정신신체의학 31(1) : 19–24, 2023
https://doi.org/10.22722/KJPM.2023.31.1.19

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ISSN 1225-6471

Physiological Predictors of Treatment Response to Biofeedback in Patients With Panic Disorder

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ABSTRACT

Objectives : Biofeedback is a useful non-pharmacological treatment for panic disorder (PD), but no studies have identified physiological markers related to the treatment response. This study investigated predictors of the treatment response for biofeedback in patients with PD.

Methods : A retrospective study based on the electronic medical records of 372 adult patients with PD was performed. Patients received biofeedback treatment at least once, and physiological markers including heart rate, heart rate variability, respiratory rate, skin conductance, skin temperature, and electromyography were collected before the treatment began. The patients were classified as responders or non-responders based on the change in Clinical Global Impression-Severity (CGI-S) score.

Results : The response rate to biofeedback treatment was 30.4%. Multivariable logistic regression analysis revealed that a higher CGI-S score at baseline and fewer benzodiazepine prescriptions were associated with a better response to biofeedback treatment. According to subgroup analyses, the baseline CGI-S score, dose of benzodiazepines, and skin conductance are candidate predictors of the response to biofeedback treatment in men, while only baseline disease severity was associated with the treatment response in women.

Conclusions : The present results suggest that skin conductance may be target marker and predictor for biofeedback in male patients with PD.

KEYWORDS : Panic disorder; Biofeedback; Treatment response; Predictor; Physiological marker.

INTRODUCTION

Panic disorder (PD) is one of the common mental disorders, and many PD patients experience significant dysfunction. Selective serotonin reuptake inhibitors, benzodiazepines, and cognitive-behavioral therapy are considered the first-line treatments for PD, but in many cases full and sustained remission is not achieved.[1)] In this situation, biofeedback, which is a non-invasive treatment that targets maladaptive physiology, can be one alternative treatment modality for PD.[2)] Physiology and psychology are closely related domains, and the physiological state influences both physical and mental health.[3)] Dysregulation of autonomic nervous system (ANS) activity serves as a biomarker for many psychiatric illnesses including PD.[4,5)]

As a self-monitoring technology, biofeedback can be helpful for patients with psychiatric disorders. Several studies have been conducted on the therapeutic utility of biofeedback for psychiatric disorders, and positive effects on symptoms such as depression and anxiety have been reported.[6-9)] A few studies have assessed the effectiveness of biofeedback for PD.[10-12)] Still, it has been rarely investigated which marker to perform biofeedback for clinical improvement.

No studies have reported predictors of the response to bio-

Received: May 1, 2023 / **Revised:** June 6, 2023 / **Accepted:** June 12, 2023
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feedback in PD patients. However, predictors of the therapeutic effectiveness of cognitive behavioral therapy, which is another type of non-pharmacological treatment, for patients with PD and anxiety disorder have been identified in some studies.[13,14] Identifying predictors of the response to biofeedback could increase its use. It will also help us understand the mechanism by which biofeedback acts therapeutically in PD. In this study, we hypothesized that certain physiological markers can predict the response to biofeedback. We attempted to identify such predictors, and assessed the associations between physiological markers and indices of the clinical severity of PD.

METHODS

1. Study population

Data were collected retrospectively from the electronic medical records (EMRs) of Seoul National University Bundang Hospital (SNUBH), Republic of Korea. We included 372 adult patients (aged ≥18 years) diagnosed with PD who received biofeedback treatment at SNUBH between December 5, 2014, and May 12, 2021, and returned to the hospital within 16 weeks of the first treatment. The diagnosis of PD was made by board-certified psychiatrists. Patients diagnosed with major psychiatric disorders, such as psychotic or neurocognitive disorder, were excluded, whereas those diagnosed with comorbid mood disorders or other anxiety related disorders were eligible. Demographic data were collected along with clinical variables including comorbidities, illness duration and medication. This study was approved by the Institutional Review Board of SNUBH (No. B-2111-719-105). The requirement for informed consent was waived because of the retrospective study design.

2. Biofeedback treatment

Biofeedback was conducted by trained medical technologists based on the biofeedback treatment protocol for PD of SNUBH; the ProComp Infiniti encoder and BioGraph Infiniti software (Thought Technology Ltd., Montreal, Canada) were used. During biofeedback, physiological data such as HRV (The standard deviation of normal to normal RR intervals), heart rate, respiratory rate, skin conductance, skin temperature, and electromyography were collected over a 5-minute period. Each treatment session lasted for 30 minutes; the basic protocol involved three sessions, but in some cases treatment was performed only once or twice according to the patient's wishes. Some patients underwent more than three treatment sessions. In treatment sessions, patients were trained to observe and alter their physiological variables. Patients were encouraged to practice on their own what they learned during the sessions.

