Research Article

Classification of Neurocognition in Japanese Patients with Schizophrenia: A Cluster Analysis

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Objectives. Cognitive functions in almost all domains are lower in patients with schizophrenia than those in healthy controls, with the severity of impairment differing between domains. Treatments are being developed to improve cognitive impairment in patients with schizophrenia. However, the pattern of cognitive impairment must be clarified to facilitate treatment. Therefore, this study aimed to classify the patterns of cognitive impairment in individuals and provide treatment suggestions.

Methods. Patients with schizophrenia were recruited from two psychiatric hospitals in Japan. Demographic and psychopathological symptoms were assessed using the Positive and Negative Symptoms Scale for Schizophrenia and neurocognitive functions, using the CogHealth battery. The following domains were assessed: processing speed, visual attention, working memory, visual learning, and spatial attention. The scores were standardised and assigned as the same-aged average score. Hierarchical cluster analysis using Ward’s method was performed based on CogHealth scores. Subsequently, one-way analysis of variance (ANOVA) and Tukey’s multiple comparisons were performed to compare the variables in each cluster.

Results. In total, 133 participants were classified into four clusters: Cluster 1 (n = 16), with severe cognitive impairment and psychiatric symptoms and the longest stay; Cluster 2 (n = 44), with moderate cognitive impairment and psychiatric symptoms; Cluster 3 (n = 42), with preserved cognitive function, except for spatial perception, and mild psychiatric symptoms; and Cluster 4 (n = 31), with only memory and spatial perception impairment and mild psychiatric symptoms.

Implications. The clusters indicate that impairment may occur in all or selective domains. Selective domain impairments may be in spatial perception or in spatial perception and memory. Therefore, it is recommended that treatments for cognitive dysfunction are developed into four subsets considering an individual’s cognitive features.

1. Introduction

Schizophrenia presents with various psychiatric symptoms—positive, negative, and neurocognitive impairment. Of these, neurocognitive dysfunction is recognised as a treatment and care target because it is related to crucial factors such as self-concept [1], community functioning, and functional outcome [2]. Neurocognitive function covers various fields. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consortium proposed a 7-domain neurocognition: speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem-solving, and social cognition [3]. Additionally, the extent of deficiency in each neurocognitive domain varies [4, 5]. Furthermore, several studies [6, 7] have highlighted that neurocognitive domains change in varying degrees over time. A narrative review by Fett et al. [7] reported a decline in memory and verbal knowledge but improvement or stability in crystallised cognitive domains. As the severity and change in each neurocognitive domain may differ, leading to diversity in neurocognition in individuals, it is necessary to measure multiple neurocognitive domains simultaneously to detect their performance and dysfunction levels.

Furthermore, neurocognitive profile patterns may vary in individuals with schizophrenia. Several reviews [7, 8] have found from two to five cognitive subtypes in schizophrenia, with three and four subtypes being predominant with
spared, mildly-impaired with verbal learning and memory impairment, moderately-impaired with global impairment, and greatly-impaired subtypes. These findings suggest that there are several neurocognitive subtypes according to domain severity and impairment.

However, existing studies have several gaps. First, neurocognition measurement instruments may be affected by individual educational levels. Second, previous long-term hospitalization is thought to affect neurocognitive function and is a risk factor for worsening neurocognition [9]; therefore, neurocognitive subtypes in patients in Asia, especially, in Japan—which has longer hospitalizations compared to other countries—may be largely different. However, no research has included Japanese samples.

It is necessary to clarify the neurocognitive subtypes of patients with schizophrenia in Japan using a tool that measures multiple neurocognitive domains without being influenced by the educational and intellectual levels to develop care strategies according to the subtypes. This is because performing tasks involving multiple cognitive batteries can be relatively difficult, as they may be influenced by participants’ educational level. Moreover, a tool that uses simple tasks to measure neurocognition will be easier for participants to understand. Therefore, this cross-sectional study aimed to clarify the neurocognitive subtypes of Japanese patients with schizophrenia and to suggest implications for practice improvement based on individual neurocognitive profiles.

