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Oral Presentations

OP-01

Globus Pallidus Structural Alterations, Motor Phenomenology and Response to Deep Brain Stimulation: a Correlation Study in a Cohort of Subjects with Generalized Dystonia

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Introduction: Deep brain stimulation (DBS) applied to the globus pallidus, pars interna, proved to be the most efficient symptomatic treatment of generalized and segmental dystonias. In this study, we specifically questioned potential correlations between structural alterations of the GPi and dystonia phenomenology and, correlations between GPi alterations and DBS outcome.

Methods: Retrospective observational study in a cohort of subjects treated with GPi DBS for generalized dystonia. Dystonia severity has been assessed by BFMDRS and motor phenotype by using a motor phenomenology evaluation grid (MPEG). MRIs have been reviewed for GPi signal and volume alterations. We compared motor scores over follow-up between the group without and with GPi alterations. We used Supervised Machine Learning algorithms and H2O Flow Open Source software to study correlation between GPi structural alterations, motor phenomenology and response to DBS. To identify the variables predicting the best dystonia severity pre-DBS and under DBS, we used Gradient Boosting Machine. Multiple correspondence analysis (MCA) was used with the statistical software R with FactoMineR package (Multivariate Exploratory Data Analysis and Data Mining) to summarize, visualize and describe the datasets and ADE4, tools for multivariate data analysis.

Results: Forty subjects (19 male, mean of age at onset, 7,5 years; at DBS surgery, 15,5 years) have been included: group A (n=21) and group B (n=15) subjects without and with structural alterations of the pallidum, respectively (MRI not available in four). Significant difference was found at one year follow-up under DBS between the two groups ($p=0,0157$) (group A, 14.84 ± 14.8 ; group B : $31,3\pm13.7$).

The MPEG allowed to collect dystonia distribution, occurrence, characteristics and associated movement disorders. For MCA, correlations between the studied variables relate to pallidal structural alterations, cranial involvement and bradykinesia. Further correlation is established between the phasic component of dystonia, rest component for dystonia and the absence of structural alterations of the globus pallidus.

Discussion: The MPEG allowed to capture dystonia and associated movement disorders and correlations with DBS target structural alterations and clinical response to DBS. GPi structural alterations do not influence dystonia severity preoperatively but therapeutical response to DBS. The variables explaining the best dystonia severity scores vary between different time points of the follow up.

OP-02

The Dutch Yips Study

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Introduction: The Yips is a neurologic movement disorder among golfers, present especially during putting, which gives the ball the wrong speed and direction. It is categorized among the group Focal Task-Specific Dystonia's (FTSD). Little is known about the prevalence of the Yips and the factors that contribute to its emergence. To investigate the prevalence of the Yips in a well-defined group of golfers and to determine potential risk factors, we performed a web-based study among all golfers of a large Dutch golf club, as part of the Dutch Yips study.

Methods: All members (n=912) of a large golf club in the eastern part of the Netherlands were approached by mailings and via the homepage of the golf club. Participants anonymously filled in a web-based questionnaire. Questions were about gender, age, golf handicap (present and best ever), dominant hand, years of playing golf, onset and duration of Yips, occurrence of Yips (putting, chipping, irons and/or driving), side affected, smoking, alcohol use, a fanaticism score on sports (VAS score), a fanaticism score on golf (VAS score), competition-tension (VAS score), possible obsessive-compulsion traits, current medication, medical history, family history of neurologic diseases, other first-degree family members with the Yips, and a validated dystonia screening questionnaire

Results: Out of 912 eligible golfers, 234 (26%) completed the questionnaire. Among them, 234, 150 (64%) were men. Mean age was 61years (range 20-84 yr). Mean handicap was 18.7 (range 0-54). There were 52 (22%) golfers who reported to suffer from the Yips. A further 20 indicated to possibly be affected by the Yips. The Yips emerged after a mean of 17 years (range 0-44 yr) of playing golf. Further data are currently being analyzed and results will be presented at the meeting.

Discussion: This part of the Dutch Yips Study attempted to provide insight into the prevalence of the Yips in an unbiased, large cohort of golf players and into factors that might be associated with its emergence. In a total of 912 eligible golfers of an average golf club, we retrieved a minimal prevalence of 5.7% with the Yips. This prevalence rate would be remarkably high for a movement disorder and particularly for a FTSD. With 400,000 golfers in the Netherlands, there could be almost 23,000 golfers affected by the Yips, and worldwide more than a million. This indicates that further studies on the pathophysiology an treatment of the Yips, and other sports-related focal dystonia's, are warranted.

OP-03

Life Satisfaction of Musicians with Focal Dystonia

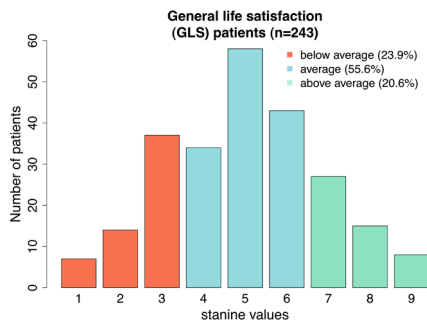
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Introduction: Musician's dystonia (MD) is a task specific movement disorder that severely impairs the ability to execute highly trained movements that in many cases leads to the end of the musician's career [1][2]. Therefore, apart from the immediate impact on musicians' professional careers, dystonia may affect general life satisfaction (GLS), especially for those who have to change their profession as a result of the disorder. Interestingly, little is known about the impact of dystonia on musicians' life satisfaction (GLS) or the satisfaction with their "job" or "health".

Methods: We asked patients with MD and a group of healthy musicians (controls) to complete a life satisfaction questionnaire [3]. We analyzed responses from those who had to change their profession and those who did not, and we assessed life satisfaction scores in relation to the duration and the course of the condition.

Results: Of the 642 patients contacted, 295 responded (46%). We excluded 52 amateur musicians and analyzed a sample of 243 patients with MD. We contacted an unknown number of healthy musicians and 57 responded. We found no differences in life satisfaction between patients and controls or between patients who had to change their profession and those who did not and no correlations between life satisfaction and the duration or the course of the disease.



Discussion: General life satisfaction and satisfaction with their job or health does not differ between musicians suffering from musician's dystonia and healthy musicians. Likewise, general life satisfaction does not differ between patients with MD and the general population. Finally, general life satisfaction does not differ between MD patients who had changed their job and those who had not. This suggests that musicians find a way to cope with dystonia, irrespective of whether they have to change their profession or not [4][5]. Patients should be made aware of self-regulatory mechanisms and the high probability of being able to cope with their situation. Physicians should support patients in proactively selecting their goals and in achieving them.

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OP-04

Pallidotomy in life-threatening dystonic storm after DBS-withdrawal

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Introduction: Dystonic storm, even called Status Dystonicus (SD), is a rare condition but carries a high mortality risk due to severe painful generalized dystonia, fever, tachycardia, tachypnea, hypertension, autonomic failure, bulbar impairment with dysarthria, dysphagia, respiratory failure, myoglobinuria and renal failure, leading to death [1]. Patients are typically treated in an intensive care unit (ICU), and in many refractory cases, surgery can be life-saving. Deep brain stimulation (DBS) of the globus pallidus internus (GPI) is the first choice, but if DBS is not available, a unilateral (or staged bilateral) pallidotomy is the next-best treatment. In patients with dystonia who are on chronic DBS, a sudden failure of the stimulation due to depletion of the battery can result in severe rebound of symptoms that develops into a life-threatening SD, necessitating an emergency replacement of the neuropacemaker. But what happens in patients on DBS who enter a SD due to removal of the hardware because of infection and cannot be re-implanted, or who cannot afford to pay for a new neuropacemaker when the battery is empty? They can die [2]. In these cases a unilateral pallidotomy may be life-saving.

Methods: The literature on surgical treatment of SD was reviewed, including surgery when a SD results from a "malignant DBS-withdrawal syndrome". Own experience is limited to two cases where a protracted severe SD leading to intensive care treatment occurred following removal of DBS.

Results: The reviewed literature is in agreement that pallidotomy is still valid in situations with SD where DBS is not possible (such as post-infection explantation of DBS hardware, or when DBS is not affordable) [1, 3-6]. In one personal case of a patient with dystonia-chorea neuro-acanthocytosis, removal of hardware due to infection led to a severe SD and ICU treatment. A new DBS was implanted too early while patient was still septic, which led to an abscess in the left pallidal area that required surgical aspiration. This patient recovered eventually and subsequently his clinical status required only a unilateral DBS contralateral to the abscess-provoked "pallidotomy". The second patient had sepsis with removal of the DBS hardware leading to a SD and was treated in ICU with tracheostomy and ventilator for several weeks, without success. A unilateral pallidotomy was performed. One day later, the SD had resolved and the patient was awake and removed from the ventilator.

Discussion: Failure of DBS in patients with dystonia can become a medical emergency. Rebound of symptoms can lead to potentially fatal SD. Emergency replacement of the neuropacemaker is necessary, and should be done as early as possible. If DBS is not possible to maintain or is not affordable, a pallidotomy may be life-saving. Pallidotomy in SD is efficacious but underused, even when needed!

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Posters

P-01

Correction of Masticatory Muscles Hypertone Using Botulinum Toxin Type A RELATOX® in Patients with Bruxism

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Introduction: As is known, malocclusion and oral parafunctions may facilitate the development symptoms of cranio-mandibular disorders. Such parafunctions as “bruxism”, “clenched jaws symptom” are accompanied by increased muscle activity and hypertrophy of masticatory muscles. Study objective: to estimate efficiency of botulinum toxin type A RELATOX® application in order to stop the pain syndrome and reduce the hypertone of masticatory muscles in patients with occlusive parafunctions under the control of superficial electromyography.

Methods: In total 24 patients with bruxism participated in the study; their average age was 40-42 years; of those 68% were females and 42% – males. All patients were divided in two groups: the patients of 1st group were receiving conventional treatment (muscle relaxants) and the patients of 2nd group – injections of BTA type A in masticatory and temporal muscles. The average dose in masticatory muscles was 30-50 units in each side, in temporal muscles – 15-20 units in each side. Superficial electromyography of masticatory, temporal and neck muscles was performed to the patients of both groups before initiation of treatment and during the treatment. The electromyography control of 2nd group patients was performed on 3, 7, 14, 21 day and once a month over the period of six month.

Results: The first signs of clinical effect appeared from the 2 to the 6th day, the maximum effect was observed on 14th day. The parameters of superficial electromyography of masticatory and temporal muscles after botulinum toxin type A RELATOX® injections showed the decrease of average amplitude of total bioelectric potential of injected muscles on average in 2-3 times which is indicative of myorelaxation. The follow-up control performed a period of 6 months gave evidence the duration of the effect's. Estimation of clinical data in patients, who received conventional neurological treatment, has shown that the effects of performed treatment was of short duration or was absent which was a cause to administer later on the BTA injections also to the patients of 1st group.

Discussion: The performed study has shown the positive action of botulinum toxin type A RELATOX® on electromyographic characteristics, reflecting functional status of masticatory muscles. It's good clinical effect allowed us not to use any medicines for a long period of time.

P-02

Successful Treatment of Hand Dystonia with Botulinum Toxin in a DYT12 Patient

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Introduction: Dystonia 12 (DYT12) or rapid-onset dystonia-parkinsonism is a rare neurological disease with onset in childhood or early adulthood. The responsible mutated gene is ATP1A3 (19q13.2) [1]. In the classical phenotype, patients develop dystonia, combined with a non-tremulous parkinsonian syndrome, postural instability, dysarthria and dysphagia [1]. The few published reports of ATP1A3-mutated patients who received pallidal surgery (GPi-DBS - deep brain stimulation, or pallidotomy) are disappointing as all implanted patients failed to improve [2] [3]. In this situation, botulinum toxin remains one of the options to treat focal dystonia.

Methods: We report the case of a 16-year old boy affected by DYT12 since he was 12 and presenting with asymmetric generalized dystonia, parkinsonian syndrome and prominent bulbar involvement. Due to a severe, particularly painful and invalidating dystonia of his left hand, he asked for botulinum toxin to relieve the symptoms. We injected 200 units of incobotulinum toxin type A (Xeomeen®) in left flexor digitorum profundus, flexor digitorum superficialis, and flexor pollicis longus, under combined ultrasound and EMG guidance to increase the chances of successful treatment. The dilution employed was 2 mL for 100 units. It has been decided to realize the injections under general anesthesia, because of the large number of injections needed and the boy's needle phobia.

Results: One month later, his left hand was free from dystonia (Fig. 1), easy to mobilize and much less painful. He was able to pick up little objects. The effect of botulinum toxin was sustained during at least three months.



Fig. 1: Left panel. Forearms before treatment, with bilateral hand dystonia. Right panel. Left hand one month after treatment (only the left hand has been injected).

Discussion: As GPi DBS is not currently demonstrated as effective in DYT12 treatment, botulinum toxin can be successfully used to selectively treat limb dystonia. Guidance techniques, such as EMG, ultrasound or both, should be used as the dystonic pattern may be complex.

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P-03

Postural Instability and Gait Disorder after bilateral Pallidotomy in Patients with Dystonia

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Introduction: Surgical treatment of dystonia can involve either deep brain stimulation (DBS) or lesioning (pallidotomy) of the globus pallidus internus (GPI). In recent years, GPi-DBS as a treatment for dystonia has been reported to cause complications of stimulation induced parkinsonism, but pallidotomy has not. Our objective is to investigate whether or not pallidotomy as a treatment for dystonia can cause postural instability and gait disorder (PIGD).

Methods: We took as our subjects 57 patients that had undergone pallidotomy procedures (32 unilateral pallidotomy, 2 simultaneous bilateral pallidotomy, 23 staged bilateral pallidotomy) between March 2015 and March 2017 at the Department of Neurosurgery, Tokyo Women's Medical University, and retrospectively examined their case files for postural instability and gait disorder. Our evaluation for PIGD used MDS-UPDRS items 3.10 (gait), 3.11 (freezing of gait), 3.12 (postural instability), 3.13 (posture), and 3.14 (bradykinesia).

Results: Among the 57 cases examined, PIGD had occurred in 6. All of these cases were ones in which the patient had undergone a bilateral pallidotomy. The mean length of the follow-up period was 21.3 ± 8.3 months. Mean scores for MDS-UPDRS items 3.10, 3.11, 3.12, 3.13, 3.14 were 2.2 ± 0.8 , 2.3 ± 0.5 , 3.5 ± 0.5 , 0.8 ± 0.8 , and 2.0 ± 1.1 , respectively. Other forms of parkinsonism observed were dysdiadochokinesia, which occurred in 4 cases, and micrographia, which also occurred in 4 cases. In all cases, oral administration of 300 mg of levodopa did not improve symptoms. In 3 cases, MRIs conducted 3 months post-surgery revealed that the lesion formed during pallidotomy had penetrated out into the globus pallidus externus (GPe). Aside from micrographia, all symptoms did not improve with time over the follow-up period. PIGD was severe in 3 cases, and had worsened to a level where assistance in daily life was required.

Discussion: It is possible for bilateral pallidotomy to cause the emergence of PIGD, which may then become refractory PIGD. Further investigations of the safety of bilateral pallidotomy is required.

