



FREEZING OF GAIT LEUVEN 2018
6-8 June BELGIUM

4th International Workshop on Freezing of Gait

June 6-8, 2018

Leuven, Belgium

KU LEUVEN



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WELCOME

Freezing of gait is one of the most fascinating, obscure but also devastating problems for people with Parkinson's disease and related disorders. In June 2018, we will hold the 4th International Workshop on Freezing of Gait to reflect on scientific progress made so far and ways to move forwards towards fuller understanding and innovative solutions for this burdensome problem.

The historic town center of Leuven in Belgium hosts the oldest university of the Low Countries, former home to Vesalius, Erasmus, Thomas More and Mercator. Set against this tranquil and medieval background at the center of Europe, we want to bring together junior and senior scholars in freezing of gait during a two-day meeting. It is our intention to particularly welcome insights and ideas from young investigators and encourage a truly multidisciplinary input and lively discussion.

In the last 10 years, freezing of gait has generated an increasing number of studies, driven by technological advance and a truly multidisciplinary interest in this field. We invite you to share these novel research paradigms and latest insights with colleagues from all over the world. We particularly welcome young investigators who want to put their research in the spotlight

PROGRAM

Pre-Workshop Symposium: June 6th 2018 Gait disorders in the Clinic

Time	Session Details
12-1pm	Registration and Coffee Reception
	Session I (1-3pm)
1pm-1.10pm	Prof Wim Vandenberghe, KU Leuven, Belgium OPENING REMARKS
1.10-1.30pm	Prof Nir Giladi, Tel Aviv University, Israel CLASSIFYING GAIT DISORDERS
1.30-2pm	Prof Simon Lewis, University of Sydney, Australia PARKINSONIAN GAITS AND ASSOCIATED FEATURES
2pm-2.30pm	Prof Bart van de Warrenburg, Radboud University Nijmegen, The Netherlands. A PRACTICAL APPROACH TO ATAXIA
2.30-3pm	Prof Alice Nieuwboer, KU Leuven, Belgium THE ROLE OF PHYSIOTHERAPY IN FALLS AND GAIT DISORDERS
3-3.30pm	Afternoon Tea & Coffee
	Session II (3.30-5.30pm)
3.30-4pm	Prof Jay Nutt, OHSU Portland, USA EMERGING THERAPIES IN GAIT DISORDERS
4-4.30pm	Prof Mark Hallett, NIH Bethesda, MD, USA PSYCHOGENIC GAIT DISORDERS AND THE COMPANY IT KEEPS
4.30-5.15pm	Prof Bas Bloem & Prof Alfonso Fasano VIDEO CASE PANEL DISCUSSION
5.15-5.30pm	Prof Wim Vandenberghe, KU Leuven, Belgium CLOSING REMARKS

FOG Workshop Welcome Dinner: June 6th 2018

Time	Session Details
4-7 pm	Registration
	Session I (6th of June 7-9.30pm)
7-7.15pm	Prof. Bart Nuttin, Research Coordinator Biomedical Group KU Leuven Prof. Alice Nieuwboer, KU Leuven, Belgium WELCOMING REMARKS
7.15pm-8.15pm	Prof Simon Lewis, University of Sydney, Australia OPENING LECTURE FREEZING OF GAIT: WHERE DO WE COME FROM AND WHERE ARE WE GOING...
8.15-9.30pm	Walking dinner at the University Hall

FOG-Workshop Day 1: June 7th 2018

Time	Session Details
	<p align="center">Session II PATHOPHYSIOLOGICAL MECHANISMS OF FREEZING OF GAIT Session chairs: Prof Simon Lewis, University of Sydney, Australia and Prof Mark Hallett, NIH Bethesda, MD, USA</p>
8.30am-10.30am	<p>What can we learn about freezing from network analysis and neurostimulation Dr. Michael Fox, Harvard Medical School, USA</p> <p>The extra-nigral pathology involved in freezing of gait Prof. Nicolaas Bohnen, Michigan University, USA</p> <p>Neurophysiological characterization of freezing episodes Dr Daniel Weiss, University Hospital Tübingen, Germany</p>
10.30-11.00am	Coffee break
	<p align="center">Session III BEHAVIORAL MANIFESTATIONS AND ASSOCIATED FEATURES Session chairs: Prof Jeff Hausdorff, Tel Aviv Sourasky Medical Center, Israel and Prof Alice Nieuwboer, KU Leuven, Belgium</p>
11.00am-1pm	<p>Sensory-motor contributions to freezing of gait Dr Q. Almeida, Wilfried Laurier University Waterloo, Canada.</p> <p>Anxiety: a modifying or causal factor? Dr. K. Ehgoetz Martens University of Sydney, Australia</p> <p>Balancing the two: postural instability and gait control in people with PD who freeze Dr. D. Peterson, Arizona State University, USA</p>
1-3pm	Sandwich lunch and poster viewing
	<p align="center">Session IV PREDICTION AND ASSESSMENT OF FREEZING OF GAIT Session chairs: Prof Fay Horak, Oregon Health & Sciences University, USA and Prof Bastiaan Bloem, Radboud University Nijmegen, The Netherlands</p>
3-5pm	<p>From genotype to phenotypical expressions of gait disturbance Prof S. Factor, Emory University School of Medicine, Atlanta, USA.</p> <p>Biomarkers of freezing of gait: the role of technology Dr. M. Mancini, Oregon Health & Sciences University, USA</p> <p>Clinical challenges for assessing freezing of gait Dr. J. Nonnekes, Radboud University Nijmegen, The Netherlands</p>

FOG-Workshop Day 2: June 8th 2018

Time	Session Details
	Session V ORAL PRESENTATIONS OF YOUNG INVESTIGATORS Session chairs: Prof Mark Hallett, NIH Bethesda, MD, USA and Prof Fay Horak, Oregon Health & Sciences University, USA
8.30am-10.30am	<p>Dr J Hamilton, Associate Director of Research program MJ Fox VISION OF RESEARCH FUNDING IN GAIT & POSTURE 8 ORAL presentations of the best ABSTRACTS</p> <ol style="list-style-type: none"> 1. The functional network signature of heterogeneity in freezing of gait <i>Dr. M. Shine</i> 2. Altered connectivity in ventral and dorsal attentional networks in Parkinson disease patients with and without freezing of gait <i>Dr. I. Maidan</i> 3. Pathology of Brainstem Noradrenergic Cell Groups Associated with Freezing of Gait in MPTP-treated Non-human Primates <i>Dr. Y. Smith</i> 4. STN Neuromodulation of beta bursts is relevant for freezing of gait in freely moving people with Parkinson's disease <i>Ms. C. Anidi</i> 5. Focal Subcortical Grey Matter Adaptations Predict Freezing of Gait in Parkinson's Disease <i>N. Paul D'Cruz</i> 6. Visual exploration during gait in Parkinson's disease: Freezer vs non-freezer response to visual cues <i>Dr. S. Stuart</i> 7. Cognitive function in people with and without freezing of gait in Parkinson's disease <i>Dr. R. Morris</i> 8. Are Hypometric Anticipatory Postural Adjustments Contributing to Freezing of Gait in Parkinson's Disease? <i>Dr. C. Schlenstedt</i>
10.40-11.00am	Coffee break
	Session VI TREATMENT OPTIONS AND WHERE THE FIELD IS HEADING NEXT Session chairs: Prof Jay Nutt, Oregon Health & Sciences University, USA and Prof Nir Giladi, Tel Aviv University, Israel
11.00am-1pm	<p>Deep brain stimulation for freezing of gait and how it may work. Prof. Jens Volkmann, University of Wuerzburg, Germany</p> <p>Aiming too high? Stimulating the spinal cord to treat freezing of gait Dr. Mandar Jog, London Health Sciences Centre in London, ON, Canada</p> <p>Rehabilitation: early intervention or if all else fails Dr Elke Heremans, KU Leuven, Belgium</p>
1-1.15	CLOSING REMARKS Prof. Alice Nieuwboer, KU Leuven, Belgium
1-2pm	Sandwich lunch

Oral presentations

List of abstracts

(in order by program schedule)

The functional network signature of heterogeneity in freezing of gait

Kaylena A. Ehgoetz Martens, Julie M. Hall, Matthew J. Georgiades, Moran Gilat, Courtney C. Walton, Elie Matar, Simon J. G. Lewis and James M. Shine

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Freezing of gait is associated with impairments across cognitive, motor and affective domains. To investigate the neural mechanisms of this heterogeneity, we used an established virtual reality paradigm to elicit freezing behaviour in 41 Parkinson's disease patients with freezing of gait in conjunction with task-based functional MRI. We first combined three unique components of the freezing phenotype – impaired set-shifting ability, step time variability, and self-reported anxiety – in a principal components analysis to estimate the severity of freezing behaviour with a multivariate approach. By combining these measures, we were then able to interrogate the pattern of task-based functional connectivity associated with freezing (compared to normal foot tapping) in a sub-cohort of 20 participants who experienced sufficient amounts of freezing during task functional MRI. Specifically, we used the first principal component from our behavioural analysis to classify patterns of functional connectivity into those that were associated with: (i) increased severity; (ii) increased compensation; or (iii) those that were independent of freezing severity. Coupling between the cognitive and limbic networks was associated with 'worse freezing severity', whereas anti-coupling between the putamen and the cognitive and limbic networks was related to 'increased compensation'. Additionally, anti-coupling between cognitive cortical regions and the caudate nucleus were 'independent of freezing severity' and thus may represent common neural underpinnings of freezing that are unaffected by heterogenous factors. Finally, we related these connectivity patterns to each of the individual components (cognitive, motor, affective) in turn, thus exposing latent heterogeneity in the freezing phenotype.

Altered connectivity in ventral and dorsal attentional networks in Parkinson disease patients with and without freezing of gait

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Background: Behavioral studies indicate that deficits in attention and executive function are associated with FOG. However, changes in the ventral and dorsal attentional networks that may contribute to FOG are unknown.

Methods: Resting-state fMRI was obtained in 20 healthy controls (HC) (age:69.7±1.3yrs; 10-men/10-women), 11 PD patients without FOG (PD-FOG) (age:74.1±1.2yrs; 7-men/4-women; UPRS3:20.7±11.0), and 26 PD patients with FOG (PD+FOG) (age:72.3±1.3yrs; 15-men/11-women; UPDRS3:33.6±13.4). Seed to voxel analysis at the whole brain level was used to quantify connectivity and compare between the groups.

Results: Changes in the ventral network were observed only in the right hemisphere seeds. The right insula showed lower connectivity with left anterior cingulate in PD compared to HC (FDRcorr:p<0.0036) and lower connectivity with left precuneus only in PD+FOG (FDRcorr:p<0.014). Right inferior parietal lobe showed higher connectivity with superior temporal gyrus (FDRcorr:p=0.036) in PD that further increased in PD+FOG. Right BA10 demonstrated higher connectivity with superior temporal and frontal gyrus (FDRcorr:p<0.0075) and lower connectivity with left precentral gyrus (FDRcorr:p=0.00073) in PD that further increased in PD+FOG. In the dorsal network, compared to HC, PD had higher connectivity between middle frontal gyrus and right putamen and superior temporal gyrus (FDRcorr:p<0.042). However, PD+FOG showed lower connectivity than PD-FOG. Higher connectivity between left inferior parietal lobe and right precuneus was found in PD+FOG, compared to HC and PD-FOG (FDRcorr:p=0.028).

Conclusions: Alterations in the resting-state functional connectivity of the attentional networks are associated with PD pathology. Interestingly, these changes are more pronounced in freezers, supporting the role of attentional networks in FOG.

Pathology of Brainstem Noradrenergic Cell Groups Associated with Freezing of Gait in MPTP-treated Non-human Primates

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Freezing of gait (FOG) is a disabling disorder commonly associated with advanced Parkinson's disease (PD). Because of the lack of animal models, little is known about the pathobiology of FOG and, for many cases, effective therapy is lacking. Revuelta and colleagues recently described FOG in the primate MPTP model of advanced PD (Revuelta et al., 2012, *Exptl Neurol* 237:464). In these animals, human FOG-like symptoms were related to the severity of parkinsonism, and were often accompanied by leg trembling. To further understand the brain pathology of FOG, we quantified the extent of degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), cholinergic neurons in the pedunculopontine tegmental nucleus (PPN) and noradrenergic neurons in the locus coeruleus (LC) of four severely parkinsonian MPTP-treated monkeys with (N=2) or without (N=2) FOG. Stereological cell counts revealed that the extent of neuronal loss in the LC, but not in the SNc or the PPN, was more severe in parkinsonian monkeys with FOG. None of these animals displayed significant loss of cholinergic cells in PPN, suggesting that FOG in MPTP-treated parkinsonian monkeys is not related to brainstem cholinergic degeneration. These data are consistent with preliminary in vivo PET and MRI data from members of our team suggesting a more profound loss of noradrenergic neurons in the LC of PD patients with FOG than patients without FOG. Overall, these data suggest that severely parkinsonian MPTP-treated monkeys may be a relevant animal model to study the brain pathology of FOG, and potentially test anti-FOG therapies.

STN Neuromodulation of beta bursts is relevant for freezing of gait in freely moving people with Parkinson's disease

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Objective: Characterize the effects of STN deep brain stimulation (DBS) on dynamic neural and kinematic features of freezing of gait (FOG) in Parkinson's disease (PD) subjects

Background: Recent studies have demonstrated that resting-state neural activity in the STN exhibits "bursts" of power in the beta-band (13-30Hz) in PD; duration of beta bursts rather than average beta power was correlated with clinical impairment^[1]. In this study, we asked whether beta burst duration during movement was relevant for FOG, during STN DBS at different frequencies.

Methods: Synchronized STN Local Field Potentials and gait kinematics were recorded in 12 PD subjects, off-medication during forward walking (FW) and stepping-in-place (SIP) tasks. Tasks were completed during NO, 60Hz, and 140Hz DBS in randomized order, on optimized settings. **Results:** Compared to Non-Freezers, Freezers experienced longer burst durations during locomotion without freezing during NO DBS in both tasks ($p < 0.001$). Freezers also experienced longer burst durations during FOG compared to locomotion without freezing ($p < 0.001$). Among Freezers, 60Hz and 140Hz significantly shortened duration of bursts and improved gait. Gait arrhythmicity showed greater improvement during 60Hz compared to 140Hz during FW ($p = 0.0174$). Subjects also spent less time freezing at 60Hz compared to 140Hz during SIP. **Conclusions:** Freezers exhibit more pathological (longer duration) beta bursts compared to Non-Freezers that are exaggerated during FOG. STN DBS shortens burst duration and improves gait in Freezers. 60Hz was superior to 140Hz in improving freezing behavior. This is the first study to demonstrate the functional relevance of beta burst duration in the pathophysiology of FOG.

References

[1] G. Tinkhauser, A. Pogosyan, S. Little, M. Beudel, D.M. Herz, H. Tan, P. Brown, *The modulatory effect of adaptive deep brain stimulation on beta bursts in Parkinson's disease* **2017**, Brain 140, 1053–1067.

Focal Subcortical Grey Matter Adaptations predict Freezing of Gait in Parkinson's Disease

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Background: Owing to its connections with motor, cognitive and limbic areas, the basal ganglia circuitry may be at the heart of Parkinson's Disease (PD) as well as Freezing of Gait (FOG). Previous studies failed to capture the precise subcortical adaptations associated with FOG. Hence, we investigated whether the morphology of subcortical nuclei differentiated between freezers and non-freezers and predicted FOG conversion.

Methods: Vertex-based grey matter analysis was performed on high-resolution T1-weighted MR images of 57 PD (36 Non-Freezers, 21 Freezers) and 19 age-matched controls. Fifteen structures were segmented using FMRIB's integrated registration and segmentation tool (FIRST)^[1]. Local volumes were assessed by vertex analysis and nonparametric permutation^[2]. Participants underwent extensive motor and cognitive assessments and were classified with the New Freezing of Gait Questionnaire (NFOG-Q)^[3] when scanned and two years later.

Results: Freezers (13 Freezers at baseline, 9 Converters) had local expansions in Right and Left Thalamus compared to Controls (P_{\max} : 0.009; P_{\max} : 0.04) and Non-Freezers (P_{\max} : 0.015; P_{\max} : 0.015) and local contractions in Right Caudate compared to Non-Freezers (P_{\max} : 0.05). At baseline, extent of Right Thalamus expansion and Right Caudate contraction predicted conversion to FOG with 85.8% accuracy. Thalamus expansions also correlated with better performance on Frontal Assessment Battery ($r = 0.58$, $P=0.009$), Trail Making Test (Part B: $r = -0.63$, $P=0.003$) and auditory Stroop while turning ($r = -0.64$, $P=0.009$).

Conclusion: Local volume changes in Thalamic and Caudate nuclei discriminate between cohorts with and without FOG and predict the conversion to FOG in PD.

References

- [1] B. Patenaude, S. M. Smith, D. N. Kennedy, and M. Jenkinson, "A Bayesian model of shape and appearance for subcortical brain segmentation," *Neuroimage*, vol. 56, no. 3, pp. 907–922, **2011**.
- [2] A. M. Winkler, G. R. Ridgway, M. A. Webster, S. M. Smith, and T. E. Nichols, "Permutation inference for the general linear model," *Neuroimage*, vol. 92, pp. 381–397, **2014**.
- [3] A. Nieuwboer *et al.*, "Reliability of the new freezing of gait questionnaire: Agreement between patients with Parkinson's disease and their carers," *Gait Posture*, vol. 30, no. 4, pp. 459–463, **2009**.

Visual exploration during gait in Parkinson's disease: Freezer vs non-freezer response to visual cues

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Introduction: Gait impairment is a core feature of Parkinson's disease (PD) with implications for falls risk. Freezing of gait (FoG) is a particularly debilitating gait impairment. Visual cues improve gait and overcome FoG episodes in PD but the underlying mechanisms are unclear. Attentional or visual processes may underpin response to visual cues, and can be studied by measuring visual exploration (saccades and fixations) when walking. Understanding how cueing influences visual exploration will help develop effective therapeutics.

Methods: Visual exploration (change (Δ) in saccade frequency (SF)) was measured using a mobile eye-tracker in 55 PD participants (36 no-FoG, 19 FoG) while walking. Task-relevance of fixation location was also examined in a sub-group of participants (13 no-FoG, 7 FoG). Participants walked with and without a visual cue under single and dual-task (forward digit-span).

Results: A visual cue increased SF in both freezers and non-freezers under both single and dual-task conditions. However, under dual-task non-freezers increased their SF significantly more than freezers in response to a visual cue (FoG: 0.54 Δ sacc/sec, no-FoG: 0.93 Δ sacc/sec, $p=.015$). Sub-group analysis demonstrated that freezers also looked at more task-relevant locations (e.g. floor) with a visual cue compared to non-freezers, particularly under single-task conditions ($p=.033$).

Conclusion: Visual cues elicit greater visual exploration during gait in both freezers and non-freezers, with more task-relevant fixations made by freezers with a cue. However, SF cue response significantly reduced in freezers with attentional distraction (dual-task). This suggests that attention may play a vital role in visual cue application in freezers.

Cognitive function in people with and without freezing of gait in Parkinson's disease

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Introduction: Impaired cognitive function is common in Parkinson's disease (PD) with previous studies suggesting cognitive differences between people with FOG (FOG+) and without FOG (FOG-) [1,2]. However, differences in cognitive function have been inconsistently reported within small cohorts. Additionally, cognitive performance has not been associated with an objective measurement of FOG. Therefore, this study aimed to i) assess a comprehensive range of cognitive domains in a large cohort of FOG+ and FOG- and ii) associate cognitive performance with FOG severity using an objective FOG measure [3].

Methods: 116 idiopathic PD (50 FOG+ [UPDRS III 46.5±13.40], 66 FOG- [UPDRS III 35.7±10.48]) completed a comprehensive cognitive battery. Six domains of cognition were assessed; global cognition, psychomotor speed, set-shifting, response inhibition, working memory and visuospatial. Objective FOG severity was assessed using wearable sensors during 360° turning [3]. To determine differences, a MANCOVA compared domains controlling for age, gender, education and disease severity, $\alpha \leq .01$ was deemed significant.

Results: There were no differences in cognitive domains between FOG- and FOG+; (Psychomotor speed [F=2.93, p=.037], global cognition [F=3.67, p=.058], set shifting [F=1.76, p=.176], response inhibition [F=2.67, p=.051], working memory [F=1.44, p=.232], and visuospatial [F=.167, p=.683]). Additionally, objective FOG severity was significantly different between groups (p<.01) but was not associated with cognitive performance.

Discussion: This is the largest study to assess a comprehensive range of cognitive domains between FOG+ and FOG-. We were unable to replicate findings of cognitive differences between groups, furthermore when using an objective FOG severity score there was no association with cognition.

References

- [1] Georgiades MJ, Gilat M, Ehgoetz Martens KA, Walton CC, Bissett PG, Shine JM, et al. Investigating motor initiation and inhibition deficits in patients with Parkinson's disease and freezing of gait using a virtual reality paradigm. *Neuroscience*. **2016**;337:153-62.
- [2] Factor SA, Scullin MK, Sollinger AB, Land JO, Wood-Siverio C, Zanders L, et al. Freezing of gait subtypes have different cognitive correlates in Parkinson's disease. *Parkinsonism Relat Disord*. **2014**;20(12):1359-64.
- [3] Mancini M, Priest KC, Nutt JG, Horak FB. Quantifying freezing of gait in Parkinson's disease during the instrumented timed up and go test. *Conf Proc IEEE Eng Med Biol Soc*. **2012**;2012:1198-201.

Are Hypometric Anticipatory Postural Adjustments Contributing to Freezing of Gait in Parkinson's Disease?

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AIM: This study investigates whether impaired anticipatory postural adjustments (APA) during gait initiation contribute to the occurrence of freezing of gait (FOG) or whether altered APAs compensate for FOG in Parkinson's disease (PD).

METHODS: Gait initiation was analyzed without and with a cognitive dual task (DT) in 33 PD subjects with FOG (PD+FOG), 30 PD subjects without FOG (PD-FOG), and 32 healthy controls (HC). APAs were characterized with inertial sensors and muscle activity of the tensor fasciae latae (TFL), gastrocnemius (GAS) and tibialis anterior (TIB) muscles with EMG recordings. Nine trials (of 190) were associated with FOG and were analyzed separately.

RESULTS: PD+FOG and PD-FOG did not differ in disease duration, disease severity, age or gender ($p < 0.05$). PD+FOG had significantly smaller APAs compared to PD-FOG (DT, $p < 0.05$). Within the PD+FOG, the medio-lateral (ML) size of APA (DT) was positively correlated with the severity of FOG (NFOG-Q) ($\rho = 0.477$, $p = 0.025$). ML APAs were larger during trials with observed FOG compared to trials of PD+FOG without FOG.

CONCLUSIONS: People with PD with a history of FOG have smaller ML APAs (weight shifting) during gait initiation compared to PD-FOG and HC. However, start hesitation (FOG) is not caused by an inability to sufficiently displace the center of mass toward the stance leg because APAs were larger during trials with FOG. We speculate that reducing the acceleration of the body center of mass with hip abductor co-contraction for APAs might be a compensatory strategy in PD+FOG, to address postural control deficits and enable step initiation.

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Delayed-onset freezing of gait after globus pallidus injury

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Neural substrates and pathomechanism of freezing of gait (FOG) remain controversial. The contribution of globus pallidus (GP) to FOG was discussed in a few case reports with GP lesions or deep brain stimulation. We report two FOG patients with GP necrosis secondary to hypoxia or carbon monoxide poisoning. The first patient is a 47-year old man presented with gait disturbance. He experienced asphyxia and lost consciousness when his house was caught by a fire at age 18. Neurologic examination was unremarkable except FOG. Brain magnetic resonance imaging (MRI) showed bilateral cystic change of GP. Dopamine transporter imaging showed decreased uptake in bilateral striatum. Dopaminergic medications were ineffective. The second patient is a 77-year old woman who visited us because of gait disturbance. She had a history of carbon monoxide poisoning at age 52. Her gait problems had started at age 70. Neurologic examination showed cognitive impairment (Mini-mental status examination = 10) and FOG. MRI showed mild periventricular white matter change and bilateral cystic change of GP. Dopamine transporter imaging showed decreased uptake in bilateral striatum. Her FOG was not improved by dopaminergic medication. In summary, the patients share common clinical features: neurologic problems limited to FOG, GP damage, long intervals between clinical events related to GP damage and FOG, and nigrostriatal denervation. Preceding GP lesions may have set subclinical conditions for gait problems that may be triggered by later dopaminergic deficiency, resulting in FOG.

