Can MRI predict olfactory loss and improvement in post-traumatic olfactory dysfunction?*

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Abstract

Background: Although most patients with post-traumatic olfactory dysfunction (PTOD) undergo MRI, there is no consensus about its diagnostic or prognostic value. The aims were: 1) to classify the extent of post-traumatic neurodegeneration; 2) to determine its relationship with chemosensory dysfunction (smell, taste, trigeminal); and 3) to establish whether MRI can predict olfactory improvement.

Methodology: We conducted a retrospective cohort study based on a series of 56 patients with PTOD. All patients underwent validated psychophysical tests of their smell, taste, and trigeminal functions, otorhinolaryngologic evaluation, and MRI. An experienced radiologist blinded to patient data evaluated 40 chemosensory-relevant brain regions according to a four-point scale (0=no lesion to 3=large lesion). Follow up data after 4 years (on average) were available in 46 patients.

Results:The cluster analysis showed 4 brain lesion patterns that differed in lesion localization and severity. They are associated with diagnostic categories: anosmia, hyposmia and normosmia. Two clusters were highly specific for anosmia (100% specificity) and could accurately predict this condition (100% positive predictive value). No clusters were associated with trigeminal or taste dysfunction. Regarding improvement, 72.7% of patients in the cluster with mild lesions experienced subjective and measurable olfactory improvement whereas this was only the case in 21.7-37.5% of patients with larger lesions. The odds of subjective smell improvement were 5.9 times higher in patients within the milder cluster compared to larger ones.

Conclusions: The analysis of brain lesions in PTOD allows corroboration of smell test results and prediction of subjective and measurable improvement.

Key words: olfaction, taste, trigeminal, head trauma, MRI

Introduction

About 56% of patients may experience olfactory dysfunction (OD) after head injury [(1)]. It often causes lesions in the orbitofrontal and temporal regions and may impact all three chemosensory senses [(2)] (olfaction, gustatory and trigeminal) with olfactory function being the most frequently impaired [(3, 4)].
Testing the chemical senses is needed because subjective evaluation is insufficient for deficit localization and quantification

[5, 6]. It is even more important in post-traumatic injury because patients may develop cognitive dysfunction and unawareness of OD [7, 8]. Currently, olfactory evaluation is based on psychophysical tests, during which patients are presented with odor stimuli and asked questions about the smell. These results are influenced by olfactory receptor genes, previous experience with the tested odor or by malingering [9-12]. Objective measurements such as olfactory-event-related potentials can overcome some of these problems but are restricted to specialist clinics [13]. A more widespread objective method to support patients' chemosensory complaints and psychophysical test results is needed, especially for medicolegal issues.

Magnetic Resonance Imaging (MRI) has the potential to supplement the diagnosis of OD as measured by psychophysical tests. For example, olfactory bulb (OB) volume appears to be associated with OD severity [14, 15] and improvement after trauma [16]. Lesion severity grading in olfactory-relevant brain areas also appears to be associated with OD [17-21]. Several knowledge gaps persist and motivate the design of the present study.

First, as the chemical senses share common brain regions, it remains unclear how trigeminal and taste functions are affected in post-traumatic OD patients. Second, there is no clear relationship between the severity of head trauma (as measured by the initial Glasgow Coma Scale, GCS) and the severity of OD [22]. Even minor head trauma can cause extensive brain lesions and severe olfactory loss [23, 24]. Third, a clinically useful staging system to classify these lesions could not only assist the diagnosis of OD, but also predict smell improvement.

The aims of our study were: 1) to classify the extent of post-traumatic neurodegeneration; 2) to study its relationship with chemosensory dysfunction; and 3) to establish whether MRI can predict olfactory improvement.

Materials and methods

Experimental design

A retrospective cohort study conducted in a tertiary care facility between December 2013 and December 2019. The study was approved by the institutional ethics review board and was conducted according to the Declaration of Helsinki on Biomedical Research Involving Human Subjects (IRB approval No: 13–161).

Study subjects

A total of 79 consecutive patients were referred to the Smell and Taste Clinic of Geneva University Hospital, Switzerland with chemosensory dysfunction after a traumatic head injury. The median time from trauma to evaluation was 8.5 months (interquartile range=12.5).

Patients underwent nasal endoscopy, olfactory, gustatory, and trigeminal psychophysical tests, and brain MRI.

Twenty-three patients were excluded because imaging was not available, with 56 patients included in the study. The median time from trauma to MRI was 8.5 months (interquartile range=13.5). Of the included patients, 46 had a follow-up visit including at least subjective evaluation of their sense of smell. Among them, 34 had smell testing as well. Follow-up visits occurred on average 47 months after the first visit (range 10-409 months, SD=61.9).

Outcome measures and procedures

Patient characteristics

The following data were recorded: age at first visit, gender, dates of first and last consultation, date of head injury, date of MRI, head injury mechanism, initial GCS (if available) and loss of consciousness. Chemosensory symptoms were codified as presence or absence of: parosmia, phantosmia, ano- or hyposmia, aroma loss, taste loss, para- and phantogeusia. Presence or absence of subjective smell improvement was recorded at follow-up visits.

Olfactory function

Patients were tested using Sniffin'Sticks (Burghart, Wedel, Germany), which includes olfactory threshold (T), discrimination (D), and identification (I). The composite TDI score differentiates anosmia (TDI <16), hyposmia (>16 TDI ≤30.5) and normosmia (TDI >30.5) [25, 26]. If each nostril was tested separately, the best score of each TDI from each nostril was used, according to established procedures [27, 28].

Gustatory function assessment

Gustatory function was assessed using Taste Strips (Burghart, Wedel, Germany), with filter paper strips soaked with four different tastes (sweet, sour, salty, and bitter) of four different concentrations [29]. A total of 32 taste strips were randomly applied on the left and right anterior third of the extended tongue. Participants identified the respective taste from a descriptor list. The sum of correct answers (range 0-32) was calculated. A cut-off ≥16 was used to discriminate normal from gustatory impairment. This threshold corresponds to the 25th percentile score of healthy subjects of 41 to 60 years of age [30].

