

Guided Poster Tours

International Congress of
Parkinson's Disease and Movement Disorders®

October 5-9, 2018

HONG KONG

www.mdscongress.org



International Parkinson and
Movement Disorder Society

International Congress of Parkinson's Disease and Movement Disorders®

Guided Poster Tour Abstracts

Guided Poster Group 1: Clinical Trials and Therapy in Movement Disorders

5 Improvements of tremor control and life quality of refractory essential tremor patients after MR-guided focused ultrasound thalamotomy – A Taiwan experience

H.C. Lai, K. Tsai, W.C. Chang, T. Taira, C.Y. Wei (Changhua County, Taiwan)

7 Specific active immunotherapy (SAIT) against alpha-synuclein with AFFITOPE® PD01A and PD03A: Results from the AFF009 phase I trial

W. Meissner, A. Pavy-Le Traon, A. Foubert-Samier, M. Galitzky, B. Laurens, U. Sabatini, S. Schmidhuber, D. Winter, G. Galabova, G. Staffler, A. Schneeberger, A. Kutzelnigg, O. Rascol (Bordeaux Cedex, France)

8 PASSPORT, An Ongoing Phase 2 Study in Patients with PSP– Baseline Characteristics

T. Dam, A. Boxer, L. Golbe, G. Höglinger, H. Morris, I. Litvan, J.C. Corvol, A. Lang, C. Bechtold, I. Qureshi, M. Grundman, B. Han, J. O'Gorman, T. Olsson, S. Budd Haeberlein (Cambridge, MA, USA)

9 A German-Austrian multicenter, non-interventional, prospective study for the treatment with abobotulinumtoxinA injections in naïve and previously treated patients suffering from cervical dystonia

W. Jost, A. Schramm, M. Müngersdorf, A. Stenner, P. Schwingenschuh, P. Maisonobe, M. Koch, B. Haslinger (Wolfach, Germany)

12 Low-Fat Versus Ketogenic Diet In Parkinson's Disease: A Pilot Randomized Controlled Trial

M. Phillips, D. Murtagh, L. Gilbertson, F. Asztely, C. Lynch (Hamilton, New Zealand)

15 Deep brain stimulation (DBS) for dyskinesic cerebral palsy: A pilot study

S. Duma, N. Mahant, A. Ha, S. Kim, A. Phu, K. Stewart, M-C. Waugh, N. Wolfe, D. Russell, B. Oowler, M. Krause, V. Fung (Westmead, Australia)

17 Zonisamide improves parkinsonism in DLB patients: A randomized phase 3 trial

M. Murata, T. Odawara, K. Hasegawa, R. Kajiwara, H. Takeuchi, M. Tagawa, K. Kosaka (Kodaira, Japan)

32 Alleviation of freezing of gait in patients with Parkinson's disease by high-frequency rTMS over SMA is associated with normalization of brain connectivity patterns

T.M. Mi, S. Garg, F. Ba, T. Wu, P.P. Liang, L.L. Gao, K.C. Li, P. Chan, M. McKeown (Beijing, China)

35 PPMI driven sample size estimation for clinical trials in Parkinson's disease

K. Marek, J. Seibyl, C. Caspell-Garcia, C. Coffey, B. Mollenhauer, K. Kieburtz, C. Tanner, L. Chahine, A. Siderowf, T. Simuni (New Haven, CT, USA)

Guided Poster Group 2: Parkinson's Disease: Clinical Trials, Pharmacology And Treatment

251 The anti-dyskinetic effect of the clinically-available 5-HT3 receptor antagonist granisetron in the 6-OHDA-lesioned rat model of Parkinson's disease

C. Kwan, I. Frouni, D. Bedard, A. Hamadjida, P. Huot (Montreal, QC, Canada)

301 Directional Lead Impedances and Their Possible Effects on Deep Brain Stimulation

L. Juarez Paz, A. Dalal Kirsch, F. Steigerwald, C. Matthies, S. Meoni, V. Fraix, T. Ten Brinke, R. de Bie, K. Wynants, D. Blum, N. Van Dyck, P.R. Schuurman, E. Moro, S. Chabardes, J. Volkmann (Valencia, CA, USA)

326 DIRECT DBS: A Prospective, Multicenter Clinical Study with Double-Blinding for a Directional Deep Brain Stimulation Lead – Therapeutic Windows with Directional Stimulation

F. Steigerwald, J. Volkmann, C. Matthies, A. Dalal Kirsch, S. Chabardes, R. de Bie, P. Schuurman, E. Moro, V. Fraix, S. Meoni, D. Blum, L. Juarez Paz, K. Wynants, N. Van Dyck (Würzburg, Germany)

341

‘PDSAFE’ – A multi-dimensional fall rehabilitation intervention for people with Parkinson’s with specialist physiotherapy training: qualitative exploration of physio’s experiences

K. Seymour, S. Hulbert, V. Goodwin, L. Rochester, A. Nieuwboer, A. Ashburn (Southampton, United Kingdom)

364

The Effect of Short Pulse Width Settings on Speech in Subthalamic Nucleus Deep Brain Stimulation for Parkinson’s disease

V. Dayal, T. Grover, E. Tripoliti, P. Limousin, T. Foltynie (London, United Kingdom)

380

Sex differences by design and outcome in the Safety of Urate Elevation in PD (SURE-PD) trial

M. Schwarzschild, E. Macklin, R. Bakshi, S. Bhattacharyya, R. Logan, A. Ascherio; on behalf of the Parkinson Study Group SURE-PD Investigators (Boston, MA, USA)

388

The highly selective 5-HT_{2A} receptor antagonist EMD-281,014 alleviates L-DOPA-induced dyskinesia in the 6-OHDA-lesioned rat model of Parkinson’s disease

I. Frouni, D. Bedard, S. Belliveau, E. Bourgeois-Cayer, A. Hamadjida, P. Huot (Montreal, QC, Canada)

394

Patient and Provider Experiences and Attitudes toward Rytary

S. Horn, D. Coughlin, J. Chou, F. Wang, M. Stacy, R. Dolhun, C. Kopil, N. Amondikar, A. Deik, H. Sarva (Philadelphia, PA, USA)

420

Mitochondrial morphometrics in idiopathic Parkinson’s disease fibroblasts

P. Antony, O. Boyd, K. Mommaerts, K. Sokolowska, M. Ostaszewski, A. Baumuratov, L. Longhino, F. Poulain, R. Krueger, R. Balling, N. Diederich (Belvaux, Luxembourg)

427

Dysphagia predicts poor outcome in late-stage Parkinson’s disease

M. Fabbri, D. Abreu, L. Guedes, M. Rosa, A. Antonini, M. Zibetti, L. Lopiano, J. Fereira, M. Coelho (Lisbon, Portugal)

Guided Poster Group 3:

Surgical Therapy: Parkinson’s Disease

512

Post-Deep Brain Stimulation Psychosis in Parkinson’s Disease: A Meta-analysis

YC. Tai, N. Mahant, B. Stubbs, A. Carvalho, YW. Chen, TY. Chen, SP. Hsu, PT. Tseng (Kaohsiung, Taiwan)

515

Motor and cognitive progression in GBA-related PD patients submitted to Deep Brain Stimulation

L. Correia Guedes, C. Silva, R. Machado Bouça, N. Gonçalves, M. Fabbri, A. Castro Caldas, P. Pita Lobo, M.M. Rosa, B. Cattoni, H. Carvalho, A. Gonçalves Ferreira, J.J. Ferreira, M. Coelho (Lisbon, Portugal)

537

Directional deep brain stimulation in Parkinson’s disease guided by local field potentials

F. Alonso-Frech, C. Fernandez-Garcia, M. Monge, M.J. Catalan Alonso, G. Foffani (Madrid, Spain)

543

Surgery-, hardware - and chronic stimulation-related adverse events following subthalamic nucleus deep brain stimulation for Parkinson’s disease

B. Gonenli Kocer, E. Ozturk, S. Comoglu, M. Sorar, H. Kertmen (Ankara, Turkey)

544

Poor responders to STN DBS in Parkinson’s disease: 1 year follow-up study

M. Zibetti, L. Ricciardi, E. Montanaro, M. Sarchioto, M. Edwards, L. Lopiano, F. Morgante (Toriino, Italy)

546

A wireless brain-spine interface alleviating gait deficits of non-human primates model of Parkinson’s disease

F. Raschella, T. Milekovic, M. Perich, S. Sun, G. Schiavone, C. Hitz, Y. Jianzhong, W. Ko, Q. Li, C. Qin, S. Lacour, J. Bloch, S. Micera, E. Bezard, G. Courtine (Geneva, Switzerland)

552

Deep brain stimulation for monogenic Parkinson’s disease: A systematic review

T. Kuusimäki, J. Korpela, E. Pekkonen, M. Martikainen, A. Antonini, V. Kaasinen (Turku, Finland)

558

Propionibacterium acnes Infection with Intracerebral Abscess in Deep Brain Stimulation

R. Lewis, F. Farrokhi, M. Marsans (Seattle, WA, USA)

563

Intraoperative Electromyography can optimize pallidotomy for Parkinson's disease and dystonias

P. Brainer, A. Campos, A. Brainer, J. Brainer, P. Brainer, P. Coutinho, C. Lima, S. Laurentino, R. Bandin, M. Andrade (Recife, Brazil)

567

The effects of deep brain stimulation of the pedunculopontine nucleus on cognition in Parkinson's disease and Progressive Supranuclear Palsy

F. Leimbach, J. Gratwicke, T. Foltynie, M. Hariz, P. Limousin, L. Zrinzo, M. Jahanshahi (London, United Kingdom)

572

Is lowering stimulation frequency a feasible option to improve speech in Parkinson's disease patients undergoing subthalamic deep brain stimulation?

M. Fabbri, M. Zibetti, G. Ferrero, A. Accornero, I. Guimaraes, M. Rizzone, A. Romagnolo, J. Ferreira, L. Lopiano (Lisbon, Portugal)

Guided Poster Group 4:

Ataxia

618

Loss of paraplegin drives spasticity rather than ataxia in SPG7: A European cohort analysis of 238 patients

G. Coarelli, R. Schule, B. vande Warrenburg, P. de Jonghe, C. Ewencyk, A. Martinuzzi, M. Synofzik, E. Hamer, J. Baets, M. Anheim, L. Schöls, T. Deconinck, B. Fontaine, T. Klockgether, MG. D'Angelo, ML. Monin, P. Charles, MT. Bassi, T. Klopstock, E. Ollagnon-Roman, C. Kamm, M. Papin, CS. Davoine, G. Banneau, S. Tezenasdu Montcel, D. Seilhean, A. Brice, C. Duyckaerts, G. Stevanin, A. Durr (Paris, France)

622

Cerebellar Ataxia case series study from southern Spain: Clinical and molecular description

A. Adarmes Gomez, S. Jesus Maestre, C. Mendez delBarrio, D. Macias Garcia, F. Carrillo Garcia, M. Carballo, P. Gomez Garre, P. Mir Rivera (Seville, Spain)

624

Genotype-phenotype correlations in 104 Uzbekish families with Spinocerebellar ataxias

F. Rakhimov, Y. Majidova, G. Rakhimbaeva (Tashkent, Uzbekistan)

626

Objective Measures of Ataxic Gait Using Wearable Inertial Sensors

M. El-Gohary, L. Horak, C. Gomez (Portland, OR, USA)

627

Multi-tiered Diagnostic Approaches Reveal a High Degree of Genetic Heterogeneity for Hereditary Cerebellar Ataxias: A Retrospective Review of an Australian Cohort

C. Kang, C. Liang, K. Ahmad, Y. Gu, SF. Siow, J. Colebatch, S. Whyte, K. Ng, P. Cremer, R. Davis, T. Roscioli, M. Cowley, J.S. Park, C. Sue, K. Kumar (Sydney, Australia)

633

MRI and behavioural account of the aging cerebellum

M. Bares, P. Filip, C. Gallea, S. Lehericy, O. Lungu (Brno, Czech Republic)

655

Transcriptional profiling of peripheral blood monocytes from child Friedreich's ataxia patient: New molecules and patterns of gene expression

H. Singh, V. Swarup, R. Singh, I. Singh, M. Faruq, S. Vivekanandhan, A. Srivastava (Delhi, India)

660

Comorbid Pediatric Early Onset Ataxia and Dystonia - Is the Cerebellum Involved?

D. Sival, M. Tijssen, D. Verbeek (Groningen, Netherlands)

663

The etiologies of chronic progressive cerebellar ataxia in a Korean population

J. Youn, M. Kim, JH. AHN, JW. Cho, JS. Kim (Seoul, Republic of Korea)

Guided Poster Group 5:

Dystonia

691

DBS neuromodulation reduces severe dystonic pain in children and young people

S. Perides, J.P. Lin, G. Lee, H. Gimeno, R. Selway, K. Ashkan, M. Kaminska (London, United Kingdom)

696

The clinical value of SPECT in identifying dystonic muscles of patients with cervical dystonia

L. Jin, L. Feng, I. Djibo, S. Chen, F. Teng, B. Li, H. Ma (Shanghai, China)

713

Characterizing Bulbar Dysfunction in X-Linked Dystonia-Parkinsonism (XDP): A Pilot Study

J. de Guzman, B. Perry, C. Go, J. Green, N. Sharma (Boston, MA, USA)

727

The association of primary dystonia with tics - chance or new syndrome?

C. Del Gamba, A. Latorre, U. Bonuccelli, R. Ceravolo, K. Bhatia (London, United Kingdom)

734

Zolpidem effect in task specific dystonia – clinical and neurophysiological study

K. Vogelnik, M. Grmek, R. Perellon Alfonso, P. Tomše, M. Trošt, M. Kojović (Ljubljana, Slovenia)

746

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

J. Krauss, C. Nicholson, M. Barbe, V. Visser-Vanderwalle, A. Kuehn, M. Poetter-Nerger, R. Jain, H. Scholtes, N. Van Dyck, A. Albanese (Hannover, Germany)

761

Comorbidity and retirement in primary focal cervical dystonia

R. Ortiz, F. Scheperjans, T. Mertsalmi, E. Pekkonen (Helsinki, Finland)

762

Frequency and Phenotypic Spectrum of KMT2B Mutations in Childhood-Onset Dystonia: Results from a Single-Centre Cohort Study

M. Carecchio, G. Zorzi, F. Invernizzi, C. Panteghini, L. Romito, F. Zibordi, V. Leuzzi, S. Galosi, P. Morana, B. Morana, C. Piano, A. Bentivoglio, C. Reale, F. Girotti, M. Topf, A. Joseph, M. Kurian, S. Lubbe, B. Garavaglia, N. Mencacci, N. Nardocci (Milan, Italy)

769

A machine learning approach to determine the important patient characteristics for tremor prevalence and tremor irregularity in dystonia

S. Balta Beylergil, L. Scorr, A. Cotton, H. Jinnah, A. Shaikh (Cleveland, OH, USA)

776

Cohort profile of the Japan Dystonia Consortium: Genetic diagnosis and characteristics of movement disorders in Japan

T. Kawarai, R. Miyamoto, A. Orlacchio, R. Kaji (Tokushima, Japan)

**Guided Poster Group 6:
Huntington's Disease**

681

Chorea and Ataxia as Manifestations of Xeroderma Pigmentosum: A Case Report

A. Jocson, K. Ngo, D. Togasaki, B. Fogel (Los Angeles, CA, USA)

805

Prediction of suicidality in Huntington disease: Analysis of Enroll-HD data using machine learning approach

Y. Seliverstov, A. Borzov, E. van Duijn, B. Landwehrmeyer, M. Belyaev (Moscow, Russian Federation)

807

Vertical and horizontal eye movements in a large cohort of early manifest Huntington's disease: Evidence from ENROLL-HD

W. Muller, M. MacAskill, L. Paermentier, T. Anderson (Christchurch, New Zealand)

809

White matter microstructural alterations in Huntington Disease: When neurodegeneration starts?

P. Azevedo, L. Piovesana, M. Nogueira, R. Guimarães, A. Amato Filho, F. Cendes, Í. Lopes-Cendes, C. Yasuda (Campinas, Brazil)

814

Interrater reliability of the Unified Huntington's Disease Rating Scale-Total Motor Score certification

J. Winder, R. Roos, J.M. Burgunder, J. Marinus, R. Reilmann (Leiden, Netherlands)

821

Cognitive Reserve and Physical Activity Modulate Functional Brain Re-organisation in Premanifest Huntington's Disease: Preliminary Evidence

M. Soloveva, S. Jamadar, G. Poudel, N. Georgiou-Karistianis (Melbourne, Australia)

823

Comparing risperidone and olanzapine to tetrabenazine for the management of Huntington's chorea

J. Schultz, J. Kamholz, P. Nopoulos, A. Killoran (Iowa City, IA, USA)

830

Driving performance of Huntington's disease gene carriers

M. Jacobs, E. Hart, Y. Mejia Miranda, G.J. Groeneveld, J. van Gerven, R. Roos (Leiden, Netherlands)

838

Cerebrospinal fluid flow dynamics in Huntington's disease evaluated by phase contrast MRI

F. Rodrigues, L. Byrne, E. De Vita, E. Johnson, N. Hobbs, J. Thornton, R. Scahill, E. Wild (London, United Kingdom)

Guided Poster Group 7:

Parkinsonism, MSA, PSP (Secondary and Parkinsonism-Plus)

927

Clinical features and natural history of pathologically-confirmed corticobasal degeneration: A Japanese validation study of CBD (J-VAC study)

I. Aiba, T. Shimohata, S. Murayama, K. Hasegawa, Y. Iwasaki, O. Yokota, H. Fujimura, M. Sakai, T. Yokota, I. Yabe, H. Takigawa, K. Sugaya, K. Mori, M. Ito, C. Ishida, M. Kobayashi, Y. Hashizume, T. Ikeuchi, M. Hasegawa, M. Yoshida, T. Komori, K. Wakabayashi, Y. Saito, A. Tokumaru, K. Sakurai, K. Nakashima (Nagoya, Japan)

929

Quantitative mobility metrics from a body-fixed sensor predict incident parkinsonism in older adults

R. von Coelln, R. Dawe, J. Shulman, L. Yu, S. Leurgans, J. Hausdorff, L. Shulman, D. Bennett, A. Buchman (Baltimore, MD, USA)

933

Apolipoprotein E and multiple system atrophy

K. Ogaki, Y. Martens, M. Heckman, S. Koga, L. Labbé, O. Lorenzo-Betancor, A. Wernick, R. Walton, A. Soto, E. Vargas, H. Nielsen, S. Fujioka, T. Kanekiyo, R. Uitti, J. van Gerpen, W. Cheshire, Z. Wszolek, P. Low, W. Singer, N. Hattori, D. Dickson, G. Bu, O. Ross (Tokyo, Japan)

939

ARISE study: Study Design and Baseline Characteristics for a Phase 2 Trial of the Anti-Tau Antibody ABBV-8E12 in Progressive Supranuclear Palsy

N. Mendonca, R. Bateman, A. Boxer, J. Braunstein, D. Claassen, D. Holtzman, D. Kerwin, B. Rendenbach-Mueller, H. Soares, D. Wang, G. Höglinger (Ludwigshafen, , Germany)

948

The characteristic of gait in progressive progressive supranuclear palsy

Y. Takamatsu, N. Matsuda, I. Aiba (Kyoto, Japan)

957

Olfactory testing in Parkinson plus syndromes

O. Abdulkarimov, F. Akhmedova (Tashkent, Uzbekistan)

964

Nilotinib for treating MSA: A preclinical proof of concept study

P. Guerin, M. Lopez-Cuina, E. Beazard, W. Meissner, P-O. Fernagut (Bordeaux, France)

974

Evolution of diagnostic certainty and PSP-predominance types in 187 pathologically confirmed PSP patients

M. Grimm, G. Respondek, I. Piot, T. Arzberger, Y. Compta, E. Englund, L. Ferguson, E. Gelpi, A. Giese, S. Roeber, D. Irwin, W. Meissner, C. Nilsson, A. Pantelyat, A. Rajput, C. Troakes, G. Höglinger (Munich, Germany)

979

Rapamycin for treating MSA: A preclinical proof of concept study

M. Lopez-Cuina, P. Guerin, E. Beazard, W. Meissner, P-O. Fernagut (Bordeaux, France)

Guided Poster Group 8: Technology

1096

The BlueSky Project: monitoring motor and non-motor characteristics of people with Parkinson's disease in the laboratory, a simulated apartment, and home and community settings

K. Erb, J. Daneault, S. Amato, P. Bergethon, C. Demanuele, T. Kangarloo, S. Patel, V. Ramos, D. Volfson, P. Wacnik, H. Zhang, D. Karlin, H. Huggins, L. Soll, G. Costante, G. Vergara-Diaz, F. Parisi, J. Banghu, C. Brooks, C. Dethridge, A. Abrami, E. Bilal, V. Caravagio, S. Heisig, R. Norel, E. Pissadaki, J. Rice, B. Ho, K. Thomas, P. Bonato (Cambridge, MA, USA)

1097

Quantitative assessment of the hand motor symptoms in Parkinson's disease based on a custom wearable device: A Proof-of-Principle Study

Q. Ye, Z. Lin, H. Dai, Y. Xiong, G. Cai (Jinjiang, China)

1103

Does the Parkinson's Kinetigraph change clinical practice?

S. Jones, C. Grose, S. Mahon, T. Williams, C. Thomas, B. Mohamed (Cardiff, United Kingdom)

1111

The use of smartphone task derived features to predict clinical scores in Parkinson's Disease (PD)

C. Lo, S. Arora, F. Baig, T. Barber, M. Lawton, A. Zhan, M. Little, M. Hu (Oxford, United Kingdom)

1113

Temporal Gait Parameters in Parkinson's Disease: A Study Using PDlogger, A Quantitative Gait Measuring Device

N. Chia, J. Derrick, V. Mikos, S. Ng, A. Tay, S-C. Yen, K. Koh, D. Tan, K. Prakash, L. Tan, W.L. Au (Singapore, Singapore)

1117

Feasibility of a multi-sensor data fusion method for assessment of Parkinson's disease motor symptoms

M. Memedi, S. Aghanavesi, D. Nyholm, F. Bergquist, M. Senek (Örebro, Sweden)

1118

Assessment of Motor Symptoms in Parkinson's disease using Flexible Wearable Sensors and Deep Neural Networks: A CIS-PD substudy

L. Lonini, A. Dai, C. Poon, N. Shawen, L. Shimanovich, T. Simuni, D. Daeschler, J. Rogers, A. Jayaraman (Chicago, IL, USA)

1124

Objective monitoring of drug response in early PD patients using remote, at-home typing data through machine learning analysis

M. Matarazzo, T. Arroyo-Gallego, P. Montero Escribano, V. Puertas-Martín, I. Butterworth, C. S. Mendoza, M.J. Ledesma-Carbayo, M.J. Catalán, JA. Molina-Arjona, F. Bermejo-Pareja, JC. Martínez Castrillo, L. López-Manzanares, A. Alonso-Cánovas, J. Herreros-Rodríguez, I. Obeso, P. Martínez Martín, JC. Martínez-Ávila, A. Gómez de-la-Cámara, M. Gray, JA. Obeso, L. Giancardo, Á. Sánchez-Ferro (Vancouver, BC, Canada)

1138

The Levodopa Response Trial and the Parkinson Disease Digital Biomarker Challenge: Monitoring symptoms of Parkinson's disease in the lab and home using wearable sensors

J. Daneault, G. Vergara-Diaz, G. Costante, E. Fabara, G. Ferreira-Carvalho, F. Golabchi, F. Parisi, S. Sapienza, Y. Chae, P. Snyder, P. Aubin, P. Banda, D. Brunner, R. Dorsey, L. Mangravite, W. Marks, E. Neto,

U. Rubin, E. Soderberg, D. Daeschler, S. Moore, S. Sieberts, L. Omberg, P. Bonato, The Parkinson's Disease Digital Biomarker DREAM Challenge Consortium (Newark, NJ, USA)

1148

The international MDSGene initiative: Systematically exploring genotype-phenotype correlations of hereditary movement disorders

S. Petkovic, S. Schaake, J. Huang, H. Madoev, A. Rasheed, C. Lill, K. Lohmann, C. Klein, C. Marras (Lübeck, Germany)

Guided Poster Group 9:

Tremor

1169

Phase-locked transcranial alternating current stimulation of the cerebellum for essential tremor

S. Schreglmann, D. Wang, E. Boyden, K. Bhatia, J. Rothwell, N. Grossman (London, United Kingdom)

1174

Gamma Knife Radiosurgery for essential and parkinsonian tremor: Long-term experience in a Spanish center

JR. Perez-Sanchez, R. Martinez-Alvarez, NE. Martinez-Moreno, I. Cuervo-Arango, G. Rey Portoles, I. Parees, A. Del Barrio, J. Alvarez-Linera, MM. Kurtis (Madrid, Spain)

1175

A new clinical and research smartphone application to assess tremor and bradykinesia in patients with movement disorders

C. Duval, J.F. Daneault, B. Carignan, C.É. Coderre, S. Bogard (Montreal, QC, Canada)

1177

Shaky legs: The clinical spectrum and treatment of orthostatic tremor; a systematic review

A. Buijink, M. Meulepas, A. van Rootselaar (Amsterdam, Netherlands)

1182

The spectrum of involuntary movements in patients with motor neuron disease – a cross-sectional study

K. Vogelnik, L. Dolenc Grošelj, B. Koritnik, L. Leonardis, J. Zidar, M. Kojović (Ljubljana, Slovenia)

1188

Imaging neurodegeneration biomarkers in Essential Tremor

S. Pietracupa, M. Bologna, G. Pasqua, S. Tommasin, N. Petsas, F. Elifani, A. Berardelli, P. Pantano (Pozzilli, Italy)

1190

Quantitative characterisation of tremor in functional and organic tremor patients

Z. Dominguez-Vega, G. Kramer, J. Elting, M. de Koning-Tijssen, N. Maurits (Groningen, Netherlands)

1203

Repetitive Transcranial Magnetic Stimulation Therapy is a Potential Therapeutic option for Primary Orthostatic Tremor

W. Hu, J. Legacy, A. Ferng, A. Wagle Shukla (Gainesville, FL, USA)

1210

Tremor in motor neuron disease may be central rather than peripheral in origin

A. Latorre, L. Rocchi, M. Stamelou, A. Batla, M. Ciocca, B. Balint, K. Sidle, A. Berardelli, J. Rothwell, K. Bhatia (London, United Kingdom)

1213

Regional homogeneity changes detected between Essential tremor with resting tremor and tremor-dominant Parkinson's disease

J. Li, Z. Lu, X. Suo, N. Li, L. Wang, J. Peng, J. Zhang, Q. Gong, R. Peng (Chengdu, China)

Guided Poster Group 10:

Parkinson's Disease: Genetics

1299

PLA2G6-related juvenile-onset Parkinsonism: clinical features and cognitive profile in a cohort of Chinese patients

C. Chen, Y.M. Sun, F.T. Liu, S.S. Luo, Z.T. Ding, J.J. Wu, J. Wang (Shanghai, China)

1304

Resistance to Parkinson's disease among LRRK2 mutation carriers is associated with higher plasma levels of urate but not its purine precursors

M. Schwarzschild, R. Bakshi, R. Logan, M. Zorlu, X. Chen, A. Ascherio, E. Macklin (Boston, MA, USA)

1307

Interest in Genetic Testing in PD Patients with DBS

A. Frait, G. Pal, L. Verhagen, D. Hall, K. Marder (Chicago, IL, USA)

1312

Application of the Movement Disorder Society Prodromal Criteria in healthy G2019S-LRRK2 carriers

A. Mirelman, R. Saunders-Pullman, R. Alcalay, S. Shustak, A. Thaler, B. Cohen, A. Hillel, T. Gurevich, D. Raymond, H. Mejia-Santana, L. Ozelius, L. Clark, M.

Gana-Weisz, A. Bar-Shira, A. Orr-Urtreger, S. Bressman, K. Marder, N. Giladi (Tel Aviv, Israel)

1326

LRRK2 and GBA genetic mutations are not uncommon in an unselected Ashkenazi elderly cohort with PD

S. Isaacson, J. Isaacson (Boca Raton, FL, USA)

1340

BDNF(V66M), EIF4G1(R1205H), VPS35(D620N) gene polymorphisms in South Indian PD Patients

T. Syed, T. S.D., S. Meka, S. Kumar, S. Thandra, V. Kutala, R. Kandadai, R. Borgihain (Hyderabad, India)

1341

Full sequencing and haplotype analysis reveals LRRK2 protective haplotype in REM sleep behavior disorder

B. Ouled Amar-Bencheikh, J. Ruskey, I. Arnulf, Y. Dauvilliers, C. Charley Monaca, V. Cochen De-Cock, J.F. Gagnon, D. Spiegelman, M. Hu, B. Högl, A. Stefani, L. Ferini-Strambi, G. Plazzi, E. Antelmi, P. Young, A. Heidebreder, B. Mollenhauer, F. Sixel-Döring, C. Trenkwalder, W. Oertel, J. Montplaisir, R. Postuma, G. Rouleau, Z. Gan-Or (Montreal, QC, Canada)

1353

Association of GBA polymorphisms and mutations with dementia in Parkinson disease: A 7-year study of three population-based incident cohorts

K. Lunde, J. Chung, I. Dalen, K. Pedersen, J. Linder, M. Domellöf, E. Elgh, A. Macleod, C. Tzoulis, J. Larsen, O. Tysnes, L. Forsgren, C. Counsell, G. Alves, J. Maple-Grødem (Stavanger, Norway)

1370

Molecular mechanisms of GCH1-associated Parkinson's disease

J. Terbeek, W. Vandenberghe (Leuven, Belgium)

Guided Poster Group 11:

Parkinson's Disease: Neuroimaging And Neurophysiology

1376

Presynaptic dopamine depletion determines the timing of levodopa-induced dyskinesia onset in Parkinson's disease

HS. Yoo, SJ. Chung, BS. Ye, YH. Sohn, PH. Lee (Seoul, Republic of Korea)

1388

Automated Differential Diagnosis of Parkinsonian Syndromes Using FDG-PET Metabolic Brain Network Analysis

T. Rus, P. Tomše, L. Jensterle, M. Grmek, Z. Pirtošek, D. Eidelberg, C. Tang, M. Trošt (Ljubljana, Slovenia)

1400

Parkinson's disease motor symptoms are linked to red nucleus volume and cerebellar metabolism

A. Bonnet, R. Sanford, A. Riou, S. Drapier, F. Le Jeune, M. Vérin, D.L. Collins (Rennes, France)

1403

Brain Network Connectivity Measured by Diffusion Tensor Imaging Predicts Prognosis in Parkinson's Disease

S.M. Fereshtehnejad, N. Abbasi, Y. Zeighami, K. Larcher, R. Postuma, A. Dagher (Montreal, QC, Canada)

1415

Longitudinal development of nigral iron load in Parkinson's Disease

S. Franthal, L. Pirpamer, C. Rodler, N. Homayoon, M. Koegl, P. Katschnig-Winter, K. Wenzel, C. Langkammer, S. Ropele, R. Schmidt, P. Schwingenschuh (Graz, Austria)

1430

Identifying the neural correlates of doorway freezing in Parkinson's disease

E. Matar, J. Shine, P. Ward, M. Gilat, K. Ehgoetz-Martens, M. Frank, A. Moustafa, S. Naismith, S. Lewis (Sydney, Australia)

1433

Abnormal Functional Connectivity in Cerebellar Locomotor Region is associated with the severity of freezing of gait in patients with Parkinson's disease

K. Bearti, A. Suppa, S. Pietracupa, N. Upadhyay, C. Giannì, G. Leodori, F. Di Biasio, N. Modugno, N. Petsas, G. Grillea, A. Zampogna, A. Berardelli, P. Pantano (Rome, Italy)

1464

Resting-state connectivity and cognitive changes in Parkinson's disease: A four-year follow-up study

HC. Baggio, B. Segura, A. Abos, A. Campabadal, C. Uribe, A.I. Garcia-Diaz, M.J. Marti, Y. Compta, F. Valldeoriola, C. Junque (Barcelona, Spain)

1479

A cortical neural signature of motor interruption in patients with Parkinson's disease and freezing of gait

J. Baarbé, M. Brown, U. Saha, K. Lizarraga, A. Weissbach, N. Drummond, C. Rinchon, P. Kapoor, J. Saravanamuttu, R. Chen (Toronto, ON, Canada)

1483

The difference in cerebellar blood flow reduction in multiple system atrophy and Parkinson's disease

N. Murakami, W. Sako, S. Haji, Y. Izumi, R. Kaji (Tokushima, Japan)

1484

Structural Abnormalities in the Cerebellar Peduncles of patients with Freezing of Gait: A Diffusion Tensor Imaging Study

K. Bharti, A. Suppa, S. Pietracupa, N. Upadhyay, C. Giannì, G. Leodori, F. Di Biasio, N. Modugno, N. Petasas, G. Grilla, A. Zampogna, A. Berardelli, P. Pantano (Rome, Italy)

Guided Poster Group 12:

Parkinson's Disease: Non-Motor Symptoms

1531

Characterization of the gastrointestinal dysfunction in mice overexpressing the human mutation (A53T) of alpha-synuclein

S. Diwakarla, R. Constable, O. Artaiz, D. Finklestein, J. Berger, J. Furness (Melbourne, Australia)

1533

Four-year course of impulsive and compulsive behaviors in Parkinson's disease

A. Erga, G. Alves, O.B. Tysnes, K. Pedersen (Stavanger, Norway)

1553

Striatal dopamine transporter availability changes reflect gastrointestinal dysautonomia severity in early Parkinson's disease

J. Hinkle, K. Perepezko, K. Mills, Z. Mari, A. Butala, T. Dawson, A. Pantelyat, L. Rosenthal, G. Pontone (Baltimore, MD, USA)

1554

Early gastrointestinal dysfunction is predictive of faster progression in Parkinson's disease

M. Camacho, J. Evans, D. Breen, G. Cummins, R. Wijeyekoon, K. Scott, T. Stoker, R. Barker, C. Williams-Gray (Cambridge, United Kingdom)

1573

Non-motor symptoms in Parkinson's Disease: Frequency, types and correlated factors compared to a group of healthy controls. Results from the COPPADIS Study Cohort

L. Planellas, M. Martí, P. Santacruz, A. Cámara, S. Jesus Maestre, F. Carrillo García, P. Mir, M. Aguilar, P. Pastor, J. García Caldentey, E. Estelrich Peyret, N. Caballol Pons, I. Legarda, B. Vives Pastor, J. Hernández Vara, G. Martí Andrés, I. Cabo, L. López Manzanares, M. Gallego-de-la-Sacristana, P. Martínez

Martín, D. Santos García, G. COPPADIS STUDY
(Barcelona, Spain)

1576

Non-motor outcomes of subthalamic DBS in PD depend on the location of volume of activated tissue

JN. Petry-Schmelzer, H. Dafsari, M. Krause, T. Dembek, A. Keyoumars, A. Rizos, M. Silverdale, J. Evans, M. Barbe, G. Fink, P. Martinez-Martin, V. Visser-Vandewalle, A. Antonini, L. Timmermann, K. Ray-Chaudhuri (Cologne, Germany)

1591

A detailed clinical study of pain in 1957 participants with Parkinson's disease

M. Silverdale, C. Kobylecki, L. Kass-Iliyya, P. Martinez-Martin, D. Grosset, M. Hu, M. Lawton, S. Cotterill, K. Ray Chaudhuri, H. Morris, F. Baig, N. Williams, L. Hubbard (Manchester, United Kingdom)

1600

Gastrointestinal Symptoms and Enteric Nerve Dysfunction in A53T Mice

R. McQuade, P. Rajasekhar, S. Diwakarla, R. Constable, D. Poole, J. Berger, D. Finkelstein, J. Furness (Melbourne, Australia)

1635

Gut microbiota geography in Parkinson's disease in the world

M. Hirayama, T. Maeda, T. Minato, M. Itoh, J. Takeda, T. Hamaguchi, M. Katsuno, K. Ohno (Nagoya, Japan)

1641

Progression of sleep disorders spectrum in Parkinson's Disease: A 5 year clinical longitudinal study

Z. Xu, K. Anderson, DJ. Brooks, N. Pavese (Singapore, Singapore)

Guided Poster Group 13:

Parkinson's Disease: Pathophysiology

1663

Bidirectional gut-to-brain and brain-to-gut propagation of α -synuclein pathology in non-human primates

ML. Arotçarena, S. Dovero, A. Prigent, M. Bourdenx, P. Aubert, I. Trigo, G. Porras, ML. Thiolat, M. Tasselli, C. Estrada, A. Recasens, J. Blesa, M. Herrero, N. Carillo, M. Vila, J. Obeso, P. Derkinderen, B. Dehay, E. Bezard (Bordeaux, France)

1666

Risk estimation in the years preceding diagnosis of Parkinson's disease in the PREDICT-PD cohort

S. Auger, D. Rack, J. Bestwick, G. Giovannoni, A. Lees, A. Schrag, A. Noyce (London, United Kingdom)

1680

Predictors of freezing of gait in newly diagnosed Parkinson's disease: Clinical, dopamine transporter imaging and CSF markers in the PPMI cohort

R. Kim, J. Lee, H.J. Kim, A. Kim, B. Jeon, U.J. Kang, S. Fahn (Seoul, Republic of Korea)

1691

Neurophysiological correlates of bradykinesia in Parkinson's disease

M. Bologna, A. Guerra, G. Paparella, L. Giordo, D. Alunni Fegatelli, AR. Vestri, J. Rothwell, A. Berardelli (Rome, Italy)

1715

Unraveling gut microbiota in Parkinson's disease and atypical parkinsonism

R. Cilia, M. Barichella, M. Severgnini, E. Cassani, C. Bolliri, S. Caronni, V. Ferri, R. Canello, S. Faierman, G. Pinelli, C. Ceccarani, G. De Bellis, L. Zecca, E. Cereda, C. Consolandi, G. Pezzoli (Milan, Italy)

1722

Association between serum Vitamin D levels and Parkinson's disease: A systematic review and meta-analysis

XY. Luo, R. Ou, HF. Shang (Chengdu, China)

1734

Antibodies to alpha-Synuclein in Parkinson disease

D. Labunskiy (Santa Rosa, CA, USA)

1750

Natural occurring antibodies reduce aggregation of α -synuclein

A. Braczynski, E. Agerschou, Y. Kronimus, W. Hoyer, R. Dodel, B. Falkenburger, J. Schulz, J. Bach (Aachen, Germany)

1757

Alpha-synuclein oligomer and rotenone treatments injury the dopaminergic neuron via inhibiting the expression of gene SEMA6D

X. Yingyu (Guangzhou, China)

Guided Poster Group 1: Clinical Trials and Therapy in Movement Disorders

5

Improvements of tremor control and life quality of refractory essential tremor patients after MR-guided focused ultrasound thalamotomy – A Taiwan experience

H.C. Lai, K. Tsai, W.C. Chang, T. Taira, C.Y. Wei (Changhua County, Taiwan)

Objective: To quantify the tremor control and life quality changes of refractory essential tremor (ET) patients after the MR-guided focused ultrasound (MRgFUS) thalamotomy in Taiwan.

Background: There were more than 1 million people suffered from ET by estimation, and near more than 60% of ET patients were refractory to medication. The uncontrollable tremor from the bilateral hands, legs, head, trunk, or even vocal cord impacted the daily regulation of patients and further affected to the social interaction. Recently review suggested that MRgFUS thalamotomy has more benefits than to other surgical approaches to mitigate ET. Here we reported the first quantitative analysis on the tremor control and life quality improvements of refractory ET patients after the MRgFUS thalamotomy in Taiwan.

Methods: Ten patients (two females, 52.3 ± 11.6 years old, one left handiness) with informed consents were recruited in this study. Different medication and dosages were given during a one-month screening period. Brain MRI, Tc99m-ECD SPECT, CT, laboratory exam, and behavioral movement test were arranged to excluded the other movement disorders. CDR, CASI, MMSE, MoCA, and NPI and recorded to estimation the psychological conditions. The scores of Clinical Rating Scale for Tremor (CRST) and Quality of Life in Essential Tremor Questionnaire (QUEST) were recorded to quantify the tremor control and life quality before and one-month after the MRgFUS thalamotomy respectively. Single-tailed pair t test was exam to CRSTs and QUESTs indices before and one-month after the MRgFUS thalamotomy.

Results: These ten patients showed refractory to different combination of medication and dosages. Brain MRI, Tc99m-ECD SPECT, CT, laboratory exam, and behavioral movement test suggested that these ten patients were ET people. CDR (0.25 ± 0.42), CASI (52.3 ± 11.6), MMSE (52.3 ± 11.6), MoCA (52.3 ± 11.6), and NPI (52.3 ± 11.6) revealed normal psychological conditions. CRST and QUEST before and one-month after the MRgFUS thalamotomy were 36.0 ± 10.2 vs. 14.2 ± 4.8 ($p < 10^{-5}$) and 65.8 ± 26.0 vs. 44.5 ± 22.6 ($p < 10^{-4}$), respectively.

Conclusions: Our results suggested that MRgFUS thalamotomy could significantly improve the tremor control and life quality of refractory ET patients in Taiwan. MRgFUS could not only mitigate ET but also the other types of tremor such as Parkinson disease. MRgFUS become a promising tool to improve tremor control and life quality of variety of movement disorders in Taiwan.

References: 1. Louis, E. D., Ford, B., Lee, H., Andrews, H. & Cameron, G. Diagnostic criteria for essential tremor: a population perspective. *Arch. Neurol.* 55, 823–8 (1998). 2. Hariz, G.-M., Bergenheim, A. T., Hariz, M. I. & Lindberg, M. Assessment of ability/disability in patients treated with chronic thalamic stimulation for tremor. *Mov. Disord.* 13, 78–83 (1998). 3. Rohani, M. & Fasano, A. Focused Ultrasound for Essential Tremor: Review of the Evidence and Discussion of Current Hurdles. *Tremor Other Hyperkinet. Mov. (N. Y.)* 7, 462 (2017).

7

Specific active immunotherapy (SAIT) against alpha-synuclein with AFFITOPE® PD01A and PD03A: Results from the AFF009 phase I trial

W. Meissner, A. Pavy-Le Traon, A. Foubert-Samier, M. Galitzky, B. Laurens, U. Sabatini, S. Schmidhuber, D. Winter, G. Galabova, G. Staffler, A. Schneeberger, A. Kutzelnigg, O. Rascol (Bordeaux Cedex, France)

Objective: Phase I study with AFFITOPE® PD01A and PD03A to assess safety and tolerability as well as immunogenicity of this approach in MSA patients.

Background: Multiple system atrophy (MSA) is characterized by the accumulation of aggregated alpha-synuclein (aSyn) in oligodendrocytes forming glial cytoplasmic inclusions. Some symptomatic treatments

are available, while disease-modification remains an urgent unmet treatment need in MSA. aSyn-targeting AFFITOPE®-based specific active immunotherapies are a novel approach aimed to achieve disease-modification in synucleinopathies.

Methods: In this 52-week phase I study (AFF009; NCT02270489), 30 early stage MSA patients on stable symptomatic therapy received four s.c. injections at 4-weekly intervals followed by a boost injection at week 36. Subjects were randomized to receive either AFFITOPE® PD01A 75 µg or AFFITOPE® PD03A 75 µg or matching placebo (adjuvant only) in a patient-blinded fashion (random assignment on a 2:2:1 basis). The study was conducted at two centers in France as part of an EU-funded program (FP7, SYMPATH Grant Agreement No. 602999). The objectives were to evaluate the safety and tolerability (primary endpoint) of repeated s.c. injections with PD01A and PD03A, and to explore the immunological response (secondary outcome). Clinical ratings of MSA symptoms were performed as exploratory endpoints.

Results: There was no significant signal in terms of safety and tolerability. Treatment-emergent adverse events (TEAE) were observed in 29 of 30 patients. Serious TEAE were recorded in all treatment groups (7/12 patients for PD01A, 2/12 patients for PD03A and 2/6 patients for placebo). Serious TEAE were mostly due to worsening of MSA symptoms. Two patients died because of worsening of MSA-related symptoms or complications and one from fatal pulmonary embolism. There were no signs on clinical examination or magnetic resonance imaging suggestive of inflammatory responses in the brain in any of the patients. PD01A was able to induce a significant and sustained immune response against aSyn protein and could be reactivated by boost injection. Antibodies induced by PD01A recognized the aSyn target epitope.

Conclusions: AFFITOPE® PD01A and PD03A had a favorable safety and tolerability profile in early MSA patients. The results of this study support further clinical development of this novel treatment approach for MSA, mainly of PD01A which was able to induce a significant and sustained immune response against aSyn.

8

PASSPORT, An Ongoing Phase 2 Study in Patients with PSP– Baseline Characteristics

T. Dam, A. Boxer, L. Golbe, G. Höglinger, H. Morris, I. Litvan, J.C. Corvol, A. Lang, C. Bechtold, I. Qureshi, M. Grundman, B. Han, J. O’Gorman, T. Olsson, S. Budd Haeberlein (Cambridge, MA, USA)

Objective: To describe baseline characteristics of the participants with progressive supranuclear palsy (PSP) enrolled in the ongoing PASSPORT (NCT03068468) phase 2 study.

Background: PSP is a rare, rapidly progressing, neurodegenerative 4-repeat tauopathy. Currently, no medications are approved for treatment of PSP. BIIB092 is a humanized IgG4P monoclonal antibody directed against N-terminal tau fragments found extracellularly (eTau) in the interstitial and cerebrospinal fluid and hypothesized to spread tau pathology between neurons. BIIB092 has been shown to suppress eTau in cerebrospinal fluid of participants with PSP.[1]

Methods: PASSPORT is a randomized, double-blind, placebo-controlled, parallel group study. Participants aged 41–86 years diagnosed with possible or probable PSP (MDS criteria [2]) are randomized to 52 weeks of treatment with BIIB092 or placebo administered intravenously every 4 weeks. Planned recruitment is 396. The primary efficacy endpoint is the change from baseline to Week 52 in BIIB092- vs. placebo-treated participants on the PSP Rating Scale (PSPRS) score. Change from baseline to Week 52 will also be evaluated on the Clinical Global Impression of Severity scale (CGI-S), Movement Disorder Society - modified-Unified Parkinson’s Disease Rating Scale Part II score (MDS-UPDRS Part II), PSP Quality of Life scale (PSP-QoL), and Repeatable Battery for the Assessment of Neuropsychological Disease Severity scale (RBANS).

Results: PASSPORT began enrolling in April 2017 and is ongoing; select baseline characteristics (age, sex, race, ethnicity, height, weight, body mass index, symptom duration) of the initial enrollees will be presented. In addition, select baseline disease characteristics (PSPRS, MDS-UPDRS Part II, CGI-S, RBANS, PSP-QoL) will be presented.

Conclusions: Baseline characteristics of enrolled PASSPORT participants will be described to provide contemporaneous information on recruitment into PSP clinical trials.

References: 1. Qureshi I, Grundman M, Tirucherai GS, et al. Multiple ascending dose study of the tau-directed monoclonal antibody BIIB092 in patients with progressive supranuclear palsy. Poster presented at 10th Clinical Trials on Alzheimer's Disease (CTAD). November 1–4, 2017. Poster LBP32. 2. Höglinger GU, Respondek G, Stamelou M, et al, for the Movement Disorder Society-endorsed PSP Study Group. Clinical Diagnosis of Progressive Supranuclear Palsy - The Movement Disorder Society Criteria. *Movement Disorders*, 2017;32(6):853-864.

9

A German-Austrian multicenter, non-interventional, prospective study for the treatment with abobotulinumtoxinA injections in naïve and previously treated patients suffering from cervical dystonia

W. Jost, A. Schramm, M. Müngersdorf, A. Stenner, P. Schwingenschuh, P. Maisonobe, M. Koch, B. Haslinger (Wolfach, Germany)

Objective: In this prospective, multicenter, non-interventional study (NCT01840462) the primary objective was effectiveness of abobotulinumtoxinA in BoNT treatment-naïve and previously treated subjects after two injection cycles. Secondary objectives included the effectiveness of abobotulinumtoxinA in different CD subtypes.

Background: Cervical dystonia (CD) is a focal dystonia prevalent in roughly 8/100,000 inhabitants, and characterised by involuntary muscle contractions that result in movement and undesired positioning of the head. Depending on the dystonic function of the affected muscles, CD can be further classified by the location (as head or neck type) and the movement (as a turn, shift, or inclination). AbobotulinumtoxinA (Dysport) has been demonstrated to be an effective treatment with a well-established safety profile for CD.

Methods: Subjects received 4 injection cycles (each 3-4 months), with 5 visits (V1-V5), resulting in a 12-16 months study program. Effectiveness was determined using the TSUI score and Quality of Life measures (CDQ-24) with the primary effectiveness variable as the difference of the total TSUI score at visit 1 (V1) and visit 3 (V3).

Results: 361 subjects were enrolled in 41 centers across Germany and Austria. 273 subjects were included in the main analysis population. At baseline, 62.6% had been previously treated with BoNT. The major primary components of CD were torticollis (64.5%) and torticaput (17.6%). Previously treated subjects showed a slight reduction of the TSUI scores (mean V1: 5.6 [SD: 3.3]; mean change V3-V1: -0.3 [SD: 2.4]), whereas BoNT-naïve subjects had a more severe baseline TSUI score (mean V1: 7.8 [SD: 4.2]) and improved much more over all cycles (mean change V3-V1: -2.6 [SD: 4.3]). Results were similar for CDQ-24.

Interestingly, improvements mainly occurred in the TSUI subscore A (amplitude of sustained posture) with mean change V3-V1 previously treated: -0.1 [SD: 1.1] and mean change V3-V1 naïve: -1.2 [1.7]. Marked differences between CD subtypes regarding effectiveness could not be determined.

Conclusions: To our knowledge this is the first large multi-centre study investigating and illustrating the effectiveness of BoNT-A in different primary components of CD over several injection cycles.

12

Low-Fat Versus Ketogenic Diet In Parkinson's Disease: A Pilot Randomized Controlled Trial

M. Phillips, D. Murtagh, L. Gilbertson, F. Asztely, C. Lynch (Hamilton, New Zealand)

Objective: To compare the plausibility, safety, and efficacy of a low-fat, high-carbohydrate diet versus a ketogenic diet in a hospital clinic of PD patients.

Background: Preliminary evidence suggests that diet manipulation may influence motor and non-motor symptoms in PD, yet conflict exists over the ideal fat to carbohydrate ratio. A low-fat, high-carbohydrate diet may trigger an insulin-induced rise in brain dopamine and enhance beneficial short chain fatty acid production in the gut. Alternatively, a high-fat, low-carbohydrate "ketogenic" diet produces ketones that may

bypass the respiratory chain complex 1 defect and stimulate mitochondrial biogenesis in central and peripheral neurons.

Methods: Single-phase, parallel-group 1:1 randomization study of 47 patients (aged 40-75 years, fulfilling UK PD Brain Bank criteria) to either a low-fat (per 1750 kcal - 42 g fat, 75 g protein, 246 g net carbohydrate, 33 g fiber) or ketogenic (152 g fat, 75 g protein, 16 g net carbohydrate, 11 g fiber) diet for eight weeks. Patients monitored blood glucose and ketones daily. Primary outcomes (assessed by an MDS-certified, diet-blinded neurologist) were within- and between-group changes in MDS-UPDRS Parts 1-4 from baseline to week 8.

Results: There were no between-group differences at baseline (Table 1). We randomized 47 patients; there was an 86% completion rate for patients commencing the diets (Figure 1). The ketogenic group maintained physiological ketosis (Figure 2). Both groups significantly decreased their MDS-UPDRS scores, but the ketogenic group decreased more in Part 1 (-4.58 +/- 2.17 vs -0.99 +/- 3.63 points, $P < 0.001$), with the largest between-group decreases observed for urinary problems, pain, fatigue, daytime sleepiness, and cognitive impairment; there were no between-group differences for Parts 2-4 (Table 2). The most common adverse effects were excessive hunger in the low-fat group and a transient, intermittent exacerbation of the PD tremor and/or rigidity in the ketogenic group (Table 3).

Conclusions: It is plausible and safe for PD patients to maintain a low-fat or ketogenic diet for eight weeks. Both diet groups significantly improved in motor and non-motor symptoms, however the ketogenic group showed greater improvements in non-motor symptoms (41% vs 11% reduction in baseline Part 1 scores). Adverse effects were generally mild and differed between the two groups.

*Presented at NANZ (Nov 2017) and ANZAN (May 2018).

13

The PDSAFE falls prevention programme for people with Parkinson's: A multicentre randomised controlled trial

A. Ashburn, R. Pickering, L. Rochester, H. Roberts, C. Ballinger, S. Hulbert, I. Marian, C. Fitton, E. McIntosh, V. Goodwin, A. Nieuwboer, S. Lamb, K. Chivers Seymour (Southampton, United Kingdom)

Objective: The aim was to examine the effectiveness of an exercise and strategy based intervention (PDSAFE) for fall reduction.

Background: Evidence suggests exercise-based interventions might reduce fall risk although research findings were inconclusive. This is the largest trial on fall prevention for people with Parkinson's.

Methods: People with a confirmed diagnosis of Parkinson's at risk of falls were randomly allocated to a two-group multi-centred, community-based (1:1) controlled trial. PDSAFE, individually tailored and structured around functional fall avoidance strategies with balance and strengthening exercises was delivered by physiotherapists in the home. The primary outcome was risk of repeat falling between 0-6 months post-randomisation using self-completed monthly falls diaries. Secondary outcomes assessed blind included: balance (Mini-BESTest); functional strength (chair stand test), disease severity (UPDRS and H&Y); falls efficacy (FES); freezing (new Freezing of Gait (NFoG) questionnaire).

Results: 541 participants were screened and recruited to pre-randomisation monitoring, 474 participants (56% male; mean age 72 years; Hoehn & Yahr 1-4) were randomised to intervention (238) or control (236). No difference in repeat falling within 6 months of randomisation was found (PDSAFE to control odds ratio 1.21, 95% CI 0.74 to 1.98, $P = 0.447$). Secondary analysis demonstrated better balance (Mini-BESTest mean difference 0.95, 95% CI 0.24 to 1.67, $P = 0.009$) and balance confidence (FES-I mean difference 1.6, 95% CI -3.0 to -0.19, $P = 0.026$), in addition near-falling was reduced with PDSAFE (odds ratio 0.67, 95% CI 0.53 to 0.86, $P = 0.001$) at 6 months. Pre-specified subgroup analysis revealed a varied PDSAFE effect according to UPDRS at baseline ($P = 0.009$) and retrospective falling recorded at trial entry ($P = 0.050$) with decreased falling among those in the moderate group and increased repeat falling following PDSAFE between 0 and 6 months among those with freezing of gait (interaction $P = 0.025$), and a trend of increasing falls with those with cognitive impairment (interaction $P = 0.088$).

Conclusions: No significant difference in the overall fall rate was found as a result of the intervention. Secondary analysis demonstrated improvements in fall risks such as balance and diverse responses in falls rate according to disease severity, freezing and cognitive deficits illustrating the heterogeneity of the sample. Future research should target specified groups.

15

Deep brain stimulation (DBS) for dyskinetic cerebral palsy: A pilot study

S. Duma, N. Mahant, A. Ha, S. Kim, A. Phu, K. Stewart, M-C. Waugh, N. Wolfe, D. Russell, B. Oowler, M. Krause, V. Fung (Westmead, Australia)

Objective: To investigate whether deep brain stimulation (DBS) is effective in reducing symptoms and improving function in dyskinetic cerebral palsy (CP).

Background: DBS targeting the internal segment of the globus pallidus (GPi) is effective for several forms of dystonia, particularly idiopathic isolated dystonia. DBS may also be helpful for some causes of chorea and other hyperkinetic disorders. A minority of people with CP have dystonia or choreoathetoid movements (labelled dyskinetic CP). Treatment options to improve function for this group are limited.

Methods: This study was a randomised, placebo-controlled, double-blinded, cross-over trial. Four participants (2M:2F, aged 11-48yr) with dyskinetic CP were included between 2010-2011. Participants underwent GPi DBS implantation and were randomised to active or sham stimulation for 3-months, following which their DBS stimulation was switched for a further 3-months. The Bourke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) was used to rate the severity of dystonia at baseline, 3-months after initial treatment; and 3-months after cross-over treatment. The study was terminated early due to slow recruitment.

Results: One participant had a reduction in BFMDRS score with active stimulation; this participant was the oldest and had the mildest BFMDRS score. The remainder of the participants had either no change, or a slight increase in BFMDRS score. Despite this, in longer term follow-up, 3 participants reported symptomatic improvement and continue active DBS treatment 7-8 years post-surgery.

Conclusions: We did not identify a benefit of GPi DBS for dyskinetic CP in our randomised controlled trial. However, 3 participants have had symptomatic improvement on long-term follow-up, consistent with other reports of benefit with GPi DBS. Limiting factors of the study include small sample size, participant heterogeneity and study design. It was noted that the final (efficacious) stimulation parameters required open label programming to achieve and were outside of those permitted by the protocol.

References: This abstract has been submitted, but not yet accepted, for presentation at the Australia and New Zealand Association of Neurology (ANZAN) Annual Scientific Meeting 2018.

17

Zonisamide improves parkinsonism in DLB patients: A randomized phase 3 trial

M. Murata, T. Odawara, K. Hasegawa, R. Kajiwara, H. Takeuchi, M. Tagawa, K. Kosaka (Kodaira, Japan)

Objective: To verify the efficacy and safety of zonisamide (ZNS) for parkinsonism in patients with dementia with Lewy bodies (DLB).

Background: DLB parkinsonism is responsive to levodopa, but the responsive rate is moderate and the higher dose has a risk of worsening underlying psychiatric symptoms. In Japan, ZNS is now available as anti-Parkinson drug. Previously, our randomized studies with Parkinson's disease showed ZNS improves motor symptoms and wearing off without affecting psychiatric symptoms[1]. Therefore, we hypothesized ZNS would improve DLB parkinsonism and conducted the randomized phase 2 trial[2]. Here, we will show results of a randomized phase 3 trial using larger number of patients.

Methods: The trial consisted of 12-week randomized double-blind confirmatory and subsequent 40-week open-label extension phases. Outpatients diagnosed with probable DLB were enrolled. The patients randomized into placebo (PLA), ZNS 25 or 50 mg/d groups and received any of drugs at fixed dose for 12 weeks in the confirmatory phase. In the extension phase, the patients received ZNS at an initial dose of 25 mg/d over 2 weeks, and then at a flexible dose of 25 or 50 mg/d depending on patients' condition. Change

from baseline (BL) in UPDRS part3 (UPDRS3) score at Week (W) 12 was the primary endpoint. Throughout the trial, UPDRS3, MMSE, NPI-10 as well as safety were evaluated.

Results: Of 373 patients screened, 351 were randomized. Patients' background for primary endpoint was following, mean age, 77.2 years; mean durations of dementia and motor dysfunction, 3.6 and 2.7 years; mean UPDRS3 score, 31.2. Although any groups showed the score reduction in UPDRS3 at W12 (change from BL; -1.4 [PLA], -4.1 [ZNS25], -4.0 [ZNS50]), the reduction in both ZNS groups was statistically greater than in PLA (figure 1). Subsequently, the UPDRS3 scores further reduced until W24-28 in both ZNS groups (-5.1 to -6.3) and then were almost constant until W52 (figure 2). In contrast, the score reduction in MMSE at W12 was greater in ZNS50 than in PLA, but in term of long-term evaluation, the scores of MMSE as well as NPI-10 were not affected by ZNS treatment. Of 335 patients for long-term evaluation, 230 completed the 52-week treatment. There was no remarkable adverse event throughout the trial.

Conclusions: Zonisamide improves DLB parkinsonism and is well-tolerated. (A part of the results has been presented at several meetings such as WCN [Sep 2017] and IAPRD [Nov 2017].)

References: [1] Murata M, Hasegawa K, Kanazawa I, et al. Zonisamide improves wearing-off in Parkinson's disease: a randomized, double-blind study. *Mov Disord.* 2015; 30: 1343–1350. [2] Murata M, Odawara T, Hasegawa K, et al. Adjunct zonisamide to levodopa for DLB parkinsonism: a randomized, double-blind phase 2 study. *Neurology.* 2018; 90: e664–e672.

