Basic and Clinical NEUROSCIENCE
November & December 2022 Volume 13, Number 6

Research Paper

Resting-state Functional Connectivity During Controlled Respiratory Cycles Using Functional Magnetic Resonance Imaging

Chan-A Park[1], **Yeong-Bae Lee**[2, 3], **Chang-Ki Kang**[4*]

1. Biomedical Engineering Research Center, Gachon University, Incheon, Republic of Korea.
2. Department of Neurology, Gil Medical Center, Gachon University College of Medicine, Incheon, Republic of Korea.
3. Neuroscience Research Institute, Gachon University, Incheon, Republic of Korea.
4. Department of Radiological Sciences, College of Health Sciences, Gachon University, Incheon, Republic of Korea.

Use your device to scan and read the article online

Citation Park, C-A., Lee, Y-B, and Kang, C-K. Resting-state Functional Connectivity During Controlled Respiratory Cycles Using Functional Magnetic Resonance Imaging. *Basic and Clinical Neuroscience, 13*(6), 855-864. http://dx.doi.org/10.32598/bcn.2022.2534.1

http://dx.doi.org/10.32598/bcn.2022.2534.1

Article info:
Received: 07 May 2020
First Revision: 23 Feb 2021
Accepted: 03 oct 2021
Available Online: 01 Nov 2022

Keywords:
Respiratory rate, Functional connectivity, Functional MRI

ABSTRACT

Introduction: This study aimed to assess the effect of controlled mouth breathing during the resting state using functional magnetic resonance imaging (fMRI).

Methods: Eleven subjects participated in this experiment in which the controlled "Nose" and "Mouth" breathings of 6 s respiratory cycle were performed with a visual cue at 3T MRI. Voxel-wise seed-to-voxel maps and whole-brain region of interest (ROI)-to-ROI connectome maps were analyzed in both "Nose>Mouth" and "Mouth>Nose" contrasts.

Results: As a result, there were more connection pairs in the "Mouth" breathing condition, i.e., 14 seeds and 14 connecting pairs in the "Mouth>Nose" contrast, compared to 7 seeds and 4 connecting pairs in the "Nose>Mouth" contrast (false discovery rate [FDR] of $P<0.05$).

Conclusion: The present study demonstrated that mouth breathing with controlled respiratory cycles could significantly induce alterations in functional connectivity in the resting-state network, suggesting that it can differently affect resting brain function; in particular, the brain can hardly rest during mouth breathing, as opposed to conventional nasal breathing.

*** Corresponding Author:**
Chang-Ki Kang, PhD.
Address: *Department of Radiological Sciences, College of Health Sciences, Gachon University, Incheon, Republic of Korea.*
Tel: *+98 (32) 8204110*
E-mail: *ckkang@gachon.ac.kr*

Highlights

- Mouth breathing increases significantly resting-state functional connectivity.
- Mouth breathing is deeply correlated with communication between the limbic system and the posterior regions.
- The brain can hardly rest during mouth breathing.

Plain Language Summary

Problems with mouth breathing have long been well studied and have a multifactorial origin attributable to physiological and mechanical etiology, but the neural correlates of functional connectivity remain unclear. The inefficient oxygen and carbon dioxide exchange created by mouth breathing adversely affects brain function. Examination of controlled breathing through the mouth found more pairs of connections between the limbic (temporal cortex) and posterior (parietal cortex). A possible cause may be different nitric oxide (NO) production. NO is produced to a greater extent in the sinuses, located in the nasal pathway, and increases oxygen transport throughout the body, making nasal breathing critical for normal brain function.

1. Introduction

Humans generally breathe through the nose, but mouth breathing is inevitable in certain circumstances such as nasal congestion. Many studies have shown that abnormal respiration via the mouth has various adverse effects on the body and brain (Chlif et al., 2009; Harari et al., 2010; Jefferson, 2010; Lessa et al., 2005; Lin & Lin, 2012). There are several reasons for the functional inefficiency of mouth breathing compared to nasal breathing. First of all, our mouth cannot obstruct viruses and germs, while the nasal passages play an important role in filtering the air before it enters the lungs. Furthermore, in mouth breathing, oxygen absorption decreases due to a large amount of air exhaled, which leaves insufficient time for oxygen absorption by the lungs. In contrast, the smaller air pathways of the nose provide greater resistance to the airflow; thus, when one breathes through the nose, the lung has more time to extract oxygen, resulting in a 10%-20% increase in oxygen uptake (Cottle, 1972, 1980). Additional deleterious effects of mouth breathing include low academic or arithmetic achievement in children who breathe with their mouth, along with deficiencies in working memory, reading comprehension, and learning skills (Kuroishi et al., 2015).

Since the introduction of a new functional technique by Ogawa et al. in the 1990s (Ogawa et al., 1990), several studies have examined the effect of respiration through nose breathing on brain function using blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) (Gozal et al., 1995, 1996; Harper et al., 1998). Some studies have compared the effects of nasal and mouth breathing using electroencephalography (EEG) (Bell et al., 1998; Lee et al., 2019) and near-infrared spectroscopy (Sano et al., 2013). Studies to examine the respiratory mechanism in the human brain have typically used the task-based imaging modality.

