Olfactory Training and Visual Stimulation Assisted by a Web-Application for Patients With Persistent Olfactory Dysfunction After SARS-CoV-2 Infection

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Abstract

Introduction

We aimed to quantify the benefit of olfactory training and visual stimulation assisted by a dedicated web application for patients who experienced olfactory dysfunction for ≥1 month after Sars-Cov-2 infection and compared it with published cohorts of spontaneous recoveries.

Materials and Methods

We performed a prospective observational study. Participants performed olfactory training and visual stimulation assisted by a dedicated web-application. Improvement was defined as a 2-point increase on a 10-point, self-assessed olfactory visual analogue scale.

Results

In total, 1155 patients were assessable. Improvement was observed in patients who trained 4 weeks and 4 to 8 weeks with high concentration oils in 63.0% (58/92) and 72.9% (137/188) respectively, whereas in historical cohorts, a spontaneous improvement was observed in 7% to 27% without training respectively ($p<.001$). The benefit was observed regardless of the duration of the olfactory dysfunction. No or mild toxicity was reported by 86.6% (662/764) of patients. Severe toxicity leading to stop training was reported in 0.5% of patients.

Conclusions

Olfactory training and visual stimulation assisted by a dedicated web application seems to accelerate olfactive improvement in persistent olfactory dysfunction following SARS-CoV-2 infection, especially after 30 days of olfactory training. Maximal duration of training appeared to be 8 weeks.

Introduction

Persistent olfactory dysfunction is a significant complication of SARS-CoV-2 infection. Olfactory training involving aromatic oils has been recommended in this situation to improve olfactory recovery after a positive randomized trial in post-infectious olfactory loss, but quantitative and comparative data after SARS-CoV-2 infection are missing. [1, 2]

We aimed to assess the dynamic and the benefit of olfactory training assisted by a dedicated web-application and compared results to previous studies of spontaneous recovery without training.

Materials And Methods

We performed an observational, real-life, data-based study on a cohort of patients who experienced at least 1 month of persistent olfactory dysfunction induced by SARS-CoV-2 infection between January 30

and June 18, 2021. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline and was approved by the French National Health Data Institute, which reviews the ethical conduct of human subject's research, data confidentiality, and safety. To participate, individuals were required to connect to the free covidanosmia.eu web-application and provide electronic agreement. Gradation of symptoms were obtained through questionnaires at baseline and weekly by the application as well as toxicity. Details of the inclusion criteria and results of interim analysis performed after a mean olfactory training time of at least 28 days with the first 548 patients were previously published. [3] Participants exposed themselves twice daily to odors from 4 high-concentration oils and visual stimulation assisted by the dedicated web-application. Improvement was defined as a 2-point increase on a 10-point, subjective self-assessed olfactory visual analogue scale. Comparison of recovery was done with previous published cohorts of post viral (SARS-CoV-2 or other virus) patients with persistent olfactory dysfunction having training or not. [2, 4, 5]

Categorical variables were summarized using frequencies and percentages and Chi-square test was employed to make comparison. The level of statistical significance was 5% for all statistical tests. To analyze predictive factors of assessment, logistic regression was used to calculate odds ratios, which were presented with CIs set at 95%. All statistical analyses were conducted with SAS (Statistical Analysis System), version 9.3 (SAS Institute Incorporated).

All experiments were performed in accordance with relevant guidelines and regulations. This study was approved by the French National Health-Data Institute, which reviews ethical conduct of human subject research, data confidentiality, and safety. All methods were carried out in accordance with relevant guidelines and regulations, other than (STROBE) guidelines.

Informed consent

was obtained from all subjects and/or their legal guardian(s).

Results

On June 18, 2021, 10084 users downloaded the web-application and 1155 patients were assessable for primary outcome assessment with a mean olfactory training duration of 30 days. The mean age was 40.3 (min 18, max 85). Table 1, Figure 1

Table 1. Patient's characteristics

Variables	N(%)
Sex:	
Male	398 (34.4)
Female	757 (65.6)
Smell level before smell dysfunction:	
In the standard	
Less developed than average	741 (64.1)
More developed than average	38 (3.3)
	376 (32.6)
Smell role before lost:	
Not care about smell	342 (29.6)
Important role	813 (70.4)
Smell level at baseline:	
0	204 (17.6)
[1-2]	614 (53.2)
[3-5]	277 (24.0)
[6-7]	60 (5.2)
Olfactory dysfunction duration	
1-2 months	128 (11.1)
2,1 to 3 months	375 (32.5)
3,1 to 6 months	404 (35.0)
6 to 12 months	248 (21.4)
Taste dysfunction:	
None	577 (50.0)
Dysfunction	578 (50.0)
Parosmia:	
No	491 (42.5)
yes	664 (57.5)
Self-assessed toxicity:	
None	546 (71.5)

