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Research paper

Prediction of residual cognitive disturbances by early response of depressive symptoms to antidepressant treatments in patients with major depressive disorder

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ABSTRACT

Background: Patients with major depressive disorder (MDD) frequently retain cognitive disturbances after recovery from mood symptoms. We investigated the relationship between early response of mood symptoms and/or remission, and residual cognitive disturbances after 6 months of antidepressant treatment.

Methods: 518 patients with MDD were followed up for 6 months after antidepressant treatment initiation (first-line or switch from a previous drug). Subjective and objective cognitive disturbances were assessed by the Perceived Deficits Questionnaire – Depression (PDQ-D) and digit symbol substitution test (DSST), respectively. Depressive symptoms, as well as remission and early response to treatment, were assessed using the Montgomery-Asberg Depression Rating Scale (MADRS). Multivariable linear and logistic regression models were used to adjust for confounders.

Results: Early response of depressive mood (≥50% reduction in MADRS score at month 1) was related with fewer residual subjective cognitive symptoms, as evaluated by the PDQ-D at month 6 ($p < 0.001$). Likewise, early remission status at month 2 was inversely associated with PDQ-D scores at month 6 ($p < 0.001$). Among patients with baseline DSST scores of ≥1 standard deviation below the norm, early response/remission was associated with better performance on the DSST at month 6 ($p < 0.05$).

Limitations: The cohort may not be representative of the general MDD patient population, and the possible influence of concomitant medications was not evaluated.

Conclusions: These findings suggest that early improvements in depressive symptoms predict better cognitive outcomes in patients with MDD. Grouping of patients by mood and cognition status in early stages of antidepressant treatments may facilitate efforts to improve long-term functional outcomes.

1. Introduction

Major depressive disorder (MDD) is a common psychiatric condition with a lifetime and 12-month prevalence of 5.7% and 2.7%, respectively, in Japan (Ishikawa et al., 2018). Patients with MDD often experience cognitive difficulties both subjectively and objectively (Srisurapanont et al., 2017). Recovery from cognitive disturbances is an important treatment goal to improve social relationships and maintain labor productivity and quality of life (QOL) in patients with MDD (Evans et al., 2014).

Disturbances of cognitive function are known to persist in some patients with MDD even after attaining remission from mood symptoms

Abbreviations: DSST, digit symbol substitution test; EQ-5D-5L, EuroQOL 5 dimensions 5-level; HAM-D-17, 17-item Hamilton Rating Scale for Depression; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; PERFORM-J, Prospective Epidemiological Research on Functioning Outcomes Related to Major Depressive Disorder in Japan; PDQ-D, Perceived Deficits Questionnaire – Depression; QOL, quality of life; SDS, Sheehan Disability Scale.

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(Rock et al., 2014; Semkovska et al., 2019). These residual cognitive disturbances have been suggested to determine long-term outcomes, including remission, relapse of depression, and social functioning (Baune and Renger, 2014; Hammer-Helmich et al., 2018; Saragoussi et al., 2017). The precise mechanisms for the lasting cognitive impairment, even in remitters from mood symptoms, are unclear. It has been suggested that neurobiological insults due to recurring depressive episodes may be responsible for cognitive impairment of MDD (Fossati et al., 2004). For example, some patients with MDD show atrophy of the hippocampus (Gorwood et al., 2008), which may be associated with lingering cognitive symptoms. It has also been reported that the functions of executive network, which consist of dorsolateral prefrontal and lateral parietal cortices and correlates positively with executive task performance, are reduced in MDD (Hamilton et al., 2013). This suggests that dysfunction of the executive network may be related to cognitive impairment in MDD. On the other hand, a decrease in brain-derived neurotrophic factor (BDNF) levels has been reported in patients with MDD (Oral et al., 2012; Teng et al., 2021). BDNF exerts multiple effects, such as synapse formation, neuroprotection, modulation of long-term potentiation (LTP) (Park and Poo, 2013), and the weakening of these effects is thought to produce cognitive impairment. Further evidence is awaited to support a direct link between hippocampal atrophy, dysfunction of the executive network, lower levels of BDNF and MDD (Gorwood et al., 2008; Hamilton et al., 2013; Marvel and Paradiso, 2004; Oral et al., 2012; Teng et al., 2021; Vythilingam et al., 2004).

Predictors of lingering cognitive symptoms would represent valuable tools to identify patients at risk for long-term functional impairments, allowing for early intervention. Previous studies have suggested that improvement in depressive symptoms during the early phase of treatment may have predictive value for long-term clinical outcomes in patients with MDD, including symptomatic remission and functional improvement (Ciudad et al., 2012; Szegedi et al., 2009). However, to our knowledge, little information is available about the predictive value of early symptomatic response and/or remission for medium- to long-term cognitive consequences in this patient group.

Cognitive disturbances in patients with MDD have been differentiated into dysfunction of subjective cognition (i.e., cognitive symptoms) and objective cognition (i.e., cognitive performance) (Serra-Blasco et al., 2019; Srisurapanont et al., 2017; Svendsen et al., 2012). As these two types of cognitive function appear to represent distinct manifestations (Srisurapanont et al., 2017; Wang et al., 2019), it is reasonable to evaluate them separately. This was taken into account when designing the Prospective Epidemiological Research on Functioning Outcomes Related to Major Depressive Disorder in Japan (PERFORM-J) (Sumiyoshi et al., 2021, 2018, 2019). PERFORM-J is a 6-month, non-interventional, prospective, longitudinal study investigating the relationship between cognitive disturbances, severity of depressive symptoms, and social functioning in patients with MDD (Sumiyoshi et al., 2021, 2018, 2019). So far, the results indicate improvements in mood symptoms and cognitive symptoms from baseline over the 6-month observation period after initiation of antidepressant treatment (Sumiyoshi et al., 2021). Specifically, cognitive symptoms at month 2, as measured by the Perceived Deficits Questionnaire – Depression (PDQ-D) (Fehnel et al., 2016; Lam et al., 2018), were found to predict social function and QOL at 6 months, as measured by the Sheehan Disability Scale (SDS) (Sheehan et al., 1996) and EuroQOL 5 dimensions 5-level (EQ-5D-5L) (Herdman et al., 2011), respectively. Also, there was a trend for higher rates of relapse into depressive episodes at month 6 in patients with higher PDQ-D scores (indicating poor subjective cognitive function) at month 2. On the other hand, psychomotor speed (attention/information processing) at month 2, as measured by the digit symbol substitution test (DSST) (Wechsler, 2006) was not associated with relapse (Sumiyoshi et al., 2021). In spite of these findings, the relationship between early improvement in mood symptoms and the residual cognitive disturbances that persists even after symptomatic remission has not yet been fully explored.

