

Efficacy of pallidal stimulation in isolated dystonia: a systematic review and meta-analysis

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The aim of this review was to provide strong clinical evidence of the efficacy of deep brain stimulation (DBS) of the globus pallidus internus (GPi) in isolated inherited or idiopathic dystonia. Eligible studies were identified after a systematic literature review of the effects of bilateral GPi-DBS in isolated dystonia. Absolute and percentage changes from baseline in the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) motor and disability scores were pooled, and associations between treatment effect and patient characteristics were explored using meta-regression. In total, 24 studies were included in the meta-analysis, comprising 523 patients. The mean absolute and percentage improvements in BFMDRS motor score at the last follow-up (mean 32.5 months; 24 studies) were 26.6 points [95% confidence interval (CI), 22.4–30.8] and 65.2% (95% CI, 59.6–70.7), respectively. The corresponding changes in disability score at the last follow-up (mean 32.9 months; 14 studies) were 6.4 points (95% CI, 5.0–7.8) and 58.6% (95% CI, 50.3–66.9). Multivariate meta-regression of absolute scores indicated that higher BFMDRS motor and disability scores before surgery, together with younger age at time of surgery, were the main factors associated with significantly better DBS outcomes at the latest follow-up. Reporting of safety data was frequently inconsistent and could not be included in the meta-analysis. In conclusion, patients with isolated inherited or idiopathic dystonia significantly improved after GPi-DBS. Better outcomes were associated with greater dystonia severity at baseline. These findings should be taken into consideration for improving patient selection for DBS.

Introduction

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements, postures or both [1]. The disorder can induce severe disability and have an important impact on patients' quality of life (QoL) [2–4]. When available medical treatment has failed, bilateral deep brain stimulation (DBS) of the globus pallidus internus (GPi) is considered safe and

effective, in particular in patients with isolated inherited or idiopathic (formerly primary) segmental or generalized dystonia [5–7].

To date, three meta-analyses have assessed the effects of DBS in patients with isolated dystonia [8–10]. These analyses calculated the change in score from before surgery to after surgery as a percentage of the baseline score. This value traditionally gives results that are considered clinically relevant for physicians, easily understood by patients and do not depend on the actual scale used to measure the outcome. However, the percentage change is highly dependent on the patient's baseline score. For the

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same absolute number of points gained on a scale, a patient with a higher baseline score will mathematically have a smaller percentage improvement than a patient with a lower baseline. Similarly, the same percentage could represent vastly different changes on the actual measurement scale, depending on where the patients started. Therefore, interpreting percentage change without knowledge of the population's baseline characteristics does not reflect the role of the initial dystonia severity in prognosis for DBS. Statistically, a method that has higher statistical power would be better, such as the absolute change in score, which is not sensitive to changes in baseline characteristics and is mathematically more appropriate in the context of a meta-analysis [11]. The absolute change better reflects improvements in health experienced by patients with dystonia after treatment with DBS, as it shows the actual number of points by which patients have improved, whereas the percentage change is skewed in favor of a lower baseline dystonia status.

Therefore, we analyzed the available data primarily using absolute changes from baseline, but also reporting the corresponding percentage change, to provide statistical validity as well as 'practical' and comparative clinical relevance for physicians. Our aims were to: (i) systematically identify and summarize all existing evidence on the efficacy and safety of bilateral GPi-DBS in isolated dystonia; (ii) synthesize the available evidence with statistical meta-analytic methods where feasible; and (iii) explore the effects of study-level covariates on study results.

Methods

Systematic review

The systematic review was based on a literature search conducted in PubMed, Embase, Medscape and the Cochrane Central Register of Controlled Trials from January 1990 to November 2015. The search dates pre-date the publication of the new classification of dystonia [1], so the classical definition of 'primary' dystonia from 1998 [12] was used for study identification and selection. Primary dystonia studies were reclassified using the new classification as isolated (inherited or idiopathic) dystonia, with further specification of idiopathic or inherited types where applicable.

Publications reporting efficacy and/or safety and/or QoL outcomes for patients with isolated dystonia treated with DBS were selected. Editorials, letters, case reports, non-systematic reviews and papers published before 1990, in a language other than English, German, French, Italian or Spanish, or reporting

results on <10 patients were excluded. Further search strategy details and the selection criteria are in Appendix S1. Precautions were taken to avoid inclusion of studies reporting results on the same patients. Authors were contacted in case of doubt.

Statistical analysis

Data on study and patient characteristics, efficacy, QoL and safety parameters were extracted. For accurate calculation of absolute changes from baseline, studies were included in the meta-analysis only if sufficient data using relevant statistical elements were reported, i.e. means and measures of precision (e.g. SDs or CIs for continuous outcomes; frequencies for binary outcomes). For studies not reporting results at study level, or when the study only reported mean changes in score but not the precision, reported individual patient data were used to derive aggregated results.

As we aimed to show corresponding percentage changes for each study included, missing data on percentage score were imputed. Mean percentage changes in scores were calculated by dividing the mean absolute change in score by the mean baseline score and multiplying by 100. The missing precision could not be approximated using available data; therefore, the median precision observed in other studies of the dataset for the same outcome was used as a proxy (a commonly used approach).

Individual study results for each outcome were pooled at 6 and 12 months and at the last mean follow-up. Fixed-effect and random-effect models were applied, using the inverse variance approach. The most appropriate model in each meta-analysis was chosen based on the presence of heterogeneity (i.e. 'statistical heterogeneity' is present when observed intervention effects are more different from each other than one would expect due to random error/chance alone [13]), assessed by Cochran's Q test and I^2 statistics. The latter measure can be regarded as the percentage of the total variability in a set of effect sizes due to true heterogeneity and interpreted according to the classification of Higgins and Thompson in 2002 (25%, low level of heterogeneity; 50%, moderate; 75%, high) [14]. In the presence of significant heterogeneity, the random-effects analysis is the preferred approach.

The effect of study characteristics on heterogeneity in the observed effects was explored using meta-regression. Based on previous literature findings and clinician input, as well as data available in identified studies, the characteristics included in the meta-regression were: duration of follow-up, baseline scores,

study location, publication year, gender split, mean age at onset of disease and surgery, duration of disease, proportion of life lived with dystonia (PLD) (defined as duration of disease divided by age at baseline, multiplied by 100), and proportion of dystonia 1 protein (DYT1)-positive patients. Due to lack of reporting in the identified studies, it was not possible to include type of dystonia, comorbidities (e.g. depression, anxiety), dystonia-related physical complications (e.g. skeletal deformities, fixed positions), medication and stimulation parameters. Meta-regression was carried out on absolute changes at the last follow-up (due to their greater statistical power [11]). Both univariate and multivariate models are presented. All analyses were implemented in STATA SE version 8.2 (Stata Corp., College Station, TX, USA).

Results

Systematic review

In total, the literature search revealed 2501 citations (initial and update search), resulting in identification of 58 relevant articles corresponding to 54 distinct studies (Fig. 1). Most were bilateral DBS of the GPi. All were uncontrolled, apart from two studies that started as randomized controlled trials for the first 3 months post-surgery before being extended as observational studies [5,15]. Another study was not a randomized controlled trial, but included a double-blind evaluation with and without stimulation 3 months post-surgery (patients served as their own control) [6].

Of the 54 studies identified, 24 reported usable data on the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) [16]; all 24 studies included movement scores (range 0–120), whereas 14 also reported disability scores (range 0–30) (see Table S1 for patient characteristics). Data of efficacy from 12 studies were not usable, as relevant data and/or statistics were insufficiently reported or not reported at all.

Ten studies reported results on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) [17]. However, in most cases, these were poorly reported, with insufficient details on changes in scores. Therefore, TWSTRS was not included in the meta-analysis.

Similarly, evidence on patient-reported outcomes (e.g. QoL) was insufficient for inclusion in the meta-analysis; only six studies reported QoL data and those that did used different outcomes and timepoints. The collected QoL data are provided in Table S2.

Safety outcomes were reported in 33 included studies and details are outlined in Table S3. To summarize, the most commonly reported adverse events (AEs) were device- or surgery-related complications/

failures (e.g. electrode or cable fracture) (reported in 23 studies), stimulation-related AEs (18 studies) and wound problems or infections (15 studies). Intracranial hemorrhages/bleedings, mostly asymptomatic, were reported in five studies. Potentially life-threatening AEs were reported in two studies, acute relapse of dystonia in four patients due to loss of stimulation following hardware issues. However, reporting of safety outcomes was generally inconsistent and not systematic, preventing detailed analysis of severity, time to resolution, relation to the procedure, device, stimulation or pre-existing condition. Therefore, safety data were excluded from the meta-analysis.

In total, the 24 studies in the meta-analysis included 523 patients (average 22 patients per study, range 10–54) with an average follow-up of 32.5 months (range 6–72 months). The BFMDRS mean score at time of surgery was 44.0 (SD 13.6; range 16.8–72.2) for movement and 11.3 (SD 3.4; range 4.7–16.5) for disability. Both genders were equally represented. Patients were on average 35.1 years old (SD 15.8; range 12.3–64.5) at time of surgery, and had on average been suffering from dystonia for 12.6 years (SD 4.8; range 5.1–24). Two studies focused only on pediatric patients (<18 years at time of surgery), but children were present in eight other studies in the meta-analysis (Table S1).

Efficacy outcomes (meta-analysis)

BFMDRS motor scores

Both absolute and percentage changes showed that DBS significantly improved motor scores at 6 months post-surgery, with continued improvement until the last follow-up. Mean absolute changes increased from a 23.8-point improvement (95% CI, 18.5–29.1) at 6 months to 26.6 points (95% CI, 22.4–30.8) at the last follow-up (mean 32.5 months, range 6–72 months) (Fig. 2a). The mean percentage improvement also increased from 59.0% (95% CI, 51.2–66.7) at 6 months to 65.2% (95% CI, 59.6–70.7) at the last follow-up (Fig. 2a). A summary of the BFMDRS motor scores at 6 months and the latest timepoints are outlined in Table 1, with full details (all timepoints) in Appendix S2.

BFMDRS disability scores

Deep brain stimulation significantly improved BFMDRS disability scores in dystonia at 6 months post-surgery, and patients continued to improve until the last follow-up. Mean absolute changes increased from a 4.8-point improvement (95% CI, 3.1–6.6) at 6 months to 6.4 points (95% CI, 5.0–7.8) at the last follow-up (mean 32.9 months, Fig. 2b). The mean percentage improvement also increased from 44.2%

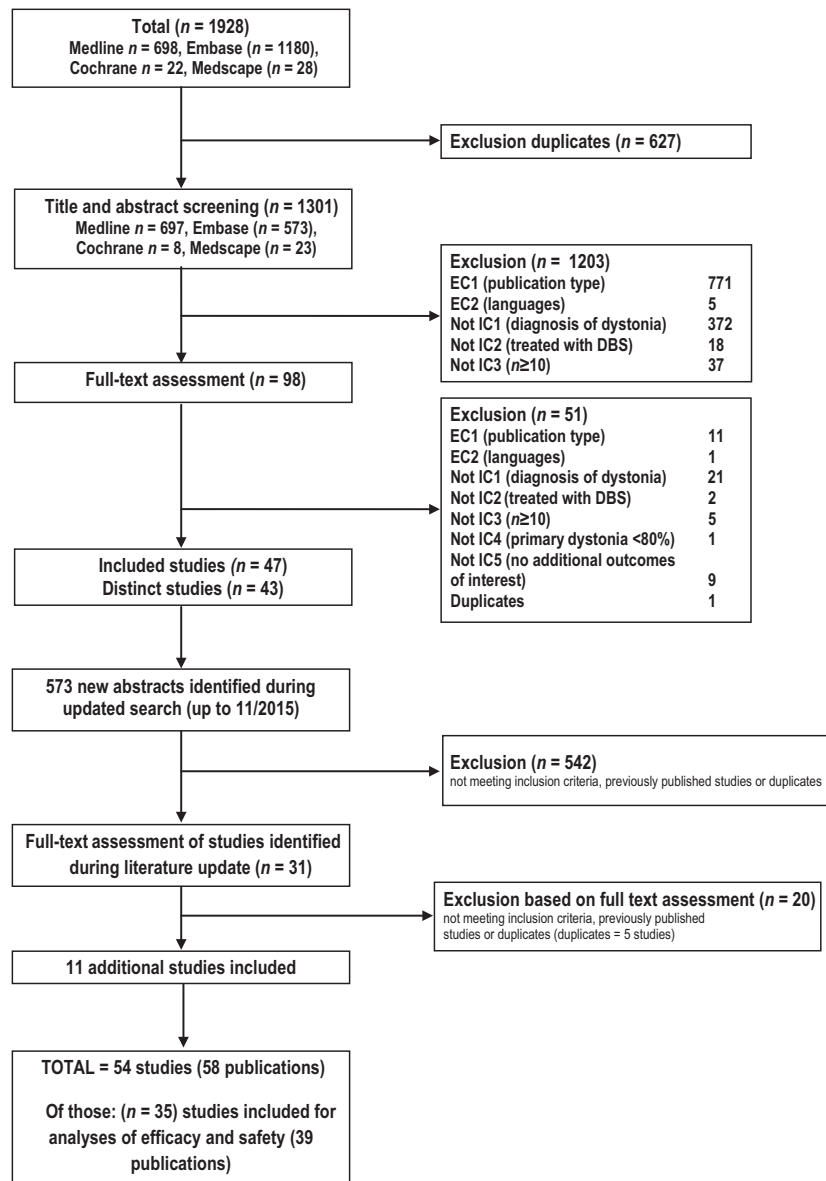


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. DBS, deep brain stimulation. EC, Exclusion criteria; IC, inclusion criteria.

(95% CI, 40.3–48.1) at 6 months to 58.6% (95% CI, 50.3–66.9) at the last follow-up (Fig. 2b). A summary of the BFMDRS disability scores at 6 months and the latest timepoints are outlined in Table 1, with full details (all timepoints) in Appendix S2.

Effect of covariates (univariate and multivariate meta-regression)

Covariates used in meta-regression models are included in Table S1. After univariate meta-regression, significantly greater improvements in BFMDRS motor and disability scores post-DBS were associated with higher BFMDRS motor and disability scores (i.e. greater impairment) at baseline, younger age at time

of surgery, younger age at disease onset, greater PLD and DYT1-positive status (Tables 2 and 3). When combined in a multivariate model (apart from DYT1-positive status, which was reported in only a subset of studies), only higher BFMDRS baseline scores remained significant, thus identifying them as the main predictors of response. As an aside, a multivariate model restricted to the three age-related covariates showed that only age at surgery remained significant.

