Clinical Initiative Stage II

Final Report

July 2011

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Stage II of the *Spinal Research* Clinical Initiative Final Report: July 2011

Executive Summary

Key Outcomes

[1] 33 papers so far published from the Clinical Initiative

[2] Improved outcome measures

a. Lower limb motor test has been developed capable of distinguishing between deficits in strength and dexterity
b. Automatic quantitative hand function test developed
c. Validation of electrical perceptual threshold (sensory) tests
d. Consolidation of other sensory tests (CHEPs
e. Methodologies implemented in Phase I/II clinical trials
f. Portable gait assessment tool developed to record time-dependant gait parameters

[3] Development and commercialisation of a upper-limb rehabilitation device (ReJoyce)

[4] In-house telerehabilitation technology developed

[5] Members of the consortium now actively engaged in clinical trials

a. Multicentre clinical trial of ReJoyce
b. Cell-based therapy in Phase I/II Balgrist

[6] Members of the consortium in consultation with the US DoD to advise on clinical trial design

[7] Improved understanding of neurophysiological changes that are important to functional recovery

Background

Spinal cord injury (SCI) is a devastating condition that results in dysfunction or complete loss of function in motor, sensory and autonomic systems – cardiovascular/bladder/bowel – that is usually enduring. During the last few decades, clinical care and management, together with rehabilitation practice, has ensured life expectancy after SCI approaches that of the able-bodied population. The socio-economic burden of SCI is enormous and unlikely to change without the advent of new reparative treatments aimed at recovery of function. Over this same period, our understanding of the underlying biology of SCI has rapidly advanced; functional recovery has been achieved in the laboratory and several of these approaches are currently being translated from bench to bedside.

Those seeking to translate the innovations of basic science into clinical practice require sensitive outcomes measures that respond to both physiological (activity of the cells) and functional changes. Unfortunately, the tools available, typically the American Spinal Injury Association (ASIA) Impairment Scale (AIS), were not designed with such use in mind and there is a recognized need to develop additional assessment tools for clinical trials with the sensitivity to pick up changes over time.

Without gold standards and surrogate markers for repair, translation is hampered. Early forays into the clinic may not prove successful and it is incumbent on all to learn as much from clinical trials, successful or otherwise. Clinical tools that allow us to look at mechanisms of change, whether such changes result in functional recovery or not, will help inform new treatment design.

In response to this need, the International Spinal Research Trust launched their Clinical Initiative, the aim of which was to identify potentially useful techniques for the assessment of functional recovery following SCI. The outcomes from this first stage were published (Ellaway *et al*., 2004).

A second stage of the International Spinal Research Trust Clinical Initiative commenced in 2006 and involved teams in London (UK), Zurich (Switzerland), Edmonton (Canada) and Glasgow (UK). The aim of this stage was to examine the psychometric properties of newly developed and improved outcome measures from Stage 1 (see Ellaway et al, 2004), particularly physiological and functional tests, during either the application of treatments expected to produce functional improvements in SCI or the natural course of recovery.

Stage 2 of the Clinical Initiative

Stage 2 of the Clinical Initiative adopted a number of strategies to examining the efficacy of the assessment tools developed in Stage one (Ellaway et al, 2004). Three of the groups (those from London and Glasgow in the UK, Edmonton in Canada) chose to apply specific rehabilitation strategies that were likely to impact favourably on outcome. The fourth group (Zurich, Switzerland) followed the course of natural recovery which is predictable in nature, albeit poor. The assessment tools could thus be evaluated in these different patient groups in advance of more invasive treatments.