P-04

Abnormal Sensorimotor Processing in Cervical Dystonia in Functional Magnetic Resonance Imaging

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Introduction: Cervical dystonia (CD) is a movement disorder characterized by involuntary muscle contractions leading to abnormal head posture. Despite predominantly focal manifestation, CD is also associated with discrete deficits in praxis and abnormal sensorimotor activation during sequential finger movements. We assessed brain activation during voluntary sequential finger tapping in CD patients while manipulating task complexity.

Methods: Participants (15 CD patients, 12 healthy controls) underwent one 3T fMRI session, during which they performed blocks of sequential finger tapping with their right hand according to visual cues. Each tapping epoch (TAP) included 4 repetitions of a 4-item sequence presented once during cue epoch (CUE). One half of the blocks consisted of a repeated simple constant sequence (CON condition), whereas the second consisted of unique pre-randomized sequences (RAN condition).

Results: In both groups, RAN-TAP was associated with increased activation in the premotor and posterior parietal cortices and decreased activation of the default mode network, whereas CON-TAP resulted in increased activation of the basal ganglia. In combined condition RAN+CON-TAP, patients activated more the left parietal operculum and less the bilateral sensorimotor cortex. During CUE, patients activated more the medial frontal cortex and activated less the left frontoparietal network. They also activated more bilateral premotor cortices during RAN-CUE, but not during CON-CUE.

Discussion: We provide evidence for differences in the cortical representation of simple and complex motor sequential movements between patients with CD and healthy controls, confirming that CD is a system-wide disorder of central motor control and planning.

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P-05

Prevalence and Natural History of X-linked Dystonia Parkinsonism in Koronadal City, South Cotabato

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Introduction: X-linked Dystonia Parkinsonism is an adult-onset, progressive, debilitating movement disorder, manifesting predominantly with dystonia in combination with parkinsonism. It was first reported in 1975 among males in Panay Island, Philippines. The region of South Cotabato in Mindanao with its capital Koronadal City, is populated by migrants from Panay Island. The estimated population of the region is 912,957 as of 2015 and the major ethnicity, comprising 51%, are from the Panay Island. This paper calls attention to this migration and aims to identify cases and describe the clinical picture of XDP in Koronadal City.

Methods: A descriptive study using the screening questionnaire for X-linked Dystonia Parkinsonism was used per barangay to look for possible cases. Cases were confirmed through a one on one interview and assessment by a movement disorder specialist.

Results: From those screened by barangay health workers, four cases of X-linked dystonia parkinsonism from Koronadal City were seen. They were all male, presenting with generalized dystonia. With a population of 174, 942 and 4 cases of XDP, the prevalence in Koronadal City is 2.28 per 100,000. All four participants with X linked dystonia Parkinsonism were male between the 41 to 50 age bracket. The clinical features of these patients shows a mean age of onset at 38.25 years old and a mean age at initial examination at 40.25 years old. The mean duration of illness from onset to present is 3.5 years and the mean duration of illness from onset to generalized dystonia is 2.75 years. Three of these patients initially presented with craniofacial symptoms like blepharospasm, facial twitching and jaw opening.

Discussion: The phenomenology of these cases is similar to the 2011 study involving 312 patients. Another 11 patients from other municipalities of South Cotabato came also for evaluation. They were not included in the screening per barangay since this study was limited to Koronadal City. An expansion of this study to involve the entire region of South Cotabato is warranted to provide a more accurate picture of the prevalence and natural history of the disease in the region. XDP has spread to different areas due to migration. With this knowledge of the migration of people from Panay Island to South Cotabato in Mindanao and the discovery of possible XDP cases through this study, research work can be triggered to expand to this region where the knowledge about the disease is few and the help extended to XDP sufferers is scarce.

P-06

Maladaptive Striatal Plasticity and Abnormal Reward-learning in Cervical Dystonia

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Introduction: In monogenetic generalized forms of dystonia, in vitro neurophysiological recordings have demonstrated direct evidence for abnormal plasticity at the level of the cortico-striatal synapse[1] [2]. It is unclear whether similar abnormalities contribute to the pathophysiology of cervical dystonia, the most common type of focal dystonia. Study objectives: To investigate whether abnormal cortico-striatal synaptic plasticity contributes to abnormal reward-learning behavior in patients with focal dystonia.

Methods: Forty patients and forty controls performed a reward-gain and loss-avoidance reversal learning task. Participant's behavior was fitted to a computational model of the basal ganglia incorporating detailed cortico-striatal synaptic learning rules. Model comparisons were performed to assess the ability of four hypothesised receptor specific abnormalities of cortico-striatal long term potentiation (LTP) and Long Term Depression (LTD): increased or decreased D1:LTP/LTD and increased or decreased D2: LTP/LTD to explain abnormal behavior in patients.

Results: Patients were selectively impaired in the post-reversal phase of the reward task. Individual learning rates in the reward reversal task correlated with the severity of the patient's motor symptoms. A model of the striatum with decreased D2:LTP/ LTD best explained the patient's behavior, suggesting excessive D2 cortico-striatal synaptic depotentiation causes biased reward learning in patients with cervical dystonia.

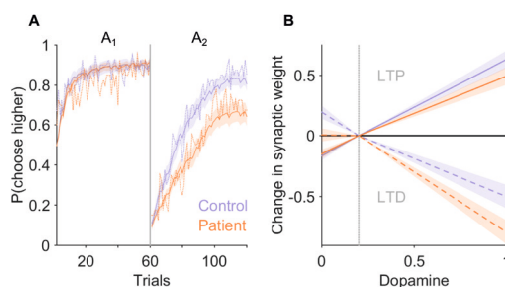


Fig. 1: (A) Average choice probability for patients and controls with model performance overlaid. (B) Dopamine-weight change curve for the optimally fitted basal ganglia model.

Discussion: Reversal learning impairment in cervical dystonia may be a behavioural correlate of D2 specific abnormalities in cortico-striatal synaptic plasticity. Reinforcement learning tasks with computational modeling could allow the identification of molecular targets for novel treatments based on their ability to restore normal reward-learning behavior in these patients.

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P-07

The Long-Term Effect of Continuous Apomorphine Treatment on Camptocormia in Parkinson's disease: a 24-months Longitudinal open, prospective Follow-up Study

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Introduction: Camptocormia in Parkinson's disease (PD) responds poorly to botulinum toxin injections, manipulation with dopaminergic treatment or deep brain stimulation. The results of our previous pilot study showed good therapeutic effect of subcutaneous apomorphine infusions in a small cohort of patients. The aim of the study was to assess the long-term effect of subcutaneous infusions of apomorphine in the treatment of camptocormia in advanced Parkinson's disease.

Methods: 11 patients with Parkinson's disease, who developed camptocormia, were treated with subcutaneous apomorphine infusion and followed-up for the period of 2 years. All patients were treated with L-DOPA and dopaminergic agonists at the time when camptocormia appeared; none of them improved following the manipulation of dopaminergic treatment or application of botulinum toxin injections. In the case of positive response to apomorphine challenge (i.e. substantial improvement of camptocormia), the treatment by continuous subcutaneous infusions of apomorphine was initiated. Apomorphine dose was gradually titrated, according to the clinical response and tolerance, up to daily dose ranging from 40 to 70 mg. All patients were regularly monitored over a 24-month follow-up period.

Results: The camptocormia improved in all patients after four weeks of continuous apomorphine treatment, and this effect remained stable over the whole follow-up period in 10 of them. In one patient, the therapy was discontinued due to loss of effect after one year; the patient later developed the clinical phenotype MSA-P type. The side effects in all patients were rare and not serious.

Discussion: Apomorphine hydrochloride in the form of continuous subcutaneous infusion can be successfully and safely used for the long-term treatment of camptocormia in the advanced stage of Parkinson's disease.

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P-08

Psychological and Environmental Factors in the Onset of Musician's Focal Dystonia: an Exploratory Grounded Theory Study

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Introduction: Musician's Focal Dystonia (MFD) is a neurological disorder with unknown pathophysiology, affecting highly skilled musicians. It has been suggested in recent studies that apart from genetic predisposition and the repetition itself, negative psychological traits and environmental contributors might be risk factors. The current study's aim was to explore these in more detail to understand their role in the onset.

Methods: Due to the study's exploratory nature, a qualitative constructivist Grounded Theory (GT) design was chosen, with the goal of generating a theory which emerges directly from the data. 12 MFD sufferers (4 females, mean age=37.5 years) were interviewed for the study. The inclusion criteria were to be a professional musician and to have been diagnosed with MFD by a medical professional. The participants were recruited from online support groups on a voluntary basis. Each interview lasted for approx. 90 minutes and their transcripts were coded following the methodology of GT.

Results: Apart from previously identified negative traits, such as anxiety, perfectionism, and neuroticism, the findings also include environmental factors, especially the negative influence of instrumental teachers. Many participants reported unattainable demands, negative emotional climate, and technique-focused teaching in their instrumental lessons. Furthermore, these characteristics seemed to have influenced their behaviours after their studies were finished, in the form of unhealthy practice habits and negative perfectionism. In addition, many participants reported personal or professional trauma before the onset of the condition.

Discussion: These findings support the theory that MFD is a multifaceted condition which could partially originate from problematic psychological traits. It also suggests that environmental factors – especially the educational approach – might be more influential than previously thought. This might have further implications not only for the current research but for the treatment strategies as well. In order to further explore these factors, the researchers are currently conducting a second interview study with medical professionals. The theoretical framework based on the findings of both studies will subsequently inform a deductive quasi-experimental study, comparing MFD sufferers with healthy control musicians.

P-09

How Satisfied are Cervical Dystonia Patients after 3 years of Botulinum Toxin Treatment?

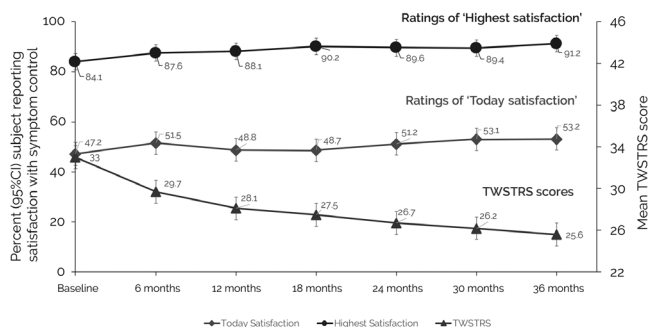
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Introduction: Cervical dystonia (CD) typically requires regular repeat injections of botulinum toxin for maintained symptomatic control. We aimed to track disease severity (as assessed by Toronto Western Spasmodic Torticollis Rating Scale [TWSTRS] scores) and patient satisfaction with abobotulinumtoxinA (AboBoNT-A) over 3 years of treatment.

Methods: INTEREST IN CD2 (NCT01753349) is an observational study following CD patients treated with BoNT-A over 3 years. At each injection visit, subject's clinical status was assessed using TWSTRS and subjects reported satisfaction with the previous BoNT-A treatment cycle in 2 ways: (1) 'Highest satisfaction', assessing the highest level of satisfaction with symptom control over the previous cycle. (2) 'Today satisfaction', assessing current satisfaction at the end of treatment cycle.

Results: 466 subjects were treated with AboBoNT-A over 3 years (median dose/number of treatment cycles: 500 units/10; 60.5% of subjects were reinjected with an interval of 12-16 weeks and 38.8% with a >16 weeks interval). Of these, 62% were female; mean age was 54.1 ± 12.9 years and median time since diagnosis was 6.5 years. Over the course of 3 years treatment, subject levels of satisfaction (both types) remained relatively stable from the first to the last injection visit [Figure1]. Ratings of highest satisfaction by time periods (84.1% - 91.2%) were higher than ratings of Today satisfaction (48.7% - 53.2%). This consistent level of satisfaction was in contrast to mean TWSTRS Total scores, which continued to decrease over the course of 3 years (from 33.0 at baseline to 25.6 at 3 years).



Satisfaction (n)	422	460	453	458	451	452	466
TWSTRS (n)	466	459	453	458	449	453	466

TWSTRS Total scores and subject satisfaction with symptom control over 3 years

Discussion: In this study, despite continued improvements in clinical features (TWSTRS) over 3 years, subject satisfaction with symptom control remained relatively constant. This may indicate that factors other than symptom control also play a role in patient satisfaction.

P-10

Factors Predicting Long-term Patient Satisfaction with Botulinum Toxin Treatment in Cervical Dystonia

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Introduction: We investigated factors influencing patient satisfaction with long-term botulinum toxin-A (BoNT-A) treatment for cervical dystonia (CD).

Methods: INTEREST IN CD2 (NCT01753349) is a 3-year observational study following CD patients treated with BoNT-A. Multivariate stepwise logistic regression analyses were used to determine potential predictors for treatment satisfaction in all treated subjects (N=995) with post-baseline assessment of treatment satisfaction and Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) scores. Satisfaction was assessed at the last visit (closest to the 3-year time point) as: (1) 'Today satisfaction', assessing current satisfaction at the end of treatment cycle, (2) 'Highest satisfaction', assessing the highest level of satisfaction over the previous cycle. In each analysis: Step 1 was a univariate logistic analysis where baseline factors that met the defined threshold of $p < 0.20$ were included in Step 2, which tested for independence of these factors. Step 3 was a multivariate stepwise logistic regression analysis of the factors retained from Step 2.

Results: Higher TWSTRS-Total score was the only factor associated in the multivariate analyses with 'Today' satisfaction (Odds ratio [95%CI]: 0.978 [0.968, 0.988] $p < 0.0001$) and was also associated with 'Highest' satisfaction (Odds ratio: 0.985 [0.971, 1.000] $p = 0.0434$). Other significant predictors for poorer 'Highest' satisfaction were: mean injection interval (weeks) prior to assessment (Odds ratio: 1.044 [1.006, 1.088], $p = 0.0308$) and number of prior treatment cycles (Odds ratio: 1.065 [1.005, 1.127] $p = 0.0301$).

Discussion: Subjects with more severe CD (higher TWSTRS-Total scores) are less likely to be satisfied with their symptom control from established BoNT-A treatment, both at peak effect and end of cycle. Likewise, those with a lower number of previous treatments and shorter treatment intervals are also less likely to be satisfied during their treatment.

P-11

Outcomes of the First-in-human Study with a Recombinant Botulinum Toxin E (rBoNT-E): Safety and Pharmacodynamic Profile of rBoNT-E Compared with abobotulinumtoxinA

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Introduction: Naturally occurring botulinum toxin serotypes have different pharmacological features and are of therapeutic interest. In particular, BoNT-E has a faster onset of action and shorter duration of effect compared with BoNT-A. We aimed to evaluate the safety of the first recombinant BoNT serotype E (rBoNT-E) and characterize its pharmacodynamic profile versus abobotulinumtoxinA (aboBoNT-A) administered to the extensor digitorum brevis (EDB) muscle of healthy males, by recording compound muscle action potential (CMAP).

Methods: 28 healthy males were randomised (3:1) in this double-blind, placebo-controlled single ascending dose study (sequential cohorts; up to 3.6ng rBoNT-E). 24 further subjects were randomised (6/treatment arm) to receive a double-blind injection of aboBoNT-A 20, 40 or 70U, or placebo. Data from active treatment groups only (rBoNT-E and aboBoNT-A) are described.

