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Differentiating The Cognitive Impairment of Clinically Stable Schizophrenia from Mild Cognitive Impairment

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Abstract

Background: Cognitive deficit is common and considered as the core feature of both mild cognitive impairment (MCI) and schizophrenia. However, only a few studies have directly compared cognitive profiles of these two conditions. The objective of the study was to compare the cognitive profiles of patients with schizophrenia to those with mild cognitive impairment (MCI).

Methods: Participants consisted of three groups; 42 normal controls, 42 patients with schizophrenia and 42 people with MCI. They were matched 1:1:1 with comparable educational levels. Cognitive functions were assessed using the Addenbrooke's Cognitive Examination III.

Results: Recall memory and naming subdomains were significantly lower in the MCI group as compared to patients with schizophrenia, but did not differ on attention, verbal fluency, clock drawing test, language and visuospatial ability. Logistic regression and diagnostic prediction model demonstrated that the MCI group is best differentiated from the schizophrenia group using recall memory and naming scores.

Conclusions: The cognitive profiles in patients with schizophrenia and MCI are different. In this study, naming and recall memory were less impaired in patients with schizophrenia than in people with MCI. The results of this study might provide some clues for clinicians on how to distinguish between cognitive impairment in elder patients with schizophrenia versus people with MCI.

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INTRODUCTION

To date, studies have demonstrated that cognitive deficits is common in schizophrenia and it is considered one of the core features. A cognitive profile is typically characterized by prominent deficits in episodic memory, executive function and attention [1, 2]. The impairments typically remain remarkably constant over the course of disease even though patients have no overt psychotic symptoms [3, 4]. Compared to normal controls, a review and meta-analysis demonstrated that individuals with schizophrenia generally perform around 1 to 1.5 standard deviations (SD) below normal controls in overall cognitive function [2, 5].

On the other hand, mild cognitive impairment (MCI) is a clinical-stage on the continuum of cognitive decline between normal aging and dementia. It is characterized by modest impairment in cognitive function that is not severe enough to require help with activities of daily living (ADL) [6, 7]. The cognitive decline can occur in a variety of cognitive domains, i.e., memory, executive function, language, attention and visuospatial ability, but impairment of episodic memory is the most commonly seen in MCI patients. Scores on cognitive assessments for patients with MCI are typically 1 to 1.5 SD below the age and education of matched controls [8].

Since both conditions had modest impairment in cognition with comparable severity, it raises to a question in clinical practice of how can we differentiate cognitive impairment in people with schizophrenia from people who have both schizophrenia and MCI.

Assume we have a chronic schizophrenic patient aged 58 years old, who has had no hallucinations or delusions for many years. Lately, he complains about mild memory loss and problem-solving ability. Functionally, he remains independent in all ADL. The brief cognitive assessment confirmed that he had lower scores than a norm value. How can we ensure that his cognitive impairment is due to schizophrenia itself or if he also has an MCI?

To solve this problem, the first question should be, are there

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any differences in cognitive profiles between schizophrenia patients and people with MCI. To our knowledge, only a few studies which have directly compared the differences in cognitive profiles between patients with MCI and those with schizophrenia [9, 10]. Therefore, the primary objective of the study was to examine the differences of cognitive profiles between patients with clinically stable schizophrenia and people with mild cognitive impairment. As an exploratory analysis, the secondary objectives were to investigate what are the best cognitive domains that can differentiate MCI from schizophrenia and examine the possibility of developing a simple diagnostic prediction rule from the cognitive profile.

METHODS

Participants

In this study, there were 126 participants consisting of 42 schizophrenia patients, 42 people with MCI and 42 elderly controls. They were matched 1:1:1 with a comparable level of education. This study was exempt from ethics approval (No. 079/2020) because we used the secondary data from our previous database [11, 12] which was approved by the Human Ethics Committee of Thammasat University (Protocol Number MTUEC-PS-6-043/59 and 151/58). The inclusion criteria for each group are as follows:All participants provided informed consent to participate.

