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<td>Author(s)</td>
<td>Mori, Asako; Okamoto, Yasumasa; Okada, Go; Takagaki, Koki; Takamura, Masahiro; Jinnin, Ran; Ichikawa, Naho; Yamamura, Takanao; Yokoyama, Satoshi; Shiota, Syouichi; Yoshino, Atsuo; Miyake, Yosie; Okamoto, Yuri; Matsumoto, Madoka; Matsumoto, Kenji; Yamawaki, Shigeto</td>
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| Relation    |                                                                                     |
Effects of behavioural activation on the neural circuit related to intrinsic motivation

Asako Mori, Yasumasa Okamoto, Go Okada, Koki Takagaki, Masahiro Takamura, Ran Jinnin, Naho Ichikawa, Takanao Yamamura, Satoshi Yokoyama, Syouichi Shiota, Atsuo Yoshino, Yoshie Miyake, Yuri Okamoto, Madoka Matsumoto, Kenji Matsumoto and Shigeto Yamawaki

**Background**

Behavioural activation is an efficient treatment for depression and can improve intrinsic motivation. Previous studies have revealed that the frontostriatal circuit is involved in intrinsic motivation; however, there are no data on how behavioural activation affects the frontostriatal circuit.

**Aims**

We aimed to investigate behavioural activation-related changes in the frontostriatal circuit.

**Method**

Fifty-nine individuals with subthreshold depression were randomly assigned to either the intervention or non-intervention group. The intervention group received five weekly behavioural activation sessions. The participants underwent functional magnetic resonance imaging scanning on two separate occasions while performing a stopwatch task based on intrinsic motivation. We investigated changes in neural activity and functional connectivity after behavioural activation.

**Results**

After behavioural activation, the intervention group had increased activation and connectivity in the frontostriatal region compared with the non-intervention group. The increased activation in the right middle frontal gyrus was correlated with an improvement of subjective sensitivity to environmental rewards.

**Conclusions**

Behavioural activation-related changes to the frontostriatal circuit advance our understanding of psychotherapy-induced improvements in the neural basis of intrinsic motivation.

**Declaration of interest**

None.

**Keywords**

Behavioural activation; intrinsic motivation; depressive disorders; imaging; functional magnetic resonance imaging; subthreshold depression.

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Thus, we hypothesised that successful behavioural activation would increase the activity of the anterior striatum, LPFC and anterior cingulate gyrus. Given previous findings that patients with MDD showed abnormal functional connectivity in the frontostriatal circuit, we predicted that functional connectivity between the LPFC and anterior striatum would be reduced in participants with subthreshold depression, and that behavioural activation would increase this functional connectivity.

### Participants

The participants were recruited over a 2-year period between 2013 and 2014 at Hiroshima University. The ethics committee of Hiroshima University approved the study (Approval number: clinical-408). The trial was registered in the UMIN clinical trials registry (UMIN000011967). Before the study, written informed consent was obtained from all participants. The Beck Depression Inventory II (BDI-II) scores and the Composite International Diagnostic Interview\(^{10,11}\) were used to recruit freshmen for an RCT of behavioural activation over a 2-year period. The Japanese version of BDI-II is routinely administered yearly to all freshmen, as part of the health check-up conducted by the Health Service Center of Hiroshima University.

The participants that were recruited in the second year participated in this functional magnetic resonance imaging (fMRI) study. A total of 59 individuals were enrolled in the 2014 RCT of behavioural activation. From this group, 29 were allocated to the intervention group and 30 were allocated to the non-intervention group. Participants in the intervention group participated in the RCT of behavioural activation comprising five weekly behavioural activation sessions. The BDI-II score was the main outcome of the RCT. Details of the RCT have been published elsewhere.\(^5\) The intervention group participants were scanned before and after behavioural activation intervention. The non-intervention group participants were scanned twice, with a 5-week interval (i.e. at the same time as the intervention group but without any intervention).

