# Freezing of gait treatment

Freezing of gait (FOG) is a devastating axial motor symptom in Parkinson's disease (PD) leading to falls, institutionalization, and even death. The response of FOG to dopaminergic medication and deep brain stimulation (DBS) is complex, variable, and yet to be optimized. Fundamental gaps in the knowledge of the underlying neurobiomechanical mechanisms of FOG render this symptom one of the unsolved challenges in the treatment of PD.

Converging evidence supports that co-stimulation of the subthalamic nucleus and the substantia nigra pars reticulata can be efficacious for the management of the resistant gait impairment in Parkinson's disease.

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From the available evidence, the stimulation effects of 63Hz or 126Hz seem to interplay with a neurophysiological continuum re- gardingthelocalstimulationeffectsonsingleunitactivityandsynaptic plasticity measures, rather than exhibiting controversial neurophysio- logical or clinical effects. However, the downstream and overal network effects of nigral stimulation are not yet characterized and may influence future stimulation protocols beyond the present knowledge. Giventheconvergingevidenceofthepresentclinicalandphysiological studies,aswellasotherrelatedstudiesregardingtheroleofSNrinPD gait pathophysiology, more detailed basic research and exploratory clinical work is warranted in order to take fulladvantage of the nigral locomotor hub for neurostimulation therapy [1)].

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included six patients (mean age 59.1 years, disease duration 16.1 years). All patients suffered motor fluctuations and dyskinesias. The best results were obtained with COMB in four patients (who preferred and remained with COMB over 3 years of follow-up) and with HF-STN in two patients. SNr stimulation alone did not produce better results than COMB or STN in any patient.

COMB and HF-STN stimulation improved PD-associated gait disorders in this preliminary case series, sustained over time. Further multicenter investigations are required to better explore this therapeutic option [2)].

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Deep brain stimulation(DBS) of the substantia nigra pars reticulata (SNr) is under consideration for the treatment of freezing of gait (FOG) in Parkinson's disease (PD). While DBS of the subthalamic nucleus (STN) is effective for the management of segmental motor symptoms and fluctuations, axial motor symptoms show limited therapeutic response as the disease progresses. One correlate of PD is that the in- hibitory basal ganglia output structures are overactive.

Since the SNr sends non-dopaminergic projections to brainstem structures involved in locomotion,combined stimulation of the SNr(usingacaudalelectrode) and STN (using rostral electrodes) was suggested to modulate locomotor integration

Twelve patients were enrolled in a 2 × 2 cross-over double-blind randomized controlled clinical trial and both the safety and efficacy of combined subthalamic nucleus and substantia nigra pars reticulata stimulation were evaluated compared with standard subthalamic nucleus stimulation. The

primary outcome measure was the change of a broad-scaled cumulative axial Unified Parkinson's Disease Rating Scale score (Scale II items 13-15, Scale III items 27-31) at '3-week follow-up'. Secondary outcome measures specifically addressed freezing of gait, balance, quality of life, non-motor symptoms and neuropsychiatric symptoms. For the primary outcome measure no statistically significant improvement was observed for combined subthalamic nucleus and substantia nigra pars reticulata stimulation at the '3-week follow-up'. The secondary endpoints, however, revealed that the combined stimulation of subthalamic nucleus and substantia nigra pars reticulata might specifically improve freezing of gait, whereas balance impairment remained unchanged. The combined stimulation of subthalamic nucleus and substantia nigra pars reticulata was safe, and of note, no clinically relevant neuropsychiatric adverse effect was observed. Patients treated with subthalamic nucleus and substantia nigra pars reticulata stimulation revealed no 'global' effect on axial motor domains. However, this study opens the perspective that concomittant stimulation of the substantia nigra pars reticulata possibly improves otherwise resistant freezing of gait and, therefore, highly warrants a subsequent phase III randomized controlled trial [3)].

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Biomechanical parameters and leg muscle activity were recorded during gait initiation in seven selected patients operated for bilateral STN stimulation, out of 204 stimulated patients, with one contact of each electrode located within the SNr. Step length, anteroposterior and vertical velocities of the centre of gravity were studied, with special reference to the subjects' ability to brake the centre of gravity fall before foot-contact, and compared to seven controls. In Parkinson's disease patients, five treatment conditions were tested: (i) no treatment, (ii) levodopa treatment, (iii) STN stimulation, (iv) SNr stimulation and (v) combined levodopa treatment and STN stimulation. The effects of these treatments on motor parkinsonian disability were assessed with the UPDRS III scale, separated into 'axial' (rising from chair, posture, postural stability and gait) and 'distal' scores. Whereas levodopa and/or STN stimulation improved 'axial' and 'distal' motor symptoms, SNr stimulation improved only the 'axial' symptoms. Compared to controls, untreated Parkinson's disease patients showed reduced step length and velocity, and poor braking just prior to foot-contact, with a decrease in both soleus (S) and anterior tibialis (AT) muscle activity. Step length and velocity significantly increased with levodopa treatment alone or in combination with STN stimulation in both natural and fast gait conditions, and with STN stimulation alone in the fast gait condition. Conversely, SNr stimulation had no significant effect on these measures in either condition. In the natural gait condition, no fall in the centre of gravity occurred as step length was low and active braking was unnecessary. In the fast gait condition, braking was improved with STN or SNr stimulation but not with levodopa treatment, with an increase in the stance leg S muscle activity. These results suggest that anteroposterior (length and velocity) and vertical (braking capacity) gait parameters are controlled by two distinct systems within the basal ganglia circuitry, representing respectively locomotion and balance. The SNr, a major basal ganglia output known to project to pontomesencephalic structures, is postulated as being particularly involved in balance control during gait. [4)].

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Results prompt consideration of a new strategy for two-stage subthalamic nucleus deep brain stimulation (STN-DBS) frequency optimization, with stimulation at 130 Hz and the usual voltage during the initial years of STN-DBS and then at 60 Hz at a high voltage in Parkinson disease patients who develop severe gait disorders [5)].

1)

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4)

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5)

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