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Disorganization of Semantic Brain Networks in Schizophrenia Revealed by fMRI

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Objectives*: Schizophrenia is a mental illness that presents with thought disorders including delusions and disorganized speech. Thought disorders have been regarded as a consequence of the *loosening of associations* between semantic concepts since the term "schizophrenia" was first coined by Bleuler. However, a mechanistic account of this cardinal disturbance in terms of functional dysconnection has been lacking. To evaluate how aberrant semantic connections are expressed through brain activity, we characterized large-scale network structures of concept representations using functional magnetic resonance imaging (fMRI). *Study Design*: We quantified various concept representations in patients' brains from fMRI activity evoked by movie scenes using encoding modeling. We then constructed semantic brain networks by evaluating the similarity of these semantic representations and conducted graph theory-based network analyses. *Study Results*: Neurotypical networks had small-world properties similar to those of natural languages, suggesting small-worldness as a universal property in semantic knowledge networks. Conversely, small-worldness was significantly reduced in networks of schizophrenia patients and was correlated with psychological measures of delusions. Patients' semantic networks were partitioned into more distinct categories and had more random within-category structures than those of controls. *Conclusions*: The differences in conceptual representations manifest altered semantic clustering and associative intrusions that underlie thought disorders. This is the first study to provide pathophysiological evidence for the *loosening of associations* as reflected in randomization of semantic networks in schizophrenia. Our method provides a promising approach for understanding the neural basis of altered or creative inner experiences of individuals with mental illness or exceptional abilities, respectively.

Key words: Thought disorder/voxelwise encoding modeling/semantic network/small-worldness

Introduction

Schizophrenia is a serious mental illness characterized by symptoms such as delusions, hallucinations, incoherent speech, and behavior. The forms and structures of thought are often disorganized in schizophrenia, as revealed in the speech of schizophrenia patients,[1–3] in which words and phrases are loosely related. Influenced by association psychology, Bleuler referred to such thought disorders as being due to a *loosening of associations*, ie, abnormalities in semantic relations between ideas. His concept of *loosening of associations* was offered as a fundamental psychopathology of schizophrenia, namely, a *disintegration of the psyche*.[4–7] As support for Bleuler's perspective, psychological studies of the priming effect have shown that, in schizophrenia patients, priming occurs even between semantically distant concepts, indicating abnormal conceptual associations.[8–13] From a complementary pathophysiological perspective, Wernicke proposed a sejunction hypothesis,[14,15] which posits a disruption of associative brain connectivity as the cause of psychosis. The neural systems supporting semantic processing are widely distributed in the cortex and encode knowledge of concepts by learning relationships between multimodal information,[16,17] whereas the connections that underwrite this learning are impaired in schizophrenia.[18,19] Although the *loosening of associations* in schizophrenia patients has been a dominant concept in psychiatry for decades, there has been little direct neurological or pathophysiological evidence to support this construct.

To characterize a *loosening of associations*—and its underlying pathophysiology—it is necessary to clarify the principles that relate the large-scale connectivity structure of neuronal representations of concepts related to human knowledge and language, ie, the “semantic brain network”. Network analysis, also referred to as graph theory, which deals with the mathematical characteristics of graphs comprising nodes connected by edges, has been applied to understanding the structure of such large-scale semantic networks.[20–22] A network structure known as small-world topology, characterized by short average path lengths and high local clustering, is frequently observed in networks formed by natural and artificial systems.[23]

Small-world structures have been observed in semantic networks based on free-association norms and text corpora.[21,24] The small-worldness in such natural language networks is interpreted as an efficient semantic association between most pairs of words or concepts.[21,24,25] Given these aspects of natural language, a network based on neuronal representations of semantic concepts should also feature a small-world structure. However, there is no direct evidence showing such homology in the human brain. Furthermore, because schizophrenia patients exhibit thought disorder, their semantic networks should have a more disorganized structure than those of neurotypical individuals.

