UK Sensorimotor Meeting 2022

Aston University Lecture theatre 2 (room 417 - 4th floor)

Monday 20th June

13:15 Yingshi Feng, Malte Kaller, Heidi Johansen-Berg

Myelin Plasticity and Sleep-Dependent Memory Consolidation

Motor learning involves both improvement during practice and offline improvement, known as consolidation, that occurs after practice. Sleep can enhance motor consolidation, during which patterns of neural activity elicited during initial learning replay during subsequence sleep. Such neural replay may evoke plasticity in the task-related circuits, thereby contributing to behavioural improvement post-sleep. We predict that sleep-dependent motor consolidation involves myelin plasticity, where motor learning induces preferential myelination of active axons, leading to alterations in conduction velocity across neuronal circuits, which may contribute to behavioural improvements.

We will use targeted memory reactivation (TMR) to boost consolidation during sleep. TMR involves repeatedly pairing a motor memory with sensory cues during initial learning. Re-presenting the sensory cues during subsequent slow-wave sleep reactivates motor representation, thereby enhancing behavioural consolidation. However, the biological mechanisms underlying TMR are unclear. Therefore, we will first use rodent models to assess myelination directly with histology and indirectly with MRI.

We will also use a transgenic mouse model (P-Myrf (−/−)) to determine whether myelin plasticity causes motor consolidation. In this model, tamoxifen-dependent knockout of myelin regulatory factor (MyRF) in oligodendrocyte (OG) precursors results in reduced capacity to form new OGs following tamoxifen administration, without any loss of existing OGs. We will inactivate MyRF at different motor learning stages and assess its impact on motor memory consolidation.

This project will unveil the role of myelin plasticity in sleep-dependent memory consolidation and provide translatable results to inspire rehabilitative treatments in disease.

13:30 Elliott Atkinson

Reliability of non-invasive assessment methods of reticulospinal tract function in humans.

Introduction

The reticulospinal tract is involved in maximal force production, and potentially a site of adaptation following resistance exercise in humans. However, the reliability of non-invasive methodologies quantifying reticulospinal tract function are yet to be assessed.

Methods

We assessed the reliability of the StartReact task (visual, auditory & startle reaction times), the interaction of auditory startles with cervico-medullary (CMEPs) and transcranial magnetic stimulation (TMS) motor evoked potentials (MEPs), and MEPs elicited by anterior-posterior TMS coil orientation (AP-TMS). Sixteen volunteers (25 ± 4 years) completed familiarisation, then two tests 7-days apart. Responses were recorded from

elbow flexors and extensors. Paired-samples t-tests assessed systematic error, random error was assessed as a coefficient of variation (CV).

Results

Although preliminary, there were no systematic differences between visits in any measure (P>0.05), except for faster extensor visual and auditory reaction times in StartReact on visit 2 (P<0.05). Reliability was excellent for extensor auditory (ICC=>0.9) and good for startle reaction times (ICC=0.75–0.9). Flexor and extensor startle-induced CMEPs, visual reaction time, and flexor auditory and startle reaction times displayed moderate reliability (IC =0.5–0.75). Flexor and extensor startle-induced MEPs and AP TMS reliability was poor (ICC <0.5). Random error was acceptable across all conditions (CV = 6-25%).

Conclusion

StartReact showed good reliability in the elbow flexors, but not in extensors. Reliability of startle-induced CMEPs for elbow flexors and extensors was good, but for TMS MEPs there was more variability. All measures displayed a relatively high degree of random error, consistent with previous assessments of neurological function.

13:45 Rachael H. A. Jones, Mark R. Baker, Stuart N Baker

Histopathologies in a Macaque Model of Motor Neurone Disease: Evidence for Prion-like Spread

Motor Neurone Disease (MND) is a rapidly progressive and ultimately fatal neurodegenerative disease, characterised by the loss of upper and lower motor neurons. The primary proteinopathy found in approximately 97% of all cases involves cytoplasmic mislocalisation and aggregation of the ubiquitous nuclear protein, TDP-43. Despite the identification of many implicated genes during the last few decades, our understanding of the mechanisms involved in the onset and propagation of pathology have advanced very little.

Translatable advancements have likely been limited due a lack of reliable animal models which accurately recapitulate this complex disorder. No model has been created to date which replicates the progressive motor weakness; characteristic histopathologies; extended pre-symptomatic phase and subsequent rapid deterioration. Rodents have been the dominant species in MND research; however, their anatomy and genetic profile differs fundamentally to humans. Crucially, they lack the direct monosynaptic connection between the upper and lower motor neurons, unique to primates.

We have harnessed a novel intersectional genetics approach to induce the overexpression of the human TDP-43 protein in a selective spinal motoneuron population in two Rhesus macaques. Focal overexpression of TDP-43 in a spinal motor pool was sufficient to induce the expression of pathological phosphorylated TDP-43 (pTDP-43) throughout the motoneurons of the cervical spine and corticomotoneuronal cells of the primary motor cortex. The detection of this histopathology in the distant giant cells of Betz in the primary motor cortex supports the idea of an axon mediated ‘prion-like’ spread, likely involving the corticospinal tract.

14:00 Stuart N. Baker, Takamichi Tohyama, Jesus Tapia Lopez.

Evidence for a dominant reticulospinal drive to voluntary movement

To make any movement, motoneurons must be recruited to fire action potentials and activate motor units in the periphery. Quantitative data on the relative importance of different sources of synaptic input to motoneurons is hard to come by. In primates, it is often assumed that the corticospinal tract provides the major input to motoneurons, but spinal cord interneurons, afferents and other descending pathways also play a role. In this study, we trained two macaque monkeys to perform elbow flexion-extension movements in response to auditory and visual cues. On some trials, the visual 'go' cue was supplemented by a loud sound (115dB); this caused reaction times to be faster, as observed previously in humans (the 'StartReact' effect). Once training was complete, animals were surgically prepared to record single unit activity from identified corticospinal neurons in the primary motor cortex (M1), and from the reticular formation (RF; gigantocellular and oral/caudal pontine nuclei). Post-cue activity in RF was enhanced by the loud sound, but suppressed in M1. We then used computational modelling to test the response of a simulated motoneuron pool to inputs which modulated as varying mixtures of the population activity recorded experimentally from M1 and RF. When the majority of input to motoneurons came from M1, reaction times were slowed by the loud sound – the opposite to what is seen experimentally. Only if the input mixture favoured the RF could the StartReact shortening of reaction times be replicated by the model. We conclude that the majority of motoneuron drive for voluntary movement, even in primates, may arise from non-corticospinal pathways.

Supported by the MRC and CONACYT, Mexico.