In the present study, we sought to test the hypothesis that early changes of depressive symptoms during treatment with antidepressants would predict the presence or absence of residual cognitive disturbances in patients with MDD. Therefore, using data from the PERFORM-J study, we investigated the relationship between improvement in mood symptoms within 1 or 2 months of antidepressant treatment initiation and subjective cognition and psychomotor speed (a domain of objective cognition) after 6 months of medication.

2. Methods

2.1. Participants and procedure

The protocol of PERFORM-J and demographic data of participants have been previously reported (Sumiyoshi et al., 2018, 2019).

Briefly, PERFORM-J (166/NRP-001) (2016–2018) was a 6-month observational, multicenter study enrolling patients from 48 psychiatric clinics in Japan. It included 518 outpatients with MDD aged 18–65 years for whom new antidepressant monotherapy was initiated (first-line or switch from a previous drug) (Sumiyoshi et al., 2019). Inclusion and exclusion criteria are provided in **Supplementary Table 1**. The details of the data collection have been described (Sumiyoshi et al., 2018).

2.2. Clinical variables

2.2.1. Depressive symptoms

The primary exposure variables were the response to treatment by month 1 (hereafter "early response") and the remission status at month 2 (hereafter "early remission") based on depressive symptoms, as evaluated by the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). The MADRS provides a physician-directed assessment of 10 pre-specified depressive symptoms (**Supp. Table 1**) on a scale from 0 (normal) to 6 (extremely ill). Changes in MADRS scores were used to obtain the following two indicators: (i) response at month 1, defined as a reduction in MADRS total score of $\geq$50% compared to baseline after the first month of treatment, and (ii) remission at month 2, defined as a MADRS total score of $\leq$10 points after the second month of treatment (Hawley et al., 2002; Zimmerman et al., 2004). For subgroup analysis, the total population was categorized into patients with none to mild (MADRS score: 0–19 points) and patients with moderate to severe (MADRS score: 20–60 points) depression at month 6.

2.2.2. Subjective and objective cognitive function

We used two different outcome variables to evaluate cognitive disturbances: (i) the PDQ-D total scores for the subjective evaluation of cognitive symptoms, and (ii) the DSST score for evaluation of objective cognitive function (psychomotor speed) (**Supp. Table 1**). Patients were considered as having residual cognitive symptoms (hereafter "residual cognitive symptoms") if the PDQ-D score was between 20 and 60 at month 6 (Wang et al., 2019). Similarly, they were categorized as having residual impairment of psychomotor speed (hereafter "impaired psychomotor speed") if their DSST value was $\geq$1 standard deviation (SD) below the norm (general Japanese population) at month 6 (Wechsler, 2006).

2.2.3. Confounding variables

In the analyses, the following items were considered as confounding variables: age (year, continuous), sex (men/women), educational level (junior college or below/university or above), duration of current depressive episode ($<$8 weeks/$\geq$8 weeks), concomitant mental disorders (yes/no), chronic pain (yes/no), history of MDD episodes (first/recurrent), switch of antidepressant (yes/no), and DSST or PDQ-D scores at baseline (continuous). For all regression models, the clinics were added as a random effect.

2.3. Statistical methods

The number of patients, mean, SD, median, minimum and maximum were analyzed for the continuous variables, while frequency and proportion (percentage) were analyzed for categorical variables. Proportion at each level of a categorical variable was calculated versus the number of patients without any missing value, and the number of missing values at each level was separately presented.

To determine whether the early improvement of depressive symptoms (i.e., response and remission) was associated with cognitive disturbances at month 6, multivariable linear regression models were used to adjust for confounders. All data were analyzed using two specific sets of questions from Model 1 and Model 2 (**Supp. Table 2**). In Model 1, the association between early improvement in depressive symptoms and cognitive disturbances at month 6 was investigated after adjusting for age, sex, educational level, and DSST or PDQ-D scores at baseline. In Model 2, further adjustments were made for MDD-related covariates such as time since the beginning of the depressive episode, concomitant mental disorder, chronic pain, history of MDD episode, and switch of antidepressant at baseline. The number of patients for each level, adjusted means, and estimated difference (with 95% confidence intervals [CI]) were reported with *p*-values. Any covariates that predicted the difference were also reported.

Multivariate logistic regression models were also developed to determine whether early improvement of depressive symptoms was associated with the presence of residual cognitive disturbances at month 6. The odds ratio (OR) of having residual cognitive symptoms (with 95% CI and *p*-value) was calculated after adjusting for age, sex, educational level, and DSST or PDQ-D scores at baseline in Model 1. In Model 2, further adjustments were made for time since the beginning of the depressive episode, concomitant mental disorder, chronic pain, history of MDD episode, and switch of antidepressant at baseline (**Supp. Table 2**).

Additional sensitivity analyses were conducted for multivariate regression analyses in the subgroups of patients with cognitive disturbances at baseline.

3. Results

3.1. Participants

We included 518 patients with MDD in the analysis, 288 (55.6%) of whom were female. The mean age (±SD) was 37.3±11.2 years. The levels of educational attainment varied across the study population, with 250 (48.3%) participants having higher education (university and above) and 268 (51.7%) patients educated to junior college level or below. Further details of baseline characteristics are shown in Table 1. A flow diagram of study participants and inclusion and exclusion criteria are presented in the Supplementary Materials (**Supp. Fig 1, Supp. Table 1**).