Mild	192 (25.1)
Moderate	23 (3.0)
Severe (leading to stop training)	3 (0.4)

The mean baseline, self-assessed olfactory score was 1.9 (SD 1.7), and this increased to 4.8 (SD 2.7) after a mean olfactory training time of 30 days. The rate of patients achieving olfactory dysfunction improvement was 75.7% (311/411) with at least 30 days training. Olfactory recovery increased dramatically from 1-day to 4 weeks training and was further asymptotic between 70% and 77% from 8-weeks training. Figure 2

Improvement was observed in patients who trained 4 weeks and 4 to 8 weeks in 63.0% (58/92) and 72.9% (137/188) respectively, whereas in historical cohorts of patients with Sars-Cov-2 or other infection's persistent olfactory dysfunction, a spontaneous improvement was observed in 7% to 43% without training or using low concentration oils respectively (p<.001). Figure 3

The duration of the training was associated with better outcomes (p<.001) and no other predictive factors were highlighted in univariate analysis. Table 2

Table 2. Logistic regression analysis for determining the predictive factors of olfactory function improvement (ie, an increase of ≥2 points on the olfactory scale).

	Univariate analysis			
Variables	RR [95%CI]	p-value	RR [95%CI]	p-value
Gender Male Female	 1 1.156 [0.896; 1.492]	0.2637		
Age	0.991 [0.981; 1.000]	0.0613	0.991 [0.982; 1.001]	0.0890
Covid test Postive test No test Yes, but Negative test Yes, but no test	 1 1.473 [0.393; 5.520] 1.350 [0.767; 2.376] 1.187 [0.731; 1.925]	0.8644		
Antecedent More 6 month (3) 1 month (0) 2 month (1) 3-6 month (2)	 1 0.631 [0.403;0.989] 0.728 [0.524; 1.011] 0.672 [0.485; 0.931]	0.0718	 1 0.588 [0.366; 0.945] 0.774 [0.541;1.108] 0.700 [0.498; 0.984]	0.0961
Smell importance In the standard Less than standard Better than standard	 1 1.138 [0.584; 2.218] 0.911 [0.702; 1.182]	0.4351		
Taste lost No Yes	 1 0.911 [0.716; 1.159]	0.4483		
Parosmie No Yes	 1 1.015 [0.796; 1.295]	0.9018		
Follow-up <28 days >=28 days	 1 2.212 [1.697; 2.833]	<0.0001	 1 2.053 [1.544; 2.730]	<0.0001

Local toxicity (nose irritation) was assessable in 764 patients. No toxicity was reported by 71.5% (546/764) of patients, and mild, moderate, and severe (leading to stop training) toxicities were reported by 25.1% (192/764), 3.0% (23/764) and 0.5% (3/764) of patients respectively.

The benefit of 30-days or more olfactory training was observed regardless of the duration of the olfactory dysfunction: 73.7% (140/190) of patients having 1-month to 2.9 months olfactory dysfunction duration and 77.1% (165/214) in 3-months to 1-year dysfunction (p=.82) as well as the mean improvement of olfactory function on olfactory scale. Figure 4

Discussion

This study is the largest that prospectively assess the benefit of olfactory training for patients who experience persistent olfactory dysfunction after SARS-CoV-2 infection.

Olfactory training and visual stimulation assisted by a dedicated web application was associated with accelerated improvement in olfaction as compared with spontaneous recovery in SARS-CoV-2 or other virus persistent olfactory dysfunction reported in literature (73% of patients with high concentration oils' training vs 43% with low concentration oils' training vs 7-27% without training. [2, 4, 5]. The maximal duration of training appeared to be 8 weeks as improvement rate became asymptotic from 8-weeks. The mean improvement in self-assessed olfactory scale scores was similar regardless of the anteriority of the olfactory dysfunction and training duration was associated with probability of recovery. No other predictive factors were highlighted such as parosmia, taste loss, gender…

As only subjective assessment was performed in our study, we probably underestimated the rate of improvement as Renaud M and al recently reported that participants tend to underappreciate the return of normosmia in subjective assessment versus objective measures. [6] So our results could be higher after objective assessment of recovery by physician using sniffing tests.