14:15 **Break – Posters**

14:45 Viviane S. G. M. Tenorio, Stuart N. Baker

Applying a Dynamical Systems Approach to Neural Recordings from Cortical and Sub-cortical Motor Centres in Awake Behaving Monkeys

In the past few years, different frameworks were proposed for how brain activity generates movements. The dynamical systems framework considers a neural population as a dynamical system that, through its different states in time generates and controls movement. A succession of states evolving through time constitutes a neural trajectory. Those trajectories will then be signatures of the neural response to a given motor behaviour. Churchland et al. found that primary motor cortical (M1) activity during reaching contained an oscillatory neural trajectory – an unexpected result for such a non-periodic behaviour. These results were achieved using an approach called joint principal component analysis (jPCA), which searches for rotational trajectories – one of the simplest dynamics. Here, we investigate whether similar oscillatory trajectories occur in other brain regions. jPCA analysis used single unit recordings from two macaque monkeys performing an elbow flexion/ extension task, taken from M1, reticular formation (RF) and spinal cord interneurons (SC). We found that brief oscillatory trajectories do occur in RF and SC as well as in M1. The trajectories in RF appeared qualitatively different from those in M1 and SC; to quantify this, we computed the resultant vector (R). This takes a value of one for perfect rotations and zero for random data. R was 0.4 for M1, ** for SC and 0.68 for RF (averages across task conditions and monkeys). Our results suggests that rotational dynamics are present at different levels of the motor system. While M1 and SC dynamics appear similar, RF

activity is closer to a pure rotation, possibly indicating that RF does not simply act to transmit M1 activity.

15:00 Lucy Dowdall and Tamar Makin

Pilot Study Investigating Integration of Somatosensory Information Following Short-Term Training with an Augmentation Device

Augmentation technology is a rapidly expanding field, and with it there is growing interest in how such devices interface with the body. When using body augmentation devices, the brain gains experience with a variety of different sensory feedback cues. It is thought that when learning to control such devices, the brain gathers information from these sensory inputs to construct an internal representation of the device. One important input is the tactile cues from when the device is worn on the body, described as intrinsic touch.

We aimed to investigate changes in somatosensory functioning following active training with a supernumerary robotic finger (the Third Thumb, Dani Clode Design) that are indicative of a sensory representation being constructed. We particularly wanted to assess integration of intrinsic touch inputs with the somatosensory inputs from the biological fingers. Participants underwent one day of motor training with the Third Thumb and a specific finger, then completed a spatiotemporal localisation task (temporal order judgement). Improvements in localisation ability were seen for the trained finger-pair, but not seen for an untrained finger-pair. This suggests integration of the intrinsic tactile feedback from the Third Thumb and somatosensory inputs from the trained finger had taken place. However, more work is needed using a larger sample who spend more time training with the Third Thumb to thoroughly explore the possibilities of this sensory representation. Future studies, using representational similarity analysis, will also determine whether the perceptual similarity between the Third Thumb and biological fingers will be reflected in the S1 hand representation.

15:15 Anna Baines, Stuart Baker

A Primate Model for the Flexor Synergy after Stroke

There are over a million stroke survivors in the UK. Some patients can become ‘stuck’ with unhelpful muscle co-contractions, whereby shoulder abductors obligatorily activate elbow flexors (‘flexor synergy’). This makes reaching and grasping almost impossible. Despite this, no animal study has ever attempted to investigate the neural source of post-stroke synergies separate from weakness. The aim was to dissociate which discrete lesions of the primary motor cortex (M1) lead to development of flexor synergy. These areas were the ‘Old’ (anterior part) and ‘New’ M1.

Two rhesus macaques were trained in a reach and grasp task. A supportive table to support the arm could be removed to discriminate synergies from weakness. Wires for electromyography (EMG) recording during active movement were implanted into 12 upper limb muscles. Video footage allowed for kinematics analysis. After baseline recording, endothelin-1 infusions produced focal ischaemic lesions of upper limb representations in each cortical area. EMG and kinematics were analysed over 15 weeks post-lesion.

The anterior Old M1 lesion did not produce muscle weakness. Progressive increases in flexor and extensor muscles in the weeks following the lesion allowed for near-normal kinematics. In contrast, the New M1 lesion led to severe and immediate weakness in all muscles. Flexors recovered back to baseline within 5 weeks. However, extensors remained

persistently lower than baseline EMG and kinematics of movements requiring extension never fully recovered. These results are consistent with anterior Old M1 functioning primarily in a suppressive role, whereas New M1 is important for movement facilitation of the upper limb.

15:30 Colin McNamara

Bidirectional continuous closed-loop modulation of neuronal oscillations in vivo via stable brain-machine feedback

Closed-loop interaction has the potential to regulate ongoing brain activity by continuously binding an external stimulation to specific dynamics of a neural circuit. As opposed to reacting episodically like other approaches, interactive modulation requires a stable brain-machine feedback loop. A highly responsive system is required to track a continuously waxing and waning oscillation and respond to any stimulation induced changes. Here, we demonstrate that it is possible to maintain oscillatory brain activity in a desired state by delivering stimulation accurately aligned with the timing of successive individual cycles. We developed and implemented a fast algorithm that responds on a cycle-by-cycle basis to stimulate basal ganglia nuclei at predetermined phases of successive cortical beta cycles in parkinsonian rats. Using this approach, we demonstrate a stable brain-machine interaction. An equilibrium emerged between the modified brain signal and feedback-dependent stimulation pattern, which led to sustained amplification or suppression of the oscillation depending on the phase targeted. Sustained beta amplification slowed movement speed by biasing the animal's mode of locomotion, demonstrating the manipulation had functional relevance. Our work supports the idea that integrating an external system within the intrinsic dynamics of a pathophysiological neural circuit can provide a "network prosthesis", whereby the closed-loop system compensates for maladaptive changes. Furthermore, our approach to bidirectionally manipulate network oscillations within their normal functional range provides a technical and conceptual platform to define the role of these activities in the function and dysfunction of memory, sleep and other fundamental brain operations.

15:45 **Break – Posters**

16:15 **Keynote talk: Andrew Jackson**

Tuesday 21st June

Presentations - Morning

9:30 **Keynote talk: Anna Kuppuswamy**

10:30 **Break - Posters**

11:00 Arora, K., Chakrabarty, S.

A Simplified Framework of Motor Control

Control of movement is commonly examined and assumed to be either cortical, spinal, or purely biomechanical in origin1,2. To achieve this separation while studying a particular level, variations, possibly introduced by the other levels, are generally either ignored or restricted. This restriction misrepresents how movements occur in realistic scenarios. We propose a framework for motor control which conceptually and mathematically accommodates the entire motor process, from cortex to the endpoint.

We suggest that motor control starts with a simple representation of endpoint coordinates at the cortical level. This is then transformed, mainly at the subcortical level, into specific movements at each involved end-effector. This transformation is proposed as a composition of stages, where each stage involves a selection from a range of possibilities that are appropriate for the task (eg. the goal of the task, the appropriate muscles to use). The components of these transformations (sensory influences, variability) are designed in line with experimental data.

Our approach accounts for sensory effects and muscle properties, along with the variability of the process (across trials and individuals). It can provide a clearer understanding of the functional deficits that occur from ALS, stroke, or sensory neuropathy introduced by the absence of components in this representation. It allows otherwise purely cortical, spinal, or biomechanical findings to be described in terms of the entire motor control system, and hence provide insights into motor control in both dynamic and passive scenarios without the need to eliminate sources of variations.

