



A return to work program improves parasympathetic activity and psychiatric symptoms in workers on sick leave due to depression

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ABSTRACT

Background: People with depression have autonomic function disturbances. In Japan, workers who take leave due to depression often undergo a work-focused intervention program called the return to work (RTW) program at a mental health hospital during their leave of absence. However, its biological efficacy remains unclear. We investigated the biological efficacy of the RTW program, including changes in autonomic nervous system (ANS) activity, in workers on sick leave due to depression in Japan.

Methods: The study involved 104 workers on sick leave due to major depressive disorder or bipolar disorder who underwent the RTW program for 3 months in Yokohama City University Hospital. The ANS activity of all patients was evaluated using heart rate variability at the beginning and end of the 3-month RTW program. Psychiatric symptoms were evaluated using the Montgomery-Åsberg Depression Rating Scale-Japanese (MADRS-J) and Social Adaptation Self-evaluation Scale (SASS). We followed up 3 months after the end of the program and investigated the association between the success in returning to work within 3 months after the end of the RTW program and several factors, including ANS activity, depressive symptoms, and demographic factors.

Results: Parasympathetic activity was significantly higher and depressive symptom severity was significantly lower at program end than at baseline. Logistic regression analysis showed that the change in depressive symptoms was significantly associated with success in returning to work.

Conclusion: We suggest that the RTW program improves parasympathetic activity as well as psychiatric symptoms. ANS activity was not a predictor of a successful return to work within 3 months after the end of the program in workers on sick leave due to depression, but further studies with a larger sample size are needed.

1. Introduction

Mental disorders such as major depression and bipolar depression are the main causes of sick leave [1, 2]. The incidence of sick leave due to a mental disorder has increased in the past 10 years [3], and lost productivity due to mental health problems and rising costs associated with poor mental health in workers have been reported [4]. In 2008, the economic burden of depression was estimated to be USD 11 billion in Japan and

about USD 7 billion in the Japanese workplace [5]. A survey of large Japanese companies showed that the average number of days of sickness absence due to mental health problems, including depression and bipolar disorder, was approximately 120 days [6]. In addition, many workers on sick leave take repeated sick leave due to depression or do not manage to return to work for a long time [7]. A previous Japanese study found that almost half of employees experienced recurrent sickness absence over a follow-up period of 8.5 years [8]. In Japan, workers who take leave due

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to depression often receive a work-focused intervention program called the return to work (RTW) program at a mental health hospital or clinic during their leave of absence. This program is quite popular for rehabilitation in Japan and generally provides cognitive behavior therapy, social skills training, office work training, and a relaxation program. Through the RTW program, the participants aim to keep a regular routine, change their ways of thinking, and learn smooth communication. The purpose of the program is to enable resumption of work and to prevent depression recurrence.

The efficacy of work-focused interventions has been investigated worldwide [9, 10]. Previous studies [9, 10] have used various scales to determine the efficacy of RTW interventions. The impact of the severity of the stress condition and baseline work-related self-efficacy were also reported as predictors of returning to work [11, 12]. On the other hand, most of the scales involved self-report measures or questionnaires, and few studies have reported the biological efficacy of RTW interventions. Patients with depression have autonomic function disturbances as important clinical symptoms; examples of such symptoms include disturbances in sleep, appetite, sexual activity, and sweat secretion as well as cardiac and gastrointestinal paresthesia [13]. In recent years, many studies have reported imbalanced autonomic nervous system (ANS) activities of patients with depression evaluated using heart rate variability (HRV) [14, 15]. In a meta-analysis, among adults without cardiovascular diseases, patients with major depressive disorder had reduced parasympathetic activity, with the change in HRV related to the underlying depression [16]. A previous study also reported that the high-frequency (HF) component of HRV, parasympathetic activity, was associated with depressive symptom severity [17].

Therefore, we investigated the biological efficacy of the RTW program, including the change in ANS activity, in workers on sick leave due to depression in Japan.

2. Methods

2.1. Participants

This study involved 104 Japanese workers on sick leave due to major depressive disorder or bipolar disorder who were in a recovery period and underwent the RTW program for 3 months in Yokohama City University Hospital. Patients were consecutively recruited. We excluded participants who were diagnosed with conditions other than major depressive disorder or bipolar depression, such as adjustment disorder or anxious disorder. Psychiatrists with sufficient clinical experience made the diagnosis based on criteria in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [18]. Patients did not have cardiovascular, respiratory, neurological, or endocrine disease or a current or past history of substance abuse that obscured diagnosis or were receiving medication for physical diseases. The study was performed in Yokohama City University Hospital in Japan, was approved by the ethics committee of Yokohama City University Hospital, and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants after they received a full explanation of the study.