Intranasal trigeminal function assessment

Intranasal trigeminal function was measured with the lateralization task. Two 250ml squeeze bottles were presented simultaneously to the nostrils. One bottle contained the target odor (30 ml eucalyptol, Sigma-Aldrich, Switzerland); the other contained 30 ml of odorless propylene glycol. Single air puffs were delivered simultaneously to each nostril by pressing both bottles at the same time. Forty pseudo-randomized stimuli were applied at 30–40s intervals; patients were blindfolded to avoid visual cues. After each stimulation, participants were asked to identify which nostril the target had been presented to. Each correct answer

yielded one point. The sum of correct identifications was calculated (score range per nostril: 0-20; total range: 0-40). A cut-off ≥32 was used to discriminate normal from impaired trigeminal function [31].

Imaging, interpretation and grading criteria

An experienced radiologist (VL) blinded to all clinical data reviewed the MRI from the closest date to the first consultation. MRI sequences used included T2-weighted (axial or coronal, 4mm slices), FLAIR (coronal or 3D, 1-4mm slices), T1-weighted (axial or 3D, 0.9-4mm slices) with or without gadolinium, SWI or T2-star (4mm slices), 3D T2 targeted on olfactory bulbs (0.6-1mm slices). Forty regions relevant for chemosensory function were evaluated per patient (20 per hemisphere), according to previously published work and corresponding to the brain regions that are currently considered as being part of the olfactory system (20, 32-34) (supplementary Figure 1). For each region, a four-point evaluation scale was used: 0 = no visible lesion; 1=suspicion of a lesion or minimal punctate lesion; 2=moderately large lesion (larger than punctate lesion in 1 limited subregion, or multiple lesions in ipsilateral non-continuous subregions); 3=large lesion (located in ≥2 ipsilateral continuous subregions) (supplementary Figure 2). The sum of all 40 scores yielded the total lesion grade as a marker of global brain lesion severity.

Statistical analysis

To classify brain lesions, we identified the appropriate number of clusters using hierarchical clustering and inspected the dendrogram, which showed four first generation clusters. Then, we defined four clusters for the K-means non-hierarchical clustering analysis. To identify brain areas that contributed the most to cluster characterization, we employed ANOVA tests to look for differences in average lesion grade between four clusters. To analyze correlation between frequency and severity of individual brain lesions, we used descriptive statistics and Spearman correlations.

Then, we compared chemosensory test scores between clusters and controlled for GCS using ANOVA and ANCOVA. Dunnett's post-hoc test was used to compare average TDI scores between groups. We used chi-square and Fischer's exact test to study associations between categories of chemosensory dysfunction and clusters. For taste and trigeminal function, we used two categories: dysfunction or normal function. We used the Cramer's V to calculate the strength of associations. Contingency tables were used to calculate the diagnostic accuracy of clusters to detect anosmia. To analyze the correlation between test scores and cumulative lesion scores, we employed Pearson's correlations. We performed a non-parametric partial correlation test and controlled for age to test whether lesion grades of individual brain areas and groups of brain areas (composite score) correlated with chemosensory function. We used multiple linear with forward regressions to test whether a model of several brain regions (predictors or independent variables) could predict chemosensory function scores (dependent variables). For this analysis, individual brain lesions were recoded into binary variables (0=no lesion, 1=lesion).

We performed chi-square tests to analyze the association between clusters and subjective olfactory improvement and binary logistic regression to identify predictors for subjective smell improvement. To test whether TDI scores at the last visit were higher compared to the first visit for each cluster, we employed a one-tailed paired t-test. For this analysis, the two large clusters were grouped because they yielded similar results throughout the study. P values < 0.05 were considered statistically significant. We performed all analyses with GraphPad Prism 8.4 and IBM SPSS statistics version 25. Adobe illustrator 2019 was used to refine the figures.

Results

Post-traumatic brain lesions cluster identification and characterization

The OB were the most frequently damaged structures followed by the frontal and orbitofrontal cortices, and finally the temporal regions. The most frequently affected regions were also the most severely damaged (Spearman r=0.9 p<0.0001) (Supplementary Figure 1). Supplemental Figure 2 illustrates examples of mild, moderate and large post-traumatic olfactory system lesions as seen in 6 different patients.

To classify these different brain lesion patterns, we used K-means cluster analysis and found four different clusters (Figure 1A). Demographic data of these 4 clusters including age, trauma mechanism, and symptoms are shown in Table 1.

To characterize these four clusters, we studied the cumulative lesion grade. ANOVA revealed a significant effect of cluster, $F(3, 53) = 89.17$, $p<0.0001$. With the exception of the comparison between clusters three and four, statistically significant differences were found between the remaining possible multiple comparisons ($p<0.05$) (Figure 1B and C). We also looked for regions that contributed the most to these clusters using ANOVA. We found 18 brain regions that had a significant effect of clusters on lesion grade. Overall, from cluster one to four, we observed increasing lesion severity and number of brain areas involved. Cluster three had large lesions in the right hemisphere (R) and cluster four had large lesions not only in the left hemisphere but also in both olfactory bulbs (OB,L) (ANOVA test $p<0.05$) (Figure 1D).

Post-traumatic brain lesion clusters are associated with OD but not taste or trigeminal dysfunction

