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Research paper

Effects of behavioral activation on default mode network connectivity in subthreshold depression: A preliminary resting-state fMRI study

Satoshi Yokoyama[a,b], Yasumasa Okamoto[a,*], Koki Takagaki[a], Go Okada[a], Masahiro Takamura[a], Asako Mori[a], Syouichi Shiota[a,b], Naho Ichikawa[a], Ran Jinnin[a], Shigeto Yamawaki[a]

[a] Department of Psychiatry and Neurosciences, Hiroshima University, Japan
[b] Research Fellow of Japan Society for the Promotion of Science, Japan

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ABSTRACT

Background: Subthreshold depression is a risk factor for major depressive disorder, and it is known to have a negative impact on quality of life (QOL). Although behavioral activation, which is one type of cognitive behavioral therapy, is an effective psychological intervention for subthreshold depression, neural mechanisms of behavioral activation are unclear. Enhanced functional connectivity between default mode network (DMN) and the other regions has been demonstrated in participants with subthreshold depression. The purpose of this study was to examine the effects of behavioral activation on DMN abnormalities by using resting-state functional MRI (rs-fMRI).

Methods: Participants with subthreshold depression ($N = 40$) were randomly assigned to either an intervention group or a non-intervention group. They were scanned using rs-fMRI before and after the intervention. Independent component analysis indicated three subnetworks of the DMN.

Results: Analyzing intervention effects on functional connectivity of each subnetwork indicated that connectivity of the anterior DMN subnetwork with the dorsal anterior cingulate was reduced after the intervention. Moreover, this reduction was correlated with an increase in health-related QOL.

Limitations: We did not compare the findings with healthy participants. Further research should be conducted by including healthy controls to verify the results of this study.

Conclusions: Mechanisms of behavioral activation might be related to enhanced ability to independently use the dACC and the DMN, which increases an attention control to positive external stimuli. This is the first study to investigate neural mechanisms of behavioral activation using rs-fMRI.

1. Introduction

Recently, it has been suggested that subthreshold depression, which is defined as clinically significant depressive symptoms not meeting diagnostic criteria for major depressive disorder (MDD: Pincus et al., 1999), is a potential risk factor for MDD (Bertha and Balázs, 2013; Jinnin et al., 2017). This condition is frequently observed among adolescents, and it is known to have a negative impact on quality of life (QOL: Bertha and Balázs, 2013). Although symptoms of subthreshold depression are less severe than those of MDD, the resulting impairments of daily life functions, including the deficit in QOL is similar to that in individuals with MDD, and significantly worse than in healthy people (Nierenberg et al., 2010). As a result, it is considered essential to elucidate the pathogenic mechanisms of subthreshold depression and to develop effective interventions. In particular, psychotherapy might be preferable for certain groups such as subthreshold cases or adolescents.

A meta-analysis (Cuijpers et al., 2007) suggested that cognitive behavioral therapy (CBT) is an effective intervention for subthreshold depression. Moreover, our previous study (Takagaki et al., 2014) on behavioral characteristics of subthreshold depression demonstrated that people with subthreshold depression are hyposensitive to reward. Therefore, a primary goal of interventions for subthreshold depression is to increase access to positively reinforcing events and activities. Behavioral activation is a CBT technique used for increasing the frequency of positive activities that lead to reinforcements in their life (Jacobson et al., 2001). The efficacy of behavioral activation matched to behavioral characteristics of clients with subthreshold depression has been confirmed in our recent randomized controlled trial (Takagaki et al., 2016), which demonstrated that behavioral activation was effective for improving depressive symptoms as well as clinical variables such as

* Correspondence to: Department of Psychiatry and Neurosciences, Graduate School of Biomedical and Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan.
E-mail address: oy@hiroshima-u.ac.jp (Y. Okamoto).

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health-related QOL and the exposure to environmental rewards (Takagaki et al., 2016). However, the underlying neural mechanisms of behavioral activation that are associated with the improvement of clinical variables are not fully understood.

A number of resting-state functional magnetic resonance imaging (rs-fMRI) studies that examined functional abnormalities of the brain and therapeutic responses in MDD have reported that depressed patients exhibit hyperactivity of the default mode network (DMN), which is composed of the medial prefrontal cortex (MPFC), the precuneus/posterior cingulate cortex (PCC), the inferior parietal lobule (IPL) and the hippocampal formation (Buckner et al., 2008). According to meta-analysis (Sundermann et al., 2014b), increased functional connectivity in the DMN regions, including the region between the anterior cingulate cortex (ACC) and the medial frontal cortex, as well as the region between the precuneus and PCC, was associated with depression. It is considered that the DMN is associated with self-referential processing (Lemogne et al., 2010). Patients with MDD often show abnormal self-focus biases, such as depressive ruminations (Grimm et al., 2009) and they focus on negative self-relevant information (Nolen-Hoeksema, 2000). Moreover, the functional connectivity between the DMN, including the ventrolateral and ventromedial prefrontal cortices, superior temporal gyri and limbic areas, and subgenual ACC, has the highest power to discriminate MDD patients from healthy controls (Zeng et al., 2014a, 2014b). Therefore, the DMN connectivity is considered to play a central role in the physiopathology of depression (Li et al., 2013).