Discussion

This systematic review and meta-analysis provides up-to-date evidence of the efficacy of bilateral GPi-DBS in patients with isolated dystonia. GPi-DBS

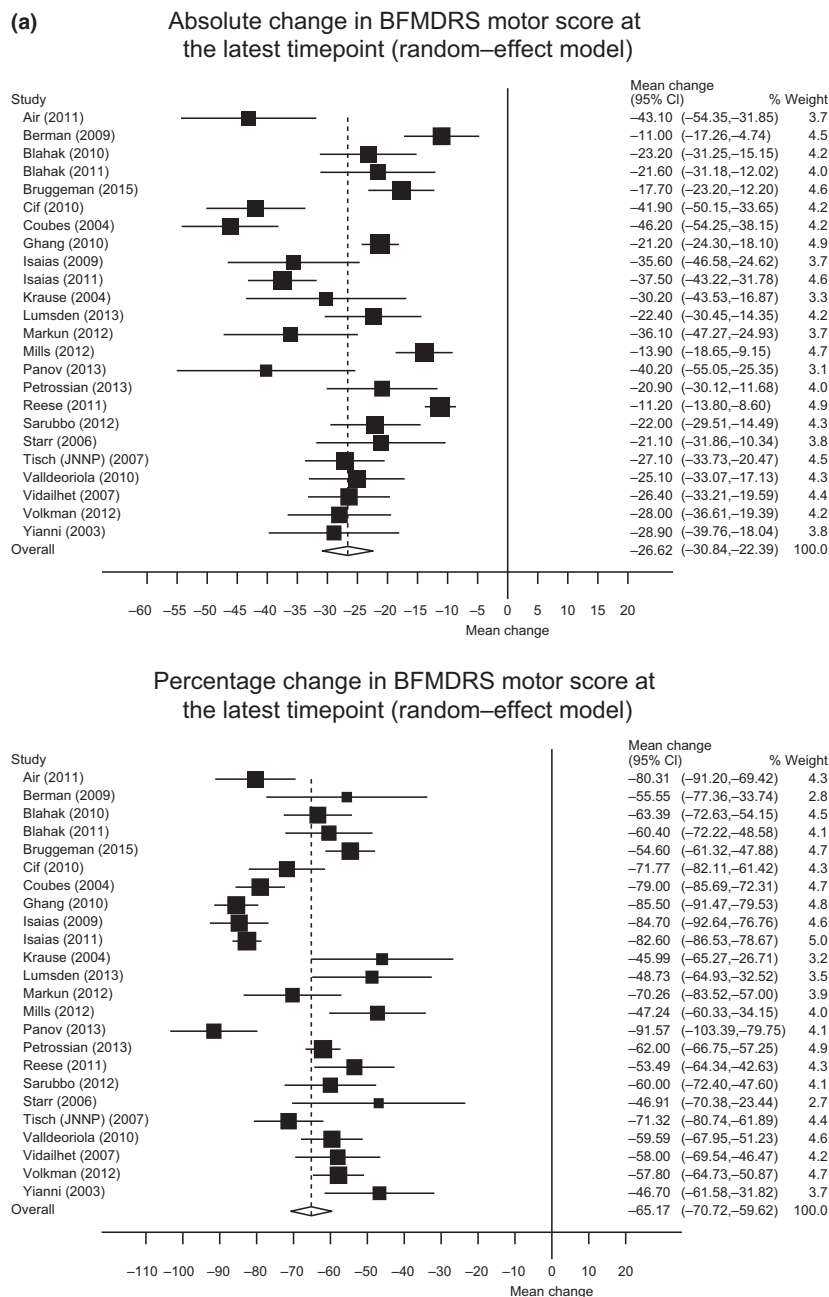


Figure 2 Forest plots of changes in Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) at last follow-up. (a) Absolute (top) and percentage (bottom) change in motor; (b) absolute (top) and percentage (bottom) change in disability. CI, confidence interval. Negative changes indicate improvement.

significantly improved both motor function and ability to perform activities of daily living in patients with inherited or idiopathic isolated dystonia, measured by absolute and percentage changes in the BFMDRS score from baseline. Large effect sizes were consistently reported, in particular with regard to the BFMDRS scores (mean changes in the BFMDRS movement score: -11.0 to -46.2 points and 46.0–91.6%; mean changes in the BFMDRS disability score: -1.9 to -10.2 points and 37.3–79.1%), and effects were maintained for up to 72 months.

Furthermore, both univariate and multivariate meta-regression indicated a significant positive correlation between a greater effect of DBS and younger age at time of surgery and greater impairment at baseline (i.e. higher BFMDRS motor and disability scores). When interpreting the results, it should be considered that patients with initial higher BFMDRS scores had more room for improvement, whereas the effect in less impaired patients might have been skewed according to a floor effect. It should also be noted that BFMDRS scores may not adequately reflect severity

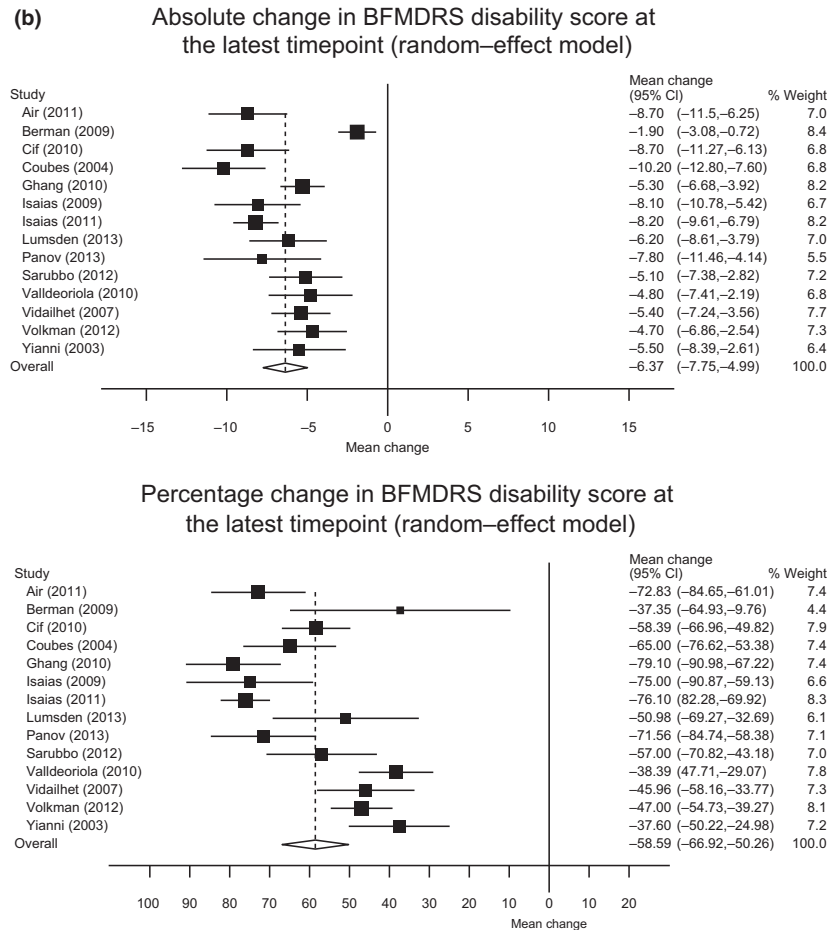


Figure 2 Continued.

of disease in focal or segmental dystonia. Only the univariate meta-regression showed a positive, significant relationship with greater PLD and DYT1-positive status.

Our findings support and expand results from previous analyses, which found consistent and large benefits across studies. One review separated patients with dystonia into two subtypes, one with good evidence of favorable outcome and one with less predictable outcome, and found that GPi-DBS was more effective long-term in patients with severe isolated (inherited or idiopathic) generalized and cervical dystonia [10]. Another meta-analysis showed that the mean percentage change in the BFMDRS score from baseline was 51.8% (range -34% to 100%) post-surgery (although it is unclear at what timepoint the data were analyzed) [8].

Although data on improvement in the TWSTRS scores in patients with cervical dystonia could not be meta-analyzed due to insufficient details on changes in scores, individual study results support the positive impact of DBS in patients with cervical dystonia, with

up to 40–70% improvements in the total TWSTRS scores.

Our univariate meta-regression showed that absolute BFMDRS motor and disability scores decreased more after DBS with greater PLD. This differs from previous analysis in children demonstrating a negative correlation between PLD and percentage BFMDRS [18]. It was argued that measuring absolute changes in BFMDRS after DBS would be a fairer representation of the effects of DBS on the most severely affected cases [18]. The patients included in our large meta-analysis were on average 35.1 years old (SD 15.8; range 12.3–64.5) at time of surgery, and had been suffering from dystonia for an average of 12.6 years (SD 4.8; range 5–24).

Although younger age at DBS surgery confers an advantage for DBS dystonia reduction, thus strongly supporting DBS in childhood, DBS is also effective in adults. Indeed, our univariate analysis demonstrated that patients with severe dystonia who have lived with dystonia for many years responded well to DBS. Other results are in contrast with previous analyses.

Table 1 Absolute and percentage changes in Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) [16] motor and disability scores (random-effects model)

	BFMDRS motor score				BFMDRS disability score			
	No. of studies	Months after surgery (mean/median) (range)	Pooled absolute mean change from meta-analysis (95% CI)	Pooled percentage mean change from meta-analysis, (%) (95% CI)	No. of studies	Months after surgery (mean/median) (range)	Pooled absolute mean change from meta-analysis (95% CI)	Pooled percentage mean change from meta-analysis, (%) (95% CI)
Analysis								
At last follow-up	24	32.5/29.5 (6–72)	–26.6 (–30.8 to –22.4)	–65.2 (–70.7 to –59.6)	14	32.9/30 (8–72)	–6.4 (–7.8 to –5.0)	–58.6 (–66.9 to –50.3)
At 6 months	10	6.6/6 (6–9)	–23.8 (–29.1 to –18.5)	–59.0 (–66.7 to –51.2)	6	6.8/6 (6–9)	–4.8 (–6.6 to –3.1)	–44.2 (–48.1 to –40.3)

CI, confidence interval.

One study found that shorter dystonia duration and lower severity score at surgery were associated with significantly greater improvements post-DBS [9], whereas in another study longer duration of symptoms correlated negatively with surgical outcome, with no effect on outcome of DYT1 [8]. However, our systematic review is more extensive than those previously published (a wider search and larger selection of databases). A novel feature of our review is that it also includes both individual patient data and results aggregated at study level; therefore, meta-analysis was the most appropriate statistical tool. Furthermore, it analyzed absolute and percentage changes.

The main limitation of our analysis is linked to the quality of data reported in available publications, which led to 38% of identified studies being excluded at the outset. In particular, no data on QoL effects could be included due to the lack of quality reporting. In addition, some efficacy data were excluded from our meta-analysis as no precision (i.e. SD, standard error or CI) was provided around the mean estimates, or results were reported as medians and ranges. Furthermore, details on patient enrolment (timing, centers) in some studies were poorly reported and, despite precautions (contact with authors, omission of papers with obvious large patient overlap), some partial overlaps, albeit very limited, may exist. The safety analysis presented specific challenges due to wide disparities in the information reported. Some studies focused on the number of events, others on the number of patients experiencing them, and others described the evolution of a few clinically interesting patients. This lack of consistency across studies, as well as the lack of detail on the events reported (type, severity, resolution, relation to surgery, device or condition), prevented meta-analysis and limited reporting to a very generic outline. The limited data also restricted the type of analyses, and subgroup analyses (e.g. by type of dystonia, adult/pediatric populations) could not be performed. Multivariate meta-regression models assessing the impact of all study characteristics were implemented. However, the overall number of studies was limited and ideally more data are necessary to properly assess the joint effect of these variables, i.e. their impact on outcome as well as their correlation with each other. Meta-regression results should only be considered as leads for further investigations and not used to draw definite conclusions.

This review has important implications for future research. In particular, improved and consistent reporting of results, including provision of precision estimates, mean and median values and ranges, is vital for inclusion of studies into meta-analyses. In addition, consistent and thorough reporting of safety data

Table 2 Impact of covariates on efficacy outcomes using univariate meta-regression of absolute changes in Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) [16] motor and disability scores at last follow-up (mean 32.5 months for motor score, 32.9 months for disability score)

Covariate	BFMDRS motor score			BFMDRS disability score		
	No. of studies	Effect (95% CI)	P-value	No. of studies	Effect (95% CI)	P-value
Baseline BFMDRS motor score	23/24	−0.55 (−0.74 to −0.36)	<0.001	13/14	−0.49 (−0.72 to −0.26)	<0.001
Age at onset	21/24	0.41 (0.20 to 0.62)	<0.001	13/14	0.10 (0.02 to 0.17)	0.010
Age at surgery	24/24	0.42 (0.23 to 0.62)	<0.001	14/14	0.11 (0.04 to 0.17)	0.001
Percentage of life with the disease	21/24	−0.38 (−0.61 to −0.14)	0.002	13/14	−0.07 (−0.16 to 0.01)	0.080*
Percentage of DYT1 + patients	17/24	−0.23 (−0.33 to −0.12)	<0.001	11/14	−0.04 (−0.07 to −0.02)	0.002

*A significance level of 10% was used due to the small number of data points in the model. CI, confidence interval; DYT1, dystonia 1 protein.

Table 3 Clinical relevance of the impact of covariates on outcomes with deep brain stimulation (DBS) in dystonia (interpretation of univariate meta-regression using absolute scores)

Covariate	Change in covariate	Clinical relevance to the outcome of DBS in dystonia	
		Effect on average BFMDRS motor score	Effect on average BFMDRS disability score
Impairment at baseline	Increase of 1 point on the average BFMDRS score at baseline	0.55-point decrease	0.49-point decrease
Age at onset of disease	Increase of 1 year in the average age at time of onset	0.41-point decrease	0.10-point decrease
Age at surgery	Increase of 1 year in the average age at time of surgery	0.42-point decrease	0.11-point decrease
PLD	Increase of 1% of life lived with the disease	0.38-point decrease	0.07-point decrease
DYT1-positive status	Increase of 1% of patients who are DYT1-positive	0.23-point decrease	0.04-point decrease

BFMDRS, Burke–Fahn–Marsden Dystonia Rating Scale [16]; DYT1, dystonia 1 protein; PLD, proportion of life lived with dystonia.

is essential. Meta-regression also indicates the need to investigate associations between DBS benefits with specific population characteristics. Finally, data gaps related to patient-reported outcomes such as QoL, which were rarely assessed [19], indicate the need for more comprehensive assessment of the impact of dystonia and DBS from the patient's perspective.