To understand whether these clusters were associated with che-

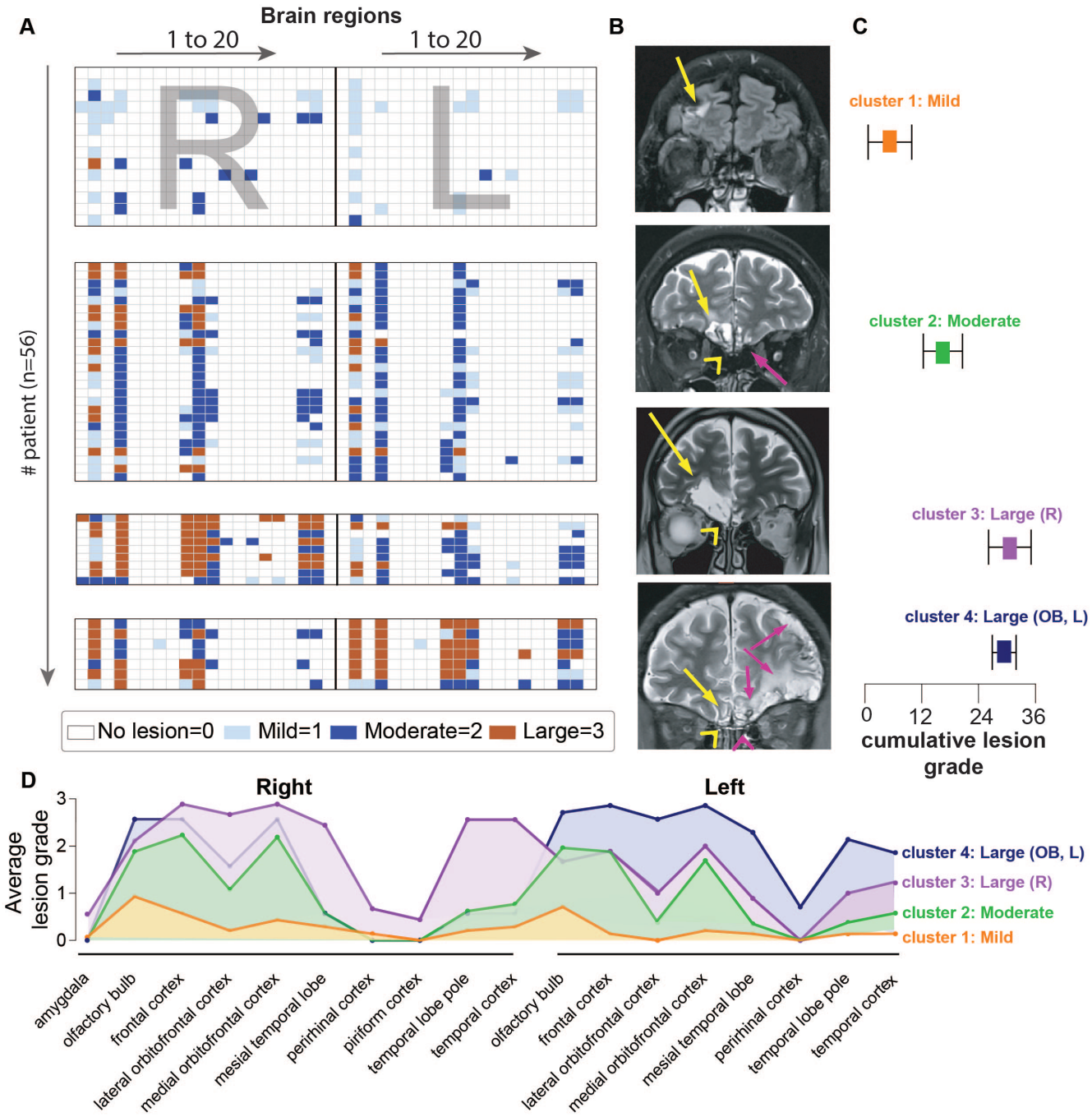

Figure 1. Brain lesion clusters differed in severity and localization. (A) Grading of lesion in right (R) and left (L) brain regions numbered from 1 to 20 according to supplementary figure A. The four large rectangles represent the four clusters found with K-means cluster analysis. The raws within each of the four rectangles represents a patient. (B) Characteristic MRI for each cluster. The first MRI (T1 flair) on top depicts a moderate lesion in the right superior frontal cortex. The second MRI (T2) represents medial orbitofrontal bilateral lesions that are mild on the left, and moderate on the right side, with a lesion in the right olfactory bulb. The third MRI (T2) shows a single large lesion in the right lateral and medial orbitofrontal cortex with ipsilateral large lesion in the olfactory bulb. The fourth MRI (T2) depicts multiple large lesions in the left frontal and orbitofrontal cortex with bilateral medial orbitofrontal and olfactory bulb lesions. Yellow arrow=right, magenta arrow = left. Arrow head = olfactory bulb. (C) Clusters and severity. The mean (± SD) cumulative lesion score was calculated from the average of patient's cumulative lesions in 40-brain areas for each cluster. (D) Clusters and 18 brain regions, in which the average lesion score was significantly different across the 4 clusters. OB=olfactory bulbs, L = left side, R=right side.

mosensory function, we used ANOVA and Dunnett's post-hoc test to uncover differences in average psychophysical test score (TDI, lateralization, and taste strips) between clusters. There was a significant effect of clusters only on the TDI score, F (3, 52) =

Table 1. Demographics, mechanism of head trauma, and symptoms in clusters.

	Mild	Moderate	Large R	Large OB, L
n	14	26	9	7
% female	42.8	26.9	55.6	42.9
Mean age (SD)	48 (15.5)	46 (16.0)	52 (15.2)	43 (11.0)
Mechanism of head trauma - % patients				
Physical assault		34.6		28.5
Motor vehicle accident	57.1	15.4	33.3	14.3
Fall from own height	21.4	34.6	44.4	42.8
Fall from higher than own height	21.4	3.8	22.2	14.3
Low energy head trauma		7.7		
Unknown		3.8		
Symptoms - % patients				
Parosmia	35.7	26.9	33.3	14.2
Phantosmia	21.4	57.7	44.4	28.6
Smell loss	92.8	96.2	88.8	100
Aroma loss	85.7	84.6	77.8	57.1
Taste loss	21.4	30.8	55.6	28.6
Phanto- or parageusia	14.3	23	44.4	14.3
Mean psychophysical test score (SD)				
TDI	18.9 (9.6)	11.9 (5.3)	12.1 (3.3)	8.9 (2.1)
Lateralization	26 (8.6)	25.8 (9.1)	30.1 (6.9)	30.4 (5.9)
Taste strips	17.1 (7.1)	18.5 (7.1)	18.3 (9.8)	12.8 (7.5)

R=Right; L=Left; OB=Olfactory bulbs; TDI=Sniffin' Sticks Threshold, Discrimination and Identification test score; SD=Standard deviation.

5.379, p=0.0027. The TDI score in the mild group was higher than the moderate (p=0.005), large R (p=0.04), and large OB,L group (p=0.003) (Figure 2A). To rule out that these clusters were not simply a reflection of head injury severity, we used ANCOVA and controlled for GCS; GCS was not significantly related to the TDI score $F(1, 28) = 0.3$, p=0.58. The cluster effect remained significant $F(3, 28) = 4.3$, p=0.013, partial eta squared value = 0.32.