Of the 59 participants, 58 completed 2 days of experiments and had complete fMRI data; one participant in the intervention group failed to complete scanning because of an incidental finding. Of the 58 participants, two were excluded from the analysis: one participant in the non-intervention group initiated psychopharmaco-therapy between times 1 and 2, and one participant in the intervention group had missing fMRI data because of scanner failure. Therefore, data from 56 remaining participants were analysed.

In addition, the Environmental Reward Observation Scale (EROS) was administered to examine the efficacy of behavioural activation. The EROS is a self-administered questionnaire that subjectively evaluates positive reinforcement associated with an action.\(^12\) Each questionnaire was completed at baseline (time 1) and after 5 weeks (time 2). The RCT inclusion criteria were 18–19 years of age and a freshman at screening, a BDI-II score of 10 or more according to the inclusion and exclusion criteria are provided in the Supplementary Methods.

Clinical measures

**Japanese version of the BDI-II**

We used the Japanese version of the BDI-II,\(^14\) the reliability and validity of which has been confirmed. The original version of the BDI-II, developed by Beck et al,\(^15\) consists of 21 items on a four-point scale to measure the severity of depression.

**Japanese version of the EROS**

We used the Japanese version of the EROS, the reliability and validity of which has been confirmed.\(^16\) The original version of the EROS, developed by Armento and Hopko,\(^12\) consists of ten items on a four-point scale to measure environmental rewards congruent with behavioural theories of depression.

### Treatment

The intervention group participated in a treatment programme comprising five weekly behavioural activation sessions conducted by a trained therapist for 60 min per session (Supplementary Methods). The non-intervention group did not receive any treatment, only the pre- and post-assessment. None of the participants received any medication until the study was completed.

### Experimental tasks

To explore neural activity associated with intrinsic motivation, the participants performed stopwatch and watch-stop tasks in an fMRI scanner, as described by Murayama et al.\(^7\) In the stopwatch task, a stopwatch was displayed on a screen. The participants were asked to press a button within 50 ms of the 5 s time point. Responses made within 50 ms of the 5 s were considered a success and a point was added to the total score, which was shown in the upper right corner of the screen. In the watch-stop task, the participants were told to press a button when the stopwatch stopped. In this task, participants did not get any points because success and failure were not distinguished. The tasks were administered once and included 30 stopwatch and 30 watch-stop task trials. The trials were pseudo-randomly intermixed. Before each task, instructions were displayed to indicate which task would be performed next. Directly after the task, the participants were asked to fill out a questionnaire indicating to what extent they enjoyed or felt bored during each task. We used the method given by Elliot et al\(^7\) to calculate the Intrinsic Motivation Inventory (IMI) as follows: question 1 (‘I enjoyed the stopwatch task’) score + question 3 (‘The stopwatch task was interesting’) score – question 2 (‘The stopwatch task was boring’) score.

### fMRI acquisition

fMRI was performed by a Magnetom Verio 3T (Siemens, Munich, Germany). Details are provided in the Supplementary Methods.

### fMRI data preprocessing and statistical analyses

Image processing and statistical analyses were carried out by Statistical Parametric Mapping (SPM12) software (Wellcome Department of Cognitive Neurology, Wellcome Trust Centre, London, UK). Details of the preprocessing steps are provided in the Supplementary Methods. To investigate the cue and feedback effects, two contrasts were calculated: (a) the cue presentation phase (i.e. cue presentation of the stopwatch task versus the watch-stop task); and (b) the feedback phase (i.e. success feedback versus failure feedback of the stopwatch task). The cue presentation phase represents mental preparation and anticipation of the upcoming task. The feedback phase represents the adjusted motivation in

**Method**

**Participants**

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Of the 59 participants, 58 completed 2 days of experiments and had complete fMRI data; one participant in the intervention group failed to complete scanning because of an incidental finding. Of the 58 participants, two were excluded from the analysis: one participant in the non-intervention group initiated psychopharmacological treatment between times 1 and 2, and one participant in the intervention group had missing fMRI data because of scanner problems. Of the 56 remaining participants, two in the intervention group and three in the non-intervention group were excluded from the analysis because of excessive motion (>4 mm) during scanning. Therefore, data from 25 individuals in the intervention group and 26 individuals in the non-intervention group were analysed.

