Deep Brain Stimulation Effects on Olfactory Dysfunction of Parkinson's Disease - A Meta-Analysis

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Abstract

Background: Non-motor symptoms in PD usually arise at very early stage and suffer the damage decades from diagnose. Deep brain stimulation (DBS) is considered as a highly efficient treatment option for PD's motor function. However, the effect of DBS on NMS, especially hyposmia, has not been fully understood and there are contradictory data among different researches.

Objective: The objective of this study was to evaluate the therapeutic effect of DBS on hyposmia in PD patients with a cohort study and identified whether the olfactory function scores influence the final surgery effect.

Methods: A meta-analysis including six studies with 326 patients were conducted to evaluate the exact therapeutic effect of DBS on hyposmia in PD. Sub-group analyses based on sample size, gender, stimulation parameters were carried out to distinguish the difference. Sensitivity analysis was conducted to evaluate studies' heterogeneity and stability. Potential publication bias were evaluated by Egger's tests and the funnel plots.

Results: Our study showed that DBS had clearly improved olfactory function in Parkinson patients ($P < 0.0001$) and the group heterogeneity as well as the publication bias advocate the convince of the result (Heterogeneity: $Chi^2 = 6.39$, $df = 5$ ($P = 0.38$); $I^2 = 22\%$). Subgroup analysis also found that different groups of gender, education level or stimulation parameters have no obvious discrepancy on olfactory function improvement except age groups.

Conclusion: In summary, this article summarize studies about DBS and hyposmia and offer evidences for the notion that DBS has authentic therapeutic value on the hyposmia in PD.

Introduction

Parkinson's disease (PD) has now risen to the second most common neuro-degenerative disease, with a prevalence of approximately 2% in persons over 65 years[1]. By 2030, the morbidity of PD is expected to double, particularly in developing countries [2]. A major challenge in PD treatment is that the neurodegenerative process begins many years in the background before motor symptoms emerge. Thus early diagnosis of PD is in vital for a favorable curative effect on this disease[3].

Non-motor symptoms (NMS) in Parkinson's disease (PD) are very common and usually emerge from the early phase of the disease. Of these features, such as sleep disturbances, constipation, cognition, and changes in mood, olfactory dysfunction seems particularly suitable for early PD diagnosis because it affects most idiopathic PD patients[1]. It has been revealed that 90% of PD patients report hyposmia before the onset of the motor symptoms[4],which can be considered as a promising marker for latent neurodegenerative process in PD and predicts the classic motor features[5]. The association of impaired olfactory function and motor function for PD is thought to be tight [6]. Rapidly increasing data showed that olfactory parameters (OT, ODI and OI) are all gradually impaired along with the neurodegenerative

progression of PD [7], and hyposmia might help to predict the latent motor function impairment based on the dysfunction degree of smell sensation [8]. In accordance with this, studies also showed that parts of pathogens in PD originated from the olfactory bulb, anterior olfactory nucleus and the brain stem[9].Then pathogens ,usually referred to α-nuclei, might retrograde from peripheral neurons to motor function regions which directly connecting the cortical motor pathways with subcortical olfactory bulb[10]. To shed light on these findings it is not unreasonable to draw this conclusion that olfactory impairment partly spurred PD procession and it was confirmed by autopsy results [6].

Deep brain stimulation (DBS) is a highly efficient treatment option which could significantly improve motor function such as rigidity, tremor, bradykinesia etc. in typical PD. Irrespective of this, the effect of DBS on NMS, especially hyposmia, has not been fully understood and contradictory data regarding the DBS treatment on olfactory function were reported by different research teams. For instance, although there are studies indicating that DBS in STN did not change the olfactory function score in the acute postoperative process [11], some other data showed that DBS treatment provides an obvious improvement in OD in the long-term follow-up (6–12 months)[12–14].

These findings together suggested that DBS could improve the olfactory function in the meanwhile with the motor function. However, these articles failed to find an innate association between DBS and olfactory function improvement in PD. To our knowledge, there is no meta-analysis regarded to this topic. So we carefully gathered the most recent studies to give a compelling evidence for this issue and performed the meta-analysis to deduce the results from eligible studies to present a quantitative calculation.

Results

Study selection and characteristics

The whole procedure of study selection was presented in Fig. 1. Based on an comprehensive combination of search keywords, we screened a number of 36 papers by articles' title and abstract, 6 of them [11–16] were picked up as they fulfilled all inclusion criteria with intact data, strict experiment design to minor publication bias in this meta-analysis. All the enrolled studies were well-controlled and meeting selection criterions. Then according to the sample size, applied frequency, width of DBS, enrolled patients of all the studies were classified to different subgroups. Groups were also divided based on pre-SST and post-SST scores as well as UPDRS-III scores (on/off modulation). Overall, 6 studies constituting 326 patients were evaluated with SST scores, UPDRS, sample size, gender, age, frequency and width of stimulation.

Study characteristics and quality assessment

The enrolled studies and detailed clinical characteristics are exhibited in Table 1. Three studies contained more than 50 patients while the other two studies had relatively smaller sample size. Two studies use relatively low stimulation frequency and three studies used higher frequency. Three articles used shorter

pulse width (mean < 60us) and others used longer index. The publication time of all papers ranged from 2004 to 2019. The number of patients enrolled ranged from 22 to 78. To evaluate the quality of related studies and patients' data, Newcastle-Ottawa Quality Assessment scores (NOS) were conducted and scores varied from 6 to 9 (information presented in Table 2), which indicated that the quality of enrolled studies was high. Exacted clinical data could be browsed in Tables 1, 2.

