Effect of high-frequency subthalamic neurostimulation on gait and freezing of gait in Parkinson's disease: a systematic review and meta-analysis

C. Schlenstedt[a,*], A. Shalash[a,b,*], M. Muthuraman[a,c], D. Falk[d], K. Witt[a] and G. Deuschl[a]

[a]*Department of Neurology, Christian-Albrechts-University, Kiel, Germany;* [b]*Department of Neurology, Faculty of Medicine, Ain Shams University, Cairo, Egypt;* [c]*Department of Neurology, Johannes Gutenberg University, Mainz; and* [d]*Department of Neurosurgery, Christian-Albrechts-University, Kiel, Germany*

The aim of this meta-analysis was to summarize the short- and long-term effects of bilateral deep brain stimulation of the subthalamic nucleus (STN-DBS) on gait and freezing of gait (FOG) in Parkinson's disease and to detect predictors of post-stimulation outcome. A comprehensive review of the literature was conducted up to October 2015 using Medline Ovid databases for studies analyzing the effect of bilateral STN-DBS on FOG and/or gait. Sixteen studies with available data for the gait item (no. 29) of the Unified Parkinson's Disease Rating Scale (UPDRS) and six studies with the FOG item (no. 14) were included. Data were summarized for the following follow-up periods: 6–15, 24–48 and >48 months. For the medication (Med)-Off/stimulation (Stim)-On condition compared with baseline Med-Off, STN-DBS significantly improved gait on average from 2.43 to 0.96, 2.53 to 1.31 and 2.56 to 1.40 points at 6–15, 24–48 and >48 months, respectively ($P < 0.05$). Pre-operative levodopa responsiveness of UPDRS-III and Med-Off severity of gait were the predictors of this beneficial effect. STN-DBS significantly improved FOG for the Med-Off/Stim-On condition compared with baseline on average from 2.26 to 0.82, 2.43 to 1.13 and 2.48 to 1.38 points at 6–15, 24–48 and >48 months, respectively ($P < 0.05$). There was no significant effect in the Med-On/Stim-On condition. This meta-analysis showed a robust improvement of gait and FOG by STN-DBS for more than 4 years in the Med-Off/Stim-On condition. No beneficial effect was found for the On state of medication. Pre-operative levodopa responsiveness of global motor performance (UPDRS-III) is the strongest predictor of the effect of deep brain stimulation on gait.

Introduction

Bilateral deep brain stimulation of the subthalamic nucleus (STN-DBS) is an efficient treatment for Parkinson's disease (PD) that improves patients' quality of life [1]. However, its effect on some important features of advanced PD is considered less favorable and shorter lasting, especially gait impairment [1–4]. Quantitative studies have shown that gait is improved in the first years after STN-DBS but worsens gradually with disease progression [2,5,6]. Gait improvement was more prominent for some gait parameters, but it was limited to the Off state rather than the On state of medication [7–11]. This effect is similar to gait response to levodopa, denoting underlying dopaminergic dysfunction [4]. Consequently, researchers have advocated different approaches to achieve a better outcome for patients with gait deficits, including the use of low-frequency stimulation (60 Hz), testing of other stimulation targets such as the

Correspondence G. Deuschl, University Hospital Schleswig-Holstein, Campus Kiel, Department of Neurology, Schittenhelmstrasse 10, 24105 Kiel, Germany (tel.: +49-431-597-8707; fax: +49-431-597-8502; e-mail: g.deuschl@neurologie.uni-kiel.de).
*These authors have equally contributed to the paper.

pedunculopontine nucleus [4] or co-stimulation of the STN and the substantia reticulata [12]. Despite significant short-term effects, long-term results showed a loss of effect and a lack of superiority in comparison to high-frequency stimulation [4,13,14]. Moreover, recent kinematic studies showed similar effects of low and high frequencies of STN-DBS on gait and posture of patients with PD [13,15].

Similarly, freezing of gait (FOG) is associated with disease severity and poor quality of life [16], and is an independent risk factor for falls [17]. FOG was reported as a side-effect of deep brain stimulation (DBS) in some studies [18]. The impact of STN-DBS on FOG is not clear. Several DBS studies report the severity of FOG as a secondary outcome [usually indicated with the Unified Parkinson's Disease Rating Scale (UPDRS) item 14 for FOG]. To the best of our knowledge, only one study exists that focuses on the effect of DBS on FOG as a primary outcome compared with best medical treatment for 1 year after surgery [19]. Larger trials with long-term follow-up and with a detailed assessment of FOG are needed to investigate the impact of STN-DBS on FOG.

The aim of this meta-analysis was to review the current literature on the effect of STN-DBS on FOG and gait to quantify its short- and long-term effects, and to determine the predictors of post-stimulation outcome.

Methods

A comprehensive review of the literature was conducted up to October 2015 using Medline Ovid databases for studies analyzing the effect of bilateral STN-DBS on FOG and/or gait. Different individual and combined terms were used, including 'deep brain stimulation', 'subthalamic nucleus', 'Parkinson's disease', 'Parkinson disease', 'gait' and 'freezing'. Studies of STN-DBS that included the FOG item 14 of the UPDRS-II and/or the gait item 29 of the UPDRS-III, pre-operatively in medication (Med)-Off and/or Med-On states and post-operatively in Med-Off/stimulation (Stim)-On and/or Med-On/Stim-On states, were included. The search was limited to studies published in English. Studies including patients with previous surgeries other than STN-DBS were excluded.

Data were extracted from retrieved studies including the number of patients, mean age, duration of disease, control group (if available), type of study, methods of assessing FOG/gait and the primary and secondary outcomes. Data were summarized for the following follow-up periods: 6–15, 24–48 and >48 months. The effect of bilateral STN-DBS was analyzed by detecting changes between the pre-operative and post-operative scores of items 14 and 29 of the UPDRS. Analysis of gait and FOG outcome in Med-Off/Stim-Off and Med-On/Stim-Off states could not be performed due to the limited number of studies. Furthermore, regression analysis was performed to detect pre-operative predictors of the effect of STN-DBS on gait at different follow-up periods, including age, disease duration and pre-operative levodopa responsiveness of gait and UPDRS-III scores. Regression analysis for effect on FOG could not be conducted due to the limited number of studies.

