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FOREWORD

Dear Colleagues,

Welcome to the 10th biennial International Motoneuron Meeting in Istanbul. I wish to thank every one of you who traveled from all around the globe to come over to the Koç University Sarıyer Campus for this meeting. As you know, the meeting and the majority of the related activities are held in the Campus where the vast majority of the participants are also accommodated. This gives us a fantastic opportunity to engage lively discussions to build upon new ideas, novel methods, and also initiate new collaborations.

This meeting has several sessions covering areas from motoneuron and motor unit research in the experimental animals and in human volunteers to disease / injury state that affect motoneurons.

I do hope that the Istanbul experience will be one of your happy memories and also hope that you will come over many more times to see the entire country and experience more of this beautiful land.

I wish to thank many people for putting this meeting together, in particular, Ms Gizem Yılmaz, meeting secretary, for her excellent work in coping with the bombardment of emails and requests; Ms Merve Evren, meeting illustrator, for her beautiful designs which made our posters, signposts, program and abstract book so attractive and professional; Ms Sevilay Akpınar, university contact person, for helping organize many unseen things including the lecture theatre, poster boards, etc. My sincere thanks also go to the members of the international committee for this meeting for their welcome support for putting the program together.

Also, my thanks go to all of our students and colleagues who helped at various stages of the work including Nazlı Başak, Hilmi Uysal, Ali Cenk Aksu, Görkem Özyurt, Ata Berk Demir, Oğuz Sebik, Aslı Aydın. Also thanks to the capable personnel of the School of Medicine including Sermin Karakale, Merve Çiğdem Atsu and Pınar Yazıcı Yaman for their help organizing airport pickups and liquid refreshments. Finally I would like to thank the Rector of this University Ümran İnan and the dean of the School of Medicine Evren Keleş for their generous support for the meeting.

Kemal S. Türker

President of the local committee

20 June 2016, Istanbul, Turkey



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ASIA



Tuesday
21 June 2016

Session 1: Introductory session

Chair: Rob Brownstone

09:00 - 09:30 Elif Vatanoğlu-Lutz Yeditepe University, Istanbul, Turkey

A brief history of medicine and neuroscience in Anatolia

E. Elif Vatanoğlu-Lutz

Yeditepe University School of Medicine, Kayışdağı, Istanbul, Turkey

The aim of this review paper is to provide an overview to the medicine and neuroscience in Anatolia.

Throughout the history, Anatolia (Asian part of Turkey) generated many important figures of neuroscience from numerous civilizations, as well as other major contributions to medicine. Anatolia pioneered both scientific and cultural perspectives during the history of civilization. In order to contribute to today's literature and plan the future projects in medicine and especially in neuroscience, it is important to remember pioneers of the past. The medical history in Anatolia can be divided into ages of Antic, Hittites, Antic Hellenistic, Roman, Byzantium and the period after the Turks had immigrated (Anatolian Selcuklu and Ottoman) to Anatolia.

First doctors had emerged during the Hittites. In the Antic Hellenistic period the diseases were considered with materialistic and rationalistic point of view instead of supernatural causes. After the Anatolia fell under Roman rule many physicians including Galen played leading roles and contributed to medicine. After the Roman Empire had divided into two, Byzantium Empire submerged first hospitals on the world begun to give service.

The Seljuk and Ottoman Period in Anatolia have started various reconstruction activities following their settlement in Anatolia. Within a short period, they built several types of artifacts such as; caravansaries, madrasahs, mosques, darüssifas. Darüssifa is one of the names given to medical and educational establishments which provided health service and treated patients in Turkish and Islamic world. In Seljuk and Ottoman darüssifas, medical subjects were taught according to research and scientific principals and surgeons were educated at medical madrasahs.

The history of neuroscience in Anatolia includes great examples of scientists that increase their knowledge by travelling to different centers in the world. This approach in continuing medical education still remains the most crucial factor in neuroscience.

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Use of different forms of brain stimulation to modulate human corticospinal excitability: a crisis in replication of results

Simon Gandevia
Neuroscience Research Australia
Sydney Australia

Research progress research requires robust findings which are corroborated by others. However, the failure to replicate findings is widespread in the biomedical sciences (e.g. Begley & Ellis, 2012; Nuzzo, 2015). Startlingly, the majority of so-called 'statistically significant' research findings are probably wrong (Ioannidis, 2005). Unfortunately, this issue impacts on our studies of cortical control of motoneurons and muscles. Because we had failed to reproduce some published findings on human motor control with transcranial magnetic stimulation (TMS; Martin et al. 2006) and because we were assured we were not alone, we did an anonymous online survey on the prevalence and causes of these reproducibility difficulties (Héroux et al. 2015). This yielded surprising results from 47 authors in the field (out of 153 approached). Respondents had a range of experience (1 to 30 years) and an average of 16 published papers (95% CI 11–22) that used TMS to modulate motor cortical excitability and hence motoneuronal output. About half the respondents could reproduce published findings but the other half could do this only sometimes or never. Also, many knew researchers who engaged in 'questionable research practices' that increase the false discovery rate (44%; range 30–81%), but fewer respondents admitted to them (18%; range 6–38%), and they went virtually unreported in publications (Héroux et al. 2015). As examples, these practices include selection of subjects, time points, and actual responses. Our on-going analysis of studies using forms of DC stimulation (responses from 154 authors) reveals similar problems with replication as well as evidence of poor research practice. Intrinsic cognitive biases combined with pressure to publish results contribute to this serious problem.

Begley CG & Ellis LM. (2012). Drug development: Raise standards for preclinical cancer research. *Nature* **483**, 531-533.

Héroux ME, Taylor JL & Gandevia SC. (2015). The use and abuse of transcranial magnetic stimulation to modulate corticospinal excitability in humans. *PLoS one* **10**, e0144151 (and PLoS ONE 11(1): e0147890. doi:10.1371/journal.pone.0147890)

Ioannidis JP. (2005). Why most published research findings are false. *PLoS Med* **2**, e124.

Martin PG, Gandevia SC & Taylor JL. (2006). Theta burst stimulation does not reliably depress all regions of the human motor cortex. *Clin Neurophysiol* **117**, 2684-2690.

Nuzzo R. (2015). How scientists fool themselves - and how they can stop. *Nature* **526**, 182-185.

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Advances/problems in our understanding of how motoneurons convert input to output

Hans Hultborn

University of Copenhagen, Denmark

In this review I will discuss a number of factors that control the “input-output” function across individual motoneurons (MNs) as well as a group of MNs comprising a single spinal motor nucleus. The main focus will be on intrinsic properties of individual MNs that can be controlled by neuromodulators. I will start with the 1) transduction of the net synaptic excitation into a frequency code (the MN’s stimulus current-spike frequency relation, as studied by current injection into the soma – and the interpretation of primary, secondary and sub-primary ranges); 2) the reduction of the afterhyperpolarization (AHP) and lowering of firing threshold during e.g. (fictive) locomotion; and not least 3) the amplification of the synaptic input at the MN’s dendritic level by voltage-gated, persistent inward currents (plateau potentials). I will also briefly discuss the effect by changing the threshold differences between MNs within the motor nucleus – a change in the “recruitment gain” – either as a consequence of a non-uniform distribution of synaptic effects to low and high threshold motor units, or as a consequence of central lesions.

NOTE

Session 2: Motoneuron / motor unit properties
Chair: Hans Hultborn

11:30 – 12:00 Rob Brownstone, University College London

Therapeutic Motoneurons?

Rob Brownstone

University College London

While there is plenty of evidence demonstrating the possibility of making “motoneurons” from a variety of cell types, is it possible to use these cells for therapeutic benefit? In this talk, I will explore the good, the bad, and the ugly that we have encountered in our endeavours to move towards translating motoneuron transplantation strategies.

NOTE

12:00 – 12:20 Pascal Legendre, Juliette Boeri and Antonny Czarnecki, CNRS UMR, Paris, France

Persistent sodium current controls motoneuron and Renshaw cell excitability at the onset of synaptogenesis in the mouse embryonic spinal cord

Juliette Boeri¹, Hervé Le Corronc¹, Christine Mouffle¹, Jean-Marie Mangin¹, Pascal Branchereau², Pascal Legendre¹, Antonny Czarnecki¹.

¹NPS, INSERM U1130/CNRS UMR 8246, Paris France

²INICIA, CNRS UMR 5287, Pessac France.

Aim: A remarkable feature of embryonic spinal cord (SC) is its endogenous ability to generate rhythmic spontaneous network activity (SNA) from E12.5 in mice. This activity is due to the presence of an early functional loop between motoneurons (MN) and gabaergic interneurons. Renshaw cell (RC) is the first gabaergic interneuron to directly contact MN at early stages of development. In the present study, we determined to what extent the intrinsic activation properties of MN *versus* RC are correlated to early embryonic SNA by comparing the development of MN and RC excitability from E12.5 to E14.5 (SNA vanishes after E14.5).

Methods: MN and RC were recorded using whole-cell patch-clamp recording in an embryonic SC open-book preparation. SNA was recorded using multiple extracellular recordings.

Results: We found that 27.5 % of MN and 63.8 % of RC fire repetitively in response to current injection at E12.5 being due to the expression of inward persistent sodium current (INaP). Although MN excitability developed in a classical way, RC excitability dramatically decreased between E12.5 and E14.5 due to an increase in potassium currents. Interestingly, at E12.5, 5 μ M riluzole (an INaP blocker) dramatically slowed down SNA whereas it had little effect on the SNA frequency at E14.5.

Conclusion: Our results indicate that INaP expressed by MN and RC plays a transitory role in the control of SNA in the embryonic SC. RC excitability declines with age contrary to MN excitability, suggesting that functional rearrangements occur during early development of the motor networks.

NOTE

Session 3: Neuromodulatory effects on motor output, from mechanisms to functional effects

Chair:

Daniel Zytnicki

14:00 – 14:30 Randall K Powers, University of Washington, Seattle, USA

Distortion of motor commands by motoneuron pool properties

Randall K Powers¹, CJ Heckman²

¹ University of Washington, Seattle, Washington, USA

² Northwestern University, Chicago, Illinois, USA

Aim: Motor commands for muscle force output are comprised of three components: excitation, inhibition and neuromodulatory drive. Our ultimate goal is to infer the time course and relative magnitude of these components based on the discharge patterns of 10 – 30 motor units obtained from multi-electrode surface EMG arrays.

Methods: We developed a pool of model motoneurons that recreates the frequency-current (F-I) and current-voltage (I-V) relations of cat medial gastrocnemius motoneurons. Each model consists of a soma compartment with spike- and AHP-generating conductances, coupled to 4 dendritic compartments with different densities of Cav1.3 channels. Models were tuned to recreate the range of input conductances observed experimentally, along with the relations between input conductance and F-I and I-V behavior. We then ‘recorded’ the models’ responses to slowly increasing and decreasing excitatory conductance commands either alone or in combination with proportional (balanced) or inverse changes in inhibition (push-pull). Total pool output was represented as the average of the smoothed firing rates of all units.

Results: The responses to conductance inputs recreated many of the features of motor unit discharge observed in humans during slowly changing isometric contractions including: 1) a rapid increase in firing rate following recruitment, 2) partial firing rate saturation with further increases in excitation and 3) ‘onion-skinning’, i.e. lower firing rates in later recruited units. The time course of average pool firing rate was a very distorted version of the time course of the excitatory command, particularly for balanced inhibition and for high levels of neuromodulation.

Conclusions: Our results show a remarkable flexibility in the command to EMG transform, which has important implications for understanding to what degree EMG patterns reflect motor command patterns.

NOTE

14:30 – 15:00 CJ Heckman, Northwestern University, Chicago, USA

Gain control in motoneurons, from cellular effects to system outputs

CJ Heckman¹

¹ *Northwestern University, Chicago, Illinois, USA*

Aim: The spinal motoneuron provides the last opportunity for motor commands to modify motor outputs before the signal is sent to muscle. The electrical properties of motoneurons are highly modifiable by brainstem neuromodulatory inputs, with axons releasing either serotonin or norepinephrine having powerful effects. These effects have been well studied over the past 25 or so years. The primary remaining question concerns the functional role of this highly flexible control of motoneuron properties. The aim of this presentation is to consider this question.

Methods: Studies were carried out in human subjects, assessing the impact of drugs that alter the effect of serotonin both positively (re-uptake blockers) and negatively (receptor blockers). The effects of these agents on the tendon tap reflex and the level of noise fluctuations during precise low force tasks were assessed. In addition, preliminary measurements motor unit discharge patterns were made using the delta F method to estimate the contribution of persistent inward currents to motoneuron output at different levels of effort.

Results: The serotonin reuptake blocker lexipro dramatically increased the amplitude of the tendon tap reflex in human subjects with spinal cord injury, while the receptor blocker cyproheptadine dramatically lowered these reflexes. Moreover, lexipro markedly increased motor output noise, while cyproheptadine markedly decreased this noise. These results are consistent with a strong tonic descending input from serotonergic systems in human subjects in the resting state. Finally, in highly preliminary studies, we considered whether increasing effort is associated with increasing gain. To assess this, we used the delta F technique to assess amplitudes of persistent inward currents at low and high efforts levels. The results suggest that the PIC does in fact increase with effort.

Conclusions: The effects of neuromodulators on motoneurons potentially induced several different electrical states, which strongly impact input-output processing. It is possible that variation in the level of brainstem serotonergic and noradrenergic system can be coupled to volition motor commands and provide variable gain control. The potential functional advantages of this gain control will be discussed.

NOTE

15:00 – 15:30 Christopher Thompson, Temple University, Philadelphia, USA

Post synaptic potentials across motoneuron populations in the cat

Thompson CK¹, Johnson MD², Negro F³, Chardon MK², Farina D³, Heckman CJ^{2,4}

¹Department of Physical Therapy, Temple University, Philadelphia PA

²Department of Physiology and ⁴Department of Physical Therapy and Human Movement Sciences, Northwestern University, Chicago IL

³Department of Neurorehabilitation Engineering, University Medical Center, Georg-August University, Göttingen Germany

Aim: Contemporary motor unit approaches are used to describe the mixture of excitatory and inhibitory post synaptic potentials (PSP) across motor unit populations evoked through transient axonal stimulation of surgically isolated cutaneous nerves in the *in vivo* cat model.