In addition, the Environmental Reward Observation Scale (EROS) was administered to examine the efficacy of behavioural activation. The EROS is a self-administered questionnaire that subjectively evaluates positive reinforcement associated with an action.\(^12\) Each questionnaire was completed at baseline (time 1) and after 5 weeks (time 2). The RCT inclusion criteria were 18–19 years of age and a freshman at screening, a BDI-II score of 10 or more according to a previous study,\(^13\) no major depressive episodes within the past year, not undergoing psychopharmacological or psychological treatment and willingness to provide informed consent. Details of the inclusion and exclusion criteria are provided in the Supplementary Methods available at https://doi.org/10.1192/bjo.2018.40.
response to the former results. The t-maps were transformed into z-scores to create a statistical parametric map for each contrast.

**Analysis of neural signals during cue presentation and feedback**

We first confirmed brain activation related to stopwatch task feedback and cue presentation versus watch-stop task feedback and cue presentation across all participants at time 1. We then performed a two-sample t-test with the subtraction images (time 2 − time 1) of the first-level contrasts in the cue presentation phase (cue presentation of the stopwatch task versus the watch-stop task) and the feedback phase (success feedback versus failure feedback of the stopwatch task), reflecting the difference between time 2 and time 1 scans to determine whether the behavioural activation intervention resulted in changes to brain activity. The imaging analysis statistical threshold was set at multiple comparisons with a cluster-extent family-wise false positive rate (FWE)-corrected significance threshold of FWE < 0.05. As we had an a priori hypothesis focused on the anterior striatum, we also performed analysis focused on the anterior striatum region of interest (ROI), which was determined by the bilateral caudate and putamen in the Automated Anatomical Labeling Atlas and bounded caudally at y = 0 to include only the anterior parts of the striatum. We report the areas that survived after multiple comparisons at the whole-brain level or ROI analysis.

**Individual difference correlation analysis**

As a treatment response measure, we calculated BDI-II score change (time 1 − time 2). For the EROS, we calculated the change score as time 2 − time 1. A high score indicated symptom improvement over time.

Changes in activation related to cue presentation, feedback and clinical response were investigated. For each group, we analysed the correlation between the clinical score and the mean values of subtraction images (time 2 − time 1) of the first-level contrasts in each contrast (cue presentation phase and feedback phase); a 6 mm sphere centred on the peak coordinate of the clusters significant at the group level was extracted. Then, Spearman correlation coefficients were calculated within each group, using SPSS statistics 21 software (Chicago, IL, USA), and P < 0.05 was considered statistically significant.

**Psychophysiological interaction analysis**

We hypothesised that behavioural activation treatment modulates neural circuits; therefore, we used the psychophysiological interaction (PPI) method. The current PPI analysis was conducted to test behavioural activation–related changes in functional connectivity from the brain region(s) where neural activation was changed after behavioural activation and associated with an improvement of the clinical symptoms. The statistical threshold for the PPI analysis was set at P < 0.05 (cluster-extent FWE-corrected). On the basis of changes in neural activity between times 1 and 2 and correlation analysis, activation of the right MFG changed after behavioural activation, and the changes in the right MFG were associated with an improvement of the clinical symptoms. Thus, we chose the right MFG (peaks at 30, 30 and 36) as a seed region. The seed was set at a 6 mm diameter centred on the peak coordinate. After extracting the time course of the seed region and the psychological vector of interest (weighting stopwatch task cue presentation with 1 and watch-stop task cue presentation with −1), the interaction term was calculated. We included the psychological vector and time course of the seed region as nuisance regressors in the general linear model and calculated the PPI contrast image. For each participant, this procedure generated a functional connectivity map identifying areas where blood-oxygen-level–dependent signal changes were coupled with the seed region as induced by cue presentation. A second-level analysis was then applied to the extracted individual images. To examine the effects of behavioural activation on functional connectivity, we performed a two-sample t-test with the PPI subtraction (time 2 − time 1) contrast between the groups.

