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Aberrant resting-state functional connectivity of major depressive disorder with higher risk of suicide

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Abstract

Aim: Suicide prevention for depressive patients is an important clinical issue in psychiatry. However, not all depressive patients plan or attempt suicide. In this study, we investigated the differences of functional brain networks between a high-risk group and a low-risk group for suicide by comparing resting-state functional connectivity (rsFC).

Methods: The subjects were 29 patients with major depressive disorder, nine of whom had attempted suicide. The suicidal ideation of all subjects was assessed with the Columbia-Suicide Severity Rating Scale, then the subjects were divided into two groups based on the most severe suicidal ideation (MSI) in their lifetime. We compared rsFC between the two groups.

Results: Of the 29 subjects, 16 were in the severe MSI group. We found that the severe MSI group members had significantly smaller rsFC in two networks: one comprised the right dorsolateral prefrontal cortex and the default-mode network, and the other comprised the left rostrolateral prefrontal cortex and the striatum, amygdala, and hippocampus. These regions are reported to be associated with rumination, retrieval suppression, and delay discounting (DD).

Conclusion: Our results suggest that functional networks related to rumination, retrieval suppression, and DD might be impaired in depressive patients with severe suicidal ideation. It might be beneficial for psychiatrists to assess these characteristics in terms of suicide prevention for depressive patients.

KEYWORDS

delay discounting, resting-state functional MRI, retrieval suppression, rumination, suicide

INTRODUCTION

Suicide is a public health problem of global importance. Over 800,000 people died by suicide in 2012, which means that every 40 s a person dies by suicide somewhere in the world.[1] A review of psychological autopsy studies, which included 3,275 suicide completers, showed that 87.3% of suicide victims had been diagnosed with a mental disorder prior to their death, and that 43.2% of suicide victims were diagnosed with an affective disorder, including depressive and bipolar disorders.[2]

However, not all people who suffer from major mood disorders plan or attempt suicide. These differences are thought to be associated with suicidal vulnerabilities of individuals. Many biological studies have been conducted to elucidate suicidal vulnerabilities. Previous studies have shown that familial and genetic predispositions, as well as early-life adversities increase the lifetime risk of suicide.[3,4] They alter responses to stress and other processes through epigenetic modification of genes and associated changes in gene expression and through the regulation of emotional and behavioral traits. Impairments of the serotonin neurotransmitter system and the hypothalamic-pituitary-adrenal axis stress-response system, inflammatory changes, and glial dysfunction in the brain are associated with the precipitation of a suicidal event.

As part of such biological studies, neuroimaging studies have also been actively conducted.[5,6] A previous study using structural magnetic resonance imaging (MRI) suggested that suicide attempters (SAs) with depression showed volume reduction or cortical thinning in frontal regions, such as ventral lateral prefrontal cortex, dorsolateral prefrontal cortex (DLPFC), and orbitofrontal cortex (OFC) compared with non-suicide attempters (NSAs) or healthy controls (HCs).[7] Other studies implicated that SAs had volume reduction in limbic regions and basal ganglia,[8–13] but a recent study found no significant volumetric differences in the caudate, pallidum, putamen, nucleus accumbens, hippocampus, amygdala, ventral diencephalon, or thalamus between SAs and NSAs.[14]

Various studies have also reported aberrant brain functions using functional MRI (fMRI) and positron emission tomography. Jollant et al.[15] investigated task-related fMRI during the Iowa Gambling Task in depressive SAs and depressive NSAs. They found activation of left lateral OFC is reduced in SAs during risky choices compared with safe choices. In another task-related fMRI study assessing emotion processing neural circuitry, reduced functional connectivity between the right anterior cingulate cortex and the bilateral insula was observed in SAs compared with NSAs when viewing 50% intensity angry faces.[16]

A significant reduction of serotonin-transporter binding potential in the midbrain, thalamus, and striatum was noted in the depressed suicidal group compared to the HC group.[17,18] Sublette et al.[19] examined the glucose metabolism of depressive SAs compared with depressive NSAs. They found that the glucose metabolic rate in SAs was lower in the right DLPFC.