Case study: Surface Emg Before, During and After FOG in a Patient with Parkinson disease

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In Parkinson’s disease, the prevalence of freezing of gait (FOG) increases with disease duration, occurring in up to 53% of the population after 5 years of illness [1]. The unpredictability of the FOG phenomenon makes it notoriously difficult to study experimentally [2].

The aim of our study was to analyze surface electromyography (SEMG) signals on one patient during normal walking, before and during FOG to understand if FOG could be predictable.

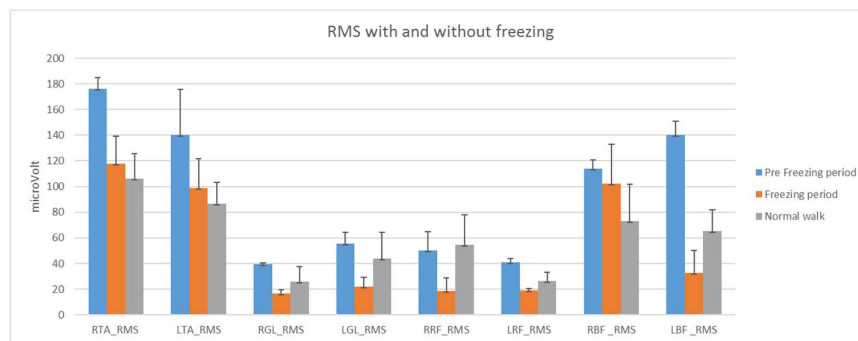


Figure 1: On the left side RMS values and on the right side PoE values extracted from each SEMG signal, before Freezing (blue), during freezing (orange) and during normal walking (grey).

One subject with 10 years of Parkinson’s disease (age 66, BMI 23.34) was recruited.

The subject was asked to walk on a 8 m gait laboratory. Gait analysis was performed with a BTS motion capture system (six cameras, 60–120 Hz) synchronized with two Bertec force plates (FP4060-10). SEMG signals of the following muscles were recorded: Rectus Femoris (RF), Biceps Femoris (BF), Tibialis Anterior (TA), Gastrocnemius Lateralis (GL) bilaterally. Root Mean Square (RMS), the peak of the envelope (PoE in microvolt), and the position of the peak of envelope (PoPE in % of gait cycle) have been extracted.

The key finding of this study is the alteration observed on the RMS value before FOG event. All muscles analyzed showed higher RMS values when compared with the RMS recorded in normal walking and during FOG.

It seems that RMS could be a key variable in identifying FOG events. We’ll increase the sample subjects in order to confirm this preliminary result.

References

- [1] N. Giladi, TA. Treves, ES. Simon, H. Shabtai, Y. Orlov, B. Kandinov, et al., *J Neural Transm* **2001a**; 108: 53–61.
- [2] A. Nieuwboer, R. Dom, W. De Weerd, K. Desloovere L. Janssens V. Stijn, *Brain* Volume 127, Issue 7, 1 July **2004**, Pages 1650–166[3] A. Burleigh-Jacobs, FB. Horak, JG. Nutt, JA. Obeso, *Mov Disord* 1997; 12: 206–15.

Subthalamic nucleus deep brain stimulation reduces freezing of gait in Parkinson's disease

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Deep brain stimulation effectively relieves most motor symptoms of Parkinson's disease, but effects on freezing of gait remain controversial with reports of improvement, worsening, and even induction post-surgery. Our objective was to evaluate the effects of bilateral subthalamic nucleus deep brain stimulation on subjective and objective freezing of gait, with a special focus on freezing of gait subtypes and patterns. VANTAGE is a multicenter, prospective, open-label, non-randomized trial that assessed motor improvement in 38 subjects with Parkinson's disease for one year post-surgery. Data collection included the freezing of gait questionnaire at baseline and 26 weeks post-implantation, and unified Parkinson's disease rating scale II item 14 scores at baseline and 12, 26, and 52 weeks post-implantation. A blinded walking test was performed by a subgroup at baseline and 12, 26, and 52 weeks post-implantation. Other gait-specific items, including unified Parkinson's disease rating scale II (falling) and III (gait and mobility of legs) and the Parkinson's disease questionnaire 39-mobility subscore. Freezing of gait questionnaire improved at 26 weeks compared to baseline. Analysis of the walking test during medication-off revealed reductions in the total walking time, number of freezing of gait episodes, and total time spent frozen at weeks 12, 26, and 52 compared to baseline. Deep brain stimulation was effective for all freezing of gait subtypes and freezing of gait-provoking circumstances (Figure 1). Subjective and objective evaluation of freezing of gait revealed that deep brain stimulation of the subthalamic nucleus reduces freezing of gait occurrence and severity within the first postoperative year.

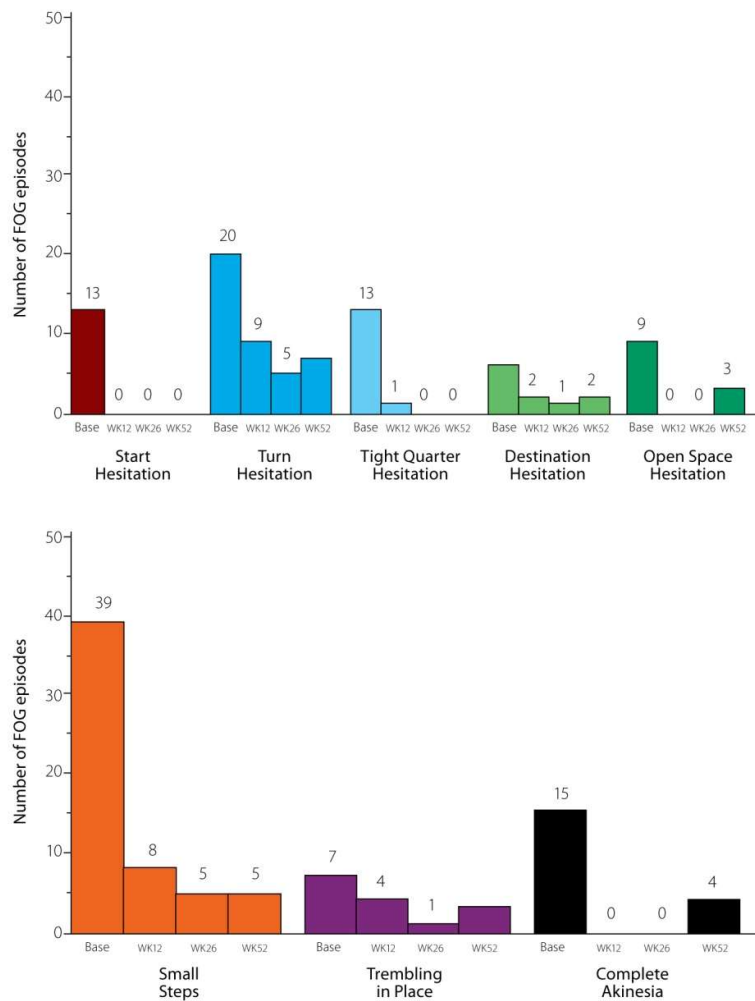


Figure 1. Manifestations and subtypes of FOG

Each FOG episode was assigned to a certain A) FOG subtype (start hesitation, tight quarter hesitation, open space hesitation, destination hesitation, and turning hesitation), and B) manifestation (small steps, trembling in place, or complete akinesia) at each visit (baseline, week 12, week 26, and week 52). The walking test data were collected from n=20 subjects (subgroup) under medication-off. Note that one FOG episode might present with more than one manifestation. FOG, freezing of gait.

Adaptations to postural perturbations in patients with freezing of gait

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Freezing of gait (FOG) is a powerful determinant of falls in Parkinson's disease (PD). Automatic postural reactions serve as protective strategy to prevent falling after perturbations. However, FoG-specific automatic postural reactions in response to perturbations are at present unclear. Therefore, adaptation patterns and neuromuscular control were compared between patients with (FOG+) and without FOG (FOG-) and healthy controls (HC) in response to perturbations. Fifteen FOG+, 13 FOG- and 22 HC were included. Participants stood on a moveable platform while several perturbations were imposed. The first anterior platform translation was retained for analysis. Center of mass (CoM) trajectories and trunk, knee and ankle angles were compared between groups using Statistical Parametric Mapping, allowing to capture changes in time. In addition, muscle activation of tibialis anterior and medial gastrocnemius was measured using EMG.

At baseline, FoG+ stood with more trunk flexion ($p=0.005$) and following a perturbation, they reacted with increased trunk extension ($p=0.004$) in comparison to HC, a pattern not observed in FoG-. The CoM pattern showed greater backward displacement in FoG- and FoG+ ($p=0.02$). Both FoG+ and FoG- showed increased co-activation of lower leg muscles compared to HCs ($p=0.010$). No differences between FoG+ and FoG- were observed.

Automatic postural reactions after a sudden perturbation are similar between subgroups with and without FOG but differ from HC. Inappropriate trunk control and muscle coordination in PD seem to increase susceptibility for balance loss. Reactive postural control, largely regulated by brain stem centers, seem to affect different mechanisms than those governing freezing of gait.

Virtual reality for rehabilitation in Freezing of Gait

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People with Parkinson's disease and freezing of gait (FOG+) have more postural instability, cognitive impairment, falls and loss of retention of learning compared to FOG-. The V-TIME randomized, controlled study showed positive effects of virtual reality treadmill training (TT+VR) on falls, over and above that of usual treadmill walking (TT)[1]. We addressed whether these treadmill interventions led to similar gains in FOG+ as FOG-.

Seventy-five FoG+ and 46 FoG- (similar age and fall rates) were randomly assigned to TT+VR or TT. Participants were assessed at baseline, post, 1 month and 6 months. Primary outcome was the Mini-Best test, capturing postural and dynamic stability. Fall risk was assessed via diaries. Secondary outcomes comprised the new freezing of gait questionnaire (NFOG-Q) and the Trail Making Test (TMT-B).

Both FOG+ and FOG- had a higher reduction of falls ($p < 0.001$) after TT+VR compared to TT. Mini-Best scores improved in both groups after training ($p = 0.001$), irrespective of study arm. Improvements were retained at 1-month, but not at 6-months in both groups. The same pattern of results was apparent for the TMT-B. NFOG-Q scores did not change after both training modes.

Overall, TT+VR was able to reduce falling more than TT in FOG+ and FOG-. Similar to FOG-, FOG+ improved postural and dynamic instability after both training modes and retained these effects briefly. Freezing scores were not helped by training and deteriorated with time. These results highlight the potential of treadmill-based rehabilitation to address gait, balance and fall risk even in FOG+, but not freezing.

References

[1] A. Mirelman, L. Rochester, I. Maidan et al., *Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial* **2016**, p1170.

The influence of an Emotion-Enriched Context on Cortical Excitability during Action Observation is switched off by freezing of gait

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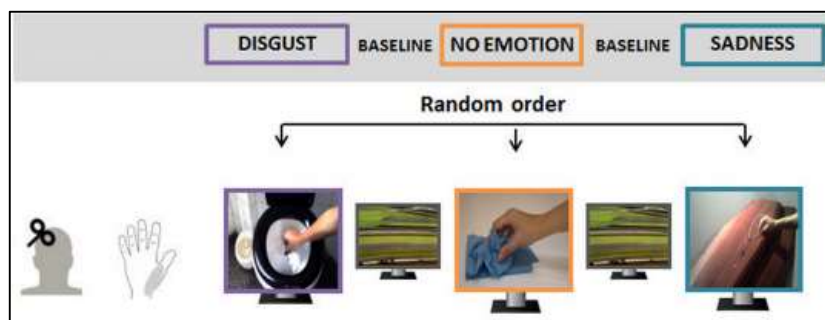
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Recent studies enhanced the role of the Mirror Neuron System (MNS) for action comprehension and prediction. Particularly the emotional information provided by the context where the observed action takes place seems to modulate motor resonance. We recently showed that a combination of negative valence/high arousal drives the greater response in the observer's MNS in a strictly muscle specific fashion¹.

Here we recruited a group of healthy subjects (HS; mean age 69,8 ±5,4) and two groups of age-matched Parkinson's disease (PD) patients with and without freezing of gait (FOG+ and FOG-). Corticospinal excitability was recorded from a muscle involved in the grasping action, the abductor pollicis brevis (APB), while subjects were watching the same reach-to-grasp movement embedded in different contexts: (i) with negative emotional valence, but different levels of arousal (sadness, low arousal; disgust, high arousal) and (ii) without emotional valence (no-emotion). Corticospinal excitability was recorded also during a baseline condition, (landscape picture).

No differences were observed at baseline condition between groups. Results from HS showed that corticospinal excitability increased in all movement conditions respect to baseline and that disgust condition enhanced corticospinal excitability more than the others. FOG- group displayed a partial reduction of this context modulation, as corticospinal increased only in the sadness condition ($p=0.04$) respect to baseline. FOG+ group did not show any differences between the various conditions (p always > 0.05). Our results support the hypothesis that FOG involves a complex interplay between motor and non-motor (i.e., affective) factors, rather than being a pure motor problem.



Caption 1: Experimental paradigm.

References

- [1] Lagravinese, G., Bisio, A., De Ferrari, A. R., Pelosin, E., Ruggeri, P., Bove, M., & Avanzino, L. (2017). An Emotion-Enriched Context Influences the Effect of Action Observation on Cortical Excitability. *Frontiers in Human Neuroscience*, 11, 504. <http://doi.org/10.3389/fnhum.2017.00504>.

Quantification of gait sub-phase durations using an ambulatory system in Parkinson's disease

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Objective: To apply for the first time in Parkinson's disease (PD) a newly developed and validated signal-processing algorithm aimed at quantifying the variability, symmetry, and regularity of gait phase/sub-phase durations during comfortable walking using an ambulatory accelerometer-based foot-mounted system. Methods: We recorded 47 seconds long gait data from 14 PD patients ((mean±std) age=67.8±10.8 years, Unified PD Rating Scale score obtained on medication (Part III)=27.8±11.6, Hoehn & Yahr stage=2.0±0.6) and 14 age-matched controls (age=68.2±10.2 years) using 4 accelerometers attached to the regular shoes of each participant [1][2]. Participants walked in straight lines at their self-selected/usual speed outside a controlled laboratory. Data processing and analyses included the following chronological steps. First, we extracted stride-by-stride left/right heel strike (HS), toe strike (TS), toe-off (TO), maximum heel clearance (MHC), and maximum toe clearance (MTC) timings. Second, using these timings, we computed the mean/coefficient-of-variation (CV) of durations of (1) left/right stride (Sr), stance (Sa), swing (Sw), and double-support (DS) phases, and (2) left/right HS to TS (HS2TS), TS to TO (TS2TO), TO to MHC (TO2MHC), MTC to HS (MTC2HS) sub-phases [3]. We also calculated symmetry and regularity ratios, and phase/sub-phase durations as percentages of Sr. Results: Compared with controls, PD patients showed significantly decreased mean value of HS2TO and increased variability of several gait phase/sub-phase durations (Table 1). Conclusions: This accelerometer-based algorithm is able to quantify disturbances in gait phase/sub-phase durations during comfortable walking in PD patients. This opens new perspectives for gait analyses in PD patients with/without freezing of gait in their ecological environment.

			PD patients	Controls	p-value
Duration values	Mean	HS2TS	0,081	0,093	<0.05
	CV (%)	Sr	3%	2%	<0.01
		Sa	4%	3%	<0.003
		Sw	6%	4%	<0.005
		DS	13%	8%	<0.0001
		HS2TS	27%	13%	<0.002
		TS2TO	4%	3%	<0.02
MTC2H	49%	34%	<0.03		
Percentages	CV (%)	Sa	3%	2%	<0.01
		Sw	7%	4%	<0.003
		DS	11%	8%	<0.03
		HS2TS	24%	11%	<0.002
		TS2TO	3%	2%	<0.01
Symmetry ratios	CV	Sr	4,3%	2,8%	<0.002
		Sa	4,3%	2,8%	<0.01
		Sw	8,2%	4,8%	<0.003
		DS	15,6%	10,9%	<0.03
Regularity ratios	Mean (-)	DS	1,0149	1,0061	<0.002
	CV (%)	Sr	4,9%	3,3%	<0.003
		Sa	4,9%	3,3%	<0.003
		Sw	8,1%	5,5%	<0.02
		DS	16,8%	10,5%	<0.002
		TS2TO	4,4%	3,4%	<0.05

Table 1: Mean values and variability of the measured gait parameters for PD patients and age-matched controls.

References

- [1] M. Boutaayamou, et al., *Medical Engineering and Physics* **2015**, pp. 226–232.
 [2] M. Boutaayamou, et al., *Biomed. Eng. Sys. Tech., Springer* **2017**, pp. 236–254.
 [3] M. Boutaayamou, et al., In *Proc. 11th Interna. Joint Conf. Biomed. Eng. Sys. Tech.* **2018**, pp. 248-255.

Multi-target transcranial direct current stimulation for freezing of gait in Parkinson's disease

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Background: Recent findings suggest that transcranial direct current stimulation (tDCS) of the primary motor cortex may ameliorate freezing of gait in Parkinson's disease. However, the effects of multitarget simultaneous stimulation of motor and cognitive networks are mostly unknown. The objective of this study was to evaluate the effects of multitarget tDCS of the primary motor cortex and left dorsolateral prefrontal cortex on freezing of gait and related outcomes.

Methods: Twenty patients with Parkinson's disease and freezing of gait received 20 minutes of tDCS on 3 separate visits. tDCS targeted the primary motor cortex and left dorsolateral prefrontal cortex simultaneously, primary motor cortex only, or sham stimulation (order randomized and double-blinded assessments). Participants completed a freezing of gait-provoking test, the Timed Up and Go, and the Stroop test before and after each tDCS session.

Results: Participants were successfully blinded to the tDCS conditions. Performance on the freezing of gait-provoking test (from 14.5 ± 9.7 to 10.3 ± 8.2 , $p = 0.010$), Timed Up and Go test (14.5 ± 9.7 to 11.5 ± 3.5 sec, $p = 0.006$), and the Stroop test (27.6 ± 13.9 to 30.7 ± 15.6 , $p = 0.016$) improved after simultaneous stimulation of the primary motor cortex and left dorsolateral prefrontal cortex, but not after primary motor cortex only or sham stimulation.

Conclusions: tDCS designed to simultaneously target motor and cognitive regions apparently induces immediate aftereffects in the brain that translate into reduced freezing of gait and improvements in executive function and mobility.

L-Dopa influence on prefrontal activation during gait in individuals with FOG

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A growing body of literature suggests that freezing of gait (FOG) in Parkinson's disease (PD) is related to prefrontal cortex (PFC) dysfunction. A few imaging studies have compared OFF and ON levodopa state in PD freezers, however, no study has used brain-imaging during gait. To test the hypothesis that dopaminergic medication improves gait and reduces PFC activation, we used wireless functional near infrared spectroscopy (fNIRS) to measure PFC oxygenated hemoglobin (HbO₂) during usual walking in 27 individuals with PD who had marked FOG (FOG-questionnaire score: 17.9±4.2). Subjects walked for 20 meters, 4 times, OFF (withdrawn for more than 12 hours) and ON dopaminergic medication. As expected, gait improved during the ON state (gait speed: Δ10.98±9.16 cm/s, p=0.0001; step length: Δ4.3±4.6 cm, p=0.001), compared to OFF. Unexpectedly, PFC HbO₂ levels were higher (p=0.017) in ON (0.17±0.26μM/L), compared to OFF (0.10±0.22 μM/L). The HbO₂ changes were associated with changes in UPDRS-III between ON-OFF, disease duration, and age (R-Square=0.35, p=0.018). Perhaps, the lower PFC activation during the OFF state reflects the reduction in gait abilities when dopamine is deprived, while during the ON state, the higher activation levels reflect better motor-cognitive synchronicity. Alternatively, perhaps higher PFC activation in ON relates to the negative effects of L-dopa on certain aspects of cognitive function. Future work in a larger sample is needed to confirm these findings and to further explore the dopaminergic effects on activation of the PFC and other brain regions in people who suffer from FOG as well as those who do not.

Multifaceted Predictive Model for Conversion to Freezing of Gait in Parkinson's Disease

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Background: The onset of Freezing of Gait (FOG) in Parkinson's disease has devastating consequences on fall risk and quality of life. A comprehensive understanding and evaluation of markers of FOG is lacking. Hence we investigated the behavioural predictors of FOG conversion.

Methods: We conducted a cohort study with a two year follow-up in sixty non-freezers when OFF-medication. Instrumented and clinical tests covered domains of disease severity, gait, cognition, affect, repeated limb movements, balance, turning and dual tasking every year. Conversion was determined by the New Freezing of Gait Questionnaire^[1]. A multivariable prediction model was built and internally validated^[2].

Results: Twelve patients (20%) developed FOG, six in each year. Seven measures including non-motor (part I) (AUC=0.73) and axial motor (part III) (AUC=0.76) of the MDS-UPDRS, relative phase error variability (AUC=0.73) and amplitude variability (AUC=0.74) while finger tapping, frequency variability while toe tapping (AUC=0.75), response time variability to the auditory Stroop while turning (AUC=0.68) and gait asymmetry while dual tasking (AUC=0.70) were included in a backward logistic regression model. The bootstrap-corrected model was able to predict one-year conversion with 89.45% accuracy. MDS-UPDRS non-motor score and auditory Stroop response time variability were selected most often (73% and 63%). Cognitive and balance measures were not found to be related to FOG conversion in this timeframe.

Conclusion: A model combining clinical and objective markers was able to predict FOG conversion in the following year with excellent accuracy. These findings indicate a breakdown in movement control as well as increased non-motor pathology prior to FOG development.

References:

- [1] A. Nieuwboer *et al.*, "Reliability of the new freezing of gait questionnaire: Agreement between patients with Parkinson's disease and their carers," *Gait Posture*, vol. 30, no. 4, pp. 459–463, **2009**.
- [2] E. W. Steyerberg, F. E. Harrell, G. J. J. . Borsboom, M. J. . Eijkemans, Y. Vergouwe, and J. D. F. Habbema, "Internal validation of predictive models," *J. Clin. Epidemiol.*, vol. 54, no. 8, pp. 774–781, **2001**.

An fMRI-compatible force measurement system for the evaluation of the neural correlates of freezing of gait in patients with Parkinson's disease

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We present a system that allows the measurement of anticipatory postural adjustment (APA) of human legs to be synchronized with the acquisition of functional magnetic resonance imaging (fMRI) data. The device is composed of MRI compatible force sensors able to measure the level of force applied by both feet (Figure 1). Here are the results of our concept-proof study to validate the system ^[1] and also preliminary results comparing Parkinson's disease patients with (FoG) and without freezing of gait (nFoG). We tested the hypothesis that FoG is related to disorders of the neural control of APA. We used the force measurement system designed to assess APA in an event-related paradigm (3T MRI, Achieva, Philips) in a group of young subjects (n=10) and elderly subjects with PD FoG (n=13) and PD nFoG (n=11). Participants performed 30 trials of a step initiation task on a force plate outside the scanner and also in a task of lifting the leg during fMRI acquisition. The results showed that the force measurement system is able to provide reliable brain functional data of the APA control in healthy and people with Parkinson's disease. FoG patients recruited more prefrontal regions to perform APA than nFoG group, which activated a brain circuitry involving the cerebellum and frontal cortex (Figure 2). The circuitry involved in the processing of APA in FoG patients is similar to what has been found during episodes of FoG ^[2]. Possibly APA shares similar neural mechanisms with FoG phenomenon.



Figure 1 - The fMRI-compatible force measurement device.

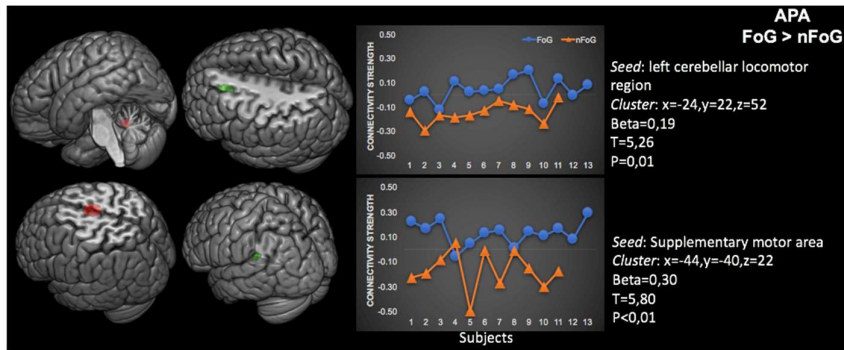


Figure 2 – Connectivity map (FoG > nFoG) during APA

References

- [1] A.C. de Lima-Pardini, R.M. de Azevedo Neto, D.B. Coelho, C.C. Boffino, S.S. Shergill, C.O. Souza, R. Brant, E.R. Barbosa, E.F. Cardoso, L.A. Teixeira, R.G. Cohen, F.B. Horak, E. Amaro Jr, *Scientific Reports* **2017**, p.1.
- [2] J.M. Shine, E. Matar, P.B. Ward, S.J. Bolitho, M. Gilat, M. Pearson, S.L. Naismith. S.J. Lewis, *Brain* **2013**, p.1204.

