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1. The physiology of the brainstem respiratory centres: Lessons from a concurrent multithreaded computational model of Rett syndrome—C.P. Arun (Ruskin Ward, Maudsley Hospital, London, United Kingdom)

Background: The brain is primarily a massively parallel computer and the brainstem is no exception. Doubtless of vital importance to life, the brainstem centres controlling respiration continue to evade precise identification. Rett syndrome (RTT) is an interesting neurodevelopmental disorder that produces characteristic neurological and behavioural features. Clinical features include autistic traits, loss of purposeful hand movements, stereotyped hand movements and life threatening respiratory rhythm disturbances. The respiratory rhythm abnormalities of RTT include hyperventilation, breath holding, apneustic breathing, etc.

Methods: We model normal mammalian respiratory rhythmogenesis as involving opposing sets of neurones, generating 'neurocomputational threads' to help model the respiratory rhythm abnormalities seen in RTT. We used Java 6 to implement concurrent multithreading of sequential slave threads for inspiration and expiration respectively, avoiding the need for a precise anatomic location for an inspiratory and expiratory centre. We allow threads to fail to generate and to lock in order to demonstrate pathophysiology.

Results: Many respiratory abnormalities of RTT can be duplicated by our model. For example, loss of generation and/or sustenance of sequential threads duplicates apnea, failure of timely termination of inspiratory threads leads to apneustic breathing, etc.

Discussion: Failure of replenishment of neurotransmitter stores may correspond to loss of 'garbage collection' of neurocomputational threads and failure of reuptake of neurotransmitters, to locking of these threads.

Conclusions: RTT affords a unique window on the workings of the respiratory centre of the brainstem. Future work using concurrent multithreading can help unravel the nature of other clinical features such as speech disturbances and hand wringing stereotypies.

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2. The StartReact effect in tasks requiring a precise endpoint—J.M. Castellote [1,2], J. Valls-Solé [3], J. Casanova-Molla [3], A. Selvi [3] ([1] National School of Occupational Medicine, Carlos III Institute of Health, Madrid, Spain, [2] Department of Physical Medicine and Rehabilitation, School of Medicine, Complutense University of Madrid, Madrid, Spain, [3] Unidad de EMG y Control Motor, Servei de Neurologia, Hospital Clínico, Universidad de Barcelona, Barcelona, Spain)

Background and aims: Many daily precision grip tasks demand a high level of dexterity with a precise endpoint. For proficiency subjects may use programmed movements to be done following an external command. Voluntary reactions can be speeded up by a startling auditory stimulus (SAS) delivered at the same time as the imperative signal, a phenomenon termed StartReact (Valls-Solé et al., 1995). It is unknown if tasks requiring a precise endpoint can also be affected by SAS. The aim of the present study is to examine how a task that requires a precise endpoint responds to a SAS delivered at different timings during the task.

Methods: We have devised a manoeuvre in which a pen had to be moved to reach endpoint targets of different sizes: 5, 10 and 20 mm diameter. The imperative signal (IS) was a weak electrical stimulus in the left index finger. The study was carried out in 8 healthy volunteers, in whom we collected 30 trials for each type of target at random. We were interested in determining the effects on movement time (MT) but also in reaching the target (target time, TT). Then, in a percentage of trials, a SAS was applied at the time of the imperative signal (SAS-0) but in others 300 ms later (SAS-300). We recorded the times of positioning of pen tip at start and end-point targets by placing adequate switches on them and on pen tip. We also recorded reaction time (RT) by an accelerometer placed at index finger. In this way, we measured RT, movement time (MT = pen tip on end target − RT) and target time (TT as RT + MT).

Results: In small size endpoint targets and for all conditions MT and TT were longer than with those medium and large size. With SAS-0 when compared to Control, there was a decrease of RT and TT in all size targets while MT was similar. There was no effect with SAS-300 when compared to control, showing similar values without any effect on reaching the endpoint target (TT).

Conclusions: Our results indicate that StartReact affects the onset of a movement intended to a precise endpoint, while subjects exert some inhibitory control at the late part of the movement. Alternatively, it is possible that certain programmed actions include a very

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effective inhibitory control over external influences, such as the startling auditory stimulus, to prevent disruption of the motor program.

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3. Brainstem reflex studies in patients with progressive supranuclear palsy and primary progressive freezing of gait—M.E. Kızıltan, A. Gunduz, G. Kızıltan, A. Tekeoğlu, M. Sohtaoğlu (Istanbul University, Cerrahpasa School of Medicine, Department of Neurology, Istanbul, Turkey)

Background and aim: Freezing of gait (FOG) is a common feature of Parkinsonian syndromes. Primary progressive freezing of gait (PPFOG) manifests predominantly as progressive freezing gait and difficulties of writing or speaking without accompanying any other movement disorders. Although FOG is mostly associated with PSP, some authors proposed that PPFOG is a distinct clinical and pathophysiological entity. Previous studies showed that startle response is absent or TCR is abnormal in most PSP patients, and its measurement has been proposed as a method of distinguishing PSP from other Parkinsonian disorders. On the other hand, startle response was found to be exaggerated in PPFOG. Based on those previous observations we aimed to investigate the characteristics of brainstem reflexes in PPFOG patients in comparison to PSP patients who had FOG and normal controls by using blink reflex (BR), trigeminocervical reflex (TCR), and acoustic startle response (ASR).

