치의학석사학위논문

Investigating the effect on whole brain functional connectivity at different sedation depth induced by nitrous oxide

아산화질소 흡입 진정법의 심도 차이에 따른 의식수준의 변화 분석 및 진정의 기전 연구

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Abstract

Investigating the effect on whole brain functional connectivity at different sedation depth induced by nitrous oxide

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Although functional connectivity has received great attention in consciousness study area, only few studies have investigated functional connectivity limited to sedation state where consciousness is maintained but impaired. The aim of the present study was to investigate the changes in functional connectivity of parietal–frontal network resulting from nitrous oxide induced

sedation state, and determine the neural correlates of cognitive impairment during transition states of consciousness.

Electroencephalography was acquired from healthy adult patients with nitrous oxide inhalation to induce cognitive impairment, and analyzed by using Granger Causality (GC). The periods of awake, sedation and recovery for GC between frontal and parietal areas in delta, theta, alpha, beta, gamma and time-domain frequency band were obtained. Kruskal-Wallis test with post-hoc analysis was conducted for GC values of each period for comparison.

As sedative state was induced by nitrous oxide inhalation, the power in low frequency band showed increased activity in frontal regions, which was reversed with discontinuation of nitrous oxide. The feedback and feedforward connections analyzed in spectral GC were differently changed in accordance with EEG frequency bands in sedative state by nitrous oxide administration. Calculated spectral GC of high frequency region in frontal to parietal direction was significantly decreased in sedative state while the spectral GC in reverse direction did not show significant change.

The frontal-parietal functional connectivity is significantly affected by nitrous oxide inhalation. It is suggested that the

significantly decreased frontal to parietal interaction may induce sedative state which can be described as impaired consciousness in accordance with the same directional decrease of interaction in the loss of consciousness induced by anesthetics.

Keywords : Sedation, Nitrous Oxide, Granger Causality, Consciousness, EEG

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I. Introduction

Nitrous oxide inhalation sedation is widely used because it provides a reversible manipulation, and the sedative effect starts rapidly as well as the effect ceases and recovered quickly. For those reasons plus its non-invasive manner, it is especially favored for both children and handicapped children. However, the precise mechanism that induces sedation during nitrous oxide inhalation is still unclear and under debate. Recently, functional magnetic resonance imaging (fMRI) investigation has been used to reveal relationship of functional connectivity of brains at the certain consciousness and sedation state.[1,2] Inducing alteration of consciousness has been told to have two main ways by suppressing the activity in relevant regions or by altering the brain communication mechanisms.[3] Considering complex nature of consciousness and dispersed brain areas in regulating various functions, the interactions between different brain regions may play critical role in maintaining normal consciousness.

Previously, general anesthetics was used and utilized to induce LOC for finding neural correlates. Among cerebral interactions

postulated to be related to conscious perception, the network between parietal and frontal area have received great attention as a critical neural correlate, especially, corti-cortical interactions play an important role in maintaining consciousness. As subjects under pharmacologically induced anesthesia also suggest the loss of frontal-parietal connectivity,[4] the patients with impaired consciousness would have a disrupted connectivity pattern in frontal-parietal network compared to healthy subjects.[5-7] Therefore, cortical functional connectivity is critical in the range of consciousness.

For investigating the role of the interactions between distant brain areas in conceptual perception, anesthesia has been instrumental in defining the differences of brain interaction between loss of consciousness (LOC) and awake state. Clinically, consciousness is maintained during sedative state, which means it can be regarded as an awake state, yet vulnerable to be lost without certain level of external stimuli in this state. Meanwhile, mild impairment of cognition is not exactly the same as the awake state, but a dynamic stage from the perspective of cognitive perception change. However, there have been few studies investigating changes of functional

connectivity limited to sedation state where consciousness is maintained but impaired. By investigating this sedation state which can be described as the state in between full consciousness and impaired cognitive states, giving information on how connections between different cortical areas are affected during the transition, it may give an insight to reveal neural correlates of consciousness more clearly.

The aim of this study was to investigate changes of the functional connectivity of parietal-frontal network in nitrous oxide induced sedative state by using Granger Causality method, and to determine the neural correlates of cognitive impairment during transitional states of consciousness. The sedative state, that consciousness was impaired but not lost, was induced by nitrous oxide inhalation.

II. Methods

1. Participants (Patient Recruitment)

With the informed consent provided according to the institutional review board approval, 20~40 year-old healthy volunteers, 8 males and 7 females, were studied with 8-channel

electroencephalography (EEG). Before clinical trial, each volunteer fasted for at least 8 hours. Volunteers who had a significant medical disease and laboratory abnormalities were excluded from the study.