Author	Ethnicity	Year	Sample size	Age(yr)	gender, Female:sex, No.[%]	Duration of disease at	Education level
M. Fabbri	UK	2014	30	61.8± 14.5	12(30)	17.1 ± 8.5	9.2 ± 1.6
M. Kronenbuerger	Germany	2010	21	67.3 ±11.1	3(21)	33.05±17	9.6 ± 1.5
Rubens Gisbert Cury	Brazil	2017	32	57.0 ± 11.9	8 (25)	11.7 ± 4.6	7.8± 2.6
T. Hummel	Germany	2004	11	57.3±11.2	5 (11)	14.7±4.5	ND
Özlem Saatçi	Turkey	2019	39	61.05 ± 9.9	12 (39)	9.3 ± 4.8	ND
Xiaodong Guo	China	2008	60	61.1± 7.8	26 (60)	11.3 ± 2.9	8.9 ± 3.2

Author	DBS operation duration (months)	UPDRS-III Off medication	UPDRS-III On medication	Pre-SST	Post-SST	Frequency (Hz)	Voltage (V)	Pulse width (us)
M. Fabbri	16±6	49.1 ± 15.7	28.1 ± 12	6.4 ± 3.0	9.4± 2.0	130±10	2.1±0.9	60.5±20.3
M. Kronenbuerger	35±29	50.2 ± 10.5	21.2±4.5	7.6± 3.0	8.5± 3.0	150.4 ±28.7	2.6 ±1.2	75.4 ±21.8
Rubens Gisbert Cury	12±6	42.8 ± 7.6	14.6 ± 7.2	7.3 ± 2.4	8.2 ± 2.1	136.2±14	2.8 ± 0.6	72.6 ± 20.7
T. Hummel	12±10	36.8±13.0	13.4±9.0	7.36±1.91	8.45 ± 2.77	130	3.1±0.3	60
Özlem Saatçi	3	23 ± 7.3	11.1 ± 5.1	7.3 ± 2.8	9.3 ± 2.4	155±25	2.4±0.9	60±20.2
Xiaodong Guo	49.8 ± 9.7	38.3±5.7	20±6	8.8 ± 2.4	7.6± 2.2	155±10	2.1±1.0	75.0±15

Table 1
Characteristics of included studies into meta-analysis

	Selection				Comparability		Outcome	
Study	Representativeness of Exposed Cohort 1	Selection of Nonexposed Group 2	Ascertartainment of Expose 3	Outcome of Interest 4	Comparability of Cohorts 5	Assessment of Outcome 6	Length of Follow-up 7	Adequency of Follow-up 8
M. Fabbri	1	1	1	1	2	1	1	0
M. Kronenbuerger	1	1	1	1	1	1	0	0
Rubens Gisbert Cury	1	1	1	1	2	0	1	1
T. Hummel	1	2	1	1	2	1	0	0
Özlem Saatçi	1	1	1	1	1	1	0	0
Xiaodong Guo	1	1	1	1	1	1	0	0

Table 2
Newcastle-Ottawa Quality Assessment Scale of included studies

Association between DBS in Parkinson patients and olfactory function

Methods described in previous section were used to evaluate the results, the association between DBS and olfactory function were assessed by forest plots. First data (Fig. 2.A) showed that all the enrolled Parkinson patients had effective DBS with improved UPDRSIII scores after the

operation (P < 0.0001).Then the relationship between DBS and olfactory function was observed, and results showed DBS had clearly positive effect on olfactory function in Parkinson patients (P < 0.0001) (Fig. 2.B). Following funnel plots showed the heterogeneity of these groups is acceptable, the P value and I^2 of this results showed they were eligible. Heterogeneities existed among different groups of UPDRS scores improvement which would be discussed in following section (Heterogeneity: Chi² = 132.9, df = 5 (P < 0.0001, I² = 96%). No notable heterogeneities were observed among these studies (Heterogeneity: Chi² = 9.39, df = 5 (P = 0.27; I² = 5%) (Fig. 2.D). Thus the result was reliable to support our conclusion and random-effect model was introduced to evaluate the possible publication bias to further confirm the hypothesis and explore clinical characters.

Association between clinic pathological features and olfactory function improvement

To further confirm the potential effect of DBS in olfactory function, the relationship between Parkinson patients' olfactory function and clinic pathological patterns including disease duration, education level, gender and average age were explored precisely. As seen in Table 2 and Figs. 3, forest plots of 6 eligible studies showed the DBS was associated with Parkinson patients olfactory function improvement (P < 0.0001). No great changes of olfactory function scores was found between different gender group (P = 0.06) or education level (P = 0.97) (Fig. 3.A, B), but in age group, it seems that age structure effected improve rates rate (P = 0.02) (Fig. 3.C). The difference may originate from the different morbidity and self-healing ability in different age and the criteria for young (< 60) and old (> 60) do have influence on the bias (P = 0.006).

