. Within 10-20 min after microinjection of muscimol (0.5%, 1.5 μl) in the M1 hand area, there was a dramatic decrease in the evoked digit muscle EMG activity evoked from F5. Behavioural deficits restricted to the hand contralateral to the injection site were observed during the recovery period immediately after recovery from sedation. Control injections of saline in M1 were without effect. In a further control experiment, we noted that EMG responses to direct stimulation of the medullary pyramid were only slightly decreased after M1 muscimol inactivation, arguing against a decrease in spinal or motoneuronal excitability as the explanation of the loss of F5-evoked activity.

In conclusion, the results argue against a direct influence of F5 on hand motoneurones via the corticospinal tract, but rather suggest that M1 plays a key role in the transmission of output from F5 to hand motoneurones.

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Repetitive transcranial direct current stimulation (tDCS) of the motor cortex: a new form of inducing ‘homeostatic-like’ timing-dependent plasticity in the human

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Plasticity in the excitability of neural circuits is necessary for learning and memory. However, it is also necessary to regulate how easy it is to make such changes in order to prevent one or a small number of inputs from dominating activity in a pathway. Several rules have been put forward to control the amount of plasticity in a circuit (metaplasticity). One of these, homeostatic plasticity, suggests that the ease with which a connection can be facilitated/suppressed depends on the previous amount of activity in the system.

Here we describe a ‘homeostatic-like’ interaction between two protocols that are currently used in the human motor cortex to produce lasting changes in corticospinal excitability. We used transcranial direct current stimulation (tDCS; 1 mA) of motor cortex in 9 healthy subjects using the method described by Nitsche & Paulus (2000). As reported previously, 5 min of anodal tDCS facilitated motor-evoked potentials (MEPs) evoked in relaxed contralateral hand muscles for the next 5 min; 10 min anodal stimulation facilitated MEPs for up to 1 h. Cathodal tDCS suppressed MEPs for similar periods.

We then investigated the effect of splitting 10 min of tDCS into two 5 min periods separated by a pause. If 5 min tDCS was followed by a rest period of 30 min, application of a second period of 5 min tDCS had the same effect as the first period of tDCS. We refer to this protocol as 5/3/5. However, the effects were quite different if the pause between two successive periods of tDCS was only 3 min (i.e. 5/3/5). In this case, the second 5 min tDCS was applied while the cortex was still facilitated/depressed following the first period of tDCS. For anodal stimulation, the second period of tDCS initially led to facilitation, but this only lasted 5 min; from 10–30 min MEPs were suppressed. With cathodal stimulation, the second 5 min tDCS no longer produced any suppression, but was followed by facilitation that was particularly evident from 10–30 min. There was no effect of the 3 min pause on the after-effects of 5 min tDCS on measures of intracortical inhibition/facilitation.

We conclude that the after-effects of tDCS depend on the excitability of the cortex at the time the stimulation is applied; a period of increased excitability reverses the effect of anodal tDCS on MEPs from facilitation to suppression. A period of decreased excitability reverses the effect of cathodal stimulation from suppression to facilitation. This is compatible with a ‘homeostatic-like’ rule governing the response of the human motor cortex to plasticity probing protocols. Furthermore, this rule appears to take into account the delay between previous activity and application of the protocol.

K. Fricke and A. Seeber contributed equally to this work.


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Physiological connectivity of an area anterolateral to the dorsal premotor cortex (PMd) to the ipsilateral primary motor cortex in human

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Paired TMS has been applied as a probe to test functional connectivity within distinct cortical areas of the motor system. Depending on the intensity of a conditioning stimulus applied to different areas of the cortical motor network both facilitation and inhibition may be detected in the primary motor cortex (M1), ipsilaterally or contralaterally to the site of conditioning stimulation. Civardi (2001) and our group (Koch; unpublished data) reported that conditioning stimuli applied to the PMd may induce opposite effects on ipsilateral M1 depending on the intensity of stimulation. Low conditioning intensities provoked inhibition with a maximum at 90% active motor threshold (AMT) which turned into facilitation when higher intensities (120% AMT and 110% RMT, respectively) were applied.

Very recently, Lemon and co-workers have demonstrated robust facilitation of M1 motor outputs to intrinsic hand muscles by conditioning the ipsilateral ventral premotor cortex (area F5) in the Macaque monkey (Cerri et al. 2003; Shimazu et al. 2004). Here we report data on an area anterolateral to the PMd in humans that elicits strong facilitation on motor outputs of the ipsilateral M1 hand area as tested with single pulse TMS.

We tested five different conditioning stimulus intensities (CSIs) (70, 80 and 90% AMT and 90 and 110% RMT, respectively). Interestingly, we found complementary results to those reported on the PMd. Repeated measures ANOVA showed that different effects were obtained depending on the CSI (ANOVA main factor F=13.2; p<0.001), with no specific time course profile. Whereas low intensities evoked facilitation of ipsilateral M1 motor output with a maximum at an interstimulus interval (ISI) of 6 ms and a conditioning stimulus intensity of 80% AMT (140% of the MEP evoked by the test pulse alone; p=0.008), higher intensities provoked inhibition (maximum: ISI 4 ms; CSI 90% RMT; 80% of the baseline MEP; p=0.04). The facilitating effect was even stronger when paired conditioning stimuli were applied (at ISIs of 1.4, 2.0 and 2.6 ms, respectively).

In a stereotactically guided (Brain Sight) control experiment the area of the conditioning stimulus turned out to be anterior-parietal to the area of Broca (area 44), in the range of what Rizzolatti and co-workers proposed to be the human homologue of monkey F5 (Rizzolatti et al. 1998). Cerri G, Shimazu H, Maier MA & Lemon RN (2003). J Neurophysiol 90, 832-842.


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Transcallosal sensorimotor integration – effects of sensory input on cortical projections to the contralateral hand

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Low amplitude vibration of forearm or hand muscles predominantly activates proprioceptive inputs that influence corticospinal projections in a focal manner, increasing output to the stimulated muscle while reducing output to neighbouring muscles [1]. Modulation of contralateral forearm muscles by vibration has also been reported on one occasion [2]. The aim of the current investigation was to investigate the effects of proprioceptive input from a hand muscle on corticospinal excitability, intracortical inhibition (SICI) and interhemispheric inhibition (IHI) targeting the homologous contralateral muscle.

Transcranial magnetic stimulation (TMS) was delivered to the left cortical hand area of ten healthy subjects and surface electromyography (EMGs) recordings taken from the right first dorsal interosseus (FDI) and abductor digiti minimi (ADM). The effect of low amplitude vibration of the left FDI on MEP amplitudes, SICI and IHI targeting the right hand was assessed.

Vibration of the left FDI caused a significant reduction in MEP amplitudes in the homologous right FDI but not in ADM. SICI and IHI targeting the right FDI were also significantly increased but were unchanged in ADM. These increases in inhibition occurred despite controlling for the amplitude of baseline MEPs.

We conclude that proprioceptive input from a hand muscle reduces the corticospinal excitability of the contralateral homologous muscle. Although vibratory input is known to affect the excitability of spinal alpha motor neurons [3], the increase in SICI suggests that at least some of this effect occurs in the cortex ipsilateral to the stimulus. The observed increase in IHI suggests that such changes may be mediated via transcallosal fibres.

These results suggest that sensory input can modulate excitability in both motor cortices simultaneously, as well as the relationship between them. Interventions which modulate this transcallosal relationship may become useful in disorders where abnormal IHI is a potential therapeutic target [4].


Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.
Globus pallidus field potentials in patients with primary dystonia

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Dystonia is thought to result from disorders of basal ganglia function, hence the globus pallidus is the preferred target for its functional surgical treatment by high frequency electrical stimulation. To explore the role of abnormal neuronal activity of the globus pallidus in the generation of dystonia in man, local field potentials (LFPs) were recorded from the globus pallidus internus (GPi) in 13 patients undergoing deep brain surgery for primary dystonia and compared with EMGs recorded from the affected muscles. Their frequency composition was analysed before and during dystonic phases, and during voluntary movements. As is often seen, in 5 patients with rhythmic bursting involuntary movements, the muscle EMG bursts were phase locked with oscillations in the contralateral pallidal LFPs at the burst frequency. But in patients with tonic dystonia without rhythmic components no significant coherence between EMGs and LFPs was seen. The most interesting features emerged, however, when the patients’ involuntary dystonic movements were compared with their voluntary movements. During both, power in the GPi LFPs increased at the movement frequencies (0.1–5 Hz), as one might expect. However, during voluntary movements power in the higher beta (25-35 Hz) and gamma (45-85 Hz) frequency bands also increased, whereas that between 8 and 20 Hz decreased. In contrast during involuntary dystonic episodes power at 8-12 Hz increased, whereas there was no increase in power at any of the higher beta and gamma frequencies. Since these higher frequencies are thought to be responsible for helping to ‘bind’ together and time accurately the elements of a complex movement, their absence during dystonia may help to explain its uncontrolled character. In addition the pathological increase in GPi LFP power at 8-12 Hz during dystonic episodes may contribute directly to them. Such frequencies may be projected to excite the muscles, but since the muscles + limb act as low pass filters, this rate may be too high to appear as tremor, but instead it may contort the limb into its dystonic postures.

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Dynamic multivariate Granger causality analysis of neural and muscular signals

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Analysis of functional coupling between muscular and oscillatory neural activity at different levels of the motor system has provided important insights into neural control of movement. One widely used method of estimating the functional coupling between two oscillatory signals is coherence estimation. However, this does not provide directional information, preventing further dissection of their relationships. Granger causality analysis has proved useful in revealing causal relationships between signals. In a recent study, it was performed for all pairwise combinations of oscillatory field potential activity in the beta (14–30 Hz) frequency range among sensorimotor cortical recording sites in monkeys (Brovelli, 2004). We have developed autoregressive (AR) models followed by Granger causality analysis to quantify coupling of five variables including pairwise and group interactions with or without conditional variables. The AR models were optimised and validated according to Akaike’s information criteria and prediction error for individual signal pairs. Their rescaling property and robustness to noise were investigated using simulated signals.

Tremor-related EMGs and local field potentials (LFPs) of the subthalamic nucleus (STN) were simultaneously recorded in Parkinsonian patients undergoing deep brain stimulation surgery. We have therefore used conditional Granger causality analysis to quantify the directional interdependence between the STN LFPs and the envelope signal of the surface EMGs related to Parkinsonian tremor. Our results from four patients showed that during persistent tremor, there was a directional causality predominantly from surface EMGs to contralateral STN LFPs corresponding to significant coherence between them at the tremor frequency. By using an adaptive Granger causality model based on autoregressive analysis with a running window, we were able to show that the LFP-EMG interdependence was bi-directional and varied with time of tremor occurrences. We conclude that the tremor-related functional correlation appeared between the STN and the contralateral muscle. This interdependence is dynamic, bi-directional, and dependent on the tremor status.


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Excitability of inhibitory neurons in the human motor cortex during static and dynamic contractions

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We investigated the nature of the supra-spinal contribution to the motoneuronal drive of the Soleus (SOL) muscle during dynamic and static contractions using sub-threshold transcranial magnetic stimuli to suppress the corticospinal output (Davey et al. 1994).

Eight healthy subjects with no history of neuromuscular disorder participated in the study. Subjects were seated with the right foot fixed to a stationary manipulandum. Surface EMG was recorded from the right SOL. Visual feedback of the ankle torque was provided via strain gauges fixed to the manipulandum. Subjects were instructed to follow a four-segment ramp and hold force trajectory using their plantar flexor muscles. The ramp was defined as a per cent of the maximum voluntary contraction (MVC) as follows: hold 5% MVC (1 s), ramp up (0.6 s), hold 15% MVC (0.9 s), ramp down (0.6 s).

Magnetic stimuli were delivered via a custom-made 90 mm double coil (batwing design) placed on the scalp and over the hot-spot of the SOL muscle. The stimulation intensity was decreased until a clear suppression of the mean rectified SOL EMG could be seen without evidence of facilitation at 15% MVC. Stimuli were delivered in the middle of each trajectory section. At least 90 stimulated trials and 90 control trials were recorded for each section in a fully randomised fashion.

The onset of the suppression was defined as the point where the ensemble-averaged SOL EMG for the stimulated trial was less than that of the control EMG for at least 5 ms. For each subject, the same analysis window was used for each trajectory section (13-24 ms wide). The suppression was expressed as a per cent change from the control EMG. A one-way ANOVA and Tukey-Kramer post-hoc test was used to compare the magnitude of the suppressions at each trajectory section (significance level α=0.05).

The background EMG for the different trajectory sections was (mean±SD): 9±2 µV, 17±3 µV, 16±3 µV and 11±3 µV. The onset of the EMG suppression occurred between 35-45 ms after the TMS stimulation. The magnitude of the suppressions was (mean±SD): 17±7%, 14±5%, 18±3% and 3±9%. No significant differences were found between the first 3 sections of the ramp (p<0.1). However, the suppression of the ramp-down section, was significantly less than the other sections (p<0.001).

The lack of a significant difference between the EMG suppression of the dynamic and static contractions (ramp-up and 15% MVC hold) suggests that the excitability of the inhibitory neurones in the motor cortex is the same in both tasks. However, when the force is decreased, the inhibitory effect of the stimulus also decreases suggesting that the cortical control of the descending part of the trajectory is different from the other sections. This result may be explained by a decreased excitability of the inhibitory neurones or a change in the cortical drive to the spinal motoneurones.


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Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.
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Histamine H3–receptor-mediated inhibition of GABA release in the vestibular nucleus in normal and labyrinthectomized rats

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Histamine depolarises vestibular neurones via H1 and H2 receptors (Wang & Dutia, 1995), and infusion of H2-receptor antagonists or H3-receptor agonists into the medial vestibular nucleus (MVN) induces a behavioural syndrome similar to that seen after unilateral labyrinthectomy (UL; Yabe et al. 1993). Presynaptic H3-receptors can act both as inhibitory autoreceptors and as inhibitory heteroreceptors, but it is not known if the latter mechanism has a role in vestibular function. To clarify this we investigated the histaminergic regulation of endogenous GABA release in superfused MVN slices.

Slices were prepared from normal male Lister hooded rats and from animals which underwent left labyrinthectomy under halothane anaesthesia either 25 h or 7 days earlier (Yamanaka et al. 2000). The animals were decapitated under halothane anaesthesia and horizontal 400–450 µm slices of the MVNs of the two sides were prepared in chilled artificial cerebrospinal fluid (aCSF; 123 mM NaCl, 5 mM KCl, 2.4 mM CaCl2, 1.3 mM MgSO4, 26 mM NaHCO3, 1.2 mM KH2PO4, 10 mM D-glucose, 100 µM glutamine). The slices were separately superfused with oxygenated aCSF at 32°C, and GABA release was determined with high performance liquid chromatography.

In samples from normal MVN slices, the GABA release evoked by a 4-min stimulus with high K+ (60 mM) aCSF was Ca2+ dependent, indicating neuronal origin. Histamine (100 µM) reduced the evoked GABA release from 36±5 fmol/mg to 18±2 fmol/mg (mean±SEM, unpaired t test, P=0.0099, df=18). The H3-agonist immepip dose-dependently inhibited evoked GABA release, with a calculated IC50 of 0.34 nM, reaching maximum inhibition (-45% to -70%, 95% confidence interval) at 10–100 nM.

In superfusates from MVNs prepared from UL animals, an imbalance in evoked GABA release (with less release from the contra-lesional MVN) was observed after 25 h (paired t test, P=0.0093, df=6) but not after 7 days. The inhibitory effect of immepip was attenuated in MVN slices from UL animals at both time points. In slices from 25 h post-UL animals, immepip (100 nM) removed the imbalance of evoked GABA release between the ipsi-lesional and contra-lesional MVNs.

