PAPER

Formulation of Mindfulness States as a Network Optimization Problem and an Attempt to Identify Key Brain Pathways Using Digital Annealer

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SUMMARY Although intervention practices like mindfulness meditation have proven effective in treating psychosis, there is no clarity on the mechanism of information propagation in the brain. In this study, we formulated a network optimization problem and searched for the optimal solution using Digital Annealer developed by Fujitsu Ltd. This is inspired by quantum computing and is effective in solving large-scale combinatorial optimization problems to find the information propagation pathway in the brain that contributes to the realization of mindfulness. Specifically, we defined the optimal network state as the state of the brain network that is considered to be associated with the mindfulness state. We formulated the problem into two network optimization problems—the minimum vertex-cover problem and the maximum-flow problem—to search for the information propagation pathway that is important for realizing the state. In the minimum vertex-cover problem, we aimed to identify brain regions that are important for the realization of the mindfulness state, and identified eight regions, including four that were suggested to be consistent with previous studies. We formulated the problem as a maximum-flow problem to identify the information propagation pathways in the brain that contribute to the activation of these four identified regions. As a result, approximately 30% of the connections in the brain network structure of this study were identified, and the pathway with the highest flow rate was considered to characterize the bottom-up emotion regulation during mindfulness. The findings of this study could be useful for more direct interventions in the context of mindfulness, which are being investigated by neurofeedback and other methods. This is because existing studies have not clarified the information propagation pathways that contribute to the realization of the brain network states that characterize mindfulness states. In addition, this approach may be useful as a methodology to identify information propagation pathways in the brain that contribute to the realization of higher-order human cognitive activities, such as mindfulness, within large-scale brain networks.
key words: *mindfulness states, minimum vertex-cover problems, maximum-flow problems, digital annealer*

1. Introduction

In this section, we first explain the background of the research in Sect. 1.1 and the purpose and possibilities of the research in Sect. 1.2. Finally, the flow of this paper is explained in Sect. 1.3.

1.1 Theoretical Background

1.1.1 Previous Research on Mindfulness and Issues

Interventions including mindfulness meditation and short-term intensive programs, such as mindfulness-based stress reduction (MBSR), have been reported to have therapeutic effects on psychosis, including depression and social anxiety [1], [2]. Mindfulness meditation, such as Zen and Vipassana, inspired by Eastern meditation techniques, involve becoming aware of the ever-changing perceptual field and paying attention to the present moment with an attitude of accepting its perceptual content without judgment [3]. The practice of mindfulness involves, in various ways, controlling the focus of attention, suppressing elaborate thoughts, and re-directing or disengaging attention after a lapse [4]. The state of *mindfulness* achieved through mindfulness meditation is mostly defined as "paying attention in a particular way: on purpose, in the present moment, and non-judgmentally" (p.4, [5]). Although the mindfulness state has attracted attention because of its effects, the mechanism of information propagation in the brain that realizes the mindfulness state is unclear. Many basic studies have been conducted accordingly in recent years. Most of the neuroscientific findings that have studied emotion regulation through mindfulness meditation are based on fMRI (e.g., [6] see above), diffusion tensor imaging (e.g., [7]), and voxel-based morphometric techniques (e.g., [8]). In addition, in recent years, many review articles have systematically summarized existing neuroscientific findings, such as those presented above [9], [10]. Tang et al. have found that the anterior cingulate cortex (ACC) and striatum of the basal ganglia are involved in attentional control; that the multiple frontal regions, limbic regions, and the striatum are involved in emotional control; and that the insula, medial prefrontal cortex (mPFC), and posterior cingulate cortex are involved

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in self-awareness. The striatum as well as the insula, medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and precuneus are involved in self-awareness [9]. According to Young et al., the caudate nucleus and several frontal regions are involved in attentional control, and the ACC and insula are involved in self-awareness. In particular, the most consistent finding in their study was the activation of the insula, which is associated with self-awareness [10].

The aforementioned studies have led to a better understanding of the individual brain regions involved in mindfulness. However, a wide range of brain regions could possibly be involved in mindfulness states. In addition, since the complex mental state of mindfulness is thought to be supported by changes in large-scale brain networks, future studies should consider comparing not only the intensity of activation in single brain regions, but also the analysis of complex networks [9]. Therefore, it has been pointed out that future research should focus on the interaction of multiple brain regions and the dynamics of their information propagation, rather than on specific brain regions [9]. Farb et al. reported enhanced functional connectivity between the right insula-left dlPFC and attenuated functional connectivity between the right insula-left vmPFC through MBSR training [11]. Tang et al. also investigated whether 11 h of integrative body mind training (IBMT) could change the phase characteristics of the anterior cingulate cortex of the brain functional network [7]. They suggested that the network properties of the resting anterior cingulate cortex were altered by brief meditation. Furthermore, Sharp et al. investigated changes in structural neuroplasticity within brain network structures after 70 minutes of mindfulness meditation training and reported an increase in structural connectivity in the right insular cortex (e.g., between the insula and OFC, between the insula and olfactory entorhinal cortex) [12]. Mooneyham et al. described the characteristics of the brain networks involved in mindfulness—the default mode network (DMN), the salience network (SN), and the central executive network (CEN). They summarized the findings related to changes in functional connectivity (FC) within and between these networks [4]. They then reported two of the most reliable findings: increased intra-network FC between the default network regions of the PCC and vmPFC, and increased inter-network FC between the dlPFC (executive) and insular cortex (attention).

The trend that suggests the need to map human cognitive activity to the state of the network, rather than to the neural activity of local brain regions, is not limited to mindfulness. There have been studies that consider brain networks within the field of complex networks; these studies analyzed the importance of influential nodes in the network, such as hub regions, as well as the state and structural characteristics of the network that characterize certain states (see, e.g., [13] for more details). For example, complex symptoms of the psyche, including illusions and delusions, are framed in terms of a breakdown in the interaction between regions within the network and in the network's widespread integration processes (e.g., [14]). In particular, the "disconnection hypothesis" in schizophrenia suggests that abnormalities in the regulation of synaptic plasticity by the ascending modulatory neurotransmitter system lead to the failure of functional integration of scattered neural systems [15]. In addition, the relationship between brain regions and cognitive functions is probably not one-to-one, but many-to-many, except for the sensory and motor regions [16]. Thus, human cognitive activity, especially higher-order cognitive activity, such as mindfulness, in which multiple cognitive functions interact, requires the conjoint functioning of brain regions that work together as a large network [17], and Olaf states that "cognitive activity is a networked phenomenon." (p.190, [18]). Olaf suggested that even in the same network state, different complex functions are achieved by different combinations of elements in the network at different times under varying input or task conditions [18]. Therefore, it is necessary to address the question of what kind of information propagation is involved in the realization of the state of the brain network corresponding to the mindfulness state. To address this problem, it has been pointed out that it is difficult to clarify the dynamics of information propagation in large-scale brain networks using existing experimental methods, and that computational modeling is important [19].

1.1.2 Our Approaches and Related Theory

In light of the above background, computer simulations have been used to investigate the propagation of information within the network structure of the brain based on our knowledge of multiple brain regions affected by mindfulness [20]. In this study, mindfulness meditation was represented as a change in the parameters of a computational model that specifies the propagation of information in the brain, and qualitative changes in the behavior of each brain region were observed by simulation [20]. We observed a behavior consistent with that reported in previous studies, suggesting that the mindfulness state may be realized by a state in which bottom-up information processing is dominant in the brain [20]. In addition, Nakamura et al. found that the brain regions that are activated by the propagation of information are those with the highest input and output in the brain network structure, and as a result, the brain network structure realized by mindfulness meditation is a state in which information is propagated to more brain regions in the network structure [21]. It is noted that the state of being consciously aware of one's own perceived sensory stimuli (meta-awareness) is important for mindfulness. The processing that rises to consciousness corresponds to a state in which information is propagated to a wide range of regions in the brain, e.g., in global neural workspace theory [22]. From this, we consider the possibility that the propagation of information to more brain regions may realize the meta-awareness that characterizes mindfulness.