Schizophrenia Group

Schizophrenia patients were recruited from the outpatient psychiatric clinic, Thammasat University Hospital, Thailand. They were diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria [7] by the consensus of two psychiatrists. The age range was 20 to 55 years old with the education level of at least four years. We limit the age to 55 years old to ensure that those patients did not also have MCI. Moreover, we intended to investigate cognitive performance in clinically stable schizophrenia as defined by no significant change in symptoms and treatment in the last 12 weeks. They had a global rating for each positive symptom of less than three points as assessed by the Scale for the Assessment of Positive Symptoms (SAPS) [13].

MCI Group

Individuals with MCI were recruited at our Memory Clinic. They were aged at least 55 years old with at least four years of formal education. We made the diagnosis of MCI using DSM-5 for minor neurocognitive disorder [7] by geriatric psychiatrist or neurologist. The diagnostic assessments included history, neurological examination, cognitive assessment and laboratory data according to the guideline of the Memory Clinic.

Normal Control Group

The cognitively healthy elderly participants were recruited among the relatives or spouses of patients of the Memory Clinic. They were aged at least 55 years old with at least four years of formal education, had no history of cognitive decline, had a normal performance on the cognitive test, and were independent in ADL.

The exclusion criteria for all groups were other major neurological disorders (e.g., dementia and stroke), other major psychiatric disorders (bipolar I disorder and major depressive disorders) and substance dependence except for nicotine.

Cognitive Assessment

The Addenbrooke's Cognitive Assessment III (ACE) was used to assess cognitive function. The ACE assessed a variety of cognitive domains including attention, verbal fluency, language, visuospatial ability, and memory. It scores ranges from 0 to 100, with a higher score indicating better cognitive function [12, 14]. The ACE has demonstrated that it is sensitive to detect cognitive impairment in both people with MCI and schizophrenia [3, 12, 14]. In this study we divided the ACE into seven subdomains: 1) attention (score range 0-18 points) 2) recall memory (0-26 points) 3) naming (0-12 points) 4) language (0-14 points) 5) verbal fluency (0-14 points) 6) clock drawing test (CDT; 0-5 points) and 7) visuospatial ability (0-11 points). More details of the tasks are provided in Table 1.

Schizophrenia patients were assessed for positive and negative symptoms using the Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS). The SAPS were reported using the sum of global rating scores, ranging from 0-20, where a higher score indicates greater positive symptom severity. The global SANS ranges from 0-25 with a higher score indicating more negative symptoms [13, 15-17].

Table 1. Score range and cognitive tasks of each cognitive domain

	Attention	Memory	Naming	Language	CDT	Verbal fluency	Visuospatial
Score range	0-18	0-26	12	0-14	0-5	0-14	0-11
Tasks	Orientation, Serial 7 subtraction, Registration of 3 items	3-word recall, Name and address recall, Famous person	Confrontation naming test	Comprehension, Writing, Word and sentence repetition, Reading	Clock drawing test	Letter fluency, Category fluency	Infinity loops copying, Cube copying, Fragmented letter, Count dots

Statistical Analysis

Exact test and analyses of variance (ANOVA) was employed to assess the difference in the demographic data between study groups. We used ANOVA with post-hoc Bonferroni test to examine the differences of each cognitive subdomain score. Multivariable linear regression analysis was used to confirm the effects of diagnostic groups on each cognitive subdomain test while adjusting for age, gender and education level. Postestimation of regression analysis was then used to demonstrate the p-value between schizophrenia and MCI group.

The secondary objective was to assess which cognitive subdomain can distinguish MCI from schizophrenia. Binary logistic regression with the stepwise forward method was employed to delineate the significant subdomains. In this analysis, the independent variable is the diagnostic group (schizophrenia vs MCI-as-reference group), and predictive variables were seven cognitive subdomain scores. We also presented the standardized coefficient of each explanatory variable to demonstrate which cognitive domains had a high magnitude in predicting MCI from schizophrenia.

Lastly, we used the predictive variables in the final model to develop a simple diagnostic prediction rule to separate MCI from schizophrenia. Cognitive domain scores were categorized into two levels using Liu's method. The score for each predictor variable was assigned and added up to obtain a total risk score. Discrimination of the risk score was presented with diagnostic accuracy indices. All data were analyzed using STATA version 14.