This is the first report of H3-mediated inhibition of GABA release in the MVN. The change in immepip potency after UL is in line with changes in H3-receptor mRNA expression after UL (Lozada et al. 2004). Changes in H3-receptor control of GABA release in the MVN may be important in the rebalancing of bilateral MVN activity after unilateral deafferentation.

Lozada AF et al. (2004). BMC Neurosci 5, 32.


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Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.

**PC11**

**Experimental approach to the investigation of human nervous disorders using transgenic or mutant mouse models**

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In vitro investigations of transgenic or mutant mouse models with defined neuronal changes revealed valuable insights into pathophysiological mechanisms at the genetic and molecular/cellular level, which may cause motor disorders. The significance of the raised data, however, often remained hypothetical with respect to the in vivo situation of the intact animal and the clinical symptomatology. We now tried to bridge the gap between the findings at the molecular/cellular level and the pathophysiological appearance by analysing the spinal and peripheral components of neuronal disorders with different system-physiological techniques in vivo. Comparative experiments were performed in wild type (WT) mice of the same strain. EMG was recorded in freely moving animals with flexible electrodes implanted into the muscles under ether anaesthesia. Acute experiments were performed in anaesthetized mice (methohexital-Na i.v., 50 mg kg\(^{-1}\) h\(^{-1}\)). Body temperature was controlled and ECG was monitored.

1. LDL receptor-related protein 1 (LRP1) knockout mice develop severe behavioural and motor abnormalities. In EMG and ECG was monitored.


Supported by the DFG Schwerpunktprogramm ‘Funktionsanalyse von definierten Mutanten’ to B.U.K.

Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.

**PC12**

**Vibro-tactile feedback cueing a step response to balance challenge**

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The use of vibro-tactile arrays to inform pilots about orientation (Rupert, 2000) has prompted investigations of their use in providing patients with supplementary information which may aid balancing (Wall et al. 2003). Published studies have used ‘steady-state’ balancing which does not reveal whether vibration feedback can be fast enough to cue a saving reaction. Accordingly, we evaluated vibratory feedback in cueing a single step balancing response to a transient perturbation. Human subjects stood facing longitudinally on a moving walkway. Body movements were transduced with gyroscopes (angular velocity), accelerometers and Fastrak® position transducers. Vibrations were generated by body movement. (i) The locus of vibration giving the shortest latency step response was determined by comparing the latencies of step responses to bursts of vibration applied to the forehead vs the xiphoid process of the sternum. Subjects were instructed to step as soon as they felt the vibration. In 7 subjects mean reaction times, from vibration to step initiation, were significantly lower for the head, 176±24 ms, compared with the trunk, 225±54 ms (t test, P<0.05). (ii) The part of the body giving the earliest signal of instability with balance challenge was determined by destabilising posture with unpredictable accelerations (4 m s\(^{-2}\)) of the walkway, forwards or backwards with trapezoidal velocity profiles peak 1.5 m s\(^{-1}\) or 1.1 m s\(^{-1}\). Subjects had to respond with a rapid step to avoid toppling.

Mounting the various transducers on ankle, hip, shoulder and head was found that the gyroscope placed on the lower part of the thigh, just above the knee, gave the earliest (48±11 ms) least ambiguous signal of the perturbation and then only to backwards walkway motions. (iii) Thereafter, the combination of signals from the thigh to trigger vibration on the forehead was used to determine whether vibratory cues could enhance the stepping response to unpredictable backwards walkway translation. The trigger for vibration was given when the gyro signal reached a subject-dependent threshold of passive leg tilt. Four normal, age-matched subjects and 3 patients with bilateral vestibular loss were tested. Reaction times were measured as latency between the onset of translation and the time for the gyro signal to reach a zero crossing signifying that a step had been initiated. There was no difference between normal reaction times with and without vibration cueing feedback (284 (SD±80) ms and 274 (±40) ms. Patients also had similar reactions, 283 (±20) ms with and 290 (±50) ms without vibration. These preliminary results suggest that vibro-tactile feedback triggered from the body’s own instability may be ineffective in shortening the latency of a step response in either normal subjects or patients with significant disorders of balance.
Supporting muscles are less active following self-triggered than externally induced unloading during human walking

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During arm movements it is known that anticipation of unloading can result in a reduction of unwanted reactions (anticipatory postural adjustments, APAs) [1]. Similarly, during gait, self-triggered electrical stimulation of the sural nerve results in smaller reflex responses as compared to computer-triggered stimulation [2]. This reduction is seen as a switch from reactive to proactive motor control. The question remains whether such a switch occurs during mechanical gait perturbations as well. In the lower limb, sudden unloading has already been used as perturbation. Upper limbs are not normally used as support during gait, except for crutch walking. Sudden unloading can then be introduced by experimentally inducing a crutch collapse.

EMG activity of 12 subjects was investigated in 8 upper arm muscles following sudden unloading, induced either by the subjects themselves or externally, during the stance phase of bilateral crutch walking on a treadmill. This unloading was caused by 7 cm shortening of the crutch. Following the self-triggered shortening of the crutch, the normalized EMG (electromyogram) activity was substantially lower in the muscles after the collapse as compared to computer-triggered shortening. The reduction was present in all muscles studied and the amount of reduction differed for the various muscles. In almost all muscles the reduction in EMG amplitude was largest in the 70 ms period just following collapse (mean of all muscles: 34%, SD 21.4%) and the difference subsided in later periods (mean 24% and 17%, SD 11% and 14%).

Upper arm supporting muscle activity following unloading during crutch-walking can effectively be reduced by anticipation of the self-triggered unloading, consistent with a switch from reactive to proactive control. Apparently, APAs during gait perturbations can be elicited in the upper limb as well, provided the arms are involved in the control of body support.


Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.
Reciprocal inhibition between knee extensors and knee flexors in humans

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The reciprocal inhibition evoked from the knee extensors to the knee flexors is particularly potent in the cat and has therefore been the subject of detailed analysis (Hultborn, 1972). More recently reciprocal inhibition has been described between various muscles in humans. Surprisingly, however, the reciprocal inhibition between knee extensors and flexors has not been studied in humans. We have therefore investigated the reciprocal inhibition between quadriceps and hamstrings in 8 healthy subjects. EMG was recorded from vastii medialis and lateralis, and the medial and lateral hamstrings. Either the femoral or sciatic nerves were stimulated using 1 ms pulses at strengths up to 2x motor threshold (MT). The femoral nerve was stimulated at the femoral triangle. The sciatic nerve was stimulated at mid-thigh level between the bellies of biceps femoris and semitendinosus. Data were collected using two approaches. In the first approach, the EMG was rectified and averaged following 100 stimuli to either the femoral or the sciatic nerve. In the second approach, the H reflexes of hamstrings and quadriceps were conditioned with stimuli to the antagonist’s nerve at various test-condition intervals.

Short latency inhibition, at strengths below 2T, was observed in the medial and lateral hamstrings upon stimulating the femoral nerve and in the vastii medialis and lateralis upon stimulating the sciatic nerve. The occurrence of short latency inhibition was observed more often in both the medial (21/31 trials) and lateral (15/22 trials) hamstrings than in vastus medialis (4/27 trials) and vastus lateralis (8/27 trials). In addition, the inhibition evoked in the hamstrings by femoral nerve stimulation was significantly larger than the short latency inhibition evoked in quadriceps by sciatic nerve stimulation (p<0.05, t test). Using H reflex testing in three subjects, increasing the stimulus strength to the femoral nerve produced a progressive reduction in the hamstring H reflex amplitude, reaching a maximum at 1.5MT and with a condition-test interval of 4 ms. In contrast, varying the stimulus strength to the sciatic nerve produced no change to the quadriceps H reflex, even at 2MT.

