SA1

Adaptations in spinal neuronal pathways in relation to motor learning and immobilization

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During voluntary movement sensory feedback from the moving limb may contribute to drive the muscle activity, correct the ongoing movement, and update the central motor commands for future movements. The sensory feedback may be modulated in various ways to ensure that it is optimally adjusted to the requirements of the performed motor task. It has been demonstrated that much of this modulation is explained by changes in presynaptic inhibition of the synapses of Ia afferents on spinal motorneurones (Hultborn et al. 1987a,b; Meunier & Pierrot-Deseilligny, 1989; Nielsen & Kagamihara, 1993b). In recent experiments we have demonstrated that the amount of presynaptic inhibition changes in relation to the recent motor activity of the subject.

In a first study, 19 healthy volunteers were asked to train a visuomotor skill task involving the ankle muscles. The position of the ankle joint was measured by a goniometer and displayed as a cursor on a computer screen located in front of the subject. Subjects were instructed to make the cursor follow a series of figures as accurate as possible by performing voluntary ankle dorsi- and plantarflexion movements. A session consisted of 8 sets of 4 min of training with 2 min of rest in between the sets. Motor performance (measured as the deviation of the ankle joint position signal from the target trajectory) was significantly improved following the visuo-motor skill task but not after a control session consisting of simple voluntary dorsi- and plantarflexion movements. The slope of the H-reflex recruitment curve and the H-max/M-max ratio were depressed after repetition of the visuomotor skill task and returned to baseline after 10 min. No changes were observed after the control session. To elucidate the mechanisms contributing to the H-reflex depression we measured the size of the long-latency depression of the soleus H-reflex evoked by peroneal nerve stimulation (D1 inhibition) and the size of the monosynaptic Ia facilitation of the soleus H-reflex evoked by femoral nerve stimulation. The D1 inhibition was increased and the femoral nerve facilitation was decreased following the visuomotor skill task, suggesting an increase in presynaptic inhibition of Ia afferents.

In a second study, 7 healthy human subjects had their ankle joint immobilized by a cast for a period of 2 weeks. Immediately following the immobilization, the size of the soleus H-reflex was significantly increased, but returned to pre-immobilization levels within a couple of days. This increase was caused in all likelihood by a decrease of presynaptic inhibition of soleus Ia afferents. In summary, these observations suggest that presynaptic inhibition of Ia afferents may be both down- and up-regulated depending on the preceding motor activity of the subject. The functional significance of these changes is unclear, but we believe that they may have some relevance for the hyperexcitability of the stretch reflex arch in patients with lesions of central motor pathways.

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

SA2

The prevalence of inappropriate muscle sequencing in recurrent shoulder instability

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Inappropriate sequencing of activation of shoulder muscles can cause shoulder instability.

The records of 868 cases of recurrent shoulder instability referred to a specialist shoulder service between 1981 and 2003 were reviewed. All patients were assessed clinically. Muscle patterning abnormality (Bayley, 1986) was identified in 387 patients (45%). Confirmatory functional electromyography was performed in 97 (25%). Inappropriate pectoralis major activation was identified in cases of anterior instability. In posterior instability, inappropriate activation of latissimus dorsi and anterior deltoid, and suppression of infraspinatus were the classical patterns. Arthroscopic assessment was performed in 179 (46%), identifying additional structural lesions of instability in 96 (54%).

All patients diagnosed with muscle patterning disorder received specialist physical therapy using biofeedback. Symptomatic improvement or stability was achieved in 85% of patients with anterior instability and 88% of those with posterior instability. Prior surgical stabilisation procedures on the shoulder reduced cure rates by 5 times for anterior and by 10 times for posterior instability.

Muscle patterning abnormalities contribute to recurrent instability of the shoulder in 45% of cases. The success of physical therapy in these patients is high.