2. Sedation Protocol & Data acquisition (Measurement of EEG signal)

We used 8-channel EEG (WEEG-8®, Laxtha Inc., Daejeon, South Korea) with its electrodes placed on the montages (Fp1, Fp2, F3, F4, P3, P4, Cz; A2 electrode for reference) to investigate the effect of nitrous oxide on the brain overall the sedation procedure. The procedure was divided into four consecutive epochs; (i) patients began to close eyes, then five to ten minutes EEG recording with no external stimulus in order to record baseline. [wake up phase] (ii) 30 vol% nitrous oxide inhalation for five minutes with the flow rate of 6.0liter per minute. (iii) 50 vol% nitrous oxide inhalation for five minutes with the same flow rate. [sedative phase] (iv) 100% oxygen inhalation for five minutes [recovery phase]. The nitrous oxide was inhaled by volunteers through facial mask under the control of flowmeter. Also, electrocardiogram and pulse oximetry

(SpO_2) of each volunteer were continuously attached to monitor vital sign during nitrous oxide sedation. The EEG was continuously recorded during the whole phases until the volunteers were transferred to the post-anesthesia care unit. Data were recorded at a sampling rate of 256Hz with a customized software.

3. EEG Data Preprocessing

The data acquired were converted to raw text files by using TeleScan software package (LAXTHA, Daejeon, South Korea), then loaded and analyzed by Matlab R2015a (Math Works Inc., Natick, MA, USA). The certain part of data was analyzed that each set of data consists three-minute spontaneous EEG recording during wake-up, sedation and recovery period from each subject. We selected the position to acquire EEG data manually which had the least artifact by researchers. The 64^{th} order of finite impulse response (FIR) notch filters (59-61 Hz and 199-121Hz) was applied to EEG data to remove the 60Hz power-line noise as well as its harmonics at 120Hz using 'firls' function provided by Matlab. Notch filtering conducted in each EEG signal of frontal and parietal areas was calculated by averaging the EEG signals of brain

areas placed (frontal: FP1, FP2, F3, F4, parietal: Cz, P3, P4). The definition of awake(AW), sedation(SE) and recovery(RE) were defined as the period before nitrous oxide inhalation started, between nitrous oxide inhalation started and ended, and after nitrous oxide inhalation ended to the end of measurement, respectively.

4. Granger Causality Analysis

The Granger Causality in the time and frequency domains, used in analyzing the result, is explained in this section. If there is two weakly stationary time X and Y which means that time series whose observations have constant means and autocorrelation, Granger Causality ($F_{Y\rightarrow X}$) is a measure of interactivity in which X is better able to predict by using available information Y than by only information apart from Y has been used.[8]

In vector autoregressive (VAR) model, stationary signal can be expressed like below:

$$\begin{bmatrix} X(t) \\ Y(t) \end{bmatrix} = \sum_{k=1}^{p} A_k \cdot \begin{bmatrix} X(t-kt_0) \\ Y(t-kt_0) \end{bmatrix} + \begin{bmatrix} E_x(t) \\ E_y(t) \end{bmatrix} \quad (1)$$

$$X(t) = \sum_{k=1}^{p} B_k \cdot X(t - kt_0) + \hat{E}_x(t) \quad (2)$$

where A_k and B_k are 2 by 2 and 1 by 1 matrices if $X(t)$ and $Y(t)$ are one-dimensional signals, p is the order of models, $E_x(t), E_y(t), \hat{E}_x(t)$ are residuals for $X(t)$ with correlated $Y(t)$, $Y(t)$ with correlated $X(t)$ and $X(t)$ with uncorrelated $Y(t)$, respectively.

GC is defined by the log-ratio calculated by dividing the variance of the unrestricted regression (1) by that of the restricted regression (2). The formula is expressed like this:

$$F_{Y \to X} \triangleq ln\left[\frac{var(\hat{E}_x)}{var(E_x)}\right] \quad (3)$$

GC is decomposed by spectral form which could explain about causal influence to particular frequency bands. Spectral GC can be thought of as measuring the proportion of power of X at the given frequency that derives from its interaction with Y.

$\mathrm{A}(\lambda)$ can be defined like below:

$$\mathrm{A}(\lambda) \coloneqq I - \sum_{k=1}^{p} e^{-i \cdot 2\pi \mathrm{f} t_0 k} A_k = \sum_{k=0}^{p} -e^{i\lambda k} A_k \quad (4)$$

where $\lambda = 2\pi \mathrm{f} t_0$ (f: frequency, t_0: *sampling time*).

