ORIGINAL ARTICLE
https://doi.org/10.30773/pi.2019.0331
Print ISSN 1738-3684 / On-line ISSN 1976-3026
OPEN ACCESS

The Role of Insular Cortex in Response to Group Therapy in Vaginismus Patients: Magnetic Resonance Spectroscopy Study

Mehmet Fatih Erbay[1] ✉ and Esra Porgalı Zayman[2]

[1]Department of Radiology, Inonu University School of Medicine, Malatya,Turkey
[2]Department of Psychiatry, Inonu University School of Medicine, Malatya,Turkey

Objective Disgust has been propounded as a potential etiological factor in certain sexual dysfunctions such as vaginismus. Studies reports that insular cortex is activated as a response to disgust. The present study aimed to investigate the predictive role of metabolites in insular cortex in response to group therapy among vaginismus patients.

Methods Study sample consisted of 51 vaginismus patients attended an ambulatory group therapy, of whom 26 benefited from 8-week group therapy and 25 were unresponsive to group therapy. All of the patients underwent H magnetic resonance spectroscopy (H-MRS), and insular cortex N-acetyl aspartate (NAA), Creatinine (Cr), Glutamine (Gln), Glutathione (GSH), Choline (Cho), Myo-inositol (mIns), Glutamate (Glu) and Lactate (Lac) concentrations were compared between the groups.

Results Comparing insular cortex metabolite concentrations between the groups, Cho was statistically significantly higher (p=0.005) but mIns was significantly lower (p=0.001) in the unresponsive to group therapy group.

Conclusion MR spectroscopy findings of the present study indicated significant metabolic changes such as increased Cho/Cr ratio and decreased mIns/Cr ratio in the insular cortex of vaginismus patients who were unresponsive to group therapy. Our results support the studies suggesting that disgust is an important emotion in vaginismus patients and also that insula plays a role in the neurobiology of disgust.

Psychiatry Investig 2020;17(6):608-612

Key Words Vaginismus, Insular cortex, Responsive to group therapy, Magnetic resonance spectroscopy.

INTRODUCTION

Vaginismus is a condition causing vaginal examination to be almost impossible due to the spasm of 1/3 of the vagina.[1] It is usually classified under the name of sexual pain disorders. Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) defines vaginismus as failure of vaginal penetration and significant fear or anxiety felt while waiting for penetration or during penetration.[2]

Recently, disgust has been propounded as a potential etiological factor in certain sexual dysfunctions such as vaginismus.[3] It is thought that disgust occurs as the first zone of defense to protect human against contamination by contagious agents.[4] A theorem asserted based on this opinion links unintentional contraction of pelvic floor muscles in vaginismus to the perception of sexual intercourse as a potential contaminator.[5] The points that need particular emphasize during treatment of vaginismus can be listed as follows; fear of penetration, phobic avoidance, disgust, and anticipatory anxiety. Among these components, disgust in particular is thought as a factor that makes treatment difficult.[1]

In the literature, disgust has been studied rather in specific phobia,[6] obsessive compulsive disorder (OCD),[7] and posttraumatic stress disorder (PTSD).[8] Its neurobiology has been investigated especially in OCD patients dwelling on the role of insular cortex.[9] A functional imaging study reported that insular cortex is activated as a response to disgust in both healthy participants and OCD patients.[10,11] Considering that disgust is a factor that makes treatment difficult, it can be thought that metabolic disorder of the insular cortex may be important role at response to group therapy in vaginismus patients.

H-magnetic resonance spectroscopy (H-MRS) is a noninvasive method for in-vivo detection of endogenous tissue metabolites. When it is applied at 3 Tesla to the human brain, it

Received: December 13, 2019 **Revised:** March 4, 2020
Accepted: April 5, 2020

✉ **Correspondence:** Mehmet Fatih Erbay, MD
Department of Radiology, Inonu University School of Medicine, 44280, Malatya, Turkey
Tel: +90 422 3410660-5710, **Fax:** +90 422 341 07 87
E-mail: drfatiherbay@hotmail.com

allows estimation of neurobiological structure of the brain at that moment based on the concentrations of 17 different neurochemical substances.[12] For this reason, we as well aimed to compare N-acetyl aspartate (NAA), Creatinine (Cr), Glutamine (Gln), Glutathione (GSH), Choline (Cho), Myo-inositol (mIns), Glutamate (Glu) and Lactate (Lac) concentrations measured in the insular cortex by HMRS between benefited from group therapy and unresponsive to group therapy.