The inhibition evoked by quadriceps in hamstring muscles observed here seems likely to be the equivalent of the 1a reciprocal inhibition observed in the cat. In contrast, caution needs to be observed in interpreting the inhibition evoked by stimulating the sciatic nerve, since such stimuli will activate afferents from many other muscles as well as the hamstring afferents. However, despite this, only small inhibitions were observed by comparison to the inhibition evoked from quadriceps to hamstring. These results show that reciprocal inhibition at this joint is not actually reciprocal i.e. not equal in both directions. The implications of this in understanding the function of reciprocal inhibition needs to be assessed.


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Poster Communications 19P

Descending control of human trapezius and serratus anterior muscles

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Trapezius (Tr) and serratus anterior (SA) are shoulder muscles which help to stabilise the scapula on the chest wall. In a previous study, we described interesting differences in the reflex properties of these two muscles (Alexander et al. 2005). Here we examine the descending control of these muscles using magnetic stimulation of the cortex. With informed consent from 14 subjects, EMG recordings were made from SA, upper Tr and lower Tr muscles using surface electrodes placed bilaterally. First, the optimal sites for stimulation of the motor cortex were examined. Using a grid marked on a cloth attached to the head, magnetic stimuli were applied to the scalp overlaying the motor cortex in different positions until the largest amplitude contralateral MEP (cMEP) was evoked for each of the three muscles studied. In these positions, the stimulator output was varied from 20 to 100% of the stimulator output. The latency at 1.2 x threshold for the cMEP was 10.4 ± 1.1, 12.3 ± 1.4 and 12.0 ± 1.1ms (mean ± S.D.) for upper Tr, lower Tr and SA, respectively. With ongoing EMG activity, the threshold of the cMEPs was approx. 40% of the stimulator output. The position of the coil was then systematically moved around the grid. The amplitudes of the cMEPs were then used to construct a surface map. The optimal site was expressed as a centre of gravity (C of G). An average site for the C of G was expressed as the mean anterior-posterior position ± SD, the mean medio-lateral position ± SD. A two-way ANOVA without replication demonstrated that the C of G for each of the muscles recorded could not be separated (SA -0.6 ± 0.8, 3.8 ± 0.5cm, upper Tr -0.5 ± 0.9, 3.7 ± 0.7 cm and lower Tr -0.7 ± 0.7, 3.7 ± 0.6cm). In 10 subjects, this experiment was repeated bilaterally for upper Tr in order to examine the symmetry of this map. In 9 of 10 subjects, the maps were asymmetrical in either the anterior posterior or the medio lateral direction by at least 1.5cm. Finally, in order to study possible ipsilateral connections, the EMG was rectified and averaged. During a weak contraction, ipsilateral responses were evoked in upper Tr at a latency of 19.0 ± 2.7ms (85% occurrence), i.e. nearly 9ms longer than the corresponding contralateral response. In contrast, no ipsilateral MEPs were evoked in SA even at high stimulator outputs and/or with ongoing EMG activity.

In conclusion, cMEPs can be evoked in both Tr and SA with latencies consistent with a direct corticospinal connection. While these experiments indicate that the optimal position to evoke MEPs in these muscles are identical, care needs to be taken when evoking MEPs from each side due to inherent asymmetries. Tr and SA differ in their bilateral descending control. Whereas such magnetic stimulation often evoked an MEP in ipsilateral Tr (albeit at a higher threshold and at a long latency), no responses were evoked in ipsilateral SA.

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PC17

Mapping the cortical representation of the lumbar paravertebral muscles in humans

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Cortical maps of muscle representations provide a tool for investigating neuroplastic changes in response to a variety of stimuli and insults. While stimulation of the cortex with TMS has identified contralateral and ipsilateral corticospinal projections to trunk muscles, to date comprehensive maps of the representation of the lumbar paravertebral muscles have not been demonstrated.

The aim of this study was to investigate the feasibility of constructing maps of the cortical representation of the lumbar paravertebral muscles in normal healthy subjects using transcranial magnetic stimulation (TMS).

Twelve normal healthy volunteers were investigated. While subjects maintained a steady level of activity in the lumbar paravertebral muscles with a forward sitting manoeuvre, TMS stimuli were applied using a biphasic Magstim stimulator to reference points on a grid applied on the cranium over the left motor cortex. Six stimuli were applied to each reference point. Using surface electromyography, motor evoked potentials (MEPs) in the lumbar erector spinae (ES) and superficial multifidus (SM) muscles were recorded bilaterally in response to these stimuli. Responses obtained from each grid point were averaged and MEP area was calculated. Responses were normalised for each subject by expressing MEP area for all stimulation sites as a percentage of the peak response. Centre of gravity (COG) was calculated using the formula presented by Wassermann et al. (1992):

\[
\text{COG} = \left[ \frac{\sum v_i x_i + \sum v_i y_i}{\sum v_i}, \frac{\sum v_i x_i y_i}{\sum v_i} \right],
\]

for scalp sites \((x_i, y_i)\) and amplitudes \((v_i)\).

It was possible to construct maps in 10 out of 12 subjects. Student’s paired t tests were performed to compare latencies and COG coordinates for each muscle. MEPs from ES had a shorter latency than those from SM (mean 1.1 ms; \(p<0.05\)). The COG of the contralateral SM was located significantly medial to that of ES (mean 0.75 cm; \(p<0.05\)).

This methodology may be useful in determining whether neuroplastic changes in the cortical representation of these muscles occur in response to acute and chronic low back pain.

Table 1. Mean COG coordinates (represented as cm from the vertex) for all muscles tested.

<table>
<thead>
<tr>
<th>Muscle group</th>
<th>A-P axis (cm ant to Vertex)</th>
<th>M-L axis (cm lateral to Vertex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONT ES</td>
<td>1.65 ± 0.92</td>
<td>3.8 ± 0.6</td>
</tr>
<tr>
<td>IPSI ES</td>
<td>2.21 ± 0.97</td>
<td>2.01 ± 0.51</td>
</tr>
<tr>
<td>CONT SM</td>
<td>1.81 ± 0.02</td>
<td>3.1 ± 0.90</td>
</tr>
<tr>
<td>IPSI SM</td>
<td>1.91 ± 0.12</td>
<td>2.21 ± 0.35</td>
</tr>
</tbody>
</table>

All values are mean±SD.


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PC18

Corticospinal excitability changes following functional electrical stimulation of the tibialis anterior muscle in healthy humans

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Studies have demonstrated that functional electrical stimulation (FES) is effective in rehabilitation [1]. FES, as well as repeated voluntary activity, has been shown to produce long lasting changes in sensorimotor excitability [2]. FES has been used for the rehabilitation of foot drop, following stroke. However, there is limited evidence comparing the effects of FES with voluntary activation of ankle dorsiflexion in healthy participants. We have used transcranial magnetic stimulation (TMS), to compare changes produced by repetitive FES to that of simple repetitive voluntary dorsiflexion.

Seven healthy volunteers received both treatments in random order: an FES and a voluntary activation session separated by at least 1 week. The voluntary exercise consisted of 30 min of repetitive dorsiflexion producing 30% of maximum voluntary torque. Strain gauge measuring the torque of ankle dorsiflexion was used to provide visual feedback and ensure that similar sustained (3 s) contractions were maintained at 11 times a minute. Using an FES device (Odstock stimulator, 04CHS, Salisbury District Hospital, Wiltshire) electrical stimulation was applied to the tibial nerve through a pair of circular electrode pads (3.8 cm) for activation of the tibialis anterior (TA) muscle, a prime ankle dorsiflexor. Automatic repetitive stimulation trains (25 Hz, 3.5 s duration, at 11 times per minute) was applied for 30 min. Similar levels of FES induced torque matching the 30% of maximum level of voluntary activation was achieved by adjusting the stimulus current. Motor-evoked potentials (MEPs) were monitored by surface electromyography of the right TA in relaxed subjects placed in a semi-reclined position. TMS was applied using a 70 mm figure-of-eight coil (rapid MagStim, in single pulse mode) over the left motor cortex (intensity 1.2 times resting motor threshold). MEPs were measured for 15 min before and for 60 min after completion of exercise. There was a significant increase in the averaged MEPs for both interventions, which were still significant at post 60 min (95 ± 58% after FES, 97 ± 20% after voluntary activation, mean ± S.D., \(P = 0.001\), repeated measures ANOVA). The magnitude of the MEP increase was not significantly different between the two treatments. There was also no significant change in MEPs monitored during tonic voluntary activation (at 20% of MVC). No significant change was observed in torque; suggesting the changes could not be attributed to exercise-induced fatigue. A persistent effect on MEPs is therefore likely to be part of the normal adaptive plasticity of corticospinal control following simple repetitive exercise. Our experiments confirm previous similar findings for FES in the healthy.