Conclusions

This meta-analysis adds further strong evidence that bilateral GPi-DBS has a significant beneficial clinical impact on patients with isolated dystonia, reflected by both absolute and percentage changes in BFMDRS from baseline. Moreover, benefits continue for successive years over a 3-year follow-up period. Greater impairment at baseline and younger age at DBS surgery were positively related to better outcomes with GPi-DBS. These findings have relevance in clinical practice regarding the timing and selection of patients with dystonia for DBS.

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Disclosure of conflicts of interest

E. Moro has received honoraria from Medtronic for consulting services and lecturing. C. LeReun received consulting fees from Medtronic International Sàrl for her work on this project. J. K. Krauss is a consultant to Medtronic and to Boston Scientific. He received honoraria from AbbVie and fees for speaking from St Jude. A. Albanese received speaker's honoraria from Ipsen, Merz, Medtronic and Boston Scientific. J.-P. Lin has received a New Service and Innovation Grant from Guy's and St Thomas' Charity G, Dystonia Society UK grants, an Action Medical Research grant, unrestricted education grants from Medtronic Ltd for educational meetings and consultancy honoraria from Medtronic Ltd. M. Vidailhet is on a Merz scientific

advisory board. She has received unrestricted research grants from ANR (French National Institute) and from AMADYS and Alliance France Dystonie (patient associations). S. Walleiser Autiero and T.C. Brionne are employees of Medtronic International Sàrl.

Supporting Information

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

Table S1. Patient characteristics at baseline of all studies included in the efficacy and safety meta-analyses.

Table S2. Quality of life after deep brain stimulation of the globus pallidus internus.

Table S3. Safety outcomes reported in bilateral deep brain stimulation of the globus pallidus internus studies.

Appendix S1. Detailed search strategy.

Appendix S2. Full results of meta-analyses regarding efficacy of deep brain stimulation in dystonia at 6, 12 and 24–36 months and at last follow-up.

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Online only

Appendix S1. Detailed search strategy

Identification of studies

Electronic databases

A systematic literature search was carried out in Medline (PubMed), Embase, Medscape (www.medscape.com) and Cochrane Central Register of controlled Trials (http://onlinelibrary.wiley.com/o/cochrane/cochrane_clcentral_articles_fs.html) in order to identify published articles which contain information on the safety and/or efficacy of DBS treatment in dystonia, and on the quality of life of dystonia patients.

Search strategy

All databases were searched for studies published from 1990 to February 2012. This search was updated (in Embase.com, covering Medline and Embase) in August 2014 and November 2015 to identify any additional relevant literature published from March 2012 – November 2015. The search strings, added by in-built filters (delimiters), for the systematic searches in Medline, EmBase, Cochrane library and Medscape are specified in Tables 1–3.

Table 1. Search string Medline

Medline	
No.	Term
1	Dystonia/de OR dystonic disorder!/de OR (dystonia OR dystonic disorder OR dyston? OR hemidyston? OR hemi()dyston? OR torticollis? OR cervical()dyston? OR blepharospasm OR meige()syndrome)/TI,AB
2	deep brain stimulation/de OR (deep()brain OR “DBS” OR pallidal()stimulation OR electrode? OR neurostim? OR electroneurostim? OR electrostim?)/TI,AB OR ((intracerebral? OR pallidal OR pallidus OR pallidum OR “GPI” OR globus(W)pallidus(W)internus or globus(W)pallidus(W)internis or globus(W)pallidus(W)interna) AND stim?)/TI,AB
3	S1 and S2
4	S3 and HUMAN=yes
5	S4 and PY=1990:2012
6	DT=EDITORIAL OR DT=LETTER
7	S5 NOT S6

Table 2. Search string EMBASE

EMBASE	
No.	Term
1	Dystonia/de OR dystonic disorder!/de OR (dystonia OR dystonic disorder OR dyston? OR hemidyston? OR hemi()dyston? OR torticollis? OR cervical()dyston? OR blepharospasm OR meige()syndrome)/TI,AB
2	brain depth stimulation/de OR (deep()brain OR “DBS” OR pallidal()stimulation OR electrode? OR neurostim? OR electroneurostim? OR electrostim?)/TI,AB OR ((intracerebral? OR pallidal OR pallidus OR pallidum OR “GPI” OR globus(W)pallidus(W)internus or globus(W)pallidus(W)internis or globus(W)pallidus(W)interna) AND stim?)/TI,AB
3	S1 and S2
4	S3 and HUMAN=yes
5	S4 and PY=1990:2012
6	DT=EDITORIAL OR DT=LETTER
7	S5 NOT S6

Table 3. Search string Cochrane Library

Cochrane Library*	
No.	Term
1	(Dystonia[ti ab kw] or dystonic disorder[ti ab kw] or distonia[ti ab kw] OR distonic disorder[ti ab kw]) OR hemidyston*[ti ab kw] OR hemi NEAR dyston*[ti ab kw] OR torticollis*[ti ab kw] OR cervical NEAR dyston*[ti ab kw] OR blepharospasm[ti ab kw] OR meige syndrome[ti ab kw]
2	deep brain stim*[ti ab kw] OR pallidal stim*[ti ab kw] OR deep brain OR intercerebell*OR pallidal OR pallidus OR pallidum OR "GPI" OR globus pallidus internus OR globus pallidus internis OR globus pallidus interna OR DBS stim*[ti ab kw] OR electrode* stim*[ti ab kw] OR neurostim*[ti ab kw] OR electroneurostim*[ti ab kw] OR electrostim*on[ti ab kw],
3	#1 and #2
* Database: Cochrane Central Register of Controlled Trials	

Table 4. Search string MedScape

Medscape*	
No.	Term
1	Dystonia (in: news & education)*
2	"Deep brain stimulation" or "DBS" or "pallidal stimulation" or electroneuro (in: news & education)
	#1 AND #2
* Difference in search term compared to other databases is due to the nature of the search option, which disallows more advanced combination of search terms.	

Delimiters

To refine the search, the following delimiters were used:

- Human
- Publication time: 1990 onwards (DBS in dystonia started in 1993)

Study selection

From all references identified in the systematic search of databases, studies were included based on the inclusion criteria specified below (see 'Inclusion criteria' and 'Exclusion criteria' below)

Eligible studies had to be published in the English or one of other major western European languages (German, French, Italian, and Spanish). The need to include full text assessment of any article in other languages was discussed with Medtronic on a case-by-case basis. The included studies report efficacy and/or safety outcomes of DBS in primary dystonia.

Study selection was accomplished through two levels of study review. Level I review was performed by scanning abstracts and titles of all the references identified in the searches. For level I review, abstracts and titles were electronically stored in a database (e.g. Reference Manager[®] 12), allowing for the identification of duplicates retrieved from the different electronic databases and then exported into a (MS-ACCESS) database, to facilitate the check of the inclusion and exclusion criteria and allow an efficient documentation. The abstracts that passed title and abstract screening were retrieved in full text for level II review, which involved a more detailed assessment of the inclusion and exclusion criteria based on the information provided in the full text of the articles. Studies passing level II review are included in the systematic review.

Study selection is summarized in the PRISMA flow chart. In cases where more than one in- or exclusion criterion applied for the non-eligibility of the study the first criterion listed was used for the flow chart.

Quality assurance

A random proportion of 10 percent of abstracts, 10% of full text papers, and 10% extracted data (including quality assessment) were subject to a double review.

For cases/papers which were flagged as questionable by the first reviewer (another 10% at least for each double review) a second opinion was obtained.

Inclusion criteria

The following inclusion criteria (IC) were applied: 1. diagnosis of isolated dystonia (IC1); 2. All/part of the subjects included in the study were treated with DBS (IC 2); 3. A minimum of 10 subjects (per arm if comparative design) included in the study: (IC3) Populations: If results reported from a mixed population include it either (IC 4):

- n isolated dystonia ≥ 10 AND total share of isolated dystonia patient $\geq 80\%$

OR

- If results are separately reported for isolated dystonia AND n isolated dystonia ≥ 10 .

Additional inclusion criteria at Level II assessment based on full text:

Safety and/or efficacy information for DBS and/or quality of life information for dystonia patients undergoing or eligible for DBS treatment (IC 5).

Exclusion criteria

1. Publication type: Editorial, Letter; Case reports, 2. Non-systematic reviews (EC 1), 3. Languages other than English, German, French, Italian, Spanish (EC 2)

Data extraction

An electronic data report form (DRF) was designed to extract data from the studies. Data extraction was performed by a research analyst and then reviewed by a *second researcher* independently to examine and confirm a fixed portion of extracted data elements. Extracted data are entered into DRF in EXCEL format. The following data elements are sought: Study ID, Author, Journal, Publication year

Study location

Study type

Study dates

Study funding

Number of patients

Study population (age, gender)

Type of dystonia

Subtypes of dystonia (genetic, pediatric/early patients, location of dystonia)

Duration of dystonia (Mean/ Median, SD, IQR, Quartiles)

HRQOL of patients eligible for DBS (baseline) (Mean/ Median, SD, IQR, Quartiles)

Primary efficacy endpoints (also for subtypes) (Mean/ Median, SD, IQR, Quartiles)

Other clinical endpoints for efficacy (and changes in HRQOL compared to baseline)

Targets of stimulation (GPI or others)

Stimulation settings

- Intensity: Amplitude/ Voltage(V)
- Pulse Duration (μ s)
- Frequency/ used for stimulation (Hz / pps)

Device manufacturer

Safety endpoints (bleedings, infection, etc.)

Instruments/ questionnaires endpoints used in study

Abstract

Specific subgroup information

Study quality appraisal

Comments

Table S1. Patient characteristics at baseline of all studies included in the efficacy meta-analysis, plus those that provided additional safety data.

Study	No. patients	Longest follow-up (months)	Body distribution (no. patients)	Gender (% male)	Age at surgery (years)	Age at onset (years)	Pediatric patients (%)	Disease duration	Life with disease (%)	Isolated (%)			BFMDRS movement score	BFMDRS disability score
										Idiopathic	Inherited (all DYT1 unless indicated otherwise)	Unknown		
Efficacy data (included in the meta-analysis)														
Air (2011) ¹	13	12	Generalized or segmental (inclusion criteria)		13.8 (children only)		100.0				77.0	23 (non-DYT1 primary dystonia)	57.1	13.3
Berman (2009) ²	11	8	Cervical (2), segmental (9)	55.0	57.9	44.3	0.0	13.6	23.0	100			16.8	4.7
Blahak (2010) ³	18	57	Segmental (16), generalized (2)	44.0	55.4	45.8	0.0	9.6	17.0			100	36.6	
Blahak (2011) ⁴	11	17	Segmental	55.0	57.6		0.0					100	35.8	
Bruggemann (2015) ⁵	54	57	Generalized (25), segmental (23), focal (6: 2 cervical, 2 truncal, 1 leg, 1 dystonic voice and head tremor)	63.0	45.6	26.4	0.0	19.2	42.0	45.6	DYT1 (8), DYT6 (9)	Non DYT (37)	32.0	8.7
Cif (2010) ⁶	26	72	Generalized (24), segmental (2)	38.0	21.6	8.1	61.5	13.5	63.0		100		57.5	14.9
Coubes (2004) ⁷	31	24	Generalized	45.0	27.5	17.8	61.3	9.7	35.0		45.0	55 (non-DYT1)	59.1	16.5
Ghang (2010) ⁸	11	24	Segmental (Meige syndrome)	18.0	58	49.4	0.0	8.7	15.0	100			24.5	6.7
Isaias (2009) ⁹	30	48	Generalized	67.0	28	14	Unclear	14	50.0		67.0	33 (non-DYT1)	44	10.6
Isaias (2011) ¹⁰	44	36	Generalized or segmental (inclusion criteria)	73.0	31	15	Unclear	15	48.0		52.0	48 (non-DYT1)	45.1	
Krause (2004) ¹¹	10	12	Generalized	60.0	29.5	15	0.0	14.5	49.0		40.0		72.2	
Lumsden	17	12	Generalized	52.9	12.3 (children	5.9	100.0	6.4	52.0		23.5		54.8	14.4

Study	No. patients	Longest follow-up (months)	Body distribution (no. patients)	Gender (% male)	Age at surgery (years)	Age at onset (years)	Pediatric patients (%)	Disease duration	Life with disease (%)	Isolated (%)			BFMDRS movement score	BFMDRS disability score
										Idiopathic	Inherited (all DYT1 unless indicated otherwise)	Unknown		
(2013) ¹²					only)									
Markun (2012) ¹³	14	32	Generalized	50.0	15.5 (children and adults)	8.1	78.6	7.9	51.0		100.0		54.6	
Mills (2012) ¹⁴	27	27	Generalized, focal and segmental (number per group unspecified)	52.0	44.6		0.0					100		
Panov (2013) ¹⁵	47	60	Generalized	64.0	16.0 (children and adults)	8.0	Unclear	8.0	50.0		100.0		43.9	10.9
Petrossian (2013) ¹⁶	12	45	Generalised (9), Focal (3)	67.0	14.3 (children and adults)	9.2	91.7	5.1	36.0		25.0		37.0	
Reese (2011) ¹⁷	12	42	Segmental (Meige syndrome)	50.0	64.5	56.2	0.0	8.3	13.0	100			21.4	
Sarubbo (2012) ¹⁸	10	60	Segmental (9), generalized (1)	30.0	45.8	29.7	0.0	16.1	35.0	100			36.9	8.9
Starr (2006) ¹⁹	14	13	Segmental (7), generalized (4), cervical (2), left hemibody (1)		31.8	20.6	35.7	11.2	35.0		73.0		47.2	
Tisch (2007) ²⁰	15	6	Generalized	33.0	42.1	18.1	6.7	24	57.0		47.0		38.9	
Valledeoriola (2010) ²¹	22	12	Generalized (22) (+2 segmental patients included in the safety analysis only)	50.0	30	20	Unclear	10	33.0		25.0		42.2	12.4
Vidailhet (2007) ²²	22	36	Generalized	50.0	31.9	13.1	9.1	18.8	59.0		32.0		46.3	11.6
Volkman (2012) ²³ *	40	60	Generalized (24), segmental (16)	68.0	36.9	20.0	Unclear	17.9	49.0	100			43.4	10
Yianni (2003) ²⁴	12	9	Generalized	50.0	31.9	19.2	8.3	12.7	40.0		17.0		65	14.7
Additional safety data														
Bittar (2005) ²⁵	12	30	Generalized (6),	16.7	34.8	27.1	8.3	7.7	22.0			100		