Moreover, DMN activity of depressive people is known to be abnormally linked to other brain regions. Hwang et al. (2016) demonstrated that subthreshold depression was associated with enhanced functional connectivity between the DMN and regions outside the DMN, similar to patients with MDD (Greicius et al., 2007). Moreover, changes in functional connectivity of the DMN were observed in an early stages of developing MDD, which might be associated with the behavioral characteristics of subthreshold depression. Therefore, investigating whether such abnormalities in the DMN are changed by behavior activation is important for understanding the neural mechanisms of behavior activation in subthreshold depression. However, to date, there are no published studies that have specifically focused on changes in spontaneous brain functions during the course of psychological treatment of subthreshold depression.

The purpose of this study was to examine the neural effects of behavioral activation on the DMN in people with subthreshold depression using rs-fMRI. The DMN can be divided along the anterior-posterior and inferior-superior axes (Allen et al., 2011). Li et al. (2013) investigated changes in the DMN subnetworks of MDD patients following antidepressant treatment, by using independent component analysis (ICA) approach. They reported that abnormalities in the posterior subnetwork were normalized after treatment, whereas there were no changes in the anterior subnetwork. CBT techniques including behavioral activation are mainly known to affect the frontal areas of the brain including the dorsal, ventral, and medial frontal cortices (DeRubeis et al., 2008; Goldapple et al., 2004; Ritchey et al., 2011; Yoshimura et al., 2014). A recent study (Shou et al., 2017) and a review (Mason et al., 2016) of predictors and mechanisms of CBT have also reported that evidence of functional connectivity resulting from CBT was most commonly found in fronto-limbic circuitry. Therefore, we hypothesize that successful behavioral activation would induce changes in functional connectivity of anterior DMN subnetwork. Based on this hypothesis and the method of previous studies (Li et al., 2013), we used only the anterior and posterior subnetworks in the analyses. We did not focus on the temporal lobes, which are also considered to be key regions within the DMN.

2. Methods

2.1. Participants

Participants with subthreshold depression were recruited among freshmen attending Hiroshima University (age = 18–19) as diagnosed by the Beck's Depression Inventory-II (BDI-II: Kojima and Furukawa, 2003) and the Japanese version of the Composite International Diagnostic Interview (CIDI: Kawakami et al., 2005). Participants scoring 10 or more points on the BDI-II at all three time points [screening (week 0): $M \pm SD = 19.30 \pm 4.27$, range = 14 to 31, conducing the CIDI (week 20): $M \pm SD = 16.28 \pm 4.53$, range = 10 to 30, and pre-intervention fMRI scanning (week 25): $M \pm SD = 15.4 \pm 3.96$, range = 10–27] were considered as having subthreshold depression. Participants that met the following criteria after the CIDI conducted by evaluators blind to the subject's assigned group were excluded from this study: (a) major depressive episode within the past one year, (b) a lifetime history of bipolar disorders, (c) taking psychopharmacological or psychological treatment within the past year, and (e) possibility of acute suicide attempts. The remaining participants with subthreshold depression ($n = 40$) were included in the study and were randomly assigned to either an intervention ($n = 19$) or a non-intervention group ($n = 21$).

The intervention group took part in five, weekly, behavioral activation sessions that were conducted by a trained therapist for 60 min per session. The Behavioral activation program (Takagaki et al., 2016) was focused on expanding positively reinforcing activities in order to increase the rate of response-contingent positive reinforcement. First, participants learned to assess their long and short-term goals, and to develop activity monitoring based on psycho-education about depression and behavioral activation (Session 1). Next, they constructed a behavioral ranking consisting of 10 tasks that gave participants a sense of reward (Session 2). Sessions 2–4 focused on behavioral experiments and increasing scheduled activities. In the last session (Session 5), they reviewed behavioral activation and developed a coping behavior plan for stressful situations in the future. Sessions 1–4 included homework. We have already conducted a randomized controlled trial to confirm the effectiveness of this program for late adolescents with subthreshold depression (Takagaki et al., 2016). This program is highly effective in significantly reducing depressive symptoms (Hedges' $g = -.90$) and increasing health-related QOL (Hedges' $g = .57$–$.77$). Participants in the intervention group completed clinical measures, and rs-fMRI scanning was conducted at pre and post intervention. None of the subjects were absent for any of the sessions. They completed all of their homework assignments. Furthermore, a trained therapist conducted the intervention, and adherence to the protocol was assessed as being 100% by two supervisors (for details see Takagaki et al. (2016)). The non-intervention group also participated identically in the study, with the exception of the intervention program. All participants provided their written informed consent before participating in the study. The study was approved by the ethics committee of Hiroshima University.

