RESEARCH PAPER

Acta Neurobiol Exp 2020, 80: 381–388
DOI: 10.21307/ane-2020-035

since 1928 ACTA NEUROBIOLOGIÆ EXPERIMENTALIS

Effects of olfactory training on resting-state effective connectivity in patients with posttraumatic olfactory dysfunction

Kianoosh Hosseini[1,2], Arash Zare-Sadeghi[3], Saeed Sadigh-Eteghad[1], Marjan Mirsalehi[4] and Davood Khezerloo[1,2]*

[1] Neurosciences Research Center, Tabriz University of Medical Sciences, Tabriz, Iran,
[2] Department of Radiology, Faculty of Paramedical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran,
[3] Finethech in Medicine Research Center, Iran University of Medical Sciences, Tehran, Iran,
[4] ENT Research Center, The Five Senses Institute, Hazrat Rasoul Akram Hospital, Iran University of Medical Sciences (IUMS), Tehran, Iran,
** Email: khezerlood@tbzmed.ac.ir*

The present study investigated if and how the smell training scheme affects resting-state effective connectivity. We focused on connectivity among brain regions that participate in olfactory-related processes, including the piriform cortex, amygdala, orbitofrontal cortex (OFC), insula, and cingulate cortex. Sixteen patients with posttraumatic olfactory dysfunctions between the ages of 18 and 36 years participated in this study. Olfactory performance of subjects was evaluated using the Sniffin' Sticks test kit and then, resting-state functional magnetic resonance imaging (fMRI) was performed. Of the 16 participants, 8 underwent olfactory training for 16 weeks and the remaining 8 did not receive the treatment (the control group). After 16 weeks, participants in both groups underwent the same procedure (smell testing and the MRI examination). Olfactory performance scores were compared between groups using an independent samples t-test. Spectral dynamic causal modeling was applied to resting-state fMRI data to identify alterations in effective connectivity due to the smell training. We found that patients in the treatment group improved in the odor discrimination task and overall olfactory function as compared to the control group. Compared to the control group, patients in the treatment group had increased self-inhibitory connectivity of the OFC and increased excitatory connectivity from the cingulate cortex to the insula. Moreover, the excitatory connectivity from the OFC to the cingulate cortex was found to be weaker following the olfactory training scheme. This study shows that a smell training scheme can cause changes in resting-state effective connectivity parameters that can be attributed to improvements in the odor discrimination task.

Key words: dynamic causal modeling, Bayesian model reduction, effective connectivity, resting-state, fMRI, smell training, olfactory dysfunction

INTRODUCTION

Olfactory disorders have extensive impacts on the lives of patients and can cause serious problems (Croy et al., 2014; Hosseini et al., 2020). Head trauma is one of the major causes of olfactory malfunctions (Howell et al., 2018) and many people lose their olfaction due to head trauma related to accidents every day (Croy et al., 2013). However, there is not a gold standard treatment for olfactory impairments (Pekala et al., 2016a). The plasticity of the brain has been investigated broadly over the past few decades and this work has shown that neuroplasticity is evident both after disease and treatment (Gilbert and Sigman, 2007; Merabet and Pascual-Leone, 2010). Many studies have shown that the olfactory system has incredible plasticity (Kollndorfer et al., 2014), which indicates that interventions that are aimed to excite smell neurons and manipulate olfactory function may retrieve smell function.

The efficacy of olfactory training as a promising therapy among patients with olfactory dysfunction has

Received 20 April 2020, accepted 6 September 2020

been demonstrated in several studies (Konstantinidis et al., 2016; Pekala et al., 2016b). In particular, Kollndrofer et al. (2014), found that smell training can cause functional connectivity adjustments in the right and left piriform cortices, which are among the major olfactory regions. However, the causal processes between brain regions associated with the olfactory system are still not clear. Further, the intrinsic network architectures of olfactory-related brain regions in patients with hyposmia and/or anosmia have not been completely identified. Spectral dynamic causal modeling (spDCM), which estimates resting-state effective connectivity, can be used to identify the neural mechanisms underlying posttraumatic olfactory loss and how a smell training scheme can modulate resting-state effective connectivity (Friston et al., 2014).