The limitation of our study is the lack of a direct comparison with a placebo group, but as olfactory training is recommended, it is not ethical to perform a new randomized trial. Another limitation is the different scales and methods used in other studies reporting olfactory function improvement.

Conclusion

Olfactory training and visual stimulation assisted by a dedicated web application seems to accelerate olfactive improvement in persistent olfactory dysfunction following SARS-CoV-2 infection, especially after 30 days of olfactory training. Maximal duration of training appears to be 8 weeks.

Declarations

Acknowledgments

We thank the users for their participation in this study as well as Magali Balavoine, MSc, from Weprom in Angers, France and the Anosmie.org patient's association. No one received compensation for their contributions. The sponsor (Weprom) designed and conducted the study; collected, managed, analyzed, and interpreted the data; prepared, reviewed, or approved the manuscript; and made the decision to submit the manuscript for publication.

Authors' Contributions

FD had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. FD contributed to the concept and design of this study. All authors contributed to the acquisition, analysis, or interpretation of data. All authors contributed to the drafting of the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. FD and ALS conducted the statistical analysis. FD, Weprom, and Kelindi provided administrative, technical, or material support. FD, SM, and HG supervised this study.

Conflicts of Interest

FD and FL are founders of Kelindi. The other authors have no conflicts of interest.