Study	No. patients	Longest follow-up (months)	Body distribution (no. patients)	Gender (% male)	Age at surgery (years)	Age at onset (years)	Pediatric patients (%)	Disease duration	Life with disease (%)	Isolated (%)			BFMDRS movement score	BFMDRS disability score
										Idiopathic	Inherited (all DYT1 unless indicated otherwise)	Unknown		
			cervical (6)											
Cacciola (2010) ²⁶	10	38	Cervical	50.0	52.9	43	0.0	9.9	19.0			100		
Chung (2015) ²⁷	25	50	Cervical	57.0	52.2	47.8	0.0	4.4	8.0			100		
Contarino (2014) ²⁸	35	12	Cervical	60.0	56.5	42.3	0.0	14.3	25.0			100		
Dinckelbach (2015) ²⁹	13	12	Cervical	46	53.9	39.2	0.0	14.7	27.0			10		
Fitzgerald (2014) ³⁰	60	60	Generalized	42.0	33.5	14.9	0.0	19.1	57.0		23 (DYT1, DYT6, DYT11)	77 (non-genetic)		
Haridas (2011) ³¹	22	24	Generalized	72.7	13.4 (children and adults)	8.5	95.5	5	37.0		77.3	22.7 (non-DYT1)	39.9	
Hung (2007) ³²	10	32	Cervical	50.0	48.7	38.7	0.0	10	21.0	100				
Kim (2012) ³³	14	31	Cervical	42.9	48.4	43.1	0.0	5.3	11.0			100		
Kiss (2007) ³⁴	10	12	Cervical	50.0	56.4	40.1	0.0	16	28.0			100		
Witt (2013) ³⁵	28	34	Cervical	47.0	56.0	45.1	0.0	13.3	24.0	100				

* See also Kupsch et al (2006)³⁶ and Müller et al (2008).³⁷ BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale

Appendix S2. Full results of meta-analyses regarding efficacy of DBS in dystonia at 6 and 12 months and at last follow-up

BFMDRS motor score

Analysis at last follow-up

All 24 studies are included in this analysis.

The last follow-up ranges from 6 months to 72 months, with a mean at 32.5 months post surgery.

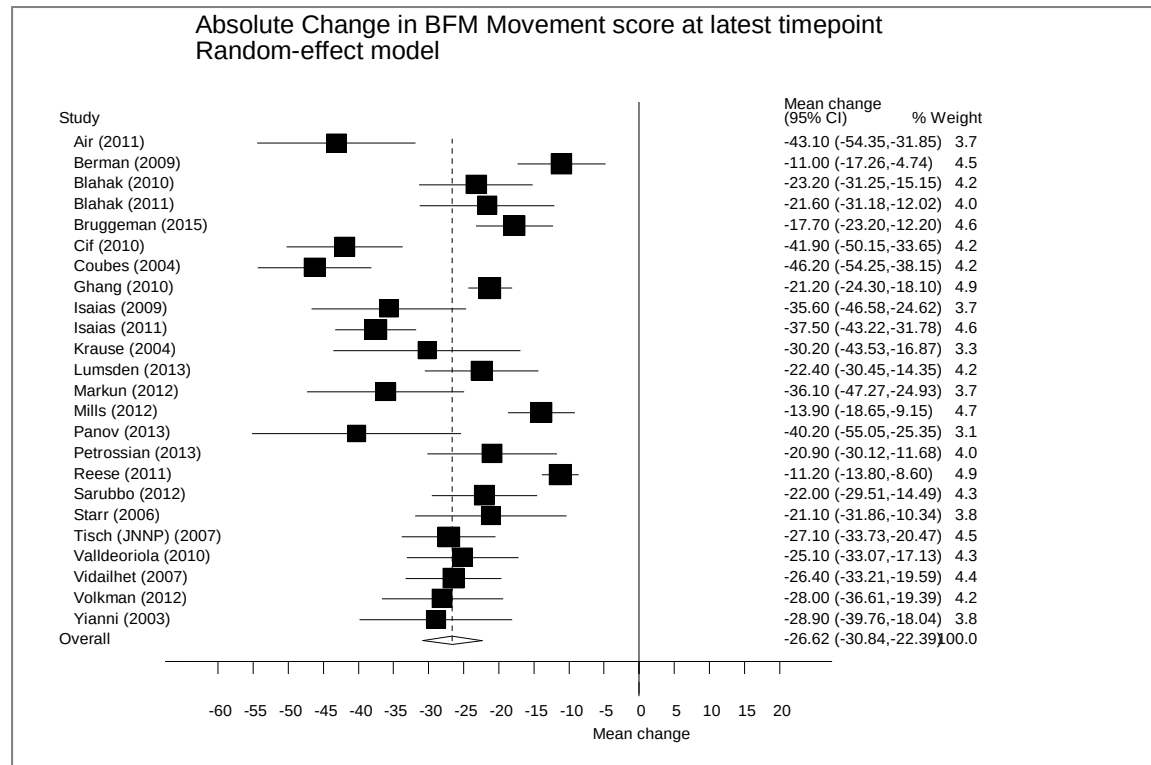
Study	ANALYSIS ON ABSOLUTE CHANGE			ANALYSIS ON PERCENTAGE CHANGE		
	Mean change from baseline (95% CI)	Weights in FE model (%)	Weights in RE model (%)	Mean change from baseline (95% CI)	Weights in FE model (%)	Weights in RE model (%)
Air (2011) ¹	-43.1 (-54.4, -31.8)	1.3	3.7	-80.3 (-91.2, -69.4)	2.5	4.3
Berman (2009) ²	-11.0 (-17.3, -4.7)	4.2	4.5	-55.5 (-77.4, -33.7)	0.6	2.9
Blahak (2010) ³	-23.2 (-31.3, -15.2)	2.5	4.2	-63.4 (-72.6, -54.1)	3.5	4.5
Blahak (2011) ⁴	-21.6 (-31.2, -12.0)	1.8	4.0	-60.4 (-72.2, -48.6)	2.1	4.1
Bruggeman (2015) ⁵	-17.7 (-23.2, -12.2)	5.4	4.6	-54.6 (-61.3, -47.9)	6.6	4.7
Cif (2010) ⁶	-41.9 (-50.1, -33.7)	2.4	4.2	-71.8 (-82.1, -61.4)	2.8	4.3
Coubes (2004) ⁷	-46.2 (-54.2, -38.2)	2.5	4.2	-79.0 (-85.7, -72.3)	6.6	4.7
Ghang (2010) ⁸	-21.2 (-24.3, -18.1)	17.1	4.9	-85.5 (-91.5, -79.5)	8.3	4.8
Isaias (2009) ⁹	-35.6 (-46.6, -24.6)	1.4	3.8	-84.7 (-92.6, -76.8)	4.7	4.6
Isaias (2011) ¹⁰	-37.5 (-43.2, -31.8)	5.0	4.6	-82.6 (-86.5, -78.7)	19.2	5
Krause (2004) ¹¹	-30.2 (-43.5, -16.9)	0.9	3.3	-46.0 (-65.3, -26.7)	0.8	3.2
Lumsden (2013) ¹²	-22.4 (-30.4, -14.4)	2.5	4.2	-48.7 (-64.9, -32.5)	1.1	3.6
Markun (2012) ¹³	-36.1 (-47.3, -24.9)	1.3	3.7	-70.3 (-83.5, -57.0)	1.7	3.9
Mills (2012) ¹⁴	-13.9 (-18.7, -9.1)	7.2	4.7	-47.2 (-60.3, -34.2)	1.7	4
Panov (2013) ¹⁵	-40.2 (-55.0, -25.4)	0.7	3.1	-91.6 (-103.4, -79.8)	2.1	4.1
Petrossian (2013) ¹⁶	-20.9 (-30.1, -11.7)	1.9	4.1	-62.0 (-66.8, -57.2)	13.2	4.9
Reese (2011) ¹⁷	-11.2 (-13.8, -8.6)	24.2	4.9	-53.5 (-64.3, -42.6)	2.5	4.3
Sarubbo (2012) ¹⁸	-22.0 (-29.5, -14.5)	2.9	4.3	-60.0 (-72.4, -47.6)	1.9	4.1
Starr (2006) ¹⁹	-21.1 (-31.9, -10.3)	1.4	3.8	-46.9 (-70.4, -23.4)	0.5	2.7
Tisch (2007) ²⁰	-27.1 (-33.7, -20.5)	3.7	4.5	-71.3 (-80.7, -61.9)	3.3	4.4

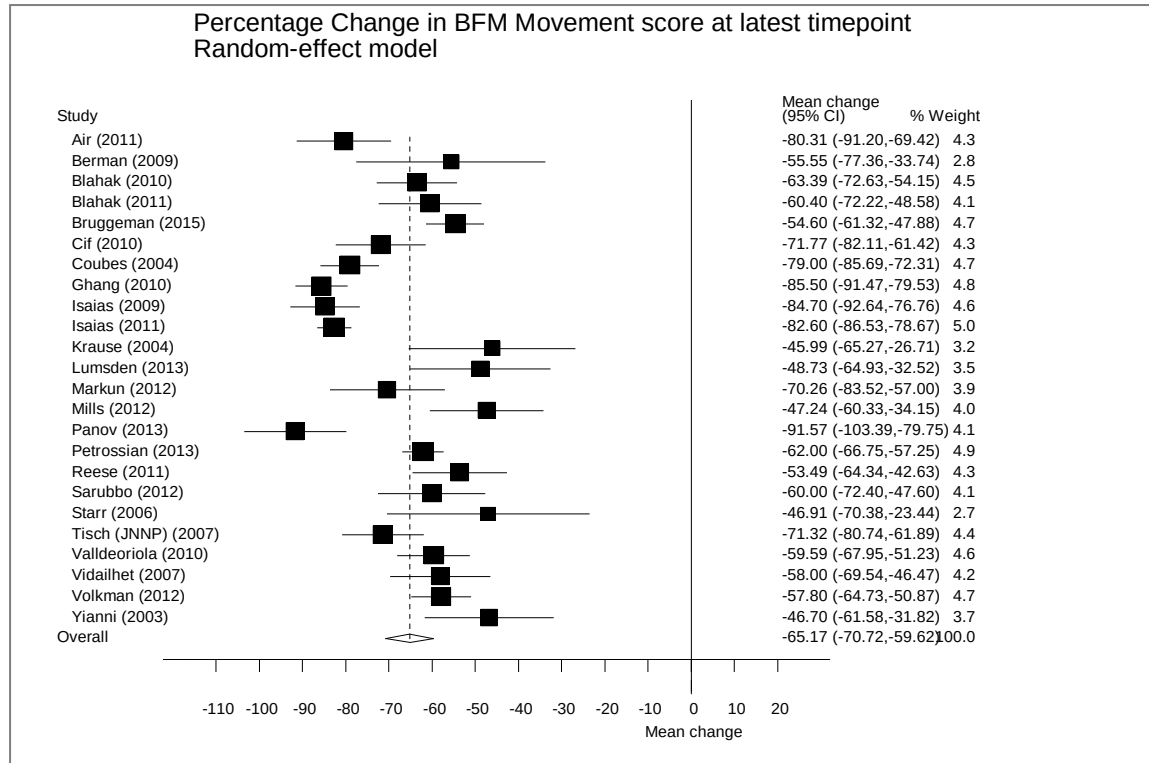
Valdeoriola (2010) ²¹	-25.1 (-33.1, -17.1)	2.6	4.3	-59.6 (-67.9, -51.2)	4.3	4.6
Vidailhet (2007) ²²	-26.4 (-33.2, -19.6)	3.5	4.4	-58.0 (-69.5, -46.5)	2.2	4.2
Volkman (2012) ²³	-28.0 (-36.6, -19.4)	2.2	4.2	-57.8 (-64.7, -50.9)	6.2	4.7
Yianni (2003) ²⁴	-28.9 (-39.8, -18.0)	1.4	3.8	-46.7 (-61.6, -31.8)	1.3	3.7
	Pooled absolute mean change (95% CI)	-21.3 (-22.6, -20.1)	-26.6 (-30.8 -22.4)	Pooled percentage mean change (95% CI)	-69.9 (-71.6, -68.2)	-65.2 (-70.7, -59.6)
	p-value	<0.001	<0.001	p-value	<0.001	<0.001
	Heterogeneity	I ² =89.4%, p-value<0.001		Heterogeneity	I ² =89.0%, p-value<0.001	

There is a high amount of heterogeneity within these data on both measures, which comes out as highly significant. The random-effect model is therefore the most appropriate one in both cases.

The meta-analysis shows a significant improvement of 26.6 points and 65.2% on the BFMDRS movement scale at the end of follow-up (on average 32.5 months post-surgery).

Individual studies results as well as the pooled estimate are displayed on the forest plots below.





Analysis at 6 months

10 studies are included in this analysis: 7 reporting data at 6 months and 3 others reporting data at 7, 8 and 9 months.