Statistical analysis

A random-effect meta-analysis was conducted using MetaEasy [20]. We used the random-effects model known as the DerSimonian and Laird method [21] because it builds on an estimate of the between-study variation in effect size and provides larger CIs for the overall effect than the fixed-effect model. The heterogeneity of study results was analyzed using the Cochrane Q and the I^2 statistics [22]. Heterogeneity was regarded as high when the I^2 was above 75%. A one-sample Student's t-test was conducted to analyze whether the mean effect significantly differed from zero. To determine predictors of the effect of STN-DBS, we first correlated different baseline variables with the magnitude of change of the gait item from baseline to different follow-up periods (Spearman's rank correlation). Second, we included those baseline variables with a significant correlation as independent variables in a multivariate backward stepwise regression analysis with the difference from baseline to follow-up (gait item) as dependent variable. The pre-defined level of significance was set at $P < 0.05$.

Results

A total of 120 studies of bilateral high-frequency STN-DBS in PD were found; 22 studies met the inclusion criteria and were included in the meta-analysis. Mean age for studies including FOG and gait data was 57.5 years (range, 55–61.4 years) and 58.4 years (range, 55–61.4 years), respectively. Mean disease duration at surgery for studies with gait and FOG data was 13.3 years (range, 6.8–16.4 years) and 13.6 years (range, 6.8–16.4 years), respectively. Mean post-operative follow-ups were at 12 months (all studies), 36 months (range, 24–45.6 months) and 60 months (range, 54–66 months). For characteristics of the included studies, level of evidence and source of funding (S5) see supplemental material online according to AMSTAR (A Measurement Tool to Assess Systematic Reviews; http://amstar.ca/Amstar_Checklist.php).

Effect of STN-DBS on gait

Sixteen studies were identified with data on gait item 29 and were included in the meta-analysis (Table S1). For the Med-Off/Stim-On condition, 632 patients from 14 studies were included for the follow-up of 6–15 months, 427 patients from nine studies for the follow-up of 24–48 months and 279 patients from nine studies for the follow-up of >48 months (Fig. 1a). There was persistent significant improvement of post-operative gait scores (Med-Off/Stim-On), maximally at 6–15 months (mean effect, 1.62; 95% CI, 1.36–1.87; $P < 0.001$), with gradual worsening of this improvement at 24–48 months (mean effect, 1.20; 95% CI, 0.88–1.53; $P = 0.023$) and >48 months (mean effect, 1.19; 95% CI, 0.96–1.42; $P < 0.001$) compared with pre-operative scores (Fig. 2). The average (SD) change in gait was −1.5 (0.3) (mean change from 2.43 to 0.96), −1.2 (0.4) (from 2.53 to 1.31) and −1.1 (0.2) (from 2.56 to 1.40) points at the different follow-up periods, respectively. However, heterogeneity was high for the follow-ups of 6–15 and 24–48 months ($P < 0.0001$) ($Q = 44.9$, $I^2 = 71\%$ and $Q = 37.83$, $I^2 = 78.85\%$, respectively) but low for the assessment at >48 months ($P = 0.228$, $Q = 10.56$, $I^2 = 24.22\%$).

For the best On condition (Med-On/Stim-On), 589 patients from 12 studies were included for the interval of 6–15 months, 407 patients from eight studies for the interval of 24–48 months and 259 patients from eight studies for a follow-up period of >48 months (Table S1). There was a non-significant effect of STN-DBS on gait scores with slight worsening to values higher than pre-operatively (Fig. 1b). The mean effects were 0.14 (95% CI, −0.06–0.34; $P = 0.153$), 0.29 (95% CI, −0.65–0.06; $P = 0.092$) and 0.45 (95% CI, −0.92–0.02; $P = 0.058$) for 6–15, 24–48 and >48 months, respectively (Fig. 3). Heterogeneity was low at 6–15 months ($P = 0.09$, $Q = 17.8$, $I^2 = 38.2\%$), whereas a moderate to high risk of heterogeneity was found for the follow-ups of 24–48 and >48 months ($P = 0.007$, $Q = 19.38$, $I^2 = 63.87\%$