The TDI score negatively correlated with the total number of brain lesions (r=-0.35; p=0.008). There was no correlation between taste or trigeminal function and lesion number (Figure 2B).

In clinical practice, OD is classified according to the TDI score. To verify whether clusters of brain lesions could assist in diagnosing OD, we used chi-square and contingency tables to analyze diagnostic accuracy. There was a statistically significant association between clusters and diagnostic categories, χ^2 (6, n=56) =15.5, p=0.015; Cramer's V=0.372, p=0.015. However, this test demonstrated violation of assumption where eight cells had an expected count of less than five; therefore, we performed a Fischer exact test, which also showed a statistically significant association (p=0.026). The ability to detect anosmia (TDI score < 16) in the large clusters (R or OB,L) was 36.4% sensitivity, 100% specificity, 30% negative predictive value (NPV), and 100% positive predictive value (PPV). There was no significant association between taste or trigeminal function and brain lesion clusters (Figure 2C).

Lesions in individual brain regions are associated with olfactory and trigeminal dysfunction

Lotsch and colleagues found that post-traumatic lesions in the right OB correlated with TDI score. To replicate this finding and extend this analysis to taste and trigeminal function, we asked whether lesion grades of individual brain areas and groups of brain areas (composite score) correlated with chemosensory function. We carried out a non-parametric partial correlation test and controlled for age. For olfaction, the TDI score negatively correlated with lesion grade in the right OB (r=-0.27, p=0.049), left medial orbitofrontal cortex (r=-0.29, p=0.035) and bilateral temporal regions and subregions (r=-0.35, p=0.001). For trigeminal, the lateralization score positively correlated with lesion grade in the left parietal cortex (r=0.27, p=0.047) and bilateral parietal cortex (r=0.28, p=0.042) (Figure 3A).

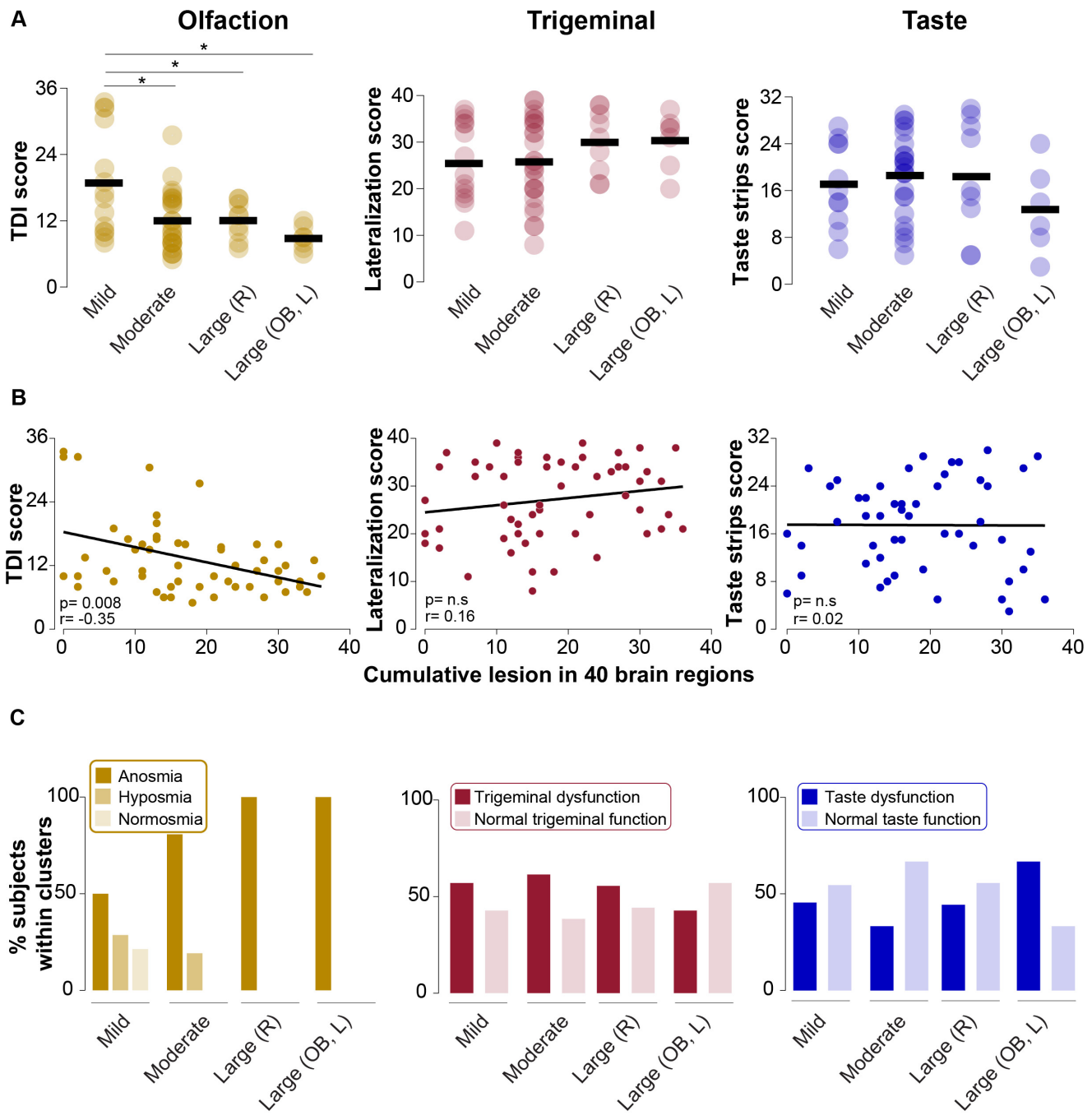

Figure 2. Olfactory function is associated with clusters that differed in brain lesion severity and localization, but not trigeminal and taste. (A) the star represent a p value <0.05. The black bar represent the mean and each color coded circle is a patient. (B) Correlation between psyhcophysical test scores and cumulative lesion in 40 brain regions. Colored round dot = patient. (C) contingency tables analysis between diagnostics and clusters.