RESULTS

Table 2 shows the baseline characteristic in the three diagnostic groups. The three groups did not differ significantly with respect to educational level. Gender was marginally significant (p = 0.049), and age was significantly different with the schizophrenia patients being younger than normal controls and MCI patients.

Table 2. Demographic data

Variables	Schizophrenia (n=42)	MCI (n=42)	Normal controls (n=42)	p-value
Gender: male (%)	10 (23.8%)	21 (50%)	16 (37.3%)	0.049
Age (years)	39.7 (13.1)	69.9 (7.7)	64.7 (7.7)	<0.001
Education (years)	11.5 (3.1)	10.2 (5.0)	10.1 (4.6)	0.25
SAPS	2.2 (2.4)	n/a	n/a	n/a
SANS	7.8 (5.1)	n/a	n/a	n/a
Duration (years)	9.3 (1.0)	n/a	n/a	n/a
Episode	2.3 (1.6)	n/a	n/a	n/a

MCI: mild cognitive impairment; SAPS: the Scale for the Assessment of Positive Symptoms; SANS: the Scale for the Assessment of Negative Symptoms; n/a: not applicable

Score Differences Between Schizophrenia, MCI and Control Groups

Table 3 illustrates the cognitive scores in each subdomain of the ACE of three groups. Overall, MCI patients had lower scores than normal controls in all cognitive subdomains. Thirty-six of our MCI patients (85.7%) had recall memory scores lower than 1 standard deviation (SD) of normal controls. People with schizophrenia had lower scores than control for attention, recall memory, and verbal fluency, but not for clock drawing test (CDT), naming, language and visuospatial ability. Contrasting people with schizophrenia and MCI, MCI patients demonstrated lower scores than schizophrenia patients on four subdomains: recall memory, naming, language and visuospatial ability, but did not differ in attention, verbal fluency, and CDT.

Table 3. Means, standard deviations (SD), and analysis of variance (ANOVA) in cognitive subdomain scores in schizophrenia, mild cognitive impairment (MCI) and normal controls

	Diagnostic groups			p-value [a]		
	Schizophrenia: mean (SD)	MCI: mean (SD)	NC: mean (SD)	Schizophrenia vs MCI	Schizophrenia vs NC	MCI vs NC
Attention	15.3 (2.1)	14.8 (1.6)	16.4 (1.5)	0.7	0.017	<0.001
Memory	18.1 (3.3)	13.9 (3.4)	20.2 (2.7)	<0.001	0.01	<0.001
Fluency	8.5 (2.7)	7.6 (2.7)	10.3 (2.0)	0.329	0.002	<0.001
CDT	4.2 (1.2)	3.8 (1.3)	4.5 (0.9)	0.27	0.65	0.01
Naming	10.9 (1.7)	8.8 (2.3)	10.6 (1.1)	<0.001	1.0	<0.001
Language	13.1 (1.5)	12.0 (1.7)	13.2 (1.2)	0.001	1.0	0.001
Visuospatial	9.9 (1.5)	9.0 (1.9)	10.3 (0.9)	0.01	0.65	<0.001
Total score	79.8 (8.7)	69.5 (8.5)	85.5 (6.6)	<0.001	0.004	<0.001

MCI: mild cognitive impairment; NC: normal controls; CDT: clock drawing test; [a]ANOVA post-hoc Bonferroni test

We employed multivariable linear regression analysis to adjust for effect of age, gender and level of education (Table 4). Postestimation analysis demonstrated that only recall memory and naming were significantly lower in patients with MCI than schizophrenia. It also should be noted that schizophrenia patients did not differ significantly from controls in the naming test.

It can be seen from the standardized coefficient (beta) that the most deficient cognitive domains in schizophrenia patients were verbal fluency (-0.54), clock drawing test (-0.44) and recall memory (-0.38). For MCI patients, the most deficient cognitive domains were recall memory (-0.71), attention (-0.42), verbal fluency (-0.47), and naming (-0.46).

Table 4. Results of multivariable linear regression analysis with each cognitive subdomain score as dependent variables and participant groups as primary explanatory variables, while adjusting for age, gender and level of education.