Sensitivity and subgroup analyses

Subgroup analysis was also performed on sample sizes and stimulation parameters such as stimulation frequency and stimulation width to explore the potential sources of heterogeneity. Table 3 and Fig. 4

present the results of subgroup analyze on relationship between Parkinson patients' olfactory function and stimulation parameters. These results also indicated that sample size (P = 0.38, Fig. 4A) and as well as stimulation width (P = 0. 08, Fig. 4B) did not obviously effect the olfactory function improvement. However stimulation frequency (P = 0. 002, Fig. 4C) influenced the heterogeneity of the study. However,

Factors	Studies	Patients	Effect model	Test for subgroup differences:	Heterogeneity:
Sample size					
>50	4	64	Odds Ratio (M-H, Randomed, 95% CI)	$Chi^2 = 50.76$, df = 41 (P = 0.18), $I^2 = 44.3\%$	$Chi^2 = 5.41$, df = 4 (P = 0.03); $I^2 = 68\%$
<150	2	262	Odds Ratio (M-H, Randomed, 95% CI)		
Modulation frequency					
>150	3	146	Odds Ratio (M-H, Randomed, 95% CI)	$Chi^2 = 0.15$, df = 1 (P = 0.61), $I^2 = 0\%$	$Chi^2 = 5.41$, df = 4 (P = 0.008); $I^2 = 68\%$
<150	3	180	Odds Ratio (M-H, Randomed, 95% CI)		
Modulation width					
<70	2	166	Odds Ratio (M-H, Randomed, 95% CI)	$Chi^2 = 3.14$, df = 1 (P = 0.002), $I^2 = 89.7\%$	$Chi^2 = 5.41$, df = 4 (P = 0.002); $I^2 = 68\%$
>70	3	160	Odds Ratio (M-H, Randomed, 95% CI)		

Table 3
Data of subgroup for analyze of sample size and stimulation paramaters effects

Publication bias

Potential publication bias was evaluated by using Begg's funnel plot and Egger's test. Final results were shown in Fig. 5A, B, C. The results manifested that there were no obvious publication bias existing in enrolled studies, and no evidence of significant publication bias were found in this paper.

As seen in Fig. 5A, B, C and Table 3 group size didn't effect Olfactory improvement after DBS operation (*Test for subgroup differences: $Chi^2 = 1.79$, P = 0.18, $I^2 = 44.3\%$*). However, the heterogeneity of UPDRS III scores existed in these subgroups (*Heterogeneity: $Chi^2 = 132.99$, P < 0.0001; $I^2 = 96\%$*), which may come from the different diagnose patterns of PD in different countries. Additionally, stimulation parameters didn't influence the conclusion. And there were little heterogeneity among these subgroups (Frequency high vs low: *$Chi^2 = 15.59$ P = 0.06, $I^2 = 64\%$;* Width long vs short: *Heterogeneity: $Chi^2 = 15.59$ P = 0.008, $I^2 = 68\%$*).With these results, the heterogeneity of tumor grades mainly resulted from the UPDRS III scores.

DBS effects on Olfactory function sensitivity and specificity

Sensitivity and specificity analyses were also conducted to find the diagnostic effect of olfactory scores in PD patients. As seen in Figs. 6, forest plot and SROC curve of 5 eligible studies showed the higher olfactory scores is highly related to lower UPDRSIII of DBS which means improvement in PD patients and indicate good potential of sensitivity and specificity to define therapeutic effect which is in coincide with our theory.

Discussion

The motor symptoms of PD are reported to only become apparent after > 80% of dopaminergic neurons in STN underwent degeneration, so pathogenesis could commence in the background decades before the clinical onset of motor PD. Nonmotor symptoms emerged from the surface long before the onset of motor PD supports this hypothesis [17]. Thus early diagnosis of PD is in vital for a favorable curative effect on this disease [3]. Different prodromal features such as sleep disturbances, constipation and changes in mood, cognition, and olfaction impairment have been noticed as markers for prediagonostic as it influences most typical PD patients and predates the process of classic motor features [6]. Actually olfactory bulb also represent gateways with direct contact between environmental toxins and neurons, and evidence indicates that environmental pathogens contribute to the proceeding of PD[17]. The researches between hyposmia and PD are far from enough.

According to Braak et al hypothesis, olfactory bulb and the dorsal motor nucleus of the vagus (DMNV) were identified as the sparkle sites at which the neurodegenerative process in PD starts and then spreads to the brainstem and cortical regions of the brain [5].The sense of smell is originated from olfactory bulb, along with olfactory tract and then to the primary olfactory cortex [18, 19]. Then olfactory sensation is usually projected from these former structures to the secondary smell centers which are generating a complex network containing functional components of behavior, emotion, smell-related feeding, autonomic status and memory [18]. Studies have found that the α-synuclein appeared in the olfactory bulb had the capacity to anterograde from the olfactory system into the temporal lobe along with the smell tract structure [20].

Recent rodent studies have demonstrated the projection neurons in thalamic nucleus and Locus ceruleus directly innervate the olfactory bulb [21],As a result, α-syn pathology could rapidly propagate from the olfactory bulb to those motor-symptom related regions. Another latest study showed that the injection of exogenous α-syn fibrils into the olfactory bulb leads to recruitment of endogenous α-syn into pathological aggregates that spread trans-synpatically to remote brain regions [22]

Our findings confirmed that the olfactory function is tightly connected with PD progression and also the prognosis results. However, it may contradict the Braak hypothesis, as they showed the stimulation of STN improved the olfactory scores, which could not be fully explained by the model that the pathogens spread from peripheral nerves to cortex via anterograde progression.

There are also lots of studies presenting that PD is tightly connected with environment factors, and microbiota is considered as an important pathogen for PD [23]. There has been mounting interest in the role of human microbiome in modulating the inflammatory milieu of the central nervous system in PD [24]. Some environmental factors, such as caffeine consumption and cigarette smoking, may alter the composition of the microbiome in the gut in a way influencing the inflammation of intestine [25]. This, in turn, results in less aggregation of α-synuclein in the endogenous nerve system (ENS), thereby lowering the risk of PD. This finding is in coincidence with the observations of an altered intestinal microbiomes in PD patients and a profound influence of gut microbiota on the activity of ENS [26]. To date, most

researches on NMS has focused on the popular area “gut-brain axis”, with other mucosal surfaces such as nasal mucosa being relatively neglected.