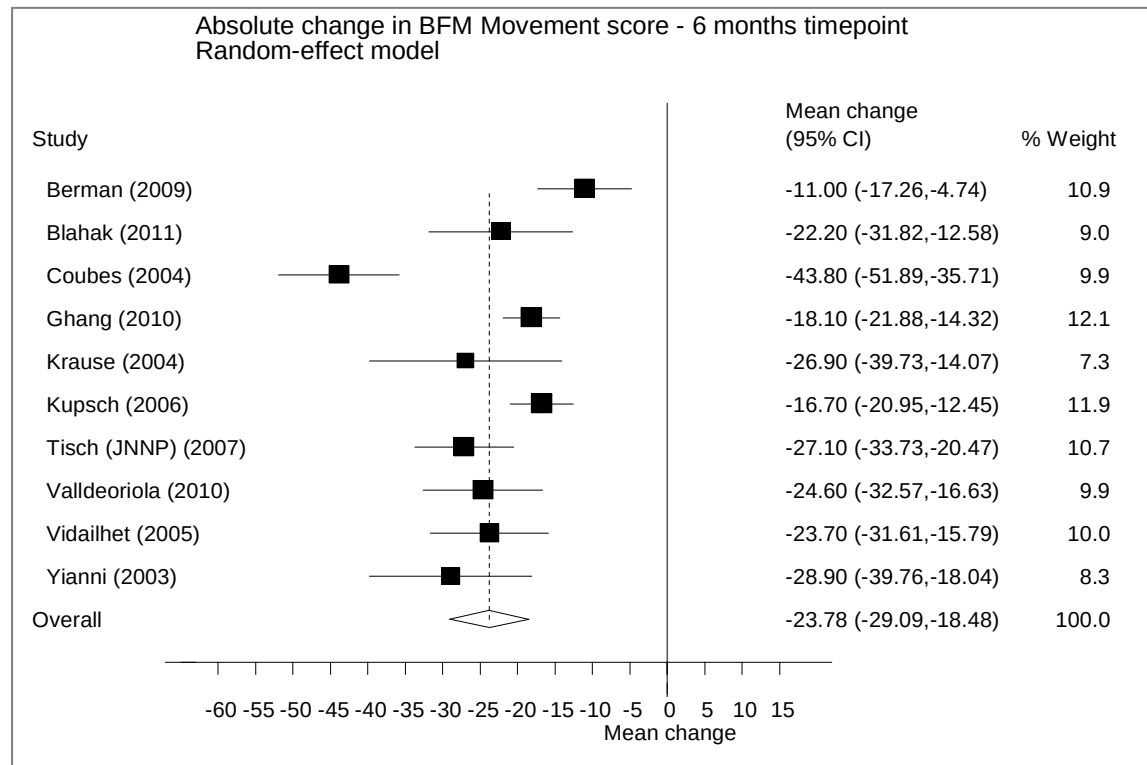
	ANALYSIS ON ABSOLUTE CHANGE			ANALYSIS ON PERCENTAGE CHANGE		
Study	Mean change from baseline (95% CI)	Weights in FE model (%)	Weights in RE model (%)	Mean change from baseline (95% CI)	Weights in FE model (%)	Weights in RE model (%)
Berman (2009) ²	-11.0 (-17.3, -4.7)	10.4	10.9	-55.5 (-77.4, -33.7)	2.0	6.4
Blahak (2011) ⁴	-22.2 (-31.8, -12.6)	4.4	9.0	-61.9 (-73.7, -50.1)	6.8	10.1
Coubes (2004) ⁷	-43.8 (-51.9, -35.7)	6.2	9.9	-74.1 (-81.2, -67.1)	19.1	11.9
Ghang (2010) ⁸	-18.1 (-21.9, -14.3)	28.4	12.1	-74.1 (-87.3, -60.9)	5.5	9.6
Krause (2004) ¹¹	-26.9 (-39.7, -14.1)	2.5	7.3	-40.5 (-60.1, -21.0)	2.5	7.2
Kupsch (2006) ³⁶ *	-16.7 (-20.9, -12.5)	22.5	11.9	-47.9 (-54.4, -41.4)	22.2	12.1
Tisch (2007) ²⁰	-27.1 (-33.7, -20.5)	9.3	10.7	-71.3 (-80.7, -61.9)	10.7	11
Valdeoriola (2010) ²¹	-24.6 (-32.6, -16.6)	6.4	10.0	-58.4 (-66.7, -50.0)	13.6	11.4
Vidailhet (2005) ²² †	-23.7 (-31.6, -15.8)	6.5	10.0	-51.2 (-59.5, -42.8)	13.6	11.4
Yianni (2003) ²⁴	-28.9 (-39.8, -18.0)	3.4	8.3	-46.7 (-61.6, -31.8)	4.3	8.9
	Pooled absolute mean change (95% CI)	-21.0 (-23.0, -19.0)	-23.8 (-29.1, -18.5)	Pooled percentage mean change (95% CI)	-59.6 (-62.6, -56.5)	-59.0 (-66.7, -51.2)
	p-value	<0.001	<0.001	p-value	<0.001	<0.001
	Heterogeneity	I ² =83.3%, p-value<0.001		Heterogeneity	I ² =82.0%, p-value<0.001	

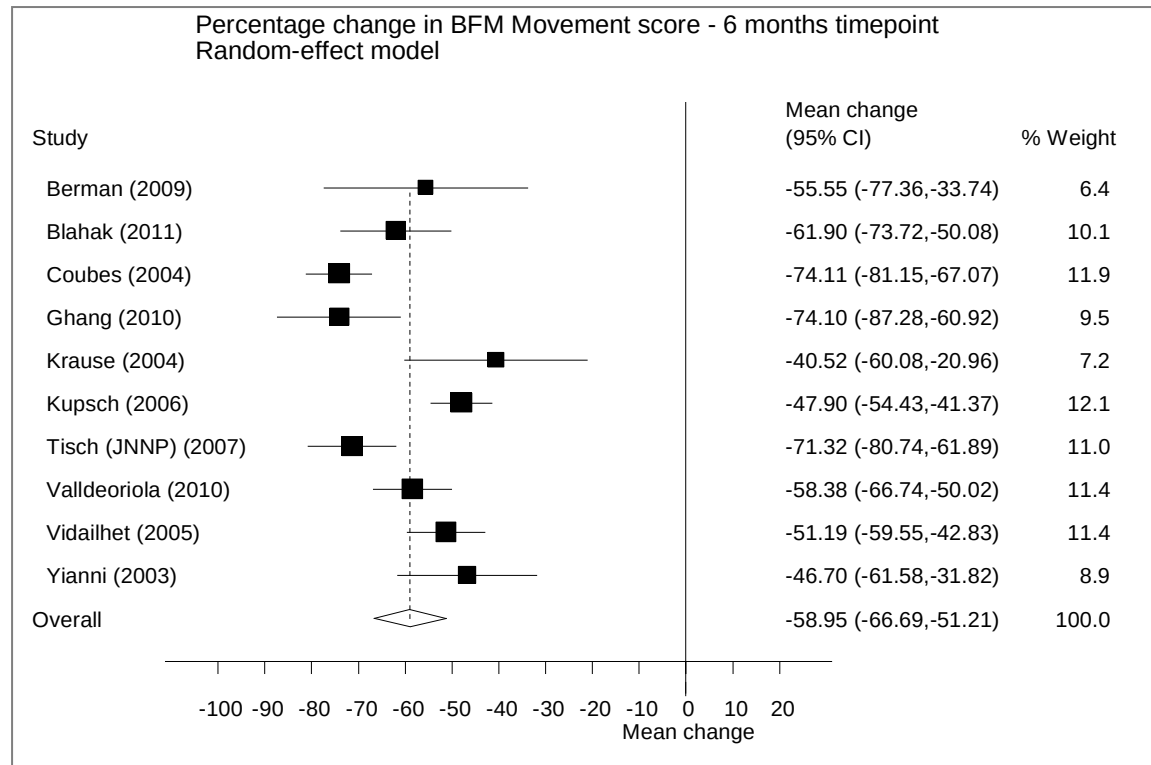
* See also Müller et al (2008)³⁷ and Volkmann (2012)²³; † data at 6 and 12 months derived from Vidailhet (2005)²², while data at 36 months (used in the analysis at latest timepoint) derived from Vidailhet 2007²²

There is a high amount of heterogeneity within these data on both measures, which comes out as highly significant. The random-effect model is therefore the most appropriate one in both cases.

The meta-analysis shows a significant improvement of 23.8 points and 59.0% on the BFMDRS movement scale 6 months post-surgery.

Individual studies results as well as the pooled estimate are displayed on the forest plots below.





Analysis at 12 months

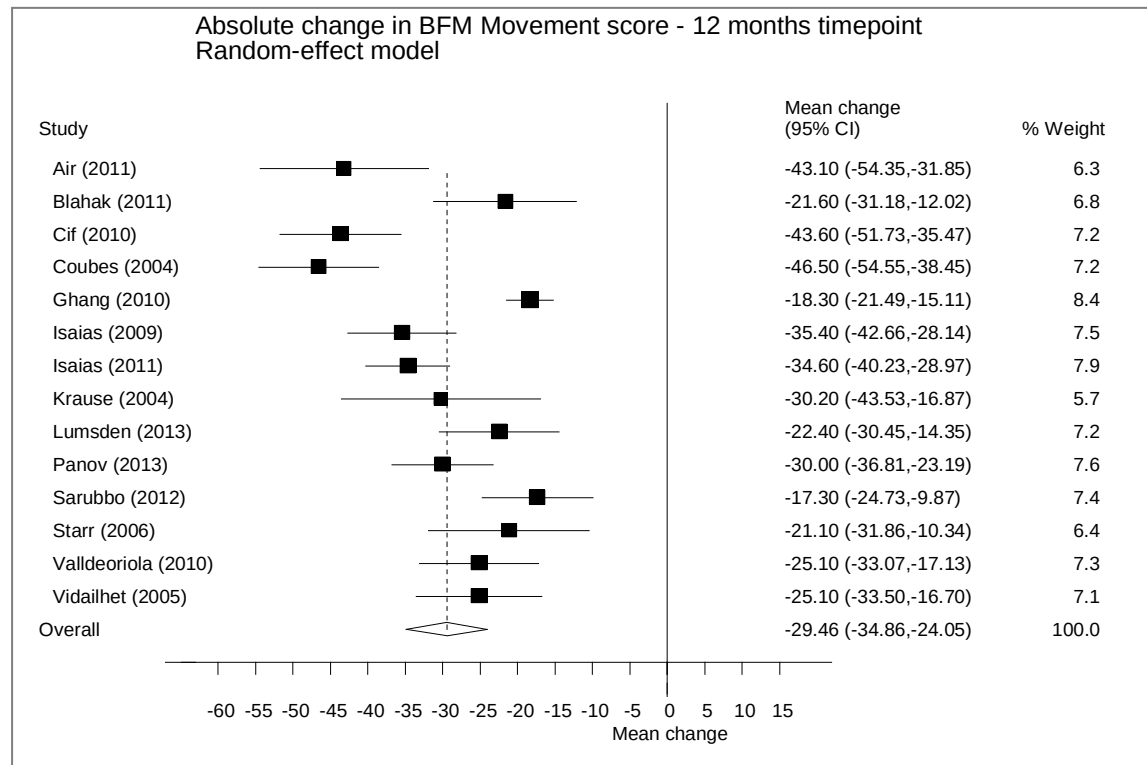
14 studies are included in this analysis: 12 reporting data at 12 months and 2 others reporting data at 13 and 17 months.

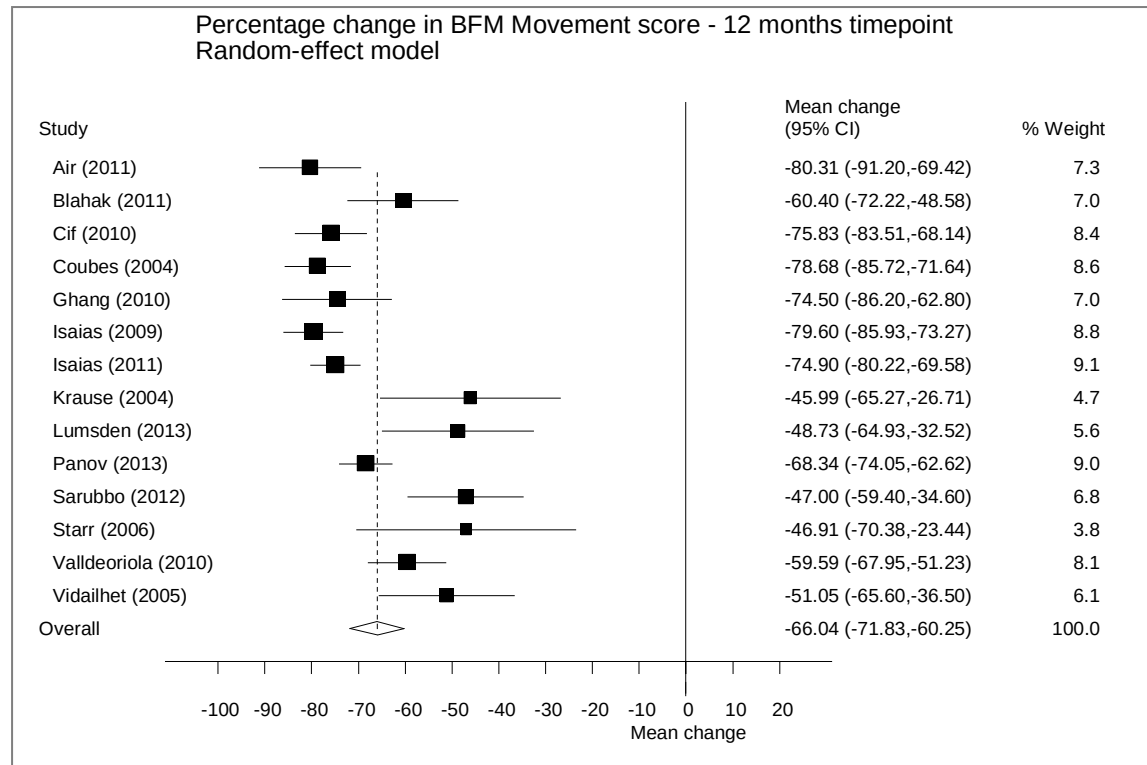
	ANALYSIS ON ABSOLUTE CHANGE			ANALYSIS ON PERCENTAGE CHANGE		
Study	Mean change from baseline (95% CI)	Weights in FE model (%)	Weights in RE model (%)	Mean change from baseline (95% CI)	Weights in FE model (%)	Weights in RE model (%)
Air (2011) ¹	-43.1 (-54.4, -31.8)	2.7	6.3	-80.3 (-91.2, -69.4)	4.6	7.3
Blahak (2011) ⁴	-21.6 (-31.2, -12.0)	3.7	6.8	-60.4 (-72.2, -48.6)	3.9	7.0
Cif (2010) ⁶	-43.6 (-51.7, -35.5)	5.1	7.2	-75.8 (-83.5, -68.1)	9.2	8.4
Coubes (2004) ⁷	-46.5 (-54.6, -38.4)	5.2	7.2	-78.7 (-85.7, -71.6)	10.9	8.6
Ghang (2010) ⁸	-18.3 (-21.5, -15.1)	33.0	8.4	-74.5 (-86.2, -62.8)	4.0	7.0
Isaias (2009) ⁹	-35.4 (-42.7, -28.1)	6.4	7.5	-79.6 (-85.9, -73.3)	13.5	8.8
Isaias (2011) ¹⁰	-34.6 (-40.2, -29.0)	10.6	7.9	-74.9 (-80.2, -69.6)	19.1	9.1
Krause (2004) ¹¹	-30.2 (-43.5, -16.9)	1.9	5.7	-46.0 (-65.3, -26.7)	1.5	4.7
Lumsden (2013) ¹²	-22.4 (-30.4, -14.4)	5.2	7.2	-48.7 (-64.9, -32.5)	2.1	5.6
Panov (2013) ¹⁵	-30.0 (-36.8, -23.2)	7.3	7.6	-68.3 (-74.1, -62.6)	16.6	9.0
Sarubbo (2012) ¹⁸	-17.3 (-24.7, -9.9)	6.1	7.4	-47.0 (-59.4, -34.6)	3.5	6.8
Starr (2006) ¹⁹	-21.1 (-31.9, -10.3)	2.9	6.4	-46.9 (-70.4, -23.4)	1.0	3.8
Valdeoriola (2010) ²¹	-25.1 (-33.1, -17.1)	5.3	7.3	-59.6 (-67.9, -51.2)	7.8	8.2
Vidailhet (2007) ²²	-25.1 (-33.5, -16.7)	4.8	7.1	-51.0 (-65.6, -36.5)	2.6	6.1
	Pooled absolute mean change (95% CI)	-26.6 (-28.5, -24.8)	-29.5 (-34.9, -24.1)	Pooled percentage mean change (95% CI)	-70.6 (-72.9, -68.3)	-66.0 (-71.8, -60.2)
	p-value	<0.001	<0.001	p-value	<0.001	<0.001
	Heterogeneity	I ² =86.8%, p-value<0.001			I ² =81.1%, p-value<0.001	

There is a high amount of heterogeneity within these data on both measures, which comes out as highly significant. The random-effect model is therefore the most appropriate one in both cases.

