Depression and Anxiety Following Deep Brain Stimulation in Parkinson's Disease: Systematic Review and Meta-Analysis

Depressão e Ansiedade após Estimulação Cerebral Profunda na Doença de Parkinson: Revisão Sistemática e Meta-Análise

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ABSTRACT

Introduction: Deep brain stimulation (DBS) is effective in advanced Parkinson's disease (PD), improving motor symptoms, fluctuations and quality of life. However, adverse psychiatric outcomes have been reported, albeit variably and in an unstandardized fashion. We aimed to summarize the published evidence on the outcomes of anxiety and depressive symptoms in Parkinson's disease patients following DBS, through systematic review and meta-analysis.

Material and Methods: PubMed was searched until May 2012 to identify studies assessing anxiety and depressive symptoms in PD patients who underwent bilateral DBS of the subthalamic nucleus (STN) or globus pallidus internus (GPi). Random effects meta-analyses were conducted for groups of at least three studies that were homogeneous regarding the design and the instruments used.

Results: 63 references were selected; 98.4% provided data on depression, and 38.1% on anxiety assessment scales. Two studies did not discriminate the target; from the remaining 61 references, short-term evaluation was performed in 37 (60.7%), mid-term in 36 (59.0%) and long-term in 5 (8.2%). Data on pre to postop variation was available in 57 (93.4%) reports and 16 (26.2%) presented STN-DBS versus different comparison groups: GPi-DBS (*n* = 4 studies, 25.0%), eligible for surgery (*n* = 6, 37.5%), and medical treatment (*n* = 7, 43.8%).

Discussion: Improvement of depression and anxiety is apparent after DBS, more pronounced in the short-term, an effect that seems to wane in later assessments. Concerning depression, STN-DBS shows superiority against medical treatment, but not when compared to eligible for surgery control groups. The opposite is apparent for anxiety, as results favor medical treatment over STN-DBS, and STN-DBS over eligible for surgery control group. Superiority of one target over the other is not evident from the results, but data slightly favors GPi for both outcomes.

Conclusion: The pattern and course of depressive symptoms and anxiety following DBS in PD is not clear, although both seem to improve in the short-term, especially depression following STN-DBS. Results are highly heterogeneous. Efforts should be carried out to standardize assessment procedures across centers.

Keywords: Parkinson's Disease; Deep Brain Stimulation; Anxiety; Depression; Meta-Analysis.

RESUMO

Introdução: A estimulação cerebral profunda (ECP) é eficaz na doença de Parkinson (DP) avançada, melhorando sintomas motores, flutuações e a qualidade de vida. No entanto, têm sido reportados efeitos adversos psiquiátricos, mas de uma forma variável e não padronizada. O objectivo deste artigo é analisar e sumarizar a evidência publicada sobre sintomas depressivos e ansiedade em doentes com DP após ECP, através de revisão sistemática e meta-análise.

Material e Métodos: A PubMed foi pesquisada até Maio 2012 para identificar os estudos que avaliaram sintomas depressivos e ansiedade em doentes com doença de Parkinson submetidos a estimulação cerebral profunda bilateral do núcleo subtalâmico (NST) ou globo pálido interno (GPi). Foram feitas meta-análises com modelo de efeitos aleatórios para grupos de pelo menos três estudos homogéneos em relação ao desenho e instrumentos utilizados.

Resultados: Foram selecionadas 63 referências; 98,4% continham dados relativos a escalas de avaliação de depressão e 38,1% relativos a ansiedade. Dois estudos não discriminavam o alvo usado; nos restantes 61 foi feita avaliação de curto prazo em 37 (60,7%), de médio prazo em 36 (59,0%) e de longo prazo em 5 (8,2%). Foram encontrados dados sobre variação pré/pós operatória em 57 (93,4%) estudos e 16 (26,2%) continham dados comparando ECP-NST versus outros grupos: ECP-GPi (*n* = 4 estudos, 25,0%), elegíveis para cirurgia (*n* = 6, 37,5%), e tratamento médico (*n* = 7, 43,8%).

Discussão: É aparente a melhoria de depressão e ansiedade após ECP, sobretudo a curto prazo, efeito que tende a esbater-se em avaliações posteriores. Em relação à depressão a ECP-NST mostrou-se superior ao tratamento médico, mas não em comparação com o grupo de controlo elegível para cirurgia. Verificou-se o resultado oposto para a ansiedade, uma vez que os resultados favorecem o tratamento médico sobre a ECP-NST, e esta sobre o grupo de elegíveis para cirurgia. Não é evidente a superioridade de um alvo sobre o outro, mas os dados favorecem ligeiramente o GPi para ambos os tipos de sintomas.

Conclusões: O padrão e curso dos sintomas depressivos e ansiedade após ECP na DP não são claros, mas ambos parecem melhorar no curto prazo, especialmente a depressão após a ECP-NST. Os resultados são bastante heterogéneos. Devem ser promovidos esforços no sentido de haver padronização de procedimentos de avaliação nos vários centros.

Palavras-chave: Doença de Parkinson; Estimulação Cerebral Profunda; Ansiedade; Depressão; Meta-Análise.

