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Efficacy of olfactory training in patients with olfactory loss: a systematic review and meta-analysis

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Abstract

Objective—Olfactory loss is a challenging clinical problem with few proven therapeutic options. Early experimental results with olfactory training (OT) suggest that this novel therapy may be an effective intervention for olfactory dysfunction of multiple etiologies. The aim of this study was to systematically review currently available studies that assess the efficacy and outcomes of OT in patients with olfactory loss.

Methods—A comprehensive systematic literature review was performed with the assistance of a reference librarian using the Medline, PsycInfo, Google Scholar, EMBASE, and Proquest databases. Eligible studies were extracted based on defined inclusion criteria and the effect of OT on objective olfactory function was evaluated qualitatively and by meta-analysis.

Results—A total of ten studies with 639 patients were identified and systematically reviewed. Sufficient data for meta-analysis was available for 3 studies. Patients receiving OT experienced a statistically significant improvement in the TDI (Threshold, Discrimination, Identification) score compared to control patients (mean difference [MD] 3.77; 95% CI 2.28–5.26). Improvement in olfactory function was observed in discrimination ([MD] 1.92; 95% CI 1.13–2.71) and identification ([MD] 1.61; 95% CI 0.55–2.68), but not in olfactory thresholds ([MD] −0.01; 95% CI −0.42–0.39).

Conclusion—Olfactory training is a promising modality for the treatment of olfactory dysfunction. Results of this systematic review and meta-analysis suggest that it may be an effective treatment for olfactory dysfunction due to multiple etiologies. Additional high quality studies are needed to define indications, outcomes, and duration of therapy for this novel therapy.

Keywords

olfactory dysfunction; hyposmia; anosmia; treatment; essential oils; smell training; rehabilitation; recovery

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INTRODUCTION

Olfactory dysfunction affects fifteen percent of the general population and continues to increase with age, affecting up to twenty-five percent of persons over the age of fifty.[1] The precise pathophysiology behind olfactory loss is poorly defined in the majority of patients. In most cases, olfactory dysfunction is acquired, often secondary to inflammatory conditions (chronic rhinosinusitis, viral infection), neurodegenerative diseases such as Parkinson's disease, or traumatic brain injury. Unfortunately, a lack of clear understanding regarding the molecular mechanisms of olfactory dysfunction has resulted in limited treatment options.

The olfactory system exhibits unique neural plasticity not found elsewhere in the central nervous system, with neurogenesis of the neuroepithelium and portions of the olfactory tract continuing throughout lifetime.[2] This suggests that certain interventions may have the potential to promote olfactory recovery by awakening olfactory neurons or modulating neural function. Olfactory training is a novel intervention that seeks to improve olfactory function by frequent sniffing and/or exposure to robust odors. Typical stimulating smells are representative of major odor categories, including flowery, fruity, aromatic, and resinous, and protocols typically require exposure to each odorant 2–4 times daily for several weeks. Clinical studies that have assessed the efficacy of olfactory training with such odors have been promising.[3–11] Whether the post-training improvements in olfaction are the result of changes at the level of the olfactory epithelium or more centrally at the olfactory bulb is still unknown. Recent studies using functional magnetic resonance imaging (fMRI) have demonstrated altered functional connectivity at the level of the cortex both before and after olfactory training.[10,11] Some studies have suggested that perhaps the act of sniffing alone, in the absence of any odor, can lead to similar results [3,11], though a recent randomized trial by Damm et al. seems to suggest that this effect is likely marginal [6].

Although generally viewed as an experimental treatment, there is mounting evidence that olfactory training may hold great potential as a treatment of olfactory dysfunction due to multiple etiologies. To date, there has been no critical review of this topic, despite several published trials that have shown positive outcomes. This evidence-based systematic review seeks to objectively evaluate current studies and assess efficacy across various etiologies of olfactory loss.

METHODS

A comprehensive systematic literature review was performed with the assistance of a research librarian, using the MedLine, EMBASE, PsycInfo, Google Scholar, and Proquest databases. The literature review was completed in April 2014 using the Medical Subject Headings (MESH) search term 'olfaction disorders'. The key search terms included 'olfactory training', 'olfactory disorders', 'olfactory rehabilitation' and 'olfactory recovery'. Exact search terms for each database are outlined in Figure 1. The literature search was developed to identify articles that included patients with olfactory dysfunction (all etiologies) who underwent olfactory training, and that included objective measurements of olfactory function. The search was limited to articles published in the English language and

to human studies. Non-human studies, single case reports, articles without objective measurements, and articles with little relevance to the study aims were excluded.