The meta-analysis shows a significant improvement of 29.5 points and 66% on the BFMDRS movement scale 12 months post-surgery.

Individual studies results as well as the pooled estimate are displayed on the forest plots below.





BFMDRS disability score

Analysis at last follow-up

All 14 studies are included in this analysis.

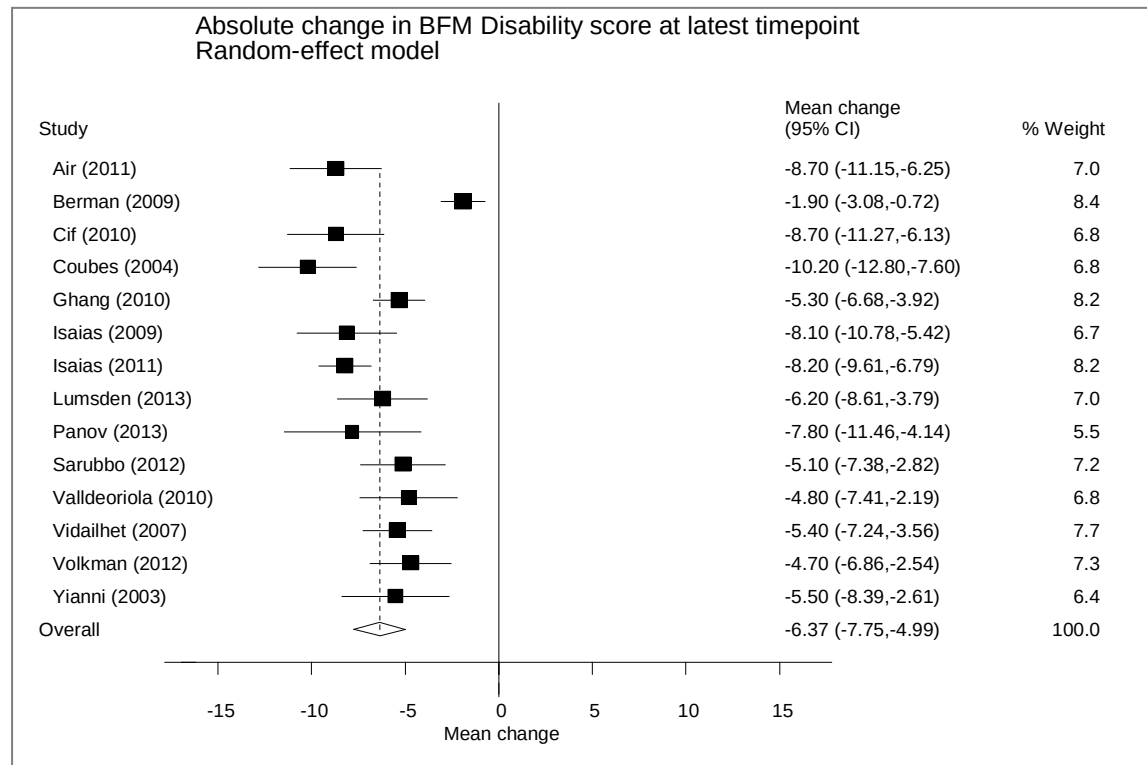
The last follow-up ranges from 8 months to 72 months, with a mean at 32.9 months post surgery.

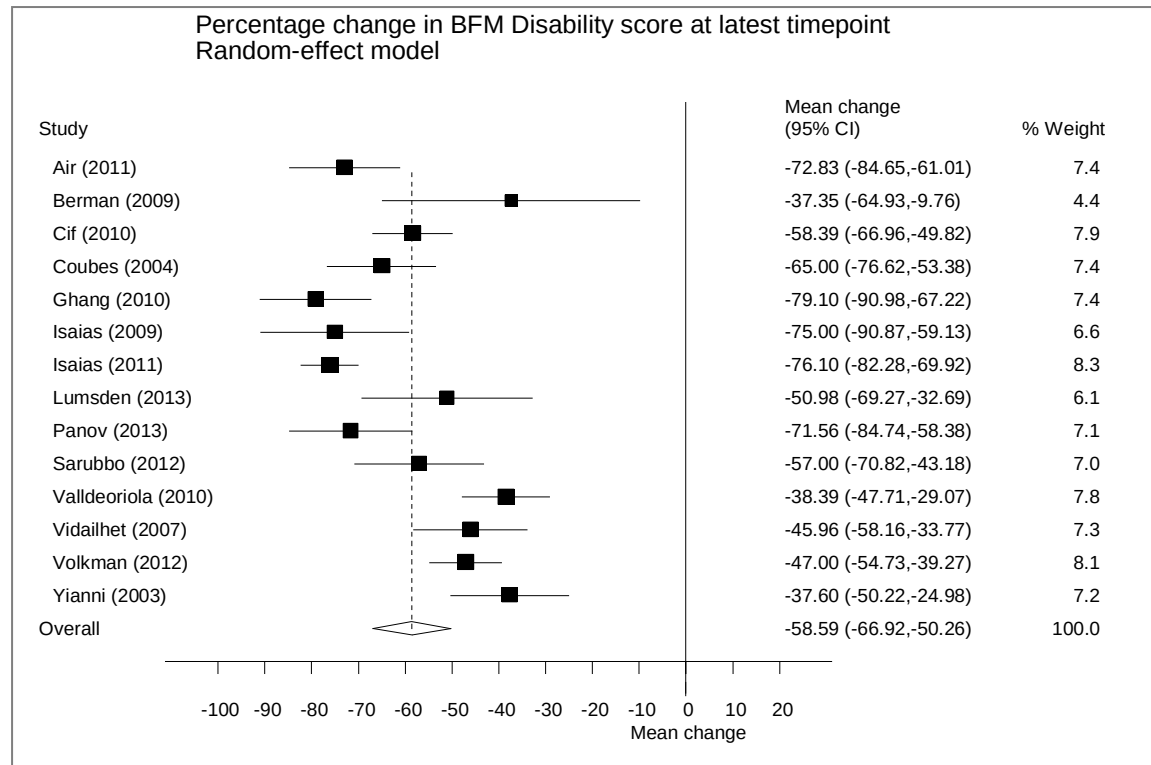
	ANALYSIS ON ABSOLUTE CHANGE			ANALYSIS ON PERCENTAGE CHANGE		
Study	Mean change from baseline (95% CI)	Weights in FE model (%)	Weights in RE model (%)	Mean change from baseline(95% CI)	Weights in FE model (%)	Weights in RE model (%)
Air (2011) ¹	-8.7 (-11.1, -6.3)	4.7	7.0	-72.8 (-84.7, -61.0)	5.9	7.4
Berman (2009) ²	-1.9 (-3.1, -0.7)	20.1	8.4	-37.3 (-64.9, -9.8)	1.1	4.4
Cif (2010) ⁶	-8.7 (-11.3, -6.1)	4.2	6.8	-58.4 (-67.0, -49.8)	11.2	7.9
Coubes (2004) ⁷	-10.2 (-12.8, -7.6)	4.1	6.8	-65.0 (-76.6, -53.4)	6.1	7.4
Ghang (2010) ⁸	-5.3 (-6.7, -3.9)	14.6	8.2	-79.1 (-91.0, -67.2)	5.8	7.4
Isaias (2009) ⁹	-8.1 (-10.8, -5.4)	3.9	6.7	-75.0 (-90.9, -59.1)	3.3	6.6
Isaias (2011) ¹⁰	-8.2 (-9.6, -6.8)	14.2	8.2	-76.1 (-82.3, -69.9)	21.5	8.3
Lumsden (2013) ¹²	-6.2 (-8.6, -3.8)	4.8	7.0	-51.0 (-69.3, -32.7)	2.5	6.1
Panov (2013) ¹⁵	-7.8 (-11.5, -4.1)	2.1	5.5	-71.6 (-84.7, -58.4)	4.7	7.1
Sarubbo (2012) ¹⁸	-5.1 (-7.4, -2.8)	5.4	7.2	-57.0 (-70.8, -43.2)	4.3	7.0
Valledeoriola (2010) ²¹	-4.8 (-7.4, -2.2)	4.1	6.8	-38.4 (-47.7, -29.1)	9.4	7.8
Vidailhet (2007) ²²	-5.4 (-7.2, -3.6)	8.3	7.7	-46.0 (-58.2, -33.8)	5.5	7.3
Volkman (2012) ²³	-4.7 (-6.9, -2.5)	6.0	7.3	-47.0 (-54.7, -39.3)	13.7	8.1
Yianni (2003) ²⁴	-5.5 (-8.4, -2.6)	3.4	6.4	-37.6 (-50.2, -25.0)	5.2	7.2
	Pooled absolute mean change (95% CI)	-5.7 (-6.2, -5.2)	-6.4 (-7.8, -5.0)	Pooled percentage mean change (95% CI)	-60.1 (-63, -57.3)	-58.6 (-66.9, -50.3)
	p-value	<0.001	<0.001	p-value	<0.001	<0.001
	Heterogeneity	I ² =83.9%, p-value<0.001		Heterogeneity	I ² =87.0%, p-value<0.001	

There is a high amount of heterogeneity within these data on both measures, which comes out as highly significant. The random-effect model is therefore the most appropriate one in both cases.

The meta-analysis shows a significant improvement of 6.4 points and 58.6% on the BFMDRS disability scale at the end of follow-up (on average 33 months post-surgery).

Individual studies results as well as the pooled estimate are displayed on the forest plots below.





Analysis at 6 months

6 studies are included in this analysis: 4 reporting data at 6 months and 2 others reporting data at 8 and 9 months.

	ANALYSIS ON ABSOLUTE CHANGE			ANALYSIS ON PERCENTAGE CHANGE		
Study	Mean change from baseline (95% CI)	Weights in FE model (%)	Weights in RE model (%)	Mean change from baseline (95% CI)	Weights in FE model (%)	Weights in RE model (%)
Berman (2009) ²	-1.9 (-3.1, -0.7)	35.1	20.4	-37.3 (-64.9, -9.8)	2.0	2.0
Coubes (2004) ⁷	-8.2 (-11.0, -5.4)	6.2	14.0	-49.7 (-57.5, -41.8)	24.7	24.7
Kupsch (2006) ^{36 *}	-4.1 (-5.3, -2.9)	35.4	20.4	-41.0 (-48.3, -33.7)	28.7	28.7
Valdeoriola (2010) ²¹	-5.8 (-8.4, -3.2)	7.2	14.8	-46.5 (-55.8, -37.2)	17.5	17.5
Vidailhet (2005) ^{22 †}	-5.1 (-7.3, -2.9)	10.3	16.5	-44.0 (-53.3, -34.6)	17.5	17.5
Yianni (2003) ²⁴	-5.5 (-8.4, -2.6)	5.9	13.8	-37.6 (-50.2, -25.0)	9.6	9.6
	Pooled absolute mean change (95% CI)	-3.9 (-4.6, -3.2)	-4.8 (-6.6, -3.1)	Pooled percentage mean change (95% CI)	-44.2 (-48.1, -40.3)	-44.2 (-48.1, -40.3)
	p-value	<0.001	<0.001	p-value	<0.001	<0.001
	Heterogeneity	I ² =79.5%, p-value<0.001		Heterogeneity	I ² =0%, p-value=0.527	