Based on these findings, recent studies have focused on functional connectivity of patients with suicidal ideation. Cao et al.[20] investigated the resting-state brain functional network connectivity in depressed patients with and without suicidal behavior using resting-state fMRI. The suicidal attempts group showed significantly decreased inter-network connectivity between the anterior default mode network and the salience network as well as the right frontal-parietal network. Jung et al.[21] investigated the differences in resting-state brain networks in patients with major depressive disorder (MDD) who had or did not have a history of suicide attempts using independent component analysis. The suicidal depressed patients' group had a decreased inter-network connectivity between the insular network and the default mode network compared with the non-suicidal depressed patients' group. These findings suggest that suicidal behavior affects various functional networks. Functional networks might partly reflect psychological phenomena related to suicidal vulnerability. Rumination and delay discounting (DD) have been reported to be related to suicidal vulnerability. Rumination, which is defined as a persistent passive focus on negative self-relevant information, is thought to be a possible cause of depression or a possible consequence of depression.[22] DD is a decreased subjective value for delayed reward relative to the same reward at present, and greater DD has been reported in psychiatric disorders.[23]

Most of the past neuroimaging studies have compared SAs with nonattempters. However, it is known that not only past suicide attempt(s), but also having severe suicidal ideation increases the risk of suicide.[24] Thus, if we divide subjects only by the history of suicide attempts, those who have no history of suicide attempts but have had severe suicidal ideation are included in the nonattempters group. Actually, there are few neuroimaging studies that compare subjects who have a history of suicide attempts or who have had severe suicidal ideation as a "high-risk group for suicide" with those who have never had a history of suicide attempts nor had severe suicide ideation as a "low-risk group for suicide."

Therefore, in this study, we tried to elucidate the differences of functional brain networks in a "high-risk group for suicide" by comparing the resting-state functional connectivity (rsFC) between those who have had a history of suicide attempts or have had severe suicidal ideation and those who have never had a history of suicide attempts nor had severe suicidal ideation.

METHODS

Subjects

The subjects were 30 patients with MDD, 10 of whom had attempted suicide within the 3 years before they were admitted to a hospital or were referred to a clinic, and the remaining 20 of whom had no history of suicidal attempts. The diagnosis of MDD was based on the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th revision.[25] One patient with attempted suicide was excluded as the patient was 79 years old and showed cognitive decline. Therefore, data derived from 29 patients were analyzed. To assess suicidal ideation, we employed the Columbia-Suicide Severity

Rating Scale (C-SSRS).[26] We used this scale because the worst-point suicidal ideation in one's lifetime (most severe suicidal ideation [MSI], lifetime) question in this scale would predict suicide attempts during the follow-up period of the study. The C-SSRS was administered to all subjects, and they were divided into two groups based on the severity of suicidal ideation at the time when their ideation was the most severe in their lifetime: the more severe ideation group (MSI 4–5) and the milder ideation group (MSI 0–3). The reason for separating the MSI scores at 3 or less and 4 or more is based on a study in which participants with the two highest levels of ideation severity (intent or intent with plan) were more likely to attempt suicide during the study period (24 weeks).[26]

Demographic data, the Japanese version of the Quick Inventory of Depressive Symptomatology (QIDS-J) scores, and medications were analyzed using Rstudio. The Wilcoxon rank sum test was applied to compare continuous variables, including age, QIDS-J score, antidepressants, and anxiolytics/hypnotics. Pearson's chi-square test was applied to examine the differences in gender and handedness composition between groups.

This study was approved by the ethics committee of the Ibaraki Prefectural Medical Center of Psychiatry and performed in accordance with the guidelines and regulations of the institution. All participants gave written informed consent prior to participation.