3.2. Residual cognitive symptoms/impaired psychomotor speed at month 6

Some patients retained cognitive symptoms despite improvement of their mood symptoms. Among the 272 patients with none to mild depression severity at month 6, 94 (34.6%) had cognitive symptoms, and 89 (32.7%) had impaired psychomotor speed (Table 2).

3.3. Multivariate linear regression models for PDQ-D score as outcome

3.3.1. MADRS-responder vs MADRS-non-responder at month 1 as a predictive variable

Response within the first month of treatment was associated with a lower PDQ-D score at month 6. In Model 1, which was adjusted for basic baseline characteristics, the adjusted mean PDQ-D score at month 6 was 14.1 for MADRS responders (at month 1) and 21.1 for non-responders ($p<0.001$; Table 3). Model 2, which included additional MDD-related covariates for adjustment returned similar results, with 17.3 and 24.2 for MADRS responders and non-responders, respectively ($p<0.001$). Together, these data indicate that the clinical response status after the first month of treatment may be a predictor of subjective cognitive function at month 6 of treatment.

Model 2 identified two confounding factors associated with cognitive symptoms at month 6: baseline PDQ-D score and the time since the

Table 1
Baseline characteristics of participants.

Characteristics	Overall (*N*=518)	Response at month 1		Remission at month 2	
		Measured by MADRS (*n*=407)		Measured by MADRS (*n*=395)	
		Yes (*n*=97)	No (*n*=310)	Yes (*n*=163)	No (*n*=232)
Socio-demographic characteristics at baseline					
Age, years (SD)					
Mean	37.3 (11.2)	38.7 (11.4)	38.2 (10.9)	38.3 (11.0)	38.4 (10.6)
Missing, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sex, women/men, n (%)					
Women	288 (55.6)	49 (50.5)	166 (53.5)	86 (52.8)	126 (54.3)
Men	230 (44.4)	48 (49.5)	144 (46.5)	77 (47.2)	106 (45.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Educational level, n (%)					
Junior college or below	268 (51.7)	45 (46.4)	158 (51.0)	74 (45.4)	119 (51.3)
University or above	250 (48.3)	52 (53.6)	152 (49.0)	89 (54.6)	113 (48.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Clinical characteristics at baseline					
PDQ-D score at baseline					
n	507	96	304	160	229
Mean	32.2	30.4	32.4	28.3	34.5
Missing, n (%)	11 (2.1)	1 (1.0)	6 (1.9)	3 (1.8)	3 (1.3)
DSST score at baseline					
Mean	72.4	74.6	71.5	75.3	69.3
Missing, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Time since beginning of current depressive episode, n (%)					
< 8 weeks	170 (32.8)	30 (30.9)	105 (33.9)	51 (31.3)	76 (32.8)
≥ 8 weeks	348 (67.2)	67 (69.1)	205 (66.1)	112 (68.7)	156 (67.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Switch of antidepressant at baseline, n (%)					
Yes	129 (24.9)	25 (25.8)	85 (27.4)	43 (26.4)	69 (29.7)
No	389 (75.1)	72 (74.2)	225 (72.6)	120 (73.6)	163 (70.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Concomitant mental disorder, n (%)					
Yes	151 (29.2)	23 (23.7)	92 (29.7)	46 (28.2)	73 (31.5)
No	367 (70.8)	74 (76.3)	218 (70.3)	117 (71.8)	159 (68.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chronic pain, n (%)					
Yes	17 (3.3)	4 (4.1)	12 (3.9)	7 (4.3)	7 (3.0)
No	501 (96.7)	93 (95.9)	298 (96.1)	156 (95.7)	225 (97.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
History of MDD episode, n (%)					
First	310 (59.8)	65 (67.0)	180 (58.1)	100 (61.3)	140 (60.3)
Recurrent	208 (40.2)	32 (33.0)	130 (41.9)	63 (38.7)	92 (39.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

DSST: Digit Symbol Substitution Test; MADRS: Montgomery-Asberg Depression Rating Scale; DQ-D; Perceived Deficits Questionnaire – Depression

Table 2
Prevalence of cognitive disturbances in patients with MDD at month 6.

	MADRS score	
	None to mild (0–19) (*n*=272)	Moderate to severe (20–60) (*n*=60)
PDQ-D score		
Without cognitive symptoms (0–19), n(%)	178 (65.5)	9 (15.0)
With cognitive symptoms (20–80), n (%)	94 (34.6)	51 (85.0)
DSST performance		
Within 1 SD below norm, n (%)	183 (67.3)	31 (51.7)
≥1 SD below norm, n (%)	89 (32.7)	29 (48.3)

DSST: digit symbol substitution test; MADRS: Montgomery-Asberg Depression Rating Scale; PDQ-D: Perceived Deficits Questionnaire – Depression.

beginning of the depressive episode at baseline. A 1-point increase of PDQ-D score at baseline was associated with an estimated increase of 0.479 in PDQ-D score at month 6 ($p<0.001$; **Supp. Table 3**). Participants with a depressive episode of 8 weeks or longer at baseline had a higher PDQ-D score at month 6 than those who initiated treatment after a shorter period of depression ($p=0.049$; **Supp. Table 3**).

3.3.2. MADRS-remitter vs MADRS-non-remitter at month 2 as a predictive variable

Remission status 2 months after treatment initiation was associated with a lower PDQ-D score at month 6. In Model 1, MADRS-remitters at month 2 had an adjusted mean PDQ-D score of 15.5 versus 22.9 for non-remitters ($p<0.001$; Table 3). Similarly, in Model 2, the PDQ-D scores of 18.9 for MADRS remitters and 26.8 for non-remitters ($p<0.001$) suggest that the MADRS remission status after 2 months of treatment is indicative of subjective cognitive function at month 6.