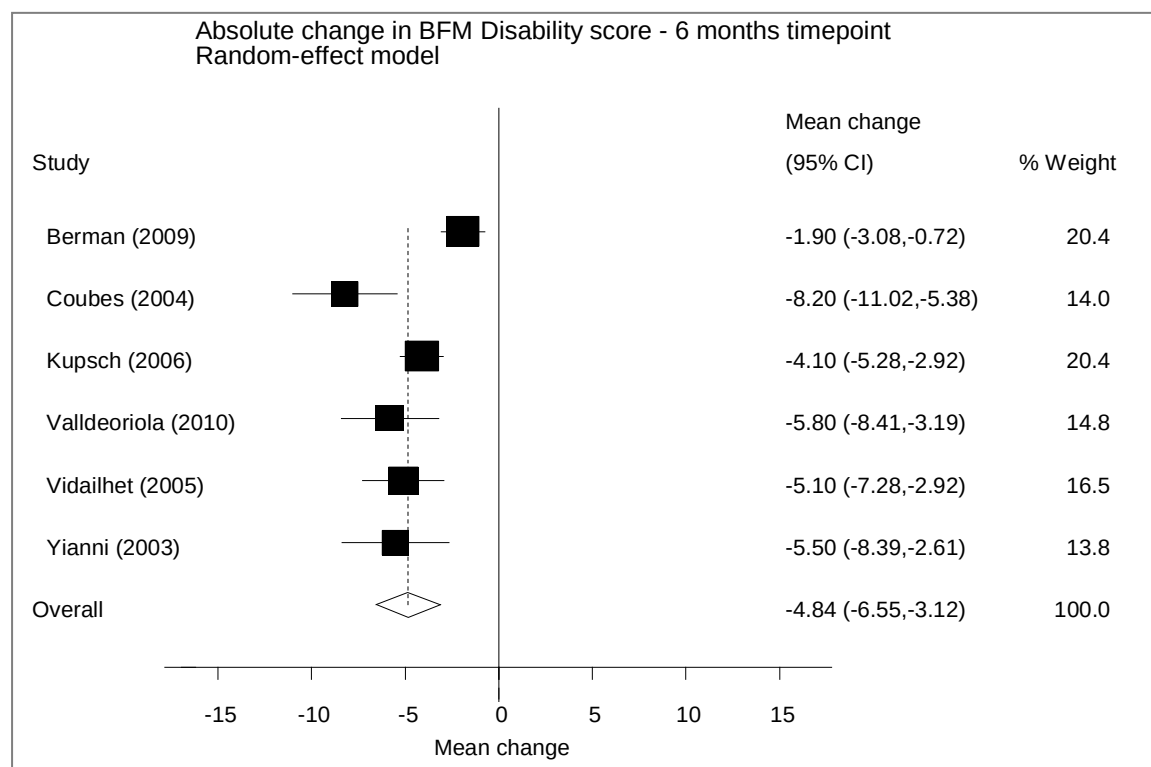
* See also Müller et al (2008)³⁷ and Volkmann (2012)²³; † data at 6 and 12 months derived from Vidailhet (2005)²², while data at 36 months (used in the analysis at latest timepoint) derived from Vidailhet 2007²²

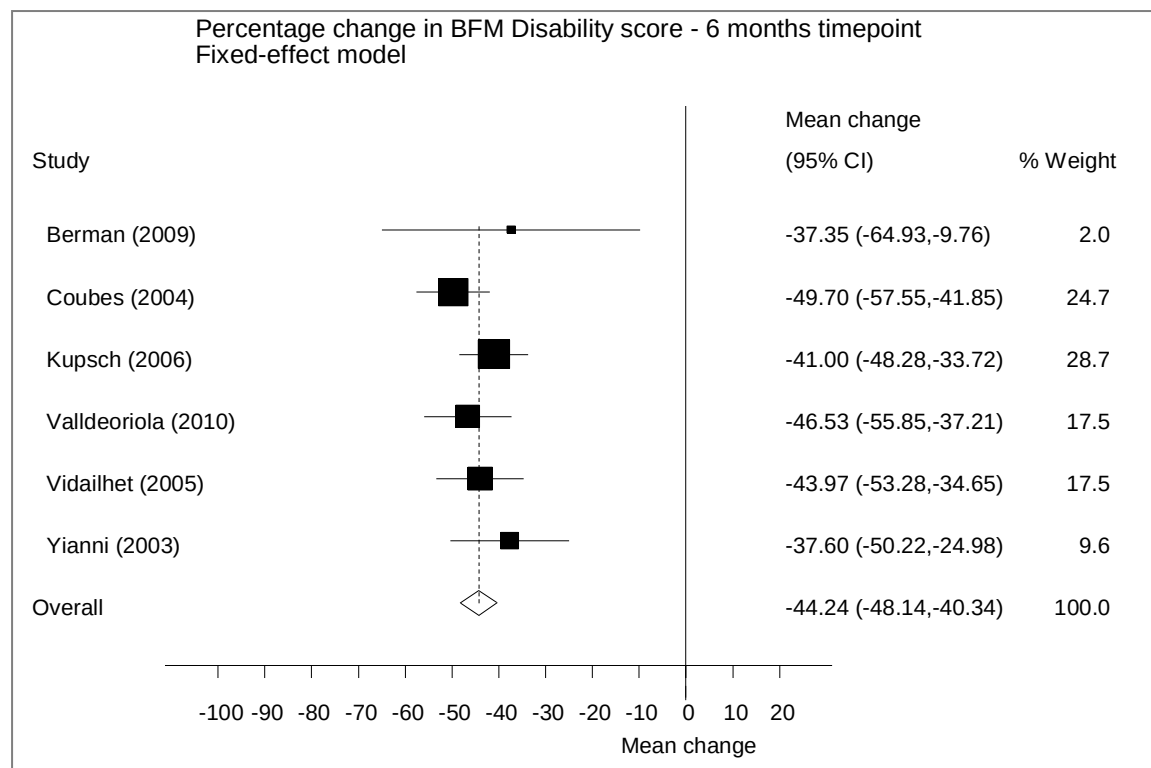
There is a high amount of heterogeneity within the absolute change data, which comes out as highly significant. The random-effect model is therefore the most appropriate one.

There is, however, no heterogeneity at all in the percentage change data, leading to both models giving identical results.

The meta-analysis shows a significant improvement of 4.8 points and 44.2% on the BFMDRS disability scale 6 months post-surgery.

Individual studies results as well as the pooled estimate are displayed on the forest plots below.





Analysis at 12 months

11 studies are included in this analysis, all reporting data at 12 months.

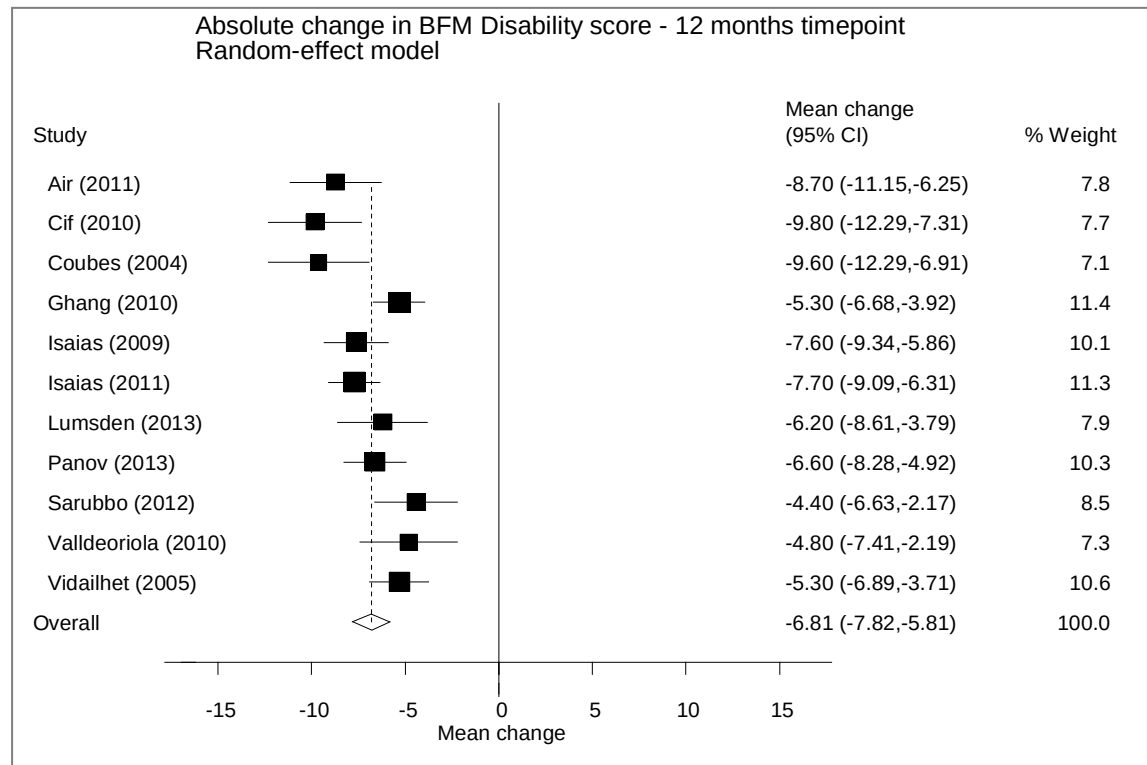
Study	ANALYSIS ON ABSOLUTE CHANGE			ANALYSIS ON PERCENTAGE CHANGE		
	Mean change from baseline (95% CI)	Weights in FE model (%)	Weights in RE model (%)	Mean change from baseline (95% CI)	Weights in FE model (%)	Weights in RE model (%)
Air (2011) ¹	-8.7 (-11.1, -6.3)	5.4	7.8	-72.8 (-84.7, -61.0)	5.3	8.6
Cif (2010) ⁶	-9.8 (-12.3, -7.3)	5.2	7.7	-65.8 (-74.3, -57.2)	10.0	9.8
Coubes (2004) ⁷	-9.6 (-12.3, -6.9)	4.4	7.1	-58.2 (-66.0, -50.3)	11.9	10.1
Ghang (2010) ⁸	-5.3 (-6.7, -3.9)	16.8	11.4	-79.1 (-91.0, -67.2)	5.2	8.5
Isaias (2009) ⁹	-7.6 (-9.3, -5.9)	10.7	10.1	-69.2 (-77.2, -61.2)	11.5	10.0
Isaias (2011) ¹⁰	-7.7 (-9.1, -6.3)	16.7	11.3	-69.0 (-75.3, -62.7)	18.7	10.6
Lumsden (2013) ¹²	-6.2 (-8.6, -3.8)	5.5	7.9	-51.0 (-69.3, -32.7)	2.2	6.3
Panov (2013) ¹⁵	-6.6 (-8.3, -4.9)	11.5	10.3	-60.6 (-66.9, -54.2)	18.1	10.5
Sarubbo (2012) ¹⁸	-4.4 (-6.6, -2.2)	6.5	8.5	-49.0 (-62.8, -35.2)	3.8	7.8
Valledeoriola (2010) ²¹	-4.8 (-7.4, -2.2)	4.7	7.3	-38.4 (-47.7, -29.1)	8.5	9.5
Vidailhet (2005) ²² *	-5.3 (-6.9, -3.7)	12.8	10.6	-46.5 (-58.8, -34.1)	4.9	8.4
	Pooled absolute mean change (95% CI)	-6.7 (-7.2, -6.1)	-6.8 (-7.8, -5.8)	Pooled percentage mean change (95% CI)	-61.8 (-64.5, -59.1)	-60.4 (-67.2, -53.7)
	p-value	<0.001	<0.001	p-value	<0.001	<0.001
	Heterogeneity	I ² =65.8%, p-value=0.001		Heterogeneity	I ² =82.3%, p-value<0.001	

* Data at 6 and 12 months derived from Vidailhet (2005)²², while data at 36 months (used in the analysis at latest timepoint) derived from Vidailhet 2007²²

There is a high amount of heterogeneity within these data on both measures, which comes out as highly significant. The random-effect model is therefore the most appropriate one in both cases.

The meta-analysis shows a significant improvement of 6.8 points and 60.4% on the BFMDRS disability scale 12 months post-surgery.

Individual studies results as well as the pooled estimate are displayed on the forest plots below.



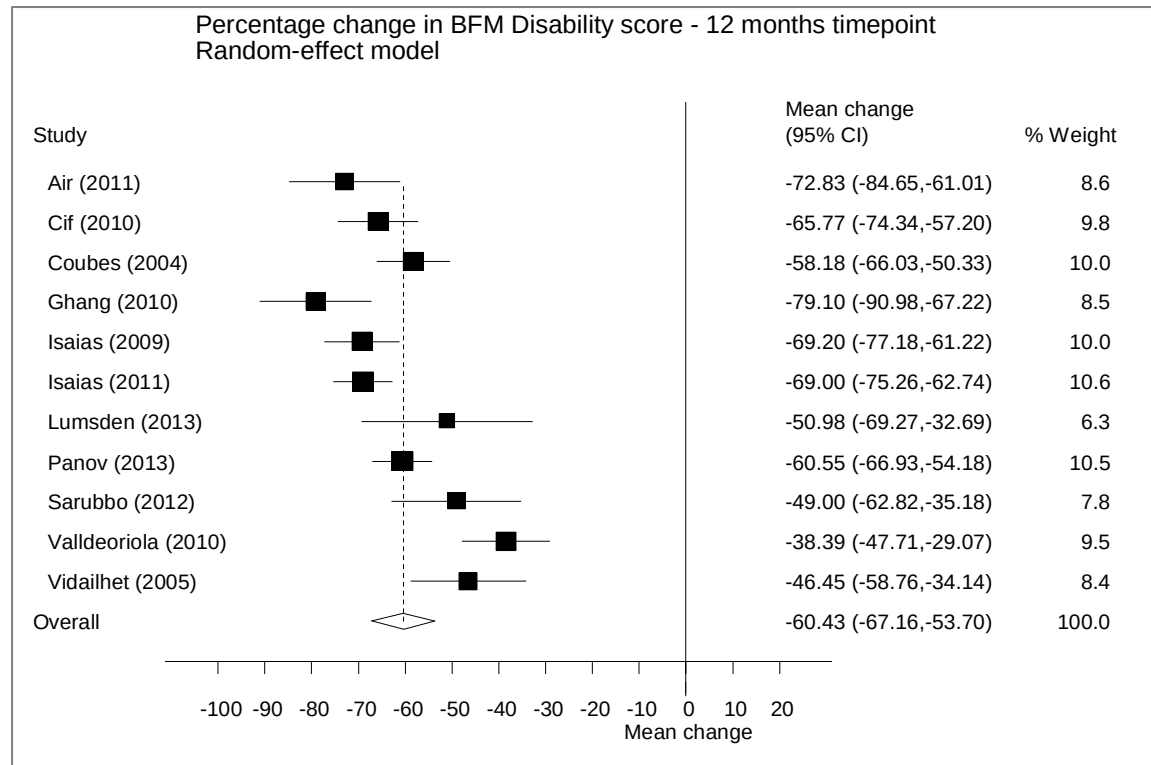


Table S2: Quality of life after GPi DBS.