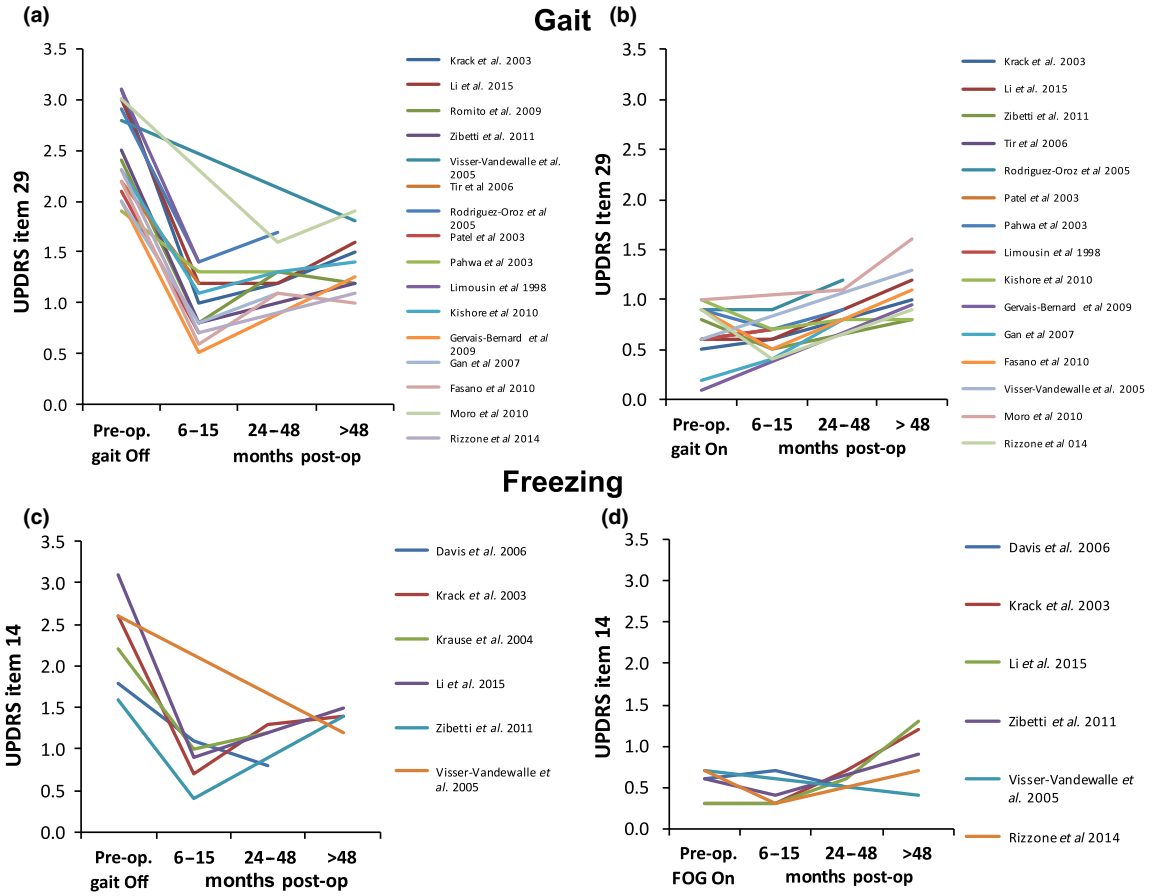

Figure 1 Short- and long-term effects of bilateral deep brain stimulation of the subthalamic nucleus on gait and freezing of gait (FOG) at different follow-up periods. (a) Gait [Unified Parkinson's Disease Rating Scale (UPDRS) item 29] baseline (Med-Off) follow-up (Med-Off/Stim-On); (b) gait (UPDRS item 29) baseline (Med-On) follow-up (Med-On/Stim-On); (c) FOG (UPDRS item 14) baseline (Med-Off) follow-up (Med-Off/Stim-On); (d) FOG (UPDRS item 14) baseline (Med-On) follow-up (Med-On/Stim-On). [Colour figure can be viewed at wileyonlinelibrary.com].

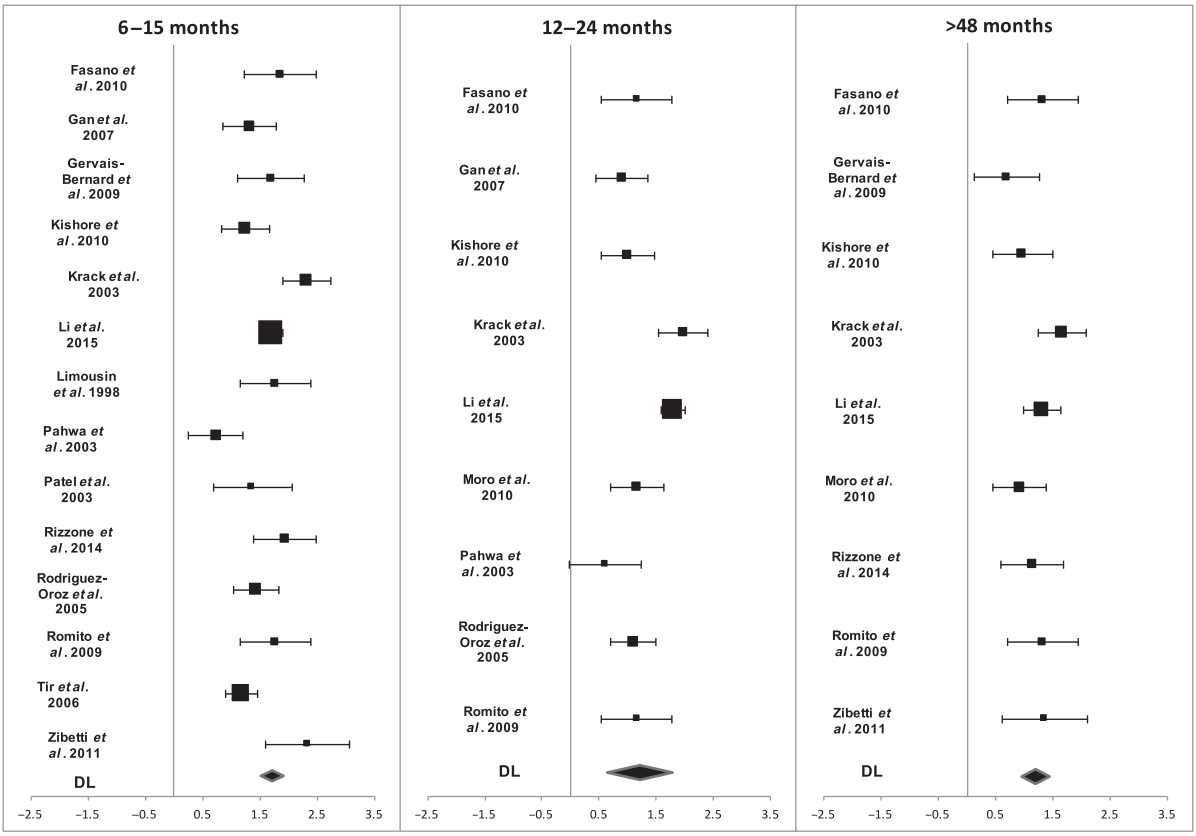

Figure 2 Summary of estimate of change in gait from pre-operative (Med-Off) to different follow-up periods (Med-Off/Stim-On). DL, DerSimonian and Laird method.

and $P = 0.0002$, $Q = 28.9$, $I^2 = 75.77\%$, respectively). The average (SD) change in gait was −0.1 (0.2) (mean change from 0.73 to 0.62), +0.2 (0.3) (from 0.75 to 0.91) and +0.4 (0.3) (from 0.71 to 1.07) points of baseline gait On state at the different follow-ups, respectively.