Recently, Huth et al[26,27] developed a method that can quantitatively evaluate the semantic representations of individual words in the brain (ie, brain word embeddings) by modeling functional magnetic resonance imaging (fMRI) brain activity using natural language processing techniques. The method inspired us to characterize semantic networks in the human brain by assessing the similarity between brain word embeddings and analyze their structural characteristics using a network analysis. Likewise, we assessed the network structure of categorical knowledge in the brains of schizophrenia patients. The contribution of this study is to clarify the structural characteristics of semantic networks in both healthy controls and schizophrenia patients based on neuronal (fMRI) responses and to quantify pathological deficits related to the *loosening of associations* in schizophrenia patients.

Materials and Methods

Data Collection

Fourteen schizophrenia patients (age 24–59 years, mean = 44.1 years; 42.9% females) and 17 healthy controls (age 26–49 years, mean = 40.2 years; 58.8% females) participated in this study. All patients were free of comorbid psychiatric disorders, and all were taking antipsychotic medications. Healthy controls were matched with the patient group by age, sex, educational background, and predicted IQ.[28] All participants provided written informed consent after receiving a complete description of the study. The experimental protocol was approved by the Committee on Medical Ethics of Kyoto University (R0809) and conducted at Kyoto University Hospital in accordance with the Code of Ethics of the World Medical Association. Psychopathological assessment was performed with the Positive and Negative Syndrome Scale (PANSS-5)[29] for patients only and the Peters et al, Delusions Inventory (PDI)[30] for all participants. PANSS-5 is a symptom rating scale for schizophrenia comprising 20 items, categorized into Positive, Negative, Disorganized/Concrete, Excited, and Depressed factors. PDI is a self-report, 21-item scale for measuring delusion proneness in the general population. Demographic data, clinical measures, and psychological tests are shown in Supplementary table 1.

Functional and anatomical MRI data were collected using a 3-T Siemens TIM Trio scanner. The participants watched soundless color movies of natural scenes projected on a screen in the MRI scanner, freely moving their gaze. The movies consisted of various types of clips (eg, animals, nature, film scenes) that lasted 10–20 s each; these movies were identical to those used by Nishimoto et al.[31] Details of MRI data collection and fMRI data preprocessing procedure are described in the Supplementary Methods and Supplementary figure 1.

Semantic Vector Construction for Movie Scenes

We manually annotated the movie scene by scene every 1 s with a description using natural Japanese language. Subsequently, the scene descriptions were transformed into word2vec[32] vector representations as previously described.[33] Word2vec is a natural language processing algorithm that represents a high-dimensional word vector space based on word co-occurrence statistics. Because this vector space effectively captures the semantic relationships between words, it can also effectively model semantic representation in the human brain.[34,35] Each description of a given scene was segmented and decomposed into words using MeCab (http://taku910.github.io/mecab). The resulting 11 132 words were projected into a word2vec vector space created from the Japanese Wikipedia corpus, and then all word vectors obtained from the description for each scene were averaged, resulting in a scene representation vector with 1000 dimensions.

Voxelwise Encoding Modeling

The multi-voxel patterns of neural activity evoked by the movie scenes were modeled as the matrix product of the scene vector matrix and the model weights. Model weights were estimated by L2-regularized linear least-squares regression. The regularization parameters were estimated by a cross-validation method. All data samples were randomly divided into training samples and test samples at a rate of 4:1 and used for model fitting and validation, respectively. This resampling was repeated 10 times. The regularization parameters, optimized according to the mean Pearson's correlation coefficient between the predicted and measured BOLD signals for the 20% validation samples, were obtained for each subject and for each dimension of the scene vectors. Prediction accuracy of the ensuing encoding modeling is described in the Supplementary Methods and Supplementary figures 2–4.

Brain Word Embeddings

The brain word embeddings of each participant were quantified using the weights of the voxel-wise encoding model. First, the top 7000 voxels showing the highest prediction accuracy were selected to create a weight matrix. Then, the original word vectors in the word2vec vector space for the top 1000 most frequent words out of the 11 132 words appearing in the descriptions of movie scenes were multiplied by the model weights to obtain a vector representation of each word in the brain.