Asymmetric subthalamic stimulation does not alleviate freezing of gait in Parkinson's disease

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Background. Patients with Parkinson disease (PD) and freezing of gait (FOG) show abnormalities in gait coordination, symmetry and rhythmicity.¹ However, the role of these gait parameters in the genesis of FOG is not clear. Several deep brain stimulation (DBS) strategies have been attempted to alleviate FOG. In an acute trial, the authors suggested that unilateral reduction of the stimulation amplitude in the subthalamic nucleus (STN) contralateral to the leg with the longer step could normalise limb coordination, improving FOG.²

We aimed at assessing the efficacy of such a strategy in the long-term in a randomized, double blind, cross over clinical trial.

Methods. PD patients with bilateral STN DBS for at least one year and FOG refractory to medications and stimulation were included. They were randomized to chronic vs. experimental stimulation (30% amplitude reduction contralateral to the least affected body side), each condition for 4 weeks. Gait analysis and FOG were assessed at normal pace, and under FOG provoking circumstances, both OFF and ON medication.

Results. The study was stopped early for futility. Of the 12 patients included, 8 opted out because of re-emerging of PD symptoms. In the 4 patients who could sustain the experimental condition, there was no change in the percent of FOG during the gait assessment, whether OFF (13.4 vs. 16.8%) or ON (19.5 vs. 19.8%) medication.

Conclusion. Most patients did not tolerate the unilateral amplitude reduction of STN DBS in the long-term. Moreover, this strategy failed to improve FOG in patients who could sustain the procedure.

References

[1] Giladi **2013**

[2] Fasano A, Herzog J, Seifert E, Stolze H, Falk D, Reese R, et al. *Mov Disord.* **2011**;26(5):844-51.

Action observation and motor imagery of freezing of gait

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Unravelling the neural underpinnings of freezing of gait (FOG) during an actual episode is hampered by the supine position required for magnetic resonance imaging (MRI). Here, we propose a novel method to study the neural underpinnings of FOG combining motor imagery and action observation of an actual episode in the MRI scanner. Participants watched a sequence of two different videos alternated with rest periods, showing a normal gait episode and a real life FOG episode in a patient with Parkinson's disease (PD). Circumstances and durations of the footage were otherwise exactly the same. Participants were asked to imagine that they were going through the same experience as the person in the video. Participants received a motor imagery training prior to the scan and were screened for motor imagery ability. All participants had high scores on the kinesthetic and visual imagery questionnaire. So far, 3 freezers (aged between 58 and 72; the New Freezing of Gait Questionnaire scores between 6-10) and 6 non-freezers (aged between 67 and 75) with PD underwent the protocol. We report on the preliminary results for the FOG > gait 2nd level contrast (p -value=.001, cluster size \geq 10). Freezers did not show any higher activations than non-freezers. Non-freezers showed greater activations in the occipital cortex, right angular cortex/inferior parietal lobe, right precentral cortex and the left cingulum than freezers (see figure 1), which could not be explained by an order effect. Lower occipital, prefrontal and parietal activation in freezers may indicate a disengagement of watching and imagining FOG.

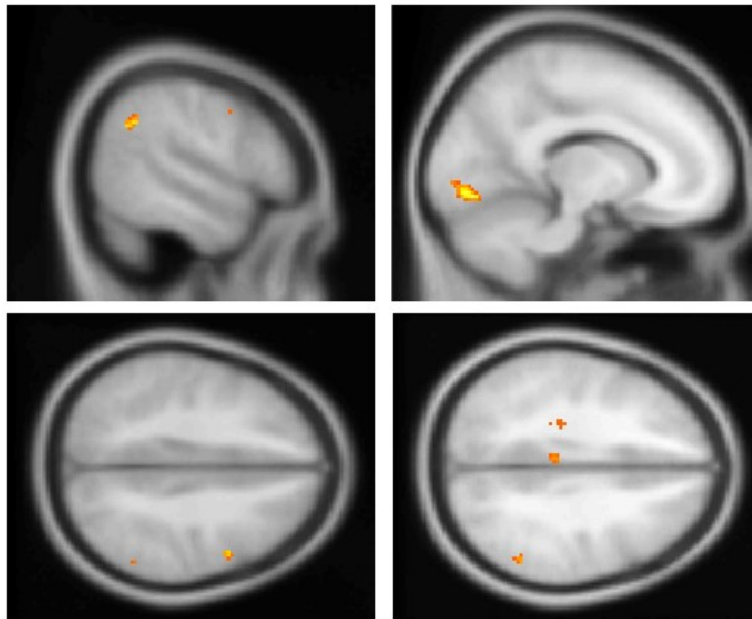


Figure 1: Higher activations for non-freezers compared to freezers for the FOG > gait contrast.

Levodopa Responsiveness of Freezing of Gait: Results Using a Levodopa Test

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Background: The responsiveness of freezing of gait (FOG) to levodopa in Parkinson's disease (PD) is heterogeneous.

Objective: To characterize levodopa response of FOG in PD using levodopa tests.

Methods: Patients were evaluated in the practically defined OFF state (no medication for at least 12 hours) using MDS-UPDRS and timed-up-and-go tests. They were then given a higher than usual levodopa dose and examined in the same way when they turned ON. Based on responsiveness they were categorized into: No FOG (NFOG) by exam and history; Responsive FOG (RFOG) defined as manifesting FOG when OFF only; Unresponsive FOG (URFOG) defined as ANY FOG in the ON state. Demographics, N-FOGQ responses, and change in MDS-UPDRS scores were compared for these groups.

Results: Fifty-three subjects were categorized as either NFOG (n=16), RFOG (n=14), or URFOG (n=23). No difference in age, gender, education, or PD family history was seen. NFOG had a shorter duration of disease (p=.04) than RFOG and URFOG who did not differ from each other. The same was true for number of falls and use of gait assist devices (p=.002). RFOG had a lower N-FOGQ score compared to URFOG (p=.002). No differences were seen with OFF or ON UPDRS scores. Change in FOG subscore was significantly less in the URFOG group.

Conclusions: FOG in PD may be responsive or unresponsive to levodopa. It appears that URFOG is more severe than RFOG. These may represent separate entities with different pathophysiology. A levodopa test should be utilized to categorize FOG for studies.

	NFOG n=16	RFOG n=14	URFOG n=23	P value
Disease Duration (Yrs)	5.9 (2.8)	10.3 (4.9)	10.7 (7.4)	.04
Falling	19%	67%	73%	.002
Use of assistive devices	13%	67%	77%	.002
N-FOGQ total	NA	18.1 (6.0)	23.0 (3.3)	.002
UPDRS part 3 OFF	30.8 (13.2)	32.7 (9.2)	33.8 (10.0)	NS
UPDRS part 3 change ON	12.4(7.4)	15.8 (7.5)	9.8 (9.2)	NS
Item 3.11 OFF (FOG)	na	1.9 (.7)	2.3 (1.3)	NS
Item 3.11 Change ON	na	1.8 (.8)	.8 (1.7)	.04

Visual cueing using laser shoes reduces freezing of gait in Parkinson patients both in the laboratory and at home

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Freezing of gait (FOG) in Parkinson's disease (PD) is common and debilitating. While the evidence for cueing efficacy is encouraging, it remains difficult to translate cueing strategies into an efficient device for use at home. Laser shoes (Figure 1) projecting visual cueing upon heel strike might offer a solution^[1] and we assessed their effectiveness in twenty-one PD patients with FOG, both in the lab and at home. In the laboratory, we measured the number of FOG episodes and the percent time frozen occurring during a standardized walking protocol. At home, the patients completed three consecutive conditions: week 1=wearing laser shoes, without cueing ('Without Cueing'); week 2=wearing laser shoes, with cueing ('With Cueing'); week 3=without laser shoes ('Follow-Up'). The primary outcome was FOG severity (New FOG Questionnaire, NFOGQ). In the lab, cueing using laser shoes was associated with a significant reduction in the number of FOG episodes, both "off" (45.9%) and "on" (37.7%) medication. Moreover, laser shoes significantly reduced the percent time frozen by 56.5% "off" medication (Figure 2).^[2] At home, FOG severity reduced significantly (NFOGQ: 20.35±5.00 Without Cueing versus 18.12±5.44 With Cueing, p=0.036) (Figure 3). Furthermore, the NFOGQ did not differ between With Cueing and Follow-Up. These findings suggest that laser shoes have potential as a mobile visual cueing device to reduce FOG in PD patients, also within their home situation, and that improvements may last beyond punctual use. Studies with longer training periods and follow-ups are needed to document the long-term efficacy, and to further study possible learning effects.



B

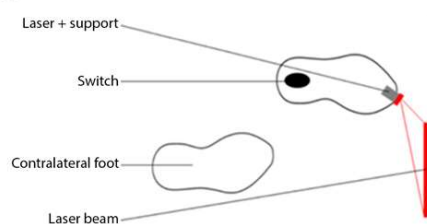


Figure 1. (A) The photograph shows the men's model of laser shoes. (B) The laser is activated during heel strike by a switch located under the sole of the contralateral foot, and appears orthogonally to the contralateral foot.

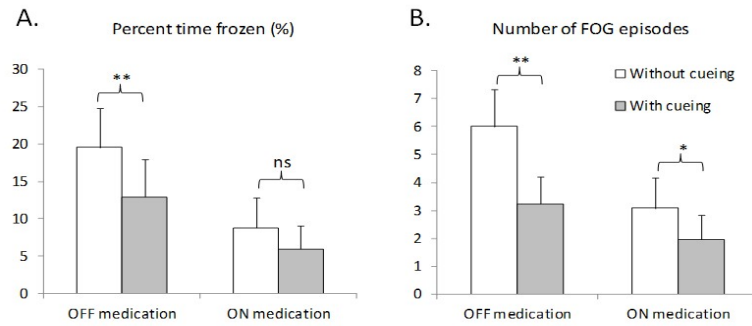


Figure 2. (A) Percent time frozen with-cueing and without-cueing, both “off” and “on” medication. (B) Number of freezing of gait (FOG) episodes with-cueing and without-cueing, both “off ” and “on” medication. **Significance at $p < 0.001$; *significance at $p < 0.05$; ns = nonsignificant.

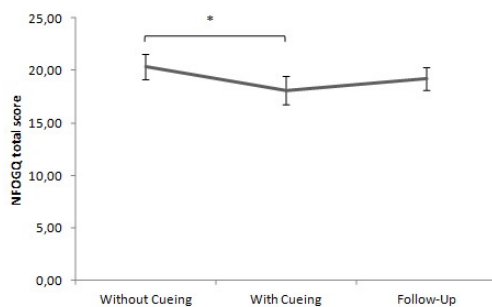


Figure 3. New Freezing Of Gait Questionnaire (NFOGQ) total score; Graphs show mean and SEM of the NFOGQ Without Cueing (week 1), With Cueing (week 2) and during the Follow-Up week (week 3); * = significant differences ($p < 0.05$).

References

- [1] Ferraye MU, Fraix V, Pollak P, et al. The laser-shoe: a new form of continuous ambulatory cueing for patients with Parkinson’s disease. *Parkinsonism Relat Disord* 016;29:127–128.
- [2] C. Barthel, J. Nonnekes, M. van Helvert, et al. The laser shoes: A new ambulatory device to alleviate freezing of gait in Parkinson disease. *Neurology*. **2018**;90(2):e164-e171.

Freezing of Gait and cognition: what can we learn from asymmetry?

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Background: Alteration of cortical circuits in PD leads to cognitive dysfunctions associated with the development of FoG. The asymmetric degeneration of the corticostriatal dopaminergic circuits affects differently cognition in PD patients with right side (RPD) and left side (LPD) motor symptoms onset.

Aim: To investigate the role of cognition and asymmetric dopaminergic depletion in FoG.

Methods: 305 retrospectively-enrolled PD patients were divided according to the presence (FoG+, n=128) or absence (FoG-, n=177) of FoG and to the side of motor symptoms onset. Several scales and test were administered to assess the clinical, motor and cognitive profile of patients: UPDRS, MMSE, FAB, WCST, TMT A-B, RAVLT, 6MWT, TUG.

Results: No differences in the prevalence of FoG was found between LPD and RPD patients. At the PD diagnosis, FoG+ patients were younger (p=0.04). L-Dopa equivalent dosage was higher in FoG+ patients (p<0.0001). FoG+ patients showed worse scores in all variables: FAB (p=0.005), TUG (p=0.017), 6MWT (p=0.046), UPDRS (total, IV, III, II, p<0.0001, p<0.0001, p=0.007, p<0.0001, respectively). Finally, FoG+ patients showed a higher percentage of deficit in WCST (p=0.018), TMT A (p=0.0013) and RAVLT (p=0.012).

Conclusions: FoG is associated with deficits in executive functions and earlier PD onset. The side of motor symptoms onset does not influence the prevalence of FoG and the related cognitive aspects. Despite higher dopaminergic therapy, FoG+ patients get worse in clinical-motor performances. Therefore, the presence of FoG defines a specific PD phenotype, in which the involvement of cortical circuits is much more pronounced than the striatal dopaminergic ones.

References

- [1] Z. Yao, Y. Shao, X. Han, *Freezing of gait is associated with cognitive impairment in patients with Parkinson disease*. *Neurosci Lett*, **2007**, p 126-130.
- [2] F. Brugger, E. Abela, S. Hägele-Link, S. Bohlhalter, M. Galovic, G. Kägi. *Do executive dysfunction and freezing of gait in Parkinson's disease share the same neuroanatomical correlates?* *J Neurol Sci*, **2015**, p 184-187.
- [3] F. Pieruccini-Faria, K.A. Ehgoetz Martens, C.R. Silveira, J.A. Jones, Q.J. Almeida. *Side of basal ganglia degeneration influences freezing of gait in Parkinson's disease*. *Behav Neurosci*, **2015**, p 214-218.

Instrumented Timed Up and Go: simple test with insights for differentiating between patients with Parkinson's disease with and without freezing of gait

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The instrumented Timed Up and Go (iTUG) is a simple clinical test that can provide information about walking, transitions and turning. It was used to evaluate fall risk in idiopathic fallers, differentiate between patients with Parkinson's disease (PD) and controls, identify differences between motor subtypes of patients with PD and demonstrate an association between cognitive and motor function. In our current study, we aimed to test if iTUG could be used to distinguish freezers from non-freezers. It included 40 patients with PD who experience freezing of gait (FOG+) and 35 without FOG (FOG-) that performed iTUG while on medication (tests with FOG episodes were excluded). Both groups were matched by age, disease duration and UPDRS part III (table 1). As seen in Table 1, iTUG total duration was longer for FOG+. There was a significant difference in their straight line walking duration and in the number of steps it took to complete the test, i.e., shorter step length. In the turn-to-walk, FOG- had a higher yaw amplitude. FOG+ were also slower in the transition from sit-to-stand. Intriguingly duration of both turns (turn-to-walk and turn-to-sit) did not differ between FOG+ and FOG-. Logistic regression separate the groups with an accuracy of 71.4%. Although it is a simple test, the iTUG managed to identify subtle differences in the way freezers and non-freezers perform this test.

	FOG+	FOG-	P-Value
Age	66.9 ± 7.6	64.6 ± 8.4	0.20
UPDRS 3	36.7 ± 14.3	35.5 ± 12.8	0.72
Disease duration	7.0 ± 3.6	6.3 ± 2.3	0.29
FOG-Q	15.7 ± 4.5		
	iTUG results		
TUG total time [sec]	11.7 ± 3.6	9.7 ± 2.4	p<0.01
Straight line walk duration [sec]	5.9 ± 2.0	4.6 ± 1.4	p<0.01
# steps in straight line walk	10.6 ± 3.3	8.0 ± 2.2	p<0.01
Vertical axis freq width [Hz]	1.6 ± 0.6	2.4 ± 1.2	p<0.01
Yaw amplitude[deg/sec]	159 ± 35	141 ± 41	0.039
Sit to stand duration [sec]	0.68 ± 0.20	0.56 ± 0.15	0.04
Turn-to-walk duration [sec]	2.0 ± 0.5	2.2 ± 0.7	0.13
Turn-to-sit duration [sec]	1.9 ± 0.6	2.1 ± 0.7	0.23

Table 1 – Demographics and results

The Interactive Walkway for an innovative evaluation of freezing of gait in Parkinson's disease patients

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Background and aim: Freezing of gait (FOG) is an important cause of falls in Parkinson's disease patients. Growing evidence suggests that challenging walking tests are more likely to reveal differences between freezers and non-freezers than standard walking tests. The Interactive Walkway (IWW; Figure 1) is an overground 8-meter walkway with projected visual context, which can be used to create challenging walking tests^[1], especially when context is presented in a gait-dependent manner using real-time processed Kinect v2 data^[2]. This study aims to assess the added value of challenging IWW tests over standard walking tests in discriminating freezers from non-freezers. Methods: 30 patients (14 freezers, 16 non-freezers) performed standard walking tests (10-meter walking test, Timed Up-and-Go test) and various challenging IWW tests (including the tests depicted in Figures 1 and 2). Discriminant analysis was used separately for either type of walking test. Results: No group differences were found for standard walking tests, but the Timed Up-and-Go test classified 6 of 14 freezers (42.9%) and 15 of 16 non-freezers (93.8%) correctly. Regarding IWW tests, freezers had significantly longer sudden-stops-and-starts initiation times ($p=0.013$) and better stepping accuracies ($p=0.002$) than non-freezers. Using these outcome measures, 10 of 14 freezers (71.4%) and 13 of 16 non-freezers (81.5%) were correctly classified. In addition, in 7.1% of IWW trials FOG-episodes occurred, mostly during tasks that included turning, while FOG only occurred once (1.2%) in standard walking tests. Conclusions: Challenging IWW tests have limited added value over standard walking tests in discriminating freezers from non-freezers and in eliciting FOG.

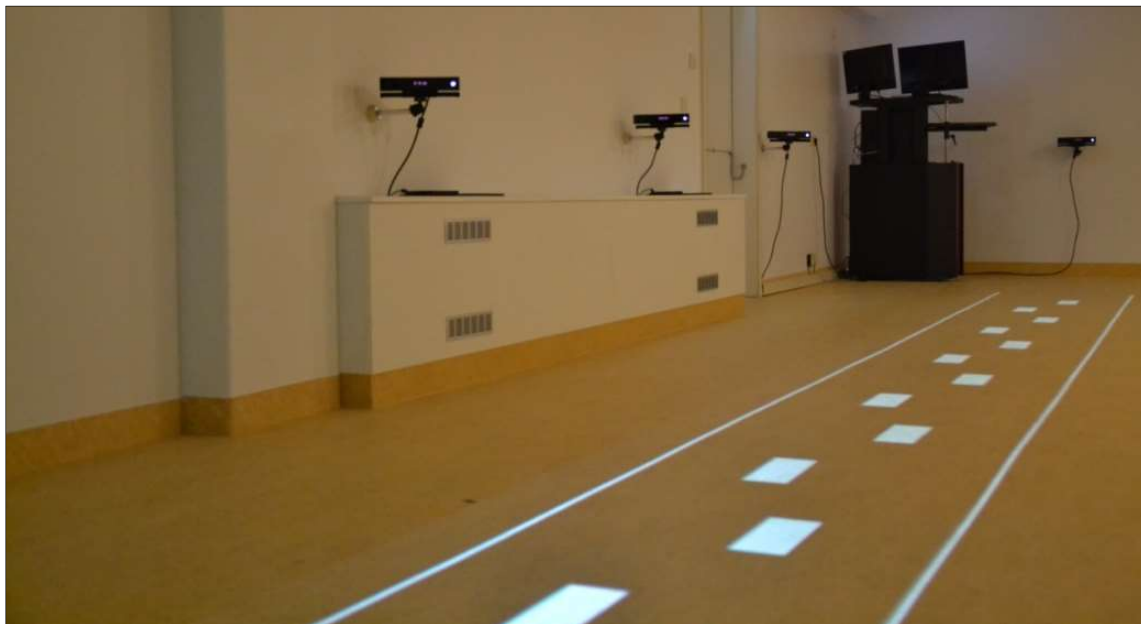


Figure 1: The Interactive Walkway with stepping stones presented on the walkway to assess stepping accuracy.

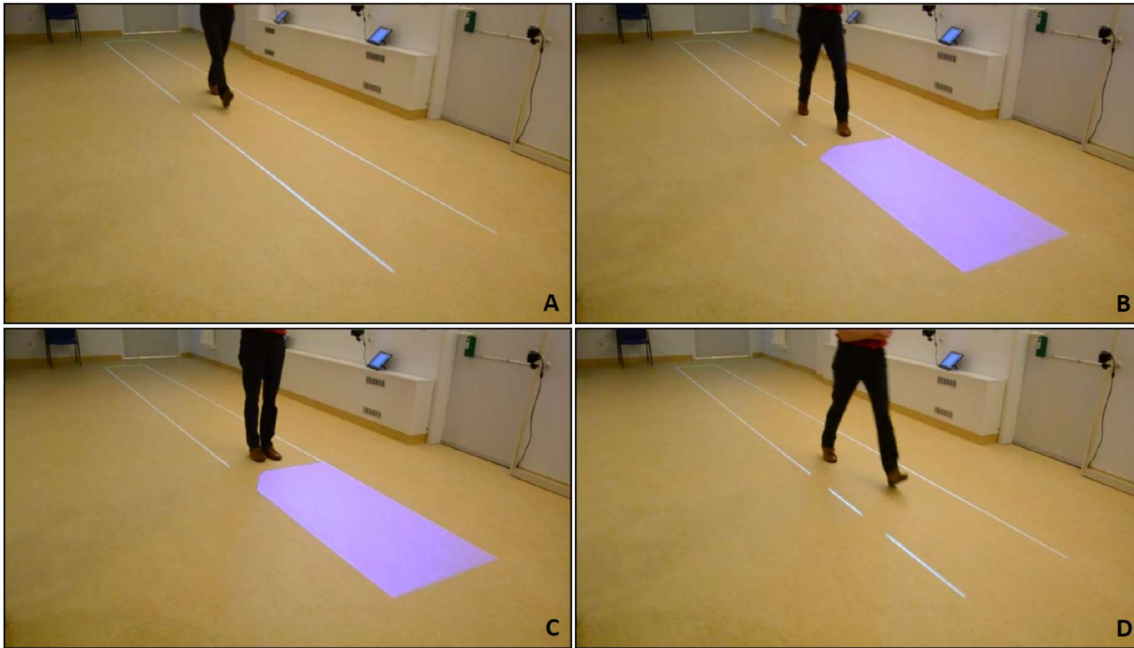


Figure 2: The sudden-stops-and-starts task on the Interactive Walkway with a stop cue suddenly appearing and disappearing to assess one's ability to suddenly stop and start (i.e., initiation time) walking.

References

- [1] D.J. Geerse, B.H. Coolen, M. Roerdink, *Walking-adaptability assessments with the Interactive Walkway: between-systems agreement and sensitivity to task and subject variations*. *Gait Posture*. **2017**;54:194-201.
- [2] D.J. Geerse, B.H. Coolen, M. Roerdink, *Kinematic Validation of a Multi-Kinect v2 Instrumented 10-Meter Walkway for Quantitative Gait Assessments*. *PLoS One*. **2015**;10(10):e0139913.

Dysfunctional Limbic Circuitry Underlying Freezing Of Gait in Parkinson's Disease

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Freezing of gait (FOG) is a poorly understood symptom affecting many patients with Parkinson's disease (PD). Despite growing evidence of a behavioural link between anxiety, attention and FOG in PD, no research to date has investigated the neural mechanisms that might explain this relationship. The present study therefore examined resting state MRI functional connectivity between the amygdala, striatum and frontoparietal attentional control network in PD patients with (freezers: n=19) and without FOG (non-freezers: n=21) in the dopaminergic 'off' state. Functional connectivity was subsequently correlated with an objective measure of FOG severity and a subjective scale of affective disorder within each group. Connectivity between the right amygdala and right putamen was significantly increased in freezers compared to non-freezers ($p < 0.01$). Furthermore, freezers showed increased anti-coupling between the frontoparietal network and left amygdala ($p = 0.011$), but reduced anti-coupling between this network and the right putamen ($p = 0.027$) as compared to non-freezers (Figure 1). Key functional connections between the amygdala, putamen and frontoparietal network were significantly associated with FOG severity and a fear of falling. This study provides the first evidence that dysfunctional fronto-striato-limbic processes may underpin the link between anxiety and FOG in PD. It is proposed that freezers have heightened striato-limbic load and reduced top-down attentional control at rest, which when further challenged by the parallel processing demands of walking may precipitate FOG.

