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Accepted Manuscript

Impact of subjective vs. objective remission status on subjective cognitive impairments in depression

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Highlights

- Objective/subjective depression severity affects subjective cognitive impairment.
- Subjective remission seems more correlated with subjective cognitive function.
- Objective remission alone does not represent favorable cognitive function.

*(Original Article)***Impact of subjective vs. objective remission status on subjective cognitive impairments in depression**

Abbreviated title: Impact of subjective versus objective depression severity on cognition

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Abstract

Objective: The impact of subjective versus objective illness severity on subjective cognitive impairment in patients with depression has not been addressed.

Methods: This study is a post-hoc analysis of our cross-sectional study in Japanese outpatients with depressive disorder (ICD-10) (Ozawa et al., 2017). The participants received assessments with the Japanese version of the Perceived Deficits Questionnaire (J-PDQ), Quick Inventory of Depressive Symptomatology (QIDS), and Montgomery-Asberg Depression Rating Scale (MADRS). First, multiple regression analysis was conducted to examine the effects of demographic and clinical characteristics, including illness severity and medications (e.g., antidepressants and benzodiazepines), on the PDQ total score. Next, we categorized the participants into 4 groups based on the presence/absence of subjective and objective symptom remission (i.e., QIDS total score of ≤ 5 and MADRS total score of ≤ 9 , respectively), and compared the differences in PDQ total scores between the QIDS- and MADRS-remitted group and the QIDS-non-remitted but MADRS-remitted group.

Results: 102 participants were included (45 men; mean $\pm$ SD age, 50.5 $\pm$ 14.7 years). Higher QIDS and MADRS total scores were significantly associated with a greater PDQ total score (both p 's <0.001), while

other factors did not exhibit any associations. The QIDS-non-remitted but MADRS-remitted group showed a significantly higher PDQ total score than that of the QIDS- and MADRS-remitted group (median 10.0 [8.0-12.0] vs. 3.0 [range: 2.0-4.0], $p < 0.001$).

Conclusions: These findings suggest that objective remission in the absence of subjective remission may not be adequate to improve subjective cognitive functioning.

Keywords: depression, illness severity, PDQ, subjective cognitive impairment

1. Introduction

Cognitive impairment is a common symptom of major depressive disorder (MDD) with prevalence rates ranging from 20% to 60% (Afridi et al., 2011; Gualtieri and Morgan, 2008). While research often prioritizes mood symptoms because of the illness's affective nature, it is also critically important to focus on cognitive impairment in light of its close associations with poor treatment response and low psychosocial functioning

(Evans et al., 2014; Story et al., 2008). Patients with MDD have reported impairment in several domains of cognition, including working memory, social cognition, reasoning/problem solving, motor speed, and attention (Bakkour et al., 2014). A meta-analysis indicated moderate impairments in several cognitive domains in patients with MDD as compared to healthy controls (Cohen's d : -0.34 to -0.54 in executive function, -0.41 to -0.50 in memory, and -0.65 in attention, respectively) (Rock et al., 2014).

Previous studies have shown that cognitive impairment remains unresolved in some patients who have already remitted from depressive episodes, although this finding has not been consistent in the literature (Baba et al., 2010; Conradi et al., 2011; Nagane et al., 2014; Paelecke-Habermann et al., 2005). One recent randomized longitudinal study, which included 712 patients with MDD, demonstrated that cognitive impairment remained unresolved in five domains (attention, response inhibition, verbal memory, decision speed, and information processing) following antidepressant treatment, even among remitted patients (Shilyansky et al., 2016). Thus, there is a clear need to attend to cognitive function in patients with MDD regardless of their remission status.