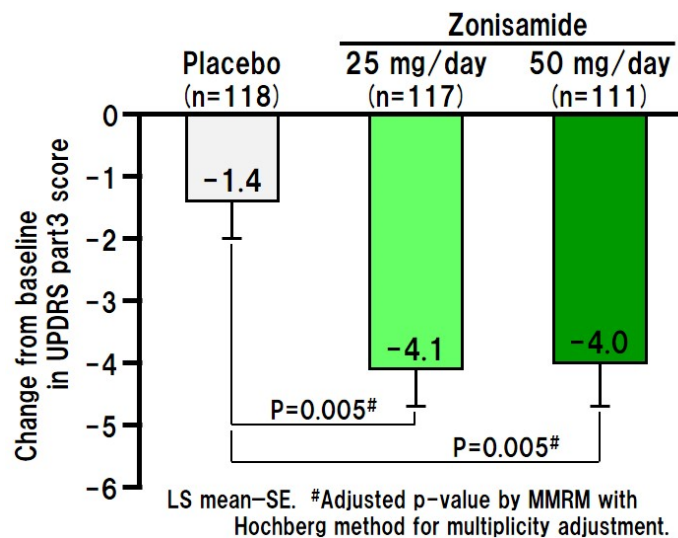


FIG. 1 (17) Change from baseline in UPDRS part3 score at Week12 [Primary endpoint]

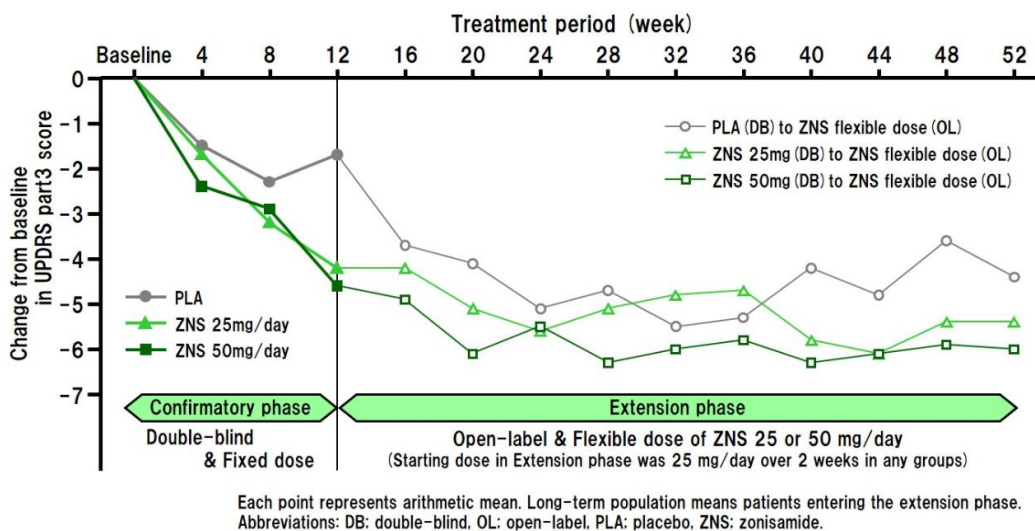


FIG. 2 (17) Time courses of change from baseline in UPDRS part3 score in Long - term population

32

Alleviation of freezing of gait in patients with Parkinson's disease by high-frequency rTMS over SMA is associated with normalization of brain connectivity patterns

T.M. Mi, S. Garg, F. Ba, T. Wu, P.P. Liang, L.L. Gao, K.C. Li, P. Chan, M. McKeown (Beijing, China)

Objective: We explored the efficacy and neural mechanisms of repetitive transcranial magnetic stimulation (rTMS) over the supplementary motor area (SMA) on freezing of gait (FOG) in Parkinson's disease (PD).

Background: FOG contributes to falls and greatly reduced mobility in PD, however, robust effective treatments remain elusive.

Methods: We first conducted a resting-state fMRI (rs-fMRI) study using a group of 40 PD patients with FOG (PD-FOG), 31 without FOG (PD-noFOG) and 30 normal controls (NC). A subset of 30 PD-FOG participated in a randomized, double-blind, sham-controlled trial to investigate the effects of rTMS on FOG. Patients were randomly assigned (with 2:1 allocation) to receive ten sessions of either verum or sham 10 Hz rTMS over SMA. The primary clinical outcome was the Freezing of Gait Questionnaire (FOG-Q). The Movement Disorder Society Unified Parkinson's Disease Rating Scale motor score (MDS-UPDRS III) and Timed Up and Go test were secondary clinical outcomes. Rs-fMRI studies were performed at baseline and after the rTMS sessions off medication. The functional connectivity between 48 ROIs that included the fronto-parietal network, frontostriatal loop, and locomotor network were assessed with a Bayesian network methodology. We used the baseline scans to create imaging biomarkers for FOG (FOGbm) and PD (PDbm) by using logistic Least Absolute Shrinkage and Selection Operator regression applied to the rs-fMRI connectivity profiles, and contrasting PD-FOG to PD-noFOG and NC respectively. These biomarkers were then interrogated to assess the effects of rTMS on connectivity patterns.

Results: The FOGbm and PDbm consisted of 14 and 16 functional connections, and included connections to/from the basal ganglia, cerebellar and thalamic regions, precuneus, anterior cingulate cortex, insula cortex and superior temporal gyrus. As anticipated, FOGbm was negatively correlated with FOGQ, and PDbm was negatively correlated with MDS-UPDRS III. After long-term follow-up, significant clinical improvements in FOG-Q, MDS-UPDRS III and several gait variables were found in the verum group. Moreover, both FOGbm and PDbm were significantly improved after verum stimulation. Neither significant clinical improvements nor biomarker changes were found in the sham group.

Conclusions: Our results suggest that high-frequency rTMS over SMA can alleviate FOG in PD through normalizing the abnormal brain functional connectivity patterns of PD-FOG and makes it not only more similar to PD-noFOG, but also more similar to NC.

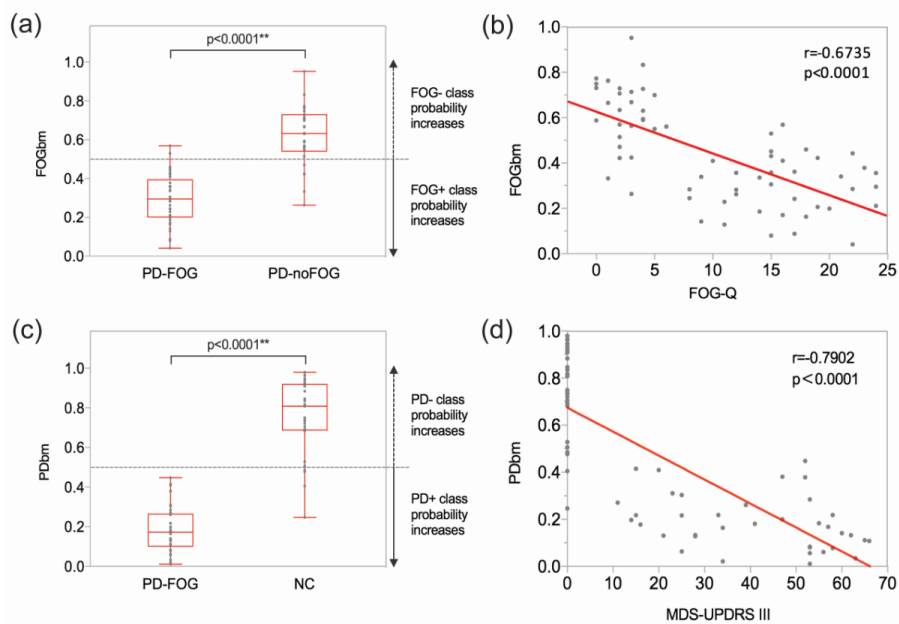


FIG. 1 (32)

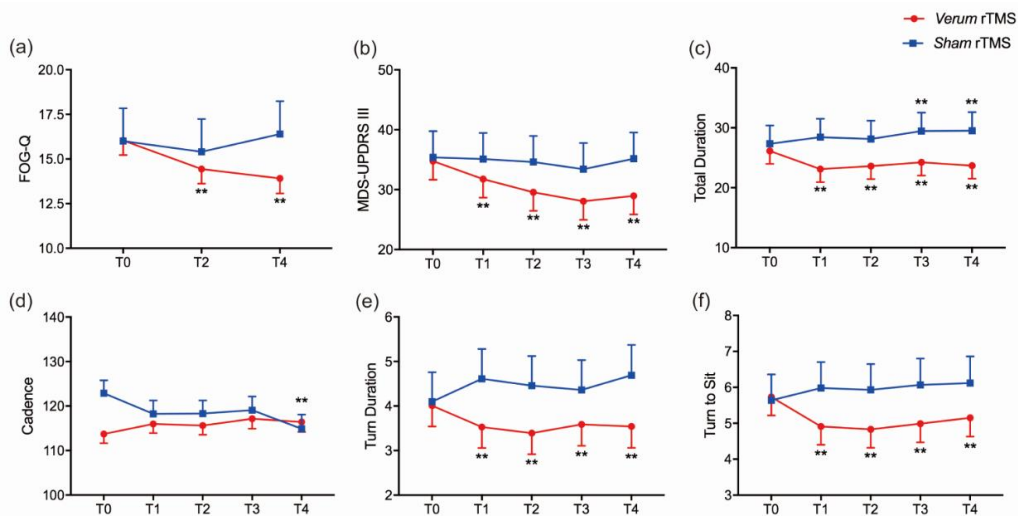


FIG. 2 (32)

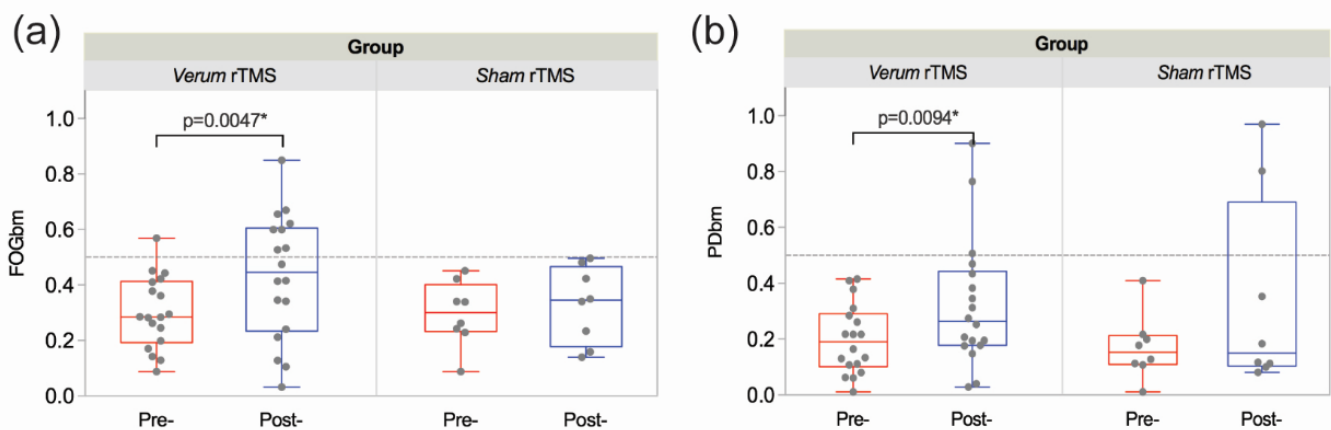


FIG. 3 (32)

PPMI driven sample size estimation for clinical trials in Parkinson's disease

K. Marek, J. Seibyl, C. Caspell-Garcia, C. Coffey, B. Mollenhauer, K. Kiebertz, C. Tanner, L. Chahine, A. Siderowf, T. Simuni (New Haven, CT, USA)

Objective: To utilize clinical, imaging and CSF data from the Parkinson's Progression Markers Initiative (PPMI) to estimate the sample size for disease modification studies in Parkinson's disease (PD) participants.

Background: The PPMI study provides longitudinal clinical and biomarker data that may be utilized to design PD therapeutic trials to assess putative disease modifying therapies. A major roadblock for these PD studies is to accurately establish the sample size required to establish drug effect and dosage in a reasonably sized Phase 2 program.

Methods: PPMI PD and healthy control participants are evaluated annually with a wide range of assessments including the MDS-UPDRS, DAT/VMAT imaging and CSF measures. PPMI subjects have been followed for more than five years. We utilized PPMI longitudinal data to establish sample size estimates for these measures for studies of up to two years duration assessing PD subjects. Given the large confound of MDS-UPDRS in subjects treated with dopaminergic therapies, we examined the sample size in treated and untreated PD after 12 month of PPMI participation. In addition, since an exponential fit of DAT imaging data provided a better fit than a linear model, we have used the exponential model to explore sample size estimates.

Results: Table 1 shows the one and two year sample size for all PD subjects evaluated for one and two years. Of the variables assessed mean putamen and striatum DAT scores allow the smallest sample size. Additional data demonstrate that DAT imaging sample size estimates may be substantially improved by utilizing an exponential fit of three scans. VMAT2 imaging may provide an alternative imaging biomarker with improved sample size estimates but additional data are required. MDS-UPDRS I-III untreated reduces sample size compared to the UPDRS for the entire group. Extending the follow up to 2 years would allow reducing the sample size by close to 50%. CSF measures would require a substantially larger sample size.

Conclusions: Sample size data can be utilized in planning future clinical trials of potential disease modifying interventions in PD. Powering the study based on DAT imaging utilizing an exponential fit can substantially reduce the sample size in the treated PD population. Extending the duration of the study to 2 years will also reduce the sample size but has to be balanced with the challenges of retention and overall cost.

TABLE 1 (35)

Variable	Column A Change from BL to Year 1		Sample Sizes Necessary to Detect 1 Year Differences				Column B Change from BL to Year 2		Sample Sizes Necessary to Detect 2 Year Differences			
	N	Mean (SD)	Reduce by 50%		Reduce by 25%		N	Mean (SD)	Reduce by 50%		Reduce by 25%	
			80% Power	90% Power	80% Power	90% Power			80% Power	90% Power	80% Power	90% Power
All PD Subjects												
Total MDS- UPDRS	334	7.45 (11.56)	306	408	1212	1622	282	10.43 (12.89)	194	260	770	1030
MDS- UPDRS Part III	334	4.51 (8.17)	416	556	1654	2212	282	6.37 (9.25)	268	358	1062	1420
Mean Putamen % Change	360	13.7 (21.7)	318	426	1266	1694	330	0.187 (0.214)	168	224	664	886
Mean Striatum % Change	360	11.5 (15.1)	220	294	874	1170	330	0.167 (0.163)	122	162	480	642
Alpha Synuclein	360	-11.33 (605.62)	358902	480468	1435598	1921860	-	-	-	-	-	-

251

The anti-dyskinetic effect of the clinically-available 5-HT₃ receptor antagonist granisetron in the 6-OHDA-lesioned rat model of Parkinson's disease

C. Kwan, I. Frouni, D. Bedard, A. Hamadjida, P. Huot (Montreal, QC, Canada)

Objective: To determine the effect of the serotonin 3 (5-HT₃) receptor antagonist granisetron, a clinically-available anti-emetic, on L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesia.

Background: Dopamine replacement with L-DOPA is the most effective symptomatic treatment for Parkinson's disease (PD), however, long-term therapy leads to dyskinesia. 5-HT₃ receptor blockade reduces dopamine levels in the striatum, which suggests that 5-HT₃ receptor antagonists could mitigate the aberrant release of dopamine that occurs in dyskinesia, thereby diminishing the severity of dyskinesia in PD. In the present study, we hypothesised that granisetron would alleviate dyskinesia in the 6-hydroxydopamine (6-OHDA)-lesioned rat.

Methods: Following 6-OHDA lesion of the right medial forebrain bundle, rats underwent the cylinder test to assess the degree of parkinsonism. Severely parkinsonian rats were selected for priming with L-DOPA to exhibit stable and reproducible abnormal involuntary movements (AIMs). On experimental days, granisetron (0.0001, 0.001, 0.01, 0.1 or 1 mg/kg) or vehicle was administered in combination with L-DOPA, and duration and amplitude of axial, limbs and oro-lingual (ALO) AIMs severity were evaluated. Following a 2-day washout period, preference for the un-lesioned forelimb was measured by the cylinder test to assess the effect of granisetron on L-DOPA anti-parkinsonian action.

Results: In combination with L-DOPA, granisetron 0.01 mg/kg significantly diminished both duration and amplitude of ALO AIMs by 46% and 50%, respectively ($P < 0.05$ and $P < 0.01$), compared to vehicle. Moreover, the anti-dyskinetic effect of granisetron was achieved without hindering L-DOPA anti-parkinsonian action.

Conclusions: Our results suggest that granisetron is a potential drug candidate to effectively alleviate L-DOPA-induced dyskinesia without impairing the therapeutic efficacy of L-DOPA. Because it is already available in the clinic, our results could quickly lead to clinical trials. Moreover, coupled with the companion Abstract on ondansetron, our results suggest that selective 5-HT₃ receptor blockade is a potentially effective anti-dyskinetic approach likely to be well tolerated by PD patients.

301

Directional Lead Impedances and Their Possible Effects on Deep Brain Stimulation

L. Juarez Paz, A. Dalal Kirsch, F. Steigerwald, C. Matthies, S. Meoni, V. Fraix, T. Ten Brinke, R. de Bie, K. Wynants, D. Blum, N. Van Dyck, PR. Schuurman, E. Moro, S. Chabardes, J. Volkmann (Valencia, CA, USA)

Objective: The objective was to characterize the possible effects that directional leads impedances have on Deep Brain Stimulation (DBS) therapy.

Background: DBS of the subthalamic nucleus (STN) has proven to be effective into treating some motor symptoms in Parkinson's Disease patients by activating neural tissue that renders therapeutic benefits while avoiding the activation of tissue that provokes side effects. The activation of tissue is defined by the amount of current applied to it, which in turn could depend on the impedance of the tissue-contact interface. Recently, directional leads have been introduced into DBS systems in order to have more selective stimulation of therapeutically relevant areas. However, the stimulation accuracy, precision and stability for these directional leads might be compromised by differences or changes on individual tissue-contact interface impedances.

Methods: DIRECT-DBS is a prospective, randomized, multi-center, double-blind study with a crossover design, for which 12 subjects have been enrolled and implanted for STN DBS with bilateral directional leads (Vercise Cartesia, Boston Scientific) connected to a pulse generator. Within the framework of the study, impedance and stimulation settings data will be collected at different time points for analysis.

Results: The collected data so far shows significant differences between ring and segmented contacts' impedances. The data also shows substantial impedance changes through time for ring and especially the segmented contacts (5.7% and 11.4% average impedance change, respectively). By calculating the equivalent current delivered by single source voltage (and current DBS systems) under these impedance changes conditions, it was found that these systems are unable to deliver the same current distribution for the desired stimulation setting when multiple contacts are needed for effective stimulation. In addition, these systems are unable to constantly deliver the desired current as opposed to DBS systems using multiple independent current sources.

Conclusions: The results suggest that in order to leverage the advantages of directional leads for an effective DBS therapy, it is fundamental to use them in combination with multiple independent current sources systems to allow for accurate, precise and stable current delivery. The clinical relevance of these findings has to be further investigated.

326

DIRECT DBS: A Prospective, Multicenter Clinical Study with Double-Blinding for a Directional Deep Brain Stimulation Lead – Therapeutic Windows with Directional Stimulation

F. Steigerwald, J. Volkmann, C. Matthies, A. Dalal Kirsch, S. Chabardes, R. de Bie, P. Schuurman, E. Moro, V. Fraix, S. Meoni, D. Blum, L. Juarez Paz, K. Wynants, N. Van Dyck (Würzburg, Germany)

Objective: To evaluate changes in therapeutic window values for changes in directional Deep Brain Stimulation (DBS) stimulation.

Background: Historically, DBS systems have delivered stimulation using cylindrical electrodes, which may stimulate neurons around the entire circumference of the lead. In this study, we test a directional DBS lead, which adds radially segmented electrodes designed for selective stimulation in directions orthogonal to the lead trajectory. One way to show clinical proof of the additional capabilities of directional leads is to examine the therapeutic windows of varying directional stimulation settings.

Methods: DIRECT-DBS is a prospective, randomized, multi-center, double-blind study employing a crossover design. A total of 12 subjects have been enrolled and implanted per standard of care with bilateral directional DBS leads (Vercise Cartesia, Boston Scientific) connected to a pulse generator providing an independent current source for each of 16 contacts. Visits occur in 3 major periods: during implant, at 3-5 months, and at 1 year. At 3 months, multiple single-day programming visits will be undertaken to optimize directional programming, based on observed clinical responses. In one of the visits, various directional stimulation settings are explored at the optimal longitudinal level, first in 90 degree increments, then in 30 degree increments. These fine explorations require precise fractionalization of the current between sets of segmented electrodes. At each of these settings, the therapeutic window is calculated as the difference between the minimum amplitude which gives full rigidity control and the minimum amplitude that elicits a limiting side effect.

Results: Examination of the results collected thus far show differences in therapeutic windows at the various directional stimulation settings. These differences can manifest in changes as small as 30 degrees in the rotational direction.

Conclusions: These results show that directional stimulation is a useful advancement in DBS technology as it may enable the user to elicit differential clinical responses which may not have been observed with other programming changes.

341

‘PDSAFE’ – A multi-dimensional fall rehabilitation intervention for people with Parkinson’s with specialist physiotherapy training: qualitative exploration of physio’s experiences

K. Seymour, S. Hulbert, V. Goodwin, L. Rochester, A. Nieuwboer, A. Ashburn (Southampton, United Kingdom)

Objective: To describe the experiences and views of physiotherapists on the specialist training and delivery of the PDSAFE intervention as part the falls prevention trial.

Background: In the United Kingdom, recent NICE guidelines state that all People with Parkinson’s (PwP) should have access to a Specialist Physiotherapist. PwP are twice as likely to fall as the healthy older population and most become repeat fallers. They present with complex pictures of motor and non-motor features and specialist physiotherapists trained in the management of falls are essential. PDSAFE provides an individualised, intensive and progressive, home-based falls prevention programme of exercises and strategies for PwP delivered by physiotherapists. All therapists completed a comprehensive training and professional development programme to become Specialists in Parkinson’s.

Methods: 541 PwP were recruited to the multi-centred, single-blinded, randomised control trial (RCT). In-depth qualitative semi-structured interviews were conducted with a sub-group of the treating physiotherapists (n= 6) and 2587 intervention sessions that were analysed. Thematic analysis was used to extract the experiences and views of the therapists.

Results: The physiotherapists were positive about the conceptual underpinning of the PDSAFE programme and its holistic, patient centred focus. The approach, focusing on strategies to enable functional activity, was seen as differing from the prevalent approach used in usual practice, which was described as being exercise driven. They identified cognitive deficits, co-morbidities and dyskinesia to be the most challenging aspects of the intervention delivery. PwP with support, good cognitive ability and motivation were likely to gain the most.

Conclusions: The physiotherapists working on the PDSAFE trial liked the treatment and highly praised the training. The physiotherapists valued the structure of the treatment programme and the clear process for progressing patients.

364

The Effect of Short Pulse Width Settings on Speech in Subthalamic Nucleus Deep Brain Stimulation for Parkinson’s disease

V. Dayal, T. Grover, E. Tripoliti, P. Limousin, T. Foltynie (London, United Kingdom)

Objective: To compare perceptual characteristics and intelligibility of speech in Parkinson’s Disease (PD) patients with Subthalamic Nucleus Deep Brain Stimulation (STN-DBS) in the acute setting at Pulse Width of 30µs (PW30) and the standard pulse parameter of 60µs (PW60).

Background: STN-DBS is an established treatment for selected PD patients, but therapy is often limited by side effects such as speech impairment. Recent studies have shown that the therapeutic window of STN-DBS using a pulse width (PW) shorter than the conventional 60µs setting significantly expands the therapeutic window, but there is limited data on the effect on speech (1).

Methods: 15 consecutive PD patients [mean age 54 ± 8; disease duration 13 ± 4 years; UPDRS-III 43 ± 9 ON, 15 ± 6 OFF] who had STN-DBS implanted and monopolar review of programming performed 2-10 days post-operatively at PW60 and PW30 were included. Assessment of speech was performed at the efficacy threshold for rigidity control using the most efficacious contact per STN on each PW condition. A speech therapist rated perceptual characteristics of speech using a 60-second monologue (MON) and a reading task (RDG), and speech intelligibility with the Assessment of Intelligibility for Dysarthric Speech scale (SIT%)(2). A paired sample t-test was used for the comparison.

Results: The perceptual speech score for the reading task (RDG) was higher at PW30 (36 ± 5/ 42) compared to PW60 (33 ± 5/ 42); p<0.01, as was the monologue score (MON; 35 ± 5/42 for PW30 vs. 32 ± 5

at PW60; $p=0.01$). The SIT% score at PW30 ($96.5 \pm 4.1\%$) was not significantly different to that at PW60 ($94.7 \pm 8.7\%$); $p>0.05$. [Figure 1] [Figure 2].

Conclusions: STN-DBS in PD patients using a PW of $30\mu\text{s}$ may improve perceptual characteristics of speech compared to conventional PW settings. Speech intelligibility as measured by the SIT% score was not significantly improved using PW30 in this cohort. However, this should be further explored in patients with symptomatic speech impairment and longer term follow up on the two conditions.

References: 1. Steigerwald F, Timmermann L, Kühn A, Schnitzler A, Reich MM, Kirsch AD, et al. Pulse duration settings in subthalamic stimulation for Parkinson's disease. *Mov Disord.* 2017;0(0):1–5. 2. Yorkston, K, Beukelman D. (1984) *Assessment of Intelligibility of Dysarthric Speech.* Austin: Pro-ed, CC Publications.

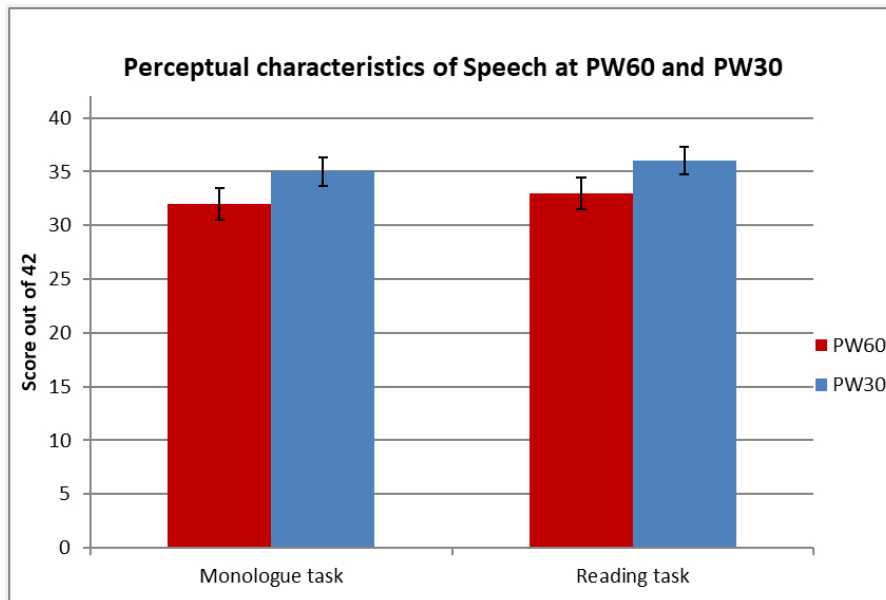


FIG. 1 (364)

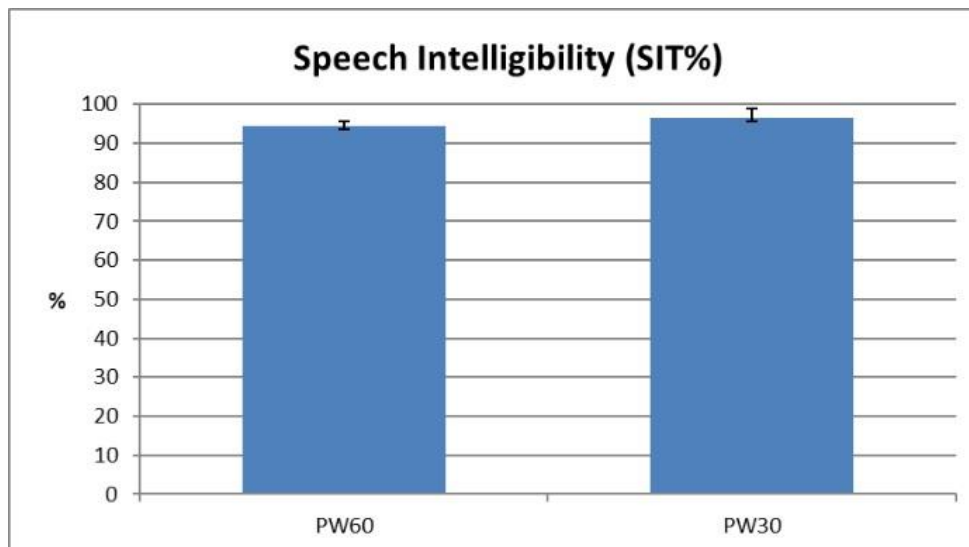


FIG. 2 (364)

Sex differences by design and outcome in the Safety of Urate Elevation in PD (SURE-PD) trial

M. Schwarzschild, E. Macklin, R. Bakshi, S. Bhattacharyya, R. Logan, A. Ascherio; on behalf of the Parkinson Study Group SURE-PD Investigators (Boston, MA, USA)

Objective: To investigate whether women and men with Parkinson's disease (PD) may differ in their biochemical and clinical responses to long-term treatment with urate-elevating inosine.

Background: Higher levels of serum or CSF urate predict a reduced risk of PD or a favorable rate of its progression (especially in men), and can confer protection against dopaminergic neuron degeneration in preclinical PD models. These findings have prompted clinical development of inosine as a urate-elevating strategy with the potential to slow PD progression. Because women on average have lower urate levels than men, a treatment that targets the same range of higher urate for both sexes should lead to a greater mean increase in women.

Methods: The SURE-PD (phase 2) trial enrolled 75 people with early PD and baseline serum urate below 6 mg/dL and randomized them to three double-blinded treatment arms: placebo or oral inosine titrated to produce mild (6.1-7.0 mg/dL) or moderate (7.1-8.0 mg/dL) serum urate elevation for up to two years. Here we report secondary analyses stratified by sex

Results: The absolute increase in serum urate induced by inosine was 20% greater in women, consistent with their expected lower urate levels at baseline. Similarly, only among women was CSF urate significantly greater on mild or moderate inosine (+88% [p<0.001] and +98% [p<0.001], respectively) compared to placebo (in contrast to men: +10% [p=0.6] and +14% [p=0.4], respectively). The previously reported trend toward slower clinical progression with increasing inosine is attributable to slower decline in women, based on slower worsening of Unified PD Rating Scale [UPDRS] score with higher inosine dosing (7.0 points/year slower rate of change on moderate inosine versus placebo; p = 0.01), with greater urate elevation (r = -0.52; p = 0.001; [figure1]), or with greater increase in plasma antioxidant capacity (r = -0.44; p = 0.006; [figure2]), whereas no significant difference was observed in men. Although kidney stones developed only among those treated with inosine and only among women, overall incidence of serious adverse events was no higher among women than men [table1].

Conclusions: Inosine produced greater increases in serum and CSF urate in women compared to men in the SURE-PD trial, consistent with the study's design. Preliminary evidence suggests that urate-elevating inosine treatment may slow clinical decline in early PD primarily or only among women.

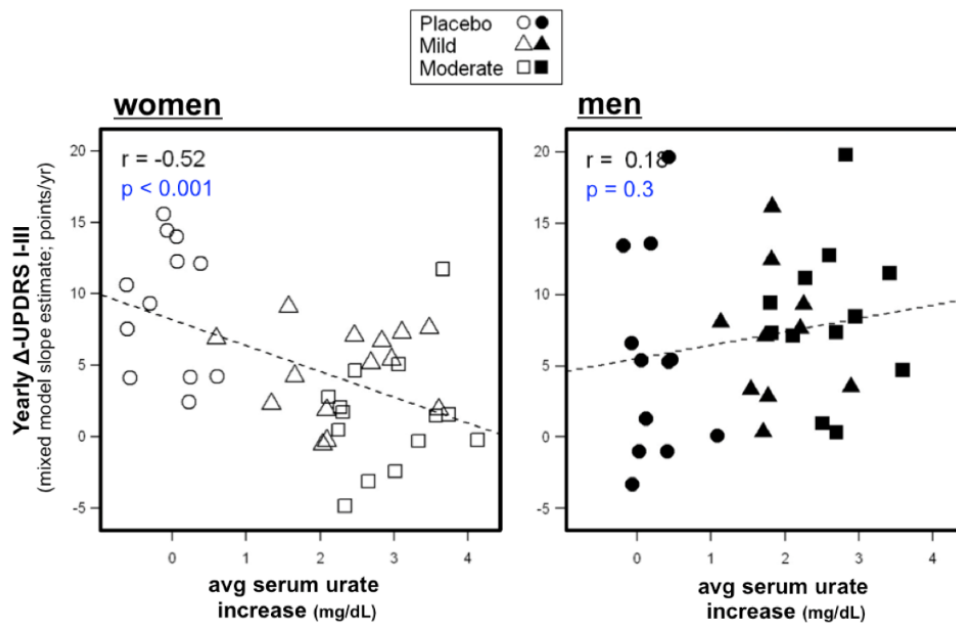


FIG. 1 (380) Relationships between change in serum urate and rate of clinical decline in women and men. For each subject the increase in serum urate from baseline to the average of on - treatment values was plotted against the individual's annualized change in total UPDRS (parts I - III) score estimated from a random - slopes mixed model. The placebo group data (circles) appear on the left of each plot given the expected lack of change in serum urate. Several men in the placebo group showed no decline during the trial (filled circles in lower left) contributing to a non - significant overall trend toward worsening with increasing urate among men.

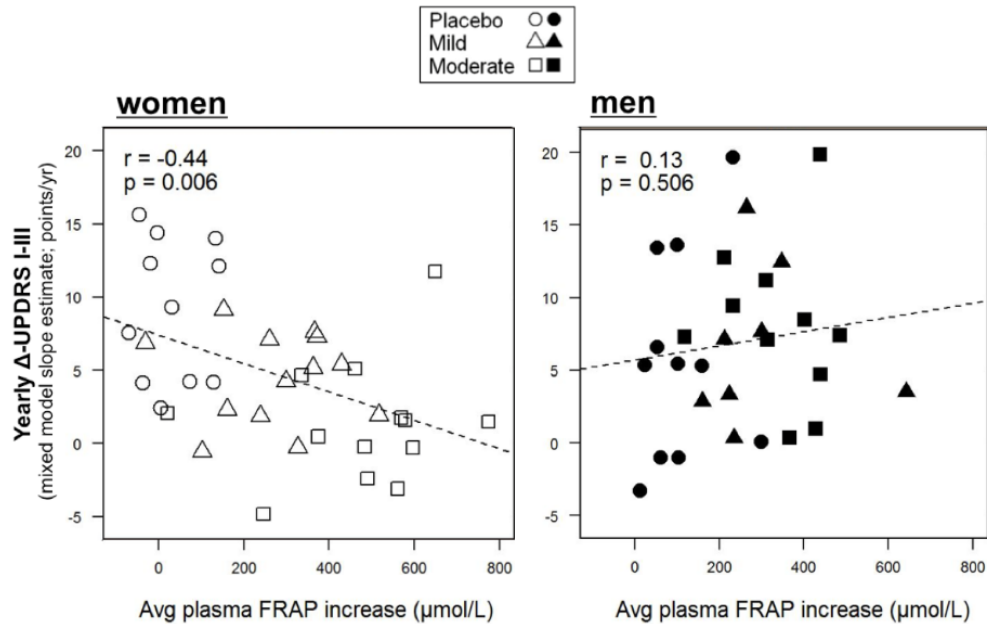


FIG. 2 (380) Relationships between change in plasma total antioxidant capacity and rate of clinical decline in women and men. For each subject the increase in plasma FRAP from baseline to the average of on - treatment (6 month and ~ 18 month visit) values was plotted against the individual's annualized change in total UPDRS (parts I - III) score estimated from a random - slopes mixed model. The placebo group data (circles) appear on the left of each plot given the lack of FRAP change as expected in this group. Several men in the placebo group showed no clinical decline during the trial (filled circles in lower left) contributing to a non - significant overall trend toward worsening with increasing FRAP (like urate) among men.

TABLE 1 (380) Serious and known hyperuricemic adverse events, by treatment group and sex.

	Treatment Group					
	Placebo		Inosine (6-7 mg/dL)		Inosine (7-8 mg/dL)	
	Women (n=13)	Men (n=12)	Women (n=14)	Men (n=10)	Women (n=14)	Men (n=12)
Serious AEs	6 (38%)	5 (33%)	1 (7%)	1 (10%)	2 (14%)	2 (17%)
Gout	0	0	0	0	0	0
Kidney stones	0	0	1 (7%)	0	2 (14%)	0

The highly selective 5-HT_{2A} receptor antagonist EMD-281,014 alleviates L-DOPA-induced dyskinesia in the 6-OHDA-lesioned rat model of Parkinson's disease

I. Frouni, D. Bedard, S. Belliveau, E. Bourgeois-Cayer, A. Hamadjida, P. Huot (Montreal, QC, Canada)

Objective: To investigate the effect of the highly-selective serotonin 2A (5-HT_{2A}) receptor antagonist EMD-281,014 at alleviating L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesia in the 6-hydroxydopamine (6-OHDA)-lesioned rat.

Background: Chronic administration of L-DOPA, the most effective symptomatic treatment for Parkinson's disease (PD), leads to motor complications such as dyskinesia in as many as 95% of patients. Previous studies have suggested that antagonising 5-HT_{2A} receptors may alleviate dyskinesia in animal models of PD, but the drugs assessed interacted with targets other than 5-HT_{2A} receptors and, as such, a 5-HT_{2A}-selective mechanism may not be the only factor underlying their effectiveness. Here, we hypothesised that EMD-281,014, a clinically-ready compound that is currently the most selective 5-HT_{2A} antagonist available, may effectively decrease dyskinesia in PD.

Methods: Rats were rendered hemi-parkinsonian by administration of 6-OHDA. They were then primed with L-DOPA to elicit stable and reproducible axial, limbs and oro-lingual (ALO) abnormal involuntary movements (AIMs). On experimental days, rats were administered L-DOPA in combination with EMD-281,014 (vehicle, 0.01, 0.03 and 0.1 mg/kg), after which ALO AIMs were assessed for 1 min, every 20 min, for 180 min. After a 72h washout period, animals were administered an acute challenge of EMD-281,014 in combination with L-DOPA and the degree of parkinsonism was assessed with the cylinder test.

Results: In combination with L-DOPA, EMD-281,014 mildly, but significantly, diminished the amplitude of dyskinesia, when compared to vehicle. Thus, EMD-281,014 (0.01, 0.03 and 0.1 mg/kg) significantly reduced cumulative ALO AIMs amplitude, when compared to vehicle, by 20%, 14% and 13%, respectively (all $P < 0.01$). EMD-281,014 (0.01 and 0.1 mg/kg) also reduced cumulative axial AIMs amplitude, by 21% and 18% (both $P < 0.05$), respectively, when compared to vehicle. Lastly, EMD-281,014 (0.01 and 0.1 mg/kg) diminished cumulative limbs AIMs amplitude, by 40% and 20% (both $P < 0.05$), respectively, when compared to vehicle. Importantly, EMD-281,014 did not hinder the anti-parkinsonian action of L-DOPA.

Conclusions: These results suggest that the highly-selective 5-HT_{2A} antagonist EMD-281,014 is a promising drug to reduce the severity of dyskinesia in PD.

Patient and Provider Experiences and Attitudes toward Rytary

S. Horn, D. Coughlin, J. Chou, F. Wang, M. Stacy, R. Dolhun, C. Kopil, N. Amondikar, A. Deik, H. Sarva (Philadelphia, PA, USA)

Objective: To survey Parkinson's disease (PD) patients and providers about their experiences using Rytary, an oral extended release carbidopa/levodopa capsule (ER C/L).

Background: ER C/L demonstrated in clinical trials to decrease OFF time and improve ON time without increasing troublesome dyskinesia when compared to other levodopa formulations (Dhall & Kreitzman 2016). However, individual provider and patient experiences vary, and barriers to using ER C/L exist.

Methods: 801 PD patients and 250 physicians, nurse practitioners, and physician assistants completed separate online nationwide surveys to determine utility, side effects, satisfaction and barriers to using ER C/L.

Results: Movement disorders specialists were 27% of provider respondents; 44% were general neurologists. The top reasons providers chose ER C/L include reducing OFF time (69%) and reducing medication dosing frequency (32%). Reduction in OFF time was reported by 74% of providers but by only 50% of patients. Among providers, 71% reported reduction in dyskinesia, whereas only 27% of patients experiencing dyskinesia reported a decrease and 32% reported worsening dyskinesia. Dry mouth (33%) and fatigue (25%) were the most common side effects reported by patients. The proportion of patients reporting improvements in quality of life, motor symptoms, and non-motor symptoms with ER C/L were 51%, 55%,

and 38% respectively. Patient perceived quality of counseling prior to initiation of ER C/L correlated positively with satisfaction ($p < 0.001$). Providers cited high cost (38%), need for prior authorization (30%), and complicated dosing and conversion processes (12%) as most common barriers. Patients reported high cost (52%), inconvenient dosing (37%) and suboptimal symptom control (32%) as challenges. Twenty-six percent of patients discontinued ER C/L; the most common reasons were side effects (40%) and suboptimal symptom control (21%).

Conclusions: These large surveys evaluated patient and provider experiences with ER C/L. Both noted reduction in OFF time as a benefit. Patients reported moderate satisfaction with motor benefits and quality of life, but less satisfaction with the effect on non-motor symptoms. Providers noted a reduction in dyskinesia greater than what patients reported. High out-of-pocket costs and complicated conversion and dosing regimens were common barriers. There is continued need for accessible symptomatic therapies for PD to serve unmet patient needs.

References: Dhall, R., & Kreitzman, D. L. (2016). Advances in levodopa therapy for Parkinson disease Review of RYTARY (carbidopa and levodopa) clinical efficacy and safety. *Neurology*, 86(14 Supplement 1), S13-S24.

420

Mitochondrial morphometrics in idiopathic Parkinson's disease fibroblasts

P. Antony, O. Boyd, K. Mommaerts, K. Sokolowska, M. Ostaszewski, A. Baumuratov, L. Longhino, F. Poulain, R. Krueger, R. Balling, N. Diederich (Belvaux, Luxembourg)

Objective: To identify mitochondrial morphometric phenotypes in fibroblasts derived from patients with idiopathic Parkinson's disease (IPD).

Background: Mitochondrial dysfunction (MD) has been proposed as cellular phenotype in patients with idiopathic Parkinson's disease (IPD). However, study results remain controversial for fibroblasts derived from IPD. Here we aim to identify mitochondrial morphometric changes that eventually can be used in cell based drug screening assays targeting IPD.

Methods: Axilla skin punch biopsy derived fibroblasts from 41 IPD patients with a mean disease duration of 6.5 years (st.dev. 5.5 years) and from 21 healthy age-matched controls (HC) were stained with Hoechst, CellMask, and TMRM. Mitochondrial morphometrics were analyzed via automated confocal microscopy and in house developed computational image analysis (figure).

Results: Significant morphometric changes were seen in IPD fibroblasts. The number of mitochondria was increased ($p=0.002$) whereas the mitochondrial morphometric complexity was substantially decreased as visualized by reduction of mitochondrial perimeter ($p=0.029$) and mitochondrial form factor ($p=0.013$). Further analysis with established algorithms from computer vision and graph theory confirmed mitochondrial fragmentation: The mitochondrial skeleton corresponding to the final chain of pixels remaining after step by step erosion of the mitochondrial mask was significantly reduced in IPD fibroblasts ($p=0.020$). The number of mitochondrial nodes in the sense of graph theory applied to the mitochondrial skeleton reflects reduced mitochondrial branching in IPD ($p=0.013$). Finally, the mitochondrial node degree representing the average branch length in the mitochondrial skeleton network was also reduced ($p < 0.001$). [figure1] Figure: (white) mitochondrial shapes, (blue) skeleton, (green) branch points, (red) endpoints. Note the reduced branching in the IPD patient sample.

Conclusions: Morphometric changes of IPD mitochondria with increased number of mitochondria on one side and reduced branching on the other side reflect mitochondrial fragmentation. This may be due to impaired mitophagy and/or also – at least temporary efficient – compensatory mechanisms, as also indicated by increased mitochondrial membrane potential. The results are in agreement with similar changes observed in submucosal enteric ganglia neurons of IPD patients (doi:10.1038/srep33117).

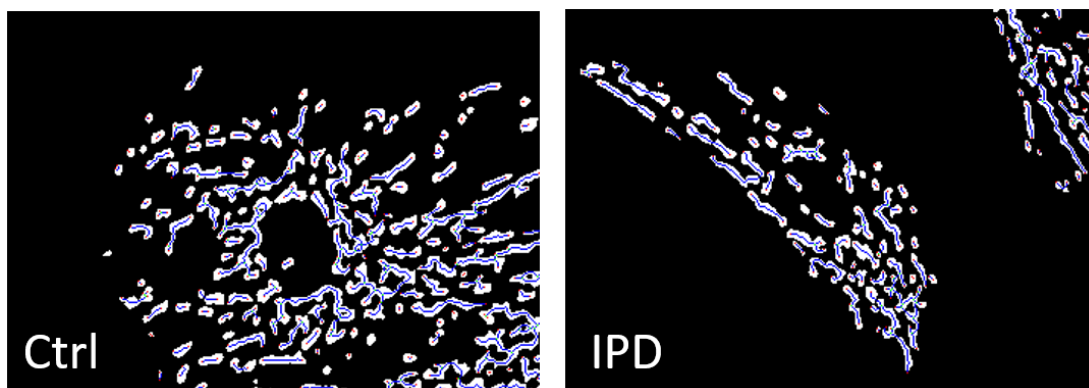


FIG 1. (420)

427

Dysphagia predicts poor outcome in late-stage Parkinson's disease

M. Fabbri, D. Abreu, L. Guedes, M. Rosa, A. Antonini, M. Zibetti, L. Lopiano, J. Ferreira, M. Coelho (Lisbon, Portugal)

Objective: to evaluate the clinical progression and prognostic factors of a late-stage PD (LSPD) population.

Background: Parkinson's disease (PD) disability milestones emerge in an exponential manner at a late stage disease [1]. Few data exists on the rate of clinical progression and prognostic factors for patients who have entered a very late stage of disease [2].

Methods: 50 LSPD patients (Schwab and England ADL Scale <50 or Hoehn Yahr Stage >3 in MED ON) and 17 advanced (AD) PD patients matched for age at disease onset underwent an acute levodopa challenge test and an extensive cross-sectional clinical assessment for motor, non-motor symptoms (NMS), quality of life (QoL) and caregiver burden. LSPD patients were also assessed at one year follow-up.

Results: LSPD patients present a more severe clinical picture, with prominent axial and NMS, that negatively influenced QoL [Table 1]. LSPD and ADPD patients' MDS-UPDRS-III score significantly improved after levodopa ($p < 0.001$) respectively 18% and 53% [Table 2]. The magnitude of levodopa response significantly correlated with motor complications in LSPD. After one-year, 20% of LSPD patients have died. Overall, after 1 year follow-up there was still clinical worsening of motor symptoms and NMS (worsening of MDS-UPDRS-III mean \pm SD 7.7 ± 10.3 , NMSS 19 ± 46 and NPI 6 ± 13), although heterogeneous [Table 1]. Nevertheless, motor fluctuations and dyskinesias improved. Functional independence worsened. Dysphagia severity at baseline significantly predicted a poor outcome (death, institutionalization or HY 5) [Table 3].

Conclusions: LSPD patients still present a significant, although heterogeneous, progression in the motor and non-motor features. Dysphagia severity was the single factor associated to progression for additional disability milestones.

References: [1] M. Coelho, J.J. Ferreira, Late-stage Parkinson disease (2012). [2] R. Cilia, E. Cereda, C. Klersy, M. Canesi, A.L. Zecchinelli, C.B. Mariani, S. Tesei, G. Sacilotto, N. Meucci, M. Zini, C. Ruffmann, I.U. Isaias, S. Goldwurm, G. Pezzoli, Parkinson's disease beyond 20 years, *Journal of neurology, neurosurgery, and psychiatry* 86(8) (2015) 849-55.

Results: Twelve studies comprising 1037 participants with PD met inclusion criteria. The cross-sectional prevalence of post-DBS psychosis was positively associated with follow-up duration and higher stimulation frequency but inversely with a higher stimulation voltage. The person-year incidence of post-DBS psychosis was positively associated with lower pre-DBS UPDRS scores. In subgroup analysis, post-DBS psychosis was associated with longer follow-up duration. Incidence was lower in studies that employed standard diagnostic criteria for psychosis but higher in patients with baseline UPDRS scores <40 and levodopa-equivalent doses <1000mg. It was noted that gait disturbance and Hoehn and Yahr stage ≥ 3 were not related to psychosis

Conclusions: A number of other findings may not have been predicted a priori and may be explicable by the complexities of DBS, including patient selection and management to attempt to reduce or treat psychosis. With early post-DBS psychosis, physicians tend to reduce the stimulating voltage but increase the stimulating frequency, which may be the reason for that prevalence of psychosis was positively associated with stimulating frequency but inversely related to the stimulating voltage. Lower dose of LEDD before or after the operation reflects that clinicians tend to reduce medication doses when patients exhibit psychotic symptoms. Those unexpected findings need to be confirmed in prospective studies.

References: 1. Constantinescu R, Eriksson B, Jansson Y, et al. Key clinical milestones 15 years and onwards after DBS-STN surgery-A retrospective analysis of patients that underwent surgery between 1993 and 2001. *Clin Neurol Neurosurg* 2017;154:43-48. 2. Castelli L, Perozzo P, Zibetti M, et al. Chronic deep brain stimulation of the subthalamic nucleus for Parkinson's disease: effects on cognition, mood, anxiety and personality traits. *Eur Neurol* 2006;55(3):136-144. 3. Qureshi AA, Cheng JJ, Sunshine AN, et al. Postoperative symptoms of psychosis after deep brain stimulation in patients with Parkinson's disease. *Neurosurg Focus* 2015;38(6):E5. 4. Voon V, Saint-Cyr J, Lozano AM, Moro E, Poon YY, Lang AE. Psychiatric symptoms in patients with Parkinson disease presenting for deep brain stimulation surgery. *J Neurosurg* 2005;103(2):246-251. 5. Cozac VV, Ehrensperger MM, Gschwandtner U, et al. Older Candidates for Subthalamic Deep Brain Stimulation in Parkinson's Disease Have a Higher Incidence of Psychiatric Serious Adverse Events. *Front Aging Neurosci* 2016;8:132. 6. Boel JA, Odekerken VJ, Schmand BA, et al. Cognitive and psychiatric outcome 3 years after globus pallidus pars interna or subthalamic nucleus deep brain stimulation for Parkinson's disease. *Parkinsonism Relat Disord* 2016;33:90-95. 7. Umemura A, Oka Y, Yamamoto K, Okita K, Matsukawa N, Yamada K. Complications of subthalamic nucleus stimulation in Parkinson's disease. *Neurol Med Chir (Tokyo)* 2011;51(11):749-755. 8. Chopra A, Abulseoud OA, Sampson S, et al. Mood stability in Parkinson disease following deep brain stimulation: a 6-month prospective follow-up study. *Psychosomatics* 2014;55(5):478-484. 9. Welter ML, Schupbach M, Czernecki V, et al. Optimal target localization for subthalamic stimulation in patients with Parkinson disease. *Neurology* 2014;82(15):1352-1361. 10. Chen CC, Lee ST, Wu T, Chen CJ, Chen MC, Lu CS. Short-term effect of bilateral subthalamic stimulation for advanced Parkinson's disease. *Chang Gung Med J* 2003;26(5):344-351. 11. Vesper J, Haak S, Ostertag C, Nikkiah G. Subthalamic nucleus deep brain stimulation in elderly patients-analysis of outcome and complications. *BMC Neurol* 2007;7:7. 12. Herzog J, Volkmann J, Krack P, et al. Two-year follow-up of subthalamic deep brain stimulation in Parkinson's disease. *Mov Disord* 2003;18(11):1332-1337.

515

Motor and cognitive progression in GBA-related PD patients submitted to Deep Brain Stimulation

L. Correia Guedes, C. Silva, R. Machado Bouça, N. Gonçalves, M. Fabbri, A. Castro Caldas, P. Pita Lobo, M.M. Rosa, B. Cattoni, H. Carvalho, A. Gonçalves Ferreira, J.J. Ferreira, M. Coelho (Lisbon, Portugal)

Objective: Our study aimed to evaluate the motor and cognitive outcome after Deep Brain Stimulation (DBS) in GBA-related PD.

Background: Parkinson's disease (PD) patients carrying a glucocerebrosidase gene mutation (GBA-related PD) have been associated to worse cognitive decline after DBS, although the overall response to DBS is still poorly understood.

Methods: Comparison of motor and cognitive outcomes between GBA-related PD and idiopathic PD (iPD) patients after subthalamic nucleus (STN)-DBS. Pre- and post-DBS MDS-UPDRS and MMSE were assessed. Post-DBS evaluations were performed in 4 conditions concerning ON/OFF medication and/or stimulation.

Results: Eight GBA-related PD and 10 iPD patients, with no significant differences in gender, age at disease onset (AO), time to DBS, pre-DBS levodopa response, follow-up post-DBS and pre- and post-DBS levodopa equivalent daily dose. Post-DBS MDS-UPDRS-III MedON/StimON was significantly different between groups (40.1 ± 9.1 GBA-PD; 28.8 ± 11.2 iPD; $P=0.05$). In GBA-related PD, post-DBS MDS-UPDRS-III MedON/StimON was worse than pre-DBS MDS-UPDRS-III MedON (40.1 ± 9.1 vs 24.5 ± 8 ; $P=0.017$). MMSE did not differ significantly between groups.

6/8 GBA-related PD patients were evaluated in the 4 post-DBS conditions. Stimulation significantly improved MDS-UPDRS-III (MedOFF/StimOFF 57.7 ± 14.8 vs MedOFF/StimON 36.7 ± 14.3 ; $P=0.026$), but the benefit with stimulation (post-DBS MDS-UPDRS-III MedOFF/StimOFF vs MedOFF/StimON) was worse compared to benefit from levodopa pre-DBS (pre-DBS MedOFF vs MedON).

Conclusions: GBA-related PD patients benefit from acute STN-DBS stimulation, although less than iPD patients. Motor symptoms of GBA-related PD seem to worsen 4.5 years after STN-DBS, whereas we found no cognitive decline. More data is warranted but available evidence do not support excluding GBA-related PD patients from DBS.

Abstract presented at the 4th Congress of the European Academy of Neurology, 16-19 June 2018, Lisbon, Portugal.

537

Directional deep brain stimulation in Parkinson's disease guided by local field potentials

F. Alonso-Frech, C. Fernandez-Garcia, M. Monge, M.J. Catalan Alonso, G. Foffani (Madrid, Spain)

Objective: Implementation of directional stimulation of subthalamic nucleus with segmented leads guided by local field potential (LFP) recordings in order to personalize DBS parameters, optimize therapeutic window and minimizing side effects.

Background: Novel directional electrodes may have the advantage over the conventional ones of avoiding adverse effects, however the programming optimization could be very time-consuming.

Methods: Since March 2016 to December 2017, 14 patients have been implanted with 28 directional Vercise Cartesia leads (Boston SC). Mean age of patients were 54,6 years (37-74 years). Mean evolution was 9,2 years (5-18). Postoperatively CT scans/ MRI fusion were performed to asses lead placement. Local field potentials of all contacts from each lead in bipolar montage were recorded 5 days after surgery to analyze beta band peaks. Therapeutic window effect for rigidity were assessed blinded to LFP results at least 1 week after surgery.

Results: No postoperative complications after directional leads implantation were observed in any patient. LFP analyses showed significant beta peaks in 100% of patients. Directional deep brain stimulation guided by LFP widened therapeutic window to 39% compared to spherical stimulation. Negative correlation between beta band and final score for rigidity was found to be statistical significant ($R -0,31$). Contacts with higher beta power were selected for chronic stimulation of the subthalamic nucleus with good clinical response, obtaining 78% improvement in UPDRS-III, 82% reduction of medication.

Conclusions: Deep subthalamic stimulation with directional leads is safe and efficient. Local field potentials and beta oscillations could optimize settings parameters and alleviating programming burden as it seems to predict the optimal directional contact for improving rigidity. In advance, these neurophysiological parameters may be taken into consideration to personalize directional stimulation and can be time saving tools for programming.

References: Directional local field potentials: A tool to optimize deep brain stimulation. Tinkhauser G, Pogosyan A, Debove I, Nowacki A, Shah S.A, Seidel K, Tan H, Brittain J.S, Petermann K, di Biase L, Oertel M, Pollo C, Brown P, Schuepbach M. *Mov Disord.* 2018 Jan;33(1):159-164.

543

Surgery-, hardware - and chronic stimulation-related adverse events following subthalamic nucleus deep brain stimulation for Parkinson's disease

B. Gonenli Kocer, E. Ozturk, S. Comoglu, M. Sorar, H. Kertmen (Ankara, Turkey)

Objective: To evaluate the adverse events (AEs) following subthalamic nucleus (STN) deep brain stimulation (DBS) for Parkinson's disease (PD) during 6 years period.

Background: The adverse events associated with DBS surgery were evaluated in 3 main categories: Surgery-, device- and stimulation-related issues.

Methods: Between 2011 and 2017, 147 consecutive patients (92 males, %62.6) who had undergone STN DBS surgery for PD in our Movement Disorders Clinic, were assessed retrospectively. Patients' characteristics including modified Hoehn and Yahr (mH&Y) stages, Unified Parkinson's Disease Rating Scale (UPDRS) part II and III scores, levodopa equivalent doses (LED) at the pre- and postoperative period were obtained from the continuous medical records. Surgery-, hardware- and chronic stimulation related AEs were also recorded after the patients' data was reviewed comprehensively.

Results: The mean age and disease duration were 54.92 ± 9.65 and 13.64 ± 6.35 years. After STN DBS, 54.44%, 55.85%, and 51.9% reduction were found on UPDRS part II, III scores and LED, respectively. There was no mortality and also persistent morbidity related to the surgery. The most surgery-related AE was perioperative confusion (8.2%) and the most hardware-related AE was lead or electrode fracture (6.1%). Chronic stimulation-related AEs including weight gain, dysarthria/dysphonia, and gait/postural instability were found 30.6%, 21.8%, and 16.3%, respectively.

Conclusions: Surgery- and hardware-related AEs are usually non-severe and non-persistent after the STN DBS surgery. Most of AEs are treatable but chronic stimulation-related axial and non-motor symptoms including gait and/or speech disturbances and weight gain may persist in the long-term period.

544

Poor responders to STN DBS in Parkinson's disease: 1 year follow-up study

M. Zibetti, L. Ricciardi, E. Montanaro, M. Sarchioto, M. Edwards, L. Lopiano, F. Morgante (Torino, Italy)

Objective: To determine which factors contribute to a poor outcome at 1 year after Deep Brain Stimulation (DBS) of the Subthalamic Nucleus (STN).

Background: The efficacy of STN-DBS for advanced Parkinson's disease (PD) has been consistently demonstrated. Yet, despite accurate selection and electrode positioning, a few patients report unsatisfactory outcome.

Methods: We conducted a retrospective analysis of prospectively acquired data at University of Turin DBS Centre. Out of 203 consecutive PD patients treated with STN-DBS, we identified those with available UPDRS II scores before surgery (T0) and at 1-year follow-up (T1) respectively in the OFF medication and in the OFF medication/ON stimulation condition. We defined as "Poor DBS Responders (Poor-DBS)" those who had <20% of improvement at UPDRS-II OFF MED/ON STIM at T1. "Poor" and "Good DBS responders (Good-DBS)" were compared for demographical, clinical, cognitive and affective variables at T0 and T1. We included in the analysis: demographical and clinical variables, Schwab-England Scale (SE), UPDRS-III (in the practically defined OFF state (OFF MED) at T0 and in OFF MED/ON STIM at T1). Psychiatric assessment included Beck Depression Inventory (BDI) and State-Trait Anxiety Inventory (STAI-X1 and X2).

Results: We retrieved baseline UPDRS II data in OFF MED from 126 subjects (Poor-DBS = 35, Good-DBS = 91). At T0 UPDRS II, UPDRS III and axial UPDRS III were significantly less impaired in poor-DBS. Motor fluctuations were also less severe in this group. UPDRS III improved at T1 in both Poor-DBS and Good-DBS ($p < 0.0001$). UPDRS II, SE, UPDRS axial score, dyskinesia score, OFF score significantly improved at T1 compared to T0 in Good-DBS. In Poor-DBS, UPDRS II significantly worsened at T1 ($p = 0.0001$), SE remained unchanged ($p = 0.7$), Axial motor UPDRS score tended to decrease but not significantly ($p = 0.06$), OFF time score was not modified ($p = 0.17$). Only dyskinesia score and total UPDRS IV were

improved at T1 in poor-DBS (respectively $p = 0.0025$ and $p = 0.0055$). Depression by BDI decreased only in Good-DBS ($p < 0.01$) whereas it remained unchanged in poor-DBS. STAI-X1 and X2 did not differ between groups.

Conclusions: Our data suggest that poor outcome on activity of daily living after STN DBS in PD might be caused by mild improvement of axial symptoms and of OFF time score, despite improvement of UPDRS-III in OFF MED/ON STIM.

546

A wireless brain-spine interface alleviating gait deficits of non-human primates model of Parkinson's disease

F. Raschella, T. Milekovic, M. Perich, S. Sun, G. Schiavone, C. Hitz, Y. Jianzhong, W. Ko, Q. Li, C. Qin, S. Lacour, J. Bloch, S. Micera, E. Bezard, G. Courtine (Geneva, Switzerland)

Objective: While levodopa and deep brain stimulation alleviate most of the symptoms associated with Parkinson's Disease (PD), axial gait disorders are less responsive to these treatments. Impairments include short and slow steps, balance deficits and freezing of gait. Using MPTP-treated non-human primates, we studied the impact of a brain-spine interface on alleviating axial gait deficits observed in PD.

Background: We have established a mechanistic and technological framework that guided the design of electrical spinal cord stimulation protocols engaging extensor and flexor muscle groups. We created an interface that linked gait events decoded from leg motor cortex activity to spatially selective stimulation protocols that reinforced the movements associated with these events. As early as 6 days after spinal cord injury, this brain-spine interface restored weight-bearing locomotor movements of a paralyzed leg in a non-human primate model of spinal cord injury [1].