Word Selection and Categorization

From the top 1000 words most frequently appearing in the scene descriptions of the movies, we manually selected 257 concrete nouns (please see the Supplementary Methods for details on this selection). We then classified the 257 words into seven lexical semantic classes based on higher taxa in the lexical hierarchy of WordNet: "artificial environment" (40 words), "body part" (35 words), "clothing" (14 words), "human" (40 words), "instrument" (36 words), "living being" (50 words) and "natural environment" (42 words) (Supplementary figure 5). Some categories were manually defined by integrating several high-level synsets that appeared in the tree graph of the 257 words in WordNet. We further classified these categories into living beings ("body part", "human", and "living being") and non-living beings ("artificial environment", "clothing", "instrument", and "natural environment") to investigate the effect of coarse-grained classification.

Network Analysis

We binarized the pair-wise distance matrix of word embeddings by proportional thresholding to construct an adjacency matrix for an unweighted undirected graph. A connection density threshold was defined to ensure that each graph had the same number of edges (Details of threshold selection are described in the Supplementary Methods). We refer to these constructed graphs based on word embeddings as semantic brain networks. We performed graph-theoretical analyses on the entire semantic brain network and the sub-networks within each category using the Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/). Then, we evaluated clustering coefficient (C), characteristic path length (L), small-worldness (*sigma,* σ), and modularity (Q). For definitions and statistical analyses of network measures, please refer to the Supplementary Methods.

Results

Analysis of the Entire Semantic Brain Network

To characterize the semantic representation of words in the brain, we used fMRI to measure brain activity in healthy controls and schizophrenia patients while they watched movies of various natural scenes. The neuronal responses to words describing the movie were estimated using standard regression analyses. This furnished a profile of word-specific activation patterns over voxels (brain word embeddings) that allowed us to construct semantic networks based upon the similarity of the patterns (figure 1A) (details of the methods employed have been described in our preprint paper: Nishida et al[35]). Briefly, we thresholded the pair-wise distance matrices of the brain word embeddings to produce adjacency matrices and analyzed the network connectivity and topology measures of the adjacency matrices (figure 1B).

To test the hypothesis that the semantic networks of schizophrenia patients have a more disorganized structure than those of healthy controls, we evaluated: (1) the clustering coefficient (C) as measures of local functional segregation; (2) the characteristic path length (L) as measures of global functional integration; and (3) the small-worldness [sigma, σ, defined as normalized C (gamma, γ)/normalized L (lambda, λ)] of the networks. We quantified these network indices using the area under the curve (AUC) expressing each index as a function of the edge-density—and assessed any differences between patients and healthy controls, and any differences in relation to a corpus-based semantic network built from word2vec[32] embeddings.

In the semantic brain networks, the areas under the curve of C, L, and σ in the schizophrenia group were significantly lower than those in the healthy group (P = .005, .011, and .003, respectively, t-test) (figure 2A). Moreover, C and L in the patient group were significantly