Predictors of beneficial effect of bilateral STN-DBS on gait

For the Med-Off/Stim-On condition, a significant correlation was found between the magnitude of change from baseline to the follow-up of 6–15 months and pre-operative UPDRS-III Med-Off (rho = −0.73, $P = 0.005$), gait Med-Off (rho = −0.80, $P = 0.001$) and levodopa responsiveness of UPDRS-III and gait (rho = 0.90, $P < 0.001$ and rho = 0.69, $P = 0.009$, respectively; Table S3). When including these variables as independent variables in a multivariate backward stepwise regression analysis only the levodopa responsiveness of UPDRS-III at baseline remained in the model with the strongest predictive capacity of the effect of DBS on gait (corrected $R^2 = 0.632$, $P = 0.002$; Table S4).

For the follow-up of 24–48 months, gait item at baseline (Med-Off, rho = −0.946, $P < 0.001$) and levodopa responsiveness of UPDRS-III and gait (rho = 0.857, $P = 0.007$ and rho = 0.922, $P = 0.001$, respectively) significantly correlated with the effect of DBS on gait. The regression analysis showed that gait item at baseline (Med-Off) and levodopa responsiveness of UPDRS-III revealed a significant model to predict the effect of DBS (corrected $R^2 = 0.871$, $P = 0.003$).

For the follow-up of >48 months, a significant correlation was found between UPDRS-III levodopa responsiveness and effect of DBS on gait (rho = 0.881, $P = 0.004$). The regression analysis indicated that the UPDRS-III levodopa responsiveness was able to predict 63% of the variance of the effect of DBS on gait and this model was significant ($P = 0.011$; Table S4).

No significant correlation with the effect of DBS was found in any condition for age at surgery, disease duration, levodopa equivalent daily dose (LEDD) and change in LEDD.

Effect of STN-DBS on FOG

Seven studies with available data of FOG item 14 were included in the meta-analysis (Table S2). For the Med-Off/Stim-On condition, 335 patients from five

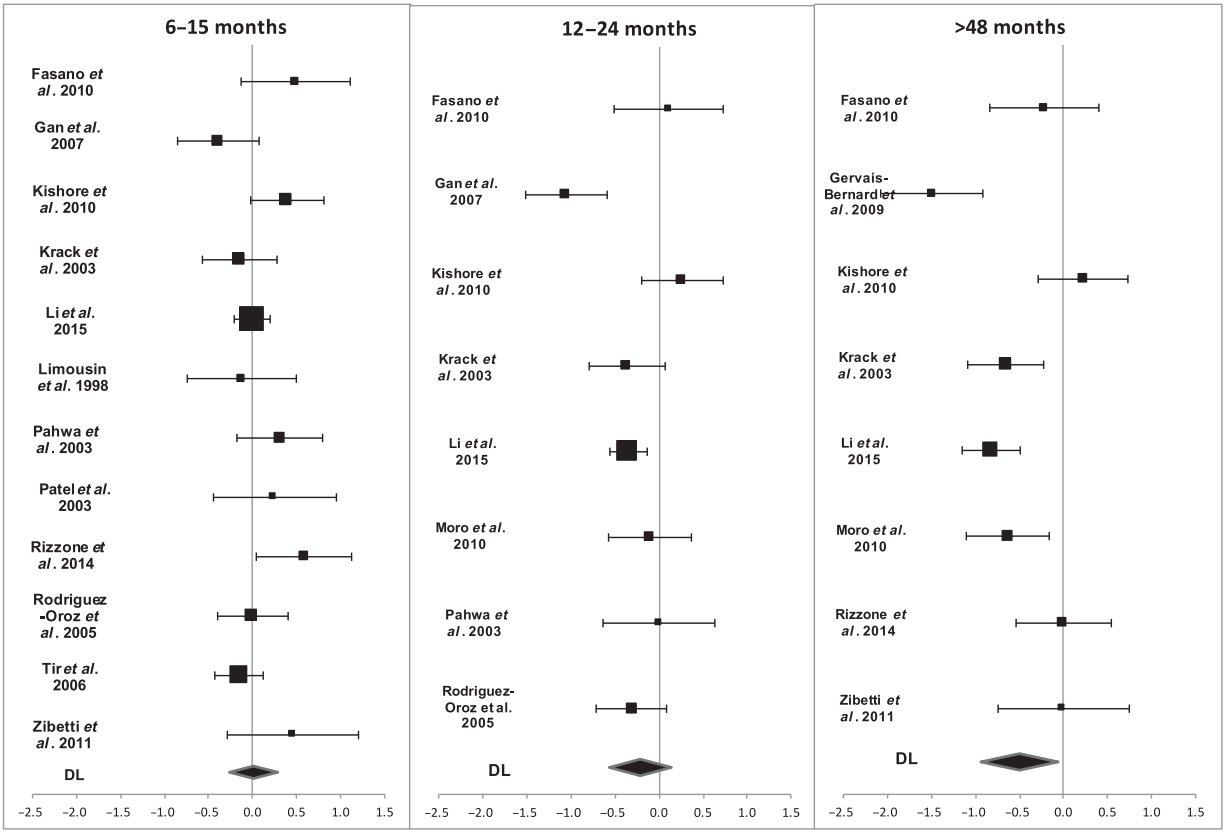

Figure 3 Summary of estimate of change in gait from pre-operative (Med-On) to different follow-up periods (Med-On/Stim-On). DL, DerSimonian and Laird method.