Methods: During tonic motor output, either the left sural nerve or a cutaneous branch of the right superficial peroneal nerve are electrically activated with single or brief trains (300Hz, 10ms) provided at ~1Hz through cuff or hook electrodes. Electromyographic activity of the left soleus (Sol) and/or medial gastrocnemius (MG) is collected using 64-channel electrode arrays and traditional fine wire electrodes. Offline, EMG signals are decomposed into corresponding motor unit (MU) discharge times and peristimulus time histograms (PSTH) and peristimulus frequencygrams (PSF) are constructed for concurrently active motor units.

Results: PSP estimates are supported through high levels of rate of agreement with fine wire recordings and similarity of similar evoked responses across trials. The majority of suprathreshold evoked responses contained a bout of excitation, however stark variability in the presence, timing, and magnitude of initial responses is observed across the motor pool. Evoked responses from MG reveal further differences in presynaptic circuitry. Clear discrepancies between probability based estimates of excitability and the PSF approach are observed.

Conclusion: We demonstrate the feasibility and utility of motor unit spike trains in the assessment of the synaptic drive to the motor pool. These data suggest the distribution of cutaneous evoked PSPs is unequal within and across the motor pool.

NOTE

Session 4 - Posters (rest of the afternoon)

Chair: CJ Heckman

Wednesday
22 June 2016

Session 5: Stimulus evoked Post-synaptic potentials in human motoneurons

Chair: Simon Gandevia

09:00 – 09:20 Kemal Türker, Koç University, Istanbul, Turkey

A brief history of the peristimulus frequencygram

Kemal S Türker

Koç University School of Medicine, Sariyer, Istanbul, Turkey

Aim: There are many neuronal circuitries in the nervous system that originate from the peripheral receptors and end in motoneurons that innervate skeletal muscles. The properties of these circuitries are usually investigated in experimental animals. These experiments can be criticized as they use general anaesthetics or work on reduced / decerebrate animals. These experiments are likely to give us erroneous results as the anaesthetics are known to work directly on neurons and affect synaptic transmission between neurons. To study the neuronal networks between the peripheral receptors and the motoneurons, therefore, we have decided to utilize healthy adult human subjects and utilize single motor unit techniques to avoid the general anesthetic and cross talk related issues.

Methods: In these experiments we used healthy adult volunteer subjects who gave informed consents to the experimental protocol. Mechanical stimulation was a computer generated force profile that activated a small mechanical vibrator connected to the area of interest via a probe. Other than the surface EMG that represents gross muscle response to the stimuli, activities of single motor units were also recorded. Subjects were asked to contract the muscle to fire a clearly identifiable motor unit at a fixed rate with the help of audio feedback. When analyzing the results, offline discrimination of the shape of action potentials was performed using pre-established templates. Data were then used to construct peristimulus frequencygrams (PSFs: **1** and **2**) and peristimulus time histograms (PSTHs).

Results: Using the PSF indicated neuronal pathways that were previously unknown. Combined approaches of the PSF and PSTH methods complement each other so that reliable neuronal circuitries that connect peripheral receptors and motoneurons of human skeletal muscles can be discovered.

Conclusions: This study aimed to standardize analysis procedures for the experiments using human motor unit. It indicates that the combined use of PSF and PSTH complement each other and discover previously unknown pathways in human subjects.

References:

1. TÜRKER, K.S. and CHENG, H.B. (1994) Motor-unit firing frequency can be used for the estimation of synaptic potentials in human motoneurons. *Journal of Neuroscience Methods*, 53:225-234
2. TÜRKER, K.S. and POWERS, R.K. (2005) Black box revisited: A technique for estimating postsynaptic potentials in neurones. *Trends in Neuroscience*, 28:379-386

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09:20 – 09:40 Monica Gorassini, University of Alberta, Canada

The use of Peristimulus Frequencygrams to examine sensory activation of motoneurons in health and neurotrauma

*Monica Gorassini,
University of Alberta, Canada*

I will discuss how the firing rate response of single motor units can reflect the profile of excitatory and inhibitory post-synaptic potentials in motoneurons that are activated by sensory inputs. I will review how changes in the membrane potential of the motoneuron are reflected in the firing rate profile of single motor units and how these profiles change in response to both spinal cord injury in the adult and to descending motor tract injury incurred near the time of birth in cerebral palsy.

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Periodontal and muscle spindle pathways to the trigeminal motoneurons

Gizem Yılmaz¹, Paulius Uginčius², Kemal S Türker¹

¹Koç University School of Medicine, Sariyer, Istanbul, Turkey

²Institute of Physiology and Pharmacology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania

Aim: In feedback control of mastication, the sensory input from the periodontal mechanoreceptors (PMRs) and the muscle spindles was investigated previously on anesthetized animals or on humans using the probability based methods such as the surface electromyogram (SEMG), peri-stimulus time histogram (PSTH) and raster dots of single motor unit (SMU) spikes. However, probability based methods are subject to errors. In this study we used precisely controlled stimuli to activate PMRs and used local anesthetic (LA) blocks. Furthermore, we compared the classic and the frequency-based methods.

Methods: Twelve consenting volunteer subjects participated in this study. Surface and intramuscular EMG of the masseter was recorded. While a selected motor unit was discharged at a fixed rate (10-25 Hz), 4-N stimuli were delivered to the upper right central incisor either as a tap (rise time of 5 ms (800 N/s)) or as a push (rise time of ~ 100 ms (40 N/s)). Each trial was repeated with local anesthetic block around the stimulated tooth. The probability based (SEMG, PSTH) and the frequency based (PSF) methods used for the analysis of results.

Results: Before local anesthesia, the tap stimuli induced inhibitory reflex; during anesthetic block, the same stimulus induced excitatory and inhibitory reflex responses. The push, however, generated a combination of inhibitory and excitatory responses that disappeared during the local anesthetic block. We found that the frequency-based method was better for indicating the duration of earlier responses and the existence, sign, and duration of later responses.

Conclusions: Current results suggest a new wiring diagram among the PMRs, spindles, and jaw-muscle motoneurons: tap stimulus activates the inhibitory reflex pathway originating from the PMR and the excitatory pathway originating from the jaw- muscle spindles. Push, on the other hand, activates both the inhibitory and the excitatory PMR pathways.

References:

1. TÜRKER, K.S. and CHENG, H.B. (1994) Motor-unit firing frequency can be used for the estimation of synaptic potentials in human motoneurons. *Journal of Neuroscience Methods*, 53:225-234
2. TÜRKER, K.S. and POWERS, R.K. (2005) Black box revisited: A technique for estimating postsynaptic potentials in neurones. *Trends in Neuroscience*, 28:379-386

NOTE

10:00 – 10:20 Utku Ş. Yavuz, University Medical Center Göttingen, Göttingen, Germany

Reflex responses of large populations of motor units as a means to estimate the distribution of afferent input

Utku Ş. Yavuz¹, Francesco Negro¹, Robin Diedrichs¹, Oğuz Sebik², Kemal S. Türker², and Dario Farina¹

¹*Institute of Neurorehabilitation Systems, University Medical Center Göttingen, Göttingen, Germany*

²*Koç University School of Medicine, Sariyer, Istanbul, Turkey*

Aim: We propose and validate a non-invasive method that enables accurate detection of the discharge times of a relatively large number of motor units during excitatory and inhibitory reflex stimulations.

Method: HDsEMG and intramuscular EMG (iEMG) were recorded from the tibialis anterior (TA), during ankle dorsiflexion performed at 10%, and 20% of the maximum voluntary contraction (MVC) force, in 9 healthy participants. The mixed nerve innervating homonymous (for excitatory reflex) or antagonist (for inhibitory reflex) muscle were stimulated with constant current stimuli. In total, 416 motor units were identified from the automatic decomposition of the HDsEMG. The iEMG was decomposed using a state-of-the-art decomposition tool and provided 84 motor units (average of two recording sites). The reflex responses of the detected motor units were analyzed using the peri-stimulus time histogram (PSTH) and the peri-stimulus frequencygram (PSF).

Results: The reflex responses of the common motor units identified concurrently from the HDsEMG and the iEMG signals showed an average disagreement (the difference between number of observed spikes in each bin relative to the mean) of $8.2 \pm 2.2\%$ for 5% MVC, $6.8 \pm 1.0\%$ for 10% MVC, and $7.5 \pm 2.2\%$ for 20% MVC for reflex inhibition; $6.5 \pm 4.1\%$, $12.0 \pm 1.8\%$, $13.9 \pm 2.4\%$ respectively for reflex excitation. There was no significant difference between the characteristics of the reflex responses, such as latency, amplitude and duration, for the motor units identified using either of the methods.

Conclusion: Results indicated that the single motor unit reflex responses can be estimated accurately and non-invasively in relatively large populations of motor units using HDsEMG. This non-invasive approach may enable a more thorough investigation of the synaptic input distribution on active motor units at low force levels. For example, it was also shown within this study that the probability density histogram of the reflex amplitudes had different distribution for bisynaptic reciprocal inhibition and monosynaptic spindle afferent input, most likely due to the differentiated synaptic distribution.

This study was supported by European Research Council (ERC, DEMOVE, No. 267888).

NOTE

Session 6: Motoneurons in spinal cord injury and stroke Chair: Randall Powers

11:00 – 11:20 Jayne Garland, Western University, Canada

Robot-assisted therapy plus repetitive TMS improves motor unit activation post-stroke

Kimberly J Miller¹, Tanya D Ivanova², Alessio Gallina³, Jason Neva³, Lara Boyd³, Carlo Menon⁴, S Jayne Garland²

¹Faculty of Health Sciences and ⁴School of Engineering Science, Simon Fraser University, Burnaby, Canada

²Department of Physical Therapy, Western University, London, Canada

³Department of Physical Therapy, University of British Columbia, Vancouver, Canada

Aim: Repetitive transcranial magnetic stimulation (rTMS) and intensive movement practice individually have been shown to augment motor function post-stroke. We compared the combined effects of robot-assisted active wrist extension movement practice (RW) and rTMS with RW alone on muscle activation and upper-extremity function post-stroke.

Methods: Thirteen participants (>1 year post-stroke) with upper-extremity motor impairment completed 2 training sessions >1 week apart: 1) rTMS+RW, where participants attempted to extend their wrist in the robot, combined with 30 trains of 5Hz rTMS over the ipsilesional primary motor cortex, and 2) Sham rTMS+RW, with RW alone. An abbreviated Wolf Motor Function Test (WMFTa) was administered and wrist extensor muscles were recorded using high-density surface electromyography (HDsEMG) during ramp-and-hold isometric contractions before and after the intervention. Single motor unit (MU) potentials were identified by decomposing HDsEMG using DEMUSE software.

Results: A total of 413 MUs were identified for all participants during both sessions. The recruitment threshold force of the MUs decreased only after rTMS+RW ($p=0.0002$), demonstrating earlier activation of MU in the ramp-and-hold contraction. The WMFTa also improved only after rTMS+RW ($P=0.04$). Modulation of MU discharge rate increased after both types of intervention ($P=0.004$) with no significant difference between conditions.

Conclusions: Motor function and motor unit recruitment were augmented after rTMS+RW, whereas motor unit discharge rate modulation improved with RW practice with or without rTMS. These data are encouraging for use in the rehabilitation of people with moderate to severe arm disability post-stroke.

NOTE

11:20 – 11:40 WZ Rymer, Rehabilitation Institute of Chicago, Chicago, USA.

Neural Origins Of Muscle Weakness In Hemispheric Stroke Survivors

X Hu, WZ Rymer, N Suresh.

Rehabilitation Institute of Chicago, Chicago, Illinois, USA

Aims: Following hemispheric stroke, there is often profound weakness for voluntary movement in contralesional muscles. We have assumed that this weakness results primarily from interruption of corticospinal projections, however disruptions of motor unit recruitment and firing rates may also contribute.

Methods: In 14 hemispheric stroke survivors, we recorded surface electromyogram signals over the first dorsal interosseous muscle using the Delsys sensor array. This array provides high-resolution signals suitable for motor unit decomposition using a template-based algorithm. We recorded EMG signals over a range of isometric forces, providing guidance to subjects through a screen-based cursor display.

Results: We were able to decompose surface EMG signals to provide up to 15 motor units spike trains for each force level generated by the FDI. We estimated recruitment force and mean firing rate for each motor unit train in both impaired and contralateral muscles, examined sequentially.

In unimpaired FDI muscles, the pattern of recruitment and firing rates displayed an onion skin arrangement, in which the first recruited motor units increased firing rates substantially with increases in voluntary force, reaching rates consistently higher than those displayed by later recruited units. In impaired muscles, the onion-skin pattern was greatly disrupted, with many motor units firing in a narrow rate range, regardless of recruitment rank order. There was also clustering of motor unit recruitment onset, with many motor units recruited over a relatively narrow force range.

Conclusions: A precise estimate of the functional impact of these disruptions on muscle force production will depend upon implementation of a model of the FDI motoneuron tool, and on potential changes in muscle fiber properties. Nonetheless it is likely that these motor unit disruptions contribute substantially to muscle weakness.

NOTE

11:40 – 12:00 K.P. Dimintiyanova, J. Wienecke, D.B. Jensen, C.F. Meehan, University of Copenhagen, Denmark.

The time course of axon initial segment plasticity following spinal cord injury in rats.

K.P. Dimintiyanova, J. Wienecke, D.B. Jensen, C.F. Meehan

University of Copenhagen.