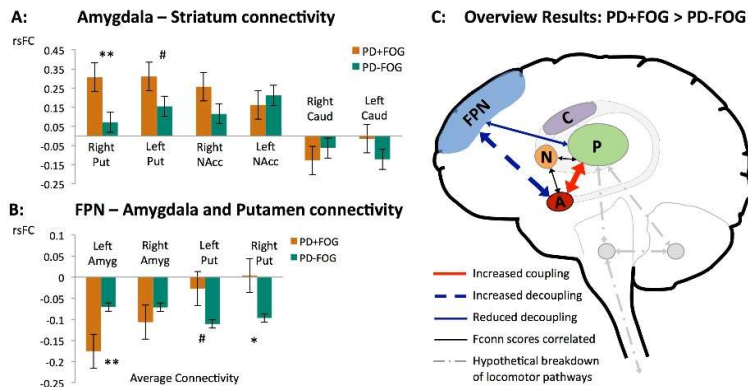


Figure 1: Overview of resting state functional MRI connectivity results

The neural effects of a randomized controlled targeted cognitive training program for the treatment of Freezing of Gait in Parkinson's disease

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This study investigated whether a cognitive training program (CT) induced neural plasticity processes associated with reduced propensity for freezing of gait (FOG) in Parkinson's disease (PD). Twenty-four patients with PD and FOG performed a virtual reality gait paradigm (VR) during functional magnetic resonance imaging (fMRI) in their "off state", before and after completing either a 7-week CT program (n=13) or an active control (AC) condition (n=11) (Figure 1A). During the VR, patients alternately depressed foot-pedals while processing cognitively demanding cues in a pseudo-random fashion. Dual task cost was calculated as the difference in coefficient of variation (CV) in footstep latencies during periods of high cognitive load compared to periods without cognitive cues (simple walking). Blood oxygen level dependent (BOLD) responses were entered in a Group x Task x Time factorial ANOVA using SPM12. As expected, CV was higher during high cognitive load compared to simple walking (t=6.35, p<0.001) and a reduction in dual task cost was found following CT ($\Delta CV = -1.16$) compared to AC ($\Delta CV = +0.54$), although the interaction was non-significant (Figure 1B). Figure 2 shows the BOLD changes associated with the factorial ANOVA on VR performance. The interaction effect of interest revealed that CT increased BOLD in the right putamen, whereas BOLD in the left superior frontal cortex and right lingual gyrus decreased (Figure 2F). Taken together, these results indicate that CT allowed patients to perform the VR in a more automatic manner^[1], thereby aiding in reducing their reliance on cognitive control to operate steps and lowering the risk for FOG^[2,3].

References

- [1] Gilat M, Bell PT, et al. *Dopamine depletion impairs gait automaticity by altering cortico-striatal and cerebellar processing in Parkinson's disease.* **2017**, Neuroimage. p.207-220.
- [2] Vandenberghe J, Deroost N, et al. *Freezing of gait in Parkinson's disease: disturbances in automaticity and control.* **2012**, Front Hum Neurosci. p.356
- [3] Lewis SJG, Shine JM. *The next step: A common neural mechanism for freezing of gait.* **2014**. Neuroscientist. p.72-82.

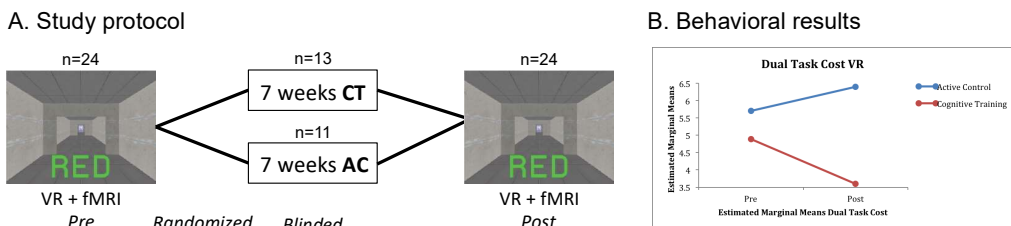
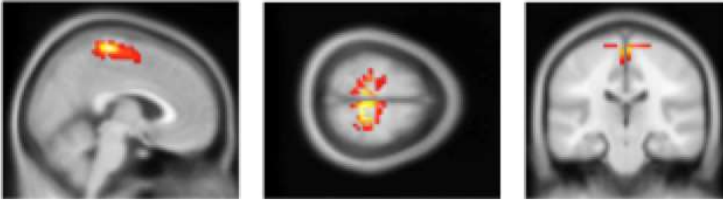
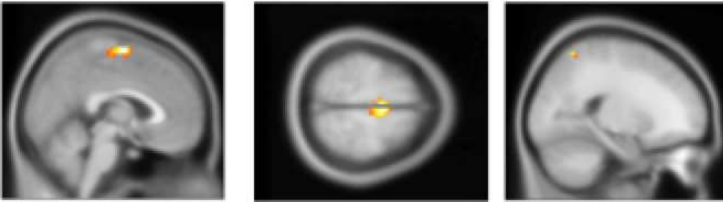


Figure 1: Study protocol (A) and behavioral outcomes on dual task cost across groups before and after the cognitive training or active control interventions (B).

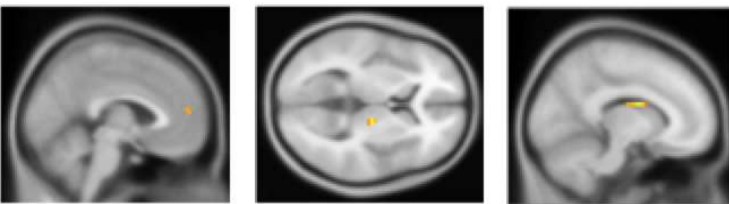
A: Main effect of performing the VR Task (F-test)



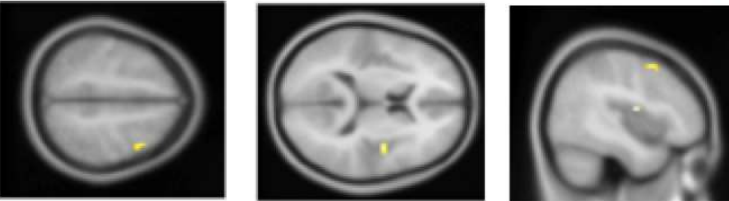
B: Main effect of Group (F-test)



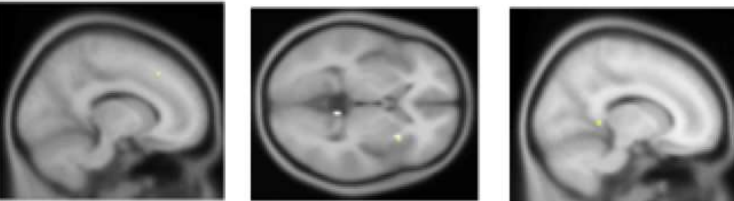
C: Main effect of Task (cues vs. walking) (F-test)



D: Main effect of Time (pre vs. post intervention) (F-test)



E: Interaction effect (F-test)



F: Interaction effect (T-test)

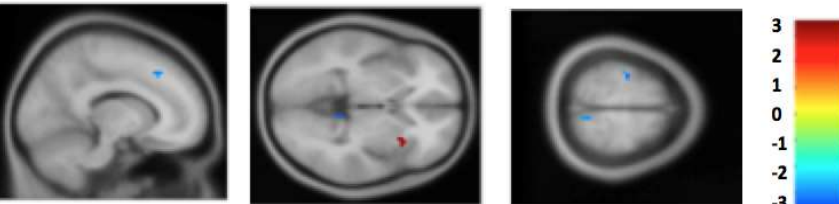


Figure 2: Changes in BOLD responses associated with the factorial ANOVA on VR performance. Labels: A = bilateral primary motor cortex; B=supplementary motor area; C=Prefrontal cortex, Right thalamus, Caudate nucleus; D=Right superior frontal gyrus, Right insula; E=Left superior frontal cortex, Right lingual gyrus, Right putamen; F=E. $p < 0.005$, $k > 10$.

Cued prolonged walking is not extra fatiguing for patients with freezing of gait

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Cueing is a valuable tool for gait rehabilitation in Parkinson's disease, but has also been found to induce fatigue compared to healthy controls. We expected that patients experiencing freezing of gait (FOG+) would suffer from more fatigue than those without (FOG-). Therefore, we studied fatigue in both groups before and after prolonged walking under various cueing conditions. Fifteen FOG+ and 13 FOG- patients, of similar age and disease severity, walked 30 minutes under 4 conditions randomly offered with one week interval between conditions. A wearable sensor system provided: 1) continuous cues; 2) intermittent cues upon cadence deviations; 3) intermittent verbal instructions upon cadence deviations; and 4) no input. Outcome measures were: 1) Multidimensional Fatigue Inventory (MFI) at baseline, 2) Visual Analog Scale (VAS) for physical and mental fatigue before and after walking, 3) heartrate before and after walking, and 4) BORG-scale after walking. We found that both groups had similar heart rates and MFI scores at baseline, except that FOG+ reported less physical activity compared to FOG- ($p=0.01$). Heartrate increased significantly less in FOG+ than FOG- during walks with continuous ($p=0.04$), intermittent cueing ($p=0.01$) and no input ($p=0.04$). FOG+ had slower gait speed ($p<0.04$) than FOG-, which was not correlated with heart rate. Perceived fatigue after walking, as assessed by the VAS and BORG-scales, was similar in both groups during all conditions. We conclude that cueing, irrespective of continuous or intermittent delivery, does not induce additional fatigue in FOG+ compared to FOG- and can thus be recommended for prolonged walks.

Prediction and pattern of progression of freezing conversion during motor task in Parkinson's disease. A six year prospective study.

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Freezing of gait (fog) strongly impact walking ability in Parkinson's disease (PD) and may occur in the early years of the disease. Freezing or festination may also be seen on upper limb or oral production. Here we prospectively study the onset of freezing or festination in a cohort of early PD patients.

A total of 24 patients with PD are currently enrolled in the study, to date 20 of them have fulfilled the complete study with assessment at diagnosis, two years and 5-6 years of diagnosis using movement analysis during motor diadochokinetic tasks with hand, foot and syllable pronunciation at 2 and 4 hertz. Subjects were assessed in "off-drug" and "on-drug" condition. None had freezing or festination at baseline. Kinematic parameters were recorded using a VICON 3D motion analysis (Oxford Metrics). Patients are defined as non-freezer, early or late converters. The following kinematic criteria will be assessed as possible predictive factor: variability of amplitude and frequency at baseline, during the five first productions at each evaluation. The progression of freezing localization in the early-converters group will be described. Clinical parameters are mds-UPDRS scores, MOCA cognitive scale, and influence of dopaminergic drugs.

This follow-up study is one of the rare studies with a long prospective follow-up allowing the assessment of freezing onset and freezing progression.

Preoperative stratification of gait outcome from subthalamic nucleus stimulation

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Introduction: Freezing of gait (FOG) constitutes a major unmet therapeutic need in advanced Parkinson's disease (PD). As patients show highly variable postoperative outcomes of FOG from standard subthalamic neurostimulation, it is highly warranted to establish predictors of the therapeutic outcome.

Methods: We conduct a prospective observational clinical study with a clinical and biomechanical characterization of gait function before and after surgery. Biomechanical measures of gait were assessed by three inertial measurement units attached to limbs and lumbar position including triaxial accelerometer, gyroscope and magnetometer. The clinical severity of FOG was assessed by the Freezing of Gait Assessment Course (FOG-AC). The preoperative visit included assessments in both 'off' and 'on' dopaminergic state. Patients were reassessed on the same measures six months after the implantation in their best individual treatment 'on medication, on stimulation'.

Results: Preoperative L-Dopa response of FAC was indicative for favorable FOG-AC outcome six months from subthalamic neurostimulation implantation. Moreover, preoperatively reduced stride length in 'off' dopaminergic state pointed to favorable outcome on FOG postoperatively.

Discussion: These preliminary observations encourage us to develop a predictive model to stratify preoperative patients with FOG for subthalamic deep brain stimulation procedures. This is crucial given that FOG in many patients dominates self-perceived impairment of health-related quality of life.

If motor control gets out of hand: increasing task complexity triggers freezing in the upper limbs in patients with PD

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Patients with Parkinson's disease (PD) suffer from upper limb problems including sudden movement arrests. Although being a debilitating symptom, the best manner to assess freezing of the upper limbs (FOUL) is not clear yet. In the current study, 49 patients with PD (63.4 ± 9.3 years, H&Y 2.1 ± 0.4 , 16 with and 33 without freezing of gait (FOG), ON medication) and 10 age-matched controls (HC) performed a freezing-provoking writing task, requiring up- and downstroke writing movements at varying sizes in-between visual target zones indicating funnel-shapes on a touch-sensitive tablet.^[1] They performed five trials at their preferred speed, i.e. Normal Funnel Task (NFT) and five trials at maximum speed, i.e. Fast Funnel Task (FFT). Based on a combination of kinematic criteria and video analysis, 123 FOUL episodes were detected during FFT and 60 during NFT. The number of patients with FOUL, number of FOUL episodes and percent time frozen were significantly higher during FFT than NFT, and in PD than HC. Most FOUL episodes occurred during writing at small (51.6%) and decreasing size (36.3%). FOUL outcomes significantly correlated with the Montreal Cognitive Assessment and New Freezing of Gait Questionnaire. As FOUL is more prevalent under higher task demands and in patients with less cognitive reserve, these data offer support for the interference model^[2] that has previously been employed to provide insight in FOG and confirm the presupposed link between FOG and FOUL.^[3] As well, this study may provide a sensitive paradigm to assess FOUL in a laboratory or clinical setting.

References

- [1] E. Heremans, E. Nackaerts, G. Vervoort, S. Vercruysse, S. Broeder, C. Strouwen, S.P. Swinnen, A. Nieuwboer, *Amplitude manipulation evokes upper limb freezing during handwriting in patients with Parkinson's disease with freezing of gait*, PLoS One **2015**, 10(11):e0142874.
- [2] S.J. Lewis, R.A. Barker, *A pathophysiological model of freezing of gait in Parkinson's disease*, Parkinsonism Relat Disord **2009**, 15, 333-338.
- [3] A. Nieuwboer, S. Vercruysse, P. Feys, O. Levin, J. Spildooren, S.P. Swinnen, *Upper limb movement interruptions are correlated to freezing of gait in Parkinson's disease*, Eur J Neurosci **2009**, 29, 1422-1430.

Depressive symptoms may predict the future development of freezing of gait in patients with Parkinson's disease: findings from a 5-year prospective study

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Prospective studies describing the natural-history of freezing of gait (FOG) in Parkinson's disease (PD) are limited and it is not clear who are the subjects that will develop FOG as the disease progresses. We aimed to explore which symptoms contribute to the future development of FOG in non-freezers. Fifty seven patients without FOG at baseline were re-evaluated five years later. At both time-points, disease severity, gait, balance, cognitive function and non-motor symptoms were assessed. The new-FOG-questionnaire (NFOG-Q) was used to distinguish people who developed freezing 5 years later (FOG+) from non-freezers (FOG-). Multivariate binary logistic regression determined independent predictors of FOG. At follow-up, 26 subjects (46%) had FOG (NFOG-Q>0) while 31 participants remained non-freezers. At baseline, FOG+ and FOG- were similar ($p>0.10$) with respect to age, gender, disease duration, LEDD, and the MoCA scores. However, FOG+ had worse scores ($p<0.05$) on the Geriatric Depression Scale (GDS) (FOG+: 5.2 ± 3.7 ; FOG-: 2.4 ± 2.0), PDQ-39, NMS-questionnaire and the Berg Balance Scale. In binary logistic regression, GDS scores and motor UPDRS (off) were the only significant independent predictors of future FOG (GDS: OR=1.42, 95% CI:1.12-1.81; $p=0.004$, UPDRS: OR=1.07, 95% CI:1.01-1.13; $p=0.02$). Moreover, 80% of the subjects who had marked depressive symptoms at baseline (GDS ≥ 5) developed FOG within the 5 years follow-up. In contrast, only 27% with GDS < 5 developed FOG ($p<0.001$). Although FOG is typically considered a motor disturbance, non-motor features, especially depressive symptoms, apparently precede the development of FOG. This early marker may help clinicians to estimate a patient's risk of converting into a "freezer".

Are different aspects of postural impairments in PD who freeze mediated by similar SMA networks dysfunctions?

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Introduction: People with Parkinson's disease (PD) who freeze exhibit deficits in postural control, including poorer anticipatory postural adjustments (APA) prior to a voluntary step [1] and automatic postural responses (APR) to a backward Push&Release [2]. However, how PD-related neuropathology contributes to this poor performance is unknown. Previous findings showed a re-organization of functional communication within the right supplementary motor area (SMA) connectivity with the pedunculo-pontine nucleus (PPN) [3] in PD who freeze. The objective of this study was to investigate whether APAs and/or APRs are associated with the SMA-brainstem networks in PD with and without freezing of gait.

Methods: Twenty-four subjects (MDS-UPDRS-III: 45.3±15) with freezing and 24 without (MDS-UPDRS-III: 37±10.3) participated in the study. Behavioral outcome measures were: 1) Amplitude of lateral APA prior to a voluntary step [1], 2) Time to stabilize equilibrium (TS) after Push&Release. Functional connectivity between SMA (ant. & posterior) [4] and the following locomotor hubs: 1) subthalamic nucleus (STN) and 2) PPN, [3] was assessed, within each hemisphere. Associations between the behavioral measures and functional connectivity within (8) regions in brain were investigated using linear partial correlations controlled for disease duration.

Results: Freezers showed a significant positive association between amplitude of APA and right aSMA-PPN connectivity (Fig.1A) and a positive association between TS and left pSMA-STN (Fig.1B).

Conclusions: Only freezers showed a relationship between postural disorders and SMA-brainstem networks. Results suggest that the hyper-direct pathway between SMA-STN may relate to APRs whereas the SMA-PPN relates to APAs prior to voluntary step initiation.

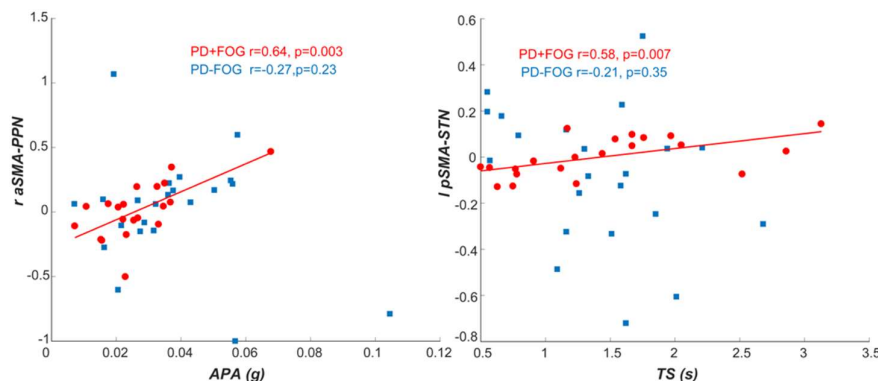


Figure 1: Linear partial correlation of A. APA before a step and right SMA-PPN, and B. Time to stabilize after a Push&Release and left SMA-STN.

References

- [1] C. Schlenstedt, M. Mancini, J. Nutt, A.P. Hiller, W. Maetzler, G. Deuschl, F. Horak, *Are Hypometric Anticipatory Postural Adjustments Contributing to Freezing of Gait in Parkinson's Disease?*, 2018, Front Aging Neurosci.
- [2] P. Carlson-Kuhta, M. El-Gohary, M. Mancini, F. Horak, J. Huisinga, *Quantifying postural stability differences in people with Parkinson's disease with and without freezing of gait, using body-worn sensors*, 2017, MDS 21st Int. Congress of Parkinson's Disease and Movement Disorders.

- [3] B. Fling, R. Cohen, M. Mancini, S. Carpenter, D. Fair, J. Nutt, F. Horak, *Functional Reorganization of the locomotor network in Parkinson patients with freezing of gait*, **2014**, PLoS One.
- [4] M. Glasser, S. Sotiropoulos, J. Wilson, T. Coalson, B. Fischl, J. Andersson, et al. *The minimal preprocessing pipelines for the Human Connectome Project*, **2013**, Neuroimage.

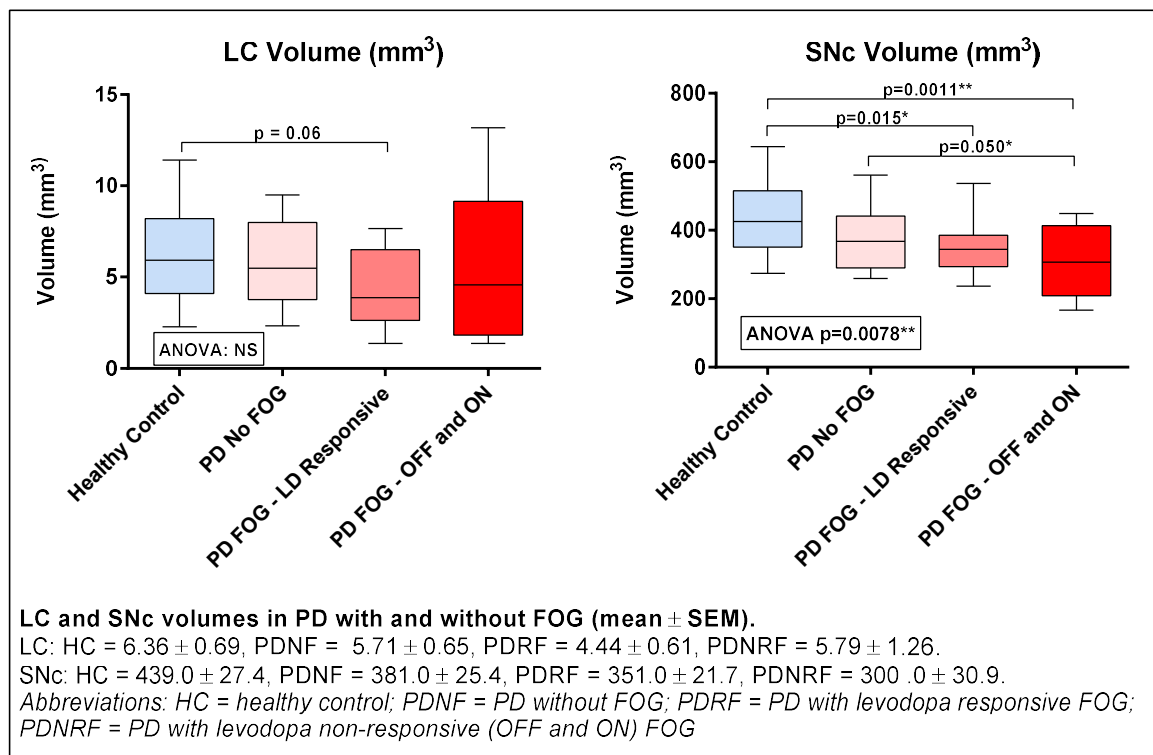
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Neuromelanin-sensitive MRI detects neurodegeneration in catecholamine nuclei in Parkinson's disease with freezing of gait

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Parkinson's disease (PD) causes progressive neurodegeneration in multiple neural systems and manifests a diverse range of phenotypic features. There is a lack of objective biomarkers for PD, and neuroimaging markers to detect and monitor features of neurodegeneration relevant to phenotype may be useful to improve clinical trial design. Both locus coeruleus (LC) and substantia nigra pars compacta (SNc) degenerate profoundly in PD and have been implicated in the pathophysiology of freezing of gait (FOG). We previously developed a novel neuromelanin-sensitive MRI (NM-MRI) method to determine LC and SNc volumes with automated image processing.[1] Here we apply this method to assess for differences in LC and SNc volumes in 19 healthy controls, 19 PD without FOG, 18 PD with levodopa responsive FOG and 11 PD with levodopa non-responsive FOG. Subjects were recruited from the Emory Movement Disorders Clinic, and PD diagnosis and FOG group were established by a movement disorders specialist using U.K. Brain Bank Criteria and FOG Questionnaire item 3 score of 2 or greater.[2, 3] NM-MRI was acquired using a Siemens Trio 3T MRI scanner, and LC and SNc volumes were determined using an explicit magnetization transfer contrast approach with demonstrated high reproducibility.[4] One-way analysis of variance was done to assess for differences in LC volumes and SNc volumes across the four groups, followed by group comparisons with false discovery rate correction.[5] Results are shown in the figure. We conclude that MRI measures of SNc and LC volume warrant further investigation as candidate neuroimaging markers for PD with FOG.