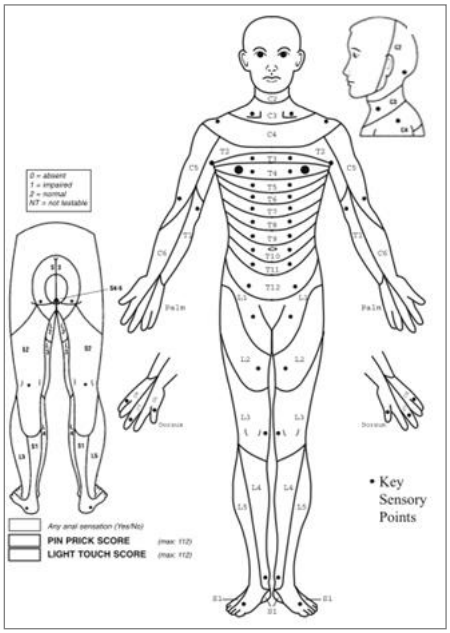
- **The London Project** led by Professor Peter Ellaway opted to apply a technique called repetitive transcranial magnetic stimulation (rTMS) to areas of the brain in stable (chronic) incomplete spinal cord injury patients following a pilot study that had shown encouraging functional improvement of upper limb function.
- **The Glasgow Project** led by Professor Bernie Conway employed robotic weight-assisted treadmill walking therapy (WAT) and compared outcomes in acute and chronic groups of incomplete spinal cord injured patients.
- **The Edmonton Project** undertook an innovative tele-rehabilitation approach using functional electrical stimulation to provide hand opening and grip, allowing stable incomplete spinal cord injured (iSCI) subjects to deploy an instrumented hand tool device for hand and arm exercises and to participate in interactive computer-generated tasks.
- **The Zurich Project** followed the natural progress of recovery in SCI subjects recruited into the European Multicentre Study for Human Spinal Cord Injury (EMSCI) and developed motor tests for the lower extremity to investigate whether an iSCI results in a comparable loss of strength and the ability to coordinate muscle groups.

The following sections of this review are based on the achievements of the four research groups who contributed to Stage Two of the Clinical Initiative.

The London Project (Professor Peter Ellaway)

The standard neurological assessment possible via the American Spinal Injuries Association (ASIA) Impairment Scale (AIS) records function of key muscle groups in the body as well as sensory impairment to light touch and pin prick tests at key points on the body. These key points have become the accepted standard across the world (*see figure, opposite*). In addition to AIS, a number of complimentary tests that give very precise information on such things as injury "level" and "completeness" have been identified. The quantitative nature of these techniques makes them ideal for research purposes but their complexity and requirement for expert interpretation is likely to limit their use as routine clinical tools.

The London group have developed a test that does not have these limitations. The test, known as the Electrical Perceptual Threshold (EPT) test, measures the minimally detectable sensory appreciation, or threshold, of a repetitive constant electrical current applied to the same key points on the skin used in the AIS. When applied, the EPT test provides a quantitative picture of a patient's skin sensitivity that can be compared with that of a normal healthy template. **The group performed numerous trials in healthy and patient groups to validate this new quantitative test, demonstrating reliability and repeatability which are important parameters for any test that will be used across multiple clinical centres.**



In this arm of the Clinical Initiative, repetitive Transcranial Magnetic Stimulation (rTMS) was applied in the hope of eliciting a beneficial effect on a group of SCI patients in line with earlier beneficial effects that had been reported in studies of stroke, Parkinson's and SCI patients. These studies allowed, therefore, (i) further investigation of the potential of rTMS as a non-invasive treatment for SCi as well as (ii) an opportunity to examine the utility of the newly-developed EPT test.

EPT is more sensitive

The EPT was found to be more sensitive that the standard AIS sensory measures routinely employed. For example, in nearly half all cases tested, the level of the spinal cord at which the EPT could detect abnormalities was higher than that defined by the AIS assessment.

One reason for this might be due to the subjective nature of AIS which relies on a patient describing whether a light touch or pin prick feels "normal". In someone with a long standing injury, the impression of what is normal may significantly change in people as they become accustomed to living with SCI. EPT by contrast measures a threshold which is not subjective in nature.

Reliability of EPT

Testing on SCI subjects and healthy volunteers allowed reliability to be assessed. It was shown that:

- In healthy subjects, EPT results matched to the corresponding key point each side of the body
- Results were consistent from day to day in control subjects demonstrating good repeatability
- This repeatability was confirmed in SCI subjects and results obtained from different assessors matched – this is known as inter- and intra-rater repeatability

The conclusion that EPT is reliability has been further strengthened by results published from an independent study.

EPT provides information on specific sensory pathways in the spinal cord

Weak electrical stimulation of the skin as used in the EPT excites nerve endings that normally respond to light touch or pressure. The sensation is likened to a light tapping on the skin. Work continues, but it is emerging that EPT can discriminate between damage to pathways that process pain or pin prick tests and the pathways that convey information about light touch and body awareness (proprioception) providing a further dimension to this test.