We have previously shown that following a complete spinal cord injury the axon initial segments (AISs) of motoneurons below the injury become longer, wider and closer to the soma (Azam et al, Proc. of the Phys. Soc. 2014). This could help to explain the hyperreflexia observed in this model.

In vitro AIS plasticity can occur within 3 hours and is dependent on L-type calcium channel activity. In the in vivo model we are using, however, hyperreflexia does not occur until 3-4 weeks post-transection. Furthermore, others have shown that, acutely following spinal cord injury there is a loss of L-type calcium channel activity which returns by 3 weeks post-injury. We therefore explored AIS plasticity at more acute time points.

We performed complete spinal transections at the S2 level in 7 adult male Wistar rats. 24 hours later the tails showed a flaccid paralysis with no signs of spasticity normally observed at later time points. Immunohistochemistry was used to label Ankyrin G as a marker of AISs and ChAT as a marker of motoneurons. AISs were measured in 3-dimensions and compared to 8 control rats. No significant differences were found between motoneurone AISs in control and spinalized rats with respect to length, distance from cell body and proximal width for both alpha and gamma motoneurons. Distal AISs were, however, significantly wider for both alpha and gamma motoneurons (26 % wider, $P < 0.0001$ and 30% wider, $P < 0.05$ respectively).

Conclusion: The AIS plasticity we have observed at more chronic time points was not observed at more acute time points before the onset of hyperreflexia. This suggests that L-type calcium channel activity is also necessary for AIS plasticity in vivo

NOTE

12:00 – 12:20 Roeland F. Prak, Christine K. Thomas, Marga Tepper, Inge Zijdwind, University Medical Center Groningen, University of Groningen, The Netherlands; University of Miami Miller School of Medicine, Miami, USA

Cortical Activation during a Sustained Maximal Voluntary Contractions with the First Dorsal Interosseous Weakened by Spinal Cord Injury

Roeland F. Prak¹, Christine K. Thomas², Marga Tepper³, Inge Zijdwind¹

¹Department of Neuroscience, University Medical Center Groningen, University of Groningen ²The Miami Project to Cure Paralysis, Department of Neurological Surgery, Physiology and Biophysics, University of Miami Miller School of Medicine, Miami, FL ³Department of Rehabilitation Medicine, University Medical Center Groningen, Groningen, The Netherlands

Introduction: In able-bodied individuals, activity of the primary and secondary motor areas contralateral to the target muscles increased progressively during sustained maximal contractions. However, little data is available on cortical activation during sustained maximal contractions with muscles weakened by spinal cord injury (SCI). A related experiment showed that at the start of a sustained contraction muscle activation was more reduced in SCI participants. We expected that this reduced muscle activation was due to use-dependent reductions in excitability on spinal levels and not due to a decline of cortical activation.

Methods: Seventeen SCI (impairment scale C/D) and able-bodied participants generated brief and sustained (2-minute) maximal contractions (MVC) with the first dorsal interosseous in a magnetic resonance imaging scanner. Force, EMG, superimposed twitches and blood-oxygenated level detection (BOLD) were recorded during the contractions.

Results: Preliminary results showed that the MVC of SCI participants was weaker and MVC-superimposed twitches were larger in SCI participants. Force decline during the sustained contraction did not differ between the two groups. Group analysis of the BOLD data showed activation of contralateral primary and secondary motor areas in both SCI and able-bodied participants. Further analysis of the BOLD data are currently performed.

NOTE

12:20 – 12:40 Bożenna Kuraszkiewicz, Jia-Jin Jason Chen, Hanna Goszczyńska, Maria Piotrkiewicz, Nalecz Institute of Biocybernetics and Biomedical Engineering, Poland and National Cheng Kung University, Taiwan

Bilateral Changes in Afterhyperpolarization Duration of Spinal Motoneurons in Post-stroke Spastic Patients

Bożenna Kuraszkiewicz¹ Jia-Jin Jason Chen² Hanna Goszczyńska¹ Maria Piotrkiewicz¹

¹Nalecz Institute of Biocybernetics and Biomedical Engineering, PAS, Warsaw, Poland

²Institute of Biomedical Engineering, National Cheng Kung University, Tainan, Taiwan

Aim: To compare afterhyperpolarization (AHP) duration of motoneurons (MNs) supplying brachial biceps (BB) at affected and contralateral side of 11 post-stroke patients with AHP estimated in BB on left, non-dominant side of 8 healthy volunteers.

Methods: Motor unit (MU) action potentials trains were recorded by needle electrodes. The after-hyperpolarization (AHP) duration was estimated by the SD-mean method developed in Warsaw Institute.

Results: AHP was estimated for 39 control and 113 patient MNs (64 and 49 from affected and contralateral side, respectively). It has been shown that the estimated AHP duration was significantly longer for patients' MNs supplying BB on the affected side, and the prolongation decreased with patient's age and disease duration. For MNs supplying contralateral muscles dependency on age generally did not differ from the control data, but data scatter was substantially bigger. The dependency of AHP duration on the disease duration, when corrected for the factor of age, have shown values higher than control for the short times after stroke, and lower than control for the longer times. Our results indicate that the spinal MNs on both sides respond to the cerebral stroke very soon with prolongation of AHP duration, which tends to decrease after the accident.

Conclusion: It is conceivable that these changes may be accelerated by the rehabilitation and presumably that is why in the recent study of Mc Nulty et al. the increase in firing rates above control values was consistently observed for the contralateral side. We suggest that the analysis of changes in AHP duration may serve as the indicator of rehabilitation effectiveness.

NOTE

Session 7: Motoneurons in ALS: (rest of the afternoon)

Chair: A. Nazlı Başak

14:00 – 14:20 A. Nazlı Başak, Boğaziçi University, Istanbul, Turkey

The Distinct Genetics of ALS in Turkey

A. Nazlı Başak

Turkey, with its wealthy historical background and unique geography at the southeastern border of Europe, forms a natural bridge between Europe and Asia. The large coastal areas at the Mediterranean Sea and extensive rural parts bordering the Near Eastern countries and the Black Sea make Turkey a rich genetic pool with a high ethnic heterogeneity. In contrast with other European populations, in which family sizes have been decreasing steadily in the last 50 years, Turkey is still very dynamic, with high birth rates and traditionally large kindreds containing several living generations and an impressive number of offspring. Because close consanguineous marriages are still part of the Turkish culture, exceeding 60% in the eastern parts of the country, the number of autosomal recessively inherited forms of diseases is in excess of what is to be expected.

The molecular basis of amyotrophic lateral sclerosis (ALS) has been extensively investigated in several populations; however, a systematic analysis in Turkey has not been reported so far. In this study, we screened 798 ALS patients for mutations, including 202 familial ALS patients from 146 families and 596 sporadic ALS cases. The most common five ALS gene mutations (C9orf72, SOD1, FUS, TARDBP, UBQLN2) together account for 36% of familial ALS in Turkey. Further, exome sequencing in consanguineous families reveals mutations in diverse genes like OPTN, SPG11, DJ1, PLEKHG5, SYNE1, TRPM7, SQSTM1, C19orf12, DNAJB2, ERLIN1 and IGHMBP2, many of them novel. The epidemiology of ALS in Turkey has features representing the pattern seen in other Caucasian populations; however, it has also specific aspects, such as the more complex nature of the disease in molecular and clinical terms. This rich spectrum reflects both the distinct genetic background and the heterogeneous nature of the Turkish population.

NOTE

14:20 – 14:40 Claire Meehan, University of Copenhagen, Denmark

What can we learn from the G127X mouse SOD1 mouse model of amyotrophic lateral sclerosis?

Claire Meehan

University of Copenhagen, Denmark

Amyotrophic lateral sclerosis is a neurodegenerative disease preferentially affecting upper and lower motoneurons. The most commonly used animal models of this disease have been the SOD-1 mutants, in particular the G93A. These mice have been used by other labs to study excitability levels of spinal motoneurons to explore a role for a hypo/hyperexcitability of the motoneurons to explain their vulnerability.

We have conducted a number of experiments over the years on an alternative SOD-1 mutant- the G127X SOD1 mouse which I will review. This mutant protein lacks enzyme activity and is unstable so rapidly degraded resulting in low expression levels. Despite this these mice develop a severe disease phenotype with a relatively long time to symptom onset (approximately 250 days old), followed by a rapid progression (around 1 week). This offers clear advantages for studying progressive changes related to symptom onset.

In vivo recordings in this mutant at adult presymptomatic mutants have shown that the motoneurons at this time point display normal intrinsic properties (Meehan et al 2010). Unlike the G93A mutant, the neurons show no impairment in repetitive firing despite slightly shorter axonal initial segments (Bonnievie et al 2012). This may be a result of the longer presymptomatic period. Increased L-type calcium channel activity is however increased (Meehan et al. 2010a). At symptom onset however, the axon initial segments now increase in size with accompanying electrophysiological correlates (Jorgensen et al 2015). Remarkably, most motoneurons are still capable of repetitive firing with normal I-f slopes. Immunohistochemistry of the nodes of Ranvier, however, show a severe disruption of the paranodal /juxta-paranodal boundaries consistent with axonal degeneration (Maglemose et al in prep). This is present even in presymptomatic mice suggesting the problems are starting distally.

NOTE

15:40 – 16:00 Marcin Bączyk, Paris Descartes University, CNRS, Paris, France

Monosynaptic excitatory inputs to spinal motoneurons are depressed in SOD1-G93A mice, model of amyotrophic lateral sclerosis

Marcin Bączyk, Marin Manuel, Clémence Martinot, Nicolas Delestrée and Daniel Zytnicki

Center for Neurophysics, Physiology and Pathology (UMR 8119), Paris Descartes University, CNRS, Paris, France

Aim: In ALS, dysfunction of the excitatory amino-acid transporter 2 in astrocytes could lead to a toxic accumulation of glutamate in the synaptic cleft of excitatory synapses. Here we investigated whether this alters the size of EPSPs in motoneurons in a mouse model of ALS.

Methods: Experiments were carried out on P45-55 SOD1-G93A mice (mSOD1) before degeneration onset and on their controls (wtSOD1 mice). Mice were deeply anesthetized with pentobarbital sodium, artificially ventilated and curarized. Intracellular recordings of triceps surae (TS) motoneurons allowed recording monosynaptic EPSPs from proprioceptive Ia afferents and from descending mediolateral funiculus (MLF).

Results: Ia monosynaptic EPSPs are significantly reduced in mutant mice compared to controls whether Ia EPSPs were induced by muscle vibration or by nerve electrical stimulation. Similarly, descending monosynaptic EPSPs from MLF were significantly reduced in mSOD1 compared to wtSOD1. The resting membrane potential of motoneurons and their input resistance were unchanged. Some motoneurons were also intracellularly filled with neurobiotin, and VGlut1 (excitatory proprioceptive inputs) and VGlut2 (other excitatory inputs) boutons were immunostained. The density (VGlut1, VGlut2) and size (VGlut1) of these boutons, on both soma and dendrites, was unchanged in mSOD1 compared to wtSOD1 mice. This indicates that the reduction of the EPSP size is not caused by neuroanatomical alterations, but rather by an impairment of the synaptic function.

Conclusions: We conclude that excitatory synapses to motoneurons are depressed in SOD1-G93A mice before the degeneration onset of the most vulnerable motoneurons. The fact that both proprioceptive and descending inputs are depressed points towards a postsynaptic mechanism.

NOTE

16:00 – 16:20 L. Martinez-Silva, CNRS / Univ. Paris Descartes, Paris, France

Excitability of adult spinal motor neurons in the fus-p525l model of amyotrophic lateral sclerosis (ALS)

*L. MARTINEZ-SILVA, D. ZYTNICKI, *M. MANUEL*

UMR 8119, CNRS / Univ. Paris Descartes, Paris, France

Aim: Alterations in motoneuron excitability have been reported in ALS, where excitotoxicity, due to a hyperexcitable state, has long been suspected as a disease mechanism. However, studies in mutant SOD1-G93A mice, show evidence that spinal motoneurons are not intrinsically hyperexcitable, and that the Fast-type motor units (MUs) are affected before their muscle fibers become denervate. In this context, the aim of this study is to analyze the excitability of motoneurons in a novel model of ALS, the FUS-P525L mouse, around the time of muscle fiber denervation.

Methods: Intracellular in vivo recordings of motor units from ankle extensor muscles (TS-MUs), and ankle flexor muscles (DP-MUs) in adult FUS-P525L mice.

Results: The excitability of motoneurons from both TS-MUs and DP-MUs is diminished at P180, where a larger proportion of motoneurons (mostly in FF and FR subpopulations) are incapable of firing repetitively in response to stationary inputs in mutants (43%) compared to controls (24%). The electrophysiological properties of the motoneurons that still fire repetitively at this age in TS-MUs and TA-MUs in FUS-P525L mice are not statistically different (Mann–Whitney U test) from their control counterparts.

Conclusions: Our results suggest that motoneuron hypoexcitability is a hallmark during the pre-symptomatic phase of ALS. However, a large portion of motoneuron is also incapable of repetitive firing at P180 in WT mice, which implies that this behaviour could be partly due to the normal aging process. For this reason experiments on younger mice (about P30) are under investigation.