Methods: Three MPTP-treated Rhesus macaque monkeys, the gold standard model for PD symptomatology, were implanted with the wireless brain-spine interface. Recordings of multi-unit activity from the left and right leg motor cortex were used to detect neural states related to flexion and extension movements of both legs while the animal walked freely overground or over a horizontal ladder. The detection of these gait events triggered the delivery of spatially selective electrical stimulation protocols that reinforced the extension and flexion movements of the legs. Stimulation protocols were delivered using an implantable pulse generator with real-time triggering capability that was connected to a custom-made electrode array. The electrode layout was based on a computational model that estimated optimal locations to target the dorsal roots of each lumbar spinal cord segment.

Results: MPTP-treated monkeys exhibited moderate to severe axial gait deficits, including short and slow steps, balance deficits, freezing of gait, and poor precision of paw placement when traversing the horizontal ladder. The brain-spine interface instantly alleviated these deficits, allowing the monkeys to increase their walking speed, improved their balance and regained coordinated gait patterns. Moreover, the brain-spine interface enabled the monkeys to regain the ability to position the paws precisely on the rungs of the horizontal ladder.

Conclusions: These preliminary results illustrate the ability of the brain-spine interface to alleviate axial gait deficits and restore visuomotor control of leg movements in MPTP-treated non-human primates, standard model for PD symptomatology. These findings open promising avenues for targeting gait deficits in people with PD, which are still resistant to current treatments.

References: [1] Capogrosso M, Milekovic T, Borton D, et al. A brain-spine interface alleviating locomotor deficits after spinal cord injury. *Nature* 2016; 539: 284-88.

552

Deep brain stimulation for monogenic Parkinson's disease: A systematic review

T. Kuusimäki, J. Korpela, E. Pekkonen, M. Martikainen, A. Antonini, V. Kaasinen (Turku, Finland)

Objective: The aim was to systematically investigate the outcome of deep brain stimulation (DBS) in genetic Parkinson's disease (PD) compared to the patients with documented negative genetic screening.

Background: DBS is an effective treatment for PD patients with motor complications (1). However, the key DBS efficacy studies have been performed in PD patients with unknown genotype but given the estimated prevalence of approximately 5–10 % of monogenic mutations, proper characterization is becoming increasingly relevant. It is also known that medication effects may vary between different mutations (2) and it can be considered possible that there are differences in the treatment response for DBS in advanced monogenic PD as well.

Methods: A PubMed search from inception to Feb 13, 2018 with key words “deep brain stimulation or DBS”, “Parkinson’s or Parkinson or Parkinsonism” and “genetic or gene”. Thirty-seven studies from years 2003-2017 were included in the systematic review.

Results: Included studies reported 168 monogenic DBS-treated PD patients and mutations were documented in six different genes. The most comprehensive published data were available for LRRK2 and PRKN mutations providing the strongest evidence of DBS-outcomes in these two patient groups. Key findings were: 1) DBS outcome appears to be poor in patients with LRRK2 R1441G mutations, excellent in patients with LRRK2 G2019S mutations and good in patients with PRKN mutations, 2) the overall benefit of DBS in SNCA, GBA and LRRK2 T2031S mutations may be decreased due to rapid progression of cognitive and neuropsychiatric symptoms, and 3) in other mutations, the motor outcome in DBS-treated genetic PD patients appears generally comparable to that of sporadic PD patients. [Table1]

Conclusions: Monogenic PD patients have variable DBS outcomes depending on the mutated gene. Most patients benefit from the operation, at least in the short-term, but the current evidence does not support or is questionable for DBS implantation for patients with T2031S or R114G mutations in the LRRK2 gene or mutations in the SNCA or the GBA genes. Apart from LRRK2 and PRKN mutations, the published literature concerning DBS is scarce which complicates the interpretation. In these patients with rarer mutations, the need for DBS should be evaluated considering the accumulating evidence from the literature and individual clinical factors.

References: 1. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2006; 355(9): 896-908. 2. Masellis M, Collinson S, Freeman N, et al. Dopamine D2 receptor gene variants and response to rasagiline in early Parkinson's disease: a pharmacogenetic study. *Brain* 2016; 139(Pt 7): 2050-62.

TABLE 1 (552)

<i>Gene</i>	<i>Studies (n)</i>	<i>Patients (n)</i>	<i>Outcome</i>
LRRK2	14	80	Mostly favourable motor outcome. Three studies with seven patients (9 % of reported patients) reported poor motor outcomes. Both patients with the T2031S mutation (n = 2) developed neuropsychiatric problems 5-7 years after implantation. The outcome seems poor in patients with LRRK2 R1441G mutations whereas it appears excellent in patients with LRRK2 G2019S mutations.
PRKN	14	54	Favourable long-term motor outcome. One study with two patients (4% of reported patients) suggested questionable benefit.
GBA	3	21	Favourable long-term motor outcome although GBA carriers developed cognitive impairment faster compared to patients without mutations.
SNCA	5	5	Favourable motor outcome. Three out of five patients developed cognitive or neuropsychiatric problems a few years after implantation.
VPS35	4	5	Favourable motor outcome in four cases and little motor benefit complicated by dysarthria in one case.
PINK1	3	3	Favourable motor outcome reported in two cases.

Propionibacterium acnes Infection with Intracerebral Abscess in Deep Brain Stimulation

R. Lewis, F. Farrokhi, M. Marsans (Seattle, WA, USA)

Objective: Propionibacterium acnes infection in DBS patients has distinct characteristics that distinguish it from the most commonly associated bacteria in postoperative wound infections, Staphylococcus aureus. Whereas S. aureus is typically presents with early fever and elevated inflammatory markers, P. acnes infections in DBS more typically present with later clinical onset and unremarkable inflammatory markers. Our objective is to highlight the unique characteristics of P. acnes infections in DBS patients. The unifying feature amongst the cases was the presentation of neurological symptoms in the absence of fever or elevated inflammatory markers.

Background: Deep Brain Stimulation (DBS) is an increasingly applied modality for treatment of movement disorders such as Parkinson's Disease and essential tremor. Although DBS has an excellent and well proven safety profile, a small risk of infection still exists. A rare and previously underreported form is noted here. Propionibacterium acnes infections in DBS patients have distinct presentation characteristics, including later clinical onset and normal inflammatory markers. We review a series of infections and the literature in an effort to raise awareness of a process that can go unnoticed and lead to devastating clinical outcomes.

Methods: We review the literature in conjunction with a series of three P. acnes DBS infections at our institution, with attention to commonalities between patients and clinical presentation.

A standard frame-based DBS surgical approach was followed on all cases. Preoperative prophylactic treatments included the use of nafcillin for Case 1, vancomycin for Case 2, and cefazolin for Case 3.

Results: Common characteristics of infections included lack of clinical history of fever, chills, or sweats. Another similarity was seen in absence of elevation in inflammatory markers. All cases showed delayed presentation months after the initial surgery and presented with slow onset of neurologic deficits.

Case 1 resulted with a 1.7 cm abscess at the tip of the implanted electrode. Case 2 developed a 2.4 cm cystic lesion around the tip of the electrode. Case 3 developed a 2.2 cm cystic lesion. All three cases yielded P. acnes in cultures of explanted leads.

Conclusions: In context of delayed and subtle neurological changes in DBS patients, infection caused by P. acnes must be taken into consideration and routinely evaluated by cranial imaging for more rapid diagnosis and to avoid additional harm.

References: 1. Bhatia R, Dalton A, Richards M, Hopkins C, Aziz T, et al. (2011) The incidence of deep brain stimulator hardware infection: the effect of change in antibiotic prophylaxis regimen and review of the literature. *British Journal of Neurosurgery* 25: 625-631. 2. Bjercknes S, Skogseid IM, Saehle T, Dietrichs E, Toft M (2004) Surgical site infections after deep brain stimulation surgery: frequency, characteristics and management in a 10-year period. *PLoS ONE* 9: e105288. 3. Gorgulho A, Juillard C, Uslan DZ, Tajik K, Aurasteh P, et al. (2009) Infection following deep brain stimulator implantation performed in the conventional versus magnetic resonance imaging-equipped operating room. *J Neurosurg* 110: 239-246. 4. Temel Y, Ackermans L, Celik H, Spincemaille GH, van der Linden C, et al. (2004) Management of hardware infections following deep brain stimulation. *Acta Neurochir* 155: 355-361. 5. Sillay KA, Larson PS, Starr PA (2008) Deep brain stimulator hardware-related infections: incidence and management in a large series. *Neurosurgery* 62: 360-367. 6. Voges J, Waerzeggers Y, Maarouf M, Lehrke R, Koulousakis A, et al. (2006) Deep-brain stimulation: long-term analysis of complication caused by hardware and surgery - experiences from a single centre. *J Neurol Neurosurg Psychiatry* 77: 868-872. 7. Fily F, Haegelen C, Tattevin P, Buffet-Batillon S, Revest M, et al. (2011) Deep brain stimulation hardware-related infections: a report of 12 cases and review of the literature. *Clinical Infectious Diseases* 52: 1020-1023. 8. Umemura A, Jaggi JL, Hurtig HI, Siderowf AD, Colcher A, et al. (2003) Deep brain stimulation for movement disorders: morbidity and mortality in 109 patients. *J Neurosurg* 98: 779-784. 9. Farrokhi FR, Gunther M, Williams B, Blackmore CC (2013) Application of lean methodology for improved quality and efficiency in operating room instrument availability. *Journal for Healthcare Quality*. 10. Hegde V, Meredith DS, Kepler CK, Huang RC (2012) Management of postoperative spinal infections. *World J Orthop* 3: 182-189.

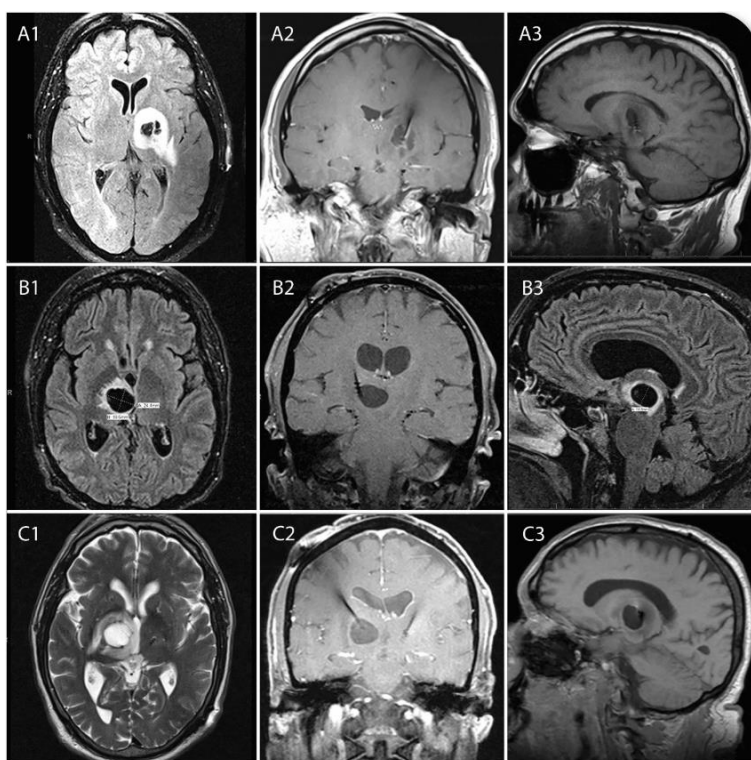


FIG 1 (558)

563

Intraoperative Electromyography can optimize pallidotomy for Parkinson's disease and dystonias

P. Brainer, A. Campos, A. Brainer, J. Brainer, P. Brainer, P. Coutinho, C. Lima, S. Laurentino, R. Bandin, M. Andrade (Recife, Brazil)

Objective: The aim of this study is show our experience in use intraoperative electromyography during stereotactic pallidotomy for Parkinson's disease and dystonia, to help care to avoid capsular injury while maximizing improvement of rigidity, bradykinesia, dystonic movements and tremor.

Background: Microelectrode techniques are used in many centers to localizing the stereotactic target to implant DBS, thalamotomy and pallidotomy, but DBS implant and radiofrequency lesions may be performed with macroelectrodes stimulation alone. Patient cooperation with physiologic testing during surgery may become limited with dyskinetic movements and motor responses may be difficult to differentiate from spontaneous movements. While general anesthesia is necessary in patients with dystonia, ENM may be even more useful.

Methods: seventy two consecutive stereotactic procedures were performed in sixty one patients between January 2004 and december 2016 . All patients had a clinical diagnosis of Parkinson's disease or dystonia for at least 5 years prior to surgery. The stimulation electrode was introduced via MRI- CT guided stereotaxis with stimulation at 5 and 100 Hz thresholds for detection of EMG responses were usually seen at 3mA. Electromyography (EMG) responses were consistently seen prior to visual observation of muscle activity. Timing of EMG response relative to stimulus aided in differentiating stimulus-related movement from spontaneous tremor. Resting spontaneous EMG activity was seen to decrease as rigidity was improved by stimulation. EMG activity related to tremor was recorded and tremor decrease by stimulation was documented by EMG recording.

Results: Sixty seven patients showed immediate postoperative neurologic improvement. One patient develop a motor deficit during surgery due to a catastrophic hemorrhage and die. Four patients developed a postoperative transient minimal contralateral facial paresis or hemiparesis due to hemorrhage at the lesion site, Treated with conservative management, the hematoma and the hemiparesis resolve six weeks after

surgery. After 5 years on average(2 to 10 years), Statistically significant improvements were seen in the UPDRS scores for activities of daily living, motor examination in the off- on states. Significant improvements were observed in dyskinesia and rigidity. Improvements in gait and posture in the off state were not statistically significant.

Conclusions: EMG recordings during stereotactic DBS have been helpful in this group of patients and have elevated the level of confidence in the safety of the site of electrode implantation, without increase in operative complications or significant surgical time.

References: Functional lesional neurosurgery for tremor-a protocol for a systematic review and meta-analysis. Schreglmann SR, Krauss JK, Chang JW, Bhatia KP, Kägi G. *BMJ Open*. 2017 May 9;7(5). Seventy years of pallidotomy for movement disorders. Cif L, Hariz M, *Mov disord* 2017 Jul;32(7):972-982. A metaanalysis comparing the results of pallidotomy performed using microelectrode recording or macroelectrode stimulation. Palur RS, Berk C, Schulzer M, Honey CR. *J Neurosurg*. 2002 Jun; 96(6):1058-62. Electromyography during stereotactic pallidotomy for Parkinson's disease. Einer WJ, Calancie B, Bowen B. *Stereotact Funct Neurosurg*. 2000;74(1):21-9. Stereotactic pallidotomy performed without using microelectrode guidance in patients with Parkinson's disease: surgical technique and 2-year results. Eskandar EN, Shinobu LA, Penney JB Jr, Cosgrove GR, Counihan TJ. *J Neurosurg*. 2000 Mar; 92(3):375-83.



FIG 1 (563)

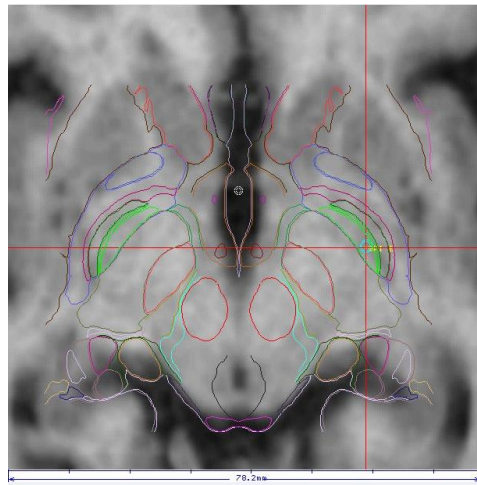


FIG 2 (563)

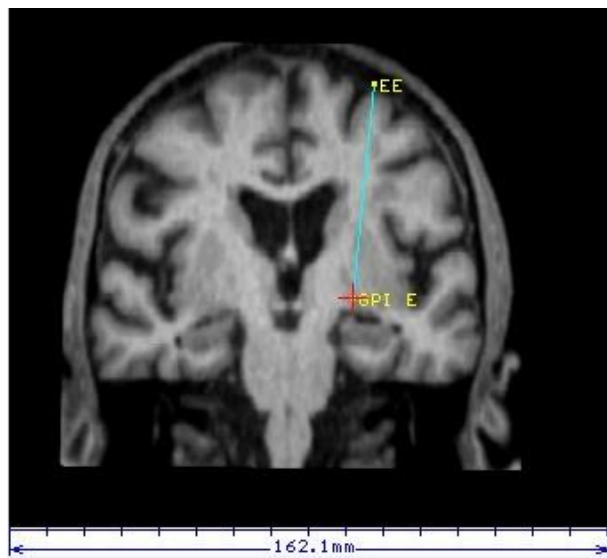


FIG 3 (563)

567

The effects of deep brain stimulation of the pedunclopontine nucleus on cognition in Parkinson's disease and Progressive Supranuclear Palsy

F. Leimbach, J. Gratwicke, T. Foltynie, M. Hariz, P. Limousin, L. Zrinzo, M. Jahanshahi (London, United Kingdom)

Objective: To investigate the effects of deep brain stimulation (DBS) of the pedunclopontine nucleus (PPN) on different cognitive domains for Parkinson's disease (PD) and progressive supranuclear palsy (PSP).

Background: DBS-PPN has been proposed as a treatment for the axial symptoms of patients with PD or PSP. The results concerning the clinical benefits of PPN-DBS are inconsistent. However, some reported evidence suggests beneficial effects of PPN-DBS on aspects of cognition.

Methods: Five patients with PD and two patients with PSP who were consecutively operated with PPN-DBS were administered a neuropsychological battery of tests assessing all major cognitive domains within one month prior to surgery and one year after surgery. Six patients had unilateral (1 right, 5 left) and one patient had bilateral PPN-DBS. None of the patients had undergone DBS at other brain targets.

Results: The majority of tests of cognition showed no significant change from before to after surgery. The only aspects of cognition that reliably declined in a proportion of the patients were processing speed

(Stroop colour naming control task, WAIS-III digit symbol) and switching category verbal fluency. None of the tests of cognition showed improved performance at one year compared to before DBS.

Conclusions: Despite the small sample size and the heterogeneity of the sample, the results indicate that PPN-DBS is generally safe from a cognitive perspective, but by contrast to previous reports, there was no evidence of improvement of any aspect of cognition assessed.

572

Is lowering stimulation frequency a feasible option to improve speech in Parkinson's disease patients undergoing subthalamic deep brain stimulation?

M. Fabbri, M. Zibetti, G. Ferrero, A. Accornero, I. Guimaraes, M. Rizzone, A. Romagnolo, J. Ferreira, L. Lopiano (Lisbon, Portugal)

Objective: To analyze the effect of low frequency (LFS) subthalamic nucleus deep brain stimulation (STN-DBS) on speech and voice in Parkinson's disease (PD) patients with medium/long term post-surgical follow-up.

Background: STN-DBS has an optimal effect on cardinal motor symptoms of PD. Nevertheless, its long-term effect on dysarthria is not clear. Few studies, with small patients samples, suggest a transient beneficial effect of LFS on PD dysarthria. Though data in this area are scarce [1].

Methods: 20 PD patients who underwent STN-DBS at least 3 years before, divided into two groups, matched for gender, age and age at disease onset (Group A: slight speech impairment [MDS-UPDRS item 2.1 \leq 2] and group B: severe speech impairment [MDS-UPDRS item 2.3 \geq 3] were tested in the following conditions: MED OFF/STIM ON (130Hz – standard frequency), MED OFF/STIM OFF and MED OFF/STIM ON (60Hz - LFS). Total electrical energy delivered was maintained constant. The following was assessed in all conditions: maximum phonation time, voice quality and stability, oral diadochokinesis, speech rate and intelligibility and MDS-UPDRS-III. Voice samples were recorded and analyzed by a speech pathologist, blinded to patients' therapeutic condition. A two weeks follow-up was performed in patients who decide to keep LFS due to a subjective and clinician rated acute improvement of speech and voice.

Results: Overall, mean (SD) age was 64.4 (\pm 5.8) years and mean disease duration 19.4 (\pm 4.5) years. Data on demographic, clinical, therapeutic characteristics and speech impairment impact on quality of life, are detailed in Table 1 [Table 1]. LFS compared to no stimulation (MED OFF/STIM ON at 60Hz vs MED OFF/STIM OFF) significantly improved voice quality, diadococinesis and intelligibility in Group A and diadococinesis and intelligibility in Group B, with a motor improvement (MDS-UPDRS-III) of 42 \pm 12% and 39 \pm 22% in the two groups, respectively. On the other hand, when comparing LFS to standard frequency stimulation, there was a significant improvement of maximum phonation time, diadococinesis and intelligibility only in Group B without significant changes of motor performance. Five Group B patients opted to maintain LFS. At two weeks follow-up, two of them were kept at 60Hz stimulation, one was switched to 80 Hz and two were switched back to 130Hz, due to tremor and wearing-off reappearance.

Conclusions: LFS could be a useful option to test for STN-DBS patients with severe speech impairment. Nevertheless, its effect on motor symptoms and motor fluctuations may not be preserved over time.

References: [1] Moreau C, Pennel-Ployart O, Pinto S, Plachez A, Annic A, Viallet F, Destée A, Defebvre L. Modulation of dysarthropneumophonia by low-frequency STN DBS in advanced Parkinson's disease. *Mov Disord.* 2011 Mar;26(4):659-63.

TABLE 1 (572)

	Group A (n=18)	Group B (n=19)	P-values
Age (yrs)	63.5 ± 5.7	65.3 ± 6.1	ns
Women (n/total (%))	3/10 (33%)	3/10 (33%)	ns
Age at disease onset (yrs)	43.6 ± 7.1	46.3 ± 6.6	ns
Disease duration (yrs)	19.9 ± 4.9	19 ± 5.2	ns
Age at DBS (yrs)	56.7 ± 8.1	58.4 ± 5.7	ns
Months after DBS	81.1 ± 36.7	82 ± 42	ns
LEDD before surgery (mg)	945 ± 337	1013.7 ± 436	ns
LEDD after surgery (mg)	680 ± 420	812 ± 610	ns
Stimulation Voltage*			
R_STN/L_STN at 130 Hz	3.4 ± 0.5 / 3.4 ± 0.4	3.4 ± 0.7 / 2.8 ± 0.8	ns
R_STN/L_STN at 60 Hz	5 ± 0.7 / 5.1 ± 0.6	4.8 ± 1 / 4.2 ± 1	
MMSE	28.6 ± 1.2	28.3 ± 1.7	ns
NFG-Q	6.4 ± 8.1	13.8 ± 7.4	0.048
SE (ON)	86 ± 6.9	81 ± 11	ns
MDS-UPDRS-I	11.4 ± 5	11.3 ± 3.6	ns
MDS-UPDRS-II	18.2 ± 4	22.5 ± 6.1	ns
MDS-UPDRS-III	22.2 ± 9.7	27.2 ± 9.8	ns
MDS-UPDRS-IV	1.6 ± 2.2	5 ± 3.6	0.035
QoL-DyS, total score	16.2 ± 16	49 ± 22.6	<0.01
Speech characteristics			
Situational difficulty	7.2 ± 6	19.2 ± 7.5	<0.01
Compensatory strategies	4.4 ± 2.9	14.8 ± 6.4	<0.001
Perceived reactions of others	2.6 ± 6.1	5.3 ± 7.8	ns
	2 ± 3.5	9.5 ± 9.5	<0.05

Table 1. Demographic, clinical, therapeutic and speech characteristics of DBS patients. Group A: PD patients with slight/moderate speech impairment (MDS-UPDRS 2.1 = 2); Group B: PD patients with severe speech impairment (MDS-UPDRS = 3); ns: not significant; Values are presented as mean ± SD, if not otherwise specified. LEDD: levodopa equivalent daily dose; R_STN: right subthalamic nucleus; L_STN: left subthalamic nucleus; NFG-Q: New freezing of gait questionnaire; MMSE: Mini mental state examination; SE: Schwab and England Scale (MED ON/STIM ON); QoL-DyS: Quality of life in the dysarthric speaker questionnaire. (*) Stimulation setting before speech assessment ⇒ Group A: two patients had a 130 Hz stimulation; Group B: two patients had a bipolar stimulation and one a double monopolar.

Guided Poster Group 4: Ataxia

618

Loss of paraplegin drives spasticity rather than ataxia in SPG7: A European cohort analysis of 238 patients

G. Coarelli, R. Schule, B. vande Warrenburg, P. de Jonghe, C. Ewencyk, A. Martinuzzi, M. Synofzik, E. Hamer, J. Baets, M. Anheim, L. Schöls, T. Deconinck, B. Fontaine, T. Klockgether, MG. D'Angelo, ML. Monin, P. Charles, MT. Bassi, T. Klopstock, E. Ollagnon-Roman, C. Kamm, M. Papin, CS. Davoine, G. Banneau, S. Tezenasdu Montcel, D. Seilhean, A. Brice, C. Duyckaerts, G. Stevanin, A. Durr (Paris, France)

Objective: The aim of this work was to delineate the clinical phenotype of SPG7 patients, integrating genetic data and follow-up examinations, taking advantage of a large multinational recruitment.

Background: The SPG7 gene was the first identified gene for inherited spastic paraplegia (HSP)1. Actually, SPG7 is a common cause of adult onset spastic ataxia 2, variably presenting either predominantly with ataxia or spasticity. It is not known whether genetic factors and/or neuropathology account for these differences.

Methods: We analyzed clinical and genetic data from 238 SPG7 patients. Neuropathological examination was performed in one case.

Results: SPG7 was a late onset (35.2 ± 14.6 years, $n=230$) and slowly progressive disease with annual SARA progression of 0.64. At onset, ataxia was present in 71 patients. Disease durations of more than 20 years ($n=58$) showed significantly increased cerebellar dysarthria ($p=.02$), deep sensory loss ($p<.001$), wasting ($p=.001$) and ophthalmoplegia ($p=.04$). Brain MRI showed cerebellar atrophy in 63% of the patients. We did not find a cluster of mutations along the gene nor phenotype correlations based on the location of the mutations in case of missense. Patients homozygous for loss of function (LOF) mutations ($n=63$) versus

those with missense variants or composite missense and LOF mutations (n=173), presented significantly more often with pyramidal signs (p=.01), pes cavus (p=.04) and diminished visual acuity (p<.0001). The missense variant A510V was the most frequent mutation (58% of patients). The presence of at least one A510V mutation was associated with later age at onset (37.14± 14 vs 32.67± 15, p=.02) and cerebellar signs at onset (p=.04), but no differences in disease severity was observed compared to patients carrying other mutations. Apparently dominant inheritance was found in 11 families (6%), more often reported in patients that had cerebellar symptoms at onset (p=.02). Neuropathological examination in a SPG7 patient (c.1749G>C; c.2181+2dup) who died at age 56, revealed a 20% pyramidal tract reduction, moderate loss of Purkinje cells, moderate neuronal loss in the substantia nigra without Lewy Body.

Conclusions: This is the first longitudinal follow-up study of a large cohort of 238 SPG7 patients, showing that LOF mutations was associated more often to spastic predominance and that at least one A510V mutation more often to cerebellar ataxia and later onset.

References: 1. Casari G, De Fusco M, Ciarmatori S, Zeviani M, Mora M, Fernandez P, De Michele G, Filla A, Coccozza S, Marconi R, Dürr A, Fontaine B, Ballabio A. Spastic paraplegia and OXPHOS impairment caused by mutations in paraplegin, a nuclear-encoded mitochondrial metalloprotease. *Cell* 1998; 93: 973–83. 2. Pfeffer G, Pyle A, Griffin H, Miller J, Wilson V, Turnbull L, Fawcett K, Sims D, Eglon G, Hadjivassiliou M, Horvath R, Németh A, Chinnery PF. SPG7 mutations are a common cause of undiagnosed ataxia. *Neurology*. 2015 Mar 17;84(11):1174-6.

622

Cerebellar Ataxia case series study from southern Spain: Clinical and molecular description

A. Adarmes Gomez, S. Jesus Maestre, C. Mendez delBarrio, D. Macias Garcia, F. Carrillo Garcia, M. Carballo, P. Gomez Garre, P. Mir Rivera (Seville, Spain)

Objective: Describe clinical features of a Cerebellar Ataxia non-Friedreich case series from southern Spain, and their molecular diagnosis.

Background: Cerebellar Ataxias are a highly heterogeneous group, the diagnosis approach constitute a challenge to neurologist, with most patients having a lack of conclusive molecular diagnosis. To our knowledge no previous case series from southern Spain has been study.

Methods: We selected cerebellar ataxia patients that have been assessed in our Unit through a systematic protocol of study. We analyzed different variables such as inheritance pattern, age of onset, different symptoms and signs, and molecular diagnosis. We compare this variables between early (<40 y) and late (>40 y) onset groups.

Results: We recruited 102 patients with a mean age of onset of 39.24 ±18.91 y, sex predominance male (51%), early onset in 52% of cases. Mean years of evolution of disease 15.64 ±10.89 y, positive familiar history in 55.9% of cases, with a distribution of inheritance pattern as follow: Autosomal dominant 30.4%, autosomal recessive 19.6%, X-link related 5.9%, and the rest 44.1% consider as sporadic in absent of other affected family members. Early onset group preserved independent walking only in 45.3%, while in the late onset group a 51% walk without support. Early onset group also have a large proportion of cases with other neurological signs associated beside than cerebellar signs (69.8% vs 57.1% in the late onset group), being pyramidal signs the most frequents ones. Regarding MRI, 76.9% of early onset group has evident cerebellar atrophy, while only 63.6% of the late onset group has this alteration. We have been able to confirm diagnosis with genetic test in 36.7% of cases. The list of diagnosis in order of frequency is: SCA3 11, FXTAS 8, SPG7 4, NPC 3, Cerebrotendinous xantomatosis 3, SCA23 2, SCA2 2, SYNE1/ARCA1 1, SPG46 1, SCA1 1, ATM 1.

Conclusions: In our case series, syndromes with early onset and autosomic recessive pattern has a major severity, being associated with others neurological signs in most of the cases. Assessed patients with a progressive cerebellar syndrome through a schematic protocol in a specialized unit have provided a molecular diagnosis in a large percentage of cases.

References: Németh AH, Kwasniewska AC, Lise S, et al. Next generation sequencing for molecular diagnosis of neurological disorders using ataxias as a model. *Brain*. 2013;136(10):3106-3118.

doi:10.1093/brain/awt236. Synofzik, Matthis, Schüle, Rebecca. Overcoming the divide between ataxias and spastic paraplegias: Shared phenotypes, genes, and pathways. *Movement Disorders*. 32- 3. 1531-8257. <http://dx.doi.org/10.1002/mds.26944>. 10.1002/mds.26944-332- 345. 2017.

624

Genotype-phenotype correlations in 104 Uzbekish families with Spinocerebellar ataxias

F. Rakhimov, Y. Majidova, G. Rakhimbaeva (Tashkent, Uzbekistan)

Objective: Spinocerebellar ataxias are neurodegenerative disorders involving the cerebellum and its connections. There are more than 30 distinct subtypes, 16 of which are associated with an identified gene. The aim of the current study was to evaluate a large group of patients from 104 Uzbekish families with spinocerebellar ataxias.

Background: The background of the current study was to evaluate a large group of patients from 104 Uzbekish families with spinocerebellar ataxias.

Methods: We studied 150 patients from 104 families with spinocerebellar ataxias who had received molecular genetic testing for spinocerebellar ataxia types 1, 2, 3, 6, 7, 8, 10, 12, 17, and dentatorubral-pallidoluysian atrophy. A statistical analysis of the results was performed using basic descriptive statistics and the correlation coefficient (r), Student's t-test, chi-square test, and Yates' correction. The statistical significance level was established for p-values <0.05.

Results: The results show that the most common subtype was spinocerebellar ataxia 3, which was followed by spinocerebellar ataxia 10. Moreover, the comparison between patients with spinocerebellar ataxia 3, spinocerebellar ataxia 10, and other types of spinocerebellar ataxia revealed distinct clinical features for each type. In patients with spinocerebellar ataxia 3, the phenotype was highly pleomorphic, although the most common signs of disease included cerebellar ataxia (CA), ophthalmoplegia, diplopia, eyelid retraction, facial fasciculation, pyramidal signs, and peripheral neuropathy. In patients with spinocerebellar ataxia 10, the phenotype was also rather distinct and consisted of pure cerebellar ataxia and abnormal saccadic eye movement as well as ocular dysmetria. Patients with spinocerebellar ataxias 2 and 7 presented highly suggestive features of cerebellar ataxia, including slow saccadic ocular movements and areflexia in spinocerebellar ataxia 2 and visual loss in spinocerebellar ataxia 7.

Conclusions: Spinocerebellar ataxia 3 was the most common subtype examined, followed by spinocerebellar ataxia 10. Patients with spinocerebellar ataxia 2 and 7 demonstrated highly suggestive features, whereas the phenotype of spinocerebellar ataxia 3 patients was highly pleomorphic and spinocerebellar ataxia 10 patients exhibited pure cerebellar ataxia. Epilepsy was absent in all of the patients with spinocerebellar ataxia 10 in this series.

626

Objective Measures of Ataxic Gait Using Wearable Inertial Sensors

M. El-Gohary, L. Horak, C. Gomez (Portland, OR, USA)

Objective: To investigate whether gait measures from wearable inertial sensors were sensitive to ataxia and related to SARA scores in patients with SCA.

Background: Clinical trials on spinocerebellar ataxias are hampered by the lack of objective measures to precisely measure the disease severity, progression, and clinical efficacy. Gait impairments precede symptoms in patients with spinocerebellar ataxia (SCA) and may be valid surrogate markers of disease severity.

Methods: Twenty one patients with SCA (mean age 61 years) and 34 control subjects (mean aged 58 years) underwent SARA testing. SARA total scores ranged from 0 (prodromal) to 25. The subjects wore 2 inertial sensors on their feet and walked for 2 minutes at their normal walking pace.

Results: Step duration, double support time, and foot angle at heel strike were all very sensitive to ataxia ($p < .02$). In addition to these gait measure, other gait measures including gait speed, cadence, foot elevation at mid-swing, and toe off angle were significantly ($p < .003$) related to the total SARA score ($r = .53 - .82$). The

figure shows the relationship between the total SARA score and double support, calculated as the percentage of gait cycle while both feet are in contact with the ground.

Conclusions: Objective measure of gait with wireless inertial sensors provides promising, practical measures of severity cerebellar ataxia for clinical trials and clinical practice. Future analysis will determine the most sensitive measures of gait in prodromal SCA, examine test-retest reliability of gait measures, and evaluate sensitivity to progression of disease.

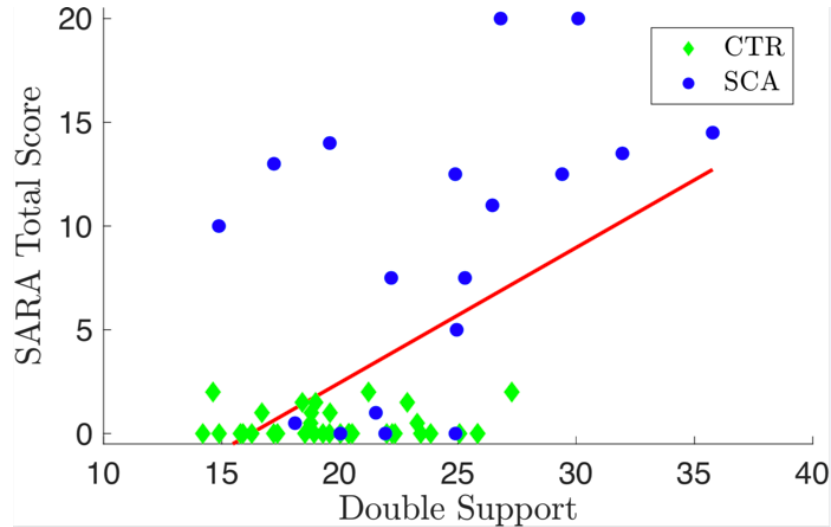


FIG. 1 (626)

627

Multi-tiered Diagnostic Approaches Reveal a High Degree of Genetic Heterogeneity for Hereditary Cerebellar Ataxias: A Retrospective Review of an Australian Cohort

C. Kang, C. Liang, K. Ahmad, Y. Gu, SF. Siow, J. Colebatch, S. Whyte, K. Ng, P. Cremer, R. Davis, T. Roscioli, M. Cowley, J.S. Park, C. Sue, K. Kumar (Sydney, Australia)

Objective: A retrospective review of the genetic spectrum in an Australian cohort of hereditary cerebellar ataxia (HCA), as well as evaluating HCA's testing modalities at the Neurogenetics Clinic of Royal North Shore Hospital.

Background: HCA is a group of diseases that are challenging to diagnose due to its clinical and genetic variability. Newer genetic testing modalities had been implemented to aid HCA diagnosis. Techniques such as next generation sequencing (NGS) targeted panels and whole genome sequencing (WGS) are known to improve the diagnostic yield of rarer HCA variants. However, their impact on HCA's genetic spectrum remains unclear.

Methods: 87 HCA affected individuals records were reviewed in order to assess genetic testing strategies. Testing modalities included triplet repeat expansion panels, NGS panels and WGS. Probands had triplet repeat expansion testing; those that tested negative had subsequent NGS targeted panels and WGS testing when available.

Results: In our cohort, 58.6% were male (51/87), average age at onset was 37.1 years (range 2-75), 66.7% were of adult onset. Of interest, the duration from onset to genetic diagnosis for sequencing variant positive individuals were averaging 26.3 years (range 1-53), which was significantly prolonged compared to triplet repeat positive individuals (averaging 10.4 years, range 1-53), with no significant difference in disease severity scales between these two groups. The detection rate in probands for triplet routine repeat expansion panels was 13.8% (11/80). NGS targeted panels yielded a further 10 patients (10/33, 30.3%), with WGS yielding 1 more diagnosis (1/3, 33.3%). NGS and WGS improved the overall diagnostic rate to 27.5% (22/80), with mutations occurring in 14 known HCA loci. We detected novel variants in ANO10 (SCAR10),

CACNA1A (SCA6), and SPG7 (HSP7) via NGS panels. We also report identifying a novel variant in PRKCG (SCA14) detected by WGS analysis.

Conclusions: Our findings highlight the genetic heterogeneity of HCAs in Australia and support the use of subsequent NGS targeted panel for patients who were negative on repeat expansion testing. Furthermore, our results suggest that individuals with sequencing variants have a less rapid disease progression, which may be of prognostic value.

TABLE 1 (627) Overall demographics and clinical manifestations of patient with suspected HCA referred to Neurogenetic Clinic, RNSH.

Variable	All patients	Triplet repeat +ve	Sequencing variant +ve	p-Value ^a
Total/probands	87/80	16/14	9/8	
Gender (M/F)	51/36	10/6	7/2	0.661
Age at onset (yrs) ^b	37.1 ± 18.9 (2-75)	36.4 ± 15.7 (8-61)	30.8 ± 15.8 (10-55)	0.411
Duration: ongoing (yrs) ^{b,c}	20.3 ± 15.7 (4-65)	13.8 ± 12.6 (4-54)	27.1 ± 16.5 (6-54)	0.033
Duration: from onset to initial presentation (yrs)	15.0 ± 16.0 (0 ^d -51)	10.1 ± 12.9 (0-51)	23.3 ± 18.1 (1-51)	0.060
Duration: from onset to diagnosis (yrs)	16.2 ± 16.7 (1-53)	10.4 ± 13.5 (1-53)	26.3 ± 17.8 (1-53)	0.028
Duration: from initial presentation to diagnosis (yrs) ^e	1.8 ± 3.4 (0-13)	1.0 ± 0.8 (0-2)	2.9 ± 4.9 (0-13)	0.252
Family history (%)	41 (47.1)	8 (50.0)	6 (66.7)	0.677
Gait ataxia (%)	84 (96.6)	16 (100.0)	9 (100.0)	-
Pyramidal signs (%)	42 (48.3)	7 (43.8)	4 (44.4)	0.688
Cerebellar atrophy on MRI (%)	36 (41.4)	8 (50.0)	3 (33.3)	0.677

+ve: positive

^a Analysis comparing Triplet repeat positive patients and sequencing variant positive patients, ^b Mean ± SD (Range) ^c Ongoing duration means disease duration from onset to 2017, ^d 0 yrs duration from initial presentation to diagnosis indicates that initial presentation to Neurogenetics Clinic and genetic diagnosis occurred in same year, ^e 4 triplet repeat expansion positive patients are removed from this analysis as they are tested from outside RNSH's Neurogenetics Clinic

TABLE 2 (627) Genetic variants identified in probands with pathogenic or likely pathogenic mutations.

(a) Triplet repeat expansions

Pt	Gene	Mode	Diagnosis	Repeats reported	Affected range	Reference
6	<i>ATXN2</i>	AD	SCA2	38	≥33	NM_002973.3
10	<i>ATXN2</i>	AD	SCA2	39	≥33	NM_002973.3
25	<i>ATXN3</i>	AD	SCA3	73	52-86	NM_004993
40	<i>ATXN3</i>	AD	SCA3	65	52-86	NM_004993
71	<i>ATNX7</i>	AD	SCA7	49	38-130	NM_000333
77	<i>ATNX7</i>	AD	SCA7	45	38-130	NM_000333
15	<i>ATXN8OS</i>	AD	SCA8	80	≥80	NG_016173
32	<i>ATXN8OS</i>	AD	SCA8	86	≥80	NG_016173
5	<i>CACNA1A</i>	AD	SCA6	22	≥20	NM_023035.2
42	<i>CACNA1A</i>	AD	SCA6	22	≥20	NM_023035.2
4	<i>FXN</i>	AR	FRDA	800	66-1700	NM_000144
51	<i>FXN</i>	AR	FRDA	1000	66-1700	NM_000144
22	<i>TBP</i>	AD	SCA17	49	≥49	NM_003194
39	<i>TBP</i>	AD	SCA17	47	≥47	NM_003194

(b) Pathogenic/likely pathogenic sequencing variants

Pt	Gene	Mode	Diagnosis	Coding change	Protein change	Reference	Previously reported
87	<i>ANO10</i>	AR	SCAR10	c.1A>T	p.(?)	NM_018075.3	Novel
30	<i>CACNA1A</i>	AD	Ataxia/ FHM1	c.1748G>A	p.(Arg583Gln)	NM_023035.2	Yes
58	<i>CACNA1A</i>	AD	SCA6	c.4415C>T	p.(Ser1472Leu)	NM_023035.2	Novel (Segregates with disease)
81	<i>DNMT1</i>	AD	ADCADN	c.1709C>T	p.(Ala570Val)	NM_001130823.1	Yes
63	<i>KCND3</i>	AD	SCA22	c.1034G>T	p.(Gly345Val)	NM_004980.4	Yes
80	<i>NPCI</i>	AR	NPC	c.3289G>A	p.(Asp1097Asn)	NM_002310.5	Yes
	<i>NPCI</i>	AR	NPC	c.3263A>G	p.(Tyr1088Cys)	NM_000271.4	Yes
66	<i>PRKCG</i>	AD	SCA14	c.448T>C	p.(Cys150Arg)	NM_002739.3	Novel
79	<i>SPG7</i>	AR	SPG7	c.1529C>T	p.(Ala510Val)	NM_003119.3	Yes
	<i>SPG7</i>	AR	SPG7	c.1745G>A	p.(Gly582Asp)	NM_003119.3	Novel (Segregates with disease and <i>in trans</i> with known pathogenic variant)

Pt: patient, *SCA*: Spinocerebellar ataxia, *FRDA*: Friedreich's ataxia, *FHM*: Familial hemiplegic migraine, *SPG*: Spastic paraplegia, *ADCADN*: autosomal dominant cerebellar ataxia with deafness and narcolepsy, *NPC*: Niemann-Pick disease type C, *AD*: autosomal dominant, *AR*: autosomal recessive, *aa*: amino acid. Table 1a details mutations of triplet repeat expansion origins; *italics*: yielded from larger NGS expansion panels. Table 1b details pathogenic or likely pathogenic sequencing variants from NGS & WGS testing; underline: result yielded from WGS testing.

633

MRI and behavioural account of the aging cerebellum

M. Bares, P. Filip, C. Gallea, S. Lehericy, O. Lungu (Brno, Czech Republic)

Objective: With the rapidly increasing average age of developed-world population and extended life expectancy, the effects of healthy aging on various brain networks are becoming of paramount importance.

Background: While the majority of current literature focuses on the supratentorial circuits, especially the prefrontal cortex, the cerebellum has largely avoided attention despite important implications.

Methods: We included 67 healthy subjects of various ages ranging from 25 to 72 volunteers (36 women, mean age 45.61; SD 14.63) to a fMRI study using a task heavily based on cerebellar functions – predictive motor timing. The subjects were supposed to hit a target moving with various speeds with a projectile released by button press. In addition to the behavioural assessment of the success rate, we performed complex fMRI analysis, utilizing an advanced method of cerebellar processing of BOLD signal and anatomical scans (voxel-based morphometry), allowing us to exclude the supratentorial structures to vastly improve the co-registration and avoid cerebellar deformation.

Results: The increasing age did not affect the success rate at all. However, this stable behavioural performance was associated with significant hyperactivation dominantly in the posterior lobes of the cerebellum. The profile of atrophy was more pronounced in the posterior cerebellum (bilateral crus I, left crus II, right lobule VI, and right lobule and vermis IX), the anterior cerebellum was affected only slightly (left lobule V). No age-related GM volume increase was found. Moreover, the extent of cerebellar grey matter volume decrease was far more significant than the general grey matter decrease in the supratentorial area and the very parts showing hyperactivation in BOLD fMRI were affected by the age-related atrophy far more than other cerebellar segments.

Conclusions: The cerebellum responds to the increasing age by hyperactivating relevant areas, thus compensating for the age-related atrophy. Interestingly, despite the vast decrease of grey matter volume, it is able to maintain stable performance even in high age.

References: Seidler RD, Bernard JA, Burutolu TB, Fling BW, Gordon MT, Gwin JT, et al. Motor control and aging: links to age-related brain structural, functional, and biochemical effects. *Neuroscience & Biobehavioral Reviews*. 2010;34(5):721-33. Filip P, Lungu OV, Bares M. Dystonia and the cerebellum: A new field of interest in movement disorders? *Clinical Neurophysiology*. 2013 124(7):1269-76. Filip P, Gallea C, Lehericy S, Bertasi E, Popa T, Mareček R, et al. Disruption in cerebellar and basal ganglia networks during a visuospatial task in cervical dystonia. *Movement Disorders*. 2017;32(5):757-68.

655

Transcriptional profiling of peripheral blood monocytes from child Friedreich's ataxia patient: New molecules and patterns of gene expression

H. Singh, V. Swarup, R. Singh, I. Singh, M. Faruq, S. Vivekanandhan, A. Srivastava (Delhi, India)

Objective: To explore peripheral biomarkers related to Friedreich's ataxia and identification of pathophysiological insights of complex phenotype

Background: Friedreich's ataxia (FRDA) causes nervous system damage and movement problems which starts in children leading to early death. Although reduction in frataxin level is responsible for FRDA, other deregulated bio-markers may also contribute in disease phenotype mediated by cellular pathways. Therefore, identification of such biomarkers can be helpful in order to understand disease etiology and development of future medications. In the present study genome-wide expression analysis was performed in FRDA child patients as compared to normal children.

Methods: Transcriptome expression profiling of FRDA and controls peripheral blood cells was performed on a cohort of 28 patients and 10 controls that was extracted from GSE11204. To calculate mRNA expression, the bioconductor R package "limma" was used. Significantly deregulated genes were filtered using unpaired Student-t test and bonferrani test. The gene list associated with FRDA was extracted from DisGeNET database (<http://www.disgenet.org>). The ontology analysis of significantly altered genes was done using String Database (string-db.org).

Results: A total of 144 genes were found to be significantly altered ($p < 1.0E-06$) in children manifest FRDA phenotype (Figure 1). Out of 144 genes, 76 genes were found to be downregulated and 68 genes were upregulated. It is also interesting to note that the identified genes were not reported earlier in FRDA provided at DisGeNET database. Genes associated with metabolic processes such as cellular metabolism of the

transition metal, lipid metabolism etc (Table 1) were found to deregulated leading to altered metabolic processes damage and affect tissues leading to neuro-and cardio-degeneration.

Conclusions: The results suggest gene expression pattern consistent with metabolic process damage leading to neuro- and cardio-degeneration complexities in FRDA. Although the development of effective therapeutics enhanced analysis is required, identified biomarkers could also provide insight into pathway based etiology and may have predictive value in future clinical trials.

TABLE 1. (655) Gene ontology analysis of differentially expressed genes (n=144) in peripheral blood cells in Friedreich's ataxia

BIOLOGICAL PROCESS (GO)			
<i>Pathway ID</i>	<i>Pathway description</i>	<i>Count in gene set</i>	<i>FDR</i>
GO:0043933	Macromolecular complex subunit organization	32	0.004
GO:0044267	Cellular protein metabolic process	43	0.004
GO:0019538	Protein metabolic process	44	0.039
GO:0043412	Macromolecule modification	35	0.039
GO:0008064	Regulation of actin polymerization or depolymerization	07	0.045
MOLECULAR FUNCTION (GO)			
GO:0044822	Poly(A) RNA binding	24	0.001
GO:0003723	RNA binding	27	0.002
GO:0004713	Protein tyrosine kinase activity	07	0.036
CELLULAR COMPONENT (GO)			
GO:0070062	Extracellular exosome	34	0.029
GO:0044421	Extracellular region part	40	0.048
GO:0030529	Ribonucleoprotein complex	13	0.049
GO:0044444	Cytoplasmic part	64	0.049

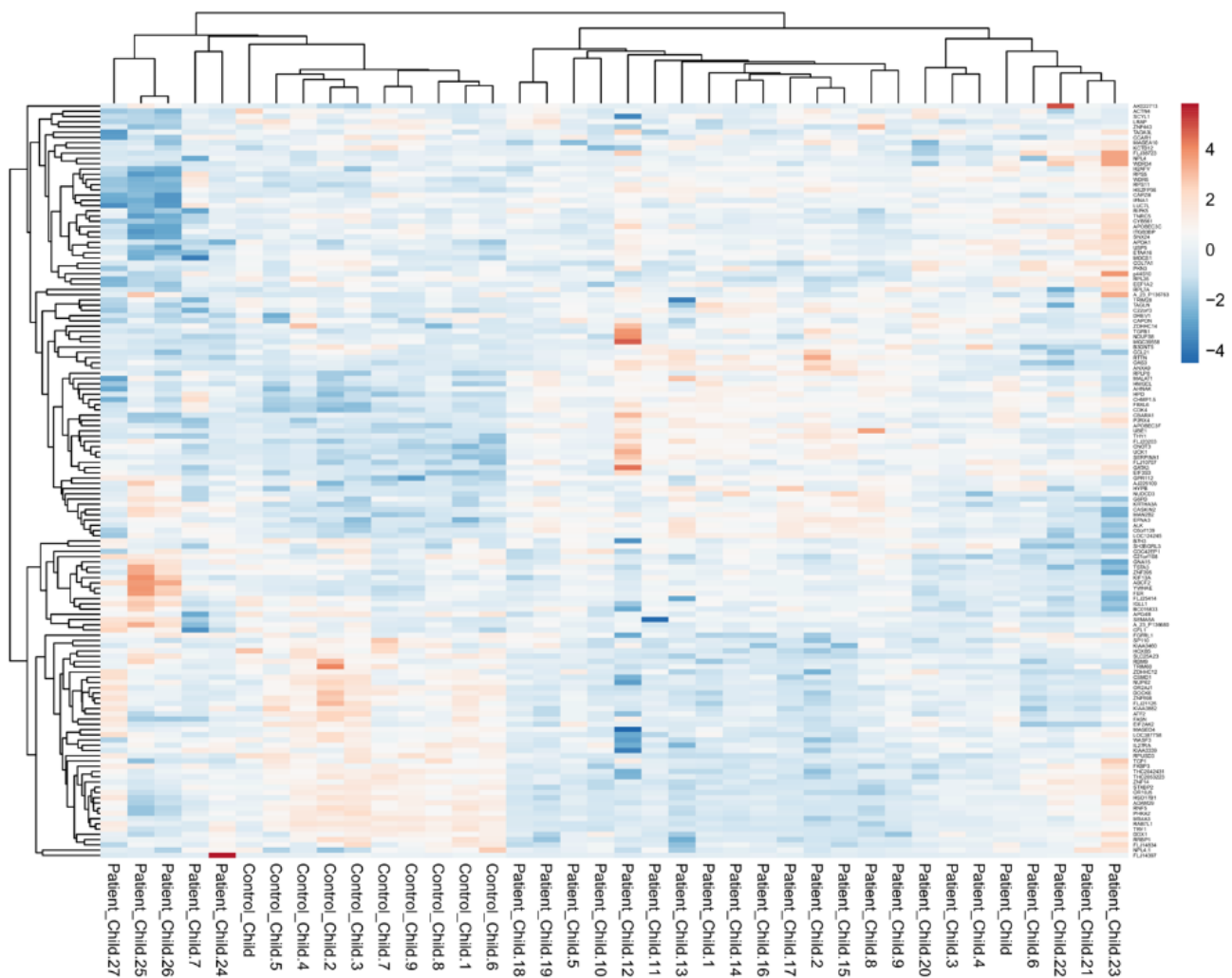


FIG. 1. (655) Heatmap of mRNA expression of significantly altered 144 genes in GSE11204 dataset Clustering the samples using -means revealed two groups, FRDA child patients (n=28) and normal children (n=10).

660

Comorbid Pediatric Early Onset Ataxia and Dystonia - Is the Cerebellum Involved?

D. Sival, M. Tijssen, D. Verbeek (Groningen, Netherlands)

Objective: In children with Early Onset Ataxia (EOA), we aimed to determine the prevalence of comorbid dystonia and to explore the pathogenesis by the shared genetic background.

Background: Recent publications in patients with cervical dystonia have indicated cerebellar Purkinje cell pathology. In pediatric EOA patients with developing cerebello-thalamo-basal ganglia motor networks, we hypothesized that the association between ataxia and dystonia could be particularly strong due to additional (mal)adaptive plasticity. In EOA children, however, the prevalence and etiology of comorbid dystonia is still unknown. We reasoned that exploration of co-expression between genes involved in EOA, AOA and dystonia disorders could provide pathophysiologic insight in shared biological pathways.

Methods: In a historic cohort of 36 well-phenotyped EOA children by 6 internationally recognized movement disorder specialists (ref 1), we retrospectively determined the prevalence of comorbid dystonia. As previously published, we determined gene co-expression by GeneNetwork* and PANTHER software (ref 2).

Results: In pediatric EOA, the prevalence of comorbid dystonic features was 67% (24/36), detected by 1-6 (mean 2) movement disorder experts. Network analysis of genes co-expressed with shared EOA and AOA genes revealed a 9 fold overrepresentation of genes involved in GABA receptor activity and subsequent network analysis of shared EOA, AOA and dystonia genes revealed an 11 fold overrepresentation of genes involved in Tricarboxylic acid (TCA), necessary for mitochondrial ATP production and GABA synthesis (the neurotransmitter of cerebellar Purkinje cells).

Conclusions: In pediatric EOA, the prevalence of comorbid dystonic features appears particularly high (EOA 67% vs AOA 14-54%), potentially due to maladaptive plasticity. Our genetic data suggest that hampered mitochondrial energy production and GABA synthesis may provide a shared disease mechanism for comorbid dystonia with EOA and AOA. These results in EOA children could support a direct (metabolic) and indirect (maladaptive plasticity) association between cerebellar Purkinje cell pathology and dystonia.

References: 1. Lawerman TL, Brandsma R, van Geffen JT, Lunsing RJ, Burger H, Tijssen MA, de Vries JJ, de Koning TJ and Sival DA. Reliability of phenotypic early-onset ataxia assessment. *DMCN* 2016;58(1):70-6. 2. Nibbeling E, Delnooz CS, de Koning TJ, Sinke RJ, Jinnah HA, Tijssen MAJ, Verbeek DS. Using the shared genetics of dystonia and ataxia to unravel their pathogenesis. *Neurosci & Biobehav Rev* 2017; 75: 22-39. *<http://129.125.135.180:8080/GeneNetwork/cytoscape.html>.

663

The etiologies of chronic progressive cerebellar ataxia in a Korean population

J. Youn, M. Kim, JH. AHN, JW. Cho, JS. Kim (Seoul, Republic of Korea)

Objective: The etiologies and frequency of cerebellar ataxias vary among countries. Our primary aim was to assess the frequency of each diagnostic group of cerebellar ataxia patients in a Korean population.

Background: The prevalence and frequency of cerebellar ataxia subtypes vary among countries. Although estimation of subtype frequency is necessary for planning a diagnostic strategy in a specific population, studies regarding epidemiology in all categories of cerebellar ataxias is surprisingly rare in Korea. Our primary aim was to assess the frequency of each diagnostic group (familial and sporadic) in a movement disorders out-patient clinic at a tertiary referral center.

Methods: We reviewed medical records of patients those who were in the process of follow-up during the period from November 1994 to February 2016. We divided patients with cerebellar ataxias into familial and non-familial groups and analyzed the frequency of each etiology. Finally, we categorized patients into genetic, sporadic, secondary and suspected genetic, but undetermined ataxia.

Results: A total of 820 patients were included in the study, among whom 136(16.6%) familial patients and 684(83.4%) non-familial cases were identified. Genetic diagnosis confirmed 98/136(72%) familial and 72/684(11%) non-familial patients. The overall etiologies of progressive ataxias consisted of 170(20.7%) genetic, 516(62.9%) sporadic, 43(5.2%) secondary and 91(11.1%) undetermined ataxia. The most common cause of ataxia was multiple system atrophy(57.3%). In the genetic group, the most common etiology was spinocerebellar ataxia(152/170, 89.4%) and the most common subtype was spinocerebellar ataxia 3. 38 of 136 familial and 53 of 684 sporadic cases(91/820, 11.1%) were undetermined ataxia.

Conclusions: This is the largest epidemiological study to analyze the frequencies of various cerebellar ataxias in a Korean population based on a large database of a tertiary hospital movement disorders clinic in South Korea. These data would be helpful for clinicians in constructing diagnostic strategies and counseling for patients with cerebellar ataxias.

References: 1. Gebus O, Montaut S, Monga B, Wirth T, Cheraud C, Alves Do Rego C, et al. Deciphering the causes of sporadic late-onset cerebellar ataxias: a prospective study with implications for diagnostic work. *J Neurol* 2017;264:1118-1126. 2. Hadjivassiliou M, Martindale J, Shanmugarajah P, Grünewald RA, Sarrigiannis PG, Beauchamp N, et al. Causes of progressive cerebellar ataxia: prospective evaluation of 1500 patients. *J Neurol Neurosurg Psychiatry* 2017;88:301-309.

691

DBS neuromodulation reduces severe dystonic pain in children and young people

S. Perides, J.P. Lin, G. Lee, H. Gimeno, R. Selway, K. Ashkan, M. Kaminska (London, United Kingdom)

Objective: This review analyses the prevalence of painful dystonia in a cohort of children undergoing neuromodulation. The aim was to better understand the dystonic pain experience and evaluate improvements one year following initiation of deep brain stimulation (DBS) therapy.

Background: Dystonic pain is reported as prevalent in genetic, acquired and idiopathic dystonic conditions. However, it is yet to be systematically evaluated. There is an overall paucity of literature evaluating the effect of DBS on dystonic pain using validated, reliable methods. The methods that have been used in the literature are varied and at times inappropriate for the population being assessed.

Methods: Dystonic pain was assessed in a cohort of children (n=144) undergoing DBS. Assessment was multi-modal, six different pain assessment methods were used: intensity (proxy- Paediatric Pain Profile- PPP and self-report - Numerical Rating Scale - NRS); parental perception (CPCHILD questionnaire); pain frequency, pain severity and analgesia use. SPSS version 21 was used to analyse both the whole cohort, and separately, by etiological sub-classification; inherited DYT-positive dystonias (n=8), inherited heredodegenerative dystonias (n=9), acquired dystonias (n=37) including Cerebral Palsy (n= 21) and idiopathic dystonias (n= 8).

Results: We found that 44.5% (63/144) of this DBS cohort reported dystonic pain. Pain improved after DBS surgery in each group. Clinically significant improvements $P < 0.001$ were noted in the whole cohort, using NRS (n=27), PPP (n=17/63) and the CPCHILD (n=48/63) assessments. Subjective reductions in frequency and severity were also reported. Very severe pain fell in 9/28 (30%) cases. Constant pain fell from 27/63 to 11/63 cases, a 40.7% reduction, and 18/63 (28.6%) became pain-free. We found a 40% reduction in children receiving daily medications and an increase of 46.1% not requiring analgesia. Whole cohort findings were comparable to results in the etiological sub-classifications, except the heredodegenerative group, where subjective improvements were noted only.

Conclusions: This is the first evaluation focusing on the impact of DBS surgery on dystonic pain in children. The multi-assessment approach in pain research reduces the risk of bias in an otherwise complex population, both to assess and to treat. Longitudinal data collection and the consideration of a multi-center research project would improve validity and reliability further. A reduction in dystonic pain should remain a goal for DBS surgery, particularly given the relationship between pain and poor quality of life, social isolation, self-perception and overall poor health status.