Accordingly, we clarified how the mindfulness state is realized in the brain and how it corresponds to the state of the network structure in the brain, which has only been partially identified in existing studies. On the other hand, as mentioned earlier, mindfulness is associated with the involvement of many brain regions; however, the identity of the important brain regions are still unclear. In addition, although Nakamura et al. discussed the mechanism of information propagation in the brain, it is still challenging to identify the information propagation pathways that contribute to the realization of a mindfulness state. To identify these pathways it is necessary to investigate options among the combinations of pathways in a large-scale network structure, and a high-power/ high-capacity computational environment is required for this purpose.

1.2 Purpose and Significance of This Study

Based on the above, we attempt to clarify what states of the brain network structure realize the state of mindfulness, formulate it as a network optimization problem, and identify the information propagation pathways in the brain network structure that contribute to its realization. It should be noted that we do not formulate our research in terms of how the brain achieves the optimal network state at "computational level." [23]. We only formulate the search for brain regions and pathways that are important in the network structure when the optimal network state is realized. Fujitsu Ltd.'s Digital Annealer (DA) is used to search for solutions to network optimization problems. Digital Annealer are made of digital circuits and can handle large problems with up to 8192 all-bit interconnections [24].

The significance of this study is as follows. This study's research approach is academically significant. Although this study focuses on mindfulness, this research approach is significant as a framework for identifying the state of brain networks that correspond to higher-order cognitive activities in humans and the information propagation pathways that contribute to their realization, independent of mindfulness. Peterson et al. point out that human higher-order cognitive activities cannot be explained by individual brain regions alone and require the interaction of multiple brain regions that collaborate as a large-scale network [17]. Therefore, human higher-order cognitive activity can be mapped as the state of a brain network realized by the interaction of multiple brain regions. The identification of information propagation pathways that contribute to the realization of such a state will lead to the elucidation of the mechanism of realization of higher-order cognitive lightening in humans. In such cases, there are many combinations of important brain regions and important information propagation pathways, such as the number of regions in a large-scale brain network structure and the number of possible pathways between regions. Therefore, the use of DA as a methodology to search for solutions is an important factor in the success of this approach.

The results obtained from this research approach may be used to examine direct intervention and treatment methods for mental disorders. A recent review by Rabipour and Raz suggests that neurofeedback may be effective for cognitive function and psychiatric disorders [25], and early studies have already shown efficacy for attention deficit disorders. Such mental disorders are known as pathologies in which interactions between domains are disrupted [14], as described in Sect. 1.1. The information on the pathways obtained from this study's methodological approach to identifying exploratory information flow from within a large network structure of higher-order human cognitive activity may be useful for direct intervention methods and treatment of mental disorders that can be associated with the above interactions between domains. Furthermore, in mindfulness, more direct interventions, such as neurofeedback, are now being tested to support people in deepening their meditation in recent years. However, many of the brain regions that are significantly activated during mindfulness are located deep within the brain. If the pathways of information propagation in the brain, that contribute to the realization of a state of mindfulness, are clarified through this research, it may be possible to identify brain regions that are involved during mindfulness. These regions are closer to the surface of the brain and contribute to the activation/deactivation of brain regions located in deeper layers.

1.3 Flow of This Paper

The flow of this paper is described below. The methodology of this study is described in Sect. 2. Next, in Sect. 3, we explain how we specified the network structure that is the subject of this study. In Sect. 4, we describe the brain network states to which the mindfulness state is thought to correspond (henceforth, the optimal network state). We also describe in Sect. 5 the Quadratic Unconstrained Binary Optimization (QUBO) model handled by the digital annealer used to find solutions to the optimization problems in this study. Then, based on the contents of Sects. 3 and 4, the formulation of the network optimization problem is explained in 6. In Sect. 7, we describe how we search for solutions using DA, outline the simulations we perform in this study, and describe the criteria for adopting the results. In Sect. 8, simulation results and discussions are presented. In Sect. 9, we benchmark the execution time of our simulation. Finally, the problem of this study is discussed in Sect. 10, and the conclusion is presented in Sect. 11.

2. Methodology

In this section, we describe the flow of the research and analysis process. Figure 1 shows the flow of this research. In this study, we first define the optimal network state in which the mindfulness state can be associated with the network structure in the brain (see Sect. 3, Sect. 4). Then, we formulate the network optimization problem, which is a type of combinatorial optimization problem, by identifying the information propagation paths in the brain network structure that contribute to the realization of the state. Specifically, we formulate the problem in the following steps (see Sect. 6). To determine the endpoint information necessary for the for-

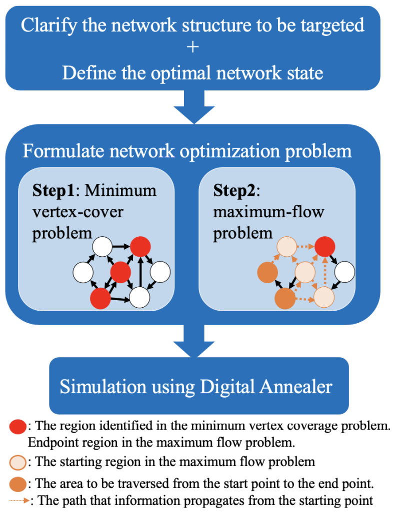

Fig. 1 Formulation of Information Propagation Pathfinding for Network Optimization and Solution Search Using Digital Annealer

mulation of the pathway problem, the brain regions that are important for the realization of the optimal network state are first identified (Step 1), and the information propagation pathways that are important for the activation/deactivation of the activities in the identified regions are determined using the identified regions as endpoints (Step 2). The purpose of Step 1 is twofold. The first is to confirm the validity of the state, clarified as the optimal network state. We assume that most of the brain regions to be identified are those that have been suggested to be involved in the mindfulness state in existing studies. The optimal network state defined in this study may be one of the brain network structures that realizes the mindfulness state if the results are consistent with previous studies, as expected. The second step is to identify the regions that are structurally important for the realization of the optimal network state, even though existing studies suggest the involvement of a wide range of regions in the realization of the mindfulness state [9]. This research aims to identify the information propagation pathways that are important for the realization of mindfulness states by formulating and discovering solutions to the network optimization problem in the above two steps.

The problem is converted to quadratic unconstrained binary optimization (QUBO) (e.g., [26], [27]) for computation using Digital Annealer. For the solution search, we use Digital Annealer inspired by quantum computing. In this study, as a benchmark, we used a computer with 24 Xeon cores and 64GB of memory to compute the same problem, and compared the computation time with that of Digital Annealer.

3. Network Structure Targeted in This Study

To explain higher-order human cognitive activities, such as mindfulness, it is necessary to understand the structure and mechanisms of neurobiological networks at a macroscopic level, rather than at a microscopic level, such as synapses and neurons [17]. Therefore, in this study, the elements of our network model were chosen according to brain parcellations based on cytoarchitecture. We did not model individual neurons, but represented each brain region using a single state variable. Specifically, we defined each region within the cortex as Brodmann area (BA). The other regions were defined as neural populations at the mesoscopic level [28]. In this study, we constructed a network structure with 64 regions as nodes. Table 1 shows the brain regions and the upper categories encompassing each area which constitute the structural network of our study. The selection criteria for 64 regions of the brain are as follows.