Model 2 returned three baseline factors positively associated with cognitive symptoms at month 6: baseline PDQ-D score ($p<0.001$), a depressive episode with duration longer than 8 weeks at baseline ($p=0.003$), and a history of recurrent depression ($p=0.015$) (**Supp. Table 4**).

For both responders at month 1 and remitters at month 2, limiting patients to those with cognitive symptoms at baseline did not change the results (Table 3). The estimated difference between the adjusted mean PDQ-D scores was increased slightly compared to the total population, and both differences remained significant (Table 3).

3.4. Multivariate logistic regression models for PDQ-D score as outcome

Achieving MADRS-response at month 1 was associated with a reduced risk of cognitive symptoms at month 6, as measured by the PDQ-D. Responders were approximately four times less likely to experience cognitive symptoms than non-responders, both in Model 1 ($p<0.001$) and Model 2 ($p<0.001$; Table 4). According to Model 2, baseline PDQ-D score ($p<0.001$) and a history of recurrent depression ($p=0.005$) confounded the risk of residual cognitive symptoms at month 6 (**Supp. Table 5**).

Similarly, achieving MADRS-remission at month 2 was associated with reduced cognitive symptoms at month 6, as measured by the PDQ-D. Remitters at month 2 were significantly less likely to have cognitive symptoms, according to both Model 1 ($p<0.001$) and Model 2 ($p<0.001$; Table 4). The results were similar when analyzing only participants with cognitive symptoms at baseline (sensitivity analysis; Table 4). Model 2 identified three confounding factors; baseline PDQ-D score ($p<0.001$), history of recurrent depression ($p<0.001$), and a depressive episode with duration longer than 8 weeks at baseline ($p=0.024$) were all associated with residual cognitive symptoms at month 6 (**Supp. Table 6**).

3.5. Effect of baseline DSST scores on residual impairment of psychomotor speeds

In the total population, we did not observe a statistically significant association between response at month 1 and impaired psychomotor speed, as measured by the DSST, at month 6 (Tables 5 **and** 6). However, among participants with impaired cognitive performance at baseline (sensitivity analysis population), DSST scores showed a meaningful association with treatment response at month 1 in both Model 1 and Model 2 (Table 5). In this subgroup, responders had a higher mean DSST score at month 6 than non-responders (Model 1: 76.1 vs 70.1, $p=0.028$; Model 2: 75.1 vs 69.5, $p=0.04$), suggesting the predictive value of MADRS response status at month 1 for psychomotor speed at month 6 only in patients with poor performance at baseline.

For the sensitivity analysis group, we identified baseline DSST score as a confounder significantly associated with better psychomotor speed at month 6 ($p<0.001$) in Model 1. Likewise, Model 2 returned a positive association between baseline DSST scores and better cognitive psychomotor speed at month 6 ($p<0.001$) (**Supp. Table 7**). Furthermore, a history of recurrent depression was associated with poor psychomotor speed at month 6 ($p=0.040$) in Model 2 (**Supp. Table 7**).

Table 3
Association between early improvement in depressive symptoms and residual cognitive symptoms at month 6.

		All Patients					Patients who had cognitive symptoms at baseline				
		N	Adjusted means	Estimate	(95%CI)	*p*-value	n	Adjusted means	Estimate	(95%CI)	*p*-value
Response at month 1											
Model 1*	Yes	79	14.1	−6.975	(−10.431, −3.520)	<0.001	58	16.1	−8.431	(−12.720, −4.143)	<0.001
	No	231	21.1	Ref			182	24.5	Ref		
Model 2**	Yes	79	17.3	−6.905	(−10.356, −3.453)	<0.001	58	19.6	−8.415	(−12.705, −4.125)	<0.001
	No	231	24.2	Ref			182	28.0	Ref		
Remission at month 2											
Model 1*	Yes	130	15.5	−7.465	(−10.315, −4.615)	<0.001	90	17.3	−9.187	(−12.749, −5.625)	<0.001
	No	188	22.9	Ref			157	26.5	Ref		
Model 2**	Yes	130	18.9	−7.920	(−10.724, −5.115)	<0.001	90	21.3	−9.292	(−12.792, −5.793)	<0.001
	No	188	26.8	Ref			157	30.6	Ref		

* Model 1: Adjusted for age (continuous), sex, clinics, education level, PDQ-D score at baseline.
** Model 2: Further adjusted for time since the beginning of current episode (≥8 weeks or <8 weeks), concomitant mental disorder, chronic pain, history of MDD episode and switch of antidepressant at baseline.
CI: confidence interval; MDD: major depressive disorder; PDQ-D: Perceived Deficits Questionnaire – Depression; Ref: Reference.

Table 4
Association between early improvement in depressive symptoms and the presence of residual cognitive symptoms at month 6.

		All Patients				Patients with cognitive symptoms at baseline			
		N	OR	(95%CI)	*p*-value	n	OR	(95%CI)	*p*-value
Response at month 1									
Model 1*	Yes	79	0.262	(0.134, 0.515)	<0.001	58	0.234	(0.113, 0.485)	<0.001
	No	231	Ref			182	Ref		
Model 2**	Yes	79	0.274	(0.140, 0.539)	<0.001	58	0.250	(0.121, 0.517)	<0.001
	No	231	Ref			182	Ref		
Remission at month 2									
Model 1*	Yes	130	0.388	(0.227, 0.664)	<0.001	90	0.340	(0.187, 0.618)	<0.001
	No	188	Ref			157	Ref		
Model 2**	Yes	130	0.341	(0.194, 0.599)	<0.001	90	0.313	(0.167, 0.586)	<0.001
	No	188	Ref			157	Ref		

CI: confidence interval; MDD: major depressive disorder; OR; odds ratio; PDQ-D: Perceived Deficits Questionnaire – Depression; Ref: Reference.
* Model 1: Adjusted for age (continuous), sex, clinics, education level, PDQ-D score at baseline.
** Model 2: Further adjusted for time since the beginning of the current episode (≥8 weeks or <8 weeks), concomitant mental disorder, chronic pain, history of MDD episode and switch of antidepressant at baseline.