MRI acquisition and preprocessing

MRI data were obtained using a 3.0-Tesla MRI scanner (Discovery MR750, GE Healthcare, USA) equipped with standard phased array head coils. For resting-state fMRI (rs-fMRI) scans, we employed a gradient-echo echo-planar imaging sequence with the following parameters: echo time (TE), 30 ms; repetition time (TR), 2500 ms; field of view (FOV), 211 × 211 mm; matrix, 64 × 64; slice thickness, 3.3 mm; and flip angle, 80°. We acquired 160 real scans with five dummy scans. During scanning of rs-fMRI, participants were instructed to rest with their eyes open and to focus on a centrally presented white cross. Three dimensional T1-weighted images were also acquired with the following parameters: TE = 2.3 ms; TR = 5.9 ms; TI = 400 ms; FOV 256 × 256 mm; flip angle 14°; and slice thickness, 1 mm.

Functional connectivity was analyzed using the CONN toolbox 17.f (http://www.nitrc.org/projects/conn), running on MATLAB R2017b (MathWorks, Inc.) on Lin4Neuro[27] based on Ubuntu 18.04 to analyze functional connectivity. The images were preprocessed using the default settings of CONN. Slice timing of functional images was corrected based on slice order followed by realignment and normalization of the images. The Artifact Detection Tools (ART) were applied for scrubbing image artifacts due to head movement using 97 percentiles in a normative sample. Signal noise from the white matter and cerebrospinal fluid were also discerned. As a result of denoising, the FCs were normally distributed. Then, we applied a band-pass filter at 0.008–0.09 Hz and smoothed data with 6-mm full width at half maximum Gaussian kernel.

Statistical analysis

For first-level analyses (within-subject analyses), we calculated Pearson's correlation coefficients between the time-course of a seed-region of interest (ROI) and the time-courses of all other ROIs and generated ROI-to-ROI connectivity matrices. We employed the atlas based on the rsFC-boundary map by Gordon et al.[28] and the subcortical atlas implemented in CONN. Then we performed Fisher's transformation to convert the correlation coefficients to normally distributed scores that were used for second-level analysis.

As second-level analyses (inter-subject analyses), we performed between-group comparisons of connectivity. Ages and doses of antidepressants (imipramine equivalent) were treated as nuisance variables. The false discovery rate (FDR) was used to correct for the multiple comparisons, with a threshold of $p < 0.05$.

RESULTS

Demographics and clinical data

Of the 29 subjects, 16 belonged to the severe MSI group (MSI = 4, 5). All nine patients with MDD who had been admitted to a hospital or clinic for suicidal attempts were in the severe MSI group. We found no statistically significant differences between the severe and the mild MSI groups in terms of age, sex, handedness, depression scale (QIDS-J), or equivalent amount of psychotropic medication (imipramine equivalent of antidepressants agents and diazepam equivalent of benzodiazepine anxiolytics and hypnotic agents) at the time of MRI scanning (Table 1). In our sample, QIDS-J and MSI score were not significantly correlated ($r = -0.009$, $p = 0.963$).

TABLE 1 Comparison of demographics and clinical data between the two groups

	MSI ≦ 3	MSI ≧ 4	*P*-value
n (male/female)	13 (10/3)	16 (10/6)	0.67
Age (years), median (interquartile range)	44 (39–48)	38.5 (33.5–51.25)	0.57
Handedness (R/L)	11/2	16/0	0.37
QIDS-J	11 (9–15)	10 (8–15.5)	1
Antidepressants[a] (mg/day)	150 (70–200)	112.5 (65–206)	0.9
Anxiolytics/hypnotics[b] (mg/day)	5 (5–8.3)	7.09 (1.25–10.11)	0.88

Abbreviations: MSI, most severe suicidal ideation; QIDS-J, Japanese version of the Quick Inventory of Depressive Symptomatology.

[a]Imipramine equivalent.

[b]Diazepam equivalent.