[1] Song, Y., Hirashima, M., & Takei, T. (2022). Neural network models for spinal implementation of muscle synergies. *Frontiers in Systems Neuroscience, 16*.
[2] De Santis, D. (2021). A Framework for Optimizing Co-adaptation in Body-Machine Interfaces. *Frontiers in Neurorobotics, 15*, 40.

11:15 Sang-Hoon Yeo

On the Encoding Capacity of Human Motor Adaptation

Primitive-based models of motor learning suggest that adaptation occurs by tuning the responses of motor primitives. Based on this idea, we consider motor learning as an information encoding procedure, that is, a procedure of encoding a motor skill into primitives. The capacity of encoding is determined by the number of recruited primitives, which depends on how many primitives are “visited” by the movement, and this leads to a rather counterintuitive prediction that faster movement, where a larger number of motor primitives are involved, allows learning more complicated motor skills. Here, we provide a set of experimental results that support this hypothesis. First, we show that learning occurs only with movement, that is, only with nonzero encoding capacity. When participants were asked to counteract a rotating force applied to a robotic handle, they were unable to do so

when maintaining a static posture but were able to adapt when making small circular movements. Our second experiment further investigated how adaptation is affected by movement speed. When adapting to a simple (low-information-content) force field, fast (high-capacity) movement did not have an advantage over slow (low-capacity) movement. However, for a complex (high-information-content) force field, the fast movement showed a significant advantage over slow movement. Our final experiment confirmed that the observed benefit of high-speed movement is only weakly affected by mechanical factors. Taken together, our results suggest that the encoding capacity is a genuine limiting factor of human motor adaptation.

11:30 Ian S. Howard and David W. Franklin

Investigating generalisation to dynamic force field adaptation across distinct gestures

Previous work has shown that distinct past and future movements act like a contextual cue, enabling the formation of distinct motor memories when the adaptation movements are preceded by unique lead-in [1] or follow-through motions [2]. Here we investigate if a set of individual gestures, with distinct and unique state trajectories, constitute their own contexts and are represented as separate memories.

To carry out this investigation we choose a set of letters of the alphabet which participants can generate with very precisely and reliably. We then examine if when a dynamic force field is applied to one of several highly trained gestures, whether or not there is transfer of dynamic learning to unperturbed gestures. We use a vbot manipulandum to implement the experiments [3]. We present results and discuss their implications.

References

1. Howard IS, Ingram JN, Franklin DW, Wolpert DM. Gone in 0.6 seconds: the encoding of motor

memories depends on recent sensorimotor States. Journal of Neuroscience. 2012; 32: 12756–12768. https:// doi.org/10.1523/JNEUROSCI.5909-11.2012 PMID: 22972999.

2. Howard IS, Wolpert DM, Franklin DW. The value of the follow-through derives from motor learning depending on future action actions. Curr Biol. 2015; 25: 397–401.

3. Howard IS, Ingram JN, Wolpert DM. A modular planar robotic manipulandum with end-point torque control. Journal of Neuroscience Methods. 2009; 181: 199–211.

11:45 Matthew Weightmann, Ned Jenkinson

Timing is everything: Event-related transcranial direct current stimulation improves motor adaptation

There is a current discord between the foundational theories underpinning motor learning and how we currently apply transcranial direct current stimulation (TDCS): the former is dependent on tight coupling of events while the latter is conducted with very low temporal resolution.

Here we aimed to investigate the temporal specificity of stimulation by applying TDCS in short epochs, and coincidentally with movement, during a motor adaptation task.

Participants simultaneously adapted a reaching movement to two opposing velocity-dependent force-fields (clockwise and counter-clockwise), distinguished by a contextual leftward or rightward shift in the task display and cursor location respectively. Brief bouts (< 3 seconds) of event-related TDCS (er-TDCS) were applied over M1 or the cerebellum during movements for only one of these learning contexts.

We show that when short duration stimulation is applied to the cerebellum and yoked to movement, only those reaching movements performed simultaneously with stimulation are selectively enhanced, whilst similar and interleaved movements are left unaffected. We found no evidence of improved adaptation following M1 er-TDCS, as participants displayed equivalent levels of error during both stimulated and unstimulated movements. Similarly, participants in the sham stimulation group adapted comparably during left and right-shift trials.

It is proposed that the coupling of cerebellar stimulation and movement influences timing-dependent (i.e., Hebbian-like) mechanisms of plasticity to facilitate enhanced learning in the stimulated context.

12:00 **Lunch**

Tuesday 21st June

Presentations – Afternoon

13:30 **Keynote talk: Robert Brownstone**

14:30 David Ó' Reilly, Ioannis Delis

A network-information theoretic framework to charecterise muscle synergies in space and time

Objective.

Current approaches to muscle synergy extraction rely on linear dimensionality reduction algorithms that make specific model assumptions. However, to capture nonlinear time-varying, large-scale, and muscle-specific interactions, a more generalised approach is required.

Approach.

We developed a novel framework for muscle synergy extraction that relaxes model assumptions by using a combination of information- and network theory and dimensionality reduction. We first quantify pairwise informational dynamics between muscles using a novel mutual information estimator. We then model these interactions as multiplex networks and identify representative modules. We employ this modularity criterion as the input parameter for dimensionality reduction.

Main results.

This novel framework captures spatial, temporal and spatiotemporal interactions across two benchmark datasets of reaching movements, producing distinct spatial groupings and both tonic and phasic temporal patterns. Readily interpretable muscle synergies spanning multiple spatial and temporal scales were identified, demonstrating significant task dependence, ability to capture trial-to-trial fluctuations and concordance across participants. Furthermore, our framework identifies submodular structures that represent the distributed networks of co-occurring signal interactions across scales.

Significance.

The capabilities of this framework are illustrated through the concomitant continuity with previous research and novelty of the insights gained. Several limitations are circumvented including the extraction of functionally meaningful and multiplexed pairwise muscle couplings under relaxed model assumptions. The extracted synergies provide a holistic view of the movement with

couplings transcending biomechanical constraints and capturing fundamental neural mechanisms. We conclude that this framework opens new opportunities for muscle synergy research, providing a bridge between existing models and recent network-theoretic endeavours.

14:45 Giulia Dominijanni, Danielle Clode, Silvestro Micera, Solaiman Shokur and Tamar R. Makin

Assessment of Augmented Hands Synergies with an Unobstrusive Setup

Extra robotic fingers (XRFs) are an emerging enhancement technology for patients and healthy individuals. Assessing the interactions between the hand and an XRF is a fundamental step to evaluate successful XRF functional integration. In a previous study, changes in biological hand kinematic synergies during intensive use of the XRF Third Thumb (TT; Dani Clode Design) were assessed by means of a data glove. However, this well-established tool presents several drawbacks when applied for augmented hands, and in particular: (i) it doesn't account for the XRF – which is especially problematic for soft devices – and (ii) its own presence potentially interferes in fine manipulation tasks. An alternative for pose estimation is made available by deep convolutional neural network-based regression, which proved to be extremely effective in tracking animals and humans body landmarks from video recordings. Newly released trained networks, together with transfer learning, have significantly reduced the amount of training data needed, making markerless pose estimation viable for any research facility. Here we combine solutions from Google Mediapipe and DeepLabCut to track the joint coordinates of the TT-augmented hand, which we can then filter and triangulate using Anipose to obtain the 3D poses and joint angles. The proposed pipeline builds on established and easily deployable resources for markerless tracking to assess the kinematics of augmented hands with a simple and unobstrusive setup that can greatly facilitate assessment and implementation of XRFs for diverse purposes and clinical groups.