The titles and abstracts of retrieved articles were reviewed by two study authors (K.P., J.T.). A full-text review was then performed on selected articles by both authors to confirm that inclusion and exclusion criteria were met. Included studies were analyzed for multiple criteria, including number of subjects, etiology of olfactory loss, presence of a control group, outcome measures, and study results. Qualitative analysis and risk of bias was assessed using the modified 8-item Jadad scale.[12] This scale assigns points in the following manner:

1. Was the study described as randomized? (0=no; 1=yes)
2. Was the method of randomization appropriate? (−1=no; 1=yes; 0=not described)
3. Was the study described as blinding? (0=no; 1=yes)
    a. Double blind=1
    b. Single blind=0.5
4. Was the method of blinding appropriate? (−1=no; 1=yes; 0=not described)
5. Was there a description of withdrawals and dropouts? (0=no; 1=yes)
6. Was there a clear description of inclusion/exclusion criteria? (0=no; 1=yes)
7. Was the method used to assess adverse effects described? (0=no; 1=yes)
8. Was the method of statistical analysis described? (0=no; 1=yes)

A quantitative assessment of publication bias was completed using Begg and Mazumdar's Rank Correlation Test and Egger's Regression using Comprehensive Meta Analysis 2.2 software (Biostat, Englewood, NJ).

Studies were chosen for inclusion in the meta-analysis based on study quality and presentation of results in a way that allowed for data extraction. Correspondence with study authors was attempted when data could not be extracted from publication alone. Data was extracted from individual studies and compiled in a standardized database using Cochrane Review Manager 5.3 software (The Cochrane Collaboration, Oxford, UK). Mean values, standard deviations, and sample sizes were used for each comparable outcome with cumulative data formatted into forest and funnel plots to demonstrate weighted effects of olfactory training and publication bias, respectively.

Results are detailed in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines for reporting systematic reviews and meta-analyses. A 95% confidence interval (CI) was reported throughout, and statistical significance was set a priori with a p value of <0.05.

RESULTS

Systematic Review

The completed literature search retrieved a total of 549 articles, with 405 remaining after removal of duplicates. 395 articles were excluded after multi-level review, with the majority excluded on the basis of relevance, as they did not include an olfactory training protocol. Ten articles were selected for full text review, with all ten being included in the final qualitative analysis. The selection process is illustrated in Figure 2.

Study details

Details regarding individual studies identified during the systematic review are shown in Table 1. The ten included articles were comprised of eight prospective studies, one retrospective study, and one multicenter crossover randomized controlled trial. As shown in Table 2, the analyzed studies included subjects with olfactory loss due to multiple etiologies, including post-infectious (7 studies), post-traumatic (4 studies), idiopathic (3 studies), Parkinson's disease (2 studies), and old age (1 study). Adequate memory and cognitive function were ensured for patient's with Parkinson's disease and old age, in order to ensure reliable olfactory testing.[4,7,13] The same basic protocol was used in the majority of studies, with four distinct scents used for training, corresponding to each of the commonly used odor categories. Twice daily exposure was utilized with different durations of olfactory training, varying from a single day to 35 weeks. Seven of ten studies performed olfactory training for between 10 and 16 weeks.

The majority of studies used the Sniffin' Sticks test to objectively assess olfactory function. Two studies utilized functional magnetic resonance imaging to demonstrate altered connectivity after olfactory training.[10,11] Kollndorfer et al. demonstrated altered functional connectivity in the piriform cortex after olfactory training in patients with anosmia secondary to upper respiratory tract infections. Prior to olfactory training, there were multiple non-olfactory areas functionally connected to the piriform cortex. After olfactory training, there was one significant functional connection to the right subgenual cortex and the other non-olfactory connections declined. Subjective estimation of olfactory function was also collected by several studies.[5,6]

Bias Assessment

Qualitative assessment of the risk of bias was performed, taking into account study type, method of sampling, attrition, and adequacy of outcome reporting. As shown in Table 3, eight studies were deemed 'low risk' for bias, while two studies were classified as 'intermediate risk'. Risk of bias was quantitatively assessed for the most common primary study endpoint (TDI score) using the Begg and Egger tests. Both tests were nonsignificant ($p = 0.31$ and $p = 0.11$, respectively). Study quality was then quantitatively assessed using the modified Jadad scale. A majority of analyzed studies were of relatively low quality, with a modified Jadad score less than three.

