Freezing of Gait: Phenomenology

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Definition Freezing of gait:

FOG is an episodic inability to generate effective stepping in the absence of any known cause other than parkinsonism or high-level gait disorders…
(Nir Giladi and Alice Nieuwboer 2008)
Phenomenology gait disturbance and freezing in Parkinson´s disease

Three clinico-phenomenological presentations of freezing:

1. **Trembling-in-place**
   Alternating trembling (3-8Hz) of legs with the feet remaining in place

2. **Shuffling**
   Shuffling forward with very short steps

3. **Akinetic freezing**
   Complete akinesia without any leg movement (least common)

**Definition Freezing of gait:**

FOG is an *episodic inability to generate effective stepping in the absence of any known cause other than parkinsonism or high-level gait disorders*…

(Nir Giladi and Alice Nieuwboer 2008)
History: 
Freezing of gait in the first descriptions of James Parkinson in 1817

“...the patient is thereby forced to step on the toes and fore part of the feet, whilst the upper part of the body is thrown so far forward as to render it difficult to avoid falling on the face....”
Jean-Martin Charcot (1877):
„…get up from the seat, hesitate for some seconds to step out, then, once started go off in spite of themselves at a rapid pace…“

William R. Gowers (1893):
„…often walks with short quick steps, leaning forward as if about to run“

André Barbeau (1972):
„…there is a possible diminuition in the late-occuring bradykinetic and hypotonic freezing episodes“
Clinical observations of **FOG Phenomenology** are important to

1. get clues on FOG pathophysiology

2. get ideas of therapeutical approaches
1. Clinical observation of **FOG Phenomenology**

The effect of L-Dopa depletion

**VS.**

L-Dopa administration on FOG
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*Case of the Frozen Addicts*, a group of young drug addicts in Santa Clara, California that were accidentally intoxicated with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and developed a severe Parkinsonian syndrome in 1982.

Nonnekes et al., 2018
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Nonnekes et al., 2018
None of MPTP-PD humans presented with the common trembling FOG phenotype in the **acute state**, but one in the L-Dopa **Longterm-State**

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1 of 7 MPTP-PD humans presented with akinetic freezing in the **acute state**

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Nonnekes et al., 2018

History:  
Freezing of gait descriptions after L-Dopa depletion Nr. 10
Freezing of gait after L-Dopa administration: Observed Improvement

Schaafsma et al. 2003

![Graph showing freezing percentages for different gait types and conditions.](image-url)
Freezing of gait after L-Dopa administration: Biphasic freezing

OFF

L-Dopa 100mg FOG

L-Dopa 200mg

Perez Parra et al., 2020
Nonnekes et al., 2020
FOG was recognized before the levodopa era, although the frequency seems to have increased since after the introduction of levodopa. There might be different phenomenological associations of freezing with acute L-Dopa depletion or acute or chronic L-Dopa administration.

Subtypes of FOG along L-Dopa response

1) Some PD patients have FOG in the Off State, but FOG responds to L-Dopa and is absent in MED On (subtype Off-FOG)

2) Some PD patients have no response and suffer from freezing in MED OFF AND MED ON (subtype Off-On-FOG)

3) In some PD patients, there is no FOG in MED OFF, but levodopa causes FOG (subtype On-FOG), sometimes in the transition phase as “biphasic FOG”
Reconciliation of the L-Dopa Paradox

Clues on pathophysiology:

Improvement-deterioration of Freezing of gait

Homeostatic Compensation with disease progression

A Untreated Parkinson disease

Cortex  

Cortex  

Cortex  

Compensatory dopamine receptor upregulation

Striatum  

Striatum  

Striatum  

Dopaminergic cell loss is greater in SN than VTA

SN  

VTA  

VTA  

Motor  

Cognitive  

Limbic

B Parkinson disease after chronic dopaminergic treatment

Cortex  

Cortex  

Cortex  

(1) Loss of compensatory dopamine receptor upregulation

Striatum  

Striatum  

Striatum  

(2) Aberrant levodopa-induced plasticity occurs predominantly within motor loops

SN  

VTA  

VTA  

Motor  

Cognitive  

Limbic

Cenci et al. 2014

Nonnekes et al. 2020
2. Clinical observation of **FOG Phenomenology**

Freezing is an episodic, ictal phenomenon - but the gait pattern beyond freezing episodes is continuously disturbed.
Continuous gait characteristics in Freezeers: I. Gait variability