When equation (4) is applied, unrestricted regression (1) is

changed like this:

$$\mathrm{A}(\lambda) \cdot \begin{bmatrix} X(\lambda) \\ Y(\lambda) \end{bmatrix} = \begin{bmatrix} E_x(\lambda) \\ E_y(\lambda) \end{bmatrix} \tag{5}$$

Let us also introduce the covariance matrix of residuals of the unrestricted regression (1) as

$$\Sigma \triangleq \mathrm{cov}\begin{pmatrix} E_x(t) \\ E_y(t) \end{pmatrix} = \begin{pmatrix} \Sigma_{xx} & \Sigma_{xy} \\ \Sigma_{yx} & \Sigma_{yy} \end{pmatrix} \tag{6}$$

The autocovariance sequence k for a covariance−stationary stochastic process u_t is defined like this:

$$\Gamma_k \triangleq \mathrm{cov}(u_t . u_{t-k}\,)(\mathrm{k} = \cdots, -2. -1. 0, 1, 2, \cdots) \tag{7}$$

For a VAR process (1), the equation (7) could be expressed by VAR parameters used in (1) by the Yule−Walker equations

$$\Gamma_k = \sum_{k=1}^{p} A_k \cdot \Gamma_{k-k} + \delta_{k0} \Sigma \ (\mathrm{k} = \cdots, -2. -1. 0, 1, 2, \cdots) \tag{8}$$

The cross−power spectral density (CPSD) is defined as the Fourier transform of the autocovariance sequence using (8):

$$\mathrm{S}(\lambda) = \sum_{k=-\infty}^{\infty} \Gamma_{k-k} \cdot e^{-ik\lambda} \ (0 \le \lambda \le 2\,\pi\,) \tag{9}$$

For a VAR process, the CPSD admits a unique spectral factorization.

$$S(\lambda) = H(\lambda)\,\Sigma\,H^{*}(\lambda) \tag{10}$$

where the transfer function $H(\lambda)$ is defined as the inverse matrix of the Fourier transform of the regression coefficients:

$$H(\lambda) \triangleq \left(I - \sum_{k=1}^{p} e^{-ik\lambda} A_k \right)^{-1} \quad (0 \le \lambda \le 2\,\pi\,) \tag{11}$$

Then the spectral GC is given by

$$f_{Y\to X}(\lambda) \triangleq ln\left(\frac{S_{xx}(\lambda)}{S_{xx}(\lambda) - H_{xy}(\lambda)\,\Sigma_{y|x} H^{*}_{xy}(\lambda)} \right) \tag{12}$$

where '$*$' denotes complex conjugation and $\Sigma_{y|x} = \Sigma_{yy} - \Sigma_{yx}\Sigma_{xx}^{-1}\Sigma_{xy}$

The 'band-limited' GC for a frequency band $[f_1, f_2]$ is calculate by obtaining the mean spectral GC across the range like this (using $\lambda_1 = 2\pi f_1 t_0, \lambda_2 = 2\pi f_2 t_0$):

$$F_{Y\to X}(f_1, f_2) = \frac{1}{\lambda_2 - \lambda_1} \int_{\lambda_1}^{\lambda_2} f_{Y\to X}(\lambda)\, d\lambda = \frac{1}{f_2 - f_1} \int_{f_1}^{f_2} f_{Y\to X}(f)\, df \tag{13}$$

The total time-domain GC can be calculated by calculating mean of all frequencies:

$$F_{Y\to X} = \frac{1}{f_N} \int_{0}^{f_N} f_{Y\to X}(f)\, df \tag{14}$$

where f_N means Nyquist Frequency.

5. Granger Causality Implementation

To analyze the EEG data acquired from subjects, 90 consecutive epochs were selected in each analysis region of subjects. To avoid nonstationary problems, the data was divided into two-second segments, and removed the average value and applied linear detrend.[9] After the pre-process, the EEG signal in each epoch was renormalized to have mean of zero standard deviation of one.

We chose epoch lengths of 2-second used in studies.[10,11] 90 segments were selected for calculation with no epoch was overlapped. Next, we calculated the best model order as given by the Akaike information criterion (AIC) in each epoch using MVGC Multivariate Granger Causality Toolbox.[12,13] The calculated model order was 25, and we used it to calculate GC value in each subject according to three different levels of consciousness (awake, sedation and recovery), direction and frequency band (delta (0.5-4Hz), theta (4-8 Hz), alpha (8-12Hz), beta (12-25 Hz), gamma (25-40 Hz) and time-domain (0.5-40 Hz)).