**Behavioural data analysis**

We calculated the response time for the stopwatch task, the success rate of the stopwatch task and IMI score. The response time for the stopwatch task was the time window between cue presentation and button press (approximately 5000 ms). One session consisted of 30 stopwatch and 30 watch-stop trials; therefore, the stopwatch task success rate was the number of successes in the stopwatch task divided by 30. The success rate was not controlled in this task; therefore, the time window for success (5000 ± 50 ms) was determined to be approximately half of the trials in the non-clinical setting sessions to obtain the greatest sense of achievement. Clinical scores were analysed by analysis of variance in SPSS 21, with group (intervention and non-intervention) as the between-participant factor and time (times 1 and 2) as the within-participant factor. A post hoc Bonferroni test was used to examine pairwise differences from the analysis of variance. In all cases, P < 0.05 was considered statistically significant.

**Results**

**Demographic characteristics**

Table 1 shows the demographic characteristics of the participants. There were no significant differences in gender or mean age between the intervention and non-intervention groups. All

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**Table 1** Demographic data and symptom profiles

<table>
<thead>
<tr>
<th></th>
<th>Intervention group</th>
<th>Non-intervention group</th>
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<tbody>
<tr>
<td></td>
<td>Time 1</td>
<td>Time 2</td>
</tr>
<tr>
<td>Mean s.d.</td>
<td>Mean s.d.</td>
<td>Mean s.d.</td>
</tr>
<tr>
<td>Age</td>
<td>18.2 0.4</td>
<td>18.2 0.4</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>16/9</td>
<td>18/8</td>
</tr>
<tr>
<td>BDI-II</td>
<td>12.8 5.3</td>
<td>7.0 6.2</td>
</tr>
<tr>
<td>EROS</td>
<td>23.2 3.4</td>
<td>25.8 4.3</td>
</tr>
<tr>
<td>Statistical value</td>
<td>−0.26, t_{20}</td>
<td>−1.05, t_{20}</td>
</tr>
<tr>
<td>P value</td>
<td>0.79</td>
<td>0.002</td>
</tr>
<tr>
<td>Post hoc comparison</td>
<td>Intervention group less than non-intervention group at time 2 (P &lt; 0.01); time 1 more than time 2 in the intervention group (P &lt; 0.01)</td>
<td>Intervention group more than non-intervention group at time 2 (P &lt; 0.01); time 1 less than time 2 in the intervention group (P &lt; 0.01)</td>
</tr>
</tbody>
</table>
participants were right-handed. There was a significant group ×
time interaction in the BDI-II scores (F(1, 49) = 11.05, P < 0.002).
The mean BDI-II scores of the intervention group at time 2 were
significantly lower than those of the non-intervention group.
BDI-II scores decreased significantly in the intervention group,
whereas there was no significant change in the non-intervention
group. For the EROS, there was a significant group × time inter-
action (F(1, 49) = 6.51, P < 0.014), indicating that the mean EROS
scores of the intervention group at time 2 were significantly
higher than those of the non-intervention group. Further, the
EROS scores increased significantly within the intervention group,
whereas there was no significant change within the non-interven-
tion group.

**Behavioural results**

Supplementary Table 1 shows the behavioural results of the partici-
pants. There were no significant main or interaction effects of group
(intervention and non-intervention) on response time in the stop-
watch task (F(1, 49) = 0.57, P = 0.46), success rate of the stopwatch
task (F(1, 49) = 1.75, P = 0.19) or IMI score (F(1, 49) = 0.04, P = 0.84).