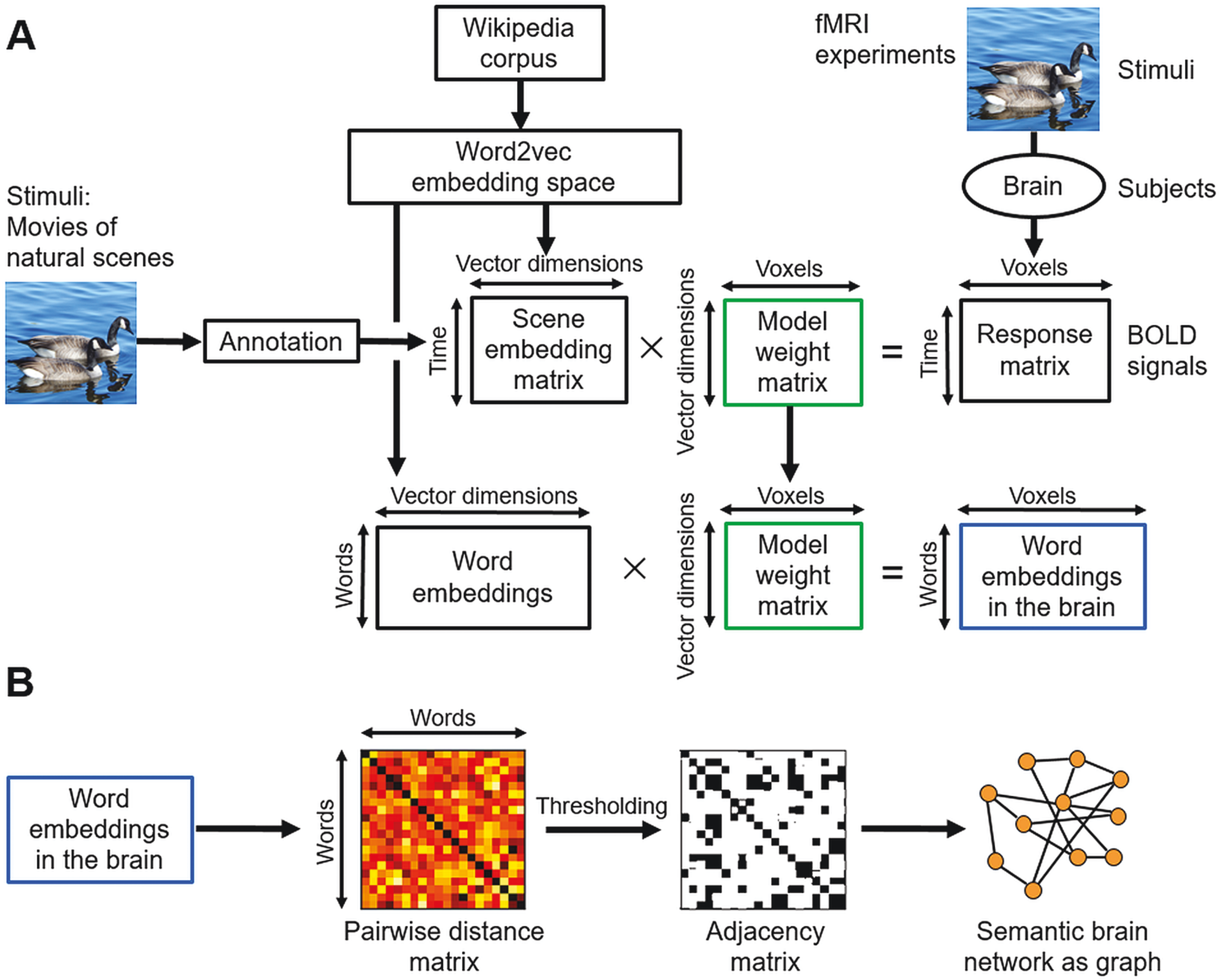

Fig. 1. Experimental procedure. (A) Schematic of encoding modeling of semantic brain representations. The model was constructed by predicting brain responses to natural movie scenes from scene embeddings using regularized linear regression. The brain word embeddings were calculated by multiplying the word embeddings in word2vec by the model weights. (B) Schematic of network analysis of semantic brain representations. We calculated the pairwise distance between brain word embeddings and applied thresholding to create the adjacency matrix of listed words. The connectivity and topology of the semantic network defined by the adjacency matrix were analyzed using graph theory.

lower than those in the word2vec embeddings ($P < .0001$ and .007, respectively, one-sample t-test), whereas those in the control group were not different from those in the word2vec embeddings ($P = .477$ and .169, respectively) (Supplementary figure 6A and B). Small-worldness σ in the patient and control groups were both significantly lower than that in the word2vec embeddings ($P < .001$ and .001, respectively) (Supplementary figure 6C).

Network analysis showed that the semantic brain networks of schizophrenia patients had a lower C, a shorter L, and a smaller σ than the corresponding networks of healthy controls or the text corpus. This indicates that the network topology of the semantic brain networks was more similar to those of random graphs (which are characterized by a small C and small L) and hence more disorganized in patients than in controls.