References:

- [1] Chen, X., et al., *Simultaneous imaging of locus coeruleus and substantia nigra with a quantitative neuromelanin MRI approach*. Magn Reson Imaging, **2014**. 32(10): p. 1301-1306.

- [2] Hughes, A., et al., *Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases*. J Neurol Neurosurg Psychiatry, , **1992**. 55(3): p. 181-184.
- [3] Giladi, N., et al., *Construction of freezing of gait questionnaire for patients with Parkinsonism*. Parkinsonism Relat Disord, **2000**. 6(3): p. 165-170.
- [4] Langle, J., et al., *Reproducibility of locus coeruleus and substantia nigra imaging with neuromelanin sensitive MRI*. MAGMA, **2017**. 30(2): p. 121-125.
- [5] Benjamini, Y., et al., *Controlling the false discovery rate in behavior genetics research*. Behav Brain Res, **2001**. 125(1-2): p. 279-84.

The Adjusted Auditory Stroop task to increase cognitive load in behavioral experiments in patients with Parkinson's disease

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Freezing of gait (FOG) can be elicited by increasing the cognitive load on persons with Parkinson's disease (PD) and FOG. In experimental behavioral studies investigating (freezing of) gait in PD, cognitive tasks are required to be auditory rather than visual, be independent of presbycusis, avoid interference with internal rhythm generation, and facilitate adding additional commands. We present the 'Adjusted Auditory Stroop task' (AAS) as a novel method suited to increase cognitive load in behavioral studies in persons with PD. In the AAS, congruent words ('man' spoken by a male voice, or 'woman' spoken by a female voice) signal participants to start or continue walking, while incongruent words (male voice saying 'woman' or female voice saying 'man') constitute stop cues. The AAS task is compared to the 'Random Numbers task' (RN), in which participants count how many times specific digits occur in a sequence of spoken, randomly ordered digits between 1 and 9. The influence of the AAS on gait parameters was measured in 20 healthy control (HC) subjects aged over 50 years and 20 persons with PD and FOG performing a simple gait task in the presence or absence of rhythmic visual cues. The AAS was compared to a condition with no additional cognitive load, and in HC additionally with the RN. Preliminary results show that both the AAS and RN influence gait parameters in HC.

Recuperation of slow walking in advanced fluctuating Parkinson's disease is associated with step/stride length improvement, rather than with cadence increase

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Previous research reported that the increment in cadence is more important than the increment in stride length in de novo PD. In this study, we aimed to investigate spatiotemporal gait features in advanced, fluctuating PD patients and to find out differences between on and off state. We studied 10 PD patients with motor fluctuation. All patients were investigated for baseline features, MMSE, UPDRS III, mHYS, NFOG-Q, gait analysis with GaitRite. Gait analysis and UPDRS III were done both in overnight levodopa off state and 200mg levodopa challenge state. Most of spatiotemporal gait parameters were significantly improved in ON state compared to OFF state except cadence and variability of stride length. Step and stride length showed negative correlation with UPDRS III after adjustment for ON/OFF state, which meant PD patients with severe motor symptoms showed shorter step and stride length (Step length - UPDRS III: adjusted correlation coefficient = -0.609, P = 0.020). Base of support and NFOG-Q total score showed negative correlation with adjustment for ON/OFF state, which meant PD patients with severe FOG showed narrower base of support. In this study, we found that improvement of step/stride length and swing/stance phase could be main features of levodopa responsive gait recovery in advanced PD patients who showed motor fluctuation. Further study is needed to investigate whether the compensatory mechanism of gait recovery is different between early stage and advanced stage of PD patients.

The ability of recognizing positive, negative and neutral facial expressions in Parkinson's disease is influenced by the presence of freezing of gait.

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Affective "Theory of Mind" (ToM) is the ability to represent own and others' emotional states and can be assessed by means of the "Reading the Mind in the Eyes test" (RMET).

A previous study showed that this ability is impaired in patients with Parkinson's disease (PD), particularly in patients with freezing of gait (FOG)¹.

We assessed, by means of RMET, whether the ability to recognize positive, negative and neutral emotional facial expressions was different between PD patients with or without FOG.

We evaluated ToM in 25 PD patients with FOG (FOG+), 28 PD patients without FOG (FOG-), and 35 age-matched healthy subjects (HS). Results confirmed that the ability to judge a person's mental state was impaired in PD patients, particularly in FOG+. Regarding the stimuli valence, HS recognized better positive compared to neutral and negative stimuli and neutral compared to negative stimuli. FOG- performed better in recognizing positive stimuli compared to neutral and negative ones; no differences emerged between neutral and negative stimuli. In FOG+ no differences emerged between the three categories of stimuli. Particularly FOG+ performance in recognizing positive and negative stimuli was significantly worse than HS and FOG- (positive: FOG+ vs HS: $p=0.001$, FOG+ vs FOG-: $p=0.045$; negative: FOG+ vs HS: $p=0.014$, FOG+ vs FOG-: $p=0.019$). FOG+ performed worse than HS also for neutral stimuli ($p=0.0001$). Our study showed that the ability to recognize positive facial expressions is preserved in PD patients without FOG. Differently, patients with FOG showed at RMET test a widespread emotional processing dysfunction.

References

[1] Raffo De Ferrari, G. Lagravinese, E. Pelosin, M. Pardini, C. Serrati, G. Abbruzzese, L. Avanzino. Freezing of gait and affective theory of mind in Parkinson disease. *Parkinsonism Relat Disord.* 2015 May;21(5):509-13. doi: 10.1016/j.parkreldis.2015.02.023. Epub 2015 Mar 4.

The transition between anticipatory postural adjustments and step execution is abnormal in Parkinson's disease with freezing of gait

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Freezing of gait (FOG) episodes are commonly evoked when individuals with Parkinson's disease (PD) attempt to initiate walking, turn, or avoid obstacles, suggesting that freezing is triggered during movement transitions. Gait initiation includes a transition from bipedal steady-state standing to single support for locomotion, which requires a coupling of anticipatory postural adjustments (APAs) with first step execution. We analyzed data from trials of self-initiated gait in individuals with (FOG+, n=11) and without FOG (FOG-, n=14). Similar to previous work, there were no significant differences in APAs between groups^[1-3]. Despite comparable APAs, the FOG+ group exhibited differences in the coupling of the APA and the first step. Step width in the FOG+ group was correlated with the magnitude of the lateral CoP shift ($p=0.016$), but not in the FOG- group. In contrast, first step length and speed were correlated with the lateral and second posterior shift in the CoP ($p<0.005$) in the FOG- group only. Abnormal coupling in the FOG+ group was associated with a significantly wider and less variable first step ($p<0.04$) that tended to be shorter ($p=0.067$). Additionally, freezing episodes captured during gait initiation were often preceded by a correct APA pattern followed by an abnormal first step execution characterized by: posterior shear forces generated under the stepping leg during unloading, a failed toe-off or short step, a simultaneous bilateral heel rise and festination of the legs (Fig. 1). These data demonstrate that FOG is associated with an impaired transition from the APA to first step execution.

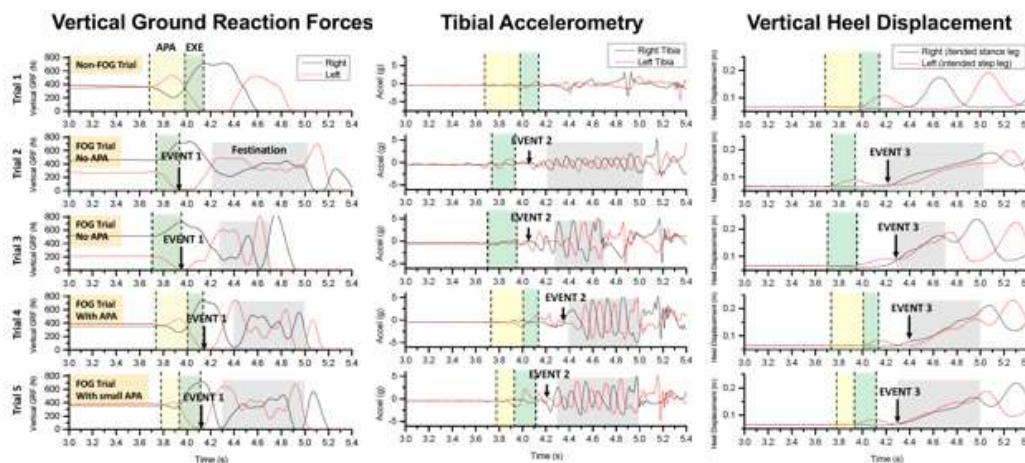


Figure 1. Examples of the vertical ground reaction forces, tibial accelerations and heel displacements associated with gait initiation trials without (top row) and with (bottom four rows) episodes of FOG.

References

- [1] Lu et al., *Effect of cue timing and modality on gait initiation in Parkinson's disease with freezing of gait*. Archives of Physical Medicine and Rehabilitation. **2017**. 98: 1291-9.
- [2] Alibiglou et al., *Subliminal gait initiation deficits in rapid eye movement behavior disorder: a harbinger of freezing of gait?* Movement Disorders. **2016**. 31(11): 1711-19.
- [3] Schlenstedt et al., *Are hypometric anticipatory postural adjustments contributing to freezing of gait in Parkinson's disease?* Frontiers in Aging Neuroscience. **2018**. 10: 1-9.

Rhythmic - auditory stimulation (RAS) with and without music feedback in gait training for people with Parkinson's disease

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Rhythmic – auditory stimulation (RAS) with functional music has been found to be effective in increasing step length and cadence in Parkinson's disease (PD) [1]. 15 patients with PD and clinically apparent slowness in walking were recruited (age: 66.5 years \pm 12.4; disease duration: 7.1 years \pm 4.6; Hoehn & Yahr 2.2 \pm 0.3). The randomized cross-over design included 3 different training modi: 1. RAS with functional music, 2. Musical feedback (MF), 3. no musical stimulation (NOM). Walking training consisted in 5 min of fast walking. Gait parameters were recorded with a sensor-based gait analyses system (RehaGait®, by Hasomed, Germany). For the MF condition, a software application created interactive music feedback that provided more complex orchestration in the music for every increase in stride length. Outcomes were compared with one-way repeated-measures ANOVAs. The main effect of the three modi on stride length was statistically significant, $F(2,28) = 6.89$, $p = .004$, $\eta^2 = .02$. Planned contrasts revealed that musical stimulations significantly increased stride length compared to NOM, $t(28) = 2.85$, $p = .008$, $\eta^2 = .22$. The mean difference between MF and RAS was also significant, $t(28) = 2.37$, $p = .025$, $\eta^2 = .17$. This pilot study provides first evidence for a clinical efficacy of sensor-based musical feedback in the gait therapy for patients with PD.

References

[1] M.H. Thaut, G.C. McIntosh, R.R. Rice, R.A. Miller, J. Rathbun, J.M. Brault, *Rhythmic auditory stimulation in gait training for Parkinson's disease patients* **1996**, *Mov Dis Mar*;11(2), p193-200.

Association between executive function and dual-task turning in people with Parkinson's Disease

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Executive function including initiation, cognitive flexibility and set-shifting is found to be impaired in people with Parkinson's Disease (PD). Gait disorder is exaggerated under dual-task condition but little is known about turning under dual-task conditions and its association with executive function. We aimed to examine the effect of cognitive dual-task on turning performance and the correlation between executive function and turning performance in people with PD. Twenty-six individuals with idiopathic PD completed two executive function tests: Mattis Dementia Rating Scale Initiation/Perseveration (MDRS-IP) and Wisconsin Card Sorting Test (WCST). Participants then completed an instrumented timed-up-and-go test in two conditions: 1) walking alone (iTUG) and with an added cognitive task (iTUG_cog) arranged in a random manner.

When compared with iTUG, there were significant reductions in the trunk range of motion and peak trunk velocity of all planes, turning duration and turn velocity in iTUG_cog condition ($p < 0.05$). WCST error scores were inversely correlated with trunk range of movement in horizontal plane and peak horizontal trunk velocity during iTUG and iTUG_cog ($r = -0.49$ - 0.51 , $p < 0.05$), and positively correlated with turn steps during iTUG_cog ($r = 0.41$, $p < 0.05$). MDRS-IP score was inversely correlated with turn step time during iTUG_cog ($r = -0.41$, $p < 0.05$). There was no association between dual-task cost of the turning parameters and executive function tests. To conclude, people with PD had poorer turning performance under cognitive dual-task condition than turning alone. PD individuals with poorer executive function was associated with more turn steps and increased turn time during cognitive-turn tasks.

The impact of freezing of gait in daily life: a wearable sensors approach

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Introduction: Although a growing number of studies focus on detecting freezing of gait (FoG) during daily activities [1], the impact of FoG and percentage of time spent freezing have not yet been reported. This pilot study investigated the impact of FoG, objectively measured with inertial sensors, on balance confidence and on mobility function during community-living in people with Parkinson's disease (PD).

Methods: Twenty-four subjects with PD (67 ± 7 years), 14 with FoG (new FoG Questionnaire (nFoG-Q) score ≥ 1 [2]), wore 3 inertial sensors attached to the feet and lumbar region for 7 days of continuous monitoring. Walking bouts, of at least 10s, were identified and features of FoG (derived by the high-low power frequency of the acceleration signals of the feet's sensors; Fig. 1A), quantity and quality [3] of mobility were extracted and averaged across the week.

Results: Time and variability of time spent freezing were associated with the nFoG-Q (Fig.1B), and to subject perception of balance (ABC: $r = -0.44$, $p < 0.05$). Results showed significant impairments in balance confidence and quality of mobility in freezers compared to non-freezers (variability of pitch angle $0.51^\circ \pm 0.05$ vs $0.95^\circ \pm 0.15$, average turning angle $97.2^\circ \pm 1.9$ vs $90.1^\circ \pm 1.2$). Gait speed ($0.85\text{m/s} \pm 0.04$ vs $0.77\text{m/s} \pm 0.06$) and quantity of mobility (# gait bouts/30min: 8.2 ± 0.9 vs 8.8 ± 0.7 , # turns/30min: 28 ± 5 vs 30 ± 6) were similar across groups.

Discussion: An objective measure of time spent freezing with wearable technology during community-living should relate to clinical, mobility and patient-related outcomes to be most useful for managing this distressing feature of mobility disability in PD.

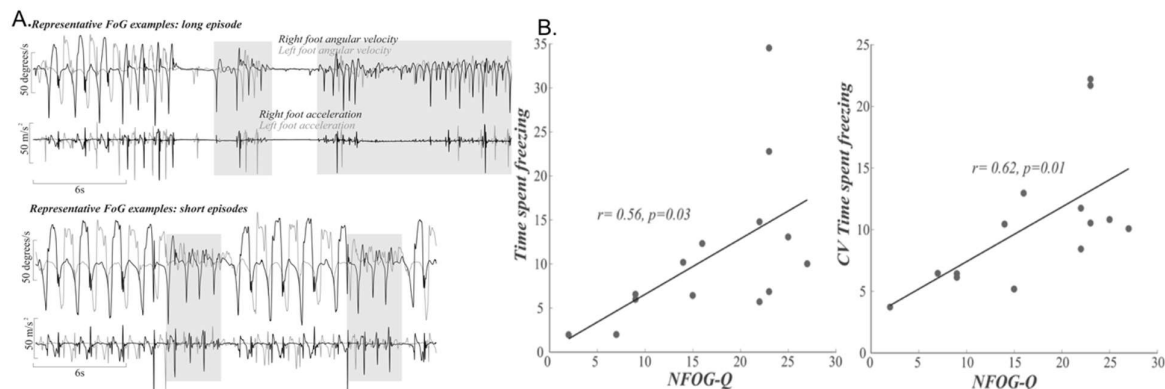


Figure 1. A) Representative examples of FoG during community-living recordings. B) Significant associations were found between the average/variability of the time spent freezing and the NFOG-Q.

References

- [1] L. Silva de Lima et al., *Freezing of gait and fall detection in Parkinson's disease using wearable sensors: a systematic review*, 2017, J Neurol, pp. 1642-1654.
- [2] A. Nieuwboer et al., *Reliability of the new freezing of gait questionnaire: agreement between patients with Parkinson's disease and their carers*, 2009, Gait Posture, pp. 459-63.
- [3] M. Mancini, A. Weiss, T. Herman, and J. M. Hausdorff, *Turn Around Freezing: Community-Living Turning Behavior in People with Parkinson's Disease*, 2018, Frontiers in Neurology.

Association of anxiety and depression with FOG subtype in Parkinson's disease

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BACKGROUND. Affective symptoms including depression and anxiety are reported to be associated with freezing of gait (FOG). **OBJECTIVE.** To determine whether anxiety or depression are associated with specific FOG subtypes (no freezing, "NOFOG" vs. levodopa-responsive freezing, "RFOG," vs. levodopa-unresponsive freezing, "URFOG") that may reflect different underlying pathophysiology.

METHODS. N=125 PD patients were assessed for depression and anxiety using a Structured Clinical Interview (SCID), the Beck Depression Inventory-II (BDI-II) and the Beck Anxiety Inventory (BAI). FOG subtype was determined with FOG-Q and self-report. Associations between the presence of RFOG or URFOG and 1) presence vs. absence of depression and anxiety on the SCID, and 2) severity of depression and anxiety on the BDI-II and BAI were determined with multinomial logistic regression. Analyses controlled for age, sex, education, MoCA score, UPDRS-III score, and PD disease duration.

RESULTS. Mean age and disease duration were 65±8 and 8±4 years. RFOG, URFOG, and depression/anxiety were present in 14%, 11%, and 18% of the sample, respectively. Current depression (SCID) was associated with significantly increased odds of RFOG (OR [95% CI]: 4.84 [1.24-19.00]; P=0.02). A similar, marginally-significant association was identified for current anxiety and RFOG (3.90 [0.92-16.50]; P=0.07). In contrast, associations between depression or anxiety and URFOG were not significant (OR: 0.91, depression; 1.05, anxiety). Similar patterns were identified for BDI-II and BAI.

DISCUSSION AND CONCLUSION. These results suggest that anxiety or depression may be differentially associated with levodopa-responsive FOG. Levodopa-unresponsive FOG may reflect distinct underlying pathophysiology with potentially less interaction with limbic cortico-basal ganglia pathways.

Table 1. Associations between depression and anxiety and FOG.

Variable	RFOG vs. NOFOG		URFOG vs. NOFOG	
	OR [95% CI]	P Value	OR [95% CI]	P Value
Current depression (SCID)	4.84 [1.24-19.00]*	0.02	0.91 [0.10-8.50]	0.93
Current anxiety (SCID)	3.90 [0.92-16.50]	0.07	1.05 [0.10-10.96]	0.97
BDI-II score ^a	1.04 [0.96-1.13]	0.37	1.06 [0.97-1.16]	0.18
BAI score ^b	1.03 [0.95-1.12]	0.44	1.02 [0.94-1.11]	0.68

^aN=111; ^bN=110. *P<0.05. Abbreviations: RFOG, levodopa-responsive freezing of gait; URFOG, levodopa-unresponsive freezing of gait; NOFOG, no freezing of gait; OR, odds ratio; SCID, structured clinical interview; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Inventory.

Directional Perception of Whole Body Perturbations is Impaired in People with Parkinson's Disease

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BACKGROUND AND OBJECTIVE: In addition to its primary motor features, Parkinson's disease (PD) may also be associated with sensory and perceptual impairments. We hypothesized that impaired perception of body motion could contribute to impaired balance and potentially falls. We tested 1) whether PD was associated with impaired directional perception of whole body perturbations, and, 2) whether these impairments were associated with impaired balance ability.

METHODS: We tested whole-body directional acuity of 18 PD patients from the PDFALLS study cohort (age 66 ± 7 y, 7 female, MDS-UPDRS-III 28 ± 12). We assessed balance ability with the Mini-BESTest,^[1] a common behavioral outcome measure. Directional acuity was measured using an adaptive testing paradigm in which participants reported whether they perceived pairs of approximately backward support-surface perturbations to be in the "same" or "different" direction (Figure 1A). Discrimination thresholds were identified separately for left and right deviations. Maximum threshold, minimum threshold, and threshold left/right asymmetry were determined and compared to existing data of $n=11$ healthy young adults (HYA). Linear regressions determined associations with clinical variables.

RESULTS: PD patients had poorer discrimination and larger thresholds than HYA, with statistically-significant increases in minimum threshold ($15 \pm 5^\circ$ vs. $10 \pm 3^\circ$, $p=0.015$, Figure 1B) and marginally-significant increases in maximum threshold ($p=0.07$) and threshold asymmetry ($p=0.16$). Statistically-significant correlations were identified between Mini-BESTest and all threshold values (minimum, $r=0.37$, $p=0.009$, Figure 1C; maximum, $r=0.50$, $p=0.002$; asymmetry, $r=0.52$, $p=0.026$).

DISCUSSION AND CONCLUSIONS: PD may be associated with deficits in directional perception of whole-body movements that may contribute to balance impairments and potentially falls.

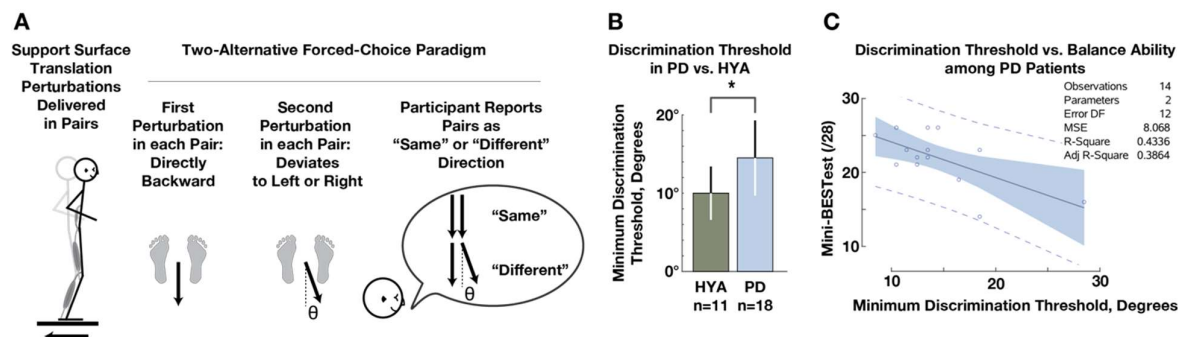


Figure 1: (A) Cartoon depicting translation perturbation paradigm. (B) Comparison of minimum discrimination threshold values identified in PD patients with historical control data from healthy young adults (HYA). * $P < 0.05$. (C) Comparison of Mini-BESTest scores and identified discrimination thresholds among PD patients.

References

[1] F. Franchignoni, F. Horak, M. Godi, A. Nardone, A. Giordano, *J Rehabil Med* **2010**, 42(4):323-31.

Effects of Rhythmic Vibratory cueing on gait in Parkinson's Disease

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Background: Improvements in gait have been observed in patients with basal ganglia movement disorders like Parkinson's Disease (PD) by providing visual cues, somatosensory cues, avoiding multi-tasking and also noted when walking on an uneven surface.

Research Question: We hypothesized that rhythmic vibratory cueing could produce improvements in gait as noted when walking on an uneven surface by engaging similar sensory afferent pathways; namely the dorsal columns and their cortical/subcortical projections.

Methods: Thirty patients with idiopathic PD walked with and without rhythmic vibratory cues. Vibratory cues were provided using an unstable multivibrator built into an ankle brace at a fixed frequency attached above the medial malleolus. Gait parameters measured included step length, stride length, time and cadence.

Results: Rhythmic vibratory cueing significantly improved the gait variables in PD patients, both on and off medication.

Significance: The results of this study provide a non-invasive intervention to improve gait in PD, which responds sub-optimally to the currently available symptomatic treatments. The encouraging results from this study merit further controlled studies evaluating the use of this gait rehabilitation technique to better understand its long-term efficacy. It also provides a potential alternative to more invasive interventions hypothesized to work via similar mechanisms, like spinal cord stimulation.



Figure 1. Stimulator as tied during evaluation and its contents

Freezing of gait is associated with changes in functional connectivity among motor, subcortical, but also higher order attention networks.