2.2. RTW program

The program was held from 9:00 am to 12:00 pm three times a week for 3 months. In the RTW program, the participants receive cognitive behavior therapy (120 min/session, 10 sessions during the 12 weeks), social skills training (120 min/session, 7 sessions during the 12 weeks), and office work training (personal computer work and reading) and take part in a relaxation program (yoga program, muscle relaxation, and breathing techniques; 4 sessions) and group discussion (5 sessions during the 12 weeks); in addition, they maintain a diary at home during the 12 weeks. Participants worked closely with psychiatrists with sufficient clinical experience, psychotherapists, and psychiatric social workers. Participants received psychological education from a psychiatrist and

psychotherapist and supportive therapy once a week during the 12 weeks from a psychiatrist.

2.3. Measurement of psychiatric symptoms

Psychiatrists with sufficient clinical experience assessed depressive symptom severity with the Montgomery-Åsberg Depression Rating Scale-Japanese (MADRS-J) [19] before the first day of the RTW program and on the last day of the 3-month RTW program, when the electrocardiogram was recorded. In addition, self-efficacy regarding social adaptation was measured at the same time by the Social Adaptation Self-evaluation Scale (SASS) [20], which is a self-report scale.

2.4. Measurement of success in returning to work

We followed up 3 months after the end of the RTW program using a postal survey to patients and investigated whether the participants succeeded in returning to work within 3 months after the end of the RTW program.

2.5. R-R interval power spectral analysis

HRV was used to investigate ANS activity before the first day of the RTW program and on the last day of the 3-month RTW program. Periodic components of HRV tend to aggregate within several frequency bands [21, 22]. ANS activity was assessed by subjecting noninvasive electrocardiogram (ECG) measurements to HRV power spectral analysis using the Fourier transform to decompose a series of sequential R-R intervals into the sum of the sinusoidal functions of different amplitudes and frequencies. This approach has confirmed validity and reliability, as demonstrated in basic physiological and clinical research [23, 24, 25]. All experimental sessions were held between 09:00 am and 12:00 pm, and participants were told not to consume caffeine or smoke from the morning on the measurement day. ECG was performed with patients in a seated position for 5 min after resting for at least 10 min beforehand. The ECG signal was amplified (BBA-8321; Bio-Tex, Kyoto, Japan) and digitized via a 13-bit analog-to-digital converter (Daq AD132; Elan, UK) at a sampling rate of 1024 Hz. The digitized ECG signal was differentiated, and the resultant QRS spikes and impulse intervals (R-R intervals) were sequentially stored on a hard disk for later analysis. Before the R-R spectral analysis, the stored R-R interval data were displayed and sequentially aligned to obtain equally spaced samples with an effective sampling frequency of 2 Hz [26] and were viewed on a computer display. Then, the direct current component and linear trend were eliminated by digital band-pass filtering between 0.03 and 0.4 Hz. The root mean square value of the R-R interval was calculated as representing the average amplitude. After being passed through the Hamming window, power spectral analysis by means of a fast Fourier transform of a consecutive 256-s time series of R-R interval data was then Fourier transformed. Low-frequency (LF) power (0.03–0.15 Hz), HF power (0.15–0.4 Hz), and total power (TP; 0.03–0.4 Hz) were calculated as indicators of both sympathetic and parasympathetic nervous system activity, parasympathetic nerve activity, and overall ANS activity, respectively.

2.6. Statistical analysis

All statistical analyses were carried out with SPSS for Windows version 24 (SPSS, Chicago, IL). A paired t-test was used to examine the change in the LF, HF, and TP components of HRV and in the MADRS-J and SASS. The Student's t-test was used to compare the MADRS-J and SASS and the LF, HF, and TP components of the HRV between the participants who could return to work 3 months after the RTW program and those who could not. In addition, the effects of ANS activities, psychiatric symptoms, and several factors on a successful return to work were assessed by forward stepwise logistic regression analysis. The dependent variable was success in returning to work within 3 months after the RTW

program; the independent variables were age, sex, diagnosis, living arrangement, annual income, the degree of change in the MADRS-J, the degree of change in the SASS, the degree of change in the lnLF, and the degree of change in the lnHF. Each value of the degree of change in the MADRS-J, lnLF, and lnHF was measured by dividing the end data by the baseline data of the 3-month RTW program. In the forward stepwise logistic regression analysis, the values at the end of the RTW program of the MADRS-J, SASS, lnLF, and lnHF were also used as independent variables. Because the HRV data were skewed, the spectral components were log-transformed prior to statistical analysis. The threshold of statistical significance was set at $P < 0.05$.