15:00 Massimo Bertoli, William Tippins, William De Doncker, Chi-Hsu Wu, Annapoorna Kuppuswamy

Can pathological fatigue be considered among agency disorders spectrum?

Chronic fatigue is one of the most debilitating symptoms among psychiatric and neurological disorders like stroke, with a major impact on quality of life.

We have recently proposed that fatigue could be the result of a poor attenuation of the sensory stream resulting in a heightened effort perception. In schizophrenic patients, an impaired sensory attenuation is also deemed to drive alterations of the sense agency, the sense of being in control of one's own actions and their consequences. Could poor sensory attenuation account for fatigue being considered among agency disorders spectrum?

We recorded the EEG in high and low fatigued post-stroke survivors while performing a modified Libet-like experiment eliciting intentional binding, an implicit measure of sense of agency based on the compression of the perceived time interval between a voluntary action (button press) and consequent high or low aversive auditory outcomes with different degrees of probabilistic control.

The task was set up to maximise the effect of intentional binding which literature has shown to be sensitive to the degree of control over the outcome and its valence.

Behaviorally, compared to low fatigue, we expect that poor sensory attenuation driving fatigue also results in a weaker intentional binding. From an electrophysiological point of view, we expect an impaired attenuation of self-generated sensory outcomes, indicated by similar stimulus intensity ratings for both low and high aversive tones as well as changes in selected event-related

potentials related to action and outcome binding (readiness potential and auditory evoked potentials N1, Tb, P2).

15:15 Jennifer L Davies

A novel system to deliver transcranial magnetic stimulation during treadmill walking

Transcranial magnetic stimulation (TMS) can be used to probe the cortical control of muscle activity. Stimulation must be delivered at a precise location over the scalp. This has largely limited its use to studying the cortical control of muscle activity in stationary conditions, and precluded study of many non-stationary functional activities. The most recent systems to allow TMS during movement have fixed the head in place relative to the upper body, restricting degrees-of-freedom of movement.

The purpose of this work was to develop a system to enable TMS during treadmill walking without restricting head movement, and to integrate this within a real-time feedback loop that allows self-paced treadmill walking, optic flow, and gait perturbations.

Sixteen healthy participants participated in studies performed as part of an iterative design process. Design objectives included supporting the weight of the stimulation coil, and maintaining coil position on the head within 3 mm of the target. The position of a custom bent batwing TMS coil (Magstim Ltd., Wales) on the head was monitored throughout the gait cycle using a neuronavigation system (Brainsight, Rogue Resolutions, Wales) while participants walked on a treadmill at their comfortable speed.

The final design maintained a stable TMS coil position in ≥96% of samples in each of six participants. The system has been integrated within a Gait Real-time Analysis Interactive Lab (GRAIL) system (Motek Medical B.V., Netherlands). This will allow TMS to be used to probe the cortical control of muscle activity during walking under a wide range of experimental conditions.

15:30 **Break – Posters**

16:00 Jenny S. A. Lee, Brenton Hordacre, Duncan Austin, John Rothwell, Nick Ward, Sven Bestmann

A Longitudinal Comparison of Cortical Excitability in Stroke and Control Populations

Background. Pre-clinical trials identify a finite “critical period” following stroke in which accelerated recovery occurs, driven by an excitable brain environment which supports neuroplasticity (Centonze et al., 2007; Zeiler et al., 2016). In rodents, this critical window occurs at approximately 14-21 days (Murphy & Corbett, 2009); in humans the presence and duration of a critical window remains undefined. Here, we examine three TMS measures of neuroplastic potential in the human primary motor cortex: response to cTBS, SICI and RMT. Data were collected 3 weeks, 6 months and 12 months post-stroke and compared to control data.

Aim: To compare longitudinal neuroplastic potential in individuals with and without stroke.

Methods. Hordacre and colleagues collected data from 31 stroke survivors and 28 control participants (Hordacre et al., 2021). In each session, resting motor threshold (RMT) was recorded, and a paired-pulse TMS protocol was applied to test short-interval intracortical inhibition (SICI). Motor evoked potential (MEP) amplitude was compared before and after continuous theta burst stimulation (cTBS) applied to ipsilesional M1.

Results. In stroke and control groups, no difference in corticospinal excitability was detected between timepoints. Group comparison revealed a sustained difference in intra-cortical inhibition between groups. No measurable difference in cTBS response or in RMT was detected.

Conclusion. This collaborative work identifies atypical inhibitory processing following stroke. No clear indication of a critical post-stroke time window was captured by three distinct measures of excitability, contributing to a growing literature characterising human post-stroke neurophysiology.

16:15 Po-Yu Fong

Cerebellar transcranial evoked potential to investigate the role of the cerebellum in visuomotor adaptation

Introduction

The cerebellum is thought to be a key structure in learning a new motor skill or adapting to a changed environment. Human neurophysiology has previously probed this using TMS over the cerebellum to suppress MEPs evoked from a second TMS pulse to motor cortex. Here we probe the effects of cerebellar TMS by recording the EEG activity that it evokes in cerebral cortex (the cerebellar transcranial evoked potential (TEP)). We ask if the cerebellar TEP can provide another possible way to investigate the role of the cerebellum in visuomotor adaptation.

Method

We first defined the cerebellar TEP in twenty-five healthy volunteers using a range of control experiments to separate the cerebellar contribution to the TEP from other non-specific inputs produced by the concurrent auditory and somatosensory effects of TMS. Fourteen healthy volunteers were enrolled in the visuomotor learning experiment using an arm reaching task. Two blocks of baseline training, two blocks of adaptation with 30 degrees visual rotation, and one block of de-adaptation (no visible cursor and visual manipulation). The cerebellar TEP was recorded before and after baseline training and after adaptation.

Result

In the contralateral frontal region, we isolated a consistent cerebellar-related positive peak after 80ms (P80) and another negative peak after 110ms (N110) that differed in location and precise timing from the auditory and somatosensory evoked activity. Intriguingly, the amplitude of P80 and N110 decreased after baseline training (i.e. during familiarisation with the manipulandum and visual feedback). The P80 increased significantly after adaptation compared with post-baseline training.

Conclusion

By using cerebellar TMS and EEG co-registration, it is possible to observe changes in the strength of cerebellar-frontal connectivity during different stages of motor learning.

16:30 Ian D. Loram, Henrik Gollee, Cornelis van de Kamp and Peter J. Gawthrop

Does human balance control require predictive or non-predictive feedback control?

Objective: To test whether human balance control requires short term prediction.