696

The clinical value of SPECT in identifying dystonic muscles of patients with cervical dystonia

L. Jin, L. Feng, I. Djibo, S. Chen, F. Teng, B. Li, H. Ma (Shanghai, China)

Objective: The aim of this study is to compare the efficacy of selecting target muscles for botulinum toxin injection by abnormal movement pattern and by SPECT combined with abnormal movement pattern.

Background: Cervical dystonia (CD) is caused by involuntary and excessive contraction of cervical muscles which leads to abnormal movement and posture. Botulinum toxin injection has become the first line treatment for CD, the critical step which decides the treatment efficacy is to accurately identify dystonic muscles. At present, dystonic muscles are selected by patients' abnormal movement pattern. However, most patients have a combination of various patterns, and the same pattern may be caused by contraction of

different muscles. SPECT imaging uses ^{99m}Tc -MIBI as a contrast agent, which can reveal abnormal contraction of the muscle. However, SPECT has not been reported to guide the treatment of CD.

Methods: Forty patients with idiopathic CD were enrolled. These patients had not received botulinum toxin injection for last 3 months. The first group: dystonic muscles were screened based on cervical dystonia pattern (n1=20). The second group: we analyzed cervical muscles with increased uptake of ^{99m}Tc -MIBI in cervical SPECT, the SPECT results combined with cervical dystonia pattern were used to determine dystonic muscles (n2=20). SPSS20.0 software was used to compare the results between the two groups after botulinum toxin injection. The TWSTRS score reduction rate and Tsui score reduction rate at the second week, the first month, the third month and the sixth month were compared.

Results: The number of botulinum toxin reinjection in 6 months was significantly higher in the first group than in the second group (13: 4). The interval between the first and the second injection of the second group was significantly longer than the first group ($p < 0.05$). There was no significant difference between TWSTRS score reduction rate and Tsui score reduction rate in the second week and the first month after treatment, $p > 0.05$. At the third month, TWSTRS score reduction rate and Tsui score reduction rate of the second group was significantly higher than the first group, $p < 0.05$. At the 6th month, although the number of follow-up in was decreased in both groups because of repeat injection (n1 = 5: n2 = 14), the TWSTRS reduction rate and the Tsui reduction rate in the second group were significantly higher than the first group, $P < 0.05$.

Conclusions: SPECT imaging can more accurately select the dystonic muscles and thus greatly improve the efficiency and remission rate of botulinum toxin treatment.

713

Characterizing Bulbar Dysfunction in X-Linked Dystonia-Parkinsonism (XDP): A Pilot Study

J. de Guzman, B. Perry, C. Go, J. Green, N. Sharma (Boston, MA, USA)

Objective: This study aims to characterize bulbar motor impairments in patients with X-linked XDP and to identify clinical correlates for prediction of aspiration.

Background: X-linked dystonia-parkinsonism (XDP) is an inherited neurodegenerative disease endemic in Panay Island, Philippines that predominantly affects males. Initial stages are characterized by focal dystonia, which then generalizes. Seven to ten years after onset, parkinsonian symptoms emerge alongside symptoms of dystonia. Around 15 years post onset, parkinsonism predominates. In approximately 28% of cases, dystonic symptoms initially manifest in the oromandibular and cervical area causing significant bulbar impairment. Over the course of the disease, most persons with XDP develop bulbar dysfunction resulting in speech and swallowing impairments. The characteristics and severity of bulbar impairment in XDP is not well understood.

Methods: Twenty-five XDP patients underwent assessments of respiratory function, speech, lip and tongue strength, diadochokinetic rates, articulation during connected speech, and swallowing function. Patient-reported measures of speech and swallowing impairment included the Communicative Participation Item Bank and the Eating Assessment Tool – 10.

Results: All participants exhibited bulbar impairment. Sixteen subjects had evidence of aspiration. The average lip and tongue strength were both reduced with respective mean values of 9.48 ± 4.03 kPa (NV= 35 kPa) and 19 ± 11.29 kPa (NV = 63 kPa). The average pause percentage for speech sample was 34.18%. The mean scores for the following questionnaires were all abnormal: EAT-10 score of 19.28 ± 10.15 (score ≥ 3 is abnormal), FOIS score of 4.88 ± 0.97 (score < 7 is abnormal), and CPIB score of 7.32 ± 7.72 (maximum score of 30 and higher scores are more favorable). Logistic regression analysis showed that the duration of illness ($p = 0.463$), site of onset ($p = 0.553$), and phase of illness (dystonic $p = 0.977$, parkinsonian $p = 0.829$, dystonia-parkinsonian $p = 0.999$) did not contribute significantly to the prediction model of aspiration. The resulting model was not statistically significant, $X^2(4) = 4.71$, $p = 0.316$.

Conclusions: Bulbar dysfunction in XDP results in speech and swallowing impairments characterized by decreased phonation time, decreased lip and tongue strength, decreased diadochokinetic rates, evidence of aspiration, and patient-reported speech and swallowing deficits.

References: Kreisler, A, Verpraet, AC, Veit, S, Pennel-Ployart, O, Behal, H, Duhamel, A, Destee, A. Clinical characteristics of voice, speech, and swallowing disorders in oromandibular dystonia. *Journal of Speech, Language, and Hearing Research*, Vol. 59, October 2016, pp. 940-949. LaPointe, LL, Murdoch, BE. *Movement disorders in neurologic disease: effects on communication and swallowing*. Plural Publishing, Inc., 2014, pp 123-159.

727

The association of primary dystonia with tics - chance or new syndrome?

C. Del Gamba, A. Latorre, U. Bonuccelli, R. Ceravolo, K. Bhatia (London, United Kingdom)

Objective: This study aimed to evaluate the association between dystonia and tics as a primary clinical entity.

Background: Primary cranio-cervical dystonia (PCCD) is an idiopathic condition, which typically occurs in late adulthood and in women more than men. Primary tics (PT) generally start during childhood/adolescence, and a later age of onset or other associated movement disorders are “red flags” to suspect secondary causes. Primary dystonia and PT are distinct entities, but nevertheless, a clinical syndrome with these two features has been described. We report a series of patients presenting both PCCD and PT.

Methods: 248 patients with PCCD attending our Botulinum toxin clinic at the National Hospital of Neurology and Neurosurgery - Queen Square, were examined for PT over a period of 4 months. Secondary tic causes were excluded by clinical interview and appropriate investigations (brain MRI, extensive blood tests, acanthocytes, genetics).

Results: We have found 16 patients (6,5%) with PCCD, also presenting PT. Thirteen patients are males while three are females. In eleven dystonia started below the age of 40. Eleven had a focal involvement, while 5 a segmental. Dystonia was found to affect neck (13), vocal cords (4), jaw (1) eyes (1) and arms (4). Six patients displayed a sensory trick. The association with tics can be stratified as follows: 3/16 patients presented tics before 21 years old, fitting Tourette’s syndrome (GTS) criteria (also presenting >1 motor tic and ≥1 vocal tic); for the other patients, we were not able to recall the onset, which was therefore more likely to fall into the Adult Primary Tics (APT) category. Most of our patients also showed psychiatric issues (hyperactivity, anxiety, depression or obsessive-compulsive features), which were generally mild.

Conclusions: We described a primary clinical entity of PCCD associated with PT. This syndrome differs from pure cranio-cervical dystonia by a higher prevalence in males and a lower age of onset. It presents a tic disorder, which, in a minority of cases resembles GTS, whereas more frequently falls into APT category.

References: Damasio J, Edwards MJ, Alonso-Canovas A, Schwingenschuh P, Kagi G and Bhatia KP. The Clinical Syndrome of Primary Tic Disorder Associated with Dystonia: A Large Clinical Series and a Review of the Literature, *Movement Disorders*, Vol. 26, No. 4, 2011. Stone LA and Jankovic J. The coexistence of tics and dystonia. *Arch Neurol* 1991;48:862–865.

734

Zolpidem effect in task specific dystonia – clinical and neurophysiological study

K. Vogelnik, M. Grmek, R. Perellon Alfonso, P. Tomše, M. Trošt, M. Kojović (Ljubljana, Slovenia)

Objective: We conducted a double blind, placebo-controlled crossover study to examine clinical and neurophysiological effect of zolpidem in patients with task specific dystonia.

Background: Task specific dystonia is disabling movement disorder that includes writer’s cramp and musician dystonia. It causes impaired hand use and may lead to the termination of professional career. Currently, there is no effective treatment. Zolpidem, a short-acting hypnotic drug that binds to GABA –A receptor benzodiazepine site, has been reported to transiently improve various movement disorders, including a proportion of patients with primary focal and generalized dystonia. The mechanisms underlying its therapeutic effects has not been investigated.

Methods: Six patients with writer’s cramp and one guitarist with musician dystonia underwent transcranial magnetic stimulation (TMS) and 18F-FDG-PET brain imaging after single 5 mg dose of

zolpidem and placebo, in four separate sessions. We measured resting motor threshold (RMT), active motor threshold (AMT), resting and active input/output (IO) curve, short interval intracortical inhibition (SICI) curve, long interval intracortical inhibition (LICI), intracortical facilitation (ICF) and cortical silent period (CSP). Clinical improvement was rated using writer's cramp rating scale (WCRS). Clinical and TMS measures were compared using paired sample t-test or repeated measures ANOVA; correlations were tested using Spearman analysis. Statistical parametric mapping was used to identify zolpidem effect on global brain metabolism.

Results: There was significant improvement on WCRS on zolpidem. Zolpidem reduced the steepness of active IO curve, while there was no difference in AMT, RMT, resting IO curve, SICI, LICI, CSP and ICF on the group level. Significant positive correlation was found between clinical improvement and enhancement of LICI on zolpidem. 18F-FDG-PET revealed that zolpidem treatment was associated with hypometabolism in primary sensori-motor cortex, cerebellum and medial temporal lobes and hypermetabolism in caput nuclei caudate, parietal cortex and frontal regions.

Conclusions: Clinical effect of zolpidem in task specific dystonia was associated with evident changes in TMS measures of corticospinal excitability and intracortical inhibition and changes in brain metabolism on brain 18F-FDG-PET. Zolpidem may be an effective treatment in a proportion of patients with task specific dystonia.

References: 1. Lin, P. T. & Hallett, M. The pathophysiology of focal hand dystonia. *J. Hand Ther. Off. J. Am. Soc. Hand Ther.* 22, 109–114 (2009). 2. Konczak, J. & Abbruzzese, G. Focal dystonia in musicians: linking motor symptoms to somatosensory dysfunction. *Front. Hum. Neurosci.* 7, (2013). 3. Depoortere, H. et al. Zolpidem, a novel nonbenzodiazepine hypnotic. I. Neuropharmacological and behavioral effects. *J. Pharmacol. Exp. Ther.* 237, 649–658 (1986). 4. Abe, K. Zolpidem therapy for movement disorders. *Recent Patents CNS Drug Discov.* 3, 55–60 (2008). 5. Miyazaki, Y. et al. Efficacy of Zolpidem for Dystonia: A Study Among Different Subtypes. *Front. Neurol.* 3, (2012). 6. Martinez-Ramirez, D., Paz-Gomez, V. & Rodriguez, R. L. Response to zolpidem in oromandibular dystonia: a case report. *Parkinsonism Relat. Disord.* 21, 154–155 (2015). 7. Sunwoo, M. et al. A Case with Improvement of Blepharospasm by Zolpidem. *J. Mov. Disord.* 4, 53–54 (2011).

746

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

J. Krauss, C. Nicholson, M. Barbe, V. Visser-Vanderwalle, A. Kuehn, M. Poetter-Nerger, R. Jain, H. Scholtes, N. Van Dyck, A. Albanese (Hannover, Germany)

Objective: The objective of this device registry entails collecting clinical outcomes, economic value and technical performance of a Deep Brain Stimulation (DBS) system capable of multiple independent current control (MICC) for use in the treatment of dystonia.

Background: 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 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.

Conclusions: Large patient data registries may facilitate insights regarding real-world, clinical use of DBS. This registry represents the first comprehensive, large scale collection of outcomes associated with

dystonia patients implanted with a DBS system capable of multiple independent current control (MICC) and will include assessment of economic value and device technical performance.

761

Comorbidity and retirement in primary focal cervical dystonia

R. Ortiz, F. Scheperjans, T. Mertsalmi, E. Pekkonen (Helsinki, Finland)

Objective: The objective of this study was to investigate comorbidities in cervical dystonia (CD) and effect of CD to retirement rate in Finland.

Background: Cervical dystonia is most common form of dystonia, the prevalence being 394 persons per million in Finland. The onset of CD is usually before 60 years of age, and even though CD does not reduce life expectancy, it may cause severe functional and psychosocial impairment in everyday life. Besides the motoric symptoms, recently non-motoric symptoms, especially psychiatric comorbidities, have been reported to occur in CD affecting substantially quality of life.

Methods: We studied the comorbidity in primary focal CD in Finland based on ICD-10 codes obtained from care registry and patient records of 937 confirmed adult primary focal CD patients between years 2007-2016. The retirement months and diagnosis of retirement were calculated from pension registry information. The results were compared to 3746 age and gender matched controls.

Results: Most prominent comorbidities with primary focal CD were depression (14%), anxiety (7%), and dorsalgia (11%)[table]. There was significantly more of retirement months before age of 65 years in CD group than in control ($32,8 \pm 67,2$ vs. $13,3 \pm 47,1$ months, $p < 10^{-5}$) [figure]. Also, the retirement age was significantly younger in CD patients compared to control group controls ($56,1 \pm 8,3$ vs. $59,8 \pm 6,7$ years, $p < 10^{-5}$). Of the dystonia patients, who were retired because of sickness, the most common retirement diagnoses were dystonia (51%), depression (14%) and anxiety (8%). Patients with anxiety and depression had more of retirement months than other dystonia patients.

Conclusions: Cervical dystonia reduces considerably working ability and leads to earlier retirement. Anxiety and depression are most notable comorbidities, and co-occurrence of them further reduces more working ability. Spinal degenerative diseases were also common with CD, but they did not affect retirement rate significantly compared with control group. Our results suggest that more health care resources should be administered in treatment of CD to longer maintain working ability of CD patients. Further, psychiatric comorbidities should be taken into consideration in CD treatment.

TABLE 1 (761) Comorbidities with cervical dystonia patients

Diagnosis	Patient n= 937	Control: Patient	p-value
Cervical disc disorders	23 (2,5%)	1:5,7	<10 ⁻⁵
Dorsalgia	100 (10,7%)	1:1,9	<10 ⁻⁵
Oth and unsp soft tissue disorders	53 (5,7%)	1:2,3	<10 ⁻⁵
Essential tremor	44 (4,9%)	1:88	<10 ⁻⁵
Tension neck	19 (2,1%)	1:4,2	<10 ⁻⁵
Major depressive disorder, single episode	91 (9,7%)	1:2,9	<10 ⁻⁵
Major depressive disorder, recurrent	58 (6,2%)	1:3,5	<10 ⁻⁵
Depressive disorders	120 (13,5%)	1:2,9	
Phobic anxiety disorders	9 (1%)	1:9	<10 ⁻⁵
Other anxiety disorders	56 (6%)	1:3,8	<10 ⁻⁵
Anxiety disorders	61 (6,8%)	1:4	
Somatoform disorders	16 (1,7%)	1:5,3	<10 ⁻⁵
Abdominal and pelvic pain	74 (7,9%)	1:2	<10 ⁻⁵

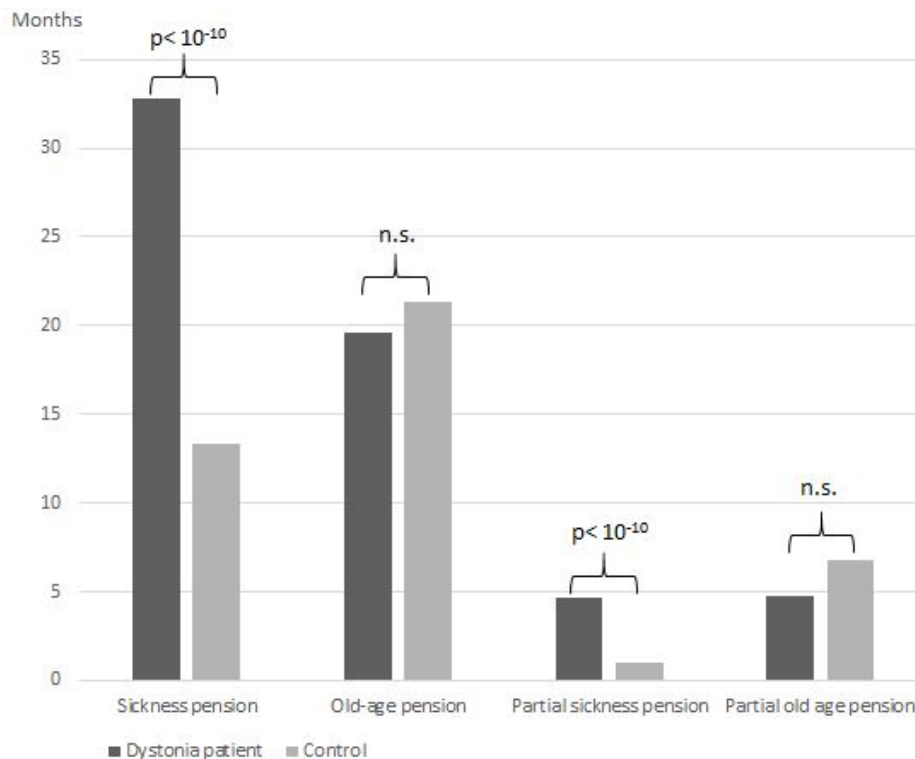


FIG. 1 (761)

Frequency and Phenotypic Spectrum of KMT2B Mutations in Childhood-Onset Dystonia: Results from a Single-Centre Cohort Study

M. Carecchio, G. Zorzi, F. Invernizzi, C. Panteghini, L. Romito, F. Zibordi, V. Leuzzi, S. Galosi, P. Morana, B. Morana, C. Piano, A. Bentivoglio, C. Reale, F. Girotti, M. Topf, A. Joseph, M. Kurian, S. Lubbe, B. Garavaglia, N. Mencacci, N. Nardocci (Milan, Italy)

Objective: To assess the frequency of KMT2B mutations in a cohort of patients with childhood-onset dystonia and characterize the related molecular and phenotypic spectrum.

Background: Heterozygous mutations in KMT2B, encoding a histone lysine methyltransferase, were recently reported as a cause of childhood-onset generalized dystonia variably associated with additional neurological and systemic features.

Methods: 55 patients (23F,22M) with genetically undefined childhood-onset dystonia were screened by means of Whole Exome Sequencing or customized gene panels including known dystonia-associated genes. KMT2B variants were confirmed by Sanger sequencing and further characterized by segregation analysis, bioinformatics tools and in silico homology modelling in some cases.

Results: 12/55 (21.8%) patients were found to carry KMT2B variants (8 missense, 3 frameshift, 1 in-frame deletion) [table 1] [figure 1], of which 5 were confirmed to be de novo, 4 were inherited from one unaffected parent and 3 were likely de novo segregating with disease status in available family members [figure 2]. All but one variant had not been reported previously. Mean age at onset was 6.5 years (range 3.5-14); mean age at last examination was 28 years (range 17-45) and mean disease duration was 22.5 years (range 2-40). 10/12 (83%) patients had lower limb presentation, 11/12 (92%) progressed to generalization with laryngeal dystonia observed in 10/12 (83%). Mild intellectual disability, short stature, minor facial dysmorphisms were recurrently observed [table 2]. Brain MRI was normal in all cases, including DWI/SWI sequences. 7/12 patients underwent bilateral pallidal DBS with excellent, long-lasting motor improvement (mean post-operative follow-up: 12 years). Additional genetic findings included a novel, de novo GNAO1 missense mutation (p.Cys215Tyr) identified in a 42-year-old male with a 30-year history of myoclonus dystonia and biallelic ATM mutations (p.Cys907*/p.Glu2052Lys) in a 40-year-old female with isolated generalized dystonia presenting at age 13.

Conclusions: Mutations in KMT2B are a relevant cause of dystonia in the paediatric population, with autosomal dominant inheritance and possible incomplete penetrance in some cases. Red flags include onset in the lower limbs, caudo-cranial spreading, oro-mandibular and laryngeal involvement, short stature and mild intellectual disability. Brain MRI in our cases did not confirm previously reported basal ganglia alterations. Childhood-onset dystonia can rarely be an atypical presentation of other genetic diseases.

References: Meyer E, Carss KJ, Rankin J, et al. Mutations in the histone methyltransferase gene KMT2B cause complex early-onset dystonia. *Nat Genet* 2017;49:223-237. Zech M, Boesch S, Maier EM, et al. Haploinsufficiency of KMT2B, encoding the lysine-specific histone methyltransferase 2b, results in early-onset generalized dystonia. *Am J Hum Genet* 2016;99:1377-1387.

TABLE 1 (762) KMT2B variants identified in the study; * based on NM_014727

Pt ID	KMT2B variant* (cDNA; protein)	Exon	Novel mut.	De novo mut.	ExAc	GnomAD	PolyPhen	SIFT	Mutation Taster	CADD phred	Protein domain or predicted protein consequences
DYT317	c.5114G>A; p.Arg1705Gln	24	N	Y	Absent	Absent	Probably damaging	Damaging	Disease Causing	34	--
DYT2102	c.2240A>G; p.Gln747Arg	3	Y	N	Absent	Absent	Benign	Tolerated	Polymorphism	14,42	--
DYT75	c.5330G>C; p.Arg1777Pro	26	Y	?	Absent	Absent	Probably damaging	Damaging	Disease Causing	25,5	FYR N-terminal domain
DYT304	c.5258T>C; p.Leu1753Pro	25	Y	Y	Absent	Absent	Probably damaging	Damaging	Disease Causing	29,3	FYR N-terminal domain
DYT958	c.4844C>T; p.Ser1615Leu	22	Y	?	Absent	Absent	Probably damaging	Damaging	Disease Causing	33	Zinc Finger (PHD-like) domain
DYT2443	c.3431A>T; p.Asp1144Val	10	Y	N	Absent	Absent	Probably damaging	Tolerated	Disease Causing	26,3	--
DYT1070	c.7292T>C; p.Leu2431Ser	31	Y	N	Absent	Absent	Probably damaging	Damaging	Disease Causing	27,6	FYR C-terminal domain
LDM397	c.3008G>A; p.Arg1003Gln	7	Y	N	Absent	Absent	Probably damaging	Damaging	Disease Causing	32	Zinc Finger (CXXC-type) domain
DYT1950	c.6210_6213delTGAG; p.Ser2070Argfs*20	28	Y	Y	Absent	Absent			Disease Causing	NA	Premature stop codon
DYT1365	c.1656dupC; p.Lys553Glnfs*46	3	Y	?	Absent	Absent			Disease Causing	NA	Premature stop codon
DYT45	c.6413dupC; p.Ala2139Glyfs*6	28	Y	Y	Absent	Absent			Disease Causing	NA	Premature stop codon
DYT123	c.5405_5429del; p.Gln1801_Ala1808del	26	Y	Y	Absent	Absent			Disease Causing	NA	In-frame deletion

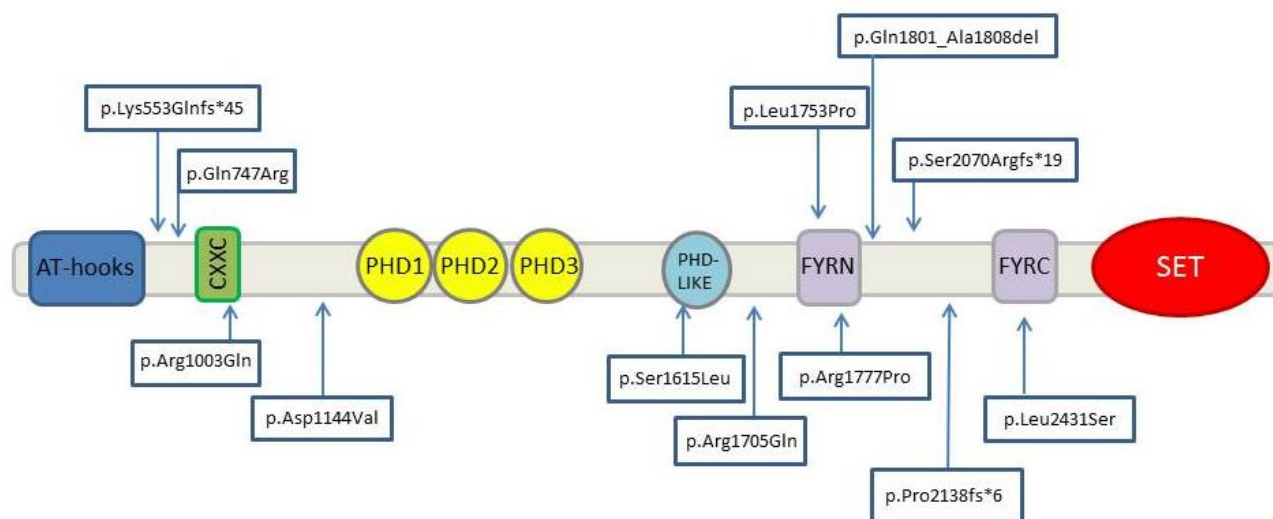


FIG. 1 (762) Position of KMT2B variants individuated in the study along the protein structure.

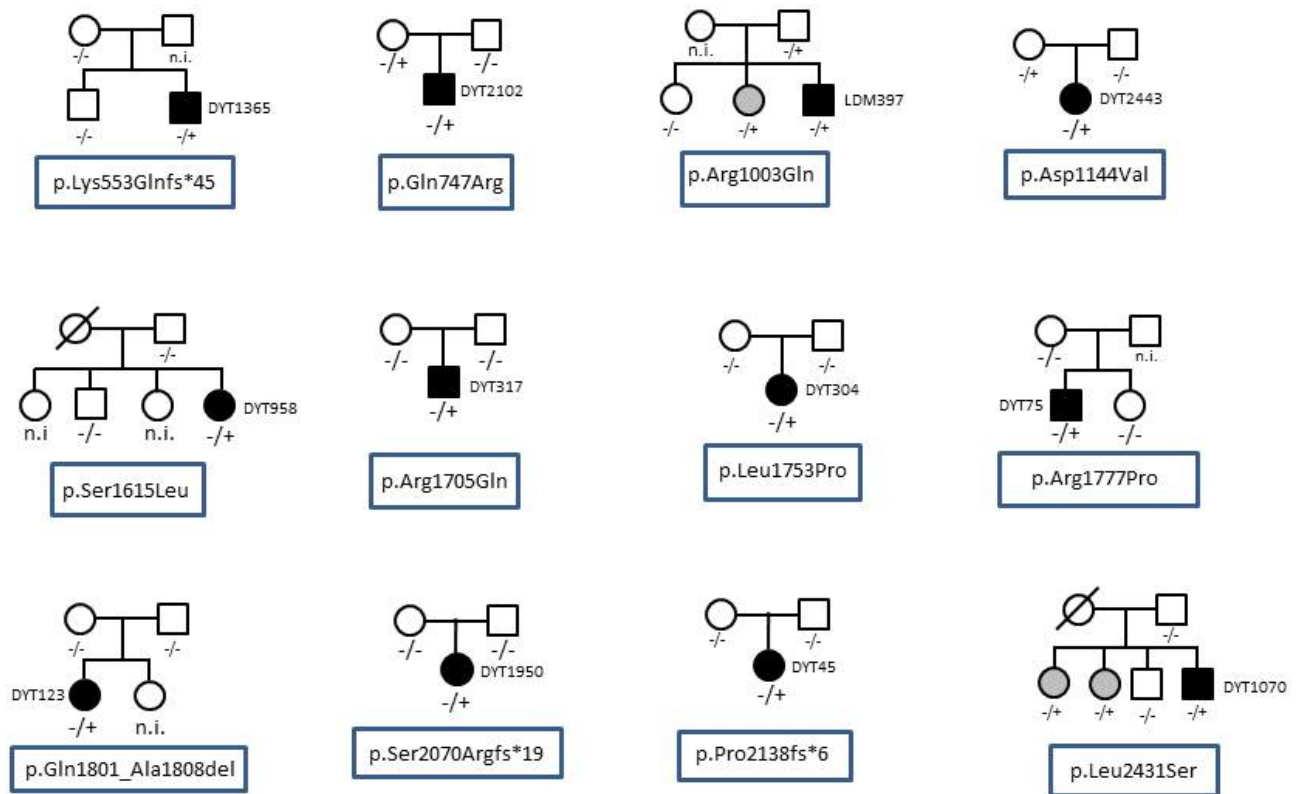


FIG. 2 (762) Family trees of patients carrying KMT2B variants; black symbols indicate patients affected by dystonia; grey symbols indicate subjects with other isolated clinical features (short stature and/or intellectual disability) at the time of examination, n.i.: not investigated.

TABLE 2. (762) clinical features of KMT23 variant carriers. AAO: Age at onset; LL: lower limbs; OM: oro-mandibular dystonia; LAR: laryngeal dystonia; CRAIN; cranial dystonia; NA: not available; ID: intellectual disability; TBZ: tetrabenazine; LD: Levodopa; * following post-surgical lenticular haemorrhage

Pt ID	DYT1070	DYT1365	DYT45	DYT317	DYT2102	DYT1950	DYT75	DYT304	DYT2443	DYT958	LDM397	DYT123
SEX	F	M	F	M	M	F	M	F	F	F	M	F
KMT23 VARIANT* (CDNA, PROTEIN)	c.7292T>C; p.Leu2431Ser	c.1656dupC; p.Lys553Glnfs*46	c.6413dupC; p.Ala2159Glyfs*6	c.5114G>A; p.Arg1705Gln	c.2240A>G; p.Gln747Arg	c.6210_6213delTGAG; p.Ser2070AArgfs*20	c.5330G>C; p.Arg1777Pro	c.5258T>C; p.Leu1753Pro	c.3431A>T; p.Asp1144Val	c.4844C>T; p.Ser1615Leu	c.3008G>A; p.Arg1003Gln	c.5405_5429del; p.Gln1801_Ala1808del
DELAYED MILESTONES	N	N	N	N	N	N	N	N	N	Y	N	N
DELAYED LANGUAGE	N	N	N	Y	N	N	N	N	N	Y	N	N
AAO (DYSTONIA)	10	4	5	6	9.5	6	3.5	4	14	7	7	4
AGE LAST EXAMINATION	45	44	35	22	24	18	25	21	16	44	17	30
DISEASE DURATION	35	40	30	16	13.5	12	21.5	17	2	37	10	26
SITE OF ONSET	LL	LL/larynx	LL	LL	NECK	LL	LL	LL	NECK	LL	LL	LL
CURRENT DYSTONIA DISTRIBUTION	GEN; +++ LAR; +++ OM	GEN; +++ OM, LAR, CRAN, AXIAL	UL; +++ LAR; ++ OM	OM; TRUNK	Generalized ++ trunk and OMD	Generalized, +++ LAR	GEN; +++ OMD	GEN; +++ OM; +++ LAR	Cervical dystonia	GEN; +++ LAR	GEN; +++LAR	GEN; +++TRUNK/CERVICAL
ID/IQ	Mild/NA	Mild/NA	N/IQ 91	Borderline/IQ 75	N/NA	Mild/IQ 69	N/IQ 96	N/NA	N/NA	Borderline/IQ 75	Mild/IQ 57	Borderline/IQ 77
SHORT STATURE	N	N	Y	Y	N	Y	Y	Y	N	Y	Y	N
ADDITIONAL NEUROL SIGNS	N	Mild bilateral ptosis, absent reflexes LL	Brisk reflexes LL	Right hemiparesis*	N	Brisk reflexes LL	Brisk reflexes LL	Microcephaly	N	Brisk reflexes LL	Mild bilateral ptosis, brisk reflexes LL Microcephaly	Subcortical myoclonus
FACIAL DYSMORPHISM	Y	Y	N	Y	N	N	N	Y	N	Y	Y	Y
BRAIN MRI	Normal	Normal	Normal	Hypoplasia cerebellar vermis	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
TRIAL OF MEDICATION	Tryhexyphenidyl (up to 12 mg/day), clonazepam 1 mg, pimoside 8 mg	Clonazepam 1.5 mg, trihexyphenidyl 18 mg, quetiapine 37.5 mg	Tryhexyphenidyl 32 mg, baclofen 75 mg, pregabalin 75 mg	Tryhexyphenidyl 18 mg, tetrabenazine 75 mg, Diazepam 10 mg, baclofen 75 mg, clonazepam 2 mg	Tryhexyphenidyl (up to 42 mg/d), baclofen 50 mg	Tryhexyphenidyl, baclofen botulinum toxin (neck)	TBZ 50 mg, diazepam 30 mg	LD, Tryhexyphenidyl 27 mg	LD, Botulinum toxin (neck)	Tryhexyphenidyl 24 mg, baclofen 50 mg, amantadine 450 mg	Baclofen 50 mg, trihexyphenidyl 130 mg	Tryhexyphenidyl up to 45 mg/day, clonazepam, botulinum toxin (neck, lower limbs)
DBS (age at surgery)	N	N	N	Y (10)	Y (16)	Y (8)	Y (10)	Y (11)	N	Y (38)	N	Y (14)

769

A machine learning approach to determine the important patient characteristics for tremor prevalence and tremor irregularity in dystonia

S. Balta Beylergil, L. Scorr, A. Cotton, H. Jinnah, A. Shaikh (Cleveland, OH, USA)

Objective: To evaluate the importance of dystonia features that can predict concurrent tremor prevalence and tremor irregularity. (2) To cluster dystonia cases based on important data-driven features using a large, multi-institutional cohort of 2362 patients, and adopting state of the art feature selection and clustering methods of machine learning.

Background: Dystonia is often accompanied by regular or irregular tremor. The dystonia features that increase the likelihood of concurrent tremor are unclear. Dystonia traits associated with irregular tremor are also not well defined.

Methods: We used a permutation-based feature selection algorithm to evaluate various dystonia attributes and select the relevant ones to be used in predicting tremor prevalence and irregularity. We performed clustering analyses to group dystonia patients into clusters with similar characteristics using an agglomerative hierarchical clustering algorithm.

Results: The first feature selection analysis indicated that body part affected by dystonia provides the most useful information for predicting tremor prevalence. Duration of dystonia, total Global Dystonia Rating Scale score, and age at dystonia onset also play a significant role in determining whether dystonia and tremor coexist. With these parameters, a random forest classifier (RFC) was able to classify a test data set with 69% accuracy. The clustering analysis yielded 4 distinct clusters with 16%, 31%, 62% and 67% tremor prevalence

rates. The second feature selection analysis showed that tremor irregularity is sensitive to the extent to which dystonia and tremor locations overlap. Investigator site is also an important feature that discriminates between regular and irregular tremor. RFC was able to predict irregularity with 79% test accuracy, and clustering analysis formed 4 distinct clusters with 28%, 76%, 79%, and 84% irregular tremor rates. Handedness, gender, and race were found unimportant for predicting tremor prevalence and irregularity in dystonia.

Conclusions: We identified the most relevant dystonia traits for predicting concurrent tremor prevalence and irregularity using modern machine learning methods. Our results also exemplify the benefit of these methods in understanding the relationship between subtypes of heterogeneous movement disorders.

776

Cohort profile of the Japan Dystonia Consortium: Genetic diagnosis and characteristics of movement disorders in Japan

T. Kawarai, R. Miyamoto, A. Orlacchio, R. Kaji (Tokushima, Japan)

Objective: To reveal molecular epidemiology of hereditary dystonia through resequencing of the currently-known dystonia genes and identification of novel genetic defects.

Background: The Japan Dystonia Consortium was established to construct a nationwide clinical and DNA database on dystonia patients, including genotype-phenotype-outcome correlations and natural course, which would contribute to elucidation of dystonia pathomechanism and refinement of guideline for dystonia.

Methods: A total of 587 patients with dystonia or other movement disorders were recruited. Patients were videotaped, which were phenomenologically examined by movement disorder specialists with long-standing experience. After phenomenological evaluation, candidate genes are chosen for sequence analysis. Direct sequencing of polymerase chain reaction products with the Sanger-based method or whole-exome sequencing was applied for genetic screening in the currently-known dystonia genes. Furthermore, whole exome trio sequencing was conducted in order to identify new genetic defect(s) in dystonia.

Results: Mutations in DYT genes have been revealed in familial and seemingly sporadic cases with dystonia, including DYT-TOR1A, DYT-THAP1, DYT-GNAL, DYT/PARK-GCH1, DYT/PARK-TH, DYT/PARK-ATP1A3, DYT/PARK-TAF1, and DYT-SGCE. In addition, we identified mutations in other dystonia or dyskinesia-associated genes, including PRRT2, MR-1, TUBB4A, KMT2B and ADCY5. Genotype –phenotype correlations in most cases were consistent with those previously reported.

Conclusions: The cohort contains enough sample power to detect novel genes for dystonia. Correct phenomenological evaluation is indispensable for variant interpretation and establishment of phenotype-genotype correlations.

Guided Poster Group 6: Huntington's Disease

681

Chorea and Ataxia as Manifestations of Xeroderma Pigmentosum: A Case Report

A. Jocson, K. Ngo, D. Togasaki, B. Fogel (Los Angeles, CA, USA)

Objective: To report a case of a 51-year-old woman with recurrent basal cell carcinoma, severe photosensitivity, and progressive chorea and ataxia caused by xeroderma pigmentosum (XP).

Background: XP is an autosomal recessive (AR) disorder associated with photosensitivity and skin malignancies. Severe cases may present with mental retardation, dwarfism, and hypogonadism. XP-A to G are due to mutations in nucleotide excision repair (NER) of ultraviolet (UV)-induced DNA lesions. Neurologic signs are found in 20% of cases. Presentations include chorea, ataxia, and peripheral neuropathy. Chorea is rare in AR ataxias, except for ataxia telangiectasia and AOA1/2; thus, XP should be on the

differential for patients with chorea and AR ataxia. MRI imaging often demonstrates diffuse atrophy; two reports note hyperostosis frontalis interna. Considerations for the pathophysiology of the neurologic syndromes include transcriptional disturbances given roles in NER and transcription initiation.

Methods: A 51-year-old woman presented with chorea and ataxia. Gait ataxia and choreiform movements in her hands began at age 39. At 46, she developed dysarthria and, at 47, generalized chorea. Mild cognitive changes have developed. She has a history with 8 basal cell carcinomas, severe photosensitivity, and premature menopause in her 30s. Her paternal great-aunt had abnormal movements and photosensitivity. Her exam was notable for skin freckling, scanning dysarthria, mild increased tone, moderate chorea of the face, trunk and limbs, and ataxic gait. MRI brain showed diffuse cerebral and cerebellar atrophy and hyperostosis frontalis interna. Huntingtin and Fragile X testing were negative. Peripheral smear, copper and rheumatologic studies, and GAD65 Ab were negative.

Results: Exome sequencing revealed two variants of uncertain significance in the ERCC4 gene (16:14029554 C>G, p.Arg589Gly, MAF 0.002%; 16:14041570 T>C, p.Ile706Thr, MAF 0.14%) as well as a previously reported mutation (16:14041848 C>T, p.Arg799Trp, MAF 0.04%) consistent with a likely pathogenic diagnosis of XP complementation group F. We suspect p.Ile706Thr to be a rare polymorphism based on its higher minor allele frequency relative to the other two variants. Supportive treatment and UV light damage prevention are recommended.

Conclusions: XP is more commonly associated with ataxia, but case reports note associations with chorea. Our patient had recurrent basal cell carcinomas, skin sensitivity, and hypogonadism that are common in XP. XP should be considered in patients with chorea and ataxia with a significant dermatologic history and hypogonadism.

References: Carre G, Merelli C, et al. "Xeroderma pigmentosum complementation group F: A rare cause of cerebellar ataxia with chorea." *Journal of the Neurological Sciences*. 2017; 37: 198-201.
Sijbers, A. M., van Voorst Vader, P. C., Snoek, J. W., Raams, A., Jaspers, N. G., & Kleijer, W. J. (1998). "Homozygous R788W point mutation in the XPF gene of a patient with xeroderma pigmentosum and late-onset neurologic disease." *Journal of Investigative Dermatology*, 110, 832–836.

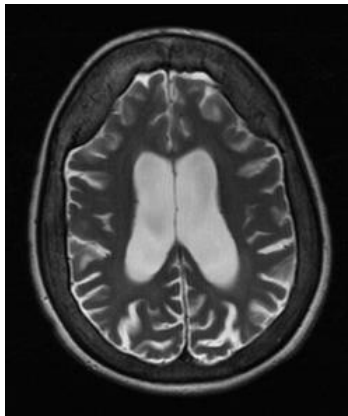


FIG. 1 (681)

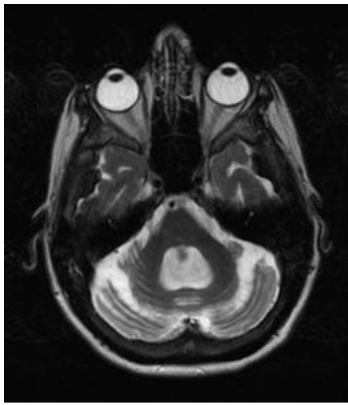


FIG. 2 (681)

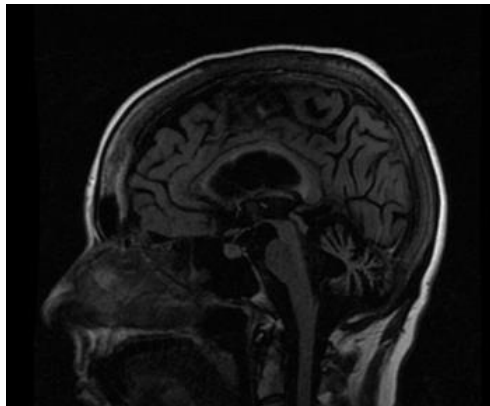


FIG. 3 (681)

805

Prediction of suicidality in Huntington disease: Analysis of Enroll-HD data using machine learning approach

Y. Seliverstov, A. Borzov, E. van Duijn, B. Landwehrmeyer, M. Belyaev (Moscow, Russian Federation)

Objective: To develop a model for prediction of suicidal ideation or suicidal behaviour in Huntington disease gene expansion carriers (HDGEC) based on Enroll-HD data using machine learning approach (MLA).

Background: Suicidal ideation and suicidal behaviour are frequently reported, severe features in HDGEC. So far, no suicidality prediction models have been developed using MLA.

Methods: We used the third Enroll-HD study periodic dataset (PDS3). The Columbia-Suicide Severity Rating Scale (C-SSRS) was used for the assessment of suicidal ideation/behaviour. HDGECs with either having no suicidal ideation or with presence of 'passive' suicidal ideations [state 1] at the 1st visit, who at the annual follow-up visit (FUP) either stayed in state 1 or worsened to 'active' suicidal ideations and/or suicidal behaviour [state 2] were included into our analysis. The PBAs scale was used to assess behavioural symptoms. Prediction algorithm was based on Boosted Trees (implementation from XGBoost Library for Python) and contained 48 variables from the PDS3. For further analysis we also used Fisher Exact test, Mann-Whitney U-test, and Holm method.

Results: Out of 8,714 subjects from the PDS3 only 377 HDGEC (114 pre-manifest; 161 males; median age 50 [20;78]; median nCAG=43 [38;65]) had state 1 at the 1st visit and either state 1 or state 2 at the FUP. At FUP, 61 HDGEC worsened to state 2 and 316 remained in state 1. Sixty four percent of the HDGECs who remained in state 1 at FUP were accurately classified (probability as having state 2 < 30%). HDGEC who worsened to state 2 were correctly predicted (probability of being classified as having state 2 > 60%) in 37.7% cases. We then compared HDGEC in state 2 at FUP who were poorly (probability <30%; 31 subjects) and well (probability >60%; 23 subjects) classified and found significant difference in the PBAs total scores

for depression, anxiety, aggression, and apathy. Well classified HDGEC had more severe scores. Further regression analysis failed to show significant linear relationship of those features with probability of being classified by the algorithm as subject in state 2 at FUP.

Conclusions: Our model for suicidality prediction in HDGEC showed relatively moderate accuracy. Further research is needed to understand the risk for development of suicidal ideation/behaviour in HDGECs without/less severe behavioural symptoms.

807

Vertical and horizontal eye movements in a large cohort of early manifest Huntington's disease: Evidence from ENROLL-HD

W. Muller, M. MacAskill, L. Paermentier, T. Anderson (Christchurch, New Zealand)

Objective: To determine, in a very large sample, how different types of eye movement are differentially impaired in early manifest HD, and determine whether vertical or horizontal eye movements are the more affected.

Background: One of the earliest signs to appear in manifest Huntington's disease (HD) is abnormality of eye movement. Vertical eye movements are reportedly affected earlier and to a greater extent than horizontal eye movements. These studies however are based on relatively small numbers of HD subjects and anecdotal observations have suggested that horizontal eye movements may be more impaired, at least in some.

Methods: Data from the clinical motor assessment component of the Unified Huntington's Disease Rating Scale (UHDRS) was obtained from the ENROLL-HD database, an international, prospective-cohort study, created for collation of HD information. We accessed the database, with permission, in December 2017. The annual motor assessment includes 6 oculomotor parameters: horizontal and vertical smooth pursuit, saccade latency, and saccade velocity, each graded in severity from 0-4. There were a total of 4752 manifest HD participants at the time of analysis with mean age of 59.2 ± 12.6 yrs and mean CAG repeat number of 44.1 ± 4.0 .

Results: Impairment in all oculomotor parameters increased in a linear fashion over the first 8 years of manifest disease. Vertical smooth pursuit and saccade velocity scores at disease onset were greater (i.e. more impaired) than horizontal scores, by a small but significant extent, but there was no difference in the rate of increase of scores over time between the two directions. There was no difference between vertical and horizontal saccade latency scores at onset and over time.

Conclusions: Vertical eye movements, with the exception of saccadic latency, are affected to a slightly greater extent than horizontal movements, and all types worsen in a linear fashion over at least the first 8 years after disease onset.

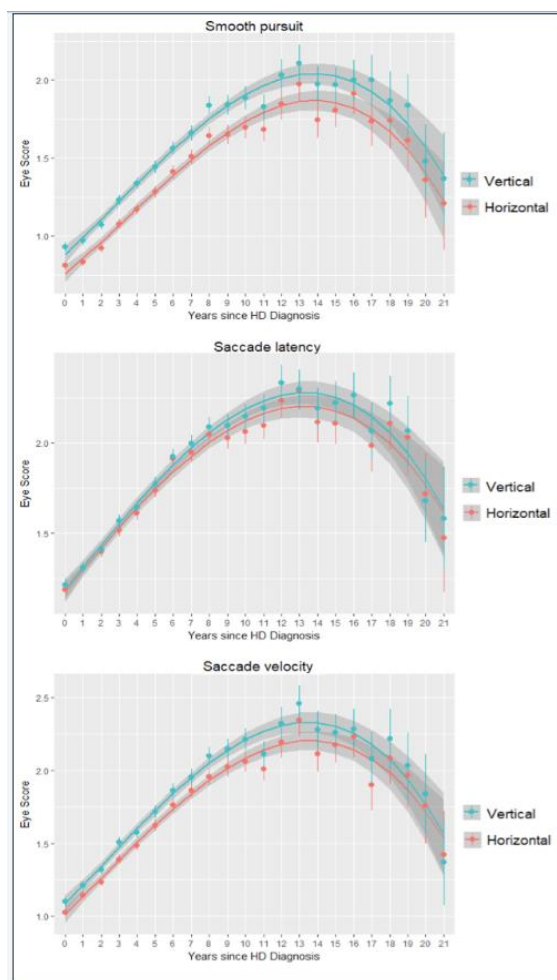


FIG. 1 (807)

809

White matter microstructural alterations in Huntington Disease: When neurodegeneration starts?

P. Azevedo, L. Piovesana, M. Nogueira, R. Guimarães, A. Amato Filho, F. Cendes, Í. Lopes-Cendes, C. Yasuda (Campinas, Brazil)

Objective: The aim of our study is to characterize in detail the white matter (WM) microstructure alterations in Huntington Disease (HD) using the diffusion tensor imaging (DTI) analysis on magnetic resonance imaging (MRI).

Background: Imaging studies in patients with HD may help to determine differential vulnerability of CNS structures to the neurodegenerative process as well as to identify precisely when neurodegeneration starts, how it progresses and the associated triggers [1].

Methods: We obtained DTI (32 directions) acquired at 3.0T from 37 healthy volunteers and 36 patients (genetically confirmed), balanced for age ($p=0.9$) and gender ($p=0.9$). Patients underwent neurological (Unified Huntington's disease rating scale – UHDRS) and cognitive (Montreal cognitive assessment – MOCA) evaluations. Diffusion Tensor Images were processed with ExploreDTI/MATLAB-2014 (www.exploredti.com). Ten tracts [3 parts of the corpus callosum (CC), Corticospinal tract (CST), Inferior Fronto Occipital (IFO) tract, Inferior Longitudinal Fasciculus (ILF), dorsal and parahippocampal cingulum (PH-CINGULUM), uncinate and body of fornix (FORNIX)] were delineated by semi-automatic deterministic tractography to yield fractional anisotropy (FA) (Figures 1 and 2). SPSS22 was used for correlations, univariate, multivariate analyses and Chi-square test.

Results: Multivariate analyses with Repeated-measures ANOVA for bilateral tracts revealed significant FA reduction mainly on cingulum and PH-cingulum ($p < 0.004$, with Bonferroni correction). MANOVA of Corpus Callosum segments and FORNIX showed reduced FA values ($p < 0.0125$ with Bonferroni correction) in patients with HD. While there was no significant correlation between FA values and CAG repeat expansion, we identified a significant correlation between UHDRS and CST (left $r = -0.575$, right $r = -0.45$, $p < 0.005$), IFO (left $r = -0.51$, right $r = -0.58$, $p < 0.002$) and left PH-CINGULUM ($r = -0.48$, $p = 0.003$). In addition, there was a positive correlation between MOCA and FA values in PH-CINGULUM (left $r = 0.54$, right $r = 0.59$, $p < 0.002$).

Conclusions: WM microstructural alterations were widespread, affecting midline and bilateral structures in patients with HD [2]. The abnormal tracts are responsible for sensorimotor integration, motor control and planning, visuospatial function and emotional processing. Prospective studies are underway in order to characterize how the pattern of WM alterations progresses over time.

References: [1] Wu D, et al. Mapping the order and pattern of brain structural MRI changes using change-point analysis in premanifest Huntington's disease. PREDICT-HD Investigators and Coordinators of the Huntington Study Group. *Hum Brain Mapp.* 2017 Oct;38(10):5035-5050. [2] Saba RA, et al. Diffusion tensor imaging of brain white matter in Huntington gene mutation individuals. *Arq Neuropsiquiatr.* 2017 Aug;75(8):503-508.

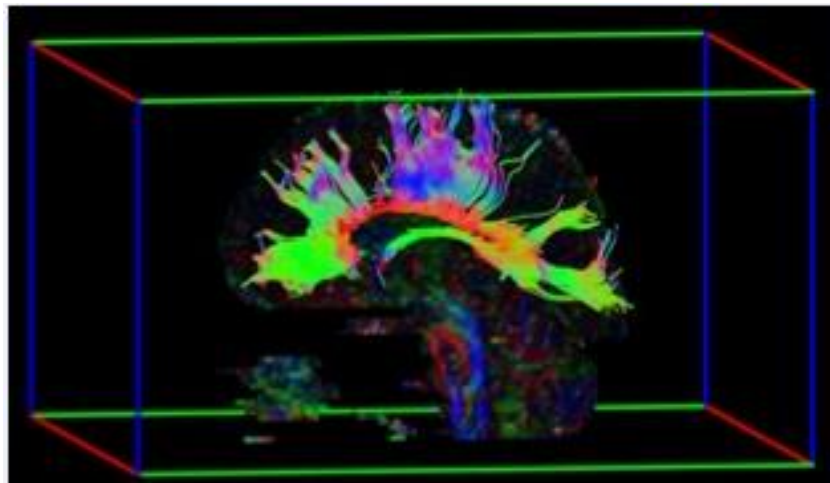


FIG. 1 (809) Midline

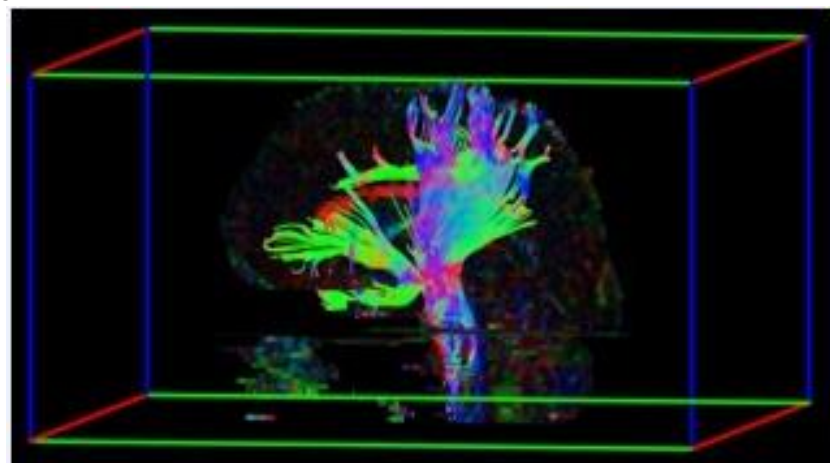


FIG. 2 (809) Lateral

Interrater reliability of the Unified Huntington's Disease Rating Scale-Total Motor Score certification *J. Winder, R. Roos, J.M. Burgunder, J. Marinus, R. Reilmann (Leiden, Netherlands)*

Objective: The aim of this study was to investigate the interrater reliability of the Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS) and of its sub-items, and to examine the performance of raters on the UHDRS-TMS certification in consecutive years.

Background: The clinical assessment of motor symptoms in Huntington's disease is usually performed with the UHDRS-TMS. A high interrater reliability is desirable to monitor symptom progression. Therefore, a teaching video and a system for annual online certification has been developed and implemented.

Methods: Data from the online UHDRS-TMS certification were used. The interrater reliability was assessed for all first-time participants ($n = 944$) between 2009 and 2016. Intraclass correlation coefficients (ICC) were calculated for each year separately and the mean was taken as the total ICC.

Results: The UHDRS-TMS (ICC = 0.847), tandem walking (0.824), pronate/supinate hands left (0.713), and retropulsion pull test (0.706) showed good interrater reliability. Poor interrater reliability was found for maximal dystonia of the left and right upper extremity (0.187 and 0.322, respectively), maximal dystonia of the left and right lower extremity (0.200 and 0.256, respectively), maximal dystonia of the trunk (0.389), tongue protrusion (0.266), and rigidity arms left (0.390). Raters performed significantly worse on follow-up certification compared to their first certification.

Conclusions: Our results suggest that the rating of 'absent-slight-mild-moderate-or-marked' dystonia is subjective and difficult to interpret, specifically on video. Therefore, changing the dystonia items of the UHDRS-TMS should be explored. We also recommend that raters should watch the UHDRS-TMS teaching video before each certification.

Cognitive Reserve and Physical Activity Modulate Functional Brain Re-organisation in Premanifest Huntington's Disease: Preliminary Evidence

M. Soloveva, S. Jamadar, G. Poudel, N. Georgiou-Karistianis (Melbourne, Australia)

Objective: In this study, for the first time we examined the relationship between cognitive reserve, sleep quality and current level of physical exercise and functional brain activity in pre-HD.

Background: It is well established that increased functional brain activity during the premanifest stage of Huntington's disease (pre-HD) is part of a compensatory process that plays early in the disease (Georgiou-Karistianis et al., 2014; Kloppel et al., 2015). However, no HD study to date has examined how to mediate functional brain activity so as to maintain cognitive function, or delay disease progression.

Methods: Pre-HD ($n = 15$; $M = 37.33$; $SD = 10.82$) and age- and gender-matched healthy controls ($n = 15$; $M = 35.60$; $SD = 10.69$) completed the Cognitive Reserve Index Questionnaire (CRIq), the Pittsburgh Sleep Quality Index (PSQI) and the International Physical Activity Questionnaire Long (IPAQ-L), as well as performed an 18-minute functional MRI (fMRI) visuospatial working memory task with low (2 items), intermediate-1 (3 items), intermediate-2 (4 items), and high (5 items) memory loads [figure 1].

Results: Pearson's correlation revealed that greater cognitive reserve (CRIq) was associated with decreased functional activity in the left posterior medial frontal cortex in pre-HD at intermediate-1 ($r = -.52$, $p = .045$) and intermediate-2 levels of memory load ($r = -.56$, $p = .030$), compared with healthy controls. Higher level of physical exercise (IPAQ-L) was related to reduced functional activity in pre-HD, in left ($r = -.52$, $p = .050$) and right ($r = -.65$, $p = .009$) anterior insula, left ($r = -.69$, $p = .004$) and right ($r = -.72$, $p = .002$) inferior frontal gyrus, left intraparietal sulcus ($r = -.64$, $p = .01$) and left dorsolateral prefrontal cortex ($r = -.57$, $p = .03$) at low memory load and right intraparietal sulcus ($r = -.61$, $p = .015$) at intermediate-1 memory load, compared with healthy controls. No significant relationship was observed between sleep quality and functional activity in any of the groups.

Conclusions: Our findings suggest that cognitive reserve and level of physical activity can modulate functional brain re-organisation in pre-HD.

References: Georgiou-Karistinis et al., 2014. Kloppel et al., 2015.

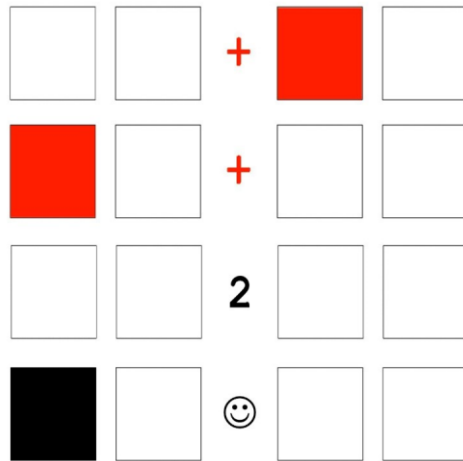


FIG. 1 (821)

823

Comparing risperidone and olanzapine to tetrabenazine for the management of Huntington's chorea

J. Schultz, J. Kamholz, P. Nopoulos, A. Killoran (Iowa City, IA, USA)

Objective: To compare the efficacy of risperidone and olanzapine to tetrabenazine (TBZ) for the management of Huntington's chorea in Enroll-HD participants.

Background: TBZ is provenly-effective and FDA-approved for the treatment of chorea in Huntington's disease (HD). Antipsychotic drugs (APD), such as Risperdal and Olanzapine, are often prescribed off-label for HD chorea, especially when psychiatric comorbidities are present. The APD' anti-choreic efficacy is presumed primarily from their long-standing use by HD experts, as they have never been evaluated in large clinical trials.

Methods: This was a retrospective analysis using the database from Enroll-HD, a longitudinal, observational study with 8714 participants. Those with manifest HD were grouped based on their use of risperidone, olanzapine, or TBZ. The effects of these anti-choreic drugs were compared using MANCOVA analyses. The primary outcome measure was the total motor score (TMS) annual rate of change between the baseline and second visits. Secondary outcome measures included TMS changes and the rates of change between the baseline and second visits of the: total chorea score, total functional capacity score, weight and body mass index (BMI). Covariates included sex, years between visits and baseline: TMS, TFC, and disease burden score. An exploratory outcome measure was the odds of having an annualized improvement in the TMS by at least 3.3 units, which was TBZ's treatment effect in the TETRA-HD study.¹

Results: The risperidone group showed an improvement in the annualized percent change in TMS of 3.9% compared to a 17.5% worsening in the TBZ group ($p=0.042$). In addition, the odds of having an annualized improvement in the TMS by at least 3.3 units was significantly higher in subjects taking risperidone (42.9%) vs those on TBZ (9.0%) ($p=0.031$). The olanzapine group increased in weight ($p=0.023$) and BMI ($p=0.022$) compared to the TBZ group. The APD and TBZ results were otherwise comparable.

Conclusions: This is the first study to provide robust, objective data on the anti-choreic effect of risperidone and olanzapine. It is also the first study to compare these APD to TBZ for their efficacy on HD chorea. Our results establish that risperidone and olanzapine are comparable to TBZ, but for some superiority to tetrabenazine on certain measures. These findings bridge the gap between expert opinion and evidence-based medicine in the management of HD chorea.

References: 1. Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington Disease: A randomized controlled Trial. *Neurology* 2006;66:366-372.

830

Driving performance of Huntington's disease gene carriers

M. Jacobs, E. Hart, Y. Mejia Miranda, G.J. Groeneveld, J. van Gerven, R. Roos (Leiden, Netherlands)

Objective: To investigate if differences in driving performance between Huntington's disease (HD) gene carriers and healthy individuals can be detected with a driving simulator. Furthermore, we wanted to determine if certain cognitive and motor symptoms contribute to driving performance in HD.

Background: The ability to drive a car is important for an individual's independence, work, and social activities. HD patients become more and more dependent in their daily life activities as the disease progresses and, for most patients, it can be difficult to quit driving.

Methods: We included 58 HD gene carriers (28 premanifest HD, 30 manifest HD) and 29 controls in this cross-sectional study. All participants were active drivers and assessed using a driving simulator, a driving history questionnaire, the Unified Huntington's Disease Rating Scale, and neuropsychological assessments. The driving simulator session included both urban and motorway scenarios.