1). Regions described by [9], [10], [29], who reviewed cognitive neuroscience studies on mindfulness and mind-wandering.
2). Other brain regions not pointed out in 1), but belonging to the category, except for areas lacking input and output.
3). Each brain region pointed out in anatomical findings [30]–[33] as having a projective relationship to each region in 1). The issues present in the above findings, which this study used to define the connection between the regions, are specified in Sect. 10.

In this study, brain regions constitute structural network nodes, and the connecting pathways constitute structural network edges. We ignored the nature of the connections between regions and created a connection matrix that was 1, if there was a projection relation from one region to another, and 0, if otherwise.

4. Defining the Optimal Network State

As mentioned in Sect. 1.1.2, mindfulness corresponds to a state in which information is propagated to the brain regions in a larger network structure. In addition, as described in Sect. 3, the brain network structure targeted in this study is defined around brain regions related to the state of mindfulness. From this point of view, we define the optimal network state to which the mindfulness state is considered to correspond as “the state in which information is propagated to all brain regions in the network structure at a certain point in time.” Figure 3 shows the optimal network state for a network structure with seven nodes. For example, Fig. 3 (A) shows that at a certain point in time, node A in the network structure will propagate information to the four red nodes via its output. Thus, the activation of nodes A, B, and C at a certain point in time, as shown in Fig. 3 (B), results in a state in which information is propagated to all brain regions, including A, B, and C. In other words, the meaning of information propagation in the graph is defined as the state in which at least one node that projects to a certain node (brain region) is adopted.

5. Digital Annealer

DA by Fujitsu Ltd. [24] aims to solve a combinatorial opti-

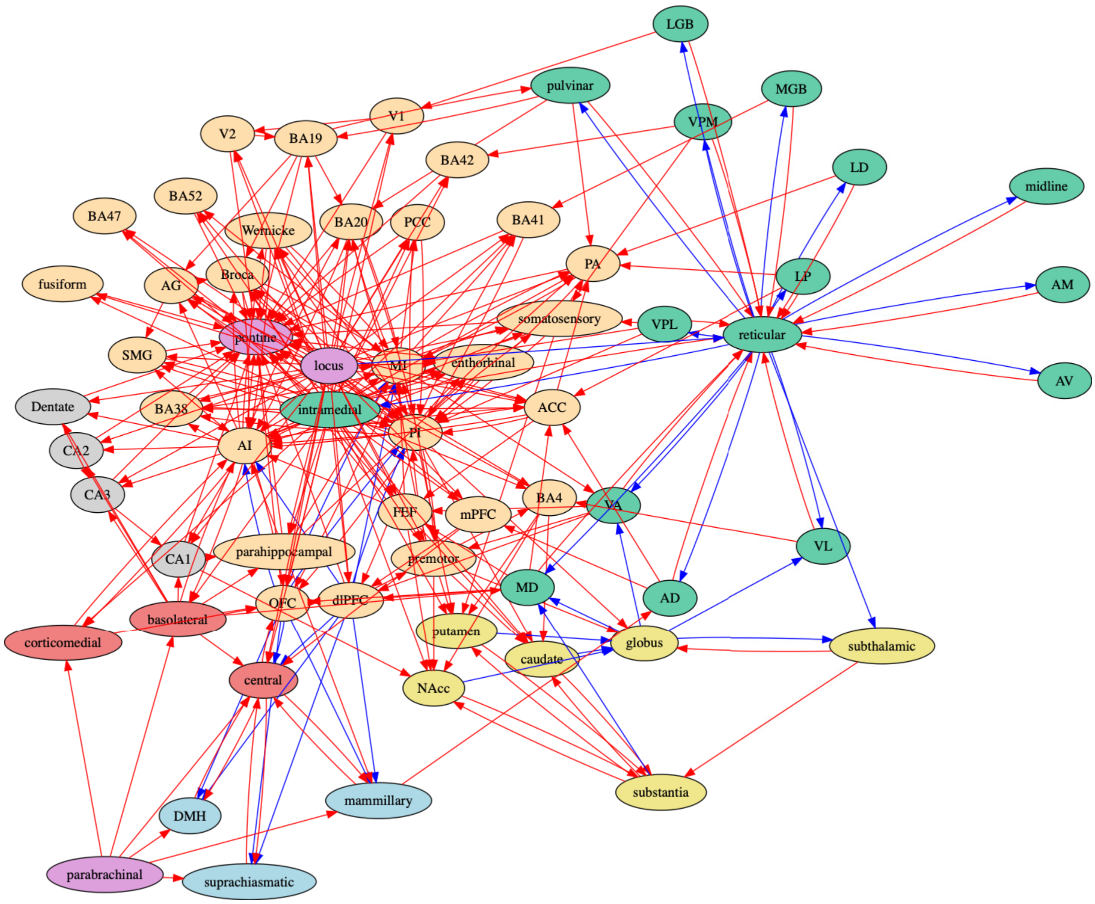

Fig. 2 Network structure. The nodes comprising the network (see Table 1) are described. The orange nodes are regions belonging to the cerebral cortex. Abbreviations: *somatosensory* = somatosensory area (BA1,2,3). *premotor* = PM (BA6). *V1* = primary visual cortex (BA17). *V2* = secondary visual cortex (BA18). *Wernicke* = Wernicke's area (BA22). *parahippocampal* = parahippocampal gyrus (BA36). *entorhinal* = entorhinal cortex (BA34). *fusiform* = fusiform gyrus (BA37). *SMG* = supramarginal gyrus (BA40). *Broca* = Broca's area (BA44, 45). The gray node is a region belonging to the hippocampus. Abbreviation: *Dendate* = the dentate gyrus. The green node is a region belonging to the thalamus. Abbreviation: *midline* = midline nuclear group. *intramedial* = intramedial nuclear group. *reticular* = thalamic reticular nucleus The red region belongs to the amygdala. Abbreviation: *basolateral* = basolateral nucleus *corticomedial* = the corticomedial nucleus. *central* = central amygdaloid nucleus The purple region belongs to pons. Abbreviation: *pontine* = pontine nuclei *locus* = locus coeruleus *parabrachial* = parabrachial nuclei. The yellow region belongs to the basal ganglia. Abbreviation: *subthalamic* = the subthalamic nucleus. *globus* = globus pallidus *caudate* = caudate nucleus *substantia* = substantia nigra. *NAcc* = Nucleus accumbens The edges in the network are described in the text. The red links indicate excitatory projections. Blue links indicate inhibitory projections.

mization problem at high speed with digital circuits inspired by quantum computing. DA can search for the minimum value of the energy function of a QUBO model. DA can only adopt the input of the QUBO model, as shown in Eq. (1):

$$E = -\frac{1}{2}\sum_{i}\sum_{j\neq i} W_{i,j}x_i x_j - \sum_{i} b_i x_i - c, \qquad (1)$$

where W, b, and c are the inputs of DA, and $x_i \in 0, 1$ is a bit. Weight matrix W reflects the quadratic coefficients of the model, while vectors b and c represent linear coefficients and a constant, respectively. The value of c, the elements in W, and the elements of b must be integers. DA calculates the global minimum value of E and outputs the value of all bits x_i when E reaches a minimum. To utilize DA, we have to transform our defined objective function into a QUBO model and to derive three necessary inputs: weight matrix W, vector b, and constant c of DA in Eq. (1). Therefore, in the following, we formulate the network optimization problem as a form of QUBO.

6. Formulation as a Network Optimization Problem

As described in Sect. 2, this study is formulated as a network optimization problem in two steps to find the information propagation pathways in the brain that contribute to the realization of a mindfulness state. We formulate a network optimization problem in two steps. In Step 1, we formulate the

Table 1 Brain regions that are included in our structural network. Abbreviation: *BA* = Brodmann area. *PA* = the parietal association area. *FEF* = frontal eie field *OFC* = orbitofrontal cortex. *MI* = middle insula *PI* = posterior insula *ITG* = inferior temporal gyrus.