Motivation: The cerebellum is relevant to balance and is associated with short term prediction. We investigate two linear (non-predictive, predictive) and one non-linear (intermittent-predictive) control models (NPC, PC, IPC) to reproduce linear and remnant components of human balance data during a disturbance rejection task.

Methods: Fourteen healthy participants, strapped to an actuated single segment robot with dynamics of upright standing, used natural haptic-visual feedback and myoelectric control signals from lower leg muscles to maintain balance (Fig. 1). An input disturbance applied stepwise

changes in external force. A linear time invariant model (ARX) extracted the delayed component of the control signal related linearly to the disturbance, leaving the remaining, larger, oscillatory remnant component. We optimized model parameters and noise (observation, motor) to replicate concurrently (i) estimated-delay, (ii) time-series of the linear component, and (iii) magnitude-frequency spectrum and transient magnitude response of the remnant component.

Results (mean±S.D., $p<0.05$): NPC produced estimated delays (0.116±0.03s) significantly lower than experiment (0.145±0.04s). There was no significant difference in estimated delay between any of PC, IPC and experiment. Overall fit (i)-(iii) was (79±7%, 83±7%, 84±6% for NPC, PC, IPC). IPC required little or no noise.

Conclusion: The inability to reproduce the experimental delays while fitting concurrently the linear and remnant response, rules NPC out as a viable explanation of this balance task.

Significance: Human balance control requires short-term prediction.

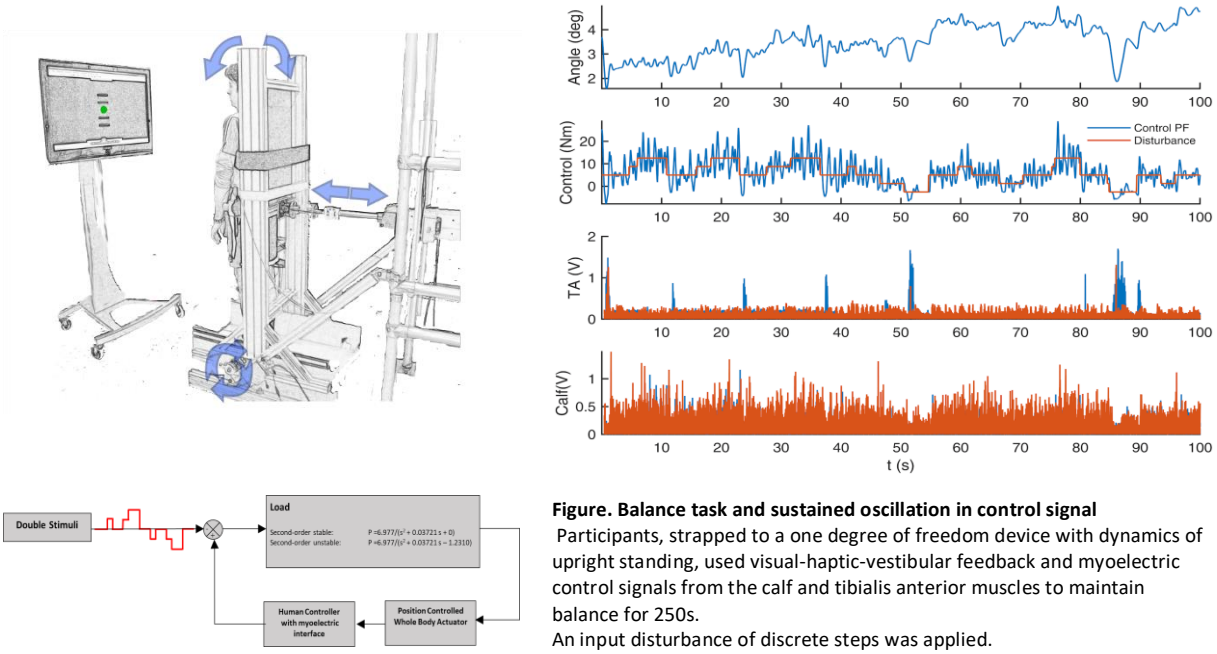

Figure. Balance task and sustained oscillation in control signal
Participants, strapped to a one degree of freedom device with dynamics of upright standing, used visual-haptic-vestibular feedback and myoelectric control signals from the calf and tibialis anterior muscles to maintain balance for 250s.
An input disturbance of discrete steps was applied.
Representative signals v time(s): row 1: forward board angle, row 2: plantar flexion control signal (blue) and forwards disturbance (red), rows 3-4: Tibialis Anterior and calf muscles rectified EMG from both legs.

16:45 Patricia Cambalova, Katie Thompson, Ioana Grigoras, Evan C Edmond, Charlotte J Stagg

Determining the test-retest reliability of controllable pulse parameter TMS (cTMS) metrics

Transcranial magnetic stimulation (TMS), a form of non-invasive brain stimulation, enables us to study the neurophysiology of the primary motor cortex (M1) by recording muscle activity induced by TMS pulses. Controllable pulse parameter TMS (cTMS) is revolutionary as it is the first TMS device that enables the modulation of pulse duration, which may selectively activate distinct neuronal populations1,2. Therefore, cTMS may facilitate breakthroughs in M1 neurophysiology, but its test-retest reliability is yet to be determined.

Here, we investigated cTMS test-retest reliability using a within-subject design, where young healthy participants completed two visits at least a week apart. On each visit, participants had cTMS at three pulse durations and completed reaction time tasks. For each pulse duration, we acquired input-output (IO) curves (Figure 1), describing muscle response changes with pulse intensity, and calculated the IO curve slopes, which reflect cortical excitability. For each duration, interim analysis showed high relative standard errors of the measurement (SEM%) and low intraclass correlation coefficients (ICC) for IO curve slopes, indicating poor test retest reliability.

Simple reaction times showed both low SEM% and high ICC, indicating good test-retest reliability. There were no significant correlations between the IO curve slope and task performance. The current small sample size (n = 7) limits our ability to draw conclusions about the test-retest reliability of cTMS metrics or the neuronal circuits activated by pulses of different durations, but data collection is still ongoing. If proven reliable, cTMS has the potential to inform about neuronal dysfunction patterns in neurological disorders.