studies at the follow-up of 6–15 months, 253 patients from four studies at the follow-up of 24–48 months and 146 patients from four studies at follow-up of >48 months were included (Fig. 1c). The mean effects were 1.82 (95% CI: 0.76–2.88; $P = 0.009$), 1.52 (95% CI: 0.74–2.30; $P = 0.009$), and 1.21 (95% CI: 0.05–2.36; $P = 0.045$), respectively (Fig. 4). The average (SD) change was −1.4 (0.5) (mean change from 2.26 to 0.82), −1.3 (0.4) (2.43–1.13), and −1.1 (0.5) (2.48–1.38) points at the different follow-up periods, respectively. Heterogeneity was high at all three follow-up periods ($P < 0.001$, $Q = 95.91$, $I^2 = 95.83\%$; $P = 0.009$, $Q = 17.33$, $I^2 = 82.69\%$ and $Q = 17.52$, $P = 0.0006$, $I^2 = 82.87\%$, respectively).

For the Med-On/Stim-On condition, FOG data of 337 patients from five studies, 244 patients from three studies and 172 patients from five studies were included for the follow-ups of 6–15, 24–48 and >48 months. No significant effect was found for any follow-up period [6–15 months: mean effect, 0.14 (95% CI, −0.17–0.46), $P = 0.278$; 24–48 months: mean effect, −0.23 (95% CI, −0.97–0.52), $P = 0.32$; >48 months: mean effect, −0.38 (95% CI, −1.03–0.28), $P = 0.188$; Fig. 5]. Heterogeneity was low for the follow-ups of 6–15 and 24–48 months ($Q = 4.15$, $P = 0.387$, $I^2 = 3.52\%$ and $Q = 3.31$, $P = 0.1909$, $I^2 = 39.6\%$, respectively), whereas a high risk of heterogeneity was found for the longer follow-up ($Q = 18.0$, $P = 0.0012$, $I^2 = 77.8\%$). The average (SD) change in FOG was −0.1 (0.1) (mean change from 0.50 to 0.40), +0.2 (0.2) (from 0.40 to 0.60) and +0.4 (0.5) (from 0.52 to 0.90) points at the different follow-up periods, respectively.

Discussion

This meta-analysis of STN-DBS effects has shown a robust improvement in gait and FOG in the Med-Off/Stim-On condition on short- and long-term assessments, whereas the effect in the Med-On/Stim-On condition is a slight worsening between the first and fourth year after surgery. Pre-operative levodopa responsiveness of the UPDRS-III is the strongest predictor of this beneficial effect on gait. The effect on FOG was similar in both conditions. Although this main finding has been shown in previous studies for

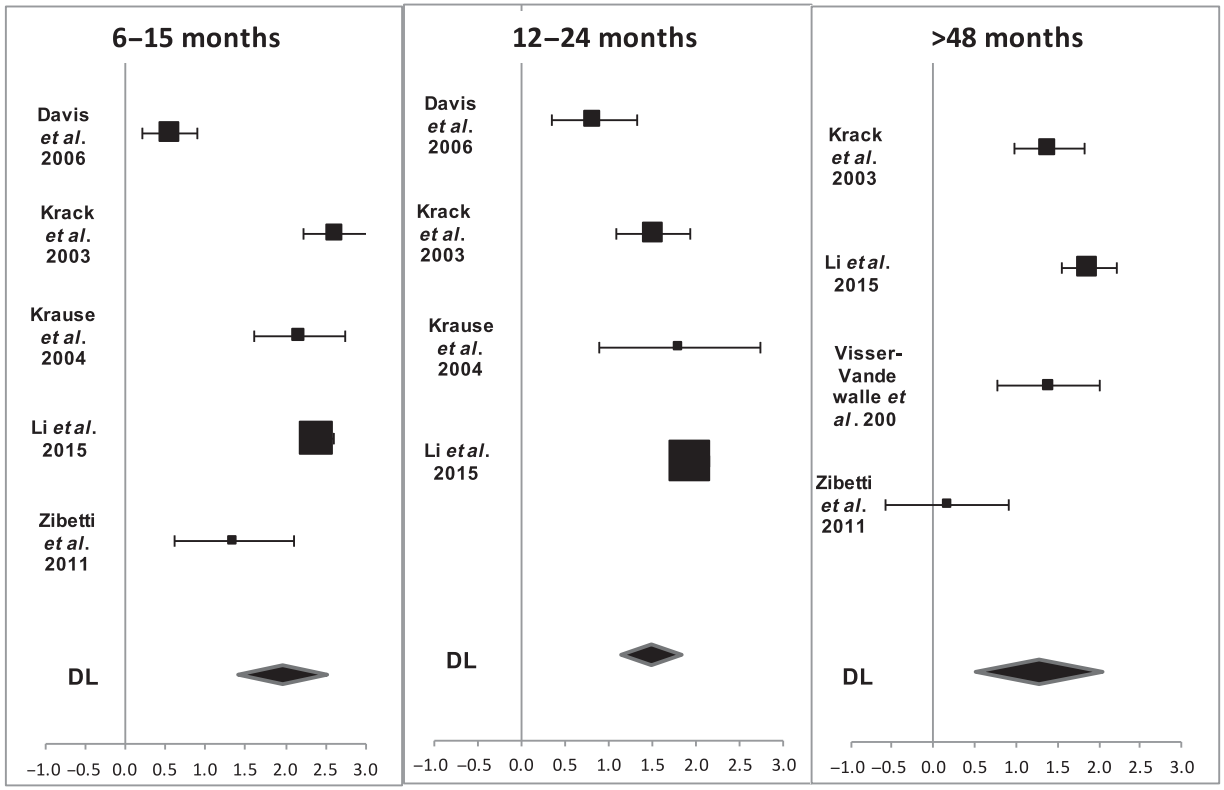

Figure 4 Summary of estimate of change in freezing of gait from pre-operative (Med-Off) to different follow-up periods (Med-Off/Stim-On). DL, DerSimonian and Laird method.