<table>
<thead>
<tr>
<th></th>
<th>Subjects with no &quot;off&quot; FOG (n=11)</th>
<th>Subjects with &quot;off&quot; FOG (n=21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average stride time (ms)</td>
<td>1,007±77</td>
<td>972±182</td>
<td>0.785</td>
</tr>
<tr>
<td>Stride time standard deviation (ms)</td>
<td>33±8</td>
<td>55±38</td>
<td>0.014*</td>
</tr>
<tr>
<td>Stride time CV (%)</td>
<td>3.3±0.7</td>
<td>6.1±5.5</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

*P<0.05

Hausdorff et al. 2003

![Gait V (m/s)](chart1)

Freezers/Fallers
Non Freezers/Fallers

![Step length (m)](chart2)

![Step time variability (%)](chart3)

![Swing time variability (%)](chart4)

Plotnik et al. 2011
Continuous gait characteristics in Freezers: II. Gait asymmetry

Plotnik et al., Parkinson´s disease 2011

Fasano et al., Neurol Science 2015
Therapeutic clue: Virtual Reality (VR) for enhanced motor learning - gait asymmetry

Different enhanced learning motor strategies by VR:

- Symmetric walk with/without sensory feedback
- Asymmetric walk
- Manipulation of foot perception in VR

Janeh et al., Cells 2019

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67.6 years ± 7 [min 49 - max 77]</td>
</tr>
<tr>
<td>Gender</td>
<td>15 male</td>
</tr>
<tr>
<td>Handedness</td>
<td>1 ambidextrous, 14 right handed</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr</td>
<td>2-3</td>
</tr>
<tr>
<td>Symptoms (duration)</td>
<td>11.5 years ± 4.9 [2-19]</td>
</tr>
<tr>
<td>Diagnosis (duration)</td>
<td>9.5 years ± 4.9 [1-17]</td>
</tr>
<tr>
<td>Gait Disturbances (duration)</td>
<td>5.5 years ± 4.4 [1-17]</td>
</tr>
<tr>
<td>Levodopa (minutes after intake)</td>
<td>58.3 minutes ± 19.8 [40-120]</td>
</tr>
<tr>
<td>UPDRS III (motor functioning)</td>
<td>25.5 ± 7.2 [12-37]</td>
</tr>
<tr>
<td>Giladi FOG questionnaire</td>
<td>27.5 ± 10.6 [12-47]</td>
</tr>
<tr>
<td>Berg Balance Score</td>
<td>24.7 ± 1.8 [19-26]</td>
</tr>
<tr>
<td>Ziegler (FOG)</td>
<td>7.2 ± 5.9 [0-17]</td>
</tr>
<tr>
<td>MOCA (cognition)</td>
<td>27.5 ± 2.0 [23-31]</td>
</tr>
<tr>
<td>Pre-SSQ (simulator sickness before experiment)</td>
<td>16.45 ± 16.59 [3.74-52.36]</td>
</tr>
<tr>
<td>Post-SSQ (simulator sickness after experiment)</td>
<td>15.21 ± 17.04 [3.74-56.1]</td>
</tr>
<tr>
<td>SUS (presence in VE)</td>
<td>3.5 ± 0.8 [1-5.83]</td>
</tr>
<tr>
<td>PDQ-39 (quality of life)</td>
<td>25.31 ± 12.83 [5.76-45.21]</td>
</tr>
</tbody>
</table>
3. Clinical observation of **FOG Phenomenology**

Freezing is a heterogeneous phenomenon - different patients exhibit different freezing patterns
Heterogeneity of FOG Phenomenology

- FOG while walking through doorway
- FOG while turning on a spot
- FOG while taking the first step after standing up
- FOG while talking when walking
- FOG with distraction as phone ringing
- FOG when being in a hurry
- FOG being anxious
- FOG while walking in the dark
- FOG while walking in a cluttered environment
- FOG while walking up a sloped surface
Heterogenity of FOG Phenomenology