Results: All rBoNT-E doses were well tolerated. Most treatment-emergent adverse events (TEAEs) were evaluated as unrelated to study treatment; no severe TEAEs or serious AEs were reported, none led to study withdrawal or death. No unexpected treatment-related toxicities were identified with rBoNT-E versus aboBoNT-A. Time to onset was faster with rBoNT-E (day 1–2) compared with aboBoNT-A (day 1–7). Maximal inhibition for rBoNT-E was dose-dependent up to 0.9 ng and achieved within approximately 1 week following injection (all doses) [Figure 1], whereas for aboBoNT-A, maximal inhibition was achieved after 2–6 weeks. The maximal effect was reached 1 week post-injection for rBoNT-E and 2–6 weeks for aboBoNT-A. Inhibition lasted ~7 weeks for 0.9 and 3.6ng of rBoNT-E, persisting until 26 weeks post-injection for aboBoNT-A subjects.

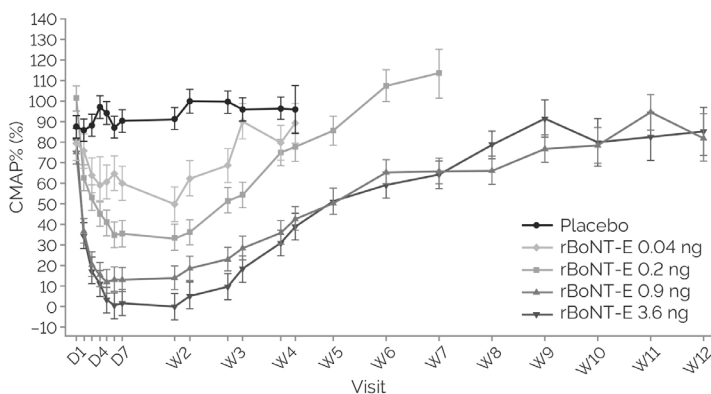


Fig. 1: Least squares mean Compound Muscle Action Potential (CMAP) for ascending doses of rBoNT-A

Discussion: A comparatively good safety profile of single intramuscular doses of rBoNT-E was demonstrated up to 3.6ng. rBoNT-E has faster onset of effect, greater and quicker peak effect and shorter duration of action versus aboBoNT-A, when injected in EDB muscles of healthy males.

P-12

Botulinum Toxin Content and Activity: Potential Implications for Duration of Efficacy in Patients with Cervical Dystonia

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Introduction: Therapeutic botulinum neurotoxin-A (BoNT-A) effects are mediated by the 150 kDa neurotoxin. Each product has a unique manufacturing process, different excipients, potency units and dosing recommendations. For example, in Canada (where clearly defined maximum dosing recommendations are provided for all 3 products), the maximum total dose for use in cervical dystonia (CD) is 1000U for abobotulinumtoxinA (aboBoNT-A, Dysport), 360U for onabotulinumtoxinA (onaBoNT-A, Botox), and 300U for incobotulinumtoxinA (incoBoNT-A, Xeomin). Light chain activity of 150 kDa BoNT-A in different products is unknown. We aimed to quantify the amount of BoNT-A protein in each vial of commercial BoNT-A product and compare light chain activity of 150 kDa BoNT-A in different products.

Methods: Quantitation of 150 kDa BoNT-A used sandwich ELISA with antibodies specific to 150 kDa BoNT-A. Commercial products were quantitated versus a calibration curve of recombinant BoNT-A. Activity was assessed using EndoPep assay. Concentration of a cleaved target was measured and quantity of 150 kDa BoNT-A determined relative to quantity of recombinant BoNT-A required for equivalent light chain activity.

Results: The amount of 150 kDa neurotoxin per potency unit of commercial product was 5.38pg for aboBoNT-A, 9.04pg for onaBoNT-A and 4.03pg for incoBoNT-A. Thus, when total recommended CD doses are given, there is more 150 kDa BoNT-A injected in aboBoNT-A ($1000\text{U} \times 5.38\text{pg} = 5.38\text{ng}$) than in onaBoNT-A ($360\text{U} \times 9.04\text{pg} = 3.25\text{ng}$) and incoBoNT-A ($300\text{U} \times 4.03 = 1.21\text{ng}$). Similar results are found at recommended initial doses (aboBoNT-A $500\text{U} = 2.69\text{ng}$ vs. onaBoNT-A $200\text{U} = 1.81\text{ng}$ vs. incoBoNT-A $200\text{U} = 0.81\text{ng}$). EndoPep assay showed no significant differences between BoNT-A products in light chain activity per ng of 150 kDa toxin.

Discussion: No differences in light chain activity were seen between BoNT-A products. However, there were greater amounts of neurotoxin in aboBoNT-A at the maximum total dose than either onaBoNT-A or incoBoNT-A. At the recommended dose, all BoNT-A products have a similar safety profile. This greater amount of neurotoxin may prolong denervation following aboBoNT-A injection, resulting in the previously observed clinically long duration of response with sustained symptom relief between injections.

P-13

Three-dimensional Analysis of Posture and Rotational Movement in Cervical Dystonia Using a Conebeam X-Ray CT Scanner

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Introduction: The combination of movements in cervical dystonia (CD) generates various clinical features. Reichel's col-cap concept [1] has renewed the comprehension of CD. Drawing on this, our studies aim at analysing the role of the lower, upper cervical spine and each intervertebral space in 3-D during usual posture and rotational movement in CD.

Methods: We recruited 10 CD patients (CD-Pt) with a tonic form (4 right, 4 left torticollis, 1 antecollis, 1 laterocollis), as well as 10 healthy subjects (H-S) matched according to age and gender. We recorded 3-D images of posture and cervical range of motion (RoM) as they were sitting, using a Conebeam x-ray CT scanner (CBCT) [2]. The analysis, which dealt with the upper, lower and intervertebral cervical spine (C0 to C4), made it possible to obtain accurate 3-D depictions of the principal and coupled movements. Cervical posture and rotational movements to the pro- and anti-dystonic sides were characterised by angular measures in degrees and two angular indexes (distance, D) and (symmetry, SI) [3]. The RoM were reported on a 3-D computer modelling [4] to analyse each CD-Pt and to compare him/her with H-S.

Results: Both CD-Pt and H-S were equally matched in gender (7 males and 3 females) and age (54.4, 54.3 years old). The mean of the TWSTRS score was 22.5/85. All the patients received their latest botulinum toxin injections at least 3 months before. Posture and movement analyses showed a significant difference between CD-Pt and H-S on the upper cervical spine ($p=0.0007$). The rotational movement of the whole cervical spine was significantly different between the two groups ($p=0.03$), particularly in the upper segment ($p=0.0005$) and notably at the C1C2 level ($p=0.01$). The involvement of the upper cervical spine was confirmed by the D ($p=0.01$) and S ($p=0.002$) indexes.

Discussion: The predominance of the dysfunction of the upper cervical spine caused by CD is demonstrated with CBCT. The intervertebral spaces C0C1 and notably C1C2, whose primary function is to orientate the head in space, are the key segment. The motion disorganisation affects the set of articulations, which provides the highest degree of mobility thanks to their specialised and richly innervate muscles [5]. Computer modelling of the vertebrae motion would make it possible to find the involved muscles and to decide on the best therapeutic option.

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P-14

A Registry of Real-World Outcomes Using Deep Brain Stimulation for the Treatment of Dystonia

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Introduction: Several studies have now published clinical outcomes using DBS for the treatment of dystonia encompassing a range of dystonic conditions including primary generalized, cervical dystonia, tardive dystonia, and other types of secondary dystonia, and all have reported effective results with use of DBS for the treatment of dystonia. Here we report the initial outcomes from a multi-center registry of dystonia patients implanted with an MICC-based DBS system.

Methods: This is a prospective, on-label, multi-center, international registry study (ClinicalTrials.gov Identifier: NCT02686125) consisting of up to 200 patients implanted with a DBS system (Vercise, Boston Scientific) for use in the treatment of dystonia followed out to 3 years (post-implant) at up to 40 sites in Europe. Study assessments conducted will be based on dystonia sub-group, classification, and age and include (but not limited to) the following: Burke-Fahn-Marsden Dystonia Rating Scale, Clinical Global Impression of Change, Global Dystonia Scale, SF-36v2 or SF-10v2 Health Survey, and Toronto Western Spasmodic Torticollis Rating Scale.

Results: Initial results of this on-going registry of DBS outcomes in dystonia patients will be reported.

Discussion: Large, multi-center patient data registries are thought to have potential for revealing insights regarding real-world, clinical use of DBS. This ongoing registry represents the first comprehensive, large scale collection of real-world outcomes associated with dystonia patients implanted with a DBS system capable of multiple independent current control (MICC).

P-15

Management of Primary and Post-paralytic Hemifacial Spasm combined with Synkinesis with Botulinum Toxin Type A

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Introduction: Clinically, facial synkinesis could be presented in both primary and post-paralytic hemifacial spasm (HFS). However, studies focused on clinical features and efficacy of HFS combined with synkinesis were seldom reported. This study is to summarize the clinical manifestation, therapeutic effect and safety of Botulinum toxin type A (BoNT-A) injection among primary and post-paralytic HFS patients with facial synkinesis.

Methods: Both primary and post-paralytic HFS patients were collected during 2009-2018 in Tongji Hospital of Tongji University. Study design could be seen in Fig 1. Synkinesis which was confirmed by video analyzing of two groups of facial muscles contributing to facial expressions was recorded according to 5 voluntary facial movements (eyebrow lifting, frowning, eye closure, teeth showing and pouting) and 3 facial regions (forehead, periocular and perioral area). According to the study design (Fig. 1), 47 primary and 7 post-paralytic HFS patients were selected for comparison of different synkinesis. 24 primary and 12 post-paralytic HFS patients with synkinesis were selected for analysis of latency, duration of effect, dosage, satisfaction score of treatment, response rate of severity of spasm and synkinesis.

Results: All 5 facial movements could induce synkinesis in both groups. Incidence rate of pouting induced eye closure were relatively high in both primary (65.31%) and post-paralytic group (91.67%). Occurrence rate of eye closure (71.43% vs. 25.53), frowning (42.86% vs. 6.38%) and teeth showing induced synkinesis (57.14% vs. 10.64) were significantly higher ($p<0.05$) in post-paralytic group. In addition, incidence rate of ocular-oral synkinesis (71.43% vs. 25.53%) and frontal-oral synkinesis (57.14% vs. 14.89%) were significantly higher ($p<0.05$) in post-paralytic group. For the efficacy of BoNT-A, latency (4.38 ± 2.17 vs. 4.67 ± 4.14 days), effective duration (3.83 ± 2.94 vs. 4.96 ± 2.48 days), dosage of injection (31.35 ± 12.30 vs. 26.98 ± 8.75 U), response rate of spasm (91.67% vs. 95.83%) and synkinesis (83.33% vs. 58.33%) were similar in both groups after BoNT-A treatment ($p>0.05$). Significant higher satisfaction score of treatment (84.79 ± 19.81 vs. 64.17 ± 31.54) and improvement of pouting induced synkinesis were seen in primary group ($p<0.05$).

Discussion: Synkinesis presented in both primary and post-paralytic HFS. BoNT-A was an efficient and safe intervention not only improving the severity of spasm, but also decreasing the severity of synkinesis.

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P-16

Effects of Botulinum Toxin Type-A on Pain and Cognitive Functions in Patients with isolated Adult-onset Cervical Dystonia

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Introduction: It is well known that botulinum toxin type-A (BoNTA) improve motor function in patients with isolated adult-onset cervical dystonia (IAOCD). However, nonmotor symptoms (NMS) are increasingly recognized as a part of IAOCD phenotype. Contrary to motor symptoms, NMS in IAOCD were rarely investigated during BoNTA treatment. The aim of present study was to investigate the effects of BoNTA on NMS, especially pain and cognitive function, in patients with IAOCD who previously were not treated with botulinum toxin.

Methods: We studied 51 IAOCD drug naive patients before and after BoNTA therapy. Severity of motor symptoms, disability and pain were assessed with Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). Cognitive functions were assessed using Cogtest, a computerized neurocognitive battery set of 5 tests examining several cognitive domains. Auditory Number Sequencing (ANS), Spatial Working Memory (SWM), Strategic Target Detection (STD), Continuous Performance Test - Flanker version (Flanker CPT) and Tower of London (ToL). Psychiatric assessment included quantitative questionnaires: Beck Depression Inventory - Second Edition (BDI-II), Beck Anxiety Inventory (BAI), Starkstein Apathy Scale (AS). Sleep quality and fatigue were determined with Pittsburgh Sleep Quality (PSQI) and Fatigue Severity Scale (FSS). Assessment was performed at baseline (before BoNTA injections) and 4 months after injections (150-200 U of onabotulinumtoxinA and/or incobotulinumtoxinA).

Results: Mean age of patients (29 female, 22 male) was 47.3 years, mean age of IAOCD onset was 44.3 years and mean disease duration 2.9 years. Significant motor score (TWSTRS) and pain amelioration ($p < 0.001$) were observed after BoNTA application. BoNTA treatment had no significant effect on any of cognitive functions assessed ($p > 0.05$). Psychiatric assessment: (BDI-II, BAI and AS score), sleep quality (PSQI) and fatigue score (FSS) did not change significantly 4 months after BoNTA treatment ($p > 0.05$)

Discussion: As expected, in addition to improvement of motor symptoms of IAOCD patients, BoNTA was significantly effective in reducing pain. But for the first time, we have shown that there was no significant impact of BoNTA therapy on cognitive function assessed with a computerized neurocognitive testing. BoNTA was ineffective in reducing anxiety, depression and apathy or fatigue and quality of sleep during this short-term treatment period. But long-term follow up of BoNTA therapy that is needed is in progress.

P-17

Oscillatory Activities Related to Tonic Dystonia and Different Pathophysiologies of Generalized Dystonia and Focal Dystonia

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Introduction: The processes of improvement with deep brain stimulation (DBS) treatment in tonic dystonia and phasic dystonia differ. It has been reported that oscillatory activities related to phasic dystonia are alpha band, but oscillations related to tonic symptoms have not been reported. We analyzed the pallidal local field potential (LFP) and found that tonic dystonia was related to delta oscillation in generalized dystonia, and delta oscillatory activity was observed in post-traumatic focal dystonia. The different pathophysiologies of the two delta oscillations will be presented.

Methods: In each patient, LFP from the internal pallidum (GPi) and external pallidum (GPe) and electroencephalography (EEG) from bilateral sensorimotor areas were recorded 5 days after DBS electrode implantation. (1) 19 patients were divided by predominant symptoms into 9 tonic patients and 10 phasic patients. In tonic patients, tonic dystonia was observed as truncal dystonia. (2) A patient with post traumatic focal dystonia had face and hand dystonia due to left-side head trauma. LFPs were recorded from bilateral GPs and sensorimotor areas.

Results: (1) Power: The predominant power was alpha band in phasic patients and delta band in tonic patients.