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SA3

Drug-induced enhancement of recurrent inhibition in humans: effects on motoneurone discharge patterns

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Almost 60 years after the Renshaw cells were first identified (Renshaw, 1946), their contribution to motor control is still

elusive. The complexity of the spinal recurrent network has led to some contradictory ideas as to how recurrent inhibition may actually influence the α motoneurone firing times (cf. Windhorst, 1996). For instance, beside a stabilizing effect on motoneurone discharge variability, positive or negative effects on motoneurone synchronous activity have both been postulated. Recurrent inhibition is not homogenously distributed among motoneurone pools. Its presence is well established among the motoneurones innervating proximal limb muscles such as extensor carpi radialis and tibialis anterior, whereas it is lacking in the intrinsic hand muscles such as abductor digiti minimi and it is a matter of debate in the facial muscles such as masseter. If recurrent inhibition does take part in the regulation of the motoneurone firing properties, the effects obtained by altering the efficacy of the spinal recurrent network can be expected to differ depending on the muscle tested.

In the present study, spinal recurrent inhibition was transiently enhanced while the discharges of pairs of motor units were being recorded in the extensor carpi radialis, the abductor digiti minimi, the tibialis anterior or the masseter muscles, during voluntary isometric contraction maintained for up to 30 min. The subjects were undergoing continuous intravenous saline (NaCl 0.9 %) perfusion interrupted by a 2 min injection of L-acetylcarnitine (L-Ac, 30 mg/kg diluted in 5 ml of saline), known to enhance cholinergic transmission from motoneurone recurrent collaterals to Renshaw cells in humans (Mazzocchio & Rossi, 1997). In control experiments involving other motor unit pairs, L-Ac injections were replaced by 2 min injections of saline performed in exactly the same conditions. The variability and synchronization of the motor unit discharges were analysed before, during and after the injection. In both the extensor carpi radialis and tibialis anterior muscles, the L-Ac injection led to (1) a significant decrease in the variability of the inter-spike intervals with no consistent changes in their mean duration and (2) a significant increase in the synchronous activity. In contrast, L-Ac injection did not alter in any way the pattern of motor unit discharge in the abductor digiti minimi and the masseter muscles. None of these changes occurred in the control experiments performed with saline injections.

The contrasting effects observed with extensor carpi radialis and tibialis anterior motoneurones known to undergo recurrent inhibition and with abductor digiti minimi motoneurones known to lack recurrent inhibition strongly suggest that Renshaw cell activity enhanced by L-Ac injection had promoted the changes in variability and synchronization in the extensor carpi radialis and tibialis anterior motoneurone pools. These data support the hypothesis that recurrent inhibition may contribute to limit the variability of steadily discharging motoneurones and to synchronize motoneurone activity. In contrast, the absence of effect of L-Ac injection in the masseter muscle argues in favour of the notion that masseter motoneurones lack recurrent inhibitory collaterals.

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SA4

Electrophysiological investigations of group II spinal reflexes in human upper and lower limbs

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In humans, electrical stimulations of various lower limb nerves helped reveal powerful excitation produced by group II afferents in motoneurones supplying knee and ankle muscles. The distribution of heteronymous group II spinal connections showed that group II from intrinsic foot muscles activate both ankle dorsiflexors and knee muscles, whereas group II from ankle dorsiflexors activate knee extensors and those from ankle plantar flexors, knee flexors. Since these combinations correspond to muscle synergies used during walking or required to maintain unstable upright stance, transmission of group II excitation from ankle to knee muscles has been investigated during various motor tasks. During both walking and standing, group II excitation is enhanced whereas group I excitation transmitted through the same interneurones was not changed as compared to that observed during tonic and voluntary co-contractions of the same muscles at matched levels of electromyogram (EMG) activity. More recent experiments, using cortical stimulation, reveal group II connections between muscles acting at the ankle joint (tibialis anterior to gastrocnemius medialis and reciprocally; see Pierrot-Deseilligny & Burke, 2005).

