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Neurocognitive impairments and quality of life in unemployed patients with remitted major depressive disorder

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ABSTRACT

Quality of life (QOL) has been reported to be impaired in patients with major depressive disorder (MDD), even after remission according to symptom rating scales. Although a relationship between QOL and neurocognitive dysfunction has been reported during depressive episodes, little is known about this relationship in remitted MDD patients. The aim of the present study was to investigate the relationship between QOL and neurocognitive dysfunction in patients with remitted MDD while controlling for confounding factors. Forty-three remitted MDD patients were assessed with neuropsychological tests and QOL, which was measured by a short-form 36-item health survey. The neurocognitive performances of the patients were compared with those of 43 healthy controls. We next evaluated the relationships between neurocognitive impairments, clinical factors, and QOL. Remitted MDD patients had poorer neurocognitive performances than healthy controls for psychomotor speed, attention, and verbal memory. Residual depressive symptoms were strongly associated with QOL. Delayed verbal recall was associated with general health perceptions, which are part of the QOL assessment, even after the effects of the residual depressive symptoms were considered. The results may indicate that clinicians should try to detect neurocognitive dysfunctions that may interfere with QOL using neurocognitive assessments in their daily practice.

1. Introduction

Major depressive disorder (MDD) is a common and severe mental disorder associated with significant impairments in psychosocial function, including quality of life (QOL) (IsHak et al., 2011). Previous studies have shown that impairments in QOL are correlated with the severity of depressive symptoms (Daly et al., 2010). However, several studies have demonstrated that MDD patients suffer from QOL impairments, even after their depressive symptoms remit, as assessed by symptom rating scales (ten Doesschate et al., 2010). Therefore, it is important to investigate the factors that affect QOL impairment in remitted MDD patients.

Neurocognitive impairment is a candidate factor that could worsen QOL in remitted MDD patients. The evidence accumulated in the past decade suggests that MDD patients present neurocognitive disturbances (Marazziti et al., 2010). While one meta-analysis has revealed that depression severity is significantly correlated with neurocognitive performances in multiple cognitive domains, which were episodic memory, executive functioning, and psychomotor speed (McDermott and Ebmeier, 2009), another recent systematic review has shown that performances on neuropsychological tests were impaired in remitted MDD patients compared with healthy control individuals in nine of the eleven studies examined (Hasselbalch et al., 2011).

However, the results of previous studies that investigated the relationship between QOL and neurocognitive dysfunction have been inconclusive (McCall and Dunn, 2003; Naismith et al., 2007; Baune et al., 2010). The previous two studies (McCall and Dunn, 2003; Naismith et al., 2007) have demonstrated a significant relationship between neurocognitive function and OQL in MDD patients; however, the most recent study (Baune et al., 2010) did not. One of the reasons for this inconsistency is that the clinical symptoms of the subjects were not controlled. The subjects in the previous two studies were not remitted, and those in the latest one were a mixed sample of remitted and symptomatic patients. Another possible reason for the discrepancies in the results in the

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previous studies is that clinical and sociodemographic factors known to correlate with QOL have not been sufficiently controlled. Recent studies have revealed that QOL in MDD patients is associated with multidimensional clinical and sociodemographic factors (IsHak et al., 2011). In a recent STAR*D report, after controlling for age and depression severity, QOL was found to be independently related to race, education, employment status, marital status, medical insurance, and general medical disorders (Daly et al., 2010). Other studies have demonstrated that QOL in MDD patients is lower if they have other psychiatric comorbidities (Brieger et al., 2002; Mittal et al., 2006).

In this study, we evaluated the relationship between neurocognitive impairments and QOL in remitted MDD patients. In order to rule out factors that affect QOL, we recruited only patients who were remitted as assessed by a symptom rating scale and who had no psychiatric comorbidities. In addition, we controlled for employment status, medical insurance, and race in remitted MDD patients.

2. Methods

2.1. Participants

Forty-three patients [10 females, 33 males; mean age (standard deviation [SD]), 38.3 (8.9) years] were recruited from outpatients of the Department of Psychiatry, Hokkaido University Hospital. All participants met the criteria for MDD according to the Diagnostic and Statistical Manual for Mental Disorders-IV, as assessed by the Mini-international neuropsychiatric interview (Sheehan et al., 1998), and at the time of entry into the study, all of them were remitted, which was defined as a score of less than 8 points on the Hamilton rating scale for depression (HAM-D; Hamilton, 1960). These clinical assessments were performed by clinical psychiatrists, and mean score of HAM-D in the participants with remitted MDD was 2.9 (2.2). All patients took a long-time absence from work (defined as 2 months or more) at the time of the study due to their previous depressive episodes, although they were of working age, which was defined as an age of 20–59 years. All participants had the same type of medical insurance because a system of public health insurance has been established for the whole nation of Japan. Forty-one patients were taking psychiatric medications at the time of entry into the study, whereas two patients were not taking any. Patients were excluded from the study if they had other Axis I disorders, personality disorders, mental retardation, previous psychotic episodes, neurodegenerative or neurological illness, severe physical illness, or history of electroconvulsive therapy within the previous year.