Results: Manifest HD drove slower compared to controls and premanifest HD when speed limits increased (80 and 100 km/h) and they had a less steady speed compared to premanifest HD on the motorway and in a 30 km/h zone. Manifest HD also had a larger standard deviation of the lateral position (i.e., more weaving of the car/less vehicle control) compared to controls and premanifest HD on the motorway. Manifest HD performed worse on all clinical assessments compared to controls. Postural instability and slower speed of processing were predictors of the driving simulator outcome measures. There were no significant differences between premanifest HD and controls.

Conclusions: Manifest HD drive more cautious in a driving simulator when speed limits increase compared to premanifest HD and controls and they have less vehicle control on the motorway. A driving simulator is able to detect differences in driving performance between manifest HD and healthy individuals. Lower performances on cognitive tasks might assist physicians in their referral for an official on-road driving test. A genetic confirmation of HD should not be decisive in the advice to cease driving. Further studies are necessary to determine if a driving simulator can be used to monitor longitudinal changes in fitness to drive. Investigating fitness to drive is important in HD, because symptoms of the disease can affect the ability to drive at a relatively young age.

838

Cerebrospinal fluid flow dynamics in Huntington's disease evaluated by phase contrast MRI

F. Rodrigues, L. Byrne, E. De Vita, E. Johnson, N. Hobbs, J. Thornton, R. Scahill, E. Wild (London, United Kingdom)

Objective: To elucidate the dynamics of CSF flow through the neuraxis in Huntington's disease (HD) using phase contrast magnetic resonance imaging (PCMRI).

Background: HD is a fatal neurodegenerative condition. Multiple targeted therapeutics are now in the early clinical stage, including intrathecally-delivered compounds. Preclinical and clinical research suggests cerebrospinal fluid dynamics may be altered in HD, which could be of paramount relevance to intrathecal drug delivery to the brain.

Methods: Ten manifest gene expansion carriers and 10 age- and gender-matched healthy controls were recruited. All participants underwent extensive clinical assessment and PCMRI at the level of the cerebral aqueduct, T1 and T8. CSF velocities and flow measurements were derived using a semi-automated method. The influence of age, gender, CAG repeat-length, serum osmolality, and brain volumes on these measurements were tested using Spearman correlations or Fisher's exact tests. Group comparisons between healthy controls and manifest carriers were achieved via two-sample Wilcoxon rank-sum tests. All tests were two-sided with a significance level of 0.05, and corrected for multiple comparisons.

Results: All participants were well matched across study groups. Measures of CSF dynamics were consistent across raters. None of the studied covariates was found to have an effect on the CSF velocities and flow measurements after corrected for multiple comparisons. No statistically significant difference was found

across groups in any of the measures studied. Sample size calculations have shown that for the most clinically significant effect size attained, 993 participants per group would be needed to show a significant difference between two groups with 90% power.

Conclusions: While external validation is required, the attained effect sizes in this exploratory study are sufficient to conclude tentatively that a clinically-relevant alteration of cerebrospinal fluid flow dynamics – i.e. one that would justify dose-adjustments of intrathecal drugs – is unlikely to exist in Huntington’s disease.

Guided Poster Group 7: Parkinsonism, MSA, PSP (Secondary and Parkinsonism-Plus)

927

Clinical features and natural history of pathologically-confirmed corticobasal degeneration: A Japanese validation study of CBD (J-VAC study)

I. Aiba, T. Shimohata, S. Murayama, K. Hasegawa, Y. Iwasaki, O. Yokota, H. Fujimura, M. Sakai, T. Yokota, I. Yabe, H. Takigawa, K. Sugaya, K. Mori, M. Ito, C. Ishida, M. Kobayashi, Y. Hashizume, T. Ikeuchi, M. Hasegawa, M. Yoshida, T. Komori, K. Wakabayashi, Y. Saito, A. Tokumaru, K. Sakurai, K. Nakashima (Nagoya, Japan)

Objective: To elucidate the clinical features and natural history of CBD.

Background: Recently, various clinical phenotypes of corticobasal degeneration (CBD) have been reported; on the other hand, the pathological background of corticobasal syndrome (CBS) is broad. Hence, the rate of antemortem diagnosis of CBD is extremely low.

Methods: Clinical evaluations were performed on patients with pathologically-, genetically-, and biochemically-verified CBD during central review and each patient’s clinical information was retrospectively studied. We analyzed the frequency of signs and clinical phenotypes, and the interval from initial symptoms to key clinical milestones. Clinical features observed in over half of patients were selected as key milestones.

Results: We identified 35 pathologically-confirmed patients, from 15 Japanese institutions. The mean age at onset was 65.0 years. The mean disease duration was 8.1 years. At initial presentation, CBS/CBD and progressive supranuclear palsy (PSP) were the most common diagnoses (19%, respectively), followed by Lewy body disease (17%) and Alzheimer’s disease (AD) (11%). CBS/CBD was the most frequent final clinical diagnosis (44%), followed by PSP (28%), AD (8%) and frontotemporal dementia (FTD) (8%). Limb rigidity, gait disturbance, and postural instability or falls were observed in more than 80% of patients with CBD. Dystonia (39%) and myoclonus (20%) were infrequently observed. In higher cortical features, both frontal executive dysfunction and general cognitive impairment were observed in more than 80% of patients, followed by speech and language impairments (77%) and behavioral changes (69%). Apraxia (48%), cortical sensory loss (20%), and the alien-limb sign (10%) were uncommonly observed. The mean intervals from the initial symptoms to onset of key clinical milestones were as follows: gait disturbance, 1.0 years; behavioral changes, 1.2 years; falls, 2.0 years; cognitive impairment, 2.4 years; speech impairment, 2.6 years; supranuclear gaze palsy, 3.1 years; urinary incontinence, 3.3 years; and dysphagia, 4.3 years.

Conclusions: The pathology of CBD was predicted antemortem in only 44% of patients. In patients with CBD, parkinsonism, frontal executive dysfunction, and general cognitive impairment were more commonly observed than the cardinal features of CBS. Behavioral changes appeared in the early stages, although the natural disease course was similar to PSP.

Quantitative mobility metrics from a body-fixed sensor predict incident parkinsonism in older adults

R. von Coelln, R. Dawe, J. Shulman, L. Yu, S. Leurgans, J. Hausdorff, L. Shulman, D. Bennett, A. Buchman (Baltimore, MD, USA)

Objective: To investigate whether body-fixed sensor mobility metrics identify older adults without a diagnosis of Parkinson disease (PD) at risk for developing parkinsonism.

Background: Parkinsonism is common in the elderly, and predicts adverse health outcomes. In prior work we showed that mobility metrics from a body-fixed sensor are related to the severity of parkinsonism in older adults without PD. However, it is not known if these metrics identify older adults at risk for developing parkinsonism.

Methods: 683 ambulatory, community-dwelling older adults without parkinsonism were evaluated annually for four parkinsonian signs (bradykinesia, tremor, rigidity, parkinsonian gait) using a modified Unified Parkinson's Disease Rating Scale. Subjects also wore a belt with a body-fixed triaxial accelerometer/gyroscope as they performed 3 motor tests (32 ft walk, standing with eyes closed, Timed Up and Go test [TUG]). Baseline measures were summarized into 12 gait scores including gait speed metrics, which quantified 5 subtasks including: a) walking, b) standing posture, plus 3 TUG subtasks: c) sit to stand transition, d) stand to sit transition, and e) turning. In a series of Cox proportional hazards models controlled for age, sex, education and race, we examined which gait scores were associated with incident parkinsonism (2 or more parkinsonian signs at a follow-up examination). Stepwise backwards elimination was performed to identify combinations of gait scores independently associated with incident parkinsonism.

Results: 139 out of 683 (20.4%) participants developed parkinsonism during 2.5 ± 1.28 years of follow-up. When modeled separately, 6 out of 12 gait scores were associated with incident parkinsonism. Two of 12 scores (stand to sit transition and turning scores) survived stepwise backward elimination, and were independently associated with incident parkinsonism ($p=0.003$ and $p<0.001$, respectively).

Conclusions: Mobility metrics derived from a wearable body-fixed sensor facilitate identification of older adults without PD at risk of developing parkinsonism.

Apolipoprotein E and multiple system atrophy

K. Ogaki, Y. Martens, M. Heckman, S. Koga, L. Labbé, O. Lorenzo-Betancor, A. Wernick, R. Walton, A. Soto, E. Vargas, H. Nielsen, S. Fujioka, T. Kanekiyo, R. Uitti, J. van Gerpen, W. Cheshire, Z. Wszolek, P. Low, W. Singer, N. Hattori, D. Dickson, G. Bu, O. Ross (Tokyo, Japan)

Objective: This study evaluated genetic associations of Apolipoprotein E alleles with risk of multiple system atrophy (MSA) and α -synuclein pathology, and also examined whether apolipoprotein E isoforms differentially affect α -synuclein uptake in a oligodendrocyte cell.

Background: Dysregulation of the specialized lipid metabolism involved in myelin synthesis and maintenance by oligodendrocytes has been associated with the unique neuropathology of MSA. We hypothesized that apolipoprotein E, which is associated with neurodegeneration, may also play a role in the pathogenesis of MSA.

Methods: One hundred sixty-eight pathologically confirmed MSA patients, 89 clinically diagnosed MSA patients, and 1,277 control subjects were genotyped for Apolipoprotein E. Human oligodendrocyte cell lines were incubated with α -synuclein and recombinant human apolipoprotein E, with internalized α -synuclein imaged by confocal microscopy and cells analyzed by flow cytometry.

Results: No significant association with risk of MSA or was observed for either Apolipoprotein E $\epsilon 2$ or $\epsilon 4$. α -Synuclein burden was also not associated with Apolipoprotein E alleles in the pathologically confirmed patients. Interestingly, in our cell assays, apolipoprotein E $\epsilon 4$ significantly reduced α -synuclein uptake in the oligodendrocytic cell line.

Conclusions: Despite differential effects of apolipoprotein E isoforms on α -synuclein uptake in a human oligodendrocytic cell, we did not observe a significant association at the Apolipoprotein E locus with risk of MSA or α -synuclein pathology.

939

ARISE study: Study Design and Baseline Characteristics for a Phase 2 Trial of the Anti-Tau Antibody ABBV-8E12 in Progressive Supranuclear Palsy

N. Mendonca, R. Bateman, A. Boxer, J. Braunstein, D. Claassen, D. Holtzman, D. Kerwin, B. Rendenbach-Mueller, H. Soares, D. Wang, G. Höglinger (Ludwigshafen, , Germany)

Objective: This double-blind, placebo-controlled phase 2 study (M15-562 ARISE study, NCT02985879) assesses the safety and efficacy of ABBV-8E12 treatment in patients with progressive supranuclear palsy (PSP) for 52 weeks.

Background: ABBV-8E12 is a humanized anti-tau monoclonal antibody being developed for the treatment of PSP and early Alzheimer's disease (AD). A phase 1 double-blind, placebo-controlled, single ascending dose study on the safety, tolerability, and pharmacokinetics of ABBV-8E12 in PSP patients (NCT02494024) was recently completed. The phase 1 results showed that ABBV-8E12, when administered as a single dose up to 50 mg/kg, exhibited an acceptable safety and tolerability profile to support repeat-dose testing in larger cohorts of patients with tauopathies. Here we present the design and baseline characteristics of the ongoing phase 2 ARISE study of ABBV-8E12 in PSP patients.

Methods: Male and female patients, at least 40 years of age, are being enrolled at approximately 40 global study sites. Prior to enrollment, patients will have had symptoms for less than 5 years and meet the NINDS-PSP criteria for possible or probable PSP. Patients will be randomized to one of two ABBV-8E12 dose arms or placebo.

Results: The primary efficacy outcome is the change from baseline to week 52 in Progressive Supranuclear Palsy Rating Scale total score. Key secondary endpoints include the Schwab and England Activities of Daily Living Scale, the Unified Parkinson's Disease Rating Scale Part II, the Clinical Global Impression of Severity and Change, the PSP-Quality of Life subscale scores, and the Visual Analog scale. Table 1 includes baseline characteristics for the first 91 enrolled patients [table1].

Conclusions: The current study is ongoing and designed to evaluate the 52-week safety and efficacy of ABBV-8E12 in PSP patients. In addition to the ongoing phase 2 study in PSP patients, a phase 2 study evaluating ABBV-8E12 in early AD patients is also currently ongoing (NCT02880956).

TABLE 1 (939) ARISE demographics and baseline characteristics

Demographics and Baseline Characteristics	N=91
Age, years, mean (SD)	68.3 (6.1)
Male, n (%)	53 (58.2%)
Race, Caucasian, n (%)	85 (94.4%)
MMSE total score, mean (SD) ^a	26.1 (3.0)
RBANS total score, mean (SD) ^b	72.6 (12.5)
PSPRS total score, mean (SD) ^c	39.0 (11.2)
SEADL score, mean (SD) ^c	57.3 (20.4)
UPDRS Part II score, mean (SD) ^d	18.7 (7.0)

^a N=90, ^b N=75, ^c N=89, ^d N=91

MMSE=Mini-Mental State Examination; PSPRS=Progressive Supranuclear Palsy Rating Scale; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; SEADL=Schwab and England Activities of Daily Living; UPDRS=Unified Parkinson's Disease Rating Scale

948

The characteristic of gait in progressive progressive supranuclear palsy

Y. Takamatsu, N. Matsuda, I. Aiba (Kyoto, Japan)

Objective: To elucidate the characteristic of gait in patients with progressive supranuclear palsy (PSP) and compare to healthy elderly and patients with Parkinson's disease (PD)

Background: Gait disturbance is one of main symptoms in PSP. PSP is a rare disease and their characteristic of gait has not been well understood. Therefore, the optimal physical therapy approach has not been established for their gait disturbance in PSP.

Methods: Subjects were PSP (n = 24, 72.9 ± 6 y/o, man/female = 18/6), PD (n = 32, 71.1 ± 9 y/o, man/female = 18/14) and neurologically healthy elderly (CON, n = 29, 71.6 ± 6 y/o, man/female = 12/17) whose modified Rankin scale (mRS) were 4 or less. Gait patterns analysis was performed by using Walk Way MW-1000 (anima inc., Tokyo) and walking speed, cadence, stride length, step width, foot angle, walking cycle time and coefficient of variation (CV) of each parameter were measured. In the statistics, one-way ANOVA with post hoc Scheffe test was performed to compare all groups. For group differences were assessed using t-test and Mann-Whitney U test. SPSS ver.23 statistical software was used to analyze the data and the criterion for significance was set at p < 0.05.

Results: There were no differences in the disease duration (PSP: 64.4 ± 53 mos., PD: 68.8 ± 56 mos.) and mRS (PSP: 3 [2.25-4], PD: [2-3]) between PSP and PD. The walking speed was lower and stride length was shorter significantly in PSP and PD than that of CON (p<0.05), but there was no difference between PSP and PD. The step width and foot angle were larger significantly in PSP than that of CON (p<0.05), but there was no difference between PD and CON. In addition, CV of walking cycle time was larger in PSP than that of CON and PD (p<0.05).

Conclusions: In PSP and PD, their walking abilities were markedly disturbed compared to CON. Furthermore, their step width, foot angle and variation of walking cycle time were significantly larger in PSP than PD. It has been reported that dentate nucleus, cerebellar white matter, putamen nucleus, and inferior olivary nucleus were pathologically involved unlike PD. Therefore, the gait of PSP might be highly unstable

by dysfunction of the cerebellum. As the result, they might increase in step width and foot angle as compensation to stable at their walking.

957

Olfactory testing in Parkinson plus syndromes

O. Abdugarimov, F. Akhmedova (Tashkent, Uzbekistan)

Objective: To determine the diagnostic utility of olfactory testing in patients with neurodegenerative Parkinsonism.

Background: Olfactory dysfunction can be identified in the vast majority of patients with Parkinson's disease (PD). Less is known about olfactory function in multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) - two atypical Parkinsonian disorders (APD) that may closely mimic PD in early disease stages – but current evidence suggests that olfactory function remains largely intact in these conditions.

Methods: The Sniffin' Sticks test battery for assessment of odor identification, odor discrimination, and olfactory threshold was applied to two independent cohorts – a screening and a validation cohort. The screening cohort included Parkinson's disease (PD) patients and healthy controls (HC) and was used to calculate optimal cut-offs for a diagnosis of PD with a sensitivity or specificity exceeding 95%. The validation cohort was used to determine the diagnostic accuracy of the newly established cut-off values in discriminating patients with PD from those with atypical Parkinsonian disorders (APD) including multiple system atrophy (MSA) and progressive supranuclear palsy (PSP).

Results: PD patients (screening cohort n520, validation cohort n547) performed significantly worse in olfactory testing than HC (n541) and patients with MSA (n523) or PSP (n523). Diagnostic performance of the identification subscore was similar to the sum score of the Sniffin' Sticks test (AUC identification test 0.94, AUC sum score 0.96). In subjects with neurodegenerative Parkinsonism, the specificity cut-off predicted a diagnosis of PD with a sensitivity and specificity of 76.6 and 87.0%, respectively. The discriminative value of this cut-off in separating PD from MSA was 76.7% (sensitivity) and 95.7% (specificity). Optimal cut-offs of the sum score provided a sensitivity and specificity for a diagnosis of PD of 78.7% and 76.1%, respectively. The positive predictive value of olfactory testing adjusted for PD prevalence in the community exceeded 95%.

Conclusions: Our data suggest that assessment of olfactory function, particularly odor identification, can be useful to discriminate PD from APDs, particularly MSA patients.

964

Nilotinib for treating MSA: A preclinical proof of concept study

P. Guerin, M. Lopez-Cuina, E. Bezard, W. Meissner, P-O. Fernagut (Bordeaux, France)

Objective: To assess the effects of nilotinib on motor behavior, α -synuclein burden and surrogate markers of neurodegeneration in a transgenic mouse model of multiple system atrophy (MSA).

Background: The pathological hallmark of MSA is the presence of α -synuclein bearing glial cytoplasmic inclusions. Treatment is available for some symptoms, in particular autonomic dysfunction, while disease modification remains an urgent unmet need. Activation of the tyrosine kinase c-Abl protein is increased in Parkinson's disease (PD) and alpha-synuclein has been identified as one of its substrates. Through C-Abl inhibition, nilotinib (a commercially available treatment for a type of leukemia) is thought to potentially counteract α -synuclein accumulation and to protect neurons from degeneration. In this regard, positive effects of nilotinib on the neurodegenerative process have been reported in preclinical models of PD. The aim of this study was to evaluate the effects of nilotinib in PLP-SYN mice, a transgenic mouse model of MSA.

Methods: Wild-type (WT) mice received daily intraperitoneal injections of vehicle and transgenic PLP-SYN received daily intraperitoneal injections of either vehicle, nilotinib 1mg/kg or 10mg/kg, for 12 weeks

since age 6 weeks. Motor behavior was assessed at baseline and every 4 weeks until termination. The histopathological analysis included cell survival in the substantia nigra pars compacta (SNpc) as assessed by the number of tyrosine hydroxylase and Nissl positive neurons. Immunoblotting was performed to measure α -synuclein load.

Results: Nilotinib was safe and well tolerated at both doses by PLP-SYN mice. There was no difference in motor performance between the different treatment groups of PLP-SYN mice. As expected, placebo-treated PLP-SYN mice showed dopaminergic cell loss in the SNpc compared to WT mice, while nilotinib failed to protect neurons from degeneration and to attenuate α -synuclein burden in PLP-SYN mice.

Conclusions: Nilotinib failed to demonstrate positive effects in a transgenic mouse model of MSA.

974

Evolution of diagnostic certainty and PSP-predominance types in 187 pathologically confirmed PSP patients

M. Grimm, G. Respondek, I. Piot, T. Arzberger, Y. Compta, E. Englund, L. Ferguson, E. Gelpi, A. Giese, S. Roeber, D. Irwin, W. Meissner, C. Nilsson, A. Pantelyat, A. Rajput, C. Troakes, G. Höglinger (Munich, Germany)

Objective: To examine the evolution of diagnostic certainty and clinical predominance types as defined by the movement disorder society (MDS) criteria for the clinical diagnosis of PSP (Höglinger et al, 2017) during the course of disease in autopsy-confirmed patients with PSP.

Background: Three degrees of diagnostic certainty ("suggestive of" = s.o., "possible", or "probable"), and definition of clinical predominance types (PSP-RS, PSP-PGF, PSP-P, PSP-F, PSP-OM, PSP-SL, PSP-CBS, PSP-PI) were implemented into the new clinical diagnostic criteria for PSP (MDS criteria for the clinical diagnosis of PSP, Höglinger et al, 2017). The evolution of diagnostic certainty and predominance types over the course of disease in PSP patients according to the MDS-criteria has not been studied so far. However, this is relevant for further understanding the natural history and clinical spectrum of PSP.

Methods: Features relevant for the diagnosis of PSP according to the MDS-diagnostic criteria were collected in 187 autopsy-confirmed PSP patients by chart review. Diagnostic certainty and PSP-predominance types according to the MDS-diagnostic criteria were determined for each patient and each year.

Results: According to the MDS-PSP diagnostic criteria, 62% (n=115) of patients had a clinical diagnosis of PSP in the first year of disease, as opposed to 14% (n=26) according to the NINDS SPSP criteria, and 98% (n=183) at final record, as opposed to 79% (n=147) according to the NINDS/SPSP criteria. A diagnosis of s.o. PSP was present in 44% (n=83) of patients in the first year. Of these, 77% (n=64) had a diagnosis of "probable" PSP at final record. In the first year of disease, the variability of predominance types was greatest, and PSP-RS represented only 11% of patients. At final record, 56% patients had a PSP-RS predominance type.

Conclusions: The conversion of s.o. PSP into possible and probable PSP in 72% of the cases shows that the concept of s.o. PSP indeed allows identification of PSP patients at a very early clinical stage. Furthermore, our data suggest that many initially variant PSP presentations converge to a PSP-RS phenotype during the course of the disease.

References: MDS criteria for the clinical diagnosis of PSP, Höglinger et al, 2017.

979

Rapamycin for treating MSA: A preclinical proof of concept study

M. Lopez-Cuina, P. Guerin, E. Bezdard, W. Meissner, P-O. Fernagut (Bordeaux, France)

Objective: To assess the effects of rapamycin on motor behavior, α -synuclein burden and surrogate markers of neurodegeneration in a transgenic mouse model of multiple system atrophy (MSA).

Background: Growing evidence suggests impairment of the autophagy-lysosomal pathway in MSA. Since this pathway has a major role in the degradation of α -synuclein, its impaired function may contribute to

the accumulation of α -synuclein in glial cytoplasmic inclusions in MSA. The mammalian target of rapamycin complex 1 (mTORC1) is a key protein complex regulating autophagy. Rapamycin is an mTORC1 inhibitor that enhances autophagy, by increasing autophagosomes and boosting lysosomal biogenesis. We here assessed if rapamycin exerts neuroprotective effects by enhancing autophagic α -synuclein clearance in a transgenic mouse model of MSA.

Methods: Wild-type (WT) and PLP-SYN transgenic mice were fed either with normal food or food enriched with 14mg/kg of rapamycin for 16 weeks since age 6 weeks. Motor behavior was assessed at baseline and every 4 weeks until termination. Histopathological analysis included cell survival in the substantia nigra pars compacta (SNpc) as assessed by the number of tyrosine hydroxylase and Nissl positive neurons, and the amount of α -synuclein aggregates in oligodendrocytes in the SNpc and the striatum after incubation of sections with or without proteinase K. Additional immunoblotting was performed to measure α -synuclein load.

Results: Rapamycin was safe and well-tolerated. There was no difference in motor performance between groups. As expected, placebo-treated PLP-SYN mice showed dopaminergic cell loss in the SNpc compared to WT mice. Rapamycin provided partial neuroprotection since the number of Nissl positive neurons in the SNpc was similar compared to WT mice, while the number of tyrosine hydroxylase positive neurons was significantly lower and not different from placebo-treated PLP-SYN mice. Rapamycin also significantly reduced the amount of α -synuclein aggregates in the SNpc, while only a trend was observed for the striatum.

Conclusions: Rapamycin partially rescued neurons in the SNpc, although they remained dysfunctional as suggested by the down-regulated tyrosine hydroxylase expression. The partial rescue was paralleled by a positive effect on the amount of α -synuclein aggregates.

Guided Poster Group 8: Technology

1096

The BlueSky Project: monitoring motor and non-motor characteristics of people with Parkinson's disease in the laboratory, a simulated apartment, and home and community settings

K. Erb, J. Daneault, S. Amato, P. Bergethon, C. Demanuele, T. Kangarloo, S. Patel, V. Ramos, D. Volfson, P. Wacnik, H. Zhang, D. Karlin, H. Huggins, L. Soll, G. Costante, G. Vergara-Diaz, F. Parisi, J. Banghu, C. Brooks, C. Dethridge, A. Abrami, E. Bilal, V. Caravagio, S. Heisig, R. Norel, E. Pissadaki, J. Rice, B. Ho, K. Thomas, P. Bonato (Cambridge, MA, USA)

Objective: We present data collected for the BlueSky Project which aims to develop novel assessments of motor and non-motor function using mobile and wearable technology.

Background: A major challenge for the management of Parkinson's disease (PD) and for clinical trials investigating new treatment strategies is to accurately monitor the severity of symptoms over time. Wearable sensors can enable the long-term monitoring of patients in the home and community settings. However, more data is needed to develop robust algorithms to accurately estimate symptom severity.

Methods: This project encompasses 4 studies that investigate motor and non-motor monitoring of healthy volunteers and people with PD experiencing motor fluctuations. In Study 1, 60 healthy volunteers donned several inertial, EMG, and ECG sensors. They were asked to perform speech tasks, a battery of scripted motor tasks, and activities of daily living (ADLs) twice in a laboratory setting. In Study 2, 35 people with PD were asked to perform the same data collection protocol as in Study 1 on two occasions: once in a practically-defined OFF state, and once in an ON state. In Study 3, 25 people with PD donned the same sensors as in Studies 1&2 plus sensors to record galvanic skin response. Subjects performed 5 repetitions of a battery of motor and speech tasks as well as ADLs over a complete medication cycle (6 hours). Subjects came back for a second visit where semi-scripted and unscripted activities were performed in a simulated apartment setting over 6 hours of continuous monitoring using the same sensors. In Study 4, 34 people with PD were asked to perform two weeks of continuous home monitoring while wearing similar devices. During

both weeks, they completed a medication log, motor diary, and QOL instruments. Both weeks of monitoring began and ended with clinic visits where they performed scripted motor tasks as well as the MDS-UPDRS.

Results: 60 healthy volunteers (aged 23-69; 33 females) and 94 people with PD were recruited (aged 42-80; 37 females; years since diagnosis 1-24 years; Hoehn & Yahr 1-3). Motor UPDRS scores were obtained in the ON and OFF states for 60 subjects. 50 subjects exhibited dyskinesia.

Conclusions: Multi-day studies using wearable sensors, even those requiring long laboratory data collections, are feasible in patients with PD. The current project has yielded large amounts of clinically relevant data that will enable us to develop robust algorithms for the estimation of motor and non-motor symptom severity.

1097

Quantitative assessment of the hand motor symptoms in Parkinson's disease based on a custom wearable device: A Proof-of-Principle Study

Q. Ye, Z. Lin, H. Dai, Y. Xiong, G. Cai (Jinjiang, China)

Objective: The objective of this study was to evaluate the feasibility of a wrist-worn wearable device to assist with the quantitative assessment of hand motor symptom, involving tremor, bradykinesia, and rigidity, in patients with PD.

Background: Currently, the clinical evaluation of PD mainly relies on the MDS-UPDRS, which is affected by the subjective judgment and clinical experience of the evaluators. Objective quantification of hand motor symptoms in PD based on wearable motion sensor technology has been the subject of several studies. However, most of the previous studies unable to measure all hand motor symptoms in a single assessment system.

Methods: In this study, a custom wrist-worn wearable device (Fig. 1) based on the nine degrees-of-freedom (9DoF) motion sensors and force sensors was proposed to capture the hand movement information during the clinical assessment tasks. Rapid hand opening/closing, tremor during rest, postural and kinetic task, and wrist rigidity movements were measured with the proposed quantification system. The multivariable regression model was used to involve quantitative tremor parameters to output quantitative tremor scores, and the multi-class support vector machine (SVM) classifier was employed to estimate the bradykinesia severity. In describing the severity of rigidity, the mechanical impedance model was applied to find an optimal quantitative evaluation index.

Results: Clinical experiments with 20 PD patients and 10 age-matched healthy controls showed that the predicted tremor scores correlated well with the clinical assessment results ($r^2=0.95$), and the proposed method can correctly distinguish the bradykinesia severity with superior classification accuracy (93.3%). The mechanical impedance correlated well with the clinical rigidity scores (Pearson correlation coefficient $r=0.872$), and it can be used as an optimal quantitative evaluation index to describe the rigidity severity.

Conclusions: The methodology described and the results presented in this study demonstrated the applicability of quantifying hand motor symptoms in PD patients with a single wearable system. Smart clothes and insoles based on motion sensors are developing and full motor assessment of the whole body of PD patients will be carried out in the near future.

References: [1] Guoen Cai, Zhirong Lin, Houde Dai, et al. Quantitative assessment of parkinsonian tremor based on a linear acceleration extraction algorithm. *Biomedical Signal Processing and Control*, vol. 42, pp. 53-62, April 2018

[2] Zhirong Lin, Houde Dai, Yongsheng Xiong, et al. Quantification assessment of bradykinesia in Parkinson's disease based on a wearable device. In *39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC'17)*, Seogwipo, South Korea, July 2017, pp. 803-806.

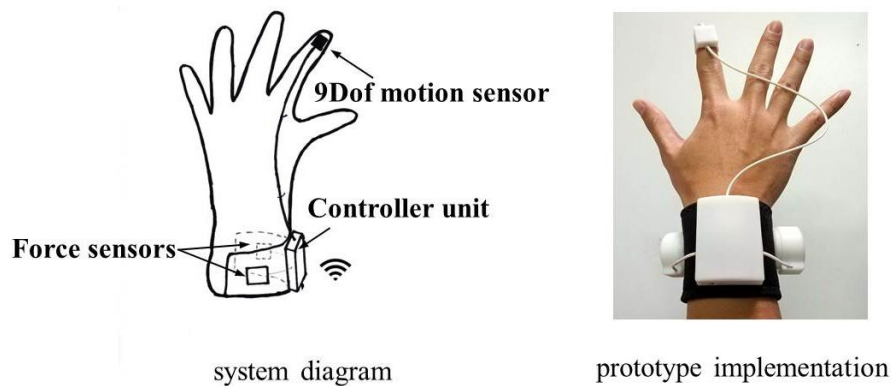


FIG 1 (1097)

1103

Does the Parkinson's Kinetigraph change clinical practice?

S. Jones, C. Grose, S. Mahon, T. Williams, C. Thomas, B. Mohamed (Cardiff, United Kingdom)

Objective: To assess whether information obtained from Parkinson's Kinetigraph (PKG) influences clinical decision-making.

Background: PKG is a relatively new technology: the device is worn continuously for 6-10 days in the home environment and records data on motor function, offers dose alerts and can register medication use. Graphical representation of motor patterns (bradykinesias and dyskinesias) is produced and information can be gained about immobility, somnolence, propensity to impulsiveness and responsiveness to medication.

Methods: A descriptive study of 70 patients attending a hospital-based movement disorder clinic between December 2015 and February 2017, all of whom had PKG data requested by the examining physician as part of routine care. All patients had a diagnosis of PD with either self-reported severe or worsening symptomatology, or an uncertain response to a treatment change and a clinical query over the next best management course. Clinicians were asked to record their proposed management before and after PKG data was available to them.

Results: Data from 70 patients were analysed. The median age was 65 years and 40 (53%) of patients were male. 68 (94%) patients were living in own home. 51 (74%) of the patients had Hoehn and Yahr rating between 2 and 3. Median time from diagnosis was 6.9 years. Increasing symptoms and wearing-off were the commonest reasons for undertaking PKG. Kinetigraph analysis was consistent with clinical impression in 53 patients (76%). It gave additional clinically-relevant information in 18 (25%) patients (unidentified brady- or dyskinesia). Clinical decision changed in 24 (34%) patients based on the results of PKG. 4 (6%) patients clinically considered to require an advanced treatment had current medication titrated instead. 5 (7%) patients in whom advanced treatments were not being considered pre-PKG, were deemed to require them and were subsequently referred. In 2 patients the PKG demonstrated a poor response to medication which led to revision of the diagnosis.

Conclusions: Patient management has actively changed based on PKG information for a significant number of patients in this clinic cohort. The PKG may allow better identification of individuals needing more complex therapies, as well as facilitating medication changes that may delay the need for such treatments. Such outcomes may improve quality of life for the individuals as well as improving cost-efficiency in the service.

1111

The use of smartphone task derived features to predict clinical scores in Parkinson's Disease (PD)

C. Lo, S. Arora, F. Baig, T. Barber, M. Lawton, A. Zhan, M. Little, M. Hu (Oxford, United Kingdom)

Objective: To capitalise on the ubiquity of smartphones and to develop tools to objectively assess symptoms associated with PD.

Background: Accurate and reproducible outcome measures resistant to the inherent inter- and intra-rater variability associated with clinician derived measures of disease change are critically needed to inform PD research.

Methods: We obtained smartphone recordings from deeply phenotyped participants enrolled in a large longitudinal cohort study involving participants with early PD and healthy controls. Participants performed tasks assessing voice, balance, gait, dexterity, reaction time, rest and postural tremor. 2674 time-synchronised recordings of all 7 tasks were analysed from 329 participants with PD (63% male, mean age 68.1 years, standard deviation 9.3 years, mean Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) III score 28.7, standard deviation 12.5). In total, 998 features were extracted. Using the smartphone-based features, machine learning algorithms were employed to predict scores derived from semi-quantitative tests of motor function, namely the Purdue pegboard test, Timed up and go and the Flamingo test as well as the MDS-UPDRS part III, Montreal Cognitive Assessment score and Beck Depression Inventory. Model accuracy was evaluated using a 10-fold cross validation scheme, whereby the data was randomly split into training and test sets comprising 90% and 10% of the data respectively.

Results: Having demonstrated around 85% sensitivity and specificity in distinguishing PD from healthy controls using smartphone motor testing, we also predict semi-quantitative tests of motor function and cognition with relatively high levels of accuracy. This includes the prediction of the motor MDS-UPDRS score with a mean absolute error of 4.9 points, within previously observed limits of inter-rater variability of between 1.7 and 5.4 points.[1]

Conclusions: Objective smartphone assessments of voice and movement accurately predict clinical scores in early PD. Advantages include low cost, high-frequency, data capture across the clinic and home environment, with the potential for individual stratification and treatment monitoring.

References: 1. Post B, Merkus MP, de Bie RM, et al. Unified Parkinson's disease rating scale motor examination: are ratings of nurses, residents in neurology, and movement disorders specialists interchangeable? *Movement disorders: official journal of the Movement Disorder Society* 2005;20(12):1577-84. doi: 10.1002/mds.20640 [published Online First: 2005/08/24].

1113

Temporal Gait Parameters in Parkinson's Disease: A Study Using PDlogger, A Quantitative Gait Measuring Device

N. Chia, J. Derrick, V. Mikos, S. Ng, A. Tay, S-C. Yen, K. Koh, D. Tan, K. Prakash, L. Tan, W.L. Au (Singapore, Singapore)

Objective: Freezing of gait (FOG) is a disabling symptom in patients with Parkinson's disease (PD). This study aims to investigate the differences in temporal gait parameters between early PD subjects and healthy controls, and between PD subjects with FOG (PD+FOG) and early PD cohort.

Background: Wearable sensors allow clinicians and researchers to objectively assess movements and analyse the gait disturbances in patients.

Methods: 137 subjects (Early PD=50, PD+FOG=25, Controls=62) were recruited from two large tertiary hospitals in Singapore. Subjects performed the 7-metre Timed Up and Go (7mTUG) while wearing the PDlogger, an in-house quantitative gait measuring device with inertia motion sensors worn over the ankles and the back of the neck. Temporal gait parameters such as stride time, angular velocity and cadence were recorded. FOG severity was expressed as the percentage of time in which FOG occurred (%FOG) in video recordings. Differences between groups were analysed using Kruskal-Wallis with post-hoc Mann-Whitney U

test to further investigate inter-group statistical significance. Bivariate associations were conducted using Spearman's rho to study the relationship between variables.

Results: There were significant differences ($p < 0.001$) in stride time, angular velocity, cadence, and 7mTUG time across all 3 groups. Post-hoc analysis revealed a longer stride time ($p < 0.001$), reduced cadence ($p < 0.001$), longer 7mTUG time ($p < 0.001$) and a higher angular velocity ($p < 0.001$) in early PD compared to healthy controls. PD+FOG had shorter stride time ($p < 0.001$), increased cadence ($p < 0.001$), longer 7mTUG time ($p < 0.001$), and reduced angular velocity ($p < 0.001$) compared to early PD cohort. There were no significant differences in temporal gait parameters between PD+FOG and healthy controls, except for the 7mTUG time ($p < 0.001$). The angular velocity was correlated with the UPDRS motor subscores for gait and balance in both early PD ($\rho = -0.417$, $p < 0.01$) and PD+FOG ($\rho = -0.785$, $p < 0.01$). The angular velocity decreased with increasing %FOG ($\rho = -0.642$, $p < 0.01$).

Conclusions: Early PD subjects demonstrated longer stride times, reduced cadence, and higher angular velocities compared to healthy controls. The angular velocities decreased with increasing disease severity and %FOG.

References: Hausdorff, J.M., Schaafsma, J.D., Balash, Y., Bartels, A.L., Guverich, T. & Giladi, N. (2003). Impaired regulation of stride variability in Parkinson's disease subjects with freezing of gait. *Exp Brain Res* (149) 187-194. DOI: 10.1007/s00221-002-1354-8. Hausdorff J.M., Ladin Z. & Wei, J.Y. (1995). Footswitch system for measurement of the temporal parameters of gait. *J Biomech* (28) 347-351. Morris, M. Iansek, R., Matyas, T. & Summers, J. (1998). Abnormalities in the stride length-cadence relation in parkinsonian gait. *Movement Disorder* (13) 61-69.

1117

Feasibility of a multi-sensor data fusion method for assessment of Parkinson's disease motor symptoms

M. Memedi, S. Aghanavesi, D. Nyholm, F. Bergquist, M. Senek (Örebro, Sweden)

Objective: To assess the feasibility of measuring Parkinson's disease (PD) motor symptoms with a multi-sensor data fusion method. More specifically, the aim is to assess validity, reliability and sensitivity to treatment of the methods.

Background: Data from 19 advanced PD patients (Gender: 14 males and 5 females, mean age: 71.4, mean years with PD: 9.7, mean years with levodopa: 9.5) were collected in a single center, open label, single dose clinical trial in Sweden [1].

Methods: The patients performed leg agility and 2-5 meter straight walking tests while wearing motion sensors on their limbs. They performed the tests at baseline, at the time they received the morning dose, and at pre-specified time points until the medication wore off. While performing the tests the patients were video recorded. The videos were observed by three movement disorder specialists who rated the symptoms using a treatment response scale (TRS), ranging from -3 (very off) to 3 (very dyskinetic). The sensor data consisted of lower limb data during leg agility, upper limb data during walking, and lower limb data during walking. Time series analysis was performed on the raw sensor data extracted from 17 patients to derive a set of quantitative measures, which were then used during machine learning to be mapped to mean ratings of the three raters on the TRS scale. Combinations of data were tested during the machine learning procedure.

Results: Using data from both tests, the Support Vector Machines (SVM) could predict the motor states of the patients on the TRS scale with a good agreement in relation to the mean ratings of the three raters (correlation coefficient = 0.92, root mean square error = 0.42, $p < 0.001$). Additionally, there was good test-retest reliability of the SVM scores during baseline and second tests with intraclass-correlation coefficient of 0.84. Sensitivity to treatment for SVM was good (Figure 1), indicating its ability to detect changes in motor symptoms. The upper limb data during walking was more informative than lower limb data during walking since SVMs had higher correlation coefficient to mean ratings.

Conclusions: The methodology demonstrates good validity, reliability, and sensitivity to treatment. This indicates that it could be useful for individualized optimization of treatments among PD patients, leading to an improvement in health-related quality of [1] M. Senek, S. M. Aquilonius, H. Askmark, F. Bergquist, R.

Constantinescu, A. Ericsson, et al., "Levodopa/carbidopa microtablets in Parkinson's disease: a study of pharmacokinetics and blinded motor assessment," *Eur J Clin Pharmacol*, Jan 18 2017. [2] C. G. Goetz, G. T. Stebbins, K. A. Chung, R. A. Hauser, J. M. Miyasaki, A. P. Nicholas, et al., "Which dyskinesia scale best detects treatment response?," *Mov Disord*, vol. 28, pp. 341-6, Mar 2013. life.

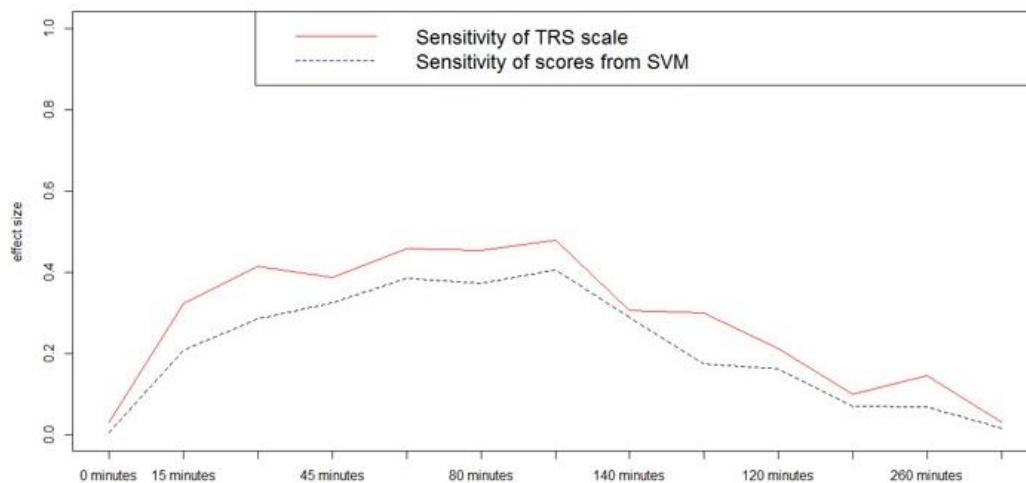


FIG. 1 (1117)

1118

Assessment of Motor Symptoms in Parkinson's disease using Flexible Wearable Sensors and Deep Neural Networks: A CIS-PD substudy

L. Lonini, A. Dai, C. Poon, N. Shawen, L. Shimanovich, T. Simuni, D. Daeschler, J. Rogers, A. Jayaraman (Chicago, IL, USA)

Objective: To develop an algorithm to characterize in-office motor symptoms of Parkinson's disease (PD) using multiple wireless sensors, and to compare symptom recognition in activities of daily living (ADLs) vs. standard clinical assessments.

Background: Objective assessment of PD motor disability could greatly impact design of PD clinical trials and clinical care. It still remains to be determined what is the minimal number of sensors necessary to provide accurate characterization of PD motor function, specifically motor fluctuations, while patients are engaged in routine activities of daily living (ADLs).

Methods: This study was conducted as a single center sub-study of the Michael J Fox Foundation (MJFF) funded clinician input study (CIS-PD). A subset of 14 participants (mean=61.6y; SD=10.1y) were fitted with 10 sensors [figure1], assessed with serial MDS-UPDRS and performed standardized ADL tasks including walking and fine dexterity movements. The tasks were performed first in the medications OFF state and then 5 more times every 30 minutes after taking medications (ON state). All exams were videotaped. An additional, single assessment was performed 2 weeks later. A clinician rated the severity of tremor, bradykinesia and dyskinesia of the upper-extremities on a scale from 0-4. We trained a convolutional neural network model to detect whether tremor or bradykinesia were present (score > 0) in 5-second recordings of the raw sensor data. A leave-one-visit-out cross validation was performed to assess the accuracy of the model at predicting symptoms at different time points.

Results: This report is limited to the analysis of the upper extremities sensors. Area under the curve (AUC) of the model, averaged across tasks and time, was 0.81 (SD=0.047) for bradykinesia detection, and 0.87 (SD=0.041) for tremor. Bradykinesia detection was higher during walking and assembling nuts and bolts (median recall=0.87); recall of tremor was comparable between walking and finger to nose tasks (0.69, p=0.48)[figure2].

Conclusions: Flexible sensors are a non-invasive method to continuously record movement data in PD. Deep networks can successfully detect PD symptoms from such data. The analysis of the full dataset and minimal number of sensors to optimize model accuracy is underway. All raw data from this study will be made publicly available by MJFF.

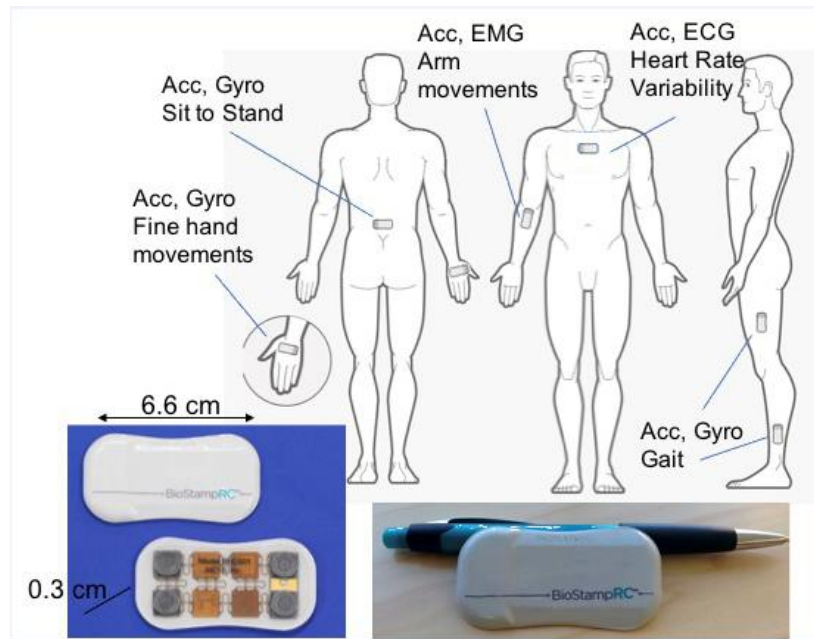


FIG. 1 (1118)

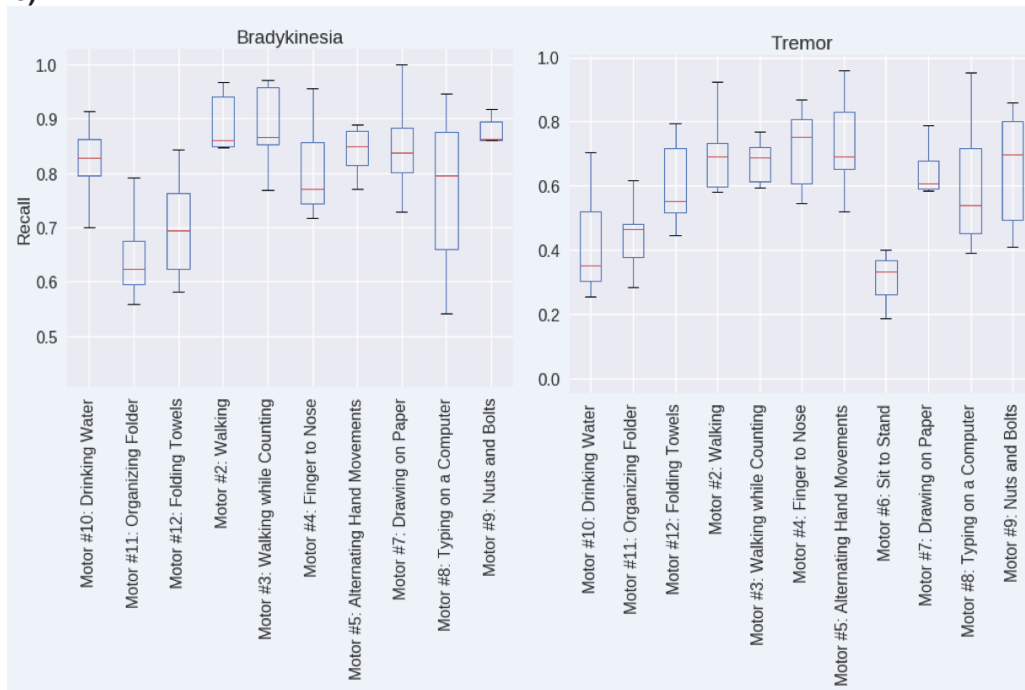


FIG. 2 (1118)

Objective monitoring of drug response in early PD patients using remote, at-home typing data through machine learning analysis

M. Matarazzo, T. Arroyo-Gallego, P. Montero Escribano, V. Puertas-Martín, I. Butterworth, C. S. Mendoza, MJ. Ledesma-Carbayo, MJ. Catalán, JA. Molina-Arjona, F. Bermejo-Pareja, JC. Martínez Castrillo, L. López-Manzanares, A. Alonso-Cánovas, J. Herreros-Rodríguez, I. Obeso, P. Martínez Martín, JC. Martínez-Ávila, A. Gómez de-la-Cámara, M. Gray, JA. Obeso, L. Giancardo, Á. Sánchez-Ferro (Vancouver, BC, Canada)

Objective: We designed an algorithm to detect response to medication in an early PD population using at-home, unsupervised, unobtrusive typing data.

Background: Advances in technology are opening a new era to remotely evaluate people with PD. In previous studies we have shown that features of in-lab keyboard typing can be used to evaluate motor skills and to classify subjects as having PD or not [1]. More recently we have shown the same capability from typing on a touch-screen based information and from keyboard data at-home [2]. We now hypothesized that typing on an electronic device, a habitual behavior, likely controlled by the nigro-striatal dopaminergic pathway, could allow for objectively and non-obtrusively monitoring parkinsonian features and response to medication in an at-home setting.

Methods: We designed a naturalistic prospective validation study to evaluate whether typing patterns changed in accordance with responsiveness to medication. 31 early PD subjects, who were going to start a dopaminergic drug, and 30 matched controls were enrolled. We remotely monitored their typing pattern over a 6-month follow-up period while antiparkinsonian medications were being titrated (fig.1). A novel deep learning algorithm (nQRNN) was developed to detect participants' outcome defined as the response to medication assessed by the UPDRS-III minimal clinically important difference (MCID) at the final visit (6 months). Further, we tested if this model could predict that outcome earlier than 6 months.

Results: The nQRNN had an overall moderate kappa agreement ($k=0.50$) and fair 0.73 area under the ROC curve with the time-coincident UPDRS-III MCID-based classification of response (fig.2). Furthermore, the nQRNN at week 3 (and beyond) could reliably predict which subjects would respond and which wouldn't. (fig.3)

Conclusions: This preliminary study suggests that a habitual task based on remotely-gathered unsupervised typing data at home allows for an accurate and predictive classification of drug response in PD. If confirmed by a larger prospective study, this approach could provide supplementary information to clinicians for a more continuous monitoring of motor symptoms of PD, thus helping to take informed decision on therapeutic strategies and disease management. Also, this tool could be useful as a cost-effective and reliable outcome measure for clinical trials to test response to medication.

References: 1. Giancardo L, Sánchez-Ferro Á, Arroyo-Gallego T, et al. Computer keyboard interaction as an indicator of early Parkinson's disease. *Sci Rep* 2016;6:34468. doi:10.1038/srep34468. 2. Arroyo-Gallego, T, Ledesma-Carbayo, M, Butterworth, I, et al. Detecting Motor Impairment in Early Parkinson's Disease via Natural Typing Interaction with Keyboards: Validation of the neuroQWERTY Approach in an Uncontrolled At-Home Setting. *JMIR* 2018 in press. doi: 10.2196/jmir.9462.

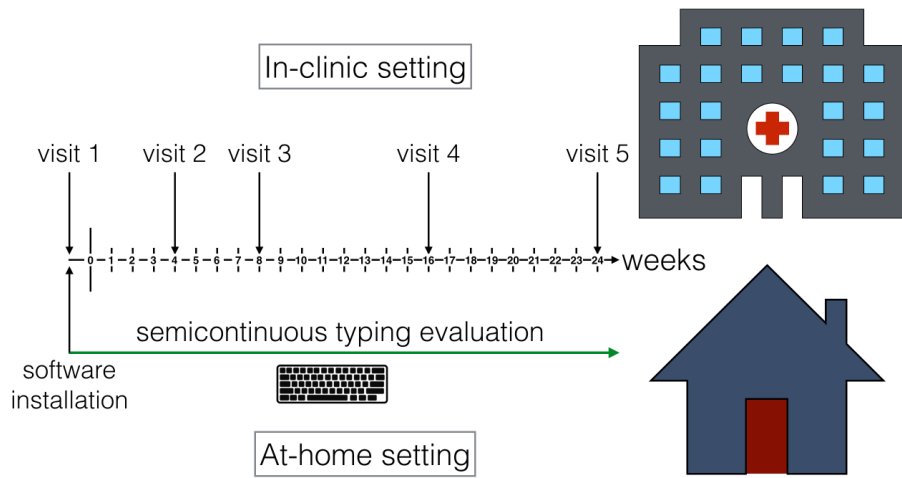


FIG. 1 (1124)

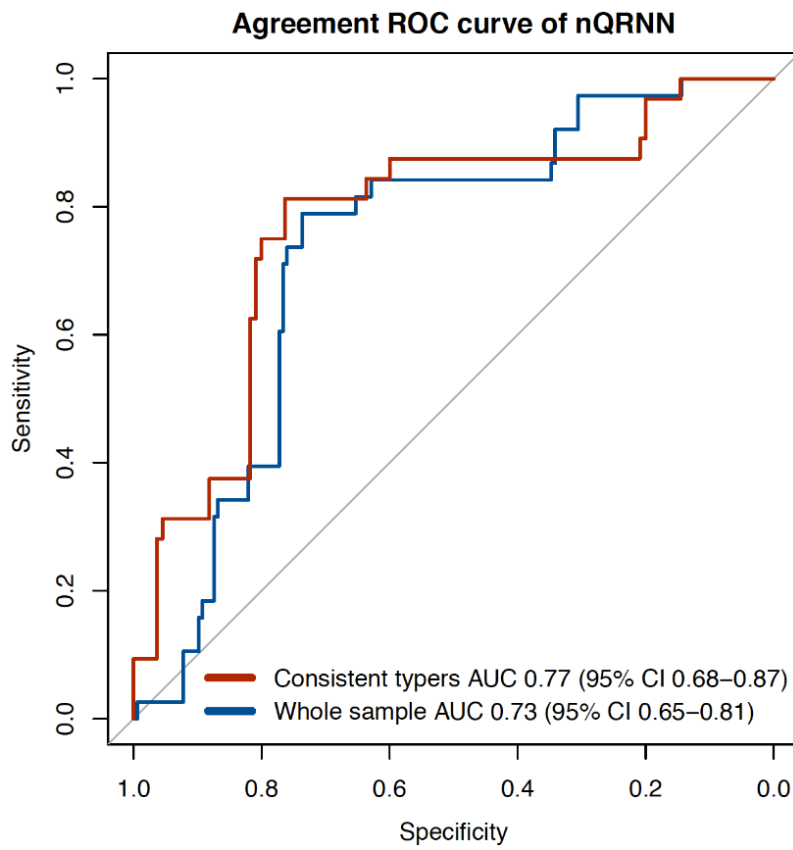


FIG. 2 (1124)

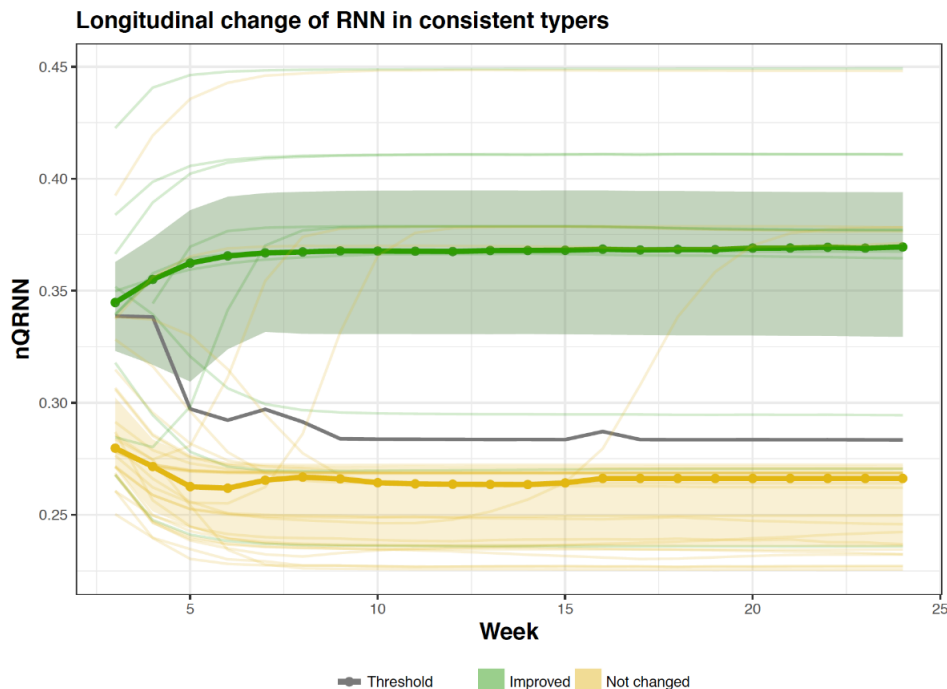


FIG. 3 (1124)

1138

The Levodopa Response Trial and the Parkinson Disease Digital Biomarker Challenge: Monitoring symptoms of Parkinson's disease in the lab and home using wearable sensors

J. Daneault, G. Vergara-Diaz, G. Costante, E. Fabara, G. Ferreira-Carvalho, F. Golabchi, F. Parisi, S. Sapienza, Y. Chae, P. Snyder, P. Aubin, P. Banda, D. Brunner, R. Dorsey, L. Mangravite, W. Marks, E. Neto, U. Rubin, E. Soderberg, D. Daeschler, S. Moore, S. Sieberts, L. Omberg, P. Bonato, The Parkinson's Disease Digital Biomarker DREAM Challenge Consortium (Newark, NJ, USA)

Objective: To leverage a community of researchers and shared wearable data to develop algorithms to estimate the severity of PD specific symptoms.

Background: People with Parkinson's disease (PwPD) often experience fluctuations in motor symptom severity. Wearable sensors have the potential to help clinicians monitor symptoms over time, outside the clinic. However, to gather accurate and clinically-relevant measures, there is a need to develop robust algorithms based on clinically-labelled data.

Methods: The Levodopa Response Trial captured three-axis acceleration from two wrist-worn sensors and a smartphone located at the waist from 29 PwPD continuously over 4 days. On day 1, in an in-clinic visit, participants performed clinical assessments and motor tasks on their regular medication regimen. During these visits, a clinician also provided symptom severity scores for tremor, bradykinesia, and dyskinesia. On days 2 & 3, sensor data was collected while participants were at home. On day 4, participants returned to the clinic for the same assessments as day 1, but arrived without having taken their medication for at least 10 hours.

Leveraging this dataset, Sage Bionetworks, the Michael J Fox Foundation and the Robert Wood Johnson Foundation launched the PD Digital Biomarker DREAM Challenge which made a subset of the data available to researchers to develop robust and accurate algorithms for the estimation of specific symptoms' severity.

Results: Teams participating in the challenge used several technical approaches, from signal processing to deep learning. 35 submissions were received for the estimation of action tremor severity. Teams achieved an area under the precision-recall curve (AUPR) of 0.444 to 0.75. As for dyskinesia during movement, 37 submissions were received and the teams achieved an AUPR of 0.175 to 0.477. Finally, 39 submissions were

received for the estimation of bradykinesia and the teams achieved an AUPR of 0.413 to 0.95. Null expectations for the testing datasets were 0.432, 0.195, and 0.266, respectively.

Conclusions: Making datasets available to the community leverages the creativity of different groups to develop robust and accurate algorithms for the estimation of PD symptom severity. This will lead to better quality and interpretability of data collected in unsupervised settings within the community.

1148

The international MDSGene initiative: Systematically exploring genotype-phenotype correlations of hereditary movement disorders

S. Petkovic, S. Schaake, J. Huang, H. Madoev, A. Rasheed, C. Lill, K. Lohmann, C. Klein, C. Marras (Lübeck, Germany)

Objective: To explore phenotype-genotype relationships of familial movement disorders, the Movement Disorder Society Genetic Mutation Database (MDSGene) extracts, summarizes, and curates published data on the phenotypic and mutational level.

Background: The increasing cost-efficiency of genetic testing has led to a substantial increase in the number of publications and the spectrum of reported variants potentially causative for movement disorders. MDSGene, launched in 2016, is a freely accessible online resource (<http://www.mdsgene.org>) that provides a systematic overview on the currently published literature on phenotype-genotype relationships in hereditary movement disorders in the English language.

Methods: Inclusion of genes into MDSGene is based on the recommendations of the MDS Task Force for Nomenclature of Genetic Movement Disorders. Data extraction and curation is performed according to MDSGene's standardized data extraction protocol optimized for hereditary movement disorders by an international team of >60 members in 13 countries including clinicians, geneticists, and epidemiologists.