It has been extensively discussed whether the pathways transmitting long latency reflexes originating from muscle stretches are transcortical (activated by group Ia afferents) or spinal (group II and/or cutaneous afferents; see Marsden et al. 1983; Matthews, 1991). The electrophysiological expertise concerning group II spinal reflexes developed in lower limb investigations has been extended to upper limb. Since the intensity of the electrical stimulation required for activating group II afferents needs to be above motor threshold (MT) and given the distribution of recurrent inhibition, which can mask hypothetical group II excitations, the study has been focused on the effects of ulnar nerve stimulation at wrist level in order to activate group II afferents from hand muscles. This stimulation has been used to condition the motor units' (MUs) firing (studied with the post stimulus time histogram, PSTH method), extracted from surface EMG of forearm and arm muscles. It has been observed that ulnar nerve stimulation produced monosynaptic group Ia excitations in the PSTHs of flexor digitorum superficialis (FDS) MUs and non-monosynaptic (mediated by propriospinal neurones) group I excitation in the PSTHs of flexor carpi radialis (FCR) MUs (see Pierrot-Deseilligny & Burke, 2005). When the stimulus intensity was above 1.2 x MT, a late peak of increased MU firing appeared in the PSTH of (i) 21 out the 28 FDS MUs (all 6 subjects) so explored, with a mean latency of 10.6 ± 0.3 ms (mean ± S.E.M.; after the monosynaptic group Ia peak) and of (ii) 20 out the FCR 24 MUs (all 7 subjects, but one) so explored, with a mean latency of 11.2 ± 0.4 ms. It was checked that these peaks were not evoked when using weaker stimuli (0.8 x MT) and after pure cutaneous stimulation (external aspect of the fifth finger), which eliminate a possible contribution of low threshold afferents (group I and cutaneous). The threshold for evoking the late peak suggests the contribution of smaller diameter afferents, probably group II afferents. To test this hypothesis, the modifications in the

latency of the monosynaptic group Ia and late and higher threshold peaks were assessed during cooling the ulnar nerve (ice pack placed against the palmar aspect of the forearm, along the nerve). In all 6 FDS MUs so studied (5 subjects), the late and higher threshold peak was significantly more delayed than the monosynaptic group Ia peak (8.0 ± 0.5 *vs* 2.6 ± 0.4 ms, respectively; $p < 0.01$, Mann-Withney *U* test). Moreover, the effects of ulnar nerve stimulation on FCR on-going EMG was tested after tizanidine oral intake (α_2 noradrenergic agonist, inhibiting group II afferent transmission; 150 μg kg^{-1}). Under these conditions, after drug intake (45-90 min), the amount of non-monosynaptic group I excitation was not statistically changed (39.9 ± 6.6 *vs* 35.0 ± 8.8% of the mean unconditioned EMG before drug intake) whereas that of the late and higher threshold facilitation was significantly decreased (11.0 ± 2.4 *vs* 44.6 ± 9.9% before drug taking; $p < 0.05$ Wilcoxon matched-pairs signed-rank test).

These results suggest that group II afferents from hypothenarian muscles produce excitation in motoneurones involving finger and wrist flexors. It was also possible to evoke a similar late and high threshold excitation in all the motor nuclei so investigated (extensor digitorum, triceps and biceps brachii), except in motoneurones supplying wrist extension. In contrast, median nerve stimulation at wrist level evoked low threshold and short latency inhibition (43/67 MUs) or late and low threshold excitation (17/67 MUs), both mainly reproduced by pure cutaneous stimulation.

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SA5

A question of balance - what happens when sensory input is reduced?

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In order to study postural maintenance we have used a substantial inverted pendulum with one degree of freedom as an unstable load. In our previous work, such a human-sized inverted pendulum has been balanced pedally (Loram et al. 2001) or manually (Lakie et al. 2003). The advantage of the manual approach is that it allows the movement not only of the load but also of the actuator (the hand) to be directly recorded and the stiffness of the coupling between actuator and load to be altered. The inverted pendulum represents the body, the hand represents the calf muscles, and the spring coupling the two represents the stiffness of the Achilles tendon and foot. It is a reductionist approach where the role of the human operator becomes solely the transformation of the available sensory data into appropriate motor acts. Because the head is stationary the sensory information that is available to the subject can be precisely controlled. Although it is not 'real' standing, dynamic ultrasonography (Loram et al. 2005) has revealed the close similarities between movements of the hand in manual balance and movements of the calf muscles in naturally standing subjects.