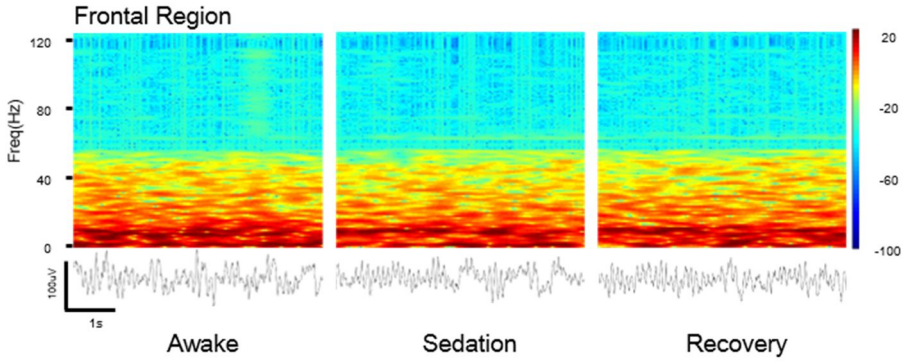
To eliminate bias of GC in each epoch, permutation technique was used.[14] For each case, one thousand random samples of each frontal

and parietal epoch were selected and pairs of frontal and parietal were mixed. After that, GC of each case was acquired in each frequency band. Because the GC of the mixed frontal-parietal is zero by definition of GC, GCs were adjusted by GCs which were calculated by mixed frontal-parietal EEG data.

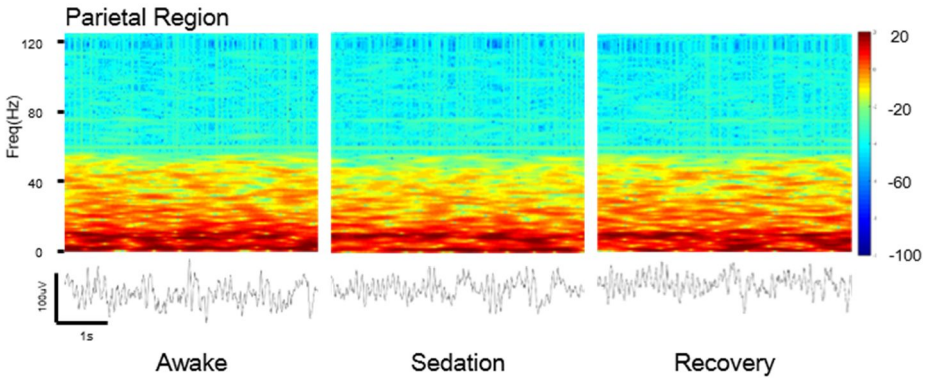
To compare the differences of connectivity at different levels of consciousness, Friedman test followed by post-hoc analysis were performed in each case. A P value less than 0.05 was considered to be statistically significant.

III. Result

As volunteers were sedated with nitrous oxide administration, the power in low frequency band tended to be increased in frontal regions, which was reversed with discontinuation of nitrous oxide. In parietal areas, however, the power at all frequency bands appeared to be significantly changed irrespective of nitrous oxide administration.



A



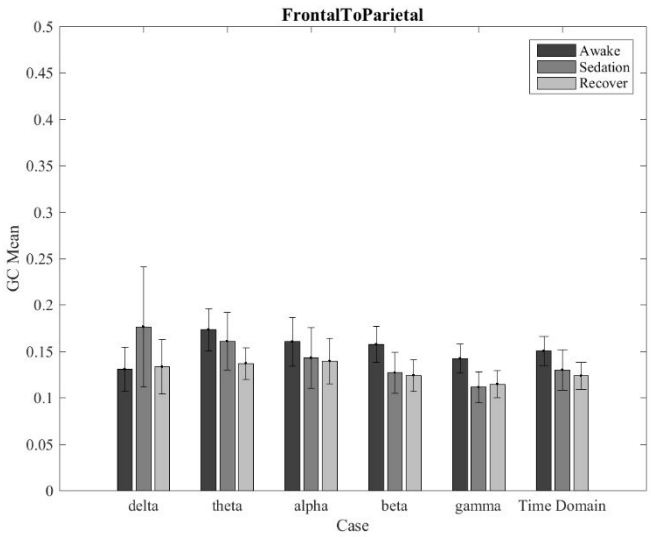
B

Figure 1. The spectorgrams and signal samples show that the overall frequency had been changed during the procedure. A and B are representatives of frontal and parietal region, respectively.