In summary, this arm of the Clinical Initiative has supported the introduction of the EPT test to provide an adjunct to the standard clinical ASIA Impairment Scale (AIS) for sensory function that is quantitative and more objective as a measure. There is greater sensitivity to the method and it has good inter-rater and intra-rater reliability and easy to perform.

The Edmonton Project (Professor Arthur Prochazka)

About a third of tetraplegic people have partly or fully paralyzed hand muscles. In most C5-C6 level injuries, the nerves innervating muscles remain intact and the muscles can therefore be activated with functional electrical stimulation (FES) applied through surface or implanted electrodes. There is growing evidence that combining FES with intensive exercise therapy (FES-ET) can significantly improve tetraplegic hand function, a high priority in this patient population.

The Edmonton group aimed to provide exercise therapy that would result in changes in hand function against which the newly developed tests could be evaluated. During the course of the project a new rehabilitation device (The ReJoyce; *see panel below*) and tele-rehabilitation technology was developed that allowed two types of rehabilitation therapy to be conducted in participants' homes with remote supervision by therapists via the Internet.

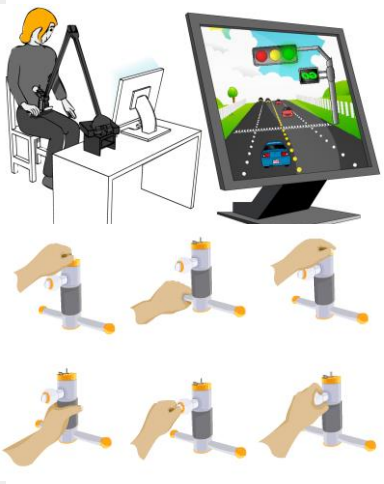
Subjects were recruited to this study with stable chronic C5- C7 level (neck) injuries that had resulted in complete or incomplete tetraplegia. These subjects had partial or complete loss of hand grasp and release.

Participants performed hand exercises supervised over the Internet. Subjects were divided into one of two rehabilitation regimes:

- **Treatment 1**: conventional hand exercises for 6 weeks, 1 hour/day, 5 days/week with off-the-shelf equipment including 20 minutes of cyclical electrical muscle stimulation
- **Treatment 2**: hand exercises for the same periods, but on the computerized "ReJoyce" exercise workstation and assisted with FES

The 'ReJoyce' workstation

ReJoyce stands for Rehabilitation Joystick for Computerized Exercise. The ReJoyce workstation comprised a spring-loaded extensible arm with attachments such as a spring-loaded doorknob, a gripper, and a pull-handle. The attachments represented activities of daily life (ADL). According to motor improvements in consecutive sessions, participants were presented with tasks of increasing difficulty. A muscle stimulator garment provided FES for hand opening and grasp, wirelessly triggered by the participant via an earpiece similar to a hearing aid that detected small tooth-clicks.



In-home tele-rehabilitation (IHT)

An Internet-based computer interface allowed therapists to supervise participants in their homes and to download their performance data. Audiovisual software was developed that guided participants through a hand function test and a variety of computer games based on activities of daily living (ADLs).

Methods of evaluating outcomes

Two methods of evaluation were used:

1) A standard upper limb functional assessment known as The Action Research Arm Test (ARAT)
2) The ReJoyce Automated Hand Function Test (RAHFT), a quantitative test of activities of daily living (ADLs) developed during this project performed on the ReJoyce workstation