Study	Sample size	QOL instrument	Score at baseline (mean $\pm$ SD)	Score at 3 months (mean $\pm$ SD)	Score at 6 months (mean $\pm$ SD)	Score at 7.5 months (mean $\pm$ SD)	Score at 12 months (mean $\pm$ SD)	Score at 17 months (mean $\pm$ SD)	Score at 36 months (mean $\pm$ SD)	Score at 60 months (mean $\pm$ SD)
Blahak 2008 ³⁸	10	SF-36 physical functioning	62.0 $\pm$ 24.8	NA	NA	80.7 $\pm$ 15.7	NA	NA	90.1 $\pm$ 9.1	NA
		SF-36 role limitation physical	5.1 $\pm$ 10.6			62.4 $\pm$ 36.1			65.0 $\pm$ 37.6	
		SF-36 bodily pain	76.3 $\pm$ 30.3			89.1 $\pm$ 18.6			88.0 $\pm$ 13.1	
		SF-36 general health	40.1 $\pm$ 23.4			64.6 $\pm$ 26.3			67.5 $\pm$ 15.0	
		SF-36 vitality	50.7 $\pm$ 16.1			64.2 $\pm$ 16.4			68.6 $\pm$ 15.3	
		SF-36 social functioning	51.5 $\pm$ 27.0			79.9 $\pm$ 25.2			83.9 $\pm$ 21.2	
		SF-36 role limitation emotional	73.7 $\pm$ 43.4			90.1 $\pm$ 16.1			90.1 $\pm$ 22.3	
		SF-36 mental health	58.4 $\pm$ 19.3			70.4 $\pm$ 19.7			77.4 $\pm$ 11.3	
		SF-36 summary physical health	46.7 $\pm$ 14.6			72.3 $\pm$ 16.4			75.9 $\pm$ 11.3	
		SF-36 summary mental health	54.7 $\pm$ 20.4			73.7 $\pm$ 17.2			77.4 $\pm$ 10.2	
Kiss 2007 ³⁴	10	SF 36 physical + mental summary	90.9 $\pm$ 11.3	NA	NA	NA	112.9 $\pm$ 18.0	NA	N.A	N.A
	10	BDI	14.2 $\pm$ 7.2				6.0 $\pm$ 3.5			
Valdeoriola 2010 ²¹	22	SF-36 physical summary	34.2	NA	45.1	NA	44.5	NA	NA	NA
	22	SF-36 mental summary	42.5		48.3		49.9			
	22	EQ-5D	0.41		0.67		0.68			
	22	VAS	40.5		69.1		65.0			
Vidailhet 2005, ³⁹ 2007 ²²	22	SF-36 general health	47 $\pm$ 24	NA	NA	NA	63 $\pm$ 27	NA	64 $\pm$ 21	NA
	22	SF-36 physical functioning	41 $\pm$ 28				62 $\pm$ 29		68 $\pm$ 32	
	22	SF-36 role physical	53 $\pm$ 43				58 $\pm$ 39		69 $\pm$ 37	
	22	SF-36 role emotional	59 $\pm$ 48				77 $\pm$ 37		71 $\pm$ 39	
	22	SF-36 social	57 $\pm$ 36				58 $\pm$ 29		63 $\pm$ 30	

Study	Sample size	QOL instrument	Score at baseline (mean $\pm$ SD)	Score at 3 months (mean $\pm$ SD)	Score at 6 months (mean $\pm$ SD)	Score at 7.5 months (mean $\pm$ SD)	Score at 12 months (mean $\pm$ SD)	Score at 17 months (mean $\pm$ SD)	Score at 36 months (mean $\pm$ SD)	Score at 60 months (mean $\pm$ SD)
	22	functioning								
	22	SF-36 body pain	39 $\pm$ 32				56 $\pm$ 36		61 $\pm$ 25	
	22	SF-36 vitality	40 $\pm$ 24				50 $\pm$ 24		47 $\pm$ 21	
	22	SF-36 mental health	54 $\pm$ 20				64 $\pm$ 23		58 $\pm$ 21	
	22	BDI	11.3 $\pm$ 7.0				8.3 $\pm$ 7.9		7.8 $\pm$ 8.0	
Volkmann 2012 ²³ *	35	SF-36 physical function	39.1 $\pm$ 22.5	NA	62.0 $\pm$ 28.7	NA	NA	NA	66.6 $\pm$ 29.5	65.0 $\pm$ 26.8
	37	SF-36 role physical	31.1 $\pm$ 37.5		64.5 $\pm$ 38.4				74.2 $\pm$ 36.2	71.8 $\pm$ 35.8
	37	SF-36 bodily pain	44.8 $\pm$ 29.6		68.3 $\pm$ 26.6				73.7 $\pm$ 28.7	73.9 $\pm$ 28.1
	37	SF-36 general health	42.2 $\pm$ 15.7		60.7 $\pm$ 22.5				67.9 $\pm$ 19.5	63.1 $\pm$ 16.8
	37	SF-36 vitality	45.7 $\pm$ 20.9		57.8 $\pm$ 21.8				64.5 $\pm$ 18.0	58.4 $\pm$ 16.3
	38	SF-36 social function	59.2 $\pm$ 36.0		76.0 $\pm$ 29.3				80.4 $\pm$ 25.4	77.9 $\pm$ 27.6
	38	SF-36 role emotional	62.3 $\pm$ 42.6		79.8 $\pm$ 35.1				79.6 $\pm$ 35.1	83.9 $\pm$ 35.2
	38	SF-36 mental health	60.0 $\pm$ 19.8		72.2 $\pm$ 21.1				76.1 $\pm$ 15.9	69.5 $\pm$ 20.2
	36	SF-36 physical summary	33.7 $\pm$ 7.7		44.1 $\pm$ 9.1					
	36	SF-36 mental summary	46.2 $\pm$ 13.2		51.8 $\pm$ 11.8					
	38	BDI	9.0 $\pm$ 6.9		6.6 $\pm$ 9.2				3.8 $\pm$ 6.3	4.7 $\pm$ 7.3
	38	BAI	12.6 $\pm$ 10.7		8.1 $\pm$ 7.3				6.1 $\pm$ 6.9	7.3 $\pm$ 8.9
	38	Brief psychiatric rating scale	27.4 $\pm$ 7.6		25.3 $\pm$ 7.1					

* Data for SF-36 physical and mental summary and brief psychiatric rating scale were taken from an earlier related paper that reported this specific information, see also Kupsch et al (2006)³⁶ and Müller et al (2008).³⁷ BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CDQ, Craniocervical Dystonia Questionnaire; EQ, EuroQol; NA, not available; QoL, quality of life; SD, standard deviation; SF, short-form; VAS, visual analog scale.

Table S3: Safety outcomes reported in bilateral GPI DBS studies.

Study	Reported safety endpoints
Air (2011) ¹ n=31	• 5 device infections in 4 patients (but none in the dystonic patients) – 3 within 3 months of surgical implantation • Additional device complications: inaccurate lead placement, lead fracture, lead extender fracture addressed with surgical revision
Berman (2009) ² n=11	• Most acute common stimulation-induced AEs: dysarthria or tonic contraction of contralateral facial or arm muscles
Bittar (2005) ²⁵ n=12	• 3 postoperative complications: – 1 electrode displacement – 2 acute rebound phenomenon (1 damaged lead connector, 1 failure of IPG battery) • 3 patients (2 with lead migration/damage, 1 with battery failure) experienced an acute ‘potentially life threatening’ relapse of dystonia
Blahak (2010) ³ n=18	• No surgical complications
Blahak (2011) ⁴ n=11	• 4 patients experienced dysarthria • 1 patient had non-dopa-responsive hypokinetic symptoms with predominant freezing of gait
Cacciola (2010) ²⁶ n=10	• 3 complications: – 2 infections: 1 infection of IPG, 1 infection of entire system – 1 lead breakage (1 year after initial placement)
Chung (2015) ²⁷ n=25	• Overall rates of AEs 28% • 2 intracranial haemorrhages (1 intracerebral haemorrhage during lead repositioning, 1 minimal subdural haemorrhage) – resolved 2 weeks post-surgery • 3 cases of stimulation-related mild dysarthria (improved after 2–4 months of stimulation parameter adjustments) • 2 hardware-related wound problems (subsided after oral antibiotics for one patient and an extension line revision operation for the other patient) • 3 cases of device discomfort (sense of tightness because of the extension line) • No life-threatening or serious AEs • All AEs subsided without permanent sequelae
Cif (2010) ⁶ n=26	• 2 extension cable breakages • 1 spontaneous early IPG dysfunction after 3 months • 2 hardware infections
Contarino (2014) ²⁸ n=35	• 1 repositioning of electrodes • 1 SAE (intraoperative hemorrhage) • Other most frequent non severe AEs: hardware related complications requiring surgery and hypophonia/dysarthria
Coubes (2004) ⁷ n=31	• 1 delayed unilateral infection of an IPG
Dinckelbach (2015) ²⁹ n=13 (same study as Volkmann 2014 ⁴⁰ but at a different timepoint)	• 5 patients with AEs: • 1 hemiparesis or stroke (resolved) • 1 exchange of extension cable • 1 tethering of extension cable

	• 1 dyskinesia due to DBS • 1 worsening of dystonia due to DBSs
FitzGerald (2014) ³⁰ n=60	• 8 infections • 6 lead revisions • 3 lead fractures • 1 lead erosion through scalp • 1 wound granuloma • 1 status dystonicus
Ghang (2010) ⁸ n=11	• 5 transient reversible AEs, e.g. slowness in walking, heaviness in legs, subtle difficulty in speaking and swallowing, fatigue, depression, and general weakness
Haridas (2011) ³¹ n=22	• 4 lead/device infections (3 patients) • 1 lead fracture • 1 suboptimal lead position • 9 lead replacements in total
Hung (2007) ³² n=10	• 1 infection (electrode removal necessary) • 2 developed moderate dysarthria
Isaias (2009) ⁹ n=30	• 8 patients experienced 11 hardware-related AEs – 5 infections (2 in the same patient) – 2 fractured extension cables – 1 scalp erosion without infection – 1 IPG replacement due to malfunction – 2 lead position revision because of lack of benefit – 3 stimulation-related AEs (speech difficulties, which were not present at baseline)
Isaias (2011) ¹⁰ n=44	• 3 worsening of symptoms (1 developed mild speech difficulty, 2 worsening of axial and limb scores) • 2 device infections, requiring antibiotics and re-implantation • 1 extension cable fracture requiring surgical replacement • No adverse neurologic events
Kim (2012) ³³ n=14	• 1 complication related to surgery (weakness in arm and focal infarction observed on brain MRI) • 1 neuropsychological problems (depression, suicide attempt) • 2 dysarthria • 1 intermittent diplopia
Kiss (2007) ³⁴ n=10	• 1 patient suffered from significant depression post-surgery (despite scoring within acceptable range on the Beck depression inventory) • 4 AEs: – 2 with dysphagia resolved change in stimulation parameters – 2 mild difficulties with swallowing

Krause (2004) ¹¹ n=17	• 1 fracture of femur • 13 scotoma • 4 CSF collections in IPG pouch • 1 Infection • 1 dysarthria
Markun (2012) ¹³ n=14	• Surgical complications: 1 stereotactic lead repositioning, 1 asymptomatic perioperative hemorrhage, 2 lead extender fractures surgically replaced
Mills (2012) ¹⁴ n=27	• Study focussing on weight, no safety reported.
Panov (2013) ¹⁵ n=47	• 4 infections requiring removal of hardware and re-implantation • 4 hardware malfunctions including lead fracture • 2 lead revision because of lack of therapeutic benefit • 1 aborted first attempt to implant because of intraoperative symptomatic venous air embolism
Petrossian (2013) ¹⁶ n=12	• No intracranial hemorrhage • No immediate postoperative complications • 5 patients experienced 7 hardware related AEs. • 4 lead fractures • 2 infections
Reese (2011) ¹⁷ n=12	• 1 infection of the right DBS electrodes (2 years postoperatively - temporarily removed and re-implanted 6 months later) • Dysarthria in some instances with stimulation intensities above the therapeutic threshold
Sarubbo (2012) ¹⁸ n=10	• No SAEs • 2 hardware related complications: 1 electrode migration, 1 dramatic re-explosion of previous symptoms after battery exhaustion • 3 transient stimulation related side-effects: 2 paresthesias, 1 dysarthria
Starr (2006) ¹⁹ n=22	• 1 symptomatic hemorrhage • 1 symptomatic hemorrhage >8.2ml • 3 repositioning of initial lead • 3 reoperation for hardware exploration • 1 lead fracture
Tisch (2007) ²⁰ n=15	• 2 developments of delayed onset akinesia
Valdeoriola (2010) ²¹ n=24	• 6 AEs: – 1 hemiparesia – 1 fracture of cable lead to acute reoccurrence of dystonic symptoms 2 months after GPi – 1 retroauricular pain in the region of the cables connecting the electrodes – 2 transitory dysphagia and dysarthria
Vidailhet (2005 ³⁹ , 2007 ²²) n=22	• 5 AEs in 3 patients: – 1 transient perioperative edema of the frontal lobe (not clinically evident) and fractured lead

	– 1 cutaneous necrosis of the scalp – 1 localized skin infection and hematoma near the neurostimulator
Volkmann (2012) ²³ (also Kupsch 2006 ³⁶ and Müller 2008 ³⁷) n=40	• 71 events over 5 years: – 22 within the first 6 months, 49 from 6 months to 5 years • 19 patients affected within the first 6 months and 32 patients from 6 months to 5 years • 26 SAEs in total: – Subcutaneous infection (7), lead dislodgement (4), lead breakage (4), stimulator malfunction (3), persistent dystonia or inpatient programming (2), persistent dystonia or electrode repositioning (2), extension cable fracture (1), cervical myelopathy (1), peripheral denervation surgery (1), depressive episode or attempted suicide (1) • 45 AEs in total: – Dysarthria (16), worsening of dystonia (7), accidental deactivation of internal pulse generator (5), dysesthesias (4), gait disorder (2), postoperative confusion (1), transient internal pulse generator malfunction (1), depressive episode (1), frequent yawning (1), partial lead breakage (1), seizure (1), seroma (1), stuttering (1), sleep disorder (1), facial weakness (1), omarthrosis (1)
Volkmann (2014) ⁴⁰ n=62	• 16 SAEs (11 related to surgery or device, 1 related to medication or stimulation, 4 related to dystonia or another disorder) • 41 AEs (6 related to surgery or device, 27 related to medication or stimulation, 8 related to dystonia or another disorder)
Witt (2013) ³⁵ n=28	• 3 asymptomatic haemorrhages • 2 lead repositioning • 1 infection after battery replacement requiring explantation
Yianni (2003) ²⁴ n=12	• 1 hardware failure: sudden cessation of DBS led to very acute severe relapse of condition • 1 rebound effect after stimulation turned off suddenly

AEs, adverse events; DBS, deep brain stimulation; SAEs, serious adverse events

References for Appendix S2

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