Subjects and method: Seven patients (mean age 69.7 ± 5.0 years; 5 males, 71.4%) with PPFOG and age and sex matched seven PSP patients and 16 normal controls were included in the study. All patient and healthy volunteers underwent BR, TCR and ASR investigations under the same conditions. We measured latency and amplitudes of BR, TCR and ASR and calculated presence and response rates. Comparisons were made by Kruskal Wallis test for quantitative data and by chi-square test for qualitative data.

Results: All 3 groups had normal BR latencies. Presence rate of TCR was lowest in PSP and highest in PPFOG ($p = 0.007$ for SC and $p = 0.023$ for SCM). ASR probability was lowest in PSP group. It was highest in PPFOG ($p = 0.005$).

Discussion: ASR habituation is thought to result from synaptic depression of brainstem interneurons localized in the pontine reticular formation. We observed exaggerated ASR in PPFOG with lack of habituation whereas probability of ASR was decreased in PSP. Results of TCR paralled those of ASR. Similarly, in literature it was dramatically low in PSP. Our findings support the marked inhibition of brainstem reflexes even in PSP with FOG probably due to atrophy and degeneration. However, interestingly, in PPFOG functions of pedunculopontine nucleus and reticular formation which are reflected by ASR and TCR seem to be unaffected and excitability is exaggerated. These, in turn, may support the idea that the pathophysiology of FOG in these two diseases also seems to differ.

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4. Trigemino cervical reflexes in spinal cord injury—A. Gündüz [1], M.E. Kızıltan [1], G.K. Tokmak [1], H. Ergin [1], N.U. Adatepe [1], N.İ. Örnek [2], H. Ünalan [2] ([1] Istanbul University, Cerrahpasa School of Medicine, Department of Neurology, Istanbul, Turkey, [2] Istanbul University, Cerrahpasa School of Medicine, Department of Physiotherapy and Rehabilitation, Istanbul, Turkey)

Background and aims: Abnormal enhancement of polysynaptic brainstem reflexes including ASR, has been previously reported in patients with spinal cord injury (SCI) (Kumru, 2009). We aimed to investigate trigeminocervical reflex (TCR) in SCI since it may reflect alterations of the brainstem neuronal networks specifically trigeminocervical motoneurons in patients with SCI.

Subjects and methods: A total of consecutive 8 patients with SCI and 12 age and sex matched control subjects were included in this study. All lesions were developed traumatically at the levels between T4-T11 and none of the patients used intrathecal baclofen. TCR was recorded over sternocleidomastoid and splenius capitis muscles by stimulation of infraorbital nerve in both groups under the same conditions. We measured and compared onset latency, amplitudes and durations of responses in both groups.

Results: Response rates of TCR seemed to be decreased in patients although it only reached statistical significance for contralateral SC response (68.8% vs. 100%, $p = 0.007$). When present, responses of SCI group seemed to evoke earlier, to have higher amplitudes and to be more persistent. Contralateral SC amplitude and duration reached significance (356.8 ± 175.7 vs. 255.5 ± 186.8, $p = 0.050$ and 77.3 ± 26.1 vs. 45.5 ± 6.3, $p = 0.000$, respectively). IL SC amplitude was also much higher in patients with SCI compared to controls (467.1 ± 331.2 vs. 191.9 ± 128.7, $p = 0.005$). Despite those tendencies, few results reached statistical significance probably because of the small sample number.

Comment: We demonstrated that SCI patients had a tendency to have decreased prevalence of TCR and when present it seemed to exaggerate. Presence was independent from the level of spinal cord injury. Neck muscles have a particular role for the maintenance of the body posture and have many connections in the reticular formation (Wilson and Peterson, 1988).

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5. The effects of transcranial magnetic stimulation on vibratory-induced presynaptic inhibition of the soleus H reflex—J. Guzmán-López [1], A. Selvi [1], J. Casanova-Molla [1], J. Costa [2], J. Valls-Solé [1] ([1] Unidad de EMG y Control Motor, Servei de Neurologia, Hospital Clínico, Universidad de Barcelona, Barcelona, Spain, [2] Hospital de Sta Maria, Lisboa, Portugal)

The soleus H-reflex can be used to assess the effect on the motoneuronal pool of conditioning volleys elicited by transcranial magnetic stimulation (TMS) in descending motor tracts. In healthy subjects, a single-pulse TMS induces two facilitatory phases of the soleus H-reflex: one at inter-stimulus intervals (ISI) between 5 and 30 ms and the other at ISIs between 80 and 110 ms. The first facilitatory phase is supposed to be due to summation of the excitatory input from the descending excitatory postsynaptic potentials (EPSP) generated by TMS and the Ia-afferents, while the mechanisms responsible for the second phase are less clear. To further investigate these mechanisms, we evaluated in 13 healthy subjects how the soleus H-reflex was modulated by conditioning single pulse TMS at ISIs from 0 to 110 ms in the presence of high frequency (80 Hz) low amplitude vibration applied to the tibialis anterior and quadriceps muscles. It is known that vibration induces inhibition of the H-reflex through several possible mechanisms: increased firing threshold of Ia-afferent fibers, presynaptic inhibition of Ia-terminals with primary afferent depolarization, and post-activation depression with dendritic hyperpolarization. A two-factor ANOVA showed a significant main effect of the vibration condition ($F[2,468] = 30.8$; $p < 0.001$) and of the ISI ($F[13,468] = 3.1$; $p < 0.001$) on the percentage change of the soleus H-reflex amplitude with respect to baseline control, without interaction between vibration condition and ISI ($F[26,468] = 1.26$; $p = 0.187$). The post hoc analysis showed that while the first facilitatory phase was unchanged by vibration stimuli, the second facilitatory