**Neuroimaging results**

Changes in brain activity between time 1 and time 2

We first confirmed brain activation related to stopwatch task feed-
back and cue presentation versus watch-stop task feedback and cue
presentation across all participants at time 1. A one-sample t-test of
the cue presentation phase in all participants at time 1 showed acti-
vation of a large cluster extending to the bilateral striatum, pallidum
and anterior cingulate gyrus brain regions related to motivation. For
the feedback phase, the prefrontal region (left IFG, right medial
frontal gyrus and left MFG) were activated with a liberal threshold
of P < 0.001. We then performed a two-sample t-test with the sub-
traction (time 2 – time 1) contrast between groups (Fig. 1 and
Supplementary Table 2). (Time 2 – time 1) changes in brain activa-
tion during cue presentation were significantly different in the right
MFG (z = 4.41, P_{FWE} = 0.029), right SFG (z = 4.38, P_{FWE} = 0.01) and
anterior cingulate gyrus (z = 4.1, P_{FWE} = 0.044). For the ROI ana-
lysis, the left putamen survived (z = 4.02, P_{FWE} = 0.018). The activity
of these clusters increased more in the intervention group compared
with the non-intervention group between time 1 and time 2 during
cue presentation. Of note, the right MFG reportedly closely over-
lapped with the LPFC in a previous study of intrinsic motivation.

![Fig. 1](image-url)
with the same contrast. No region survived during the feedback phase in the whole-brain or ROI analyses.

Correlational analysis

Fig. 2 shows the significant positive correlations between changes in right MFG activation and the EROS in the intervention group ($P = 0.019, \rho = 0.465, 95\% CI = 0.086–0.727$), whereas the correlation was not significant in the non-intervention group ($P = 0.825, \rho = 0.046, 95\% CI = -0.348 to 0.426$). The positive correlation in the intervention group indicates that the participants with a greater clinical improvement (i.e., activation control after behavioural activation) had more changes in the right MFG. There was no significant correlation between changes in right SFG activation ($P = 0.598, \rho = -0.111, 95\% CI = -0.485 to 0.2972$), anterior cingulate gyrus activation ($P = 0.483, \rho = -0.147, 95\% CI = -0.512 to 0.2634$) and left putamen activation ($P = 0.175, \rho = -0.280, 95\% CI = -0.608 to 0.1295$) and the EROS in the intervention group. There was no significant correlation between changes in these regions and the BDI-II score.

Changes in functional connectivity between time 1 and time 2

The results are shown in Fig. 3 and Supplementary Table 3. Whole-brain PPI analyses revealed a single cluster extending to the right posterior cingulate cortex (PCC) that was more functionally connected to the right MFG, in which neural activity increased during stopwatch task cue presentation relative to watch-stop task cue presentation after behavioural activation compared with the non-intervention group ($z = 4.5, P_{FWE} = 0.005$).

Discussion

In this study, we examined neural changes related to successful behavioural activation in individuals with subthreshold depression. We examined people with subthreshold depression in relation to their BDI-II scores (i.e. a BDI-II score of 10 or more).

Our results revealed significant clinical and neural effects of behavioural activation on subthreshold depression. We showed that the activity of the regions related to intrinsic motivation increased during cue presentation in the intervention group compared with the non-intervention group, and that the improvement in subjective sensitivity to environmental rewards was positively correlated with increased right MFG activity. In addition, we observed that functional connectivity between the right MFG and right PCC during cue presentation increased after behavioural activation in the intervention group compared with the non-intervention group. These results indicate that behavioural activation affects intrinsic motivation by increasing functional connectivity between the MFG and PCC in the right hemisphere.

The changes in brain activity between times 1 and 2 support our hypothesis that behavioural activation improves neural intrinsic motivation. The identification of the MFG as an intrinsic motivation-related region in this study is supported by a previous study that used an identical contrast in the same task; the MFG in our study closely overlaps with the LPFC, which was reported as a region for cognitive/motivational preparation for an upcoming task. The putamen, anterior cingulate gyrus and SFG are parts of the neural reward network. The putamen has an important role not only in motor planning and execution of movement, but also in non-motor functions such as cognition. Because behavioural activation improves cognitive flexibility through behavioural experimentation, it is reasonable that we found a neural change after behavioural activation in the cue presentation phase, which requires cognitive preparation. As our behavioural activation programme was developed as a short-term intervention, cognitive control of an upcoming task, which is a function of the prefrontal region, might have improved initially. We might detect neural changes in the feedback phase if the participants continued behavioural activation independently over a longer period.