2. Materials and Methods

2.1. Participants. Participants were recruited from two psychiatric hospitals in Japan. The inclusion criteria were (a) diagnosis of schizophrenia, (b) treatment in a hospital or outpatient setting, and (c) consent from the patients and their doctor. The exclusion criteria were (a) inability to walk independently, (b) age <20 years, (c) treatment with lobotomy, and (d) presence of comorbidities, such as neurological diseases, intellectual disability, and substance-related disorder. Furthermore, all eligible candidates treated in the enrolled hospitals were invited by their doctor and included in the study only if they gave their consent to participate. A total of 133 patients were enrolled in this study. This study was conducted as part of a previously published project [10] and used a part of the data as a secondary analysis.

2.2. Measurements

2.2.1. Demographics. The following demographic data and treatment-related information were obtained: age, sex, age of onset of schizophrenia, duration of illness, length of hospital stay, treatment site, and type and dose of medications. Antipsychotic doses were calculated as chlorpromazine equivalents (first-generation and second-generation antipsychotics), anxiolytic medications as diazepam equivalents, and anti-Parkinsonian medications as biperiden equivalents.

2.2.2. Psychiatric Symptoms. Psychiatric symptoms were measured using the Positive and Negative Syndrome Scale (PANSS), which comprises the positive, negative, and general psychopathology subscales and 30 items rated from 1 (absent) to 7 (severe) based on the symptom severity over the previous week. In this analysis, the three subscales and the overall PANSS scores were used. The scale has good validity and reliability [11].

2.2.3. Neurocognitive Function. Neurocognitive function was measured using the CogHealth battery (Cogstate, Melbourne, Australia), which has good reliability and validity [12]. The following five tasks were assessed using a personal computer: speed of processing (reaction time), visual attention (reaction time), working memory (reaction time and accuracy), visual learning (accuracy), and spatial attention (reaction time).

Generally, all tasks in the CogHealth battery test require the participants to indicate their responses by pressing the “yes” or “no” buttons. We selected this battery for the study, as its rules and tasks are easy to understand and perform. To monitor the speed of processing tasks, the participants were asked to press the “yes” button quickly when the trump appearing on the display was turned up. This indicated their reaction time. Similarly, for the visual attention task, they were asked to press the “yes” button quickly when the turned-up trump was red. This demonstrated their reaction time. Furthermore, in the working memory task, the participants were asked to press the “yes” button if the trump was the same as the previous one. If it was not the same, they were directed to press the “no” button. This captured both their reaction time and accuracy. Additionally, in the visual learning task, the participants were asked to press the “yes” button if the trump had already been displayed in the present session. They were requested to indicate “no,” if it had not been displayed. This task scored their accuracy. For the spatial attention task, they were asked to press the “yes” button quickly if a trump moving in a zigzag manner reached a displayed line. This indicated their reaction time.

To help the participants understand the rules of each task and response method, researchers explained the procedures and the interface. Furthermore, the participants were given time to practice all the tasks once before the actual experiment. Upon confirming that the participants understood the rules, the cognitive battery test was started. It required approximately 20 minutes to complete.

The scores obtained in CogHealth were standardised by setting the mean score to 100 and the standard deviation (SD) to 10. Standardisation was performed based on data of more than 30,000 healthy individuals from the CogHealth database. Furthermore, as CogHealth scores are not influenced by both participants’ educational level and practice effect, they were comparable with those of healthy individuals without direct investigation of the scores of age-matched healthy individuals. Higher scores indicated better neurocognitive function.

2.3. Procedure. The study procedure was in accordance with a previously published study [10]. Data were collected in the following sequence: demographics, psychiatric symptoms, and neurocognitive function. Interviews and measurements
of psychotic symptoms and neurocognitive function were conducted for approximately one hour, in a private meeting room to ensure privacy. All interviews and measurements were conducted by the first author. All data were collected between January 2009 and October 2012.