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Figures

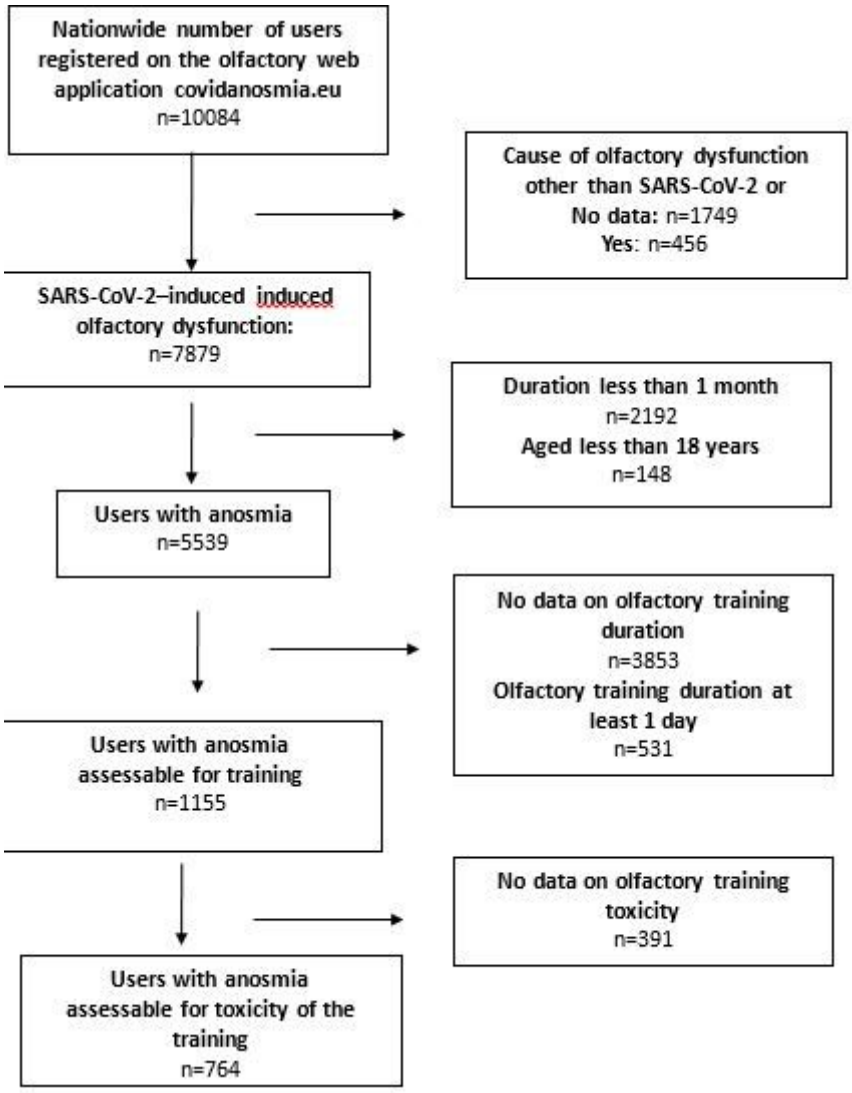

Figure 1

Flowchart of the study

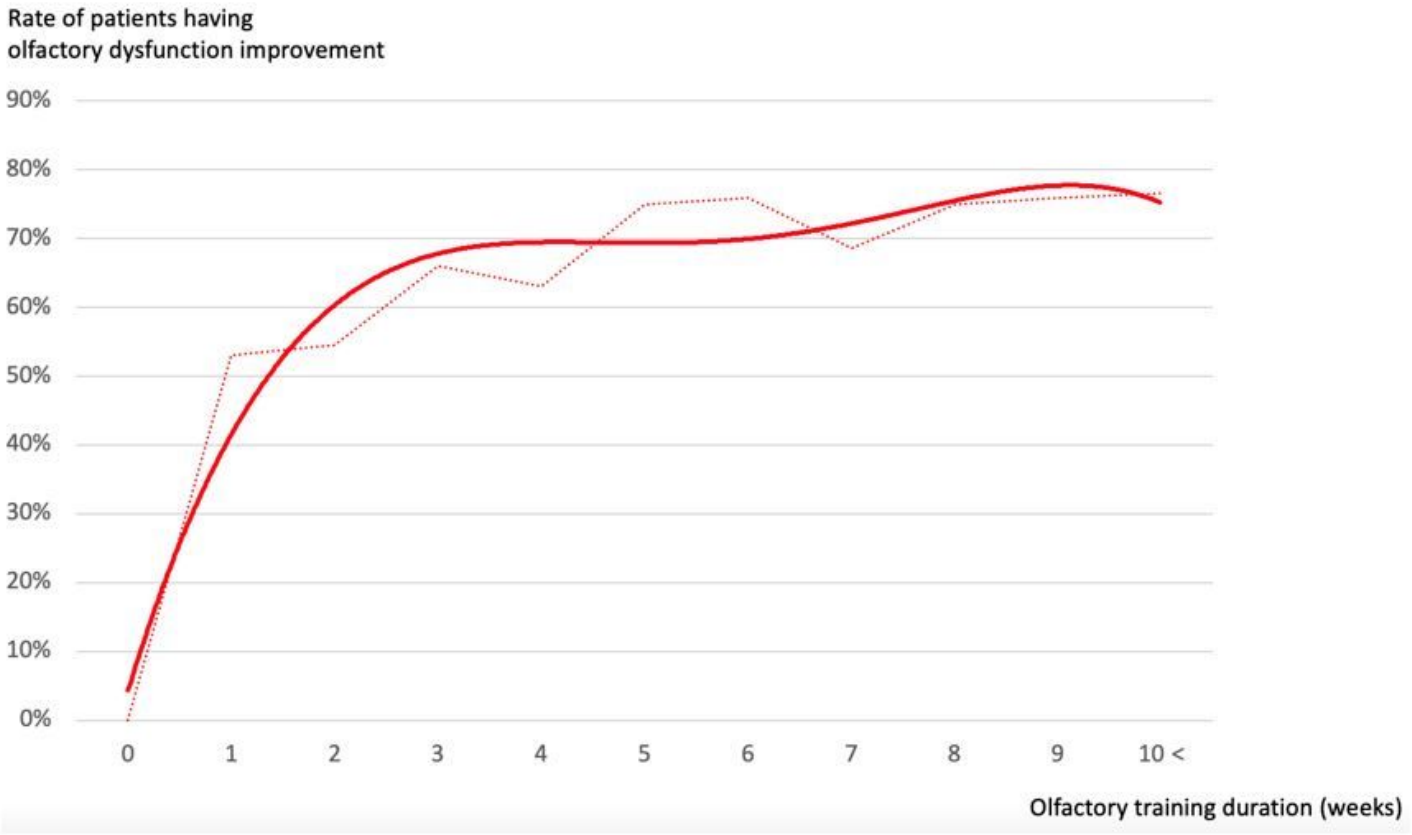

Figure 2

Improvement rates per weeks of olfactory training. Improvement of olfactory dysfunction over duration of training in patients with persistent olfactory dysfunction after Sars-Cov-2 infection by high concentration oils (1155 patients). dotted curve = raw data, continuous line = polynomial smoothed curve.