To study whether we could predict TDI score and trigeminal test score based on presence or absence of individual brain lesions, we used multiple linear forward regressions. For olfaction, the strongest predictor was bilateral frontal cortex lesions. To verify this finding, we performed a backward regression, which also pointed towards the frontal cortex as only predictor. A significant regression equation was found ($F(1, 54) = 11.15$ $p=0.002$; $R=0.41$, $R^2=0.17$, adjusted $R^2=0.16$). The predicted TDI score was equal to 18.6 – 1.5x (x=lesion grade in bilateral frontal cortex from 0 to 6). TDI scores decreased by 1.5 points for each supplementary degree of lesion in the frontal cortex on both sides.

For trigeminal function, we performed the same procedure. The identified predictors were lesion grade in the bilateral frontal cortex and left parietal cortex. The parietal cortex was the best contributor to the model and was statistically significant. A sig-

Table 2. Predictors of subjective olfactory improvement.

	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Cluster mild (vs others)	7.7	1.6-35.5	**0.009**	5.9	1.1-33.9	**0.048**
Gender	2.5	0.7-8.5	0.146	4.2	0.8-22.6	0.093
Initial TDI score	1.1	1.0-1.3	**0.024**	1.2	0.9-1.4	0.079
Age	0.99	0.9-1.0	0.741	0.9	0.9-1.0	0.281
Parosmia	0.4	0.1-1.6	0.230	1.1	0.2-6.3	0.904

Table 3. Proposed MRI classification and clinical significance.

Stage	Name	Cumulative lesion grade	Predominant Localization	Diagnostic value	Prognostic value
I	Mild	0-13 points	Olfactory bulbs Medial orbitofrontal cortex	Residual olfactory function **possible**.	-72.7 % of patients will experience smell improvement -odds of improvement 5.9 times higher compared to other categories. -TDI change of + 4.7 points
II	Moderate	14-24 points	Olfactory bulbs Frontal cortices Medial orbitofrontal	Residual olfactory function **possible**.	-62.5-78.3% of patients will experience absence of improvement - 89.7% accuracy in detecting patients without improvement.
III	Large	24 points and over	Olfactory bulbs Frontal cortices Medial orbitofrontal cortex Lateral orbitofrontal cortex Mesial temporal lobes Temporal lobe pole Temporal cortex	Residual olfactory function **unlikely**.	-same as stage II.

nificant regression equation was found (F (2, 53) = 3.43 p=0.04; R=0.34, R^2=0.11, adjusted R^2=0.081). The predicted trigeminal scores were equal to 23.965 ±0.7x (x=lesion grade in bilateral frontal cortex from 0 to 6) ±9.8x (x=lesion in left parietal cortex: presence=1/absence=0). The score was higher by 9.8 points with lesions in the left parietal cortex compared to without.

Post-traumatic brain lesion clusters can predict long-term smell improvement

Spontaneous recovery may occur in 10-36% of patients [22, 35]. To study whether MRI findings could predict smell improvement, we first analyzed the association between brain lesion clusters and long-term subjective smell improvement using chi-square test. There was an association between subjective smell improvement and clusters, χ^2 (3, n=46) =8.574, p=0.036; Cramer's V=0.432, p=0.036; Fischer exact test=8.18, p=0.036. We observed that 72.7% of the mild cluster experienced subjective improvement after an average of 47 months (min=10; max=409, SD=61.9), which is much higher than previously described. In the moderate and large clusters, only 21.7-37.5% experienced a subjective improvement (Figure 3B). Patients with subjective smell improvement had greater improvement in smell testing score (mean=6.3; SD=5.0) compared to those without (mean=1.17; SD=5.2; P=0.007) (Figure 3C). Regarding measurable improvement between the first and last consultations, we observed a statistically significant increase in TDI mean score (±SD) of 4.7±6.8 and 3.1±4.6 for the mild and moderate clusters, respectively. However, no significant improvement was noted for the pooled large cluster (1.8±6.5) (Figure 3D and E).

To analyze whether the mild cluster could be a predictor of subjective smell improvement, we recoded the cluster variable into binary variables (1=mild, 2=other clusters) and performed a binary logistic regression. Other potential predictors described in the literature were added to the model (parosmia, gender, TDI score, and age) [36]. In the univariate model, classifying patients into mild versus larger clusters could identify patients without improvement with 89.7% accuracy and patients with improvement with 47.1% accuracy (OR=7.7, 95% CI=1.6-35.5, p = 0.009). In the multivariate model, we found that the odds of experiencing subjective smell improvement were 5.9 times higher in patients within the milder cluster compared to larger ones after controlling for other potential predictors (Table 2). A summary of the findings and their clinical significance is shown in Table 3.

