Residual Memory Impairment in Remitted Depression May Be a Predictive Factor for Recurrence

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ABSTRACT

Objective: Memory impairment in remitted depression is reported to be related to the number of previous depressive episodes. A recent report hypothesized that each depressive episode increases the risk of memory impairment during remission, which further increases the risk of recurrence. We investigated whether the risk for recurrence increased as a function of memory impairment at remission.

Method: One hundred ten participants with *DSM-IV-TR* major depressive disorder (MDD) after remission (defined as a score ≤ 7 on the Hamilton Depression Rating Scale) were recruited between April 2004 and March 2012 and were followed up prospectively. All patients were divided into 2 groups: those who had memory impairment and those who had no memory impairment after remission. (Memory impairment was determined with the Wechsler Memory Scale-Revised.) The time to recurrence of depression (a score ≥ 4 on the Clinical Global Impressions-Severity of Illness scale) was compared between the groups prospectively. Kaplan-Meier survival curves, log-rank test for trend for survivor functions, and Cox proportional hazard ratio (HR) estimates for a multivariate model were conducted to examine the risk of recurrence by presence of memory impairment after remission.

Results: One hundred nine participants completed this study. In the follow-up period, recurrence occurred in 25 (55.6%) of the 45 patients with memory impairment and 21 (32.8%) of the 64 patients with no memory impairment. In the Kaplan-Meier survival estimates for time to incidence of recurrence in patients with and without memory impairment, the cumulative probability of developing a recurrence for patients with memory impairment was higher than for patients with no memory impairment (log-rank test: $\chi^2_1 = 4.63$, $P = .03$). Survival analysis was also performed using Cox proportional hazards regression in a multivariate model. The presence of memory impairment remained significantly associated with incidence of recurrence (HR = 2.55; 95% CI, 1.30–4.99; $P = .006$).

Conclusions: The presence of residual memory impairment in patients with remitted MDD may increase the risk of recurrence.

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It is widely accepted that most patients with major depressive disorder (MDD) will experience recurrence, and longitudinal cohort studies have reported recurrence rates that ranged from 80% to 95%.[1–3] A recent review[4] reported that risks for recurrence of depression were residual symptoms, more than 3 prior depressive episodes, chronic depression, family history, comorbidity, and late onset. In addition, another systematic review[5] indicated that the number of previous depressive episodes was the most important clinical predictor of recurrence of depression. However, the relationship between the recurrence of depression and clinical characteristics has yet to be fully explained.

One clinical characteristic of MDD is memory impairment exhibited in depressed patients.[6,7] Recently, evidence has suggested that memory impairment in depression may improve with adequate treatment but may also partially remain even after remission from a depressive episode.[8–14] In addition, the residual memory impairment in remitted MDD is present even in younger patients compared with matched healthy controls.[15] Taken together, these reports indicate that there is a group of patients with remitted MDD who have impaired memory functions.

Recently, we investigated memory impairments in patients with multiple-episode MDD during the remitted state.[16] In multiple-episode MDD, memory impairment remained during remission, in contrast to findings in single-episode MDD. Therefore, it was suggested that multiple depressive episodes increase residual memory impairment during remission. These findings confirm results reported by Kessing.[17] He indicated that cognitive functions of patients with multiple episodes were significantly more impaired than those in patients with a single episode or controls. Also in this study, within patients, the number of prior episodes seemed to be associated with cognitive outcome. In addition, a review[18] regarding the relationship between cognitive function and remitted depression indicated a hypothesis that each depressive episode increases the risk of cognitive impairment during remission, further increasing the risk of recurrence. The recurrence of depression would be expected to result in repeated insults to the brain.[19] However, it is unclear whether memory impairment reflects an underlying neural vulnerability for the subsequent recurrence of depression. Alexopoulos et al[20] reported that executive dysfunction but not memory impairment was associated with depressive recurrence in geriatric depression. In youth and middle-aged patients, on the other hand, a recent study[21] found no evidence that cognitive functioning was related to recurrence of depression.

The aim of the present study was to clarify whether residual memory dysfunction in remitted MDD is associated with

subsequent recurrence. Thus, we investigated the risk for recurrence in patients with remitted MDD who had impaired memory functions compared to those without. This study is a part of the Juntendo University Mood Disorder Project (JUMP).

Clinical Points

- Although most patients with depression will experience recurrence, the predictive factor for recurrence has not been fully explained.
- A group of patients with remitted depression have impaired memory functions.
- The memory impairment in remitted depression may be a predictive factor for recurrence.