Increasing the smell training period and changing odors during training can increase the chance of therapeutic success (Altundag et al., 2015). Thus, it is critical to evaluate how the olfactory training scheme can alter effective connectivity. Modeling the direct causal relationship between various olfactory-related brain areas among patients who are subjected to the treatment may allow researchers to design and study optimized therapies for patients with anosmia and hyposmia. Examining olfactory-related brain connections will also add to the body of knowledge on compensatory top-down neural processes.

In this study, we were interested in two questions: First, we aimed to identify the most probable causal relationship among the five brain areas that are implicated in olfactory-related processes, the piriform cortex (PC), amygdala (AMY), orbitofrontal cortex (OFC), insula, and cingulate cortex (Fjaeldstad et al., 2017; Zou et al., 2018; Han et al., 2019). Second, we examined whether and how an olfactory training scheme modifies the effective connectivity between these regions. To achieve these objectives, two groups of patients with posttraumatic smell loss (a group who received smell training and a group that did not underwent an fMRI experiment before and after a 16-week smell training.

METHODS

Participants

Nineteen patients were recruited. Two subjects were removed from the study due to incomplete fMRI experiments and another subject was excluded due to excess head motion during fMRI data acquisition. The final sample size was 16 patients. Two patients were hyposmic, characterized by a partial loss of smell function, and the remainder were anosmic, characterized by a complete loss of olfactory function following head trauma (16 males; mean age=25.93; SD=5.24 years). The following exclusion criteria were applied: nasal septum deviation, psychologic diseases, sinusitis, tumor, alcohol consumption, upper respiratory tract infection, nasal surgery, polyps, congenital anosmia, structural changes in the brain, and working in places such as dye or heavy metal factories. The study protocol was evaluated and approved by the regional ethics committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1398.022). All subjects provided written informed consent before inclusion.

Study design

As the first step, olfactory performance of the 19 patients was measured to determine the severity of olfactory malfunction by an expert specialist. Then, patients were randomly assigned to one of two groups. The first group was the control group, wherein patients did not receive the training (n=8; mean age=25 years; average duration of olfaction malfunction=10 months). The second group was the treatment group, wherein participants were trained, (n=8; mean age=27.8 years; average duration of smell malfunction=9 months). Next, patients performed the resting-state fMRI experiment. Then, patients in the treatment group were taught to implement the olfactory training scheme for 16 weeks. After 16 weeks, subjects underwent the smell testing and the MRI examination again, using procedures that were similar to those implemented prior to the training.

Olfactory performance assessment

Olfactory function was assessed using the Sniffin' Sticks test kit (Burghart Instruments, Wedel, Germany), which includes three subtests to measure odor threshold, odor discrimination, and odor identification. The test uses pen-like devices for odor presentation (Kobal et al., 1996; Hummel et al., 1997). All tests were implemented by a standardized computerized test protocol (Frasnelli et al., 2012). Odor detection thresholds were measured for each odor with a single-staircase, 3-alternative forced-choice procedure. For odor discrimination, subjects were exposed to 16 triplets of odorants. Three pens were consecutively presented to the patients and two of the pens had similar odors and the other one had a different odor. Then, patients were instructed to choose the distinct one. To evaluate odor identification, patients were

given 16 pens that included common odors and were asked to identify each of the odorants from a list of four descriptors. Scores of the odor detection thresholds can range from 1 to 16, and scores on the other subtests can range from 0 to 16. Thus, the scores of all three subtests are summed to give a threshold detection identification (TDI) score. Subjects with a score of 30.5 or more can be considered as normal and the ones with a score between 16.5 and 30 can be considered hyposmic. Scores lower than 16 indicate functional anosmia (Kobal et al., 2000).

Olfactory training

The smell training was performed over a period of 16 weeks. The patients who were randomly assigned to the training group were instructed to smell four odors twice each day. Patients felt the scents without recognizing and naming them. These odorants were phenyl ethyl alcohol (PEA, rose), eucalyptol (eucalyptus), citronellal (lemon), and thyme extract (thymus vulgaris). The odorants were chosen based on Henning's smell prism (Altundag et al., 2015). Subjects implemented the training before breakfast in the morning and again in the evening before sleeping (Altundag et al., 2015). Each session lasted five minutes. Every session was a rotation of the same sequence of odorants, each odorant was smelled for ten seconds with time intervals of ten seconds between odors.