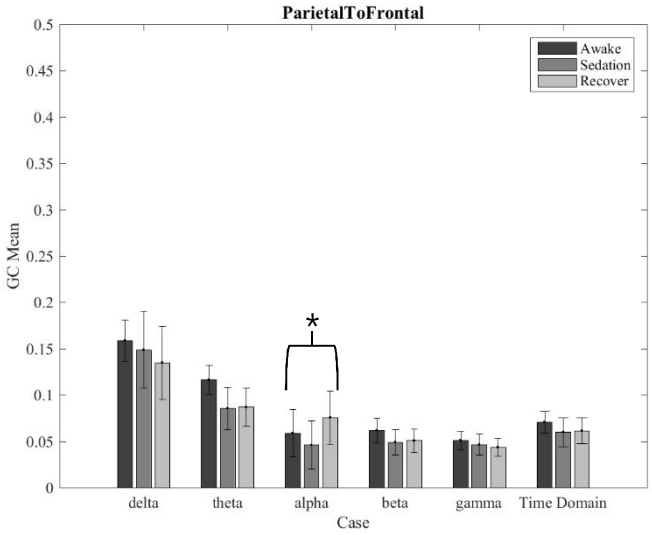
Consciousness requires feedforward and feedback interactions between frontal and parietal cortex.[15,16] GC, statistical analysis

methods for the estimation of the causality between two different time signals, has been widely used to investigate brain interaction between two different brain areas.[17] Especially, spectral GC, a measure of estimating the causality carrying the information of the directions of interactions between two different signals in frequency domain, can be very useful to evaluate brain synchrony between two different brain areas at specific frequency bands. Therefore, to confirm the direction and strength of brain interactions associated with nitrous oxide induced sedation between frontal-parietal area, spectral-GC were calculated and averaged across the subjects in this study. As shown in *Fig. 2*, spectral-GC was changed variously at different sedative levels in the direction from parietal to frontal, and frontal to parietal, respectively. Spectral-GC in the direction from frontal to parietal was not significantly changed during nitrous oxide administration in all frequency bands. Interestingly, sedative states contributed to decrement in spectral GC except at delta frequency band. However, sedative state related changes in parietal to frontal spectral-GC were only significant in alpha band. Decrement of spectral GC at other frequency bands was observed in the direction from parietal to frontal bands although the amount

was statistically insignificant. These results suggest that feedback and feedforward connections were differently changed in accordance with EEG frequency bands in sedative state by nitrous oxide administration.



A



B

Figure 2. Spectral-GC has different values according to the states and direction. **A:** Except for the delta band, spectral-GC decreased gradually through the sedative states in feedback direction. **B:** In feedforward direction, only alpha band showed statistically significant change. * Shows statistically significant changes ($P < 0.05$).

IV. Discussion

Recent studies suspect that frontal-parietal interactions are key aspects in consciousness transition. The GC method was used to analyze interactions between frontal and parietal areas during

nitrous oxide sedation. The result shows that frontal–parietal interactions were differently changed in accordance with the range of frequencies and directions.

There have been a number of methodologies to study interactions between different brain areas.[18–20] Synchrony and correlation are those of traditional methods to identify functional connectivity without or with less about direction which is an important part of analysis. On the other hand, by using GC, deriving directionality information from data is possible and relatively simple that it does not require the constraint of the prior on underlying structural connectivity. However, implementing GC requires delicate interpretation procedures that the GC estimates may reflect substantial biased estimates of values from the violation of the assumption of the original data itself and data preprocessing steps such as band pass filtering. This misinterpretation might lead to a spurious relationship between two unrelated events. To avoid such limitations, a new algorithm to estimated 'unbiased' GC is here described. They subtract the mean of GC estimates after permuting original time series 1000 times from original GC estimates. Unbiased GC estimates reflect more accurate relationship between

two related events when applied to simulated time series data. The present study used unbiased GC estimates with algorithm proposed by *Barnett et al* to investigate the change of functional connectivity between frontal and parietal areas during the sedation phases.

Studies concerning on anesthetic induced unconsciousness proposed that frontal–parietal relationship is one of the key aspects of loss of consciousness. However, the analysis of frontal–parietal interactions in sedative states, which can be described as an impaired consciousness, was not conducted especially in uses of nitrous oxide inhalation. It is important to study the similarities and differences in the brain interactions of frontal–parietal area between impaired consciousness and fully unconsciousness to understand the underlying mechanism of consciousness.

Nitrous oxide administration appears to weaken the strength of connections between frontal and parietal area. However, the communications between frontal to parietal connections and parietal to frontal connections are not related in proportional manner. Large scale frontoparietal network is believed to play a critical role in conscious perception.[21]

In this regards, our finding seems contradictory to the hypothesis

that the frontoparietal network serves to maintain consciousness since the overall connectivity between frontal and parietal regions was not significantly affected during sedation. In accordance with our results, default mode network involving frontoparietal network, known to be activated at wakeful rest state,[22] showed functional connectivity during light sedation similar to that of awake state. Taken together, sedative state may be induced although the overall frontoparietal network is not significantly disrupted.