METHODS

For the mean insular cortex metabolite change determined by MRS to be 6.5 units in the vaginismus patients, at least 23 patients was required to be enrolled into each group by taking α as 0.05 and 1-β (power) as 0.80 in the power analysis. Patients were selected among the subjects who have been diagnosed with vaginismus based on DSM-5 diagnostic criteria on an interview performed by a psychiatrists using SCID and who had participated in a sexual therapy program moderated by a trained psychiatrist. Twenty-six patients that have benefited from 8-week therapy and 25 patients with failed sexual penetration after 8-week group therapy, who were considered as the unresponsive to group therapy group, were enrolled into the study. Golombok Rust sexual satisfaction scale female version was applied to each patient before and after therapy. Response to treatment was determined as sexual penetration formation and a decrease in vaginismus subscale scale scores. HMRS was planned in the patients who had no history of medication in the last 3 months, were not smokers and have given informed written consent. All of the patients completed HMRS scanning, and none of the patients were excluded. All of the patients and the controls underwent detailed examination and clinical evaluation to exclude any neurological or psychiatric comorbidity. Patients with clinically significant major depressive disorder, bipolar disorder and/or psychotic disorder, history of clinically significant personality disorder, substance abuse or addiction, history of seizure or any other neurological disorder, closed head trauma together with loss of conscious, and mental retardation were excluded.

Study protocol was approved by the local Ethics Committee of Inonu University School of Medicine (protocol no: 2019/115). The study was performed in accordance with the principals of "Helsinki Declaration of Human Rights-2013" as well as "Good Clinical Practice." The study was financially supported by Inonu University Research Projects Unit with the project no 2019-1855.

1H-MRS neuroimaging procedures

All patients underwent MRS imaging at the Inonu University School of Medicine, Radiology Department on a 3T MR device (Magnetom Skyra-Siemens, Erlangen, Germany) using of a 20-channel phase array head coil. To determine voxel localisation and exclude parenchymal lesions, T1-weighted sagittal three-dimensional magnetisation-prepared rapid-acquisition gradient echo and T2-weighted fluid-attenuated inversion recovery axial-sagittal images were obtained, respectively (TR: 2,300 ms; TE: 2.98 ms; slice thickness: 1 mm; FOV 256 mm; matrix size: 240×256). After ruling out pathological lesions on the T2 sequence, thin slice images (1 mm) at three orthogonal planes (sagittal, axial and coronal) were obtained by multiplanar reconstruction. We placed a single 13×10×7 mm volume of interest in left insular cortex (Figure 1). We made manual shimming to enhance local magnetic homogeneity in the voxel. Subsequently, single voxel spectroscopy-short echo spectroscopic imaging was performed using a point-resolved spectroscopy sequence (TR: 20,00 ms, TE: 30 ms). After the imaging procedure, the spectroscopic data sets were transferred to a work station, and peak metabolite ratios were calculated automatically using software (Syngo.via, SiemensHealthineers, Erlangen, Germany). The integral values of the metabolites were proportionate to that of Cr, which was used as the reference metabolite.[13]

Statistical analysis

Statistical analyses were performed using the Statistical Program for Social Sciences for Windows, version 17.0, software (SPSS Inc., Chicago, IL, USA). Normality of the data distribution was assessed using the Shapiro-Wilk test. The data were summarized with median, minimum and maximum values and Mann Whitney U test was used for comparison because data not following a normal distribution. Categorical variables were indicated by number and percentage. Pearson exact test was used in the comparisons. A p-value <0.05 was considered significant.