Category	Included brain region
Cerebral Cortex	somatosensory area (BA1, 2, 3), primary motor area (BA4), PA (BA5, 7), PM (BA6), FEF (BA8), dlPFC (BA9, 46), OFC (BA11, 12) insula (AI, MI, PI; BA13, 14), primary visual cortex(BA17), secondary visual cortex (BA18), visual association area (BA19), ITG (BA20), Wernicke's area (BA22), PCC (BA23, 31), mPFC (BA10, 24, 25, 32), ACC (BA24, 32), enthorhinal cortex (BA34), parahi-ppocampal gyrus (BA36), fusiform gyrus (BA37), temporal pole (BA38), angular gyrus (BA39), supramarginal gyrus (BA40), prim-ary, auditory area (BA41, 42), primary gustatory area (BA43), Broca's area (BA44, 45), Inferior frontal gyrus (BA47), BA52
The thalamus	anterodorsal nucleus (AD), anteroventral nucleus (AV), anteromedial nucleus (AM), dorsomadial nucleus (DM), midline nuclear gr-oup, intramedial nuclear group, lateral dorsal nucleus (LD), lateral posterior (LP) nucleus, ventral anterior nucleus (VA), ventral pos-terior nucleus (VL), ventral posterolateral nucleus (VPL), ventral posteromedial nucleus (VPM), lateral geniculate body(LGB), med-ial, geniculate body (MGB), pulvinar, thalamic reticular nucleus
Hippocampus	CA1, CA2, CA3, dentate gyrus
Hypothalamus	Mammillary body, suprachiasmatic nucleus, dorsomedial hypothalamic nucleus (DMH)
Basal ganglia	subthalamic nucleus, putamen, globus pallidus, caudate nucleus, substantia nigra, Nucleus accumbens
Amygdala	Basolateral nucleus, corticomedial nucleus, central amygdaloid nucleus
Pons	Pontine nuclei, locus coeruleus, parabrachial nuclei

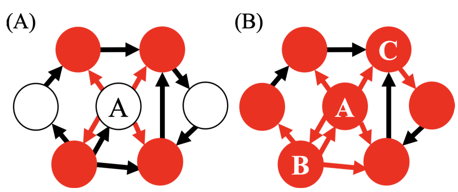

Fig. 3 Optimal network state in a network structure consisting of seven nodes. (A) Information is propagated through node A to four nodes. (B) As in (A), information is propagated to all brain regions, including nodes A, B, and C themselves, via nodes A, B, and C. *Red nodes*: Nodes where information is propagated via nodes A, B, and C (nodes A, B, and C themselves are included). *Red edge*: The edge through which information is propagated through nodes A, B, and C. *Black edge*: Edge that is not traversed when the information of all nodes is propagated through nodes A, B and C.

minimum vertex cover problem to find the brain regions that are structurally important for the realization of the optimal network state within the target network structure described in Sect. 3 and Sect. 4 (see Sect. 6.1). Then, in Step 2, the information propagation pathways in the brain that contribute to the activation of the brain regions identified in Step 1 are identified and formulated as a maximum-flow problem (see Sect. 6.2).

6.1 Step1: Minimum Vertex-Cover Problem

The minimum vertex cover problem is originally a type of network optimization problem for undirected graphs, which is to find a point coverage of minimum size such that the set of vertices in an undirected graph covers all edges when all edges from those vertices are collected. In this study, we formulated the minimum vertex cover problem in directed graphs as a problem of investigating the minimum number of nodes required to achieve the optimal network state in the network structure of this study, and the location of those nodes. The problem is to find the minimum number of nodes required to achieve the optimal network state in the network structure.

In the following sections, the objective function and constraints are described in Sect. 6.1.1, and the transformation to QUBO, which is necessary to find the optimal solution by Digital Annealer, is described in Sect. 6.1.2.

6.1.1 Objective Function and Constraints

We formulated the minimum vertex cover problem with the objective function (Eq. (2)) and constraints (Eq. (3)) as follows:

$$min \sum_{i=1}^{N} x_i \tag{2}$$

$$\sum_{j \in \Lambda_i} x_j \geq 1 \tag{3}$$

First, we explain Eq. (2). The variable x_i is a binary variable ($x_i \in 0, 1$), which indicates whether the region R_i is adopted. $i = 1, \ldots, N$ is the region number assigned to each brain region, and N indicates the number of brain regions in this study. In this paper, the number of regions is 64. Equation (2) expresses the objective function of minimizing the number of brain regions to be selected. Next, we explain Eq. (3). Λ_i is a set of region numbers projected to the region R_i. $\sum_{j \in \Lambda_i} x_j$ indicates the total value of the variables x_j for the regions to be input to the region R_i. In other words, Eq. (3) expresses the constraint that for any brain region R_i in the brain network structure, it has input from at least one of the regions R_j that project to region R_i. Here, we define the propagation of information by the fact that a path is adopted from one node to another in this study. Equations 2 and 3 are combined to formulate the problem of identifying the brain regions that are important for information propagation to all brain regions.

6.1.2 Transforming to the QUBO Model

We first convert the inequality constraint condition in Eq. (3) from the previous section into an equality constraint using the slack variable s_k. Then, we formulate the minimum vertex-cover problem, which is defined by the Hamiltonian of the constraints and the objective function described in

Eq. (2) and Eq. (3) of the previous section.

$$F_v = A_v \sum_{i=1}^{N} x_i + B_v \sum_{i=1}^{N} \left(\sum_{j \in \Lambda_i} x_j - \sum_{k=1}^{N(\Lambda_i)-1} s_k - 1 \right)^2 ,. \quad (4)$$

The terms in $A_v \sum_{i=1}^{N} x_i$ expresses the objective function of Eq. (2), and the term in $B_v \sum_{i=1}^{N} \left(\sum_{j \in \Lambda_i} x_j - \sum_{k=1}^{N(\Lambda_i)-1} s_k - 1 \right)^2$ expresses the inequality constraint of Eq. (3) using the slack variable. It is expressed as an equality constraint using s_k, which means slack variable. $\sum_{k=1}^{N(\Lambda_i)-1} s_k$ means that for each brain region, there are $N(\Lambda_i) - 1$ binary variables s_k are slack variables. The total number of all slack variables is 224. In other words, they are generated to mean the same state as the equality-transformed state of the inequality constraint using the slack variables shown in Eq. (3). The A_v and B_v in each term are the coefficients.

6.2 Step2: Maximum-Flow Problem

The brain regions identified by the minimum vertex cover problem represent the minimum number of brain regions necessary for the realization of the optimal network state. Although many brain regions are involved in the mindfulness state, the brain regions identified in this study are considered to be the brain regions that are more important for the realization of the resulting state in the brain network structure (see Sect. 1.1). Mindfulness meditation as a means of realizing a mindfulness state can be regarded as a form of attentional training directing attention to one's own sensory information. The optimal network state was achieved when more input flowed into the identified brain regions. In this study, we attempted to identify the information propagation pathways that contributed to the realization of a mindfulness state by formulating a maximum-flow problem, in which the flow rate was increased in the brain regions identified by the minimum vertex-cover problem. The starting-point was from some thalamic nuclei through which sensory information passed (i.e., LD, LP, VPL, VPM, MGB, and LGB) [30], [34]. The maximum-flow problem attempts to maximize the flow rate between the start and end points of a network when there is a limit (capacity) to the flow rate through each branch of the network.