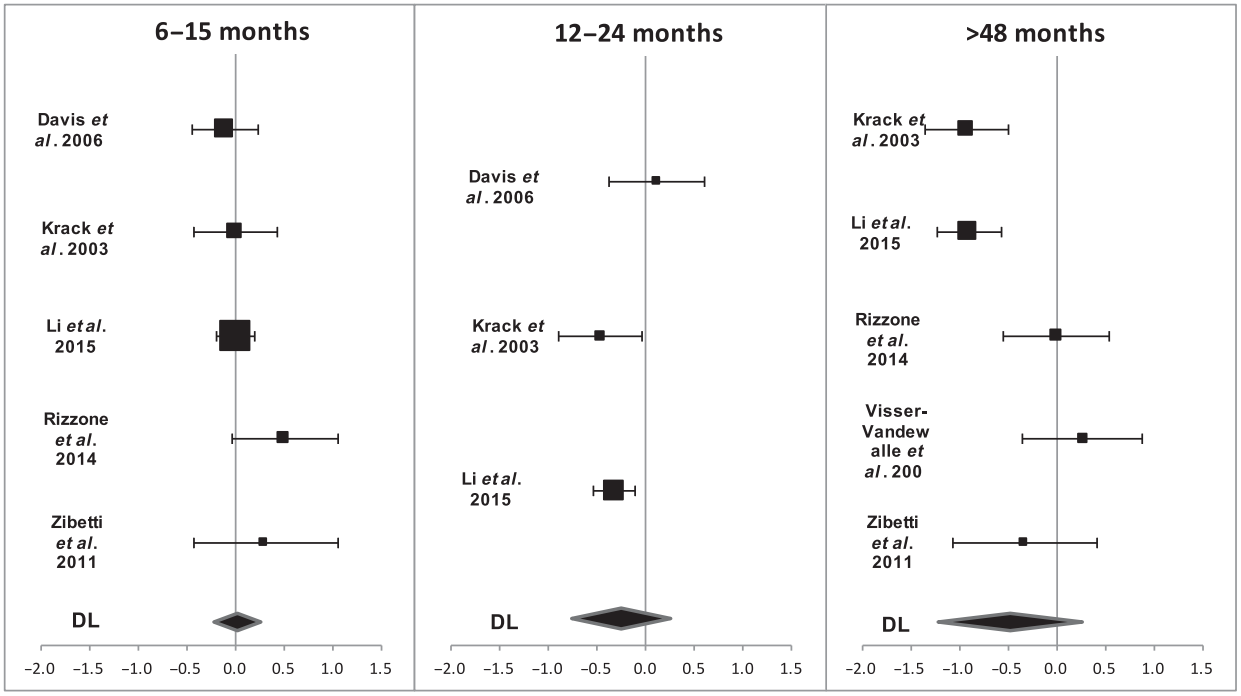

Figure 5 Summary of estimate of change in freezing of gait from pre-operative (Med-On) to different follow-up periods (Med-On/Stim-On). DL, DerSimonian and Laird method.

shorter intervals, it has never been studied and confirmed with meta-analytical methods.

Measuring gait and FOG in both conditions is a surrogate parameter for the two important extremes of mobility for the stimulated patient, i.e. the situation when medications have the best or worst effects. This illustrates the patient's spectrum of mobility. When looking at Fig. 1 for both gait and FOG, the patients apparently have only very mild symptoms that cannot be significantly improved with STN-DBS.

Gait, freezing and posture lose their dopa sensitivity with progression in PD [3,23–25]. The current data show that the same also applies to STN-DBS, whereas other symptoms like rigidity and tremor can still be treated long-term [1]. The amount of improvement compared with the baseline Off for gait is ~60% at 1 year and is reduced to ~45% at >48 months. This improvement is attributed to the favorable effect of STN-DBS on some gait parameters such as stride length, gait velocity and duration, and associated cognitive functions as explored by previous studies [7–11]. Gait improvement was attributed to the dopaminergic-like effect of DBS, whereas gradual diminution of response was attributed to the natural progressive course of the disease and the emergence of non-dopaminergic aspects, cognitive decline and co-existence of co-morbidities [3,23–26]. The long disease duration in the studies included here (mean 13 years) might explain the development of non-dopaminergic aspects of gait unresponsive to levodopa.

However, deleterious effects of STN-DBS on postural control and gait were found with regard to step initiation [27], balance confidence [28], anticipatory postural adjustments [29], compensatory stepping [30] and reaction time during postural perturbations [31,32]. It is unknown whether these effects are related to DBS or to disease progression. In contrast, a role of lowered LEDD post-stimulation in gradual gait worsening is unlikely as demonstrated by the lack of correlation between gait changes post-operatively and LEDD decrease. Thus, further studies are warranted to investigate possible mechanisms leading to worse gait performance under combined treatment.

Remarkably, although pre-operative gait severity played a role as a predictor at the follow-up of 24–48 months, levodopa responsiveness of the UPDRS-III was the strongest predictor of the short- and long-term effects of DBS on gait, indicating that the higher the response of motor performance to levodopa, the more beneficial the effect of DBS on gait. However, the patients had only a mild gait disturbance and almost no freezing in the On state of medication at baseline. This certainly reflects the selection performed by the centers.

The predictive capacity of levodopa responsiveness is in line with other studies and indicates the dopaminergic-like effect of STN-DBS as the main mechanism of its beneficial effect on gait. Consistent with this, Kleiner-Fisman *et al.* [33] reported that pre-operative levodopa responsiveness was the only predictor of post-stimulation motor outcome rather than pre-operative demographic criteria and LEDD dosage. However, pre-operative levodopa responsiveness of gait was previously described as a predictor for short-term (3-month) improvements in the Med-Off state [34,35]. Age and disease duration at surgery were not related to the short- or long-term effects of DBS on gait. It has to be taken into account that the range of age in the included studies was small, representing the specific selected subject population for DBS and this has to be considered when interpreting the results of the correlation analysis [36]. However, our results are consistent with other studies, showing that these variables are not predictors of the effect of DBS on global motor performance [23,36–39]. One study described disease duration as a predictor for post-stimulation gait improvement after 3 months [34]. The short follow-up period might explain this different finding and older patients are expected to have less improvement of axial/PIGD (postural instability and gait difficulty) symptoms [37].