Statistics

Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, USA) version 26.0 was used for statistical analysis. To evaluate olfactory function, mean and standard deviation (SD) were computed. To compare olfactory performance scores between groups, an independent samples t-test was performed. Additionally, the paired student's t-test was used to compare olfactory performance scores of each group before and after the 16-week period. The level of significance for statistical tests was set at α=0.05.

Image acquisition

All MRI data acquisitions were performed on a 3 Tesla Prisma System (Siemens Medical Solution, Erlangen, Germany) using a 64-channel head coil. 3D high-resolution structural images were obtained using an MPRAGE sequence in the sagittal plane. For the T1-weighted scan, repetition time (TR), echo time (TE), and slice thickness were 1800 ms, 3.53 ms, and 1.0 mm, respectively. Resting-state functional data were acquired using a gradient-recalled, echo-planar imaging (EPI) sequence (TR=2100 ms; TE=30 ms; flip angle=90 degrees; field of view (FOV)=256 mm × 256 mm; number of slices=36; slice thickness=3 mm). Subjects were instructed to close their eyes and not think of anything specific during the resting-state scan.

fMRI data analysis

FMRIB Software Library v6.0 (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) was used to perform brain extraction using BET and to preprocess the data. Preprocessing consisted of high-pass filtering (cut-off period=100 s), motion correction, slice timing correction, spatial smoothing (FWHM=5 mm), and normalization to the Montreal Neurological Institute (MNI) template, using the FEAT tool. To diminish the potential impact of head motion on the data, subjects who had a mean absolute motion value greater than 1.0 mm were excluded (n=1).

Five regions of interest (ROIs) were selected based on their potential roles in olfaction: the AMY and PC were selected as primary olfactory areas, and the insula, cingulate cortex, and OFC were selected as secondary olfactory areas (Seubert et al., 2013; Fjaeldstad et al., 2017). To create the masks of the five areas, WFU PickAtlas (http://fmri.wfubmc.edu/software/PickAtlas), executed in MATLAB software (Matlab 9.4.0, Release 2018a, Mathworks Inc., Sherborn, MA, USA), was used. Three of the five ROIs (insula, AMY, and OFC) were defined using the AAL atlas (Tzourio-Mazoyer et al., 2002). For the PC, we drew two-spherical shapes with a 10-mm radius in the right and left hemispheres at the following coordinate locations: Right: MNI 17 0 -20; Left: MNI -17 -3 -18. The cingulate cortex mask was created using the IBASPM 71 atlas. A GLM analysis was performed using SPM12 toolbox (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/), implemented in MATLAB software. Nuisance regressors consisted of the six head motion parameters, as well as, cerebrospinal fluid (CSF) and white matter (WM) regressors. BOLD timeseries of the aforementioned five ROIs were extracted.

Dynamic causal modeling (DCM) is a method that can be used to infer the causal influences among neural units or populations (Friston et al., 2003; Stephan and Friston, 2011). We implemented spectral dynamic causal modeling with our five ROIs (Friston et al., 2014). Given that no previous studies have examined olfactory-related information flow in patients with posttraumatic olfactory dysfunctions, we employed an explor-

atory approach to examine effective connectivity network reorganization among the five ROIs in response to smell training. Thus, we defined a fully connected model in which each region was connected to all other regions. After specifying the full model, the DCM was inverted or estimated for every subject.

To identify commonalities and differences across patients, we took subject-specific connectivity parameters to the group level and tested for group effects using a hierarchical regression model. This regression model was performed using the parametric empirical Bayes (PEB) framework, implemented in DCM12.5 (Zeidman et al., 2019). Mean connectivity across subjects, the main effect of time, the main effect of treatment, and the interaction between time and treatment were entered as regressors in the second level design matrix. As mentioned above, no particular hypothesis or model space was set, and we treated all possible reduced models of the full PEB model as being equally likely *a priori*. Here, a reduced model is one in which certain parameters, relating to particular connections, are switched off by fixing them at zero. We used Bayesian model reduction (BMR), an automatic search procedure, to make a quick and efficient comparison of a large number of reduced models (Friston and Penny, 2011; Zeidman et al., 2019). BMR identifies the models that offer the best trade-off between accuracy (explained variance) and complexity (using the fewest effective connections). We report connection strengths obtained from the output of this search.