2.4. Statistical Analysis. Hierarchical cluster analysis was performed using Ward’s method to classify participants in clusters based on the six CogHealth scores. A dendrogram was used to determine the optimal number of clusters and all measures among these clusters were compared using the chi-square test and one-way analysis of variance (ANOVA) and Tukey’s test for multiple comparisons. Neurocognitive function scores of the participants were compared with the average score of 100 healthy controls using a t-test.

All statistical analyses were performed using SPSS version 23.0 (SPSS, Chicago, IL, USA) and the significance level was set at 5%.

2.5. Ethical Consideration. This research protocol received approval by the ethical committee associated with the researchers’ institution and the hospitals where the participants received treatment. Participants and their physicians were fully informed about the study’s objectives, methods, and the measures in place to safeguard their personal data, all of which were detailed in provided documents. We emphasised the participants’ autonomy, ensuring that they could freely choose to participate or decline without facing any adverse consequences. In order to formalise their consent, all participants and their physicians were asked to complete consent forms when agreeing to participate in this study.

To uphold privacy, all investigations and interviews conducted throughout the study took place in a confidential, private setting. Additionally, participants were reassured that they could take breaks as needed during interviews to ensure their comfort and well-being.

3. Results

3.1. Characteristics of Participants. A total of 133 participants completed the questionnaires. As shown in Table 1, average age, chlorpromazine dose, and total PANSS score were $50.7 \pm 15.4$ years, $676.0 \pm 541.2$ mg, and $61.3 \pm 15.0$, respectively. The neurocognitive domain scores are shown in Table 2 and Figure 1.

3.2. Cluster Analysis. Based on the dendrogram, the participants were grouped into four clusters. The multiple comparison test results are shown in Tables 1 and 2. The chi-square test found no differences in sex between the four clusters ($p = 0.834$), whereas there was a significant difference in the ratio of inpatients to outpatients between the clusters ($p < 0.001$). ANOVA demonstrated age differences ($p < 0.001$), duration of illness ($p < 0.001$), length of stay ($p < 0.001$), negative scale ($p < 0.001$), general psychopathological scale ($p < 0.001$), total PANSS score ($p < 0.001$), and all CogHealth scores ($p < 0.001$) among the four clusters.

3.2.1. Cluster 1 (Severe Impairment). All CogHealth scores in cluster 1 were lower than those in the other three groups ($p < 0.001$). In demographics, age and length of stay were also longer than those in the other three groups ($p < 0.001$). Furthermore, all were inpatients, and the ratio of inpatients was higher than that in clusters 3 and 4. Regarding psychiatric symptoms, negative, general psychopathological, and total PANSS scores were more severe than in clusters 3 and 4 ($p < 0.01$). Therefore, this group was classified as having severe impairment.

3.2.2. Cluster 2 (Moderate Impairment). All CogHealth scores in cluster 2 were lower (range: 82.2–94.1) than those in clusters 3 and 4 and in healthy controls ($p < 0.001$) (Table 2), and the difference in the degree of neurocognitive dysfunction ranged from approximately $-2$ to $-1$SD of that in healthy controls. In demographics, the average age was higher than that in clusters 3 and 4 ($p < 0.001$). The ratio of inpatients was higher than that in clusters 3 and 4. The length of stay in this group was shorter than that in cluster 1, although it was longer than that in clusters 3 and 4. In psychiatric symptoms, negative symptoms, general psychopathological symptoms, and total PANSS score in this group were more severe than those in clusters 3 and 4, but were similar to those in cluster 1. Therefore, this group was classified as having moderate impairment.

3.2.3. Cluster 3 (Only Spatial Attention Impairment). In this group, visual attention and visual learning scores were higher than those in healthy controls ($p < 0.001$), and spatial attention was lower than that in healthy controls ($p < 0.001$) (Table 2). The average age and length of stay were lower than those in clusters 1 and 2, while the ratio of outpatients was higher than that in clusters 1 and 2. Negative, general psychopathological, and total PANSS scores in this cluster were lower than those in clusters 1 and 2 ($p < 0.05$). Therefore, this cluster was classified as having only spatial attention impairment.