Our finding is partly coordinately with above theory that olfactory function scores reflect the prognosis of PD. But why DBS could improve smell sensation if it was impaired by microbiome without antibiotics. So we think the mechanism of PD is far more complicated by using one singe model to elaborate.

Here we adopt an idea of paper that patients with PD contain highly heterogeneous symptoms and display capricious involvement of different neuro-regions during the early phases of disease and this heterogeneity can be partly explained by defining PD into a PNS- first and a CNS-first subtype [27]. According to this review, PD patients with olfactory function early impaired onset may possible belong to the PNS-first subtype. Conceivably, the olfactory bulb could sometimes be affected without involvement of the ENS, and vice versa α-syn may retrograde along with the vagus nerve to the central neuron systems resulting in the motor symptoms come first. And this could be advocated by the newly finding that risk of PD is significantly lowered in patients undergoing the vagotomy operation [28]. And in other patients, the initial pathology could arise within the CNS and reach the olfactory bulb via anterograde spreading. And that may explain the effect of DBS on olfactory function.

Convincing evidence studies have demonstrated that STN-DBS had a neuroprotective efficacy and might exhibit a modifying effect on the progress of the Parkinson’s disease [29, 30]. What was the most important finding in our study was that DBS could bring an improvement in all olfactory parameters compared to the preoperative period. And the improvement were not effected by different age, gender or education level. High-frequency STN-DBS stimulated the hippocampal neurogenesis was reported more beneficial in some researches [31], but it was not obvious within our meta-analysis. The major strength of our study is that it is the first cohort study to report the relationship with DBS and hyposmia. However, follow-up period of most studies was limited to three months and thus only the acute effects of STN-DBS could be observed which can be considered as a weakness of the study. Samples size of included studies are also limited and further research with more patients and accurate definition of olfactory function is needed which is our next goal to archieve.

Despite these limitations our meta-analysis gives a critical hint that future studies are needed to evaluate correlation of the non-motor symptoms and STN-DBS treatment in PD patients. This could be also helpful to call on the importance of early stage PD and give a hope to cure the hyposmia resulting from the neurodegeneration process.

Conclusion

This article indicates that DBS has clearly positive effect on hyposmia accompanied with Parkinson’s patients and stimulation parameters such as the frequency & pulse width do not influence the final results of DBS’s effect on hyposmia. The olfactory function scores could partially predict the final improvement of UPDRSIII scores in PD patients

Methods And Materials

Literature search strategy

A meta-analysis and systematic review was performed according to the recommends of Cochrane guidelines. Data extraction was systematically conducted among PubMed, Web of Science and EMBASE/Medlin, with various combinations of key words: [“Parkinson”, “PD”] AND [“Deep Brain Stimulation,” “DBS”] and [“Dysosmia”, “Olfactory disorder”, “Smell disorder” AND “Olfactory dysfunction”] with no language restrictions, and eliminate papers focusing on other Parkinson syndrome keywords. The search results was finally renewed till Mar. 1, 2020. References consists of PD related clinical cases, experimental studies and review articles were also enrolled to enrich additional patients’ data.

Inclusion criteria

Our purpose of this study was to clarify whether DBS enabled to improve the olfactory function among Parkinson patients. Therefore, the criteria for enrolled studies was based on: (1) studies should concern about the relationship between DBS and clinical outcomes of olfactory function within PD patients. (2) Parkinson should be diagnosed by the United Parkinson’s Disease Rating Scale (UPDRS). (3) Patients should undergo bilateral STN-DBS surgery in standard center. (4) Olfactory evaluation was assessed by Standard Olfactory Function Test such as stiff sticks’ test (5) the data should contain detailed information to explore further relationship between different factors. Studies without meeting any one of the above inclusion criteria would be excluded.

Data extraction

Two authors assessed included studies independently and selected appropriate cases. Any divergences between two authors were overcame by discussion and consensus. In these studies, data was extracted including following information: corresponding author’s name, number of enrolled patients, country of the population and the year of publication, sample size, patients’ age, education level, UPDRS scores (on/off stimulation), DBS parameters, olfactory parameters (OT, ODI and OI) and prognosis outcomes. When univariate analysis and multivariate analysis were both fit in include studies, we prefer the former results to be conducted in the study. If the necessary information could not be obtained directly within the studies, we sent email to the related corresponding author to fetch the original research data, otherwise the item was signed as “Not Documented (ND)”.

Statistical analysis

The Revman software (version 5.3) was introduced to lead the statistics work among the whole process of meta-analysis. Odds risks (OR) with 95% confidence intervals (CIs) were used to estimate the potential relationship between DBS and clinical pathological outcomes in forest plots. I^2 test and Q test were

calculated and conducted to evaluate heterogeneity in the results. If the I^2 test (> 50%) or the Q test (P < 0.05) were abnormal, indicating a significant heterogeneity existing among the selected studies, we preferred to a random-effect model to evaluate the results, and otherwise the fixed-effect model would be performed. Sub-group analyses including sample size, gender, stimulation parameters were conducted. Sensitivity analysis was introduced to analyze the heterogeneity and stability of enrolled data. In the meanwhile, potential publication bias were further evaluated by the funnel plots and Egger's tests. At the end of paper, effect of olfactory scores about diagnostic specificity and sensitivity were also shown by forest plot and SROC curve.

Abbreviations

SST, Sniffin' Sticks odor-identification test; PD, Parkinson's disease, STN: subthalamic nuclei oriented; OT: Odor threshold; ODI: odor discrimination; OI: odor identification; TDI: Threshold, Discrimination; Identification

Declarations

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Conflicts of interest

The authors have no conflicts of interest to disclose.