In this study, we considered the flow rate and capacity as processing resources devoted to information propagation in the brain. In the nervous system, the firing of neurons depends on metabolic resources (oxygen and glucose) carried by the blood flow, and there are limited metabolic resources that can be used at any given time [35]. Therefore, it may be reasonable to set a capacity for the flow rate between each brain region. On the other hand, since this study constructs the network structure at a mesoscopic level and specifies the projection relations between brain regions, it is difficult to map the flow rate to the entity of the nervous system, and in this sense, there is an interpretability issue. In addition, when formulating this as a maximum-flow problem in this study, it is important to note that the constraints described in Eq. (6) are insufficient to formulate the conservation of input and output quantities (see Sect. 10).

In the following sections, the objective function and constraints are described in Sect. 6.2.1, and the transformation to QUBO, which is necessary to find the optimal solution by Digital Annealer, is described in Sect. 6.2.2.

6.2.1 Objective Function and Constraints

We formulated the maximum-flow problem with the objective function (Eq. (5)) and constraints (Eq. (6)) as follows:

$$max \sum_{j=1}^{C} y_{ig_j} \quad (5)$$

$$\sum_{i,j \neq s,t} \left(\sum_{i \in \partial_+(v)} y_{ji} - \sum_{i \in \partial_-(v)} y_{ij} \right)^2 = 0 \quad (6)$$

First, y_{ij} represents the flow rate from region R_i to region R_j. It is a binary variable ($y_{ij} \in 0, 1$), meaning that the flow rate from region R_i to region R_j should be adopted. $i, j = 1, \ldots, N$ denotes the region number assigned to each brain region. The variable C refers to the capacity of the pathway between each brain region. It is thought that $\sum_{j=1}^{C} y_{ij}$ expresses the amount of processing resources allocated from region R_i to region R_j. Next, we explain Eq. (5). y_{ig_j} is a variable that represents the flow rate from region R_i to the brain region R_{g_j} identified by the minimum vertex cover problem. In this paper, we refer to R_{g_j} as the "target region." In other words, y_{ig_j} is a binary variable that indicates whether the flow from region R_i to the target region R_{g_j} should be adopted or not. Equation (5) expresses the objective function for maximizing the flow rate to the target region R_{g_j}. Next, we explain Eq. (6). where s, t denote the region number of the starting point and the region number of the ending point, respectively. $i \in \partial_+(v)$ indicates the region number where the input to region R_i is located, and $i \in \partial_-(v)$ is the region number where the output from region R_i is located. Then, Eq. (6) expresses the constraint for any region R_i in the brain network structure except the start and end points, the flow rate $\sum_{i \in \partial_+(v)} y_{ji}$ flowing into the region and the flow rate $\sum_{i \in \partial_-(v)} y_{ji}$ flowing out of the region conserved.

6.2.2 Transforming to the QUBO Model

Similar to the minimum vertex-cover problem, the objective function and constraints of (5) and (6) above were converted to the QUBO form.

$$F_m = A_m \sum_{j=1}^{C} y_{ig_j} + B_m \sum_{i,j \neq s,t} \left(\sum_{i \in \partial_+(v)} y_{ji} - \sum_{i \in \partial_-(v)} y_{ij} \right)^2 , \quad (7)$$

The term in $-A_m \sum_{j=1}^{C} y_{ig_j}$ represents the objective function of Eq. (5), and the term in $B_m \sum_{i,j \neq s,t} \left(\sum_{i \in \partial_+(v)} y_{ji} - \sum_{i \in \partial_-(v)} y_{ij} \right)^2$ expresses the constraints of Eq. (6). The A_m and B_m in each term are the coefficients.

7. Optimal Solution Search Using DA

We use DA to search for the optimal solution to the network optimization problem formulated in Sect. 6. DA repeats for a number of iterations to minimize the energy of the model, thus finding the compensation parameters as corresponding binaries. Algorithms of the calculation in DA are described in [24] (for implementation, refer to the DA webservice [36]. The *iteration* was set by the convergence of the solution, and the number of runs was set to 50 to compare the computation time on the benchmark for both the minimum vertex coverage and maximum flow problems.

We performed simulations by varying the values of the QUBO coefficients (A_v, B_v, A_m, B_m) for each optimization problem in an exploratory manner. The obtained candidate solutions were checked to determine whether they were feasible (the constraint condition was satisfied when the value of the energy function was minimized) or optimal (the objective function was minimized when the value of the energy function was minimized). The coefficients were adopted when they were the most feasible and optimal solutions. Although there were multiple optimal solutions for both problems, the brain regions and information propagation pathways selected in the multiple optimal solutions tended to identify a common region or pathway. Therefore, the optimal solution that is most consistent with existing research is selected as the result and discussed in the following sections.

8. Results and Discussion

In this section, the results and discussion of the minimum vertex cover problem tackled in Step 1 and the maximum-flow problem tackled in Step 2 are presented in Sect. 8.1 and Sect. 8.2, respectively. Finally, a comprehensive discussion based on the results of both network optimization problems is provided in Sect. 8.3.

8.1 Results and Discussion of Minimum Vertex-Cover Problem

In this section, we describe the results of annealing runs for the minimum vertex cover problem. When the energy function in Eq. (1) was minimized (E_{min} = 6960), there existed a feasible solution with the minimum objective function. Figure 4 plots the value of the energy function and the value of the objective function after searching for a solution by annealing for the number of runs under the condition of QUBO at A_v = 870 and B_v = 850 of Eq. (4). The minimum value is plotted in red and indicated by a dotted line. The value of the objective function is 8, which means that eight brain regions were selected as the minimum number of brain regions necessary for the propagation of information to all brain regions in this problem. The selected brain regions are the primary somatosensory area, the dorsolateral prefrontal cortex (dlPFC), orbitofrontal cortex (OFC), anterior insula (AI), middle insula (MI), subthalamic nucleus, thalamic reticular nucleus, and intramedial nuclear group. Of the above eight brain regions, AI, MI, OFC, and dlPFC were the brain regions suggested to be activated during mindfulness (e.g., [9], [10]). Since the results of identifying brain regions important for achieving the state of mindfulness as a minimum vertex coverage problem are consistent with existing studies, we consider the optimal network state described in Sect. 4 to be valid in this study.

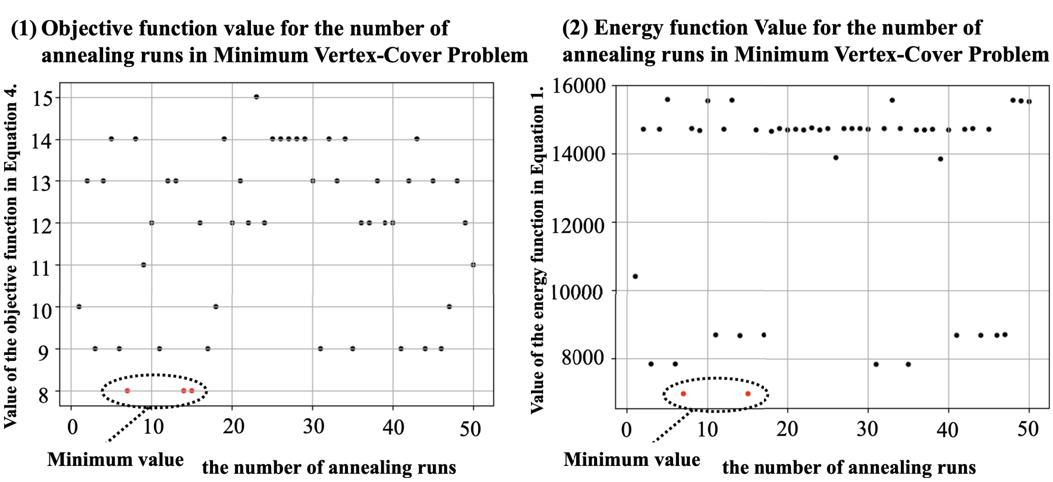

Fig. 4 Simulation results for Minimum Vertex-Cover Problem. The horizontal axis shows the number of simulation runs. The vertical axis is the optimal solution adopted in one simulation. The search for the optimal solution is performed for *iteration* in a single simulation, and the points plotted as values indicate the minimum value when *iteration* are turned. The figure reveals the results after 50 runs, and the number of times it was run at each iteration. A_v is the coefficient of the objective function (first term) in Eq. (4), and B_v is the coefficient on the constraints (second term) in Eq. (4). (1) Value of the objective function F_v in Eq. (4). (2) Value of energy function E in Eq. (1). The minimum value of each is circled in red in the top dotted line of the plot. The number of variables defined by the formulation was 286.