Qualitative Assessment

The primary endpoint for the majority of studies was change in the TDI score, with >6 TDI points (6 studies) or >5.5 TDI points (1 study) considered a significant improvement in olfactory function (Table 4). Five of these studies used a control group. The prospective study by Fleiner et al.[8] compared olfactory training to olfactory training with the addition of oral corticosteroids, whereas the study by Geißler et al.[9] was a single arm study with all patients receiving olfactory training. Fleiner et al. reported a relatively low rate of improvement (10.7%) after olfactory training across patients with olfactory loss due to multiple etiologies, though this increased to 33% with the additional of oral corticosteroids.[8] A significant difference in the number of patients with clinically significant improvement (>5.5–6 TDI points) was observed in all but one study that included a control group. These studies included patients with olfactory loss due to multiple etiologies, including post-infectious, post-traumatic, idiopathic, and Parkinson's disease. Schriever et al.[13] did not identify a significant improvement in function after olfactory training in their cohort of patients with advanced age. The majority of studies did not present etiology-specific outcomes. Konstantinidis et al., in one of the largest studies, reported improvement in 68% of patients with post-infectious olfactory loss (33% for control group) versus improvement in 33% of patients with post-traumatic olfactory loss (13% for the control group).[5]

Quantitative Assessment and Meta-analysis

Three studies included sufficient data for inclusion in the meta-analysis. Patients receiving olfactory training experienced a statistically significant improvement in the TDI (Threshold, Discrimination, Identification) score compared to control patients (mean difference [MD] 3.77, 95% CI 2.28–5.26) (Figure 3). Significant heterogeneity was observed, with an I^2 statistic of 73%, however, this was likely due to the small number of included studies focusing on multiple etiologies. Within the individual components of the TDI score, olfactory training resulted in improvement in discrimination (MD 1.92, 95% CI 1.13–2.71) and identification (MD 1.61, 95% CI 0.55–2.68), but not olfactory thresholds (MD −0.01; 95% CI −0.42–0.39) (Figure 4).

The majority of included studies identified a clinically meaningful change in the TDI score as one of the study endpoints. The three studies eligible for meta-analysis set this threshold as an improvement of greater than 5.5 points[7] or of greater than 6 points.[5,6] When data was analyzed based on this metric, there was a statistically significantly effect of olfactory training when compared to control patients (Odds ratio 2.75,95% CI 1.60–4.73) (Figure 5).

DISCUSSION

The current systematic review and meta-analysis suggests that olfactory training may be an effective intervention for patients with olfactory dysfunction. Interestingly, the effect appeared to persist across multiple different etiologies, including post-infectious, post-traumatic, and Parkinson's disease. Most studies reported positive outcomes in olfaction without significant adverse effects. Only Schriever et al. reported no improvement in olfactory function after training.[13] However, the study results did show a decline in olfactory function in the control group, while function in the training group remained

essentially stable.[13] The meta-analysis was consistent with the reported results of individual studies, with improvements in TDI score largely due to changes in the discrimination and identification components, but not the threshold component. Conversely, threshold was the only component that demonstrated a statistically significant improvement in the study by Kollndorfer et al, perhaps due to the small sample size analyzed.[11]

Olfactory dysfunction is a problem with a variety of proposed etiologies, with post-infectious, post-traumatic, and chronic inflammatory (rhinosinusitis, rhinitis) causes being among the most common. Olfactory loss affects many realms of daily life, adversely impacting enjoyment of foods and fragrances and reducing the retrieval of olfaction-associated memories. In addition, olfactory dysfunction can be hazardous due to an inability to sense noxious chemicals, smoke, and spoiled food. Prior studies have reported that 25% to 33% of patients with olfactory dysfunction have symptoms of depression, and 27% to 30% indicate severe distress on general quality of life questionnaires due to their reduced sense of smell.[14] Further, physiologic anorexia, common in geriatric populations, may be partly due to diminished olfaction.[14,15] Olfactory loss can be an early sign of neurodegenerative disease and anosmic patients display reduced grey and white matter volumes compared to healthy controls.[16] Fortunately, recovery of olfactory function is possible with some etiologies, particularly patients with post-infectious olfactory dysfunction where spontaneous rates of recovery as high as 35% over one year have been reported.[17]