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INTRODUCTION

Parkinson's disease (PD) is a common, disabling neurodegenerative condition characterized by motor and non-motor symptoms, including cognitive and behavioral.[1] Deep brain stimulation (DBS) has proved effective in advanced PD, as motor symptoms, fluctuations, disability and quality of life improve in patients carefully selected for the procedure.[2-4] Recently, the efficacy of DBS has been also demonstrated in PD with early motor complications,[5] suggesting that the universe of potential surgical candidates is wider than previously established. However, concerns have been raised about potential cognitive and psychiatric adverse effects in PD patients following DBS, and some data even suggested that consequences might vary according to the chosen target, namely the subthalamic nucleus (STN) or the globus pallidus internus (GPi).[6-8] On the other hand, several studies found no significant adverse psychiatric outcomes following DBS in PD.[9-11] Accurate knowledge on this theme is paramount, as several authors have demonstrated that non-motor symptoms (NMS), namely depression and anxiety, impact significantly on the quality of life and illness-related distress of PD patients.[12-14] In fact, the importance of NMS in PD led to the recent proposal of an integrated assessment approach as part of the clinical routine.[15] Nonetheless, the outcomes concerning depression and anxiety in PD after DBS remain incompletely clarified, as several different assessment methods have been used, and results have been reported under diverse formulas. Data have been reviewed systematically in two previous publications concerning psychiatric outcomes in patients undergoing bilateral DBS, but one study published in 2006 was limited to patients having STN-DBS,[16] while the other, published in 2007, jointly analyzed results in several disorders, including PD;[17] in addition, new research data in PD have been published since then, thus justifying re-appraisal of findings. We aimed at systematically reviewing the literature and summarizing the evidence by meta-analysis, in order to establish state of the art knowledge concerning anxiety and depression following DBS in PD.

MATERIAL AND METHODS

PubMed was searched from inception until May 2012, using the search expression "("deep brain stimulation" OR "subthalamic stimulation" OR (stimulation AND ("subthalamic nucleus" OR "globus pallidus"))) AND (parkinson disease OR parkinson's disease)", to identify studies that assessed anxiety and depressive symptoms in PD patients who underwent bilateral DBS.

A total of 3 276 references were screened by one of 3 reviewers (MIC, AM, AO), following the same exclusion criteria defined a priori, as follows: 1) language other than English, Portuguese and Spanish; 2) non-human data; 3) disorders other than PD; 4) studies not concerning DBS; 5) studies not conveying original data (reviews, systematic reviews, meta-analysis, book chapters, letters to the editor with no original data); 6) case reports; and 7) reports with no data on the outcomes of interest, namely: 7.1) no clinical outcome at all (e.g. image methods for target location); 7.2) clinical outcome other than psychiatric; 7.3) psychiatric outcome not objectively assessed by psychometric instrument. This approach intended to include only references with objective and potentially comparable data. References were then restricted to those reporting on bilateral stimulation surgery performed on the most relevant DBS targets in PD (STN and GPi), with no previous lesion surgery, and only depression and anxiety were considered psychiatric outcomes. Study design details were used to exclude publications not enrolling participants consecutively or randomly selected. One additional reference was excluded as it focused on DBS "on" *versus* "off" comparison only. Duplicate references were eliminated by comparing titles, authors, centers and sample details. A total of 63 studies[3,10,18-78] assessing depression and/or anxiety following DBS (STN and/or GPi) in consecutive samples of PD patients were found. The flow-chart depicting reference selection and exclusion is presented in supplementary material online (Appendix 1).

Data on depression and anxiety assessment scales were collected from the eligible studies along with DBS target and follow-up time. Five aspects were considered in order to group and analyze data: 1) Main outcome: depression or anxiety; 2) DBS target: STN and GPi were individually considered; 3) Follow-up time: three main periods were considered: up to 6 months after surgery (short-term follow-up); between 6 months and 3 years (mid-term follow-up); and more than 3 years (long-term follow-up); within each defined time period we selected the data referring to the longest follow-up for analysis, whenever data was available for different moments after the intervention; 4) Assessment scale(s) employed; 5) Study design: two main types of information were sought: the change of variables of interest with the exposure to the procedure (follow-up studies with pre- and post-operative data) and the difference between groups concerning the response to DBS (studies with different types of comparators).

Information on these five aspects is detailed in supplementary material online (Appendix 2) for each one of the 63 references. Eleven of them[3,22,36,52,61,67,69,70,73,76,78] presented data in a non-comparable way, with a total of 52 references allowing quantitative analysis.

DBS *versus* controls and STN-DBS *versus* GPi-DBS were considered comparisons of interest, so in studies with other comparators only the information concerning the DBS group was collected. "On" state evaluation was considered in studies reporting "on" *versus* "off" state comparison. In partial duplicates with patients overlapping but with different assessment scales,[39,53] follow-up time[20,31] or comparison groups,[77] a selection of relevant data was performed for each one, and only specific duplicated information was excluded.

Forest-plots were used to summarize the findings from all eligible studies and random effects meta-analysis (DerSimonian and Laird method) was performed for groups

of at least three comparable studies. The I^2 statistic was used to quantify heterogeneity. Original data concerning different strata from the same studies were assumed as different samples, strata being defined by age,[47] single or multiple recording electrodes,[44] and center (in one collaborative study).[77] The pre to postoperative variation was calculated from "postop score – preop score". Differences between STN-DBS and the comparison groups were calculated by "STN score – comparator score". The effect size (ES) and corresponding 95% confidence interval (CI) were extracted whenever provided in the original reports or computed using the published data considering matched and independent samples, respectively (adopted formulas detailed in appendix 2 online). Test-retest coefficients have been collected for the several psychometric instruments.[79-90]

RESULTS

From the original 63 references, nearly all (*n* = 62, 98.4%) provided data on depression, and 24 (38.1%) on anxiety assessment scales. STN-DBS was performed in 60 studies (95.2%) and GPi-DBS in 9 (14.3%); the overlap between target groups corresponds to STN *versus* GPi comparison studies and two additional reports[3,76] that did not discriminate data by target, thus not suitable for comparison. From the remaining 61 references, short-term evaluation was performed in 37 (60.7%), mid-term in 36 (59.0%) and long-term in 5 (8.2%). Data on pre to postop variation was available in 57 (93.4%) reports and 16 (26.2%) presented STN-DBS *versus* different comparison groups: the comparators were groups of patients submitted to GPi-DBS (4 studies, 25%), eligible for surgery (EFS) (6 studies, 37.5%) and medical treatment (MT) (7 studies, 43.8%). The results on depression and anxiety assessment scales from the 52 comparable studies are described henceforth.