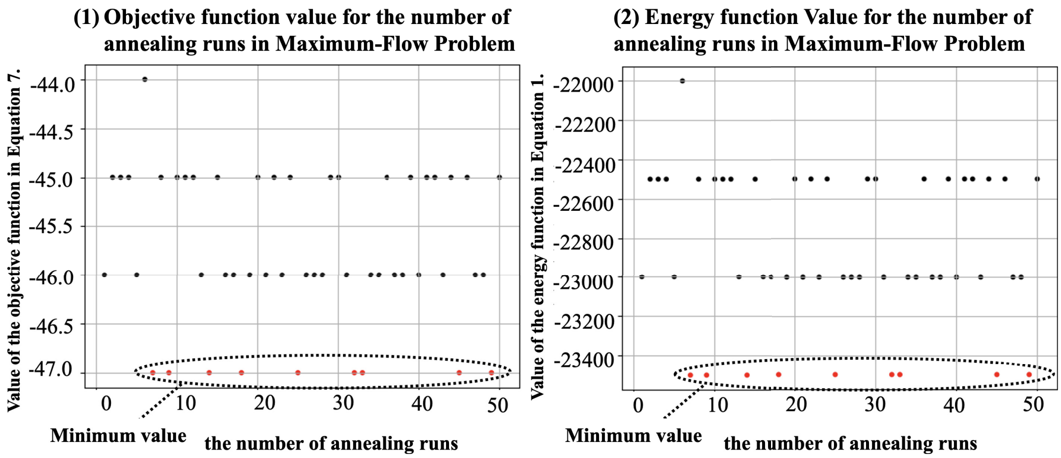

Fig. 5 Simulation results of Maximum-Flow Problem when the endpoint is set to AI. The horizontal axis shows the number of simulation runs. The vertical axis is the optimal solution adopted in one simulation. The search for the optimal solution is performed for *iteration* in a single simulation, and the points plotted as values indicate the minimum value when *iteration* are turned. The figure shows the results after 50 runs, the number of times it was run this time. A_m refers to the coefficient of the objective function (first term) in Eq. (7), and B_m is the coefficient on the constraints (second term) in Eq. (7). (1) Value of the objective function F_m in Eq. (7). (2) Value of energy function E in Eq. (1). The minimum value of each is circled in red in the top dotted line of the plot. The number of variables defined by the formulation was 1305.

8.2 Results and Discussion of Maximum-Flow Problem

In this study, among the brain regions identified in Sect. 8.1, we used four target brain regions, AI, MI, OFC, and dlPFC, and determined the pathways and flow rates between each brain region identified to maximize the amount of input to each brain region. The reason for limiting the endpoints here to four of the eight regions identified in the minimum vertex coverage problem is that information propagation pathways that activate the identified regions as endpoints will achieve a state of mindfulness. Therefore, we focused on four regions that have already been suggested to be significantly activated in the mindfulness state in previous studies (e.g., [9], [10]).

In the following sections, we mainly discuss the results with the AI as the endpoint, by using Sect. 8.2.1 to explain the results with the AI as the endpoint and Sect. 8.2.2 to explain the results with the other regions as the endpoints. This is because AI is the area where the most suggestive considerations can be made for the information propagation pathways that contribute to the realization of a state of mindfulness. Existing research suggests AI as the area most involved with the state of mindfulness [10].

8.2.1 Results and Discussion When AI is Used as the Endpoint

In this section, we describe the results of annealing for $A_m = -500$ and $B_m = 2300$ in Eq. (7) when the endpoint is AI when C is set to 5. This means that there is a binary variable y_{ij} for capacity $C = 5$ for the pathway between each brain region. The determination of the value of C was done in an exploratory manner, checking the consistency of the obtained results with existing previous studies and the execution time. For the maximum flow problem, the number of binary variables required is $261 \times C$. The maximum number of variables in a problem that can be handled by a digital annealer is 8192. While checking the resulting paths and flow rates between regions against existing studies, we have included the results for $C = 5$ as a value of capacity that prevents the number of variables from becoming larger than necessary. When $C = 5$, the number of binary variables is 1305. In the following sections, we report the results of one of the multiple optimal solutions obtained. However, it should be noted that the results reported in the following sections show the same trend for other solutions that existed multiple times within the number of runs.

As a result of the simulation, when the energy function of Eq. (5) is minimized ($E_{min} = -23500$), there are several feasible solutions with a minimum objective function. Figure 5 plots the value of the energy function and the value of the objective function after searching for a solution by annealing for the number of runs under the condition of QUBO at $A_m = -500$ and $B_m = 2300$ in Eq. (7) when the target region is AI. The minimum value is plotted in red and indicated by a dotted line. The minimum value of the objective function is -47, which is an average of 60% of the maximum flow rate (number of paths $\times$ number of capacities, C) in the target area, AI. Table 2 shows the coupling between each region employed when $C = 5$, $A_m = -500$ and $B_m = 2300$ in Eq. (7) and the flow C_{emp} are allocated between each region (the flow actually employed within the capacity $C = 5$). Figure 6 visualizes the information shown in Table 2 in a network structure.