Cognitive function can be evaluated with subjective and/or objective assessment measures in depression (Antikainen et al., 2001; Svendsen et al., 2012). Previous studies that investigated the concordance between

subjective and objective cognitive function in older adults has produced highly varied findings (Burmester et al., 2016). As for mood disorders, one study reported the positive association between subjectively and objectively assessed cognitive functions in patients with bipolar disorder (Arts et al., 2010). Recent evidence suggests that subjectively assessed cognitive measures are more closely correlated with general functioning and depressive symptoms than objective measures in patients with MDD (Potvin et al., 2016; Zlatař et al., 2018). The symptomatology of depression has similarly been assessed with subjective and/or objective assessment scales (Trivedi, 2009). However, the degree of concordance between subjective and objective measures in assessments of illness severity varies (Carter et al., 2010; Tada et al., 2014; Uher et al., 2012). Thus, it is plausible that subjective and objective illness severity has different effects on subjective cognitive impairment in patients with MDD. Furthermore, while objectively assessed cognitive impairment appears to be affected by the severity of depression, duration of illness, and medications used (Borkowska and Rybakowski, 2001; Federico et al., 2017; Gorenstein et al., 2006; Hasselbalch et al., 2011; Tourjman et al., 2018), it remains unclear which demographic and clinical factors affect subjective cognitive impairment.

In this study, we therefore explored factors associated with subjective cognitive impairment and

investigated differences in the impact of subjective versus objective illness severity on subjective cognitive impairment in patients with MDD.

2. Methods

2.1. Study design and participants

We conducted a post-hoc analysis of the data from our previous cross-sectional study investigating factors associated with resilience in patients with depression. The research conditions have been described in detail elsewhere (Ozawa et al., 2017). Briefly, the study was conducted between November 2014 and September 2016 at 10 psychiatric hospitals and clinics in Japan. One hundred and twelve outpatients aged ≥ 18 years with a diagnosis of depressive disorder based on the International Classification of Disease and related Health Problems, 10th Revision (ICD-10) (World Health Organization, 1993) participated in the study. Patients with a history of epilepsy or organic mental disorders, mental retardation, active substance abuse, or those judged to have active suicidal ideation or severe physical impairments by their treating psychiatrists were excluded. The participants were assessed with the Japanese version of the Quick Inventory of Depressive Symptomatology (QIDS) (Rush et al., 2003) for subjective symptomatology, the

Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) for objective symptomatology, and the Japanese version of the Perceived Deficits Questionnaire (J-PDQ) (Sullivan et al., 1990) for subjective cognitive impairment. The J-PDQ consists of 20 items, and each item is scored on a 5-point scale with a total score ranging from 0-80; higher scores indicate greater levels of subjective cognitive impairment. The PDQ was translated into Japanese by two authors (CO and YM) and then back-translated into English by another two (EBR and HU), who were not aware of the original English version. The scale's developer (M. J. Sullivan) confirmed the back-translated version with regard to accuracy and context. The participants were asked to fill in the J-PDQ at baseline and 3-5 days later. The internal consistency of the J-PDQ was examined with Cronbach's alpha coefficient and test-retest reliability of the J-PDQ scores at baseline, and follow-up was addressed using the intra-class correlation coefficient (ICC). Cronbach's alpha coefficient and the ICC were found to be high at 0.94 and 0.93, respectively. Other participant information collected included age, sex, duration of illness, and prescribed psychotropic medications. We calculated daily doses of antidepressants in imipramine equivalents (IMIE) (Inagaki and Inada, 2018), benzodiazepines in diazepam equivalents (DZPE) (Inada and Inagaki, 2015), and antipsychotics in chlorpromazine equivalents (CPZE) (Inada and Inagaki, 2015).

The original study was approved by the institutional review board at each participating site, and all participants provided written informed consent after receiving detailed information about the study.