phase was clearly inhibited, when vibration was applied to TA or to Quadriceps muscle. These results suggests that a conditioning single pulse TMS induces a transient suppression on the vibration-induced inhibition of the H-reflex. The fact that similar results were obtained with vibration of TA and Quadriceps muscles across all ISIs ($p = 0.39$) supports the notion that inhibition mediated through presynaptic inputs from propriospinal interneurons must play a major role in vibration induced depression of the H-reflex. It would be very unlikely that TMS overcomes the effect of vibration up to the extent of inducing a facilitation of the same amplitude as in baseline conditions during the first phase. Our results are consistent with the second phase of H-reflex facilitation by TMS is being reflex in origin and likely mediated by the terminals that remain inhibited by vibration, and we propose that TMS causes a transient depolarization of the presynaptic inhibitory neurons.

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6. Auditory startle reflex in cerebrovascular disease—M.E. Kızıltan, M.S. Sevindik, M. Bozluolay (Department of Neurology, Cerrahpasa Faculty of Medicine, Istanbul University, Istanbul, Turkey)

Objectives: Cerebrovascular diseases (CVD) are an important cause of motor disability and rehabilitation is only possible through a better understanding of the mechanisms underlying the recovery of motor functions after brain injury. In the presented study we aimed to investigate the properties and interactions of reticulospinal tract and corticospinal tract with the help of auditory startle reflex (ASR) which is an involuntary rapid contraction of muscles against a sudden sound and believed to play a role in conducting voluntary movements and transcranial magnetic stimulation (TMS) in CVD patients with different lesion sites and chronicity.

Methods: We have included 44 CVD patients and 18 age and sex matched healthy controls. According to the site of the lesion patients were divided into anterior ($n = 24$, 54.5%) and posterior ($n = 20$, 45.5%) circulation groups and according to chronicity they were divided further into acute and chronic groups. In patients and controls the properties of ASR and single pulse TMS was noted.

Results: Overall the ASR was found to be enhanced on the symptomatic site of patients compared to controls and asymptomatic site. The exaggeration of ASR was most obvious in chronic posterior circulation group and in distal muscles of all patient groups. The ASR probability on the asymptomatic site was mildly decreased in all patient groups, most apparent being in acute anterior circulation patients. MEP responses could not be elicited in most of the patients at distal muscles. Lineer regression analysis of MEP amplitudes and ASR probabilities showed that the patients with high MEP amplitudes at distal muscles ended up to have decreased ASR and this relationship was found to be statistically important in patients with anterior circulation infarction and in patients with temperature and pain loss on the clinically affected site.

Conclusions: In conclusion we have found that the ASR is enhanced on the clinically affected site of CVD patients and the properties of ASR differs according to the clinical signs, chronicity of the disease and lesion site. Patients with abolished MEP responses suggesting corticospinal tract injury had enhanced ASR indicating that the innervation of the reticulospinal tract remains active through which a rehabilitation potential is possible.

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7. Deficient prepulse inhibition of blink reflex in narcolepsy-cataplexy: Evidence of pedunculopontine involvement—B. Frauscher [1], W. Löscher [1], L. Ehrmann [1], V. Gschliesser [1], E. Brandauer [1], B. Högl [1], M. Kofler [1,2] ([1] Department of Neurology, Innsbruck Medical University, Innsbruck, Austria, [2] Department of Neurology, Hochzirl Hospital, Zirl, Austria)

Background and aims: Hypocretin deficiency plays a major role in the pathophysiology of narcolepsy-cataplexy. In animal models, hypocretinergic projections to the pedunculopontine nucleus (PPN) are directly involved in muscle tone regulation mediating muscle atonia – a hallmark of cataplexy. We hypothesized that PPN function, tested with prepulse inhibition of the blink reflex, is altered in human narcolepsy-cataplexy.

Methods: Blink reflex, prepulse inhibition of the blink reflex, and blink reflex excitability recovery were measured in 20 patients with narcolepsy-cataplexy and 20 healthy controls.

Results: Blink reflex characteristics (R1 latency and amplitude, and R2 and R2c latency and area-under-the-curve) did not differ between patients and controls ($P > 0.05$). Prepulse stimulation significantly increased R2 and R2c latencies and reduced R2 and R2c areas in patients and controls. However, the R2 and R2c area suppression was significantly less in patients than in controls (to 69.8 ± 14.4% and 74.9 ± 12.6%, respectively, vs. 34.5 ± 28.6% and 43.3 ± 29.5%; $P < 0.001$ each). Blink reflex excitability recovery, as measured by paired-pulse stimulation, which is not mediated via the PPN, did not differ between patients and controls ($P > 0.05$).

Conclusions: Prepulse inhibition is clearly altered in narcolepsy-cataplexy, whereas unconditioned blink reflex and its excitability recovery were normal. Since the PPN plays a crucial role in prepulse inhibition, these results concur with functional involvement of the PPN in the pathogenesis of narcolepsy-cataplexy.