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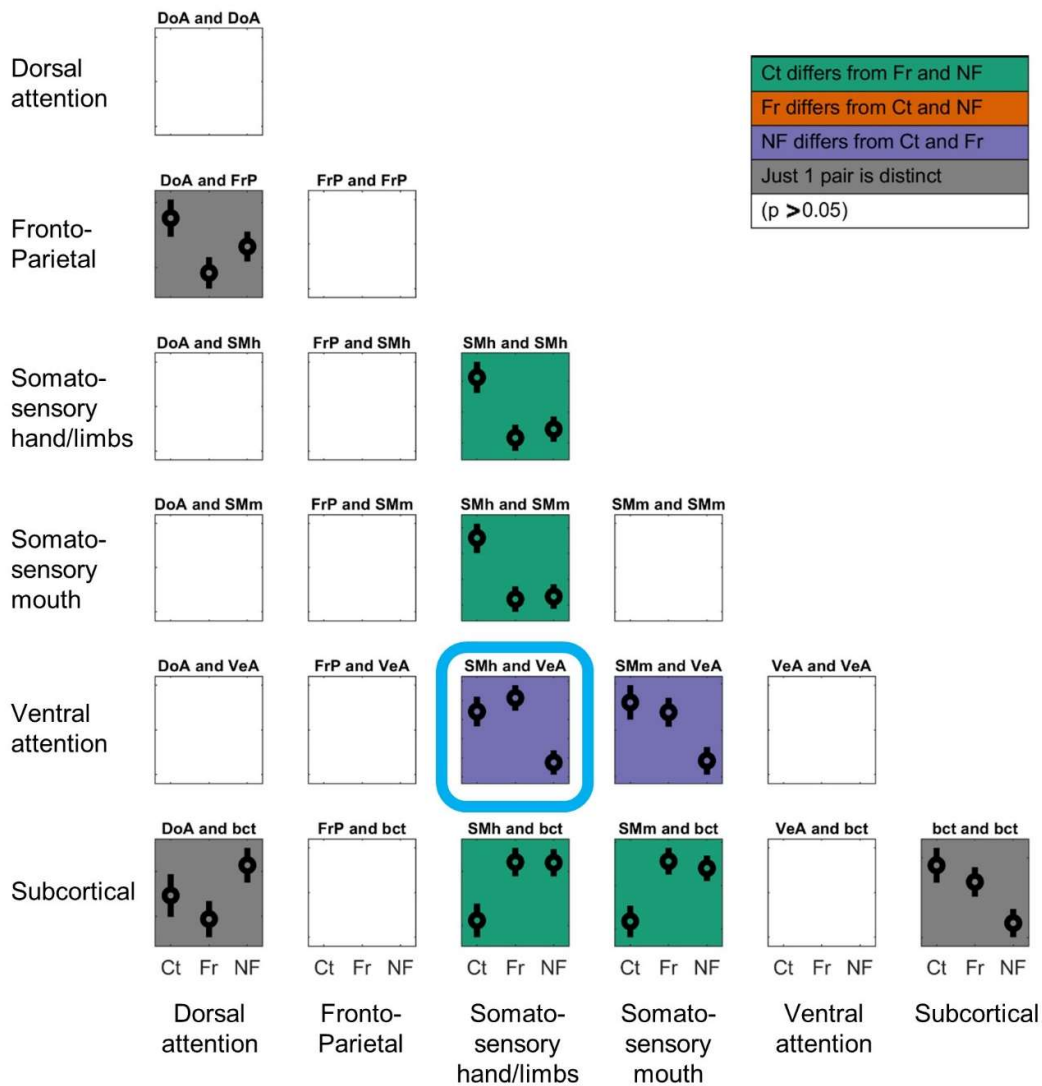
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Introduction: Freezing of gait (FOG) is a disorder where impaired mobility cannot be explained by peripheral or central motor deficits only, suggesting the involvement of non-sensorimotor, heteromodal-association cortices in this disorder ^[1]. In this study, we aimed to determine whether differences in brain network-network connectivity among motor and higher-order association areas is related to FOG in Parkinson's disease.

Methods: We used resting state functional MRI data from an ongoing study on aging and mobility from OHSU (41 controls (CT), 49 freezers (Fr) and 49 non-freezers (NF)). Data was processed using a slightly modified version of the workflow pipelines from the Human Connectome Project ^[2] plus in-house denoising methods ^[3]. Timecourses were strictly scrutinized for head movement. Surviving frames (5 minutes of data, frame displacement ≤ 0.3 mm) were used to characterize functional connectivity (FC) using a pre-defined set of Regions of Interest (ROIs) that also groups ROIs into functional networks, including motor and attention networks ^[4]. Differences in FC secondary to diagnosis (Ct, Fr, NF), functional network, and their interaction were identified using a repeated measures ANOVA.

Results: We found significant differences for diagnosis ($p < 0.0218$), networks ($p < 1e-6$) and their interaction ($p < 1e-6$). Post hoc analysis revealed strong differences in FC within sensorimotor and subcortical areas. The strongest differences, however, were found between the sensorimotor cortex and the ventral attention network, a network involved in multisensory integration, detecting unattended or unexpected stimuli and triggering shifts of attention ^[5-8].

Conclusion: These observations highlight the importance of handling sensory information for successful gait.



Caption 1: Differences in functional connectivity for Controls (Ct), freezers (Fr) and non-Freezers (NF) per functional network. Each box shows the distributions of functional connectivity (mean plus minus 1.75 standard error) for each group across functional networks. Significant differences (corrected for multiple comparisons) are highlighted according to the legend in the top-right box.

References

- [1] Nutt JG. *Higher-level gait disorders: An open frontier*. *Mov Disord*. **2013**;28: 1560–1565. doi:10.1002/mds.25673
- [2] Glasser MF, Sotiropoulos SN, Wilson JA, Coalson TS, Fischl B, Andersson JL, et al. *The minimal preprocessing pipelines for the Human Connectome Project*. *Neuroimage*. Elsevier Inc.; **2013**;80: 105–24.
- [3] Miranda-Domínguez Ó, Feczko E, Grayson DS, Walum H, Nigg JT, Fair DA. *Heritability of the human connectome: a connectotyping study*. *Netw Neurosci*. MIT Press; **2017**; 1–48.
- [4] Gordon EM, Laumann TO, Adeyemo B, Huckins JF, Kelley WM, Petersen SE. Generation and Evaluation of a Cortical Area Parcellation from Resting-State Correlations. *Cereb Cortex*. **2014**;26: 288–303
- [5] Downar J, Crawley AP, Mikulis DJ, Davis KD. A multimodal cortical network for the detection of changes in the sensory environment. *Nat Neurosci*. **2000**;3: 277–283
- [6] Vossel S, Geng JJ, Fink GR. *Dorsal and ventral attention systems: distinct neural circuits but collaborative roles*. *Neuroscientist*. 2014;20: 150–159.
- [7] Corbetta M, Shulman GL. *Control of goal-directed and stimulus-driven attention in the brain*. *Nat Rev Neurosci*. **2002**;3: 201–215.
- [8] Calvert GA, Thesen T. *Multisensory integration: Methodological approaches and emerging principles in the human brain*. *J Physiol Paris*. **2004**;98: 191–205.

The effect of cholinergic system innervation on turning characteristics in Parkinson disease patients with and without freezing of gait

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Objective: Freezing of gait (FOG) in Parkinson disease (PD) is often triggered by turning movements. Improved understanding of underlying pathophysiological mechanisms may lead to better treatment options. We investigated the effect of cholinergic system loss on turning characteristics in PD subjects.

Methods: PD patients *with* (PD-FOG+; N=15, 69.0±6.5 years old, 9.5±4.9 years duration, 3.0 median H&Y) and *without* FOG (PD-FOG-; N=50, 66.5±6.1 years old, 5.2±3.4 years duration, 2.5 median H&Y) and normal control (NC; N=26, 67.4±6.4 years old) subjects walked up straight to a cone, turned around it (180°) as closely as possible, and then walked away. Assessments were performed in dopaminergic “off” and “on” states. Brain cholinergic system integrity was assessed *in vivo* in 36 PD subjects using [¹⁸F]FEOBV PET.

Results: ANOVAs did not show differences in turning characteristics between PD-FOG- and NC subjects. PD-FOG+ subjects, however, made wider turns (F=12.3, p<0.001) and took longer to turn around the cone compared to PD-FOG- subjects (F=18.5, p<0.001). Repeated measures ANOVA did not show changes in turning characteristics for the PD-FOG- subjects after intake of dopaminergic medications; however, turning time became faster for PD-FOG+ subjects in the on state (F=4.2, p=0.021). Across all PD subjects, increased cuneus (r=-0.430, p=0.011) and precuneus (r=-0.356, p=0.039) cholinergic innervation was associated with shorter turning time when in the dopaminergic on state.

Conclusions: Under optimized dopaminergic treatment, turning time is inversely correlated with cholinergic innervation of the precuneus and cuneus. Adjunct cholinergic therapy may improve turning characteristics in PD and may potentially mitigate FOG symptoms.

Altered effective connectivity contributes to micrographia in patients with Parkinson's disease and freezing of gait

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Recently, it was shown that patients with Parkinson's disease (PD) and freezing of gait (FOG) can also experience freezing episodes during handwriting and present writing problems outside these episodes. So far, the neural networks underlying increased handwriting problems in subjects with FOG are unclear. This study used dynamic causal modeling of fMRI data to investigate neural network dynamics underlying freezing-related handwriting problems and how these networks changed in response to visual cues. Twenty-seven non-freezers and 10 freezers (all right-handed) performed a pre-writing task with and without visual cues in the scanner. The results showed that freezers and non-freezers were able to recruit networks involved in cued and uncued writing in a similar fashion. Whole group analysis also revealed a trend towards altered visuomotor integration in freezers. Next, we controlled for differences in disease severity between both patient groups using a sensitivity analysis. For this, a subgroup of 10 non-freezers matched for disease severity was selected by an independent researcher. This analysis further exposed significantly weaker coupling in mostly left hemispheric visuo-parietal, parietal-supplementary motor area, parietal-premotor, and premotor-M1 pathways in freezers compared to non-freezers, irrespective of cues. Correlation analyses revealed that these impairments in connectivity were related to writing amplitude and quality. Taken together, these findings show that freezers have reduced involvement of the supplementary motor area in the motor network, which explains the impaired writing amplitude regulation in this group. In addition, weaker supportive premotor connectivity, may have contributed to micrographia in freezers, a pattern that was independent of cueing.

Can Exercise Improve Functional Brain Connectivity in PD with Freezing of Gait?

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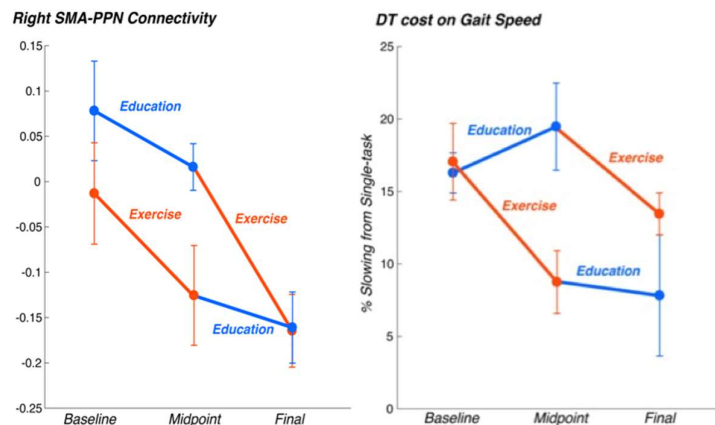
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Introduction: We have previously shown that the right medial frontal cortex functional connectivity with the mesencephalic locomotor region is hyperactive in subjects who have Parkinson's disease (PD) and FoG, with greater functional connectivity (rsfMRI) related to greater FoG [1]. We hypothesized that rehabilitation focused on reducing this top-down control by increasing automatic control of posture and gait with dual-task practice would help normalize brain connectivity.

Methods: In this cross-over design, 29 people with PD+FoG (age 68 ± 7 , MDS-UPDRS III: 47 ± 15) completed 6 weeks of Agility Boot Camp exercise and 6 weeks of Education, with the order of first intervention randomized. Outcome measures (Off medication) were: 1) rsfMRI: right SMA-PPN connectivity in 13 subjects, 2) dual-task cost on gait speed, and 3) an objective measure of FoG from inertial sensors [2]. A linear mixed-model was used with order of treatment and treatment as fixed factors, subjects as random factor, and baseline values as covariates.

Results: The right SMA-PPN connectivity showed a significant effect of exercise ($F=6.9$, $p=0.01$). Dual-task cost on gait speed showed a significant order effect ($F=7.6$, $p=0.009$). The FoG Ratio showed no treatment nor order effects, although PD with more severe FoG improved more after exercise ($r=-0.57$, $p=0.002$).

Conclusions: Functional connectivity in the right locomotor network can be improved with agility exercise. The order effect found in dual-task cost of gait speed was likely due to a carry-over improvement when exercise was first. These findings will help plan a larger intervention study to improve mobility in PD with FoG.



References

- [1] B. Fling, R. Cohen, M. Mancini, S. Carpenter, D. Fair, J. Nutt, F. Horak, *Functional Reorganization of the locomotor network in Parkinson patients with freezing of gait*, **2014**, PLoS One.
- [2] M. Mancini, K. Smulders, R. Cohen, F. Horak, N. Giladi, and J. Nutt, *The clinical significance of freezing while turning in Parkinson's disease*, **2017**, Neuroscience.

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Neural and kinematic features of different forward walking tasks in Parkinson's disease

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Objective: Investigate neural and kinematic features of different forward walking tasks in Parkinson's disease (PD).

Background: Freezing of gait (FOG) in PD is hard to elicit in the clinic because it is usually experienced in turns and among obstacles^[1,2], although gait asymmetry and arrhythmicity are greater in PD freezers (F) versus non-freezers (NF) in 'normal' walking.^[3,4] We developed a turning and barrier course (TBC) that elicits FOG.^[5] Here we demonstrate that the TBC highlights kinematic and neural differences between F and NF.

Methods: Beta band fluctuations (beta bursts) from synchronized STN Local Field Potentials and gait kinematics were recorded in 12 PD (6F) subjects, off-medication, off deep brain stimulation, who performed forward walking (FW), walking in ellipses and figures of eight through narrow openings, in a turning and barrier course (TBC).

Results: Gait was more arrhythmic for F and NF during TBC than FW ($p < 0.05$). F and NF had slower shank angular velocity during ellipses compared to FW ($p = 0.008$, $p < 0.001$), and in figure eights compared to ellipses ($p = 0.035$, $p < 0.001$). F exhibited slower shank angular velocity and longer beta burst durations during figures eights, followed by ellipses, followed by forward walking ($p < 0.05$). F were more arrhythmic and asymmetric in FW ($p < 0.05$) and more arrhythmic in figure eights ($p = 0.009$).

Conclusions: The TBC elicited more gait abnormalities in F and NF than FW; walking through narrow openings in figure eights highlighted pathological kinematic and neural features of FOG.

References

- [1] N. Giladi, D. McMahon, S. Przedborski, E. Flaster, S. Guillory, V. Kostic, S. Fahn, *Motor blocks in Parkinson's disease*. **1992**, *Neurology* 42(2), p333–339.
- [2] J. Schaafsma, Y. Balash, T. Gurevich, A. Bartels, J. Hausdorff, N. Giladi, *Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease*. **2003**, *Eur. J. Neurol.* 10(4), p391–398.
- [3] M. Plotnik, N. Giladi, Y. Balash, C. Peretz, J. Hausdorff, *Is freezing of gait in Parkinson's disease related to asymmetric motor function?* **2005**, *Ann. Neurol.* 57(5), p656–663.
- [4] M. Plotnik, J. Hausdorff. *The role of gait rhythmicity and bilateral coordination of stepping in the pathophysiology of freezing of gait in Parkinson's disease*. **2008**, *Mov. Disord.* 23, S444–450.
- [5] J. Syrkin-Nikolau, M.M. Koop, T. Prieto, C. Anidi, M.F. Afzal, A. Velisar, Z. Blumenfeld, T. Martin, M. Trager, H. Bronte-Stewart, *Subthalamic neural entropy is a feature of freezing of gait in freely moving people with Parkinson's disease*. **2017**, *Neurobiology of Disease* 108, p288–297.

A prospective study of falls in relation to freezing of gait and motor fluctuation in Parkinson's disease

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Introduction: Falls are a disabling feature of Parkinson's disease (PD). In this prospective study, we investigated: (1) in which motor state patients with PD fall most often; and (2) whether freezing of gait (FOG) and dyskinesias contribute to falls.

Methods: Patients with PD who had fallen at least once in the previous year and had wearing-off were recruited. During six months, patients complete a standardized fall report. We analyzed data regarding fall circumstances and motor state at the time of each first 10 falls.

Results: We included 36 patients with PD (34 freezers), with mean \pm SD age of 67.5 ± 6.3 years and disease duration of 12.4 ± 4.1 years. 50% had Hoehn & Yahr (HY) 2 at ON-state and 56% had a HY 4 at OFF. All 36 patients fell at least once during the follow-up period (total number of falls: 252; mean \pm SD: 19.03 ± 33.9). Falls at ON were 50% of the total falls, followed by Transition (30%) and OFF (20%). Overall, 69% of falls were related to FOG, 28% were unrelated to FOG and 3% were related to dyskinesia. There was a significant relationship between motor state and circumstances, showing that FOG-related falls happened mostly at OFF-state.

Conclusion: This study showed that patients with PD fall mostly at ON. Additionally, FOG is an important contributor to falls in patients with PD. This information may assist clinicians in optimizing medication to prevent further falls.

Freezing of Gait as an early herald sign of dementia in parkinsonism: a retrospective case-control study in PD and DLB patients.

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Freezing of gait (FoG) is a disabling and common disorder of late Parkinson's Disease (PD), yet it results more common in atypical parkinsonisms. A severe and early FoG is a red flag, suggesting an alternative diagnosis to PD. Recent studies indicate cognitive impairment as an independent risk factor contributing to the occurrence of FoG, but its exact pathophysiology is not well understood. Dementia with Lewy Bodies (DLB) is a parkinsonism characterized primarily by cognitive decline. Therefore, to support the cognitive model of FoG, we assessed its frequency in 19 patients with DLB compared to 19 control PD patients within 2 years from symptom onset and with at least 5 years follow-up. The two groups were matched by age and motor presentation at onset, disease severity and disease duration. Presence and severity of FoG was identified as those with a score of 1 or greater on item 14 of the Unified Parkinson's Disease Rating Scale (UPDRS III).

At T0 68,4% DLB and 10,5% PD patients experienced $FoG \geq 1$. The prevalence of FoG increased with disease progression (94,7% DLB and 47,3% PD subjects had $FoG \geq 1$ at T5). DLB showed also a more severe FoG ($FoG \geq 2$) than PD (21% at T0 and 52,6% vs 10,5% at T5) consistently with previous studies reporting FoG prevalence in DLB.

This is the first study looking specifically at FoG in DLB, identifying it as a frequent and early feature of DLB and emphasizing the crucial role of cognitive impairment in the occurrence of this mysterious phenomenon.

Using machine learning to automatically predict an incoming freezing episode

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External cues (e.g., rhythmic auditory stimulation) can help patients experiencing freezing of gait (FOG) to resume walking. Automatic freezing detection via wearable sensors has already been studied extensively [1]. However, systems for FOG detection identify a FOG episode only after it has already happened. In this study instead a new approach, for the prediction of incoming FOG (before it actually happens) is presented. Prediction of FOG might enable preventive cueing, reducing the likelihood that FOG will occur. The presented approach represents the evolution of our previous work [2]. It is based on machine learning and wearable sensors (see Figure 1). The CuPiD data set was used for our analyses. Eleven PD subjects were considered. Several features were extracted from movement signals (accelerations and angular velocities) recorded by inertial sensors. Several machine learning algorithms were developed and tested for FOG prediction. Results provide preliminary evidence on the feasibility of automatically predict FOG. Our solution provides a continuous score representing the risk (probability) of an incoming FOG. Different thresholds on this probability may be chosen to favor sensitivity to incoming FOG episodes or robustness against possible false positives (situations where the system would predict a FOG episode that was not going to happen). Technological issues faced during the study are also presented, together with suggestions for future studies regarding standardization and evaluation criteria.

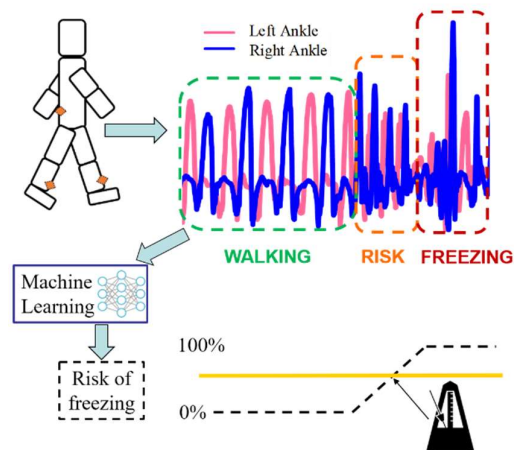


Figure 1: workflow of the proposed automatic solution.

References

- [1] A.L. Silva de Lima et al., *J Neurol* **2017**, p1642–54.
- [2] L. Palmerini et al., *Front Neurol* **2017**.

Validity study of wearable accelerometer for estimating gait in Parkinson's disease

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Background: Gait disturbance presenting as hypokinetic, short step gait and freezing of gait is major symptoms in Parkinson's disease (PD). Till now, it is difficult to measure gait disturbance objectively. Recently development of wearable device can enable quantification of gait. However, there were few reports of validation of wearable accelerometer for gait in PD. The purpose of our study is to evaluate the validity of tri-axial wearable accelerometer in gait performance in PD.

Methods: Fifty patients with PD were enrolled in our study. All participants were performed three-dimensional (3D) motion capture, while walking with three-axial accelerometer. We look for the peaks called a minimum that represents the initial contact of the leg and maxima that represents the final contact by using integration and differentiation. We evaluate the correlation between 3D motion capture and wearable accelerometer. We also calculate the mean error rate of wearable accelerometer compared to 3D motion capture.

Results: All gait parameters from wearable accelerometer were highly correlated with 3D motion capture. The mean error rate of wearable accelerometer for step time, stride time, stride length and walking speed were 3.87 ± 14.38 , 5.64 ± 4.41 , 4.46 ± 4.79 and 4.96 ± 4.83 .

Discussion: Our results proved that wearable accelerometer showed the highly valid tool for estimating gait in PD. Mean error rate of accelerometer revealed less than 10 percent based on 3D motion capture. Wearable accelerometer can enable long-term monitoring of gait and assessing gait state in free living environments.

Diagnostic accuracy of wearable accelerometer on ankle and knee for detecting freezing of gait in Parkinson's disease

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Background: Freezing of gait (FOG) is common symptom in late stage of Parkinson's disease (PD), which affects the falling and quality of life. The wearable accelerometer has been proposed to objective quantification of the gait status in PD. Despite many reports, best site of wearable device and accuracy has been showed inconsistent results. Our purpose here is to evaluate the sensitivity and specificity of wearable accelerometer in ankle and knee for detecting FOG episodes.

Method: We enrolled 43 patients with PD who showed FOG on routine clinical examination. The wearable three-axial accelerometer was applied to both knee and ankle. The participants were asked to walk, sit and stand freely with accelerometer for thirty minutes. We used frequency-based method which detects phase difference from accelerometer. We set the total number by video analysis as gold standard, and calculate the sensitivity and specificity of wearable accelerometer.

Results: Total number of FOG episode in 43 patients was 353. The sensitivity and specificity of accelerometer on ankle were 92.1% and 78.6%. The sensitivity and specificity of accelerometer on knee were 72.3% and 89.8%. In ROC analysis, the value of the AUC was 0.91 on ankle and 0.85 on knee.

Discussions: We found that accelerometer showed the acceptable sensitivity and specificity for detecting FOG. Accelerometer on ankle showed higher sensitivity than specificity and that of knee showed higher specificity than sensitivity. Our result support that ankle is the more sensitive site for detecting FOG in PD for screening test.

Anticipatory postural responses prior to protective steps are similar in people with PD who do and do not freeze

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Background: Protective stepping after a loss of balance is related to falls. Anticipatory postural adjustments (APAs) prior to protective stepping can negatively impact steps¹, have been shown to be altered in people with PD², and may be related to freezing of gait (FOG)³. However, whether people with PD and FOG (FOG+) exhibit altered APAs compared to people with PD and no FOG (FOG-) is unknown. Purpose: Determine the impact of freezing status on APAs prior to protective steps, thus improving our understanding of the link between FOG and APAs.

Methods: Twenty-eight people with PD (13 FOG+) experienced 50 support surface translations (25 forward, 25 backward, 15cm & 56cm/s, random order) resulting in protective steps. The size of medio-lateral center of pressure movements prior to the protective step (i.e. APAs), and the percentage of trials with an APA were calculated via force-plates. FOG status was assessed at the time of testing as well as 3.25(+/-0.43) years later. Participants without FOG at testing, but *with* FOG at follow-up were identified as “converters”.

Results: The size and percentage trials with an APA were similar in FOG+ and FOG-, even after excluding converters from the FOG- group ($p>0.27$ for all; Fig.1). Outcomes were similar between forward and backward protective stepping. No group by direction interactions were observed.