The authors would like to acknowledge Neil Shneider

NOTE

16:20 – 16:40 Anton Filipchuk, Fanny Gaudel, Cécile Brocard, Sylvie Liabeuf, Jacques Durand, CNRS-AMU, Institute of Neurosciences Timone, Marseille, France

Early pathological signs in presymptomatic motoneurons in ALS transgenic mice

Anton Filipchuk, Fanny Gaudel, Cécile Brocard, Sylvie Liabeuf, Jacques Durand

Institute of Neurosciences Timone (INT) UMR 7289 CNRS-AMU 27 Bd Jean Moulin 13005 Marseille France

ALS pathology takes place very early in motoneurons in the standard transgenic mouse model of the disease. These transgenic mice carrying a superoxide dismutase 1 (SOD1) mutation develop hindlimb paralysis and died from respiratory failure after several months of “apparently” normal life. However changes in excitability and dendritic morphology of motoneurons occur very early during the postnatal period. In this work we aim to determine whether a specific population of motoneurons is affected in SOD1 neonate mice. In normal mice, we recently classified spinal motoneurons into three types according to their discharge firing patterns (transient, delayed onset, sustained). In the present work we found that, in SOD1 mice, motoneurons develop more dendritic branches in the three groups. However motoneurons with sustained firing type have the greatest dendritic extensions suggesting differential compensatory growth in SOD1 motoneurons. The delayed onset firing group, corresponding to the largest motoneurons (having the highest rheobase and the lowest input resistance) was the most affected group in SOD1^{G93A-low} mice. The gain (F/I curves as measured in the steady state) and the rheobase significantly decreased in this group whereas both electrical parameters remain unchanged in the sustained firing type. This strongly suggests that the delayed onset firing subtype of motoneurons become hypoexcitable very early in neonate SOD1 mice. In the SOD1^{G93A-high} mice, we found that the sustained firing group exhibited a higher gain at the second postnatal week explaining some discrepancies between different studies. We propose that the hyperexcitability of this subgroup of motoneurons may reflect a compensatory mechanism to balance the hypo-excitability measured in the largest SOD1 motoneurons at an earlier stage.

NOTE

16:40 – 17:00 Vibhu Sahni , Sara J. Shnider, Denis Jabaudon , Janet Song, and Jeffrey D. Macklis, Geneva University Hospital, Geneva, Switzerland

Molecular development of corticospinal connectivity: Implications for organization of motor control circuitry and motor neuron disease

Vibhu Sahni¹, Sara J. Shnider¹, Denis Jabaudon^{1,2}, Janet Song¹, and Jeffrey D. Macklis^{1†}

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² Current address: Department of Basic Neurosciences, University of Geneva, and Clinic of Neurology, Geneva University Hospital, Geneva, Switzerland

The corticospinal system is the principal motor system for controlling movements that require the greatest skill and flexibility. It originates with corticospinal motor neurons (CSMN) that reside in the cerebral cortex and extend axons to the brainstem and spinal cord, forming the corticospinal tract (CST). For precise motor control, CSMN axons must specifically target distinct segments – from brainstem, to cervical, thoracic, and lumbar spinal cord. The molecular basis for this segmentally specific connectivity is unknown.

CSMN degeneration in motor neuron diseases (MNDs) such as amyotrophic lateral sclerosis (ALS) causes spasticity and paralysis. However, MNDs do not affect all CSMN equally. In bulbar forms of ALS, for instance, CSMN projecting to the brainstem degenerate, causing craniofacial weakness and spasticity, while in hereditary spastic paraplegia (HSP), lumbar-projecting CSMN degenerate, causing leg weakness and spasticity. The basis for this heterogeneity in different MNDs is unknown.

We isolated functionally distinct CSMN subpopulations during development – bulbar-cervical-projecting (CSMN_C) and thoraco-lumbar-projecting (CSMN_L) CSMN – and identified differentially expressed genes between them. Using this approach, we identified novel controls that direct CSMN axons to appropriate spinal levels – bulbo-cervical extension and innervation by CSMN_C and thoraco-lumbar extension and innervation by CSMN_L. Together, these controls constitute new mechanisms directing CSMN axonal targeting, the first for any spinal-projecting motor pathway. These results lay the foundation for investigating the development and regeneration of precise corticospinal circuitry. Additionally, these data identify potentially novel mechanisms underlying vulnerability of specific CSMN subtypes in MNDs.

NOTE

17:00 – 17:20 Pembe Hande Ozdinler, Northwestern University, Chicago, USA (via Skype)

Understanding the cellular and molecular basis of upper motor neuron vulnerability in ALS

P. Hande Ozdinler

Northwestern University, Chicago, USA

Upper motor neurons have a unique ability to collect and integrate cerebral cortex's input, which is required to initiate and modulate voluntary movement. Their degeneration has an immense impact on motor neuron circuitry, leading to paralysis in hereditary spastic paraplegia (HSP) and primary lateral sclerosis (PLS) patients. In addition, progressive degeneration of cortical and spinal motor neurons is characteristic of amyotrophic lateral sclerosis (ALS). Therefore, upper motor neurons are clinically relevant and important neuron populations that require attention. Understanding cellular and molecular mechanisms responsible for their vulnerability is required to bring a mechanistic insight for their selective vulnerability and progressive degeneration, and to build effective and long-lasting treatment strategies. We have generated novel tools and model systems in an effort to shed light onto these neuron populations that are limited in numbers and embedded within the complex structure of cerebral cortex. Our ongoing efforts began to reveal cellular events that occur very early in the disease as well as canonical pathways and protein networks that become primarily affected as disease progress. Our findings not only suggest novel targets for future treatment strategies, but also reinforce the importance of their health for building effective solutions to the motor neuron diseases.

NOTE

Thursday
23 June 2016

Session 8: Motoneurons in general

Chair: Monica Gorassini

*09:00 – 09:20 Mouloud Bouhadfane, Frédéric Brocard, Jacques Durand, CNRS-AMU,
Institute of Neuroscience Timone, Marseilles, France*

A review of 40 years of NMDA receptors in motoneurons: where, when and why?

*Mouloud Bouhadfane, Frédéric Brocard & Jacques Durand
Institute of Neurosciences Timone (INT), P3M team, UMR 7289 CNRS-AMU 27 Bd Jean Moulin
13005 Marseille France*

In vertebrates, N-methyl-D-aspartic acid (NMDA) receptors are present on most neonate and adult motoneurons. In neonate, their role in the growth of motoneurons has been well established as well as their participation to synaptic and rhythmic activities in spinal cord and brainstem. However their precise function in motoneurons is not well understood. At the motoneuronal level, NMDA receptors have been masked for a long time by several factors or parameters including experimental conditions. For example, NMDA oscillations are sensitive to temperature, expressed at temperature $> 28^{\circ}\text{C}$ in neonate rodents. In adult animals, they have been detected at the Ia synapse between proprioceptive primary afferents and spinal motoneurons. They are also present at the synapse between motoneurons and renshaw cells. However their role at the different sites is not determined. Indeed endogenous NMDA oscillations were recorded in both spinal cord and brainstem motoneurons. In some spinal motoneurons, membrane potential can switch from oscillations to bistable state with stabilization at a depolarized level for several seconds. In adult animals the involvement of NMDA receptor in signal amplification and dendritic integration has been investigated in different species. Multistable state and plateau properties induced by NMDA receptor activation will be discussed in relation with processing information in the different dendritic arborizations of motoneurons. Here I'll summarize the main findings obtained with NMDA receptors activation in neonate and adult motoneurons with special attention on oscillations and bistable state.

NOTE

The role of SK channels in initiating motoneuron bursting in the spinal cord

Amr Mahrous, Sherif Elbasiouny

Department of Neuroscience, Cell Biology and Physiology, Wright State University, Dayton, Ohio, USA.

Aim: Motoneuron bursting activity in the spinal cord represents the basis for generating motor behaviors. To generate this wide range of behaviors, the motor output of the spinal cord has to be graded and patterned in several ways. The rhythmic left-right alternating bursting, known as fictive locomotion, is one of the most intensely characterized behaviors in the spinal cord. However, other motor behaviors which require synchrony between both sides of the body, such as hopping, remain poorly understood.

The small conductance Ca^{2+} -activated K^+ channels (SK channels) are major regulators of repetitive firing in motoneurons. Recent studies showed that cholinergic modulation of SK channels is involved in regulating fictive locomotion. We attempted to study the role of SK channels in generating synchronized bursting activity in the spinal cord.

Methods: We used the in vitro sacral cord preparation from adult mice. This region of the adult spinal cord can be reliably maintained in vitro for several hours. In addition, the preparation allows for different pharmacological manipulations of the SK channels. Synchronized bursting activity was induced pharmacologically and the motor output was measured from both the ventral roots as well as single motoneurons.

Results: Using multiple approaches, we showed that SK channel inhibition initiates synchronized bursting in the disinhibited spinal cord. In addition, we were able to change the burst amplitude in a dose-dependent fashion using a direct antagonist of the channel as well as physiological inhibition through the muscarinic receptors.

Conclusions: Inhibition of SK channels is critical to induce synchronized bursts in the spinal cord, and the availability of SK channels contributes to grading the amplitude of the motor output.

NOTE

09:40 – 10:00 Anna Kaczmarek, Svenja Schneider, Laura Torres-Benito, Vanessa Grysko, Aaradhita Upadhyay, Markus Riessland, Kathryn J. Swoboda, Brunhilde Wirth; University of Cologne, Germany; The Rockefeller University and Massachusetts General Hospital for Children, USA

SMA modifier MOD2 improves motor neuron length and neuromuscular junction size

Anna Kaczmarek¹, Svenja Schneider¹, Laura Torres-Benito¹, Vanessa Grysko¹, Aaradhita Upadhyay¹, Markus Riessland², Kathryn J. Swoboda³, Brunhilde Wirth¹

¹Institute of Human Genetics, Institute for Genetics and Center for Molecular Medicine Cologne, University of Cologne, Germany, ²Laboratory of Molecular and Cellular Neuroscience, The Rockefeller University, New York City, USA, ³Massachusetts General Hospital for Children, Boston, USA

Spinal muscular atrophy (SMA) is a common recessive neuromuscular disease caused by reduced levels of survival motor neuron (SMN) protein leading to degeneration of spinal motor neurons (MNs). Homozygous *SMN1* deletions and 1-4 copies of *SMN2* copy gene lead almost inevitably to SMA, except rarely when individuals remain lifelong asymptomatic.

We identified reduced MOD2 expression in five asymptomatic individuals carrying homozygous *SMN1* deletions. MOD2 is a neuronal calcium sensor protein. MOD2 suppression restores axonal length of MN-like cells and SMA zebrafish model. Moreover, MNs derived from SMA-*Mod2*^{KO/wt} mouse embryos showed significantly longer axons than SMA MNs. SMA-*Mod2*^{KO/wt} mice showed unchanged mean survival, although few mice survived >20 days. The mean weight of SMA-*Mod2*^{KO/wt} mice was increased. We observed larger AChR clusters at neuromuscular junctions (NMJ) of the *Transversus abdominis* muscle from PND10 SMA-*Mod2*^{KO/wt} mice. Based on our in vitro evidence of impaired endocytosis in SMA MN-like cells, we analyzed the endocytotic FM1-43 dye uptake upon electrical stimulation at NMJ. The FM1-43 uptake was reduced in SMA NMJs and elevated to control levels in SMA-*Mod2*^{KO/wt} NMJs. Despite improved NMJs, muscle fiber size and motoric abilities were not improved upon MOD2 reduction. Taken together, our data show that MOD2 reduction positively affects MN development and function in SMA mice, but is unable to rescue the severe SMA phenotype – possibly due to impairment of other organs. Therefore, a milder SMA model more closely resembling the human phenotype is required.

NOTE

Session 9: Motoneurons and sports sciences

Chair: Inge Zijdewind

10:30 – 10:50 Piotr Krutki, Włodzimierz Mrówczyński, Marcin Bączyk, Dawid Łochyński, Jan Celichowski, Poznan University of Physical Education, Poland

Adaptations in electrophysiological properties of motoneurons after weight-lifting training in rats

Piotr Krutki¹, Włodzimierz Mrówczyński¹, Marcin Bączyk², Dawid Łochyński², Jan Celichowski¹

¹ Department of Neurobiology, Poznan University of Physical Education, Poland

² Department of Motor Rehabilitation, Poznan University of Physical Education, Poland

Aim: Long-lasting resistance training, with repeated short-term and high-intensity exercises, is responsible for an increase of muscle mass and force, however particular types of motor units respond differently to this kind of training. The aim of this study was to determine whether such training induces adaptations in electrophysiological properties of motoneurons innervating the trained muscles.

Methods: The study was performed on adult Wistar rats. Animals from the training group were subjected to a five-week voluntary progressive weight lifting program, while control rats were restricted to standard cage activity. Intracellular recordings from spinal MNs were made under pentobarbital anaesthesia. Passive and threshold membrane properties were measured, and rhythmic firing of MNs was analyzed.

Results: 5-week weight-lifting training evoked adaptive changes in either fast or slow-type motoneurons. A shortening of the rise time of action potentials, an increase of input resistance, an increase of the maximum frequencies of rhythmic firing, and an increase in the slope of the frequency-current relationship were observed. Moreover, an increase in the input resistance and a decrease in the minimum currents required to evoke rhythmic firing were noticed in fast-type motoneurons only.

Conclusions: The study indicates higher excitability of fast-type motoneurons, and higher susceptibility of either fast or slow-type motoneurons to an increased or decreased intensity of stimulation in response to the training. Higher maximum firing rates of MNs as well as higher discharge frequencies evoked at the same level of membrane depolarization imply higher levels of tetanic forces developed by motor units.

Supported by the National Science Center grant 2013/11/B/NZ7/01518.

NOTE

10:50 – 11:10 Jan Celichowski, Dawid Łochyński, Dominik Kaczmarek, Włodzimierz Mrówczyński, Wojciech Warchoń, Joanna Majerczak, Janusz Karasiński, Michał Korostynski, Jerzy Zoladz, Poznań University of Physical Education, Poland and University School of Physical Education, Kraków, Poland

Contractile properties of motor units and expression of myosin heavy chain isoforms in rat fast muscle after weight-lifting training

Jan Celichowski¹, Dawid Łochyński¹, Dominik Kaczmarek¹, Włodzimierz Mrówczyński¹, Wojciech Warchoń¹, Joanna Majerczak, Janusz Karasiński, Michał Korostynski, Jerzy Zoladz

¹Department of Neurobiology, Poznań University of Physical Education, Poland,

²Department of Muscle Physiology, University School of Physical Education, Kraków, Poland

Aim: Dynamic resistance training increases the force and speed of muscle contraction, but little is known about modifications to the contractile properties of the main physiological types of motor units (MUs) which contribute to these muscle adaptations. Although the contractile profile of MU muscle fibers is coupled to myosin heavy chain (MyHC) protein expression, it is not well understood if MyHC transition is a prerequisite for modifications of MU contractile characteristics.