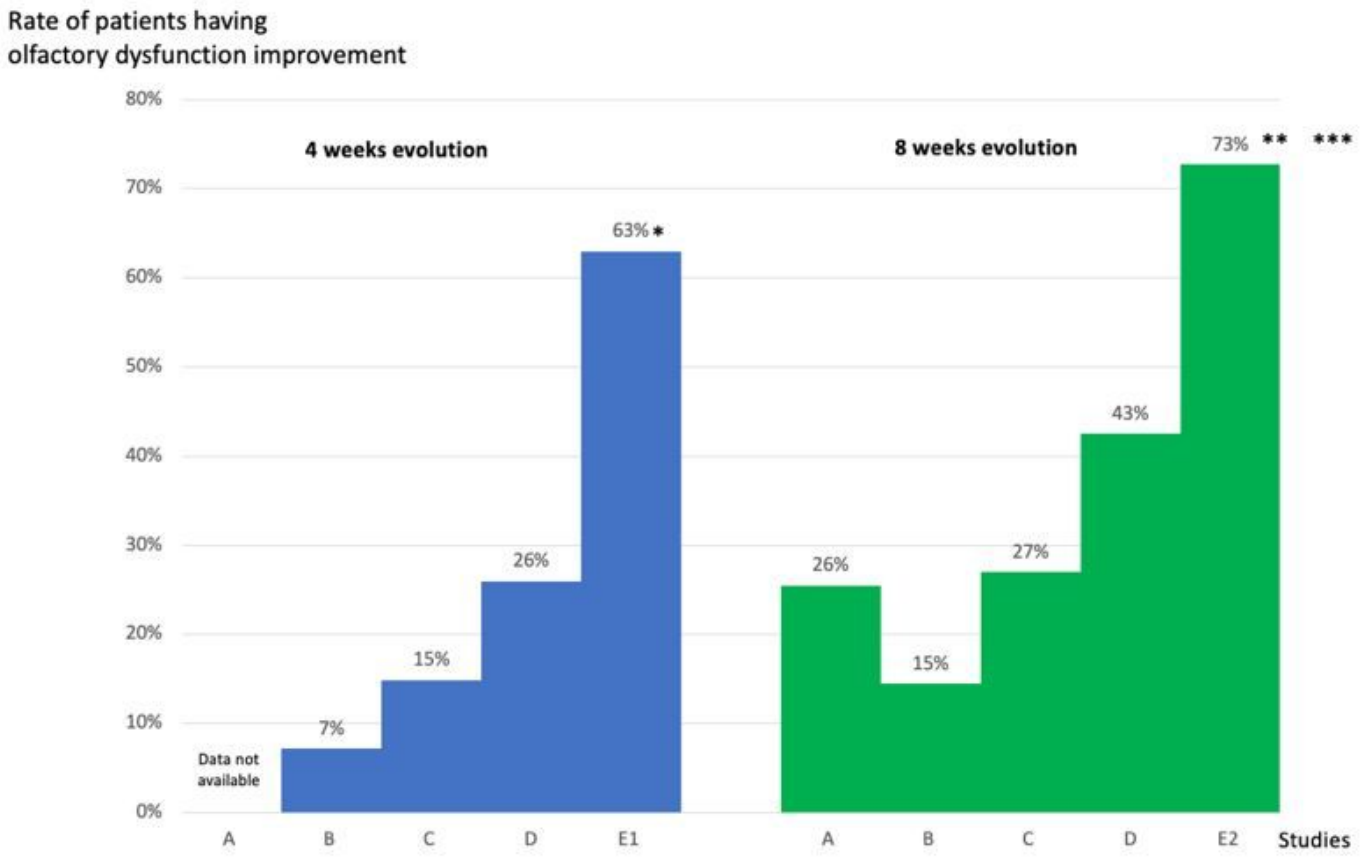

Figure 3

Rates of patients with persistent olfactory dysfunction reporting olfactory improvement at 4 and 8 weeks according to different studies. A) 4 and 8 weeks improvement rates without olfactory training in SARS-Cov-2 olfactory dysfunction = spontaneous improvement (47 patients). [4] B) 4 and 8 weeks improvement rates without olfactory training in olfactory dysfunction from other infections = spontaneous improvement (55 patients). [5] C) 4 and 8 weeks improvement rate with olfactory training using low concentration oils in olfactory dysfunction from other infections (74 patients). [2] D) 4 and 8 weeks improvement rate with olfactory training with high concentration oils in olfactory dysfunction from other infections (70 patients). [2] E1) 4 weeks olfactory training with high concentration oils in SARS-Cov-2 olfactory dysfunction (92 patients, Current study) E2) 8 weeks olfactory training with high concentration oils in SARS-Cov-2 olfactory dysfunction (188 patients, Current study) * 4 weeks' improvement rates comparisons: p(CHI-2 test) <.001 for E1 vs A, E1 vs B, E1 vs C, and E1 vs D ** 8 weeks' improvement: p(CHI-2 test) <.001 for E2 vs A, E2 vs B and E2 vs C *** 8 weeks' improvement: p(Chi-2 test) = .02 for E2 vs D