RESULTS

Olfactory performance

The average time period between the two olfactory performance testing sessions was 19 weeks. At the first testing session (before the training), patients in the control and treatment groups did not show significant differences in T, I, D, and TDI scores. Control patients showed no significant improvements in olfactory function values at the second testing session as compared to the first session. At the second smell testing, there was a significant difference between groups in terms of D ($p<0.001$) and TDI ($p<0.033$) scores wherein participants in the treatment group had higher scores than participants in the control group. Participants in the treatment group were significantly better at the odor discrimination task after the smell training scheme as compared to before ($p<0.005$). Overall olfactory performance (TDI scores) were significantly better after training in the treatment group ($p<0.039$). However, no significant changes were seen in the odor detection threshold and identification tasks between groups in the second olfaction testing session. Detailed results regarding the olfactory testing can be found in Table I.

Bayesian model reduction

The evidence of all reduced PEB models was compared using the BMR method. No single model can be reported as a winning model (probability larger than 0.95), which is likely due to the large number of models evaluated. Bayesian model averaging (BMA) was then performed over the 256 models from the final iteration of the automatic search over the reduced models. Common – i.e. mean – connectivity parameters across all subjects before and after the smell training are shown in Fig. 1. In this figure, each row indicates a given target region and each column indicates the source region for each connection. Although with Bayesian analysis there is no concept of significance, we report the parameters with posterior probabilities of more than 0.80 ($p>0.80$) for clarity. Connection strengths are provided in each square, in which a negative value indicates that a given connection inhibits the target region. Conversely, a positive value indicates an excitatory connection.

Table I. Detailed results regarding the olfactory testing of participants in each group before and after the training scheme.

Groups	Control		Treatment	
	mean (SD) Before	mean (SD) After	mean (SD) Before	mean (SD) After
Threshold	2.34 (2.39)	1.68 (1.94)	1 (0)	2.64 (3.22)
Discrimination	6.37 (2.61)	5.37 (1.30)[a]	5.71 (1.70)*	8.14 (1.34)*[a]
Identification	3.87 (2.41)	6 (3.89)	5.71 (2.13)	7.57 (2.99)
TDI	12.59 (5.05)	13.06 (4.37)[a]	12.42 (2.52)*	18.35 (4.19)*[a]

* marks significant differences before and after the olfactory training in different groups; [a] indicates significant differences between groups.

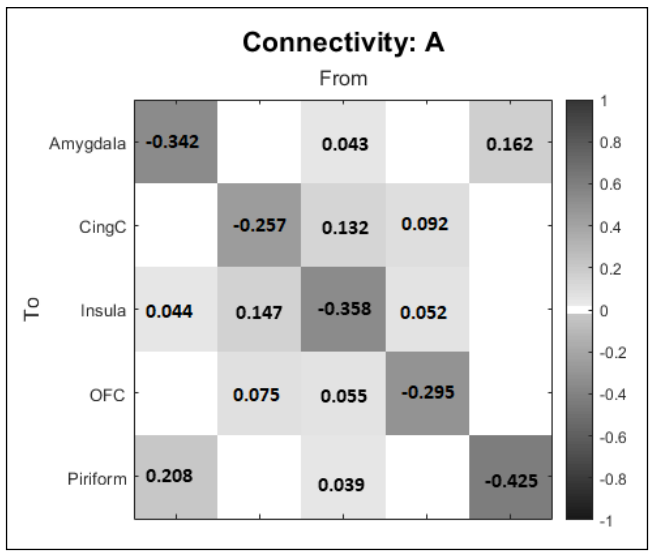

Fig. 1. Intrinsic connectivity parameters that are common among all subjects before and after the training. Parameters that have posterior probabilities (Pp) above 0.8 are reported. Regions: amygdala; (CingC) cingulate cortex; insula; (OFC) orbitofrontal cortex; piriform cortex.

Fig. 2 demonstrates differences in the intrinsic connectivity parameters across subjects by time, group (treatment or control), and the time by group interaction. The main effect of time shows whether or not there was a difference between pre-test and post-test time points, averaged across the groups. We found that no connection was significantly altered over time. The main effect of group demonstrates whether there is a difference between the two groups, averaged over pre-test and post-test time points. Our results show that the strength of the self-inhibitory connection of insula varies between groups. This group difference may originate from the fact that the examined subjects were all posttraumatic and the extent of their injuries varied across subjects. The interaction of time and group tests whether there is a distinction between groups at the second fMRI examination but not the first one, or vice versa. There was a significant time by group interaction for three connections. In the treatment group, the self-inhibitory connection of the OFC and the connection from the cingulate cortex to the insula increased and, oppositely, the connection from the OFC to the cingulate cortex diminishes (Fig. 3).