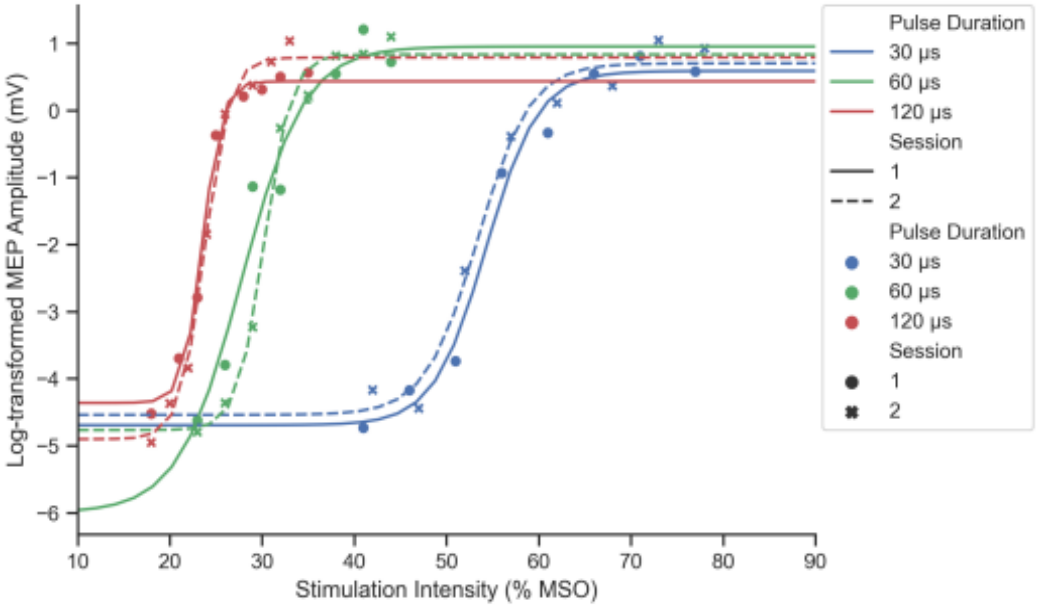

Figure 1: Representative input-output (IO) curves of one subject for pulse durations 30 (blue), 60 (green) and 120 (red) ∝s acquired in session 1 (solid line) and 2 (dashed line). The markers represent log-transformed mean amplitude of motor evoked potentials (MEPs) elicited by TMS pulses of various intensities. MEPs were recorded using electromyography (EMG) and the mean MEP amplitude is calculated from the 10 trials recorded at each TMS pulse intensity. The lines show sigmoid curves of best fit to the mean MEPs.

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17:00 Germann M, Maffitt N, Poll A, Raditya M, Ting SJ & Baker SN

Pairing transcranial magnetic stimulation and loud sounds produces plastic changes in motor output

Most current methods for neuromodulation target the cortex. Approaches for inducing plasticity in sub-cortical motor pathways such as the reticulospinal tract could help to boost recovery after damage. In this study, we paired loud acoustic stimulation (LAS) with transcranial magnetic stimulation (TMS) over the motor cortex in healthy humans. LAS activates the reticular formation; TMS activates descending systems, including corticoreticular fibers. Two hundred paired stimuli were used, with 50 ms interstimulus interval at which LAS suppresses TMS responses. Before and after stimulus pairing, responses in the contralateral biceps muscle to TMS alone were measured. Ten and 20 minutes after stimulus pairing ended, TMS responses were enhanced, indicating the induction of long-term potentiation. No long-term changes were seen in control

experiments which used 200 unpaired TMS or LAS, indicating the importance of associative stimulation. Following paired stimulation, no changes were seen in responses to direct corticospinal stimulation at the level of the medulla, or in the extent of reaction time shortening by a loud sound (StartReact effect), suggesting that plasticity did not occur in corticospinal or reticulospinal synapses. Direct measurements in monkeys undergoing a similar paired protocol revealed no enhancement of corticospinal volleys after the paired stimulation, suggesting no changes occurred in intracortical connections. The most likely substrate for the plastic changes, consistent with all of our measurements, is an increase in the efficacy of corticoreticular connections. This new protocol may find utility, as it seems to target different motor circuits compared to other available paradigms.

Wednesday 22nd June

Presentations - Morning

9:30 Brownson-Smith, R., Orange, S., Saxton, J., Temesi, J

The effect of exercise before and/or during taxane chemotherapy on peripheral neuropathy symptoms, fatigue and quality of life in breast cancer patients: a systematic review and meta-analysis

Introduction: Taxanes are they are among the most neurotoxic substances, with taxane-based chemotherapy often leading to dose-limiting peripheral neuropathy (1). Reviews of literature indicate that exercise at any point throughout and after taxane chemotherapy can improve peripheral neuropathy and quality of life (2). However, a review is yet to be conducted that investigates how exercise only before and/or during taxanes impacts these outcomes.

Objective: The purpose of this systematic review and meta-analysis was to estimate the effect of exercise undertaken before and/or during taxane chemotherapy on peripheral neuropathy symptoms, fatigue and quality-of-life.

Methods: On the 27 September 2021 six databases were systematically searched to identify randomised controlled trials (RCTs) of exercise interventions delivered before and/or during taxane-based chemotherapy for breast cancer. Within the search, three key concepts were used “breast cancer”, “exercise”, “chemotherapy”/”taxane” in addition to their synonyms and controlled vocabulary. Eligible studies required at least one of the following outcomes; peripheral neuropathy symptoms (sensory, motor and autonomic), fatigue or quality-of-life. Participants needed to have a breast cancer diagnosis, be receiving only a chemotherapy regime containing taxanes and be randomised into either a group receiving an exercise intervention before and/or during treatment or control/usual care. Two independent reviewers screened the search results and extracted data from eligible trials. A meta-analysis was performed when the same outcome was assessed in two or more studies. Standardised mean differences (SMDs) with 95% confidence intervals (CIs) were pooled using random effects models. The review was registered via PROSPERO (CRD42021272036).

Results: Six RCTs met the inclusion criteria including a total of 690 participants, with 355 of those being in a control/usual care group and 335 receiving an exercise intervention. A

significant standardized mean difference in CIPN symptoms was found between groups from baseline (SMD; -0.71, 95% CI: -1.24 to -0.17; I2= 76.86%; four RTCs; n=141), in favour of exercise before and/or during chemotherapy, compared with usual care. There was no evidence for an effect of exercise on fatigue (SMD; -0.66, 95% CI: -3.09 to 1.77, I2= 96.2%; three RCTs; n=366 participants) or quality of life (SMD; 0.58, 95% CI: -0.91 to 2.08; I2= 98.25%; two RCTs; n=207 participants).

Conclusion: The findings indicate that exercise before and/or during taxane chemotherapy for breast cancer does have an effect on symptoms of peripheral neuropathy. Therefore, exercise before and/or during a chemotherapy regime may be effective in the management of neurotoxic side effects. However, substantial heterogeneity was consistent throughout the analysis, this may be due to the large amount of variability in exercises performed during the included interventions. Therefore, further investigations into specific exercise protocols with larger sample sizes may further inform the best practices for breast cancer patients.

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9:45 Laura Alvarez Hidalgo & Ian S. Howard

Using a gain scheduling controller with an inverted pendulum as a model of human balancing behaviour

The human brain provides an effective means of stabilizing our posture and balancing the body and objects we hold. To gain theoretical understanding of the control mechanisms involved, here we examine approaches to balancing using an inverted pendulum.

To studying balancing tasks in robotic systems, we describe a new pendulum system that enables us to easily record the position of the cart and the pendulum rod angle to vertical during operation. We designed a controller that operates in two different control modes for two distinct operating conditions; a static cart balancing mode and a moving cart balancing mode. The first mode balanced the pendulum while maintaining the cart stationary at it starting position. The second mode balanced the pendulum while the cart moved at a requested speed. We show both modes of control for the inverted pendulum maintained its balance. However, there was a difference in behaviour in the presence of disturbances between the controller modes. While set up for position control, the system was more responsive and resistant to perturbations than when it was set to velocity control.