Depression:

a) Pre – postop variation:

i) STN-DBS (Fig.s 1 and 2):

1. Short-term follow-up: meta-analysis was performed on Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HDRS) and Montgomery-Åsberg Depression Rating Scale (MADRS) data. Summary effect size (ES) regarding BDI samples pointed to improvement (-3.05, I^2 = 68.8%). Only slight improvement occurred in the other groups, with ES = -0.286 for HDRS (I^2 = 70.5%) and ES = -0.763 for MADRS (I^2 = 0%). Improvement is apparent in all the remaining samples, with the only exception of one Geriatric Depression Scale (GDS) sample.
2. Mid-term follow-up: meta-analysis was performed on BDI and MADRS data only, with summary ES showing very slight improvement, along with high heterogeneity of the results: -0.37 (I^2 = 72.1%) and -0.636 (I^2 = 79.1%), respectively. In the remaining samples, four showed improvement and depression levels worsened after surgery in five.
3. Long-term follow-up: meta-analysis was performed only on BDI data. Summary ES indicated very slight depression improvement: -0.222 (I^2 = 40.9%). Additionally, the Zung-d sample showed improvement and the remaining Hospital Anxiety and Depression Scale – depression part (HAD-d) sample worsened.

GPi-DBS (Fig. 3):

4. Short-term follow-up: meta-analysis was conducted for BDI data and summary ES revealed depression improvement, despite high heterogeneity (summary ES = -3.101, I^2 = 57.9%). The remaining two samples showed improvement as well.
5. Mid-term follow-up: depression, as assessed by the several instruments, improved in all the three samples.

b) STN *versus* comparator (Fig. 4):

MT group:

1. Short-term follow-up: two samples (assessed with MADRS and Zung-d) showed a trend towards medical treatment superiority. The remaining seven favored STN-DBS.
2. Mid-term follow-up: both groups favored STN-DBS.

EFS group:

3. Short-term follow-up: in this single MADRS sample, medical treatment was superior.
4. Mid-term follow-up: two samples (BDI and MADRS) slightly favored STN-DBS. The remaining three samples (from HAD-d and also BDI and MADRS groups) pointed to medical treatment superiority, a tendency that is stronger in HAD-d sample.

GPi group:

5. Short-term follow-up: one BDI sample favored STN and the other one, along with the HDRS sample, favored GPi-DBS.
6. Mid-term follow-up: both BDI samples showed GPi-DBS superiority. Conversely, in the HDRS sample, STN-DBS was superior.

Anxiety

Pre – postop variation:

STN-DBS (Fig. 5):

7. Short-term follow-up: one single sample from State and Trait Anxiety Inventory – Trait part (STAI-t) group revealed anxiety worsening following STN-DBS, with all the remaining studies showing improvement after the intervention.
8. Mid-term follow-up: meta-analysis was performed on State and Trait Anxiety Inventory – State part (STAI-s) and STAI-t data. Summary ES demonstrated slight anxiety improvement in STAI-s group and moderate worsening in STAI-t group: -0.930 (I^2 = 0%) and 1.595 (I^2 = 64.2%), respectively. Hospital Anxiety and Depression Scale – Anxiety part (HAD-a) single sample showed worsening. The remaining samples presented anxiety improvement.
9. Long-term follow-up: STAI-t single sample showed no change. Additionally, one sample assessed by