This work was completed as partial fulfillment for the MSc in Neurorehabilitation.

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Locognostic acuity differs between the vertical and horizontal axes of dermatomes of the human abdomen

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The precision of tactile point localization (locognosia) has been reported to vary between the transverse and longitudinal axes of the arm (Hamburger, 1980). We have investigated whether comparable directional differences in locognostic acuity are present in the abdomen, whilst additionally attempting to replicate Hamburger’s findings for the upper limb.

Twenty-nine (13 female, 16 male, aged 18-26 years) healthy, subjects participated. A 7x7 cross of stimulus points (13 points, 5 mm separation), was drawn on the shaved skin of (a) the dorsal surface of the non-dominant forearm and (b) the anterior aspect of the ipsilateral abdomen at the level of the T10 dermatome. The axes of the cross were orientated (a) transversely and longitudinally for the arm and (b) vertically and horizontally for the abdomen. In each trial, a brief tactile stimulus was first applied, with a von Frey hair (rating 150 mN), to the central locus of the cross (reference), followed, after 1s, by a stimulus to one of the 13 test loci. The test region was obscured from the subject’s view. The subject was required to state the direction (e.g. ‘more distal’ for the longitudinal axis of the arm) of the test locus relative to the reference locus, using a 2-alternative, forced-choice procedure. The four region-axis combinations were tested separately in each subject. Each test locus received 10 stimuli (total 70 stimuli per axis). For each subject, at each test locus, the probability of a specified directional response was calculated. The interval of uncertainty (IU, a measure of locognostic discriminatory threshold) was estimated from standard psychophysical functions (probability of specified directional judgement versus stimulus locus).

Statistical analysis (2-way, repeated measures ANOVA) of IU values indicated a significant main effect of axis (P < 0.001) whereas there was no significant (P = 0.128) effect of body region. Paired t-tests, with Bonferroni correction, indicated that IU values (a) for the upper arm were smaller (i.e. locognosia more accurate; P < 0.001) in the transverse than longitudinal axis, confirming Hamburger’s (1980) findings, and (b) for the T10 dermatome were smaller (P < 0.001) in the vertical than horizontal axis.

Thus, differential, directional locognostic acuity is a feature of abdominal dermatomes, as well as the upper arm. We believe that this characteristic probably results from the receptive fields of local sensory neurons being oval-shaped and similarly aligned, which favours better tactile localization in the direction of their narrower dimension.


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A comparison between young and older human subjects of movements of the body and of the centre of pressure during quiet standing

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Measurements were made of movements of the centre of pressure (COP) and of 14 body markers during periods of standing with eyes open or closed in two groups: young (mean age 29 years) and older (mean age 72 years). The measurements were used to assess whether an inverted pendulum model, with movement only at the ankles, adequately described the observations, and also whether the amplitudes and the nature of the movements differed between groups. The older group showed significantly increased medio-lateral movements of the COP compared to the young (root mean square amplitude in mdeg: 200 ± 15 (mean ± SEM) vs 153 ± 11 with eyes open and 216 ± 16 vs 165 ± 10 with eyes closed). There was no significant difference from the young group in the anterior-posterior plane. In the ML plane in the older group the pendulum model was significantly more successful than for the young in accounting for movements of the COP (r = 0.976 ± 0.003 vs 0.954 ± 0.006). In all conditions the pendulum model explained more than 93% of the variance of the position of the COP and more than 80% of the variance of body markers’ positions. However, there was also evidence for more complex movements in which hip angle changes were correlated with the angle changes at the ankles. In some subjects the hips were consistently used to move the centre of mass in the same direction as the ankles (‘hip strategy’; Nashner & McCollum, 1985) but, in contrast to previous studies (Day et al. 1993; Gatev et al. 1999), we also found subjects in whom the movements were correlated in the opposite direction. In older subjects ‘hip strategy’ was more common with eyes closed than with eyes open.

Frequency of the pendulum movements was measured as described by Loram et al. (2001) and was not significantly different in young and old subjects (group means ranged from 0.295 to 0.334 Hz). Also following the methods of Loram et al. (2001, 2005) extracts were taken from pendulum angle records and from COP records around times of peak pendulum velocity and were averaged. Plotting the average pendulum movement against average COP excursion produced graphs that were very similar for old and young subjects (Fig. 1).
Altered ankle joint kinematics during dynamic activity in subjects with functional ankle instability (FAI)

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FAI is a term used to describe patients who sustain multiple ankle inversion injuries with slight or no external provocation (Konradsen & Magnusson, 2000). It is a common cause of residual disability following ankle sprains, affecting up to 60% of individuals who suffer an initial ankle sprain (Kannus & Renstrom, 1991). Previous research has suggested that FAI may be associated with altered feed-forward motor control. The purpose of this study was to investigate dynamic movement control during functional activities in FAI subjects compared with controls.

We compared kinematic profiles of FAI (n=24) and control (n=22) subjects during 3 dynamic functional activities; treadmill walking at 4 km h\(^{-1}\), 1 m jump for distance, and 30 cm lateral hop. FAI subjects met the inclusion criteria described by Caulfield & Garrett (2004), whilst control subjects had no history of ankle sprain. Kinematic data were recorded using a CODA MPX30 3D motion capture system (Charnwood Dynamics Ltd, UK) at a sampling rate of 200 Hz. Average values from 10 trials of each activity for hip, knee and ankle joint 3D angular displacements were calculated for each subject and group mean time averaged profiles were calculated for the period from 200 ms prior to and following initial contact (IC). Differences in FAI and control group time averaged profiles were tested for statistical significance using independent two-sided t tests.

1. Walking (24 FAI and 22 control subjects): FAI subjects exhibited a decrease in toe clearance during the time period 150 ms to 100 ms pre IC (P<0.05). They also exhibited a more inverted position of the ankle joint during the time period 95 ms pre IC to 50 ms post IC (P<0.05).

2. 1 metre jump for distance (11 FAI and 13 control subjects): FAI subjects exhibited a significant increase in ankle joint inversion during the period 70 ms pre initial contact (IC) to 30 ms post IC (P<0.05).

3. Hopping (13 FAI and 16 control subjects): FAI subjects exhibited a significant increase in ankle joint inversion during the time period 10 ms pre IC to 200 ms post IC (P<0.05).

A more inverted position of the ankle joint upon IC will cause the subtalar joint axis to remain in a more lateral position. Consequently a greater external inversion load may be exerted on the ankle joint, increasing the potential for a repeated inversion injury. The timing of the observed changes suggests an alteration in feed-forward control. The fact that FAI subjects have shown a consistent change in movement control in 3 separate functional activities suggests a possible position error in motor programming.


This study was supported by the Irish Research Council for Science, Engineering and Technology.

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Acute and acute residual effects of vibration on neuromuscular performance during fatiguing knee extension exercise

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The aim of this study was to determine whether vibration alters the time course of neuromuscular fatigue during exercise and in early recovery in man. Eight subjects (4 males, 4 females, 23 ± 2 years, 171 ± 3 cm, 70 ± 2 kg) completed two trials (vibrated or non-vibrated) of unilateral knee extension exercise to volitional fatigue, separated by at least 3 days.