Coherence: In phasic dystonia, coherence between GPi and MCx (motor cortex) in the alpha band was significant, but in tonic dystonia, there was no coherence between GPi and MCx in the delta band. (2) Power: Delta powers were observed in bilateral GPi and GPe and left MCx. Significant coherence between GPi and MCx and between GPe and MCx was observed on the affected side, but not on the unaffected side.

Delta GPi oscillatory activities were prominent in tonic patients, and alpha GPi oscillatory activities were prominent in phasic patients. Delta oscillatory activities were observed in tonic dystonia with truncal dystonia and in focal dystonia, but coherence between GPi and MCx in the two delta oscillatory activities differed, with no significant coherence in truncal dystonia and significant coherence in focal dystonia.

Discussion: Tonic dystonia is related to delta oscillatory activities, but coherence between GPi and MCx in truncal dystonia and focal dystonia differs. Different pathophysiological cortico-pallidal oscillations are related to truncal and focal dystonia.

P-18

Usefulness of Single-photon Emission Computed Tomography in Identifying Dystonic Muscles in Patients with Cervical Dystonia: A Pilot Study

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Introduction: The key point for botulinum toxin type A (BTX-A) injection in treating cervical dystonia (CD) is to accurately identify dystonic muscles. The purpose of this study was to evaluate the usefulness of single-photon emission computed tomography (SPECT) in identifying target muscles in CD patients.

Methods: Eighteen patients were included into the study group, in which target muscles were selected according to clinical evaluation combined with SPECT. While 18 patients in our database of CD were continuously selected as the control group, in which target muscles were selected according to clinical evaluation. All patients were followed-up at two weeks, one month, three months and six months after BTX-A injection. The primary outcomes were the reduction rates in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) and Tsui score at one month after injection.

Results: At two weeks and one month, no differences in the reduction rates in TWSTRS and Tsui scores were observed between the two groups ($P > 0.05$). At three months, the reduction rates in TWSTRS ($67.3 \pm 22.3\%$ versus $45.3 \pm 18.3\%$, $P = 0.003$) and Tsui score ($69.7 \pm 22.9\%$ versus $47.3 \pm 15.8\%$, $P = 0.002$) were significantly higher in the study group. At six months, the reduction rates in TWSTRS ($64.3 \pm 20.1\%$ versus $32.6 \pm 9.2\%$, $P = 0.004$) and Tsui score ($65.8 \pm 22.1\%$ versus $37.2 \pm 9.2\%$, $P = 0.013$) were still higher in the study group. The number of patients receiving re-injection within six months was significantly lower in the study group than in the control group (22.2% versus 72.2% , $P = 0.007$). Also, the re-injection interval was significantly longer in the study group (166.8 ± 26.7 days versus 131.3 ± 38.3 days, $P = 0.003$). In the study group, there were significantly more deep cervical muscles were injected, which concerns especially semispinalis capitis, longissimus capitis and obliques capitis inferior muscles. SPECT and electromyography were consistent in identifying dystonic muscles ($\text{Kappa}=0.777$, $P < 0.001$).

Discussion: SPECT is a useful method for screening target muscles in CD. It helps clinicians draw a "blueprint" for the distribution of dystonic muscles before BTX-A injection.

P-19

Discovering Neuro-Stimulation Targets Using Structural Similarity of Connectome Profiles: Potential Application to Facilitate Functional Recovery in Stroke-induced Hemidystonia

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Introduction: In primary dystonia, Deep Brain Stimulation (DBS) of the GPi provides good to excellent results in the majority of patients. However, in stroke-induced hemidystonia, contralateral GPi DBS is significantly less effective and several groups have attempted multi-target DBS (GPi+Vim) to improve outcomes. To date, our efforts to choose the optimal target(s) for hemidystonia remains clinically-driven likely resulting in suboptimal outcomes. Here, we propose a connectome-based individualised approach to find candidate brain regions for neurostimulation using structural similarity of connectivity profiles. Our hypothesis is two-fold: 1) connectivity of a region contributing to functional recovery will be similar to that of the lesioned area and 2) possible candidate regions with similar incoming and outgoing connectivity profiles may include multi-level neighbours located in non-adjacent regions but in a higher level in the hierarchical structure of the connectivity

Methods: With the cat and macaque connectomes, areas that showed evidence of functional compensation following a lesion or regions that demonstrated to facilitate functional recovery with neurostimulation were assumed to be our optimal target. We used connectome profiles to see if our predicted optimal targets based on structural similarity would match with those previously found target regions. We evaluated connectome profiles based on three criteria to measure structural similarity: matching index (quantifies the overlap in afferent and efferent connections between two areas) including level d-neighbours, non-metric multidimensional scaling (NMDS), and hierarchical proximity (HP)

Results: In both cat and macaques, using the matching index including multi-level neighbours, incoming connection similarity was a better predictor for the candidate region for functional recovery compared to that of outgoing connections. Predicted candidate regions involved in functional recovery from previous literature are identified. However, similar afferent and efferent connectivity included multiple competing regions, which could be resolved by incorporating hierarchical 'proximity' in the connectome profile

Discussion: Here, we demonstrate how the connectome profiles can be used as a good proxy to assess potential target areas which can facilitate functional recovery using the cat and macaque connectome. Future studies should replicate these findings in a multimodal hemidystonia connectome dataset and assess target feasibility.

P-20

Effects of Deep Brain Stimulations on Speech in Isolated Generalized Dystonia

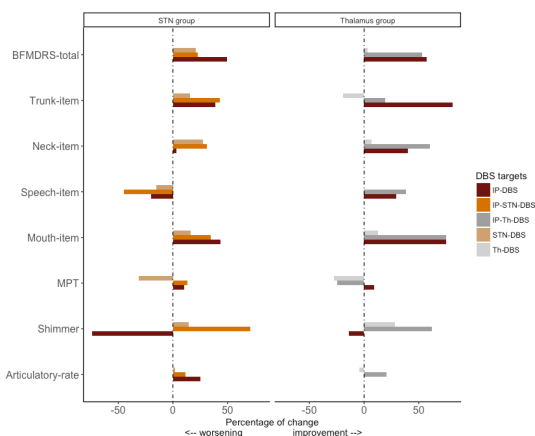
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Introduction: Hyperkinetic dysarthria is often present in Isolated Generalized Dystonia (IGD). This study aimed at evaluating the effects of IP-DBS associated whether with thalamus DBS (Th-DBS) or subthalamic nucleus DBS (STN-DBS) on the clinical assessment and acoustic features of speech in patients with IGD.

Methods: We recorded speech samples of 11 patients with IGD pre- and post-surgery: all patients benefited from IP-DBS; six patients underwent an additional electrode implantation into the STN and the remaining 5 patients, into the thalamus. The neurological assessment was performed using the Burke-Fahn-Marsden Dystonia Rating Scale (BFM-DRS). Three speech production tasks were performed: maximum phonation time (MPT), sustained vowel /a/ and oral diadochokinesis, the latter allowing for the calculation of voice quality (shimmer and jitter) and articulatory rate (syllables/sec). DBS effects (pre vs. post) were estimated with percentages of change and compared using non-parametric Wilcoxon's tests.

Results: For all patients, no change was induced for the acoustics features following IP-DBS, except for the shimmer that worsened. However, improvements of the BFM-DRS global score ($p=0.001$), trunk ($p=0.05$) and mouth items ($p=0.05$) were noticed. Regarding STN-DBS and Th-DBS, the majority of variables improved whether the stimulation was alone or combined with IP-DBS; in this latter case, improvements were systematically better than alone. More specifically: 1/ MPT worsened following both STN-DBS or Th-DBS, and additionally in the combined IP-TH-DBS condition; 2/ for the STN-DBS group, the BFM-DRS speech item worsened post-surgery whatever the DBS targets (Fig. 1, left panel); and 3/ for the Th-DBS group, the BFM-DRS trunk item and the articulatory rate worsened only under the Th-DBS condition (Fig. 1, right panel).



Discussion: So far, no study explored the effects of DBS in two targets on speech in IGD. Our findings confirmed the beneficial effect of IP-DBS, while questioning its impact on voice quality. Interestingly, STN-DBS and Th-DBS alone seem to be deleterious to aero-phonatory control.

P-21

Dystonia-like Movements and Altered Striatal Dopaminergic Neurotransmission Elicited by Peripheral Nerve Crush in a DYT1 Mouse Model

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Introduction: DYT1 dystonia is caused by a GAG deletion in the *Tor1a* gene, the penetrance of the typical human limb onset dystonia is present in only 30 % of mutation carriers. Since external triggers such as trauma and repetitive limb overuse are linked to dystonia-onset, a “two-hit” hypothesis for developing dystonia involving genetic predisposition and environmental factors has emerged. hΔGAG3 mice express the human mutated torsinA without developing overt dystonia. A peripheral nerve lesion was used to demonstrate that dystonia-like movements can be elicited in hΔGAG3 mice, leading to a striatal dopaminergic dysregulation.

Methods: Frequency and duration of dystonia-like movements in hindlimbs of wild type (wt) and hΔGAG3 mice were assessed during a tail suspension test (TST) using a newly developed 0-5 point scoring system. Nerve conduction studies were performed 10 weeks post sciatic nerve crush in order to quantify the functional recovery. HPLC and qPCR were used to analyse the striatal dopaminergic system.

Results: The TST showed dystonia-like movements induced by sciatic nerve crush in both hΔGAG3 and wt mice. Whereas the dystonic symptoms in littermate controls declined over the time period of 12 weeks, the transgene animals continued to present pronounced dystonia-like movements (week 12: 2.10 ± 0.30 vs 0.40 ± 0.20 , $p < 0.0001$). Electroneurography showed that recovery of the sciatic nerve was not different after crush injury comparing hΔGAG3 with wt mice (nerve conduction velocity: $23.97 \text{ m/s} \pm 1.80 \text{ m/s}$ vs $25.30 \text{ m/s} \pm 2.80 \text{ m/s}$). A hyperdopaminergic state was found via HPLC in the contralateral striatum of naïve hΔGAG3 mice compared to wt mice (1.15 ± 0.12 vs 1.00 ± 0.06). A significant dopaminergic depletion seen in wt mice after nerve injury (0.79 ± 0.06) was not recorded in hΔGAG3 mice (1.03 ± 0.18 , $p < 0.05$). qPCR did not reveal any significant changes of DA receptors DRD1-5 in the contralateral striatum of hΔGAG3 and wt mice after sciatic nerve crush.

Discussion: Abnormal movements, which fit the phenotypical description of dystonia, were induced by peripheral trauma in genetically predisposed DYT1 animals, supporting the “two-hit” hypothesis. HPLC analysis suggests that an altered dopaminergic neurotransmission in hΔGAG3 may represent one of the pathomechanisms involved in DYT1 development.

P-22

Long-term Safety and Efficacy of incobotulinumtoxinA for the Treatment of Blepharospasm in Botulinum Toxin-naïve Subjects: Results of a Phase III Study

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Introduction: IncobotulinumtoxinA, a botulinum neurotoxin type A (BoNT-A) free from complexing proteins, is efficacious in subjects with blepharospasm, also referred to as benign essential blepharospasm. This study was the first randomised, placebo-controlled, Phase III study with an open-label extension period (EP) in toxin-naïve subjects (NCT01896895).

Methods: Subjects (18–80 years of age) with blepharospasm, Jankovic Rating Scale (JRS) severity subscore ≥ 2 , and no treatment for blepharospasm with any BoNT serotype within the past ≥ 12 months (toxin-naïve), were enrolled in Greece, Malaysia and Sri Lanka. In the main period (MP), subjects were randomized (1:1:1) in a double-blind manner to single intramuscular injections of incobotulinumtoxinA 25 U (12.5 U/eye), 50 U (25 U/eye), or placebo, with a subsequent observation period (OP) of 6–20 weeks. Subjects with a need for re-injection (JRS severity subscore ≥ 2 , confirmed at final MP visit) were eligible for the EP: a single dose of incobotulinumtoxinA ≤ 70 U (≤ 35 U/eye) with a 6–20-week OP. The primary endpoint was change from baseline in JRS severity subscore at MP Week 6. Safety was monitored.

Results: Overall, 61 subjects were randomised (mean 55.0 years of age; 59.0% female); 55 completed the MP, and 39 entered and completed the EP. At MP Week 6, JRS severity subscore was significantly improved from baseline with incobotulinumtoxinA 50 U versus placebo and numerically improved with incobotulinumtoxinA 25 U versus placebo (Table). Over the EP, sustained improvements from the MP and EP baseline were seen with incobotulinumtoxinA ≤ 70 U (Table). In the MP, more adverse events (AEs) were reported with incobotulinumtoxinA 50 U (42.1%) versus 25 U (31.8%) or placebo (30.0%). AEs were less frequent in the EP (all incobotulinumtoxinA-treated: 28.2%). Most AEs were mild to moderate in severity.

Table: Change in Jankovic Rating Scale severity subscore during the MP and EP

Double-blind MP endpoints				
	Placebo (n=18)	IncobotulinumtoxinA		
		25 U (n=21)	50 U (n=17)	
Change from MP baseline ^a to MP Week 6 (primary endpoint)				
LSM (95% CI)	-0.6 (-1.0, -0.1)	-1.0 (-1.5, -0.6)	-1.8 (-2.3, -1.3)	
LSM difference vs. placebo (95% CI)	—	-0.5 (-1.1, 0.2)	-1.2 (-1.9, -0.6)	
p-value	—	0.1452	0.0004	
Open-label EP endpoints				
	Placebo (MP) changed to incobotulinumtoxinA ≤ 70 U (EP) (n=16)	IncobotulinumtoxinA 25 U (MP) changed to incobotulinumtoxinA ≤ 70 U (EP) (n=14)	IncobotulinumtoxinA 50 U (MP) changed to incobotulinumtoxinA ≤ 70 U (EP) (n=9)	All treatments (MP) changed to incobotulinumtoxinA ≤ 70 U (EP) (n=39)
Change from EP baseline ^b to EP Week 6				
Mean (SD)	-1.1 (1.16)**	-1.3 (0.73)**	-1.1 (0.99)*	-1.2 (0.96)***
Change from EP baseline ^b to EP final visit				
Mean (SD)	-0.8 (0.93)**	-0.6 (1.01)*	-0.9 (0.93)*	-0.7 (0.94)***
Change from MP baseline ^a to EP final visit				
Mean (SD)	-0.9 (0.68)***	-0.9 (0.95)**	-1.4 (1.13)**	-1.0 (0.90)***

JRS severity subscore range: 0 (no spasms) to 4 (severe spasms)

*p<0.05; **p<0.01; ***p<0.0001

^aMP Day 1; ^bEP Day 1. The last day of the MP was the first day of the EP if all inclusion/exclusion criteria for the EP were met; *n=15; **n=8; ***n=37

CI, confidence interval; EP, extension period; LSM, least squares mean; MP, main period; SD, standard deviation

Discussion: IncobotulinumtoxinA showed sustained efficacy in toxin-naïve subjects with blepharospasm. Long-term safety results were in line with the known safety profile.

Funded by Merz Pharmaceuticals GmbH.