DISCUSSION

The main aim of this study was to model the effective connectivity between five regions implicated in olfactory-related processes (PC, AMY, OFC, insula, and cingulate cortex), and to investigate whether and how smell training affects connectivity. We found that overall olfactory performance significantly increased among patients who trained for about four months. For the patients in the control group, in contrast, no meaningful change was seen in their overall olfactory function. Results of the olfactory training treatment group confirm those of prior published studies (Altundag et al., 2015; Pekala et al., 2016a). According to prior studies (Kollndorfer et al., 2014, 2015), we now know that smell training can alter functional connectivity networks. However, we do not know the directional effects among olfactory-related regions in the brain. We used dynamic causal modeling to model the underlying processes that occur at the neuronal level. Understanding how neural elements interact with one another via their afferent and efferent connec-

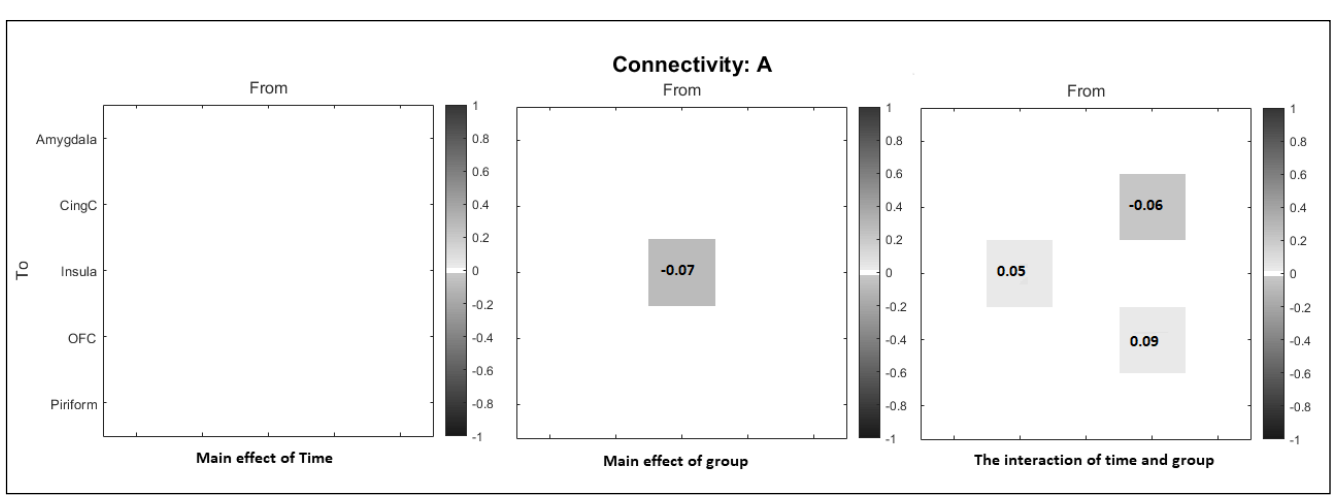

Fig. 2. Intrinsic connectivity parameters that were affected by the olfactory training (p>0.80). Regions: amygdala; (CingC) cingulate cortex; insula; (OFC) orbitofrontal cortex; piriform cortex.