Table 5
Association between early improvement in depressive symptoms and psychomotor speed at month 6.

		All patients					Patients with impaired psychomotor speed at baseline				
		N	Adjusted means	Estimate	(95%CI)	*p*-value	n	Adjusted means	Estimate	(95%CI)	*p*-value
Response at month 1											
Model 1*	Yes	78	82.6	3.010	(−0.884, 6.905)	0.129	40	76.1	5.979	(0.655, 11.303)	0.028
	No	236	79.6	Ref			132	70.1	Ref		
Model 2**	Yes	78	83.2	2.939	(−0.954, 6.832)	0.138	40	75.1	5.600	(0.272, 10.927)	0.040
	No	236	80.2	Ref			132	69.5	Ref		
Remission at month 2											
Model 1*	Yes	132	81.5	2.442	(−0.753, 5.638)	0.134	65	75.4	5.987	(1.643, 10.332)	0.007
	No	191	79.1	Ref			116	69.4	Ref		
Model 2**	Yes	132	82.6	2.696	(−0.475, 5.866)	0.095	65	74.2	5.327	(0.969, 9.686)	0.017
	No	191	79.9	Ref			116	68.9	Ref		

CI: confidence interval; DSST: Digit Symbol Substitution Test; MDD: major depressive disorder; Ref: Reference.
* Model 1: Adjusted for age (continuous), sex, clinics, education level, DSST score at baseline.
** Model 2: Further adjusted for time since the beginning of the current episode (≥8 weeks or <8 weeks), concomitant mental disorder, chronic pain, history of MDD episode and switch of antidepressant at baseline.

Table 6
Association between early improvement of depressive symptoms and the presence of impaired psychomotor speed at month 6 (logistic regression).

		All patients				Patients with impaired psychomotor speed at baseline			
		N	OR	(95%CI)	*p*-value	n	OR	(95%CI)	*p*-value
Response at month 1									
Model 1*	Yes	78	0.746	(0.368, 1.512)	0.415	40	0.610	(0.277, 1.342)	0.218
	No	236	Ref			132	Ref		
Model 2**	Yes	78	0.757	(0.368, 1.558)	0.448	40	0.616	(0.274, 1.387)	0.240
	No	236	Ref			132	Ref		
Remission at month 2									
Model 1*	Yes	132	0.861	(0.486, 1.526)	0.608	65	0.700	(0.357, 1.374)	0.298
	No	191	Ref			116	Ref		
Model 2**	Yes	132	0.842	(0.472, 1.502)	0.560	65	0.734	(0.367, 1.468)	0.379
	No	191	Ref			116	Ref		

CI: confidence interval; MDD: major depressive disorder; OR; odds ratio, DSST; Digit Symbol Substitution Test; Ref: Reference.
* Model 1: Adjusted for age (continuous), sex, clinics, education level, DSST score at baseline.
** Model 2: Further adjusted for time since the beginning of the current episode (≥8 weeks or <8 weeks), concomitant mental disorder, chronic pain, history of MDD episode and switch of antidepressant at baseline.

Similar to the response status, the remission status at month 2 lacked a significant association with impaired psychomotor speed at month 6 in the total population (**Tables 5 and 6**). In the sensitivity analysis, however, remission at month 2 was associated with DSST outcome at month 6 in Model 1 with a score of 75.4 and 69.4 for remitters and non-remitters, respectively (p=0.007), and 74.2 versus 68.9 (p=0.017) in Model 2. Thus, in this subpopulation, MADRS remission status at month 2 may predict the objective cognitive performance at month 6.

According to Module 2 there were two confounding factors associated with psychomotor speed at month 6: recurrence of depression with poor psychomotor speed (p=0.017) and a higher baseline DSST score with improved psychomotor speed (p=0.001) (**Supp. Table 8**).

4. Discussion

Improvement of depressive symptoms in the early stages of antidepressant treatment was associated with a reduced risk of residual cognitive symptoms after 6 months in patients with MDD. This was

particularly relevant to subjective measures of cognitive function. On the other hand, a similar association was noted at 6 months for psychomotor speed (objective cognitive function) in patients who showed poor performance at baseline.

After 6 months of therapy, a third of patients with none-to-mild depression retained subjective (35%, n=94/272) and/or objective (33%, n=89/272) cognitive disturbances despite amelioration of depressive symptoms (**Table 2**). These proportions are similar to the observations by Wang et al. (2019) who found that after 6 months of treatment with antidepressants, 32.4% of patients with MDD had persistent cognitive symptoms. The residual impairment in the cognitive domain (psychomotor speed) presented here is also in line with previous observations (Rock et al., 2014; Semkovska et al., 2019) that demonstrated persistent objective cognitive impairment in a proportion of remitted patients, despite recovery from mood symptoms. Several studies have shown that patients with MDD in remission still exhibit poor psychomotor speed, attention, and/or verbal memory performance (Murrough et al., 2015; Rock et al., 2014; Shimizu et al., 2013). Together, these data indicate that patients with MDD may require extended treatment (>6 months) coupled with additional intervention to recover from cognitive disturbances.

A limitation associated with measuring subjective aspects of cognition include over-estimation of cognitive difficulties in patients who do have the ability to cope with their issues. Therefore, the concurrent assessment of objective cognitive function, as performed in the current study, may provide a more accurate reflection of the patient's cognition. Furthermore, previous work suggests that objective and subjective cognitive disturbances represent distinct clinical manifestations (Srisurapanont et al., 2017). Thus, Sawada et al. (2019) found that patients who recovered from objective, but not subjective assessment elicited worse PDQ scores than those who recovered both objectively and subjectively. The present study used longitudinal assessment of both subjective cognitive symptoms and objective cognitive performance, thus providing a comprehensive picture of cognitive dysfunction in patients with MDD. In particular, the Japanese DSST norms enabled us to categorize the cognitive performance into normal versus below-normal levels.