The regions in the path from the start point to the end

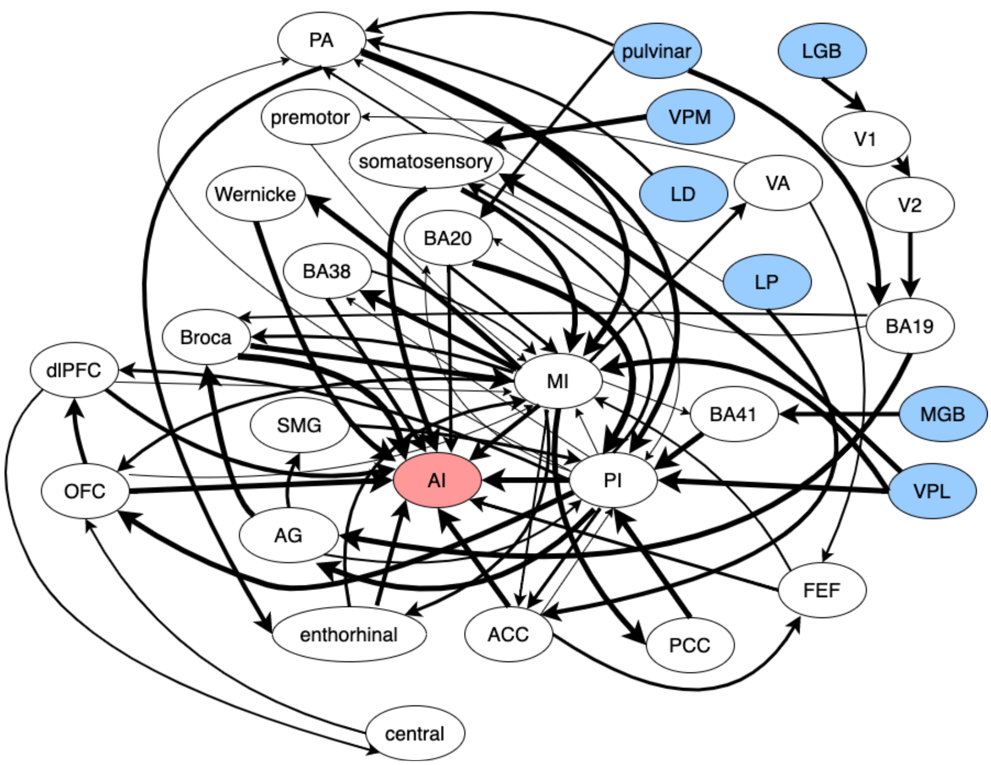

Fig. 6 Network obtained for the maximum flow problem when AI is used as an endpoint. The blue nodes indicate the starting region and the red node indicate the ending region. Please refer to the caption of Fig. 2, as the abbreviations for the areas listed in the nodes are the same as in Fig. 2. The thickness of the edges refers to the magnitude of the flow rate employed. See Table 2 for the flow rate specifically employed to join each region.

Table 2 The pathways and flow that contribute to maximizing the flow rate to the AI. The identified pathways between brain regions are decomposed by capacity and displayed as “input area-output area” See Table 1 for brain region names.

flow: C_{emp}	Connections between brain regions in the identified pathways
C_{emp} = 5	Broca-MI, MI-BA38, PI-AI, MI-BA20, PCC-PI, BA41-PI, Wernicke-MI, OFC-AI, BA20-PI, pulvinar-BA19, ACC-AI Broca-AI, VPL-PI, AG-Broca, PA-MI, somatosensory-MI, MI-Wernicke, PA-PI, VPL-MI, VPL-somatosensory, PI-OFC BA19-AG, MI-PCC, somatosensory-AI, PI-AG, VPM-somatosensory
C_{emp} = 4	V2-BA19, LGB-V1, MGB-BA41, PI-enthorhinal, BA38-AI, dlPFC-AI, OFC-dlPFC, LP-ACC, enthorhinal-AI, MI-AI V1-V2
C_{emp} = 3	enthorhinal-MI, BA20-MI, MI-OFC, SMG-PI, BA20-AI, LD-PA, PI-somatosensory, AG-SMG, pulvinar-BA20, MI-enthorhinal, PI-ACC, MI-VA, PI-dlPFC, pulvinar-PA, MI-Broca, ACC-FEF, FEF-AI
C_{emp} = 2	VA-FEF, BA19-BA20, somatosensory-PA, central-OFC, AG-PI, BA38-MI, dlPFC-central, BA19-Broca, MI-ACC, FEF-MI
C_{emp} = 1	MI-BA41, somatosensory-PI, LP-PA, PI-MI, PI-BA38, PM-MI, PI-PA, OFC-MI, ACC-PI, VA-PM, dlPFC-MI, PI-BA20

point were an average of 50% of the brain regions in the entire network structure. The identified pathways from start to end contained an average of 26.9% of all connections in the network structure. The overall trend suggests that, among the pathways that contribute to the maximum amount of input to AI after sensory information is transmitted through mindfulness meditation, significant flow volume is allocated to the connections in the pathways where sensory information is transmitted bottom-up, including the sensory cortex and thalamus.

Especially, we found that in the context of flow (processing resources devoted to neural activity) devoted to each brain region in the pathway from start to finish, a large amount of flow was devoted to PI-AI connections (see Table 2), and a relatively large amount was devoted to connectivity relationships, especially between brain regions containing AI. Previous studies have suggested that changes in functional connectivity in the brain through mindfulness meditation include increases between the posterior and anterior insulae [4]. In addition, mindfulness meditation has been shown to increase structural connectivity in the right insular cortex (e.g., between the insular cortex and the OFC, and between the insular cortex and the olfactory entorhinal cortex) [12]. Accordingly, these results show a trend similar to existing studies.

Among the pathways from the start point to the end point identified by the maximum-flow problem, those with particularly high flow rates devoted to the connections between each brain region in the pathway include "VPL-PI-enthorhinal-MI-BA38-AI" and "VPL-PI-somatosensory-PA-MI-OFC-AI." These pathways are known to enhance functional connectivity [4] and structural connectivity [12] between brain regions partially through mindfulness meditation in previous studies, including connections between the PI-olfactory cortex, insula and OFC, but as a whole are pathways that contribute significantly to maximizing AI activity. In addition, brain regions in the cerebral cortex contribute to AI activation through PI and MI in the insular cortex, suggesting that PI, MI, and AI play important roles in information processing in the brain during the mindfulness state. Although it is difficult to identify the different functional roles of the insular cortex in the realization of mindfulness states in the present study, previous studies suggest that the PI constitutes the primary interoceptive region and its receptive field, while the AI is involved in the integration of internal and external signals (e.g., [37]).

8.2.2 Results and Discussion When Other Brain Regions are Used as Endpoints

In addition to the above, we also determined the pathways and flow rates that contribute to the maximization of the flow rate to the target region in other brain regions identified by the minimum vertex-cover problem, such as MI, OFC, and dlPFC, which have been shown to be significantly activated during mindfulness. The results are shown in Fig. 5. On an average, 60% of the maximum flow to each brain region was observed, and an average of 30% of the pathways and an average of 50% of the regions in the network structure were identified. In particular, the dlPFC results showed that the identified pathways from the beginning to the end of the network were characterized by the involvement of the sensory cortex and insular cortex. In addition, the connections between brain regions with high flow rates in the identified pathways included the primary system sensory cortex-MI and AI-basolateral nucleus of the amygdala. Although previous studies have shown that the dlPFC itself is a brain region that is closely related to top-down attention control (e.g., [38]) top-down emotion regulation, and bottom-up emotion regulation (e.g., [29]). In this study, we found that the dlPFC was not associated with top-down emotion regulation in mindfulness meditation participants. Increased activity in the amygdala has also been reported during mindfulness [29]. In the present study, we considered the possibility that the activation of the dlPFC during mindfulness meditation was achieved by a state in which the activity of the sensory cortex and insular cortex was dominant. In addition, the results are consistent with an increase in the activity of the amygdala, since, as mentioned above, significant flow volume is devoted to the AI-amygdala flow.

8.3 General Discussion

In this study, the search for information propagation paths that contribute to the realization of the optimal network state (i.e., to the state of the target network structure), which is considered to correspond to the mindfulness state, was formulated using two network optimization problems: the minimum vertex-cover problem and the maximum-flow problem. The simulation was performed by annealing using Digital Annealer, which is a powerful tool for large-scale combinatorial optimization problems, to achieve a realistic simulation in a short time.

As a result, eight brain regions were identified in the minimum vertex-cover problem, including brain regions that have been suggested to be significantly activated in the mindfulness state in a previous study. The results include four regions suggested by previous research to be significantly activated in the mindfulness state, and we consider the possibility that their activation may result in the optimal network state defined in this study.

Then, in the maximum flow problem, based on the results in the minimum vertex coverage problem, a pathway was identified that included connections between brain regions where existing research suggested enhanced functional and structural connections within partial networks. The results for AI suggest that brain regions in the cerebral cortex contribute to the activation of AI, while PI and MI in the insular cortex contribute to the activation of AI. Further, results suggest that PI, MI, and AI play important roles in information processing in the brain during the mindfulness state. In addition, as for the activation of the dlPFC, significant flow volumes are allocated to the AI-amygdala and other areas when the maximum flow into the dlPFC is realized, suggesting that the activation of the dlPFC is a result of bottom-up emotional control by mindfulness meditation.