In agreement with our results, a recent prospective controlled study by Vercruysse *et al.* [19] reported decreased occurrence and severity (by 34%) of FOG at 1 year post-STN-DBS, and this effect was correlated to LEDD change and On/Off fluctuation. Similarly, Niu *et al.* [8] and Fasano *et al.* [3] reported significant improvement of Off and On FOG, compared with baseline, and attributed this to reduced LEDD and improvement in cognitive functions.

It has to be taken into account that, as most of the included studies did not include a control group, a comparison of the effect of STN-DBS with best medical treatment could not have been performed and, in this sense, this meta-analysis is uncontrolled. Therefore, the effects of STN-DBS cannot be interpreted in relation to the effects of best medical treatment.

In conclusion, this rigorously performed meta-analysis shows that gait and FOG can be improved by high-frequency STN-DBS for more than 4 years in the Med-Off/Stim-On condition. Surprisingly, no beneficial effect of STN-DBS was found for the Med-On/Stim-On condition. This is probably due to the preselection of patients who suffered from freezing in the Off condition but not in the On condition. The pre-operative levodopa responsiveness of global motor performance was the strongest predictor of the effect of DBS on gait; it showed better predictive capacity

than severity of gait affection and levodopa responsiveness of gait in this selected subject population. These results confirm the lack of a synergistic effect of both medication and DBS. Although the UPDRS is a useful scale to assess multivariate aspects of PD, it shows only limited information about gait and FOG. More specific gait features (e.g. gait variability, gait asymmetry), which are related to FOG and falls, are not detected with the UPDRS. Future long-term studies should therefore analyze the effect of STN-DBS on gait and FOG as a primary outcome and with more sensitive measures. UPDRS subitems should at least be listed to allow the estimation of effects in meta-analyses such as this.

Acknowledgements

C.S. was funded by the Coppenrath-Stiftung, Geeste/Groß-Hesepe, Niedersachsen, Germany.

Disclosure of conflicts of interest

G.D. has received co-funding for the EARLYSTIM study from Medtronic. The other authors report no financial or other conflicts of interest. G.D. has received lecture fees from Medtronic, Almirall and Desitin and has been serving as a consultant for Medtronic, Sapiens and Boston Scientific. He received royalties from Thieme publishers. He is a government employee and receives, through his institution, funding for his research from the German Research Council, German Ministry of Education and Health and Medtronic.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Characteristics of studies included with gait scores (item 29).
Table S2. Characteristics of studies of freezing of gait (FOG) outcome (item 14) that were included in the meta-analysis.
Table S3. Correlation (Spearman) between the magnitude of change from baseline to follow-up in gait (effect of deep brain stimulation: follow-up gait value minus baseline value) and different variables.
Table S4. Results of the multivariate backward stepwise regression analysis with the magnitude of change from baseline to follow-up in gait (effect of deep brain stimulation: follow-up value minus baseline value) as dependent variable and different variables as independent variables.
Table S5. Source of funding of the included studies.

References

1. Deuschl G, Agid Y. Subthalamic neurostimulation for Parkinson's disease with early fluctuations: balancing the risks and benefits. *Lancet Neurol* 2013; **12:** 1025–1034.
2. Potter-Nerger M, Volkmann J. Deep brain stimulation for gait and postural symptoms in Parkinson's disease. *Mov Disord* 2013; **28:** 1609–1615.
3. Fasano A, Aquino CC, Krauss JK, Honey CR, Bloem BR. Axial disability and deep brain stimulation in patients with Parkinson disease. *Nat Rev Neurol* 2015; **11:** 98–110.
4. Collomb-Clerc A, Welter ML. Effects of deep brain stimulation on balance and gait in patients with Parkinson's disease: a systematic neurophysiological review. *Neurophysiol Clin* 2015; **45:** 371–388.
5. Fasano A, Daniele A, Albanese A. Treatment of motor and non-motor features of Parkinson's disease with deep brain stimulation. *Lancet Neurol* 2012; **11:** 429–442.
6. Stolze H, Klebe S, Poepping M, *et al*. Effects of bilateral subthalamic nucleus stimulation on parkinsonian gait. *Neurology* 2001; **57:** 144–146.
7. Ferrarin M, Rizzone M, Bergamasco B, *et al*. Effects of bilateral subthalamic stimulation on gait kinematics and kinetics in Parkinson's disease. *Exp Brain Res* 2005; **160:** 517–527.
8. Niu L, Ji LY, Li JM, *et al*. Effect of bilateral deep brain stimulation of the subthalamic nucleus on freezing of gait in Parkinson's disease. *J Int Med Res* 2012; **40:** 1108–1113.
9. McNeely ME, Earhart GM. Medication and subthalamic nucleus deep brain stimulation similarly improve balance and complex gait in Parkinson disease. *Parkinsonism Relat Disord* 2013; **19:** 86–91.
10. Johnsen EL, Mogensen PH, Sunde NA, Ostergaard K. Improved asymmetry of gait in Parkinson's disease with DBS: gait and postural instability in Parkinson's disease treated with bilateral deep brain stimulation in the subthalamic nucleus. *Mov Disord* 2009; **24:** 590–597.
11. Seri-Fainshtat E, Israel Z, Weiss A, Hausdorff JM. Impact of sub-thalamic nucleus deep brain stimulation on dual tasking gait in Parkinson's disease. *J Neuroeng Rehabil* 2013; **10:** 38.
12. Weiss D, Walach M, Meisner C, *et al*. Nigral stimulation for resistant axial motor impairment in Parkinson's disease? A randomized controlled trial. *Brain* 2013; **136** (Pt 7)**:** 2098–2108.
13. Khoo HM, Kishima H, Hosomi K, *et al*. Low-frequency subthalamic nucleus stimulation in Parkinson's disease: a randomized clinical trial. *Mov Disord* 2014; **29:** 270–274.
14. Sidiropoulos C, Walsh R, Meaney C, Poon YY, Fallis M, Moro E. Low-frequency subthalamic nucleus deep brain stimulation for axial symptoms in advanced Parkinson's disease. *J Neurol* 2013; **260:** 2306–2311.
15. Vallabhajosula S, Haq IU, Hwynn N, *et al*. Low-frequency versus high-frequency subthalamic nucleus deep brain stimulation on postural control and gait in Parkinson's disease: a quantitative study. *Brain Stimul* 2015; **8:** 64–75.