There have been some attempts to relate early response of depressive symptoms to treatment with subsequent outcomes in patients with MDD (Ciudad et al., 2012; Szegedi et al., 2009). For example, Ciudad et al. (2012) found that patients with an early response to treatment, defined as $a \geq$ 50% improvement in the 17-item Hamilton Rating Scale for Depression (HAM-D-17) from baseline to week 6, elicited a greater improvement in social functioning, as measured by the Social and Occupational Functioning Assessment Scale, and quality of life, as measured by the EQ-5D than non-early responders. Similarly, Szegedi et al. (2009) reported the predictive value of early treatment response with outcomes. These previous studies report patients who achieved a ≥20% reduction in HAM-D-17 within two weeks of antidepressant treatment predicted a stable response or remission with ≥81% or ≥87% sensitivity, respectively (Ciudad et al., 2012; Szegedi et al., 2009). The results of the current study extend these previous findings by focusing on subjective and objective measures of residual cognitive disturbances, and highlight the importance of early symptom response and remission for decreasing the risk of lingering cognitive disturbances in the treatment of MDD.

Data presented in this study agree with previous findings that recurrence of depressive episodes worsens subsequent cognitive function in patients with MDD (Gorwood et al., 2014; Semkovska et al., 2019). For example, Gorwood et al. (2014) reported an association between the speed at which patients with MDD completed tests of attention/processing speed (i.e., Trail Making Test A and B) and the number of depressive episodes they experienced in the past. This association was independent of treatment or remission status, suggesting that depressive episodes have a cumulative negative impact on long-term cognitive consequences (Gorwood et al., 2014). This concept may be supported by a meta-analysis by Semkovska et al. (2019) who found persistent and cumulative cognitive impairment in remitters from major depressive episodes, especially regarding long-term memory, attention, and processing speed. Furthermore, longer duration of illness has been shown to negatively affect performance on cognitive tests (Semkovska et al., 2019). Overall, early intervention into mood symptoms in patients with MDD may produce long-term cognitive benefits.

As mentioned previously, the precise mechanisms for the lasting cognitive impairment, even in remitters, from mood symptoms are unclear. It has been suggested that neurobiological insults due to recurring depressive episodes may be responsible for cognitive impairment of MDD (Fossati et al., 2004). For example, some patients with MDD show atrophy of the hippocampus (Gorwood et al., 2008), which may be associated with lingering cognitive symptoms. However, a direct link between MDD and hippocampal atrophy, the dysfunction of the executive network, or lower levels of BDNF has not yet been established (Gorwood et al., 2008; Vythilingam et al., 2004). Sleep deprivation has been associated with mood disturbances in patients with mood disorders (Marvel and Paradiso, 2004). As sleep has been found to promote memory development, it is speculated that poor sleep conditions associated with MDD may worsen cognitive function (Goel et al., 2009). Comparatively, our data suggest that residual cognitive disturbances affect the relationship between recurring depressive episodes and long-term functional outcomes in patients with MDD.

When only patients with impaired cognitive performance (psychomotor speed) at baseline were included in the analysis, early improvement of depressive symptoms by antidepressant treatment was associated with a greater improvement in cognitive performance at month 6. These results are in line with previous findings that the treatment effect is more pronounced in patients with cognitive decline at treatment initiation than those without cognitive impairment (Barczyk et al., 2020; Groves et al., 2018; Murrough et al., 2015). Thus, early evaluation of depressive symptoms may be useful for predicting cognitive performance, particularly in patients who elicit cognitive impairment at the start of antidepressant treatment.

Whereas the present study demonstrates that an early treatment response, in terms of depressive symptoms, can predict fewer residual cognitive disturbances, previous studies have highlighted that cognitive symptoms at baseline can predict worse clinical outcomes and functional impairment in patients with MDD (Chokka et al., 2019; Haro et al., 2019; Wang et al., 2019). The exact relationship between the presence of cognitive and depressive symptoms and their predictive value for treatment response requires further analysis.

The limitations of the present study should be considered. Firstly, it included only outpatients younger than 65 years of age, most of whom had relatively high levels of educational attainment which may limit the generalizability of the results. Secondly, due to the observational nature of this study, the possible influence of concomitant medications, including additional antidepressants, was not evaluated. As the enrolment criteria for the PERFORM-J study were broad, various classes of antidepressants were used (including selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, noradrenergic and specific serotonergic antidepressants, and tricyclic antidepressants) (**Supp. Fig 3**) and they could have either a pro- or anti-cognitive effect. In order to prevent over-adjustment, only a limited number of potentially confounding variables were accounted for in the analysis, including concomitant mental disorders and chronic pain. As a result, concomitant medications were not included for the current evaluation. Thirdly, we did not determine whether specific depressive symptoms (e.g., insomnia, concentration) were associated with cognitive impairment. Future studies examining the relationship between MADRS sub-scores and PDQ-D scores should address this issue. Fourthly, only psychomotor speed was used to assess objective cognitive function. However, performance on the DSST has been shown to provide a good estimate of a range of other cognitive domains, including memory and executive function, in patients with MDD (Jaeger, 2018). Finally, a study duration

longer than 6 months might be required for a full recovery of cognitive disturbances, therefore, the current results may represent interim outcomes.

In conclusion, early changes in depressive symptoms were shown to predict residual cognitive disturbances, especially subjective cognition, in patients with MDD who initiated medication with antidepressants. Objective cognition at month 6 was correlated with early clinical response or remission in patients exhibiting poor cognitive performance to begin with. These findings from a real-world setting may help clinicians identify patients at risk of developing lingering cognitive disturbances, and initiate targeted intervention to improve long-term outcomes. Further, the results of this study suggest that, in terms of decreasing the likelihood of residual cognitive problems, switching of antidepressant drugs or add-on therapies, (e.g., cognitive remediation and neuromodulation) could be beneficial for patients who do not show early response to ongoing antidepressant treatments.

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Declaration of Competing Interest

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Dr. Hoshino, Mishiro, Dr. Fujikawa and Dr. Fernandez are employees of Takeda Pharmaceutical Company Limited.