However, when we narrow and directly compare functional connectivity at different frequency bands according to consciousness level, there was a significant difference of functional connectivity at alpha band. In consistent with our finding, functional connectivity in the posterior cingulate cortex was significantly reduced during light sedation.[23] Alpha power substantially decreases when nitrous oxide was administered during sevoflurane anesthesia.[24] Alpha rhythm in the posterior brain regions disappears and emerges in the frontal area, called as anteriorization, during the transition of anesthesia by propofol.[25] This anteriorization is understood as the disruption of thalamic nuclei projecting to the posterior cerebral cortex by anesthetic agents. Thalamocortical

connections are believed to be critical in maintaining consciousness.[26] This synchronization is phase locked at the alpha frequency range (8–12Hz).[27] Interestingly, nitrous oxide at high concentration suppresses the excitation of the thalamic relay nucleus induced by peripheral nociceptive inputs.[28] Taken together, it can be speculated that nitrous oxide disrupts the excitability of posterior thalamic nuclei and suppresses the parietal regions, which is phase locked at alpha frequency range to the thalamus.

The feedforward interaction was significantly decreased in alpha frequency band while the feedback interaction did not show significant changes in the sedative state. Since the synchronization of interactions of each brain area is the key for maintaining consciousness,[29] this disruption of frontal–parietal connectivity balance can lead such impaired consciousness. In previous studies of frontal–parietal brain interactions during general anesthesia, decreased feedback connectivity has been associated with loss of consciousness.[30] Contrary to previous finding, although nitrous oxide also decreases feedback connectivity at most frequency ranges, the decrement was not significant. Instead, feedforward connectivity was decreased especially at alpha frequency band

during nitrous oxide administration. Thus, it can be assumed that nitrous oxide impairs consciousness in a different way which other general anesthetics exert. It remains unclear whether the strength of connectivity in the direction from parietal to frontal area is significantly affected during nitrous oxide administration. It may be thought that nitrous oxide selectively disrupts the information projecting from the thalamus to the parietal area compared to the frontal area although a further study should explore to address the exact sedation mechanism.

Although statistically insignificant, we have found that increased synchronization between the frontal and parietal regions was only observed at delta band in the direction from frontal to parietal area. Meanwhile, this increment was not observed at delta band in the reverse direction. Nitrous oxide at high concentration (> 50%) induces delta oscillation, presumably by blocking excitatory inputs from the brainstem to the cortex. A slow–delta power was substantially increased and delta oscillation was also induced at the transition to nitrous oxide during sevoflurane anesthesia.[24] It is unclear how delta oscillation during nitrous oxide administration can be linked to impaired consciousness. Previous studies have shown

that synchronization between frontal and parietal cortical area in delta frequency range plays a critical role in decision making.[31] The executive frontal area and the sensory processing area located in the parietal area is phase locked at delta frequency range, integrating information during attention and decision making task.[32] Increased delta oscillation during nitrous oxide administration seems to contradict with the findings in previous studies.[33] This may be explained by compensatory synchronization increment from the executive regions toward parietal area with less activated during sedative state considering that brain interactions are reciprocally regulated, although this should be investigated in a future research.[34]

However, there is some limitation in this study. Subjects were inhaled nitrous oxide at a fixed concentration. Since the effect of nitrous oxide varies across the subjects, there may be individual variations in the strength of frontoparietal network during nitrous oxide administration, which may confound the results. However, bispectral index (BIS) value remained above 80 for all subjects during the experiment although there were slight differences in response to verbal command during the administration of nitrous

oxide, indicating that all subjects were subject to conscious sedative state during the experiment.

V. Conclusion

In summary, frontoparietal network is affected by nitrous oxide inhalation although the overall effect is not significant. These results suggest that sedative state induced by nitrous oxide is related to the disruption of frontoparietal network in a similar way that anesthetics induce LOC.

References

1. Martuzzi R, Ramani R, Qiu M, Rajeevan N, Constable RT: Functional connectivity and alterations in baseline brain state in humans. NeuroImage 2010; 49: 823-834

2. Greicius MD, Kiviniemi V, Tervonen O, Vainionpää V, Alahuhta S, Reiss AL, Menon V: Persistent default-mode network connectivity during light sedation. Human Brain Mapping 2008; 29: 839-847

3. Brown EN, Lydic R, Schiff ND: General Anesthesia, Sleep, and Coma. New England Journal of Medicine 2010; 363: 2638-2650

4. Lee U, Ku S, Noh G, Baek S, Choi B, Mashour GA: Disruption of Frontal–Parietal Communication by Ketamine, Propofol, and Sevoflurane. The Journal of the American Society of Anesthesiologists 2013; 118: 1264-1275

5. Boly M, Tshibanda L, Vanhaudenhuyse A, Noirhomme Q, Schnakers C, Ledoux D, Boveroux P, Garweg C, Lambermont B, Phillips C, Luxen A, Moonen G, Bassetti C, Maquet P, Laureys S: Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient.