METHOD

Subjects

A total of 110 inpatients with MDD (56 men and 54 women; mean age = 48.4 years; age range, 23–65 years) after remission were recruited from the Juntendo Koshigaya Hospital in Saitama, Japan, between April 2004 and March 2012 and entered the JUMP. Diagnoses were made according to the *Diagnostic and Statistical Manual for Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*).[22] Patients were excluded if they had a comorbid Axis I disorder, a history of other psychiatric disorders, severe or acute medical illnesses, or neurologic disorders or used any drugs that may trigger depression.

All patients were on antidepressant medications throughout the time of present study. For analysis purposes, the doses of antidepressants were converted to an equivalent dose of imipramine.[23] The number of depressive episodes, total duration of depressive episodes, and age at onset were confirmed via medical records. Depressive symptoms were assessed using the Hamilton Depression Rating Scale (HDRS),[24] and remission was defined as an HDRS score of 7 points or less.[25] Memory function was assessed immediately after remission as a baseline.

A total of 248 healthy participants were recruited as a control group. Controls who had any history of depression or met the exclusion criteria used for patients were excluded (n = 37 for all exclusions). Two hundred eleven healthy controls (96 men and 115 women; mean age = 48.3 years; age range, 18–65 years) matched for age, duration of education, and distribution of gender were recruited. All controls were working at least part-time or were students and had memory function assessments.

The present study was approved by the Medical Ethics Committee of Juntendo University and was performed in accordance with the regulations outlined by Juntendo University, Saitama, Japan. All participants provided written informed consent.

Evaluation of Memory Function

Memory function was measured by using the logical memory delayed recall subtest of the Wechsler Memory Scale-Revised (WMS-R),[26] because this subtest was significantly associated with the number of episodes of MDD in our recent research.[16]

Logical memory is a task of verbal memory in which subjects perform free recall of given sentences immediately after they listen to short stories. The examiner reads 2 stories, stopping after each story for an immediate free recall. The second portion of the logical memory test involves recall of the stories after a 30-minute delay. The logical memory delayed recall subtest has shown sufficient reliability to be interpreted on its own.[27]

Definition of Comparison Groups

Immediately after remission as baseline, we divided all patients with MDD into 2 groups: those with impaired memory function compared to healthy controls (memory impairment group) and those with no memory impairment (no memory impairment group). The memory impairment group was defined as the subjects with logical memory delayed recall scores lower than the mean – 1 standard deviation in healthy controls.

Follow-Up Evaluation

All participants were followed up prospectively, and their clinical state was evaluated. The participants were followed from the date they were registered, immediately after remission, until recurrence of their depression or March 2012. The follow-up evaluations were conducted every few weeks by experienced psychiatrists in our hospital. Recurrence of depression was defined as a Clinical Global Impressions-Severity of Illness scale (CGI-S) score greater than or equal to 4.[28] We determined recurrence of depression to include relapse, which has been widely described as depression occurring within 4 to 6 months after remission.[4,25,29]

Statistical Analysis

We compared age, HDRS score at hospital admission, HDRS score at baseline, age at onset, education, number of episodes, total duration of depressive episodes, duration of current depressive episode, daily dose of antidepressants at baseline, and duration of follow-up period between the memory impairment group and the group with no memory impairment using the 2-tailed unpaired Student *t* test. Chi-square (χ^2) tests were used to compare the frequencies of gender, family history, and recurrence of depression.

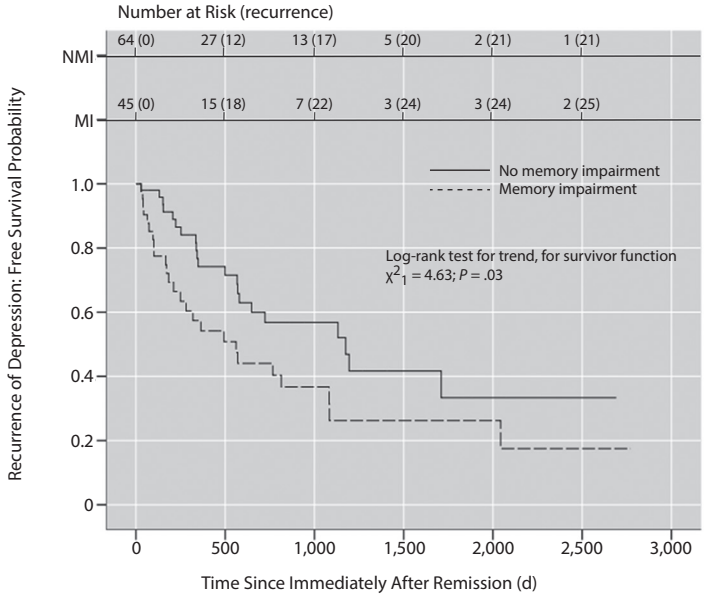
Analyses focused on incident recurrence of depression. Kaplan-Meier survival curve and log-rank comparisons were used to compare time to recurrence between groups. Subjects were censored on loss of follow-up or at the end of the present study (ie, March 2012). We used Cox proportional hazard ratio (HR) estimates for a multivariate model and examined the risk of recurrence related to the memory impairment group. A significance level of $P < .05$ was used. Statistical procedures were performed using the Japanese version of SPSS v15 (SPSS Japan Inc, Tokyo, Japan).