Torque, knee joint angle, and vastus lateralis surface EMG activity were recorded simultaneously during metronome-guided knee extension exercise at 35% of one repetition maximum (1RM), completed with (Vb+) or without (Vb−) superimposed vibration-like stimulation (10 Hz, rapid variable resistance) of the leg. Isometric (maximum voluntary contraction, MVC) and dynamic (1RM) strength were tested pre- and post-exercise. Median spectral frequency (MDF) and mean amplitude of mus-
Electromyographic power spectrum profiles and changes in knee extensor strength after surgery

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We have studied neuromuscular changes and adaptation of the knee extensors in thirty one patients (25 males, 6 females), 30 ± 8 years, body mass 76 ± 9 kg, height 1.75 ± 0.10 m (mean ± SD) following anterior cruciate ligament reconstruction (ACLR). A major rehabilitative goal is to restore optimum functional performance. We reported (Drechsler et al. 2005), that at 3 months post surgery, the knees were stable and most patients (n = 27) were pain free with minimal swelling; they had achieved full activation but still had muscle weakness. At both 1 and 3 months post surgery, the surface electromyographic (EMG) median frequency and amplitude were significantly lower (P<0.05) in the injured compared to the uninjured limb. Further work has shown that there were no significant differences in these parameters between the uninvolved limbs and those of 20 age-matched and recreationally active control subjects.

Detailed analysis of individual EMG power spectrum plots at maximum voluntary isometric contraction (MVIC) and linear regression analysis were then used to investigate whether any independent variables tested 1 month after ACLR could predict 1 year functional status using the Hughston Clinic Knee Questionnaire (Hooper et al. 2002) completed 1, 3 and 12 months after surgery. Muscle function tests included quadriceps femoris MVIC twitch superimposition and Fast Fourier Transformation of surface EMG recordings (5000 cycles per s, filter 10-250 Hz) of rectus femoris to determine median frequency and amplitude at MVIC. In addition to the reduced median frequencies observed, paired t tests showed that the magnitude (mv²) of the EMG power density spectrum during MVIC was consistently and significantly lowered (P<0.001) in the injured compared to the uninjured limb, 1 month after surgery. Step-wise forward linear regression analysis showed that the functional questionnaires (step 1), combined with activation or strength level (step 2) assessed 1 month after ACLR were the most effective estimates of functional status 1 year after surgery (R=0.80, adjusted R²=0.59, F₁,₁₂=13.9, P<0.0001).

Our results showed restoration of volitional quadriceps activation, lowered motor unit firing rates and a significant reduction in the magnitude of the frequency spectra after ACLR. Regression analysis showed that functional status combined with activation/strength assessment at 1 month can predict knee function 1 year after surgery. These findings suggest changes in patterns of activation and in the recruitment patterns of Type 11b fast contracting muscle fibres (Pette & Vrbová, 1999). In addition, analysis of the individual power spectrum plots may help to identify an inability to increase motor unit firing capability which could be addressed by selective intervention.


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remained stable and below 200 mU l\(^{-1}\) for the FC group, whereas mean skin temperatures were elevated by 8-10 °C for the CON group. 

The aim of the current study was to investigate the prolactin response to moderate passive heating is mediated by facial skin rather than core temperature, and selective cooling of the face is associated with improved perception of thermal comfort. These results indicate that the temperature of only a small part of the skin (~10%) can have a disproportionately large effect on the hormonal and perceptual responses to heat stress. Christensen SE et al. (1985). Acta Endocrinol 109, 458–462. 

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24P

PC25

The importance of skin temperature in modulating the hormonal and perceptual responses to heat stress: effects of face-cooling during passive heating

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A rise in body temperature as a result of passive heating is a potent stimulus for prolactin secretion (Christensen et al. 1985) and selective face-cooling (FC) is known to attenuate the prolactin response to hyperthermia (Brisson et al. 1991). However, there is some debate as to the role that skin temperature may play in modulating the perceptual and hormonal responses to heat stress. The aim of the current study was to investigate the prolactin response to heat stress where skin temperature is high and core temperature is low due to effective sweating, and the effect that FC would have. Sixteen, non-heat-acclimatised human volunteers (11 male, age: 29±9 years; BMI: 23±2 kg m\(^{-2}\), mean±SD) underwent a passive heat exposure for 60 min in a sauna maintained at 58°C (13% relative humidity). Subjects were allocated to one of two experimental conditions and groups were matched for sex, age and body mass index; one group received face-cooling every 5 min (FC) whilst the other received none (CON). Heat loss mechanisms were effective in minimising the rise in core temperature to ~0.25°C with no difference between groups, whereas mean skin temperatures were elevated by 8-10°C for the 60 min duration (range: 38.7–40.3°C). Levels of prolactin remained stable and below 200 mU l\(^{-1}\) for the FC group, whereas concentrations increased by more than 100% to ~450 mU l\(^{-1}\) for the CON group (P<0.05; independent t test). The heart rate response was sensitive to heat stress with a peak increase of 24 beats min\(^{-1}\) above resting levels by 60 min in both conditions; however, no differences were observed between groups. Ratings of overall discomfort and thermal comfort were significantly lower (P<0.05; one-way ANOVA) for FC, indicating an improved comfort with the thermal environment. We suggest that a significant component of the prolactin response to moderate passive heating is mediated by facial skin rather than core temperature, and selective cooling of the face is associated with improved perception of thermal comfort. These results indicate that the temperature of only a small part of the skin (~10%) can have a disproportionately large effect on the hormonal and perceptual responses to heat stress.


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Prior disruption of blood–brain barrier integrity compounds hypoxic headache; exercise, heat and free radicals as ‘vasogenic primers’

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Using a combination of exercise and heat stress, the present study examined whether prior disruption of blood–brain barrier (BBB) integrity in normoxia would alter individual susceptibility to neurovascular headache initiated during subsequent exposure to inspiratory hypoxia. Eleven males aged 24 ± 2 years (mean ± S.D.) were randomly assigned to complete two trials separated by 4 weeks recovery. During the experimental trial (EXP), subjects rested in normoxia (PRE-N) before being immersed supine in water (39°C) for 30min followed by 45min of cycling (35°C) at 60% of their previously determined peak oxygen uptake (PRIMER-N). Subjects were then exposed to normobaric hypoxia (12% O\(_2\) at 25°C) where they rested for 8h (POST-H). The control trial (CON) incorporated the hypoxic exposure without prior immersion or exercise. Headache scores were assessed using a clinically validated visual analog scale. Venous blood samples were mixed \(\alpha\)-phenyl-\(\alpha\)-tert-butylnitrone (PBN) prior to X-band electron paramagnetic resonance spectroscopy, Additional samples were assayed for S100β, neuron specific enolase (NSE), myoglobin and endotoxin according to established techniques following correction for plasma volume shifts (Bailey et al. 2005). Exercise-heat stress increased the serum concentration of S100β and PBN-adducts (Table 1), whereas no changes were observed in NSE, myoglobin or plasma endotoxin. These increases were compounded during subsequent exposure to hypoxia and were associated with a marked increase in the severity and incidence of hypoxic headache (HH).
In conclusion, exercise-heat stress increased BBB permeability and free radical generation independent of neuronal or sarcolemmal membrane damage. The increased susceptibility to HH suggests that this condition may have a vasogenic basis.

Table 1. Neuro-metabolic responses to hypoxia following prior exposure to heat and exercise

<table>
<thead>
<tr>
<th>Trial</th>
<th>CON (n = 11)</th>
<th>EXP (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>PRE-N</td>
<td>PRIMER-N</td>
</tr>
<tr>
<td>Headache score (mm)</td>
<td>2 ± 3</td>
<td>1 ± 3</td>
</tr>
<tr>
<td>SII01 (μL/L)</td>
<td>0.04 ± 0.05</td>
<td>0.03 ± 0.04</td>
</tr>
<tr>
<td>PBN-addicts (arbitrary units)*</td>
<td>5014 ± 1659</td>
<td>4883 ± 1279</td>
</tr>
</tbody>
</table>

Values are means ± SD; *main effects for trial and stage (P < 0.05, two-factor repeated measures ANOVA); different between PRE-N for a given trial (P < 0.05, Bonferroni corrected Wilcoxon matched pairs signed Ranks test); different between trial for a given stage (P < 0.05, Mann-Whitney U test).


Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.

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Cerebral haemodynamics during exercise and hypoxia; ‘downstream’ consequences for pulmonary function

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A reduction in cerebral oxygenation may contribute to brain swelling and neurovascular headache (Bailey et al. 2005) which in severe cases may progress to pulmonary oedema. This suggests that remote pulmonary complications may have a neurogenic basis. The present study combined exercise and hypoxia to effect changes in cerebral oxygen (O2) delivery and examined implications for cerebral autoregulation and pulmonary function in individuals susceptible to hypoxic headache (HHS) compared to those who are resistant (HHR). Eighteen males aged 26 ± 6 years (mean ± SD) were examined at rest in normoxia (N-REST), after 6h passive exposure to 12% O2 (H-REST) followed by a maximal cycling test (H-EXERCISE). Middle cerebral artery blood flow velocity (transcranial doppler) and mean arterial blood pressure (plethysmography) were recorded continuously during an acute hypotensive challenge to calculate a dynamic rate of cerebral autoregulation (ROR). Transepithelial nasal potential difference (NPD) recordings were obtained as an indirect measure of alveolar ion transport. Dyspnoea and headache ratings were recorded according to established clinical guidelines.

Six subjects were excluded from overall analyses due to experimental complications. Table 1 identifies that cerebral autoregulation was impaired in the HHS group as indicated by the greater decrease in ROR during passive exposure to hypoxia and lack of increase following exercise. Dyspnoea ratings were elevated and a negative relationship was observed between the increase (H-REST minus N-REST) in ratings and decrease in ROR (r = -0.81, P = 0.05). In contrast, there were no detectable differences observed in NPD.

These findings suggest that a transient impairment in cerebral autoregulation may contribute to the sensation of breathlessness in hypoxia and exercise. The lack of change in NPD tentatively excludes interstitial pulmonary oedema as a contributory factor.

Table 1. Cerebro-pulmonary function during hypoxia and exercise in HHS

<table>
<thead>
<tr>
<th>Condition</th>
<th>N-REST</th>
<th>H-REST</th>
<th>H-EXERCISE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>HHS</td>
<td>HHR</td>
<td>HHS</td>
</tr>
<tr>
<td>ROR (sec)*</td>
<td>0.27 ± 0.08</td>
<td>0.24 ± 0.05</td>
<td>0.18 ± 0.05</td>
</tr>
<tr>
<td>Total NPD (mV)</td>
<td>-17.3 ± 5.4</td>
<td>-23.3 ± 5.4</td>
<td>-19.1 ± 7.4</td>
</tr>
<tr>
<td>Dyspnoea (mmHg)</td>
<td>0 ± 3</td>
<td>0 ± 0</td>
<td>31 ± 24</td>
</tr>
</tbody>
</table>

Values are means ± SD; HHS (n = 6); HHR (n = 6); *main effect for group and main effects for condition and group (P < 0.05, two-way repeated measures ANOVA)


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Interactions between muscle performance and blood pressure

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This study investigates the relationship between systemic blood pressure, force output and fatigue in the human adductor pollicis muscle, a hand muscle in which fatigue-resistant oxidative fibres predominate, and the tibialis anterior muscle, which contains predominantly fatigue-prone glycolytic fibres. Previously, we showed that as the local perfusion pressure of the contracting adductor pollicis declines within the physiological range, its force output is reduced [1] and it fatigues faster [2]. Systemic blood pressure (BP) increases when a muscle is voluntarily contracted and continues to increase as the muscle fatigues [2]. Here we investigate how that increase in systemic BP affects muscle performance.

Subjects (N=6, 27–55 years) sat with the hand at heart level while supramaximal stimulation of the ulnar nerve produced repeated (1 Hz) tetanic contractions (5 at 40 ms) of adductor pollicis. Isometric force output gradually declined indicating a progressive muscle fatigue. After 2 min of these contractions force had declined by an average of 15%. We then raised BP by having subjects make a sustained isometric voluntary contraction of a thigh muscle. As systemic BP rose (29 ± 2.9 mmHg; mean ± S.E.M.), force output from adductor pollicis increased to recover 39 ± 5.8% of the lost force. When the leg contraction was stopped and systemic BP fell back to normal levels, force output from the hand muscle again fell gradually. Control experiments in which local perfusion pressure in the hand was kept constant despite the increase in systemic blood pressure confirmed that the
increased force output was a consequence of the greater systemic BP and not corollary neural drive to the muscle. The electrical stimulation of adductor pollicis by itself did not cause systemic blood pressure to rise. Equivalent findings were observed in 3 subjects when tibialis anterior was electrically stimulated at its motor point and systemic blood pressure was increased by a voluntary contraction of adductor pollicis. These results do not support the notion that autoregulation of muscle blood flow maintains muscle performance across the physiological range of blood pressures. The increase in systemic blood pressure that is produced as a corollary of the voluntary contraction of a muscle improves muscle performance, offsetting but not cancelling the fatigue-related decline in muscle performance. This behaves as if sensory information about muscle performance serves as the feedback ‘signal’ that controls the extent of the blood pressure rise during muscular work. Our results suggest that working muscles would fatigue approximately twice as fast without this feedback control.


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**PC30**

**The identification of large conductance potassium channels in human intervertebral disc cells**

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Classically associated with control of membrane potential in excitable cells, the calcium-activated large conductance potassium channel (MaxiK, otherwise known as BK) has more recently been identified in cells of connective tissues, namely chondrocytes [1] and osteoblasts [2]. However, no studies have identified the expression of this channel, or indeed any other ion channel, in the human intervertebral disc (IVD) which contains chondrocyte-like cells.

Our aim is to identify the expression of ion channels in the IVD. To date we have used reverse transcription polymerase chain reaction (RT-PCR) to examine the expression of MaxiK channels in normal and degenerate IVDs.

Fourteen human IVD samples were chosen for analysis. These included 4 non-degenerate (mean age 51 years) and 10 degenerate (mean age 43 years) discs. Tissues were analysed for features of degeneration and separated into nucleus pulposus (NP) and annulus fibrosis (AF) tissue, and cells and RNA directly extracted. RT-PCR was conducted using primers for the alpha subunit of the MaxiK channel. GAPDH was used as a housekeeping gene and normal articular chondrocyte and the neuroblastoma cell line SH-SY5Y as positive controls.

RT-PCR confirmed MaxiK channel expression in the degenerate IVD, both in the AF and NP. However, no expression of the channel was observed in the normal tissue, irrespective of disc region.

We have shown for the first time that human IVDs express MaxiK channels and that the level of expression is not dependent on disc region or patient age. In addition we have demonstrated that these channels are not expressed in normal disc, but are only present in the degenerate IVD. These findings have implications for understanding the phenotype of cells within the normal and degenerate IVD. Furthermore it is hoped that as we expand the repertoire of ion channel markers it will help elucidate the pathophysiology of IVD degeneration.