Authors' contribution

The clinical cases and papers were summarized by Ms. Chu, Ms Tian, Dr. Feng Li and Prof. Xu. Dr. C. Li wrote the main part of the manuscript including introduction results, methods and materials, abstract and Dr. C. Zhang revised the paper. All authors reviewed the manuscript.

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Figures

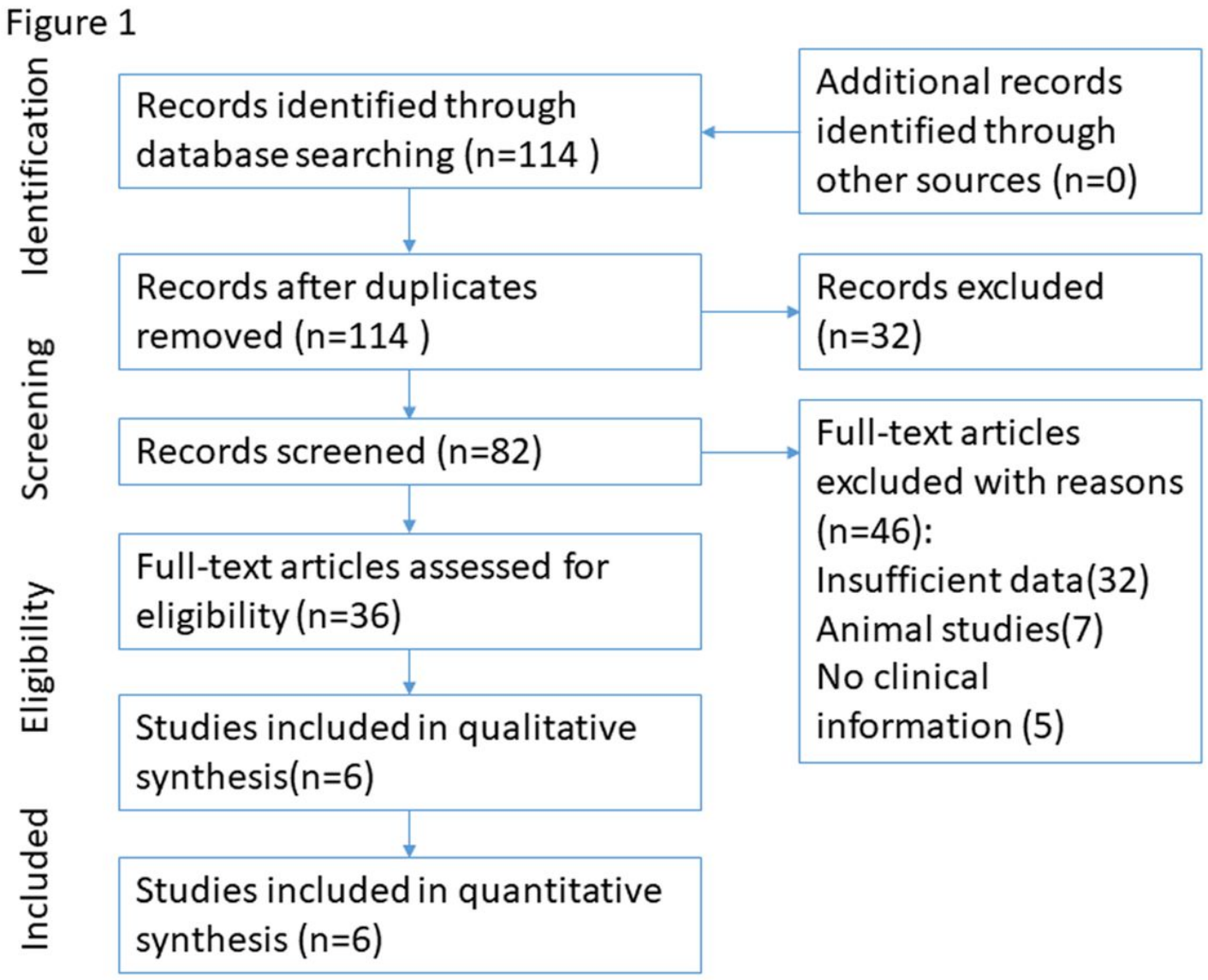


Figure 1

Flow chart for selection of studies;