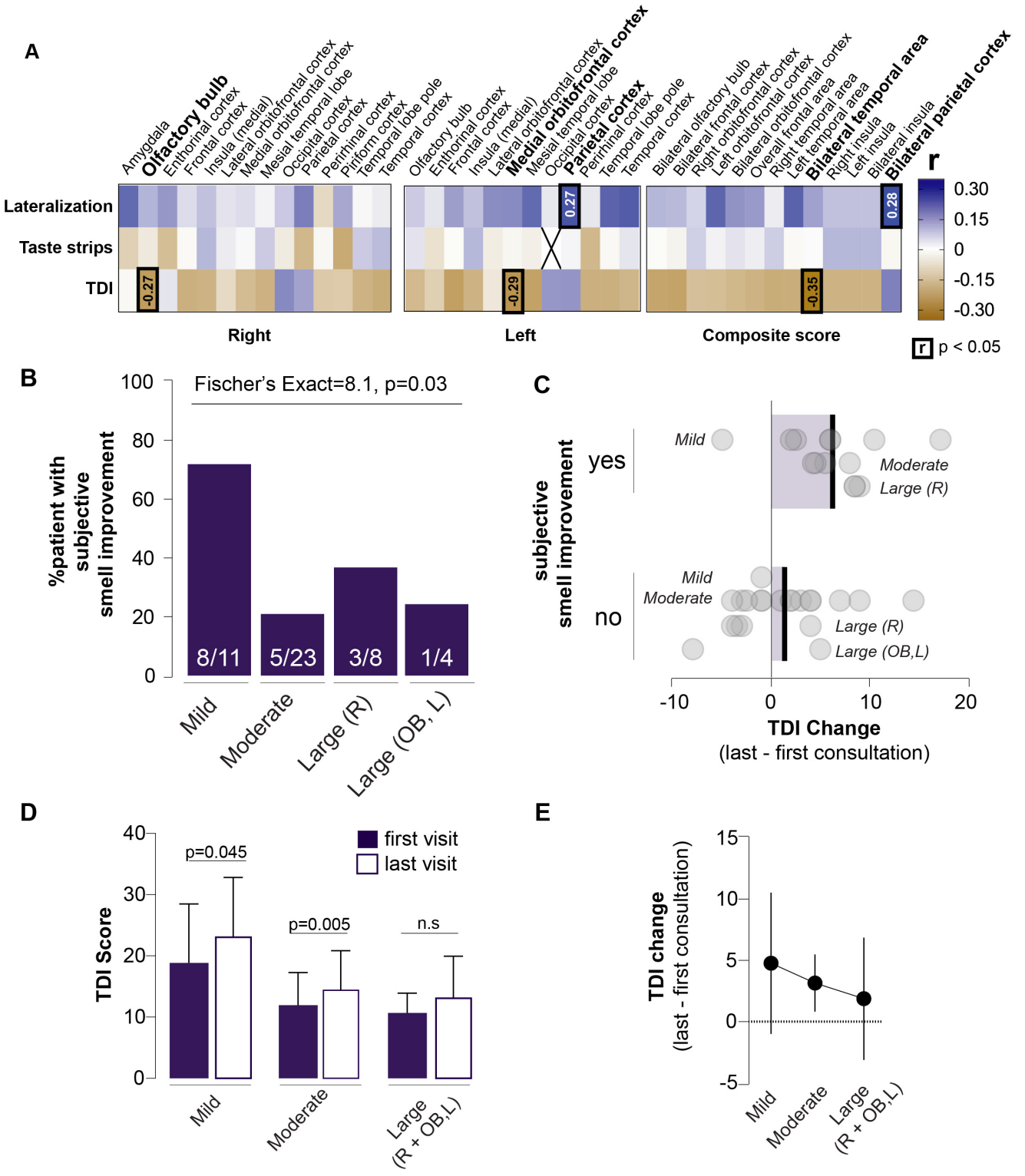

Figure 3. MRI findings correlates with trigeminal / olfactory function and may predict olfactory improvement (A) Intercorrelation matrix between psychophysical tests and lesion grading in individual brain regions. (B) Subjective smell improvement in the clusters. The number within the bars are the number of patients with improvement divided by the total number of patients in this group. (C) TDI change in patients with and without subjective improvement (D) Average TDI score at the first and last consultations in the clusters (±SD). (E) Average TDI score difference between the first and last consultation (±SD). The two large clusters were grouped for the analysis in figure D and E.

Discussion

In this study, we analyzed 40 brain areas relevant to the chemical senses, performed a cluster analysis, and identified four clusters of brain lesion patterns that differed in lesion severity and localization: I) mild; II) moderate; III) large right hemisphere; and IV) large olfactory bulbs and left hemisphere. These clusters correlated with OD severity and could accurately predict the presence of anosmia if patients belonged to cluster III or IV independently of head trauma severity. Regarding prognosis, the odds of improvement were much higher for cluster I.

Most post-traumatic patients with OD will undergo an MRI that is necessary for several reasons: a) the history or/and physical examination may suggest other differential diagnosis, b) because even minor head trauma can cause large brain lesions, a physician need to exclude brain lesions explaining present or developing subtle changes in behavior and other neurological issues, which is often misdiagnose until an MRI is performed. However, in present guidelines, there is currently no consensus about how to interpret these results beyond the reasons raised above [37, 38]. Longdon and colleagues created the Barcelona olfactory neuro-imaging score based on post-traumatic changes of the olfactory sulcus, OB, orbitofrontal cortex and temporomedial cortex. Although they showed an association between their score and subjective smell loss severity, the subjects were not assessed with psychophysical tests or followed up [19]. Altigechi et al. showed that more anosmic patients had an abnormal MRI compared to hyposmic patients. They only distinguished abnormal versus normal MRI findings, a binary measure that may be insufficient to capture subtle diagnostic or prognostic differences [17]. Yousem and Rombaux showed that damage to the olfactory bulb and tracts correlated with deficits in olfactory function [14, 15]. Lotsch and colleagues used an algorithm based on MRI of 11 olfactory-relevant brain areas and showed that it could accurately predict the presence of anosmia from the degree of damage [21]. In a follow-up study they showed that different olfactory symptoms had different brain lesion profiles with a right OB lesion being most commonly associated with anosmia [20], a finding that we reproduced in this study. Furthermore, our proposed staging system could classify patients that may still retain a functional sense of smell after trauma (clusters I/II), and those that are unlikely to have one (clusters III/IV) with high accuracy. This may assist the management of trauma-related medicolegal cases and support the diagnosis of anosmia.

Regarding long-term prognosis, 10-36% of patients with post-traumatic OD recover after 2-3 years [22, 35]. Factors such as residual olfactory function, smoking, age and parosmia may affect improvement rate [39]. Rombaux et al. showed that larger OB volumes were associated with better olfactory improvement after trauma [16]. Altundag et al. also found that OB volume may affect improvement along with other imaging features such as cribriform plate fracture, OB encephalomalacia, siderosis, and olfactory fossa depth [40]. Our study complements these findings, by showing that different brain lesion patterns could predict smell improvement more robustly than previously described non-imaging factors. Another factor that cannot be measure yet in clinical setting is the integrity of olfactory axons. As the vulnerability of these axons may varies across individuals, it is difficult to predict whether they are intact in clusters with mild or moderate lesions, perhaps explaining some variability in this group [41]. Combining MRI with innovative techniques to assess olfactory axon integrity may help to better predict olfactory improvement in the future [42]. More importantly, this study showed that MRI can even more accurately detect patients that do not improve. It is highly important because there is currently no cure, therefore some patients have to accept this debilitating condition and go forward with their lives.