Recently, a neuroimaging-based assessment method for resting-state human brain function was introduced. Increased neuronal activity has been noted in the default mode network (DMN) during the resting state rather than during tasks (Gusnard et al., 2001; Raichle et al., 2001). This network includes the prefrontal cortex (PFC) and posterior cingulate cortex (PCC) medially, and the parietal and temporal cortices laterally. Functional connectivity (FC) analysis is typically performed using the DMN seeds or region of interest (ROI)-based correlation of fMRI BOLD signals throughout the brain during the resting state (Fransson & Marrelec, 2008). A resting-state fMRI study has investigated the relationship between respiratory motion and BOLD signals using low-frequency components analysis in a time series (Birn et al., 2006). However, most resting-state fMRI experiments were conducted only in the nasal breathing condition (Fransson & Marrelec, 2008; Greicius et al., 2003; Gusnard et al., 2001; Raichle et al., 2001; van de Ven et al., 2004; Wu et al., 2014).

It is known that mouth breathing could make one susceptible to mandibular and vertical craniofacial growth, and adversely affects various cognitive functions. Based on previous studies, we hypothesize that the resting-state

FC of mouth breathing with controlled respiratory cycles can be identified and distinguished from that of normal nasal breathing because of the detrimental influence of mouth breathing on brain function. In this study, we aimed to examine the resting-state FC of the two breathing modes to investigate the unclear but undeniable effects of mouth breathing on DMN.

2. Materials and Methods

Study subjects and data acquisition

Eleven healthy young subjects (seven men and four women; Mean±SD age: 33.27±4.76 years) participated in this experiment and their written consent was taken after the study was explained to them. The study protocol followed the Declaration of Helsinki and was approved by the Institutional Review Board (GDIRB2013-23). The exclusion criteria were a history of neurological or psychiatric diseases and any respiratory disorders. The experiment was conducted using a 3T magnetic resonance imaging (MRI) (Siemens Verio, Erlangen, Germany) with a 12-channel radio-frequency head matrix coil. All participants were given a pair of earplugs and underwent two MRI imaging sequences. At first, a T1-weighted anatomical imaging sequence of three-dimensional magnetization prepared rapid gradient echo was acquired for the anatomical reference. Secondly, BOLD fMRI sequence of two-dimensional echo planar imaging (EPI) was obtained for the functional imaging with a repetition time (TR) of 3000 ms, echo time (TE) of 30 ms, imaging resolution of 3×3×3 mm, imaging slices of 46 to cover the whole brain (138 mm in the z-axis), and flip angle (FA) of 90°.

Each participant breathed only through their mouth or nose depending on the visual cue presented through a beam projector at the beginning of each session. During the session, the color of a cross placed in the center of the screen (red and blue, corresponding to inhalation and exhalation, respectively) was changed every 3 s, and the subjects were asked to maintain a constant breathing cycle (i.e., approximately 0.3 Hz) following the cross color. The protocol followed what was used in a previous study, in which subjects were asked to keep their eyes open and fixated on the cross, and the results showed the highest reliability during the examination of the within-network connections as well as the DMN, the attention network, and auditory connectivity (Patriat et al., 2013). The subjects were instructed not to move their head as much as possible and stay awake throughout the data acquisition process. Each subject bit a cylindrical plastic bar to ensure that the mouth remained open and prevent systematic motion artifacts that could unexpectedly increase upon the changing of breathing modes during the two resting-state sessions ("Nose" and "Mouth" breathing conditions). The order of the sessions was randomly assigned between subjects. Each session included the collection of 102 dynamic data volumes for about 5 min.

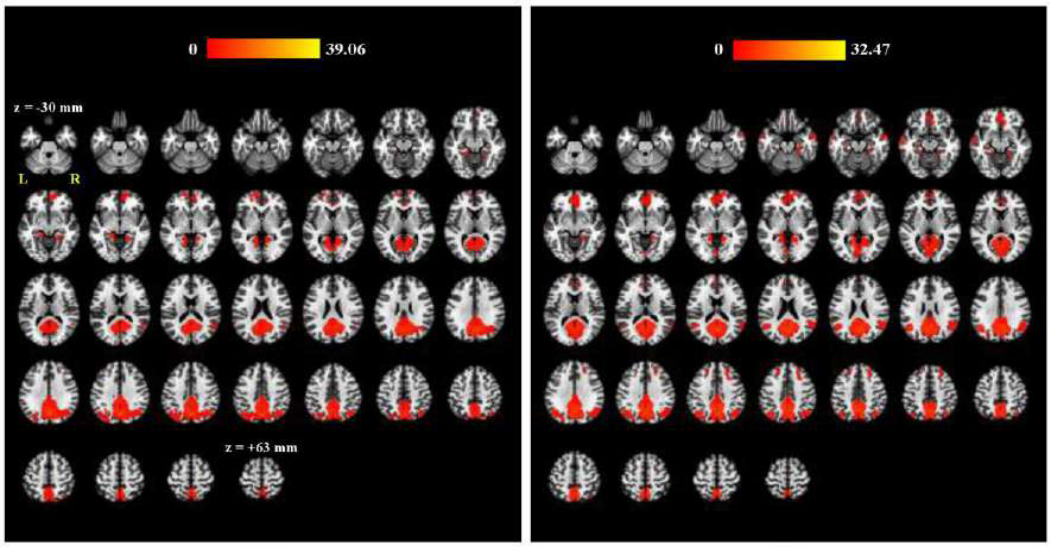
Data processing and statistical analysis