Correlations Between Psychological Variables and Network Measures

To test for a link between the characteristics of the entire semantic brain networks and thought disorder-like symptoms, Spearman rank correlation analyses between PDI scores andthe AUCs of network measures (C, L, and σ) were performed across all participants from both the schizophrenia and healthy control groups because delusional thinking is regarded as a continuum between normality and pathology.[30] For PANSS-5, correlation analyses were performed between the scores (five subscales and total score) and the AUCs of network measures only in the schizophrenia group. Although there were no significant correlations between any network measures and the scores of PANSS-5 items (the relationships between PANSS-5 Disorganized/

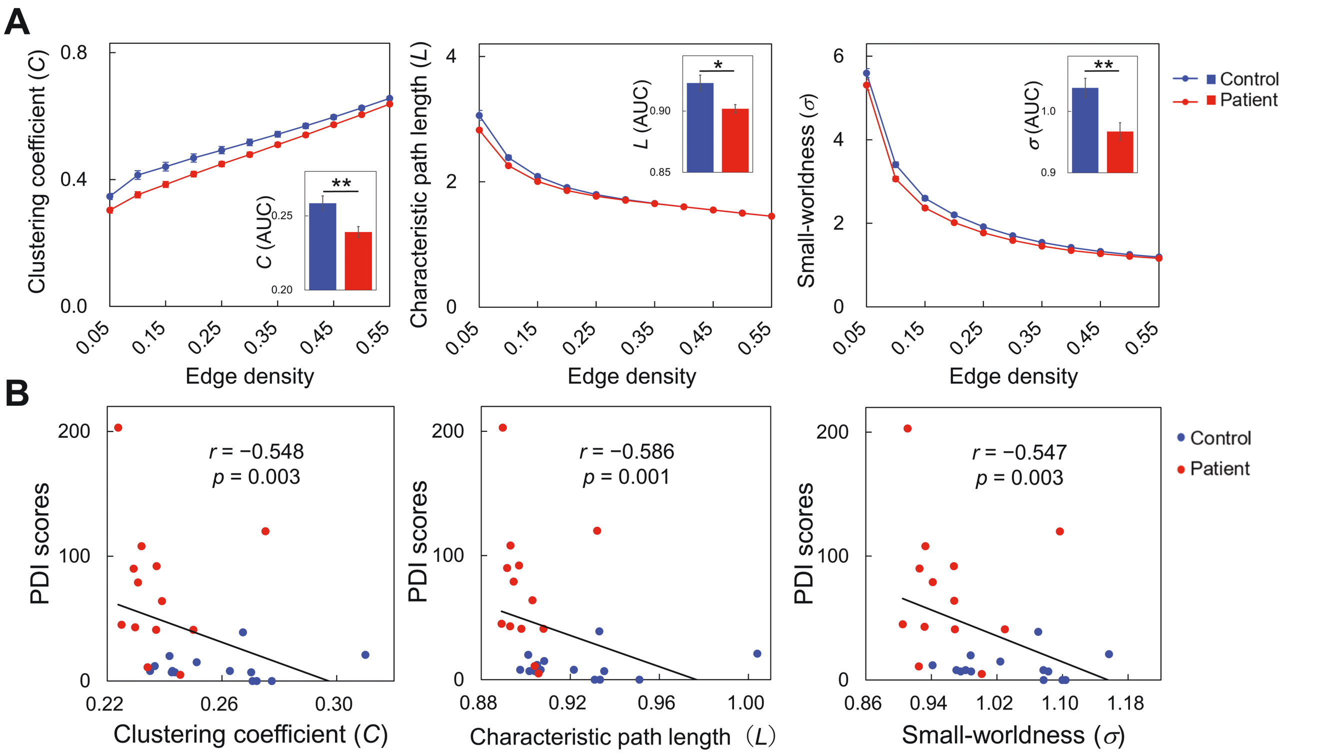

Fig. 2. Topological properties of semantic brain networks and correlations with the PDI scores. (A) Network measures, namely, clustering coefficient (*C*), characteristic path length (*L*), and small-worldness (*σ*), across a range of edge densities. Plots and bars depict network measures and their AUCs, with red indicating schizophrenia patients and blue indicating healthy controls. Data are presented as the mean ± s.e.m. Indicators above each pair of bars denote the significance of the between-group differences (*$P < .05$, **$P < .005$, *t*-tests). AUC, area under the curve. (B) Correlations between the PDI scores and network measures. Scatter plots show significant correlations between Peters et al. Delusions Inventory (PDI) scores and the AUCs of *C*, *L*, and *σ* in all participants ($P < .05$, false discovery rate [FDR] corrected). The red and blue points represent the data from individual schizophrenia patients and healthy controls, respectively (see online version for colors).