2.2. Clinical measures

2.2.1. Japanese version of the Beck's Depression Inventory-II (BDI-II)

The BDI-II is widely used scale for assessing symptoms that consist of 21 self-report items. The items are scored using a 4-point scale. The Japanese version of the scale has demonstrated reliability and validity (Kojima and Furukawa, 2003).

2.2.2. Japanese version of the Behavioral Activation for Depression Scale (BADS)

The BADS (Kanter et al., 2007) measures the frequency of activation, and consists of 25 items that are rated on a 7-point scale (0: Not at all to 6: Completely). Four subscales of BADS are Activation (AC: 7 items) representing focused, goal-directed activation and completion of scheduled activities, Avoidance/Rumination (AR: 8 items) representing avoidance of negative aversive states and engaging in rumination, Work/School Impairment (WS: 5 items), and Social Impairment (SI: 5 items). We used only the BADS-AC subscale, because our program focused on increasing access to positively reinforcing activities to

improve the rate of response-contingent positive reinforcement. The Japanese version of the BADS has demonstrated reliability and validity (Takagaki et al., 2013).

2.2.3. Japanese version of Environmental Reward Observation Scale (EROS)

The EROS (Armento and Hopko, 2007) is used to assess exposure to environmental rewards deemed essential for increasing response-contingent positive reinforcement. Items were composed of behaviors and positive affects as a consequence of rewarding environmental experiences (Armento and Hopko, 2007). The original version of the scale consists of 10 items that are scored on a 4-point scale (1: Strongly disagree to 4: Strongly agree). The Japanese version of EROS has demonstrated reliability and validity (Kunisato et al., 2011).

2.2.4. Japanese EuroQOL-5 Dimension (EQ-5D)

The EQ-5D (Euroqol Group, 1990) was developed to assess health-related quality of life and consists of 5 self-report items (3-point scale) and a visual analogue scale (VAS). The self-report items reflect health scored from 0 (death) to 1 (perfect health). VAS evaluates health status as ranging from 0 (worst imaginable health state) to 100 (best imaginable health). The Japanese version of the EQ-5D has demonstrated reliability and validity (Nishimura et al., 1998).

2.3. fMRI data acquisition

Imaging data were acquired using a 3.0T SIEMENS MAGNETOM with a 12-channel head coil (Siemens, Munich, Germany). Resting-state echo planar imaging (EPI) acquired for approximately 10 min for each participant (40 slices; TR/TE = 2500/30 ms; thickness = 3.2 mm; FOV = 212 × 212 mm; flip angle = 80°; matrix = 64 × 64; 244 volumes). During the rs-fMRI scans, participants were instructed to keep looking at a central fixation point, to keep still, to stay awake, and not to think about anything specific. Anatomic T1-weighted images were acquired using an MPRAGE sequence (192 slices; TR/TE = 2300/2.98 ms; thickness = 1 mm; FOV = 256 × 256 × 192 mm; flip angle = 9°; matrix = 256 × 256). All participants had not used nicotine or alcohol because the law prohibits people under 20 from taking these substances in Japan, and these compliances were confirmed by the investigators. Moreover, participants had not used caffeine at least 3 days prior to the scanning session.

2.4. fMRI data preprocessing

Preprocessing was performed via Statistical Parametric Mapping software (SPM8: www.fil.ion.ucl.ac.uk/spm). The first four volumes of rs-fMRI data were discarded to ensure signal equilibrium and participants' adaptation to scanning noise. After this the remaining 240 images were first time-corrected for each participants (slice timing) and subsequently realigned by using rigid body transformation. The T1-weighted anatomical volume was coregistered to the mean image created by the realignment procedure and was normalized to the Montreal Neurological Institute (MNI) space using a tri-linear interpolation. All functional images were then smoothed using 6-mm full-width at half-maximum Gaussian kernel.

2.5. Independent component analysis and selection on networks-of-interest

We performed group-ICA using the GIFT-software (http://icatb.sourceforge.net/l). ICA is a data-driven technique for identifying functional connectivity patterns in resting-state fMRI (Beckmann, 2012). As head motion may have both noise and neuronal effects on functional connectivity measures (Satterthwaite et al., 2012; Zeng et al., 2014a, 2014b), we confirmed that there were no differences in head motion parameters by comparing the groups as well as pre-intervention and post-intervention before performing ICA. Based on previous studies (Allen et al., 2011; Manoliu et al., 2013), we decomposed our data into 75 components based on the infomax-algorithm (Calhoun et al., 2001). It has been demonstrated that decomposing into 75 components is optimal for detecting between-group differences and for avoiding false positive results (Abou-Elseoud et al., 2010). The reliability and robustness of the estimated components were subsequently maximized by running 20 iterations of the ICA using the ICASSO toolbox (Himberg et al., 2004). Then, to identify DMN components, we performed multiple spatial regression analyses on spatial maps of the 75 components using three DMN templates, reflecting anterior, inferior posterior, and superior posterior subnetworks. These templates were chosen from T-maps of 28 resting-state networks available on Internet (Allen et al., 2011: http://mialab.mrn.org/data/hcp/RSN_HC_unthresholded_tmaps.nii). We selected the three DMN components having the highest correlation coefficients (component 13: .47, $p < .05$; component 56: .45, $p < .05$; component 39: .32, $p < .05$) with the templates. The amplitude of each component is known to reflect the contribution of each voxel to the distribution and the coherent activity within that component and therefore, it is interpreted as a functional connectivity (Manoliu et al., 2013).