A MATLAB-based CONN FC toolbox software (www.nitrc.org/projects/conn) was used for preprocessing, denoising, and statistical analysis. For preprocessing, we discarded the first two volumes for MRI signal stabilization, and then we realigned the other functional volumes to the first volume as a reference for head motion compensation. They were co-registrated to the structural volume, segmented the grey and white matters and cerebrospinal fluid (CSF) regions, normalized to the EPI template of 2×2×2 mm and smoothed with a Gaussian kernel of 8 mm full width half maximum. For denoising BOLD signals, white matter and CSF were considered additional confounds, and linear regression was used for this denoising process. Then, band-pass filtering of 0.008 to 0.09 Hz was performed to remove the subject's estimated motion parameters and other artificial effects.

For statistical analysis, the strength and significance of ROI pairs within all subjects' data in the "Nose" and "Mouth" breathing conditions were calculated by CONN toolbox. To reduce the skewness of the distribution of connectivity values caused by motion and or physiological noise sources, linear detrending was applied, which made the histogram of mean BOLD signals approximately centered and normalized for the regression processing after temporal preprocessing. To measure the level of linear association of the BOLD time series, a bivariate correlation was used to conduct the first-level analysis, in which the effect size is the correlation coefficient (Whitfield- Gabrieli & Nieto-Castanon, 2012).

In the CONN toolbox, 163 ROIs consist of the following items: an atlas for cortical and subcortical regions from FMRIB Software Library (FSL) Harvard-Oxford Atlas and cerebellar regions from the automated anatomical labeling (AAL) atlas (atlas.nii), and an atlas for networks (networks.nii) including medial PFC (MPFC), PCC, right lateral parietal (RLP), and left lateral parietal (LLP) regions. In total, 132 ROIs were obtained from atlas.nii, and 31 ROIs in 8 networks from networks.nii (Whitfield- Gabrieli & Nieto-Castanon, 2012).

First, the PCC among the DMN hubs was selected to construct a seed-to-voxel FC map in each "Nose" and



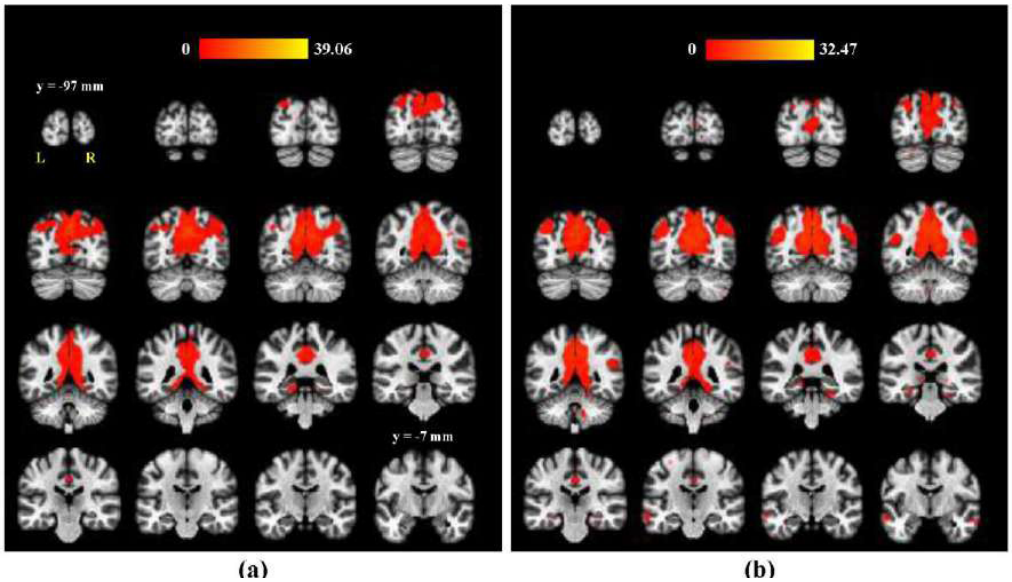
NEUROSCIENCE

Figure 1. Seed-to-voxel maps using the main effect of PCC in the DMN during "Nose" (a) and "Mouth" (b) Breathing conditions

The maps are obtained at a height threshold FDR of P<0.05 and cluster-sized extent threshold FDR of P<0.05, with 1000 simulations for non-parametric statistics, in the axial view. The internal distance between adjacent slices is 3 mm. The color bar represents statistical t values.

A, P, R, and L: anterior, posterior, right, and left; PCC: posterior cingulate cortex; DMN: default mode network; FDR: false discovery rate.