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**PC31**

**Recombinant human growth hormone (rhGH) - effects on anthropometric, exercise and psychological profiles**

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This study was designed to investigate the short term effects (6 days) of recombinant human (rh) growth hormone (GH) administration (0.056 mg/kg/day) combined with weight training on body composition, exercise and psychological profile and compare it with weight training alone. Previous work has shown an improvement in these parameters in GH deficient individuals (Caneo et al. 1991a, b), but not trained athletes (Crist, 1988; Irving, 2004). The subjects who took part in this study, were twenty-four self-prescribing weight lifters (rhGH), aged between 20 and 48 years, and the results were compared with twenty-four non-drug-using age-matched exercise controls (EC). The dosages were administered under the supervision of the authors in the morning, before any training sessions and an administration diary was recorded. Group differences were analysed using a two-way (group x time) repeated measures ANOVA. Between-group differences were analysed using an independent t test. Within-group differences were analysed using a paired t test followed by a post-hoc Bonferroni test. Data for psychological profiles were analysed using a non-parametric-related samples t test. Between-group differences were analysed using a Kruskal-Wallis test. Body fat (%) diminished within the rhGH group (19.1 ± 5.1 vs 18.1 ± 5.1 vs 18.2 ± 5.0%, p<0.05) and compared with the EC group (18.1 ± 5.1 vs 22.3 ± 3.3%, p<0.05) and strength (one repetition maximum; bench press (BP) and squat (S)) (BP; 106 ± 18 vs 113 ± 19 vs 112 ± 18 kg; S; 143 ± 27 vs 164 ± 26 vs 163 ± 25 kg, p<0.05) and power (high intensity cycle ergometry) (1345 ± 216 vs 1466 ± 257 vs 1497 ± 253 W, p<0.05) increased within the rhGH group and compared with the EC group (BP; 113 ± 19 vs 97 ± 24 kg; S; 164 ± 26 vs 141 ± 34 kg, p<0.05). A Hospital Anxiety and Depression Scale questionnaire (Zigmond & Snaith, 1983) was significantly decreased in both anxiety (A) and depression (D) symptoms within the rhGH group (A: 6.8 ±
Increased brain uptake and brain to blood efflux transport of $^{14}$C-GABA in spontaneously hypertensive rats
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Despite constant production and release from the neurons, brain interstitial fluid concentration of GABA is normally kept low and within narrow limits (Hoop et al. 1999). However, during both acute and chronic hypertensions, the protective function of the blood-brain barrier (BBB) is altered and the BBB is disrupted in spontaneously hypertensive rats (SHR) (Al-Sarraf & Philip, 2003; Ueno et al. 2004). In this study, brain uptake and brain-to-blood efflux transport of $^{14}$C-GABA were studied in SHR compared to normotensive Wistar Kyoto (WKY) rats. Rats were anesthetized intraperitoneally with urethane (1.25-1.5g/kg). To study brain uptake and efflux of $^{14}$C-GABA, in situ brain perfusion technique was used. The uptake of $^{14}$C-GABA into CSF and brain regions was found to be significantly greater in SHR when compared to the corresponding regions in WKY rats (p<0.05). Although the study of BBB integrity using $^{3}$H-manitol revealed increased paracellular permeability at the brain capillaries of SHR compared to WKY rats, this was found to be only partially responsible for the increased $^{14}$C-GABA uptake. The study of brain-to-blood efflux transport of $^{14}$C-GABA (after loading of brain with $^{14}$C-GABA by vascular perfusion) revealed that the half-time of elimination was significantly faster in SHR (5.35 ± 0.66 min) than in WKY rats (14.83 ± 1.94 min), (p<0.001). HPLC analysis revealed that GABA concentrations in brain extracts and CSF of SHR were similar to those in WKY rats (p>0.05). The faster efflux in SHR might be, at least partially, responsible to compensate for increased uptake of this neurotransmitter and to preserve the protective function of BBB towards GABA. The protective function of the blood-CSF barrier towards GABA appears to be also preserved, since systemic infusion of GABA within a wide range of administered doses (0.004-5.00 mg/kg) produced an increase in GABA CSF.
concentration from around 0.5 microM to only 11 µM, and the obtained pattern of CSF GABA concentrations under these conditions did not differ between SHR and WKY rats, as revealed by HPLC.


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**PC35**

**Role of T-type calcium current in GABA\(_A\)-induced [Ca\(^{2+}\)]\(_i\) rise in D-hair sensory neurons**

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Recently, the T-type calcium current was shown to be part of the machinery of mechanotransduction of low threshold sensory neurons, the Down hair neurons (Shin et al. 2003). Identification of D-hair neurons, in vitro, led us to analyse the molecular mechanisms involving T-type IC\(_{\text{a}}\) in mechanotransduction (Dubreuil et al. 2004). Biophysical properties of T-type IC\(_{\text{a}}\) supported the hypothesis that it could confer excitability to peripheral GABAergic receptors. Intracellular Ca\(^{2+}\) measurements were performed on dissociated D-hair neurons, loaded with Fura 2, and identified by their rosette-like growth after treatment with NT-4. The emission fluorescence from the soma was acquired with a PM tube and the resulting (340/380nm) emission ratio was converted into [Ca\(^{2+}\)]\(_i\). In D-hair cells isolated from adult mice, GABA (100µM) induced a 47 ± 15% increase in [Ca\(^{2+}\)]\(_i\) relative to basal values \((n=4)\), while it was unable to modify [Ca\(^{2+}\)]\(_i\) in non D-hair neurons. SR-95531 (20µM) blocked GABA-induced [Ca\(^{2+}\)]\(_i\) increase, suggesting that the receptor involved in the GABA stimulation was the GABA\(_A\) receptor. Muscimol (20µM), a specific GABA\(_A\) receptor agonist, also produced a 47 ± 5% increase in [Ca\(^{2+}\)]\(_i\) \((n=8)\). When the second peak of the response to muscimol was expressed as a percentage of the first muscimol-induced [Ca\(^{2+}\)]\(_i\) increase, nickel (50µM) and mibebradil (10µM), two known blockers of T-type calcium channels, inhibited this response by 89 ± 2% \((n=8)\) and 92.5 ± 4% \((n=3)\), respectively. TTX (100nM-500nM) inhibited muscimol-induced [Ca\(^{2+}\)]\(_i\) increase by 49 ± 7% \((n=9)\). Using a video-imaging system, nickel-sensitive muscimol-induced increase in [Ca\(^{2+}\)]\(_i\) was also found to be in neurites suggesting a functional co-localisation of the GABA\(_A\) receptors and the T-Type [Ca\(^{2+}\)] channels in this subcellular compartment.


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**PC36**

**Motor effects of systemic and intracerebroventricular inhibition of nitric oxide synthesis in rodents**

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Systemic injections of nitric oxide synthase (NOS) inhibitors have been shown to decrease exploratory behaviour and to induce catalepsy in a dose-dependent manner in male albino-Swiss mice. This effect may be related to motor impairments since these drugs can induce catalepsy in rodents. The objectives of these experiments was to compare the effects of two NOS inhibitors in mice in tests aimed to investigate exploratory behaviour and to assess motor control. We also investigated if these effects were centrally mediated. The acute effects of the NOS inhibitors NG-nitro-L-arginine (L-NOARG, 10-80 mg/kg i.p.) and 7-nitroindazole (7-NIO, 3-30 mg/kg i.p.) on exploratory activity were analysed in an open field arena. Drug effects on catalepsy were examined in the hanging-bar and wire-ring test. Footprint pattern after treatment with the two NOS inhibitors was evaluated and the results compared with those obtained with the dopamine D2 receptor antagonist Haloperidol (1-2 mg/kg i.p.). Sub-chronic (twice a day for 4 days) effects of L-NOARG (40 mg/kg) or 7-NIO (30 mg/kg) were also tested in the open field arena and catalepsy test. For i.c.v. injection mice were anaesthetized with 2.5% 2,2,2-trifluoroethanol (250 mg/kg, i.p.) and fixed in a stereotaxic frame. A stainless steel guide cannula (0.7 mm OD) was implanted at the right lateral ventricle (coordinates:AP= -1.0 mm from bregma, L= 1.6 mm, D=3.5 mm).

L-NOARG and 7-NIO decreased locomotion and rearing in the open field arena. Both drugs induced catalepsy in the hanging-bar test but did not change footprint pattern. The cataleptic effect of L-NOARG in the hanging-bar and wire-ring tests were highly correlated \((r=0.927)\). Similar effects were found after intracerebroventricular (i.c.v.) injection of L-NOARG (50-200 nmol) or NG-nitro-L-arginine methyl ester (L-NAME, 100-200 nmol). The exploratory and cataleptic effects of L-NOARG and 7-NIO provided evidence for tolerance after sub-chronic treatment. These results confirm that inhibition of neuronal NO formation induces impairment of exploratory behaviour. This effect does not seem to involve aspects evaluated by footprint analysis, such as weight support, trunk stability and foot placement. They could, however, be related to drug-induced catalepsy. These results suggest that interference with the striatal formation of nitric oxide may induce significant motor effects in mice.

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