RESULTS

The study comprised 25 unresponsive to group therapy vaginismus patients and 26 patients benefit to the group therapy. The median age of the groups was 27 (19−45) years and 28 (22−41) years, respectively; there was no statistically significant difference between the groups (p=0.125). However, significant difference was determined between the groups in terms of education level (p=0.018). Of the unresponsive to group therapy group, 20% was secondary school graduate, 40% was high school graduate and 40% was college graduate; whereas 30.8% of treatment responders were high school graduates and 69.2% were college graduates.

In the group that responded to group therapy, the Golombok Rust sexual satisfaction scale vaginismus subscale score

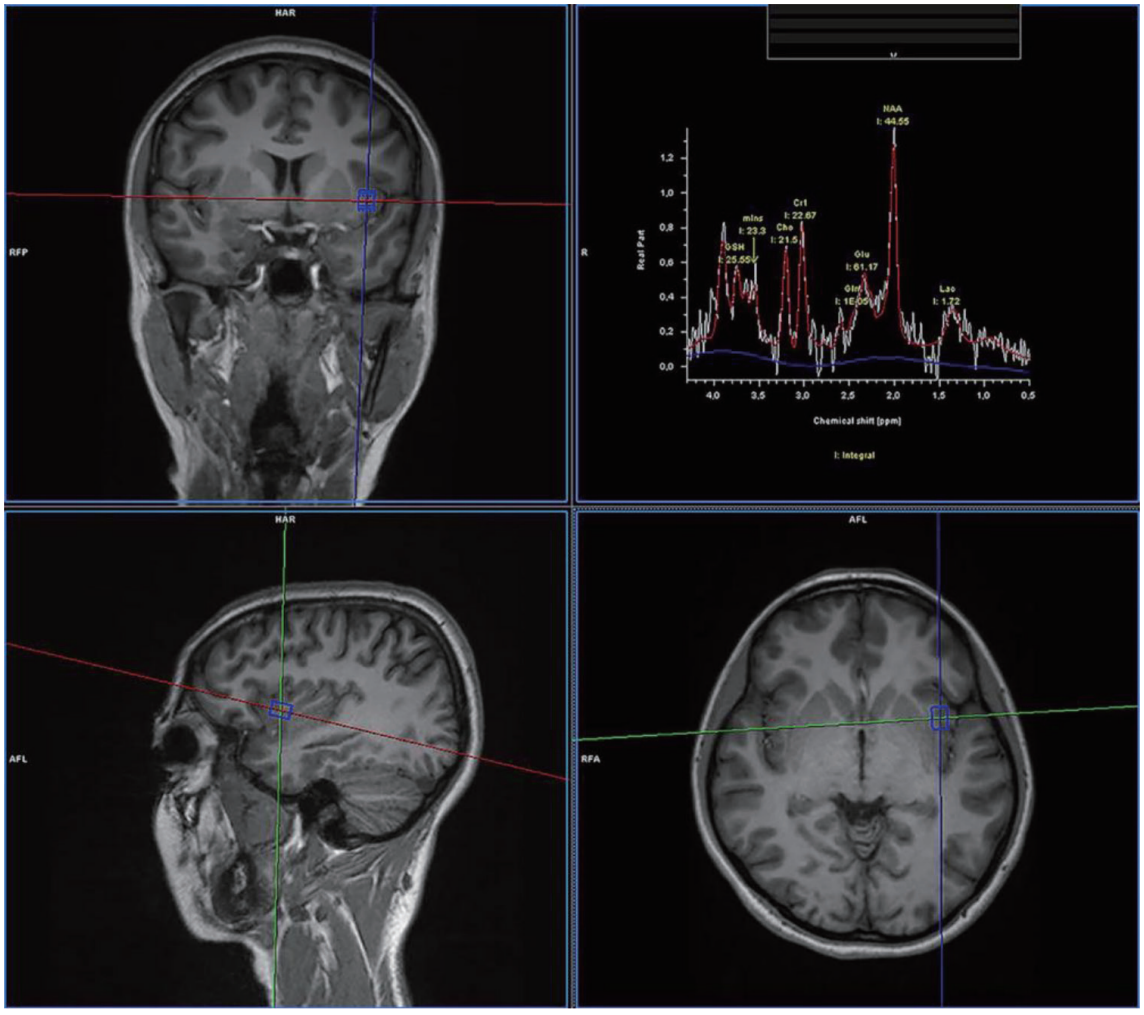

Figure 1. Voxel placing in left insula in 3 orthogonal planes and MR spectra. MR: magnetic resonance.

was 6.08±3.15 at before therapy, 3.52±2.97 at after therapy. The difference between them was statistically significant (p=0.0001). In the group that did not respond to group therapy, Golombok Rust sexual satisfaction scale vaginismus subscale score of 6.18±3.12 at before therapy, was 5.89±2.56 at after therapy. The difference between them was not statistically significant (p=0.77). There was no difference between the two groups in terms of pre-therapy scale scores (p=1.00).