Olfactory loss is a challenging clinical problem with few proven therapeutic options. A wide range of treatment modalities for anosmia and hyposomia including corticosteroids, theophylline, antibiotics, and acupuncture have been attempted. However, a gold standard for therapy has not been identified. Corticosteroids can frequently improve olfactory function, however, the effect is often short-lived and disappears with discontinuation of treatment. Long-term improvement with the use of maintenance intranasal steroids has also been reported.[18] While not the focus of this review, it is notable that the study by Fleiner et. al did show additional improvement in olfactory function with the combination of topical corticosteroids and olfactory training, compared to olfactory training alone.[8] The results of this particular study suggest that combination therapy may be more effective than olfactory training alone. Theophylline is another pharmacologic agent with potential efficacy for olfactory dysfunction. In mice, this nonspecific phosphodiesterase inhibitor was found to increase olfactory sensitivity while simultaneously decreasing olfactory thresholds.[19,20] Theophylline theoretically increases olfactory sensitivity by modulating signal transduction in the olfactory epithelium. However, human studies have been limited by utilization of subjective assessments of olfactory function rather than objective measures of evaluation.[21,22] Unfortunately, none of these interventions have demonstrated lasting clinical efficacy, thus making olfactory training a realistic therapeutic alternative with great potential in patients with olfactory dysfunction due to multiple etiologies.

The mechanism by which olfactory training improves olfactory function remains largely hypothetical, and is likely dependent, in part, on the etiology of smell loss. For example, the mechanism through which olfactory loss occurs after upper respiratory infection has yet to be clearly elucidated, despite the frequency at which this diagnosis is encountered. While

olfactory neurons are known for their neural plasticity, repeated or severe insults often result in a lack of neuronal regeneration, and a persistence of olfactory dysfunction. Several studies have attempted to elucidate whether olfactory improvements after training are more centrally or peripherally mediated. Wang et. al demonstrated that repeated odor exposure can improve olfactory sensitivity as assessed by electrolfactogram and olfactory event-related potential recordings.[23] A majority of studies to date have highlighted a lack of improvement in olfactory thresholds, which are thought to be mediated at the level of the olfactory epithelium, while functional MRI studies have identified cortical changes after olfactory training that may be more centrally mediated.[10,11] Finally, some studies that have evaluated training without clinically significant odorant exposure have demonstrated higher rates of olfactory improvement than currently reported rates of spontaneous remission.[6] This suggests that sniff training alone, even in the absence of high odor concentrations, could result in some improvements in olfactory function.

Several limitations prevent us from making generalized recommendations based on the results of this systematic review. Despite the inclusion of ten studies with nearly 650 patients, lack of control groups and insufficient quantifiable data prevented inclusion of most studies in the meta-analysis, thus limiting the power of the study as a whole. With a limited number of studies within each etiology, it also remains difficult to determine the most appropriate indications for olfactory training. Finally, though the majority of studies were prospective in nature, many met with challenges in controlling for placebo effect, citing the possibility of easy detection of odorless training jars by subjects or relatives during the long-term daily training program. As a way to circumvent this problem, Damm et al. employed a high odor olfactory training group and a low odor olfactory training group in an attempt to more accurately control for the placebo effect.[6] Additional high quality double-blinded and placebo-controlled studies are needed to further define the indications, outcomes, and duration of therapy for olfactory training.

The current systematic review represents the most comprehensive analysis to date on the use of olfactory training in the treatment of olfactory dysfunction. The majority of studies identified a clear objective functional benefit with olfactory training compared to placebo. While additional high quality studies are needed, the current review suggests that olfactory training may represent a promising intervention for patients with olfactory dysfunction due to multiple etiologies.

CONCLUSION

Current evidence suggests that olfactory training may be beneficial to patients with olfactory loss. Additional randomized controlled trials that include patients with olfactory dysfunction due to multiple etiologies will ultimately be needed to confirm therapeutic effect and protocols.