Methods: MU contractile properties, the mRNA expression of MyHC, parvalbumin, and sarcoendoplasmic reticulum Ca²⁺ pump isoforms, as well as the MyHC protein content after 5 weeks of volitional weight lifting training were studied in rat medial gastrocnemius.

Results: The training had no effect on MyHC profiling or Ca²⁺ handling protein gene expression. Maximum force increased in slow (by 49%) and fast MUs (by 21%). Within fast MUs, the maximum force increased in most fatigue-resistant and intermediate but not most fatigable MUs. Twitch contraction time was shortened in slow and fast fatigue-resistant MUs. Twitch half-relaxation was shortened in fast most fatigue-resistant and intermediate MUs. The force-frequency curve shifted rightward in fast fatigue-resistant MUs. Fast fatigable MUs fatigued less within the initial 15 seconds while fast fatigue-resistant units increased the ability to potentiate the force within the first minute of the standard fatigue test.

Conclusions: At early stage of resistance training, modifications to the contractile characteristics of MUs appear in the absence of MyHC transition and the upregulation of Ca²⁺ handling genes.

NOTE

Session 10: Motoneurons in Parkinson's disease and Cerebral Palsy

Chair: Claire Meehan

11:10 – 11:30 Jessica M. Wilson, Northwestern University, Chicago, USA

Facilitation of motoneuron excitability in Parkinson's disease

Jessica M. Wilson, Northwestern University, Chicago, USA

While the loss of dopaminergic neurons in the brain is the primary cause of Parkinson's disease (PD), serotonergic and noradrenergic brainstem networks also degenerate early in disease progression (Braak et al. 2003, 2004). The loss of these networks contribute to many of the non-motor symptoms of PD including cognitive deficits, depression, and sleep disturbances (Chaudhuri, 2006) but the effects of monoaminergic degeneration on spinal motoneuron excitability in PD are unknown. My doctoral thesis investigated the hypothesis that spinal motoneuron excitability would be reduced with a loss of serotonin and norepinephrine. However, we found that despite the loss of these neurotransmitters, spinal motoneuron excitability was significantly hyperactive in mild-moderate PD patients OFF-medication compared to control subjects. We used two well-validated measures to assess motoneuron excitability in biceps brachii: the tonic vibration reflex (TVR) and the delta-F calculation for estimating intrinsic excitability (Kiehn & Eken 1996; Gorassini et al. 1998, 2002). We found a facilitated TVR in individuals with PD compared to healthy controls, characterized by an increase in the maximum amount of torque generated during the vibration as well as five seconds after (hangabout). This increase in torque was accompanied by an overall increase in EMG in biceps, triceps and brachioradialis. Within the upper limb of healthy individuals, delta-F values are higher in extensor muscles (triceps brachii) than flexor muscles (biceps brachii). However, delta-F values in the biceps of individuals with PD were found to be nearly double the values found in healthy controls, thus equalizing the flexor/extensor gradient that has been observed in healthy individuals. Based on the increased TVR and delta-F values we've observed, we believe spinal motoneurons in PD are hyperexcitable compared to those in healthy individuals, at least in biceps brachii. The mechanisms behind this paradoxical change in motoneuron excitability are still unknown. One possibility is that spinal reciprocal inhibition is significantly decreased in PD, and that this disinhibition of motoneuron excitability might mask the effects of the loss of monoaminergic drive.

NOTE

Serotonin sensitivity of spinal motoneurons from hypoxia-ischemia rabbit model of cerebral palsy

Katharina Quinlan^{1*}, Alexander Drobyshesky²

¹*Department of Physiology Northwestern Feinberg School of Medicine*

²*Department of Pediatrics NorthShore University HealthSystem, and University of Chicago*

Aim: Serotonin profoundly increases motoneuron excitability. The rabbit hypoxia-ischemia (H-I) model of cerebral palsy shows increased spinal serotonin. Hypertonicity of limb muscles correlated with increased serotonin levels determined by HPLC and more serotonin immunopositive fibers. Blocking serotonin receptors with intrathecal methysergide *in vivo* decreased muscle stiffness of rabbit kits affected by H-I. However, changes in gene expression of 5HT2 receptors and 5HT transporter suggest H-I affected spinal cords could be less responsive to serotonin. This work tested responsiveness of spinal motoneurons to serotonin (specifically 5HT2 receptor agonists) in control and H-I affected rabbit kits.

Methods: Lumbar spinal motoneurons were targeted for whole cell patch clamp in transverse spinal cord slices from control (sham operated and unaffected kits) and H-I affected rabbits at postnatal day 0-5.

Results: Motoneurons from H-I affected rabbits have higher input resistance, larger amplitude after-spike after hyperpolarization (AHP), and smaller current amplitude at firing onset (I-on) than controls. Motoneurons respond to bath perfusion of 0.3uM alpha-methyl-5HT (5HT2 agonist) and 10uM citalopram (selective serotonin reuptake inhibitor) with increased input resistance, reduced I-on and increased AHP duration. Preliminary results show H-I affected motoneurons are less responsive to 5HT2 agonists than controls. However, input resistance, I-on and AHP are all altered in the baseline measurements of control vs H-I motoneurons, suggesting properties of H-I motoneurons are influenced by higher basal levels of serotonin.

Conclusions: Lumbar motoneurons from H-I affected rabbits show baseline properties that align with increased serotonergic tone, and are less responsive to exogenous 5HT2 agonist application. Future work will verify current results and test sensitivity of H-I affected motoneurons to inhibition of serotonergic receptors.

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POSTERS

1. Spontaneous synaptic excitation in spinal motoneurons in an adult mouse model of amyotrophic lateral Sclerosis

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Aim: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by adult onset of its clinic symptoms and selective loss of motoneurons. Glutamate induced excitotoxicity is hypothesized to play an important role in the death of the motoneurons in ALS. However, studies thus far have not found hyper-excitability in the intrinsic properties of motoneurons in an adult ALS mouse model with G93A mutated SOD1 protein (mSOD1^{G93A}). In this study, we conducted a comprehensive investigation on the excitability of the motoneurons in the spinal cord of the adult mSOD1^{G93A} mouse in order to identify any possible abnormality contributing to the excitotoxicity.

Methods: All studies were carried out in an *in vitro* preparation of the sacral spinal cord of mSOD1^{G93A} mice and their non-transgenic littermates with ages between 50 – 90 days. Two recording methods were applied to measure compound action potentials recorded from ventral roots and of synaptic, and intrinsic properties in single motoneurons using intracellular recordings.

Results: The root recordings showed increased responsiveness of the motoneurons to repeated stimulation of the dorsal roots in the mSOD1^{G93A} motoneurons, suggesting increased excitatory synaptic input. The intracellular recording identified an oscillation in excitatory postsynaptic potentials (EPSPs) that is initiated in the spinal network and dependent on the activation of NMDA receptors. The oscillation is more active in the mSOD1^{G93A} motoneurons. No significant changes were found in the fast EPSPs and intrinsic properties in the mSOD1^{G93A} motoneurons in comparison to their non-transgenic littermates. These data suggest an increased excitability in the synaptic properties in adult mSOD1^{G93A} motoneurons.

2. ONWebDUALS: the European project funded by national agencies under the patronage of Joint Programme – Neurodegenerative Disease Research (JPND)

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Aim: Present understanding of the risks factors related to ALS is incomplete, presumably because they have never been integrated with phenotype-genotype patient profiles. The aim of the presented project is to define specific risk factors taking into account the genotype-phenotype background.

Methods: In the frame of the project we have built a standardized patient questionnaire and an ALS domain ontology representing the body of medical knowledge related to this disorder. The ontology will serve as a formal basis for the construction of standardized E-health record of de-identified ALS patients, implemented in a European ALS web-database. The database is intended to include a population of about 3000 patients, derived from the consortium participants and from other European centers. The information on the possible risk factors included in the database will be analyzed to search for causal relationships between individual risk factors and ALS genotype-phenotype.

Results: The project started at March 1st, 2015. The preliminary version of patient questionnaire was accepted in June and its final version, in November 2015. The collection of patients' data is continued since June. The building of ontology is now in advanced stage, which allowed the start of web-database construction ahead of time. At present the preliminary version of web-database is tested with the available patients' data.

Conclusion: The project will be funded until the end of February, 2018. However, we anticipate that the research based on our database will continue beyond this date.

3. The effects of a single session of spinal manipulation on strength and cortical drive in athletes

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Objective: Over the past ten years several research groups have demonstrated that spinal manipulation can change various aspects of nervous system function. The primary objective of this study was to investigate whether a single session of spinal manipulation increases muscle power, strength, and cortical drive and reduces fatigue in highly trained athletes.

Method: Soleus evoked V-wave and maximum voluntary contraction (MVC) of the plantar flexors were recorded from 12 elite Tae Kwon Do athletes using a randomised controlled crossover design. Interventions were either a single session of spinal manipulation or a passive movement control. Outcomes were assessed pre intervention and at three post intervention time periods; immediately post, post 30 minutes, and post 60 minutes. A multifactorial repeated measures ANOVA was conducted to assess within and between group differences. Time and session were used as factors. A priori pairwise comparisons of the pre and post intervention data were carried out when an interactive effect was present. Significance was set at $P \leq 0.05$.

Results: Spinal manipulation resulted in increased maximum force ($p < 0.01$) and V-waves ($p < 0.01$) over time compared to the control intervention. Force and V-Waves increased at all post intervention recordings in the SM group and decreased in the control group. Between group differences were significant for all time periods ($p < 0.05$) except for the post 60 force measurements ($p = 0.065$). There was an $8.65 \pm 8.08\%$ increase in force immediately after SM ($p < 0.01$) and a non-significant decrease of $2.71 \pm 9.60\%$ after the control. V-waves increased by $33.72 \pm 46.29\%$ after SM ($p < 0.01$) and decreased by $13.32 \pm 17.72\%$ after the control intervention ($p = 0.3$).

Conclusion: Spinal manipulation appears to increase strength and cortical drive, and prevent fatigue in highly trained athletes. The strength findings lasted for 30 minutes and the cortical drive increase persisted for at least 60 minutes. Chiropractic care may play a role in enhancing athletic performance. Further research is required to investigate this potential role.

4. The effects of aging on spinal motoneurons in aged C57BL/6J mouse

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We have previously found differences in action potentials/axon initial segments (AIS) in a symptomatic ALS model. How mouse motoneurons age normally however, is unknown. Therefore, we conducted intracellular recording in C57BL/6J mice at different ages (6 at 100 days, 6 at 300-400 days and 6 at 600-750 days).

Action potentials had significantly lower amplitudes in 600-750 day old mice vs. 100 day old mice ($P<0.0001$) with significantly reduced rates of rise ($P<0.005$). Rates of fall were also significantly slower in 600-750 day old mice vs. 100 day old ($P<0.005$) and action potential width were significantly wider. The rate of rise of the IS component was not significantly different at any age.

AHP amplitudes were significantly larger at 300-400 days vs. 100 days ($P<0.05$) but not significantly so at 600-750 days. AHP durations were significantly shorter at 300-400 days ($P<0.05$) vs 100 days but returned to 100 day levels at 600-750 days. These changes appeared not to influence the current-frequency slopes which were not significantly different.

Immunohistochemistry was performed on 6 mice at 300-400 days and 7 at 600-750 days to label AISs and motoneurons with antibodies against Ankyrin G and ChAT respectively. AISs were slightly shorter (approx. 4 %, $P<0.05$) and wider (12%, $P<0.0001$) in the aged mice. Nodes of Ranvier of motor axons in the ventral roots were labeled for KV1.2, Caspr and voltage-gated sodium channels which showed a clear breakdown of the juxtaparanode-paranodal boundary in aged mice.

Conclusions:

The changes related to amplitude/rate of rise of action potentials, and AISs however are opposite to what we have observed in symptomatic ALS mice suggesting these changes do not represent accelerated aging

5. Long latency reflexes obtained from trapezius in the patients with parkinson's disease and cerebellar dysfunction

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Aim: Enhanced long latency reflexes obtained from distal muscles have been observed in many studies in patients with Parkinson's disease (PD) however long latency reflexes obtained from axial muscles have not been evaluated. In this study, long latency reflexes (LLRs) from both distal and axial muscle were evaluated in patients with PD with and without postural dysfunction and in patients with coordination disturbance due to cerebellar disease.

Methods: Thirty-three patients with PD, 9 patients with cerebellar ataxia and 22 healthy volunteers were included in the study. LLRs recorded from ipsilateral thenar and from bilateral trapezius muscles. LLRs of thenar muscles were evoked by the electrical stimulation of ipsilateral median nerve at the wrist. LLRs of trapezius were recorded from ipsilateral and contralateral trapezius muscles by the same stimulation procedure. Latencies and amplitudes of second component of LLRs obtained from thenar and trapezius muscles were analyzed.

Results: In patients with PD, second component of LLR obtained from thenar muscle showed significant shortening in the onset latencies and significant increase in the amplitudes. Mean latency of first component of trapezius-LLR in patients with PD showed significant prolongation. However, in patients with postural dysfunction, absence of first and/or second components of LLR obtained from trapezius was most conspicuous abnormality (50% vs 14.6% for first and 42.9% vs 20.8% for second component). In patients with cerebellar ataxia, LLRs obtained from thenar muscle was normal however long latency reflexes could not be recorded in any patients.

Conclusions: LLRs obtained from distal extremity muscle and axial muscle showed different features in patients with PD. LLRs obtained from trapezius showed most marked abnormality in the patients with postural instability. These responses can reflect the physiology of neural circuits responsible for postural arrangements. Additionally, cerebellar pathways may have a role in the generation of LLRs obtained from trapezius.