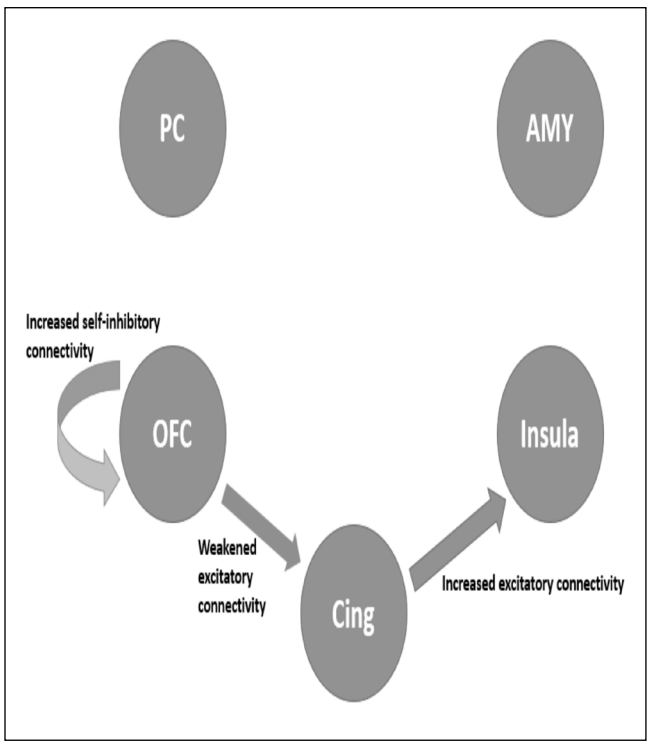

Fig. 3. The connectivity diagram of the effects found for the interaction of time and group. Regions: amygdala; (CingC) cingulate cortex; insula; (OFC) orbitofrontal cortex; piriform cortex.

tions can assist us in evaluating the organization and reorganization of brain networks in terms of their quantitative and qualitative characteristics.

This study showed meaningful improvements in olfactory performance after a 16-week smell training scheme. First, the training group achieved a better TDI score in comparison to the control group. Second, patients who received the therapy showed better discrimination among odors than patients in the control group. However, there was no significant increase for the odor identification task. These results differ from previous studies in various ways. For example, a prior study by Altundag et al. (2015), showed that subjects in the conventional olfactory training group, which was similar to the treatment in this study, showed significant improvement in both discrimination and identification (DI) tasks. This discrepancy may arise from the power of the study and the number of subjects or the trend of performing smell training. Additionally, Altundag et al. (2015), trained patients with different kinds of odors and used a longer training time than in our study. Our findings are consistent with most of the reported outcomes of individual studies in terms of not obtaining considerable changes in the odor threshold task. Alterations in odor thresholds are thought to depend on peripheral changes in the olfactory system (Altundag et al., 2015), whereas DI tasks are thought to rely on higher cognitive processes. However, one study reported a significant increase in the odor threshold task following an odor training (Kollndorfer et al., 2014). Therefore, more investigations are needed to evaluate whether the odor threshold score can be improved by smell training.

We compared the full PEB model with thousands of reduced models using Bayesian model reduction, and then reviewed the weighted averages of the parameters over models. We found the most likely directional causal relationship (mean connectivity parameters across all subjects before and after the olfactory training scheme) of the selected regions. Further, our results demonstrated a strengthening of the excitatory connection from the cingulate cortex to the insula among patients who received the olfactory training scheme. Our findings demonstrate that the smell training scheme is associated with changes in effective connectivity, as compared to the control group that did not include training. To our knowledge, the insula is engaged during olfactory-related processes but its role in olfaction is not clearly identified (Uddin et al., 2017). Bsteh et al. (2019) found that alterations in the DI tasks are correlated with gray matter atrophy in the cingulate cortex along with other regions. However, in that study, the authors did not evaluate the association between DI tasks and different regions, separately (Bsteh et al., 2019). To-date, the directed causal influences between the insula and the cingulate cortex have not been studied in healthy nor patient subjects. Alterations in intrinsic connectivity strengths and/or directionality can shed light on the inherent functional organization of the brain (van den Heuvel and Hulshoff, 2010). Our results suggest that improvements in the odor discrimination task may be attributed to the aforementioned changes in connectivity parameters among subjects in the treatment group.

Our study showed an increase in self-inhibitory connectivity of the OFC among patients in the treatment group. This result suggests a re-organization of OFC functioning the smell training scheme. This finding is consistent with previous studies, in particular, studies on patients with OFC lesions have shown that this region plays a fundamental role in odor discrimination (Potter and Butters, 1980; Zatorre and Jones-Gotman, 1991). There is also evidence that the OFC is involved in processes related to odor discrimination learning (Gottfried et al., 2002b). Given that scores of the discrimination task increased significantly among patients in the treatment group, we can conclude that a strengthening of self-inhibitory connectivity of the OFC may have likely been one of the causes. According to previous studies, the OFC, as one

of the secondary olfactory areas, engages in various tasks such as odor discrimination, identification, and memory (Gottfried et al., 2002a).