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Search Terms for Databases
PubMed ("Olfaction Disorders"[Mesh] OR olfaction disorders[tiab] OR olfactory dysfunction[tiab] OR olfactory[tiab] OR smell[tiab] OR "smell disorder*"[tiab] OR cacosmia[tiab] OR cacosmias[tiab] OR dysosmia[tiab] OR dysosmias[tiab] OR paraosmia[tiab] OR anosmia[tiab]) AND ("Recovery of Function"[Mesh] OR olfactory training[tiab] OR "Patient Education as Topic"[Mesh] OR training[tiab] OR olfactory recovery[tiab] OR rehabilitation[tiab]) AND ("humans"[MeSH Terms] AND English[lang]) AND "humans"[MeSH Terms] NOT (Dog OR mouse OR animal OR mice)=200 results
Google scholar ("olfactory training" OR "olfactory rehabilitation") -animal -rat -mouse -mice -dog -ant –bee=178 results
Proquest MJSUB.EXACT.EXPLODE("Olfactory Perception") AND ("olfactory training" OR "olfactory rehabilitation" OR "olfactory recovery" OR training)) NOT (animal OR mouse OR rat OR mice) =80 results
PsycInfo MJSUB.EXACT.EXPLODE("Olfactory Perception") AND ("olfactory training" OR "olfactory rehabilitation" OR "olfactory recovery" OR training) NOT (animal OR mouse OR rat OR mice)=68 results
EMBASE ("olfactory training".mp. OR "olfactory rehabilitation".mp. OR recovery of function.mp.) AND (olfaction disorders.mp. or smelling disorder/ OR "olfactory dysfunction".mp.)= 23 Results

Figure 1.
Details of database search algorithms.

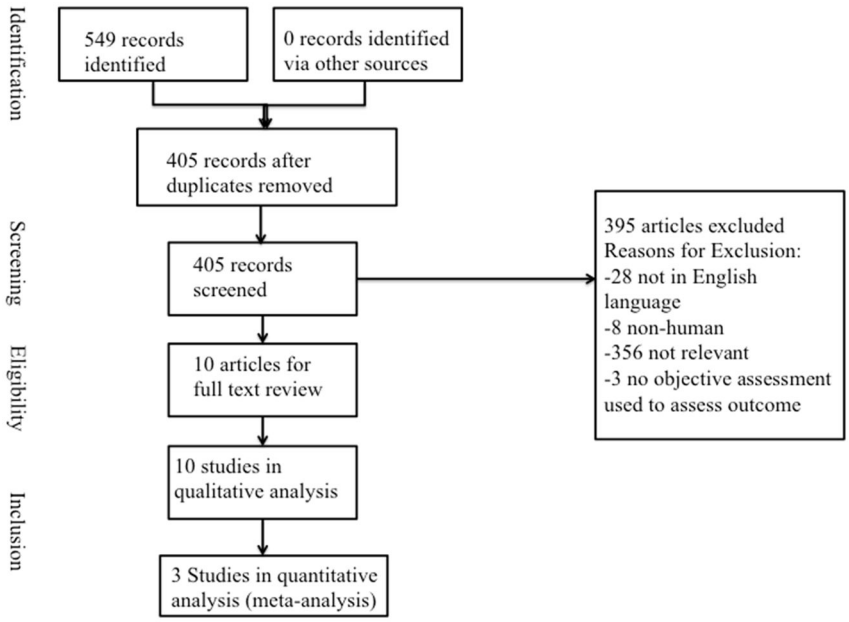

Figure 2.
Article selection process for systematic literature review.

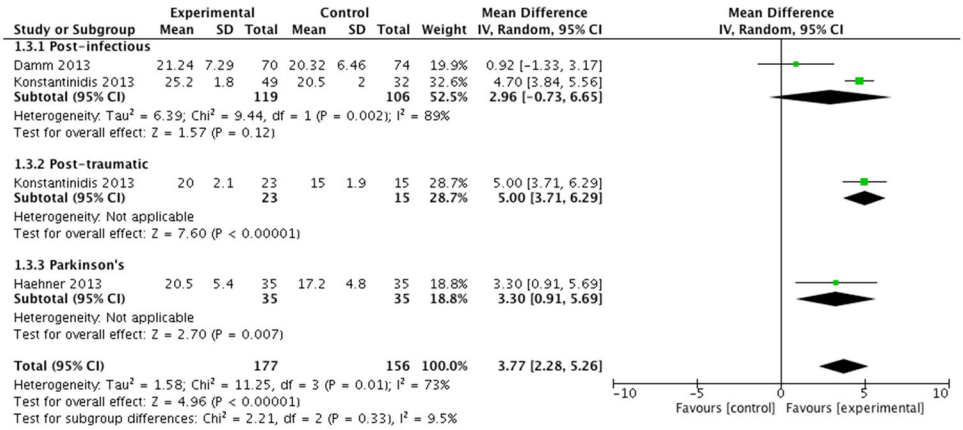

Figure 3.