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8. The blink reflex to median nerve stimuli in brainstem disorders—L. Leon, J. Casanova-Molla, J. Valls-Solé (Unitat d'EMG, Servei de Neurologia, Hospital Clinic, Barcelona, Spain)

Background and aims: Orbicularis oculi responses can be elicited by electric stimuli over the supraorbital nerve (trigeminally-induced blink reflex or TBR) as well as over peripheral nerves such as the median nerve at the wrist (somatosensory blink reflex or SBR). Both reflex responses are likely to be organized at the brainstem level but, due to different afferent pathways and probably also different interneuronal integration circuits, they may have a different behavior in brainstem disorders. We examined the differences between TBR and SBR in relation to brainstem lesion topography (upper vs lower lesions and intra-axial vs extra-axial lesions).

Patients and methods: We studied a total of 22 patients presenting disorders involving the brainstem (8 with mesencephalic focal lesions, 7 with Wallenberg's syndrome, 5 with Miller–Fisher syndrome and 2 with Bickerstaff brainstem encephalitis). In all patients we performed various neurophysiological tests intended to define and classify the lesion site and other characteristics. We report here only the results of examining the SBR and the TBR. The same tests were done in 12 control subjects. Subjects were sitting comfortably with recording electrodes attached to the lower eyelid over the orbicularis oculi muscles and stimulation electrodes attached to the skin overlying the supraorbital and median nerves of both sides. After setting the appropriate intensity for each stimulus, subjects were presented with random order stimulation to record up to 5 orbicularis oculi responses to each stimulation site.

Results: The SBR was absent or abnormally reduced in patients with mesencephalic lesions and normal in patients with medullary infarcts. The SBR was abnormal in upper brainstem intra-axial lesions (Bickerstaff's encephalitis) while it was normal in lesions involving the oculomotor nerves only (Miller–Fisher's syndrome). The TBR was normal in upper brainstem lesions and showed various abnormalities in lower brainstem lesions.

Conclusions: The SBR is abnormal in intra-axial upper brainstem lesions. It can be a complementary test to the battery of brainstem reflexes in the characterization of brainstem disorders.

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9. Atypical stimulus-sensitive myoclonus presenting abnormal sensory-motor integration in a case of congenital hemiatorophy of cerebellum—N. Murase, J.C. Rothwell, K. Bhatia (Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, United Kingdom)

Background and aims: Some diseases with cerebellar pathology such as a celiac disease, are associated with stimulus-sensitive cortical reflex myoclonus. It has therefore been suggested that disordered output of the cerebellum may be one factor that increases the excitability of sensorimotor cortex leading to muscle jerks. Here we present a case of stimulus-sensitive myoclonus due to congenital cerebellar hemiatrophy.

Methods: The patient is a 24-year-old female with normal developmental milestones and cognitive function. Myoclonus appeared when she was 15 years old in her left arm and spread gradually to involve her left leg. She has a positional and action tremor with myoclonic jerks, which sometimes appear stimulus-sensitive and are not relieved by alcohol. She also has horizontal positional nystagmus and jerky smooth pursuit. Her MRI showed left cerebellar hemiatrophy. Jerk-locked back averaging was difficult because of unclear EMG onset. Median nerve SEP, C-reflex, short-interval intracortical inhibition (SICI), short-interval afferent inhibition (SAI), and blink reflexes were examined.

Results:

- SEP and C-reflex: N20-P26 amplitude was 10 μV (borderline) on both sides and there was no C reflex.
- SICI: there was no inhibition in either hemisphere; indeed there was facilitation in the right hemisphere at all inter-stimulus intervals (ISI) from 1 to 5 ms.
- SAI: inhibition was absent bilaterally, and was replaced by facilitation in both hemispheres at ISI 4, 6, 23, 25 and 30 ms. In the right hemisphere, SAI responses often consisted of a double MEP, with the usual short latency MEP at 20–25 ms after the test TMS pulse, followed by a second response some 40 ms later. The probability of evoking this second MEP was more than 50% at ISIs of 4, 6, 10 and 23 ms.
- Blink reflex: left side stimulation produced an late R2 (ipsilateral) and there was reduced paired pulse suppression at an ISI = 500 ms.

Conclusions: Absent motor cortex SICI, replaced by facilitation, is consistent with a cortical origin of the muscle jerks from the right hemisphere. Although there was no C-reflex, the lack of SAI in the right hemisphere suggests a hyperexcitable short latency sensory input to motor cortex, again consistent with a cortical origin of the muscle jerks. The double MEP responses evoked from during SAI have not been described previously but reflect a tendency for excitation to reverberate in the cortex at about 25 Hz. Finally, increased excitability of the blink reflex is consistent with removal of a cerebellar influence on brainstem circuits.

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10. Sensorimotor interaction and motor learning in facial muscles—G. Pilurzi [1,2], A. Hasan [2], E. Tolu [1], F. Deriu [1], J.C. Rothwell [2] ([1] Department of Biomedical Sciences, University of Sassari, Sassari, Italy, [2] Sobell Department of Neuroscience and Movement Disorders, Institute of Neurology, University College London, London, United Kingdom)

Background and aim: Integration of sensory information with motor output is thought to be important in motor learning. In limb muscles, this is studied using the short afferent inhibition (SAI) paradigm, to assess sensorimotor interaction, and paired associative stimulation (PAS), to evaluate LTP-like plasticity. As far as we know, SAI and PAS paradigms have never been used in the territory of the cranial nerves. The present study was aimed at testing in normal subjects whether sensorimotor interaction and LTP-like plasticity can be observed in facial muscles as well as in limb muscles.