"Mouth" breathing condition for the second-level analysis. Note that the PCC was selected since it usually plays the role of a hub seed for resting-state fMRI seed-to-voxel FC analysis (Whitfield- Gabrieli & Nieto-Castanon, 2012). The maps were obtained at a false discovery rate (FDR)-corrected height threshold of P<0.05, and an FDR-corrected cluster-sized extent threshold of P<0.05, with 1000 simulations for non-parametric statistics. Second, the ROI-to-ROI FC was computed in the entire brain to show the correlation between all ROI seeds, and ana-



NEUROSCIENCE

Figure 2. Seed-to-voxel maps using the main effect of PCC in the DMN during "Nose" (a) and "Mouth" (b) Breathing conditions

The maps are obtained at a height threshold FDR of P<0.05 and cluster-sized extent threshold FDR of P<0.05, with 1000 simulations for non-parametric statistics, in the coronal view. The internal distance between adjacent slices is 6 mm. The color bar represents statistical T values.

A, P, R, and L: anterior, posterior, right and left; PCC: posterior cingulate cortex; DMN: default mode network; FDR: false discovery rate.

Table 1. ROI-to-ROI connections of the entire brain using a second-level group

Contrast	Pair Connection	Statistics (t)	P	
			Uncorrected	FDR
Nose>Mouth	PaCiG (R) – Visual Lateral§	5.99	0.0001	0.0110
	aPaHC (R) – Accumbens (L)	5.70	0.0001	0.0162
	Salience Anterior Insula§ – OP (L)	5.46	0.0001	0.0225
	Visual Lateral§ – Fronto Parietal PPC§	4.72	0.0004	0.0335
Mouth>Nose	SPL (R) – Language pSTG§	6.42	0.0000	0.0047
	SPL (R) – PT (R)	6.10	0.0001	0.0047
	SPL (R) – toMTG (R)	5.55	0.0001	0.0066
	SPL (R) – pSTG (L)	4.75	0.0004	0.0159
	SPL (R) – toMTG (L)	4.19	0.0009	0.0305
	Precuneus – aMTG (R)	5.82	0.0001	0.0136
	Precuneus – Cerebellar Anterior§	4.54	0.0005	0.0440
	Dorsal Attention IPS§ – toMTG (R)	5.80	0.0001	0.0141
	Dorsal Attention IPS§ – toMTG (L)	5.30	0.0002	0.0143
	Dorsal Attention IPS§ – Language pSTG§	4.36	0.0007	0.0387
	Default Mode PCC§ – Cerebellar Anterior§	5.18	0.0002	0.0274
	Default Mode PCC§ – aMTG (R)	4.85	0.0003	0.0274
	PostCG (R) – Cereb45 (R)	5.04	0.0003	0.0413
	toMTG (R) – TOFusC (L)	4.24	0.0009	0.0463

NEUROSCIENCE

Analysis of all selected ROI seeds (one-sided positive and seed-level FDR-corrected threshold of P<0.05, "Nose>Mouth" and "Mouth>Nose" contrasts).

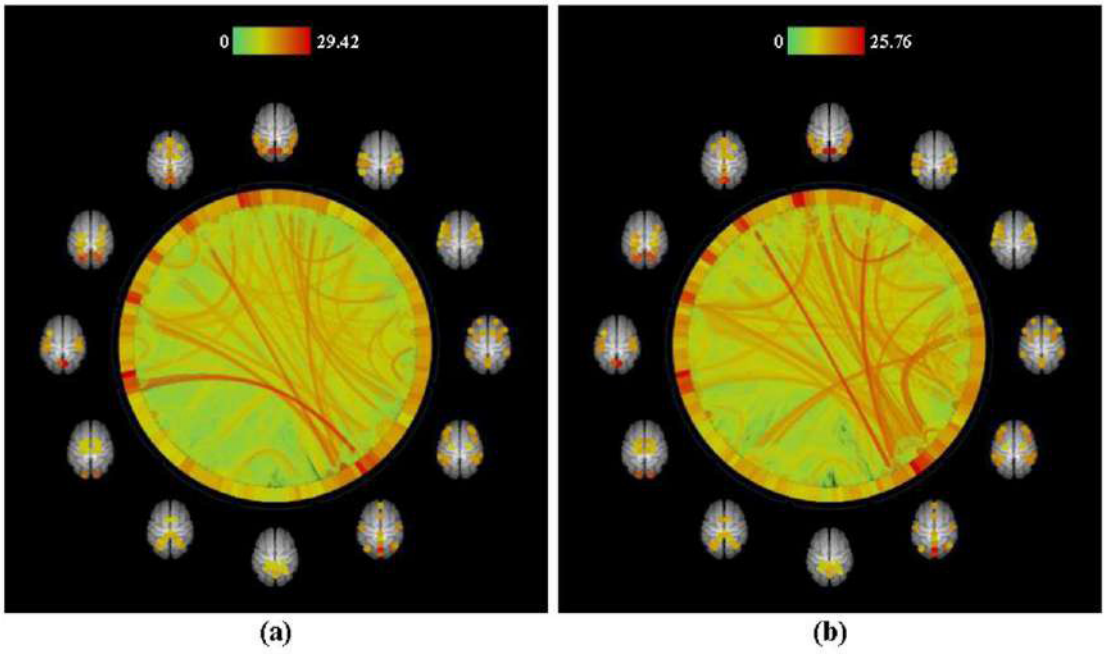
FDR: false discovery rate; ROI: region of interest; R and L: right and left; PaCiG: paracingulate gyrus; aPaHC: parahippocampal gyrus (anterior division); OP: occipital pole; PPC: posterior parietal cortex; SPL: superior parietal lobule; pSTG: superior temporal gyrus (posterior division); PT: planum temporale; toMTG: middle temporal gyrus (temporooccipital part); aMTG: middle temporal gyrus (anterior division); IPS: intraparietal sulcus; PCC: posterior cingulate cortex: PostCG: postcentral gyrus; Cereb45: cerebellum 45; TOFusC: temporal occipital fusiform cortex; §: network