Here, we discuss the challenges that exist in the results obtained from the formulation of the maximum-flow problem and the results of this study. As can be seen from Fig. 5, multiple optimal solutions were obtained within the number of runs, which means that there may be multiple patterns of information propagation in the brain that lead to the same result. It remains to be determined which result is the most valid. Another issue is that among the identified routes, there are multiple routes from the starting point to the end point. In other words, regarding formulation in this study, it is difficult to uniquely consider the path from the start point to the end point, which contributes to the realization of the optimal network state.

On the other hand, it is rare to uniquely identify the information propagation path that contributes to the realization of an object. This holds true for those that can be viewed as a network-like phenomenon, such as a mindfulness state. The results of the present study are significant in that the partial information propagation pathways, that are important for the state of a particular brain network structure, were realized from the pathways and regions in the vast network structure of the brain. This was done in a manner that was consistent with the findings of previous studies. In the future, the obtained findings will contribute to basic research on the realization mechanism of the mindfulness state by mapping each information propagation pathway and the role of information propagation between regions.

9. Comparison of Computation Time by Benchmark

We used a computer with Intel 24 Xeon cores and 64GB of memory as a benchmark to compute the problem, and compared the computation time with that of Digital Annealer for two network optimization problems considered in this study. In this section, we will refer to a computer with 24 Xeon cores and 64GB of memory as the baseline. Specifically, the minimum vertex cover problem was transformed into an energy function and annealed under the QUBO of Eq. (4) ($A_v = 870$, $B_v = 850$), where the eight brain regions described in Sect. 8.1 were chosen. The maximum-flow problem was transformed into an energy function and annealed under the QUBO of Eq. (7) ($A_m = -500$, $B_m = 2300$) described in Sect. 8.2. The number of runs was 50, and the *iteration* was unified at 10^6.

We can see that the minimum vertex-cover problem can be solved by Digital Annealer in about 44.18 minutes in the baseline and 3.47 seconds in the runtime environment using Digital Annealer, which is more than 700 times faster than baseline. For the maximum-flow problem, the baseline time was 3.77 hours, and the execution time with Digital Annealer was 4.27 seconds, indicating that Digital Annealer could solve the problem more than 3000 times faster than the baseline. The network structure used in this study, which consists of 64 brain regions, is not a network structure for the entire brain, and is smaller than the nodes and possible pathways across the entire brain. Thus, significant execution time will likely be required to obtain the optimal solution to the problem at the baseline. In the future, when the identification of important brain regions and important information propagation paths in a larger-scale brain network structure is exploratively combined and solved as an optimal problem, the search for optimal solutions using Digital Annealer will be effective.

10. Limitations and Future Works

Several issues for future research exist in this study. The first issue is the challenge that exists in the network structure of this study. The neuroanatomy textbook adopted in this study [30]–[32] does not provide a clear methodology for obtaining individual findings. These findings may include morphological information on the structure of individual neurons and nerve fiber projections, as well as information from diffusion-weighted imaging, which has limited image resolution. At the same time, morphological findings on neuronal structures and nerve fiber projections, for example, may be obtained from the brains of non-human primates. It is not clear whether all the findings in the neuroanatomy textbook used in this study are related to connectivity in the human brain. Another strong assumption is whether the projective relationships described in the neuroanatomy textbooks in this study, including morphological findings, are projective relationships between individual cells. In that case, these projective relationships are also true for relationships between regions. The source and destination regions indicated by the terms used in the multiple findings employed in this study may not be the same as the actual extent to which the projection relations exist. Therefore, the neuroscientific validity of the connections adopted in this study remains questionable.

The second issue is the definition of the optimal network state. We defined the optimal network state as “the state in which information propagates to all brain regions in the target network structure at a certain point in time.” This helps simplify the problem. The optimal network state in this study assumes a mapping between the static network state and the mindfulness state at a certain point in time. The possibility of mapping the dynamic network state to the mindfulness state, and the question of what kind of brain network structure is associated with mindfulness state in the first place, needs to be clarified in more detail through further neuroimaging studies in humans. In the present study, there is a possibility that the optimal network state corresponds to the mindfulness state, in that the resulting brain regions selected and the connections between brain regions included in the pathway are consistent with previous studies.

The third issue is the neuro-scientific relevance of the constraints in the maximum flow problem. In this study, flow rate and capacity are regarded as processing resources allocated to information propagation in the brain, and a conservation law of input-output quantity is established in the constraint condition described in Eq. (6). It is considered necessary to improve this constraint condition in the future in a way that is more in line with the propagation of information in the nervous system. On the other hand, since this study constructs the network structure at the mesoscopic level and specifies the projection relationship between brain regions, it is difficult to map the flow rate to the entity of the nervous system, and in this sense, there is an interpretability issue.

The fourth issue is a challenge that exists in the simulation results obtained. The results show that there are multiple optimal solutions for both problems. This result means that the optimal solution obtained in this study may have fallen into the local optimal solution. In contrast, the results obtained in the present study are consistent with those of previous studies in identifying regions and pathways, suggesting that the present study may be effective as an exploratory approach to identify the information flow in the brain network that contributes to the realization of the target state (mindfulness state in the present study). In addition, the simulation results of the minimum vertex coverage problem in Fig. 4 show that out of 50 simulations, there are only 8 feasible solutions that satisfy the constraint conditions. If the constraint is not satisfied, the value of the energy function is reflected in the value multiplied by $B_v = 850$ to the second-order term of the QUBO, resulting in a biased energy function value of 14000 to 16000 and only two optimal solutions. In this sense, the reliability of the simulation results in Fig. 4 remain an issue. In the future, we would like to improve the formulation of the constraint conditions for the minimum vertex coverage problem and consider formulations that converge more easily to the optimal solution.

Finally, we discuss the issue of the fact that the formulation assumes a two-body problem. In this study, the path identification problem, which contributes to achieving a state of mindfulness, is formulated by implicitly reducing it to a two-body problem. In addition, when solving optimization with the Ising model, as in the current DA, it is necessary to reduce the multi-body problem to a two-body problem through preprocessing and formulation. This should be studied in the future, taking into consideration the possibility that the problem can be reduced to a multi-body problem.

11. Conclusion

In this study, we defined the optimal network state to realize the mindfulness state as "the state in which information propagates to all brain regions" formulated it as a combinatorial optimization problem, transformed it into QUBO, and searched for the optimal solution using Digital Annealer. As a result, eight brain regions were identified, most of which were consistent with the brain regions likely related to the mindfulness state in existing studies. We then formulated the maximum-flow problem for the insula, dlPFC, and OFC, which are suggested to be particularly involved in the mindfulness state. We tried to identify the information propagation pathways in the network structure that contribute to the state in which more input flows into these brain regions (i.e., the state in which the optimal network state is achieved). These results suggest that brain regions in the cerebral cortex contribute to the activation of AI, while PI and MI contribute to the insular cortex. In addition, activation of the dlPFC and OFC is thought to be mediated by activation of the insula. In addition, it was suggested that the mindfulness state may be realized by the state in which the bottom-up processing of sensory information is more dominant than the state in which the top-down processing of information, such as from the dlPFC, is dominant at a certain point in time. This finding supports the existing studies that have identified only partial brain regions involved in mindfulness, and enables us to identify important brain regions and partial information propagation pathways in the brain network structure in more detail. Thus, we can contribute to the development of basic neuro-scientific research on mindfulness and to more direct interventions and support for the realization of mindfulness. In addition, our approach is effective as an exploratory approach to elucidate the brain regions and information propagation pathways that are important for the realization of higher-order cognitive activities in humans. This is realized by information propagation dynamics in a large-scale brain network structure.

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