Human Brain Mapping 2009; 30: 2393-2400

6. Cauda F, Micon BM, Sacco K, Duca S, D' Agata F, Geminiani G, Canavero S: Disrupted intrinsic functional connectivity in the vegetative state. Journal of Neurology, Neurosurgery & Psychiatry 2009; 80: 429-431
7. Soddu A, Vanhaudenhuyse A, Bahri MA, Bruno M-A, Boly M, Demertzi A, Tshibanda J-F, Phillips C, Stanziano M, Ovadia-Caro S, Nir Y, Maquet P, Papa M, Malach R, Laureys S, Noirhomme Q: Identifying the default-mode component in spatial IC analyses of patients with disorders of consciousness. Human Brain Mapping 2012; 33: 778-796
8. Granger CWJ: Investigating Causal Relations by Econometric Models and Cross-spectral Methods. Econometrica 1969; 37: 424-438
9. Hesse W, Möller E, Arnold M, Schack B: The use of time-variant EEG Granger causality for inspecting directed interdependencies of neural assemblies. Journal of neuroscience methods 2003; 124: 27-44
10. Barrett AB, Murphy M, Bruno M-A, Noirhomme Q, Boly M,

Laureys S, Seth AK: Granger causality analysis of steady-state electroencephalographic signals during propofol-induced anaesthesia. PloS one 2012; 7: e29072-e29072

11. Olbrich E, Achermann P, Meier PF: Dynamics of human sleep EEG. Neurocomputing 2003; 52-54: 857-862
12. Barnett L, Seth AK: The MVGC multivariate Granger causality toolbox: A new approach to Granger-causal inference. Journal of Neuroscience Methods 2014; 223: 50-68
13. Akaike H: A new look at the statistical model identification. Automatic Control, IEEE Transactions on 1974; 19: 716-723
14. Karniski W, Blair RC, Snider AD: An exact statistical method for comparing topographic maps, with any number of subjects and electrodes. Brain Topography 1994; 6: 203-210
15. Kusse C, Shaffii-Le Bourdiec A, Schrouff J, Matarazzo L, Maquet P: Experience-dependent induction of hypnagogic images during daytime naps: a combined behavioural and EEG study. Journal of Sleep Research 2012; 21: 10-20
16. Dehaene S, Changeux J-P: Experimental and theoretical approaches to conscious processing. Neuron 2011; 70: 200-227
17. Chen Y, Bressler SL, Ding M: Frequency decomposition of

conditional Granger causality and application to multivariate neural field potential data. Journal of Neuroscience Methods 2006; 150: 228-237

18. Bullmore E, Sporns O: Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci 2009; 10: 186-198

19. Groß J, Kujala J, Hämäläinen M, Timmermann L, Schnitzler A, Salmelin R: Dynamic imaging of coherent sources: studying neural interactions in the human brain. Proceedings of the National Academy of Sciences 2001; 98: 694-699

20. Liao W, Ding J, Marinazzo D, Xu Q, Wang Z, Yuan C, Zhang Z, Lu G, Chen H: Small-world directed networks in the human brain: multivariate Granger causality analysis of resting-state fMRI. Neuroimage 2011; 54: 2683-2694

21. Markus S, Tobias HD, Andreas KE: Spectral fingerprints of large-scale neuronal interactions. Nature Reviews Neuroscience 2012: 13; 121-134

22. Philipp GS, Renate W, David H, Victor IS, Henning P, Carolin T, Florian H, Michael C: Development of the Brain's Default Mode

Network from Wakefulness to Slow Wave Sleep. Cerebral Cortex 2011: 21; 2082-2093

23. Greicius MD, Kiviniemi V, Tervonen O, Vainionpää V, Alahuhta S, Reiss AL, Menon V: Persistent default-mode network connectivity during light sedation. Human brain mapping 2008; 29: 839-847

24. Pavone KJ, Akeju O, Sampson AL, Ling K, Purdon PL, Brown EN: Nitrous oxide-induced slow and delta oscillations. Clinical Neurophysiology 2015; 127: 556-564