In balancing an inverted pendulum, and in real standing, the active postural muscles exhibit repeated impulsive surges of activity which change the length (bias) of the series elastic component (s.e.c.). These purposive, bias adjustments occur more frequently than body sway and they must be pre-planned by the nervous system which has available recent sensory information concerning sway (Lakie et al. 2003; Loram et al. 2005). It is well known that impoverished sensory information leads to impaired control of balance. How does the frequency of these bias adjustments relate to the quantity of sensory information available? Craik (1947) was the first to investigate this question using an entirely different task which was visually controlled manual tracking of a moving target. He reasoned that if corrective manual adjustments depended on the visual detection of a disparity then an increase in visual gain would cause error to accrue more rapidly with a consequent increase in the frequency of adjustments. In fact, he found that the frequency of manual adjustments was substantially independent of visual gain. Accordingly, he concluded that a central movement planning process rather than the availability of sensory data limited the frequency of adjustments. Here we investigate the 'Craik' question in a balancing task. We systematically reduced the availability of sensory information from the visual, vestibular and somatosensory senses. If it is necessary that sensory information must attain a threshold value (or a critical signal/noise ratio) before a balancing impulse can be generated then a reduction in sensory information should reduce the frequency of bias adjustments.

Ten subjects performed simple tasks analogous to human standing with specific senses operating. In every case balancing was controlled by a spring of inadequate stiffness for passive stability (nominally 85% of the load stiffness). This stiffness simulates the stiffness of the s.e.c. which we believe is limited by the tendon and foot. Subjects balanced by manually altering the length of the spring (bias adjustments). The sensory information that was available to them could be purely visual, purely vestibular, purely proprioceptive or a combination of two or more of these. The movement of the body or load (sway) and the bias adjustments were recorded. Subsequent analysis showed that the mean frequency of bias adjustments (~2.4 s^{-1}) decreased trivially as sensory information was limited. Therefore the mean duration (~400 ms) of bias adjustments is not determined by the need to reach a sensory threshold. Reducing sensory information always increased mean sway size and this is presumably due to poorer judgement in the planning of each bias adjustment. In additional experiments, measurements of bias adjustments in the triceps surae were made in standing subjects with and without vision. The mean bias adjustment frequency was 2.6 Hz in both cases. Manual balancing and real standing appear to operate on similar principles. We suggest that the frequency of bias adjustments is related to a central planning time which is common to vision, vestibular and proprioceptive senses and has much in common with intermittency in the voluntary control of constant force (Slifkin et al. 2000) as well as in manual tracking of a visual target. Sway of the inverted pendulum or postural sway of the body may be a consequence of purposive centrally controlled repetitive adjustments in muscle output which act to regulate position and velocity and thus underlie the maintenance of posture.

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SA6

The vestibular system, virtual head motion, and action

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Vestibular information contributes to a number of brain functions. These include balance, gaze, navigation, self and non-self motion perception, voluntary movement, spatial orientation, and autonomic control. There is a major obstacle to isolating and studying the vestibular contribution to these brain functions. Any real movement or force that is applied to perturb the vestibular organs also evokes responses from many other sensory receptors making it difficult to extract the vestibular component. A way around this is to bypass the process of mechanical activation of the vestibular organs and perturb the vestibular system by stimulating behind the ears with small direct electrical currents. It turns out that this galvanic vestibular stimulation (GVS) technique has the same frequency-modulating effect on the vestibular afferents as natural movement, and is interpreted by the brain as such.

With anatomical knowledge of the hair cell alignment in the vestibular organs, we can calculate the direction of the natural movement that would produce the same signal that GVS evokes (Fitzpatrick & Day, 2004). Vectorially summing the responses to GVS from the entire semicircular canal neurone population reveals a virtual rotation about an axis in the mid-sagittal plane of the head at an angle of 18.8 deg with respect to Reid's plane. It is not as clear for the otolith organs but the vectorial sum suggests a small lateral acceleration. It is simply the idiosyncrasies of the vestibular anatomy that define these virtual head movements evoked by GVS.

We have used this model of GVS to investigate vestibular influences on three different brain functions in healthy human subjects. A perceptual task involved judging the extent and direction of externally imposed body movement in the world. GVS revealed a process that transformed the vestibular signal from head to world coordinates and extracted the horizontal plane component of the total signal (Day & Fitzpatrick, 2005). A similar vestibular coordinate transformation process was found for a bipedal balance task, except in that case the extracted component was in the vertical plane. In addition, a short-latency otolith contribution to balance control was revealed (Cathers et al. 2005). A voluntary movement task consisted of a goal-directed movement of the upper body while GVS was applied. The instantaneous GVS current was determined by the angular velocity of the head. The resulting modification of the trajectory demonstrated that voluntary movements, in which the head is transported in space, are under the on-line control of vestibular reafference (Day & Reynolds, 2005).