Comparing insular cortex metabolite concentrations between the groups, it was observed that Cho concentration was statistically significantly higher but mIns concentration was statistically significantly lower in the unresponsive to group therapy group (p=0.005 and p=0.001, respectively) (Table 1).

DISCUSSION

To our knowledge, the present study is the first study comparing insular cortex metabolite concentrations between unresponsive to group therapy and benefit to the group therapy vaginismus patients. Our results indicate high Cho and low mIns concentrations in the insula of the unresponsive to group therapy vaginismus patients.

Being considered as an important factor in the development of various mental disorders, disgust has attracted the investigators' attention. In one of these studies, increased hemodynamic responses were detected in the anterior insula and putamen via functional MR imaging along with the presentation of the pictures of facial expressions of disgust.[14] Insular activation was observed also during stimulation with bad odor. Earlier studies indicate the importance of basal ganglia and insula for the emotion of disgust.[15] Survey studies, exposure studies and neurobiological experiments provide evidences that disgust is a core feeling in OCD, certain phobia (blood and injection phobia, spider phobia) and eating disorders.[16]

Disgust may cause sexual problems by preventing sexual arousal and by motivating avoidance of sexual intercourse. Earlier studies demonstrated that women with vaginismus show tendency to feel extreme disgust against sexual stimulators.[17]

Table 1. Comparison of brain metabolite ratios measured in insular cortex between groups

	Unresponse to group therapy group (N=25)			Responsive to group therapy group (N=26)			p value
	Median	Minimum	Maximum	Median	Minimum	Maximum	
Age	27.00	19.00	45.00	28.00	22.00	41.00	0.125
NAA/Cr	1.76	1.49	2.67	1.73	1.16	3.20	0.610
Cho/Cr	1.16	0.86	1.59	0.98	0.63	1.43	0.005
mIns/Cr	1.09	0.18	1.70	1.49	0.66	3.50	0.001
Lac/Cr	0.23	0.00	0.71	0.22	0.00	1.08	0.532
Glu/Cr	2.64	1.29	4.52	2.94	0.98	4.76	0.132
Gln/Cr	0.16	0.00	2.59	0.00	0.00	1.24	0.058
GSH/Cr	1.02	0.09	1.73	0.96	0.57	2.11	0.836

N: number of samples, NAA: N-asetyl aspartate, Cho: choline, Cr: creatine, Lac: lactate, mIns: myoinositol, Glu: glutamate, GSH: glutathione, Gln: glutamine

There are numerous studies verifying the opinion that the difficulty women experience with vaginal penetration during vaginismus occurs partially because of disgust.[18]

The opinion whether disgust makes the treatment difficult is debatable. The fact that some patients do not show improvement even they have completed the group therapy sessions while some patients showing improvement in the first sessions of group therapy could be attributed to various factors, one of which is disgust.[1]

An important outcome of the present study is impaired insular cortex metabolism observed in the unresponsive to group therapy patients. Because of documented relationship between this region and disgust, this can be considered responsible for unresponsive to group therapy in the patients. This result is consistent with both the studies stating that disgust is an important feeling in vaginismus patients and the studies suggesting that insula plays a role in the neurobiology of disgust.[9,18]