Figure 2

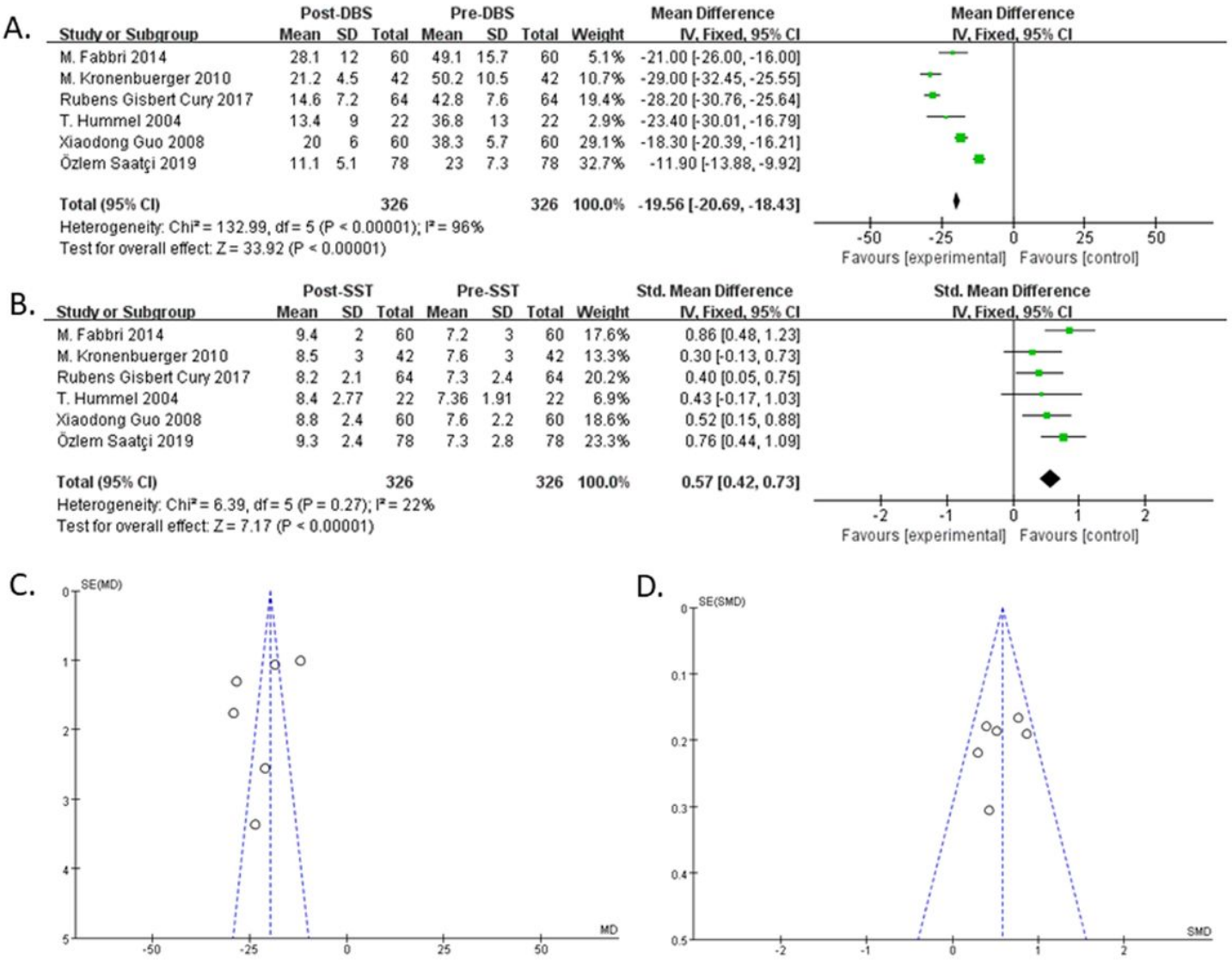


Figure 2

A Forest plot of studies evaluating the DBS's effect on involved PD patients' UPDRS III scores; B. Forest plot of studies evaluating the DBS's effect on PD patients' olfactory function; C. Funnel plot for publication bias test of DBS and UPDRSIII scores D. Funnel plot for publication bias test of DBS and olfactory funtcion related studies.