Methods: Motor evoked potentials (MEPs) were evoked in the depressor angulis oris (DAO) muscle of 7 subjects. MEPs were recorded from the contralateral DAO at rest and during 10% maximal voluntary contraction (active condition). SAI was tested in 5 subjects, by pairing electrical stimulation (ES, intensity 3 times the perceptual threshold) of the facial nerve, with magnetic stimulation (TMS, 120% of motor threshold intensity) of the facial motor cortex. Intervals between ES and TMS were 5, 10, 15, 20, 25 and 30 ms. The LTP-like plasticity protocol (200 pairs of ES and TMS, 20 ms ISI, at 0.25 Hz) was tested in X subjects by evoking twenty MEPs in both resting and active conditions, before and at 0, 20 and 30 min after paired stimulation.

Results: Facial nerve stimulation in the SAI paradigm had no significant affect on MEP amplitude, either in the active or in the relaxed DAO muscle. By contrast MEP amplitude at rest showed a trend of facilitation ($p < 0{,}072$) after the PAS protocol administration. When tested at rest this effect was observed at baseline and after 10 min. On the contrary MEP amplitude recorded during activity was significantly enhanced at 10 ($p < 0{,}026$) and 30 ($p < 0{,}014$) minutes after PAS. There was a significant difference between the time course in resting and active conditions ($p < 0{,}019$).

Conclusions: These data show that there is no short latency afferent inhibition in the facial motor cortex, yet despite this, there is evidence for maintained LTP-like plasticity. Further studies are needed to understand how and why PAS works in facial muscles despite the absence of SAI. A larger sample is also required to confirm the PAS effect on resting DAO MEPs. A second point to be clarified is why the PAS time course at rest is different from that operating during active condition.

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11. The effects of the StartReact paradigm in homonymous contralateral muscles—A. Selvi [1], J. Costa [2], J. Valls-Solé [1] ([1] Unidad de EMG y Control Motor, Servei de Neurologia, Hospital Clínico, Universidad de Barcelona, Barcelona, Spain, [2] Hospital de Sta Maria, Lisboa, Portugal)

Introduction: Ballistic movement execution is faster when the imperative signal (IS) is accompanied by a loud auditory stimulus

(the StartReact effect). In focal tasks, excitation is increased in the muscles expected to react and decreased in others such as, for instance, the homonymous muscles of the contralateral side. The contrast between the increase and decrease of excitability in homonymous muscles is likely much more marked in SRT than in CRT. We reasoned that, if inhibition is not fully accomplished, some remaining activity would be seen in the muscles not to be responding in a StartReact paradigm using SRT and CRT.

Subjects and methods: In 11 volunteers, we studied the EMG and movement occurring in the forearm muscles of the side contralateral to the one requested to react in SRT and CRT. In 25% of the trials, the IS was accompanied by a SAS.

Results: As expected, reaction time was shorter for trials with SAS than for trials without SAS. This was the case for both, SRT and CRT although the percentage shortening was significantly less for CRT. In no-SAS trials, contralateral activity was absent in SRT, 4% of trials in ART and 18% of trials in CRT. In SAS trials, contralateral activity was seen in 52% of the trials in SRT, in 61% in ART and in 79% in CRT.

Conclusions: The difference between SAS and no-SAS trials in contralateral EMG activity may be explained by the fact that SAS causes precipitated execution preventing the inhibitory action to be fully implemented. Contralateral hand activity could also be a startle-related response but the fact that it is seen in a significant number of trials with no SAS and the fact that it takes a distribution of the triphasic pattern in a few cases makes it unlikely.

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12. The importance of neurophysiological studies in the diagnosis of orthostatic tremor—S. Yagüe[1,2], M. Veciana[2], J. Pedro[2], E. Cases[2], S. Jaumà[2], J. Campdelacreu[2], J. Montero[2] ([1] USP-Instituto Universitario Dexeus, Barcelona, Spain, [2] Hospital Universitario de Bellvitge, Barcelona, Spain)

Background and aims: Orthostatic tremor (OT) is a rare motor disorder characterized by unsteadiness on standing that characteristically decreases markedly on sitting or walking. The diagnosis depends on electromyographic confirmation of a typical 13–18 Hz pattern. It has been assumed an OT generation in the bilaterally projecting brainstem centers regulating stance or tone. Our objective was to present two cases of orthostatic tremor and the neurophysiological studies performed for the diagnosis.

Methods: We describe two patients.The first is a 47-year-old woman that complains of unsteadiness in the lower limbs over 13 years, initially while standing, with increasing disability while walking, and chairbound for the last 6 months. She claimed of postural tremor in the upper limbs associated with weight-bearing. The second is a 42-year-old woman that has a ten-year history of tremor, first involving the arms, and unsteadiness in the lower limbs while standing, that was relieved by sitting, walking or leaning against objects.

Results: Electromyographic (EMG) studies in both patients by recording from tibialis anterior and gastrocnemius revealed a typical 14–16 Hz rhythmic tremor in the lower limbs in orthostatism, which began several seconds after they stood and disappeared while the patients decided to sit down. In patient one tremor was easily provoked in their arms with isometric activation and resolved with isotonic work. After transcranial magnetic stimulation tremor was suppressed and reset: the tremor rhythm post-stimulus differed from the predicted tremor rhythm. EEG back-averaging recorded from the scalp showed an oscillatory activity time-locked with the tremor in the leg.