For connectivity between the OFC and the cingulate cortex, our spectral dynamic causal modeling results demonstrated a weakened connection from the OFC to the cingulate cortex after the training scheme. Along with the OFC, the cingulate cortex plays a role in olfactory memory. As discussed above, the correlations of the DI tasks with the cingulate cortex along with our findings suggest that the cingulate cortex and OFC may be involved in processes related to odor DI. This finding suggests that improved odor discrimination may related to a reduced strength of the excitatory influence of the OFC on the cingulate cortex, as well as other alterations in effective connectivity. Based on studies showing that the OFC plays a role in both DI tasks, we anticipated an enhancement in the odor identification score following the treatment (Gottfried et al., 2002a). However, only the odor discrimination task of the participants in the treatment group enhanced after the training. We assume that this inconsistency may arise from different effects of training on regions and their connections.

This study highlights the importance of resting-state effective connectivity in understanding olfactory network functioning in posttraumatic olfactory dysfunction patients, and how a smell training scheme can affect the network. Moreover, further knowledge in the causal relationships between primary and secondary olfactory areas can successfully assist in the design of new and improved versions of the smell training that are able to result in better outcomes. The number of patients and the inclusion of subdivisions of the cingulate cortex, insula, OFC in the network were the limitations of the present study. Addressing these limitations can help draw more detailed conclusions regarding not only the effectiveness of the training scheme, but also, olfactory data computations in the brain. One of the advantages of Bayesian methods is that adding additional subjects in the future is straightforward. Increasing the sample size can also lead to enhanced sensitivity.

CONCLUSION

Results of the present study demonstrate that a smell training scheme can alter effective connectivity parameters. In particular, we observed alterations in the parameters of the OFC self-connection, the connection from the OFC to the cingulate cortex, and from the cingulate cortex to the insula. We studied posttraumatic patients with olfactory dysfunction since the efficacy of the olfactory training scheme on such patients has not been previously evaluated. The present study supports the notion that resting-state effectivity connectivity network studies can provide further information regarding the reorganization of olfactory-related processes in the brain after trauma and training, thereby allowing researchers to design more optimized training.

ACKNOWLEDGEMENTS

This work was supported by the Neurosciences Research Center of Tabriz University of Medical Sciences and the Vice Chancellor for Research of Tabriz University of Medical Sciences. We would also like to thank Dr. Peter Zeidman for his help in dynamic causal modeling and feedback on the manuscript.

REFERENCES

Altundag A, Cayonu M, Kayabasoglu G, Salihoglu M, Tekeli H, Saglam O, Hummel T (2015) Modified olfactory training in patients with postinfectious olfactory loss. Laryngoscope 125: 1763–1766.

Bsteh G, Steiger R, Tuovinen N, Hegen H, Berek K, Wurth S, Auer M, Pauli F Di, Gizewski ER, Deisenhammer F, Berger T, Scherfler C (2019) Impairment of odor discrimination and identification is associated with disability progression and gray matter atrophy of the olfactory system in MS. Mult Scler J 26: 706–715.

Croy I, Bojanowski V, Hummel T (2013) Men without a sense of smell exhibit a strongly reduced number of sexual relationships, women exhibit reduced partnership security – A reanalysis of previously published data. Biol Psychol 92: 292–294.

Croy I, Nordin S, Hummel T (2014) Olfactory disorders and quality of life-an updated review. Chem Senses 39: 185–194.

Fjaeldstad A, Fernandes HM, Hartevelt TJ Van, Gleesborg C, Møller A, Ovesen T, Kringelbach ML (2017) Brain fingerprints of olfaction: a novel structural method for assessing olfactory cortical networks in health and disease. Sci Rep 7: 42534.

Frasnelli J, Lundström J, Schöpf V, Negoias S, Hummel T, Lepore F (2012) Dual processing streams in chemosensory perception. Front Hum Neurosci 6: 288.

Friston K, Penny W (2011) Post hoc Bayesian model selection. Neuroimage 56: 2089–2099.

Friston KJ, Harrison L, Penny W (2003) Dynamic causal modelling. Neuroimage 19: 1273–1302.

Friston KJ, Kahan J, Biswal B, Razi A (2014) A DCM for resting state fMRI. Neuroimage 94: 396–407.