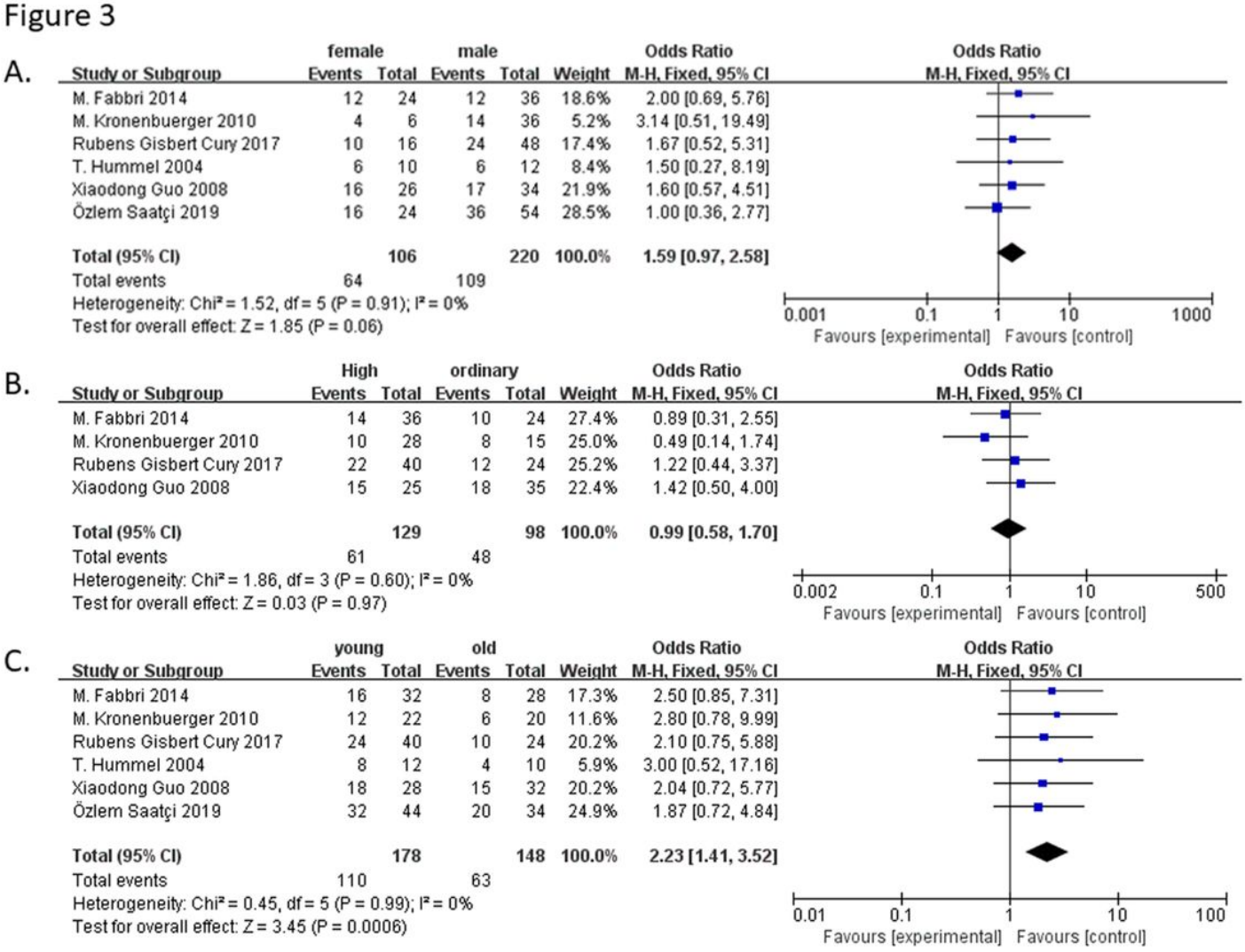


Figure 3

Association between DBS and clinical pathological features in PD patients: A. Gender; B. Education Level; C. Age

Figure 4

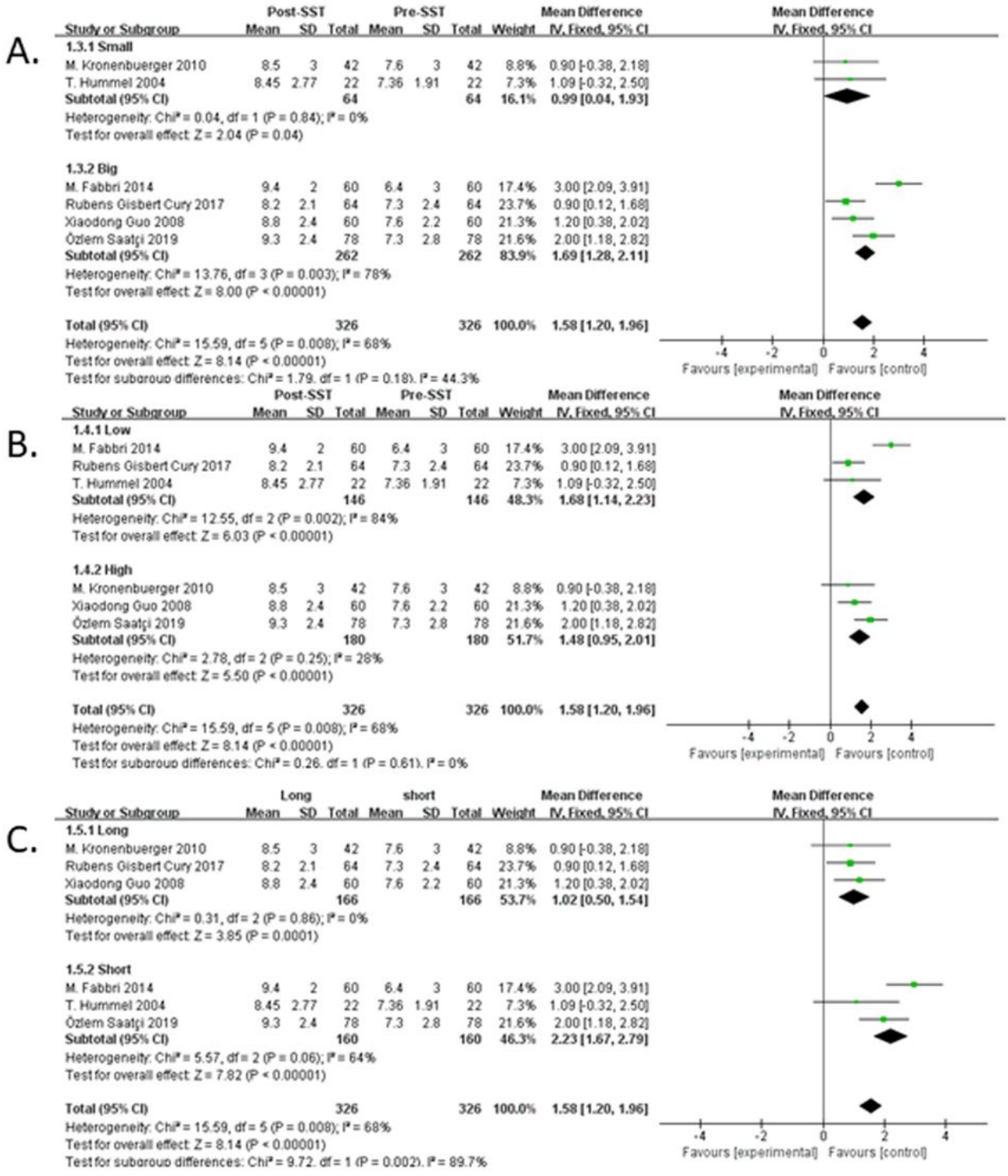


Figure 4

Subgroup analysis of DBS's effect with sample size, stimulation frequency and width: A. sample size; B. stimulation frequency; C. stimulation width.