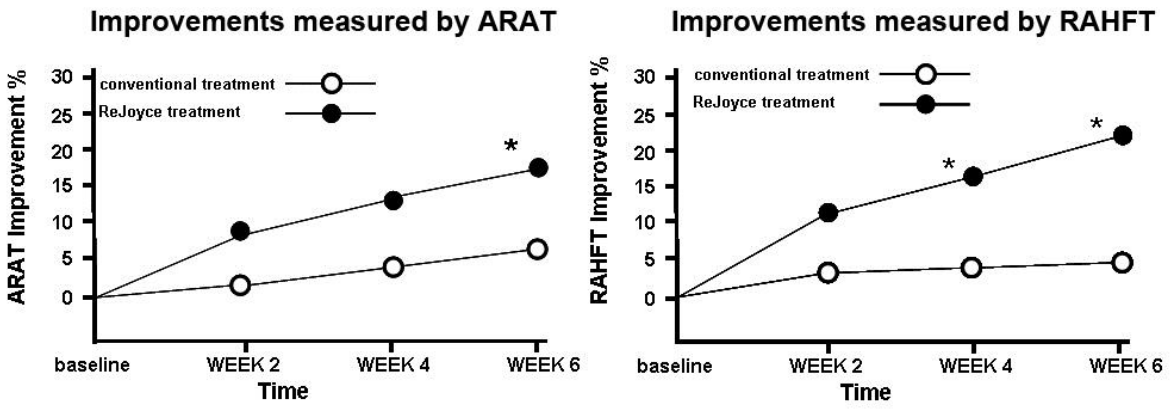
In addition to these functional tests, electrical perceptual thresholds (EPTs; as discussed earlier) and electrical recordings measuring changes in connectivity between the brain and the muscles of the upper limb were carried out before and after treatment.

Results

The figure below shows the functional improvements as evaluated with the ARAT and RAHFT for the two treatments. The mean improvements in the ARAT after the six-week treatment periods were 7.3% for the conventional treatment (-**o**- open symbols) and 17.2% for the ReJoyce treatment (-●- closed symbols). Likewise, an improvement in the RAHFT of 5.0% (open) was observed for the conventional treatment and 22.0% for the ReJoyce treatment (closed).

Statistical analysis showed there was a significant difference between the two treatments, with **subjects given rehabilitation via the ReJoyce system performing functionally better than those who had received conventional rehabilitation therapy**.

In the ReJoyce group, but not in those subjects given conventional treatment, the biceps and muscles of the wrist also showed increased responsiveness to electrical activity arising



from the brain, suggestive of improved connectivity, and whilst this did not reach statistical significance the trend was clear in the ReJoyce group but not in the conventional treatment group.

What was interesting was these functional and electrical connectivity improvements did not result in statistically significant changes in the electrical perceptual threshold (*see earlier section*). The lack of statistically significant changes in EPTs indicated either that these rehabilitation methods did not change sensory pathways from skin to brain, or that the EPT method did not have sufficient resolution to detect any changes that may have occurred.

Conclusions

The improvements seen in the functional tests for the ReJoyce group (*see figure, above*) easily exceeded the minimal clinically important difference. These functional improvements were correlated with improvement trends in the connectivity in biceps and the wrist extensors, representing the C5 and C6 segments of the spinal cord.
Regarding the EPT results, there was no indication that the 6 weeks of treatment had changed the sensory thresholds, although significant improvements in motor function had occurred. Some of the subjects reported that a small amount of cutaneous sensation in the tested arms had returned, but this has yet to be explored systematically.

We conclude that both treatments (ReJoyce + FES + teletherapy, and conventional exercise + teletherapy) resulted in functional improvements in hand function. The ReJoyce treatment produced larger gains than the conventional treatment (17.3%, easily exceeding the minimal clinically important difference of 10%).

The ReJoyce workstation is now commercially available and has been adopted in a number of SCI centres around the world. An international multicentre trial has now commenced involving groups in Canada, the US and Australia.

The Glasgow Project (Professor Bernard Conway)

Weight assisted treadmill training is a recognized rehabilitation concept that can help improve walking gait in patients with incomplete paraplegia. This approach to gait rehabilitation can be accomplished by providing patients with intensive gait training in which a body weight support system is used in conjunction with a moving treadmill. The training is provided either via manual assistance or robotic devices that assist the patient to move their legs. In this component of the Clinical Initiative a robotic driven gait device (Lokomat; *see below*) was used to provide gait training for incomplete spinal cord injury patients. For the purpose of this study the Lokomat provided an intervention on which an evaluation on the effectiveness of a battery of assessment tests able to identify changing functional outcome or physiology were investigated. A number of Quantitative Sensory Tests developed from phase 1 of the ISRT Clinical Initiative were included together with standard clinical assessments, gait outcome measures and additional sensory and motor assessments.