lyze the global characteristics of human brain networks in each "Nose" and "Mouth" breathing condition, as well as in the "Nose>Mouth" and "Mouth>Nose" contrasts. The connectome maps are obtained at an FDR-corrected height threshold of P<0.05.

3. Results

In the seed-to-voxel map, DMN hubs including the MPFC, PCC, and right and left LLP areas were significantly and positively correlated during the resting-state "Nose" and "Mouth" breathing conditions (Figures 1 and 2). The ratio and number of cluster voxels in the frontal medial cortex (FMC) during the "Nose" condition were 7% of the FMC and 68 voxels (Figure 1a), while those during the "Mouth" condition were 37% of the FMC and 367 voxels (Figure 1b). In the precuneus, the ratio and number of cluster voxels during "Nose" condition were 93% of the precuneus and 5211 voxels (Figure 2a), while those during "Mouth" condition was 92% of the precuneus and 5147 voxels (Figure 2b). Additionally, neither "Nose>Mouth" nor "Mouth>Nose" contrast made a statistical difference on the seed-to-voxel FC analysis.

Figures 3 and 4 showed the connectome maps obtained from the ROI-to-ROI group analysis. There were more resting connections between all ROI seeds during the "Mouth" breathing condition compared to the "Nose" condition (Figure 3). As shown in Figure 4, there were 14 seeds and 14 connection pairs in "Mouth>Nose" contrast, but only 7 seeds and 4 connection pairs in the "Nose>Mouth" contrast. In partic-



NEUROSCIENCE

Figure 3. ROI-to-ROI functional connectivity-based three-dimensional rendering connectome maps during "Nose" (a) and "Mouth" (b) breathing conditions

The rings are obtained at an FDR-corrected height threshold of P<0.05. The color bar represents statistical t values.

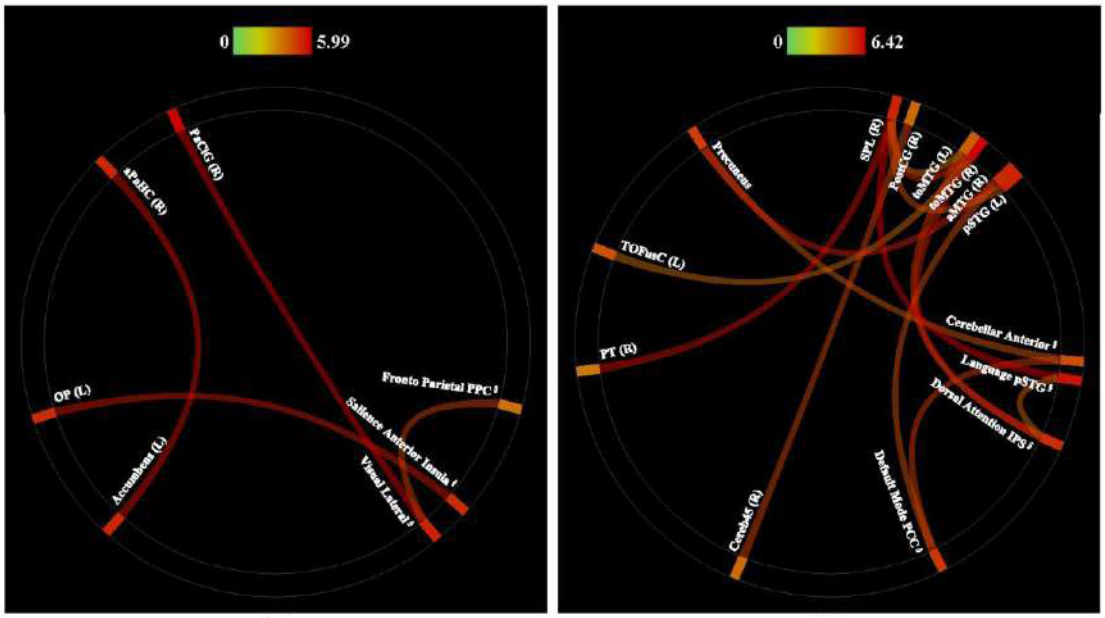
FDR: false discovery rate; ROI: region of interest.

ular, in the "Mouth>Nose" contrast, the right superior parietal lobule (SPL) seed was connected to 5 seeds: the posterior superior temporal gyrus (pSTG) of the language network, the right planum temporale (PT), both right and left temporooccipital middle temporal gyrus (toMTG), and the left pSTG. Statistical results for the connection pairs, including t and P values, are summarized in Table 1.