P-23

Duration of Effect of incobotulinumtoxinA for the Treatment of Blepharospasm in Botulinum Toxin-naïve Subjects: Results from a Phase III Study

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Introduction: The efficacy of incobotulinumtoxinA, a botulinum neurotoxin type A (BoNT A) free from complexing proteins, was investigated in a randomised, placebo-controlled, prospective, Phase III study in toxin-naïve subjects with blepharospasm (NCT01896895). Subjects who had not received BoNT-A treatment for blepharospasm within at least 12 months prior to enrolment were considered treatment-naïve. We report a sub-analysis of the flexible re-injection interval that was employed in this study to mirror clinical practice.

Methods: Treatment-naïve subjects (18–80 years of age) with blepharospasm and Jankovic Rating Scale severity subscore ≥ 2 were enrolled in Greece, Malaysia and Sri Lanka. In the double-blind main period (MP), subjects were randomized (1:1:1) to single intramuscular injections of incobotulinumtoxinA 25 U (12.5 U/eye), 50 U (25 U/eye), or placebo. During a subsequent observation period of 6–20 weeks, the patient's subjective assessment of onset and waning of effect was recorded.

Results: Overall, 61 subjects were randomised (mean 55.0 years of age; 59.0% female) and included in this analysis. Data are reported as median (first quartile, third quartile). The treatment interval was longer with incobotulinumtoxinA 50 U (20 [6.1, 20.6] weeks) and 25 U (11 [6.1, 19.6] weeks) compared with placebo (6 [0, 19.2] weeks). During the MP, time to onset was shorter with incobotulinumtoxinA 50 U (5.0 [3.0, 10.0] days) and 25 U (7.0 [4.0, 22.0] days) compared with placebo (14.0 [4.0, 42.5] days). Time to waning was similar between treatment groups (incobotulinumtoxinA 50 U: 12.0 [8.0, 17.9] weeks; 25 U: 11.0 [3.0, 18.0] weeks; placebo: 11.5 [5.0, 18.2] weeks).

Discussion: IncobotulinumtoxinA had a sustained duration of effect in toxin-naïve subjects with blepharospasm, with a median treatment interval of 20 weeks and time to waning of 12 weeks with 50 U.

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P-24

Dystonia in Children with Cerebral Palsy: A Commonly Overlooked Feature

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Introduction: Cerebral Palsy is a group of disorders that can be expressed mainly as spasticity, but also as dystonia, athetosis, several other movement disorders, or even a combination of all of them. As the most common disability in the pediatric population, the disorder itself is very heterogeneous, and sometimes unpredictable. There are some classifications, but is very common, in the clinical practice, the polarization between “spastic cerebral palsy” and “dystonic cerebral palsy”. Although the true proportion of dystonic phenomena in children with cerebral palsy has not yet been established, it is estimated that this frequency is being neglected. This brings important repercussions for children and their families, as it implies a series of consequences, such as frustrating results due to poorly indicated surgeries, functional impairment, pain and even cognitive impairment.

Methods: This review was conducted using the PubMed during the period from 1990 to January 2019. The research included definition and classification of cerebral palsy, etiology and presence of the dystonic phenomenon.

Results: After the research, 52 articles endured the criteria for the final work. In all these articles, there were considerations about the dichotomic classification between spastic cerebral palsy and dystonic cerebral palsy, considerations about the need for new approaches for the classification and treatment of cerebral patients with dystonia.

Discussion: In just 3 decades, knowledge of movement disorders in children (including dystonia) has increased dramatically. We know more about the genetic aspects, imaging methods, prognosis, and we begin to advance in therapeutics. But we may have to go back to the basics and address some issues, such as the classification and recognition of dystonia in the context of cerebral palsy. In the present literature review, it is observed that the incidence of dystonia can vary from 30 to 70% in children with cerebral palsy, and in at least 40% of them, there is coexistence with spasticity, which can mask the treatment, and misdirect the healthcare professional. We propose to go back to the basics: to examine the patient very carefully, to film, when possible, to correctly classify the patient, and with this starting point, to conduct his multidisciplinary treatment.

P-25

Deep Brain Stimulation in Generalized Dystonia: 5-year Follow-up

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Introduction: Author presents a group of patients with generalized dystonia treated with pallidal (GPi) deep brain stimulation (DBS).

Methods: 32 patients (18 male, 16 female) age from 6 to 64 (mean 27,3) affected by dystonia were treated with DBS GPi. The patients were evaluated with the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), Unified Dystonia Rating Scale (UDRS) and the SF-36 scale before treatment and 9 and 24 months after the procedure. The permanent electrodes were implanted to GPi in all patients. The target was identified with direct and indirect method. Intrastimulus macrostimulation and microrecording were used for neurophysiological evaluation of the target.

Results: No serious morbidity or mortality were reported in the group. IPG chest hematoma was reported at the region, where internal pulse generator was implanted. One patient died at the follow-up period (not related to the DBS procedure or treatment). Most significant factor that influenced efficacy of the treatment was the etiology of dystonia. The differences between the groups are presented. Better results were achieved in primary and DY-T1 generalized dystonia group.

Discussion: DBS GPi is a safe and effective method of dystonia treatment. Application of this method of treatment in generalized dystonia and dystonia in neurodegeneration with brain iron accumulation is legitimate. The improvement in both functional and quality of life scales were significant in both groups.

P-26

Subthalamic Nucleus or Globus Pallidus Pars Interna Deep Brain Stimulation for NBIA-related Dystonia

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Introduction: Emerging conservative treatment of Neurodegeneration with Brain Iron Accumulation (NBIA) gives new insight, but surgical treatment of dystonic symptoms remains an option. The authors present a group of patients with clinically and radiologically diagnosed NBIA (genetically confirmed PANK2 mutation), treated with deep brain stimulation (DBS).

Methods: 16 patients with confirmed PANK2 mutation (NBIA-PKAN) were treated with deep brain stimulation in 2008 and 2014. Age of the patients varied from 8 to 27 years. The clinical condition of patients was evaluated with scales and video recorded. At all cases the permanent electrodes were implanted to the subthalamic nuclei. The surgical procedure was undertaken under general anesthesia in six cases. Subthalamic nucleus was a surgical target among 12 patients and globus pallidus pars interna in 4 patients. The target was identified with direct and indirect method. Intrastimulus macrostimulation and microrecording were used for neurophysiological evaluation of the target. Postsurgical local field potentials were recorded in all cases.

Results: Neither neurological deterioration nor surgical complication were noted among the group. Caregivers of the patients noted subjective improvement of the clinical state of the subjects that was confirmed with tailored scales. There were no significant differences in efficacy between subthalamic and pallidal groups.

Discussion: DBS reduces dystonia symptoms among NBIA patients. The technique carries minimal surgical risk, and improves quality of life of the patients and their caregivers.

P-27

Pallidal Deep Brain Stimulation for Ephedrone Parkinsonism: report of 2 cases

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Introduction: Injections of self-prepared methcathinone hydrochloride (ephedrone) might induce manganese encephalopathy that may result in clinical signs of motor parkinsonism.

Methods: The authors present a history of two patients diagnosed with ephedrone parkinsonism treated with bilateral pallidal (GPi) deep brain stimulation (DBS). A 27-year-old female and 32-year old male patients with previous polysubstance dependence, who administered self-designed ephedrone derived from Sudafed using potassium permanganate and revealed significant clinical symptoms of manganese-induced parkinsonism. Pharmacological treatment was ineffective. The patients were qualified to GPi DBS. Clinical status was evaluated with UPDRS part III, balance test, saccadometry. The permanent electrodes were implanted to GPi in all patients. The target was identified with direct and indirect method. Intraoperative macrostimulation and microrecording were used for neurophysiological evaluation of the target.

Results: No adverse events related to the procedure were recorded. The postoperative 12-month follow-up revealed improvement in rigidity and bradykinesia. Slight improvement was also observed in lower-limb dystonia, gait disturbances and postural instability.

Discussion: The authors assume that GPi DBS might be considered as a safe treatment option for ephedrone parkinsonism.

P-28

Body Concept and Quality of Life in Patients with Idiopathic Dystonia

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Introduction: Patients with dystonia experience unusual postures and disfigurement. Few reports are available about the patients' self-perception of the body and its association with quality of life. The aim of the study was to examine changes in the body concept in relation to quality of life and severity of dystonia.

Methods: Our cohort consisted of twenty patients with idiopathic dystonia resistant to medical therapy who were planned for pallidal deep brain stimulation (Gpi-DBS). The results were compared to 25 healthy controls. The patients were assessed with the Frankfurt Body Concept Scale, the SF-36 Health Survey, as well as the Hamilton Depression Scale, the Beck Depression Inventory, the Social Phobia Inventory and the Social Interaction Anxiety Scale. The disease severity was evaluated with the Burke-Fahn-Marsden Dystonia Rating Scale and the Toronto Western Spasmodic Torticollis Rating Scale.

Results: Our results showed that the patients with dystonia had a significantly impaired body concept in eight out of nine subscales in comparison to healthy controls. The differences were most pronounced for the subscales general health, body care and taking care of body functioning, physical efficacy, sexuality, and physical appearance ($p < 0.001$). Furthermore, all 8 subscales of the SF-36 exhibited significantly lower values in patients with dystonia compared to controls. We also found significant positive correlations between the SF-36 and the body concept subscales. Impairment of body concept was not associated with disease severity or levels of social anxiety symptoms. However, there was a significant association between self-rated depression and disease severity. Our patients suffered from elevated depression and social anxiety symptoms except social interaction anxiety.

Discussion: We conclude that patients with dystonia have significant body concept impairment which interferes with quality of life in both physical and emotional domains. Future studies should focus on assessing these symptoms after adequate therapeutic management of motor symptoms.

P-29

Central Effects of Botulinum Toxins?

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Introduction: In the last decade there is a growing evidence that after peripheral application botulinum toxin A (BoNT-A) enters the CNS. Evidence for that is coming from studies in vitro, behavioral studies on experimental animals and finally enzymatic activity of BoNT-A was found in the CNS - in the form of enzymatically cleaved SNAP25, protein necessary for exocytosis of neurotransmitter vesicles. Cleaved SNAP25 was found in ventral and dorsal horn of the spinal cord, in sensory and motoric ganglia in a brain stem, and in dura mater. This raises a question of what might be central effect of BoNT-A on sensory and motoric functions?

Methods: Since 2005 we investigated the effect of BoNT-A on experimentally induced pain in rat. Most convincing evidence were our observations of antinociceptive effect of BoNT-A on different models of bilateral and 'mirror pain'. Since bilateral and especially "mirror" pain could be only of central origin, peripheral application of BoNT-A should have no effect on this type of pain.

Results: In models of bilateral and 'mirror pain' we demonstrated that the unilateral peripheral application of BoNT-A diminished pain on the ipsilateral, but on the contralateral side as well. Colchicine, an axonal transport blocker, when injected into the ipsilateral sciatic nerve, prevented the effect of the peripheral BoNT-A injection on both sides. These results demonstrate the necessity of retrograde axonal transport and crucial role of the central nervous system for the antinociceptive activity of BoNT-A. On the other hand observation of BoNT-A enzymatic activity, i.e. presence of cleaved SNAP25 in motor part of the CNS suggests that same action of BoNT-A on motor system should exist as well. In our preliminary experiments, that are still in progress, up to now, we did not find evidence that toxin from CNS affects normal motor activity. However, BoNT-A from CNS significantly attenuated experimentally induced localized muscular spasm.

Discussion: Further research on direct central or peripheral mechanisms might have significant impact on our understanding of pharmacology and clinical potential of BoNTs.

P-30

Finger Joint Laxity in Musician Focal Dystonia

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Introduction: The aim of the present study is to evaluate the finger joint laxity prevalence in musicians affected by focal dystonia compared to a healthy control population. The joint hypermobility Syndrome (JHS) is a connective tissue disease that cause a joint flexibility and is associated to chronic pain. The JHS cause abnormal posture and can induce poor proprioception, poor postural perception and motor control [1] Focal dystonia (FD) in musicians is a movement disorder characterized by irregularity in play due to involuntary muscle contraction and maintained both in the hand and in the arm [2]. About 1% of professional musicians suffer from this rare pathology [3].

Methods: Sixteen musicians affected by FD, referred to the 'Sol Diesis Service' of Fondazione Don Carlo Gnocchi, were included in the study. All musical instruments and type of FD were included. All musicians (DYS) and a hundred healthy control subjects (CNT) were evaluate by using Hakim-Grahame Questionnaire (HGQ), Beighton Scale (BS) [4] and the Hand Joint Laxity Scale (HJLS) that we have elaborated in order to study wrist and all fingers joints: we assigned a score of 1 if the passive range of motion was out of the normal range given by literature. The data were statistically analyzed with the Fisher test, Wilcoxon rank test corrected by Bonferroni

Results: CNT and DYS were homogeneous for age, gender, lateral preference. We did not find any significance difference between DYS and CNT group for HGQ, BS and HJLS total score. We instead have found that the sum of the metacarpophalangeal joints (MP score) ($p=0.0000$) and proximal interphalangeal joints (PIP score) ($p=0.015$) were significant different compared to the control group.

Discussion: Dystonic patients have greater laxity and instability at MP and PIP joints compared to the control healthy group so we could assume that laxity could be a risk factor for FD. A larger sample is necessary to conform this association.

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P-31

Mirror neuron system integrity in cervical dystonia

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Introduction: Cervical Dystonia (CD) is a movement disorder characterized by involuntary movements and postures of head and neck that, in the absence of clear brain damage, determines faulty sensorimotor integration and impaired motor planning affecting social life activities. Botulinum neurotoxin is the first line treatment with clinical improvement in about 60%; to increase clinical results rehabilitative approaches are needed.

Currently, new rehabilitative interventions are available based on the motor resonance mechanism activated by the Mirror Neuron System (MNS), a movement observation and execution matching system [1]. The MNS based rehabilitative approaches have proved to be useful in stroke [2] and Parkinson's disease [3] but no data are available in patients with CD. To exploit the MNS in rehabilitation of CD, we investigated its functional integrity in a group of CD patients.

Methods: Twenty-five healthy adults (HC, mean age [SD]= 56.12 [20.04]; 15 females) and 22 subjects with CD (mean age [SD]= 46.95 [9.19] 15 females). All subjects received a functional MRI (fMRI) examination on a 1.5 scanner. The fMRI task consisted of 2 runs: 1. subjects observed ("Observe" condition) and 2. subjects executed right hand grasping movements ("Move" condition), as in [4]. fMRI data were analysed with SPM12, according to the General Linear Model. A mixed factorial ANOVA, Group (2 levels: HC, CD) by Task (2 levels: Move, Observe), was carried out. To identify MNS, a conjunction analysis was performed between activations of the two conditions "Move" and "Observe", separately for each group using an inclusive mask with both conditions ($p < 0.05$ FWE corrected).

Results: No significant differences between the two groups were found in terms of age. Despite the visual inspection of fMRI data suggested a different pattern of activation in the ventral premotor cortex between the two groups, the statistical analysis did not show significant differences (Figure 1).

Discussion: Our results showed substantial preservation of the MNS in CD. This data suggest the possibility to implement motor control and rehabilitation exercises based on the execution/observation matching system.

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KMT2B Gene Related Dystonia: A New Entity With Severe Dystonia Improving with Deep Brain Stimulation

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Introduction: Childhood onset dystonias are disabling disorders with limited medical resources for their treatments. Mutations in lysine methyltransferase 2B (KMT2B) gene have been recently incriminated in complex childhood onset dystonia. Due to the recent description of the condition, clinical response to deep brain stimulation (DBS) remains little known and reported.