2.6. Statistical analyses

Voxel-wise one-sample *t*-tests were used to identify the spatial pattern of each DMN component (multiple comparisons with $p < .05$ family-wise-error correction on the peak- and cluster-level). We then used the mask obtained from one-sample *t*-test results corresponding to each components for the following brain analysis. Each mask was created by combining the spatial maps of the two groups obtained from one-sample *t*-test results for each components within intervention and non-Intervention groups, respectively. Intervention effects on clinical states such as depressive symptoms were examined by using two-way analyses of covariance (ANCOVAs), with groups and time points as independent variables and clinical scores (e.g. BDI-II) as dependent variables. Age and gender were included in the analyzed model as covariates. Bonferroni corrected post-hoc tests ($p < .05$) were conducted to specify significant group and time effects. For the whole brain analysis, we decided on a cut off threshold of $p < .001$ uncorrected and a spatial extent of 10 voxels ($k > = 10$) to avoid Type II errors (Lieberman and Cunningham, 2009). And similar ANCOVA models were applied to the amplitude of the voxels within each component in order to examine the effect of the intervention on each DMN component. Finally, we calculated correlations between the degree of changes in functional connectivity, by subtracting the pre-component image from the post-component image using ImCalc on SPM within the resulting areas of ANCOVAs interaction, and clinical scores within each group. The statistical threshold for these correlation analyses was set at $p < .05$.

3. Results

3.1. Subnetworks of the DMN in subthreshold depression

Three components of the DMN subnetworks were identified in all participants (Fig. 1): component 13 representing the anterior DMN (aDMN) had the highest amplitude in ACC and MPFC, component 56 representing the inferior posterior DMN (ipDMN) had the highest amplitude in PCC, and component 39 representing the superior posterior DMN (spDMN) had the highest amplitude in precuneus.

3.2. Intervention effects on clinical scores

Results of ANCOVAs conducted on scores of most clinical scores assessment scales (BDI-II, BADS-AC EROS and VAS of EQ-5D) showed significant interactional effects between group and time (Table 1; BDI-II: F (1, 36) = 7.34, $p < .05$, *partial* η^2 = .17; BADS-AC: F (1, 36)

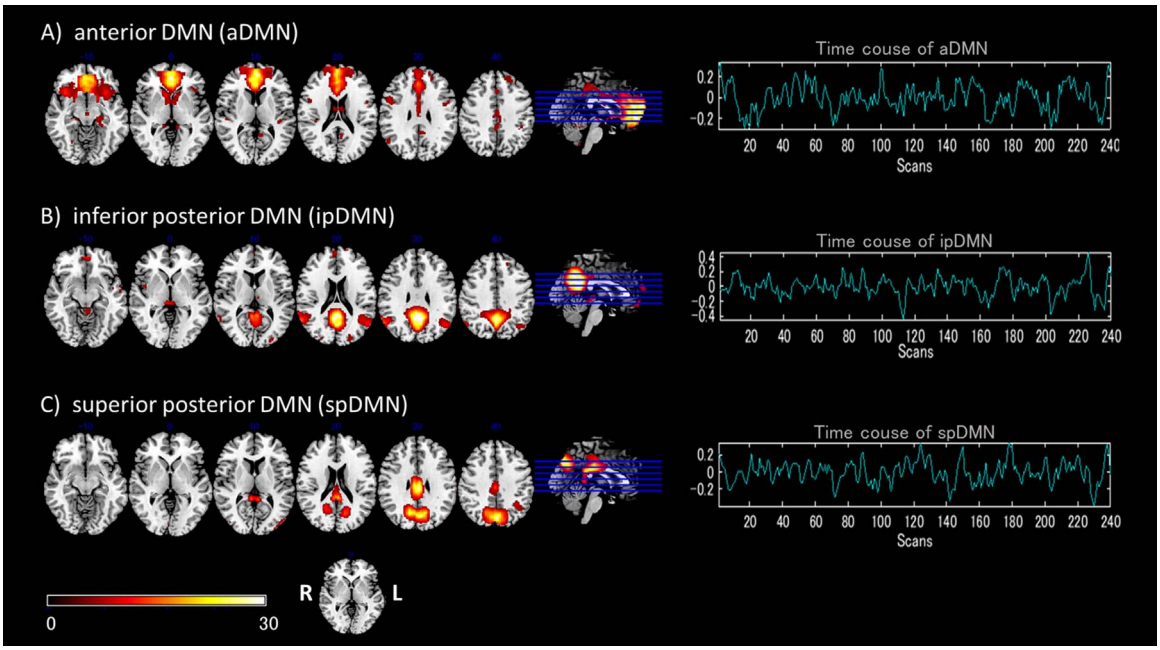


Fig. 1. T-maps and the corresponding time courses of three components reflecting the default mode subnetworks (DMN) in all participants (one-sample *t*-test, $p < .05$ family-wise-error correction on the voxel-level and $p < .05$ family-wise-error correction on the peak- and cluster-level). (A) Anterior DMN (aDMN); (B) Inferior posterior DMN (ipDMN); (C) superior posterior DMN (spDMN). Color scales represent t-values from 0 to 30.