TABLE 2 Regions in which rsFC significantly decreased in severe MSI group

ROI	Centroid of ROI (MNI coordinates)			*t*-value	p-FDR
Seed: rt. DLPFC					
rt. precuneus	12	−52	35	3.97	1.56×10^{-2}
lt. precuneus	−11	−52	37	4.61	8.90×10^{-3}
rt. medial OFC	7	48	−10	4.15	1.24×10^{-2}
lt. medial OFC	−6	55	−11	4.41	1.16×10^{-2}
lt. subgenual ACC	−7	38	−9	4.26	1.24×10^{-2}
lt. pregenual ACC	−6	45	6	3.34	4.24×10^{-2}
rt. superior frontal gyrus	21	33	42	4.13	1.24×10^{-2}
lt. superior frontal gyrus	−20	30	46	5.09	5.2×10^{-3}
rt. hippocampus	30	−19	−19	4.21	1.24×10^{-2}
lt. hippocampus	−22	−22	−17	3.92	1.64×10^{-2}
rt. parahippocampal gyrus	20	−11	−25	3.88	1.67×10^{-2}
lt. parahippocampal gyrus	−21	−13	−24	4.03	1.45×10^{-2}
rt. middle temporal gyrus	58	−7	−16	3.66	2.74×10^{-2}
lt. middle temporal gyrus	−53	−11	−16	3.56	3.27×10^{-2}
Seed: lt. RLPFC					
rt. amygdala	23	−4	−18	4	2.22×10^{-2}
lt. amygdala	−23	−5	−18	5.08	7.6×10^{-3}
rt. accumbens	9	12	−6	3.99	2.22×10^{-2}
lt. accumbens	−9	11	−7	3.61	4.62×10^{-2}
rt. putamen	25	2	0	4.31	1.27×10^{-2}
rt. hippocampus	26	−21	−14	4.51	1.18×10^{-2}
rt. thalamus	11	−18	7	3.61	4.62×10^{-2}

Abbreviations: ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; FDR, false discovery rate; MSI, most severe suicidal ideation; OFC, orbitofrontal cortex; RLPFC, rostrolateral prefrontal cortex; ROI, region of interest; rsFC, resting-state functional connectivity.

rsFC

In the rsFC comparison, we found differences in two networks. The first was the network between the right DLPFC (MNI coordinates [31, 40, 26]) and the bilateral hippocampus, precuneus, superior frontal gyrus, medial OFC, posterior middle temporal gyrus, left subgenual anterior cingulate cortex (ACC), and left pregenual ACC, with significantly lower rsFC in the severe MSI group (Table 2 and Figure 1). These regions belong to the default-mode network. The second was the network between the left rostrolateral prefrontal cortex (RLPFC) (MNI coordinates [−29, 51, 10]) and the bilateral amygdala, hippocampus, putamen, and nucleus accumbens, where rsFC was significantly lower in the severe MSI group (Table 2 and Figure 2).

DISCUSSION

In the present study, we compared rsFCs between severe MSI and mild MSI groups. We found that severe MSI groups had significantly smaller rsFCs in two networks: one is the network between the right DLPFC and regions comprising the default-mode network, and the other is the network between the left RLPFC and the striatum, amygdala, and hippocampus.

The default-mode network is associated with internally oriented mental activities, including past remembering, future thinking, social cognition, mental imagery, and mind wandering.[29] One of the psychological phenomena thought to be related to DMN is rumination. One study suggests that rumination is associated with greater severity and duration of depressive episodes in adults, and prospectively increases the risk of depressive relapse.[30] Also, rumination has garnered attention as a factor that may increase vulnerability to suicidal ideation and attempts.[31] To date, the most consistent neural correlates of rumination have been regions within the DMN and subgenual prefrontal cortex.[32,33]

Retrieval suppression is known to be associated with rumination. When people encounter an unwelcome reminder, they strive to limit awareness of the unwanted memory by stopping its retrieval. This retrieval stopping process is known as "retrieval suppression."[34] Retrieval suppression engages the right lateral prefrontal cortex; the prefrontal cortex suppresses the hippocampal activity that supports retrieval.[35] Controlling unwanted