KMT2B gene related phenomenology and initial and long-term outcomes with DBS are reported in this work.

Methods: Based on common phenomenology, molecular analysis for KMT2B gene mutations was performed in 18 patients recruited at 4 European centers. All patients underwent DBS to the globus pallidus, pars interna and dystonia evolution was monitored by alterations of the Burke Fahn Marsden's dystonia rating scale (BFMDRS).

Long term follow up with DBS was defined equal or superior to 5 years.

Results: Eighteen subjects (15 females), aged 5 to 44 years, shared similar phenomenology including short stature, severe, generalized dystonia with cranial and laryngeal involvement. MRI documented signal alterations on T2* and SWI sequences in a subset of them (8/12). Pyramidal signs and slow vertical saccades were associated findings. Mean of age at disease onset was 4.7 years. Mean of follow up with DBS was 5.8 years (range 0.1 to 22 years). At baseline, mean preoperative BFMDRS-M score was 84.5/120, 51.5/120 at 6 months, 54.5/120 at 1 years, 46/120 at 5 years. Concerning long- term follow up group (n=8), the last score was 56.5/120. DBS effect is very limited on laryngeal dystonia. In 4 patients, DBS has been administered for Status Dystonicus with systematic control of the episodes. Instantly, under DBS, patients developed freezing of gait.

Discussion: KMT2B gene related dystonia, is a severe disorder with childhood, gait or laryngeal onset, generalization and systematic, severe, laryngeal involvement, resembling whispering dysphonia. Short stature and young face are clues for diagnosis. Given the systematic worsening of dystonia and response to DBS except on laryngeal dystonia, surgical treatment should be proposed early in the evolution of the disease.

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Cerebral Cavernous Malformations and Movement Disorders

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Introduction: Cerebral cavernous malformations (CCM) most frequently become manifest by seizures, focal neurologic deficits and headaches. Movement disorders (MDs) secondary to CCM have only been rarely described in thalamic, basal ganglia and brainstem CCM. Owing to their rarity, natural history and optimal treatment of associated MDs remains unclear.

Methods: In this study we included all patients with MDs associated to a CCM that presented in our department over a period of 10 years.

Results: We encountered a total of 6 patients (5 women and 1 man). Mean age was 38,5 years (range: 16-77 years). In all cases radiographic sign of previous hemorrhage was evident. MDs included the following with CCMs in various locations: hemiparkinsonism – anterolateral pontomesencephalon (1); chorea – subthalamic region (1); tremor – subthalamic region/dentothalamic pathways (2); dystonia – putamen/thalamomesencephalic (2). Two patients underwent surgical removal of the CCM with subsequent resolution of MDs. One patient had radiosurgery with disappearance of tremor but occurrence of spasticity. In three patients with moderate severity of MDs a wait and see strategy was adopted.

Discussion: Treatment of MDs secondary to CCM is challenging because of their location. The optimal strategy can be chosen only on an individual basis. Location of the CCM, bleeding history, symptom severity and duration are factors that should be considered. Surgery remains a primary therapeutic option possibly providing cure in experienced neurosurgical centers. Stereotactic radiosurgery can be used in deep seated or surgically inaccessible CCM.

From Non-rechargeable to Rechargeable Technology: Insights and Management of Pallidal Deep Brain Stimulation in Dystonia after Switching to a Rechargeable Implantable Pulse Generator

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Introduction: Patients with pallidal deep brain stimulation (DBS) for dystonia often need continuous increase of their stimulation intensities to maintain a stable therapeutic effect. Non-rechargeable implantable pulse generators (IPG) have traditionally been used and after such IPG replacements, a decrease of stimulation intensities of about 20% frequently could be achieved. Here, we aimed to evaluate the management of stimulation intensities after switching from NRC to RC IPG compared to previous RC-to-RC replacements.

Methods: Patients with dystonia and pallidal DBS, who were switched from a NRC to RC IPG technology were identified. Modifications of stimulation intensities with otherwise stable settings during NRC battery life and during the observation period of RC use were analysed. Changes in stimulation intensities before/after switch from NRC to RC IPGs were calculated and compared with modifications of settings before/after NRC-to-NRC IPG replacements. Statistical analysis was performed using the Wilcoxon rank test for paired variables and Mann-Whitney-U-test.

Results: Eleven patients (7 men; mean age at DBS 50.3 \pm 11.7 years; mean DBS duration 120 \pm 33 months) were included. Mean battery life of NRCs was 20.6 \pm 6.5 months. RC observation period was 69.5 \pm 19.1 months. In the NRC-to-NRC setting, mean increase during battery life was 1.14V ($p<0.05$). Stimulation intensity was reduced by 19.4% ($p<0.005$) when restarting with a new IPG. In the NRC-to-RC constellation, during the RC observation period stimulation intensities were increased in 7 patients and reduced in 4 (overall mean decrease 0.1V; $p=0.48$). Management of stimulation intensity when switching from NRC to RC was heterogeneous: in 7 patients a mean reduction by 19.5% was performed, in 2 there was no change, and 2 had mild mean increase of 1.3%. Overall mean reduction was 12.2% ($p<0.05$), which was significantly less than in the NRC-to-NRC situation ($p<0.05$).

Discussion: Switching from NRC to RC IPGs in pallidal DBS for dystonia needs more variability and individualized adaptation than in classical NRC-to-NRC replacements. Indeed, after the replacement stimulation intensities were not reduced as much as previously. Over one third of the patients reduced stimulation intensities over time. These heterogeneous results might reflect neuroplasticity effects but also technical aspects of RC DBS systems.

From Constant Voltage Non-rechargeable to Constant Current Rechargeable Chronic Deep Brain Stimulation Systems in Dystonia: Feasibility and Practical Implications

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Introduction: Technological advances in deep brain stimulation (DBS) systems for movement disorders have led either to 'constant-voltage' (CV) systems or, more recently developed 'constant-current' (CC) DBS systems. Furthermore, rechargeable systems (RC) are getting more and more used compared to the former solely available non-rechargeable systems (NRC). Switches between different systems might be necessitated in clinical practice, however there is no official recommendation, how to proceed and adapt stimulation settings in such cases. We aimed to assess practical feasibility of switches from CV NRC to CC RC DBS.

Methods: We prospectively collected data from 7 consecutive patients (7 men, mean age at DBS implantation 50.4 +/- 16.9 years) with chronic bilateral DBS for dystonia (target: 6 globus pallidus internus, 1 thalamic nucleus ventralis intermedius) who underwent implantable pulse generator (IPG) replacement with switch from a VC NRC system (Activa® PC; Medtronic®) to a CC RC System (Vercise® RC; Boston Scientific®). Systematic assessment before and after IPG replacement was performed.

Results: DBS system switches were performed after mean chronic DBS duration of 116.3 +/- 50.4 months. No perioperative complications occurred. The clinical outcome was stable overall with mild improvements or deteriorations, which could be dealt with on short-term follow-up. Patients were satisfied with the new RC IPG.

Discussion: This study adds some more evidence for the feasibility of switches between different DBS systems (CV to CC, NRC to RC, different manufacturers) and indicates how the management might be planned. An individual approach is required.

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Botulinum Toxin Therapy of Hemifacial Spasm: Bilateral Injections can Reduce Facial Asymmetry

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Introduction: Botulinum toxin (BT) is the treatment of choice for hemifacial spasm (HFS). When BT is injected into the affected side, patients may experience increased facial asymmetry. We wanted to evaluate in a prospective, randomised, placebo-controlled study whether bilateral BT injections may reduce this facial asymmetry.

Methods: We treated 19 HFS patients with unilateral (UBT) and 24 with bilateral (BBT) BT therapy using CBTX-A (Lanzhou Biological Products Institute, Lanzhou, China). BT doses on the affected side were standard doses, on the non-affected side they were one-third of these doses. Facial asymmetry was studied with the Sunnybrook Facial Grading System (SFGS), the Facial Clinimetric Evaluation Scale (FaCE), the Symmetry Scale for Hemifacial Spasm (SSHS) and a self-assessment scale. All these scales were used at baseline and 1, 2, 4 and 8 weeks after injection and at the final visit before subsequent therapy.

Results: There was no difference between UBT and BBT in baseline demographics including age, gender, affected side and disease duration. As shown in SFGS and SSHS, BBT facial asymmetry, whilst UBT increases it. Both effects are more pronounced during voluntary facial movements than at rest. BT effect delay, BT effect duration, adverse effect frequency and severity were not affected. FaCE total score, some of its subscores and the self-assessment scale did not show an effect.

Discussion: BBT may improve the outcome of BT therapy for HFS without producing additional adverse effects. This strategy, however, raises drug costs (by about a third). Using even higher doses in the non-affected side may intensify the improvement even further. Future studies may also monitor the patient's quality of life and the naïve public's overall perception of the patient's facial expression.

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Hengli®: Pharmacology and Formalized Clinical Review of the Chinese Botulinum Toxin Drug

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Introduction: Botulinum toxin (BT) therapy has expanded tremendously and so have BT drugs. Hengli® (LAN, Lanzhou Institute of Biological Products, Lanzhou, Gansu Province, was licensed in 1997 and widely used since then in China. It is not yet available in Europe and North America. This review summarises the pharmacology of LAN and provides a formalised review of its clinical applications.

Methods: This review is based upon a data base search in PubMed (National Center of Biomedical Information, United States National Library, Medicine and National Institutes of Health) and in Chinese Science and Technology Paper Citation Database on 01.07.2018. Retrieved publications were identified by their authors and publication years and classified according to their indications and designs.

Results: LAN consists of botulinum neurotoxin, complexing proteins and excipients. Its pharmacology is similar to onabotulinumtoxinA. 360 publications on Hengli® were retrieved. 18 were dealing with ophthalmological, 257 with neurological, 9 with urological and 16 with autonomic disorders. 46 publications were on aesthetic use and 15 on other uses. 73 of the publications were randomised controlled trials, 46 interventional studies, 23 observational studies and 10 case studies. In addition, 18 reviews and 2 guidelines were retrieved. 352 publications were from China and 8 from the rest of the world.

Discussion: Hengli® is pharmacologically similar to onabotulinumtoxinA. Its use is documented in most BT therapy indications. Most of the studies originate from China. Most studies have a relatively low quality level - similar to other BT drugs. For world-wide registrations large multi-center high quality studies will have to be designed. Systematic adverse effects different from other BT drugs could not be detected.

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Comparing Hengli® With onabotulinumtoxinA and incobotulinumtoxinA: Identical Potency Labeling in the Mouse Diaphragm Assay

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Introduction: Botulinum toxin (BT) is provided by several manufacturers producing a number of different drugs. Their potency is given in internationally standardised mouse units (MU). Clinical practice, however, reveals that the potency labelling of different BT drugs may not be identical. Hengli® (LAN, Lanzhou Institute of Biological Products, Lanzhou, Gansu Province, China) is now widely used, but data directly comparing its potency labelling with other BT drugs are lacking.

Methods: The BT potency of different BT drugs was measured in the Mouse Diaphragm Assay (MDA) commercially provided by Toxogen, Hannover. The MDA measures the latency to the 50% twitch force reduction (paresis time, PT) of the electrically stimulated mouse phrenic nerve-hemidiaphragm preparation which was previously shown to correlate with BT potency. BT drugs tested were LAN, onabotulinumtoxinA (ONA, Botox®, Allergan, Dublin, Ireland) and incobotulinumtoxinA (INCO, Xeomin®, Merz Pharmaceuticals, Frankfurt/M, Germany). Normal distribution data analysis was performed by ANOVA followed by Bonferroni for equal variance (PT for 20MU) and Games-Howell for heterogeneous variance (60MU) as post-hoc test. Kruskal-Wallis was performed over non-normal distribution data (100MU and 140MU). The significance level was set to $p \leq 0.05$.

Results: The overall PT were 77.2 ± 25.2 min (LAN), 105.1 ± 43.4 min (ONA) and 86.3 ± 29.3 min (INCO) (n.s.). PT for 20MU were 112.7 ± 8.0 min (LAN), 169.7 ± 28.9 min (ONA) and 132.3 ± 1.5 min (INCO) (ONA vs LAN, $p=0.021$, INCO vs ONA/INCO vs LAN n.s.). PT for 60MU were 82.0 ± 1.0 min (LAN), 105.3 ± 10.1 min (ONA) and 84.7 ± 4.2 min (INCO) (n.s.). PT for 100MU were 66 ± 6.1 min (LAN), 69.7 ± 1.5 min (ONA) and 66.0 ± 7.0 min (INCO) (n.s.). PT for 140MU were 48.0 ± 2.0 min (LAN), 74.7 ± 0.6 min (ONA), 62.3 ± 2.1 min (INCO) (ONA vs LAN, $p=0.021$, INCO vs ONA/INCO vs LAN n.s.).

Discussion: Results presented here do not reveal differences in potency labelling between ONA, INCO and LAN. A trend towards stronger LAN effects in low and high doses was not significant.

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IncobotulinumtoxinA for Hypersalivation in Patients with Amyotrophic Lateral Sclerosis

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Introduction: Botulinum toxin can be used to reduce hypersalivation. We wanted to study whether incobotulinumtoxinA (INCO, Xeomin®, Merz, Frankfurt/M, Germany) can be used for this in patients with Amyotrophic Lateral Sclerosis (ALS).

Methods: 14 patients with ALS (8 males, 6 females, 57.4±16.2 years) received ultrasound-guided injections of INCO 100MU in both parotid glands and INCO 50MU in both submandibular glands. Saliva production was measured gravimetrically with the Cotton Swab Test CST an electronic precision scale. Subjective saliva production was monitored with the Drooling Frequency Scale (DFS) and the Drooling Severity Scale (DSS). Normally distributed data were analyzed by the t-test. Two-sided p-values <0.05 were considered statistically significant.

Results: As shown in Figure 1, saliva production was 4.1±1.3g (mean±standard deviation) before INCO. At week 4 it was 3.1±1.3g (-24.4%, p=0.04), at week 8, 2.6±0.3g (-36.6%, p=0.01) and at week 12 3.4±1.6g (-17.1%, n.s.). As shown in Figure 2, DSS was 5.0±0.5 before INCO. It was reduced to 4.0±0.5 (-20%, p=0.03) at week 4, to 4±0.0 (-20%, p=0.04) at week 8 and to 3.5±0.6 (-28%, p=0.04) at week 12. As shown in Figure 3, DFS was 4.0±0.0 before INCO. It was reduced to 2.1±1.5 (-47.5%, p=0.01) at week 4, to 2.5±0.4 (-37.5%, p=0.04) at week 8 and to 3.7±0.6 (-7.5%, n.s.) at week 12. Adverse effects did not occur.

Discussion: INCO is effective and well tolerated for saliva reduction in patients with ALS 4 and 8 weeks after application. 12 weeks after application the effect starts to wear off.

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Dystonia Treated with Botulinum Toxin: Quality of Life and Caregiver Burden

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Introduction: Dystonia is a common chronic movement disorder producing abnormal postures and pain. Health related Quality of Life (HrQoL) may be reduced, but may be improved by Botulinum Toxin (BT) therapy. We wanted to study how BT therapy of dystonia affects patients and the caregivers.