Ehgoetz Martens et al, MDS 2018:
41 PD Patienten (68.4 Jahre, 9.9. Jahre Krankheitsdauer, Hoehn & Yahr 2.6 Jahre)

„Asymmetric-Motor Subtype“

FOG while walking through doorway
FOG while turning on a spot
FOG while taking the first step after standing up

„Anxious Subtype“

FOG while talking when walking
FOG with distraction as phone ringing
FOG when being in a hurry
FOG being anxious

„Sensory Attention Subtype“

FOG while walking in the dark
FOG while walking in a cluttered environment
FOG while walking up a sloped surface
Heterogeneity of FOG
„Freezing-Subtypes“ exhibit different characteristics

Dopa-Response Freezing in subtypes

Different strategies:
Asymmetric-motor and sensory attention subtype:
„Metronome“ or „stepping over someones feet“
Anxious subtype:
„Take a deep breath“

Motor Performance of subtypes

Ehgoetz Martens et al, MDS 2018
Motor learning strategies (MLS)

MLS are observable therapeutic actions in which therapists consider task and client-specific factors to select and to apply evidence-based practice and feedback variables for optimal motor learning.

Porras et al. Neurology 2018

<table>
<thead>
<tr>
<th>Variable</th>
<th>Distance (m)</th>
<th>Task (N)</th>
<th>Main trainings focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Session 1</td>
<td>1000</td>
<td>40</td>
<td>Movement endurance, coordination, strength training of the lower extremity</td>
</tr>
<tr>
<td>Session 2</td>
<td>1250</td>
<td>50</td>
<td>Introduction to dual tasks situations during walking in everyday life. E.g. avoiding obstacles while walking or reacting on instruction during walking</td>
</tr>
<tr>
<td>Session 3</td>
<td>1500</td>
<td>60</td>
<td>Advanced exercises on dual tasks situations while walking and mediation of task managing strategies. E.g. focusing the the foodstep rolling behavior.</td>
</tr>
<tr>
<td>Session 4</td>
<td>1750</td>
<td>70</td>
<td>Combining complex dual task situations and mediation and the use of coping strategies. E.g. walking with shopping bags and reacting to direction signs right in a otherway they were pointing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FoG-Q ≥ 10 severe freezer [N = 9]</th>
<th>FoG-Q &lt; 10 slight freezer [N = 8]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>baseline</td>
<td>post</td>
</tr>
<tr>
<td>Velocity (m/s)</td>
<td>.89 (.19)</td>
<td>1.10 (.18)*</td>
</tr>
<tr>
<td>Cadence (steps/min)</td>
<td>98.5 (8.6)</td>
<td>108.0 (7.7)*</td>
</tr>
<tr>
<td>Step length (cm)</td>
<td>54.08 (9.20)</td>
<td>61.20 (8.68)</td>
</tr>
<tr>
<td>DSP (sec)</td>
<td>0.391 (.062)</td>
<td>0.329 (.034)*</td>
</tr>
<tr>
<td>%CV Gait left leg</td>
<td>6.31 (1.63)</td>
<td>4.99 (3.16)</td>
</tr>
<tr>
<td>%CV Gait right leg</td>
<td>7.90 (5.95)</td>
<td>3.85 (1.85)</td>
</tr>
<tr>
<td>step length dom (cm)</td>
<td>55.89 (8.41)</td>
<td>63.86 (7.94)*</td>
</tr>
<tr>
<td>Step length weak (cm)</td>
<td>52.27 (10.08)</td>
<td>58.54 (9.70)</td>
</tr>
</tbody>
</table>

Wollesen et al. in submission 2020
Clinical observations of FOG Phenomenology

1. L-Dopa administration can distinguish freezing subtypes - Pathophysiological clues on possible dopaminergic action on
   1) basal ganglia segregated motor, cognitive, limbic loops
   2) maldaptive neuroplasticity of postsynaptic receptors

2. Gait pattern beyond freezing episodes is continuously disturbed - Therapeutic clues on e.g. training of gait asymmetry

3. Freezing is a heterogeneous phenomenon - Therapeutic clues on individualised motor training strategies as precision medicine
Thanks for your attention!