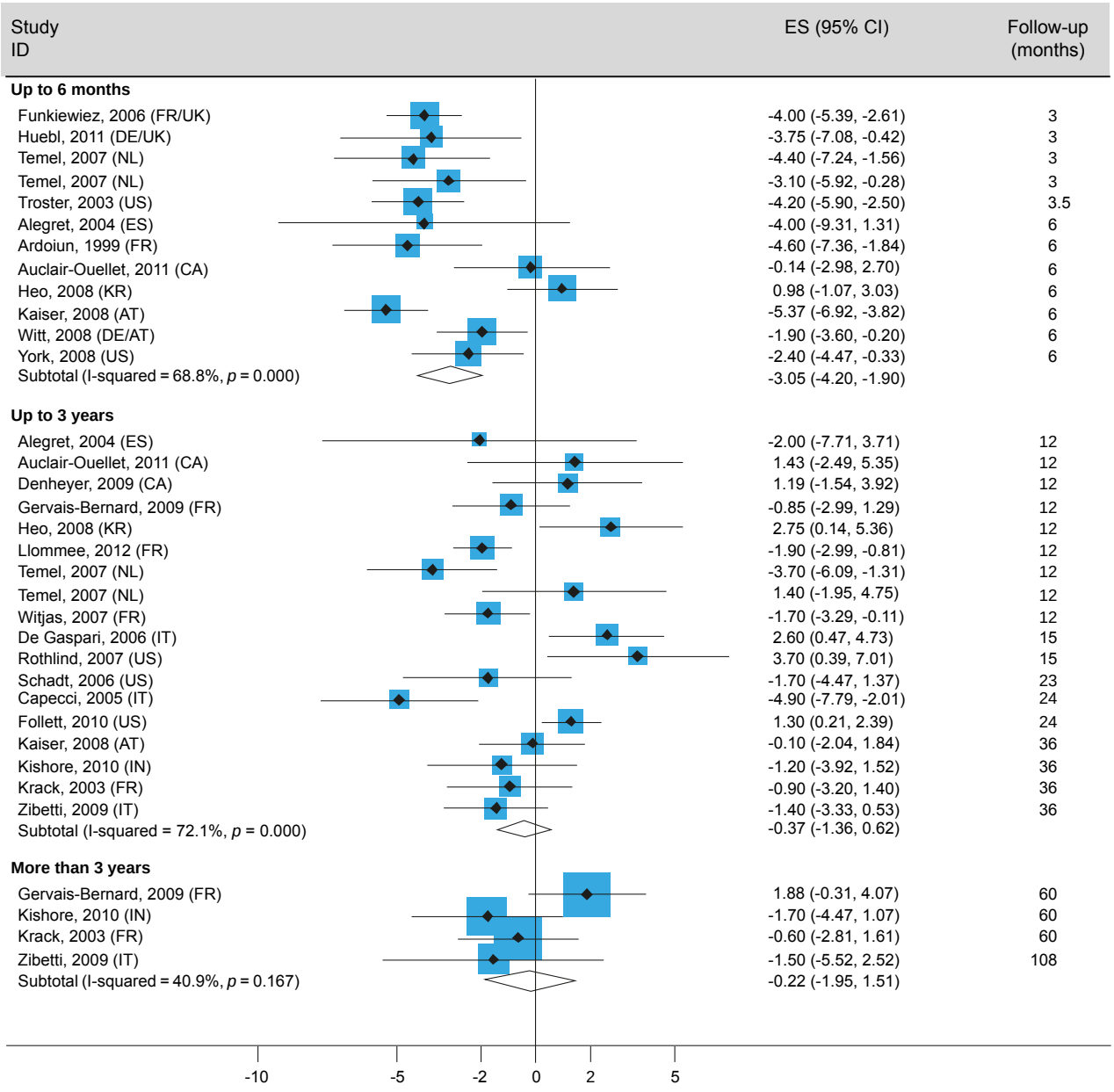

Figure 1 - Beck Depression Inventory (BDI) forest-plot. BDI results following subthalamic stimulation with data grouped and analyzed by follow-up time periods. Effect size and 95% confidence interval are presented for each sample. Overall measure is presented for each time period.

HAD-a worsened and the remaining two (STAI-s and Zung-a groups) improved.

GPi-DBS (Fig. 3):

10. Short-term follow-up: the only existing sample performed Beck Anxiety Inventory (BAI) and anxiety seemed to improve.
11. Mid-term follow-up: the only existing sample performed STAI-s and STAI-t and both improved.

c) STN *versus* comparator (Fig. 4):

MT group:

1. Short-term follow-up: the single BAI sample results favored STN-DBS. The remaining groups apparently showed medical treatment superiority.

EFS group:

2. Short-term follow-up: the only existing sample performed Association for Methodology and Documentation in Psychiatry – Anxiety part (AMDP-AT) and the results favored STN-DBS.
3. Mid-term follow up: one sample from STAI-s group favored medical treatment. The remaining two samples (from HAD-a and STAI-t groups) pointed towards STN-DBS superiority.

GPi group:

4. Mid-term follow-up: the only existing sample revealed GPi-DBS superiority, as assessed by the STAI-s and STAI-t.

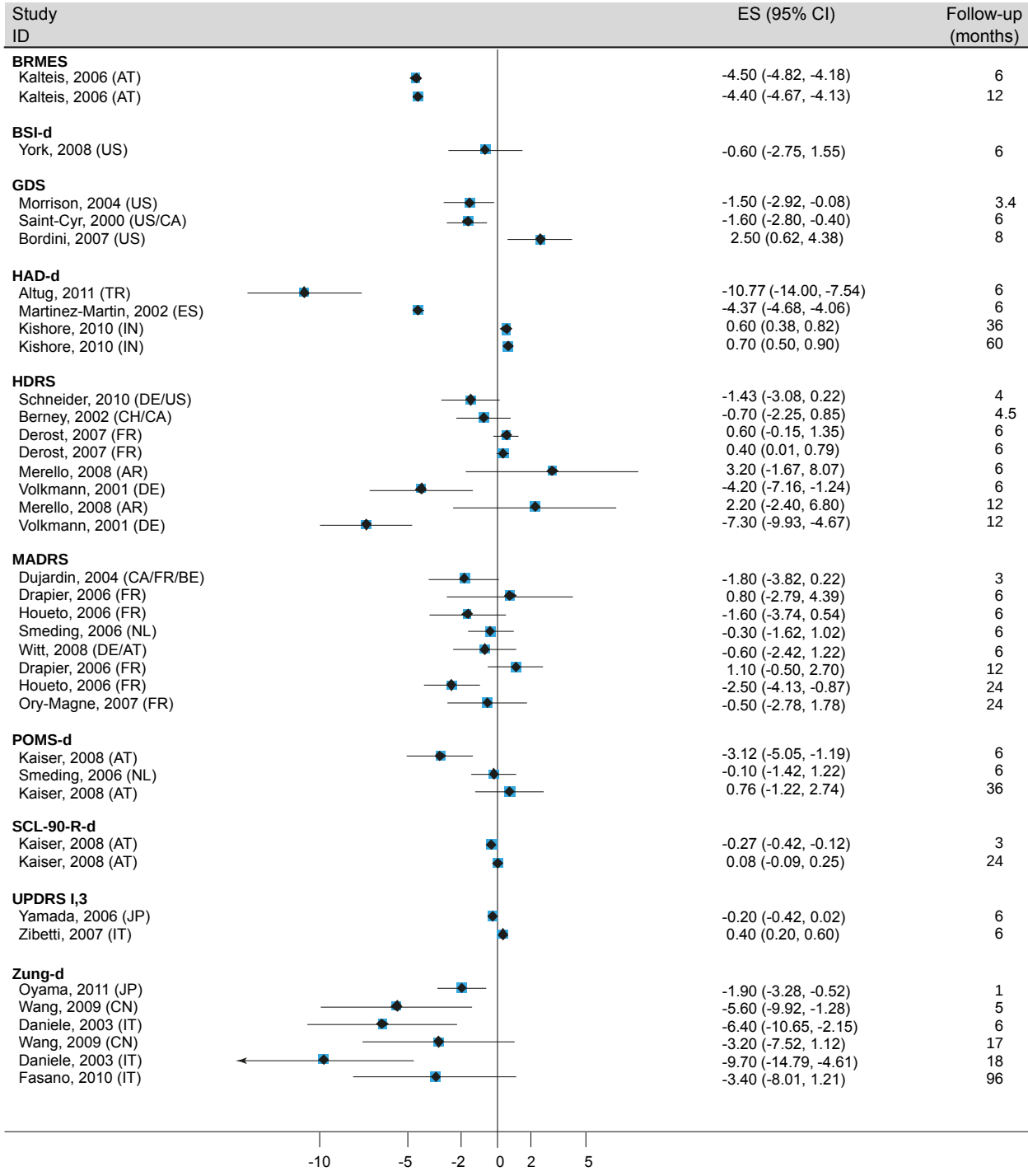

Figure 2 - Other depression psychometric scales forest-plot. Depression assessment results following subthalamic stimulation with data grouped and analyzed by psychometric instrument and sorted by ascending follow-up time. Effect size and 95% confidence interval are presented for each sample.

Abbreviations: BRMES: Bech-Rafaelsen Melancholia Scale; BSI-d: Brief Symptom Inventory – depression part; GDS: Geriatric Depression Scale; HAD-d: Hospital Anxiety and Depression scale – depression part; HDRS: Hamilton Depression Rating Scale; MADRS: Mongomery-Åsberg Depression Rating Scale; POMS-d: Profile Of Mood States – depression part; SCL-90-R-d: Symptom CheckList 90 Revised – depression part; UPDRS I,3: Unified Parkinson's Disease Rating Scale, part I, item 3; Zung-d: Zung self-rating depression scale.

DISCUSSION

Overall, objectively assessed symptoms of depression and anxiety apparently improve after DBS, with effects being more pronounced in the short-term and becoming weaker with longer follow-up. Nonetheless, results are highly heterogeneous, both across studies and psychometric instruments. Concerning depression, STN-DBS shows superiority against medical treatment, but not when compared to eligible for surgery control groups, especially in the short-term. The opposite effect occurs for anxiety, as the results favor medical treatment over STN-DBS, and STN-DBS when compared with eligible for surgery control