Taste function was globally preserved across different brain lesion severity grades. This may indicate that taste scores rely less on higher order taste centers such as the orbitofrontal cortex. Another explanation is that taste may be more resistant to brain trauma, given its bilateral central projection, contrasting with olfaction, in which projections are mostly unilateral. Finally, the peripheral taste system (cranial nerves VII, IX, and X) could be less susceptible to head injury compared to olfaction in which the olfactory axons can be sheared even with mild trauma [23, 41]. Regarding the trigeminal system, higher lesion grades in the left parietal cortex correlated with higher intranasal trigeminal function. In mild traumatic head injury, patients may have decreased pain inhibition, which may explain the high prevalence of post-traumatic headache [43, 44]. These mechanisms may explain the increased intranasal trigeminal sensitivity after brain injury. Another explanation is that anosmia itself may alter activation in trigeminal central pathways or in the periphery [45], which may also increase trigeminal sensitivity [46].

Limitations of the study include biases inherent to the retrospective design. We limited selection and misclassification bias by consecutively recording data in the electronic medical records during visits and then into a study database. Regarding this bias, there was no statistical psychophysical testing score difference between the excluded and included subjects. Loss to follow-up rate was 17.9%, which is acceptable [47]. Limitation in our statistical approach is inherent to the K means clustering method, in which the investigator can decide about the K number of clusters. To partly address this problem, we performed a hierarchical clustering analysis and analyzed the dendrogram. In addition, MRI findings were evaluated by a single experienced observer, therefore inter-observer reliability could not be tested. However, most published studies on MRI of olfactory dysfunc-

tion have used a single reader approach or they do not mention at all who rated the MR images [48-51]. A single reader approach is often used in the literature when the reading task is very time consuming, and the single reader is highly skilled at this task. Also, by including precise illustrations of the assessed brain areas on MRI (Supplementary Figure 1) and of the criteria used to score and classify MRI abnormalities (Supplementary Figure 2 and Table 3), we have provided a basis for future prospective studies using the proposed classification. A prospective follow-up study with a larger sample size would be necessary.

Conclusion

Staging of MRI brain lesion may be used as an objective marker to complement the diagnosis of olfactory dysfunction in post-traumatic patients and may predict olfactory improvement.

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Authorship contribution

JWH, BNL, VL, MH, JNL, MB designed the study, collected, and analyzed the data, drafted and revised the manuscript and approved the final version. RS, PS, DD, JR collected the data, drafted, and revised the manuscript and approved the final version.

Conflict of interest

None.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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SUPPLEMENTARY MATERIAL