Concrete scores and the network measures are shown in Supplementary figure 7), all the network measures (*C*, *L*, and *σ*) were negatively correlated with PDI scores ($r = −.548$, $−.586$, and $−.547$, $P = .003$, $.001$, and $.003$, respectively, at a false discovery rate [FDR] of 0.05) (figure 2B).

Modularity (Q) With Categories Predefined as Communities

It remained unclear whether the semantic structures were lost at all semantic scales or whether some semantic structures were preserved in the networks of schizophrenia patients. To address this question, we calculated the modularity (*Q*)[36] of the semantic networks by predefining coarse categories selected from WordNet—a lexical database of semantic relations between words—as communities to reflect the precision with which the network was partitioned into coarse categories. We found that the AUC of *Q* was significantly higher in the schizophrenia group than in the healthy group when each category was predefined as a community ($P = .006$, *t*-test) (figure 3A). Thus, patients' semantic representations were not entirely disorganized; coarse categories were preserved.

Network Analysis Within Each Category

Network analysis within each category showed that in most categories, *σ* values were significantly lower in the schizophrenia group than in the healthy group, or tended to be lower at an FDR of 0.05 (figure 3B; please see the Supplementary Results and Supplementary figures 8 and 9 for within-category analysis of *C* and *L*). The results showed the tendency of more random network topology within each category in schizophrenia patients than in healthy controls, suggesting that the representation of word concepts in schizophrenia does not preserve normative semantic associations at a within-category level.

These results held true for the network analyses within further coarse graining of categories (Living/Non-living), as shown in the Supplementary Results and Supplementary figures 10 and 11.

Discussion

Since the inception of schizophrenia as a nosological entity, two foundational ideas have dominated: (1) Bleuler's formulation of psychopathology in terms of a disintegration of psychological processing,[4] and (2) Wernicke's