4. Discussion

To demonstrate whether mouth breathing changes resting-state FC in the human brain, we examined FC networks in both "Mouth>Nose" and "Nose>Mouth" contrasts using seed-to-voxel and ROI-to-ROI analyses using 3T fMRI. To the best of our knowledge, no experimental study has investigated FC differences between nasal and mouth breathing during the resting state using fMRI. In the seed-to-voxel second-level results (Figures 1 and 2), the PCC seed positively correlated with other DMN hubs not only in the "Nose" but also the "Mouth" breathing condition, as previously shown in many seed-based correlation analysis studies (Fransson & Marrelec, 2008; Gusnard et al., 2001; Raichle et al., 2001).

The resting connection patterns based on connectome maps from "Nose" and "Mouth" breathing conditions were different, as shown in Figure 3. To confirm the statistical difference between the two breathing conditions, we additionally conducted ROI-to-ROI analysis in both "Nose>Mouth" and "Mouth>Nose" contrasts. For ROI-to- ROI FC connectome analysis, in the "Mouth>Nose" contrast in the entire brain, the right SPL seed had the maximum number of connections (Table 1 and Figure 4). In detail, the seed was linked to right PT, right and left to MTG, and left pSTG, but was mostly located in the temporal parietal cortex. This connecting network indicates that mouth breathing is deeply correlated with communication between the limbic system and the posterior regions (temporal and parietal cortices), as shown in recent studies (Park & Kang, 2017; Zelano et al., 2016). Although previous studies have used task-based fMRI and intracranial EEG, which differ from the present experiment, the results proved that the limbic system, including the hippocampus, was associated with and or influenced by a cognitive task, in a differential way between nasal and mouth breathing. Furthermore, nasal breathing is a critical source of the production of nitric oxide (NO) which is an essential vasodilator that regulates vascular smooth muscles and then oxygen delivery and increases the oxygen transport throughout the human body (Džoljić et al., 2015; Lundberg et al., 2015). However, mouth breathers with a limit to producing NO due to the pathway blockade have a lower oxygen con-



NEUROSCIENCE

Figure 4. ROI-to-ROI 3-dimensional rendering connectome maps in "Nose>Mouth" (a) and "Mouth>Nose" (b) contrasts

The rings are obtained at an FDR-corrected height threshold of P<0.05. The color bar represents statistical t values.

FDR: false discovery rate; ROI: region of interest; R and L: right and left; PaCiG: paracingulate gyrus; aPaHC: parahippocampal gyrus (anterior division); OP: occipital pole; PPC: posterior parietal cortex; SPL: superior parietal lobule; pSTG: superior temporal gyrus (posterior division); PT: planum temporale; toMTG: middle temporal gyrus (temporooccipital part); aMTG: middle temporal gyrus (anterior division); IPS: intraparietal sulcus; PCC: posterior cingulate cortex: PostCG: postcentral gyrus; Cereb45: cerebellum 45; TOFusC: temporal occipital fusiform cortex; §: network.

centration in their blood than nasal breathers (Lundberg et al., 1996; Lundberg et al., 2015).

In this study, mouth breathing during the resting state produced more BOLD-based connection pairs between the limbic system (temporal cortex) and the posterior part (parietal cortex), but not the anterior part (frontal cortex), compared to conventional nasal breathing during the resting state. In the previous study, however, the oxygen load in the PFC was correlated with different patterns between nasal and mouth breathing (Sano et al., 2013). The disparity between these studies may come from the different signals examined in this study, namely the connection pattern between contrasts.

Although the present result provides a new finding about the effects of mouth breathing on the brain, we should note that no physiological data, including real respiratory and cardiac signals, have been used as covariates for FC analysis in resting-state fMRI studies (Birn, 2012; Birn, et al., 2008; Birn, et al., 2008; Khalili-Mahani et al., 2013). However, this type of noise would not have produced false positive results in the current experiment, since heart rate has only local effects due to the beating of blood vessels (Chang et al., 2009; Dagli et al., 1999), and small fluctuations in end-tidal CO2 during normal breathing at rest occurred at a frequency range of 0 to 0.05 Hz (Wise et al., 2004). Further studies should be undertaken using resting-state fMRI without controlled respiration cycles (closed eyes), to focus on voluntary self-control respiration through the nose or mouth. In addition, breath-dependent brain activation should be investigated in further studies with multiple and appropriate task-rest sessions to examine how brain activation is affected by breathing type.

5. Conclusion

In conclusion, we examined the resting-state FC during mouth versus nasal breathing, demonstrating that mouth breathing induced significantly increased FC in several ROIs in the entire brain compared to nasal breathing. When we investigated the effect of mouth breathing using the FC analysis, the node with more connections with ROIs in mouth breathing, and specifically during the resting state with controlled respiration, was revealed to be the SPL, suggesting that habitual mouth breathing could affect the functional

brain relationships of those regions. Therefore, our result suggests that the role played by acute mouth breathing in the resting brain is unexpected but crucial, since it is widely known that mouth breathing due to nasal obstruction has adverse health effects. As a consequence of long-term (habitual) mouth breathing, irreversible effects on brain function can induce cognitive problems. These considerations could underline the opportunity of undertaking further investigations of the principles underlying the observed resting-state difference between the two breathing manners for both research and clinical purposes.

