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Asian pearls

Enhancing attention and memory of individuals at clinical high risk for psychosis with mHealth technology

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ABSTRACT

Background: Cognitive impairment has adverse impact on the social and role functions of those at clinical high risk for psychosis and it has become an important target for intervention. Mobile health applications are user-friendly, real-time, personalized and portable in administering cognitive training and have promising application prospects in the field of mental health.
Methods: Eighty CHR subjects were randomized into an intervention group and a control group. CHR subjects of the intervention group performed attention and memory training via a Specific Memory Attention Resource and Training (SMART) application in their smart phones for 10 min per day, five days per week for three months. Both groups were followed up for three months. At baseline and follow-up phases, cognitive function was measured using the MATRICS Consensus Cognitive Battery (MCCB). In the follow-up, the intervention group completed the Mobile Application Rating Scale (MARS) to provide feedback to improve SMART.
Results: There is a significant group by time interaction effect in the Attention/Vigilance domain, which is significantly better in the intervention group than in the control group at 3- month follow-up. The improvement in Attention/Vigilance in the intervention group is significantly related to the amount of cognitive training time. Global Assessment of Function (GAF) reduction rate at baseline could predict the improvement of Attention/Vigilance. MARS results indicate that CHR subjects were receptive of SMART.
Conclusion: Mobile technology can be applied to improve cognitive function of CHR individuals, especially in the Attention/Vigilance domain.

1. Introduction

Neurocognitive studies in the clinical high risk for psychosis (CHR) patients have consistently demonstrated small-to-medium impairments across most neurocognitive domains – attention/vigilance, working memory, processing speed, visual learning, verbal learning, and reasoning (Bora et al., 2014; Carrión et al., 2011; Fusar-Poli et al., 2012; Giuliano et al., 2012; Lencz et al., 2006; Wood, 2010; Zheng et al., 2018). Moreover, CHR individuals who convert to psychosis show more severe neurocognitive deficits at baseline than non-converters in nearly all domains (Bora et al., 2014; Fusar-Poli et al., 2012; Giuliano et al., 2012; Seidman et al., 2017; Velthorst et al., 2019; Woodberry et al., 2010). Psychiatric interventions (medication and psychotherapy) with CHR patients show some evidence of improving subthreshold psychotic symptoms. However, their cognitive performance remains impaired during illness progression, predicting poor occupational and functional outcome and conversion to psychosis (Ising et al., 2015; Preti and Cella, 2010; Sommer et al., 2016). Thus, cognitive enhancement or remediation has become a major goal of intervention of schizophrenia spectrum disorders.

With the rapid development of technology, computer-assisted cognitive remediation (CACR) shows improvement in

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neuropsychological functioning among schizophrenia patients with moderate effects on global cognition, and evidence of cognitive and social gains in CHR patients. Most common CACR includes Cognitive Remediation Therapy (Fan et al., 2017), Cognitive Enhancement Therapy (Eack et al., 2010), and Cognitive Adaption Training (Hansen et al., 2012). Targeted cognitive training (TCT) studies with CHR youth have evidenced significant cognitive and daily functioning improvement (Hooker et al., 2014; Nahum et al., 2014).

Expanding computer-assisted training techniques, mobile health (mHealth) technology has provided a new mode to conduct cognitive training. mHealth-based interventions among psychotic patients have yielded significant reduction in the severity of clinical symptoms, the number of acute inpatient admissions, drop-out rates, and increased treatment compliance (Ben-Zeev, 2012; Granholm et al., 2012; Schlosser et al., 2016). Regular follow-up treatment of specific clinical and cognitive symptoms using text messaging present the best risk/benefit ratio in a CHR population, improving social functioning (Oorschot et al., 2012; Torous et al., 2014) and reducing risk of transition to a primary psychotic disorder (Oorschot et al., 2012). An mHealth-based non-stigmatizing health technology that is well integrated into patients' everyday activities and that targets neurocognitive function can be a promising adjunctive preventive intervention for CHR individuals. Therefore, the purpose of our study was to examine if an mHealth application-Specific Memory and Attention in Real Time (SMART) could improve CHR patients' cognitive function. We also strived to seek users' feedback on SMART in order to improve its interface and function.