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SA7

Premotor–motor connectivity in human and primate

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Humans and other primates demonstrate an exquisite ability to precisely shape their hand when reaching out to grasp an object. Here we used a recently developed transcranial magnetic stimulation (TMS) protocol to examine how information about the geometric properties of an object is transformed into specific motor programs controlling hand shape. Pairs of TMS pulses (suprathreshold followed by subthreshold) were delivered at precise intervals to detect changes in the excitability of cortico-cortical inputs to motor cortex when subjects prepared to grasp different objects. We found that at least 600 ms prior to movement, there is an enhancement in the excitability of these inputs to the corticospinal neurons projecting from motor cortex to the specific hand muscles that will be used for the grasp. This enhancement was seen only with pulses delivered with an inter-stimulus interval of 2.5 ms, which is most likely to reflect the facilitation of the second indirect wave of corticospinal activity (the I2 wave). These changes were object- and muscle-specific and the degree of modulation in the inputs was correlated with the pattern of muscular activity used later by individual subjects to grasp the objects. In a number of control experiments we demonstrated that no change in excitability was observed during object presentation alone, under conditions in which subjects imagined grasping the object, or prior to movements involving the same muscles but without an object. This demonstrates a specific cortico-cortical mechanism subserving the transformation from the geometrical properties of an object to the outputs from motor cortex prior to grasp. This mechanism is not involved in movements that do not involve grasp of a physical object.

We have now extended these findings to show that excitability of cortico-cortical inputs to the primary motor cortex during visuomotor grasp is transient and occurs in strict temporal relation to the upcoming movement. When subjects see an object but are instructed not to grasp until they are cued to do so, muscle-specific facilitation is observed just at the moment when the movement is cued, long before any overt muscle activity is observed. Paired-pulse modulation of M1 excitability occurred only prior to the movement cue, but not after it. If TMS delivery was used as the cue to grasp a very short time after object presentation (50 or 100 ms), facilitation was absent. It first appeared for TMS cueing movement > 150 ms after presenta-

tion. The effect was present when predictable TMS was delivered at the cue to grasp, but was abolished when TMS was given at random in relation to that cue. Our results indicate that the motor cortex does not maintain a state of readiness from object presentation until cue to grasp, but rather excitation occurs only when execution of grasp is required. We suggest that commands related to the selection of appropriate hand shape are stored upstream from M1 and are 'released' to M1 immediately prior to grasp execution.

Parallel experiments in both anaesthetised and awake behaving monkeys show that single pulse stimulation of the hand representation in the ventral premotor cortex (area F5) can activate neurones in the hand region of primary motor cortex (M1) and that single-pulse stimulation of area F5, while evoking few or no motor effects alone, is able to modulate powerfully outputs from M1 to hand motoneurones and hand muscles. This modulation is seen mainly in terms of the later I wave discharges from M1 corticospinal neurones, suggesting that cortico-cortical inputs from premotor areas have particularly strong inputs to these neurones via late-I wave circuits. We have speculated that it is these inputs, no doubt among others, that are selectively enhanced during object grasp and which are particularly sensitive to the paired-pulse TMS protocol described above.

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SA8

The Nick Davey Memorial Lecture 'From muscle spindles to spinal cord injury'

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All of those that knew Nick Davey would have been saddened and shocked by the news of his untimely death early this year. This lecture will review the contributions made by Nick to our understanding of the human motor system and the impact of central nervous system disorders.

An early project involved the role of the muscle spindle and its gamma motoneurone innervation in the control of movement. The discharges of gamma motoneurones became synchronised following acute spinal cord section in the cat and that synchrony was dependent specifically on the integrity of descending monoaminergic tracts (Davey & Ellaway, 1988). The work led to studies of motoneurone discharge in Parkinson's disease. The finding also had implications for human spinal cord injury and was the starting point for Nick's many contributions to the impact of spinal cord injury on the voluntary control of skeletal muscle in man (Davey et al. 1990).