Gilbert CD, Sigman M (2007) Brain States: top-down influences in sensory processing. Neuron 54: 677–696.

Gottfried JA, Deichmann R, Winston JS, Dolan RJ (2002a) Functional heterogeneity in human olfactory cortex: An event-related functional magnetic resonance imaging study. J Neurosci 22: 10819–10828.

Gottfried JA, O'Doherty J, Dolan RJ (2002b) Appetitive and aversive olfactory learning in humans studied using event-related functional magnetic resonance imaging. J Neurosci 22: 10829–10837.

Han P, Hummel T, Raue C, Croy I (2019) Olfactory loss is associated with reduced hippocampal activation in response to emotional pictures. Neuroimage 188: 84–91.

Hosseini SF, Kamrava SK, Asadi S, Maleki S, Zare-Sadeghi A, Shakeri-Zadeh A (2020) A multimodal MR-compatible olfactometer with real-time controlling capability. J Med Eng Technol 44: 317–323.

Howell J, Costanzo RM, Reiter ER (2018) Head trauma and olfactory function. World J Otorhinolaryngol Head Neck Surg 4: 39–45.

Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G (1997) "Sniffin" sticks'. Olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem Senses 22: 39–52.

Kobal G, Hummel T, Sekinger B, Barz S, Roscher S, Wolf S (1996) "Sniffin" Sticks': Screening of olfactory performance. Rhinology 34: 222–226.

Kobal G, Klimek L, Wolfensberger M, Gudziol H, Temmel A, Owen CM, Seeber H, Pauli E, Hummel T (2000) Multicenter investigation of 1,036 subjects using a standardized method for the assessment of olfactory function combining tests of odor identification, odor discrimination, and olfactory thresholds. Eur Arch Otorhinolaryngol 257: 205–211.

Kollndorfer K, Kowalczyk K, Hoche E, Mueller CA, Pollak M, Trattnig S, Schöpf V (2014) Recovery of olfactory function induces neuroplasticity effects in patients with smell loss. Neural Plast 2014: 1–7.

Kollndorfer K, Fischmeister FPS, Kowalczyk K, Hoche E, Mueller CA, Trattnig S, Schöpf V (2015) Olfactory training induces changes in regional functional connectivity in patients with long-term smell loss. NeuroImage Clin 9: 401–410.

Konstantinidis I, Tsakiropoulou E, Constantinidis J (2016) Long term effects of olfactory training in patients with post-infectious olfactory loss. Rhinology 54: 170–175.

Merabet LB, Pascual-Leone A (2010) Neural reorganization following sensory loss: the opportunity of change. Nat Rev Neurosci 11: 44–52.

Pekala K, Chandra RK, Turner JH (2016a) Efficacy of olfactory training in patients with olfactory loss: a systematic review and meta-analysis HHS Public Access. Int Forum Allergy Rhinol 6: 299–307.

Pekala K, Chandra RK, Turner JH (2016b) Efficacy of olfactory training in patients with olfactory loss: a systematic review and meta-analysis. Int Forum Allergy Rhinol 6: 299–307.

Seubert J, Freiherr J, Djordjevic J, Lundström JN (2013) Statistical localization of human olfactory cortex. Neuroimage 66: 333–342.

Stephan KE, Friston KJ (2011) Analyzing effective connectivity with fMRI. Wiley Interdiscip Rev Cogn Sci 1: 446–459.

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M (2002) Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15: 273–289.

Uddin LQ, Nomi JS, Hébert-Seropian B, Ghaziri J, Boucher O (2017) Structure and function of the human insula. J Clin Neurophysiol 34: 300–306.

van den Heuvel MP, Hulshoff Pol HE (2010) Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol 20: 519–534.

Zeidman P, Jafarian A, Seghier ML, Litvak V, Cagnan H, Price CJ, Friston KJ (2019) A guide to group effective connectivity analysis, part 2: Second level analysis with PEB. Neuroimage 200: 12–25.

Zou L quan, Zhou H yu, Zhuang Y, Hartevelt TJ van, Lui SSY, Cheung EFC, Møller A, Kringelbach ML, Chan RCK (2018) Neural responses during the anticipation and receipt of olfactory reward and punishment in human. Neuropsychologia 111: 172–179.