Another important point is the fact that impairment in insula was detected in Cho and mIns metabolites. Cho is required for the synthesis and secretion of acetylcholine,[19,20] which is a critical neurotransmitter that mediates memory storage. Cho has significant effect on the developing brain, thus any Cho disorder is potentially devastating.[21] It has been suggested that high Cho concentrations indicate increased cell transformation.[22] Several MRS studies performed on anxiety patients report elevated Cho levels in some regions of the brain. The authors attributed this to the changes in myelination or signal conduction.[23] This is consistent with the results of the present study. High Cho levels in the insula indicates impaired metabolism of this region in treatment-resistant vaginismus patients as well as this region's causing unresponsive to group therapy by playing a role in higher commitment of fear and anxiety to memory.

mIns is the biologically most active stereoisomer of the cerebral inositol. Intracellular phosphatidyl inositol, which is bond to various neurotransmitters such as serotonin, dopamine and glutamate and accordingly changes the concentrations of various neurotransmitters in the brain including serotonin, is the component of second messaging system.[24] A study investigating postmortem depression patients found low mlnsconcentrations.[25] Mlns has not been studied enough in anxiety disorders or in other psychiatric disorders. Although it is difficult to establish a causal relationship between vaginismus and mlns and/or unresponsive to group therapy based on the outcomes of the present study, it can be considered as its neurobiological reflection. However, whether or not the outcomes are incidental needs to be verified in repeated and longitudinal studies to establish a causal relationship.

A significant feature that makes the study outcomes powerful is the exclusion of psychiatric comorbidity, which might influence the results. Nevertheless, the study has some limitations as well. First is the small sample size of the study group. Second, only the insular cortex was investigated excluding the other regions. Third, the outcomes do not reflect a causal relationship because of the cross-sectional design of the study.

In addition, the education levels of the group that responded to group therapy were higher. This may have led to more adaptation to therapy and a greater understanding of cognitive expressions. This can be a confounding factor in interpreting the results. Comparisons between cases in which education levels are equal will enable more accurate interpretation of the results.

In conclusion, the results of this MRS study revealed the existence of metabolic changes in the insular cortex of vaginismus patients who were unresponsive to group therapy. These changes may lead to better understanding of physiopathological mechanisms of unresponsiveness in the vaginismus patients who do not benefit from group therapy. The reproducibility of our results would be possible with further investigations with respect to this subject. Our preliminary findings are not sufficient to establish a causal relationship between vaginismus, disgust and insular cortex. However, we think that our results are of importance as the first study providing information about

the chemical microstructure of insular cortex by MRS method and that might be focus of interest for further investigations regarding this issue.

Acknowledgments

This project was supported by the Inonu University Scientific Research Projects Unit (project ID: 1855; project code: TSA-2019-1855).

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: all authors. Data curation: Esra Porgalı Zayman. Formal analysis: Mehmet Fatih Erbay. Investigation: Mehmet Fatih Erbay. Methodology: Esra Porgalı Zayman. Project administration: Esra Porgalı Zayman. Resources: Mehmet Fatih Erbay. Software: Mehmet Fatih Erbay. Supervision: Esra Porgalı Zayman. Validation: Mehmet Fatih Erbay. Visualization: Mehmet Fatih Erbay. Writing—original draft: Mehmet Fatih Erbay. Writing—review & editing: Mehmet Fatih Erbay.

ORCID iDs

Mehmet Fatih Erbay https://orcid.org/0000-0002-1596-3147
Esra Porgalı Zayman https://orcid.org/0000-0003-1551-6782