2.2 Statistical analysis

Spearman's correlation analysis was used to examine the relationship between the J-PDQ total scores and the QIDS or MADRS total scores. Then, multiple linear regression analysis (forced entry model) was performed to identify factors that were associated with the J-PDQ total score. The following factors were included as independent variables: age, sex, duration of illness, IMIE, DZPE, CPZE, and total scores on the QIDS or MADRS. The Shapiro-Wilk test was used to test continuous variables for normality. Next, we categorized the participants into four groups based on the presence/absence of subjective symptom remission (i.e., a QIDS total score of ≤ 5) (Trivedi et al., 2006) and objective symptom remission (i.e., a MADRS total score of ≤ 9) (Zimmerman et al., 2004). Due to non-normal distribution of the data, differences in the J-PDQ total scores were compared between three groups (the QIDS- and MADRS-remitted group, the QIDS-non-remitted but MADRS-remitted group, and the QIDS-remitted but MADRS-non-remitted group) using a Kruskal-Wallis test. Moreover, the QIDS- and MADRS-remitted group was compared with the QIDS-non-remitted but MADRS-remitted group and the QIDS-remitted but

MADRS-non-remitted group using Mann-Whitney's U test, with Bonferroni correction applied. A p-value of <0.05 was considered statistically significant (two-tailed). These statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY) and PRISM Version 7 (GraphPad Software, Inc, San Diego, CA).

3. Results

3.1 Participants characteristics

One hundred participants were included in the original study, and two additional participants, whose data became available after the study's final analyses, were also included in the present study. One participant did not complete the QIDS questionnaire. Thus, the data from 102 and 101 participants were used for the analyses with respect to the MADRS and QIDS scores, respectively. Demographic and clinical characteristics of the participants are summarized in Table 1.

Insert Table 1 Here

3.2 Factors associated with subjective cognitive impairment

The MADRS and QIDS total scores were significantly correlated with the J-PDQ total scores ($r=0.635$, $p<0.001$ and $r=0.789$, $p<0.001$, respectively); the greater correlation was found in the QIDS total scores compared to the MADRS total scores (Figures 1 and 2). Next, in a multiple linear regression analysis including the MADRS total scores for symptom severity, there was a significant positive association with the J-PDQ total scores ($\beta=0.621$, $p<0.001$) (Table 2). Similarly, greater QIDS total scores were associated with greater J-PDQ scores ($\beta=0.838$, $p<0.001$) while female sex was associated with lesser J-PDQ scores ($\beta=-0.138$, $p=0.029$) (Table 3). Other factors, including medications, did not exhibit any significant associations with the J-PDQ total scores.

Insert Figures 1 and 2, and Tables 2 and 3 Here

3.3. Subjective cognitive impairment by subjectively or objectively assessed remission status

Of the 101 participants, 33 (32.7%), 25 (24.8%), and 4 (4.0%) participants were categorized into the QIDS- and MADRS-remitted, the QIDS-non-remitted but MADRS-remitted, and the QIDS-remitted but MADRS-non-remitted groups, respectively. A Kruskal-Wallis test found a statistically significant difference in the J-PDQ total score among the three groups ($p < 0.001$). The QIDS-non-remitted but MADRS-remitted group showed a significantly higher J-PDQ total score than the QIDS- and MADRS-remitted group, even after Bonferroni correction ($p < 0.017$ [$0.05/3$]) (Table 4). However, no significant difference was found in the J-PDQ total score between the QIDS-remitted but MADRS-non-remitted group and the QIDS- and MADRS-remitted group (Table 5).

Insert Tables 4 and 5 Here

4. Discussion

This study examined factors associated with subjective cognitive impairment in patients with MDD. To the best of our knowledge, this is the first study to investigate the impact of subjective versus objective differential remission status on subjective cognitive impairment in patients with MDD. We found that greater illness severity assessed subjectively and objectively was significantly associated with subjective cognitive impairment. Furthermore, subjective cognitive impairment remained when a patient's remission status was confirmed by their physician but not by the patient's subjective assessment.