Conclusions:

1. The diagnosis of OT critically depends on EMG confirmation of the high-frequency (14–16 Hz) EMG pattern, because other symptoms during stance can occur with similar complaints.
2. The tremor appears to be best expressed when the contracted muscles are loaded. Whatever its location, the oscillator probably does not project directly onto motoneurons when subjects make voluntary isotonic contractions.
3. The EMG bursts are time-locked in all 4 limbs, therefore the remor could be generated by a central oscillator.
4. In agreement with some authors, transcranial magnetic stimulation of one cortical leg area resets OT. It can be speculated that the OT generator receives a modulating input from the motor cortex.
5. The confirmation of a cortical oscillatory activity time-locked to tremor discharges in lower limbs could be interpreted as possible involvement of a thalamo-motor cortex loop, as a part of the central oscillatory generator.

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13. Trigemino-cervical reflex: Clinical and neuroradiological links—D.Y. Demiray, M. Kiziltan, S. Saip, U. Uygunoğlu, G. Kizildas, M. Sohtaoğlu (Istanbul University, Cerrahpasa Medicine Faculty Neurology Department, Turkey)

Background: Trigemino-cervical reflex (TCR) is considered to be head protective reflex as well as head and neck postural responses. It is believed that TCR is mediated by polysynaptic brainstem neuronal pathways including trigeminal afferents, trigeminal nuclei and motor neurons of neck muscles. In an attempt to increase our knowledge about the mechanism and alteration of TCR, we studied the trigemino-cervical reflex and the conventional blink reflex (BR) in neurobehcet (NB), multiple sclerosis (MS), and ischemic stroke patients with brainstem involvement. We also recorded the blink reflex to study the association between two different trigeminal reflexes.

Method and patients: We studied 51 patients with focal brainstem lesions and 30 healthy individuals in the control group. All patients underwent a dedicated MRI study of the brainstem and the whole series of brainstem tests, currently used in clinical neurophysiology: early (R1) and late (R2) blink reflex and TCR which were bilaterally recorded from sternocleidomastoid and splenius capitis. P values <0.01 were considered statistically significant.

Results: We studied 30 normal subjects (age 43.16 ± 15.21, range: 21–75 years; 19 women, 11 men), 20 MS (age 32.75 ± 8.6, range: 20–56 years; 11 women, 9 men), 19 stroke (age 56.42 ± 12.46, range: 29–76 years; 5 women 14 men) and 12 NB (age 35.41 ± 8, range: 23–48 years; 4 women, 8 men) patients. All patients had brainstem lesions. Supratentorial lesions were observed in all MS patients and 41% of Neurobehcet patients. We detected statistically significant differences in TCR and blink reflex results among the patient and control groups. Comparison with control data revealed that brainstem involvement is related with abnormal TCR and blink reflex results.

Discussion: Our study suggests that TCR is more sensitive to brainstem lesions than the R2 component of blink reflex. Multiple sclerosis patients had more trigeminal reflex abnormalities compared with others. Its reason may be the widespread distribution of the lesions.

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14. Vestibular modulation of theta band oscillations in human pedunculopontine nucleus—N. Yousif, A. Bronstein, J. Naushahi, D. Nandi, B. Seemungal (Centre for Neuroscience, Imperial College London, United Kingdom)

Background and aims: The pedunculopontine nucleus (PPN) is a new deep brain stimulation (DBS) target, thought to be particularly for useful in ameliorating gait disturbance in Parkinson's disease. Recent evidence shows a prominent theta (4–7 Hz) rhythm in the PPN (Tsang et al., Neurology, 2010; Simon et al., J. Neurophysiol., 2010; Shimamoto et al., JNNP, 2010). Given that theta activity is modulated by vestibular signals elsewhere in the brain, e.g. hippocampus, (Shin, Synapse, 2010; Chen et al., Neuroimage, 2010), we assessed whether vestibular signals modulate PPN theta activity.

Methods: We recorded local field potentials (LFPs) in three patients with implanted bilateral subthalamic nucleus (STN) and PPN DBS electrodes at 2000 Hz and filtered at 0.5–500 Hz at rest and during passive, yaw-plane whole body rotations (i.e., vestibular stimulation) at 0.2 and 0.4 Hz with eyes closed and then open with manifest vestibular ocular reflex activation (i.e., nystagmus) and then with VOR suppression (VORS). Frequency power spectra and the average power across a 1–1000 Hz frequency range were obtained.

Results: PPN LFPs showed significant modulation during vestibular activation (rotations) compared to rest with power changes ca. four times larger than those found in the STN. The PPN LFP was dominated by theta (4–7 Hz) activity which was enhanced during all tasks compared to rest (including eyes open vs. closed at rest) except for VORS where there was a clear reduction in theta activity and this was more prominent for 'fast' (i.e., 0.4 Hz rotations) rotations. The pattern of theta activity was the same for right and left PPN including task-dependent modulation. To rule out the possibility that this theta activity was purely driven by nystagmus, we recorded LFPs during optokinetic nystagmus (OKN). OKN was associated with a *decrease* of theta power compared to rest.