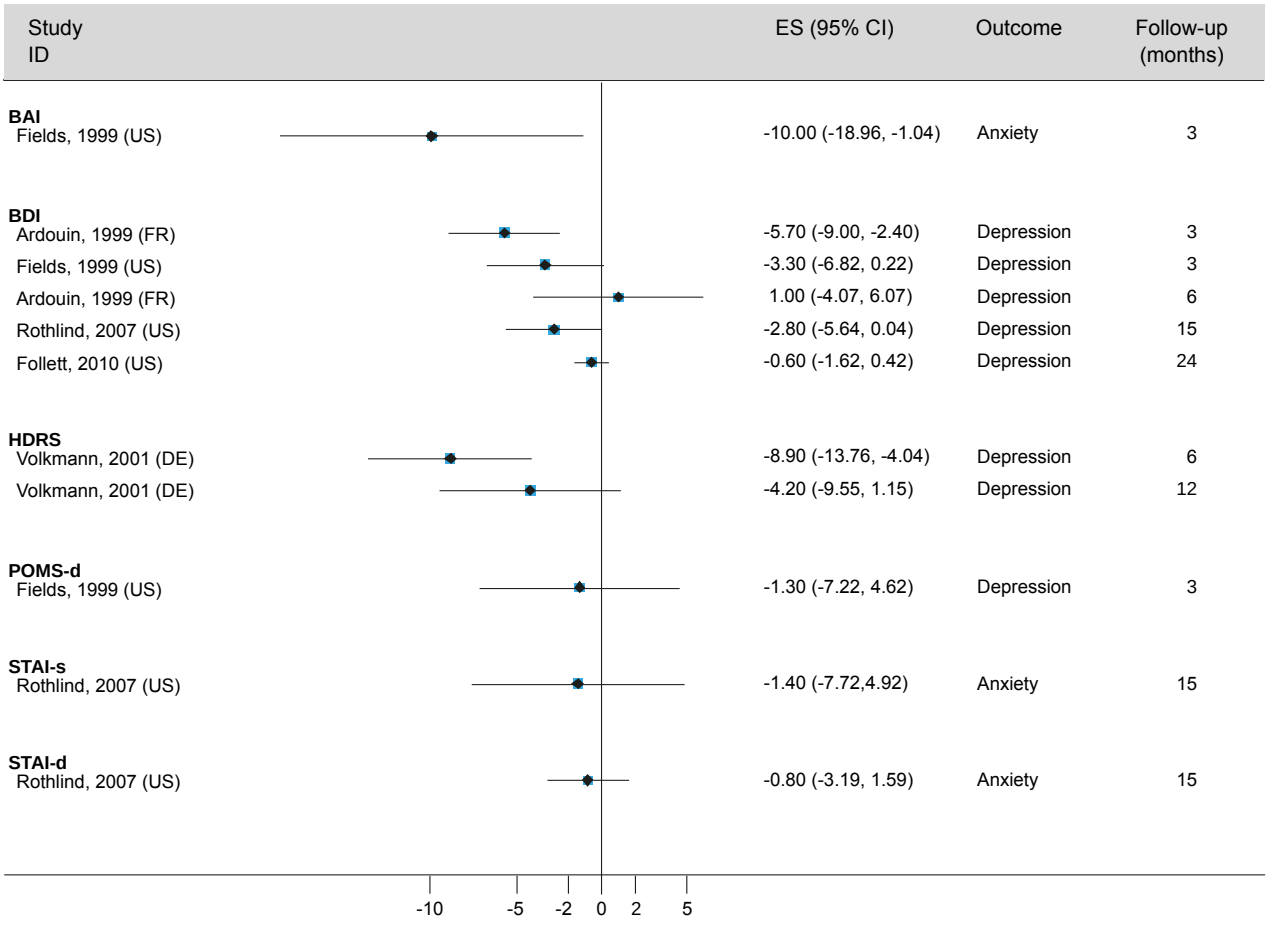

Figure 3 - GPi stimulation outcomes forest-plot. Depression and anxiety assessment results following pallidal stimulation with data grouped and analyzed by psychometric instrument and sorted by ascending follow-up time. Effect size and 95% confidence interval are presented for each sample.

Abbreviations: BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; HDRS: Hamilton Depression Rating Scale; POMS-d: Profile Of Mood States – depression part; STAI-s: State and Trait Anxiety Inventory – state part; STAI-t: State and Trait Anxiety Inventory – trait part.

group. Superiority of one target over the other is not evident from the results, due to significant heterogeneity of findings and paucity of data, but overall findings slightly favor GPi for both outcomes.

Among the included comparison studies, two randomized clinical trials on STN-DBS *versus* MT and STN-DBS *versus* GPi-DBS were found. Witt and coworkers[10] conducted a randomized multicenter trial comparing best medical treatment (BMT) and bilateral STN-DBS, with depression and anxiety assessments as specific secondary outcomes. They concluded in favor of DBS safety at short-term follow-up (6 months), in carefully selected patients. The authors adopted "major psychiatric illness - such as history of or current psychosis or history of or current severe depression diagnosed by a psychiatrist" as exclusion criteria. A recent randomized multicenter clinical trial compared STN-DBS and GPi-DBS,[29] and the authors found a modest difference between the two groups favoring GPi-DBS with regard to depression. The results from both randomized studies conform to our general findings.

From the 63 included references, 33 (52.4%) were published since 2007, when the most recent meta-analysis to the best of our knowledge was performed, highlighting the need of evidence re-appraisal. The present work focused on depression and anxiety following bilateral DBS in PD, objectively assessed by psychometric instruments, thus avoiding bias due to purely subjective clinical evaluation. In many of the excluded references, information was reported on DBS side effects (including psychiatric), without a standard definition of the clinical outcomes (concepts such as "slight disturbance of humor" or "mild depression" without further specification are hardly comparable). Additionally, this type of result contains no reference to the potential amelioration of any preoperative mild depressive symptoms following DBS. Therefore, in the present systematic review, the evaluation of the overall depression and anxiety levels following DBS was intended.

We speculate that the differences between STN-DBS, BMT and EFS groups might not be completely related to the effects of the therapeutic intervention by itself. In our 10-year experience with DBS in PD, we observed that patients who fail to meet the criteria for DBS frequently become depressed (unpublished data). A similar effect could occur with patients allocated to BMT, as opposed to those having