Several studies have investigated the impact of illness severity on cognitive function in patients with MDD (Austin et al., 2001; Hasselbalch et al., 2011; McDermott and Ebmeier, 2009). For example, Lawrence and colleagues conducted a cross-sectional study that investigated the relationship between subjective cognitive impairment assessed with the PDQ and illness severity in depressed employees (Lawrence et al., 2013). They found that greater severity of depression was significantly associated with more severe subjective cognitive impairment even after controlling for covariates such as age, sex, and antidepressant use. This finding held across all of the PDQ's four subscales (attention/concentration, retrospective memory, prospective memory, and planning/organization). Consistent with these findings, we found significant

associations between greater illness severity and overall subjective cognitive impairment, as well as impairments in the J-PDQ's four domains in Japanese patients with MDD (Supplementary Tables 1-8).

Since the impact of illness severity on cognitive impairment may differ across individual cognitive domains in patients with MDD (McDermott and Ebmeier, 2009), regular and comprehensive assessment of cognitive function would help identify and address clinical needs on an individual basis.

Of particular note is that participants who remitted objectively but not subjectively indicated worse subjective cognitive performance than those who remitted subjectively as well as objectively. Although subjective and objective measures of depression severity may be interchangeable (Bernstein et al., 2010; Rush et al., 2006), they may not necessarily be equivalent in their quality and clinical relevance (Carter et al., 2010; Tada et al., 2014; Uher et al., 2008; Uher et al., 2012). For example, Zimmerman and colleagues compared symptom profiles of depression in patients in subjective remission and patients who, according to the Hamilton Rating Scale for Depression (HAM-D), were considered to be in objective remission (Zimmerman et al., 2012). Approximately half of the objectively remitted patients (63/140) were not in subjective remission. Patients' assessments of their symptoms may be intrinsically affected by negatively biased cognitive processes, such as hopelessness and low self-esteem, as well as psychomotor retardation

(Beevers and Miller, 2004; Crane et al., 2007). Thus, physicians need to be aware of both subjective and objective perspectives in determining illness severity, which may also have relevance for prognosis (Tada et al., 2014).

In the present study, duration of illness and medications used were not associated with subjective cognitive impairment. Previous studies have also generally failed to find correlations between duration of illness and cognitive function (Biringer et al., 2007; Lampe et al., 2004; Verdoux and Liraud, 2000). Our results are in agreement with these findings, although previous studies have used objective assessment measures. The effects of antidepressants on cognitive function still remain inconclusive in patients with MDD (Hasselbalch et al., 2011). Notably, a recent meta-analysis reported that antidepressants have positive effects on cognitive function in patients with depression (Prado et al., 2018), with the exception of tricyclic antidepressants (TCAs). In our study, only 11 participants used TCAs, which might have resulted in the non-significant result. The association between cognitive impairment and benzodiazepines has been well documented (Barker et al., 2004; Pomara et al., 2015; van der Sluiszen et al., 2017). While we did not find any association between use of benzodiazepines and cognitive impairment, it should be noted that clinical evidence discourages routine use of benzodiazepines in light of various, sometimes serious, side effects,

including falls and dependence (Soyka, 2017; Wagner et al., 2004). Sex was significantly associated with subjective cognitive impairment only in the linear regression analysis wherein QIDS total score was entered as an independent variable but not in the analysis with MADRS total score. However, no significant association between sex and subjective cognitive impairment was found in the univariate linear regression analysis in which sex was entered as an independent variable (data are not shown). This may imply potential difference in the effect of sex on the QIDS and MADRS total scores. There was a difference in the coefficient of sex between the linear regression analyses wherein the MADRS and QIDS total scores were entered as an independent variable (i.e., -0.618 and -4.050, respectively) (Tables 2 and 3). Furthermore, there was a difference in the coefficient of sex between the linear regression analyses wherein the MADRS and QIDS total scores were entered as a dependent variable and other variables (i.e., age, sex, duration of illness, IMIE, CPZE, and DZPE) as independent variables (i.e., -0.82 and 1.29, respectively) (data are not shown). Such differences in the association between sex and the QIDS or MADRS total score may have resulted in the different impact of sex on J-PDQ total score that we found in this study.