Lokomat training and subject details

18 incomplete spinal cord injury patients completed a six week Lokomat programme (one hour of Lokomat training 5 days per week, giving a potential maximum of 30 training sessions per recruit). Assessments were performed on each subject before, during and after training (pre-training; mid-training; post-training, respectively).

At the onset of Lokomat training, body weight support of up to 80% was provided to each participant. As training progressed the % body weight support was reduced in relation to a patient's ability to step without knee buckling during the stance.

Subjects were defined as either acute (<six months' post injury) or chronic (>six months post injury). There was a mix of neck and back injuries in the subjects recruited.

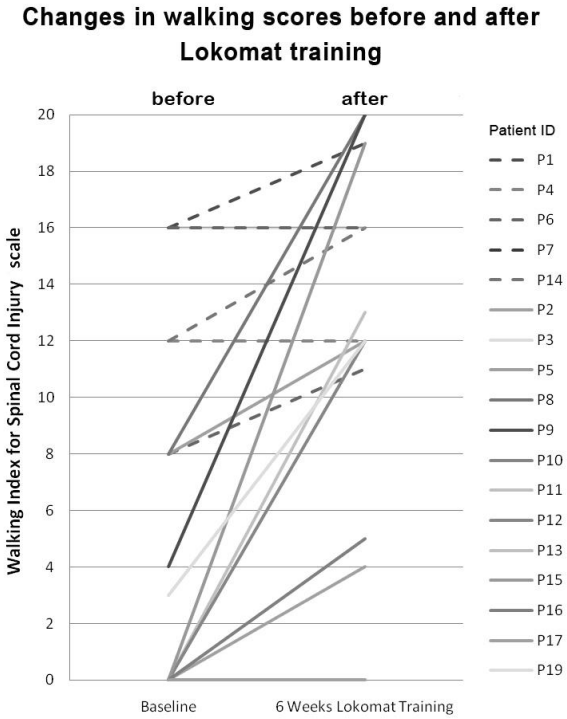
Results

Functional (locomotor) changes during training

As a first analysis, a standard scoring system, the Walking Index for SCI, or WISCI, was used to assess walking ability. The WISCI scores improved following Lokomat training for

the majority of patients recruited to the study. At the onset of training 8 patients were non-ambulatory as indicated by a WISCI score = 0. Three of these patients remained non-ambulatory with the remaining 5 non-ambulatory subjects demonstrating improved scores by the end of the Lokomat training. Of the acute patients who were ambulatory (5 subjects) at pre-training only 1 failed to show any improvement in their WISCI score post-training.
All chronic subjects were ambulatory at the start of training and either demonstrated no change in WISCI score (2 subjects) or only modest changes post-training when compared with acute subjects.

The changes in WISCI score strongly support the notion that **functional walking capability improves more readily in the acute patients** over the six-week training period (compare level of change in solid lines (acute) compared to dotted (chronic); *see figure*).



As the WISCI scores do not provide an insight into all parameters of gait additional gait analysis assessments were conducted to give a more quantitative assessment of the changes in gait pattern occurring over the training period.

Quantifiable parameters such as walking speed (estimated over a calibrated distance of 6m), double support time (i.e. time during which both feet are in contact with treadmill), stride length and cadence or stepping rate, were calculated. Subjects were also video taped from a head-on and side view camera position during these assessments.

Importantly, significant differences in all the above parameters can be identified when comparisons are made between data obtained from pre-training and post-training assessment points in acute patients. In contrast, no significant changes were observed in the chronic subject group.

For the acute patient group, significant differences in walking speed, stride length and cadence were established within the first 3 weeks of training **with no further significant change occurring over the second three weeks of training**. The double (feet)

support time on the other hand displayed a significant difference only when comparisons were performed between pre- and post-training assessments.

The study clearly demonstrated that different parameters of gait change at different rates and times and are more evident in acute than chronic patients;

- The increases in speed, stride length and cadence are acquired predominately during the first three weeks of training and level off
- Thereafter, decreases in double support time begin to show significant change from baseline measures

This new understanding may have important implications to how we design and tailor rehabilitation strategies in the future. In clinical trials in spinal cord injury where walking ability may be expected to change over time the incorporation of quantitative assessment of gait should be included alongside functional assessments such as WISCI. It is also crucial that these tests are applied at intervals which allow an adequate picture of the progressive nature of any treatment or recovery effects. The gait analysis tool used here is inexpensive, simple to use and easy to interpret.