3. Clinical and psychological factors

To evaluate the severity of panic, the Clinical Global Impression-Severity (CGI-S) scale was completed during a visit just before the initial biofeedback, and at a visit scheduled for around 12 weeks thereafter. If the CGI-S score was not obtained at the outpatient visit, two independent psychiatrists evaluated it based on the medical records. To measure interrater reliability, the intraclass correlation coefficient was calculated (r=0.913) for two independent raters based on the CGI-S scores of 20 patients. Only those with the CGI-S score ≥3 at baseline were included in this study. The Panic Disorder Severity Scale (PDSS) and Beck Depression Inventory-II (BDI-II) were completed before the initial biofeedback treatment.

The CGI-S is a seven-point scale for illness severity. The scale is completed by clinicians based on observed and reported symptoms. Scores range from 1 (*Not ill at all*) to 7 (*Extremely ill*). The PDSS is a 5-point scale developed to assess the severity of seven dimensions of PD (and associated symptoms). The internal consistency coefficient of the Korean version of the PDSS was reported to be 0.83.[15] The BDI-II is a 21-item self-report questionnaire that measures depressive symptoms. The Korean version of BDI-II showed high internal consistency (Cronbach's alpha coefficient=0.946).[16]

Antidepressant and benzodiazepine doses at the time of the first session were recorded and converted into dose equivalents of escitalopram and alprazolam, respectively.[17,18]

4. Statistical analysis

Comparing CGI scores after treatment to the baseline, responders were defined as those who had a decrease of 2 or more points. Student's t-test (for continuous variables) and the χ^2 test (for categorical variables) were used to compare responders and non-responders. Multivariable logistic regression was performed to identify predictors of the response to biofeedback. The backward elimination method was used to identify appropriate variables for the analysis. Subgroup analysis according to sex was also performed, because there are sex differences in the normal ranges of physiological variables related to the ANS.[19] Partial correlation analysis was used to evaluate the associations among physiological markers obtained during biofeedback treatment, the PDSS score, and the CGI-S score at baseline, with adjustment for age, sex and the BDI-II score. P-values<0.05 were considered statistically significant. All analyses were performed using IBM SPSS Statistics for Windows software (version 26.0; IBM Corp., Armonk, NY, USA).

RESULTS

1. Demographic and clinical characteristics

After reviewing the EMRs, 372 patients were included in the study, 113 (30.4%) of whom were classified as responders. In total, 151 patients (40.6%) were male and the mean age at the initial biofeedback treatment was 41.76±12.23 years. Table 1 shows the demographic and clinical characteristics of the responders and non-responders. The proportion of people who received more than two treatment sessions was higher in the former group (79/113 vs. 151/259; p=0.034). Responders were prescribed fewer benzodiazepines than non-responders (0.32± 0.30 vs. 0.43±0.54; p=0.011). The mean CGI-S score of the responders at baseline was 4.93, whereas that of the non-responders was 4.58 (p<0.001). There was no statistically significant difference between the two groups in any of the physiological variables.

2. Predictors of biofeedback treatment response

Multivariable logistic regression was performed to identify predictors of the response to biofeedback. There was a significant association between the treatment response and baseline CGI score (Table 2). There was a trend toward an association between baseline skin conductance and the treatment response. The use of fewer benzodiazepines was associated with a better response to biofeedback treatment. The number of sessions was weakly related to treatment response, although it was not statistically significant. Subgroup analysis was conducted to determine predictors of the treatment response according to sex (Table 3). For men (n=151), the benzodiazepine dose, baseline CGI-S score, and skin conductance were significant predictors of the response to biofeedback. For women (n=221), only the CGI-S score at baseline was a significant predictor of the treatment response.

3. Correlation analyses

Table 4 shows the correlations between the physiological variables measured during biofeedback treatment, PDSS score,

Table 2. Logistic regression analysis of the variables associated with the treatment response in patients with PD

Predictors	OR	95% CI	p-value
Sex (men)	0.66	0.40−1.08	0.098
Number of sessions (2 or more)	1.66	1.00−2.74	0.050
Benzodiazepine	0.40	0.21−0.77	0.006*
CGI-S score at baseline	2.89	1.90−4.41	<0.001*
Duration of treatment	1.01	1.00−1.02	0.074
SC	1.20	1.00−1.45	0.051

Only variables finally selected by backward elimination are included in the table. Duration of treatment, duration from initial biofeedback treatment to the point of re-evaluation of CGI-S; Benzodiazepine, prescribed dose of benzodiazepines (total dose equivalent to that of alprazolam). *p<0.05. OR, odds ratio; CI, confidence interval; CGI-S, clinical global impression severity scale; SC, skin conductance