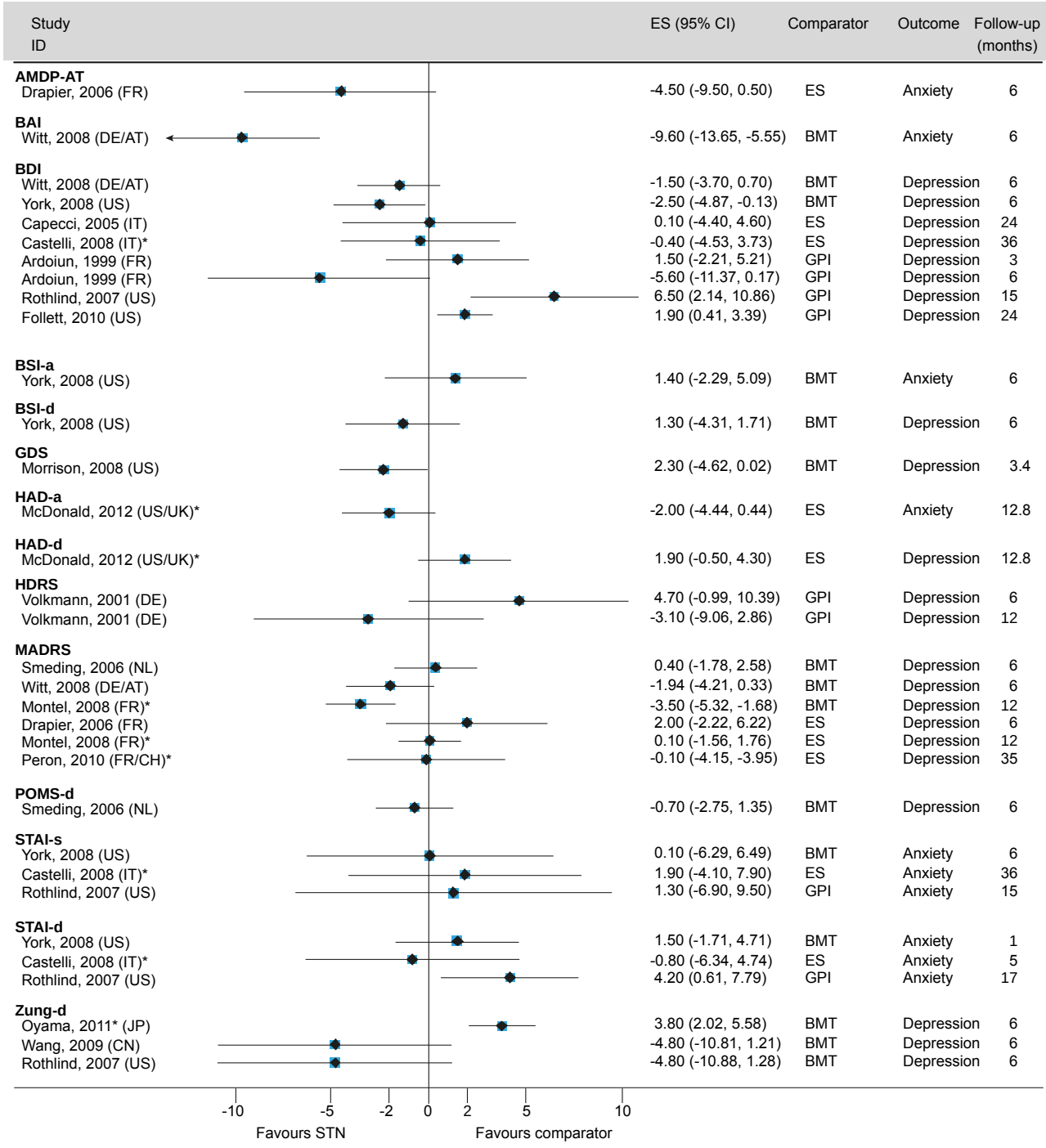

Figure 4 - Subthalamic stimulation *versus* comparators forest-plot. Depression and anxiety comparison results following subthalamic stimulation *versus* comparison groups. Data was grouped and analyzed by psychometric instrument and sorted by ascending follow-up time. Effect size and 95% confidence interval are presented for each sample.

Abbreviations: AMDP-AT: Association for Methodology and Documentation in Psychiatry – anxiety part; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; BSI-a: Brief Symptom Inventory – anxiety part; BSI-d: Brief Symptom Inventory – depression part; GDS: Geriatric Depression Scales; HDRS: Hamilton Depression Rating Scale; POMS-d: Profile Of Mood States – depression part; STAI-s: State and Trait Anxiety Inventory – state part; STAI-t: State and Trait Anxiety Inventory – trait part.

DBS or EFS (who can eventually decide to have surgery) in clinical trials. On the other hand, anxiety might increase in patients undergoing surgery due to the perceived risks but also expectations related to possible benefits. This would explain higher anxiety levels in the DBS groups. In any event, currently available data does not allow further exploration of these hypotheses.

One might also wonder about possible bias related to dropouts by suicide, since postoperative outcomes would then be wrongly estimated.[10,28,29,33,35,65] However, a large multicenter study[91] found that the completed suicide rate following subthalamic DBS in PD is less than 0.5%, suggesting that suicide occurrences are unlikely to influence data significantly in this regard.