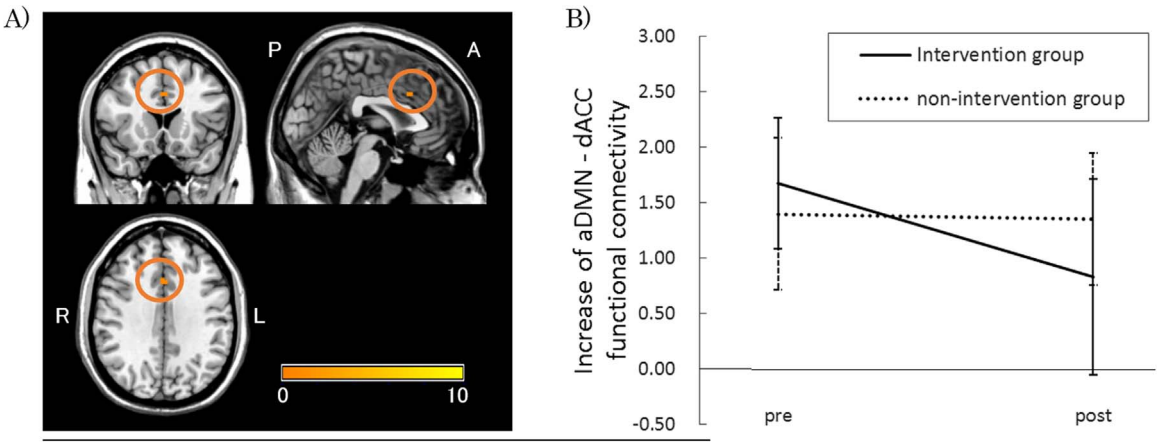
$= 26.00$, $p < .001$, *partial* $\eta^2 = .42$; EROS: $F(1, 36) = 6.67$, $p < .05$, *partial* $\eta^2 = .16$; VAS of EQ-5D: $F(1, 36) = 12.23$, $p < .001$, *partial* $\eta^2 = .25$). Post-hoc analysis with Bonferroni correction indicated significantly lower BDI-II and higher EROS and VAS scores at post-intervention in the intervention group compared to the non-intervention group (BDI-II: $p < .01$, *partial* $\eta^2 = .14$; EORS: $p < .05$, *partial* $\eta^2 = .12$; VAS of EQ-5D: $p < .001$, *partial* $\eta^2 = .30$). There were also significant improvements in the intervention group at post-intervention compared to pre-intervention (BDI-II: $p < .001$, *partial* $\eta^2 = .36$; BADS-AC: $p < .001$, *partial* $\eta^2 = .55$; EROS: $p < .01$, *partial* $\eta^2 = .24$; VAS of EQ-5D: $p < .01$, *partial* $\eta^2 = .19$). BADS-AC score of the non-intervention group at pre-intervention was higher than that of the intervention group ($p < .01$, *partial* $\eta^2 = .18$). Therefore, we used the BADS-AC score at pre-intervention as a covariate in the subsequent analysis. These ANCOVAs are described in the next section. Moreover, there was a significant reduction of VAS in the non-intervention group ($p < .05$,

Table 1
Characteristics and the results of ANCOVAs for each clinical scores.

	Intervention group (n = 19)		Non-intervention group (n = 21)		Group differences	
	Pre	Post	Pre	Post	$t/F/\chi^2$ values	*Post-hoc comparison*
Age	18.21 (0.42)		18.19 (0.40)		0.15[*]	
Gender (f/ m)	6/13		7/14		0.01[n.s.]	
BDI-II	15.42 (4.14)	9.26 (6.68)	15.38 (3.89)	14.38 (6.58)	7.34[*]	Intervention < Non-intervention at post [**] Post < pre at intervention [**]
BADS-AC	10.58 (4.90)	18.63 (6.66)	15.33 (5.99)	14.86 (5.46)	26.00[**]	Intervention < Non-intervention at pre [**] Pre < post at intervention [**]
EROS	22.11 (2.77)	25.42 (4.74)	22.38 (4.26)	22.19 (4.25)	6.67[*]	Non-intervention < Intervention at post [*] Pre < post at intervention [**]
EQ-5D total	0.90 (0.12)	0.90 (0.12)	0.86 (0.12)	0.84 (0.14)	0.14[n.s.]	
VAS	65.05 (15.17)	75.68 (9.43)	66.19 (13.68)	58.90 (16.18)	12.23[**]	Non-intervention < Intervention at post [**] Pre < post at intervention [**] Post < pre at non-intervention [*]

Note: BDI-II = Beck's Depression Inventory-II; BADS-AC = Behavioral Activation for Depression Scale- Activation; EROS = Environmental Reward Observation Scale; EQ-5D = EuroQOL-5 Dimension; VAS = visual analogue scale

[n.s.] $p > .10$.
[*] $p < .05$.
[**] $p < .01$.