3.2.4. Cluster 4 (Memory and Spatial Attention Impairment). In this cluster, speed of processing, visual attention, and reaction time in the working memory task were better than those in the healthy controls ($p < 0.001$) (Table 2). However, accuracy in the working memory task, visual learning, and spatial attention were lower than that in the healthy controls ($p < 0.001$). The average age and length of stay were lower than those in clusters 1 and 2 ($p < 0.05$) and the ratio of outpatients was higher than that in clusters 1 and 2. However, it was similar to those in cluster 3. In psychiatric symptoms, negative, general psychopathological, and total PANSS scores were better than those in clusters 1 and 2 ($p < 0.05$) but were similar to those in cluster 3. Therefore, this cluster was classified as having memory and spatial attention impairment.
<table>
<thead>
<tr>
<th>Table 1: Demographics and psychiatric symptoms by clusters (n = 133).</th>
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</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
</tr>
<tr>
<td>n = 133</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
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<tr>
<td><strong>Treatment site</strong></td>
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<tr>
<td><strong>Age (years old)</strong></td>
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<td><strong>Age of onset (years old)</strong></td>
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<tr>
<td><strong>Duration of illness (years)</strong></td>
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<td><strong>Length of stay (months)</strong></td>
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<td><strong>FGA (mg)</strong></td>
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<td><strong>SGA (mg)</strong></td>
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<tr>
<td><strong>Total chlorpromazine equivalent (mg)</strong></td>
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<tr>
<td><strong>Biperiden (mg)</strong></td>
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<tr>
<td><strong>Diazepam (mg)</strong></td>
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<tr>
<td><strong>Psychiatric symptoms</strong></td>
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<tr>
<td><strong>Positive scale</strong></td>
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<tr>
<td><strong>Negative scale</strong></td>
</tr>
<tr>
<td><strong>General psychopathological scale</strong></td>
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<tr>
<td><strong>PANSS total</strong></td>
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*ab,c* The different letters mean significant differences between letters. *Gender and treatment site were analysed by chi-square test. The rest of variables was analysed by one-way analysis of variance. FGA: first-generation antipsychotics. SGA: second generation antipsychotics.
Table 2: Cognitive score across subtypes (n = 133).

<table>
<thead>
<tr>
<th>Cognitive function</th>
<th>Overall (n = 133)</th>
<th>Cluster 1 (n = 16)</th>
<th>Cluster 2 (n = 44)</th>
<th>Cluster 3 (n = 42)</th>
<th>Cluster 4 (n = 31)</th>
<th>F</th>
<th>P&lt;sup&gt;6&lt;/sup&gt;</th>
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<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Speed of processing</td>
<td>94.5</td>
<td>11.4</td>
<td>76.3</td>
<td>8.6</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>89.4</td>
<td>8.1</td>
</tr>
<tr>
<td>Visual attention</td>
<td>98.2</td>
<td>9.8</td>
<td>80.8</td>
<td>7.7</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>94.1</td>
<td>4.8</td>
</tr>
<tr>
<td>Woking memory—reaction time</td>
<td>96.1</td>
<td>7.9</td>
<td>85.0</td>
<td>5.4</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>92.5</td>
<td>6.1</td>
</tr>
<tr>
<td>Working memory—accuracy</td>
<td>89.5</td>
<td>14.6</td>
<td>67.8</td>
<td>4.5</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>81.5</td>
<td>10.9</td>
</tr>
<tr>
<td>Visual learning</td>
<td>95.4</td>
<td>11.3</td>
<td>85.0</td>
<td>7.7</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>91.6</td>
<td>9.3</td>
</tr>
<tr>
<td>Spatial attention</td>
<td>86.6</td>
<td>12.4</td>
<td>67.8</td>
<td>8.5</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>82.2</td>
<td>11.4</td>
</tr>
</tbody>
</table>

*a*comparing to 100 as a average score of healthy control using t-test. *b,c,d* one-way analysis of variance. *a,b,c* the different letters mean significant differences between letters.
4. Discussion

This study aimed to clarify the clusters of neurocognition in patients with schizophrenia and to compare the features between the clusters. Three findings emerged: (1) there are groups with selective and total impairments, (2) all clusters have spatial attentional dysfunction, and (3) groups with selective impairment and selective hyperfunction could be further divided into two groups.