The above results illustrate that over the six weeks of Lokomat training, significant changes in functional walking and in the quality of the over-ground stepping could be measured in acute incomplete spinal cord injured patients.

Quantitative Sensory Testing and Somatosensory Evoked Potentials.
In addition to the locomotor assessments above, complex electrophysiological measurements (for which this group has particular expertise) were also taken during the course of the study to examine changes in the patterns and strengths of electrical signals associated with sensory function. These electrical measurements can provide a diagnostic signature of neurological changes that can help interpret functional changes in a way that does not require subjective interpretations and reporting by the patient, which are often variable.

One such technique, known as the somatosensory evoked potential, or SSEP, records small electrical signals that can be picked up on the scalp when a peripheral nerve in the body is stimulated by a small electrical current. This technique is widely used to monitor the health and status of the connections between the body and the brain.

The SSEP signature (the shape and timing of the recorded signal) can be analysed to provide information on the path the signal has taken to get from the body to the brain and

how this might have been disturbed after injury, disease or reorganisation during treatments.

Perhaps not surprisingly the group found that the SSEPs were different in SCI patients compared to normal subjects. It was both distorted and took longer for the signals to come through. In acute patients, the signature changed over the course of training indicating changes were taking place in the nervous system.

What is important to determine is whether analysing parts of the SSEP signature can predict with accuracy likely functional outcomes. To explore this further the group examined the correlation between aspects of the signature pre-training and the gait analysis data on walking speed, double support time, stride length and cadence. Results indicate that significant correlations can be established between specific SSEP components and the gait parameters tested.

They found that the parts of the signature that relate to how the brain processes the signal best predict improvements in walking suggesting that it is reorganisation and interpretation of sensory information coming from the body that plays an important role in recovery of walking.

Recommendations

The study demonstrates that quantitative assessments such as gait analysis, EPT and SSEP can play an important adjunct role to more established clinical and functional outcome measures in monitoring changes in the status and physiology of spinal cord injured patients participating in intervention studies. The tests employed provide in all cases additional insight into the recovery profile and importantly assist in suggesting what physiological mechanisms may be participating in the recovery process. Determining what assessment tests to include in an interventional trial will very much depend on the functional objective of the trial. The assessments employed in this arm of the Clinical Initiative were primarily considered to be relevant to locomotor recovery over a relatively short training period of six weeks. This study does not make any claim in relation to the benefits of Lokomat training other than the tests we employed successfully detected changes in function and physiology over the period of the intervention. This study recruited 18 patients over a two-year period from a single clinical centre. Single centre studies in spinal cord injury will always be restricted to small subject numbers and where possible multi-centred collaboration based on use of common assessment methodologies should be encouraged.

The Zurich Project (Dr Huub van Hedel)

Muscle strength is one important aspect of functions such as walking but it is equally important that this is associated with fine control of muscle movement. The ability to respond to changes in terrain or operate controls needed for driving require this fine control. Indeed, after an incomplete SCI, gross motor function appears rather clumsy, which could be caused by either a lack of strength, muscle coordination (both in timing and grouping) or both.

However, clinically, only strength is quantified using the international standard ASIA Impairment Scale which as indicated is only one of the components involved in recovery of motor function. There is no generally accepted clinical test that distinguishes between loss of strength and/or coordination in the field of SCI. It is therefore still an unresolved question whether an incomplete SCI affects muscle strength and coordination to a similar degree.

In general, the neuronal circuitry responsible for muscle strength is located in the spinal cord and the muscle itself, whilst changes to finer responses such as control of muscles are likely to involve changes in the higher brain centres. Understanding the contributions to functional recovery from both these mechanisms will inform the design of future treatments and clinical trials.

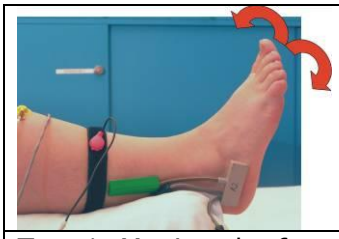
The aim of this study was to develop a variety of reliable and quantifiable techniques capable of distinguishing these various important aspects of motor function, specifically a patient's ability to control parameters such as speed of a movement, control over the degree of movement and timing of movements and not just strength of movement. In addition, they wished to relate recovery to changes in neuronal activity.