REFERENCES

1. Kadir ZS, Sidi H, Kumar J, Das S, Midin M, Baharuddin N. The neurobiology and psychiatric perspective of vaginismus: linking the pharmacological and psycho-social interventions. Curr Drug Targets 2018;19:916-926.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington D.C: American Psychiatric Publication; 2013.
3. Tybur JM, Lieberman D, Kurzban R, DeScioli P. Disgust: evolved function and structure. Psychol Rev 2013;120:65-84.
4. Curtis V, de Barra M, Aunger R. Disgust as an adaptive system for disease avoidance behavior. Philos Trans R Soc B 2011;366:389-401.
5. deJong PJ, vanLankveld J, Elgersma HJ, Borg C. Disgust and sexual problems-theoretical conceptualization and case illustrations. Int J Cogn Ther 2010;3:23-39.
6. Bianchi K, Carter M. An experimental analysis of disgust sensitivity and fear of contagion in spider and blood injury phobia. J Anxiety Disord 2012;26:753-776.
7. Olatunji BO, Lohr JM, Sawchuk CN, Tolin DF. Multimodal assessment of disgust in contamination-related obsessive-compulsive disorder. Behav Res Ther 2007;45:263-276.
8. Engelhard IM, Olatunji BO, de Jong PJ. Disgust and the development of posttraumatic stres among soldiers deployed to Afghanistan. J Anxiety Disord 2011;25:58-63.
9. Viol K, Aas B, Kastinger A, Kronbichler M, Schöller HJ, Reiter EM, et al. Erroneously disgusted: Fmrı study supports disgust-related neural reuse in obsessive-compulsive disorder (OCD). Front Behav Neurosci 2019;24;13:81.
10. Knowles KA, Jessup SC, Olatunji BO. Disgust in anxiety and obsessive-compulsive disorders: recent findings and future directions. Curr Psychiatry Rep 2018;20:68.
11. Oaten M, Stevenson RJ, Williams MA, Rich AN, Butko M, Case TI. Moral violations and the experience of disgust and anger. Front Behav Neurosci 2018;12:179.
12. Tkac I, Öz G, Adriany G, Uğurbil K, Gruetter R. Invivo 1H NMR spectroscopy of the human brain at high magnetic fields: metabolite quantification at 4T vs. 7T. Mag Reson Med 2009;62:868-879.
13. Angelie E, Bonmartin A, Boudraa A, Gonnaud PR, Mallet JJ, Sappey-Mariner D. Regional differences and metabolic changes in normal aging of the human brain: proton MR spectroscopic imaging study. AJNR Am J Neuroradiol 2001;22:119-127.
14. Phillips ML, Young AW, Senior C, Brammer M, Andrews C, Calder AJ, et al. A specific neural substrate for perceiving facial expressions of disgust. Nature 1997;389:495-498.
15. Vaitl D, Schienle A, Stark R. Neurobiology of fear and disgust. Int J Psychophysiol 2005;57:1-4.
16. Schienle A, Walter B, Stark R, Vaitl D. A questionnaire for the assessment of disgust sensitivity. Clin Psychol Psychother 2002;31:110-120.
17. Borg C, de Jong PJ, Schultz WW. Vaginismus and dyspareunia: automatic vs. deliberate disgust responsivity. J Sex Med 2010;7:2149-2157.
18. vanOverveld M, de Jong PJ, Peters ML, vanLankveld J, Melles R, ter Kuile MM. The Sexual Disgust Questionnaire; a psychometric study and a first exploration in patients with sexual dysfunctions. J Sex Med 2013;10:396-407.
19. Zeisel SH. The fetal origins of memory: the role of dietary choline in optimal brain development. J Pediatr 2006;149:131-136.
20. Zeisel SH, da Costa KA. Choline: an essential nutrient for public health. Nutr Rev 2009;67:615-623.
21. Murata T, Kimura H, Kado H, Omori M, Onizuka J, Takahashi T, et al. Neuronal damage in the interval form of CO poisoning determined by serial diffusion weighted magnetic resonance imaging plus 1H-magnetic resonance spectroscopy. J Neurol Neurosurg Psychiatry 2001;71:250-253.
22. Ende G, Braus DF, Walter S, Weber-Fahr W, Henn FA. The hippocampus in patient streated with electroconvulsive therapy: a proton magnetic resonance spectroscopic imaging study. Arch Gen Psychiatry 2000;57:937-943.
23. Trzesniak C, Araújo D, Crippa JA. Magnetic resonance spectroscopy in anxiety disorders. Acta Neuropsychiatr 2008;20:56-71.
24. Camfield DA, Sarris J, Berk M. Nutraceuticals in the treatment of obsessive-compulsive disorder (OCD): a review of mechanistic and clinical evidence. Prog Neuropsychopharmacol Biol Psychiatry 2011;5:887-895.
25. Coupland NJ, Ogilvie CJ, Hegadoren KM, Seres P, Hanstock CC, Allen PS. Decreased prefrontal myo-inositol in major depressive disorder. Biol Psychiatry 2005;57:1526-1534.