3. Results

The participants' characteristics are listed in Table 1. The total number of participants included in the analysis was 104; of these, 75 (72.1%) were men and 29 (27.9%) were women. The study participants ranged in age from 27 to 57 years, with a mean age $\pm$ standard deviation (SD) of 43.0 ± 8.3 years. Overall, 85 participants (81.7%) were diagnosed with major depressive disorder and 19 (18.3%) were diagnosed with bipolar disorder. In addition, 44 participants (42.3%) were not married and 23 participants (22.1%) were living alone. Mean annual income $\pm$ SD was 6.28 ± 2.09 million Japanese yen (about USD 56,000).

All HRV components and MADRS-J and SASS scores at the baseline and at the end of the RTW program are listed in Table 2. The HF component of HRV was significantly higher at the end than at the beginning ($P = 0.014$). The MADRS-J score was significantly lower at the end than at the beginning ($P < 0.001$). The SASS score was also significantly higher at the end than at the beginning ($P < 0.001$).

We were able to follow up 88 participants 3 months after the program; 60 succeeded in returning to work. Of these 60, 42 (70.0%) were male and 18 (30.0%) were female. The beginning and end MADRS-J, beginning SASS, and ANS activities were not significantly different between the patients who could return to work and those who could not. The end SASS score of the participants who could return to work tended to be higher than that of those who could not (35.68 ± 7.32 versus 32.61 ± 5.95 , $P = 0.055$). The results of forward stepwise logistic regression analysis between success in returning to work and several independent variables (age, sex, diagnosis, living arrangement, annual income, the degree of change in the MADRS-J, the degree of change in the SASS, the degree of change in the lnLF, and the degree of change in the lnHF) are summarized in Table 3. The logistic regression analysis showed that the degree of change in the MADRS-J was significantly associated with returning to work ($P = 0.020$) (Table 3). There were no associations

Table 1
Baseline characteristics of the participants (N = 104).

	N	%
Age (years)		
20–29	8	7.69
30–39	23	22.12
40–49	48	46.15
≥ 50	25	24.04
Sex		
Male	75	72.12
Female	29	27.88
Diagnosis		
Major depressive disorder	85	81.73
Bipolar disorder	19	18.27
Marital status		
Married	60	57.69
Not married	44	42.31
Living arrangement		
Living alone	23	22.12
Not living alone	81	77.88
Annual income (million Japanese yen)		
< 6	46	44.23
≥ 6	58	55.77

Table 2

Comparison of the log-transformed power values of the LF, HF, and TP frequency bands, the MADRS-J, and the SASS of participants between the beginning and end of the program (N = 104).

	At the beginning of the program	At the end of the program	P
MADRS-J	14.51 ± 6.16	9.29 ± 5.00	$< 0.001^a$
SASS	30.87 ± 7.06	35.08 ± 6.89	$< 0.001^a$
lnLF	4.94 ± 1.28	5.00 ± 1.34	0.612
lnHF	4.28 ± 1.12	4.58 ± 1.16	0.014^a
lnTP	5.48 ± 1.11	5.65 ± 1.16	0.114

Data are presented as mean $\pm$ standard deviation.

ln, natural log-transformed; HF, high frequency; LF, low frequency; TP, total power.; MADRS-J, Montgomery-Åsberg Depression Rating Scale-Japanese; SASS, Social Adaptation Self-evaluation Scale.

^a Significant difference ($P < 0.05$; paired t-test analysis).

Table 3

Forward stepwise logistic regression analysis of the correlation between success in returning to work within 3 months after the RTW program and several independent variables (N = 88).

Independent variable ^a	Odds ratio (95% CI)	P value
The degree of change in the MADRS-J, total score	0.158 (0.033, 0.750)	0.020 ^b

ln, natural log-transformed; HF, high frequency; LF, low frequency; MADRS-J, Montgomery-Åsberg Depression Rating Scale-Japanese; SASS, Social Adaptation Self-evaluation Scale.

^a Independent variables are age, sex, diagnosis, living arrangement, annual income, the degree of change in the MADRS-J, the degree of change in the SASS, the degree of change in the lnLF, and the degree of change in the lnHF.