6. Slow motor units of rat soleus muscle: sex differences and force summation

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Aim: The study on the rat soleus muscle was performed: 1) to compare contractile properties of slow motor units (MUs) between males and females; 2) to determine effects of the summation of forces generated by several MUs.

Methods: Experiments were performed on adult Wistar rats under general anesthesia. MUs were functionally isolated by electrical stimulation of single axons from the ventral roots of spinal nerves. A mathematical decomposition of tetanic contractions into twitch-shape responses to individual stimuli was performed. Cumulative forces of several co-active MUs were compared to the algebraic sum of the forces of individual MUs.

Results: The contraction time parameters were significantly longer in female MUs. No sex differences were observed in twitch forces, but tetanic forces were twice higher in males. The decomposition of tetanic contractions revealed higher variability between parameters of the decomposed responses for males than for females. Effects of the summation of MU forces of twitches and fused tetani revealed a high degree of linearity. However, relaxation of tetanic contractions was faster than that predicted by the linear summation, and a tendency to shorten relaxation with an increasing number of co-active MUs was noted.

Conclusions: 1) Sexual dimorphism of rat soleus implies several variations in motor control processes that should be taken into consideration while interpreting results of studies performed on males or females. 2) Almost linear summation of soleus slow MUs distinguish this muscle from the previously investigated rat medial gastrocnemius as well as from its feline counterpart.

7. Adaptation of motor units contractile properties to the treadmill endurance training

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Aim: Changes in contractile properties of motor units (MUs) in the medial gastrocnemius (MG) muscle of rat evoked by the treadmill endurance training of variable duration were studied.

Methods: Functionally isolated MUs were electrophysiologically investigated in MG in 4 groups of rats: untrained – control (C) and trained: 2 weeks (2W), 4 weeks (4W) or 8 weeks (8W). The intensity of training increased progressively. Finally, rats from 2W group covered on average a total distance of 5.5 km, 4W - 21 km, 8W - 56 km.

Results: Trained rats had lower body mass in comparison to C. Proportions of MUs were also changed: participation of fast fatigable (FF) MUs decreased, whereas of fast resistant (FR) increased as compared to C. Slow MUs proportion increased only in 8W. The main changes in contractile properties were noted for FR MUs and included: shortening of twitch time parameters, decrease of the twitch-to-tetanus ratio, increase of stimulation frequencies at the steep part of the force-frequency relationship. The fatigue resistance of FR MUs in trained groups as well as ability to potentiate the force of unfused tetanic contractions within the fatigue test increased.

Conclusions: Endurance training evoked an adaptive changes in contractile properties of MUs, mainly of FR type. The first changes appeared within 2 weeks of the training and elicited physiological transformation within fast MUs.

National Science Center grant 2013/09/B/NZ7/02555.

8. A comparison of motor unit size index and muscle strength in elite athletes

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Aim: The importance of the motor unit is basic element in the production of force or movement. Determining the number and size of motor units are studied for the diagnosis of disease and neurophysiological assessment. Exercise-induced skeletal muscle adaptations specially increase muscle force by recruiting more motor units or by increasing firing frequency of motor units are studied for many years. The purpose of this study was to investigate the basis of neural component of increase in muscle strength in elite athletes.

Methods: Twenty six male participants (athlete group n=16, control group n=10) with no neurological disorders or injuries of the lower extremities took part in the study. Their mean \pm SD age, height and body mass were 23.73 ± 4.67 years, 177.80 ± 9.18 cm., 74.53 ± 13.86 kg. Muscle activity was also recorded through surface electromyography electrodes placed on rectus femoris muscle in the dominant leg of all participants. The MUNIX derived from mathematical equations. The compound muscle action potential was evoked by stimulation of the femoral nerve with stimulator (1ms pulse; Medelec Synergy, UK). Surface Interference patterns were recorded 300ms epoch. 5s. leg extension contractions and 5 different levels contractions were recorded. 20s. Rest was allowed between each contraction. Leg extension strength was quantified using force transducer (DATALOGTypeNo.MWW8).

Results: Athletes had significantly ($p=0.01$) greater isometric strength and MUSIX than control subjects. There were no significant difference between groups in MUNIX ($p=0.915$). Also there are a significant difference in ICMUC [define] %75 and %100 maximal voluntary contraction (MVC) between athletes and control subjects ($p=.001$, $p=.005$). There were no significant difference between groups in ICMUC %10MVC and %25MVC ($p=0.274$, $p=0.247$).

Conclusions: The increase of muscle strength that occurred due to training, via neuromuscular components, it was thought that MUSIX to be associated with changes in the strength of elite athletes, determining the size of motor units and involved in a contraction of motor units explained by MUSIX and ICMUC methods.

9. ERLIN1 Mutations as a Cause of Slow Progressive ALS in a Large Turkish Pedigree

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Motor neuron disorders are complex diseases where different gene mutations may result in the same phenotype making clinical diagnosis challenging. The heterogeneity of ALS within itself is also highlighted by the growing list of genes linked to both familial and sporadic forms of the disease. The era of high-throughput sequencing enabled more detailed and sophisticated research in understanding the genetic deformities behind these complex diseases. Identification of ALS genes contributing to other motor neuron diseases like PMA, HSP etc., expanded the concept of ALS and suggested possible subtypes. Here, we report the results of exome sequencing analyses in a large consanguineous Turkish pedigree with four living affected members displaying early onset ALS with slow progression. We performed exome sequencing in three affected and three unaffected members of the family and identified the novel homozygous p.Val94Ala (c.T281C) mutation in the *Endoplasmic Reticulum Lipid Raft-Associated Protein 1* (*ERLIN1*) gene as the possible cause of the disease in the family. We have further validated the segregation of the candidate gene mutation with the disease in a total of 25 members of the family using Sanger sequencing. ERLIN1, implicated in ERAD control, encodes a prohibitin-domain containing protein localized to the ER that forms a ring-shaped complex with ERLIN2. *ERLIN1* has been previously shown to cause pure HSP, however we suggest that *ERLIN1* gene mutations may also contribute to an atypical form of ALS.

10. Exome sequencing coupled with homozygosity mapping is a powerful combination to unravel the genetics of recessively inherited neurological diseases.

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Autosomal recessive forms of ALS are caused by rare homozygous mutations in diverse genes like *OPTN*, *SPG11* and *ALS2* which are not only functionally diverse, but also too complex to be investigated by conventional PCR-based methods. In order to unravel the genetic variations, not detected by conventional techniques, we performed whole exome sequencing analysis. The high consanguinity rates in Turkey helped us to narrow down the candidate mutation list and identify novel mutations by mapping the homozygous segments in the sample data, identical by descent. Variants obtained from WES were used in homozygosity mapping with three different tools: PLINK, H3M2 and HomozygosityMapper. First, we tested the reliability of the above tools using recessive cases in which the causative loci were already known. This enabled us to optimize our own parameters resulting in a better fit with our exome data. Using this optimized method, we were able to identify homozygous mutations in the *c19orf12* and *DNAJB2* genes in four affected families. *C19orf12* mutations, previously shown to give rise to Neurodegeneration with Brain Iron Accumulation 4 (NBIA4), were identified in three pedigrees, mimicking juvenile onset ALS. The homozygous mutation in the *DNAJB2* gene, known to cause distal spinal muscular atrophy or autosomal recessive Charcot-Marie-Tooth Disease Type 2T in literature, was identified in a family with a slowly progressive distal motor neuropathy.. Exome sequencing coupled with homozygosity mapping is a powerful combination to uncover the genetics of recessively inherited heterogeneous motor neuron diseases with difficult differential diagnosis.

11. Blood RNA biomarkers in prodromal park4 and rbd show role of COMPLEXIN-1 loss for risk of Parkinson's disease

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Parkinson's disease (PD) is a frequent neurodegenerative process of old age. Accumulation and aggregation of the lipid-binding SNARE complex component alpha-synuclein (SNCA) underlies this vulnerability and defines stages of disease progression. In view of physiological SNCA roles in blood to modulate vesicle release, we studied blood samples from a large Turkish pedigree with *SNCA* gene duplication (PARK4 mutation), to identify effects of SNCA gain-of-function as potential disease biomarkers. The expression levels of other Parkinson's disease genes were not, but complexin-1 (*CPLX1*) mRNA downregulation was correlated with genotype. In global RNAseq profiling of blood from presymptomatic PARK4, bioinformatics detected significant upregulations for platelet activation, hemostasis, lipoproteins, endocytosis, lysosome, cytokine, toll like receptor signalling and extracellular pathways. Strong *SPP1*, *GZMH*, and *PLTP* mRNA upregulations were validated in PARK4. When analysing cases with REM sleep behaviour disorder (RBD), the most specific known prodromal stage of general PD, only blood *CPLX1* levels were altered. Validation experiments confirmed an inverse mutual regulation of *SNCA* and *CPLX1* mRNA levels. In the 3'-UTR of the *CPLX1* gene we identified a SNP that is significantly associated with PD risk. Our data define *CPLX1* as PD risk factor and provide functional insights into the role and regulation of blood alpha-synuclein levels. The novel blood biomarkers of PARK4 in this Turkish family may become useful for PD prediction.

12. Comparison of homozygosity mapping algorithms and application to recessive ataxias

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Ataxias are a diverse group of genetically heterogeneous neurodegenerative disorders. The significant overlap in the phenotype of patients with different types of ataxia and the manifestation of ataxic features as additional symptoms to other neurological diseases make the precise clinical diagnosis challenging. Thus, after the elimination of common late-onset spinocerebellar ataxias, still a high number of genetically undiagnosed ataxia patients remain. Recent progress in next generation sequencing (NGS) technologies coupled with homozygosity mapping, made the molecular diagnosis of patients with overlapping phenotypes more straightforward. Among these, whole-exome sequencing (WES) enables us, not only to detect the causative mutations in rare genes that cannot be analyzed by conventional methods, but it also characterizes these diseases at genetic level.

In the framework of this study, WES was applied to ataxia patients with a recessive inheritance pattern, along with their family members. Data analysis included homozygosity mapping with three tools: PLINK, H3M2 and HomozygosityMapper. Since these use different algorithms to reduce the target area, we performed an initial check for the optimization of the above tools for reliability on sample data, containing already identified homozygous mutations in consanguineous families. This work flow helped to identify disease causative mutations and genes (*SYNE1*, *SACS*, *SETX*) in five distinct ataxia families with a recessive inheritance pattern. Our findings show the usefulness of the approach which would be universally applicable to other recessive disorders.

13. Modified MUNIX Algorithm for Estimating T Response Motor Unit Number in Spasticity

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Aim: There are several methods for understanding quantitative feature of motor neuron pool in the literature. Motor Unit Number Index (MUNIX) is one of these algorithm and its method based on muscle voluntary contraction. In this way, MUNIX algorithm is widely used in clinics. In our study, MUNIX algorithm was modified for understanding not only quantitative feature of motor neuron pool but also understanding its excitability feature.

Methods: Motor unit numbers of Rectus femoris muscle were calculated by MUNIX algorithm. MUNIX algorithm was modified for calculate the motor unit number that triggered by the force which is applied to the Patellar tendon (MUNIXT). CMAP area and power parameters were changed with T response area and power in the new algorithm. In both cases, the correlation of MUSIX values in both algorithm was examined and high correlation was observed between them ($R=0.886$). For that reason MUNIX was used for verification of modified algorithm.

Results: The mean \pm sd MUNIX was calculated 274.42 \pm 55.33 in normal group and 221.6 \pm 54.42 and in spasticity group. MUNIXT was calculated 33.12 \pm 15.25 in normal group and 130.64 \pm 33.42 in spasticity group. Statistically significant difference was found in MUNIXT ($p<0.001$). Excitability percentage of motor unit pool is %14 \pm 7 in normal group and %56 \pm 12 in spasticity group.

Conclusions: It is known that there is a significant decrease in M responses while T responses decrease in spasticity. Our study indicates that, enhancement of T response is related with motor unit numbers which are triggered by reflexes. With this way, it can be helpful to explain the increasing excitability of motor neuron pool in spasticity.

14. Investigation Of Motor Unit Number And Size Index Of Rectus Femoris Muscle In Cerebral Spasticity

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Aim: Spasticity is a motor impairment due to lesions in the brain and spinal cord. The relation between M responses and reflex response changes due to the excitability of motor neuron pool is not known exactly. It is reported that M response amplitudes in spasticity are lower than the average of normal subjects. Motor neuron number estimation techniques is one of the methods for assessing motor neuron pool and MUNIX is the most suitable method for proximal muscles. In this study, M response amplitudes, MUNIX and MUSIX are examined in spasticity group and normal subjects.

Methos: The cerebral spasticity group consisted of 12 patients and normal group consisted of 12 individuals. EMG recordings were made using a Synergy EMG device and analysis were performed in MATLAB. Muscle activity was recorded through surface electromyography electrodes placed on Rf and Bf muscles. MUNIX and MUSIX were calculated in MATLAB.

Results: The mean±sd values of M responses was measured 21.71±4.24mV, MUNIX was calculated 274.42±55.33 and MUSIX was calculated 43.28±6.62 uV in normal group. The mean±sd values of M responses was measured 16.73±3.67mV, MUNIX was calculated 221.6±54.42 and MUSIX was calculated 37.00±6.49 uV in spasticity group. There were significant differences between groups in MUNIX, MUSIX and M responses (respectively, $p<0.01$, $p<0.05$, $p<0.05$).

Conclusions: There is a significantly decreasing in MUNIX and MUSIX for Rf muscle in spasticity group. These findings support the idea that there can be changes in the motor neuron pool in spasticity. Also these findings suggesting that there can be relation between the changes in the excitability and quantitative of motor neuron pool.

15. Spinal manipulation increases maximum bite force in healthy individuals

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ABSTRACT

Objectives:

Motor control of the jaw may be affected by disorders of the spine and nervous system. If chiropractic care alters sensorimotor integration and motor control it may have an impact on the function of the muscles of mastication. The aim of this study was to understand the influence of chiropractic care on total maximum bite force.