Dr. Fernandez holds restricted shares from GSK and Takeda Pharmaceutical Company Limited.

Dr. Hammer-Helmich is an employee of H. Lundbeck A/S.

Dr. Ge was an employee of Lundbeck Singapore Pte Limited at the time of the analysis.

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Supplementary materials

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References

Barczyk, Z.A., Douglas, K.M., Porter, R.J., 2020. Baseline predictors of cognitive change in the treatment of major depressive episode: systematic review. BJPsych Open 6, e131.

Battisti, W.P., Wager, E., Baltzer, L., Bridges, D., Cairns, A., Carswell, C.I., Citrome, L., Gurr, J.A., Mooney, L.A., Moore, B.J., Peña, T., Sanes-Miller, C.H., Veitch, K., Woolley, K.L., Yarker, Y.E., 2015. Good publication practice for communicating company-sponsored medical research: GPP3. Ann. Intern. Med. 163, 461–464.

Baune, B.T., Renger, L., 2014. Pharmacological and non-pharmacological interventions to improve cognitive dysfunction and functional ability in clinical depression–a systematic review. Psychiatry Res. 219, 25–50.

Chokka, P., Bougie, J., Proulx, J., Tvistholm, A.H., Ettrup, A., 2019. Long-term functioning outcomes are predicted by cognitive symptoms in working patients with major depressive disorder treated with vortioxetine: results from the AtWoRC study. CNS Spectr. 24, 616–627.

Ciudad, A., Alvarez, E., Roca, M., Baca, E., Caballero, L., Garcia de Polavieja, P., Casillas, M., Valladares, A., Gilaberte, I., 2012. Early response and remission as predictors of a good outcome of a major depressive episode at 12-month follow-up: a prospective, longitudinal, observational study. J. Clin. Psychiatry 73, 185–191.

Evans, V.C., Iverson, G.L., Yatham, L.N., Lam, R.W., 2014. The relationship between neurocognitive and psychosocial functioning in major depressive disorder: a systematic review. J. Clin. Psychiatry 75, 1359–1370.

Fehnel, S.E., Forsyth, B.H., DiBenedetti, D.B., Danchenko, N., François, C., Brevig, T., 2016. Patient-centered assessment of cognitive symptoms of depression. CNS Spectr. 21, 43–52.

Fossati, P., Harvey, P.O., Le Bastard, G., Ergis, A.M., Jouvent, R., Allilaire, J.F., 2004. Verbal memory performance of patients with a first depressive episode and patients with unipolar and bipolar recurrent depression. J. Psychiatr. Res. 38, 137–144.

Goel, N., Rao, H., Durmer, J.S., Dinges, D.F., 2009. Neurocognitive consequences of sleep deprivation. Semin. Neurol. 29, 320–339.

Gorwood, P., Corruble, E., Falissard, B., Goodwin, G.M., 2008. Toxic effects of depression on brain function: impairment of delayed recall and the cumulative length of depressive disorder in a large sample of depressed outpatients. Am. J. Psychiatry 165, 731–739.

Gorwood, P., Richard-Devantoy, S., Baylé, F., Cléry-Melin, M.L., 2014. Psychomotor retardation is a scar of past depressive episodes, revealed by simple cognitive tests. Eur. Neuropsychopharmacol. 24, 1630–1640.

Groves, S.J., Douglas, K.M., Porter, R.J., 2018. A systematic review of cognitive predictors of treatment outcome in major depression. Front. Psychiatry 9, 382.

Hamilton, J.P., Chen, M.C., Gotlib, I.H., 2013. Neural systems approaches to understanding major depressive disorder: an intrinsic functional organization perspective. Neurobiol. Dis. 52, 4–11.

Hammer-Helmich, L., Haro, J.M., Jönsson, B., Tanguy Melac, A., Di Nicola, S., Chollet, J., Milea, D., Rive, B., Saragoussi, D., 2018. Functional impairment in patients with major depressive disorder: the 2-year PERFORM study. Neuropsychiatr. Dis. Treat. 14, 239–249.

Haro, J.M., Hammer-Helmich, L., Saragoussi, D., Ettrup, A., Larsen, K.G., 2019. Patient-reported depression severity and cognitive symptoms as determinants of functioning in patients with major depressive disorder: a secondary analysis of the 2-year prospective PERFORM study. Neuropsychiatr. Dis. Treat. 15, 2313–2323.

Hawley, C.J., Gale, T.M., Sivakumaran, T., 2002. Defining remission by cut off score on the MADRS: selecting the optimal value. J. Affect. Disord. 72, 177–184.

Herdman, M., Gudex, C., Lloyd, A., Janssen, M., Kind, P., Parkin, D., Bonsel, G., Badia, X., 2011. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual. Life Res. 20, 1727–1736.

Ishikawa, H., Tachimori, H., Takeshima, T., Umeda, M., Miyamoto, K., Shimoda, H., Baba, T., Kawakami, N., 2018. Prevalence, treatment, and the correlates of common mental disorders in the mid 2010′s in Japan: the results of the world mental health Japan 2nd survey. J. Affect. Disord. 241, 554–562.

Jaeger, J., 2018. Digit symbol substitution test: the case for sensitivity over specificity in neuropsychological testing. J. Clin. Psychopharmacol. 38, 513–519.

Lam, R.W., Lamy, F.X., Danchenko, N., Yarlas, A., White, M.K., Rive, B., Saragoussi, D., 2018. Psychometric validation of the Perceived Deficits Questionnaire-Depression (PDQ-D) instrument in US and UK respondents with major depressive disorder. Neuropsychiatr. Dis. Treat. 14, 2861–2877.

Marvel, C.L., Paradiso, S., 2004. Cognitive and neurological impairment in mood disorders. Psychiatr. Clin. North Am. 27, 19–36 vii-viii.

Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.

Murrough, J.W., Burdick, K.E., Levitch, C.F., Perez, A.M., Brallier, J.W., Chang, L.C., Foulkes, A., Charney, D.S., Mathew, S.J., Iosifescu, D.V., 2015. Neurocognitive effects of ketamine and association with antidepressant response in individuals with treatment-resistant depression: a randomized controlled trial. Neuropsychopharmacology 40, 1084–1090.