25. Vijayan S, Ching S, Purdon PL, Brown EN, Kopell NJ: Thalamocortical Mechanisms for the Anteriorization of Alpha Rhythms during Propofol-Induced Unconsciousness. The Journal of Neuroscience 2013; 33: 11070-11075

26. Laureys S, Faymonville ME, Luxen A, Lamy M, Franck G, Maquet P: Restoration of thalamocortical connectivity after recovery from persistent vegetative state. The Lancet 2000; 355: 1790-1791

27. Satu P, Matias P: New vistas for α-frequency band oscillations. Trends in Neurosciences 2007; 30: 150-158

28. Kawamoto T, Shingu K, Mori K: Effects of nitrous oxide on the somatosensory evoked response in cats. Journal of anesthesia 1990; 4: 51-60

29. Sheeba JH, Stefanovska A, McClintock PVE: Neuronal Synchrony during Anesthesia: A Thalamocortical Model. Biophysical Journal 2008; 95: 2722-2727

30. Lee U, Kim S, Noh G, Choi B, Hwang E, Mashour GA: The directionality and functional organization of frontoparietal connectivity during consciousness and anesthesia in humans. Consciousness and Cognition 2009; 18: 1069-1078

31. Náchera V, Ledberg A, Deco G, Romo R, Coherent delta-band oscillations between cortical areas correlate with decision making. Proceedings of the National Academy of Sciences. 2013; 110: 15085-15090

32. Jacobs J, Kahana MJ, Ekstrom AD, Fried I: Brain Oscillations Control Timing of Single-Neuron Activity in Humans. The Journal of Neuroscience 2007; 27: 3839-3844

33. Schacka B, Witte H, Helbig M, Schelenzc C, Specht M: Time-variant non-linear phase-coupling analysis of EEG burst

patterns in sedated patients during electroencephalic burst suppression period. Clinical Neurophysiology 2001; 112: 1388-1399

34. Lewis MD, Todd RM: The self-regulating brain: Cortical-subcortical feedback and the development of intelligent action. Cognitive Development 2007; 22: 406-430

국문초록

아산화질소 흡입 진정법의 심도 차이에 따른 의식수준의 변화 분석 및 진정의 기전 연구

Investigating the effect on whole brain functional connectivity at different sedation depth induced by nitrous oxide

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의식 영역의 연구에 있어서 뇌의 각 부분의 기능적 연결성이 큰 관심을 받아왔으나 의식이 존재하지만 손상된 상태의 의식에 관한 기능적 연결에 관한 연구는 알려진 바가 드물다. 이 연구의 목적은 아산화질소의 흡입에 의해 유도되는 진정상태에서 뇌의 전두-측두 네트워크에서 변화하는 기능적 상호작용을 분석하고, 의식의 변화

과정과 의식의 손상 상태에 있어서 신경적 상관관계성을 알아보고자 한다.

건강한 성인에서 아산화질소의 흡입으로 손상된 의식 상태가 유도되었고 뇌파를 기록하였다. 수집된 뇌파 데이터는 방향성을 가지는 Granger Causality (GC) 방법을 통해 계산되었다. 각성, 진정, 회복상태에서 전두와 측두의 방향성을 가지는 델타, 세타, 알파, 베타, 감마 뇌파의 GC 값이 계산되었으며, Kruskal-Wallis 테스트와 사후검정 방법을 통해 각 상태에서의 GC 값을 비교하였다.

아산화질소의 흡입에 의한 진정상태에서 전두 영역의 저주파수 밴드의 강도가 증가하였으며, 반대로 아산화질소의 중단으로 강도가 다시 회복되는 것을 관찰할 수 있었다. GC 로 계산된 진정상태에서의 전두-측두의 양성되먹임과 음성되먹임 뇌파 상호작용이 아산화질소의 흡입에 따라 변화하는 것을 보였으며, 전두에서 측두로 가는 고주파수 영역의 GC 값은 델타 뇌파를 제외하고 유의미하게 감소하지만, 측두에서 전두 방향의 GC 값은 알파 뇌파의 유의미한 감소 및 증가 추세를 제외하고는 유의미한 방향성과 변화를 가지지 않았다. 종합적으로, 아산화질소의 흡입에 따라 전두-측두 기능적 연결성의 유의미한 변화가 관찰되었다. 전두에서 측두로 가는 상호작용의 유의미한 감소가 손상된 의식으로 표현할 수 있는 진정 상태를 유도하는 것으로 생각되며, 이는

전신마취에서의 전두 측두 방향의 상호작용 감소에 의한 의식 소실과 유사한 방향성을 가진다.

주요어 : Sedation, Nitrous Oxide, Granger Causality, Consciousness, EEG
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