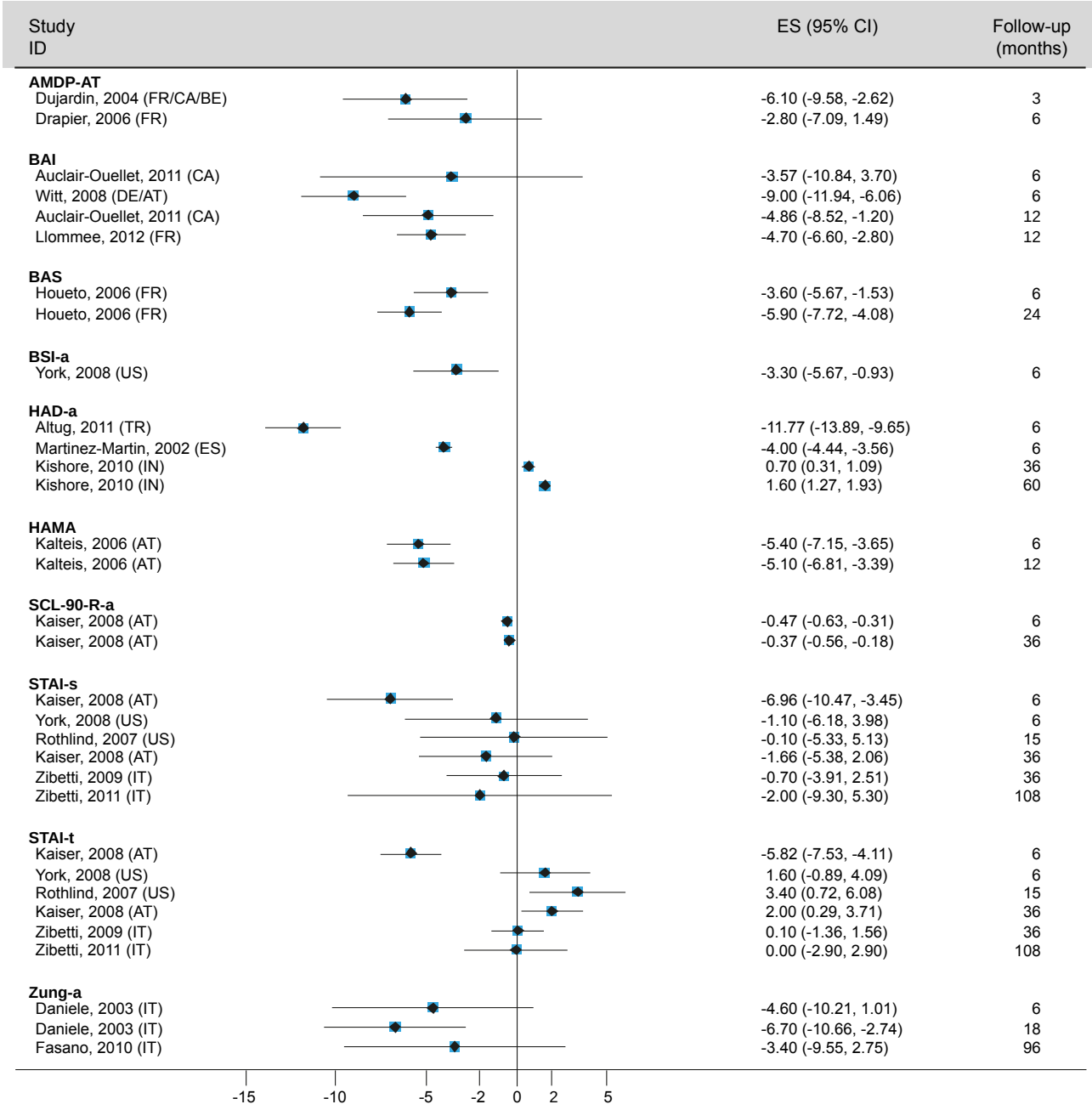

Figure 5 - Anxiety psychometric scales forest-plot. Anxiety assessment results following subthalamic stimulation with data grouped and analyzed by psychometric instrument and sorted by ascending follow-up time. Effect size and 95% confidence interval are presented for each sample.

Abbreviations: AMDP-AT: Association for Methodology and Documentation in Psychiatry – anxiety part; BAI: Beck Anxiety Inventory; BAS: Brief Scale for Anxiety; HAD-a: Hospital Anxiety and Depression scale – anxiety part; HAMA: Hamilton Anxiety scale; SCL-90-R-a: Symptom CheckList 90 Revised; STAI-s: State and Trait Anxiety Inventory – state part; STAI-t: State and Trait Anxiety Inventory – trait part; HDRS: Hamilton Depression Rating Scale; POMS-d: Profile Of Mood States – depression part; Zung-a: Zung self-rating anxiety scale. ascending follow-up time. Effect size and 95% confidence interval are presented for each sample.

We found that there are no long-term studies comparing the several therapeutic strategies for PD that adequately report objective data concerning anxiety and depression. Moreover, no long-term studies approaching this issue in GPi-DBS were found, and even short- and mid-term information regarding this target relies only on a few published studies. From the 63 references included only 9 (14.3%) reported on GPi-DBS. Therefore, there is a clear imbalance between the number of studies published concerning STN and GPi reporting objective psychometric data, thus limiting the strength of any comparative analysis. Measuring the outcome of either target could be important, since it has been suggested that patients undergoing either STN-DBS or GPi-DBS might fare differently with regard to mood following surgery.[29] This could be important in order to tailor the procedure (i.e. target choice) for each patient, considering the individual psychopathological profile.

CONCLUSIONS

The conclusions of the present systematic review are naturally limited by the small amount and specificities of the available publications, namely taking into account that most of the investigations do not have a comparator, and the heterogeneity of methods and presentation of the findings. An important issue identified by this systematic review is the wide range of psychometric instruments used in the setting of DBS in PD, with a total of 11 scales for depression and 10 for anxiety, considering those with quantitative and comparable results only. We emphasize that the high number of instruments reported, some of them involving a small number of subjects, limits the robustness of any conclusions extracted from the results. Thorough analysis of available psychometric instruments might contribute to the rational choice of scales to use, by narrowing the number of options. For example Williams and collaborators[92] have recently studied 9 depression assessment scales for use in PD patient populations. They concluded that the instruments analyzed show validity provided that specific cutoff values are used, with the exception of the item "depression" of Unified Parkinson's Disease Rating Scale[92]; the authors suggest that the 30-item GDS could be the most balanced choice in PD.[92]

In summary, no definitive conclusions can be drawn from this meta-analysis, although the available data suggests that depressive symptoms and anxiety improve following DBS at short-term, despite the significant heterogeneity of published results. Evidence is more ample concerning the improvement of depressive symptoms following STN-DBS. Our findings are consistent with the notion that DBS in PD is a safe procedure with regard to depression and anxiety, regardless of the target chosen. It seems clear that organized scientific efforts should be carried out in order to reach consensus and issue recommendations on the use of a small number of validated scales that would allow proper assessment and reporting of data in this setting. Recent evidence suggests that non-motor symptoms in PD fluctuate, namely psychiatric.[93] Thus, it could also be important to define the importance of accurate assessment of the severity of these symptoms both in "on" and "off" states, and their influence on the quality of life before and after DBS.

CONFLICTS OF INTEREST

The authors have no competing interests to declare.

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