Forest plot for TDI Score. TDI = Threshold/Discrimination/Identification; SD = standard deviation; CI= confidence interval

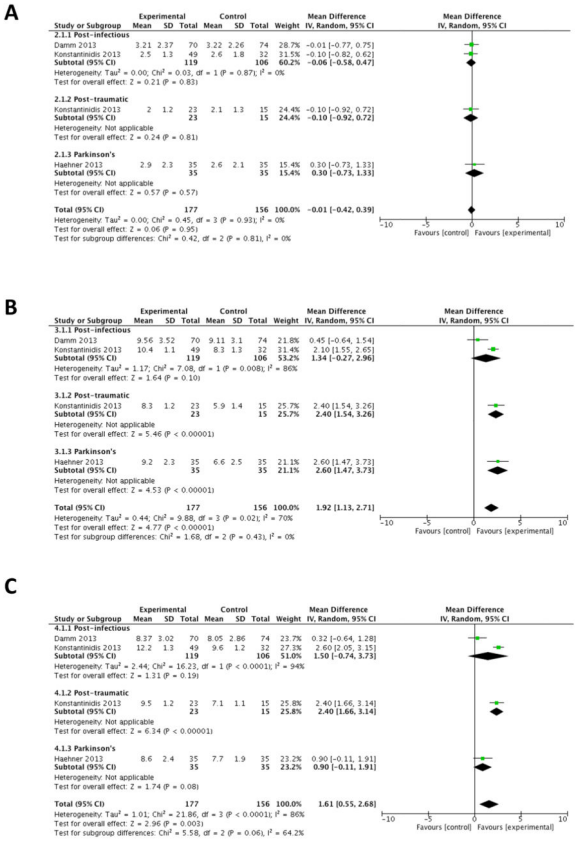

Figure 4.

(A) Forest plot for threshold component of TDI Score. (B) Forest plot for discrimination component of TDI Score. (C) Forest plot for identification component of TDI Score.

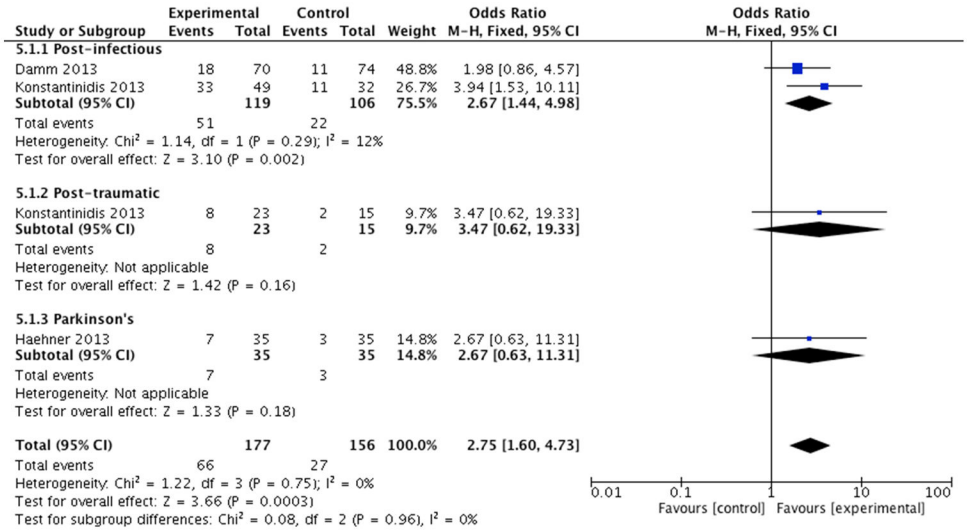

Figure 5.

Forest plot for percent of participants that experienced a functionally significant improvement in TDI Score, defined as an improvement of > 5.5–6.0 points.