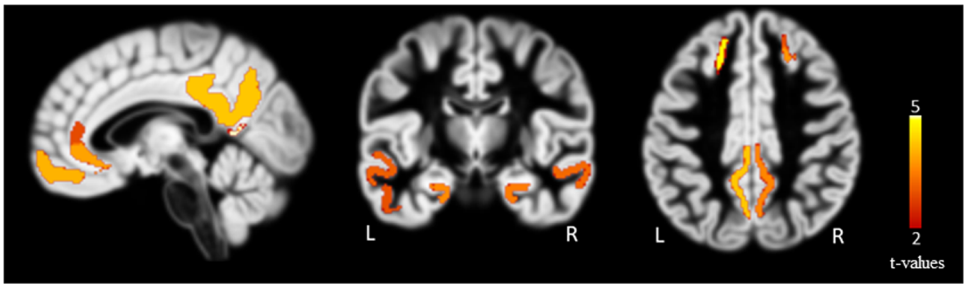

FIGURE 1 Regions in which rsFC significantly decreased with rt. dorsolateral prefrontal cortex (DLPFC) seed in severe most severe suicidal ideation (MSI) group. rsFC, resting-state functional connectivity.

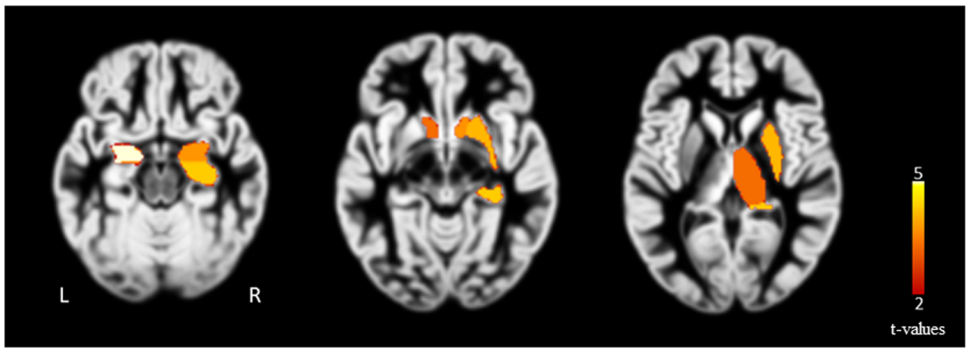

FIGURE 2 Regions in which resting-state functional connectivity (rsFC) significantly decreased with lt. rostrolateral prefrontal cortex (RLPFC) seed in severe most severe suicidal ideation (MSI) group.

memories has been associated with increased dorsolateral prefrontal activation and reduced hippocampal activation.[36] These studies suggest that the right DLPFC is involved in suppressing the mental response to the repeated recollection of past painful experiences (i.e., rumination).

In the present study, the rsFC between the regions consisting of the DMN and the right DLPFC was significantly lower in the severe MSI group. These regions are related to rumination and retrieval suppression. Our findings suggest that patients with severe MSI have difficulty suppressing the focus on their depressive symptoms or rumination, which may lead to strong suicidal thoughts or suicide attempts.

In addition to the DMN-right DLPFC network, we found decreased rsFC of the left RLPFC-striatum/amygdala network in the severe MSI group. This network is known to be related to DD. DD refers to a phenomenon in economic decision-making in which an individual's valuation of a future reward declines as the delay of reward delivery increases.[37] An individual's preference for an immediate reward, which can be measured using a behavioral index of discounting rate, has been considered as an indicator of one's impulsivity in decision-making.[38] In addition to depressive disorders, individuals with impulse-control disorders, including attention-deficit hyperactive disorder, substance abuse, pathological gambling, and smoking, exhibit steeper reward discounting than HC.[39–45] Studies have consistently shown that DD involves cortical-basal ganglia circuits.[46] These circuits consist of two networks: a valuation network consisting of the ventral striatum, amygdala, hippocampus, ventromedial prefrontal cortex, and posterior cingulate cortex,[47–49] and a control network consisting of the dorsal striatum, dorsal anterior cingulate cortex, lateral prefrontal cortex, and the posterior parietal cortex[47,50–52]