Table 1. MDD Patient (N = 109) Demographics and Clinical Information

Variable	MI, n = 45	NMI, n = 64	*P* Value
Baseline			
Age, mean (SD), y	54.9 (8.3)	44.7 (10.3)	<.01[a]
Sex, female/male	24/21	30/34	.51[b]
Education, mean (SD), y	13.1 (2.1)	14.0 (2.3)	.04[a]
Age at onset, mean (SD), y	48.5 (10.4)	40.7 (11.3)	.01[a]
Number of episodes, mean (SD)	2.0 (1.2)	1.7 (1.3)	.52[a]
Total duration of depressive episodes, mean (SD), mo	26.0 (45.2)	21.7 (26.6)	.63[a]
Duration of current depressive episode, mean (SD), mo	8.0 (8.0)	10.0 (12.0)	.36[a]
HDRS score at hospital admission, mean (SD)	21.0 (8.3)	16.2 (8.4)	.01[a]
HDRS score immediately after remission, mean (SD)	4.1 (6.7)	3.3 (2.3)	.72[a]
Family history, n (%)	6 (13.3)	13 (20.3)	.34[b]
Logical memory score on WMS-R, mean (SD)	5.3 (3.0)	19.7 (5.0)	<.01[a]
Daily dose of antidepressants, mean (SD), mg[c]	155.1 (57.0)	138.8 (72.6)	.27[a]
During follow-up period			
Recurrence of depression, n (%)	25 (55.6)	21 (32.8)	.02[b]
Duration of follow-up period, mean (SD), d	554.1 (658.7)	673.5 (610.3)	.38[a]

[a]Two-tailed unpaired Student *t* test.
[b]χ^2 test.
[c]Antidepressants were converted into equivalent doses of imipramine.
Abbreviations: HDRS = Hamilton Depression Rating Scale, MDD = major depressive disorder, MI = memory impairment, NMI = no memory impairment, SD = standard deviation, WMS-R = Wechsler Memory Scale-Revised.

Figure 1. Kaplan-Meier Survival Curve of Time to Incidence of Recurrence by Memory Impairment After Remission From Depression



Abbreviations: MI = memory impairment, NMI = no memory impairment.

RESULTS

During the follow-up period, 1 patient withdrew consent to this research. The final study comprised 109 patients with MDD (55 men and 54 women; mean age = 48.6 years; age range, 23–65 years).

Baseline Characteristics and WMS-R Score of Study Subjects

Memory function, as assessed with the logical memory delayed recall subtest of the WMS-R, was 13.7 ± 8.3 (mean ± SD) for patients with remitted MDD and 18.1 ± 8.1 for healthy controls. Therefore, we divided all MDD patients into the memory impairment group (n = 45) and the group with no memory impairment (n = 64) using the cutoff point of 10.0, which is defined as the mean – 1 SD of the WMS-R scores for healthy controls.

The variables of gender, number of episodes, total duration of depressive episodes, duration of current depressive episode, family history, HDRS score, and daily dose of antidepressants did not differ significantly between those with and without memory impairment (Table 1). Patients in the memory impairment group were significantly older ($P < .01$) and had an older age at onset ($P < .01$) and a shorter education ($P < .04$) than those in the group with no memory impairment.

Incidence of Depressive Recurrence: Kaplan-Meier Survival Curves

In the follow-up period, 46 (42.2%) of the 109 patients with MDD experienced recurrence. Recurrence of depression occurred in 25 (55.6%) of the 45 patients in the memory impairment group and in 21 (32.8%) of the 64 individuals in the group with no memory impairment. Figure 1 presents the Kaplan-Meier survival estimates for time to incidence of recurrence for each group during the present study period. The cumulative probability of developing a recurrence of depression for memory impaired patients was higher than that for individuals with no memory impairment. This survival difference was statistically significant using the log-rank test ($\chi^2_1 = 4.63$, $P = .03$).

Incidence of Depressive Recurrence: Cox Proportional Hazard Ratio Estimates for a Multivariate Model

Survival analysis was also performed using Cox proportional hazards regression in a multivariate model. For this model, we selected clinical features (number of depressive episodes, duration of current depressive episode, family history, and age at onset) and memory impairment as covariates because these variables (except memory impairment) had been previously indicated as predictors of recurrence.[4]

As shown in Table 2, the variable of memory impairment remained significantly associated with the incidence of recurrence (HR = 2.55; 95% CI, 1.30–4.99; $P = .006$). Age at onset, number of depressive episodes, family history, and duration of current depressive episode were not associated with recurrence of depression in the multivariate model.