Table 1

Qualitative Assessment for Risk of Bias

Study	Method of Data collection	Method of Sampling	Attrition (loss to follow-up)	Adequacy of Outcome Report	Risk of Bias
Hummel et al 2009	Prospective	Not reported	Not reported	Complete	Intermediate
Fleiner et al 2012	Retrospective, Non-blinded	Non-randomized	None after exclusion	Complete	Low
Konstantin idis et al 2013	Prospective	Subject preference	4% (5 patients)	Complete	Low
Haehner et al 2013	Prospective Non-blinded	Consecutive, Controlled	Not reported	Complete	Low
Damm et al 2014	Single-blind multicenter controlled trial	Randomized	None	Complete	Low
Borromeo et al 2013	Prospective	No control group	None	Complete	Intermediate
GeiBler et al 2014	Prospective	Non-randomized, no control group	Not reported	Complete	Low
Schriever et al 2014	Prospective	Not reported	48% (22 patients)training group didn’t follow protocol not included in analysis	Complete	Low
Kollndorfer et al 2014	Prospective	Not reported	36% due to incomplete fMRI measure ments	Complete	Low
Knudsen et al 2015	Prospective	Not reported	Not reported	Complete	Low

Table 2

Quantitative assessment for Study Quality

Study	Modified Jadad points
Damm et al 2014	5.5 points
Kollndorfer et al 2014	3 points
Knudsen et al 2015	3 points
Hummel et al 2009	2 points
Konstantinidis et al 2013	2 points
Haehner et al 2013	2 points
Fleiner et al 2012	2 points
GeiBler et al 2014	2 points
Schriever et al 2014	1.5 points
Borromeo et al 2013	1 point

Table 3

Organization of Studies by Cause of Olfactory Dysfunction

Etiology	Number of studies
Post-infectious	7 Hummel 2009 Konstantinidis 2013 GeiBler 2014 Fleiner 2012 Damm 2014 Borromeo 2013 Kollndorfer
Post-traumatic	4 Hummel 2009 Konstantinidis 2013 Fleiner 2012 Borromeo 2013
Parkinson's disease	2 Haehner 2013 Knudsen 2015
Old age	1 Schriever 2014
Idiopathic	3 Hummel 2009 Fleiner 2012 Borromeo 2013

Table 4

Study results

Study	Patients	Etiology of Olfactory Dysfunction	Length of Intervention	% Improved
Hummel 2009	56, I=40, C=16	• post-infection • post-traumatic • idiopathic	12 weeks	*>6 TDI points* • control (6%) • training (30%)
Konstantinidis 2013	119, post-URI I=49, C=32, post-traumatic I=23, C=15	• post-infectious • post-traumatic	16 weeks	*>6 TDI points* • post-infectious training (68%), post-infectious control (33%) • post-traumatic training (33%), post-traumatic control (13%)
Haehner 2013	70, I=35, C=35	• Parkinson's disease (stable on medication)	12 weeks	*>5.5 TDI points* • training (20%) control (9%)
GeiBler 2014	39, I=39	• post-infectious	32 weeks	• training (79%) >6 TDI points • training (56%)
Fleiner 2012	46, I=28, I+steroids=18	• sinonasal • post-infectious • post-traumatic • idiopathic	8 months (35 weeks)	*>6 TDI points* • training (10.7%) • training + steroids (33%)
Knudsen 2015	60, I_{PD}=34, C_H=26, C_{PD}=20	• Parkinson's disease	Same day training session	• improvements statistically significant but not noted for I_{PD} and C_H. $Control_{PD}$ (0%)
Schriever 2014	91, I=43, C=48	• Old age	12 weeks	• no significant improvement (>6 TDI points) • C(worsened TDI scores) • I (improved TDI scores)
Damm 2014	144, I_H=70, I_L=74	• post-infectious	16 weeks	• high training(63%) • low training (19%)

Study	Patients	Etiology of Olfactory Dysfunction	Length of Intervention	% Improved
Borromeo 2013	I=3	• idiopathic • post-traumatic • post-infectious	10 sessions over 10 weeks	• improvement in all aspects of CCCRC (100%)
Kollndorfer 2014	I=11	• post-infectious	12 weeks	• olfactory threshold improvement (85%) • fMRI changes (100%)