The results of our study must be interpreted in light of some limitations. First, our study was a post-hoc analysis of a cross-sectional study, and the topic addressed herein was not our primary focus in the original study. Furthermore, objective cognitive impairment was not evaluated in this study because the original

study focused on subjective cognitive impairment but not objective cognitive impairment in patients with MDD. Future work will be needed to compare the interplay between symptoms and cognition, both of which may be assessed subjectively as well as objectively. Second, there is a possibility that confounding factors we did not evaluate, including other modes of treatment—e.g., psychotherapy, number of depressive episodes, and number of previous hospitalizations (Hasselbalch et al., 2011)—may have affected the results. Third, the sample size was relatively small. In addition, there were only four participants in the QIDS-remitted but MADRS-non-remitted group, which may have caused a type II error. Thus, further investigations using larger samples are needed. Moreover, we were unable to examine which factors in the QIDS and MADRS affected the J-PDQ due to the small sample size, which clearly warrants further investigations. Fourth, the generalizability of our findings may be limited given the characteristics of participants, who were Japanese outpatients capable of consenting to participation in the research. Finally, subjective versus objective differentials in MDD may well be affected by personality, which was not addressed.

In conclusion, greater illness severity, both subjectively and objectively, seems to negatively affect subjective cognitive impairment in patients with MDD. Furthermore, objective remission in the absence of

subjective remission may not represent favorable outcomes in terms of subjective cognitive function.

Although future prospective studies are necessary to confirm these preliminary findings, the results of this study underscore the importance of focusing on both subjective and objective perspectives to enhance the efficacy of any treatment for patients with MDD.

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Contributors

Drs. Sawada, Yoshida, and Uchida contributed to and have approved the design and the protocol of the study and the literature search. Drs. Sawada, Yoshida, and Uchida undertook the statistical analysis. Drs. Sawada, Yoshida, and Uchida wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of interest

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Figure legends

Figure 1. Relationship between MADRS and PDQ total scores (n=102)

Spearman's correlation analysis found a significant correlation between the MADRS and the J-PDQ total scores ($r=0.635$, $p<0.001$).

Abbreviations: J-PDQ, Japanese version of Perceived Deficits Questionnaire; MADRS, Montgomery-Asberg Depression Rating Scale

Figure 2. Relationship between QIDS and PDQ total scores (n=101)

Spearman's correlation analysis found a significant correlation between the QIDS and the J-PDQ total scores ($r=0.789$, $p<0.001$).

Abbreviations: J-PDQ, Japanese version of Perceived Deficits Questionnaire; QIDS, Quick Inventory of Depressive Symptomatology

Table 1. Demographic and clinical characteristics of participants (N=102)

Characteristics	
Age, years	50.5±14.7 (21-90)
Males	45 (44.1)
Duration of illness, years	4.0 (2.0-8.3)
MADRS total score	6.5 (3.0-17.0)
QIDS total score	9.0 (4.0-14.0) ^a
J-PDQ total score	23.5 (12.8-36.0)
Daily doses of antidepressants, IMIE	90.6 (62.5-153.1)
Daily doses of antipsychotics, CPZE	0.0 (0.0-37.5)
Daily doses of benzodiazepines, DZPE	5.0 (0.0-10.0)
Use of any antidepressants	88 (86.3)
Use of any antipsychotics	34 (33.3)
Use of any benzodiazepines	74 (72.5)

Values are shown as mean±S.D. (range), median (interquartile range), or n (%).

^a. The data were available for 101 participants.

Abbreviations: CPZE, chlorpromazine equivalents; DZPE, diazepam equivalents; IMIE, imipramine equivalents; J-PDQ, Japanese version of Perceived Deficits Questionnaire; MADRS, Montgomery-Asberg Depression Rating Scale; QIDS, Quick Inventory of Depressive Symptomatology; S.D., standard deviation

Table 2. Factors associated with subjective cognitive impairment in a multiple linear regression analysis, including MADRS total scores for symptom severity (N=102).