We present results of experiments run on the inverted pendulum system. The preliminary results from our initial controller implementations indicate that robust balancing is harder to achieve when the system is in movement than when it is static. In on-going experiments, we will compare these results with how the people performs on similar balancing experiments, to gain insight into the operation of the human sensori-motor system on such tasks.

10:00 Hélio V. Cabral, Giacomo Nardese, Jacques Abboud, Paul Hodges, Deborah Falla, Alessio Gallina

Spatial and temporal characteristic of lumbar pain induced by low-frequency sinusoidal electrical stimulation

Painful electrical stimulation can be used to study motor adaptation to movement-evoked pain. Our aim was to characterize the spatial and temporal characteristics of pain experimentally induced in different lumbar regions using low-frequency sinusoidal electrical stimulation.

Twenty participants (8 females) participated in the study. Low-frequency (4Hz) sinusoidal painful electrical stimulation was delivered to 3rd lumbar vertebra (L3), posterior superior iliac spine (PSIS), and sacrum (with interelectrode distance 1 or 3 cm). For each condition, we gradually increased the stimulation intensity until the participant reported a pain intensity of 3/10, then the stimulation was applied for 60s. Participants reported pain intensity at 5s and every 10s, and indicated on a body chart the area, location and depth of the painful area at the end. Habituation over time, location and depth of the perceived pain were compared between conditions using the Friedman test.

Pain was localized around the stimulation location. Participants reported pain more cranially ($p<0.001$) when stimulation occurred at L3, and more laterally ($p<0.001$) when stimulating the PSIS. Pain was deeper when stimulating the sacrum with electrodes 3cm apart ($p<0.001$). Pain area was similar in the four conditions ($p=0.461$). Habituation occurred faster when stimulating L3 and PSIS (20s, $p<0.01$) than sacrum at 1 or 3cm (50s, $p<0.05$, figure).

Low-frequency sinusoidal electrical stimulation can induce pain in different lumbar regions. Due to the deeper sensation and the stability of pain ratings over time, stimulating the sacrum with electrodes 3cm apart may be the most appropriate setup to study motor adaptation to pain.

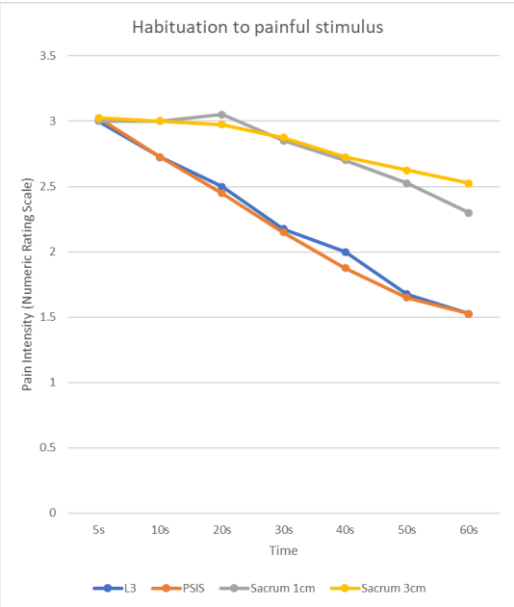

Figure: Habituation of pain ratings over time, N=20 participants. Significant habituation (decrease of reported pain compared to 5s) was identified at 20s for L3 and PSIS, and at 50s for sacrum.

10:15 Sebastian Sporn

Dopamine shaping motor skill learning

Accumulating evidence points to dopamine being involved in both invigorating movements and shaping motor skill learning. However, it is unclear if the same dopaminergic mechanism underlies both aspects of motor control. Recent findings suggest that both are shaped by similar dopamine-mediated computations, whereas others identify distinct dopamine pathways involving different brain areas. Importantly, the role of dopamine to movement vigour and motor skill learning has predominantly been assessed in isolation using different reward structures. This may account for the diverging results seen in the literature. Here we used a complex sequential reaching task in which rewards were based on movement times (MT). Crucially, MTs could be reduces via both: 1) movement vigour related to increased muscular effort and 2) a reduction in dwell times through movement fusion. Movement fusion describes the learning-dependent process of blending discrete movements into skilled, continuous actions. Therefore, this task enabled us to use the same reward structure to simultaneously investigate movement vigour and motor skill learning. 92 participants were randomly assigned to a reward and no reward group and were given either 1.5mg of haloperidol or a placebo. In line with previous work, our results show that reward invigorates performance and that the D2 antagonist haloperidol affects MT irrespective of reward. Importantly, it impaired movement vigour only when reward was available and had no modulatory effect on movement fusion. Thus, we illustrate that whilst both strategies are reward sensitive, they rely on dissociable dopaminergic mechanisms. These results have important implications for understanding dopamine-linked movement disorders.

10:30 **Break – Posters**

11:00 **Keynote talk: Chris Miall**

12:00 **End! Go to the pub!**

Posters

Maria Molina Sanchez

Exploring motor control and representation of an extra robotic finger, following intensive training

Augmentative devices, like extra robotic fingers, have a plethora of potential applications, such as substituting loss of function or assisting in manual labour. But what processes support successful motor control and generalisation of training in motor augmentation? Here we investigated the behavioural motor consequences of intensive training with an extra robotic finger (Third Thumb, by Dani Clode), a 3-D printed prosthesis worn on the right hand and controlled by two pressure sensors underneath the big toes. Participants were trained to use the Third Thumb in a set of sensorimotor tasks over 7 days. Before and after training they completed two different motor tasks, aimed to assess generalisation of training in 1) a regular scenario, where the controllers were under the big toes and the Third Thumb was worn on the right hand. In this scenario participants also completed the tasks under increased cognitive load, and 2) two alternative scenarios in which either the controllers or the Third Thumb were moved to a different body part. Following intensive

training, participants' performance in both motor tasks is predicted to improve for the regular and alternative scenarios. These results will suggest that participants are able to create a motor plan for the toes, integrate the somatosensory feedback from the hand and adapt it to different environments. Thus, they will support the idea an internal sensorimotor model of the Third Thumb is created. Ongoing neuroimaging investigations, using representation similarity analysis, will aim to establish a neural correlate to the behavioural findings.

Edmund da Silva, Lucy Dowdall, Dani Clode, Tamar Makin

Development of a prototype artificial feedback system for a supernumerary robotic finger, the Third Thumb

The Third Thumb (Dani Clode Design) is a supernumerary robotic finger that is worn on the side of the hand. Here, tactile feedback cues are received as a natural by-product of how the device is worn directly on the body. This haptic feedback, known as intrinsic touch, has been relatively underexplored compared to artificial forms of sensory feedback. Therefore, the aim of this project is to develop a prototype artificial feedback system to offer an effective comparison between artificial and intrinsic feedback for the Third Thumb to understand their relative benefits and limitations.

In order to make effective future comparisons between the artificial and intrinsic feedback, the design of the Third Thumb cannot be changed to implement the artificial feedback. The current thumb has a soft tip that improves its ability to grip objects. In the first step to providing artificial feedback, a pneumatic deformation sensor will be developed to replace this soft tip. This will provide a pressure data output when the tip of the thumb is deformed during contact with an object, providing a means for artificial feedback to be delivered to the user.