BA	Side	Z	p	K_E	x	y	z
32	L/R	3.98	0.000	10	0	18	34

Fig. 2. *The dACC in the aDMN component that showed a significant interaction between group and time.* A) T-map of the activation greater or equal to 10 voxels reported at the threshold $p = .001$, uncorrected. BA = Brodmann area; L = Left; R = Right; Z = Z value of the peak activation within the cluster; p = Uncorrected p value at peak level. Coordinates for the peak voxel are listed as MNI coordinates. A color scale represents t –value from 0 to 10. B) The change of dACC within the aDMN of each group. Error bars represent standard deviations. aDMN = anterior default mode network; dACC = dorsal anterior cingulate.

partial $\eta^2 = .11$).

3.3. Changes in DMN subnetworks after behavioral activation

The results of ANCOVAs are shown in Fig. 2. It can be seen that there is a significant interactional effect in the dorsal ACC (dACC) within the aDMN component ($p < .001$ uncorrected, $k > = 10$). Fig. 2B shows the coherent activity of the dACC within the aDMN component, which implies a functional connectivity between the dACC and this component, in both groups at each time point. Post-hoc analysis revealed that the aDMN-dACC connectivity was significantly reduced in the intervention group ($p < .001$ uncorrected, $k > = 10$). There were no significant interactions, or main effects of group or time in the ipDMN or the spDMN.

3.4. Correlations of the DMN subnetworks with clinical scores

We conducted correlation analyses with differences between pre and post intervention in aDMN-dACC functional connectivity and clinical data in order to explore associations between changes in aDMN-dACC connectivity and treatment response. We found a significant negative correlations between change in aDMN-dACC functional connectivity and VAS changes of EQ-5D in the intervention group (Fig. 3: $r = -.61$, $p < .01$), which remained significant after controlling for BDI-II score ($r = -.62$, $p < .01$). Other clinical scores were not correlated with change of the aDMN-dACC functional connectivity either both group (BDI-II: $r = .12$, *n.s.*, $r = -.17$, *n.s.*; BADS-AC: $r = -.02$, *n.s.*, $r = .36$, *n.s.*; EROS: $r = .08$, *n.s.*, $r = .06$, *n.s.*; EQ-5D: $r = -.23$, *n.s.*, $r = .10$, *n.s.*; intervention and control group, respectively).

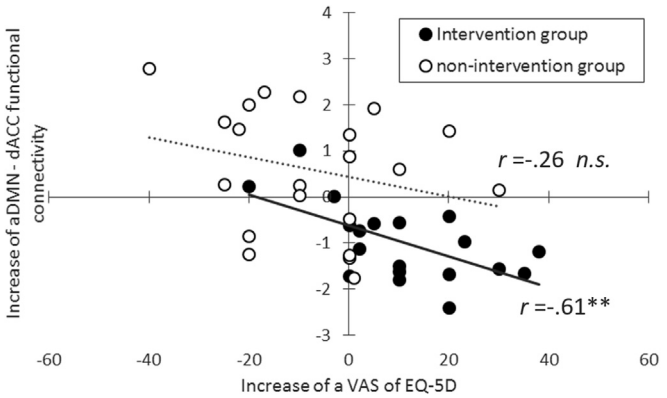


Fig. 3. *A scatter plot of correlations between the changes of aDMN-dACC functional connectivity and a VAS of EQ-5D in each group.* Black = intervention group, and white = non-intervention group. aDMN = anterior default mode network; dACC = dorsal anterior cingulate cortex; VAS = visual analogue scale; EQ-5D = EuroQOL-5 Dimension. $^{n.s.}p > .10$, $^{**}p < .01$.

4. Discussions

There were two main findings of this study. Firstly, among the three subnetworks of the DMN that identified by ICA in participants with subthreshold depression, behavioral activation might have specifically reduced the functional connectivity in the aDMN subnetwork with the dACC at least compared to non-intervention, although it is not possible to make any inferences about causation. Secondly, the reduction in the connectivity between the aDMN and the dACC was negatively correlated with the increase in subjective health-related QOL of the intervention group. This is the first study using rs-fMRI to report the effect of behavioral activation on spontaneous brain functions in people with subthreshold depression.