The control group consisted of 43 healthy volunteers [18 females, 25 males; 38.7 (10.7) years] selected from the control pool recruited from the community with an advertisement. They were also interviewed with the Mini-International Neuropsychiatric Interview by psychiatrists to confirm that they had no Axis I psychiatric disorders. They were matched with the patients in terms of age and education level. The matching was performed on the group level. MDD patients and controls were required to be native Japanese speakers due to the nature of the verbal tests; all of them belonged to the Mongoloid race.

2.2. Materials

2.2.1. Neuropsychological assessment

The neuropsychological test battery in our hospital consisted of the following five tests (Toyomaki et al., 2008).

1) *Wisconsin card sorting test (WCST)*: A computerized Japanese Keio-University version was used (Kashima and Kato, 1995). The number of categories achieved and perseverative errors of Nelson were used as measures of executive functioning.
2) *Continuous performance test (CPT)*: A computerized A–X CPT was administered for approximately 7 min. Several characters were presented at the center of a display. The subjects were instructed to respond as quickly as possible to "X," which appeared immediately after "A." The target stimulus was presented 70 times. Each stimulus was presented for 100 ms with an interstimulus interval of 1500–2000 ms. There were very few omission errors in the results. Therefore, we summed the omission and commission errors. The average reaction time was used as a measure of psychomotor speed. The total number of errors was used as a measure of attention.
3) *Trail making test (TMT)*: Both parts of TMT consisted of 25 circles distributed over a sheet of paper. In Part A, the circles were numbered 1–25. The participant was required to draw lines in order to connect the numbers in ascending order. In Part B, the circles included both numbers (1–13) and 12 hiragana (Japanese cursive syllabary) letters, and the participant was required to draw lines with the added task of alternating between the numbers and letters. Part A measured psychomotor speed and attention, whereas Part B required more mental flexibility, the ability to shift attention, and strategy. Therefore, the subtracted time (TMT-Part B minus TMT-Part A: TMT Part B-Part A) was used as a measure of executive functioning.
4) *Word fluency test (WFT)*: Each participant had to say as many words as possible beginning with the "Shi," "I," or "Re" sounds in 60 s. The total number of words was used as a measure of verbal fluency, which is a part of executive functioning.
5) *Auditory Verbal Learning Test (AVLT)*, which was adapted from the Repeatable Battery for the Assessment of Neuropsychological Status, Japanese version (Yamashima et al., 2002). Each participant was required to learn a 10-item word list over four trials (trials 1–4), and they were then assessed 30 min later (trial 5). The number of recalled words in trial 1 was used to indicate immediate recall. The number of recalled words in trial 5 indicated delayed recall.

2.2.2. Clinical measures

Each participant's age, sex, years of education, age at first episode, duration of illness, and number of episodes were noted. Furthermore, after the tests, they took the Beck Depression Inventory-Second Edition (BDI-II), which is a self-rating depressive symptom scale used for clinical assessment (Beck et al., 1996; Kojima et al., 2002).

2.2.3. QOL measures

QOL was measured with the validated Japanese version of the generic short-form 36-item health survey v2 (SF-36) in the MDD patient group (Fukuhara et al., 1998a, 1998b).The survey contained 36 self-administered questions that quantify health-related QOL and assess eight scales of the following physical and mental domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). The scores of the eight scales were standardized with Japanese population norms to obtain mean scores of 50 and SDs of 10 (norm-based scoring: NBS).

2.3. Procedure

Before the assessments, a description of the study was given to all participants and written informed consents were obtained from them. The Hokkaido University Hospital Ethical Committee approved this study. All procedures were conducted in accordance with the Declaration of Helsinki. Following the receipt of the informed consent, an experienced examiner who was blind to each participant's diagnostic classification administered the neuropsychological test battery. Approximately 60 min were necessary to complete all tests and questionnaires.

2.4. Statistical analyses

First, all the data for MDD patients were compared with those for the matched healthy controls. The results of the groups, except for neuropsychological tests scores, were compared with unpaired two-tailed *t*-tests for continuous variables or chi-square tests for categorical variables. The equality of variance was checked with Levene's test. Welch's test was performed if the homogeneity of variance assumption was not accepted. *P* values less than 0.05 were considered statistically significant. The results of neuropsychological tests between the two groups were compared using a one-way analysis of variance that included age, gender, and education as covariates (ANCOVA). In the comparison of neurocognitive performances, Bonferroni corrections were applied, and *P* values less than 0.0056 (0.05/9=0.0056) were considered statistically significant. The effect sizes (Cohen's *d* value) were calculated to estimate the magnitude of the differences between the groups.

Next, to investigate the relationship between QOL and clinical factors or neurocognitive functions, using the SF-36 subscales as dependent variables, single linear regression analyses were conducted using age, gender, years of education as covariates (multiple regression analyses by forced entry method). In each model, we used one of the neuropsychological test scores that showed significant differences between MDD patients and healthy controls or the clinical variables (age at first episode, duration of illness, number of episodes, HAM-D scores, and BDI-II scores) as an independent variable.

For the final step, a multiple regression analysis was conducted with a forced entry method in which the scores for the SF-36 subscales that were significantly related to the neuropsychological test score were used as dependent variables to find variables that could best predict the SF-36 score. As independent variables in this step, we choose age, gender, years of education (entering these three factors as covariates), clinical, and neuropsychological variables that were significantly related to the SF-36 score in the prior single linear regression analyses. Independent variables were selected on the condition that the mutual correlation coefficients in Pearson correlation were −0.5 to 0.5 considering multicollinearity.

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