Table 1. Demographic, clinical and physiological characteristics of responders and non-responders

	Responders (n=113)	Non-responders (n=259)	Analysis	
			t or χ^2	p-value
Age (years)	41.49±11.75	41.88±12.45	-0.282	0.778
Sex (male)	41 (36.3)	110 (42.5)	1.249	0.264
Duration of illness (1 year or more)	25 (22.1)	60 (23.2)	0.048	0.826
Comorbid mood disorder	34 (30.1)	91 (35.1)	0.898	0.343
Number of sessions (2 or more)	79 (69.9)	151 (58.3)	4.494	0.034*
Antidepressant (mg)	8.74±5.69	9.43±8.27	-0.927	0.355
Benzodiazepine (mg)	0.32±0.30	0.43±0.54	-2.545	0.011*
CGI-S score at baseline	4.93±0.59	4.58±0.68	5.055	<0.001*
Physiological variables				
SDNN (ms)	37.85±24.92	38.63±29.76	-0.244	0.807
HR (per minute)	72.25±11.59	72.04±11.91	0.158	0.875
RR (per minute)	14.81±2.71	14.78±2.44	0.129	0.897
SC (μS)	1.38±1.56	1.09±1.14	1.767	0.079
ST (℃)	32.96±2.15	32.84±2.12	0.513	0.608
EMG (μV)	6.84±3.66	7.12±4.30	-0.591	0.555

Data given as mean±standard deviation. The Student's t-tests were applied for the comparison of means and Pearson's χ^2 tests were applied for the comparison of proportions. Comorbid mood disorder, mood disorders including major depressive disorders and bipolar disorders. Antidepressant, prescribed dose of antidepressants (total dose equivalent to that of escitalopram); Benzodiazepine, prescribed dose of benzodiazepines (total dose equivalent to that of alprazolam). *p<0.05. CGI-S, clinical global impression severity scale; SDNN, standard deviation of normal to normal RR intervals; HR, heart rate; RR, respiratory rate; SC, skin conductance; ST, skin temperature; EMG, electromyography

Table 3. Subgroup analysis by sex of the variables associated with the treatment response in patients with PD

Predictors	Male (n=151)			Female (n=221)		
	OR	95% CI	p-value	OR	95% CI	p-value
Number of sessions (2 or more)				1.75	0.94−3.25	0.078
Benzodiazepine	0.30	0.10−0.86	0.025*	0.51	0.23−1.12	0.094
CGI-S score at baseline	5.90	2.32−14.99	<0.001*	2.21	1.36−3.58	0.001*
SC	1.35	1.03−1.76	0.028*			

Only variables finally selected by backward elimination are included in the table. Different variables were selected according to sex. Benzodiazepine, prescribed dose of benzodiazepines (total dose equivalent to that of alprazolam). *p<0.05. OR, odds ratio; CI, confidence interval; CGI-S, clinical global impression severity scale; SC, skin conductance

Table 4. Partial correlation analysis (n=121) of the associations among the physiological markers, the PDSS score, and the CGI-S score at baseline (controlling for age, sex and BDI-II score)

	CGI score at baseline	PDSS score
SDNN		
Coefficient	-0.001	0.025
p-value	0.990	0.792
HR		
Coefficient	0.144	-0.101
p-value	0.121	0.277
RR		
Coefficient	0.021	0.250
p-value	0.825	0.006*
SC		
Coefficient	0.016	0.049
p-value	0.862	0.602
ST		
Coefficient	-0.266	0.167
p-value	0.004*	0.071
EMG		
Coefficient	0.048	-0.073
p-value	0.604	0.435

*p<0.05. SDNN, standard deviation of normal to normal RR intervals; HR, heart rate; RR, respiratory rate; SC, skin conductance; ST, skin temperature; EMG, electromyography

and CGI-S score at baseline (controlling for age, sex, and the BDI-II score). The PDSS score was not obtained for all participants; thus, 121 patients were included in the correlation analyses. A higher baseline CGI-S score was associated with lower skin temperature, and a higher PDSS score was associated with a higher respiratory rate. No other physiological variables showed significant correlations with the PDSS score or baseline CGI-S score.

DISCUSSION

This study investigated the treatment response to biofeedback of patients with PD, and the clinical and physiological markers thereof. Biofeedback improved clinical symptoms in 30.4% of the patients. More severe illness and fewer benzodiazepine prescriptions emerged as candidate predictors of the treatment response to biofeedback in patients with PD. The number of sessions and skin conductance did not show a statistically significant correlation with the treatment response, but tended to be higher in the responder group. According to the subgroup analysis, skin conductance, the CGI-S score at baseline, and the dose of benzodiazepines prescribed were related to the treatment response in men, while for women only disease severity showed an association. In the analysis of physiological variables and clinical severity, skin temperature and respiratory rate were associated with the CGI-S and PDSS scores, respectively.