The artificial feedback will be provided using a high-speed pneumatic system that uses compressed air and soft silicon actuators to achieve vibrotactile feedback. The frequency of vibration of the silicon actuators will be proportional to the pressure sensed on the tip of the Third Thumb. These actuators will be tested on different points of the body to identify the optimum location to deliver this vibrotactile feedback.

Laura-Ashleigh Bird, Jordan Taylor, Tamar R Makin, & Dorothy Cowie

Sensorimotor adaptation: a developmental insight into implicit and explicit contributions to learning

People have a remarkable capacity to behave flexibly, adapting their motor actions to achieve a desired end-goal. To successfully adapt their behaviour individuals must update their internal model of how their motor commands affect the environment. This is achieved by using sensory information to map the updated spatial relationship between the body and the desired target. Whilst historically sensorimotor adaptation was thought to be an implicit process, recent findings suggest adults can use explicit strategies to facilitate this learning process. Despite being studied extensively in adults, our understanding of sensorimotor adaptation in childhood is limited. Here we use a classical error-based learning task in which participants were required to overcome a 45-degree rotation using ballistic reaches. Forty children (5-9 years) and forty adults were split into two conditions: aiming and non-aiming. Before reaching to the target using a digital pen and tablet, participants in the aiming condition were asked to verbally report their aiming direction relative to numbered landmarks. Despite no differences in baseline performance, results showed significant differences between the aiming and non-aiming condition in both adults and children. Participants in the aiming condition showed significantly higher adaptation (adults 49º, children 50º) compared to those in the non-aiming condition (adults 34º, children 28º). However, only participants in the non-aiming conditions showed aftereffects. Arguably this suggests that participants in the aiming condition were reliant on the landmarks and therefore did not update their internal model. Closer inspection revealed that both groups were able to use explicit strategies to facilitate their performance, but children were slower

to adapt and showed less adaptation overall. Further analyses will investigate the developmental trajectory of motor adaption to determine when children's performance becomes adultlike.

Butler, PB; Sakanaka, TE; Rajkowska, N; Cunningham, R; Loram, I

Which clinical test of trunk control in children with neurodisability provides the optimal basis for creation of a quantified assessment?

Background Children with neurodisability such as cerebral palsy (CP) frequently find it challenging to maintain an upright head and trunk posture. This problem increases with the severity of disability and adversely impacts a child's engagement in daily functional activities, such as head control, communication, sitting and feeding. Many clinical tests of trunk control exist but all are qualitative tests leading to an element of subjectivity. A quantified, user-friendly assessment would have the advantage of directing intervention more accurately with measurable outcome. This study was to determine which clinical test provided the optimal basis for creation of a quantified assessment of head/trunk control using a machine learning approach. Method A database (Cochrane Library, Google Scholar and PubMed) search was made to identify existing validated clinical tests that had i) the potential for use with children of all ages (0-18 years), ii) were appropriate for all forms of neurodisability and iii) had no limitations in terms of secondary issues such as poor vision or learning disability. It was also essential that the test had clear specifications amenable to quantification. The search also extended to the test databases held by the physiotherapy professional organisations in the UK, US, and Australasia. Results Five tests were identified: Gross Motor Function Measure2, Trunk Control Measurement Scale3, Trunk Impairment Scale4, Sitting Assessment for Children with Neuromotor Dysfunction5 and the Segmental Assessment of Trunk Control (SATCo)6. Of these, the only test that met all the criteria was the SATCo. It can be used for all age groups and disabilities, does not require a child to understand and follow instructions and does not need prior independent sitting ability. Discussion In addition to fulfilling the criteria defined, the SATCo has the merit that it defines postural control as ability to align head and trunk posture with the gravitational vertical1. It considers the head/trunk as seven discrete segments (head, upper-, mid-, and lower-thoracic, upper- and lower lumbar and full trunk control) and evaluates static, active, and reactive trunk control at each segment. This provides a wealth of information that is not available in the other tests that consider the trunk as a single unit. These factors, together with the specific guidelines for scoring, mean that the SATCo shows the greatest potential in a machine learning context. Work is now in process to create a quantified assessment tool of trunk control suitable for routine clinical use in children with neurodisability, using the SATCo as the basis of this tool.

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L. Lasanudin, C. McCardle, M.A. Savage, A. Kraskov

Morphometrics of the pyramidal tract axons in human and non-human primates.

The corticospinal tract (CST) is known to accomplish a number of different functions potentially due to the wide range of fibre diameters present in the tract as shown by anatomical studies.
Here we re-analysed non-human primate (NHP) light microscopy data from Firmin et al1, using a state of the art deep learning technique2. A 3D convolutional neural net (CNN) was trained on manually segmented images (n=7) denoting axon and myelin regions of interest. The CNN was then applied to the full data set (n=110). This created a cohort of more than

100,000 labelled axons. This is two orders of magnitude larger than original LM dataset where only a small part of each image was analysed due to very time-consuming manual labelling and measuring procedure.
We also analysed human medullary pyramid tissue, obtained from Newcastle Brain Tissue Resource. We showed the standard methods for preserving and storing brain tissue (fresh freezing or formalin-fixed paraffin-embedded), did not maintain intact axon morphology suitable for automatic segmentation and morphometry analysis applied to either light (LM) or electron (EM) microscopy images.
However, our preliminary EM imaging of human medullary pyramid tissue which was specifically fixed and prepared for EM, shows intact axon morphology. This suggests that this protocol may be suitable for automatic segmentation and morphometry analysis. We plan to re-apply the same protocols to human amyotrophic lateral sclerosis (ALS) patient tissue. We will compare CST axons morphometry between ALS and control subjects to identify what features are most affected by disease.

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Anne M.E. Baker, Natalie J. Maffitt, Alessandro Del Vecchio, Katherine M. McKeating, Mark R. Baker, Stuart N. Baker and Demetris S. Soteropoulos

Neural Dysregulation in Post-COVID Fatigue

Following infection from SARS-CoV-2, a substantial minority of people develop lingering after-effects known as ‘long COVID’. Fatigue is a common complaint with substantial impact on daily life, but the neural mechanisms behind post-COVID fatigue remain unclear.
We recruited 37 volunteers with self-reported fatigue after a mild COVID infection and carried out a battery of behavioural and neurophysiological tests assessing the central, peripheral and autonomic nervous systems.
In comparison to age and sex matched volunteers without fatigue (n=52), we show underactivity in specific cortical circuits, dysregulation of autonomic function, and myopathic change in skeletal muscle. Cluster analysis revealed no sub-groupings, suggesting post-COVID fatigue is a single entity with individual variation, rather than a small number of distinct syndromes. Based on our analysis we were also able to exclude dysregulation in sensory feedback circuits and descending neuromodulatory control.
These abnormalities on objective tests may indicate novel avenues for principled therapeutic intervention, and could act as fast and reliable biomarkers for diagnosing and monitoring the progression of fatigue over time.