Results: MDSGene currently contains >750 variants reported in >3900 movement disorder patients in >650 publications including Parkinson's disease (PINK1, Parkin, DJ-1, SNCA, VPS35, LRRK2), atypical Parkinson's disease (SYNJ1, DNAJC6, ATP13A2, FBXO7), dystonia (TOR1A, KMT2B, THAP1, GNAL, ANO3), paroxysmal movement disorders (PNKD, PRRT2, SLC2A1), and familial brain calcification (PDGFB, PDGFRB, SLC20A2, XPR1). Detailed clinical information contains motor and non-motor signs of movement disorders.

Conclusions: The MDSGene database represents an important research tool and allows for easy online access to a wealth of carefully curated clinical and genetic information. It is projected to contain all major hereditary movement disorders by the year 2021 and thus is ideally positioned to become a leading resource for genetic counseling as well as clinical trial design.

Guided Poster Group 9: Tremor

1169

Phase-locked transcranial alternating current stimulation of the cerebellum for essential tremor

S. Schreglmann, D. Wang, E. Boyden, K. Bhatia, J. Rothwell, N. Grossman (London, United Kingdom)

Objective: To test whether hand tremor can be mitigated by delivering an electrical stimulation to the ipsilateral cerebellum, phase-locked to the tremulous hand movement.

Background: Essential Tremor (ET) is believed to originate from oscillatory neuronal network activity involving cortex, thalamus and cerebellum. tACS has been devised as a safe and non-invasive means to deliver weak, exogenous and periodic electric fields through cutaneous electrodes to the human brain in order to modulate oscillatory network activity.

Methods: We tested this stimulation modality on postural tremor in ET patients (n=11) in a quadruple replication, semi-randomized block-design including six phase-locked, one non phase-locked stimulation and one sham condition.

Each block of stimulation included 15s of baseline period, 30s of stimulation period and 15s of post stimulation period. Tremor activity measured by a tri-axial accelerometer was used to compute the instantaneous tremor phase in real-time using a Hilbert transformation-based algorithm implemented on a microcontroller (Arduino Due). A sinusoidal voltage waveform was generated a) with a frequency equalling the tremor frequency adjusted to have a fixed lag of 0°, 60°, 120°, 180°, 240° or 300° relative to the instantaneous tremor phase (phase-locked condition), b) at the tremor frequency without adjustment (non phase-locked condition), c) and dropped to zero after the initial 5 s ramp-up period (sham condition). The stimulation signal was fed to an isolated current source DS4 (Digitimer Ltd., Welwyn Garden City, UK). Stimulation was delivered just above the individual cutaneous sensory threshold via an active (30x30mm) and return (50x50mm) skin electrode placed over the lateral cerebellar hemisphere and contralateral, frontal cortex.

After removal of sessions with baseline tremor amplitude ± 2 SD of mean baseline recordings per subject, offline analysis was done using MatLab (The MathWorks). Changes in tremor amplitude were calculated as z-scores \pm SD.

Results: Phase-locked stimulation was achieved reliably throughout the phase-spectrum. A comparison of tremor amplitude across all blocks showed a significant reduction in tremor amplitude during phase-locked (-2.22 ± 1.5) versus non phase-locked stimulation (-0.94 ± 0.92 ; $p=0.01$; paired t-test).

Conclusions: Our data provide first evidence that phase-locked tACS can modulate ET tremor amplitude, most likely by influencing network activity via cerebellar cortical stimulation.

1174

Gamma Knife Radiosurgery for essential and parkinsonian tremor: Long-term experience in a Spanish center

JR. Perez-Sanchez, R. Martinez-Alvarez, NE. Martinez-Moreno, I. Cuervo-Arango, G. Rey Portoles, I. Parees, A. Del Barrio, J. Alvarez-Linera, MM. Kurtis (Madrid, Spain)

Objective: To describe the experience of a single Spanish center in gamma knife thalamotomy (GKT) as treatment of refractory tremor in patients with Essential Tremor (ET) and Parkinson's Disease (PD).

Background: GKT is a minimally invasive stereotactic surgical option to treat medically refractory tremor in patients with ET and PD, particularly indicated for elderly and fragile patients. Recent studies have shown good results in terms of safety and efficacy (1,2). However, long-term evidence is limited, especially for PD tremor.

Methods: During a 5-year period (2013-2017), 12 patients underwent unilateral GKT and were followed-up for at least 12 months with motor and neuropsychiatric evaluations. Five patients had asymmetric tremor predominant PD, 4 cases had intractable ET and 3 patients had ET-PD. Mean age was 78.8 ± 6.8 years old (6 patients >75 years old). 2 patients were on anticoagulants. Leksell Gamma Knife was used to target the ventral intermediate nucleus with a radiation dose of 130 Gy. Efficacy was scored based on subscales of the Fahn-Tolosa-Marin (FTM) tremor rating scale, target-side tremor subscales of the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS), and EuroQoL-5D to assess quality of life.

Results: Median follow-up duration was 22 months (12-54 months). After GKT, 11 patients (91.7%) improved their tremor scores. 6 patients (50%), 3 PD, 2 ET and 1 ET+PD reported tremor eradication or minimal symptoms. Tremor improvement was sustained at the end of follow-up in 10 out of 11 patients (90.9%). Mean FTM scores improved significantly: for hand postural tremor, from 2.86 pre to 1.14 ($p=0.006$); for kinetic tremor, from 3.14 to 1.29 ($p=0.007$); for handwriting, from 2.57 to 1.29 ($p=0.016$); and for drinking, from 3.14 to 1.71 ($p=0.015$). Mean motor UPDRS scores significantly decreased: for rest tremor in the targeted upper limb, from 3.00 to 0.71 ($p=0.001$); and for overall tremor in the target-side, from 10.29 to 2.14 ($p=0.002$). EuroQoL-5D ameliorated from 8.89 to 6.56 ($p=0.027$). No severe adverse events

occurred. Three patients reported transient hand paresthesias, cognitive disturbances without changes in neurophysiological tests and depression, respectively.

Conclusions: This study suggests that GKT is a safe and long-term efficacious treatment option for medically refractory ET, and may be considered for asymmetric tremor predominant PD, especially in patients who are elderly, on anticoagulants or have high surgical risk that contraindicates DBS.

References: 1. Martínez-Moreno NE, Sahgal A, De Salles A, Hayashi M, Levivier M, Ma L, Paddick I, Régis J, Ryu S, Slotman J, Martínez-Álvarez R. Stereotactic radiosurgery for tremor: systematic review. *J Neurosurg.* 2018 Feb 23:1-12. 2. Niranjana A, Raju SS, Kooshkabi A, Monaco E, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for essential tremor: Retrospective analysis of a 19-year experience. *Mov Disord.* 2017;32(5):769-777.

1175

A new clinical and research smartphone application to assess tremor and bradykinesia in patients with movement disorders

C. Duval, J.F. Daneault, B. Carignan, C.É. Coderre, S. Bogard (Montreal, QC, Canada)

Objective: Determine the ability of on-board gyroscopes in smartphones to assess the performance of rapid alternating movements (RAM) during fast repetitive pronation-supination movements at the wrist, a measure of core bradykinesia.

Background: Smartphones are now ubiquitous, and possess several sensors capable of measuring tremulous activity and voluntary movements with relatively good accuracy. Following our work on the validation of smartphone accelerometers for the assessment of abnormal tremors (1,2), we developed a free smartphone application for patients, physicians and researchers who are interested in the assessment of abnormal tremors and bradykinesia. The app can characterize several characteristics of rest, kinetic and postural tremors and quantify characteristics of bradykinesia from RAM such as mean and maximal velocity of pronation-supination movements of the hand using onboard gyroscopes. However, the accuracy of gyroscopes to assess RAM performance during a fast repetitive pronation-supination movements of the forearm remains to be determined.

Methods: The accuracy of the gyroscopes of two smartphones, one iPhone 6s and one Android LG-D852 (Android 6.0) was assessed against an optical rotational encoder having an accuracy of 0.33 deg. Both phones were linked and held against a ball attached to the optical rotational encoder. Once recording initiated, the phones were pronated and supinated simultaneously with the ball. 5 trials of thirty seconds were performed, each having different amplitudes, velocity and variability characteristics. From those, analysis was done on 5-second epochs. First, the rotational axis was automatically detected. Second, differences in sampling rate were adjusted and signals from rotational encoders were differentiated to velocity and aligned with data from both smartphones. Correlation was used to assess agreement between signals; rotational encoders versus iPhone and Android, as well both smartphones against each other.

Results: Mean correlations between time series of both smartphones were $r = 0.997 \pm 0.003$. Mean correlations between time series from the rotational encoder and those from the iPhone and Android phone were $r = 0.909 \pm 0.100$ and 0.910 ± 0.099 , respectively. All correlations were significant at $p < 0.05$.

Conclusions: Our results demonstrate the ability of on-board gyroscopes in smartphones to assess RAM performance during fast repetitive movements at the wrist. This will enable us to propose a proven method to assess core bradykinesia in patients with movement disorders.

References: 1. Daneault JF, Carignan B, Codère CÉ, Sadikot AF, Duval C. (2013) Using a smart phone as a standalone platform for detection and monitoring of pathological tremors. *Front Hum Neurosci.* 18;6:357. 2. Carignan B, Daneault JF, Duval C (2015) Measuring tremor with a smartphone. *Methods Mol Biol.* 1256:359-74.

1177

Shaky legs: The clinical spectrum and treatment of orthostatic tremor; a systematic review

A. Buijink, M. Meulepas, A. van Rootselaar (Amsterdam, Netherlands)

Objective: To provide a systematic literature overview of orthostatic tremor (OT).

Background: Orthostatic tremor (OT) is characterized by a high-frequency tremor of the leg muscles during stance, resulting in an unsteady feeling. The pathophysiology is still not understood. Treatment options are limited and are often unsatisfactory. A systematic literature review on primary OT is lacking the literature.

Methods: Here we review data of a total of 617 OT-patients, with a focus on primary OT, retrieved after a systematic search in Pubmed (583 individual patients from 45 case reports, 20 case series, and 7 therapeutic trials) and from a questionnaire-based study in Dutch OT-patients (n=34).

Results: Overall, 67% of identified OT patients is female; mean age at onset is 57 (17-81) years. Most patients were primary OT cases, however this distinction is not always made. Six percent (22 of 390 cases) has a positive family history for OT. Mean delay to diagnosis is 7.7 years (n=268). A substantial number of patients reports falls. Quality of life is affected. Clonazepam is the most prescribed drug but is not always effective. Trials report a possible positive effect of gabapentin. Deep brain stimulation (DBS), performed in a limited number of patients, has shown a positive effect.

Conclusions: OT can be disabling and is under-recognized. The most effective treatment remains uncertain, with some evidence for clonazepam and gabapentin. DBS provides an alternative for drug-resistant and disabling OT, although long term effects are still unknown. To gain more insight in OT, it is of importance to differentiate primary OT from OT-plus and secondary OT. Increasing awareness for OT will shorten the delay in time to diagnosis and possibly lead to development of better treatment options.

1182

The spectrum of involuntary movements in patients with motor neuron disease – a cross-sectional study

K. Vogelnik, L. Dolenc Grošelj, B. Koritnik, L. Leonardis, J. Zidar, M. Kojović (Ljubljana, Slovenia)

Objective: To describe prevalence, clinical characteristics and electrophysiological findings of involuntary movements in patients with motor neuron disease (MND).

Background: Involuntary movements are not considered typical finding in MND. However, we have frequently observed involuntary jerks in patients with otherwise typical MND.

Methods: Sixty-five consecutive patients followed in MND outpatient clinic were clinically examined by movement disorders experts and video-recorded. The presence and quality of involuntary movements was noted and severity was graded on a scale from + to +++. Movements were further classified in one of the following: minipolymyoclonus, thumb rest tremor, large amplitude irregular hand tremor and regular small amplitude hand tremor. In proportion of patients, surface poly-electromyography (EMG) and accelerometry were performed.

Results: 44/65 patients had involuntary movements. 27 had non-rhythmical, small amplitude, random finger jerks present at rest and/or activation, suggestive of minipolymyoclonus. Tremor, defined as rhythmic, oscillation of a body part, was noted in 34 patients. Action hand tremor was big amplitude and irregular in 17 patients, while 11 patients had more regular and smaller amplitude tremor. All except one tremor patient able to perform finger to nose test also had intention tremor component. (Table 1). 17 patients had thumb rest tremor, almost always associated with pseudo-dystonic thumb posture (16/17). Accelerometry confirmed the presence of tremor with frequencies ranging from 4 – 7.5 Hz. Poly EMG showed that patients were almost never in a state of complete relaxation. Tremor and minipolymyoclonus were commonly associated with firing of enlarged motor units (MU) (Figure 1 and 2).

Conclusions: Contrary to widespread belief, involuntary movements are present in the majority of patients with MND. Based on the analysis of EMG and accelerometry recording, we hypothesize that pseudodystonic thumb posture, thumb “rest” tremor, minipolymyoclonus and irregular large-amplitude

tremor are part of the same spectrum of involuntary movements. These arise from incomplete muscle relaxation at rest and firing of enlarged MUs on the background of reduced recruitment pattern on attempted activation. Regular lower amplitude tremor is probably of central origin.

References: 1. Bhat, S., Ma, W., Kozochonok, E. & Chokroverty, S. Fasciculations masquerading as minipolymyoclonus in bulbospinal muscular atrophy. *Ann. Indian Acad. Neurol.* 18, 249–251 (2015). 2. Spiro, A. J. Minipolymyoclonus. *Neurology* 20, 1124 (1970). 3. Tremor & Essential Tremor. Available at: <https://www.movementdisorders.org/MDS/About/Movement-Disorder-Overviews/Tremor-Essential-Tremor.htm>. (Accessed: 8th January 2018). 4. Mills, K. R. The basics of electromyography. *J. Neurol. Neurosurg. Psychiatry* 76, ii32-ii35 (2005). 5. de Carvalho, M., Eisen, A., Krieger, C. & Swash, M. Motoneuron firing in amyotrophic lateral sclerosis (ALS). *Front. Hum. Neurosci.* 8, (2014).

TABLE 1 (1182)

Subject No. / sex / involuntary hand or finger movement	Muscle power ¹ / spasticity ² / reflexes ²	Polymyoclonus (PMMC) / rest (R), action (A) or both (R+A) / symmetry (S) or asymmetry (A)	Rest thumb tremor	Pseudo-dystonic thumb posture	Large amplitude, irregular tremor/ rest (R), action (A), / intention tremor (finger-to-nose test)	Small amplitude, irregular tremor/ rest (R), action (A), / intention tremor (finger-to-nose test)
1 / NO	4 / 0 / 3					
2 / NO	4 / 1 / 3					
3 / YES	2,5 / 2 / 3	PMMC++ / R+ A / S	NO	NO	YES / A / YES	NO / NO / NO
4 / YES	2,5 / 2 / 3	PMMC++ / A / A	NO	NO	NO / NO / NC	NO / NO / NC
5 / YES	1,5 / 0 / -1	NO	YES++ ⁴	YES	NO / NC ⁵ / NC	NO / NC / NC
6 / YES	2 / 2 / 3	PMMC++ / A / A	NO	NO	NO / NO / NO	NO / NO / NO
7 / NO	4 / 1 / 3					
8 / NO	4 / -1 / 0					
9 / YES	2,5 / 1 / 2	YES / R + A / A	YES+	YES	YES / A / NC	NO
10 / YES	2,5 / 1 / 3	NO	NO	NO	YES / A / NC	NO
11 / YES	2 / -1 / 0	PMMC++ / R + A / S	YES++	YES	NO / NO / NC	NO / NO / NC
12 / NO	3,5 / 0 / 1					
13 / NO	0 / 3 / 3					
14 / NO	4 / 2 / 3					
15 / YES	4 / 1 / 3	NO / NO / NO	YES++	YES	NO / NO / NO	NO / NO / NO
16 / YES	2,5 / 0 / 3	PMMC+ / A / A	NO	NO	NO / NO / NC	NO / NO / NC
17 / YES	4 / 1 / 3	NO	NO	NO	NO / NO / NO	YES / A / YES
18 / NO	1,5 / -1 / 1					
19 / NO	1 / -1 / 0					
20 / YES	2,5 / -1 / 0	PMMC++ / R + A / S	YES++	YES	NO / NO / NC	NO / NO / NC
21 / YES	3,5 / 2 / 2	PMMC+ / R + A / S	NO	NO	NO / NO / NC	NO / NO / NC
22 / YES	2,5 / 1 / 3	NO	NO	YES	YES / A / NC	NO / NO / NC
23 / YES ⁶	4 / 2 / 3					
24 / NO	3,5 / 0 / 0					
25 / YES	4 / 3 / 4	NO	NO	NO	NO / NO / NO	YES / A / YES
26 / NO	4,5 / 1 / 3					
27 / YES	1,5 / 0 / 2	PMMC++ / R / A	YES	YES	NO / NC / NC	NO / NC / NC
28 / YES	4,5 / -1 / 2	PMMC+ / R / A	NO	NO	NO / NO / NO	NO / NO / NO
29 / NO	4,5 / 3 / 3					
30 / YES	5 / 0 / 0	NO	NO	NO	NO / NO / NO	YES / A / YES
31 / YES	3 / -1 / 0	PMMC++ / R + A / S	YES++	YES	YES / A / YES	NO / NO / NO
32 / YES	4 / 0 / 0	NO	NO	YES	NO / NO / NO	YES / A / YES
33 / YES	1,5 / 3 / 3	PMMC++ / R / S	YES++	YES	YES / A / NC	
34 / YES	4 / -1 / 2	NO	NO	NO	YES / A / YES	NO / NO / NO
35 / NO	4,5 / 1 / 2					
36 / YES	2,5 / 2 / 3	PMMC+ / A / S	NO	NO	NO / NO / NC	NO / NO / NO
37 / YES	4 / -1 / 0	NO	NO	NO	NO / NO / NC	YES / A / NC
38 / YES	3,5 / 1 / 3	NO	NO	NO	YES / A / YES	NO / NO / NO
39 / YES ⁷	3 / -1 / 0					
40 / NO	4,5 / 1 / 2					
41 / YES	0 / 4 / 3	PMMC+ / R / S	NO	NO	NO / NC / NC	NO / NO / NO
42 / YES	2,5 / 1 / 3	PMMC++ / R + A / A	YES+	NO	YES / A / YES	NO / NO / NO
43 / NO	3,5 / 0 / 3					
44 / NO	0 / 4 / 4					
45 / NO	4,5 / 2 / 3					
46 / NO	4 / 3 / 3					
47 / YES	4,5 / 3 / 3	PMMC+ / A / A	NO	YES	NO / NO / NO	NO / NO / NO
48 / YES	3,5 / 0 / 4	PMMC++ / R + A / S	YES	YES	NO / NO / NO	NO / NO / NO
49 / YES	4 / 0 / 0	PMMC++ / R + A / S	NO	YES	NO / NO / NO	YES / A / YES
50 / NO	4 / 3 / 3					
51 / YES	5 / 0 / 3	PMMC+ / A / S	YES++	YES	YES / A / YES	NO / NO / NO
52 / YES	3,5 / 1 / 3	NO	NO	NO	YES / R+A / NO	NO / NO / NO
53 / YES	4 / -1 / 2	PMMC+ / R+A / A	YES	YES	YES / A / NO	NO / NO / NO
54 / YES	4 / 0 / 3	PMMC+ / R+A / S	NO	YES	YES / A / YES	NO / NO / NO
55 / YES	4,5 / -1 / 3	PMMC++ / R + A / S	YES++	YES	YES / A / YES	NO / NO / NO
56 / YES	4,5 / 0 / 0	PMMC+ / R + A / S	YES+	YES	YES / A / YES	NO / NO / NO
57 / YES	4,5 / 1 / 3	PMMC+++ / R + A / S	YES++	YES	YES / A / YES	NO / NO / NO
58 / NO	2 / 0 / 1			YES		
59 / YES	3,5 / 0 / 3	NO	NO	NO	NO / NO / NO	YES / A / YES
60 / YES	4,5 / 0 / 3	PMMC+ / A / A	NO	YES	NO / NO / NO	YES / A / YES
61 / YES	4,5 / 0 / 2	NO	NO	NO	NO / NO / NO	YES / R + A / YES
62 / YES	3,5 / 1 / 2	PMMC++ / R + A / S	YES	YES	YES / A / YES	NO / NO / NO
63 / NO	3,5 / 0 / 2					
64 / YES	5 / 0 / 2	NO	NO	NO	NO / NO / NO	YES / A / YES
65 / YES	4 / 0 / 0	PMMC+ / R + A / A	YES	YES	NO / NO / NO	YES / A / YES

¹Grading of muscle power using the Medical research council scale ²Ashworth scale ³upper extremity reflexes were graded using a 0 to 5 scale ⁴severity of involuntary movements was graded on a scale from + to +++ not capable of performing ⁵did not consent to video recording.

Figure 1: Patient 27. Resting thumb tremor is associated with repetitive doublets – sequential firings of a motor unit potential. Upper line represents EMG recording of the right long extensor digitorum muscle, lower three lines show accelerometry recordings from the patient's right thumb.

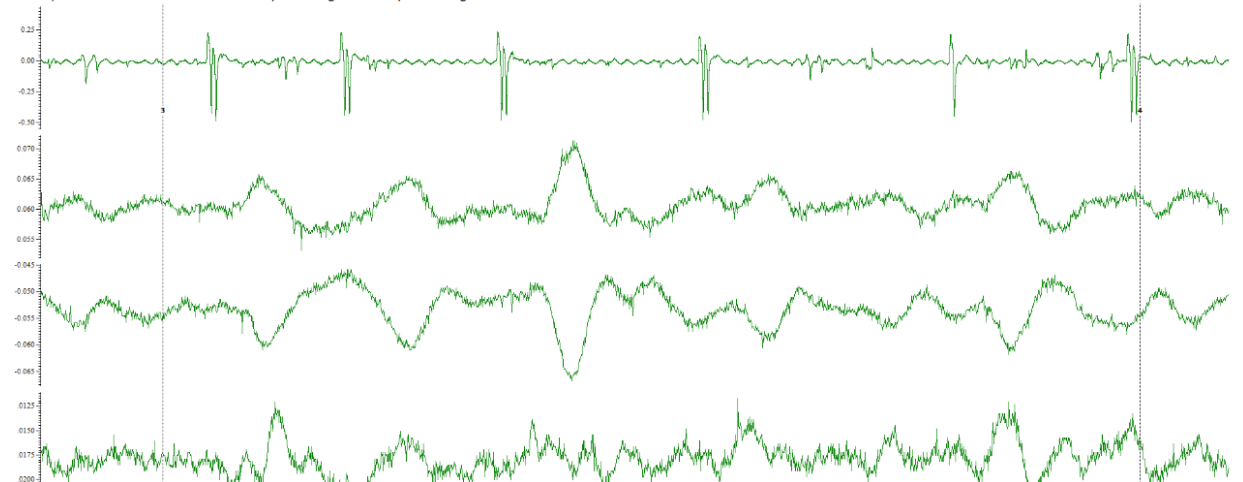


FIG. 1 (1182)

Figure 2: Patient 22 – wrist dorsiflexion. Upper 4 lines - EMG, lower 3 lines - accelerometry recordings. Firing of presumably enlarged motor units in tremor producing muscles and co-activation of agonist and antagonist muscles together with co-contraction of the resting limb muscles are seen.

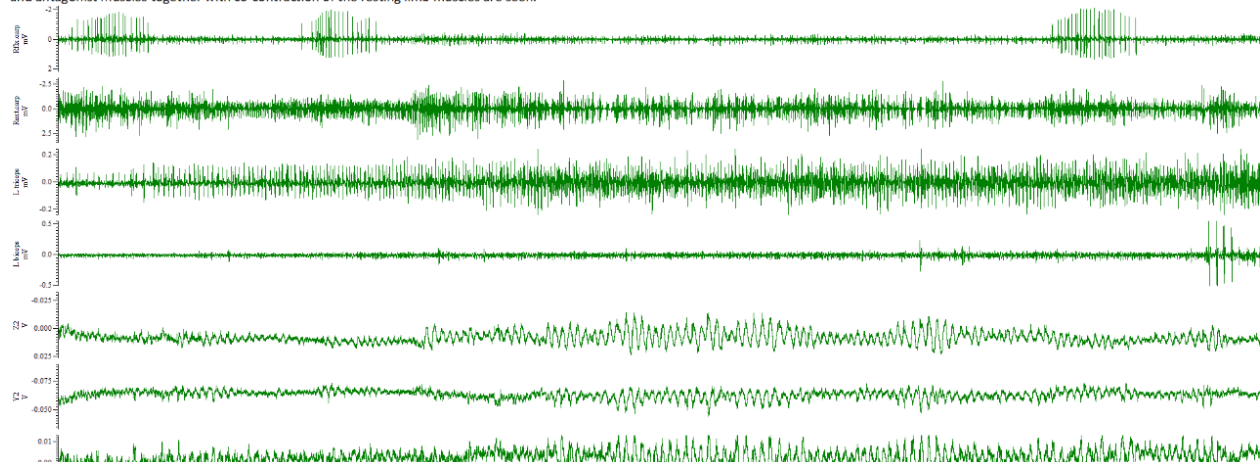


FIG. 2 (1182)

1188

Imaging neurodegeneration biomarkers in Essential Tremor

S. Pietracupa, M. Bologna, G. Pasqua, S. Tommasin, N. Petsas, F. Elifani, A. Berardelli, P. Pantano (Pozzilli, Italy)

Objective: To find neuroimaging biomarkers of neurodegeneration in patients with essential tremor (ET).

Background: ET is one of the most common movement disorder. The disease progression over time, the increased prevalence with age and the increased risk of degenerative disorders associated with ET, such as Parkinson's and Alzheimer's diseases, support the neurodegenerative hypothesis. Furthermore, previous imaging and pathological studies demonstrate brain structural changes in patients with ET.

Methods: We studied 19 ET patients and 15 healthy subjects (HS). Tremor was assessed by means of Fahn-Tolosa-Marin Tremor Rating Scale (FTM-TRS) and accelerometric measures. We ruled out cognitive impairment using by Montreal Cognitive Assessment (MoCA). Patients were also assessed using the Frontal Assessment Battery (FAB) and Beck Depression and Anxiety Inventories (BDI-BAI). Participants

underwent a standardized 3T-MRI protocol. Total grey matter (GM) and white matter (WM) volume were assessed by means of SIENAX (FSL toolbox), cortical thickness (Cth) using by CAT 12 (SPM 12 toolbox) and subcortical volumes using by FIRST-FSL. Finally, we assessed iron deposition obtained from SWAN images in seven specific Regions of Interest (ROIs): thalamus, putamen, globus pallidus, caudate, substantia nigra, red nucleus and dentate nucleus. We then investigated possible correlations between clinical scores and accelerometric measures of tremor and neuroimaging data.

Results: No differences in total GM, WM and Cth were found between the two groups. Moreover, no differences in terms of iron accumulation were observed between ET patients and HS. Subcortical volumes analysis demonstrated significant differences in thalamus volume bilaterally ($p < 0.015$) in the comparison CS>ET, positively correlating with MoCA. By contrast, thalamus volumes did not correlate with tremor severity, as assessed by clinical scores and accelerometric measures.

Conclusions: Apart for the observation of thalamic atrophy, our study indicates no structural brain abnormalities supporting neurodegenerative hypothesis in ET. Thalamic atrophy positively correlated with cognitive measures in patients, providing further insight into the pathophysiological mechanisms of the disease. However, the lack of correlation between tremor severity and thalamic volume indicates that structural abnormalities does not necessarily play a key role in generating tremor in this condition.

1190

Quantitative characterisation of tremor in functional and organic tremor patients

Z. Dominguez-Vega, G. Kramer, J. Elting, M. de Koning-Tijssen, N. Maurits (Groningen, Netherlands)

Objective: To quantify tremor characteristics using inertial sensors in functional and organic tremor patients and to present the differences in tremor quantification between these two groups, during long term tremor recordings and to determine the minimum number of days necessary to obtain reliable estimates.

Background: Distinguishing tremor types is important for treatment and prognosis. One major distinction is between tremor with an organic cause (organic tremor; OT) and functional tremor (FT). FT tends to have less stable characteristics compared to organic tremor; exhibiting frequent interruptions, irregularities and frequency changes [1]. Fluctuations in tremor characteristics affect all patients, making it difficult to assess these from a momentary observation in the clinic. Long-term continuous monitoring would facilitate overall occurrence and treatment response assessment.

Methods: Inertial sensor data were recorded from 44 tremor patients (16 FT, 28 OT) during unconstrained activities of daily living during 30 days, each day over a 10-hour period. Sensors were attached to the dorsal side of the forearm (close to the wrist). Start and end of recording per day were obtained from electronic patient diaries. The accelerometer signal and a tremor identification algorithm [2] implementing the periodogram were used to identify time windows with tremor, from which the percentage of tremor and tremor frequency variability were calculated per patient across all days. Non-parametric distributions were generated and Z-tests performed to determine whether estimates of tremor characteristics obtained from the first 3, 5, 7 or 10 days were representative of estimates obtained from any 3, 5, 7 or 10 days within the 30 days.

Results: Tremor percentage ranged from 10 to 34% for FT patients and from 4.7 to 70.0% for OT patients. Frequency variability ranged from 0.6 to 2.1 Hz for FT patients and from 0.4 to 1.5 Hz for OT patients. Seven days of tremor recording were the minimum number of days resulting in a non-significant Z-test, meaning that seven days are the shortest period of time needed to obtain reliable estimates of tremor characteristics.

Conclusions: Using long-term recordings with inertial sensors, fluctuations in tremor characteristics over the days could be observed in FT as well as OT patients based on percentage of tremor and tremor frequency variability. Seven days of recording are sufficient to determine these characteristics reliably.

References: [1] P. E. O'Suilleabhain and J. Y. Matsumoto, "Time-frequency analysis of tremors.," *Brain*, vol. 121 (Pt 11), pp. 2127–34, Nov. 1998. [2] O. Martinez Manzanera, J. W. Elting, J. H. van der Hoeven, and N. M. Maurits, "Tremor Detection Using Parametric and Non-Parametric Spectral Estimation Methods: A Comparison with Clinical Assessment," *PLoS One*, vol. 11, no. 6, p. e0156822, Jun. 2016.

Repetitive Transcranial Magnetic Stimulation Therapy is a Potential Therapeutic option for Primary Orthostatic Tremor

W. Hu, J. Legacy, A. Ferng, A. Wagle Shukla (Gainesville, FL, USA)

Objective: Determine whether low frequency repetitive transcranial magnetic stimulation (rTMS) therapy to the cerebellum improves symptoms in primary orthostatic tremor (POT)

Background: POT is a rare disabling tremor disorder characterized by high frequency tremor appearing in the legs upon standing. Treatment opportunities for POT are poor. Previous research found an increased cerebellar activity and low frequency rTMS reduces increased brain excitability.

Methods: Patients diagnosed with POT participated in a randomized double-blind placebo-controlled crossover-design study. All subjects received single session of real and sham rTMS session delivered to each cerebellar hemisphere on two separate days in random order. Nine hundred pulses were delivered consecutively to each side at a frequency of 1 Hz and at an intensity of 90% of the resting motor threshold (hand motor area). The primary outcome was the mean difference between the two arms for the Fullerton Advanced Balance Rating Scale (FABRS) standing score and the blinded video-rated standing duration measured immediately after rTMS (T1) and 60+ minutes after rTMS (T2) compared to before rTMS therapy (baseline, T0).

Results: 10 POT subjects (6 females and 4 males, mean age 70.2 ± 8.0 years, mean disease duration 13.5 ± 5.8 years) participated and tolerated the therapy well. Compared to baseline, subjects randomized to the real arm improved significantly on the FABRS standing score (baseline score 1.3; T1 score 2.3; $p = 0.02$) at T1 than those in the sham arm. With regards to video-rated standing duration time, there was mean increase of 126.0 ± 172.8 sec in the real arm compared to 12.9 ± 49.9 sec in the sham arm that approached significance ($p = 0.11$). However, at an individual level, there were 8/10 subjects in the real arm showed improvement (figure). No significant improvements were seen at T2.

Conclusions: Low frequency rTMS to cerebellum is a promising therapy for POT however requires confirmation in a larger follow-up study. A longer duration of rTMS will likely result in longer benefits.

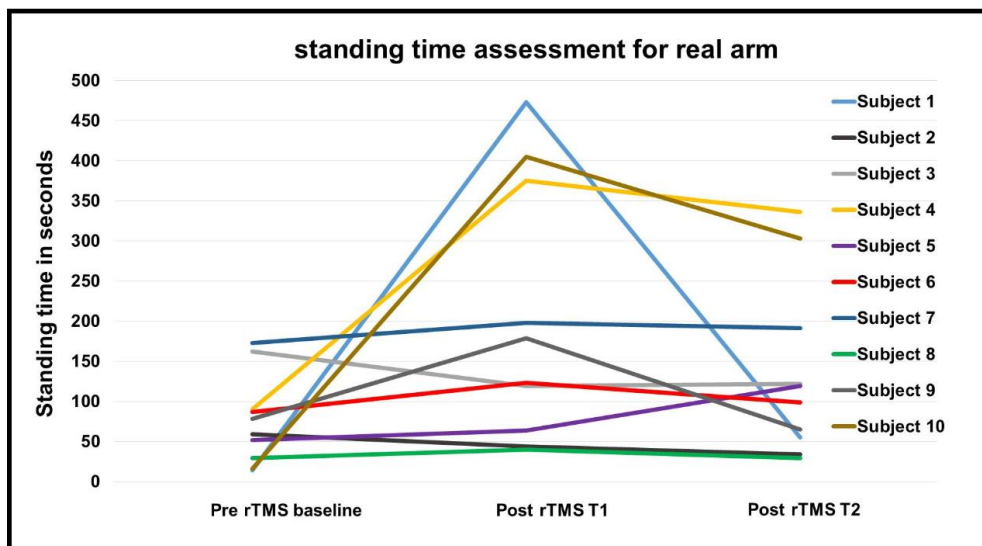


FIG. 1 (1203)

Tremor in motor neuron disease may be central rather than peripheral in origin

A. Latorre, L. Rocchi, M. Stamelou, A. Batla, M. Ciocca, B. Balint, K. Sidle, A. Berardelli, J. Rothwell, K. Bhatia (London, United Kingdom)

Objective: To investigate the pathophysiology of action tremor in motor neuron disease (MND).

Background: MND refers to a spectrum of degenerative diseases affecting motor neurons. Recent clinical and postmortem observations have revealed considerable variability in the phenotype (1). Rhythmic involuntary oscillations of the hands during action, resembling tremor, can occur in MND, but its pathophysiology has not yet been investigated.

Methods: One hundred and twenty consecutive MND patients were screened for tremor. Twelve patients with action tremor and no other movement disorders were found. Ten took part in the study. Tremor was recorded bilaterally using surface electromyography and triaxial accelerometer, with and without a variable weight load. Power spectra of rectified electromyography and accelerometric signal were calculated. To investigate a possible cerebellar involvement, eye blink classic conditioning (EBCC) was performed in five patients.

Results: Action tremor was present in about 10% of our population. All patients showed distal postural tremor of low amplitude and constant frequency, bilateral with a small degree of asymmetry. Two of them showed also simple kinetic tremor. A peak at the electromyography and accelerometric recordings ranging from 4 Hz to 12 Hz was found in all patients. Loading did not change peak frequency in either the electromyographic or accelerometric power spectra. Compared with healthy volunteers, patients had a smaller number of conditioned responses during EBCC.

Conclusions: our data suggest that MND patients can present with action tremor of a central origin, possibly due to a cerebellar dysfunction. This evidence supports the novel idea of MND as a multisystem neurodegenerative disease and that action tremor can be part of this condition.

References: 1. Sabatelli M, Conte A, Zollino M. Clinical and genetic heterogeneity of amyotrophic lateral sclerosis. *Clinical genetics*. 2013;83(5):408-16.

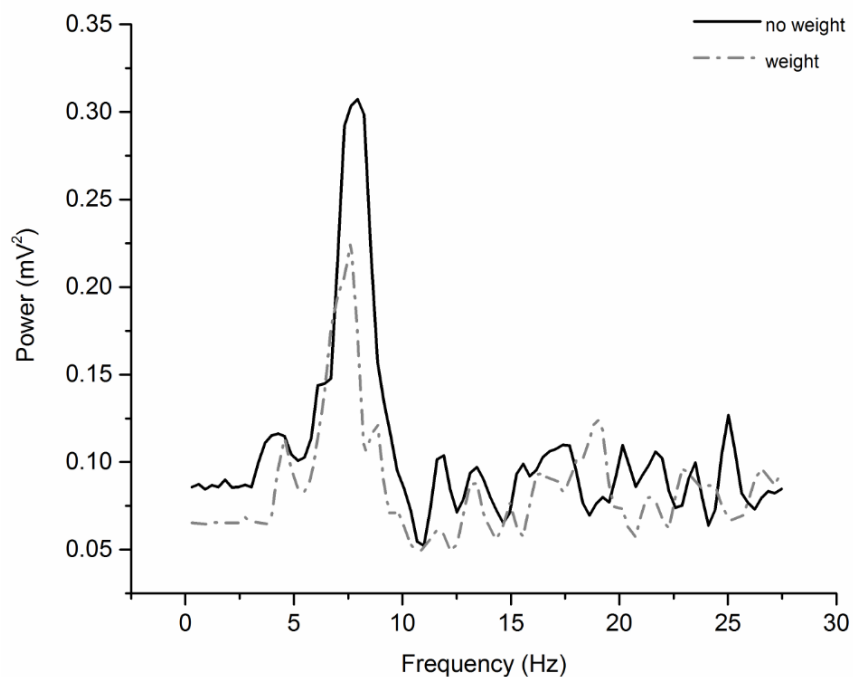


FIG. 1 (1210)

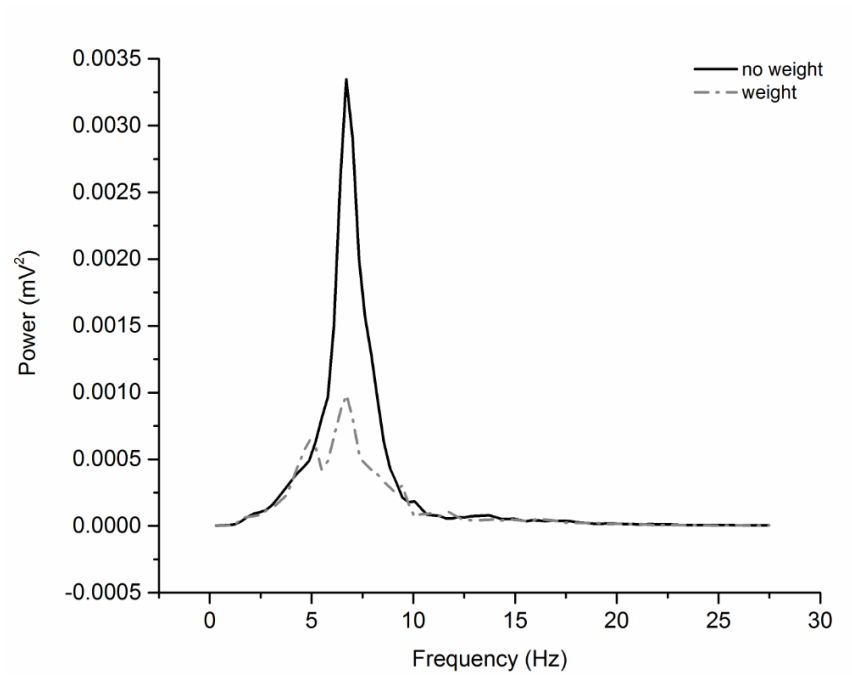


FIG. 2 (1210)

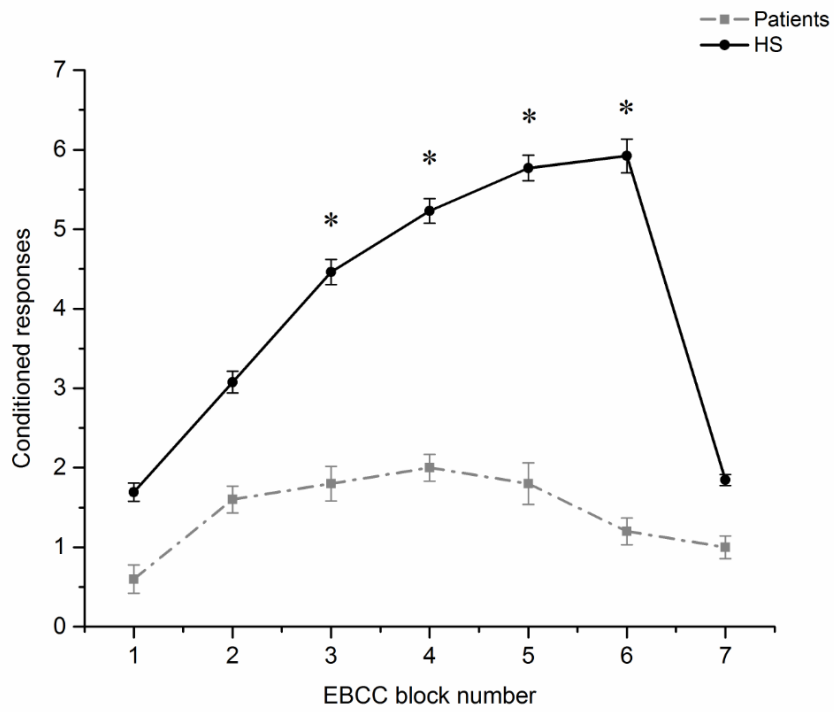


FIG. 3 (1210)

1213

Regional homogeneity changes detected between Essential tremor with resting tremor and tremor-dominant Parkinson's disease

J. Li, Z. Lu, X. Suo, N. Li, L. Wang, J. Peng, J. Zhang, Q. Gong, R. Peng (Chengdu, China)

Objective: To explore neural activity patterns in the essential tremor (ET) with resting tremor (rET) and tremor-dominant Parkinson's disease (tPD) by using resting-state functional magnetic resonance imaging (rs-fMRI) and regional homogeneity (ReHo) method.

Background: Differentiating between rET from tPD may be challenging in the early phases of the diseases. Although some imaging studies have indicated that there are differences between rET and tPD, little is known about the rs-fMRI findings.

Methods: Our study conducted rs-fMRI with a ReHo method to investigate the modulations of neural activity in 58 ethnic Han Chinese subjects comprising 19 patients of rET, 24 patients of tPD and 25 age- and gender-matched healthy controls. Differences were compared by two-sample t tests (corrected with AlphaSim, $p < 0.05$). All participants underwent clinical assessment and the correlation with ReHo was analyzed.

Results: Compared with healthy controls, rET patients and tPD patients both displayed ReHo alterations in left inferior temporal gyrus and right inferior orbitofrontal lobe. In addition, rET patients exhibited more ReHo changes in the inferior temporal gyrus, while tPD patients in extensive cortical and sub-cortical areas, including frontal, temporal, putamen, cingulum, precuneus, and cerebellum, which are involved both in basal ganglia and the cerebello-thalamo-cortical (CTC) loops. Direct comparison between rET and tPD displayed significant differences in the primary visual cortex, and in brain regions within the so-called default mode network (DMN, e.g., precuneus, cingulum).

Conclusions: Our results indicated the rET and tPD share common patterns of ReHo abnormalities in the temporal and orbitofrontal lobe, which may contribute to the broad spectrum of olfactory, visual, emotional and behavioral disturbances observed in these two diseases. In addition, we found disorder-specific involvement of temporal in rET and the basal ganglia and the CTC loops in tPD. These findings provide new evidence regarding the shared and specific neuropathological mechanisms that underlie rET and tPD.

**Guided Poster Group 10:
Parkinson's Disease: Genetics**

1299

PLA2G6-related juvenile-onset Parkinsonism: clinical features and cognitive profile in a cohort of Chinese patients

C. Chen, Y.M. Sun, F.T. Liu, S.S. Luo, Z.T. Ding, J.J. Wu, J. Wang (Shanghai, China)

Objective: Among young or juvenile onset Parkinson (PD) patients, we assessed cognitive and clinical performances, comparing homozygotes and compound heterozygotes who carry PLA2G6 pathogenic mutations with non-carriers and age-matched healthy controls.

Background: Phospholipase A2 Group 6 (PLA2G6) is the causative gene for three recessively inherited neurodegeneration disease, namely infantile neuroaxonal dystrophy (INAD) and neurodegeneration associated with brain iron accumulation (NBIA) and PLA2G6 -linked juvenile onset dystonia-parkinsonism (PARK14). Although the phenotypic spectrum of PARK14 had different features from classic Parkinson's disease, no quantitative study has been conducted in comparing clinical manifestations and cognitive profiles between cohorts of PLA2G6-related cases and other young onset Parkinson's disease cases.

Methods: We collected 10 Chinese patients with homozygous or compound heterozygous PLA2G6 mutations from the outpatient neurology clinics of Huashan Hospital consecutively who met the MDS diagnostic criteria of clinically probable PD or established PD with an age at onset of younger than 40 years old. Pathogenicity of the PLA2G6 mutations was evaluated by enzyme activity. Unified Parkinson Disease

Rating Scale Part III (UPDRS-III) and neuropsychological performance of the patients was measured. The neuropsychological scores of age and sex matched healthy controls was also collected.

Results: PLA2G6-related Juvenile onset Parkinson's disease (PARK14) patients had no statistical difference in age at onset of PD, gender, disease duration and age at examination compared to noncarriers. More pyramid signs ($P < 0.001$), dyskinesia ($P = 0.019$), higher Beck depression inventory scores ($P = 0.002$) and higher RBD questionnaire scores ($P = 0.046$) were observed in PLA2G6 mutation carriers. Carriers developed posture instability ($P = 0.029$) and dyskinesia ($P = 0.030$) more quickly. They performed poorer than noncarriers on the Mini-Mental State Examination ($P = 0.005$) and were more likely to receive lower scores on other neuropsychological tests. PARK14 patients had a remarkable impairment in language domain ($P = 0.015$). No significant difference was observed in attention, execution, memory and visuospatial cognitive domains.

Conclusions: In this study, PARK14 patients demonstrated poorer cognitive performance and motor performance than did noncarriers, especially in language domain, suggesting a more rapid disease progression and a different pattern of cognitive impairment. A longitudinal follow-up and a functional imaging study is required to confirm these findings.

Impairment in different cognitive domains

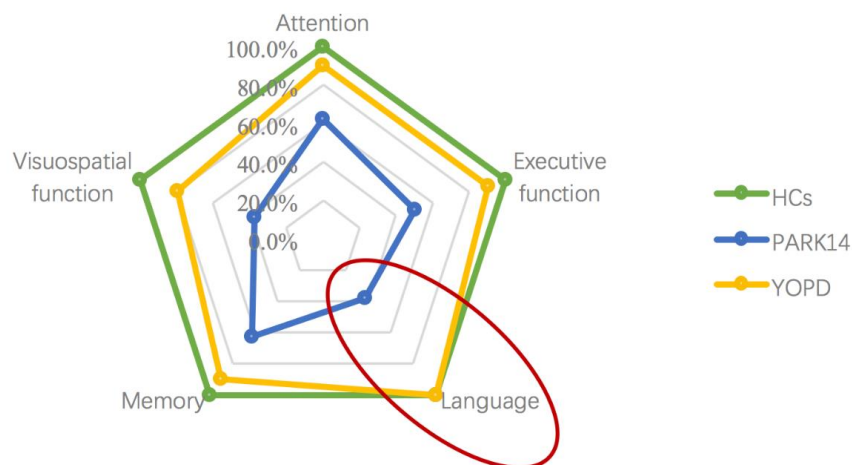


FIG. 1 (1299)

1304

Resistance to Parkinson's disease among LRRK2 mutation carriers is associated with higher plasma levels of urate but not its purine precursors

M. Schwarzschild, R. Bakshi, R. Logan, M. Zorlu, X. Chen, A. Ascherio, E. Macklin (Boston, MA, USA)

Objective: To determine whether plasma purine concentrations differ between people with Parkinson's disease (PD) and matched controls among carriers of pathogenic mutations in Leucine-Rich Repeat Kinase 2 (LRRK2) gene.

Background: LRRK2 mutations (mLRRK2) are the most common genetic cause of PD but are incompletely penetrant. Understanding the genetic and environmental factors that reduce LRRK2 mutation penetrance could help predict and possibly prevent development of PD among healthy people who are at high risk due to a mLRRK2. Urate is an endogenous purine with antioxidant, Nrf2 activator and neuroprotectant properties, and elevated serum or CSF concentrations are predictive of a reduced risk of idiopathic PD and a slower rate of PD progression.

Methods: Urate and other purines were measured in plasma samples by enzymatic and HPLC-UV/ECD assays. Baseline levels from 380 subjects (120 mLRRK2+PD-, 120 mLRRK2+PD+, 70 mLRRK2-PD-, 70 mLRRK2-PD+) matched for key covariates from the LRRK2 Cohort Consortium (LCC) and from 1,053

subjects (241 mLRRK2+PD-, 210 mLRRK2+PD+, 202 mLRRK2-PD-, 400 mLRRK2-PD+) in the Parkinson Progression Marker Initiative (PPMI) database were compared, adjusting for age and sex.

Results: Among mLRRK2 carriers in the LCC, unaffected subjects had higher levels of urate \pm SE (5.0 ± 1.3 mg/dL) than those with PD (4.2 ± 1.2 mg/dL) by 0.8 mg/dL after adjusting for sex and age ($p < 0.0001$). There was no significant difference between urate's purine precursors hypoxanthine and xanthine. A smaller difference was observed among subjects without a mLRRK2; plasma urate in unaffected subjects was 0.4 mg/dL greater than in PD ($p = 0.02$). Similarly, among mLRRK2+ (in contrast to mLRRK2-) subjects in the PPMI cohort, those who were unaffected had higher levels of urate than those with PD (by 0.4 mg/dL) after adjusting for sex and age ($p < 0.001$); adjusting further for BMI yielded the same result ($p < 0.001$).

Conclusions: The reproducible finding of higher plasma urate levels among those resistant to PD despite a LRRK2 mutation supports the hypothesis that higher urate is a marker and possibly a mediator of the incomplete penetrance of LRRK2 mutations.

1307

Interest in Genetic Testing in PD Patients with DBS

A. Frait, G. Pal, L. Verhagen, D. Hall, K. Marder (Chicago, IL, USA)

Objective: Determine interest in genetic testing (GT) among PD patients with DBS.

Background: About 26-29% of PD patients who undergo DBS have a mutation in one of three genes: glucocerebrosidase (GBA), leucine-rich repeat kinase 2, and parkin. As access to GT for PD increases, it is critical to understand the current knowledge base regarding GT in PD subjects and their expectations regarding how genetic information impacts their treatment.

Methods: Consecutive non-demented PD patients with bilateral STN-DBS were recruited. The Genetic Attitude Questionnaire (GAQ) - an assessment of GT knowledge - was administered to subjects. Demographic and clinical data were compared using student t-test or Mann-Whitney U as appropriate. Subjects were dichotomized according to whether they did or did not want GT. Correct genetic knowledge responses were quantified for all subjects and then compared using chi-square tests according to desire to obtain GT and GBA mutation status. Identical analysis was performed for reasons for desiring GT. A multivariate logistic regression model was used to identify predictors of desire to obtain GT.

Results: One hundred subjects were enrolled and complete GAQ data were available for 88 (Table 1). Fourteen respondents (16%) were GBA mutation carriers. The mean percent of correct responses for all subjects regarding genetic knowledge was 58.5% (Fig 1). Genetic knowledge was not significantly higher in subjects who desired GT ($p > 0.05$) nor among GBA mutation carriers ($p > 0.05$). Fifty-three subjects (60%) would opt for GT if it could predict their response to DBS. Subjects who desired GT were more likely than those who did not to be aware that genes have been identified which confer a higher risk of developing PD ($p = 0.02$). Both those who desired GT and those who did not were more likely to consider eligibility in clinical trials an important consideration in making their decision (95.83% and 76.67%) (Fig 2). In a multivariate logistic regression model, age, disease duration, sex, UPDRS-III scores, HY stage, and GBA mutation status were not predictive of desire to obtain GT (p 's > 0.05).

Conclusions: Most patients would want GT if it could predict response to DBS. Knowledge gaps were identified in this advanced PD cohort. Desire to be eligible for clinical trials was associated with the desire for GT.

TABLE 1 (1307)

Table 1	
Age, mean (sd)	63.67 (7.72)
Sex, n (%)	
Male	59 (67.0)
female	29 (33.0)
Ethnicity, n (%)	
Caucasian	76 (86.4)
AA	1 (1.1)
Hispanic	2 (2.3)
Other	3 (3.4)
Missing(6)	
Age of onset, mean (sd)	47.02 (9.24)
Disease duration, mean (sd)	16.54 (6.28)
UPDRS 3, mean (sd)	24.24 (11.11)
HY, n (%)	
1	1 (1.1)
2	57 (64.8)
3	18 (20.5)
4	9 (10.2)
5	3 (3.4)
Median (IQR)	2 (1)
Family diagnosed with PD, n (%)	
No	66 (75.0)
Yes	22 (25.0)

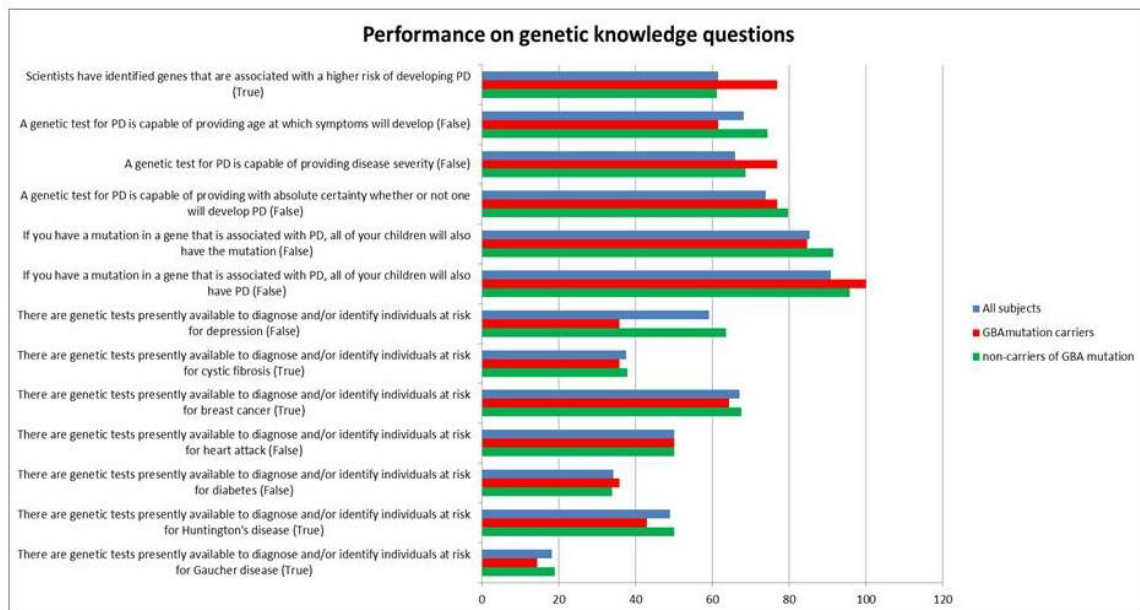


FIG. 1 (1307)

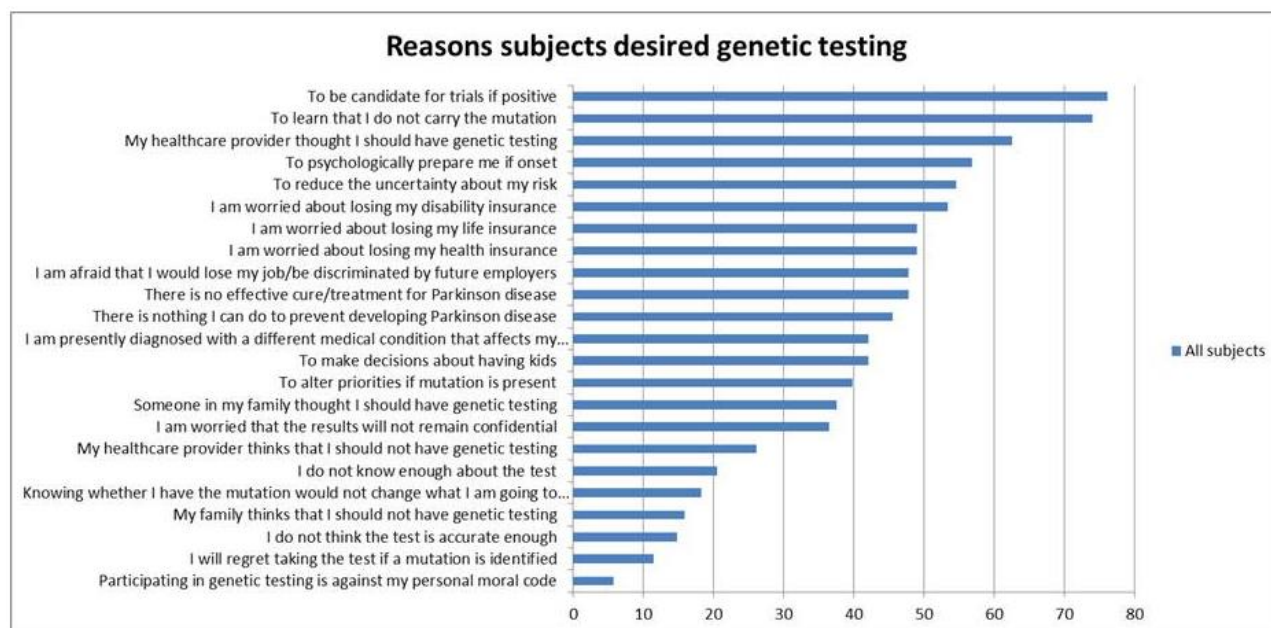


FIG. 2 (1307)

1312

Application of the Movement Disorder Society Prodromal Criteria in healthy G2019S-LRRK2 carriers

A. Mirelman, R. Saunders-Pullman, R. Alcalay, S. Shustak, A. Thaler, B. Cohen, A. Hillel, T. Gurevich, D. Raymond, H. Mejia-Santana, L. Ozelius, L. Clark, M. Gana-Weisz, A. Bar-Shira, A. Orr-Urtreger, S. Bressman, K. Marder, N. Giladi (Tel Aviv, Israel)

Objective: To evaluate the MDS prodromal criteria in first-degree relatives of Ashkenazi Jewish G2019S-LRRK2 PD patients, who are considered a population at risk for developing PD, and assess the sensitivity and specificity of the criteria in identifying phenoconverters.

Background: The pathological changes of Parkinson's disease (PD) can start decades before the appearance of cardinal motor symptoms. Detecting patients at the premotor stage will be crucial for future clinical trials aiming at modifying progression at the earliest stages of the disease. In 2015 the Movement Disorder Society (MDS) Task Force recommended research criteria for the estimation of prodromal PD.

Methods: Participants were evaluated longitudinally over a period of 5 years (average follow-up 49.2±12.3months). Likelihood ratios (LR) and probability estimations were calculated based on the MDS criteria markers and examined for each assessment point.

Results: 120 healthy carriers (HC) (49.53±13.36yrs; 50%F) and 111 healthy non-carriers (HNC) (48.43±15.79yrs; 48%F) participated in this study. Probability scores without genetic status were already significantly higher in HC than HNC (p=0.038). Twenty participants (8.6%) met criteria for probable prodromal PD at baseline, 17 were HC. Participants who reached the threshold were older (p<0.0001), had higher UPDRS-III (p<0.001), lower cognitive function (p=0.001) and more non-motor symptoms (p<0.0001), compared to those who did not. Ten participants were diagnosed with incident-PD within 5 years from baseline resulting in a specificity of 93.85%(95%CI:90.83-96.86), sensitivity of 80%(95%CI:55.21-100%), PPV of 34.78% (95%CI:15.31- 54.24) and NPV of 99.13% (95%CI:97.94-100). All 10 phenoconverters were G2019S-LRRK2 carriers.

Conclusions: The results showed the utility of using the criteria and high sensitivity and specificity in identifying prodromal PD in this high risk unique cohort. These results may be valuable for disease prevention and future disease modification clinical trials.

1326

LRRK2 and GBA genetic mutations are not uncommon in an unselected Ashkenazi elderly cohort with PD

S. Isaacson, J. Isaacson (Boca Raton, FL, USA)

Objective: Analysis of positive LRRK2 and GBA gene mutations, demographic characteristics, and family history in 1200 consecutive Ashkenazi patients with PD who had genetic testing for LRRK2 and GBA mutations.

Background: Patients with Parkinson's disease who are of Ashkenazi Jewish descent may have a LRRK2 and/or GBA gene mutation. Approximately 30-40% of unaffected LRRK2 gene carriers and approximately 8% of GBA gene carriers may develop clinical motor PD during their lifetime. It is unknown if PD diagnosis occurs earlier in life due to the LRRK2 or GBA gene, or if elderly have lower vs. higher risk.

Methods: Genetic testing was conducted at our site through the MJFF PPMI genetic screening program. We reviewed prodromal clinical characteristics of unaffected relatives of PD patients and also of patients already diagnosed with PD who were found to have the LRRK2 and/or GBA gene mutation associated with Ashkenazi PD. We also compared these gene positive to those who were tested but did not have these gene mutations. We also compared PD gene-positive and gene-negative with a family history of PD to those without.