	Schizophrenia [a]			MCI [a]			Schizophrenia vs MCI	Adjusted R^2 (%)
	Coefficient	Beta [b]	p-value	Coefficient	Beta [b]	p-value	p-value [c]	
Attention	-0.83	-0.21	0.134	-1.63	-0.42	<0.001	0.191	13.3%
Memory	-3.29	-0.38	0.002	-6.19	-0.71	<0.001	0.01	40.9%
Fluency	-3.14	-0.54	<0.001	-2.75	-0.47	<0.001	0.637	28.4%
CDT	-1.09	-0.44	0.002	-0.69	-0.28	0.004	0.258	19.9%
Naming	-0.49	-0.12	0.33	-1.96	-0.46	<0.001	0.009	38.2%
Language	-0.65	-0.19	0.116	-1.27	-0.38	<0.001	0.174	34.7%
Visuospatial	-1.66	-0.5	<0.001	-1.21	-0.36	<0.001	0.359	24.0%

MCI: mild cognitive impairment; CDT: clock drawing test. [a]Normal controls as a reference group, [b]Beta = standardized coefficient, [c]Postestimation of linear regression.

Results of Binary Logistic Regression Analysis and Diagnostic Prediction Rule

In our secondary objective, we attempted to examine the best cognitive domains that distinguish cognitive impairment in MCI from schizophrenia. Table 5 illustrates the results of stepwise forward logistic regression analysis with MCI and schizophrenia as dependent variables (MCI as the reference group) and the seven cognitive subdomains as predictive variables. The final model consisted of two variables, recall memory and naming. It can explain 30% of the variance in the data with an area under the receiver operating characteristics (AuROC) of 85%. The lower scores on these cognitive domains were associated with an MCI diagnosis. The recall memory had largest effect size in predicting schizophrenia vs MCI with standardized coefficient of 0.48, followed by naming (0.34).

Table 5. Best cognitive domain predictors using stepwise forward logistic regression analysis

	Odds Ratio (OR) [95% CI]	Standard errors (SE)	P-value	coefficient	Standardized coefficient
Memory score	1.36 [1.14-1.62]	0.12	0.001	0.31	0.48
Naming score	1.47 [1.11-1.95]	0.21	0.007	0.39	0.34

Area under the receiver operating characteristics (AuROC) 0.85; Pseudo R^2 30.5%; Mild cognitive impairment (MCI) as a reference group

We used the Liu method to estimate the cut-off point for recall memory and naming tasks. The cut-off score for naming was < 10 points and < 15 for recall memory. Then a score of 0/1 was given for each cognitive domain. The total risk score ranges from 0 to 2 points (Table 6). With the cut-off score of ≥1 point, or in simple terms, patients with either naming < 10 points or recall memory < 15, are more likely to have a diagnostic of MCI with a sensitivity of 81%, specificity of 78.6%, and positive predictive value of 79.1% (for classification performance of the diagnostic prediction rule, please see Table 7).

Table 6. Best subdomain predictors in binary scale with odds ratios (OR), coefficients, and assigned item scores using logistic regression analysis

	Odds Ratio (OR) [95% CI]	Standard errors (SE)	P-value	Coefficient	Score
Memory					
< 15 points	9.51 [2.93-30.88]	5.72	0.005	2.25	1
≥ 15 points	reference	reference	reference	reference	0
Naming					
< 10 points	5.32 [1.65-17.12]	3.17	<0.001	1.67	1
≥ 10 points	reference	reference	reference	reference	0

Schizophrenia as a reference group; Pseudo R^2 28.0%

Table 7. Classification performance of the diagnostic prediction rule for separate mild cognitive impairment from schizophrenia

Prediction rule	MCI	Schizophrenia	Total
Positive (≥ 1 points)	34	9	43
Negative (0 points)	8	33	41
Total	42	42	84

Sensitivity 81%; specificity 78.6%, likelihood ratio if test positive (LR+) 3.78, positive predictive value (PPV) 79.1%, negative predictive value (NPV) 80.5%

DISCUSSION

The main objective of this study was to investigate the differences of cognitive profiles between individuals with MCI and schizophrenia. The results demonstrated that schizophrenia and MCI had major differences in naming and recall memory domain. The scores of both domains were lower in patients with MCI than schizophrenia. There were also trends toward lower language and visuospatial ability scores in MCI patients as compared to schizophrenia patients with statistical significance using univariable analysis ($p = 0.001$ and 0.01) but not in multivariable analysis.