Of note, the change in right MFG was activation positively correlated with the EROS after behavioural activation. This might reflect an improvement in cognitive control (i.e. MFG function); therefore, the participants might have been able to act in a mood-independent manner. Consequently, they might have had more opportunities to receive rewards.

Interestingly, the intervention group exhibited increased connectivity in the right MFG (LPFC) and PCC compared with the non-intervention group, although they did not show changes in connectivity between the LPFC and anterior striatum. The PCC is not only part of the default network, but is also part of the frontoparietal network. The cluster detected in our study is
located in the dorsal PCC, which is connected with the dorsolateral prefrontal cortex. Enhancement of this connectivity after behavioural activation is consistent with the neurocognitive model of depression in which altered communication between a control system (i.e. the frontoparietal network) and the network engaged in internal thought (i.e. the default network) underlies depressive symptoms.

In addition, the dorsal PCC plays an important role in spatial navigation. Behavioural activation intends to increase the likelihood that an individual will engage in pleasurable activities, including going for a walk, exercise and painting, which require spatial navigation. To undertake more of these activities, individuals need to make a precise activity plan of when, how and with whom they will attempt these activities. The connectivity between the PCC and the LPFC might play a role in such cognitive control of spatial information.

Our findings should not be expanded to depression because the focus of our study was subthreshold depression. However, our results were in line with neural changes related to psychotherapy for depression, which suggests an improvement in top–down regulation via the prefrontal region. In a systematic review comparing studies on the effects of psychotherapy and drug treatment, IFG and SFG activity increased more with psychotherapy than with antidepressants. Dichter et al reported that MFG activity during a monetary anticipation phase increased more in a behavioural activation group compared with a control group, suggesting behavioural activation-related neural changes in a reward task. We previously reported that IFG activity during loss anticipation increased after behavioural activation. Although this study focused on intrinsic motivation, the neural change pattern is in line with previous studies that focused on monetary rewards (i.e. intrinsic motivation).

Several of our findings were contrary to our expectations. We found little evidence of neural change during feedback. This may be explained by several reasons. First, previous studies revealed a dissociation of the mental process during the anticipatory phase from that during the feedback phase in patients with MDD pathophysiology, indicating altered activity that was specific to the anticipatory phase. If this holds true for subthreshold depression, neural changes after behavioural activation might first appear in the cue presentation phase, the cue presentation phase represents cognitive preparation for an upcoming task, which is equivalent to the anticipatory phase. Second, behavioural activation encourages individuals to select a behaviour of their own preference and to evaluate the consequences of their actions. Repeating this process improves one’s ability to predict the results of a chosen action and enhances reward sensitivity. After behavioural activation, the neural changes observed during the cue presentation phase might reflect an improvement in reward anticipation. Finally, contrary to behavioural activation practised in daily life, the tasks were selected for the participants in this fMRI experiment (i.e. forced choice). Murayama et al used a modified stopwatch task to examine whether self-determined choice facilitates prefrontal activation compared with forced choice. Therefore, the participants may not have felt a strong sense of accomplishment during the feedback phase even if they successfully accomplished the task, as the experimental situation was not natural or applicable to their daily lives.

This study had several limitations. First, as we focused on participants with subthreshold depression, we are unable to generalise our findings to patients with MDD. However, neural circuit changes similar to those underlying the efficacy of behavioural activation in patients with subthreshold depression might occur in patients with MDD; the neural circuit changes after behavioural activation observed in our study overlapped with regions related to the intrinsic reward network. Second, we did not include healthy controls in our study; to date, no study specifically focused on intrinsic motivation has investigated neural changes in patients with subthreshold depression versus healthy controls. Further study of healthy controls is required to determine the accuracy of our findings, particularly in individuals without depression.

Although several limitations should be taken into consideration, to the best of our knowledge, this is the first report revealing the neural effects of behavioural activation in terms of intrinsic motivation. These findings provide further understanding of the neural mechanisms underlying the effects of behavioural activation.

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Supplementary material

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