Age of the participants was significantly different between the memory impaired group and the group without memory impairment. Therefore, we analyzed using the covariates that selected the age of participants instead of the age at onset. The

Table 2. Cox Proportional Hazard Ratio Estimates for a Multivariate Model of Predictors of Time to Depressive Recurrence

Variable	HR	95% CI	*P* Value
Age at onset	0.97	0.94–1.00	.090
Number of depressive episodes	0.98	0.72–1.32	.884
Family history	1.07	0.44–2.62	.870
Duration of current depressive episode	1.00	0.98–1.03	.833
Memory impairment	2.55	1.30–4.99	.006

Abbreviations: CI = confidence interval, HR = hazard ratio.

results were not changed. Thus, an association between the memory impairment and the incidence of recurrence was significant (HR = 2.86; 95% CI, 1.37–5.94; *P* = .005).

DISCUSSION

The present prospective study investigated the incidence of the recurrence of depression in memory impaired and non–memory impaired patients with remitted MDD over a longitudinal period. The main findings of the present study indicated an increase in risk of recurrence as a function of residual memory impairment. In addition, memory impaired patients were nearly 3-fold as likely to have a risk of recurrence. Taken together, these results suggest that residual memory impairment in patients with remitted MDD may be a predictive factor for recurrence of depression.

The number of previous episodes of MDD has been found to be the most important clinical predictor of recurrence.[5] Our previous study[16] indicated that MDD patients with multiple depressive episodes showed residual memory impairment over a long period after remission, while the patients with a single episode improved up to a healthy level. In addition, a recent review[18] hypothesized that each depressive episode increases the risk of cognitive impairment during remission, further increasing the risk of recurrence. Although a small number of studies[20,21,30,31] regarding the relationship between the recurrence of depression and cognitive function have been documented, their results did not reach a consensus. Possible causes considered were the influence of age (ie, late-life MDD or early-life MDD), duration of follow-up, and domain of cognitive function (ie, executive function, attention, or memory).[20,21,30,31] Alexopoulos et al[20] suggested that executive dysfunction in remitted MDD, but not memory impairment, was found to be associated with recurrence. The results are not consistent with our study. The reason for this discrepancy may be partly caused by the difference in age of participants. The patients in the previous study were only geriatric individuals. A part of the DELTA (Depression Evaluation Longitudinal Therapy Assessment) study,[21] which was a large prospective study, determined the relationship between memory impairment and recurrence of depression within 2 years in 137 youth and middle-aged patients with recurrent moderate-to-severe MDD. The results indicated that memory functioning was not related to recurrence of depression. These findings are also inconsistent with the results of our research. The reason for the discrepancy between the 2 studies is unclear, but the present JUMP study differed from the DELTA study in aspects such as the follow-up period and the clinical characteristics of participants. The follow-up period in the present study was longer (within 8 years) than that of the DELTA study (within 2 years). In addition, at baseline of the DELTA study, the duration of the remitted state, which ranged from 10 weeks to 2 years, was inconsistent. Memory impairment in youth and middle-aged patients with MDD may fluctuate a few years after remission.[15] Therefore, our participants consisted of only MDD patients immediately after remission. Moreover, in the present JUMP study, clinical evaluations were conducted continuously by experienced psychiatrists at the same hospital. In particular, follow-up evaluation was carried out every few weeks, which more closely approximates the clinical situation in contrast with the 3 follow-up assessments (3, 12, and 24 months) in the DELTA study.

There are important limitations to our prospective cohort study. First, all patients were treated with 1 or 2 different antidepressants that may have had deleterious effects on cognition. Although no significant differences between daily doses of antidepressant were confirmed between memory impaired and non–memory impaired patients with MDD, memory dysfunction in our patients may have been influenced by an adverse effect of anticholinergic medications. Accordingly, drug-free euthymic patients should be investigated in future research. Second, the age of participants was not matched between the memory impaired group and the group without memory impairment. In future research, matched-age participants should be studied. Third, participants in the present study consisted of both those with a first episode of MDD (n = 49) and those with multiple episodes of MDD (n = 60). When we excluded those with multiple episodes, the fundamental results using survival analysis could not confirm our results (data not shown), suggesting that the small size for these analyses (memory impaired patients, n = 17; patients without memory impairment, n = 32) may explain the discrepancy. In future research, a larger patient population should be used.

In conclusion, our JUMP study found an association between memory impairment in remitted MDD and risk for recurrence. There was a greater risk of depressive recurrence in MDD patients with memory impairment. This finding suggests that memory impairment in remitted MDD may predict future recurrence.

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