Decreased functional connectivity between the aDMN and the dACC following behavioral activation, implies that activity pattern of the dACC was de-synchronized with the time series of our aDMN component. On the other hand, behavioral activation had no effect on posterior subnetworks of the DMN (i.e. the ipDMN, or the spDMN). Antidepressants and psychotherapy (e.g. cognitive therapy) is known to work through different mechanisms (DeRubeis et al., 2008). A number of previous studies that examined neural responses to CBT have demonstrated functional brain changes in the dorsal, ventral, and medial frontal cortices (DeRubeis et al., 2008; Goldapple et al., 2004; Ritchey et al., 2011; Shou et al., 2017; Yoshimura et al., 2014) and dorsal/pregenual ACC (Fu et al., 2013; Konarski et al., 2009) related to treatment. CBT-related changes were most commonly observed in the DMN regions, which include the MPFC, PCC, hippocampus, and ACC sub-regions including dorsal, subgenual, and ventral (as review: Franklin et al., 2015). As already mentioned, DMN connectivity is deeply involved with depressive self-referential processing such as rumination (Li et al., 2013; Sundermann et al., 2014a; Zeng et al., 2014a, 2014b). Moreover, the decrease in dACC activity at resting-state following CBT could be conceptualized as the result of CBT improving a

putative 'dorsal cognitive circuit', important in cognitive control and effortful regulation of emotion (Franklin et al., 2015). These findings might suggest that there is a neural circuit of behavioral activation in common with CBT. Whereas one previous study has shown that antidepressants act on the posterior DMN (Li et al., 2013). Goldapple et al. (2004) reported that depressed subjects have shown decreases of activation in the dorsal, medial and ventral prefrontal cortices, in addition to increases of activation in the hippocampus and in the dorsal cingulate cortex after CBT. They also obtained different patterns after paroxetine treatment, including increases in the prefrontal cortex and decreases in the hippocampus and subgenual cingulate. A subsequent study by Kennedy et al. (2007) compared CBT to venlafaxine and replicated these findings, which again suggested different types of neural changes following CBT and pharmacotherapy. Unlike other psychiatric disorders, including obsessive-compulsive and panic disorders, the mechanisms of pharmacological medication and psychotherapeutic treatment in depression seem to be divergent, or only partly overlapping (Barsaglini et al., 2014). Our results suggested that behavioral activation might act differently to pharmacotherapy, by changing the anterior subnetwork of the DMN, which supported our hypothesis and findings of previous studies investigating the neural responses to CBT.

Generically speaking, the dACC is known as a core region of the salience network (SN: Menon and Uddin, 2010), which is typically distinguished from the DMN. However, in this study, ICA analysis of our data on participants with subthreshold depression identified the DMN and the dACC as identical component. ICA is a data-driven analysis method and our data points were composed mainly of subjects with subthreshold depression who had not been subjected to an intervention (pre-intervention and non-intervention conditions), which resulted in the dACC being included in the aDMN "component". It has been reported that increased functional connectivity is observed between the DMN and other regions, which the included bilateral middle frontal gyrus, left superior frontal gyrus, right inferior frontal gyrus, ventral striatum, thalamus, parahippocampus, and insula, in people with subthreshold depression (Hwang et al., 2016) and that functional connectivity between the DMN and the SN is stronger in patients with MDD than in healthy participants (Manoliu et al., 2013). These findings suggested that enhanced functional connectivity between the DMN and the dACC in the SN might be closely associated with the pathology of subthreshold depression. The SN, which anchors the dACC and the anterior insula, is known to be involved in the detection of salient stimuli and events (Seeley et al., 2007) in order to guide behavior (the ACC is involved in action selection in particular: Rushworth, (2008), and play a central role in biased negative informative processing in depression (Hamilton et al., 2012). High aDMN-dACC connectivity during the resting-state might reflect co-working of internal self-reference processing (DMN) and the detection of these internal stimuli (SN). In addition, the SN critically contributes to switching between the DMN and the executive network, so the dACC and anterior insula are uniquely positioned to initiate control signals that deactivate the DMN and activate the executive network (Seeley et al., 2007). Therefore, individuals with enhanced connectivity of the two networks, DMN and SN, might be contribute to directing attention to internal-self stimuli, without awareness of external stimuli as a consequence of deactivation in the executive network that contributes to the control of active attention. Again, our results revealed that the contribution of the dACC absorbed in the aDMN component has decreased following behavioral activation. This indicated that the dACC might not have been included in the aDMN component after intervention, as it is originally defined. Our behavioral activation program was developed for the purpose of increasing participants' access to positive activities, which was accompanied by reinforcements from their environment (Takagaki et al., 2016). Results indicated an increase in these activities and an increase in exposure to environmental rewards (Table 1), suggested that this purpose was adequately achieved. The dACC would be activated when detecting the reward and selecting behavior, and would be required to control aDMN deactivation. Such practices might have increased opportunities for activating the dACC and deactivating the DMN. The mechanisms of behavioral activation might be related to enhanced ability to independently use the dACC and the DMN, which advanced the control of attention favoring positive stimuli from the external environment. The use of a placebo and comparison with other psychotherapies are expected to further clarify this interesting mechanism.