Research often receives a boost with the emergence of new techniques. Nick was quick to exploit the potential of transcranial magnetic stimulation of the brain to test the integrity of the corticospinal tact in spinal cord injury and relate it to deficit in voluntary control of movement. The use of TMS led to an understanding of how the surviving connections from brain to muscle adapt to spinal cord injury and how this plasticity of central nervous system function may impact on any residual ability to move (Davey et al. 1998). It led to the expectation that a certain amount of recovery from spinal cord injury might be possible if this plasticity could be manipulated. Most recently his research showed that magnetic stimuli repeated at low rates and with a specific pattern can have a therapeutic effect. Clinical assessments and functional tests of motor performance improved and these were accompanied by physiological changes in the pathway from the motor cortex to motoneurones (Belci et al. 2004). A practical application of his research came in a Clinical Initiative funded by the International Spinal Research Trust to develop improved physiological tools for the assessment of the level and completeness of spinal cord injury in terms of sensorimotor function (Ellaway et al. 2004).

Nick Davey's contributions to understanding sensorimotor systems and the impact of disease and stress were not limited to spinal cord injury. They included studies on arthritis, chronic fatigue, back pain, schizophrenia and even the weightless conditions experienced in parabolic aircraft flight.

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SA9

Controlling uncertainty in volitional movements

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Sensory and motor uncertainty form fundamental constraints on human performance. I will first show that the CNS reduces the uncertainty in estimates about the state of the world by using a Bayesian combination of prior knowledge with an estimate of the uncertainty of its own sensors. I will then describe how the brain evaluates errors in terms of a loss function. Finally, I will describe how signal-dependent noise on the motor output places constraints on performance. Given these constraints features of goal-directed movement arise from a model in which the statistics of our actions are optimized. Together these studies provide a probabilistic framework for sensorimotor control.

SA10

Low frequency stimulation of the Pedunculopontine nucleus alleviates Parkinsonian akinesia. Translational research from monkey to man

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We have been studying the role of the brainstem Pedunculopontine nuclei (PPN) in the control of locomotion and posture. Our results show that in the intact normal monkey low frequency (10 Hz) stimulation of the PPN increases motor activity significantly, whereas high frequency stimulation reduces it. Giving the monkey MPTP produces Parkinsonian akinesia, but we have shown that this can be alleviated by injecting bicuculline or by unilateral low frequency electrical stimulation in the PPN. These results imply that Parkinsonian akinesia is at least partly the result of excessive inhibition of the PPN by descending GABAergic projections from the basal ganglia that can be bypassed by stimulating the PPN directly. The increase in movements probably occurs both by stimulating the PPN's ascending projections to engage surviving dopaminergic mechanisms in the basal ganglia, but also by stimulating PPN projections descending to brainstem locomotor and postural centres, 'downstream' from the dopaminergic systems (Nandi et al. 2002a,b; Jenkinson et al. 2004, 2005).

What is really exciting is that these results suggested strongly that PPN stimulation might be clinically effective in treating akinesia in advanced Parkinson's disease and other akinetic disorders. Late in the disease many patients develop akinesia that is not alleviated by any current drug or deep brain stimulation treatment (Kleiner-Fisman et al. 2003), but our results suggested that PPN stimulation might change all this. This problem is so serious that, already on the basis of our monkey findings, two groups have implanted stimulating electrodes in the PPN in akinetic Parkinsonian patients (Mazzone et al. 2005; Plaha & Gill, 2005). Both studies show that low (10 Hz) frequency stimulation of the PPN, as predicted from our monkey experiments, greatly alleviates the gait freezing and postural instability of Parkinsonian patients that is both so highly disabling and resistant to conventional surgery. We have described the effects of PPN stimulation combined with L-Dopa therapy in the Parkinsonian monkey (Jenkinson et al. 2005). We confirm that driving the PPN at 10 Hz does alleviate akinesia at least partly via a non-dopaminergic pathway (Jenkinson et al. 2005).

This rapid translation of monkey experiments in the laboratory to the alleviation of human suffering in the clinic confirms our belief in the enormous value of animal research to the human condition. It is particularly important to emphasise this at a time when animal experiments are so strongly under attack in the UK.

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