Among the candidate predictors of a treatment response, the most influential was the CGI-S score at baseline. In a previous study of cognitive behavioral therapy for patients with PD, more severe illness was associated with a response to treatment.[20] In another study related to depression, those with more severe illness at baseline showed a greater response and the author argued that these results may be due to differences in underlying biological mechanisms between cases with more severe symptoms and cases with milder symptoms.[21] There is a possibility that the results of our study can be explained in a similar context.

The benzodiazepine dose was also related to the treatment response. However, caution is needed when interpreting this result because the patients were prescribed drugs by various clinicians. One explanation for the relationship between benzodiazepines and the treatment response is that the benzodiazepine dose depends not only on the severity of PD but also on other psychiatric symptoms such as insomnia and anxiety[22]; the patients in this study prescribed high-dose benzodiazepines typically had these comorbidities, and the effectiveness of biofeedback may be compromised in such patients. Additionally, the treatment effect was relatively higher in those who completed more than one session, probably because they learned about various relaxation techniques, including progressive muscle relaxation, and received autogenic training. Also, such patients were highly motivated and showed high adherence.

Among the physiological variables assessed in this study, only skin conductance showed a weak relationship with the treatment response. In previous studies on panic disorder, some have shown a relationship between HRV and treatment outcomes.[12,23] However, other markers reflecting ANS and physiological markers as predictors of the response to biofeedback treatment have not been investigated in PD patients. High skin conductance is an indicator of ANS hyperarousal,[2] which is in turn associated with several psychiatric symptoms such as anxiety.[9,24] In a previous study, electrodermal activity predicted the effectiveness of antidepressants in patients with major depressive disorder.[25] The heart rate reflects the perceived threat level, whereas electrodermal activity reflects anxiety (especially anticipatory anxiety).[26] In another study, skin conductance declined linearly with relaxation, although the slope was less steep for PD patients than controls.[27] The results of these studies support an association between panic and skin conduction. The sex differences in skin conductance as a predictor observed in our study may be attributable to differences in electrodermal activity and clinical characteristics of PD between men and women.[28,29] Based on our results, skin conductance may be a candidate predictor of the response to biofeedback in men. However, a longitudinal study of changes of skin conductance after biofeedback is required to verify this.

Our correlation analysis suggested that physiological markers of symptom severity may differ from those predicting the treatment response. Also, the physiological variables associated with the CGI-S and PDSS scores differed, although both low body temperature and high respiratory rate are associated with ANS hyperarousal.[2] A meta-analysis indicated that baseline respiratory abnormalities were specific to PD.[30] In another study, patients with anxiety had a lower surface body temperature than controls;[31] however, the evidence that changes in skin temperature are more specific in PD than other diseases is currently insufficient. Previous studies reported correlations between CGI-S and PDSS scores,[32] although it should be noted that while the PDSS is specific to PD, the CGI-S is not. A large-scale longitudinal study is needed to validate the above findings.

This study had several limitations. First, it used a retrospective design; in particular, many of the CGI-S scores were obtained retrospectively, and their reproducibility may be limited because they were rated by several different clinicians. Next, this study has a limitation in defining responders by using CGI-S instead of the PDSS, which is specific to panic disorder. In addition, it is difficult to clearly distinguish between the treatment effect of biofeedback and pharmacotherapy. In a previous study, skin conductance was identified as a possible indicator predicting treatment response of medication in patients with PD.[33] Furthermore, the number of patients may have been insufficient to capture all of the potential physiological predictors of the treatment response. It should also be noted that, although the patients were encouraged to practice biofeedback, their practice performance was not formally evaluated; this is important because practice may have a significant influence on outcomes. Finally, only patients who visited the clinic at least once after biofeedback treatment were included in the study; no analysis was conducted on those who dropped out, which may have affected the results, given the possibility that such patients may have had more severe symptoms.

To the best of our knowledge, this is the first explorative study to identify physiological predictors of the response to biofeedback treatment among patients with PD. A therapeutic effect of biofeedback treatment was also confirmed. The results could facilitate personalized biofeedback treatment for PD patients; for example, biofeedback should be considered for male patients with high skin conductance. Longitudinal studies may shed more light on the relationship between changes in symptoms and physiological variables.

Acknowledgments

This study was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (NRF-2020 R1A2C1102105).

Conflicts of Interest

The authors have no financial conflicts of interest.

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