Towards this last objective, the group developed a new protocol for assessing "test signals" generated by transcranial magnetic stimulation (TMS) of the brain. TMS is non-invasive and harmless and serves only to induce the sort of signals naturally sent by the brain down the spinal cord to the body except in a predefined and controlled manner. Initially this procedure was used to assess the quality of the pathways down which the signal passed. Unfortunately, TMS in patients is far less reliable than in healthy volunteers or patients with other neurological disorders on whom this technique was originally developed. The new procedure, described below, has made these tests reliable enough for clinical application.

Refinement of the standard transcranial magnetic stimulation assessment measure

When lifting the foot, the brain controls muscles that are necessary for this function by generating nerve pulses that are transmitted down to the spinal cord and the individual muscles. This signal pathway can be tested by applying transcranial magnetic stimulation (TMS) to the scalp, over the brain area where the target muscle is controlled. In the brain, the magnetic pulse generates an electrical pulse that continues its course to the target muscle. This method has the advantage that it is possible to measure the time it takes the pulse to reach the muscle (latency) and the amount of activity generated once there (the amplitude of the Muscle Evoked Potential or MEP), amongst other parameters, and as such provides an assessment of the "quality" of the connection and course taken between brain and muscle. This is similar in concept to the analysis of SSEP signatures discussed earlier although this time the signal is going from brain to body rather than body to brain.

For healthy subjects, the technique has good reliability. However, for SCI patients, such tests are inconsistent and poorly correlate with functional outcomes. The new protocol developed by the Zurich group uses a specially designed device, where the subject is asked to exert a constant force against a set or variable resistance whilst the TMS test is performed (Figure 1: right hand panel). Under these modified test conditions, the group found that the measurements became reliable enough for application to clinical studies.



Test 1. Moving the foot rhythmically up and down at the right frequency.

Test 2. Measuring foot lifter and calf muscle strength.

Figure 1: Torque Device

The new procedure allowed the group to define a pathological delay in signal transfer from brain to muscle of 19.5ms for every metre in body height. In addition, the protocol allowed signals to be measured in subjects from whom signals are often difficult to record.

Impairment in muscle strength and coordination after incomplete SCI

With the new assessment in place the group could address the first objective of determining the relative contribution of strength versus dexterity to motor function. Two tests were developed to distinguish between strength and coordination. Each test was performed lying down, required only a minimal amount of strength and focussed on the ankle muscle groups for several reasons, including: (i) both para- and tetraplegic subjects

could be assessed, (ii) activity in these muscles is considered important predictor for walking capacity after SCI.

Two tests were developed to assess the ability to accurately activate the ankle muscle groups:

1. somewhat simpler, rhythmic movement test and
2. a more complex, a-rhythmical torque tracking task that required continuous visual feedback and attention.

For the first test, the subjects performed ankle movements at different frequencies (e.g. 0.8, 1.6, 2.4 Hz) by following computer generated tones. The subjects performed the movements as accurately as possible and with the maximum range of motion (ROM) they could achieve. Ankle joint movements were recorded using monitors, which allowed the accuracy of the movement frequency, the ROM and the movement velocity to be determined. **With this technique, both muscle strength and accuracy could be reliably assessed.**

The incomplete SCI subjects, who had reduced muscle strength on the ankle, could perform the ankle movements with high accuracy but with significantly reduced ROM and movement velocity compared to healthy subjects.

Muscle strength was not found to be related to the time or quality of the signal passing from the brain to the muscle as determined by TMS tests described above, however, the velocity of that movement did. So signal processing in the brain and spinal cord played an important role in speed of movement. Interestingly, the time taken for the signal to reach the muscle didn't change as patients showed recovered function but the size of the signal did increase and this increase seemed to be related to speed of movement. This is a clear indication and measurement of a neurological change in the brain and spine circuits corresponding to a functional improvement.