The dACC plays a critical role in the development of cognitive control skill that are required for adaptive functioning (Ordaz et al., 2013). Moreover, it is known that dACC activity increases with aging (Rubia, 2013) from childhood (9–17 years) to adulthood (18–26 years). One model of adolescent brain development (Crone and Dahl, 2012) describes the gradual development of the cognitive control system (dACC, dorsolateral PFC and the parietal cortex) interacting with social-affective processing and leading to increased adaptive adult functioning such as social motivation and tendencies to explore, take risks and try new things. Additionally, within-functional networks (including the DMN) are enhanced during development from early adolescence to late adolescence (Fair et al., 2008; Kelly et al., 2009; Saverino et al., 2015). A recent study on enhanced connectivity of depressed youth in remission (Jacobs et al., 2014) has also reported hyper-connectivity of the DMN and SN, whereas young adolescents with depression did not shown significant differences in resting-state DMN connectivity compared to health young adolescents (Pannekoek et al., 2014). Because the participants in this study were late adolescents, changes in DMN-dACC connectivity might be critical to many domains of adaptive adult functioning. Therefore, we suggest that future studies investigate other age groups such as children and adults with and without depression by using the research design developed in this study.

Certain late adolescents with subthreshold depression show increased depressive symptoms and develop a major depressive episode during the natural course of one year (Jinnin et al., 2017). Therefore, it is significant that behavioral activation results in positive changes in many clinical variables for late adolescents. Results also indicated an association between changes in connectivity within the aDMN component and VAS score of EQ-5D, which is a measure of health-related QOL. This was not the case between connectivity and other clinical variables such as the BDI-II, BADS, or EROS. Recently, QOL has been recognized as a more pertinent outcome measure because improvement of QOL is important in clinical settings as well as improvements of symptoms (Satomura et al., 2014). Individuals with subthreshold depression have lower depressive symptoms than patients with depression. Nevertheless, functional impairments in subthreshold depression are severe and serious (Bertha and Balázs, 2013; Nierenberg et al., 2010). Our previous study (Takagaki et al., 2016) reported that behavioral activation for subthreshold depression improves health-related QOL. Therefore, it is significant that changes in functional connectivity, possible caused by behavioral activation, were linked to the positive effects experienced by the participants. Faget-Agius et al. (2016) investigated brain functions associated with the QOL of schizophrenia patients using whole-brain single photon emission computed tomography in the resting-state. Their result indicated that not only the prefrontal area but also areas of the DMN such as precuneus (Buckner et al., 2008) and areas co-activating with the DMN such as parahippocampal gyrus (Greicius et al., 2003) were related to QOL. Although there are still few studies on the relationship between QOL and brain functions, our results showing that a change in the aDMN-dACC connectivity was associated with health-related QOL also where quite consistent with their results. As discussed in the previous paragraph, the reduction in aDMN-dACC functional connectivity would have advanced the control of attention to positive stimuli, and both the DMN and the dACC are associated with better prediction of treatment outcome (Fu et al., 2013; Ritchey et al., 2011). It is possible that increased awareness of positive stimuli in the reward acquisition process, which was associated with a reduction in aDMN-dACC connectivity following our behavioral activation program might result in an enhanced outlook on

health in life.

The results of this study are constrained by several limitations. Firstly, we did not compare the enhanced functional connectivity between the DMN and the dACC found in people with subthreshold depression with healthy participants. Moreover, we used thresholds recommended for balancing Type I and Type II error (Lieberman and Cunningham, 2009). Our findings must be considered preliminary because we did not use correction methods for multiple comparisons. The detection of intervention effects should be re-examined using more severe thresholds or correction for multiple comparisons to avoid Type I errors. Although abnormal change in functional connectivity of the DMN in people with subthreshold depression have already demonstrated in a previous study (Hwang et al., 2016), further research should be conducted by including healthy controls to verify the results of this study. Second, we did not examine the function of aDMN-dACC using measures of directing attention to internal-self stimuli, or awareness of external stimuli. There is a need to conduct a mediation analysis, particularly with regard to the association with health-related QOL. Nevertheless, we could not conduct such a mediation analysis because of the small sample size. The assessments of such psychological functions are necessary in order to examine the consideration that we have stated in the discussion. Thirdly, the lack of a placebo group makes it difficult to attribute the findings of this study to any specific treatment effects. This is because the effects of other specific factors, known to be related to the treatment efficacy of psychotherapy independently of its orientation (CBT, Psychodynamic treatment etc.) cannot be discounted. Fourth, we focused on subthreshold depression and did not include clinical course data (e.g. development of MDD) in our analyses. The study how behavioral activation and brain function are related to future depression is also required in the future. Finally, our sample was not population-based, and participants were students of the same university, limiting the generalizability of our findings. Nevertheless, the homogeneity of the sample might also be a strength of this study because it diminished the possible effects of demographic variables as confounds.

5. Conclusions

Behavioral activation induced a specific reduction in functional connectivity between the aDMN subnetwork and the dACC compared to the non-intervention group, which was negatively correlated with an increase of subjective health-related QOL in the intervention group. Mechanisms of the therapeutic efficacy of behavioral activation might be related to enhancing the ability for independently using the dACC and the DMN, which might advance an attention control directed at positive stimuli in the external environment. These findings contribute to our understanding of neural mechanisms of behavioral activation on subthreshold depression.

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