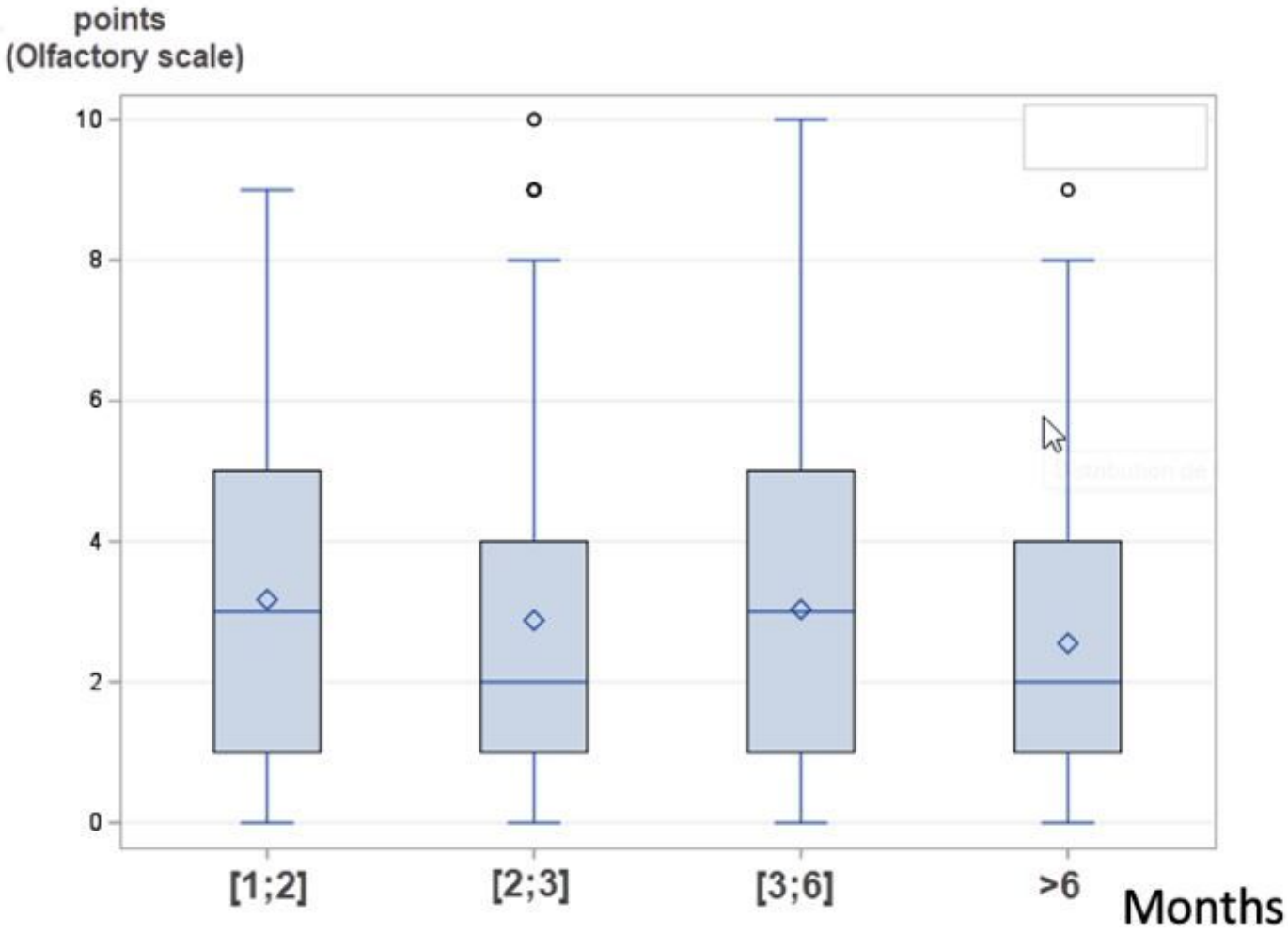

Figure 4

Mean improvement of olfactory function stratified by the duration of persistent olfactory dysfunction. Improvement was assessed with a self-assessed olfactory scale of 0-10 after olfactory training. The benefit of 30-days or more olfactory training was observed regardless of the duration of the olfactory dysfunction.