Methods:

Thirteen participants (age 18-65 years) with subclinical pain were recruited from the faculty and students at Koç University in Turkey to participate in this randomized controlled crossover trial. Maximum bite force was measured before and immediately after a session of chiropractic care consisting of spinal manipulation of dysfunctional joints, or a sham control session that involved passive movement but no spinal manipulation. Participants were randomly assigned to receive the chiropractic or control intervention first, and there was a 1 week washout period between interventions. Repeated measures ANOVA was used to compare data between the 2 sessions. Post-hoc t-tests were used to compare within and between group differences when a significant group by time interaction was found.

Results:

There was a significant effect of the chiropractic intervention compared to the control intervention on maximum bite force [$F(1,12)=5.09, p<0.043$]. Maximum bite force increased by an average of 11.0% (S.D. 18.6, $p=0.038$) following the chiropractic intervention and remain unchanged following the control intervention (0.2% increase, S.D. 7.4%, $p=0.88$). There was no significant difference in maximum bite force between baseline recordings ($p=0.44$).

Conclusions:

The results of this study suggest that a single session of chiropractic care increases maximum bite force in healthy individuals. Further studies are now required to better understand the underlying mechanism for this change and to investigate whether chiropractic care may play a role in improving motor control in the muscles of mastication in individuals who have disorders of the stomatognathic system.

16. Local cohort and population-specific alternative allele frequencies help drastically reduce the number of false positive variants

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Abstract

The importance of allele frequency in population genetics and association mapping has pushed for large international genomic sequencing initiatives which aimed to determine the genetic diversity within different human populations. Although such efforts have proved to be useful, there is still a lot to be done, especially in the case of large and heterogeneous populations, as in the case of Turkey. The high error rate and cost of next generation sequencing (NGS) technologies have, until now, made allele frequency calculations quite a cumbersome task. With advances in this field, it is now possible to perform deeper sequencing to lower the error rate at a fraction of the cost. However, due to the large amount of data produced calculating allele frequencies still remain a challenging endeavour. Having considered these facts, we have set to determine the impact of calculating cohort and population-specific allele frequencies on the number of remaining candidate variants in targeted NGS data, such as large panels of genes associated with specific diseases and whole exome sequencing (WES). Elimination of false positive variants was improved compared to using normal population allele frequencies from international efforts, such as the 1000 genomes project, and thus the number of remaining candidate variants was reduced significantly. Elimination rates changed depending on the capture kit due to kit specific errors and cohort/population-specific polymorphisms. Fast and accurate calculations of local allele frequencies in different patient and healthy sample cohorts, along with the design of automated systems for such efforts, will provide crucial knowledge bases for both clinical diagnosis and research purposes.

17. Changes in H-reflex and V-waves following spinal manipulation

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Abstract

Objective: Over the past decade there has been a growing body of research demonstrating neural plastic changes following spinal manipulation. This current study sought to investigate whether spinal manipulation leads to neural plastic changes involving cortical drive and the H-reflex pathway to a lower limb muscle.

Method: Soleus evoked V-wave, H-reflex, and M-wave recruitment curves and maximum voluntary contraction (MVC) in surface electromyography (SEMG) signals of the plantar flexors were recorded from ten subjects before and after manipulation or control intervention. Dependent measures were H reflex area under curve normalized to Mmax (Harea/Mmax), Normalized MVC, H-reflex threshold, V wave normalized to Mmax (V/Mmax), M wave slope and H reflex slope. Dependent measures were compared with 2-way ANOVA and Tukey's HSD as post hoc test, p was set at 0.05.

Results: Spinal manipulation resulted in increased MVC (measured with SEMG) by $59.5 \pm 103.4 \%$ ($p = 0.03$) and force by $16.05 \pm 6.16 \%$ ($p = 0.0002$), increased V/Mmax ratio by $44.97 \pm 36.02 \%$ ($p = 0.006$), and reduced H-reflex threshold ($p = 0.018$). Following the control intervention, there was a decrease in MVC (measured with SEMG) by $13.31 \pm 7.27 \%$ ($p = 0.001$) and force by $11.35 \pm 9.99 \%$ ($p = 0.030$), decreased V/Mmax ratio ($23.45 \pm 17.65 \%$; $p = 0.03$) and a decrease in the median frequency of the power spectrum ($p = 0.04$) of the SEMG during MVC.

Discussion: The H-reflex pathway is involved in the neural plastic changes that occur following spinal manipulation. The improvements in MVC following spinal manipulation are likely attributed to increased descending drive and/or modulation in afferents. Spinal manipulation appears to prevent fatigue developed during maximal contractions. Spinal manipulation appears to alter the net excitability of the low-threshold motor units, increase cortical drive, and prevent fatigue.

18. Changes in cortico-muscular coherence while modulating force during isometric ramp contractions

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Aim: Muscle actions predominantly generate motion, but humans can also modulate constant or variable force outputs during isometric contractions. The relationship between brain activity and muscle activity can be investigated by calculating the cortico-muscular coherence (CMC). The CMC for controlling variant force during isometric contractions is not yet fully understood. Therefore, this study aimed to investigate whether the modulation of steadily increasing or decreasing force output influences the CMC.

Methods: Thirteen healthy adults performed isometric dorsiflexions by following a trace of the force output of their right tibialis anterior (TA). The task consisted of 1) ramp up for 10 s until the target intensity was reached (10% or 30% MVC); 2) hold the intensity for 30 s and 3) ramp down for 10 s back to the resting state. Electroencephalography (EEG) from FCz, Cz, C1, C2 and CPz (located over the motor and sensorimotor areas) and electromyography (EMG) from the tibialis anterior muscle were recorded during these actions. CMC at the beta band (15-30 Hz) was calculated between each EEG channel and the EMG from TA.

Results: The CMC during constant force (0.54 ± 0.09) was significantly lower when compared to force up (0.58 ± 0.08) and force down (0.59 ± 0.09) for all EEG locations. The increase in CMC during ramp contractions suggests higher demands for modulating variable force, which occurs regardless of the contraction intensity.

Conclusion: The CMC for modulating force output during ramp contractions increases in comparison to steady isometric force output. Our results contribute to the understanding of the supraspinal participation to control movements in healthy humans.

19. Whole-body vibration induces a short or long latency muscular reflex depending on vibration acceleration

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Aim: Whole-body vibration (WBV) induces a reflex response in muscles. The physiological mechanisms underlying this reflex have been explained by activating muscle spindles (stretch-induced reflex) or osteocytes (bone myoregulation reflex). WBV-induced muscular reflex (WBV-IMR) latency was reported to be significantly longer than latency of T-reflex as a stretch-induced reflex or nearly equal to T-reflex latency in the literatures. Hypothesis of this study was that WBV activates different receptors or reflex pathways depend on vibration intensity. Aim of this study was to test this hypothesis.

Methods: This study was conducted on 14 healthy adults. WBV was applied at various frequencies (25, 29, 33 and 37 Hz) and amplitudes (0.15 and 2.90 mm). The right soleus Treflex latency was determined before and during WBV. WBV-IMR latency of the right soleus was determined using two different vibration intensity: weak vibration (range of acceleration amplitude: 0.16-0.54g) and powerful vibration (range of acceleration amplitude: 4.59-6.33g). T-reflex latency and WBV-IMR latency were determined by using cumulated average method.

Results: T-reflex latency was 34.0 ± 3.1 ms before WBV and 34.6 ± 2.4 ms during WBV ($p > 0.05$). WBV-IMR latency was 34.2 ± 2.7 ms for weak vibration. It was not statistically different from T-reflex latency. WBV-IMR latency was 43.6 ± 2.9 ms for powerful vibration. It was longer than T-reflex latency ($p = 0.001$).

Conclusions: WBV may induce muscular activity through different receptors or reflex pathways, depending on the vibration acceleration. This study suggests that weak vibration activates muscle spindles, but powerful vibration may activate other receptors such as osteocytes.

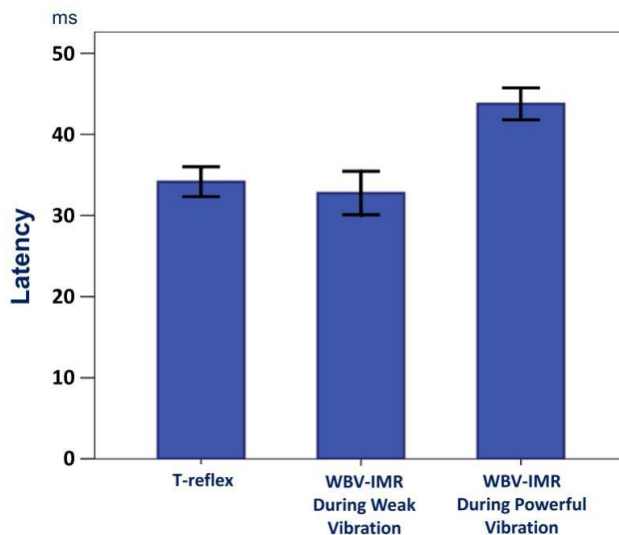


Fig 1. T-reflex latency is nearly equal to latency of whole-body vibration induced muscular reflex (WBV-IMR) elicited by weak vibration, significantly shorter than latency of WBVIMR elicited by powerful vibration.

20. Muscular activation strategies of six leg muscles on stable and unstable surface

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Aim: Balance ability is an important indicator for soccer performance and it can be assessed via different measurement protocols. Electromyography (EMG) allows to record and evaluate muscular electrical activity during different tasks. This evaluation could give significant information about the effectiveness of the training program or decision making of training characteristics. In this study, we compared muscular activation strategies of six support leg muscles during the same task but on different surfaces.

Methods: We recorded EMG activity of 10 soccer players' six support leg muscles (RF: Rectus Femoris, VL: Vastus Lateralis, VM: Vastus Medialis, BF: Biceps Femoris, TA: Tibialis Anterior, GM: Gastrocnemius Medialis) on two different surfaces (stable and BOSU ball) during uni-pedal stance by using a wireless EMG system.

Results: Recorded EMG activity showed statistically significant differences when the applied stability condition changed by affecting involving regimes of muscles. Four muscles' (VM, BF, TA, GM) activation patterns were significantly different on stable and unstable surfaces (BOSU ball).

Conclusions: Considering important role of selected muscles for the stabilization of support leg during soccer game, activation strategies of leg muscles on BOSU ball can be evaluated as an indicator of soccer performance skills such as passing, shooting or dribbling. This study emphasizes the necessity of a controlled research design including different training protocols which allows eliciting detailed results.

21. Reflex responses of the human masseter muscle to electrical lip stimulation

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Aim: Mildly painful electrical stimuli to the lip evoke short-lasting biphasic inhibitory responses in the masseter muscle. Most commonly used technique for the recording of jaw reflexes is surface electromyography (SEMG). Together with the classical analyses, we have used a discharge rate method, a peristimulus frequencygram (PSF), for the error-free estimation of masseter single motor unit (SMU) responses and examined the genuineness of these responses to uncover the true postsynaptic potentials in a trigeminal motor nucleus in human (1, 2).

Methods: We have recorded masseter SMU reflex responses in 12 normal subjects (aged between 19–31 yrs) during mildly painful electrical lip stimulation using silver fine-wire electrodes and SEMG electrodes. Bite force was registered simultaneously with the recording of motor unit activity. We have compared reflex responses obtained by using the PSF, peristimulus time histogram (PSTH) and the SEMG techniques.

Results: Using the discharge rate method (the PSF), we found that the electrical lip stimulation only generates a single long-lasting or compound inhibitory response which is followed by late long-lasting excitation in the masseter motor units, indicating only one or two pathways exist between the mechanoreceptors in the lip and the motoneurons of the masseter muscle. The other analyses methods (PSTH and SEMG), however, displayed up to five significant peaks and troughs which would have been taken as five different neuronal pathways connecting the stimulated afferents and motoneurons under investigation should PSF was not available.

Conclusion: Considering the great number of jaw reflex studies, which have used the SEMG technique and came up with the erroneous conclusions about numerous pathways connecting trigeminal afferents to trigeminal motoneurons, a novel PSF technique combined with classical muscle activity recording techniques would imply on the re-drawing the neuronal pathways of the trigeminal nerve that are frequently used to judge neuromuscular disorders of the trigeminal region.

References:

3. TÜRKER, K.S. and CHENG, H.B. (1994) Motor-unit firing frequency can be used for the estimation of synaptic potentials in human motoneurons. *Journal of Neuroscience Methods*, 53:225-234
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22. The reflex circuitry originating from the cutaneous receptors of the hand to the first dorsal interosseus muscle

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Aim: There are many neuronal circuitries in the nervous system that originate from the peripheral receptors and end in motoneurons that innervate skeletal muscles. The properties of these circuitries are usually investigated in experimental animals. These experiments can be criticized as they use general anaesthetics or work on reduced / decerebrate animals. These experiments are likely to give us erroneous results as the anaesthetics are known to work directly on neurons and affect synaptic transmission between neurons. To study the neuronal networks between the peripheral receptors and the motoneurons, therefore, we have decided to utilize healthy adult human subjects and utilize single motor unit techniques to avoid the general anesthetic and cross talk related issues.

Methods: In these experiments we used healthy adult volunteer subjects who gave informed consents to the experimental protocol. Mechanical stimulation was a computer generated force profile that activated a small mechanical vibrator connected to the area of interest via a probe. The interval between the stimuli was randomly altered between 0.8 and 1.2s to avoid predictive stimulus application. Profile of the stimulus was maintained using a Proportional-Integral-Derivative (PID) controller system based on the LabView® software. Other than the surface EMG that represents gross muscle response to the stimuli, activities of single motor units were also recorded using custom-made intramuscular fine wire bipolar electrodes made of two Teflon® insulated silver wires to study responses of motor neurons to the stimuli. Subjects were asked to contract the muscle to fire a clearly identifiable motor unit at a fixed rate with the help of audio feedback. When analyzing the results, offline discrimination of the shape of action potentials was performed using pre-established templates. Data were then used to construct peristimulus frequencygrams (PSFs: 1 and 2) and peristimulus time histograms (PSTHs). The reflex was considered to be a significant event only when it was larger than the error box before the reaction time set for that stimulus.