Before discussing the three main findings, it should be mentioned that sex, type and Number of antipsychotics did not influence the cluster structure, whereas the treatment site did. In this study, sex ratio did not differ between clusters. However, clusters 1 and 2 exhibited worse negative symptoms which are well-known influencing factors of neurocognitive level. Au-Yeung et al. [13] conducted a moderator analysis in a meta-analysis and found no moderating effects of sex on the relationships between neurocognition and negative symptoms, which is concordant with our results. Therefore, sex may not have influenced neurocognitive cluster structure in this study. Additionally, both first-generation and second-generation antipsychotics did not differ between the four clusters. This result is inconsistent with a previous meta-analysis that examined differences in effects between first-generation and second-generation antipsychotics on global cognition and reported that second-generation has higher effects than first-generation antipsychotics [14]. However, no difference was found in long-term effects [15]. Thus, as this study analysed long-course participants who have had schizophrenia for nearly 24.5 years, the antipsychotic therapies did not influence the neurocognitive cluster structure.

The treatment site ratio was significantly different between clusters 1 and 2 than clusters 3 and 4. Particularly, cluster 1 included only inpatients, but clusters 2, 3, and 4 were composed of both inpatients and outpatients. Therefore, it can be concluded that inpatients and outpatients had a common neurocognitive profile except for those in cluster 1. This may be because of the high hospitalization in Japanese psychiatric medication. Japan is well-known for having one of the highest numbers of long-term inpatients in the psychiatric care system [16]. This implies that even if the patients’ symptoms alleviate to the extent that they can maintain their lives, they may have to stay in hospitals due to

![Figure 1: Neurocognitive domains by the clusters.](image-url)
a lack of environmental support. This may be the reason why clusters 2, 3, and 4 had both inpatients and outpatients.

Participants’ neurocognitive profiles were of four types; considering neurocognitive domain deficits, there were profiles with selective impairment (clusters 3 and 4) and total impairment (clusters 1 and 2). All four subtypes had neurocognitive dysfunction in at least one domain. Vaskinn [17] examined neurocognitions in 223 participants with schizophrenia (average age: 30.8 ± 9.5) and found three subtypes: intact, intermediate, and impaired. None of the domains in the intact subtype were lower than −0.8 SD of those in healthy individuals; three neurocognitive domains in this subtype were significantly lower than those in healthy individuals. Ho et al. [18] found the “Preserved group” subtype and six neurocognitive domains of which, four were lower than those of healthy individuals. Therefore, our findings are consistent with those of the previous studies. Rodriguez et al. [19] examined 67 individuals with first-episode schizophrenia and identified three subtypes, with two having deficits in more than one domain and one having deficits in all six domains compared to those of healthy individuals. Considering this, the profiles with decline in one or more neurocognitive domain functions may be observed from the disease onset.

Second, spatial attentional dysfunction was observed in all the clusters. Several studies have reported that individuals with schizophrenia show impaired or delayed reaction times compared to those of healthy individuals during spatial scanning tasks [20, 21]. Furthermore, Canu et al. [22] compared visual scanning in individuals with schizophrenia, attention-deficit/hyperactivity disorder, and autism spectrum disorder, and healthy controls and found that a delay in reaction time could distinguish schizophrenia from other conditions. Studies have found that impairments in spatial attention and scanning may be disease specific [23]. Therefore, a delay in spatial attention was common among all cognitive subtypes in this study. To the best of our knowledge, this is a novel finding as no study has used the spatial attention task to explore cognitive subtypes.