Conclusions: This is the first demonstration of vestibular modulation of PPN activity (in either animals or humans). Human PPN activity is increased during vestibular activation with a relative suppression of theta during VORS. This pattern of a reduction of activity during VORS compared to VOR is seen in the vestibular nuclei. Thus, the PPN may represent an important component of vestibular processing within the brainstem. We speculate that given the role of the vestibular system in balance and posture, PPN DBS may be work to improve gait and balance control via vestibular circuits.

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15. Functional mapping of monaural auditory brainstem responses—P. zu Eulenburg [1], W. Mueller-Forell [2], M. Dieterich [3] ([1] Department of Neurology, Johannes Gutenberg-University, Mainz, Germany, [2] Department of Neuroradiology, Johannes Gutenberg-University, Mainz, Germany, [3] Ludwig-Maximilians University, Munich, Germany)

Introduction: The auditory brainstem circuits on the basis of rat and cat experiments include the dorsal and ventral cochlear nuclei, the superior and medial olivary nuclei, the lateral lemniscal nucleus and the inferior colliculus. The aim of this fMRI study was to determine whether an auditory broadband stimulus which covers all frequencies of human hearing can induce significant ponto-medullary BOLD responses in humans to reveal the entire auditory pathway after monaural stimulation. If so could one also demonstrate a right ear preference for the processing of monaural signals in right-handers? (Hugdahl, 2008).

Methods: The differential effects of continuous monaural auditory broadband stimulation on activation of the auditory circuits in the brainstem were studied in 18 right-handed and 16 left-handed healthy volunteers in a clinical 1.5 T scanner. The protocol included 141 volumes in alternating blocks of seven images at rest, six during stimulation. Random effects statistical analysis was done with SPM5 ($p < 0.001$) after preprocessing with a toolbox for cerebellar and brainstem responses (Diedrichsen, 2006). We also obtained a high-resolution sagittal T1-weighted image to test for morphological differences in brainstem anatomy between the groups of left-and righthanders.

Results: One sample *t*-test over all subjects and stimulations showed a significant activation of the cochlear nuclei, the olivary complex and the inferior colliculi bilaterally. Unilateral stimulation of the auditory afferences revealed a response of the ispsilateral cochlear nucleus and the contralateral inferior colliculus for all subjects. Righthanders showed a significantly stronger activation of the right cochlear nucleus in a between group comparison over all stimulations. Statistical testing for the side of stimulation between the groups revealed a significant activation of the left lateral lemniscal nucleus for righthanders after stimulation of the right ear.

Conclusions: This is the first demonstration by means of fMRI that monaural broadband stimulation can elicit significant activations of all known relay stations in the auditory brainstem. Unilateral white noise showed significant crossed activations of the ipsilateral cochlear nuclei and the contralateral inferior colliculus despite anatomically known bilateral ascending projections from the cochlear nuclei. This pattern of crossed activations has already been observed for the cortical processing of acoustic stimuli and seems to be dependant on the character of the acoustic stimulus. Laterality as measured by handedness scores gave a predominant BOLD response in the right cochlear and the left lateral lemniscal nucleus for righthanders when compared to lefthanders. Our finding might reflect the right ear preference in righthanders.

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16. Increasing clinical variety of brainstem infarcts—F. Thömke, J.J. Marx (Department of Neurology, University Medical Center of the Johannes Gutenberg-University Mainz, Germany)

Background and aims: Classical crossed brainstem syndromes and lacunar brainstem syndromes are well known consequences of brainstem infarcts. With the widespread use of magnetic resonance imaging (MRI), an increasing variety of clinical manifestations of brainstem infarcts were recognized. This prompted us to review this topic.

Methods: Review of possible clinical manifestations of brainstem infarcts based on MRI findings.

Results: Previous knowledge and more recent findings indicate the existence of 3 main groups of brainstem infarcts.

- **Classical crossed brainstem syndromes** are due to *infarcts, which involve intra-axial cranial nerve segments and long tracts.* A variety of more than 25 classical brainstem syndromes have been described and were named according to their first describer(s). They are used as eponyms to characterize a complex neurological state.

Signs and symptoms of an eponym, however, may differ between different papers and some eponyms used to characterize a certain neurological state differ from the original description. Except for Wallenberg's syndrome, classical brainstem syndromes are rarely seen in clinical practice.

- **Lacunar brainstem syndromes** are the consequence of *infarcts, which involve long tracts and spare intra-axial cranial nerve segments.* This group includes pure motor or pure sensory stroke, dysarthria-clumsy hand syndrome, or ataxic hemiparesis. Such infarcts may also cause body lateropulsion with or without limb ataxia, internuclear ophthalmoplgia, skew-torsion sign, or ocular tilt reaction. Small deep infarcts, which solely affect certain nuclei, may be followed by horizontal or vertical gaze palsies, upbeat nystagmus, isolated facial palsy, pseudoneuritis vestibularis, or isolated vomiting. Lacunar syndromes are more frequent than classical brainstem syndromes.
- **Isolated cranial nerve dysfunctions** are due to *infarcts, which involve intra-axial cranial nerve segments and spare long tracts*, and were reported for 3rd, 4th, 5th, 6th, 7th, or 8th nerves. This is the clinical manifestation of some percent of infarcts in the vertebrobasilar territory.

Conclusions: Except for classical brainstem syndromes and lacunar syndromes, a considerable number of infarcts in the vertebrobasilar territory manifest themselves as isolated cranial nerve palsies or isolated ocular motor dysfunctions.