^b Significant difference ($P < 0.05$; forward stepwise logistic regression analysis).

between the HF and LF components of HRV and the success in returning to work. In addition, in forward stepwise logistic regression analysis using the values at the end of the RTW program of the MADRS-J, SASS, lnLF, and lnHF as independent variables, no variables were associated with success in returning to work.

4. Discussion

Although the RTW program is quite popular for rehabilitation in workers on sick leave due to depression in Japan, few studies have investigated the clinical efficacy of the Japanese RTW program. This is the first study to investigate the ANS activity of workers on sick leave due to depression who underwent the Japanese RTW program and its effects on biological factors such as ANS activity. During the RTW program, the HF component of HRV and the MADRS-J and SASS scores improved. In addition, the degree of change in the MADRS-J was associated with success in returning to work within 3 months after the program. Our results suggest that the RTW program might improve parasympathetic activity in workers on sick leave due to major depression or bipolar disorder, as well as the depression symptoms and self-esteem regarding social adaptation.

This study suggested that the RTW program improved HF, which reflects parasympathetic activity. A low HRV indicative of decreased vagal cardiovascular modulations is an indicator of stress vulnerability and a low capacity for parasympathetic inhibition of autonomic arousal in emotional regulation [27, 28]. Thus, we believe that the RTW program may be able to improve parasympathetic activity and thereby affect individuals' ability to cope with stress and control their emotions.

In this study, the RTW program improved depressive symptoms evaluated by the MADRS-J. A previous study in Japan also reported that the RTW program improved depressive and anxiety symptoms evaluated by Kessler-6, which is a questionnaire and self-report measure [29]. In

the present study, we found an improvement in depressive symptoms using an objective scale, which was evaluated by a psychiatrist with sufficient clinical experience. Additionally, Ito et al. [29] also reported that the RTW program improved the social adaptation of individuals evaluated by the SASS. Because our improvement in the SASS was identified in a larger sample than in Ito et al. [29], our results enforce the findings of their study.

In logistic regression, there was a significant association between the success in returning to work and the degree of improvement in depression symptoms, which we evaluated using the MADRS-J. In a previous study [30], participants whose psychiatric symptoms on the MADRS were significantly improved showed greater success in returning to work than participants who showed a small improvement in psychiatric symptoms. Our results are thus consistent with those of the previous study. On the other hand, our study was unable to identify an association between ANS activity and success in returning to work within 3 months after the RTW program. In addition, there were no associations of other factors, including age, sex, diagnosis, living arrangement, and annual income, with success in returning to work within 3 months after the RTW program. In a previous study [11], sex and age were not associated with returning to work after an RTW program. Although the effects of living arrangement and diagnosis on sick leave due to depression have been investigated, no conclusion was reached [7, 31]. In the present study, we revealed only an association between psychiatric improvement and returning to work after the RTW program, and there were no associations of other factors, including ANS activity, with returning to work within 3 months after the RTW program. We believe that future studies with a larger sample size are needed to investigate whether ANS activity can affect individuals' ability to return to work.

Our study has some limitations. We did not investigate the ANS activity at 3 months follow-up after the RTW program. Studies to evaluate changes in more detail by increasing the number of evaluation time points are needed. In addition, because we did not use a control group, we did not compare ANS activities and psychiatric symptoms between patients who participated in the RTW program and those who did not. We did not rule out the effect of time, and improvements in parasympathetic activity and depressive symptoms may occur during the natural course of a depressive episode. There is also the possibility that the ANS activities and psychiatric symptoms changed as a result of the focused attention received in the group. A randomized controlled clinical trial with a randomly sampled control group of untreated persons is necessary in any future work. In addition, we did not elucidate the effects of medications that might influence ANS activity. Finally, we did not match the environmental and occupational factors of the workers on sick leave.

In conclusion, our study suggests that the RTW program improves both parasympathetic activity and psychiatric symptoms. ANS activity was not a predictor of returning to work within 3 months after the program in workers on sick leave due to depression in the present study but further studies with a larger sample size and longer follow-up period are needed to clarify the association between ANS activities and returning to work in workers on sick leave due to depression.

Declarations

Author contribution statement

Saki Hattori: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Ikuko Kishida, Akira Suda, Chiaki Kawanishi, Yoshio Hirayasu: Conceived and designed the experiments; Performed the experiments; Wrote the paper.

Masatoshi Miyauchi, Yohko Shiraishi, Mami Fujibayashi, Natsuki Tsujita, Chie Ishii, Toshio Moritani: Contributed reagents, materials, analysis tools or data.

Yusuke Saigusa: Analyzed and interpreted the data.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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