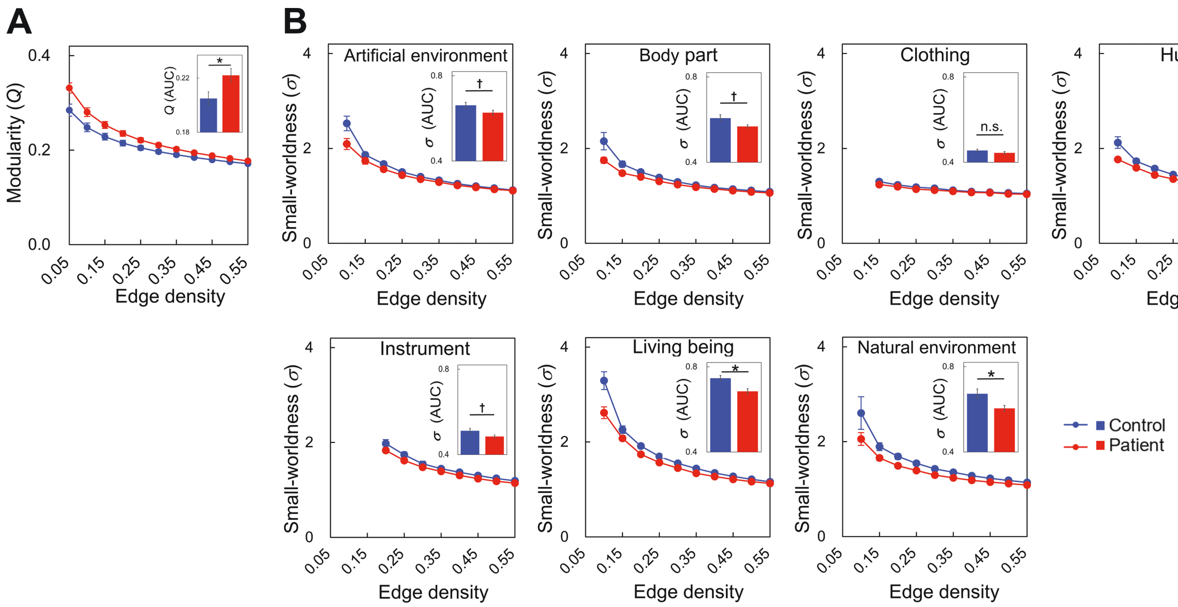

Fig. 3. Categorical distinctness and the internal structures in the semantic brain networks. (A) Modularity (Q) with the categories predefined as communities. (B) Small-worldness (σ) within categories of the semantic brain network. Plots and bars depict network measures and their AUCs, with red indicating schizophrenia patients and blue indicating healthy controls, respectively (see online version for colors). Data are presented as the mean ± s.e.m. Indicators above each pair of bars denote the significance of the between-group comparisons ($^{*}P < .05$, $^{\dagger}P < .1$, t-test). In the range of edge densities for which σ could be calculated, σ values were significantly lower in the schizophrenia group than in the healthy group in the "living being", "natural environment", and "human" categories ($P < .005$, .02, and .02, respectively, t-test), and tended to be lower in the "body part", "instrument", and "artificial environment" categories ($P = .04$, .06, and .08, respectively) at an FDR of 0.05. AUC, area under the curve; n.s., not significant.

formulation of pathophysiology in terms of a disruption of associative brain connectivity.[14] Over a century later, we are now in a position to test how one underlies the other using neuroimaging technology. In this study, we constructed semantic networks based on brain word embeddings derived from distributed neuronal responses as measured by fMRI, and then characterized the integration of these networks using graph theory.

Our study demonstrates, for the first time, that semantic networks in the healthy human brain have small-world properties similar to those of natural languages.[21] This suggests that small-worldness is a universal property in large-scale networks related to semantic knowledge. As an analogy to the natural language semantic network, the small-worldness of the semantic network in the neurotypical brain suggests that mental concepts are also organized into specific semantic domains, whereas semantically distant but associatively-related concepts are globally connected, which enables coherent thought and speech.

Conversely, the semantic networks of schizophrenia patients were more disorganized, with a lower clustering coefficient, characteristic path length, and small-worldness. The decreased clustering coefficient suggests that concepts are less prone to form specific semantic domains with each other. The reduced path length suggests that schizophrenia patients are more likely to relate distant concepts. The disintegration of the semantic network of schizophrenia patients suggests that the representations of concepts become relatively indistinct in their brains. These network properties may manifest as semantic priming for a wider range of dissimilar concepts.[8–13] Crucially, these network measures were negatively correlated with the severity of delusions, which supports the construct and predictive validity of our network characterization. The co-occurrence of intruding knowledge may cause confusion in the understanding of context, leading to the emergence of delusional beliefs.[37–39]

Modularity, which indicates the degree to which a network is distinctly partitioned into basic-level categories derived from a standard lexical database, was higher in the schizophrenia patients than in the healthy controls. Thus, patients' semantic representations were not entirely disorganized; coarse categories were preserved, which is consistent with previous psychological studies.[40,41] At the same time, the internal structure within the categories was more random, which may contribute to the overall randomization of the entire semantic network. We have reported in a preprint paper (Nishida et al[42]) that the overall distribution of semantic representation differs between schizophrenia patients and healthy control based on the same subject data as in the present study. In the present study, we further examined the network connections of individual word pairs to reveal more detailed structural difference between the two groups. The findings in the present study indicate that the abnormal internal