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17. Masseter reflex abnormalities with meso-diencephalic lesions—F. Thömke [1], P. Stoeter [2], J.J. Marx [1] ([1] Department of Neurology, University Medical Center of the Johannes Gutenberg-University Mainz, Germany, [2] Institute for Neuroradiology, University Medical Center of the Johannes Gutenberg-University Mainz, Germany)

Background and aims: According to current knowledge, unilateral masseter reflex (MassR) abnormalities indicate ipsilesional brainstem lesions between the levels of 5th and 3rd nerve nuclei, provided that 5th nerve functions are intact. We re-discuss possible suprasegmental influences on the MassR based on occasional observations of single patients with unilateral meso-diencephalic lesions and ipsi- or contralesional MassR abnormalities.

Methods: Occasional observation of 4 patients with MRI-documented acute unilateral meso-diencephalic infarcts rostral to the 3rd nerve nucleus level with contralesional (3 patients) or ipsilesional (1 patient) MassR abnormalities.

The MassR was elicited by a brisk tap with a reflex hammer on the patient's jaw and recorded simultaneously on both sides with surface electrodes placed over the muscle belly (bandwidth 20–2000 Hz). The recording was triggered at the moment of the mechanical tap by a signal from a piezo-electric element mounted in the hammer. Latency refers to the onset of the electromyographic response. Mean latencies were calculated from 10 successive events. MRI: Axial and sagittal high-resolution T1- and T2-weighted MRI (slice thickness: 3 mm) before and after intravenous Gadolinium was done with a 1.5 Tesla superconducting system in 3 patients. One patient had T1- and T2-weighted imaging with 5 mm slice thickness using a 1.0 Tesla superconducting system.

Results: Three patients had contralesional and one ipsilesional MassR abnormalities. Two had an abnormal delay of the MassR latency and the other 2 loss of the MassR. Re-examinations were done in 3 patients and documented normalization in 2 and improvement in one patient.

Conclusions: Normalization or improvement MassR abnormalities were seen in all re-examined patients indicating acute lesions. Bilateral and predominantly contralateral excitation of masseter motoneurons occur after transcranial magnetic stimulation of the motor cortex, but lesions of descending projections from the motor cortex seem unlikely to cause MassR abnormalities, as supratentorial lesions are not followed by MassR abnormalities. Impaired facilitation of masseter motoneurons may be another possible mechanism of abnormal MassR findings. In animals, MassR facilitation was shown to be mediated by a projection from the amygdala via interneurons to contralateral trigeminal motoneurons. If a similar connection also exists in humans, it may be affected by meso-diencephalic lesions causing MassR abnormalities due to impaired MassR facilitation. Depending on the site of the lesion, i.e. before or after the crossing of this projection, MassR abnormalities may be contralesional or ipsilesional.

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18. Where is my hand? The blink reflex evoked by hand stimulation is increased when the hand enters the peripersonal space surrounding the face—C. Sambo, M. Liang, G.D. Iannetti (Department of Neuroscience Physiology, Pharmacology, University College London, United Kingdom)

Background: Electrical stimulation of the hand elicits a blink reflex that has the features of a startle response. In a Sherringtonian sense, this is a defensive reflex, probably mediated by a brainstem circuit.

Objectives: To explore whether the magnitude of the blink reflex evoked by hand stimulation is dependent on the position of the hand, i.e. whether its magnitude is different when the stimulated hand is inside or outside the area of peripersonal space surrounding the face.

Methods: In 15 healthy participants we recorded the electromyographic activity from the orbicularis oculi muscles in response to electrical stimulation of the median nerve at the left and right wrist. In accordance with previous reports, six participants (40%) showed a reproducible hand-evoked blink reflex. In these responders we recorded the blink reflex elicited by the stimulation of the right and left median nerve, while the subjects were sitting with their arm either extended, with the hand close to the ipsilateral knee ('far' condition), or flexed with the hand close to the ipsilateral side of the face ('near' condition), in alternated trials. Furthermore, in these subjects we recorded the early (R1) and late (R2) responses of the blink reflex elicited by the electrical stimulation of the supraorbital nerve, in the same two conditions ('far' and 'near'). The magnitude of the response was analysed using a repeated-measures, two-way ANOVA, with 'recording side' (two levels: 'ipsilateral' and 'contralateral') and 'hand position' (two levels: 'far' and 'near') as factors. Furthermore, to disclose the time course of the effects of 'recording side' and 'hand position' on the reflex response, we performed the same repeated-measures ANOVA, but using each time point of the averaged reflex response, as implemented in LetsWave.

Results: The magnitude of the blink reflex was significantly larger (+66.8 ± 21%) when the stimulated hand was inside the area of peripersonal space surrounding the face (main effect of 'hand position', $p = 0.002$), both in the ipsilateral and the contralateral recording side (no interaction between the two factors, $p = 0.32$). By contrast, the magnitude of the blink reflex evoked by the electrical

stimulation of the supraorbital nerve was not modulated by the position of the hand.

Conclusions: This result provides strong evidence that the neural circuits mediating the blink-reflex evoked by hand stimulation undergo significant top-down modulation, in that their excitability is increased when the stimulated hand enters the peripersonal space surrounding the face. Thus, this modulation is dependent on the knowledge of *where* the eliciting stimulus is located, not only according to a somatotopic, but also to a space-based, egocentric frame of reference.

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