Both groups contained a select group of unusually severe freezers based on NFOG-Q scores at baseline (TMR, 22.3 ± 6.0; ARTI, 21.6 ± 5.7), some of whom must have had FOG episodes lasting >30 seconds. Moreover, the Hoehn and Yahr stages in both groups ranged from 3 to 4, indicating a moderate to severe degree of postural instability. Considering this severe level of disability, our concern relates to the requirements and feasibility of the ARTI intervention in such an extremely fall-prone cohort. Patients were asked to perform high-level balance exercises, that is, weighted lunges and squats on unstable surfaces, which could lead to falls and should therefore not translate to self-administration without expert supervision. Notably, adherence rates were exceptionally high (100% for 612 ARTI sessions) and adverse events scarce for such high-risk activities, although it remains unclear how these were monitored.

The primary outcome was the New Freezing of Gait Questionnaire (NFOG-Q). Recent work comparing consecutive measurements in 2 independent PD populations without intervention showed that the NFOG-Q has a minimal detectable change (MDC) of 9.95 points. This is larger than the reported effect of ARTI (4.7 points). The authors did not refer to this work, but calculated the MDC using pre- and postassessments of their own active control intervention (2.7 points). Thus, although the ARTI intervention seemed to significantly improve several outcomes, the conclusion that the intervention effectively reduced FOG is likely confounded by test-retest error.

Furthermore, the FOG ratio, an objective measure of FOG severity, strongly deteriorated in controls (12.8 preintervention vs 20.9 postintervention), which is unexpected during this brief trial duration (3 months), particularly because controls received an active intervention. This unexplained worsening in controls may have inflated the effect of the ARTI intervention on this outcome. Also, participants had abnormal FOG-ratio values (average of 20.9), whereas they were ON medication, which is much higher than those reported in patients OFF medication in the initial FOG-ratio validation article (0-13). Inconsistencies also exist between the trial registration and the reported outcome measures, including those for gait, balance, and fMRI analyses, hinting toward selective reporting. Further, the statistical analyses did not account for baseline performance, and the reported outcome measures, including those for gait, balance, and fMRI analyses, hinting toward selective reporting. Further, the statistical analyses did not account for baseline performance, and the statistical analyses did not account for baseline performance.

Given these issues, we caution the clinical interpretation of this article. PD patients with FOG typically have severe balance impairment, which greatly amplifies their fall risk. The described intervention seems hazardous, based on images provided in the supplementary material, whereas the efficacy for reducing FOG appears uncertain. Therefore, we believe that caution and further studies are warranted before advocating the ARTI intervention for people with FOG.

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Reply to: ‘Letter to the Editor on “A Randomized Controlled Trial of Exercise for Parkinsonian Individuals With Freezing of Gait”’

We read with interest the comments of Nonnekes et al1 on the safety of our adapted resistance training with instability (ARTI) for people with Parkinson’s disease (PD) and freezing of gait (FOG [freezers]) and the methodological issues related to our trial. We are confident that ARTI is safe if implemented with expert supervision and the strict safeguards we suggested. Challenging interventions, safely implemented, have been suggested to decrease FOG severity.2,4 ARTI is challenging and complex, but it has a hierarchical progression strongly based on the safety and motor abilities of each participant (see Supplementary File). ARTI was implemented in a one-to-one fashion with constant supervision of experienced physical therapists to ensure the safety of the participants. Adverse events were monitored by the first author (C.S.B.) during each session and in the time period surrounding each session.

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between sessions. There was only one adverse event possibly related to ARTI (ie, acute sciatica), which was reported to the review board. Adherence was high, which can be attributed to the challenging and motivating nature of the intervention.

It is not clear to us why Nonnekes et al attribute the differences we obtained in the New Freezing of Gait Questionnaire (NFOGQ) to measurement error, as our pre-post data had an intraclass correlation coefficient = 0.83, and pre-test mean (sd) values are within the range presented in the literature and are very consistent between groups (Table 3). Our paper showed within- and between-group statistical differences in NFOGQ score (primary outcome—Table 3) (−4.4, P < 0.0001 and −4.8, P = 0.069, respectively). The paper by Hulzinga and colleagues was not available when our study was designed and registered on June 1, 2018. We remain confident that ARTI improves FOG, although not to the 9.95 points suggested by Hulzinga and colleagues. It is possible that FOG ratio has higher sensitivity than NFOGQ to detect changes in FOG severity, but the benefits of ARTI on FOG ratio do need replication. We also acknowledge that the “FOG severity” section was misleading as NFOGQ and FOG ratio were both inadvertently presented as primary outcomes.

We do not understand the criticism about inconsistencies between registered and reported outcomes. NFOGQ and 18 secondary outcomes are listed in the trial registration. In this paper, we reported the primary and specific secondary outcomes directly associated with our FOG-related hypotheses (motor symptoms, anticipatory postural adjustments, cognitive inhibition, quality of life, and locomotor-area brain activation).

We did not consider baseline differences, as mixed-model assumptions were not violated. We have now performed an analysis on the difference in change score (NFOGQ) over 3 months (−0.3 [control] vs. −4.4 [ARTI]), and results were also significant, P < 0.001. Finally, we made a mistake when updating the number of participants in the trial. Otherwise, the Consort figure is accurate.

In summary, we are confident that ARTI is safe when administered by trained, experienced, rehabilitation professionals in a one-to-one training program and should be used as no other treatment shows comparable results, although larger trials are needed to confirm our findings.

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Letter to the Editor on “Copathology in Progressive Supranuclear Palsy: Does It Matter?”

It was with great interest that we read the manuscript by Lukic et al about the significance of copathology in progressive supranuclear palsy (PSP). Copathology was found in the majority of PSP cases (92%), mainly in the form of Alzheimer’s disease (AD) pathology (84%) and rarely of Lewy body disease (LBD) pathology (8%). However, the presence of copathology did not have an impact on the progression of the disease.

Recently, we analyzed in our Brain Bank the case of a patient with corticobasal syndrome (CBS) with neuropathological features not only of PSP but also of LBD and AD. In fact, although CBS has well-recognized clinical signs, the underlying pathology may be difficult to predict in vivo. It may be associated with a diverse constellation of conditions that include corticobasal degeneration, PSP, frontotemporal dementia, or AD, but LBD and mixed simultaneous pathologies have been rarely described.

The patient was a woman who died at 83 years of age, 8 years after she was diagnosed with CBS. She initially presented with frontalis muscle hyperactivity, left-limb ideomotor apraxia, slow vertical saccades but otherwise normal eye movements, left predominant akinetic-rigid parkinsonism, and short step gait with turning en bloc (Video 1, Segment 1). Brain MRI revealed right frontoparietal atrophy without midbrain atrophy. There was no benefit using levodopa (up to 1500 mg/day), and over the years progressive cognitive...