Ethical Considerations

Compliance with ethical guidelines

The study protocol was approved by the Ethics Committee of the Gachon University Gil Medical Center (IRB: GDIRB2013-23).

Funding

This work was supported by the National Research Foundation of Korea (NRF) grant from the Korean government (MSIT) (2020R1A2C1004355)

Authors' contributions

Conceptualization: all authors; Methodology, writing the original draft, writing, review, and editing: Kang CK and Park CA; Investigation: Park CA; Funding acquisition and resources: Lee YB and Kang CK; Supervision: Kang CK.

Conflict of interest

The authors declare no conflict of interest.

References

Bell, I. R., Kline, J. P., Schwartz, G. E., & Peterson, J. M. (1998). Quantitative EEG patterns during nose versus mouth inhalation of filtered room air in young adults with and without self-reported chemical odor intolerances. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology, 28*(1), 23-35. [PMID]

Birn, R. M. (2012). The role of physiological noise in resting-state functional connectivity. *NeuroImage, 62*(2), 864-870. [DOI:10.1016/j.neuroimage.2012.01.016] [PMID]

Birn, R. M., Diamond, J. B., Smith, M. A., & Bandettini, P. A. (2006). Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. *NeuroImage, 31*(4), 1536-1548. [DOI:10.1016/j.neuroimage.2006.02.048] [PMID]

Birn, R. M., Murphy, K., & Bandettini, P. A. (2008). The effect of respiration variations on independent component analysis results of resting state functional connectivity. *Human Brain Mapping, 29*(7), 740-750. [DOI:10.1002/hbm.20577] [PMID] [PMCID]

Birn, R. M., Smith, M. A., Jones, T. B., & Bandettini, P. A. (2008). The respiration response function: The temporal dynamics of fMRI signal fluctuations related to changes in respiration. *NeuroImage, 40*(2), 644-654. [DOI:10.1016/j.neuroimage.2007.11.059] [PMID] [PMCID]

Chang, C., Cunningham, J. P., & Glover, G. H. (2009). Influence of heart rate on the BOLD signal: The cardiac response function. *NeuroImage, 44*(3), 857-869. [DOI:10.1016/j.neuroimage.2008.09.029] [PMID] [PMCID]

Chlif, M., Keochkerian, D., Choquet, D., Vaidie, A., & Ahmaidi, S. (2009). Effects of obesity on breathing pattern, ventilatory neural drive and mechanics. *Respiratory Physiology & Neurobiology, 168*(3), 198-202. [DOI:10.1016/j.resp.2009.06.012] [PMID]

Cottle, M. H. (1972). Nasal breathing pressures and cardiopulmonary illness. *Eye, Ear, Nose & Throat Monthly, 51*(9), 331-340. [PMID]

Cottle, M. H. (1980). A consideration of nasal, pulmonary and cardio-vascular interdependance and nasal-pulmonary function studies. *Rhinology, 18*(2), 67-81. [PMID]

Dagli, M. S., Ingeholm, J. E., & Haxby, J. V. (1999). Localization of cardiac-induced signal change in fMRI. *NeuroImage, 9*(4), 407-415. [DOI:10.1006/nimg.1998.0424] [PMID]

Džoljić, E., Grbatinić, I., & Kostić, V. (2015). Why is nitric oxide important for our brain? *Functional Neurology, 30*(3), 159-163. [PMID] [PMCID]

Fransson, P., & Marrelec, G. (2008). The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis. *NeuroImage, 42*(3), 1178-1184. [DOI:10.1016/j.neuroimage.2008.05.059] [PMID]

Gozal, D., Omidvar, O., Kirlew, K. A., Hathout, G. M., Hamilton, R., & Lufkin, R. B., etal. (1995). Identification of human brain regions underlying responses to resistive inspiratory loading with functional magnetic resonance imaging. *Proceedings of the National Academy of Sciences of the United States of America, 92*(14), 6607-6611. [DOI:10.1073/pnas.92.14.6607] [PMID] [PMCID]

Gozal, D., Omidvar, O., Kirlew, K. A., Hathout, G. M., Lufkin, R. B., & Harper, R. M. (1996). Functional magnetic resonance imaging reveals brain regions mediating the response to resistive expiratory loads in humans. *The Journal of Clinical Investigation, 97*(1), 47-53. [DOI:10.1172/JCI118405] [PMID] [PMCID]

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the United States of America, 100*(1), 253-258. [DOI:10.1073/pnas.0135058100] [PMID] [PMCID]

Gusnard, D. A., Raichle, M. E., & Raichle, M. E. (2001). Searching for a baseline: Functional imaging and the resting human brain. *Nature Reviews. Neuroscience, 2*(10), 685-694. [DOI:10.1038/35094500] [PMID]

Harari, D., Redlich, M., Miri, S., Hamud, T., & Gross, M. (2010). The effect of mouth breathing versus nasal breathing on dentofacial and craniofacial development in orthodontic patients. *The Laryngoscope, 120*(10), 2089-2093. [DOI:10.1002/lary.20991] [PMID]