Results: Over 1200 patients underwent genetic testing after clinical counseling for LRRK2, and approximately half of these for GBA gene too. Of 350 unaffected relatives with a PD family history tested, 32 had LRRK2 gene mutation and 150 were also tested for GBA with 10 with a GBA gene mutation. Of 850 patients with PD, approximately 50% of patients reported a known family history of PD. Of patients with a family history, 48 had LRRK2 gene and 18 had GBA gene. Of patients with PD not reporting a family history of PD, 24 had LRRK2 gen and 12 had GBA gene.

Conclusions: Routine gene testing of patients with PD who have Ashkenazi heritage (ie one grandparent) may be of value as these genes seem relatively common in patients reporting a known family history of PD and ven in those unaware of a PD family history, As new therapies enter clinical development, PD patients of Ashkenazi descent will need counseling that LRRK2 and GBA gene mutations are not uncommon, have autosomal dominant inheritance to to their children, and may be amenable to trials of emerging therapies seeking to slow or retard progression of PD.

1340

BDNF(V66M), EIF4G1(R1205H), VPS35(D620N) gene polymorphisms in South Indian PD Patients

T. Syed, T. S.D, S. Meka, S. Kumar, S. Thandra, V. Kutala, R. Kandadai, R. Borgihain (Hyderabad, India)

Objective: To investigate the association of BDNF(V66M), EIF4G1(R1205H) and VPS35(D620N) polymorphisms in South Indian PD patients.

Background: Parkinson's disease (PD) is the most common form of movement disorder that embroiled multiple neuro-anatomical areas, due to various genetic and environmental factors. Advances in genetic analysis, Next Generation Sequencing, and Genome Wide Association Studies helps to identify the risk genes and understand the pathological pathway associated with PD development and progression. BDNF plays a role in differentiation, survival and maintenance of neurons in central and peripheral nervous system. In PD, the expression of BDNF (Brain Derived Neurotropic factor) NA is decreased there by making it a susceptible candidate gene. Studies have revealed that EIF4G1 (Eukaryotic Translation Initiation Factor 4 Gamma 1) variants may impair the ability of cells to rapidly and dynamically respond to stress, thus probably participating in PD development. Variations in VPS35 (Vacuolar Protein Sorting-Associated Protein 35) may disrupt the retrograde transport system and thereby contributing to dopaminergic neuronal cell death in PD.

Methods: A total of 168 PD patients and 151 age and ethnicity matched controls were included in the study. Blood samples were collected after taking the consent. DNA was isolated genetic analysis was done by PCR-RFLP method.

Results: The frequency of genotypic distribution of BDNF (V66M) polymorphism among the PD cases and controls were: C/C – 60.1 % and 67.5%, C/T – 28.6% and 26.4%, and T/T was 11.3 % and 5.9% respectively. The Allelic frequency distribution of C & T alleles in cases and controls were C- 74.4 % and 80.7%, T allele – 25.5% and 19.2% respectively. The Fishers exact test revealed that, there is a borderline significant difference between cases and controls (C/C versus C/T+T/T, OD 1.44, CI at 95% 0.95-2.18, P value 0.058. The frequencies of GG genotype of EIF4G1 (R1205H) and CC of VPS35 (D620N) polymorphisms among PD cases and controls are 100 %. There is no occurrence of mutant either in cases or in controls.

Conclusions: From the results we conclude that BDNF (V66M), EIF4G1 (R1205H) and VPS35 (D620N) polymorphisms are not associated with the PD risk in South Indian population.

1341

Full sequencing and haplotype analysis reveals LRRK2 protective haplotype in REM sleep behavior disorder

B. Ouled Amar-Bencheikh, J. Ruskey, I. Arnulf, Y. Dauvilliers, C. Charley Monaca, V. Cochen De-Cock, JF. Gagnon, D. Spiegelman, M. Hu, B. Högl, A. Stefani, L. Ferini-Strambi, G. Plazzi, E. Antelmi, P. Young, A. Heidbreder, B. Mollenhauer, F. Sixel-Döring, C. Trenkwalder, W. Oertel, J. Montplaisir, R. Postuma, G. Rouleau, Z. Gan-Or (Montreal, QC, Canada)

Objective: To examine the role of LRRK2 mutations and variants in susceptibility for RBD.

Background: Rapid eye movement (REM)-sleep behavior disorder (RBD) is, in most cases, a prodromal synucleinopathy, likely to progress to either Parkinson's disease (PD), dementia with Lew-bodies (DLB) or multiple system atrophy (MSA) in rare cases. There is only partial overlap between the genetics of RBD and PD. LRRK2 mutations that are known to cause PD are rare in RBD, yet thus far no comprehensive, full sequencing study of LRRK2 was performed in RBD.

Methods: A total of 350 RBD patients, diagnosed by clinical interview and polysomnography according to the International Classification of Sleep Disorders, version 2 (ICSD-2) criteria, and 869 controls participated in the current study. The full coding sequence, exon-intron boundaries and 5' and 3' untranslated regions of LRRK2 were sequenced using targeted next-generation sequencing with molecular inversion probes (MIPs). Regression and burden models were used to examine the association between LRRK2 variants and RBD.

Results: None of the known PD-causing LRRK2 pathogenic mutations was identified in RBD patients. Interestingly, the haplotype that includes the variants p.N551K-p.R1398H-p.K1423K was associated with a reduced RBD risk (OR=0.66, 95% CI 0.44-0.98, p=0.0055 for the tagging p.N551K substitution). In addition, a common variant, p.S1647T, was nominally associated with risk for RBD (OR=1.28, 95% CI 1.05-1.56, p=0.029), but was not significant after correction for multiple comparisons. Burden analysis identified associations with domains and exons that were derived by the variants of the protective haplotype, and no burden of other rare variants was identified.

Conclusions: Carriage of the LRRK2 p.N551K-p.R1398H-p.K1423K haplotype is associated with a reduced risk for RBD. However, the known PD-causing LRRK2 mutations probably have minor or no role in RBD. Additional studies are needed to replicate these results and to identify the mechanism associated with reduced risk for RBD.

1353

Association of GBA polymorphisms and mutations with dementia in Parkinson disease: A 7-year study of three population-based incident cohorts

K. Lunde, J. Chung, I. Dalen, K. Pedersen, J. Linder, M. Domellöf, E. Elgh, A. Macleod, C. Tzoulis, J. Larsen, O. Tysnes, L. Forsgren, C. Counsell, G. Alves, J. Maple-Grødem (Stavanger, Norway)

Objective: To study the effect of GBA variants on dementia in three deeply phenotyped population-based prospective cohorts of patients with incident Parkinson disease.

Background: Dementia is among the most common and severe non-motor symptoms of Parkinson disease (PD), affecting nearly 20% of all patients within the first 5 years of the disease, and the majority of patients if they survive for more than 10 years after diagnosis. Both polymorphisms and mutations in GBA may influence the development of dementia in patients with Parkinson's disease, but few longitudinal studies have investigated the role of GBA variant subcategories in disease heterogeneity and progression.

Methods: Three Northern European population-based studies (the Swedish NYPUM study, the Norwegian ParkWest study and the Scottish PINE study) designed to determine the incidence, neurobiology and prognosis of Parkinson disease were analyzed for GBA genetic variants by SNP genotyping assays or whole exome sequencing. A total of 442 patients and 419 controls were followed for seven years and dementia was diagnosed using established criteria. GBA variant carriers were analyzed as one group, and subcategorized into "polymorphism" or "deleterious mutation" carriers. Associations between GBA carrier status and dementia were assessed with Cox survival analysis.

Results: A total of 12.0% of patients with Parkinson's disease were carriers of a GBA variant, and nearly half of these (22/53) progressed to dementia during follow-up. Carriers of deleterious GBA mutations (adjusted HR 3.81, 95% CI 1.35 to 10.72; $P = .011$) or polymorphisms (adjusted HR 1.79; 95% CI 1.07 to 3.00; $P = .028$) progressed to dementia more rapidly than non-carriers.

Conclusions: GBA variants are of great clinical relevance for the development of dementia in Parkinson disease, especially due to the relatively higher frequency of these alleles in patients with Parkinson disease compared to other risk alleles.

1370

Molecular mechanisms of GCH1-associated Parkinson's disease

J. Terbeek, W. Vandenberghe (Leuven, Belgium)

Objective: To unravel the molecular mechanisms by which loss of GCH1 function enhances the risk of Parkinson's disease (PD).

Background: Loss-of-function mutations in GCH1 are the most common cause of autosomal dominant DOPA-responsive dystonia (DRD), a non-neurodegenerative movement disorder. GCH1 encodes GTP cyclohydrolase 1, the rate-limiting enzyme in the biosynthesis of tetrahydrobiopterin (BH4). BH4 is an essential cofactor for tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of dopamine. Recent genetic evidence indicates that GCH1 mutations also increase the risk of PD. The mechanisms by which GCH1 mutations predispose to nigrostriatal cell death, are unknown.

Methods: We cultured skin fibroblasts from 2 patients (Patient 1, Patient 2) with the same heterozygous missense mutation in GCH1 (p.Y75S; c. 224A>C) and from 2 healthy age-matched controls (Control 1, Control 2). Patient 1 was a 42-year-old male who developed clinically typical DRD at the age of 8 years and had severely abnormal dopamine transporter (DAT) imaging at the age of 37 years. Patient 2, the 63-year-old mother of Patient 1, developed clinically typical DRD at the age of 8 years and had normal DAT imaging at the age of 60. We induced GCH1 expression in the fibroblasts by 24-hour treatment with interferon-gamma. We assessed apoptosis using TUNEL staining, western blotting for PARP and immunostaining for cleaved caspase 3.

Results: GCH1 abundance after IFN-gamma treatment was lower in the mutant fibroblasts than in their respective controls. Moreover, GCH1 abundance was lower in Patient 1 than in Patient 2. Fibroblasts from Patient 1 were more susceptible to staurosporine- and H₂O₂-induced apoptosis than those of Control 1. By contrast, staurosporine- and H₂O₂-induced apoptosis did not differ between Patient 2 and Control 2. The survival defect of fibroblasts of Patient 1 was rescued by incubation with sepiapterin, a precursor of BH4 via the GCH1-independent salvage pathway, indicating that the survival defect was caused by BH4 deficiency.

Conclusions: The clinical phenotypes of the 2 GCH1 mutant patients correlated with the susceptibility of their skin fibroblasts to apoptosis in vitro. As skin fibroblasts do not produce dopamine, our findings suggest that GCH1 mutations can impair cellular survival via mechanisms unrelated to dopamine synthesis defects.

**Guided Poster Group 11:
Parkinson's Disease: Neuroimaging And Neurophysiology**

1376

Presynaptic dopamine depletion determines the timing of levodopa-induced dyskinesia onset in Parkinson's disease

HS. Yoo, SJ. Chung, BS. Ye, YH. Sohn, PH. Lee (Seoul, Republic of Korea)

Objective: To investigate whether dopaminergic function in the nigrostriatal system is associated with the timing of levodopa-induced dyskinesia (LID) onset in Parkinson's disease (PD).

Background: LID is one of the most debilitating effects of levodopa therapy, and is associated with a poor quality of life and health-related costs. In terms of pathogenesis, two main factors are involved in the development of LID. The first is nigral dopaminergic denervation of the striatum presynaptically, and the second consists of plastic changes in striatal dopaminergic neuron cell signalling that leads to abnormal basal ganglion firing patterns postsynaptically. Striatal dopaminergic depletion is required for the development of LID and predicts LID in patients with PD. Reduced presynaptic dopaminergic activity plays an important role in the development of LID in PD.

Methods: From among 412 drug-naive PD patients who underwent a dopamine transporter (DAT) PET scan during their baseline evaluation, we enrolled 65 patients who developed LID during a follow-up period of > 2 years. Based on the time from PD onset, LID was classified as early, intermediate or late onset. We then compared DAT availability in the striatal subregions of the patients in the three groups.

Results: Patients with de novo PD with LID had lower putaminal DAT activity than those without LID [Figure 1]. The demographic characteristics did not differ among the early-onset, intermediate-onset, and late-onset groups except for earlier intervention of levodopa therapy in the early LID onset group ($p = 0.001$). After adjusting for age at PD onset, gender, timing of levodopa therapy from PD onset, and the severity of PD motor symptoms, DAT activity in the posterior putamen was found to be significantly lower in the early LID onset group than in the late LID onset group ($p = 0.017$) [Table 1]. Multivariate linear regression analysis showed that low DAT activity in the posterior putamen was significantly associated with the early appearance of LID in the early LID onset group ($\beta = 16.039$, $p = 0.033$).

Conclusions: This study demonstrated that low DAT activity in the posterior putamen at baseline is a major risk factor for the early onset of LID in patients with PD, suggesting that the degree of presynaptic dopaminergic denervation plays an important role in determining the timing of LID onset.

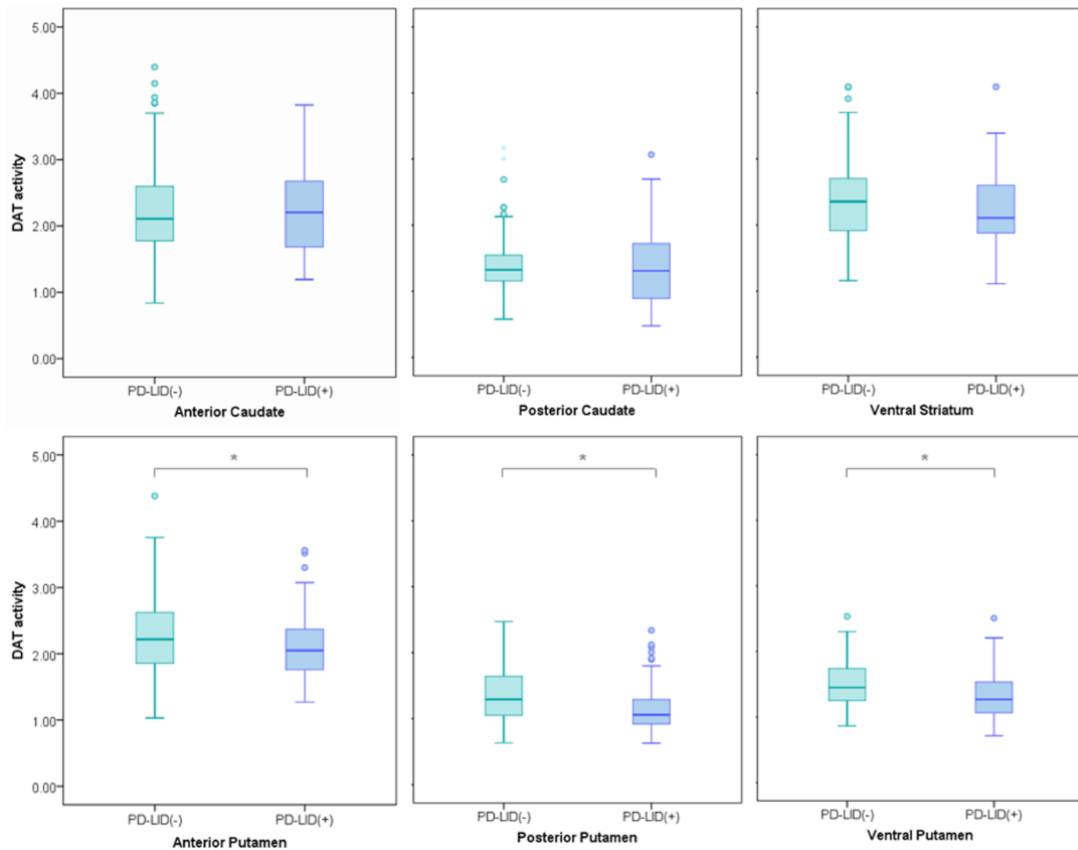


FIG. 1 (1376)

TABLE 1 (1376) Initial striatal DAT activities in the patients with Parkinson disease with levodopa-induced dyskinesia

	Early-onset LID group (n=21)	Intermediate-onset LID group (n=22)	Late-onset LID group (n=22)	p value	p*	p†	p‡
Whole caudate	1.77 (0.14)	1.88 (0.12)	2.14 (0.12)	0.139			
Anterior caudate	1.99 (0.15)	2.10 (0.13)	2.41 (0.13)	0.113			
Posterior caudate	1.19 (0.13)	1.32 (0.11)	1.46 (0.11)	0.333			
Whole putamen	1.36 (0.10)	1.55 (0.08)	1.67 (0.08)	0.072			
Anterior putamen	1.87 (0.12)	2.07 (0.10)	2.25 (0.11)	0.082			
Posterior putamen	0.94 (0.09)	1.18 (0.07)	1.30 (0.08)	0.020	0.139	0.017	0.792
Ventral putamen	1.19 (0.09)	1.33 (0.07)	1.44 (0.07)	0.106			
Ventral striatum	2.15 (0.14)	2.15 (0.12)	2.39 (0.13)	0.325			

Values are expressed as the estimated mean (standard error) and adjusted for age at PD onset, gender, time duration between the PD onset and the initiation of levodopa therapy, and initial UPDRS-III score.

DAT dopamine transporter, *LID* levodopa-induced dyskinesia

* Early-onset LID group vs. intermediate-onset LID group

† Early-onset LID group vs. late-onset LID group

‡ Intermediate-onset LID group vs. late-onset LID group

1388

Automated Differential Diagnosis of Parkinsonian Syndromes Using FDG-PET Metabolic Brain Network Analysis

T. Rus, P. Tomše, L. Jensterle, M. Grmek, Z. Pirtošek, D. Eidelberg, C. Tang, M. Trošt (Ljubljana, Slovenia)

Objective: To discriminate among parkinsonian patients using an automated network analysis of FDG-PET brain images.

Background: Clinical differentiating among parkinsonian syndromes: Parkinson's disease (PD), multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) may be challenging early in disease course. Disease specific metabolic brain patterns were identified for PD, MSA and PSP using Scaled Subprofile Modelling/Principal Component Analysis of FDG-PET images: PD related pattern (PDRP), MSA related pattern (MSARP) and PSP related pattern (PSPRP) (Poston KL, et al. 2010). Additionally, a probabilistic algorithm for the classification of individual patients with clinically uncertain parkinsonism was developed based on the expression of metabolic covariance patterns specific for PD, MSA and PSP (Tang CC, et al. 2010).

Methods: 137 patients with parkinsonism (disease duration 4.9 ± 4 years) and uncertain clinical diagnosis underwent diagnostic FDG-PET. A network analysis was performed and the expressions of PDRP, MSARP and PSPRP were calculated using Topographic Profile Rating method. A probability for PD, MSA and PSP was calculated using the two stage logistic algorithm that distinguishes between PD and atypical parkinsonian syndrome (APS) in the first stage, and between MSA and PSP in the second. The calculated diagnosis was then compared to final clinical diagnosis made 21.4 ± 13 months after imaging.

Results: Among 137 patients, 38 were excluded for alternative (not PD, MSA or PSP) diagnosis. Among 99 patients 66 were clinically diagnosed with PD, 17 with MSA and 16 with PSP. Automated algorithm diagnosed 57 patients with PD, 9 with MSA, 18 with PSP. Results were indeterminate in 15 cases. Discriminative measures of diagnostic accuracy for the first stage (PD vs atypical parkinsonian syndrome (APS)) and the second stage of diagnostic algorithm (MSA and PSP) are presented in table 1 (PPV – positive predictive value, NPV – negative predictive value). [table 1]

Conclusions: FDG-PET brain imaging with an automated differential diagnostic algorithm (Tang CC, et al. 2010) is a reliable tool for the improvement of early diagnosis in patients with uncertain parkinsonism.

References: 1. Poston KL, Eidelberg D. FDG PET in the Evaluation of Parkinson's Disease. *PET Clin.* 2010;5(1):55-64. 2. Tang CC, Poston KL, Eckert T, et al. Differential diagnosis of parkinsonism: a metabolic imaging study using pattern analysis. *Lancet Neurol.* 2010;9(2):149-58.

TABLE 1 (1388)

	PD vs APS	MSA	PSP
Sensitivity	83.3%	72.7%	86.7%
Specificity	93.9%	94.4%	64.3%
PPV	96.5%	88.9%	72.2%
NPV	73.8%	85.0%	81.8%

1400

Parkinson's disease motor symptoms are linked to red nucleus volume and cerebellar metabolism

A. Bonnet, R. Sanford, A. Riou, S. Drapier, F. Le Jeune, M. Vérin, D.L. Collins (Rennes, France)

Objective: To investigate the involvement of the red nucleus (RN) and cerebellum in the motor symptoms of Parkinson's disease (PD).

Background: Numerous studies have shown that the cerebellum is involved in PD, but its precise role remains unclear in this disease. As the red nucleus (RN) is intricately connected to the cerebellum, this structure has also been hypothesized to be involved in PD. Studies have reported greater RN volume in Parkinsonian patients compared with controls, and a positive correlation between disease severity and RN volume. However, these findings need to be verified, as sample sizes were small, resulting in poor statistical power.

Methods: We retrospectively examined 72 patients with PD. All patients had undergone whole-brain T1-weighted (T1w) and T2w MRI and 18F-fluorodeoxyglucose PET (18F-FDG PET). For each patient, RN volume was automatically estimated from the T2w MRI scan, and cerebellar metabolism was extracted from the 18F-FDG PET scan for each of the lobes. We assessed the correlations between RN volume, cerebellar metabolism and PD motor symptoms, as measured by the Unified Parkinson's Disease Rating Scale Part III off medication (UPDRS-III OFF).

Results: We observed a significant positive correlation between the RN volume and the UPDRS-III OFF score (squared-r = 0.09, p = 0.009), and between left anterior cerebellar lobe metabolism (which is involved in sensory-motor processes and motor skills learning) and the UPDRS-III OFF score (squared-r = 0.10, p = 0.001). In addition, we found a significant positive correlation between the RN volume and left anterior cerebellar lobe metabolism (squared-r = 0.07, p = 0.036).

Nevertheless, the multivariate analysis showed that both RN volume (squared-r = 0.11, p = 0.035) and left anterior cerebellar lobe metabolism (squared-r = 0.06, p = 0.003) had significant independent effects on the UPDRS-III OFF score.

Conclusions: These results indicate that cerebello-rubral pathways, but also RN and cerebellum independently, play a role in the motor symptoms of PD, which is likely to be compensatory. Thus, they demonstrate the need for therapies targeting these structures.

References: 1. Wu T, Hallett M. The cerebellum in Parkinson's disease. *Brain* 2013;136:696-709. 2. Colpan ME, Slavin KV. Subthalamic and red nucleus volumes in patients with Parkinson's disease: do they change with disease progression? *Parkinsonism Relat Disord* 2010;16:398-403.

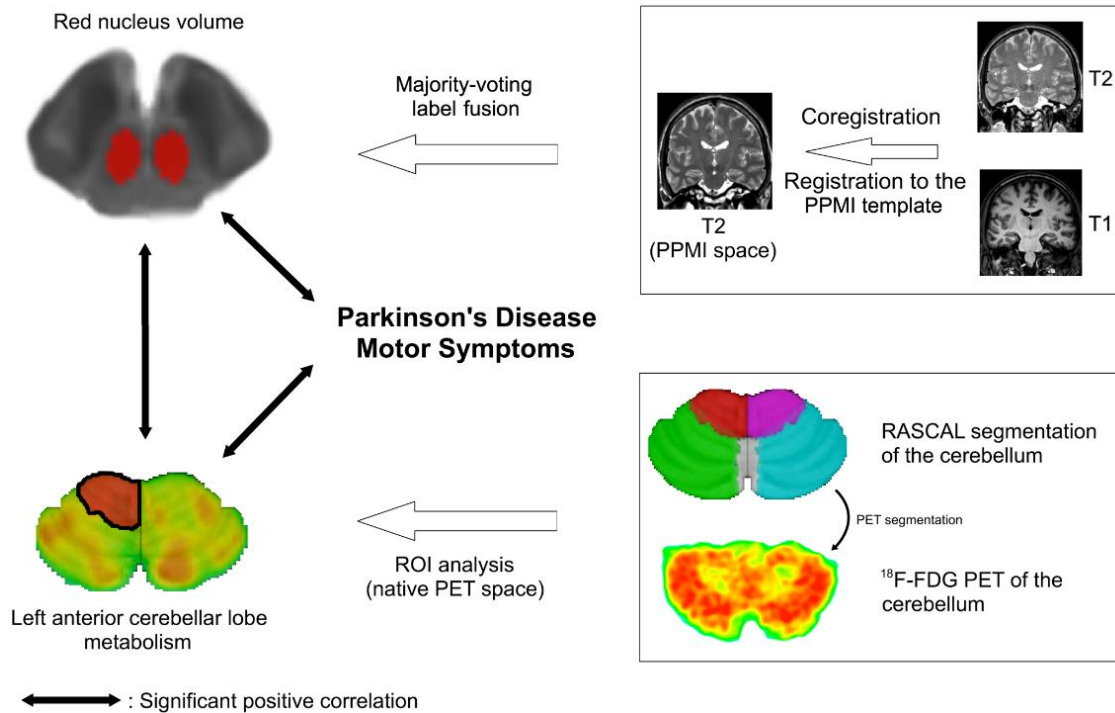


FIG. 1 (1400)

Brain Network Connectivity Measured by Diffusion Tensor Imaging Predicts Prognosis in Parkinson's Disease

S.M. Fereshtehnejad, N. Abbasi, Y. Zeighami, K. Larcher, R. Postuma, A. Dagher (Montreal, QC, Canada)

Objective: We aimed to explore whether network connectivity structure as measured by diffusion tensor imaging (DTI) are associated with progression rate of motor and non-motor outcomes in Parkinson's disease (PD). Secondly, we investigated if brain connectivity measures can differentiate clinical subtypes of PD.

Background: PD is a complex neurodegenerative disorder that varies considerably in its clinical manifestations and prognosis. Investigating biomarkers to predict PD progression, therefore, is of high priority for research and clinical practice.

Methods: This study includes 144 de novo PD patients recruited in the Parkinson's Progression Markers Initiative (PPMI). A comprehensive set of clinical features including both motor and non-motor symptoms was evaluated at baseline and annual follow-up visits. We used diffusion-weighted MRI (DW-MRI) scans obtained at entry, when participants were at the early drug-naïve stage. Mean diffusivity maps were computed for each participant in six regions of interest in the basal ganglia. For analysis of disease progression, we created a global composite outcome (GCO) as a single numeric indicator of prognosis. We also classified the PPMI population based on multi-domain clinical criteria into three subtypes: 'mild motor-predominant', 'intermediate' and 'diffuse malignant'.

Results: Baseline mean diffusivity of globus pallidus was significantly associated with worsening of motor severity ($r=0.27$, $p=0.001$), cognition ($r=-0.18$, $p=0.040$), and GCO ($r=0.30$, $p<0.0001$) after 4.5 years follow-up. After regressing out the effect of aging, network global efficacy at baseline significantly predicted decline in MoCA ($r=0.21$, $p<0.05$), and increase in GCO ($r=-0.17$, $p<0.05$). Disruption in a sub-cortical network consisting of basal ganglia, thalamus and hippocampus at baseline was significantly associated with being subtyped as 'diffuse malignant' versus 'mild motor-predominant' after 4.5 years (corrected $p<0.05$) [Figure 1].

Conclusions: DW-MRI measures of diffusivity and network connectivity (both whole brain and basal ganglia) demonstrated significant associations with progression of motor and non-motor features, and clinical subtypes of PD after 4.5 years. DW-MRI measures could be used as prognostic biomarkers in clinical trials starting from the early de novo stage of PD.

References: 1. Fereshtehnejad SM, et al (2017). Clinical criteria for subtyping Parkinson's disease: biomarkers and longitudinal progression. *Brain*, vol. 140, no. 7, pp. 1959-1976. 2. Zalesky A, et al. (2010). Network-based statistic: identifying differences in brain networks. *Neuroimage*, vol. 53, no. 4, pp. 1197-207.

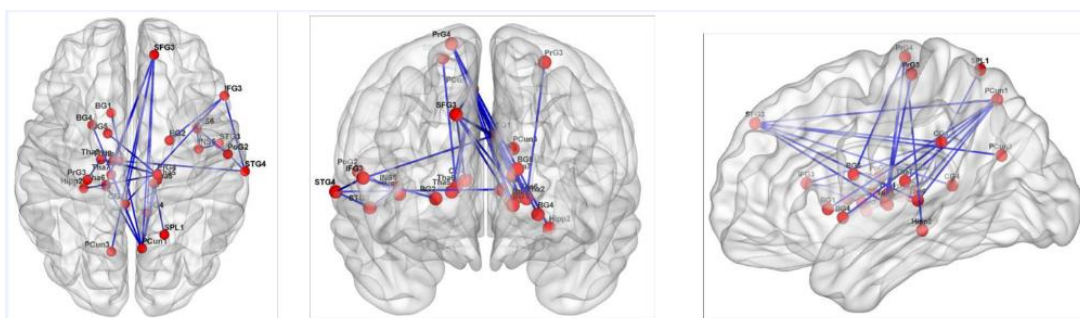


Figure 1. Sub-network consisting of basal ganglia, thalamus and hippocampus at entry to differentiate clinical subtypes after 4.5 years of follow-up in PPMI

(corrected p -value <0.05)

FIG. 1 (1403)

1415

Longitudinal development of nigral iron load in Parkinson's Disease

S. Franthal, L. Pirpamer, C. Rodler, N. Homayoon, M. Koegl, P. Katschnig-Winter, K. Wenzel, C. Langkammer, S. Ropele, R. Schmidt, P. Schwingenschuh (Graz, Austria)

Objective: We for the first time investigated longitudinal changes of nigral iron load in Parkinson's disease (PD) measured by Quantitative Susceptibility Mapping (QSM), a highly iron-sensitive MRI method, and its relation to clinical variables.

Background: Iron accumulation in the substantia nigra (SN) is discussed to be an important factor in the pathogenesis of PD. Former studies, based on histological and imaging techniques, showed higher concentrations of iron-ions in the basal ganglia, especially in the substantia nigra of parkinsonian patients compared to healthy controls. However longitudinal data are sparse.

Methods: We included 52 PD-patients (36 male, mean age $62,6 \pm 10,7$; mean disease duration 4,1 years) and 29 healthy controls (HC) (13 male; mean age $68,1 \pm 9,1$). All subjects underwent a clinical examination and a 3T MRI scan at baseline and after a follow-up period of approximately 2 years. Nigral iron concentration was determined by QSM. For cross-sectional group comparisons we performed one-way ANOVAs corrected for age and gender, for longitudinal comparisons repeated-measure ANOVAs corrected for age, gender and between-scan-time and for clinical correlations Spearman correlations. To achieve normal distribution QSM values were logarithmised, significances were corrected with Bonferroni correction for multiple comparisons.

Results: QSM values in total SN, SN pars compacta (SNc) and SN pars reticulata (SNr) were significantly higher in PD compared to HC ($p < 0.001$) at baseline and follow-up. There were no significant group differences in longitudinal QSM-change. QSM values in PD tended to increase in SNc and decrease in SNr, in HC they tended to decrease in SNc and SNr. There was no significant correlation for QSM change and change in clinical parameters (MDS-UPDRS, FTM-tremor rating scale, Non Motor symptoms questionnaire, MMSE, LED).

Conclusions: We confirmed higher nigral iron load in PD compared to HC. However there was only a not significant trend for stronger shortterm longitudinal increase of iron concentration in SNc in PD compared to HC. This might be due to relatively long baseline disease duration in our PD subjects and suggests nigral iron accumulation as an early factor in the pathogenesis of PD.

References: This abstract has previously been presented at the 4th Congress of the European Academy of Neurology, 16 - 19 June 2018 and at the 15th Annual Meeting of the Austrian Society of Neurology, 21-23 March 2018.

1430

Identifying the neural correlates of doorway freezing in Parkinson's disease

E. Matar, J. Shine, P. Ward, M. Gilat, K. Ehgoetz-Martens, M. Frank, A. Moustafa, S. Naismith, S. Lewis (Sydney, Australia)

Objective: We aimed to combine a previously validated virtual reality gait paradigm with functional Magnetic Resonance Imaging (fMRI) to investigate the neural correlates underlying doorway-provoked freezing behaviour in Parkinson's disease. Based on previous models we predicted that disturbances in connectivity of the hyperdirect pathway would correlate with the motor disturbance observed in response to doorways.

Background: Freezing of gait (FOG) in Parkinson's disease (PD) is frequently triggered upon passing through narrow spaces such as doorways. Often this freezing behaviour is improved with dopaminergic treatments. Despite being common the neural mechanisms underlying freezing are poorly understood due to the inherent limitations accompanying the functional imaging of gait. We have previously shown that freezing behaviour can be reliably modelled in a scanner using a virtual reality (VR) paradigm wherein subjects use foot-pedals to pass through a virtual corridor. Using this method, we have found that changes in

activation within fronto-parietal networks contributes to freezing of gait generally but doorway-freezing specifically has not been studied.

Methods: In our study, nineteen patients who experience FOG performed a lower limb motor sequencing task wherein foot-pedals were used to navigate a series of wide and narrow doorways within a previously validated VR environment. Patients underwent testing both 'ON' and 'OFF' their medications and task performance together with blood oxygenation level dependent (BOLD) signal changes, were compared within each patient.

Results: Patients demonstrated significantly longer 'footstep' latencies in the OFF state compared to the ON state as they passed through a doorway in the VR environment ($p < 0.05$). As with real FOG, this motor disturbance was primarily triggered by narrow doorways rather than wide doorways in the OFF state (Fig 1). fMRI analysis revealed that this footstep prolongation on passing through doorways was associated with specific hypoactivation in the pre-supplementary motor area (pSMA) bilaterally ($p < 0.05$; Fig 2). Furthermore, task-based functional connectivity analyses revealed that increased latency in response to doorways was inversely correlated with the degree of functional connectivity between the pSMA and the subthalamic nucleus (STN) across both hemispheres ($r = 0.441$, $p < 0.05$). Conversely, increased frequency of prolonged footstep latency was associated with increased connectivity in bilateral STN ($r = 0.575$, $p = 0.01$).

Conclusions: The findings of this study suggest that the effect of perceptual cues on triggering FOG reflects impaired processing within the pSMA and its normal signalling with the STN thus implicating the 'hyper-direct' pathway in the pathophysiology of this phenomenon.

References: 1. Shine, J. M. et al. Modeling freezing of gait in Parkinson's disease with a virtual reality paradigm. *Gait Posture* 38, 104-108, doi:10.1016/j.gaitpost.2012.10.026 (2013). 2. Matar, E., Shine, J. M., Naismith, S. L. & Lewis, S. J. Virtual reality walking and dopamine: opening new doorways to understanding freezing of gait in Parkinson's disease. *J Neurol Sci* 344, 182-185, doi:10.1016/j.jns.2014.06.054 (2014).

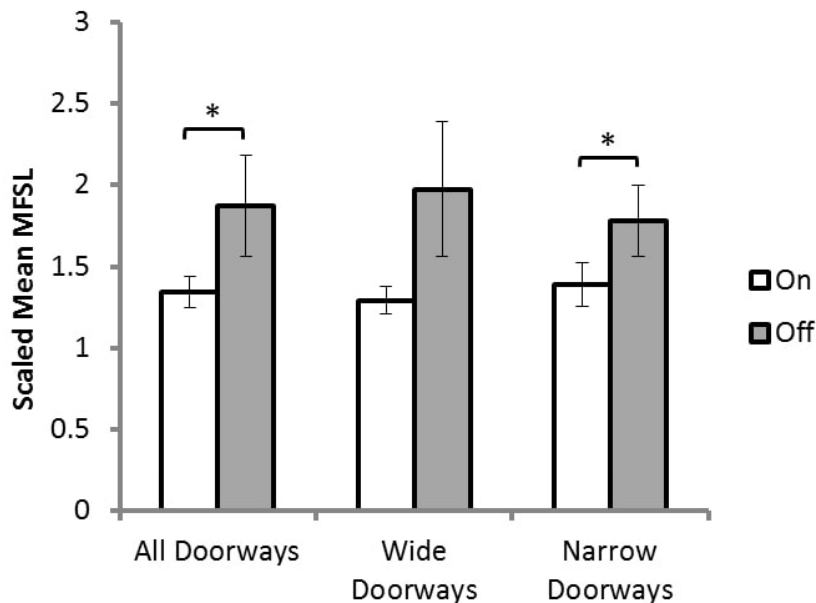


FIG. 1 (1430)

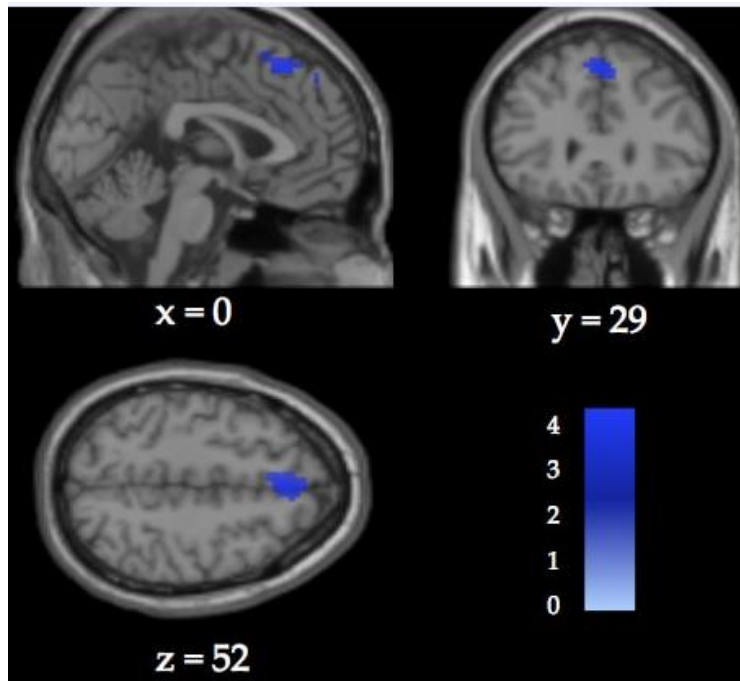


FIG. 2 (1430)

1433

Abnormal Functional Connectivity in Cerebellar Locomotor Region is associated with the severity of freezing of gait in patients with Parkinson's disease

K. Bearti, A. Suppa, S. Pietracupa, N. Upadhyay, C. Giannì, G. Leodori, F. Di Biasio, N. Modugno, N. Petsas, G. Grillea, A. Zampogna, A. Berardelli, P. Pantano (Rome, Italy)

Objective: We aim to analyze cerebellar functional connectivity (FC) in PD patients with FOG (PD-FOG).

Background: Freezing of gait (FOG) is a disabling disorder frequently affecting patients with Parkinson's disease (PD) and consists of transient inability to start or maintain locomotion [1]. The pathophysiological mechanism of FOG has not yet been identified. Although recent studies with magnetic resonance imaging (MRI) have shown alterations in several cortical and subcortical brain areas of patients with FOG, the cerebellum, a key structure in posture and gait control, has only been partially studied [2].

Methods: We recruited 15 PD-FOG, 16 PD without FOG (PD-nFOG) patients, and 16 age-matched healthy subjects (HS). The motor and cognitive impairment of patients was evaluated with validated clinical scales. FOG severity was assessed by the FOG Questionnaire (FOG-Q). Resting-state fMRI data were acquired using a high field magnet (3 Tesla, Siemens, Verio). By using the FSL software we located a seed region on the cerebellar locomotor region (CLR) and obtained FC maps of the CLR with the whole brain. The z scores of clusters showing significant differences in FC between PD-FOG patients and HS were correlated with scores at FOG-Q in SPSS toolbox.

Results: The two subgroups of patients showed decreased FC of the CLR with the prefrontal cortex (superior, middle and inferior frontal gyrus) of both the cerebral hemispheres. In addition, only PD-FOG exhibited increased FC of CLR with the cerebellar vermis, cerebellar lobules left VI, IX, and right crus I-IV, VI, VII b as well as with the parieto-occipital cortex (both fusiform gyrus and lateral occipital cortex bilaterally and right lingual gyrus) [figure1].

FC of the CLR with cerebellar and posterior cortical areas in PD-FOG positively correlated with the FOG-Q score [figure2].

Conclusions: Our results suggest that the altered functional connectivity of the cerebellum may contribute to the pathophysiology of FOG; in particular, FC of the CLR, correlated with FOG severity,

supporting the hypothesis that abnormal cerebellar function can contribute to the genesis of FOG in patients with PD.

References: 1. Giladi N, McDermott MP, Fahn S, Przedborski S, Jankovic J, Stern M, et al. Freezing of gait in PD: prospective assessment in the DATATOP cohort. *Neurology*. 2001;56:1712–21. 2. Tessitore A, Amboni M, Esposito F, Russo A, Picillo M, Marcuccio L, et al. Resting-state brain connectivity in patients with Parkinson’s disease and freezing of gait. *Parkinsonism Relat Disord*. 2012;18:781–7.

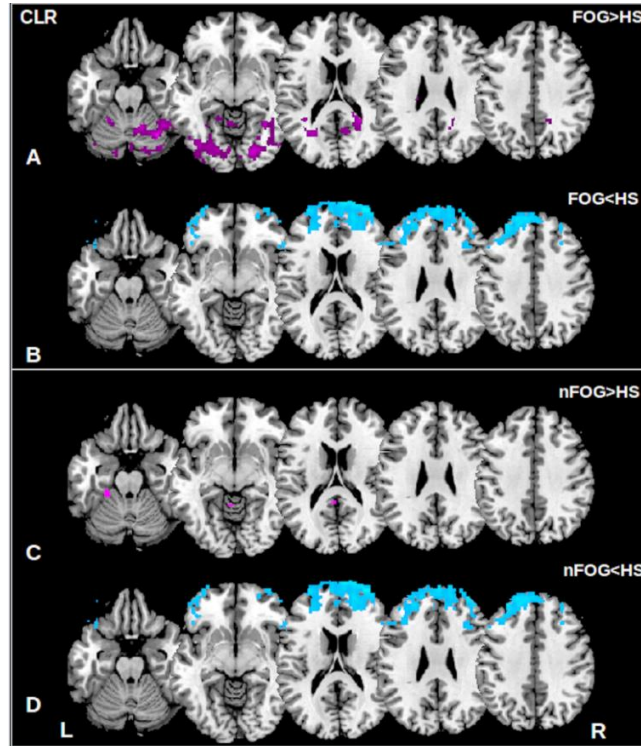


FIG. 1 (1433)

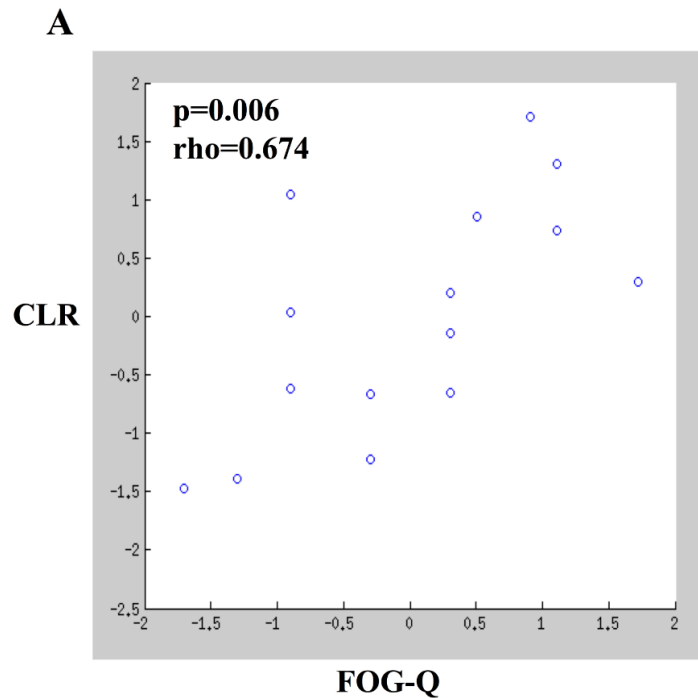


FIG. 2 (1433)

1464

Resting-state connectivity and cognitive changes in Parkinson's disease: A four-year follow-up study
HC. Baggio, B. Segura, A. Abos, A. Campabadal, C. Uribe, A.I. Garcia-Diaz, M.J. Marti, Y. Compta, F. Valldeoriola, C. Junque (Barcelona, Spain)

Objective: To study functional connectivity changes using graph theory and their association with cognitive evolution in a sample of non-demented Parkinson's disease (PD) and matched healthy controls (HC) after a four-year follow-up.

Background: Previous studies demonstrated that cognitive deficits in PD are associated with alterations in different parameters derived from resting-state functional connectivity. Evidence regarding the relationship between connectivity changes and cognitive evolution is nonetheless very scarce.

Methods: A final sample of 27 HC and 45 matched PD patients, assessed twice at an interval of approximately four years, was included. Resting-state fMRI was used for functional connectivity analysis. Connectivity matrices, obtained after parcellating the brain into 246 regions using the Brainnetome atlas, were used to compute graph-theory parameters that describe network organization (path length, clustering coefficient, modularity, small-world coefficient). For cognitive assessment, a thorough neuropsychological battery was used, and tests were subsequently grouped into four cognitive domains (attention/working memory, executive function, memory, and visuospatial/perceptual function). A repeated-measures general linear model was used to test group and time effects, as well as group-by-time interactions.

Results: Analysis of cognitive data in patients showed a significant effect of time for executive function ($p=.004$) and visuospatial/perceptual scores ($p=.015$). Significant effects of group ($p=.034$, patients performing worse than controls), time ($p=.006$), and group-by-time interaction ($p=0.027$) were found. Connectivity parameters showed significant effects of group for clustering coefficients and modularity ($p=.023$ and $p=.045$, respectively, with patients showing higher values). For path lengths, a significant effect of time was found ($p=.022$, both groups showing increasing values). When performing correlations between longitudinal cognitive and connectivity changes, we found that differences in executive function scores correlated significantly and positively with differences in clustering coefficients ($r=0.404$, $p=0.007$), modularity ($r=0.384$, $p=0.011$), and small-world coefficients ($r=0.335$, $p=0.028$).

Conclusions: Our findings indicate that functional connectivity changes explain executive function in PD patient's evolution.

1479

A cortical neural signature of motor interruption in patients with Parkinson's disease and freezing of gait

J. Baarbé, M. Brown, U. Saha, K. Lizarraga, A. Weissbach, N. Drummond, C. Rinchon, P. Kapoor, J. Saravanamuttu, R. Chen (Toronto, ON, Canada)

Objective: To investigate whether cortical oscillations involved in sensorimotor and perceptual processes [alpha (8-12 Hz), low beta (13-20 Hz) and high beta (21-35 Hz)] change during interruptions of motor output in Parkinson's disease (PD) patients with freezing of gait (FoG).

Background: FoG is a debilitating symptom in PD and can often be resistant to treatment. FoG is often triggered by narrow passageways and crowded rooms, and its incidence can be reduced by visual aids that prompt rhythmic stepping. Sensory influence on FoG suggests that sensory, perceptual and/or motor processes in the cortex may be intrinsically involved in FoG pathophysiology.

Methods: We recorded 64 channel electroencephalography in 10 PD patients (68 years old \pm 6; disease duration: 9 years \pm 5; UPDRS-III on medication: 27 \pm 9; UPDRS-III off medication: 31 \pm 8; levodopa equivalent dose: 880 mg \pm 420) and 9 healthy controls (67 years old \pm 6). Six patients had FoG confirmed by the New Freezing of Gait Questionnaire and neurologist assessment. While seated, participants manipulated foot pedals to walk through a virtual environment (VE). Participants completed 4 sets of 5 minutes walking within the VE. Doorways within the VE were used to trigger motor interruptions (MI). We also had participants intentionally stop to assess cortical activity unique to MI. Alpha, low beta and high beta were

determined pre MI (-1200 to -600 ms), upon onset of MI (-300 to 300 ms), during MI (600 to 1200 ms), during an active state and upon intentionally stopping. Cortical activities were assessed in predetermined premotor/frontal (F1,Fz,F2,FC1,FCz,FC2), motor (C1,Cz,C2) and parietal (CP1,CPz,CP2,P1,Pz,P2) clusters.

Results: Patients with FoG experienced a total of 38 MI (mean duration 2.5 s). MI influenced alpha power within premotor/frontal ($p=0.042$; Onset MI<During MI) and motor clusters ($p=0.016$; Pre MI>Onset MI; Onset MI<During MI). Onset of MI affected low beta power in motor ($p=0.022$; Onset MI<During MI) and parietal clusters ($p=0.039$; Onset MI<During MI). MI did not induce changes to high beta power within any of the clusters, but intentional stopping increased alpha, low beta and high beta in all clusters ($p<0.001$).

Conclusions: Alpha and low-beta oscillations in motor areas may be important predictive signals of MI in patients with PD and FoG. Uniquely, the absence of high beta distinguishes MI from intentional stops. These findings may be useful for the development of closed-loop brain stimulation or biofeedback strategies to alleviate FoG.

1483

The difference in cerebellar blood flow reduction in multiple system atrophy and Parkinson's disease

N. Murakami, W. Sako, S. Haji, Y. Izumi, R. Kaji (Tokushima, Japan)

Objective: The aim of this study is to determine if cerebral blood flow (CBF) reduction in the cerebellum could be a tool for differential diagnosis between patients with multiple system atrophy (MSA) and patients with Parkinson's disease (PD).

Background: MSA is the neurodegenerative disease showing progressive atypical parkinsonism, which is frequently misdiagnosed as PD, especially in case without cerebellar symptom or atrophy. The accurate tool for differential diagnosis between MSA and PD could facilitate clinical trials of disease modifying therapy.

Methods: Twenty one patients with PD were diagnosed as clinically established PD or clinically probable PD (10 men and 11 women with a mean age of 67.7 ± 12.3 years), fifteen patients with MSA with predominant parkinsonian features (MSA-P), six patients with MSA with predominant cerebellar ataxia (MSA-C) were diagnosed as probable or possible MSA (11 men and 10 women with a mean age of 65.2 ± 9.3 years), fifteen patients with progressive supranuclear palsy (PSP) were diagnosed as probable or possible PSP (5 men and 10 women with a mean age of 73.7 ± 6.1 years) according to the internationally established criteria were included in this study. All patients underwent N-isopropyl-[123I] p-iodoamphetamine (IMP) single photon emission computed tomography (123I-IMP SPECT) and data were analyzed using three-dimensional stereotactic surface projection (3D-SSP) software. Area under curve (AUC) of receiver operating characteristic (ROC) of CBF reduction in the cerebellum was assessed.

Results: Cerebellar perfusion was significantly decreased in the MSA-P ($P < 0.001$, one-way ANOVA; $P < 0.001$, post hoc, Dunnett), MSA-C ($P < 0.001$, post hoc, Dunnett) compared with the PD. There was no difference in cerebellar perfusion between PSP and PD ($P = 0.598$, post hoc, Dunnett). Specificity of CBF reduction in the cerebellum for MSA-P vs PD was 1.00, while sensitivity was 0.67. CBF reduction may be an optimal tool for differentiating between MSA-P and PD (AUC = 0.849).

Conclusions: In conclusion, our findings suggested that CBF reduction in the cerebellum using 123I-IMP SPECT could be a useful tool for differentiating between MSA-P and PD.

1484

Structural Abnormalities in the Cerebellar Peduncles of patients with Freezing of Gait: A Diffusion Tensor Imaging Study

K. Bharti, A. Suppa, S. Pietracupa, N. Upadhyay, C. Gianni, G. Leodori, F. Di Biasio, N. Modugno, N. Petasas, G. Grilla, A. Zampogna, A. Berardelli, P. Pantano (Rome, Italy)

Objective: We used diffusion tensor imaging (DTI) to investigate cerebellar structural connectivity by evaluating white matter properties along the superior (SCP), middle (MCP), and inferior cerebellar peduncles (ICP) in patients with Parkinson's disease (PD) and freezing of gait (FOG).

Background: FOG is a disabling disorder frequently affecting patients with PD characterized by a transient inability to start or maintain locomotion [1]. The pathophysiological mechanism of FOG has not yet been identified. Although recent structural studies have shown some cerebellar white matter alterations in patients with PD and FOG, the cerebellum, a key structure in posture and gait control, has only been partially studied [2].

Methods: Fifteen patients with FOG (PD-FOG), 16 with no FOG (PD-nFOG) and 16 healthy subjects (HS) underwent a DTI study. We quantified the fractional anisotropy (FA) and mean diffusivity (MD) on the Superior (SCP), Middle (MCP), and Inferior cerebellar peduncles (ICP) by using FSL toolboxes. The results were FWE-corrected at a significance level of $p < 0.05$. For the correlation analysis, the time series extracted from the FA and MD values of three cerebellar peduncles (SCP, MCP, and ICP) were correlated with the clinical scales: Severity of FOG (FOG-Q), Unified Parkinson's Disease Rating Scale, Mini-Mental State Examination, Frontal Assessment Battery, Hamilton Depression Scale using Spearman's correlation in SPSS software.

Results: PD-FOG patients showed lower FA in the Superior Cerebellar Peduncle (SCP) and the Middle Cerebellar Peduncle (MCP) than both PD-nFOG and HS [figure1A][figure1B]. PD-FOG also showed higher MD in the Superior Cerebellar Peduncle (SCP) than PD-nFOG [figure1C]. FA at the Middle Cerebellar Peduncle (MCP) negatively correlated with FOG-Q in PD-FOG ($p = 0.009$; $\rho = -0.595$) [figure2A] and MD at the Superior Cerebellar Peduncle (SCP) positively correlated with FOG-Q in PD-FOG ($p = 0.04$; $\rho = 0.642$) [figure2B].

Conclusions: Our results suggest the loss of fibers connecting the cerebellum with other brain structures in PD-FOG patients. Significant correlations support the role of the cerebellum in FOG pathogenesis, therefore underlines the importance of cerebellum with regards to locomotion.

References: 1. Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A. Freezing of gait: moving forward on a mysterious clinical phenomenon. *Lancet Neurol.* 2011;10:734–44. 2. Youn J, Lee J-M, Kwon H, Kim JS, Son TO, Cho JW. Alterations of mean diffusivity of pedunculopontine nucleus pathway in Parkinson's disease patients with freezing of gait. *Parkinsonism Relat Disord.* 2015;21:12–7.

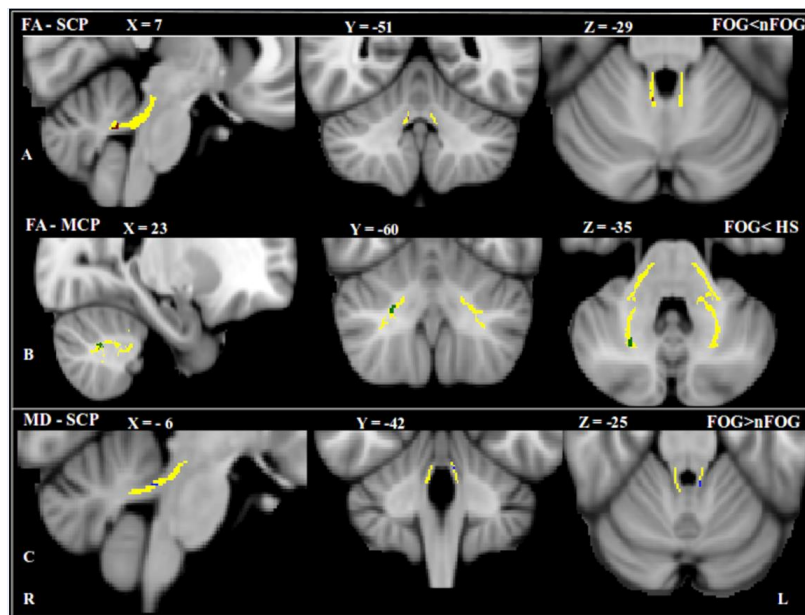


FIG. 1 (1484)

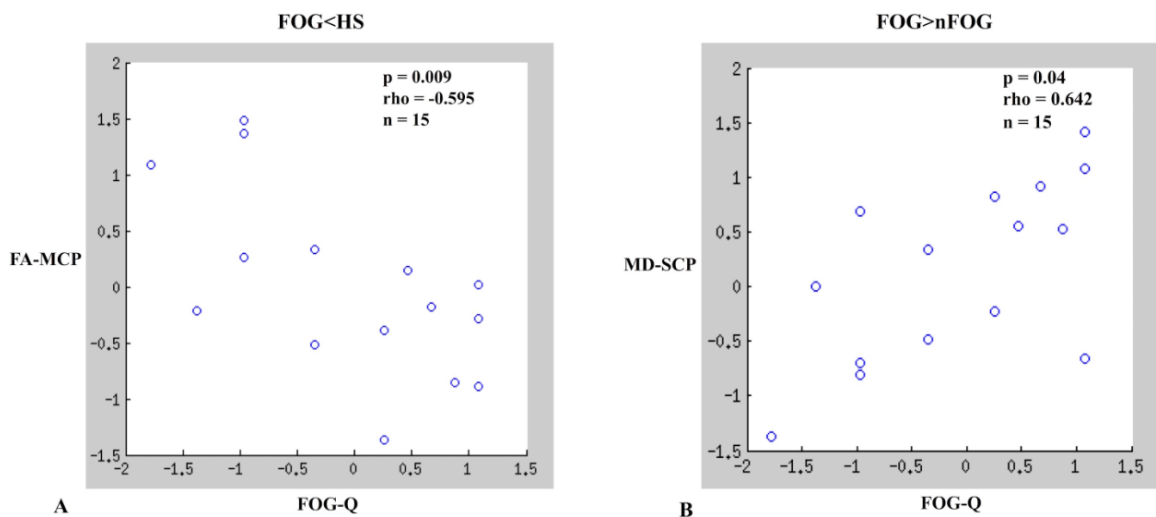


FIG. 2 (1484)

Guided Poster Group 12: Parkinson's Disease: Non-Motor Symptoms

1531

Characterization of the gastrointestinal dysfunction in mice overexpressing the human mutation (A53T) of alpha-synuclein

S. Diwakarla, R. Constable, O. Artaiz, D. Finklestein, J. Berger, J. Furness (Melbourne, Australia)

Objective: The aim of this study was to determine if mice overexpressing the human mutation of alpha-synuclein develop gastrointestinal (GI) dysfunction, and to understand the time course of events in relation to central nervous system (CNS) dysfunction.

Background: GI dysfunction, such as prolonged GI transit time and constipation, has been associated with the pathological changes seen in the brain, and often precedes the onset of motor symptoms in Parkinson's disease (PD) by decades. A hallmark of PD is the aggregation of the protein alpha-synuclein in various regions of the brain, which has been strongly linked to nerve cell death. Aggregates of alpha-synuclein are also found in the enteric nervous system of PD patients and may be a cause of enteric neuron damage and subsequent GI dysfunction.

Methods: We performed a complete characterization of the GI phenotype in the A53T mouse model of PD, which overexpresses the human mutation of alpha-synuclein driven by the mouse prion promoter. GI and motor function were monitored at one month intervals from 18-80 weeks. Constipation, colon motility, and GI transit were assessed using the fecal pellet output test, bead expulsion test, and whole-gut transit test, respectively. Motor deficits were monitored using the beam traversal test.

Results: When compared with WT mice, A53T mice developed progressive GI dysfunction from 58 weeks of age, which included reduced colon motility and whole gut transit ($P < 0.05$). Interestingly, motor deficits were observed prior to the onset of GI symptoms in A53T mice from 32 weeks of age, indicating that in this mouse model CNS dysfunction precedes the manifestation of GI symptoms.

Conclusions: Mice overexpressing the human mutation of alpha-synuclein, driven by the mouse prion promoter, develop GI dysfunction after the onset of motor deficits. Although this model may not fully reproduce the human condition, it continues to serve as a useful tool to understand both the CNS and GI dysfunction associated with PD.

1533

Four-year course of impulsive and compulsive behaviors in Parkinson's disease

A. Erga, G. Alves, O.B. Tysnes, K. Pedersen (Stavanger, Norway)

Objective: To (1) determine the longitudinal risk of ICBs for patients compared to controls, (2) determine the stability and transition probabilities of ICBs over the course of four years.

Background: Impulsive and compulsive behaviours (ICBs) include a range of behavioural addictions and related behaviours, that are common in Parkinson's disease (PD), affecting between 14 - 30 % of patients. A major limitation in previous research is use of cross-sectional or retrospective designs, and the course of ICBs is largely undescribed in the current literature.

Methods: Data from the Norwegian ParkWest study, a population-based longitudinal cohort study of the incidence, neurobiology and prognosis of PD in Western Norway were used in this study. Patients were included five years after diagnosis and inclusion in the ParkWest study and followed prospectively for four years. At study entry, 125 patients and 159 normal controls were included. Standardized clinical rating scales were used to evaluate motor severity, global cognitive function and depressive symptoms. ICBs were evaluated using the short version of the Questionnaire for Impulsive-Compulsive Disorders in PD (QUIP). The development of ICDs was investigated using Markov chain analysis, with ICD status and dropout/dementia as endpoint states.

Results: Although ICBs were consistently more frequent in PD than controls, the risk of ICBs decreased over time. The transition probability for patients with ICBs at baseline was 42.9 % for recovery of ICB symptoms, 36.3 % for persistent ICBs and 20.8 % for development of dementia or drop out from the study. Patients who were ICB negative at baseline had an estimated transition-probability of 14.2 % to develop ICBs, 64.9 % to remain without these symptoms and 20.9 % for development of dementia or drop out from the study.