Variables	B	β	95%CI	p-value
Age, years	-0.099	-0.100	-0.261-0.063	0.226
Sex				
Male	Reference			
Female	-0.618	-0.021	-5.269-4.034	0.793
MADRS total score	1.001	0.621	0.739-1.264	<0.001*
Duration of illness, years	-0.197	-0.083	-0.582-0.187	0.310
Daily doses of antidepressants, IMIE	-0.004	-0.028	-0.028-0.019	0.719
Daily doses of antipsychotics, CPZE	-0.003	-0.010	-0.045-0.040	0.903
Daily doses of benzodiazepines, DZPE	-0.026	-0.014	-0.335-0.283	0.867

* p-value of <0.05

Abbreviations: CI, confidence interval; CPZE, chlorpromazine equivalents; DZPE, diazepam equivalents; IMIE, imipramine equivalents; MADRS, Montgomery-Asberg Depression Rating Scale

Table 3. Factors associated with subjective cognitive impairment in a multiple linear regression analysis, including QIDS total scores for symptom severity (N=101).

Variables	B	β	95%CI	p-value
Age, years	0.005	0.005	-0.123-0.134	0.933
Sex				
Male	Reference			
Female	-4.050	-0.138	-7.678- -0.423	0.029*
QIDS total score	2.022	0.838	1.704-2.340	<0.001*
Duration of illness, years	-0.023	-0.010	-0.325-0.279	0.878
Daily doses of antidepressants (IMIE)	-0.016	-0.103	-0.034-0.003	0.097
Daily doses of antipsychotics (CPZE)	-0.009	-0.036	-0.043-0.024	0.569
Daily doses of benzodiazepines (DZPE)	-0.097	-0.052	-0.336-0.142	0.422

* p-value of <0.05

Abbreviations: CI, confidence interval; CPZE, chlorpromazine equivalents; DZPE, diazepam equivalents; IMIE, imipramine equivalents; QIDS, Quick Inventory of Depressive Symptomatology

Table 4. Comparison of J-PDQ total scores between the QIDS- and MADRS-remitted group and the QIDS-non-remitted but MADRS-remitted group

Variables	QIDS- and MADRS-remitted (n=33)	QIDS-non-remitted but MADRS-remitted (n=25)	z-score	p-value
J-PDQ total score	11.0 (5.50-17.50)	25.0 (17.00-31.50)	-4.063	<0.001*
MADRS total score	3.00 (0.50-4.50)	3.00 (2.00-4.00)	-0.740	0.459
QIDS total score	3.00 (2.00-4.00)	10.00 (8.00-12.00)	-6.504	<0.001*

Values are shown as median (interquartile range).

Differences were compared by using Mann-Whitney's U test.

* p-value of <0.05

Abbreviations: J-PDQ, Japanese version of Perceived Deficits Questionnaire; MADRS, Montgomery-Asberg Depression Rating Scale; QIDS, Quick Inventory of Depressive Symptomatology

Table 5. Comparison of J-PDQ total scores between the QIDS- and MADRS-remitted group and the QIDS-remitted but MADRS-non-remitted group

Variables	QIDS- and MADRS-remitted (n=33)	QIDS-remitted but MADRS-non-remitted (n=4)	z-score	p-value
J-PDQ total score	11.0 (5.50-17.50)	17.00 (13.50-32.50)	-1.886	0.058
MADRS total score	3.00 (0.50-4.50)	15.50 (12.00-18.25)	-3.265	<0.001*
QIDS total score	3.00 (2.00-4.00)	5.00 (4.25-5.00)	-2.349	0.018

Values are shown as median (interquartile range).

Differences were compared by using Mann-Whitney's U test.

* p-value of <0.05

Abbreviations: J-PDQ, Japanese version of Perceived Deficits Questionnaire; MADRS, Montgomery-Asberg Depression Rating Scale; QIDS, Quick Inventory of Depressive Symptomatology