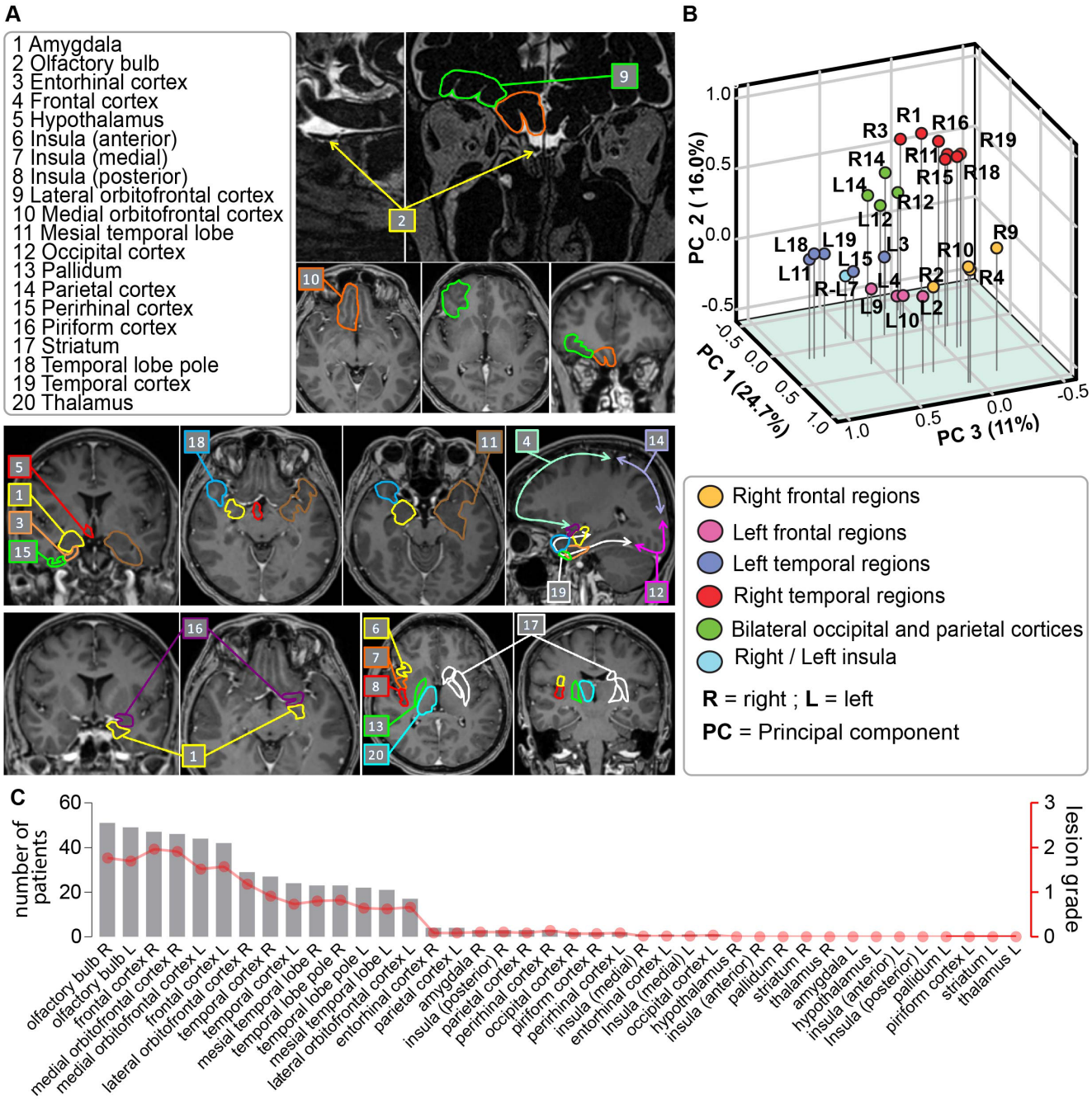

Figure S1. Characterization of post-traumatic brain lesions. (A) 20 chemosensory-relevant brain regions. (B) Principal component analysis of inter-correlation matrix of 40 brain regions (20 per hemispheres). Right and left brain regions are numbered from 1 to 20 according to Figure 1A. Regions without any lesion across all participants were excluded because of inability to perform the anaylsis. To understand the complex pattern of brain lesions after head injury, we performed an inter-correlation matrix and principal component analysis. We found that sets of brain regions shared similar occurrence and severity of lesions. In the principal component space, the closer two regions are, the stronger the positive correlation is. For example, the olfactory bulbs (OB) are close to each other. A lesion in the left OB correlates highly with a lesion in the right, and vice versa. On the other hand, a lesion in the right lateral orbitofrontal cortex is unlikely to be associated with a lesion in the left mesial temporal lobe. (C) Severity and frequency of post-traumatic brain lesions in patients with chemosensory complaints. R=right side, L=Left side.

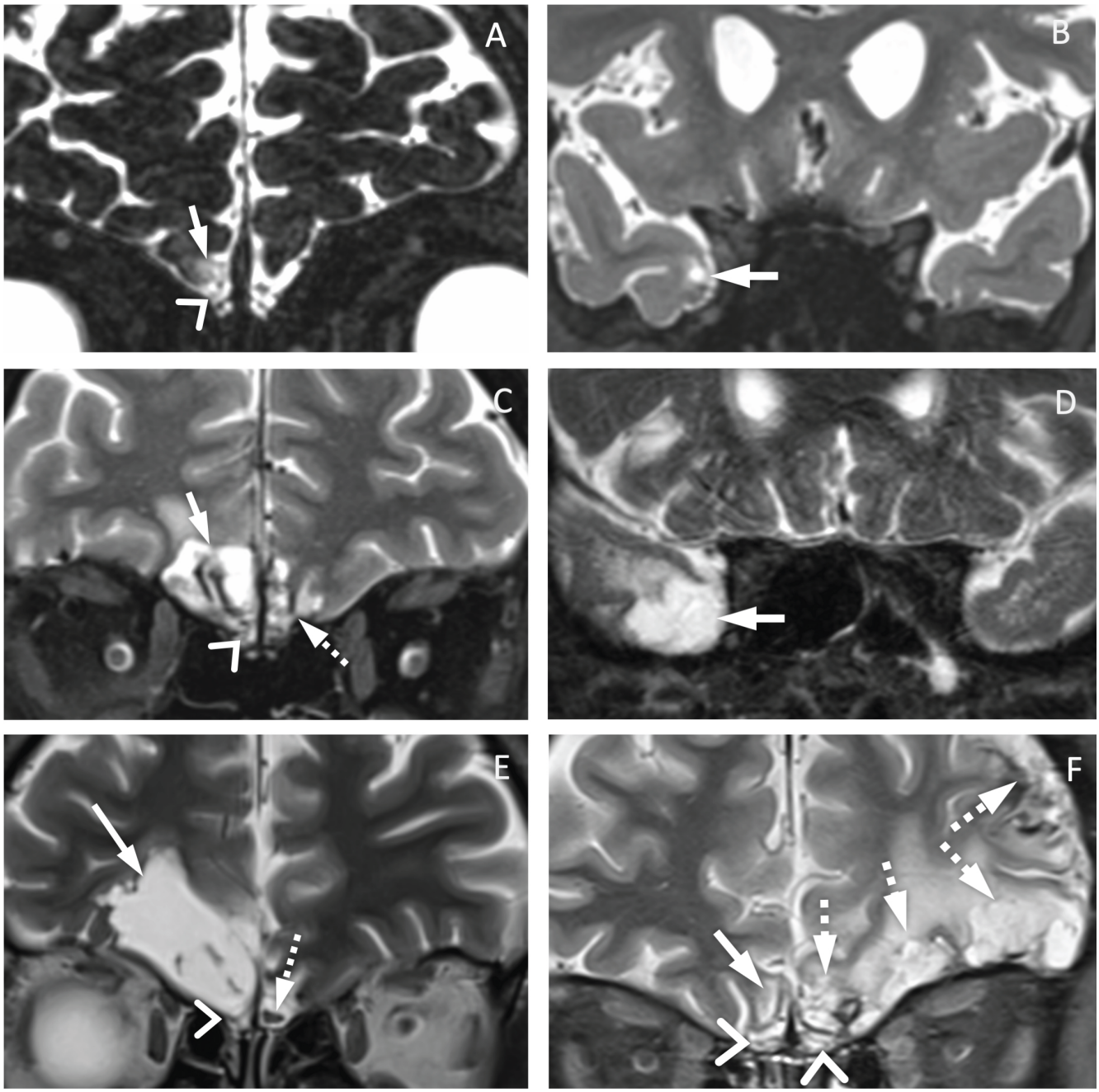

Figure S2. Coronal T2-weighted images in six different patients illustrating mild lesions (A and B), moderate lesions (C and D) and large (E and F) post-traumatic lesions along the olfactory pathways. (A) Unique mild lesion in the right medial orbitofrontal gyrus (arrow) associated with a right olfactory bulb lesion (arrowhead). (B) Unique mild right temporal lobe pole lesion (arrow). (C) Mild medial orbitofrontal lesion on the left (dashed arrow) and moderate medial orbitofrontal lesion on the right (arrow). Lesion in the right olfactory bulb (arrowhead). D. Single right moderate temporal lobe pole lesion (arrow). (E) Large right medial and lateral orbitofrontal lesions (arrow) with large lesion in the ipsilateral olfactory bulb (arrowhead). Normal left olfactory bulb (dashed arrow). (F) Multiple large left orbitofrontal and temporal lobe lesions (dashed arrows) and moderate right medial orbitofrontal lesion (arrow) with bilateral olfactory bulb lesions (arrowheads).