Methods: For this, all patients were assessed with the Burke-Fahn-Marsden Scale (BFM movement 0-120, BM impairment 0-30) for their dystonia, with the Montreal Cognitive Assessment (MoCA 0-30) for cognitive functioning, with the Beck Depression Index (BDI 0-63) for mood and with the WHO short form 36 (SF-36 0-100) for HrQoL. Primary caregivers were examined with the Caregiver Burden Inventory (CBI 0-88) for caregiver burden, the BDI and the SF-36.

Results: So far, 100 patients were tested (age 64.2±11.5 years, 74% females, 26% males). 56% suffered from cervical dystonia, 15% from blepharospasm. Dystonia severity was mild to moderate (BFM movement 12.1±13.7, min 0.5/max 72, BFM impairment 2.5±4.1, min 0/max 29). Cognitive functioning was normal (MoCA 25.3±3.2), so was mood (BDI 11.2±8.8) and HrQoL (SF-36 49.7±10.9). Also, 85 caregivers were recruited (age 62.1±13.8 years, 66% males, 34% females). Caregiver burden was normal in most patients (CBI 8.1±9.7, (min 0/max 48), and so was mood (BDI 5.8±5.7, min 0/max 23) and HrQoL (SF-36 55.2±9.7).

Discussion: Dystonia patients suffer from mildly reduced HrQoL even under BT therapy. Caregiver burden could not be detected. Further analysis will explore caregiver burden in specific dystonia manifestations such as generalised dystonia.

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Botulinum Toxin Therapy in Patients with Oral Anticoagulation: Is it Safe?

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Introduction: When used therapeutically botulinum toxin (BT) has to be injected into its target tissues. All manufacturers warn not to do so in patients with oral anticoagulation to avoid haematoma. We wanted to study the haematoma frequency (HF) in patients with anticoagulation receiving intramuscular BT therapy.

Methods: 32 patients (16 females, 16 males, age 69.3 ± 10.0 years) with blepharospasm (n=6), hemifacial spasm (n=8), post-stroke spasticity (n=16) and cervical dystonia (n=2) received BT therapy (needle size 27G, post-injection tissue compression) whilst on anticoagulation (anticoagulation group, AG). 32 patients matched for disease, target muscles, age and gender received identical BT therapy without anticoagulation (control group, CG). Anticoagulation was performed with phenprocoumon. International normalised ratio (INR) at the time of BT injection was in all patients within recommended margins of 2.0 and 3.0 (mean 2.6 ± 0.27).

Results: Overall haematoma frequency (HF) was 3.0% in AG and 1.8% in CG (not significant). All hematomas occurred in blepharospasm patients (AG 5.2%, CG 2.6%, not significant) and hemifacial spasm patients (AG 3.9%, CG 2.9%, not significant). In cervical dystonia and spasticity there were no haematomas. Throughout an observation period of 4 years, none of the haematomas was surgically relevant in both groups. In cervical dystonia and spasticity there were no haematomas.

Discussion: Haematomas are a rare complication of BT therapy, mainly occurring in periocular injections. Anticoagulation only marginally increases HF, provided INR is controlled and appropriate injection techniques are used. Surgically relevant haematomas do not occur. Interruption of the oral anticoagulation to perform BT therapy does not seem justified.

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A Brief History of Neurologic Botulinum Toxin Therapy in Germany

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Introduction: Botulinum toxin (BT) has long been infamous in food safety and biological warfare. In the early 1970's Alan B Scott of San Francisco invented its therapeutic use originally in extraocular eye muscles to treat strabismus using a therapeutic BT type A preparation provided by Edward J Schantz and Eric A Johnson. Subsequently a large number of medical indications based on motor and glandular hyperactivity and - most recently - chronic migraine are now treated by BT therapy. BT's highly specific and elaborate mechanism of action BT represents a completely novel therapeutic principle which will have consequences far beyond existing indications.

Methods: BT therapy entered neurology through Stanley Fahn in New York from where C David Marsden brought it to London. From here neurological BT therapy came to Germany through Reiner Benecke and Dirk Dressler. Ophthalmological BT therapy was brought directly to Germany by Peter Roggenkämper, a fellow of Scott. By the early 1990's several users in Germany had learned about BT therapy and made the country one of the most productive countries in clinical BT science - backed up by a long tradition of solid basic BT research.

Results: For several years now, however, BT therapy in Germany has been stagnating due to a lack of reimbursement for the medical treatment and due to off label use challenges.

Discussion: BT is a safe and effective therapeutic tool in a variety of neurologic and nonneurologic syndroms.

Impact of Pallidal Deep Brain Stimulation on Activities of Daily Living in Patients with Craniocervical Dystonia – a Multi-center Survey

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Introduction: Pallidal deep brain stimulation (DBS) is an effective treatment option for severe craniocervical dystonia (CD) when botulinum toxin treatment has failed. Dysarthria has been described as a common side effect of pallidal stimulation in generalized dystonia. However, only in patients with focal dystonia it has been recognized that mild bradykinesia up to full parkinsonian phenotype may occur with chronic pallidal DBS. Here, we assess the impact of pallidal DBS on activities of daily living (ADL) in patients with primary CD.

Methods: We conducted a multi-center survey in a cohort of 51 patients (mean age 58±10) with primary CD who underwent pallidal DBS with stable stimulation parameters for at least 3 months. The survey included a questionnaire with 34 items of ADL. Patients were asked to rate subjective changes in ADL compared to the pre-operative state based on a 5-point-Likert-scale (improved; no change; mild, moderate or severe deterioration). Furthermore, a rating of an overall post-operative improvement of dystonia was assessed via a visual analogue scale.

Results: Patients reported a mean subjective improvement of dystonia by 62% (±26) with pallidal DBS. ADL improvement was reached on average in 11 out of 34 items, whereas a mean of 8 items deteriorated in a range from mild to severe. Among the top3 ADL items, which improved most consistently were 'cut food with knife and fork' (55%), 'hold and read a newspaper' (51%), 'use a spoon to eat a soup' (49%). On the other hand, activities which deteriorated post-operatively included 'handwriting' (58%), 'general mobility' (51%) and 'speaking loud and clearly on the phone' (49%). Worsening in ADL items related to bradykinesia (17 out of 34 items) was mentioned by 80% of patients, again from mild to severe.

Discussion: Our results emphasize that despite an overall functionally meaningful improvement in dystonia by pallidal DBS certain ADL that require fine motor skills can deteriorate post-operatively. Bradykinesia should be discussed as a potential side effect when counseling patients before DBS surgery. It will be important to evaluate to which extent stimulation parameters and even more importantly electrode location contribute to these side effects.

Precise Classification and Related Responsible Muscles of Cervical Dystonia

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Introduction: To analyze the precise classification of cervical dystonia (CD), the distribution of responsible muscles for each subtype and the improvement of symptoms after botulinum toxin (BTX) injection.

Methods: Clinical data of CD patients treated with BTX between March 2010 and March 2017 in Shanghai Tongji Hospital were assessed by the col-cap concept (laterocaput, laterocollis, torticaput, torticollis, anterocaput, anterocollis, retrocaput, retrocollis, sagittal shift forwards, lateral shift, sagittal shift backwards). The responsible muscles according to EMG of each patient, as well as their symptom relief after BTX injection (evaluated by Tsui score) were analyzed.

Results: A total of 207 CD patients (88 males and 119 females) with 451 treatments were included. Among them, 255 cases were single col-cap subtype, 163 cases were combination of two subtypes, 21 cases were combination of three subtypes, and 12 cases were head tremor subtype. In single col-cap subtype, torticaput is the most common (23.92%), followed by torticollis (12.30%). Sagittal shift forwards (0.68%) and lateral shift (0.23%) are the less common. In complex subtypes (combination of two or three subtypes), torticaput combined with torticollis is the most common (28.26%), followed by torticaput combined with laterocaput (19.02%). A total of 165 patients completed video follow-up, Tsui scores were significantly reduces after BTX treatment in torticollis, torticaput, laterocollis, laterocaput and retrocaput. In rotation and lateral flexion subtypes, common responsible dystonic muscles include sternocleidomastoid, trapezius, splenius capitis, semispinalis capitis, levator scapulae and scalenus. Torticaput subtype may also involve obliquus capitis inferior, and torticollis subtype may involve splenius cervicis.

Discussion: In single col-cap subtype, torticaput is the most common, followed by torticollis. In complex subtypes, torticaput combined with torticollis is the most common, followed by torticaput combined with laterocaput. In all 11 subtypes, torticollis, torticaput, laterocollis, laterocaput and retrocaput have better therapeutic effect with BTX.

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Precise Surface Positioning of the Obliquus Capitis Inferior Muscle

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Introduction: To clarify surface positioning of obliquus capitis inferior (OCI) muscle and provide accurate puncture path for botulinum toxin (BTX) injection in cervical dystonia (CD) patients.

Methods: Firstly, reconstruction of OCI was performed in 17 CD patients who underwent cervical CT scan. Surface projection of the start and stop points of OCI was found and the relationship between OCI and surface markers was analyzed. Secondly, 10 healthy volunteers were examined by B-ultrasound to determine the thickness and depth of OCI and the distribution of adjacent muscles and blood vessels. Finally, 20 CD patients with OCI spasm were injected with BTX under electromyography guidance using the puncture path summarized from above data.

Results: OCI was located at the oblique transverse plane between spinous process of axis (C2) and tragus of the same side. The surface distance between C2 spinous process and tragus was 13.58 ± 0.98 cm. The surface distance between C2 spinous process and transverse process of atlas (C1) was 4.13 ± 0.54 cm. The surface distance between C2 spinous process and the midpoint of OCI was 2.55 ± 0.27 cm. B-ultrasound showed that OCI was covered by semispinalis capitis muscle (SECM), under OCI was the atlantoaxial joint and the vertebral artery was located at the superior lateral part of OCI. The thickness of OCI was 4.32 ± 1.18 mm and its depth was 20.11 ± 3.88 mm. We suggested the injection path for OCI as follow: the puncture site is the inner 1/5 between C2 spinous process and tragus. The needle is inserted along the sagittal plane and passes through trapezius, splenius capitis and SECM. B-ultrasound confirmed that BTX was successfully injected into OCI using this puncture path in all the 20 CD patients.

Discussion: We suggested a useful and precise surface positioning method and puncture path for OCI.

Influence of Early Traumatization on Development of Musicians' Dystonia

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Introduction: Musician's dystonia represents a special case of focal dystonia. It is described as a task-specific movement disorder which presents itself as muscular incoordination or loss of voluntary fine-motor control of extensively trained movements whilst a musician is playing the instrument. Musician's dystonia is experienced as highly stressful, leads to great impairment and often ends a musician's career. Besides heterogeneous assumptions about pathophysiology there are up to our knowledge no etiological explanatory models. Based on longterm experience from our musician's' medicine outpatient clinic, we assume a link between (early) psychic traumatisatisation and focal dystonia.

Methods: We conducted a psychodynamic based qualitative investigation on six professional musicians (5 male, 1 female, age 30-57) with focal dystonia, by employing a semi-structured episodic interview (Flick et al., 2012). This interview aims at investigating personal experiences both in episodic and semantic memory and is based on a standardized manual. We utilised items from the *Childhood Trauma Questionnaire* (Bernstein & Fink, 1998) as well as the *PITT* manual (Reddemann, 2014) to conceive a personal questionnaire made of six blocks and 30 items. Each interview audio file was transcribed using *Conversation Analytic Transcription System 2* (Selting et al., 2010) by employing the software „easytranscript“ (ISConsult, 2017).

Results: We derived one generalized etiological model describing contributing factors in the etiological understanding of focal dystonia from the six case studies by implementing grounded theory methodology (Glaser & Strauss, 1967). We found at least one traumatisatisation in each case, occurring between the age of three and sixteen years. All traumatisatisation events took place in familiar environments. In five cases perfectionistic behaviour occurred as coping strategies, in all cases resulting episodes of high tension finally led to first symptoms of focal dystonia. Concerning affect regulation, heterogeneous results were found. Summing up, we propose a link between traumatisatisation and focal dystonia which is moderated by coping behaviour.

Discussion: Our results reveal the severe consequences for traumatised musicians. We see focal dystonia as a result of a multifactorial etiological process which includes the way of practicing, the relation between teacher and pupil, a healthy lifestyle and mental hygiene. We suggest a preventive health care system which is integrated in conservatories' educational concept.

Elevated Muscular Coactivation and Higher Temporal Variability in Musicians Affected by Bow Arm Dystonia

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Introduction: Musicians' dystonia (MD) is characterized by a loss of voluntary control and deficient muscular coordination of extensively trained movements during instrumental playing (1). The present study was motivated by the obvious lack of an objective measurement tool for evaluating the quality of bowing performance in string players. It aimed to assess kinematic and electromyographic features of bow strokes performed by violinists and violists affected by bow arm dystonia, compared to healthy controls.

Methods: Seven affected and 20 healthy string players participated in the study. The task consisted of simple bowing on a single string at a given velocity. A 3D motion capture system was used to record bowing movements. Temporal variability, an indirect indicator for motor disturbances (2), was computed in order to evaluate the musicians' performance during the repetitive movements. Simultaneously, muscular activity of essential flexors and extensors of the right arm was recorded using surface electromyography. Antagonistic muscular coactivation and temporal variability were analyzed in a multilevel linear model framework.

Results: The results revealed generally higher forearm coactivation during upstrokes as compared to downstrokes in both groups. Whereas coactivation levels of the upper arm did not significantly differ between groups, we found increased forearm coactivation in patients. Furthermore, affected musicians executed bow strokes with higher temporal variability than healthy controls, especially during fast playing.

Discussion: While higher temporal variability has frequently been reported in pianists with MD (see 2, 3), this is the first study confirming this result in string players' bow arm dystonia. Increased coactivation may represent an adaptive motor control strategy that is applied in order to reduce noise entering the motor system. This is in accordance with the Predictive-control hypothesis (4). Building on these results we introduce a novel attempt to quantifying dystonic symptoms in string players by means of simple kinematic measures. To show that this approach can serve as a measurement tool in clinical practice, however, a deeper systematic exploration is necessary in order to confirm its validity and reproducibility.

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Video-based Assessment of the Long-term Development of Musicians' Dystonia in Keyboard Players

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Introduction: Musicians' dystonia (MD) is a focal and task-specific form of dystonia affecting the voluntary control of muscles or muscle groups in the embouchure, hand or forearm used in highly precise and extensively trained movements required while playing a musical instrument.(1) To our knowledge there is no study assessing the long-term development of MD in a larger cohort without the use of patient-subjective evaluation methods. This retrospective observational study aimed to show the long-term development of symptoms of MD in keyboard players by means of a video rating procedure. Furthermore, the study assessed the influence of patient-specific factors and the applied therapy (Botox, Trihexyphenidyl, Retraining) on the development of symptoms.

Methods: Video assessment was done by 6 carefully instructed pianists, rating a total of 266 videos from 80 patients, recorded over a period of almost 20 years. Raters evaluated short clips of patients playing c-major scales on a grand piano by acoustic (temporal irregularity of notes) and visual criteria (motor impairment of movement). Development of symptoms was evaluated by comparing the rating of the first and the last video in each patient.