There are only a few studies which directly compared cognitive profile in patients with MCI and patients with schizophrenia. A study by Kazui et al. compared indices of the Wechsler Memory Scale (WMS-R) in schizophrenia patients and amnestic MCI patients. The results demonstrated the same pattern as our study, that delay recall scores in the amnestic MCI group were significantly lower than in patients with schizophrenia [10]. Our results are also in accordance with a study by Kanchanatawan; using the Consortium to Establish a Registry for Alzheimer's disease (CERAD) indicated that schizophrenia patients are best separated from amnestic MCI patients by the Boston Naming Test [9].

It is interesting to note that patients with schizophrenia had comparable naming scores compared to normal controls (10.9 vs 10.6 points), whereas patients with MCI had a significantly lower score than normal controls (8.8). This suggests that anomia might be a feature that is found only in the MCI group. Concerning recall memory, both schizophrenia and MCI patients displayed lower recall memory scores than normal controls, but the degree of impairment was more severe in the MCI group. Previous studies and reviews illustrated that the major cognition deficits in schizophrenia are episodic/recall memory, executive function and attention, while language (excluding verbal fluency) is usually the smallest deficit [1, 2, 5]. A study by Goldberg et al. using Boston Naming Test also revealed that schizophrenia patients had similar scores when compared with normal controls [18]. On the other hand, though, recall memory test is the most common and prominent cognitive impairment in MCI [8, 19]. Many studies also revealed that language deficits including naming performance are often found in MCI [20-22].

Our secondary objective was to examine the best predictors and the possibility of using cognitive profiles to separate people with schizophrenia from MCI. From the logistic regression model and diagnostic prediction rule, they confirmed that naming and recall memory are the two key factors segregating schizophrenia from MCI. Recall memory seemed to be a slightly better predictor than naming with the standardized coefficient of 0.48 vs 0.34.

In this study, we demonstrated that it might be possible to establish a simple diagnostic prediction rule from the profile of cognitive impairments with acceptable diagnostic accuracy. Our prediction rule is simple, patients who have a recall memory score lower than 15 points or a naming lower than 10 points have a high probability of having MCI condition with positive predictive value (PPV) of 79.1%. However, we intended to develop this prediction rule as an exploratory analysis. We acknowledge that it needs further studies to develop a more valid and reliable prediction rule with larger sample sizes. External validity is also needed.

Limitation

There were some limitations in this study. Firstly, our schizophrenia participants were clinically stable with low positive symptoms; therefore, these results might not be applied to patients who had severe persistent psychotic symptoms, patient in inpatient department or long-term institute. Secondly, schizophrenia patients in this study were younger than MCI. Although, ideally, the best method to assess the differences in cognitive function is to match both level of education and age of the subjects. However, as previously mentioned, we decided to restrict the age of the schizophrenia group to lower than 55 years old to avoid the possibility that some participants might also have MCI. Finally, currently, MCI can be classified into four subtypes 1) MCI, amnestic, single domain 2) MCI, amnestic, multiple domains 3) MCI, non-amnestic, single domain and 4) MCI, non-amnestic, multiple domains [23]. Our results demonstrated that the majority of the participants had deficits in memory which could be considered as amnestic subtypes; however, the two latter non-amnestic subtypes might show different cognitive profiles. Furthermore, the next step and future studies are to clarify the difference in the cognitive profiles of elderly schizophrenic patients combined with MCI compared to elderly patients with schizophrenia diagnosis alone.

The main strengths of this study rest on the matching of the level of education between groups because most studies demonstrated that most cognitive tests are correlated with the level of education including the ACE [12]. Another strength is that our schizophrenia samples were clinically stable; therefore, the cognitive assessment process would not be influenced by the psychotic symptoms. Finally, we also developed a diagnostic prediction rule using cognitive profiles, which demonstrated the possibility of using cognitive subdomains to predict MCI from schizophrenia.

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