Conclusions: FOG+ and FOG- exhibited similarly sized APAs prior to protective stepping. In mild to moderate PD, an inability to couple APAs with stepping³, rather than inappropriately sized APAs^{4,5}, may be more important for FOG.

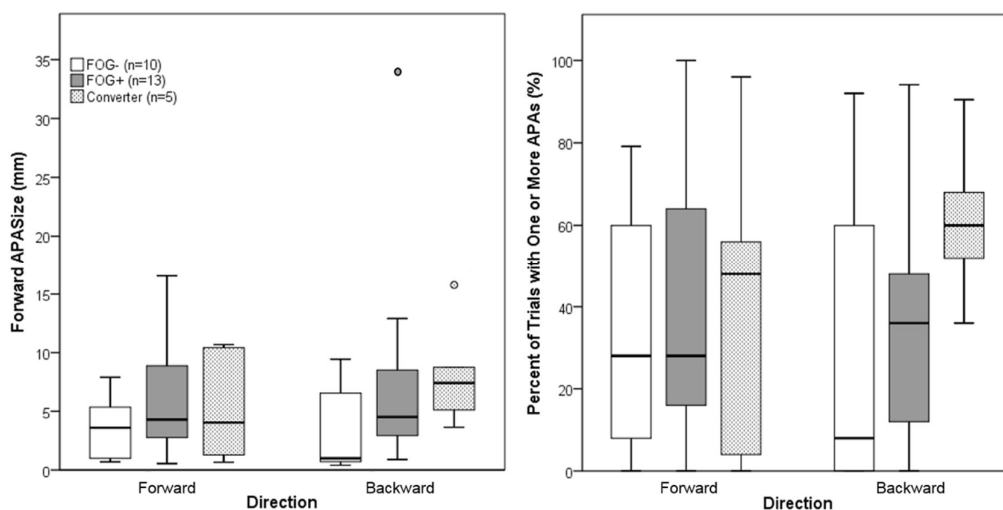


Figure 2: Box plots of APA size (A) and percentage of trials with (B) an APA during forward and backward protective stepping. Participants identifying as freezers at the time of testing (FOG+), those who did not (FOG-), and those who converted from FOG- to FOG+ over the 3.25 year follow up period (Converter) are shown.

References:

- [1] King LA, St. George R.J., Carlson-Kuhta, P., Nutt, J.G., Horak, F.B. (2010) Preparation for compensatory forward stepping in Parkinson's disease *APMR*. 91(9); 1332-8
- [2] Schlenstedt C, Mancini, M. Horak FB, Peterson DS, (2017). Anticipatory postural adjustment during self-initiated, cued, and compensatory stepping in healthy older adults and patients with Parkinson's Disease. *APMR*. 98(7) 1316-1324

- [3] Jacobs JV, Nutt JG, Carlson-Kuhta P, Stephens M, Horak FB. (2009) Knee trembling during freezing of gait represents multiple anticipatory postural adjustments *Exp Neurol.* 215(2) 334-41
- [4] Lu C, Amundsen Huffmaster L, Tuite PJ, Vachon JM, MacKinnon CD (2017) *APMR.* 98(12)91-9
- [5] Schlenstedt C, Mancini M, Nutt J, Hiller AP, Maetzler W, Dueschl G, Horak FB. (2018) *Frontiers.*

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Self-warning enables independent control of externally cued gait initiation in people with PD

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Externally generated cues improve the timing and magnitude of anticipatory postural adjustments (APAs) during gait initiation in people with Parkinson's disease (PD) and freezing of gait (FOG)^[1]. However, the efficacy of external-cueing is lost when individuals with PD and FOG self-trigger the external "go" cue^[2]. We examined if a self-warning cue, delivered before an external "go" cue, can be used to facilitate APA and step generation. Ten people with PD (9 male, 7 with FOG, tested OFF PD medications) initiated gait in seven conditions where the warning (W) and "go" (G) cues were absent (N), externally-triggered (E), or self-triggered (S) with a button press. Each self-triggered condition included a sham condition (s) where the tone was not provided with the button press. All cues were 80 dB tones. The conditions were: two self-initiated baselines (NWNG, EWNG), two self-triggered "go" conditions (EWSG, EWSG(s)), a traditional external cue condition (EWEG), and two self-triggered warning conditions (SWEG, SW(s)EG). Durations and peak amplitudes of ground reaction force (GRF) and center of pressure (COP) components were compared across conditions using repeated measures ANOVAs. Results demonstrated that peak APA magnitudes were significantly increased ($p < 0.05$) compared to baseline (NWNG) for all external "go" cue conditions (EWEG), including the self-warning conditions (SWEG, SW(s)EG). When the "go" cue was self-triggered (EWSG, EWSG(s)), no increase was observed. These findings demonstrate that a self-triggered warning cue, followed by an external "go" cue, allows for independent control of cueing to facilitate gait initiation in people with PD.

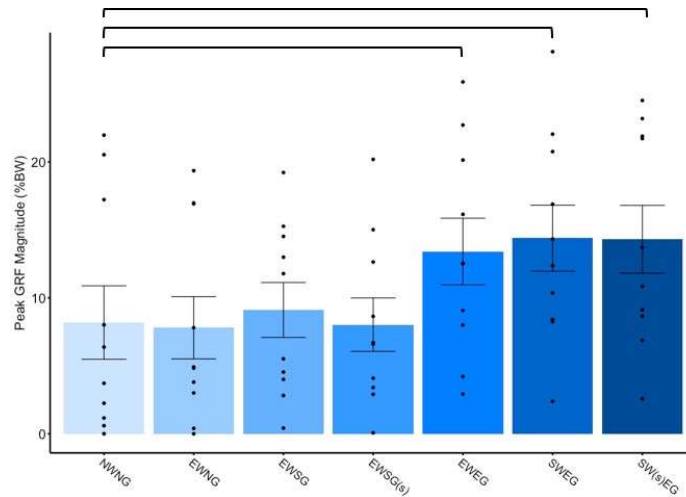


Figure 1: Average peak ground reaction force magnitude of the step leg loading by condition. Significant differences from baseline (NWNG) indicated with a horizontal bar ($p < 0.05$).

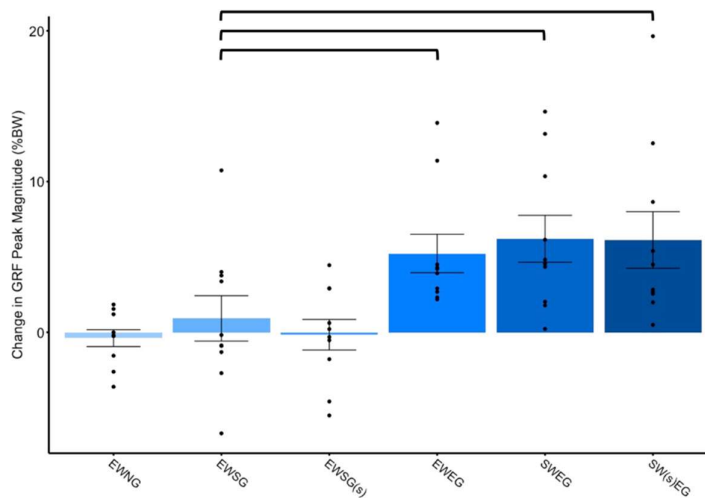


Figure 2: Average change in peak ground reaction force magnitude of loading the stepping leg from baseline (NWNG) by condition. Significant differences from the external-warning, self-go cue condition (EWSG) are indicated with a horizontal bar ($p < 0.05$).

References

- [1] Rogers, M.W., et al., *Postural preparation prior to stepping in patients with Parkinson's disease*. Journal of Neurophysiology, **2011**. 106(2): p. 915-24.
- [2] Petrucci, M.N., et al., *Effectiveness of self-triggered versus externally-triggered cueing for improving gait initiation in persons with Parkinson's disease and freezing of gait*. 45th Annual Society for Neuroscience, Chicago, IL, October 17-21, **2015**.

Action Observation and Motor Imagery in Parkinson's Disease patients with postural instability and gait disorders: functional brain plasticity during a motor task and a dual-task after six weeks of training

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Background and objective. To assess brain functional changes following action observation training (AOT) and motor imagery (MI) associated with exercises to improve balance and gait in PD patients. **Methods.** 11 PD patients were randomized into 2 groups: AOT-MI-group performed a 6-week training consisting of AOT-MI combined with practicing the observed/imagined actions; LANDSCAPE-group performed the same exercises combined with landscape-videos observation. Exercises were increasingly difficult up to include dual-task during complex gait and balance tasks. At baseline (T0) and week 6 (W6), patients underwent clinical assessments, including gait evaluation with stereophotogrammetry with and without a dual-task. Functional MRI (fMRI) tasks consisted of 1) foot anti-phase movements (motor-task) and 2) foot anti-phase movements while counting backwards by threes starting from 100 (dual-task).

Results. At W6, both groups showed a better gait and balance, but the AOT-MI group showed significant gait improvement relative to the LANDSCAPE group particularly during dual-task. During the Timed-Up-and-Go with and without dual-task, AOT-MI group showed an improvement of gait parameters also during the turn phase. AOT-MI group relative to LANDSCAPE group showed a decreased fMRI activity of the fronto-striatal network during the motor-task and of the fronto-temporal network during the dual-task. FMRI changes were correlated with clinical improvements.

Discussion and conclusion. A combined cognitive and motor physiotherapy approach can improve gait and balance and optimize brain plasticity not only during a motor-task but also a dual-task in PD, which is one of the most challenging situation for patients with postural instability.

Bilateral hyper-synchronization of frontal lobe activation in Parkinson's disease patients with freezing of gait during straight line walking and turning

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Background: Recent studies implicate altered frontal lobe function in freezing of gait (FOG) in the subset of Parkinson's disease (PD) patients with the symptom (PD+FOG). Association between level of synchronization in bilateral frontal lobe activity and FOG has not previously been assessed. The present study focuses on the contribution of interhemispheric cortical dynamics to FOG in PD. In view of evidence that FOG is associated with asymmetric and uncoordinated gait, we hypothesize that interhemispheric synchronization, as reflected in electroencephalography (EEG) signals, will differ in PD+FOG as compared with the subset of PD patients without FOG (PD-FOG), particularly over frontal lobes.

Methods: We examined 9 PD+FOG (age 66.3±7.6 y) and 6 PD-FOG (age 69.5±7.6 y) patients during: 1) one minute of quiet standing; 2) back-and-forth straight-line corridor walking which could be separated into turning and walking periods. EEG signals were recorded with a 32-electrode array (sampling rate: 2048 Hz). The Fourier-mode phase synchronization (PS) method was used to quantify synchronization in periodic cortical activation between (inter-hemispheric PS; IPS. PS ranges from 0 to 1, representing null to maximal synchronization, respectively. Theta (3.9-7.8 Hz), alpha (7.8-15.6 Hz), beta (15.6-31.2 Hz) and gamma (31.2-62.4) bands were evaluated.

Results: PD+FOG and PD-FOG groups were not significantly different in whole brain IPS across tasks (Mann-Whitney U : $p \geq .093$). Regarding homologous lobes' comparisons, significant group differences were found solely for the frontal lobes. Specifically, when analyzing only signals recorded over frontal lobes, IPS was elevated in the PD+FOG group as compared to the PD-FOG group in the beta band during turns (Mann-Whitney U : $p = .039$) and in the gamma band during turns and straight-line walking (Mann-Whitney U : $p = .020$ and $p = .034$, respectively). **Conclusions:** This study supports existent evidence of frontal lobe inter-hemispheric hyper-synchronization as a defining characteristic of PD patients suffering from FOG. The hyper-synchronization in the beta band in turning is consistent with earlier findings about the relation between elevated beta-band activity and motor deficits in PD, and with the fact that turning is a strong FOG-episode trigger. The temporal dynamics of this hyper-synchronization have yet to be elucidated; for example, future work should examine how levels of cortical synchronization vary prior to and during freezing episodes.

Transcranial direct current stimulation improves dual task performance in Parkinson's disease patients with freezing of gait

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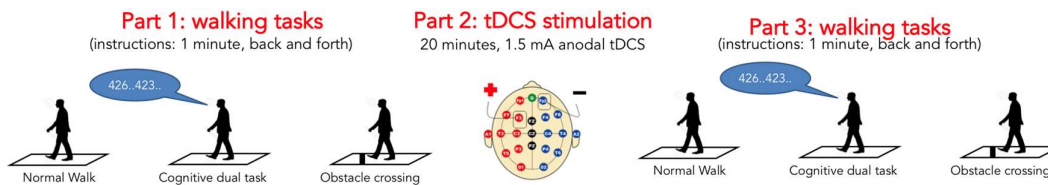
Background. Freezing of gait (FOG) is a frequent and disabling symptom of Parkinson's disease (PD) whose pathophysiological basis is still obscure. The use of transcranial direct current stimulation (tDCS), as a tool for improving motor and cognitive performances is increasing [1]. Nevertheless, the effect of tDCS on gait during dual task performance in PD patients with FOG has never been explored.

Aim. To determine the impact of a single session of tDCS on dual task in PD patients with FOG.

Methods. 10 PD patients with FOG (FOG+; mean age \pm SD, 70.1 \pm 3.84) and 10 PD patients without FOG (FOG-; mean age \pm SD, 72.8 \pm 6.87) were recruited for this study. In two separate days, subjects received real and sham stimulation with tDCS (20 minutes, 1.5 mA) targeting the left dorsolateral prefrontal cortex (dlPFC). Kinematic parameters were assessed via GAITRite instantly before and after tDCS, under different walking condition: (I) usual; (II) while performing a cognitive task; (III) while negotiating obstacles.

Results. After real tDCS, in PD FOG+, stride velocity, step length, step time and stance time improved during cognitive dual task condition and crossing velocity increased during obstacle negotiation. No effects were observed after sham tDCS. Finally, no changes were detected in PD FOG- group.

Discussion. Neuromodulation of the left dlPFC through tDCS seems to be an effective means to improve kinematic parameters during obstacle crossing and cognitive dual task, thus representing a possible adjunctive method to neurorehabilitation of PD patients with FOG.



Caption 1: Experimental protocol.

References

[1] J. Zhou, Y. Hao, Y. Wang, A. Jor'dan, A. Pascual-Leone, J. Zhang, J. Fang, B. Manor. Transcranial direct current stimulation reduces the cost of performing a cognitive task on gait and postural control. *Eur J Neurosci*. 2014; 39(8):1343-1348. doi:10.1111/ejn.12492.

Development and Initial Validation of New Methods for Quantifying Freezing of Gait among Patients with Parkinson's Disease

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One approach for evaluating FOG is a performance-based clinical test (i.e., gait initiation, turning 360° clockwise and counter-clockwise, doorway passing, and turning 180°; under 3 conditions: single, dual motor, and dual motor with cognitive loading ^[1]). FOG severity is rated based on the observed frequency. To enhance the ability to automatically quantify FOG severity, we developed and validated a new objective method using multiple wearable sensors and a paired algorithm for segmenting and evaluating each part of this FOG-provoking test. Two groups of patients with PD were examined while wearing 3 inertial sensors (lower back and above each ankle): 1) 18 PD patients with FOG and 11 patients without FOG performed the test "on" medications; and 2) 14 different PD patients with FOG performed the test "on" and "off" medications. Compared to video-analyses, the algorithm showed excellent reliability and correlations (ICC (3,1) >0.9; r > 0.97, p < 0.001) for both test and 360° turn durations. Algorithm-derived total test duration was differentially related to the difficulty of the test condition (40.55±15.1 sec vs. 45.43±19.44 sec vs. 73.73±52.50 sec; p < 0.001) Turn duration and smoothness of movement were different among patients with and without FOG across all three conditions of the test (p < 0.05). Comparing "on" vs. "off", the clinical test score in the most challenging condition was only marginally different (p = 0.057). In contrast, algorithm-derived metrics changed significantly (p < 0.05) in "on" vs. "off" in all three test conditions (e.g., see Figure 1). These findings suggest that automatic quantification could potentially improve the objective assessment of FOG.

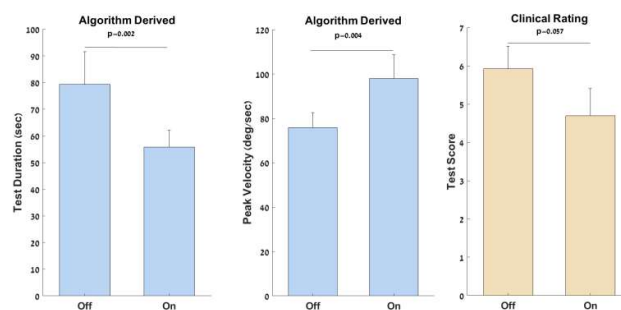


Figure 1: Example of the effects of anti-parkinsonian medications on two of the instrumented outcomes (blue bars) and the conventional clinical score in the most difficult condition (3). Note that a significant "on" vs. "off" effect was only observed for the instrumented scores.

References

[1] K. Ziegler, F. Schroeteler, A.O. Ceballos-Baumann, U.M.Fietzek, *A New Rating Instrument to Assess Festination and Freezing Gait in Parkinsonian Patients*. 2010. *Mov Disord*, 25, 1012-1018.

Surrogate Markers for Freezing of Gait Severity

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Background: A major barrier to the development of effective therapies for FOG is the lack of validated objective outcome measures. Since FOG is episodic and variable, a surrogate marker of FOG severity is an ideal outcome measure.

Methods: We recruited 17 Parkinson's disease (PD) subjects without FOG, and 16 subjects with PD and dopa-responsive FOG. Gait analysis was performed ON and OFF dopaminergic drugs, +/- dual task. FOG severity groups were defined as: severe (FOG-OFF), mild (FOG-ON) and PD-control.

Results: The total-UPDRS and FOG score were: PD-control group 24.9 and 0, FOG-ON 24.58 and 0.85, FOG-OFF 41.25 and 2.38. Overall the dual task condition improved the ability of each marker to differentiate between FOG severity groups. Turn duration was the only marker that was able to differentiate between all severity groups (control vs OFF $p=.027$, control vs. ON $p=.045$, ON vs OFF $p=.06$); area under the ROC curve (control vs OFF .87, control vs. ON .71, ON vs OFF .75). Step length variability (CV) in the dual task condition was superior at differentiating between control and ON. Multiple parameters showed responsiveness at differentiating between the ON and OFF groups, however dual task interference variables were not as responsive.

Conclusions: Dual task turn duration was superior at differentiating FOG severity groups. Dual task step length CV appeared to be most specific for FOG as it differentiated between similar groups with and without FOG. Further analysis of this data set may lead to validation of a surrogate marker of FOG severity.

Pedunculo pontine nucleus functional connectivity with cortex is increased in Parkinson's disease patients with Freezing of Gait

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Introduction: There are currently no effective therapies for Parkinson disease (PD) patients with freezing of gait (FoG). However, neuroimaging biomarkers for FoG may help inform novel brain stimulation targets and treatment strategies. In particular, structural and functional connectivity of the pedunculo pontine nucleus (PPN) and cortical regions are disrupted in patients with FoG. While previous studies have restricted their connectivity analysis to specific PPN connections and small sample sizes, we performed a seed (PPN) to voxel connectivity analysis in a large sample of PD freezers and non-freezers.

Methods: Resting state functional magnetic resonance imaging (RS-fMRI) data was collected from 32 Parkinson patients with FoG and 26 PD patients without FoG. Seed-based functional connectivity was used to compare the groups (CONN toolbox (v17, seed (left and right PPN) to voxel approach, FWE corrected, $p < 0.05$).

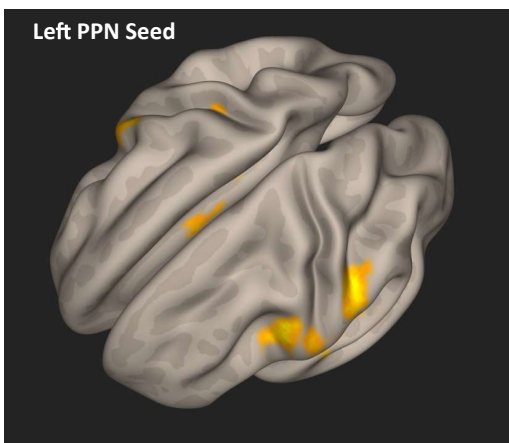


Figure 1: Regions with greater connectivity in PD FoG patients.

Results: PD patients with FoG had significantly higher connectivity between the left PPN and a network of regions including the primary motor cortex, inferior frontal gyrus, anterior cingulate and insular cortex. These FoG patients had significantly lower connectivity between the left PPN and the cerebellum and frontal pole.

Conclusions: These data support and extend previous studies that have demonstrated FOG patients have greater PPN functional connectivity than PD patients without FOG. Whereas previous studies have focused on regions involved with motor execution, our results indicate FoG patients have strengthened PPN coupling with regions typically associated with cognitive control. These results add to an emerging literature that indicates FOG is related to increased reliance of cortical control during gait.

Automatic auditory cues system for Parkinson's disease

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⁵ *Maspark project: 436/C/2014 - Freezing In Parkinson's Disease: Improving Quality Of Life With An Automatic Control System. Fundació Marató de TV3 Grant 201404.31.32.*

Among Parkinson's disease (PD) symptoms, freezing of gait (FOG) is one of the most disabling. This paper presents a new Mobility Aid System during daily living, through rhythmic auditory cueing automatic system.

METHODS: We enrolled Parkinson's disease patients with moderate to severe disease and motor symptoms without dementia or auditory deficit. All patients signed informed consent. During eight days the parameters of the patient's gait were monitored through a sensor in their activities of daily life. During half of those days (4 and 4 in random order) the mobility aid system was activated. After a wash-out period a subgroup of patients wear the mobility aid system for 30 days at their whim at home.

RESULTS: In the first pilot study, fourteen patients were included, 7 (50%) of them with FOG. When we compared the gait pattern with or without the mobility aid system, we found that when the mobility aid system was activated, the speed of the step was less variable ($p = 0.019$). No other statistical significance was found. In the subgroup ($n=7$ (71% with FOG),) that carried the mobility aid system for 30 days, a significant improvement was observed in the motor subscale of the quality of life (QoL) PDQ-39 ($p = .043$).

CONCLUSIONS: The mobility aid system is a device based on information and communication technology that includes a wide range of functionalities to offer comprehensive and customizable care, and which seems to alleviate the impact of PD gait disorders on the QoL of people with PD.

Project Holocue: on-demand and assist-as-needed patient-tailored cues to alleviate and prevent freezing of gait

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Freezing of gait (FOG) is one of the most disabling motor symptoms of Parkinson's disease and a major cause of falls. With Holocue, we aim to alleviate and ultimately prevent FOG by presenting patient-tailored cues at the right times and locations. To this end, we have built the Holocue-application for Microsoft HoloLens (Fig. 1a), an untethered non-occluding headset with a holographic display unit. HoloLens is unrivaled for its inside-out environmental tracking, providing information about a person's physical surrounding (Fig. 1b). This allows for blending holographic visual content with one's environment, called mixed reality, such as 3D cues on the floor to step over (Fig. 1c). We have currently implemented on-demand cues in Holocue, based on voice commands, which may help alleviate FOG episodes after they occurred. In a future scenario, we may even be able to prevent FOG with Holocue by detecting where and when FOG could occur. Although challenging, preventive cueing seems technologically feasible considering that the HoloLens contains very rich environmental and movement data, affording an identification of freeze-prone locations ('where', like a narrow passage; Fig. 1b) and/or prediction of FOG ('when', like predictive pre-FOG changes in movement characteristics), respectively. If successful, Holocue has the potential to radically change the prevention of FOG by automatically presenting patient-tailored cues at the right times and locations (before FOG occurs). If not successful, the developed routine to collect both environmental and movement data at least facilitates basic research aimed at better understanding the causes and circumstances of FOG in real-life settings.



Figure 1. Principle investigator wearing the HoloLens (panel A). In panel B, a first-person's view of the 3D triangulation mapping of the physical surrounding is shown, with clear differences between a corridor with fire-doors being fully opened (inset) or semi-closed (main picture), with the latter potentially being an identifiable freeze-prone location. In panels C, intelligent 3D mixed-reality horizontal bars are depicted, again seen through HoloLens, for a straight path (top) and a curved path (bottom), as dynamically controlled by the heading direction. In panels D, 3D (stair illusion, top) and 2D (stepping stones, bottom) mixed-reality visual cues are depicted, as seen through HoloLens, which are anchored to the ground.

Investigating the therapeutic and transcortical effects of spinal cord stimulation for gait dysfunction in Parkinson's disease and cortical-basal degeneration patients

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Benefits of dopaminergic therapy and deep brain stimulation are limited and unpredictable for axial symptoms in Parkinson disease (PD).^[1] Spinal cord stimulation (SCS) may be a new therapeutic approach for PD^[2,3] and parkinsonian syndromes, such as cortical-basal degeneration (CBD), however the mechanism is unclear.