Results: Intra-rater reliability and inter-rater concordance were high and medium, respectively. In 65%-70% of the patients at least one of the rating criteria improved. Development of symptoms was not dependent on patient-specific temporal factors (age, time to treatment, duration of treatment) and on the type of therapy applied. The initial severity of symptoms was the only significant explanatory variable for the development of symptoms: patients having a higher severity of initial symptoms showed better improvement during treatment.

Discussion: This study provides a new perspective on the course of MD in keyboard players by using methods other than self-report in a larger cohort. Video rating was shown to be a reliable method to evaluate MD in keyboard players. The majority of patients improved during therapy. The course of symptoms is difficult to predict and is very individual.

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Tongue Involvement in Embouchure Dystonia: New Results Using Real-time MRI of Trumpet Players

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Introduction: The embouchure of a brass musician is of utmost importance for tone production and quality of playing. It requires skilled coordination of lips, facial muscles, tongue, oral cavity, larynx and breathing and has to be maintained by steady practice. This paper features the use of real-time MRI to analyse differences in tongue movements between healthy trumpet players and professional players with embouchure dystonia (EmD) which is a highly task-specific movement disorder and so far has rarely been studied in trumpet players despite the fact that its diagnosis is a severe threat to a professional career.

Methods: Real-time MRI videos (with sound recording) were acquired at 55 frames per second, while 10 healthy subjects and 4 patients with EmD performed a defined set of exercises on an MRI-compatible trumpet inside a 3 Tesla MRI system. To allow for a comparison of tongue movements between players, temporal changes of MRI signal intensities were analysed along 7 standardized positions of the tongue using a customised MATLAB toolkit. Detailed results of movements within the oral cavity during performance of an ascending slurred 11-note harmonic series are presented.

Results: Playing trumpet in the higher register requires a very precise and stable narrowing of the free oral cavity. For this purpose the anterior section of the tongue is used as a valve in order to speed up airflow in a controlled manner. Conversely, the posterior part of the tongue is much less involved in the regulation of air speed. The results further demonstrate that healthy trumpet players control movements of the tongue rather precisely and stable during a sustained tone, whereas trumpet players with EmD exhibit much higher variability in tongue movements.

Discussion: Control of the anterior tongue in trumpet playing emerges as a critical feature for regulating air speed and, ultimately, achieving a high-quality performance. In EmD the observation of less coordinated tongue movements suggests the presence of compensatory patterns in an attempt to regulate (or correct) pitch. Increased variability of the anterior tongue could be an objective sign of dystonia that has to be examined in further studies and extended to other brass instruments and may be also a potential target for therapy options.

Long-term Treatment of Task-specific Dystonias with Botulinumtoxin

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Introduction: Botulinumtoxin is the standard treatment for the task-specific dystonias musician's dystonia (MD) and writer's cramp (WC). The aim was to assess 1a) a correlation between the amount of BTX and the treatment-duration (time) and 1b) whether patients can be classified into two groups depending on the amount of BTX; 2) a positive correlation between the interval between consecutive treatments and time.

Methods: We included 234 musicians with MD and 17 non-musicians with WC and obtained the amount of Botulinumtoxin and of injected muscles per treatment and time between consecutive treatments. We applied a median-split to separate patients into a high-BTX and a low-BTX group.

Results: For MD we found an increase of the BTX-amount for all musicians and in the high-BTX group and a decreasing amount the low-BTX group. The time interval between consecutive treatments increased for all MD-patients and for the high-BTX group. In WC, the BTX-amount decreased with time for all non-musicians. The time interval between consecutive treatments increased in the high-BTX group.

Discussion: The change in the amount of BTX given per muscle and treatment differs between the high- and the low-BTX group in MD, whereas in WC no difference between groups can be seen. The interval between consecutive treatments increases the high-BTX group in MD and WC. Further studies should aim at finding predictors that allow for a classification of each patient into the high- or low-BTX group early in treatment. This would have consequences for the counseling of patients and for the treatment plan.

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Real-Time MRI Visual Feedback in Tongue Thrust and Embouchure Dystonia: Implications for Treatment?

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Introduction: Tongue thrust (reverse swallow) is a movement disorder in which orofacial muscular control is imbalanced, resulting in impaired muscle control of the tongue. Embouchure dystonia comprises a constellation of dysfunctions in various combinations of muscles controlling the lips, face, throat, and in some cases, the tongue. Treatment strategies for these disorders using visual feedback have not involved observing structures within the mouth. We employ a novel approach using real-time MRI (RT-MRI) visual feedback.

Methods: We obtained RT-MRI videos of two brass players, one with tongue thrust (Case 1), and another with tongue-involved embouchure dystonia (Case 2), playing a sustained note on an MRI-compatible French horn. The initial performances demonstrated abnormal positioning of the tongue and poor sound quality. The subjects viewed RT-MRI images of a healthy performer demonstrating typical tongue positioning during the same exercise. The patients mimicked the same tongue positioning in a series of subsequent experimental exercises while observing their MRI images in real time. For Case 1, the subject attempted to play the note while mimicking the tongue position of the healthy performer. For Case 2, an exercise progression was employed consisting of 1) mimicking the healthy example tongue position using vocalization of "EH" with relaxed lips (not playing), 2) repeating 1 but with the lips brought closer together, and 3) repeating the same tongue position while gently touching the mouthpiece to the lips, accompanied by non-buzzing, gentle airflow (no vocalizing).

Results: RT-MRI video recordings of Case 1 demonstrate that during playing with feedback, the subject had adequate motor control of the tongue to mimic the elite, healthy subject, and sound quality improved. In Case 2, using the 3 step exercise progression, similar motor control mimicking the healthy performer was demonstrated in steps 1 and 2, but upon introduction of mouthpiece contact in stage 3, the tongue resumed its abnormal position.

Discussion: Our observations demonstrate that the acquisition of appropriate motor strategies for tongue control appear to be possible in both patients. However, increasing levels of task specificity with the dystonia patient progressively interfere with preserving these movement strategies. We posit that a longitudinal, repeated intervention study might assist the appropriate strategies to be better preserved.

From Dystonic to Epileptic Status: The vulnerability of Patients with DystoniaV. Muoio¹, P. Moreno-Granjeiro², S. Amorim², B. Monaco²¹*Medicine School, University of Sao Paulo/ Universidade Nove de Julho, Sao Paulo, Brazil,* ²*University of Sao Paulo, Sao Paulo, Brazil*

Introduction: We report a case of a 9-year-old child who developed epileptic status following TMS (Transcranial magnetic stimulation) for dystonic status.

Methods: Conducted a survey of the patient's chart, accompanied by our team, from the year 2013 to the present moment.

Results: A 9-year-old male patient admitted under our care from a remote area of Brazil. He had the diagnosis of cerebral palsy secondary to neonatal anoxia (Ashworth Scale 2), a discreetly diminished cognition, but well adapted to school activities. Medical reports from the original service reported only spasticity, with no dystonic phenomena. After pulmonary bacterial infection, he presented dystonic movements, which in one week, progressed to dystonic status. He was then transferred to our service, where he was admitted in a septic shock, with hemodynamic instability, rhabdomyolysis, renal function limitation and dystonic status. The patient was then compensated for his sepsis (with good outcome), and received early care for the dystonic status (with stable evolution). As there was no satisfactory improvement of his dystonic condition, an electrode placement for deep brain stimulation (DBS) was indicated. This procedure, however, was contraindicated by pediatrics. It was then chosen by treatment with TMS (transcranial magnetic stimulation), which quickly reversed the dystonic status, but at the end of the session, the patient evolved into an epileptic disease. The status was quickly treated, and the patient progressed very well. Six years after the event, the patient regained his basic status, studying normally, maintaining his rehabilitation routine and without dystonic phenomena.

Discussion: Transcranial magnetic stimulation is a very safe tool that can be very useful in treating patients with dystonia, even in selected cases of status. However, it is important to remember that patients, especially pediatric patients, may present instability or brain immaturity, which can lead to complications such as seizures and epileptic status.

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Genetic and Clinical Investigation of Young Onset Generalized and Segmental Dystonia in Korea

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Introduction: Dystonia is clinically heterogenous movement disorder and can present with various other movement disorders. The indications for genetic testing and which genes should be tested were not clearly elucidated yet. In this study, we performed whole exome sequencing (WES) in Korean patients with young-onset dystonia, and investigated important factors associated with WES in dystonia.

Methods: We recruited patients with young-onset (< 40 years of onset age), segmental or generalized dystonia by new MDS dystonia classification at Samsung Medical Center from 2015 to 2018. We excluded subjects with mutation in TOR1A and for persistent dystonia, PANK2 for the eye-of-tiger sign in brain MRI, PRRT2 for paroxysmal dystonia, and SGCE for myoclonus-dystonia syndrome, or subjects with focal or 2ndary dystonia. We performed WES in all enrolled subjects and confirmed with Sanger sequencing.

Results: Of total 33 recruited subjects, we found out 10 (30%) pathogenic or likely pathogenic variants related with dystonia. When we reviewed the 10 patients with relevant variants, brain imaging was helpful in 3 subjects (HTRA1, SCL20A and WDR45), clinical characteristics (paroxysmal presentation) in 2 subjects (ADCY5, and ATP1A3), and head circumference in 1 subject (PTEN). Based on our results, WES has a positive diagnostic yield of >30% for patients with young age onset dystonia. Positive diagnostic rate was highest among childhood onset dystonia (46%). Generalized dystonia and combined other neurologic manifestations are more likely to yield a positive result.

Discussion: Clinical exome sequencing suggests broadening of disease spectrum and uncover diagnosis of young age dystonia. Genetic diagnosis should be considered in early onset, generalized dystonia combined with other neurologic manifestations.

Unilateral pallidal deep brain stimulation in lateralized cervical dystonia: A pilot study in three patients

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Introduction: Deep brain stimulation of globus pallidus internus (GPi-DBS) is an accepted treatment for medically refractory cervical dystonia (CD). Given current concept of dystonia pathophysiology and evidence of bilateral muscle involvement in CD, mostly bilateral GPi-DBS is used. Only few cases of unilateral GPi-DBS for CD are described in the literature reporting controversial approach. We aimed to evaluate possible effect of unilateral GPi-DBS in CD patients. [1][2][3][4][5]

Methods: We assessed 3 patients with pharmacoresistant CD who underwent implantation of bilateral GPi-electrodes (mean age at surgery 46.3 years; disease duration 4.0 years). Two patients with isolated CD had already experience of bilateral GPi-DBS with mean duration of 34 months (predominant left or right sided torticollis). The third patient with right sided torticollis was recently operated, and had structural MRI abnormality - a small lacunar cyst in left posterior putamen. We provided patients with different variants of DBS settings, which included bilateral or unilateral for each hemisphere stimulation. Patients were advised to use each settings' variant for at least one month except in cases of marked dystonia deterioration.

Results: In all 3 patients a unilateral GPi-DBS was effective. Two CD patients with no evidence of structural lesion of basal ganglia preferred unilateral to bilateral stimulation. One of these patients also reported a dissolution of stimulation-induced chronic fatigue that he experienced following bilateral GPi-DBS and that could not be eliminated by thorough stimulation adjustments. In both patients, the most effective appeared to be stimulation of GPi contralateral to head turn (ipsilateral to contracted SCM muscle). Stimulation of GPi in ipsilateral to torticollis hemisphere was barely effective and induced deterioration of CD. In patient with small putaminal cyst, we saw an opposite situation. CD motor scores under the optimized settings did not differ significantly whether with unilateral or bilateral stimulation. Overall clinical improvement comprised $59.6 \pm 7.9\%$ according to TWSTRS, and $68.8 \pm 12.9\%$ according to Tsui scale.

Discussion: A unilateral stimulation might be used in lateralized CD. In some cases, unilateral GPi-DBS may be even more efficient compared to bilateral or allow to avoid stimulation-induced side effects. Nevertheless, it remains unclear which hemispherical side is more beneficial for stimulation regarding CD lateralization. Studies in larger population of CD patients are necessary.

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Muscular weakness and atrophy during and after the termination of Botulinum toxin Type A injections in patients with focal hand dystonia

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Objectives: The injection of Botulinum toxin (BTX) Type A remains one of the most efficient symptomatic treatments of focal hand dystonia. However, BTX injections may introduce side effects in some cases, such as muscular weakness or atrophy. The aim of the current investigation has focused on two different aspects. First, to develop assessments that can estimate retrospectively the muscular atrophy and weakness, and second, to assess the degree and the course of those side effects after the termination of the BTX therapy.

Methods: Ten healthy subjects participated at two different time points in order to test the reliability of our assessments. Afterwards, thickness and strength upper limb asymmetry was compared between 20 healthy musicians and 20 musicians diagnosed with focal hand dystonia who had received BTX injections. Ultrasonography was used to estimate muscular atrophy and a custom-made strength device was used to assess muscular strength of the fingers.

Results: Our selected assessments (thickness and strength), which focused exclusively on the evaluation of the M. flexor digitorum muscle (profound and superficial), indicated excellent test-retest reliability (ICC > 0.92). Concerning group differences, data analyses are still in progress. However, preliminary results indicated a significant muscular atrophy and weakness among the affected musicians who received BTX injections. Finally, the exact effect of dosage and the number of injections as well as the course of the side effects after the termination of BTX injections are still in progress.

Conclusion: The current study provides reliable ultrasonographic and strength assessments which could be used for more targeted evaluations of the finger flexor muscles in healthy controls but also in individuals suffering from various neuromuscular diseases. Muscular atrophy and weakness seem to be potential side effects, however, not to a degree that would affect daily activities. Exact numbers and potential development of those side effects after treatment termination will be presented at the conference.

New Classification of the Yips Phenomenon Based on Musician's Dystonia

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Objectives: Yips is usually described as focal dystonia, or choking under pressure, or as lying on a continuum between both. Based on the common occupational conditions across musicians and athletes, the present exploratory study aimed to investigate whether musicians diagnosed with focal dystonia and golfers affected with yips, can be similarly subclassified based on their psychological profiles.

Methods: Twenty healthy musicians, 20 musicians with focal dystonia, 20 healthy golfers, and 20 yips-affected golfers went through a test battery including three psycho-diagnostic standardized questionnaires (the Competitive Trait Anxiety Inventory, the Frost's Multidimensional Perfectionism Scale, and the Stress Coping Questionnaire), measuring trait cognitive and somatic anxiety, perfectionistic tendencies and different stress coping strategies.

Results: Findings based on a clustering procedure suggest that similar to musician's dystonia, yips-affected golfers can be classified into those with and those without specific elevated perfectionistic, stress and anxiety traits. The roles of these different psychological profiles as possible triggering factors of the yips are compared with those of musician's dystonia.

Conclusions: The current study suggests that the yips phenomenon might cover a broader range of different subtypes of movement disturbances than those already suggested in the literature. Finally, a theoretical model, which explains the role of the different triggering factors in the discrimination of the different subtypes, is suggested. A better classification and understanding of the different subtypes of yips could lead to a more accurate diagnosis and to the design of more individualized treatment intervention.