Figure 5

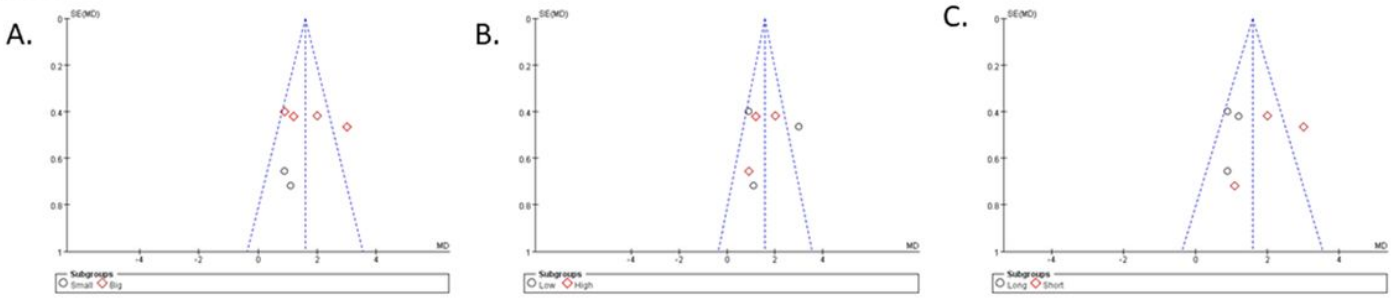
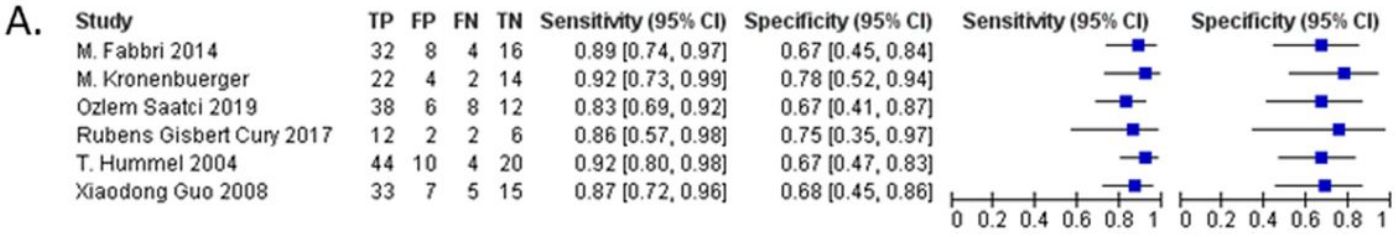


Figure 5

Funnel plot for publication bias test of related studies: D. sample size; E. stimulation frequency; F. stimulation width.

Figure 6



Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
M. Fabbri 2014	32	8	4	16	0.89 [0.74, 0.97]	0.67 [0.45, 0.84]
M. Kronenbuerger	22	4	2	14	0.92 [0.73, 0.99]	0.78 [0.52, 0.94]
Ozlem Saatci 2019	38	6	8	12	0.83 [0.69, 0.92]	0.67 [0.41, 0.87]
Rubens Gisbert Cury 2017	12	2	2	6	0.86 [0.57, 0.98]	0.75 [0.35, 0.97]
T. Hummel 2004	44	10	4	20	0.92 [0.80, 0.98]	0.67 [0.47, 0.83]
Xiaodong Guo 2008	33	7	5	15	0.87 [0.72, 0.96]	0.68 [0.45, 0.86]

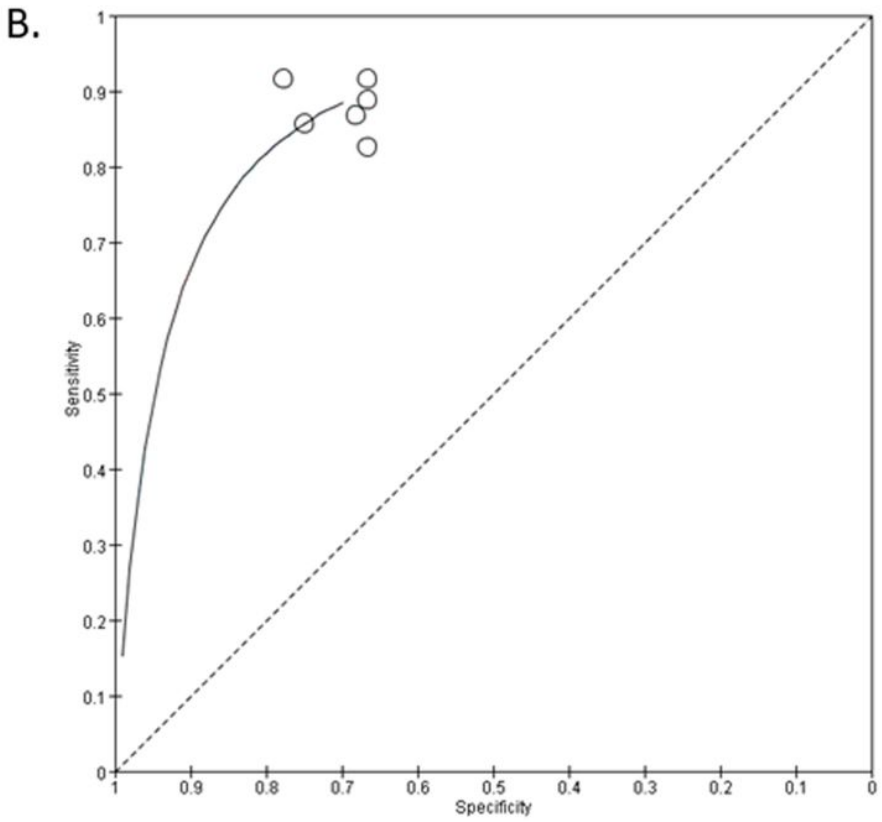


Figure 6

Diagnosis effect of olfactory scores in PD patients