Harper, R. M., Gozal, D., Bandler, R., Spriggs, D., Lee, J., & Alger, J. (1998). Regional brain activation in humans during respiratory and blood pressure challenges. *Clinical and Experimental Pharmacology & Physiology, 25*(6), 483-486. [DOI:10.1111/j.1440-1681.1998.tb02240.x] [PMID]

Jefferson, Y. (2010). Mouth breathing: Adverse effects on facial growth, health, academics, and behavior. *General Dentistry, 58*(1), 18-80. [PMID]

Khalili-Mahani, N., Chang, C., van Osch, M. J., Veer, I. M., van Buchem, M. A., & Dahan, A., et al. (2013). The impact of "physiological correction" on functional connectivity analysis of pharmacological resting state fMRI. *NeuroImage, 65,* 499-510. [DOI:10.1016/j.neuroimage.2012.09.044] [PMID]

Kuroishi, R. C., Garcia, R. B., Valera, F. C., Anselmo-Lima, W. T., & Fukuda, M. T. (2015). Deficits in working memory, reading comprehension and arithmetic skills in children with mouth breathing syndrome: Analytical cross-sectional study. *Sao Paulo Medical Journal = Revista Paulista De Medicina, 133*(2), 78- 83. [PMID]

Lee, K. J., Park, C. A., Lee, Y. B., Kim, H. K., & Kang, C. K. (2020). EEG signals 35. during mouth breathing in a working memory task. *The International Journal of Neuroscience, 130*(5), 425–434. [DOI:10.1080/00207454.2019.1667787] [PMID]

Lessa, F. C., Enoki, C., Feres, M. F., Valera, F. C., Lima, W. T., & Matsumoto, M. A. (2005). Breathing mode influence in craniofacial development. *Brazilian Journal of Otorhinolaryngology, 71*(2), 156-160. [PMID]

Lin, C. K., & Lin, C. C. (2012). Work of breathing and respiratory drive in obesity. *Respirology (Carlton, Vic.), 17*(3), 402-411. [PMID]

Lundberg, J. O., Settergren, G., Gelinder, S., Lundberg, J. M., Alving, K., & Weitzberg, E. (1996). Inhalation of nasally derived nitric oxide modulates pulmonary function in humans. *Acta Physiologica Scandinavica, 158*(4), 343-347. [DOI:10.1046/j.1365-201X.1996.557321000.x] [PMID]

Lundberg, J. O., Gladwin, M. T., & Weitzberg, E. (2015). Strategies to increase nitric oxide signalling in cardiovascular disease. *Nature Reviews. Drug Discovery, 14*(9), 623–641. [DOI:10.1038/nrd4623] [PMID]

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences of the United States of America, 87*(24), 9868-9872. [DOI:10.1073/pnas.87.24.9868] [PMID] [PMCID]

Park, C. A., & Kang, C. K. (2017). Sensing the effects of mouth breathing by using 3- tesla MRI. *Journal of the Korean Physical Society, 70*(12), 1070-1076. [DOI:10.3938/jkps.70.1070]

Patriat, R., Molloy, E. K., Meier, T. B., Kirk, G. R., Nair, V. A., & Meyerand, M. E., et al. (2013). The effect of resting condition on resting-state fMRI reliability and consistency: A comparison between resting with eyes open, closed, and fixated. *NeuroImage, 78,* 463-473. [DOI:10.1016/j.neuroimage.2013.04.013] [PMID] [PMCID]

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America, 98*(2), 676-682. [PMID] [PMCID]

Sano, M., Sano, S., Oka, N., Yoshino, K., & Kato, T. (2013). Increased oxygen load in the prefrontal cortex from mouth breathing: A vector-based near-infrared spectroscopy study. *Neuroreport, 24*(17), 935-940. [DOI:10.1097/WNR.0000000000000008] [PMID] [PMCID]

van de Ven, V. G., Formisano, E., Prvulovic, D., Roeder, C. H., & Linden, D. E. (2004). Functional connectivity as revealed by spatial independent component analysis of fMRI measurements during rest. *Human Brain Mapping, 22*(3), 165. [DOI:10.1002/hbm.20022] [PMID] [PMCID]

Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connectivity, 2*(3), 125-141. [DOI:10.1089/brain.2012.0073] [PMID]

Wise, R. G., Ide, K., Poulin, M. J., & Tracey, I. (2004). Resting fluctuations in arterial carbon dioxide induce significant low frequency variations in BOLD signal. *NeuroImage, 21*(4), 1652-1664. [PMID]

Wu, X., Yu, X., Yao, L., & Li, R. (2014). Bayesian network analysis revealed the connectivity difference of the default mode network from the resting-state to task-state. *Frontiers in Computational Neuroscience, 8,* 118. [DOI:10.3389/fncom.2014.00118]

Zelano, C., Jiang, H., Zhou, G., Arora, N., Schuele, S., & Rosenow, J., et al. (2016). Nasal respiration entrains human limbic oscillations and modulates cognitive function. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 36*(49), 12448-12467. [PMID] [PMCID]

This Page Intentionally Left Blank