The hypothesis is SCS reduces freezing of gait (FOG) episodes and improves gait measures known to be affected in parkinsonian syndromes by modulating transcortical circuits that play a key role in the pathophysiology of gait disorders over a 12-month period.

Three PD and two CBD patients with significant gait dysfunction and FOG underwent mid-thoracic SCS; an additional 15 PD patients are being recruited. Nine settings (200-400 μ s/30-130 Hz) at suprathreshold intensity were tested in the first month post-SCS surgery. Patients completed ambulatory walking tasks over a Protokinetics Zeno Walkway that measured spatiotemporal gait parameters and FOG detection using foot pressures were analyzed to determine which SCS setting induced the best motor response compared to pre-SCS. Patients utilized their best setting at-home; gait and cortical excitability effects of SCS using paired-pulse transcranial magnetic stimulation were measured at 3-, 6- and 12-months of SCS use.

Preliminary results demonstrate that 300 μ s/60Hz elicited a mean 30% improvement in gait measures and FOG elimination in the first month for PD patients. Significant improvements in gait, bradykinesia, posture and elimination of foot drag in the CBD patient was established at 3-months. Changes in transcortical excitability were observed at 3-months in both populations.

The therapeutic potential of SCS can be optimized to each patient's characteristics.

References

- [1] EM. de Andrade, MG. Ghilardi, RG. Cury, et al. *Spinal cord stimulation for Parkinson's disease: a systematic review*. **2016**.
- [2] O. Samotus, A. Parrent, M. Jog, *Spinal cord stimulation therapy for gait dysfunction in advanced Parkinson disease patients*. **2017**.
- [3] CP. Souza, C. Hamani, CO. Souza, et al. *Spinal cord stimulation improves gait in Parkinson's disease patients previously treated with DBS*. **2016**.

Different patterns of brain activity during lower limb movements in Parkinson's disease patients with and without freezing of gait

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Background and objective. To date, few studies investigated task-based fMRI alterations underlying gait difficulties in Parkinson's disease (PD) patients with FoG (PD-FoG). The aim of the study is to assess brain fMRI activity during a feet movement task in PD-FoG patients, PD patients without FoG (PD-noFoG) and healthy controls.

Methods. 10 PD-noFoG, 17 PD-FoG patients and 18 matched healthy controls were recruited. PD-FoG were divided into 9 mild and 8 moderate PD-FoG according to the median NFOG-Q value. Patients underwent motor (Timed-Up-and-Go test, 10-meters-walking test, UPDRSIII) and neuropsychological evaluations assessing executive-attentive, visuo-spatial and memory domains. Both patients and controls performed fMRI task consisting of alternate feet dorsal/plantar flexion according to an auditory stimulus of 0.5 Hz.

Results. PD patients groups were similar for all motor variables except for the presence of FoG. PD-FoG patients performed worse in executive-attentive, visuo-spatial and memory functions relative to controls. fMRI results showed decreased activity in sensorimotor areas in PD-FoG and PD-noFoG patients relative to controls; PD-noFoG patients showed an increased activation of frontal-striatal network while PD-FoG subjects had an increased parieto-occipital and cerebellar cortices recruitment. Comparing patient groups, PD-FoG showed a decreased basal ganglia activity relative to PD-noFoG. Analysing PD-FoG subgroups, mild PD-FoG subjects revealed an increased fronto-parietal activation relative to moderate PD-FoG patients.

Discussion and conclusion. This study revealed the presence of two different patterns of brain activity during feet movements in PD-FoG and PD-noFoG patients, suggesting a compensatory role of parieto-occipital network to overcome the fronto-striatal failure in PD-FoG subjects.

Clinical trial protocol: Restitution of oral transport, penetration and aspiration with nigral stimulation in Parkinson's disease?

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Objective: In this randomized controlled clinical trial, we aim to characterize the differential effect of subthalamic nucleus (STN) or subthalamic nucleus and substantia nigra pars reticulata (STN+SNr) deep brain stimulation (DBS) on dysphagia in Parkinson's disease (PD) as primary interest.

Background: Dysphagia is a frequent symptom in late-stage PD and highly associates with mortality and quality of life. It represents an urgent unaddressed therapeutic need as conventional treatments (dopaminergic medication, STN-DBS) have limited effect on dysphagia. Attempts have been made to modulate non-dopaminergic pathways for resistant symptoms in PD^[1]. As such, the SNr may modulate brainstem activity via its monosynaptic projections to the superior colliculus (SC) and the pedunculopontine nucleus (PPN). There is evidence that swallowing associates to neuronal integration upon the SNr-SC pathway^[2].

Methods: In this double-blind randomized controlled study, we aim to investigate 20 patients with idiopathic PD with disease duration of ≥ 5 years, DBS ≥ 6 months and clinical dysphagia with a penetration-aspiration scale (PAS) ≥ 3 . First, we test the effect of StimOff, STNmono, and SNrmono on swallowing. The active treatment starts with a baseline assessment. Then, we will randomize patients to either 'standard-STN' or 'STN+SNr' for eight weeks. The primary endpoint hypothesizes on a two-point improvement on the PAS.

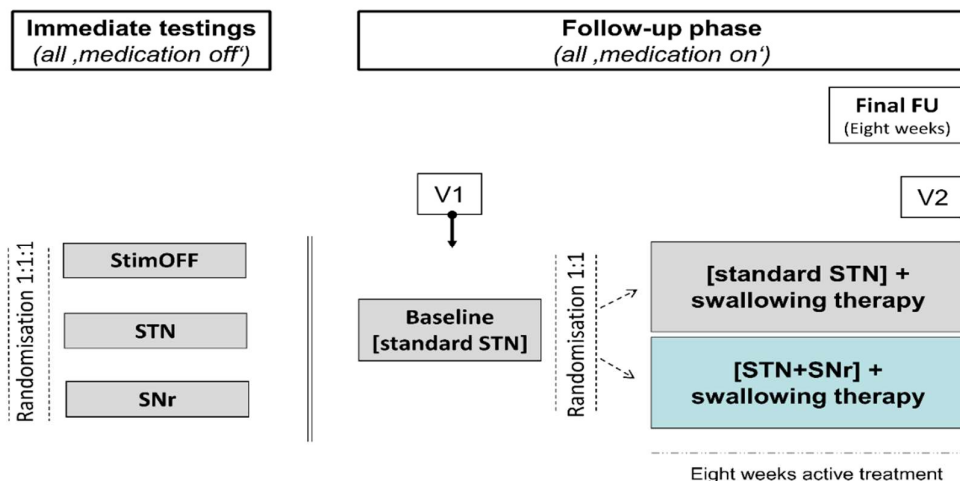


Figure 1: Study design with the two parts 'Immediate testing' and 'Follow-up phase'

A sample size of 10 per group will have 81% power to reject the null hypothesis ($H_0: p=0.5$ vs $H_1: p \leq 0.17$) that an observation in Experimental Group (STN+SNr) is less than in Standard Group (standard-STN) ($p < 0.05$).

Results: The clinical trial is currently active.

References:

- [1] Weiss D, Walach M, Meisner C, Fritz M, Scholten M, Breit S, et al. Nigral stimulation for resistant axial motor impairment in Parkinson's disease? A randomized controlled trial. *Brain*. 2013

[2] Rossi MA, Li HE, Lu D, Kim IH, Bartholomew RA, Gaidis E, et al. *A GABAergic nigrotectal pathway for coordination of drinking behavior.* Nat Neurosci. **2016**

Cortical signatures of repetitive finger movement and transition to freezing in upper limb movement in patients with Parkinson's disease

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Introduction: Freezing phenomena in Parkinson's disease (PD) constitute an important and largely unaddressed therapeutic need. The cortical electrophysiological signature of freezing phenomena is largely unknown. We hypothesize that the event-related desynchronization (ERD) and event-related synchronization (ERS) observed during regular fingertapping ^[1] deteriorate in the transition period between regular tapping and freezing.

Methods: We tested 14 patients with idiopathic PD with deep brain stimulation of the subthalamic nucleus (STN-DBS) and 13 age- and gender-matched healthy controls (HC) during biomechanically registered self-paced repetitive tapping of the right index finger. We applied time-frequency analysis to determine the cortical activity during tapping and freezing episodes. In particular, we focused on cortical ERD/ERS patterns of the individually-determined responsive beta frequency band.

Results: In preliminary analysis, we observe beta band modulation preceding the finger taps in terms of ERD/ERS. Beta band modulation is attenuated in the transition period and during freezing itself. Further, we investigate if the impairment in cortical beta band amplitude modulation in PD can be used as robust feature in order to predict freezing events of individual patients and on single trial level.

Conclusion: Our preliminary findings support that pathological attenuation of cortical beta band modulation in PD may provide a useful surrogate in order to predict freezing of upper limb movement.

References

[1] Stegemöller EL, Allen DP, Simuni T, MacKinnon CD. *Altered premotor cortical oscillations during repetitive movement in persons with Parkinson's disease*. Behav. Brain Res. **2017**; 317: 141–146.

The Minimal Clinically Relevant Change of the FOG-Score

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Despite the tremendous advances in the field of FOG research, the clinical assessment of FOG remains a challenge. Previously, we developed an evaluation instrument, that recently received a limited recommendation from the MDS scale committee, i.e. the FOG-score.^[1,2] Main critique point was the lack of responsiveness data. Here, we present data on the minimal clinically relevant change (MCRC).

We obtained ethical approval from the TUM/EC. Patients were evaluated before and 30 minutes after taking a regular levodopa dose according to their individual regime by means of direct and post-hoc video assessment. Additionally, both patient and expert rater assessed the change in FOG on a 7-step Likert-typed scale [-3;+3]. The MCRC was calculated using the ROC approach with the expert's rater evaluation as event value (rating of >0).

40 patients (29 male/11female) were recruited, 36 were able to complete all tasks. Mean Hoehn and Yahr stage (OFF) was 3. Patients scored an average of 11 points on the FOG-Score. Mean Change in FOG-Score was 4.5. The MCRC was calculated as a change of 2 points (sensitivity 0.7; specificity 0.93; PPV 0.78; NPV 0.89), see Figure 1.

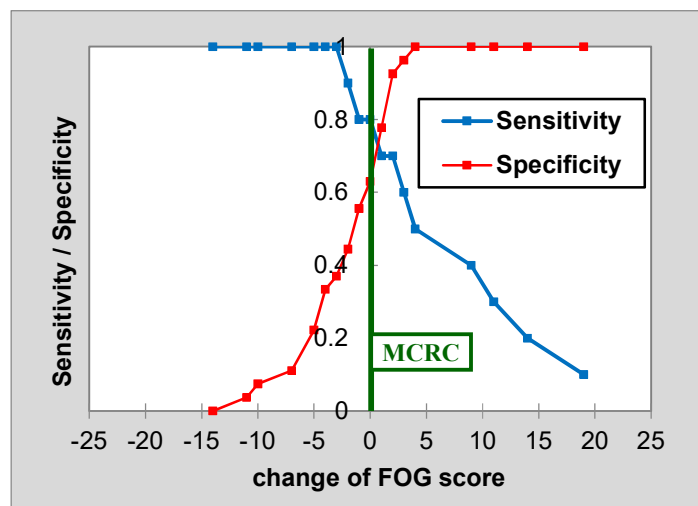


Figure 1: Sensitivity and Specificity

This is the first report of the MCRC of a clinical evaluation instrument for FOG. The value of two demonstrates that the FOG-score is able to detect subtle mild changes that were considered relevant by the bystanding expert. Our data support the further use of the instrument in clinical research.

References

- [1] K. Ziegler, F. Schroeteler, A.O. Ceballos-Baumann, U.M. Fietzek, *A New Rating Instrument to Assess Festination and Freezing Gait in Parkinsonian Patients*. **2010**, *Mov Disord*, 25(8) pp1012-8.
- [2] B. Bloem, J. Marinus, Q. Almeida et al. *Measurement Instruments to Assess Posture, Gait, and Balance in Parkinson's Disease: Critique and Recommendations*. **2016**, *Mov Disord*, 31(9) pp1342–55.

Split-Belt-Treadmill to modulate Freezing and Freezing-related Gait Deficits in Parkinson's disease: Feasibility of a Study Protocol

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INTRODUCTION: Freezing of gait (FOG) is associated with asymmetric gait and difficulty with motor switching. The aim of this study is to investigate whether adapting to modulations imposed by a Split-Belt-Treadmill, improves walking ability and reduces FOG.

METHODS/DESIGN: This randomized controlled trial is currently conducted at the KU Leuven, Belgium and CAU Kiel, Germany. Sixty-four patients with Parkinson's disease with FOG (PD+FOG) and 64 healthy controls (HC) will be randomly assigned into four 30-minutes (6x5min) intervention groups: A) Split-Belt ratio 1:2; B) Split-Belt ratio 3:4; C) Split-Belt changing ratios; D) Tied-Belt. For the Split-Belt condition the belt's velocity of the side with the longer step length will be reduced. The following tests will be conducted before and after the training and after 24h: Overground and Split-Belt-Treadmill gait analysis (assessing gait asymmetry, variability, bilateral coordination and step length), 1-minute 360° turning in place under single and dual task (Stroop test) condition, postural sway analysis and cognitive assessment.

RESULTS: Walking on a Split-Belt-Treadmill was feasible for all included participants so far and no adverse events (e.g. falls) occurred during testing/training. Seven freezers (with mild to severe NFOGQ scores 11-24) and 5 healthy controls underwent the protocol. However, study protocol was long and had to be reduced to avoid fatigue.

DISCUSSION: This implicit learning protocol was found feasible for patients and may help patients with FOG to adapt to gait perturbations. Preliminary results will be presented if data of the first included participants appear to be robust.

Acknowledgement: This project is funded by the Jacques & Gloria Gossweiler Foundation

Turning problems and Freezing Of Gait in Parkinson's Disease: A systematic review and meta-analysis.

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Objective: To understand the differences of step and rotational parameters between freezers and non-freezers during turning and determine the influence of turn angle and turn characteristics on Freezing Of Gait (FOG).

Data Sources: Pubmed and Web of Science

Study Selection: Case-control studies that examined the differences in turning while walking between freezers and non-freezers. Two reviewers selected studies independently.

Data Extraction: Methodological quality was evaluated by two independent reviewers using the STROBE checklist for case-control studies. Mean differences and 95% confidence intervals were calculated for turn duration, peak turn velocity, number of steps and cadence. Center of mass deviation, segmental rotation, phase coordination and FOG-frequency were also extracted. When possible, different turning angles or spatial confounds were compared.

Data Synthesis: Sixteen studies met the inclusion criteria. FOG occurred in 38.2% of the freezers. Turning in freezers was characterized by an increased turn duration, cadence and number of steps and a decreased peak turn velocity. Qualitative analysis showed that results concerning step width, step length and step time variability were inconsistent. Turning was characterized by an increased head-pelvis coupling and worse coordination in freezers compared to non-freezers. A decreased medial deviation of the Center of mass was present prior to a FOG-episode.

Conclusions: Both step and rotational parameters differed in freezers compared to non-freezers while turning. These differences increased with increasing task complexity (i.e. larger turning angle or spatial confounds during turning).

Good vibrations: cortical activity response to tactile cues in Parkinson's freezers and non-freezers

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Introduction: Difficulty turning often presents in Parkinson's disease (PD) and can result in freezing episodes or falls. Cueing strategies can mitigate mobility deficits, but the underlying mechanisms involved in response are unclear. Theories suggest executive-attentional processes, stemming from the pre-frontal cortex (PFC), may play a vital role. This study aimed to evaluate the effect of tactile biofeedback and metronome-like cueing on PFC activity during turning in people with PD.

Methods: PFC activation when turning was recorded in 10 healthy older adults and 28 PD participants (OFF-medication, MDS-UPDRS: 42.5±13.8, age: 67.3±5.6years, 16 freezers, 12 non-freezers) using mobile functional near infra-red spectroscopy (fNIRS). Inertial sensors measured turns. Participants walked then turned (180°, 360°) with and without biofeedback or metronome-like tactile cueing. The primary outcome was cortical activation, specifically change in oxygenated hemoglobin (HbO₂) 6sec prior-to and during turning.

Results: Unlike older adults, PFC activation significantly increased during compared to prior-to turns in PD, with greater activation for sharper turns (180° vs 360°, $p=.021$). Reduced PFC activation occurred with metronome-like cueing in PD, whereas response to biofeedback depended upon freezing status ($p=.033$). Specifically, PFC activation decreased in freezers with biofeedback, whereas the opposite occurred in non-freezers (Figure1). Better executive function (TMT-B) related to lower PFC activation with biofeedback prior-to turns in freezers (180°; $\rho=-.73$, $p=.011$, 360°; $\rho=-.85$, $p=.002$).

Conclusions: These preliminary findings demonstrate that PFC response to biofeedback may differ between freezers and non-freezers. Furthermore, tactile biofeedback or metronome-like cueing may reduce PFC activation when turning in freezers, which may improve movement control.

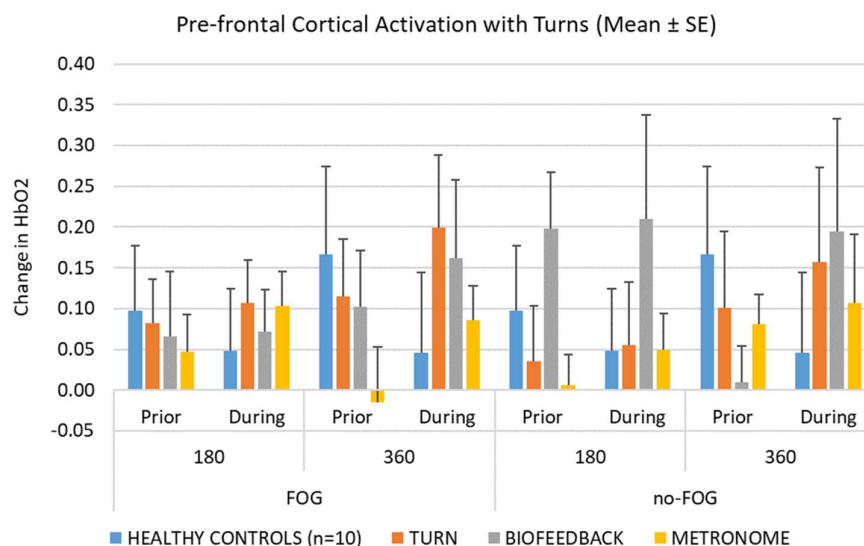


Figure 3 - Cortical activation when turning in Parkinson's disease

Objective markers of turning in idiopathic Parkinson's disease with freezing of gait

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Objective: To develop objective measures of turning in Parkinson's disease (PD) patients with or without freezing of gait (FOG).

Introduction: PD patients face lifestyle limiting changes due to gait problems. FOG in PD commonly occurs during turning, compounding the risk of falling from concurrent postural instability. In order to develop treatments, objective markers of turning are needed that can be subsequently employed in clinical trials to monitor therapeutic efficacy.

Methods: PD subjects provided written consent after IRB approval. Subjects walked on a 20'x4' Zeno pressure sensor impregnated mat (Protokinetics) in the levodopa ON-state. We studied 180-degree pivot turns to identify changes in FOG.

Results: 34 PD FOG and 38 PD no-FOG subjects with similar ages and disease duration (FOG 9.2±0.8 years; no-FOG 7.2±1.0 years; p=0.14) were analyzed. PD-FOG subjects had higher motor UPDRS and FOG-Q scores. PD-FOG subjects took longer to turn (FOG 4.11±0.23s; no-FOG 3.44±0.09s; p=0.01), took more steps (FOG 7.34±0.62; no-FOG 5.37±0.14; p=0.003) with shorter mean length (FOG 77±2cm; no-FOG 90±3cm; p=0.002) and longer mean width of turning (FOG 33±2cm; no-FOG 28±1cm; p=0.03). Gait cycle time (FOG 1.06±0.04s; no-FOG 1.18±0.03s; p=0.01) and swing time (FOG 0.26±0.02s; no-FOG 0.34±0.01s; p<0.001) were shorter in FOG, while stance time (FOG 0.82±0.02s; no-FOG 0.86±0.02s; p=0.26) was similar and there was no difference in stride-stride variability in these measures.

Conclusion: PD-FOG patients took wider shorter turns with more steps that had shorter time period and shorter swing time. These measures may help test therapeutic efficacy in future clinical trials.

FOG detection via EEG analysis in local-moving experiment

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Several cueing-strategies, e.g. rhythmic auditory or visual cues, may help PD patients overcome FOG. The feasibility of these cues would be further improved if they were applied in an on-demand manner (i.e. cueing only occurs when FOG is detected, and preferably predicted). Current studies on FOG detection mainly utilize 3D gyroscopes or accelerometers for movement patterns. However, these studies are limited by their ability to at best detect, but not predict FOG. The possibility of using electroencephalography (EEG) to predict FOG (detect the transition between normal walking and FOG) was proposed by Handojoseno ^[1]. In his study, 4-channel EEG data was acquired and analyzed, which is not yet accurate enough for FOG prediction. Our study therefore focuses on the real-time detection and prediction of FOG, with 64-channel EEG, ECG and motion sensor data. Fifteen patients with idiopathic Parkinson's disease at off-medication state were asked to execute three tasks in place (two minutes per task) at each session: stepping, normal half turning, and rapid half turning. The following data were acquired during the sessions: 64-channel EEG data (ActiCap), the motion data from 6 accelerometers (TMSi; applied above ankles, knees, and metacarpophalangeal joints) and 8 footswitches (TMSi; 4 per foot), EMG data (TMSi; 1 sensor per forearm), and 3-lead ECG data. The experiment was videotaped, and two independent raters annotated the presence of FOG via the videos. Rapid half turning especially evoked FOG during our measurements. The FOG episodes will be correlated with the EEG signals in our analysis.

References

- [1] A. M. Ardi Handojoseno, James M. Shine, Moran Gilat, Tuan N. Nguyen, Yvonne Tran, Simon J.G. Lewis, Hung T. Nguyen, *Using EEG spatial correlation, cross frequency energy, and wavelet coefficients for the prediction of Freezing of Gait in Parkinson's Disease patients*. Engineering in Medicine and Biology Society (EMBC) **2014** 36th Annual International Conference of the IEEE, pp. 4119-4122, 2014, ISSN 1557-170X.

Both frequency and duration of freezing of gait is related with falling severity in recurrent fallers with Parkinson's disease

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Falls are a common and disabling symptom in patients with Parkinson's disease (PD). To prevent falls in PD patients, it is important to understand the related factors with falling frequency and severity, but there was no study focusing on these relationships.

In this study, we recruited 66 recurrent PD fallers. Parkinsonism was evaluated with the Unified Parkinson Disease Rating Scale (UPDRS) part 3 and the Hoehn and Yahr (HY) stage. Additionally, freezing of gait (FOG), postural instability, general cognition and psychiatric symptoms were checked using FOG questionnaire (FOGQ), Tinneti balance assessment tool, Korean version of Montreal cognitive assessment (MoCA-K) and neuropsychiatric inventory (NPI), respectively. We performed partial Spearman correlation analysis to investigate associated factors with falling frequency and severity.

For enrolled subjects, mean age was 70.6 ± 7.9 , and disease duration was 11.5 ± 4.5 years. Mean UPDRS part 3 score was 23.0 ± 9.1 , and mean HY stage was 2.3 ± 0.6 for parkinsonian symptoms. Falling severity was correlated with both frequency and duration of FOG, while falling frequency with Tinneti balance score and camptocormia even after controlling age, education year, disease duration, levodopa equivalent daily dose, MoCA-K and NPI score. However, tremor, bradykinesia, rigidity and axial sub-scores of UPDRS-III were not associated with falling frequency and severity. Our results indicate that FOG and postural instability are two major factors related with falling severity and frequency. In particular, FOG is associated with falling severity, thus FOG should be treatment target to minimize the trauma from falls.

Video presentations

List of videos

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**Freezing of gait in challenging activities:
analysis of freezing during backward gait whilst playing tennis**

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**Clinical Assessment and Functional Management in Upper Limb Freezing in
Parkinson's Disease: a successful external cues interference**

Tamine T.C. Capato^{1,2,4}, Jorik Nonnekes⁴, Monica Haddad³, Egberto R. Barbosa³, Bastiaan R. Bloem⁴

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Unilateral FOG: search for correct diagnosis

Philip Bourgeois¹, Winny Depaepe¹, Ilse Vandenbroucke¹

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Freezing of Gait as a Complication of Multiple Sclerosis

Urban M. Fietzek¹, Mario Paulig¹, Patrick Fischer¹, Andres O. Ceballos-Baumann^{1,2}, Oliver Neuhaus³

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Perceptual gait training for Freezing of Gait (FOG)

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