Results: *Using both PSTH and PSF simultaneously indicated neuronal pathways that were previously unknown in many of the pathways investigated. Combined approaches of these two analyses methods complement each other so that reliable neuronal circuitries that connect peripheral receptors and motoneurons of human skeletal muscles can be discovered.*

Conclusions: *This study aimed to standardize the stimulation, recording and analyses procedures. This approach has shown that all of these variables could be standardized and the results of such price procedures can be reliable and the experiments repeatable.*

References:

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6. TÜRKER, K.S. and POWERS, R.K. (2005) Black box revisited: A technique for estimating postsynaptic potentials in neurones. *Trends in Neuroscience*, 28:379-386

23. Investigating Renshaw Cell Circuitry in Human Neuromuscular System

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Background: Among many interneurons that synapse onto motor neurons, the Renshaw cells have been investigated in mammals, especially in cats. These cells are situated in the ventral horn of the vertebrate spinal cord and provide a suitable model for studying circuits in the spinal cord. Animal studies have suggested that these cells are inhibitory to the motor neurons of the homonymous muscle motor neurons. However, their function in human motor system is not so certain as conflicting results are obtained by various investigators. In this study, we hypothesize that the activation of the Renshaw cells *via* antidromically stimulated larger motor axons will lead to an inhibition of smaller motor neurons.

Materials and Methods: The experimental procedure was approved by the Human Ethics Committee of Koç University. Surface electrodes were placed on tibialis anterior muscle. Sterile bipolar intramuscular electrodes were placed *via* a surgical needle. Subjects were asked to contract their muscles while common peroneal nerve was stimulated with constant current stimulator and single motor unit potentials were recorded.

Results and Discussions: As a consequence of stimulation of larger motor axons, the motor unit activity which corresponds to the H-reflex was delayed by several milliseconds. The peristimulus time histogram (PSTH) showed an inhibition and subsequent facilitation of motor neuron activity. As it is stated in the hypothesis, Renshaw cells do generate a short lasting inhibition of the motor neurons of the homonymous muscles. This inhibitory input seems to delay the timing of the H-reflex by several milliseconds indicating that the Renshaw inhibitory and spindle excitatory inputs arrive in the motor neurons almost simultaneously.

Conclusion: Low intensity stimulation of Ia afferents induce the H-reflex. If the cathode position and the stimulus intensity are optimized, the stimulus now can activate both the spindle primary (Ia) afferents and the largest motor axons. The activity of motor axons induces an antidromic activation of the Renshaw cells that then can cause an inhibition on the ongoing activity of the motor neuron. This method can be used to investigate the distribution and modulation of the Renshaw inputs to various sized motor neurons in human subjects.

24. Chiropractic alters TMS induced I-wave excitability and cortical silent period duration

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Abstract

The objective of this study was to construct peristimulus time histogram (PSTH) and peristimulus frequencygram (PSF) using single motor unit recordings to further characterize the previously documented immediate sensorimotor effects of spinal manipulation. Single pulse transcranial magnetic stimulation (TMS) via a double cone coil over the tibialis anterior (TA) motor area during weak isometric dorsiflexion of the foot was used in fourteen subjects. On two separate days several hundred stimuli were delivered at a frequency of about 0.3Hz and the intensity set at active motor threshold before and after either a spinal manipulation of dysfunctional spinal segments or a control intervention. The order of the interventions was randomized. TA electromyography (EMG) was recorded with surface and intramuscular fine wire electrodes. Three subjects also received sham double cone coil TMS pre and post a spinal manipulation intervention. The single motor unit data were analysed from the constructed PSF and PSTH. From the averaged surface EMG data motor evoked potentials (MEPs) and cortical silent periods (CSP) were constructed and analysed. 16 single motor units were identified for the spinal manipulation intervention and seven single motor units were identified for the control intervention. Following spinal manipulations there was a shortening of the silent period and an increase in the single unit I-wave amplitude. No changes were observed following the control condition. The results provide evidence that spinal manipulation of dysfunctional spinal segments reduces the TMS-induced cortical silent period, and increases low threshold motoneurone excitability. A significant increase in the level of excitation and a decrease in the level of inhibition may increase subject's confidence to move his/her leg after the manipulation. This manipulation may be used to strengthen weakened muscles in human subjects.

25. Fifteen minutes of active recovery after an exhaustive endurance task enhances the recovery capacity of the CNS but not that of the muscle 24h later

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Aim: The fast recovery after exhaustive exercise is important for both training and competition. However, the mechanisms underlying recovery are not yet fully understood. Especially, the role of the central nervous system (CNS) in driving recovery is unknown. Thus, the aim of this study was to demonstrate the active role of the CNS on fatigue recovery processes. We hypothesized that an active recovery treatment vs. control would modulate differently the recovery capacity of the CNS and thus induce differences in voluntary activation of the knee extensors measured with transcranial magnetic stimulation (VATMS) after a fatiguing cycling task.

Methods: We measured VATMS, isometric maximal voluntary contraction (MVC) and potentiated twitch at rest (Ptw) induced by peripheral nerve stimulation (11 subjects, cross over design) before and after a fatiguing cycling task (12.5km uphill time trial), after an active (15 min cycling at 100 W) or passive (15 min sitting) recovery treatment, and 24h later, before and after a fatiguing task (1 min MVC).

Results: With ANOVAs, we observed a time and task effect for VATMS, explained by a higher VATMS measured after the 1 min MVC with the active recovery treatment 24 h after the time trial. However, no comparable effects were observed for Ptw.

Conclusion: VATMS was higher after the active recovery treatment when compared to passive control 24h after the fatiguing exercise but peripheral fatigue was not affected. These results indicate that the CNS recovery may be independent from the muscle recovery after an exhaustive endurance exercise. This demonstrates the need for optimised recovery strategies targeting both peripheral and central components of muscle performance.

26. Learning to walk on a slack-line induces highly task-specific neural plasticity

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Aim: There is growing evidence that improvements in performance after short-term balance training occur only in trained tasks [1, 2]. A neuronal origin for this task-specificity has been suggested but not yet demonstrated. In the present study we tested the hypothesis that learning to walk on a slackline induces neural adaptations mediating performance improvements exclusively for this task.

Methods: We measured the amplitude of H-reflexes in the soleus muscle during a trained (slackline) and an untrained balance task (tilt-board) before and after six weeks of slackline training in a training (N=15) and control group (N=13). To ensure identical pre-post conditions, stimulations were applied during the preparatory phase of the balance task, i.e. just before the foot of the subject touched the balance device. Background EMGs, knee and ankle angles were measured at the time of stimulation. To assess the effect of training on performance, the number of steps on the slackline and the duration of equilibrium on the tilt-board were measured.

Results: Mixed design ANOVAs showed: i) an increase in performance only in the training group and only for the trained task. ii) No effect of time for background EMGs, knee and ankle angles, indicating comparable stimulation conditions pre vs. post-training. iii) A reduction of the H-reflex only in the training group and only during the trained task.

Conclusion: We assume that the modulation of the H-reflex most probably reflects training-induced neural plasticity, which might partly explain the specificity of the performance improvement observed on the behavioural level.

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27. Aggregating stimulus increases the activity in motoneurons causing spasm

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Aim: Discrepancy in dental occlusion is trigger mechanism for Muscle Pain Dysfunction Syndrome (MPDS). Premature contacts may stimulate neural mechanism in masticatory system. MPD syndrome will be developed if premature contacts are not removed from the occlusion. We use T-Scan occlusal analysis system to find and remove premature contacts from the occlusion. Usually this action is useful for rapidly treating MPDS. The purpose of this study is to evaluate the longevity of reduced disclusion distance in treating and removing myofascial pain dysfunction symptoms following the T-Scan-based, immediate complete anterior guidance development (ICAGD) coronoplasty. This measured occlusal adjustment has been shown to reduce sharply the muscle hyperactivity of myofascial pain.

Methods: Myofascial pain symptomatic patients were recruited as per the diagnostic criteria for temporomandibular disorders(TMDs), including the clinical protocol and assessment instruments outlined by the international RDC/TMD consortium network (version: January 20, 2014) to assess the efficacy of reduced disclusion time in left and right lateral excursions to resolve the myofascial pain symptoms. As per the inclusion and exclusion criteria, 20 cases were treated with ICAGD in two visits, each 1 week apart. Recall disclusion time measurements were recorded every 3 months over 3 years. The RDC/TMD questionnaire was used for symptom assessment at every recall visit. ICAGD brought pretreatment prolonged disclusion time down to <0.4 s, as quantified from T-Scan force and time data records, while the subjects were assessed for symptom relief.

Conclusion: The results indicate that ICAGD reduces the musculoskeletal symptoms of myofascial pain, such that this methodology increases clinical therapeutic success.

28. The sensitized motoneuron as a possible missing link in the development of myofascial trigger points?

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Aim: Myofascial trigger points (mTp) are a very common source of referred pains. Until now the focus in the etiology of mTp has been on the permanently contracted muscle fibers which lead to nociceptive changes. However, the possibility that a sensitized motoneuron innervating the region of the mTps could be involved in this phenomenon should also be considered. This possibility should be assessed by online research. In addition, the poster should give a simple overview of the possible connections between referred pain and the failure of inhibitory input on the motoneuron and be an incentive for more research in this field.

Methods: The hypothesis that the development of mTp is, in part, due to a sensitization of motoneurons was compared with the result of online research of the literature in that field (Pubmed, Cochrane, CHBD, Hubmed, Medline, DIMDI; keywords: myofascial-and- motoneuron-and- sensitization, or-excitation, or- inhibition).

Results: There is no sound proof of the existing hypotheses that the development of mTp happens only on the muscular level. The literature lacks references for sensitization effects of motoneurons with mTp involved. The positive clinical effects of oral splints which profoundly changes the reflex input on the trigeminal motoric system could be evidence for a reflexive inhibition on a motoneuron which is sensitized and exhibits a dysfunctional motor endplate.

Conclusions: There is no research considering the sensitized motoneuron as a possible missing link in the development of mTp. Therefore, this poster should be a call for further research in this field.

29. Directed differentiation of corticofugal projection neurons from endogenous cortical progenitors

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Specific classes of neurons are selectively vulnerable in distinct neurodegenerative, developmental, and acquired diseases of the CNS. In particular, for this work, corticospinal motor neurons (CSMN) degenerate in amyotrophic lateral sclerosis (ALS) and other motor neuron diseases, and loss of motor function in spinal cord injury results from damage to CSMN axons. Directed differentiation of new neurons with appropriate identity, maturity, circuit connectivity and function from endogenous local progenitors offers a potential therapeutic approach for functional repair of diseased or injured neuronal circuitry.

Recent work by our lab and others has begun to identify central elements of a combinatorial “molecular logic” of stage-, state-, and area-specific controls over development of broad classes and specific subtypes of cortical projection neurons. Here, we target endogenous cortical progenitors present in postnatal and adult brain to direct their differentiation into corticofugal (cortical output) projection neurons; CSMN belong to this class. Application of a select combination of central and complementary transcriptional controls in cultured cortical progenitors directs acquisition of cardinal morphological, molecular, and electrophysiological features of corticofugal projection neurons. We employ synthetic modified RNA technology to enable temporal and dose control to mimic the *in vivo* expression dynamics of the relevant transcriptional regulators. Ongoing work will further assess fidelity of their differentiation, integration, and function within complex cortical circuitry in both developing and the diseased brain.

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32	Dennis Bo	Jensen	Copenhagen University
33	Fulya	Akçimen	Boğaziçi University
34	Cengiz	Tataroğlu	Adnan Menderes University
35	Cemile	Koçoğlu	Boğaziçi University
36	Kadir	Ozkan	Harvard University/Boğaziçi Üni
37	Anderson	Souza Oliviera	Aalborg University
38	Sara	Goltash	Copenhagen University
39	Claire	Francesca	Copenhagen University
40	Muhammed	Hadzipasic	Yale School of Medicine
41	Jessica	Wilson	Northwestern University
42	Hamid	Hamzeiy	Boğaziçi University
43	CJ	Heckman	Northwestern University
44	Utku	Yavuz	University Medical Center of Goettingen
45	Amr	Mahrous	Wright State University
46	Kristina	Diminityanova	Copenhagen University
47	Christopher	Thompson	Temple University
48	İlhan	Karacan	Bağcılar Araştırma Hastanesi
49	Muharrem	Çidem	Bağcılar Araştırma Hastanesi
50	Suna Lahut	Ömür	Boğaziçi University
51	Vibhu	Sahni	Harvard University
52	Serdar	Gözler	İstanbul Aydın University
53	Roeland	Prak	University Medical Center Groningen
54	Mehmet Cemal	Kahya	İzmir Katip Çelebi Üniversitesi
55	Aleyna	Eray	Boğaziçi University
56	İlayda	Ateş	Boğaziçi University

57	Kübra	Çelikbaş	Boğaziçi University
58	Selin	Gök	Boğaziçi University
59	Meltem	Işık	Boğaziçi University
60	Kaan	Şen	Boğaziçi University
61	Ismail	Bayram	Anadolu University
62	Nazlı	Başak	Boğaziçi University
63	Hilmi	Uysal	Akdeniz University
64	Paulius	Ugincius	Lithuanian Academy of Health Sciences
65	Hayri	Ertan	Anadolu University
66	Kemal S.	Türker	Koç University
67	Gizem	Yılmaz	Koç University
68	Görkem	Ozyurt	Koç University
69	Ata Berk	Demir	Koç University
70	Aslı	Aydın	Koç University
71	Oğuz	Sebik	Koç University

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