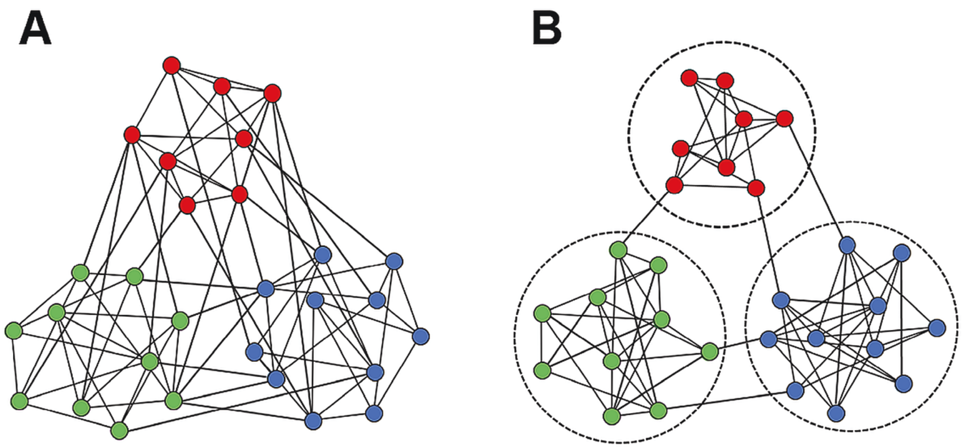

Fig. 4. Schematic depictions of different semantic brain networks. (A) Schematic of the small-world structure of a healthy control semantic brain network. (B) Schematic of the modular structure and within-category randomization of a schizophrenia patient semantic brain network. Different colors represent different categories that serve as predefined modules (see online version for colors). Dashed circles represent rigid modular structures.

structure of categories is the essence of the deficits of semantic brain representations of schizophrenia patients and, furthermore, that the semantic network structure is more random. In contrast, the modularity in patients' brains increased at a certain level of coarse graining, such as Living/Non-living things, suggesting that patients have a stronger tendency to relate individual concepts within a coarse category, while exhibiting difficulty distinguishing individual concepts within a coarse category, because of the randomness of the semantic associations within the category (figure 4A and B).

This study has a few limitations. First, participants were able to move their eyes freely and fixation was not required during the experiments. Therefore, possible behavioral differences between groups, as well as differences in attention set in the patients, may have affected the recorded fMRI signal. We consider that the differences in the semantic network structures reported here reflect all possible subject-group differences that were involved in the fMRI signals for semantic representation, including both behavioral and cognitive ones. An important point is that these subject-group differences were not due to trivial factors such as the noise level of the raw fMRI or the accuracy of the model fitting (see the Supplementary Methods and Supplementary figures 1–4). Our future work will incorporate eye movement data into the encoding model to distinguish between behavioral and cognitive factors. Second, the patients were taking antipsychotic medications, which may have affected their neuronal responses to the movies and the subsequent processing of the stimuli in a drug-specific manner. Indeed, dopamine antagonists have been reported to alter the resting state fMRI network.[43] To address this limitation, we hope to perform the same experiments using drug-naive schizophrenia patients in future research. An additional limitation is the variability in patient age, which may have confounded severity, chronicity, and burden. Educational factors may also be linked to functional brain networks. Future studies should recruit more participants to investigate the effects of these subject-specific factors on semantic brain network changes.

In conclusion, this is the first study to construct semantic networks based on brain responses and to quantitatively evaluate the differences in network structure between schizophrenia patients and healthy controls. Whereas the semantic networks of healthy controls' brains showed high small-worldness, as did natural language networks, the semantic networks of schizophrenia patients' brains were relatively disorganized. Moreover, the semantic representations in the brains of schizophrenia patients showed distinct division into coarse-grained categories with indistinct and random within-category structure. In schizophrenia patients, these structural abnormalities can be characterized as both impaired semantic clustering and associative intrusions, which may contribute to thought disorders such as delusions and derailment. We identified disorganization of the knowledge system related to the *loosening of associations* in schizophrenia patients by combining two techniques: semantic encoding modeling of fMRI responses and graph-theoretical analysis. Our method offers a promising approach to explore the altered or creative inner experiences of individuals with mental illness or exceptional abilities, respectively, which thus far, have been accessible only through verbal reports and behavior.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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