Third, our study found two subtypes (clusters 3 and 4): selective impairment and selective hyperfunction. Cluster 4, which comprised 23.3% of participants, showed impairments not only in accuracy of working memory, learning, and spatial attention but also in hyperfunctions in speed of processing, visual attention, and reaction time of working memory. Ho et al. [18] examined neurocognition in outpatients and found that even preserved groups had impaired memory, motor tasks, fluency, and symbol cording. Rangel et al. [24] examined neurocognition in outpatients and found four clusters of memory and executive impairment subtypes. Rodriguez et al. [19] found a cluster of impaired selective domains which included memory and working memory. In this study, Cluster 4 constituted the majority of outpatients. Considering the above, the cluster showing impairments in both working memory and learning in this study was consistent with the findings of previous studies. As for domains with hyperfunction, Helldin et al. [25] examined 291 patients and found that 24% and 18% had above average working memory and speed of processing, respectively, while healthy controls had average levels of both. Miskowiak et al. [26] examined clusters by neurocognitive profiles and found that the intact group outperformed in working memory. Furthermore, Rodriguez et al. [19] found one of three subtypes that coexisted not only in impaired learning but also in hyper-functional vigilance compared to that of healthy individuals. Villa et al. [27] examined the children of patients with schizophrenia, grouped their neurocognition into three clusters, and found that the children had high attention and working memory performance. Our findings are concordant with those of previous studies that reported high working memory performance and processing speed as common features in patients with mild disease severity and their children.

Cluster 3 had impairment only in spatial attention. Rangel et al. [24] explored subtypes based on cognition and emotional cognition but not spatial attention and found four subtypes of which, one did not have any impairment. This suggests that a subtype exists that maintains neurocognitive levels.

4.1. Limitations. This study had several limitations. First, owing to its cross-sectional design, it could not be clarified whether this subtype structure is stable over a long period. Future longitudinal studies are needed to confirm these results using data from participants in various institutions across the country.

4.2. Conclusion. This study explored the neurocognitive subtypes of schizophrenia, included spatial attention for the first time, and found four subtypes: severe impairment, moderate impairment, only spatial attention impairment, and memory and spatial attention impairment. Nursing and rehabilitation strategies for individuals with schizophrenia should be designed according to these four subtypes.

4.3. Implications for Nursing Practice. Psychiatric nursing for people with schizophrenia has two main strategies: interventions for enhancing their abilities such as neurocognition and interventions to compensate for neurocognitive function impairment. Both care strategies should be developed using the four neurocognitive profiles found in this study.

Care aimed at compensating for neurocognitive dysfunction, such as spatial attention, is a fundamental aspect of patient care. It should focus on environmental arrangements, such as placing target materials (e.g., medication for medication schedule reminders) in a location where patients naturally look, regardless of the subgroup [28].

For both severe and moderate subgroups, it is essential to provide individuals with adequate time to think and respond. This is crucial for compensating for their lower speed
of processing and memory function, preventing them from making mistakes or providing incorrect answers. Considering the high ratio of inpatients, communication or re-habilitation should be done gradually.

In the case of the memory and spatial attention impaired subgroup, their strengths, such as better attentional and vigilance function, can be utilised for compliance with cognitive training. This opens up the possibility to improve neurocognition significantly. Studies have shown that better neurocognitive function at baseline predicts higher adherence to participation in cognitive remediation therapy, and this high engagement in therapy is associated with improvements in neurocognition [29].

Among all the elements of cognitive remediation, discussions related to applying real-world settings have been linked to improvements in memory [30]. In addition, both physical exercise [31] and smoking cessation [32] are recognised as potent treatment strategies for improving working memory and learning, which are more impaired among this subgroup. Therefore, for this subgroup, it is recommended to facilitate their participation in cognitive rehabilitation and to modify their lifestyle to increase physical exercise and quit smoking.

Data Availability

Research data are not shared.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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References