For the second test, the subjects performed a tracking task, with the same torque measurement device as used for the assessment of strength and MEPs. A blue trace was displayed on a monitor representing the amount of torque the subject should apply. Eight trajectories were performed and both the learning rate and performance were quantified by calculating the error between the desired and performed trajectory. Similarly to the simpler task, despite marked impairment in strength (65-75% torque of healthy values), task performance improved at a similar rate and the final performance equalled that of the healthy subjects **indicating that, although strength was significantly affected,**

cortical control over partially paralyzed muscles was intact. This lack of difference, however, is unlikely to be due to insensitivity in the test, as significant deteriorations in accurate muscle coordination were also found in stroke versus incomplete SCI subjects, both for the simple task, as well as for the more complex task. Furthermore, healthy elderly subjects were found to perform less well compared to young subjects. In other words, the test was able to pick up deficits in performance in subjects where deficits in brain regions are affected (i.e. stroke and the elderly).

These findings could have consequences for rehabilitation training programmes and experimental interventions that are being translated from bench to bedside, as in contrast to patients with stroke, patients with an incomplete SCI might benefit from interventions that focus on improving muscle strength.

Through this work the group have demonstrated that the dynamic muscle strength parameters they have developed are far more sensitive in distinguishing the degree and level of paralysis and are more closely related to electrophysiological measures of neuronal damage than existing and routinely used techniques. These simple methods could therefore act as routine surrogate measures of neuronal recovery, either spontaneous or after treatment.

Specific methods developed as a result of this study have now been incorporated in a proposed Phase I/II clinical trial on an anti-Nogo antibody therapy developed by Novartis.

General conclusions

The Clinical Initiative has furnished a number of novel and improved physiological and functional methods of assessment that are appropriate for monitoring recovery (or deterioration) in spinal cord injury. It is unlikely, for several reasons, that any single test will emerge either for application in clinical trials for repair or in newly developed rehabilitation strategies. The choice of test(s) to supplement AIS assessments will depend first on the physiological system to be tested, whether it is sensory, motor or autonomic. Second, it will depend on the level and completeness of the spinal cord lesion. Third, the anticipated improvements in function or connectivity will be factors, although these may be hard to estimate. For example, the improvements may be restricted to particular types of movement or changes in connectivity within specific cerebrospinal pathways. Finally, consideration will need to be given to a raft of incidental but clinically and socially important factors. These include the time available for the test to be undertaken, the tolerance of subjects to protracted or intrusive tests especially if the SCI is acute and if other health and safety issues are present, and finally, the cost of administering tests in terms of time, apparatus and personnel. The current toolkit employed by the Clinical Initiative focussed on functional and physiological assessment. Improved imagining of the spinal cord would bring much needed data on the anatomical substrate that these tests explore. Clinicians, scientists and physiotherapists are in the vanguard of reparative clinical trials, but we lack gold standards and the confidence of significant clinically-meaningful changes in outcome measures. In the earliest forays into trials, it is incumbent on all to ensure the trial data collected can feed back into the translation and optimisation of new approaches and not merely to set our sights on distinguishing whether a treatment has been successful or not. Improving outcome measures is a way forward in achieving this goal.

Dr Mark Bacon
Director of Research, Spinal Research **Jul 2011**

If you would like to discuss this report please contact
Dr Mark Bacon on: 020 7653 8935 or email mark@spinal-research.org

List of publications arising from Part II of the Clinical Initiative

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2. Clarke, C.J.G.S., Allan DB, Conway BA, *Correlations between recovery of ambulatory capacity and lower-limb somatosensory evoked potentials in incomplete spinal cord injury.* Archives of Physical Medicine and Rehabilitation, 2010. **91**(10).
3. Curt, A., et al., *Recovery from a spinal cord injury: significance of compensation, neural plasticity, and repair.* J Neurotrauma, 2008. **25**(6): p. 677-85.
4. Ellaway, P., *Quantitative tests of sensory, motor and autonomic function*, in *Essentials of Spinal Cord Injury*, V. Fehlings, Boakye, Rossignol, Ditunno, Burns, Editor. 2011, Theme Publishers.
5. Ellaway, P.H., et al., *Development of quantitative and sensitive assessments of physiological and functional outcome during recovery from spinal cord injury: a clinical initiative.* Brain Res Bull. **84**(4-5): p. 343-57.
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