16. Perez-Lloret S, Negre-Pages L, Damier P, *et al*. Prevalence, determinants, and effect on quality of life of freezing of gait in Parkinson disease. *JAMA Neurol* 2014; **71:** 884–890.
17. Latt MD, Lord SR, Morris JG, Fung VS. Clinical and physiological assessments for elucidating falls risk in Parkinson's disease. *Mov Disord* 2009; **24:** 1280–1289.
18. Follett KA, Weaver FM, Stern M, *et al*. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2010; **362:** 2077–2091.
19. Vercruysse S, Vandenberghe W, Munks L, Nuttin B, Devos H, Nieuwboer A. Effects of deep brain stimulation of the subthalamic nucleus on freezing of gait in Parkinson's disease: a prospective controlled study. *J Neurol Neurosurg Psychiatry* 2014; **85:** 871–877.
20. Kontopantelis E, Reeves D. MetaEasy: a meta-analysis add-in for Microsoft Excel. *J Stat Softw* 2009; **30:** 1–25.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7:** 177–188.
22. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21:** 1539–1558.
23. Fasano A, Romito LM, Daniele A, *et al*. Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. *Brain* 2010; **133:** 2664–2676.
24. Krack P, Batir A, Van Blercom N, *et al*. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 2003; **349:** 1925–1934.
25. Vercruysse S, Gilat M, Shine JM, Heremans E, Lewis S, Nieuwboer A. Freezing beyond gait in Parkinson's disease: a review of current neurobehavioral evidence. *Neurosci Biobehav Rev* 2014; **43:** 213–227.
26. Zibetti M, Merola A, Rizzi L, *et al*. Beyond nine years of continuous subthalamic nucleus deep brain stimulation in Parkinson's disease. *Mov Disord* 2011; **26:** 2327–2334.
27. Rocchi L, Carlson-Kuhta P, Chiari L, Burchiel KJ, Hogarth P, Horak FB. Effects of deep brain stimulation in the subthalamic nucleus or globus pallidus internus on step initiation in Parkinson disease: laboratory investigation. *J Neurosurg* 2012; **117:** 1141–1149.
28. St George RJ, Carlson-Kuhta P, Nutt JG, Hogarth P, Burchiel KJ, Horak FB. The effect of deep brain stimulation randomized by site on balance in Parkinson's disease. *Mov Disord* 2014; **29:** 949–953.
29. St George RJ, Carlson-Kuhta P, Burchiel KJ, Hogarth P, Frank N, Horak FB. The effects of subthalamic and pallidal deep brain stimulation on postural responses in patients with Parkinson disease. *J Neurosurg* 2012; **116:** 1347–1356.
30. St George RJ, Carlson-Kuhta P, King LA, Burchiel KJ, Horak FB. Compensatory stepping in Parkinson's disease is still a problem after deep brain stimulation randomized to STN or GPi. *J Neurophysiol* 2015; **114:** 1417–1423.
31. Shivitz N, Koop MM, Fahimi J, Heit G, Bronte-Stewart HM. Bilateral subthalamic nucleus deep brain stimulation improves certain aspects of postural control in Parkinson's disease, whereas medication does not. *Mov Disord* 2006; **21:** 1088–1097.
32. Hausdorff JM, Gruendlinger L, Scollins L, O'Herron S, Tarsy D. Deep brain stimulation effects on gait variability in Parkinson's disease. *Mov Disord* 2009; **24:** 1688–1692.
33. Kleiner-Fisman G, Fisman DN, Sime E, Saint-Cyr JA, Lozano AM, Lang AE. Long-term follow up of bilateral deep brain stimulation of the subthalamic nucleus in patients with advanced Parkinson disease. *J Neurosurg* 2003; **99:** 489–495.
34. Yamada K, Goto S, Hamasaki T, Kuratsu JI. Effect of bilateral subthalamic nucleus stimulation on levodopa-unresponsive axial symptoms in Parkinson's disease. *Acta Neurochir* 2008; **150:** 15–22; discussion.
35. Charles PD, Van Blercom N, Krack P, *et al*. Predictors of effective bilateral subthalamic nucleus stimulation for PD. *Neurology* 2002; **59:** 932–934.
36. Shalash A, Alexoudi A, Knudsen K, Volkmann J, Mehdorn M, Deuschl G. The impact of age and disease duration on the long term outcome of neurostimulation of the subthalamic nucleus. *Parkinsonism Relat Disord* 2014; **20:** 47–52.
37. Welter ML, Houeto JL, Tezenas du Montcel S, *et al*. Clinical predictive factors of subthalamic stimulation in Parkinson's disease. *Brain* 2002; **125:** 575–583.
38. Tsai ST, Lin SH, Chou YC, *et al*. Prognostic factors of subthalamic stimulation in Parkinson's disease: a comparative study between short- and long-term effects. *Stereotact Funct Neurosurg* 2009; **87:** 241–248.
39. Castrioto A, Lozano AM, Poon YY, Lang AE, Fallis M, Moro E. Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation. *Arch Neurol* 2011; **68:** 1550–1556.