Oral, E., Canpolat, S., Yildirim, S., Gulec, M., Aliyev, E., Aydin, N., 2012. Cognitive functions and serum levels of brain-derived neurotrophic factor in patients with major depressive disorder. Brain Res. Bull. 88, 454–459.

Park, H., Poo, M.-m., 2013. Neurotrophin regulation of neural circuit development and function. Nat. Rev. Neurosci. 14, 7–23.

Rock, P.L., Roiser, J.P., Riedel, W.J., Blackwell, A.D., 2014. Cognitive impairment in depression: a systematic review and meta-analysis. Psychol. Med. 44, 2029–2040.

Saragoussi, D., Touya, M., Haro, J.M., Jönsson, B., Knapp, M., Botrel, B., Florea, I., Loft, H., Rive, B., 2017. Factors associated with failure to achieve remission and with relapse after remission in patients with major depressive disorder in the PERFORM study. Neuropsychiatr. Dis. Treat. 13, 2151–2165.

Sawada, K., Yoshida, K., Ozawa, C., Mizuno, Y., Rubinstein, E.B., Suzuki, T., Mimura, M., Uchida, H., 2019. Impact of subjective vs. objective remission status on subjective cognitive impairments in depression. J. Affect. Disord. 246, 99–104.

Semkovska, M., Quinlivan, L., O'Grady, T., Johnson, R., Collins, A., O'Connor, J., Knittle, H., Ahern, E., Gload, T., 2019. Cognitive function following a major depressive episode: a systematic review and meta-analysis. Lancet Psychiatry 6, 851–861.

Serra-Blasco, M., Torres, I.J., Vicent-Gil, M., Goldberg, X., Navarra-Ventura, G., Aguilar, E., Via, E., Portella, M.J., Figuereo, I., Palao, D., Lam, R.W., Cardoner, N.,

2019. Discrepancy between objective and subjective cognition in major depressive disorder. Eur. Neuropsychopharmacol. 29, 46–56.
Sheehan, D.V., Harnett-Sheehan, K., Raj, B.A., 1996. The measurement of disability. Int. Clin. Psychopharmacol. 11 (Suppl 3), 89–95.
Shimizu, Y., Kitagawa, N., Mitsui, N., Fujii, Y., Toyomaki, A., Hashimoto, N., Kako, Y., Tanaka, T., Asakura, S., Kusumi, I., 2013. Neurocognitive impairments and quality of life in unemployed patients with remitted major depressive disorder. Psychiatry Res. 210, 913–918.
Srisurapanont, M., Suttajit, S., Eurviriyanukul, K., Varnado, P., 2017. Discrepancy between objective and subjective cognition in adults with major depressive disorder. Sci. Rep. 7, 3901.
Sumiyoshi, T., Watanabe, K., Noto, S., Sakamoto, S., Moriguchi, Y., Hammer-Helmich, L., Fernandez, J., 2021. Relationship of subjective cognitive impairment with psychosocial function and relapse of depressive symptoms in patients with major depressive disorder: analysis of longitudinal data from PERFORM-J. Neuropsychiatric Dis. Treat. 17, 945–955.
Sumiyoshi, T., Watanabe, K., Noto, S., Sakamoto, S., Moriguchi, Y., Okamoto, S., 2018. Prospective epidemiological research on functioning outcomes related to major depressive disorder in Japan (PERFORM-J): protocol for a Prospective Cohort Study. JMIR Res. Protoc. 7, e161.
Sumiyoshi, T., Watanabe, K., Noto, S., Sakamoto, S., Moriguchi, Y., Tan, K.H.X., Hammer-Helmich, L., Fernandez, J., 2019. Relationship of cognitive impairment with depressive symptoms and psychosocial function in patients with major depressive disorder: cross-sectional analysis of baseline data from PERFORM-J. J. Affect. Disord. 258, 172–178.
Svendsen, A.M., Kessing, L.V., Munkholm, K., Vinberg, M., Miskowiak, K.W., 2012. Is there an association between subjective and objective measures of cognitive function in patients with affective disorders? Nord. J. Psychiatry 66, 248–253.
Szegedi, A., Jansen, W.T., van Willigenburg, A.P., van der Meulen, E., Stassen, H.H., Thase, M.E., 2009. Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder: a meta-analysis including 6562 patients. J. Clin. Psychiatry 70, 344–353.
Teng, Z., Wang, L., Li, S., Tan, Y., Qiu, Y., Wu, C., Jin, K., Chen, J., Huang, J., Tang, H., 2021. Low BDNF levels in serum are associated with cognitive impairments in medication-naïve patients with current depressive episode in BD II and MDD. J. Affect. Disord.
Vythilingam, M., Vermetten, E., Anderson, G.M., Luckenbaugh, D., Anderson, E.R., Snow, J., Staib, L.H., Charney, D.S., Bremner, J.D., 2004. Hippocampal volume, memory, and cortisol status in major depressive disorder: effects of treatment. Biol. Psychiatry 56, 101–112.
Wang, G., Si, T.M., Li, L., Fang, Y., Wang, C.X., Wang, L.N., Tan, K.H.X., Ettrup, A., Eriksen, H.F., Luo, S., Ge, L., 2019. Cognitive symptoms in major depressive disorder: associations with clinical and functional outcomes in a 6-month, non-interventional, prospective study in China. Neuropsychiatr. Dis. Treat. 15, 1723–1736.
Wechsler, D., 2006. Wechsler Adult Intelligent Scale, 3rd Edition. Nihon Bunka Kagakusha Co. Ltd, Tokyo, Japan.
Zimmerman, M., Posternak, M.A., Chelminski, I., 2004. Derivation of a definition of remission on the Montgomery-Asberg depression rating scale corresponding to the definition of remission on the Hamilton rating scale for depression. J. Psychiatr. Res. 38, 577–582.