Structural and functional connectivity between the striatum and lateral prefrontal cortex has been negatively associated with discounting rates.[53] Li et al.[54] found that the FC between the valuation network and the control network was negatively correlated with discounting rates. That is, the smaller the rsFC between the valuation network and the control network, the larger the discount rate. In our results, the rsFC between the left RLPFC, which is part of the control network, and the valuation network was significantly smaller in the severe MSI group. These results suggest that the severe MSI group might have a larger discount rate and be more likely to make impulsive decisions. Making a choice according to a long-term goal at the expense of an immediately available reward is accompanied by an increased negative functional interaction between the nucleus accumbens (NAcc) and the anteroventral PFC.[55] The left anteroventral PFC (MNI coordinates [−28, 56, 4]) reported in their study is almost the same region as the left RLPFC (MNI coordinates [−29, 51, 10]), in which we found significant differences between the two groups. Our results suggest that the high suicide risk individual (severe MSI) might be more likely to make impulsive and short-sighted decisions when making decisions that involve a temporal component. Because of these biological characteristics, they might have difficulty coping with distress from a long-term perspective, leading to serious suicidal ideations or to impulsive suicide attempts.

In this study we treated patients with history of suicidal attempt and those with severe suicidal ideation as a high-risk group for suicide. The neuroimaging findings of our study were similar to previous studies in which only suicidal attempters were included. Cao and colleagues reported that suicidal attempters showed decreased FC between left superior frontal gyrus and right anterior cingulate gyrus.[56] Stange et al. showed the decreased FC between right middle frontal gyrus/inferior frontal gyrus and DMN.[57] These results are in line with our results, which indicates that individuals with severe suicidal ideation might have altered functional network similar to suicidal attempters.

There are several limitations in our study. First, our sample size was small, so it limits the generalization of the result. Second, there was no HC group in this study. We evaluated the intensity of suicidal ideation by semi-structured interviews (C-SSRS) and selected subjects not only based on their history of suicide attempts, but also based on previous severe suicidal ideation. This allowed us to compare MDD patients with a high risk of suicide with MDD patients with a low risk of suicide. Including a control group may allow evaluation of the interaction between MDD traits and suicide risk.

Lastly, though we speculate that rumination, retrieval suppression, and DD might influence suicidal ideation based on our results, we did not directly assess these tendencies. Future studies focusing on severe suicidal ideation as well as rumination, retrieval suppression, and DD would shed more light on the neural substrate of suicide.

In conclusion, our results suggest that functional networks related to rumination, retrieval suppression, and DD might be impaired in depressive patients with severe suicidal ideation. It might be beneficial for psychiatrists to assess these characteristics to prevent suicide in depressive patients.

AUTHOR CONTRIBUTIONS

Hirokazu Tachikawa: conceptualization; supervision; writing—review and editing. Yuki Shiratori: conceptualization. Kazuhiro Ishikawa: data curation; data analysis; writing—original draft. Hitoshi Usuniwa: data curation; data analysis. Noriko Yamada: data curation. Chie Yaguchi: data curation. Yuki Shiratori: data curation. Noriko Sodeyama: data curation. Kiyotaka Nemoto: data analysis; methodology; writing—original draft. Takafumi Hori: writing—review and editing. Tetsuaki Arai: writing—review and editing. Kikuko Kodama: writing—review and editing.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS APPROVAL STATEMENT

This study was approved by the ethics committee of the Ibaraki Prefectural Medical Center of Psychiatry and performed in accordance with the guidelines and regulations of the institution.

PATIENT CONSENT STATEMENT

All participants gave written informed consent prior to participation.

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