Conclusions: These findings suggest that ICBs can develop in the later stages of PD, and have a high probability to remain stable once developed.

References: 1. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Archives of neurology* 2010;67(5):589-595. 2. Erga AH, Alves G, Larsen JP, Tysnes OB, Pedersen KF. Impulsive and Compulsive Behaviors in Parkinson's Disease: The Norwegian ParkWest Study. *Journal of Parkinson's disease* 2017;7(1):183-191.

1553

Striatal dopamine transporter availability changes reflect gastrointestinal dysautonomia severity in early Parkinson's disease

J. Hinkle, K. Perepezko, K. Mills, Z. Mari, A. Butala, T. Dawson, A. Pantelyat, L. Rosenthal, G. Pontone (Baltimore, MD, USA)

Objective: To test the hypothesis that constipation and gastrointestinal (GI) dysautonomia may be correlated with nigrostriatal dopaminergic (DA) dysfunction in PD.

Background: Constipation is a prodromal feature of PD and the GI tract is implicated in the pathogenesis of PD. Autopsy evidence supports nigral degeneration as a correlate of late-life constipation (Petrovitch et al., 2009), but no studies have demonstrated ante-mortem relationships between nigrostriatal dysfunction and GI dysautonomia in PD. However, it was recently demonstrated in rodents that nigral projections regulate gastrointestinal motility via DA receptors on neurons in the dorsal vagal complex (Anselmi et al., 2017).

Methods: The Scale for Outcomes in Parkinson's disease for Autonomic Symptoms (SCOPA-AUT) assesses dysautonomia in the multi-center Parkinson's Progression Marker Initiative (PPMI). We used linear mixed-effects (LME) models and reliable change indices (RCIs) to examine longitudinal associations between dysautonomia and dopamine transporter (DAT) striatal binding ratios (SBRs) measured by single-photon emission computerized tomography (SPECT) in PPMI participants over four years (n=397 at baseline).

Results: Adjusted LME models of longitudinal data [table1] showed that constipation—but not orthostatic hypotension or urinary dysfunction—was associated with reduced SBR in both caudate ($P < 0.001$) and putamen ($P = 0.022$). In both regions, SBR reductions between baseline and 4-year follow-up were significant and measurable ($P < 0.0001$), with larger decline and variances in the caudate nucleus [figure1]. Logistic regression adjusting for disease duration and baseline SCOPA-GI score showed that 4-year change in caudate—but not putamenal —SBR was significantly associated with RCI-indicated progression of GI dysautonomia ($P = 0.007$), but not other types of dysautonomia [table2]. The association remained after adjusting for the use of medications or supplements to control constipation. Consistent with prior PPMI reports, motor impairment progression was not associated with SBR reduction.

Conclusions: GI dysautonomia correlates with reduced striatal DAT availability in PD and constipation may be most closely associated with caudate-DAT reductions. Worsening GI dysautonomia may accompany advancing nigral degeneration or changes in nigrostriatal dopamine function.

References: Anselmi L, Toti L, Bove C, Hampton J, Travaglini RA. A Nigro-Vagal Pathway Controls Gastric Motility and is Affected in a Rat Model of Parkinsonism. *Gastroenterology* 2017; 36138–3. Petrovitch H, Abbott RD, Ross GW, Nelson J, Masaki KH, Tanner CM, et al. Bowel movement frequency in late-life and substantia nigra neuron density at death. *Mov. Disord.* 2009; 24: 371–376.

TABLE 1 (1553)

Table 1: Adjusted linear mixed-effect models of DaTscan uptake and measures of dysautonomia

Independent variable	Caudate SBR		Putamen SBR	
	Beta-coefficient (95% CI)	<i>p</i>	Beta-coefficient (95% CI)	<i>p</i>
SCOPA-AUT measures				
Total (mean score per question)	-0.05 (-0.11 to 0.002)	0.052	-0.02 (-0.05 to 0.01)	0.232
SCOPA-GI (mean)	-0.07 (-0.11 to -0.03)	0.001	-0.04 (-0.06 to -0.01)	0.003
SCOPA-CV (mean)	0.01 (-0.04 to 0.05)	0.905	-0.01 (-0.03 to 0.02)	0.574
SCOPA-U (mean)	-0.02 (-0.05 to 0.01)	0.209	0.003 (-0.01 to 0.02)	0.725
Dysphagia (mean)	-0.01 (-0.05 to 0.02)	0.450	-0.02 (-0.04 to -0.003)	0.021
Constipation (mean)	-0.05 (-0.09 to -0.03)	***	-0.02 (-0.04 to -0.003)	0.022
MDS-UPDRS part I (non-motor)				
Constipation problems	-0.03 (-0.05 to -0.01)	***	-0.01 (-0.02 to -0.001)	0.031
Lightheadedness standing	-0.01 (-0.03 to 0.01)	0.228	-0.0002 (-0.01 to 0.01)	0.964
Urinary problems	-0.02 (-0.03 to -0.0002)	0.047	-0.006 (-0.01 to 0.003)	0.202
MDS-UPDRS part III	-0.001 (-0.002 to 0.001)	0.348	-0.004 (-0.001 to 0.0003)	0.261

SCOPA-AUT and MDS-UPDRS non-motor estimates are adjusted for baseline DaTscan measures, age, disease duration, MDS-UPDRS III, GDS, STAI (State), UPSIT score, RBD sleep questionnaire score. RBD sleep questionnaire estimates are adjusted by the same covariables (except total SCOPA-AUT score is used in lieu of RBD score).

******* $p < 0.001$

TABLE 2 (1553)

Table 2: Reduced caudate SBR in early PD over four years is associated with clinically significant worsening of gastrointestinal dysautonomia

Scale	Caudate SBR change			Putamen SBR change	
	Reliable change, n (%)	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
SCOPA-AUT (total)	63 (28.3)	0.29 (0.10 to 0.81)	0.021	1.26 (0.20 to 8.38)	0.805
SCOPA-GI	104 (47.5)	0.25 (0.09 to 0.67)	0.007	0.32 (0.05 to 1.90)	0.215
SCOPA-CV	70 (32.0)	0.59 (0.21 to 1.57)	0.292	1.00 (0.17 to 6.06)	0.998
SCOPA-U	38 (17.4)	0.31 (0.08 to 1.08)	0.070	2.37 (0.24 to 25.01)	0.463
MDS-UPDRS III (total)	131 (59.8)	0.61 (0.23 to 1.61)	0.323	0.52 (0.08 to 3.07)	0.471

Reliable change was scored as a binary outcome variable (0 or 1) based on whether reliable change index (RCI) exceeded 1.96 (indicating statistical significance at $p < 0.05$).

One logistic regression model was constructed for each scale with reliable change in that scale as the dependent variable. The four independent variables shared by all models were (1) four-year change in caudate SBR; (2) four-year change in putamen SBR; (3) disease duration; (4) baseline section/scale score.

Figure 1: Distribution of SBRs at baseline and 4-year follow-up (n=180)

Graphical representation of Baseline vs. 4-year comparison column in Table 3.

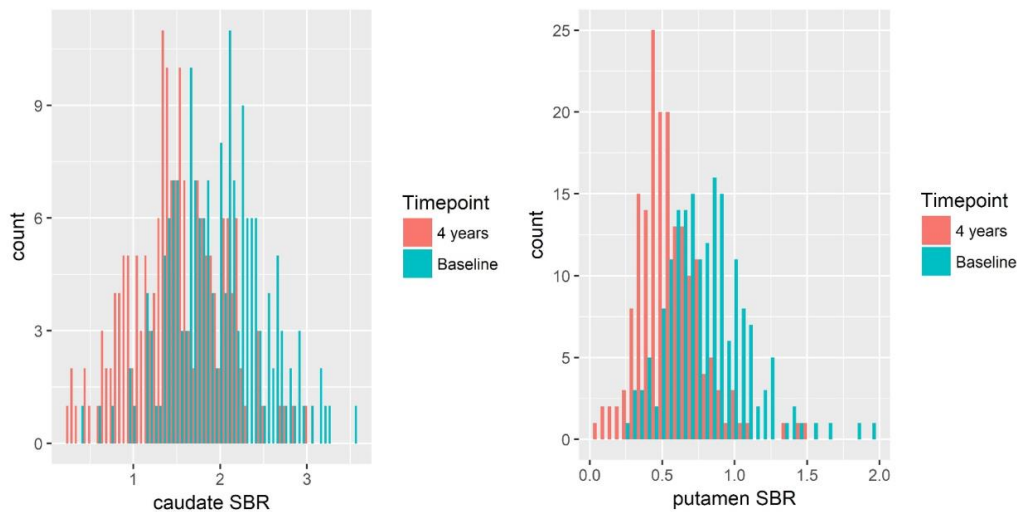


FIG. 1 (1553)

1554

Early gastrointestinal dysfunction is predictive of faster progression in Parkinson’s disease

M. Camacho, J. Evans., D. Breen, G. Cummins, R. Wijeyekoon, K. Scott, T. Stoker, R. Barker, C. Williams-Gray (Cambridge, United Kingdom)

Objective: To evaluate whether constipation at time of diagnosis has prognostic significance in terms of motor and cognitive progression in PD.

Background: There is evidence that PD pathology may start in the gut before spreading to connected areas of the nervous system. Constipation is one of the most common non-motor symptoms experienced by patients with PD and is often present before diagnosis. Moreover, it has a significant impact on quality of life. However, constipation is not a universal feature in early PD patients, suggesting that gut involvement is heterogeneous in PD and may characterize different subtypes with different progression rates.

Methods: We studied a newly diagnosed community-based cohort of 281 IPD patients (PICNICS, Parkinsonism: Incidence and Cognitive Heterogeneity In Cambridgeshire) and followed them up prospectively every 18 months with standardized assessments including the MDS-UPDRS, ACE-R and PDQ-39. According to scores on the MDS-UPDRS constipation item at baseline visit, we stratified the sample using two different cut-offs: mild to high (score of ≥ 1 ; n=78) and moderate to high (score ≥ 2 ; n=35) constipation and followed the natural progression of PD for up to 108 months after diagnosis.

Results: At baseline, 27.8% of patients had mild to high constipation and 12.5% of patients had moderate to high constipation. Regardless of cut-off scores, constipated and non-constipated patients did not differ in age, education level, disease duration, disease stage (Hoehn and Yahr), number of comorbidities and L-dopa equivalent daily dose. Patients with moderate to high constipation had significantly higher disease severity (MDS-UPDRS total) and worse quality of life (PDQ-39), whereas there were no between-group differences in the group with mild to high constipation. Survival analysis showed that patients with moderate to high constipation had an earlier onset of PD related dementia (according to MDS criteria) and more rapid progression to development of postural instability (Hoehn and Yahr stage 3). No differences were observed in mortality between groups.

Conclusions: Constipation only affects one third of PD patients at diagnosis, but its severity at baseline seems to predict a faster motor and cognitive progression.

1573

Non-motor symptoms in Parkinson's Disease: Frequency, types and correlated factors compared to a group of healthy controls. Results from the COPPADIS Study Cohort

L. Planellas, M. Martí, P. Santacruz, A. Cámara, S. Jesus Maestre, F. Carrillo García, P. Mir, M. Aguilar, P. Pastor, J. García Caldentey, E. Estelrich Peyret, N. Caballol Pons, I. Legarda, B. Vives Pastor, J. Hernández Vara, G. Martí Andrés, I. Cabo, L. López Manzanares, M. Gallego-de-la-Sacristana, P. Martínez Martín, D. Santos García, G. COPPADIS STUDY (Barcelona, Spain)

Objective: The aim of this study is to describe the prevalence and burden of NMS in a group of PD patients without dementia compared to an age-matched control group.

Background: Non-motor symptoms (NMS) are frequent in patients with Parkinson's disease (PD) and impact quality of life.

Methods: This is a descriptive study conducted in Spain using data from the baseline visit of the COPPADIS-2015 Study (Santos García et al. BMC Neurol 2016;16:26), an observational, descriptive, 5-year follow-up, national, multicenter, evaluation study. The prevalence and burden of NMS were evaluated using the Non-Motor Symptoms Scale (NMSS), a scale that assess 30 non-motor items grouped in 9 domains.

Results: 696 patients (mean age 62.77 ± 9.03 , males 59.7%) and 206 controls (mean age 61.16 ± 8.45 , males 49.8%) were included in the analysis. NMS were more prevalent in PD patients than controls (total prevalence: 99.3% vs 84.9%, $p < 0.0001$). The mean number of domains affected was 5.74 ± 2.10 in PD group vs 3.25 ± 2.24 in control group ($p < 0.0001$). PD patients had higher prevalence and burden of NMS in all domains and also in all items except "difficulty falling asleep" and "altered sexual interest". Fatigue (62.2%), nocturia (61.2%) and urinary urgency (60.5%) were the most common NMS in the PD group while nocturia (43.2%), difficulty falling asleep (34.0%) and altered interest in sex (32.0%) were the most frequent in control group. Among patients, females had higher scores than males in items related to mood while males had higher scores in daytime sleepiness and sialorrhea. Postural instability and gait difficulty (PIGD) phenotype was associated with higher total NMSS score than tremor dominant PD (51.31 ± 40.96 vs 40.07 ± 34.82 ; $p = 0.004$) and higher scores in sleep/fatigue, mood/apathy, gastrointestinal and miscellaneous domains too.

Conclusions: In our study PD patients have more NMS with higher NMSS scores than controls. Moreover, our results suggest that NMS could be influenced by gender and PD phenotype.

1576

Non-motor outcomes of subthalamic DBS in PD depend on the location of volume of activated tissue

JN. Petry-Schmelzer, H. Dafsari, M. Krause, T. Dembek, A. Keyoumars, A. Rizos, M. Silverdale, J. Evans, M. Barbe, G. Fink, P. Martinez-Martin, V. Visser-Vandewalle, A. Antonini, L. Timmermann, K. Ray-Chaudhuri (Cologne, Germany)

Objective: To investigate the impact of stimulation location on non-motor symptoms (NMS) in PD patients with DBS in the subthalamic nucleus (STN) via an analysis of volumes of activated tissue (VAT).

Background: STN-DBS improves non-motor and motor symptoms. In a recent study, we showed that NMS improvement is higher with a more anterior, ventral and medial position of the active contact, whereas motor symptoms improve more with a more posterior and lateral position of the active contact. However, investigating only electrode locations neglects the spatial extent of electrical stimulation, which also depends on the stimulation parameters. We thus conducted an investigation into the spatial distribution of NMS improvement in the STN using VATs.

Methods: Clinical data was collected from an ongoing prospective, open-label, multicenter study (Cologne, London, Manchester) including 92 patients with bilateral STN-DBS. The following scales were collected at preoperative baseline (MedON) and on follow-up (FU) six months after surgery (MedON/StimON): SCOPA-motor examination (SCOPA-motor), -activities of daily living (ADL), NMSScale (NMSS), NMSQuestionnaire (NMSQ), Hospital Anxiety and Depression Scale-anxiety and depression subscales (HADS-A/-D). Wilcoxon signed-rank test was used to test for significant changes between baseline and follow-up and Bonferroni-correction was applied for multiple comparisons. Individual VATs, based on the stimulation parameters used in clinical setting, were calculated in MNI space (ICBM 2009b) as described elsewhere (1). To analyse the relationship between VATs and change scores, we employed probabilistic stimulation maps and projected them on the DISTAL-Atlas (2).

Results: All outcomes, besides HADS-D, improved significantly at FU. Probabilistic stimulation maps showed higher improvement of NMS for stimulation localized in the limbic and associative STN, whereas motor symptoms improved more for stimulation localized in the motor STN.

Conclusions: Our preliminary results support the finding that the non-motor outcome after DBS may depend on the location of neurostimulation. DBS in non-motor STN subregions was associated with bigger improvement of NMS. The underlying mechanisms and clinical relevance of our results should be investigated in future studies.

References: 1 Horn, A., Reich, M., Vorwerk, J., Li, N., Wenzel, G., Fang, Q., . . . Fox, M. D. (2017). Connectivity predicts deep brain stimulation outcome in Parkinson's disease. *Ann Neurol*. doi:10.1002/ana.24974. 2 Ewert, S., Plettig, P., Li, N., Chakravarty, M. M., Collins, D. L., Herrington, T. M., . . . Horn, A. (2017). Toward defining deep brain stimulation targets in MNI space: A subcortical atlas based on multimodal MRI, histology and structural connectivity. *Neuroimage*. doi:10.1016/j.neuroimage.2017.05.015.

1591

A detailed clinical study of pain in 1957 participants with Parkinson's disease

M. Silverdale, C. Kobylecki, L. Kass-Iliyya, P. Martinez-Martin, D. Grosset, M. Hu, M. Lawton, S. Cotterill, K. Ray Chaudhuri, H. Morris, F. Baig, N. Williams, L. Hubbard (Manchester, United Kingdom)

Objective: We performed a large clinical study to investigate potential factors contributing towards pain in Parkinson's disease (PD).

Background: The causes of pain in PD are not well understood. Although peripheral factors such as rigidity, reduced joint movements and poor posture may contribute towards the development of pain, central mechanisms including altered nociceptive processing may also be involved.

Methods: We recruited 1957 PD participants who had detailed assessments of pain, motor and non-motor symptoms. The King's Parkinson's Pain scale was used to quantify different subtypes of pain.

Results: 85% of participants reported pain (42% with moderate to severe pain). Pain influenced quality of life more than motor symptoms in a multiple regression model. Factors predicting overall pain severity included affective symptoms, autonomic symptoms, motor complications, female gender and younger age, but not motor impairment or disease duration. There was negligible correlation between the severity of motor impairment and the severity of musculoskeletal or dystonic pain as well as between the severity of OFF period motor problems and the severity of OFF period pain or OFF period dystonic pain. Features of central sensitization, including allodynia and altered pain sensation were common in this population. The use of drugs targeting central pain was very low.

Conclusions: Pain in PD cannot be explained by peripheral factors. Central causes may play a much more important role than previously considered. These results should lead to a major shift in the investigation and management of this common and disabling symptom.

1600

Gastrointestinal Symptoms and Enteric Nerve Dysfunction in A53T Mice

R. McQuade, P. Rajasekhar, S. Diwakarla, R. Constable, D. Poole, J. Berger, D. Finkelstein, J. Furness (Melbourne, Australia)

Objective: To investigate the relationship between α synucleinopathy-induced enteric neuropathy and gastrointestinal dysfunction in A53T mice.

Background: Approximately 80-90% of PD patients suffer from GI symptoms including dysphagia (swallowing difficulty), gastroparesis (slowed stomach emptying) and chronic constipation. Importantly, these GI symptoms often precede the onset of motor deficits by decades (1). GI function is primarily controlled by the enteric nervous system (ENS), a subdivision of the autonomic nervous system, and its central nervous system (CNS) connections. Beginning in the oesophagus and extending down to the anus, the ENS is embedded in the lining of the GI tract and interacts with the CNS through parasympathetic (vagus and pelvic nerves) and sympathetic (prevertebral ganglia) connections to regulate contraction, relaxation, secretion and absorption throughout the GI tract. It is well established that changes at the level of the ENS have functional GI consequence (2). Whilst the identification of abnormalities in the ENS of PD sufferers was discovered over 30 years ago and these changes have been acknowledged as a key contributor in the manifestation of PD-induced GI dysfunction, the relationship between α synuclein aggregation, ENS deterioration and the onset of GI dysfunction remains unclear.

Methods: Male and female human α synuclein overexpressing transgenic (A53T) mice and WT littermate controls aged 7 months were euthanised by cervical dislocation and the entire colon was removed. Colons were arranged horizontally in organ-bath chambers and the contractile activity of each colon was video recorded and used to construct spatiotemporal maps using in-house edge detection software. Separate segments of colon tissue were loaded with a high-affinity Ca^{2+} indicator, Fluo-4 and optically probed via in situ calcium imaging to evaluate electrically excitable in the ENS.

Results: α -synuclein overexpressing transgenic mice (A53T) had significantly reduced colonic motor activity compared to WT mice, this loss was primarily due to a reduction in the number and proportion of short propagating contractions. Changes in colonic motor activity demonstrated in A53T mice corresponded with altered Ca^{2+} signalling at the level of the myenteric plexus.

Conclusions: Our research investigating motor patterns in isolated colon indicate that GI dysfunction in A53T human α synuclein overexpressing transgenic mice is intrinsically mediated by the ENS.

References: 1. Fasano A, Visanji NP, Liu LW, Lang AE, Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. *The Lancet Neurology*. 2015;625-39. 2. Wood JD. Enteric Nervous System: Neuropathic Gastrointestinal Motility. *Digestive diseases and sciences*. 2016:1-14.

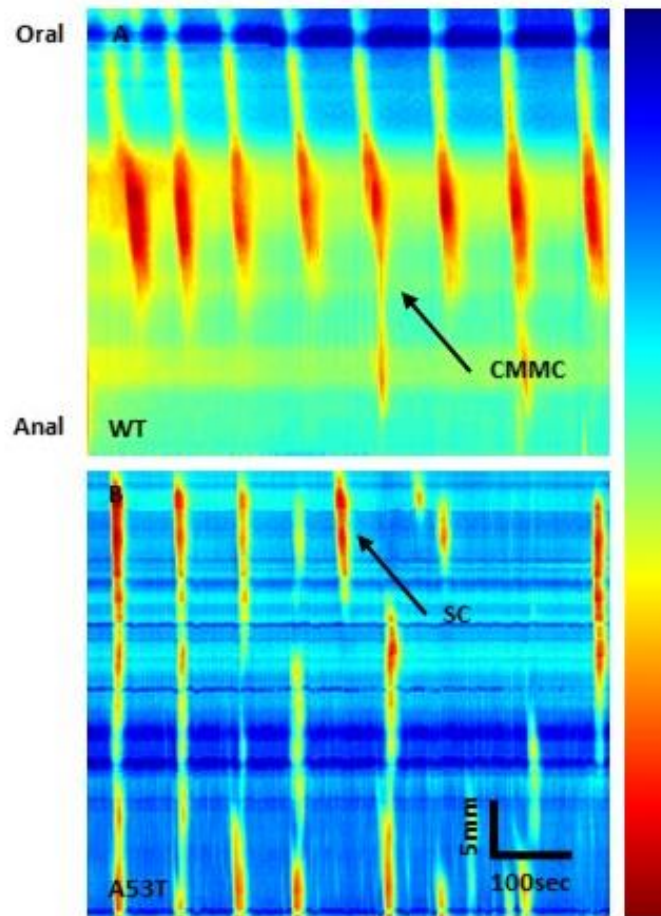


FIG. 1 (1600)

1635

Gut microbiota geography in Parkinson's disease in the world

M. Hirayama, T. Maeda, T. Minato, M. Itoh, J. Takeda, T. Hamaguchi, M. Katsuno, K. Ohno (Nagoya, Japan)

Objective: The 16 rRNA analysis and the shotgun metagenome analysis in our cohort were compared with 5 previous reports by others.

Background: In PD patients, the frequency of constipation is higher than control. People who received total vagotomy for the purpose of treating duodenal ulcers in the past have a 50% reduction in the incidence of PD. These facts suggest that the changes in intestinal environment may be involved in the development of PD. It has been clarified that the intestinal microbiota is related to various diseases. Compositional changes of intestinal bacteria in PD have been reported in many countries.

Methods: In the 16s rRNA analysis, the V3-V4 regions were amplified by PCR and 300-bp pair-ends were sequenced with Illumina MiSeq. The obtained data were analyzed by Qiime 2. In the shotgun metagenome analysis, 150-bp pair-ends of the whole metagenome were sequenced with Illumina HiSeq 2500. The obtained data were analyzed by MetaPhlAn 2. We also obtained raw sequencing datasets in the past reports from the GEO database and others. For each downloaded dataset, 16S rRNA analysis and the shotgun metagenome analysis were performed using Qiime 2 and MetaPhlAn 2, respectively.

Results: The compositions of microbiota varied widely between countries. The difference in controls between countries was larger than the difference between healthy and PD individuals in each country. In

Finland, *Prevotella* was the major intestinal bacterial species. However, in Germany, Japan, and the USA, the ratio of *Prevotella* was small. In Japan, the ratio of *Bifidobacterium* was higher than those in other countries.

Conclusions: Differences in microbiota compositions between healthy and PD individuals have been reported in many countries. However, since the microbiota composition in controls in each country varies greatly, it is unlikely that specific bacteria are uniquely changed in PD. In the future, functional analysis, not taxonomic analysis, of shotgun metagenome datasets will elucidate intestinal dysbiosis that is unique to PD.

1641

Progression of sleep disorders spectrum in Parkinson's Disease: A 5 year clinical longitudinal study

Z. Xu, K. Anderson, DJ. Brooks, N. Pavese (Singapore, Singapore)

Objective: To investigate longitudinal changes in the prevalence of different sleep disorders in the PPMI cohort of patients with Parkinson's Disease (PD).

Background: Sleep disturbances are common in advanced PD but they are frequently present also in the early and prodromal stages of disease. However, little is known about the prevalence and potential interactions between different types of sleep disorders and their evolution over time, particularly in the natural history of early PD.

Methods: Data was obtained from the Parkinson Progression Markers Initiative (PPMI) database. REM sleep behavior Disorder (RBD), excessive daytime sleepiness (EDS), and insomnia were defined using the RBD Screening Questionnaire (>5), Epworth Sleepiness Score (> or = 10) and UPDRS Part 1.7 (> or = 2).

Results: Two hundred and eighteen PD patients with a completed 5 year-clinical follow-up were included. At baseline, 55.5% PD patients did not report any sleep complaint. 31.7% of PD patients reported 1 sleep disorder: 12.8% reported insomnia only, 10.6% reported RBD only, and 8.3% EDS only. 11.5% PD patients reported 2 sleep disorders: 5.0% reported EDS and RBD, 4.1% reported both insomnia and RBD, and 2.3% reported both insomnia and EDS. Only 1.4% PD patients reported all 3 sleep disorders. At 5 years, the percentage of patients with no sleep complaints was reduced to 30.3%. 39.0% PD patients reported 1 sleep complaint: 19.3% reported insomnia only, 11.0% reported RBD only, and 8.7% reported EDS only. 23.4% of PD patients reported 2 sleep disorders: 10.6% reported insomnia and EDS, 7.3% reported insomnia and RBD, and 5.5% reported RBD and EDS. 7.3% PD patients reported 3 sleep disorders. The largest increase in reported prevalence was seen for insomnia, followed by EDS and then RBD. At baseline, 20.6% of PD subjects reported insomnia which increased to 55.5% at 5 years ($p<0.001$); 17.0% of PD subjects reported EDS which increased to 32.1% at 5 years ($p<0.001$); 21.1% of PD subjects reported RBD, which increased to 31.2% at 5 years ($p=0.005$).

Conclusions: Although sleep disorders are common in early PD, one-third of PD patients in the PPMI cohort remained free of sleep complaints 5 years after disease onset. Amongst the sleep disorders studied, the greatest reported increase in prevalence over the 5-year period was observed for insomnia, followed by EDS and RBD. The number of patients with multiple sleep disorders was relatively low suggesting that they can have different pathogenesis.

PD: Spectrum of sleep disorders at baseline

PD: Spectrum of sleep disorders after 5 years

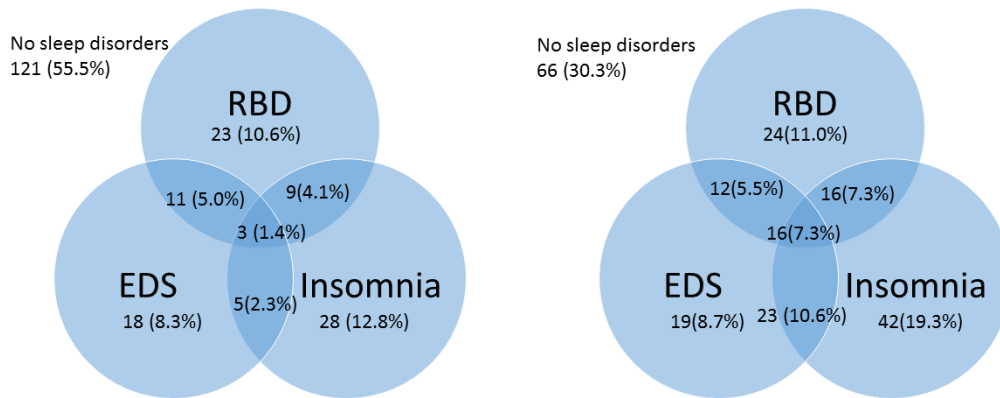


FIG. 1 (1641)

Graph showing the percentage of PD subjects reporting the presence of various sleep disorders across time

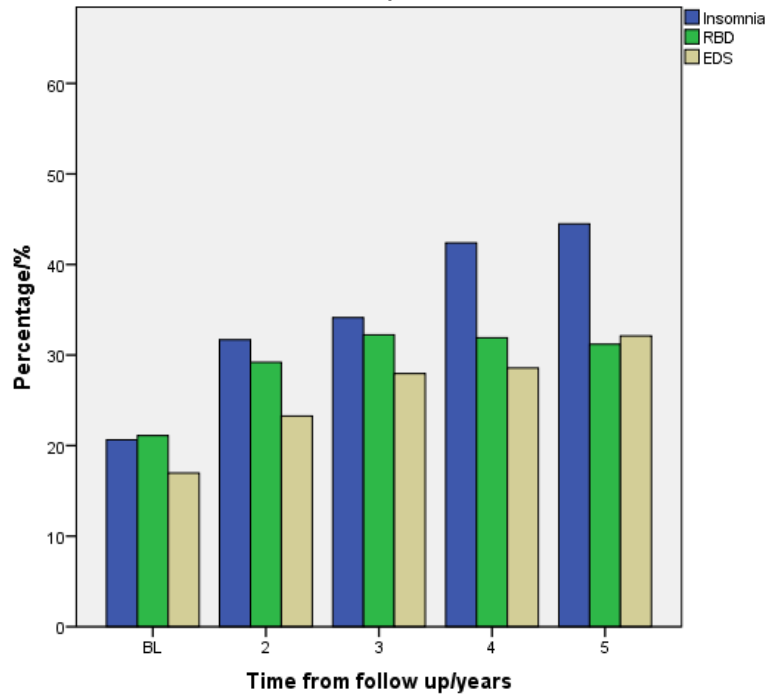


FIG. 2 (1641)

Graph showing the percentage of healthy controls reporting the presence of various sleep disorders across a 5 year period

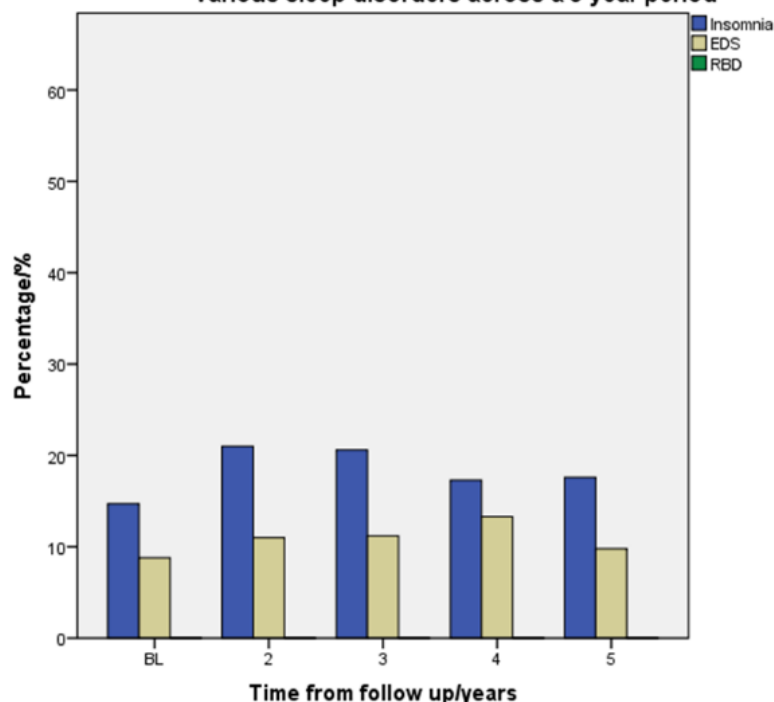


FIG. 3 (1641)

Guided Poster Group 13: Parkinson's Disease: Pathophysiology

1663

Bidirectional gut-to-brain and brain-to-gut propagation of α -synuclein pathology in non-human primates

ML. Arotçarena, S. Dovero, A. Prigent, M. Bourdenx, P. Aubert, I. Trigo, G. Porras, ML. Thiolat, M. Tasselli, C. Estrada, A. Recasens, J. Blesa, M. Herrero, N. Carillo, M. Vila, J. Obeso, P. Derkinderen, B. Dehay, E. Bezard (Bordeaux, France)

Objective: The prototypic synucleinopathy Parkinson's disease (PD) is hypothesized to spread out from the enteric nervous system (i.e. the gut) via the vagal nerve up to the central nervous system (Lionnet et al., 2017). Such popular hypothesis is supported by indirect clinical evidences and by experimental data showing gut-to-brain transfer of synucleinopathy using either viral vector delivery of synuclein or recombinant synuclein preformed fibrils.

Background: The aim of this study was to test the alternate hypothesis that synucleinopathy can indeed develop upward but also downward, i.e. from the gut to the brain but also from the brain to the gut.

Methods: To this end, we used our primate model of synucleinopathy obtained with administration of α -synuclein species contained in PD-derived Lewy bodies (LB) (Recasens et al., 2014). We examined in non-human primates, (i) if LB administration in the ventral wall of the stomach (n=5) leads to central nervous α -synuclein aggregation and possibly nigrostriatal degeneration and (ii) if LB administration in the striatum (n=6) might lead to synucleinopathy into the enteric nervous system. Two years after injection, extensive analysis was performed to assess qualitatively, quantitatively and spatially in the whole brain and in the enteric nervous system the extent and pattern of lesion as well as the occurrence of synucleinopathy using both biochemical and histochemical procedures.

Results: Enteric injection of LB in non-human primates results in enteric nervous system pathology and nigrostriatal lesion in keeping with the well-accepted hypothesis. However, striatum LB-injected animals, in addition to the expected nigrostriatal degeneration, showed also enteric nervous system pathology at the stomach level.

Conclusions: This study establishes that α -synuclein species might move up and down the neural axis in non-human primates questioning (i) the hypothesis of a peripheral origin of synucleinopathies (ii) and the specificity of enteric nervous system as biomarker of early/presymptomatic PD.

References: [1] A. Lionnet, L. Leclair-Visonneau, M. Neunlist, S. Murayama, M. Takao, C.H. Adler, P. Derkinderen, T.G. Beach, Does Parkinson's disease start in the gut?, *Acta Neuropathol*, 135 (2018) 1-12. [2] A. Recasens, B. Dehay, J. Bove, I. Carballo-Carbajal, S. Dovero, A. Perez-Villalba, P.O. Fernagut, J. Blesa, A. Parent, C. Perier, I. Farinas, J.A. Obeso, E. Bezard, M. Vila, Lewy body extracts from Parkinson disease brains trigger alpha-synuclein pathology and neurodegeneration in mice and monkeys, *Ann Neurol*, 75 (2014) 351-362.

1666

Risk estimation in the years preceding diagnosis of Parkinson's disease in the PREDICT-PD cohort

S. Auger, D. Rack, J. Bestwick, G. Giovannoni, A. Lees, A. Schrag, A. Noyce (London, United Kingdom)

Objective: To test and refine the use of probability-based algorithms to identify individuals at high-risk of developing Parkinson's disease (PD).

Background: Neurodegeneration preceding a formal diagnosis of PD is associated with identifiable motor and non-motor features. Evidence-based algorithms have been developed to attempt identifying individuals in this pre-diagnostic phase according to exposure to common risk factors and results of simple screening tests. Two notable approaches to risk estimation are the PREDICT-PD algorithm (Noyce et al 2013) and the MDS research criteria (Berg et al 2015).

Methods: The PREDICT-PD pilot cohort comprised 1,323 healthy 60 to 80 year olds who completed annual online surveys and a keyboard-tapping task. Here, we considered those in the cohort who were diagnosed with PD during follow-up and tracked their risk estimation in the years preceding formal diagnosis, according to both the PREDICT-PD and MDS research criteria algorithms. A key difference between the MDS and PREDICT-PD algorithms, is that whereas PREDICT-PD previously only used demographic information, environmental exposures and simple symptomology to estimate risk with tapping speed, hyposmia and REM sleep behaviour disorder as intermediate outcome markers, MDS-criteria combines an extensive set of clinical and radiological tests. PREDICT-PD scores are also not updated in the known absence of a risk factor and are based on odds ratios, rather than likelihood ratios. We sought to refine the PREDICT-PD algorithm's risk estimation by including our motor and non-motor intermediate markers (hyposmia and REM sleep behaviour disorder) in the risk score.

Results: 8 people in the PREDICT-PD cohort have been diagnosed with PD from a total 864 with follow-up at year 4. For these 8 with PD, mean probability risk score was higher over the 4 years according to the MDS criteria than with PREDICT-PD basic score (25.5% vs 8.4%), both of which were higher than the rest of the cohort (2.7% & 2.8% respectively, both $p < 0.0001$). Incorporating intermediate markers into the PREDICT-PD algorithm produced markedly greater probability risk scores than without for PD patients (38.7% vs 8.4%, $p < 0.0001$), with values remaining greater than healthy comparators' (6.6%, $p < 0.0001$).

Conclusions: Probability-based algorithms offer a means of identifying people at highest risk of developing PD prior to a formal diagnosis. Their accuracy can be significantly improved by incorporating simple, remotely administered screening tests.

References: Noyce AJ, Bestwick JP, Silveira-Moriyama L, et al. 2013. PREDICT-PD: Identifying risk of Parkinson's disease in the community: methods and baseline results. *J Neurol Neurosurg Psychiatry*. Berg D, Postuma R, Adler C, et al. 2015. MDS research criteria for prodromal Parkinson's disease. *Movement Disorders*.

Predictors of freezing of gait in newly diagnosed Parkinson's disease: Clinical, dopamine transporter imaging and CSF markers in the PPMI cohort

R. Kim, J. Lee, H.J. Kim, A. Kim, B. Jeon, U.J. Kang, S. Fahn (Seoul, Republic of Korea)

Objective: To examine whether clinical, dopamine transporter (DAT) imaging and cerebrospinal fluid (CSF) markers can be used to predict the later development of FOG individually and in combination in patients with newly diagnosed Parkinson's disease (PD).

Background: Various clinical factors have been suggested as predictors of FOG, but their predictive value remains unclear. Although presynaptic striatal dopamine depletion and CSF β -amyloid 1-42 (A β 42) is considered to have a role in the development of FOG, they have not been investigated as a means of predicting FOG.

Methods: This retrospective cohort study included a total of 393 patients with newly diagnosed PD without FOG at baseline. Data were obtained from the Parkinson's Progression Markers Initiative (PPMI) database. Data up to 4 years of follow-up were included. The development of FOG was defined to be present if the score was 1 or higher either for the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) item 2.13 or item 3.11 at any point during the follow-up period. Cox regression models were performed to identify the factors predictive of FOG. Based on these results, we constructed a predictive model for the development of FOG.

Results: During a median follow-up of 4.0 years (mean 3.0 years), 136 subjects developed FOG, and its cumulative incidence was 17, 21, 28, and 37% at 1-, 2-, 3- and 4-year follow-up, respectively [Figure 1]. The development of FOG was associated with postural instability gait difficulty (PIGD) score (hazard ratio [HR] 1.494; confidence interval [CI] 1.282–1.741; $p < 0.001$), caudate DAT uptake (HR 0.581; 95% CI 0.408–0.827; $p = 0.003$), CSF A β 42 (HR 0.997; 95% CI 0.996–0.999; $p = 0.009$) and, to a lesser extent, male sex (HR 1.512; 95% CI 1.007–2.271; $p = 0.046$), MDS-UDPRS motor score (HR 1.022; 95% CI 1.000–1.045; $p = 0.046$), and Montreal Cognitive Assessment score (HR 0.927; 95% CI 0.860–0.995; $p = 0.035$) [Table 1]. The combined model integrating the PIGD score, caudate DAT uptake and CSF A β 42 achieved a better prediction accuracy (area under the curve 0.755; 95% CI 0.700–0.810) than any factor alone [Figure 2].

Conclusions: We found clinical, DAT imaging and CSF markers as predictors of FOG in patients with newly diagnosed PD. The development of FOG within 4 years after diagnosis of PD can be predicted with acceptable accuracy using our risk model.

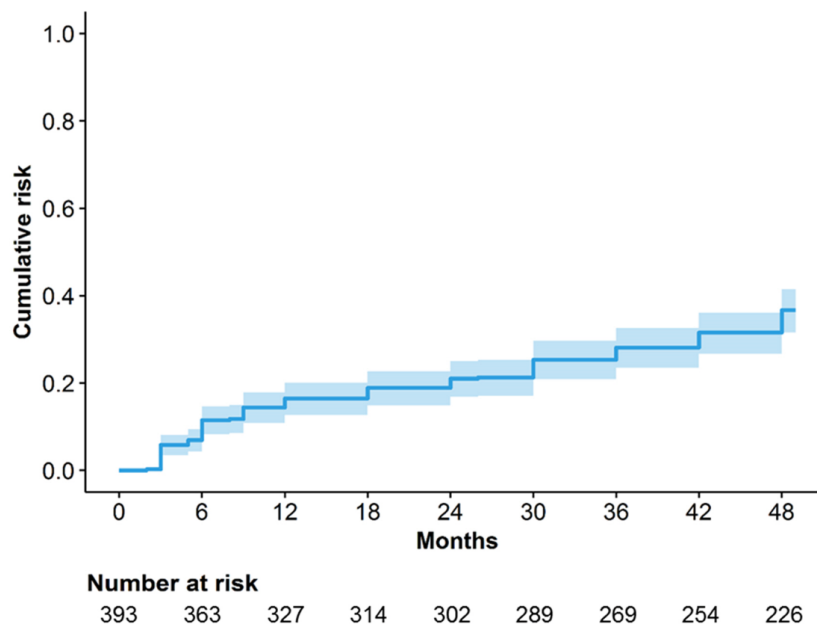


FIG. 1 (1680)

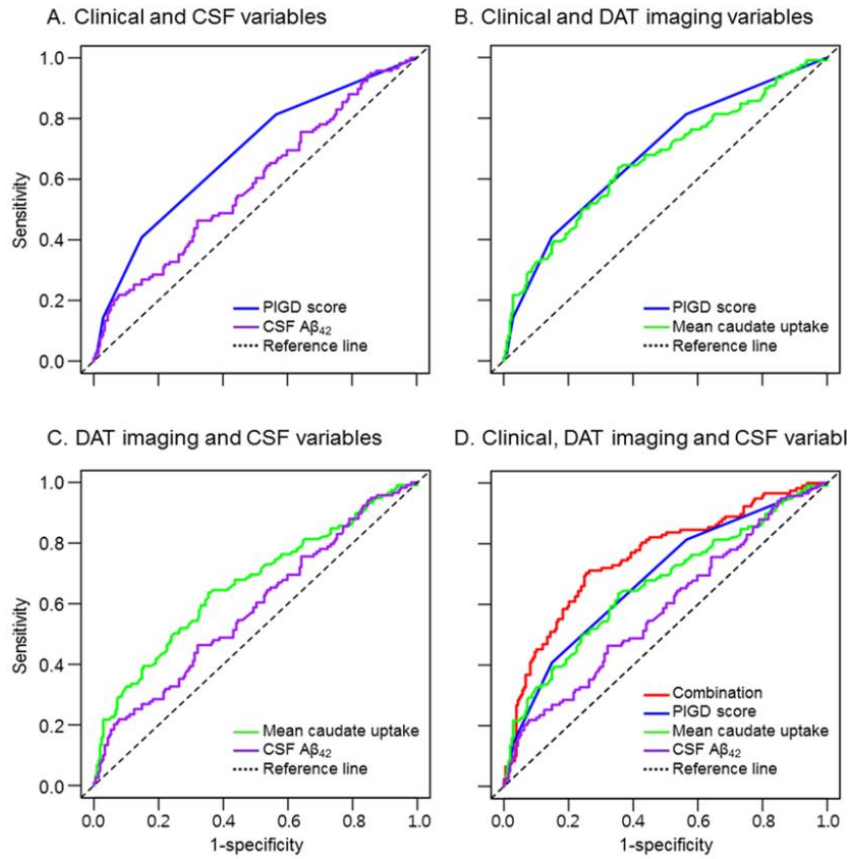


FIG. 2 (1680)

TABLE 1 (1680) Results of the Cox regression analyses for potential predictors of FOG

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Clinical variables				
Male sex	1.560 (1.066–2.284)	0.022	1.512 (1.007–2.271)	0.046
Disease duration	0.941 (0.844–1.049)	0.272		
Age at onset	1.025 (1.007–1.043)	0.006	–	–
MDS-UPDRS motor score	1.042 (1.023–1.061)	<0.001	1.022 (1.000–1.045)	0.046
Tremor score	0.995 (0.947–1.046)	0.858		
PIGD score	1.539 (1.347–1.758)	<0.001	1.494 (1.282–1.741)	<0.001
MoCA score	0.899 (0.843–0.957)	0.001	0.927 (0.860–0.995)	0.035
UPSIT score	0.975 (0.955–0.996)	0.019	–	–
RBDSQ score	1.084 (1.020–1.152)	0.009	–	–
ESS score	1.074 (1.026–1.124)	0.002	–	–
GDS score	1.082 (1.016–1.153)	0.015	–	–
STAI score	1.007 (0.998–1.017)	0.143		
SCOPA AUT score	1.042 (1.017–1.068)	0.001	–	–
DAT imaging (striatal binding ratio)				
Mean caudate uptake	0.478 (0.342–0.667)	<0.001	0.581 (0.408–0.827)	0.003
Mean putamen uptake*	0.301 (0.149–0.610)	0.001		
CSF marker (pg/mL)				
A β ₄₂	0.997 (0.995–0.999)	0.003	0.997 (0.996–0.999)	0.009
α -synuclein	1.000 (1.000–1.000)	0.088	–	–
Total tau	0.991 (0.980–1.001)	0.078	–	–
Phosphorylated tau	0.977 (0.957–0.998)	0.033	–	–
A β :tau ratio	0.993 (0.940–1.049)	0.790		

FOG=freezing of gait. HR=hazard ratio. CI=confidence interval. MDS-UPDRS=Movement Disorders Society Unified Parkinson's Disease Rating Scale. PIGD=postural instability gait difficulty. MoCA=Montreal cognitive assessment. UPSIT=University of Pennsylvania Smell Identification Test. RBDSQ=REM Sleep Behavior Disorder Screening Questionnaire. ESS= Epworth Sleepiness Scale. GDS=Geriatric Depression Scale. STAI= State-Trait Anxiety Inventory. SCOPA AUT= Scale for Outcomes in Parkinson's disease-Autonomic. DAT=dopamine transporter. A β ₄₂= β -amyloid 1-42.

1691

Neurophysiological correlates of bradykinesia in Parkinson's disease

M. Bologna, A. Guerra, G. Paparella, L. Giordo, D. Alunni Fegatelli, AR. Vestri, J. Rothwell, A. Berardelli (Rome, Italy)

Objective: In the present study we aimed to investigate whether objective measures of bradykinesia in Parkinson's disease have any relationship with neurophysiological measures in primary motor cortex as assessed by means of transcranial magnetic stimulation techniques.

Background: Many neurophysiological abnormalities have been described in the primary motor cortex of patients with Parkinson's disease (Bologna et al., 2016). However, it is unclear whether there is any

relationship between them and bradykinesia, one of the cardinal motor features of the condition (Espay et al., 2011).

Methods: Twenty-two patients with Parkinson's disease and 18 healthy subjects were enrolled. Objective measurements of repetitive finger tapping (amplitude, speed and decrement) were obtained using a motion analysis system. The excitability of primary motor cortex was assessed by recording the input/output curve of the motor-evoked potentials and using a conditioning-test paradigm for the assessment of short-interval intracortical inhibition and facilitation. Plasticity-like mechanisms in primary motor cortex were indexed according to the amplitude changes in motor-evoked potentials after the paired associative stimulation protocol. Patients were assessed in two sessions, i.e. 'OFF' and 'ON' medication. A canonical correlation analysis was used to test for relationships between the kinematic and neurophysiological variables.

Results: Patients with Parkinson's disease tapped more slowly and with smaller amplitude than normal, and displayed decrement as tapping progressed. They also had steeper input/output curves, reduced short-interval intracortical inhibition and a reduced response to the paired associative stimulation protocol. Within the patient group, bradykinesia features correlated with the slope of the input/output curve and the after-effects of the paired associative stimulation protocol. Although dopaminergic therapy improved movement kinematics as well as neurophysiological measures, there was no relationship between them.

Conclusions: Neurophysiological changes in primary motor cortex relate to bradykinesia in patients with Parkinson's disease, although other mechanisms sensitive to dopamine levels must also play a role.

References: Bologna M, Suppa A, Conte A, Latorre A, Rothwell JC, Berardelli A. Are studies of motor cortex plasticity relevant in human patients with Parkinson's disease? *Clin Neurophysiol.* 2016;127:50-9. Espay AJ, Giuffrida JP, Chen R, Payne M, Mazzella F, Dunn E, et al. Differential response of speed, amplitude, and rhythm to dopaminergic medications in Parkinson's disease. *Mov Disord.* 2011;26:2504-8.

1713

Microbiota DNA in the blood of patients with Parkinson's disease

S.Q. Xu, Y.W. Qian, X.D. Yang, S.D. Chen, Q. Xiao (Shanghai, China)

Objective: The aim of this study was to explore the blood microbiota compositions in Chinese patients with Parkinson's disease (PD).

Background: Emerging evidences suggest that the microbiota present in the feces plays a role in PD. However, the alterations of the microbiome in the blood of PD patients remains unknown.

Methods: Microbiota communities in the blood of 45 patients and their healthy spouses were investigated using high-throughput Illumina Hiseq sequencing targeting the V3-V4 region of 16S ribosomal RNA (rRNA) gene. The relationships between the microbiota in blood and PD clinical characteristics were analyzed.

Results: No difference was detected in the structure and richness between PD patients and healthy controls. Genera *IsotERICOLA*, *Cloacibacterium*, *Enhydrobacter*, and *Microbacterium* were enriched in the blood of PD patients, whereas genus *Limnobacter* was enriched in the healthy controls after adjusting for age, gender, body mass index (BMI), and constipations. Furthermore, not only genera *Cloacibacterium* and *IsotERICOLA*, which were identified enriched in the PD patients, but also genera *Paludibacter* and *Saccharofermentans* were positively associated with disease duration. Some specific genera in the blood were related to mood disorders.

Conclusions: We give direct evidences firstly to support the hypothesis that the identified microbiota in the blood are associated with PD. Additionally, some microbiota in the blood are closely related to PD clinical characteristics. Elucidating these differences in the blood microbiomes will provide a foundation to improve our understanding the role of the microbiota in the pathogenesis of PD.

1715

Unraveling gut microbiota in Parkinson's disease and atypical parkinsonism

R. Cilia, M. Barichella, M. Severgnini, E. Cassani, C. Bolliri, S. Caronni, V. Ferri, R. Canello, S. Faierman, G. Pinelli, C. Ceccarani, G. De Bellis, L. Zecca, E. Cereda, C. Consolandi, G. Pezzoli (Milan, Italy)

Objective: (1) To evaluate the differences in gut microbiota among Parkinson's disease (PD), atypical parkinsonism (i.e. multiple system atrophy [MSA] and progressive supranuclear palsy [PSP]) and healthy control subjects (HC). (2) To investigate whether specific microbiota taxa may act as modulators of disease progression and clinical phenotype.

Background: Recent evidences support the hypothesis that PD pathology originates into the gut and propagates to the brain by different pathophysiological pathways. However, findings are heterogeneous probably due to the presence of several confounders.

Methods: We recruited patients with idiopathic PD (n=193, of whom 39 were de novo), PSP (n=22), MSA (n=22), and HC (n=113). Several confounders have been taken into account, including pharmacological therapy and dietary habits. Information on the type of lactation were also recorded. Early-onset PD (≤ 50 ys) were screened for mutations on parkin, DJ-1, PINK-1 genes.

Results: Despite simple non-parametric comparison of PD patients and HC showed several differences in relative taxa abundances, the number of significant comparisons was greatly reduced after adjusting for multiple confounders. We observed a constant effect of age on almost all abundances. The use of COMT inhibitors appeared to influence the level of several taxa.

Overall, PD patients had increased Verrucomicrobia, Christensenellaceae, Lactobacillaceae, and decreased Lachnospiraceae and Ruminococcaceae than HC. Reduced level of Lachnospiraceae was significant in all PD duration strata, while many of these differences were associated with disease progression. De novo PD differed from HC only by lower abundance in Lachnospiraceae. Compared to PD, Lachnospiraceae and Ruminococcaceae were not significantly lower in MSA, while in PSP cases other genera of Ruminococcaceae and Lactobacillaceae were higher and comparable, respectively. Increased Lactobacillaceae, Christensenellaceae, Verrucomicrobia and decreased Lachnospiraceae were associated with worse disease severity, including intellectual impairment and other non-motor symptoms, and axial features (gait disturbances and postural instability).

Conclusions: Gut microbiota may play a role in the pathogenesis of PD and act as modulators of individual differences in disease severity, especially non-dopaminergic features (cognitive functions and axial symptoms).

1722

Association between serum Vitamin D levels and Parkinson's disease: A systematic review and meta-analysis

XY. Luo, R. Ou, HF. Shang (Chengdu, China)

Objective: The aim of this systematic review and meta-analysis was to evaluate the association between serum vitamin D levels and the risk and severity of PD.

Background: Vitamin D is an important molecule involving in the development and regulation of brain. Several studies have focused on exploring the relationship between serum vitamin D levels and Parkinson's disease (PD), but the conclusion remains ambiguous yet.

Methods: We searched observational studies that explored the association between serum vitamin D levels and PD based on Pubmed, EMBASE and Cochrane library. The quality of included studies was evaluated by using Newcastle-Ottawa Scale. Statistical analysis of this meta-analysis was performed by Stata version 12.0 and R software.

Results: 22 studies with a total of 3516 PD patients and 3481 controls were included. Our meta-analysis revealed that compared with controls, PD patients had lower vitamin D levels (WMD -5.21, 95% CI -6.48, -3.94), especially in higher latitude regions (WMD -5.53, 95% CI -7.49, -3.57). Assay methods contributed

significantly to high heterogeneity. Furthermore, PD patients with deficient vitamin D levels had advanced risk (OR 2.08, 95% CI 1.35, 3.19) than those patients with insufficient levels (OR=1.73, 95% CI 1.41, 2.12). In addition, Vitamin D levels was also related to PD severity (WMD-5.69, 95% CI-8.42, 2.96), and the summary correlation coefficient showed strong negative correlation ($r=-0.609$, 95% CI-0.76, -0.39). Moreover, the pooled effect size revealed that vitamin D concentrations were also negatively related to mUPDRS scores ($r=-0.36$, 95% CI-0.53, -0.16), but not associated with duration ($P=0.37$) and age ($P=0.49$).

Conclusions: Vitamin D levels are inversely associated with the PD risk and severity. Our results may provide a update evidence to better explore the effect of vitamin D on PD and prompt the adjunctive therapeutic decisions about vitamin D application.

1734

Antibodies to alpha-Synuclein in Parkinson disease

D. Labunskiy (Santa Rosa, CA, USA)

Objective: Alpha-synuclein (α -syn) plays a very important role in pathogenesis of Parkinson's disease (PD). There are enough evidence of neuroinflammation in the brain tissue of many neurodegenerative diseases, including PD. Many researchers found lymphocytes and macrophages infiltration in basal ganglia of the brain samples of patients died from PD complications. On the same time, systematical study of α -syn in the brain, serum and CSF of these patient still not performed.

Background: Under our observations were 56 PD patients, 39 men and 17 women, ages from 44 to 83 years old. Control group comprised from 124 healthy donors/ Also we used paraffin slices of cerebellum, brain stem and basal ganglia from patients died from PD complications.

Methods: We produced an enzyme-linked immunosorbent assay (ELISA) for measuring α -syn AAB (IgG) in the serum and CSF of PD patients. Also immunohistochemical study of the brains of 4 patients died from PD. We used antibodies marked by fluorescein-isotiocyanate (FITC). Control slices of the brain tissue were taken from person died from PD and from non-neurological causes.

Results: Anti α -syn AAB were increased in 86 percent PD patients, both men -89 per cent and women - 74 per cent) Confocal luminescence was revealed fluorescence in substantia nigra, globus pallidum and locus cereleum in the brain histological samples received from dead PD patients. The histological brain samples from dead patients without any neurological diseases did not revealed any immunofluorescence in basal ganglia or any other brain region.

Conclusions: The studies of immune response in neurodegenerative disorders is a new part of pathogenetic approach to this problem. Antibodies to α -syn probably play an important role in clinical picture and complications of PD.

References: Elevated Serum α -Synuclein Autoantibodies in Patients with Parkinson's Disease Relative to Alzheimer's Disease and Controls. Shalash A, Salama M, Makar M, Roushdy T1, Elrassas H, Mohamed W, El-Balkimy M, Abou Donia M. *Front Neurol.* 2017 Dec 22;8:720. doi: 10.3389/fneur.2017.00720. eCollection 2017.

1750

Natural occurring antibodies reduce aggregation of α -synuclein

A. Braczynski, E. Agerschou, Y. Kronimus, W. Hoyer, R. Dodel, B. Falkenburger, J. Schulz, J. Bach (Aachen, Germany)

Objective: We tested naturally occurring antibodies (nAbs) against α -synuclein both in vitro as well as in HEK293T cells to determine binding, cell viability and capacity to reduce α Syn aggregation.

Background: Parkinson disease (PD) is the second frequent neurodegenerative disorder and causes severe motor disturbances. nAbs are part of the innate immune system. They are produced without contact to the specific antigen they recognize and are polyclonal. Variation in specific nAbs levels are described for α Syn and tau. PD patients have lower levels of α Syn specific nAbs. nAbs- α Syn are thought to decrease the

load of α Syn deposits in the brain, but the mechanism of action is fairly unclear. Therefore we want to elucidate the behavior of nAbs- α Syn in cell culture systems.

Methods: We isolated nAbs- α Syn from intravenous Immunoglobulins (IVIG) using column affinity purification. Recombinant human α Syn was coupled to AminoLink Plus coupling resin. IVIGs were incubated in the column repeatedly followed by a pH dependent elution step. nAbs- α Syn from several purification rounds were pooled to reach reasonable protein concentrations. We tested the pooled antibodies to both in vitro as well as in HEK293T cells.

Results: nAbs- α Syn could be isolated from human IVIGs. They bound monomeric α Syn in a dot blot as well as in an ELISA against α Syn. nAbs- α Syn did not affect cell viability as tested in a Cell Titer Blue and an LDH Assay. In an in vitro Thioflavin T aggregation assay they inhibited fibrillation of α Syn. In a cell culture system of HEK293T cells transfected with EGFP-tagged α Syn we saw a reduction of aggresome load as visible by fluorescence microscopy.

Conclusions: nAbs- α Syn inhibited aggregation of α Syn both in vitro and in cell culture systems. These findings have to be corroborated further. Next, we want to analyze the effects of nAbs- α Syn in a Parkinson mouse model and describe the binding behavior of nAbs- α Syn to different conformational α Syn forms. As an outlook, we want to understand the mechanism of action of nAbs- α Syn to better extent and hopefully add antibodies to improved treatment of PD patients.

1757

Alpha-synuclein oligomer and rotenone treatments injury the dopaminergic neuron via inhibiting the expression of gene SEMA6D

X. Yingyu (Guangzhou, China)

Objective: To investigate the expression of Semaphorin6D (SEMA6D) and its interaction with Plexin-A1 in cellular Parkinson's disease(PD) models induced by α -synuclein and rotenone.

Background: In order to uncover the molecular pathological process in Parkinson's disease (PD), we employed a microarray analysis upon the alpha-synuclein oligomer induced cellular PD model and investigate the significant differentially expressed genes(DEGs) screened from the microarray analysis.

Methods: SY-SH5Y cells cultured in vitro were divided into three groups: normal control group, α -synuclein oligomer-induced group, rotenone-induced group. The last two groups were treated with α -synuclein oligomer and rotenone respectively to establish the cellular PD models. The mRNA levels of SEMA6D and plexin-A1 were evaluated using real-time polymerase chain reaction analysis(rt-PCR), and the determinations had also been made on related proteins by Western blot analysis. The interaction between SEMA6D and Plexin-A1 was validated by co-immunoprecipitation. Immunofluorescence and co-focusing experiment were used to investigate the co-location of SEMA6D and PlexinA1 inside the cell.

Results: As the result showed, the expression of SEMA6D was significantly decreased in cellular PD model. KEGG Pathway analysis showed that SEMA6D was closely related to the network of MARK pathway. Comparing with the normal control group, the expressions of SEMA6D in cellular PD model groups were down-regulated obviously. Immunoprecipitation analysis and Immunofluorescence co-localization analysis confirmed that the association of SEMA6D with Plexin-A1 was reversed in PD models.

Conclusions: α -synuclein and rotenone treatments inhibit expression of SEMA6D and its interaction with Plexin-A1. The decline of their interaction could trigger the MAPK signaling pathway, which is associated with the progress of PD. Our results suggest that SEMA6D is a critical factor in the pathogenesis of PD, and therefore could be an important drug target for novel treatments towards PD.