2. Method

2.1. Subjects

We recruited 80 CHR patients from 2017 to 2019 on a continuous basis in two hospitals in China: Shanghai Mental Health Center (SMHC) (n = 65) and Suzhou Guangji Hospital (n = 15). The recruitment and assessment procedures were the same across the two sites. The inclusion criteria were: 1) first time mental health help-seeker at either hospital, 2) male or female between ages 14 and 45, 3) meeting diagnostic criteria for a prodromal syndrome; If under the age of 19, meeting diagnostic criteria for Schizotypal Personality Disorder *or* the diagnostic Criteria for Prodromal Syndromes (COPS), 4) no prior psychiatric treatment, 5) no DSM IV Axis I mental retardation, or affective psychoses or psychosis NOS, 6) no DSM IV Alcohol or Drug Dependence in the past 3 months and no use on the day of assessment – clearly not high or hung-over, 7) not having taken any medication that could affect cognitive function or psychotropic drugs, 8) no current or past HIV infection, 9) IQ > 69, 10) no past or current history of a clinically significant central nervous system disorder that may contribute to prodromal symptoms or confound their assessment, 11) no history of Traumatic Brain Injury that was rated as 7 or above on the Traumatic Brain Injury screening instrument (signifying a significant brain injury with persistent sequelae), 12) no visual or hearing impairment, or 13) no other issues that researchers deemed not fit for this project.

The study protocol was approved by the ethic committee of Shanghai Mental Health Center, and informed consent was obtained from each participant. This trial had been registered at Chinese Clinical Trial Registry (ChiCTR2000031741).

2.2. Instruments

2.2.1. Diagnosis, symptom and cognition assessment

CHR patients were identified by a panel of clinicians using a validated Chinese version of the Structured Interview for Prodromal Symptoms (SIPS) (Miller et al., 2003; Zheng et al., 2012). Psychotic symptoms were assessed using the Scale of Prodomal symptoms (SOPS) in the SIPS. Cognitive domains were measured by a validated Chinese version of MATRICS Consensus Cognitive Battery (MCCB) (Shi et al., 2015).

2.2.2. Specific memory and attention in real time (SMART) application

The SMART application was modified based on an existing application, Learn, Assess, Manage, Prevent (LAMP) (Torous et al., 2019) by researchers from Florida A&M University, Beth Israel Deaconess Medical Center, Shanghai Mental Health Center, and a technology company located in New Hampshire. SMART1.0 is available in both android and IOS versions. For this present study, subjects used the IOS version either with their own phones or ones borrowed from the researchers. SMART is available in both English and Chinese.

SMART consists of five sections: "S" provides user guides on how to use this APP, seek immediate support, and provides user information. "M" includes symptom survey, test environment, health data, and cognitive games. We used cognitive games to conduct cognitive training in our study. There are nine memory games (n-back, spatial span, simple memory, series 7, visual spatial tasks, digit span forward and backward, cats and dogs, time series, and n-back new) and five attention games (trails B new, trails B, jewelry A, jewelry B, and 3 D image). "A" provides a fun scratcher game to increase user interest. "R" allows researchers to increase item difficulty. "T" displays user training results, including scores, training time, and ranking.

2.2.3. Mobile application rating scale (MARS)

MARS is a 20-item scale used to rate mobile health applications on four key criteria: aesthetics, engagement, functionality, and information, as well as a final section on potential impact on a user's knowledge, attitudes, and intention to change (Stoyanov et al., 2015). MARS has been validated in different countries with appropriate psychometric properties. MARS uses likert-scale format (e.g., 1 = not satisfactory to 5=excellent). MARS total score is the sum of the average scores of the four key criteria. With written permission of the authors, we translated MARS into Chinese following international translation standards (Bracken and Borona, 1991). The sample Cronbach alpha was 0.87.

3. Procedure

3.1. Research design

At baseline, trained clinician researchers conducted MCCB assessment with all CHR subjects, who were then randomly assigned to either the SMART intervention group (n = 40) or the control group (treatment-as-usual) (n = 40), according to the random number table. The information of group allocation was kept blind to the MCCB and the SIPS assessment personnel. The SMART group practiced the cognitive games 10 min per day, five days per week for three months. Daily total time and total scores were recorded on the server side, which allowed researchers to monitor subjects' daily SMART activities. Subjects in the control group did not receive SMART training and were treated in their natural settings. Nevertheless, researchers maintained weekly contact with them to attempt to keep the same contact frequency as the intervention group. At 3-month follow-up, all subjects completed MCCB assessment for cognitive function, and the intervention group also completed MARS survey for user attitude and feedback to SMART. Please refer to Fig. 1 for study flowchart.

3.2. Statistical analyses

We used SPSS 26 to conduct data analyses. Chi-square analysis was used to examine the association between categorical variables. For continuous variables, we first examined distribution by Shapiro-Wilk. When scores were normally distributed, a repeated measurement analysis of variance (ANOVA) test was used to examine the interaction of group by time, independent sample t tests were used to examine between group differences, and paired sample t tests to examine within group differences. For non-normal distribution, median numbers were

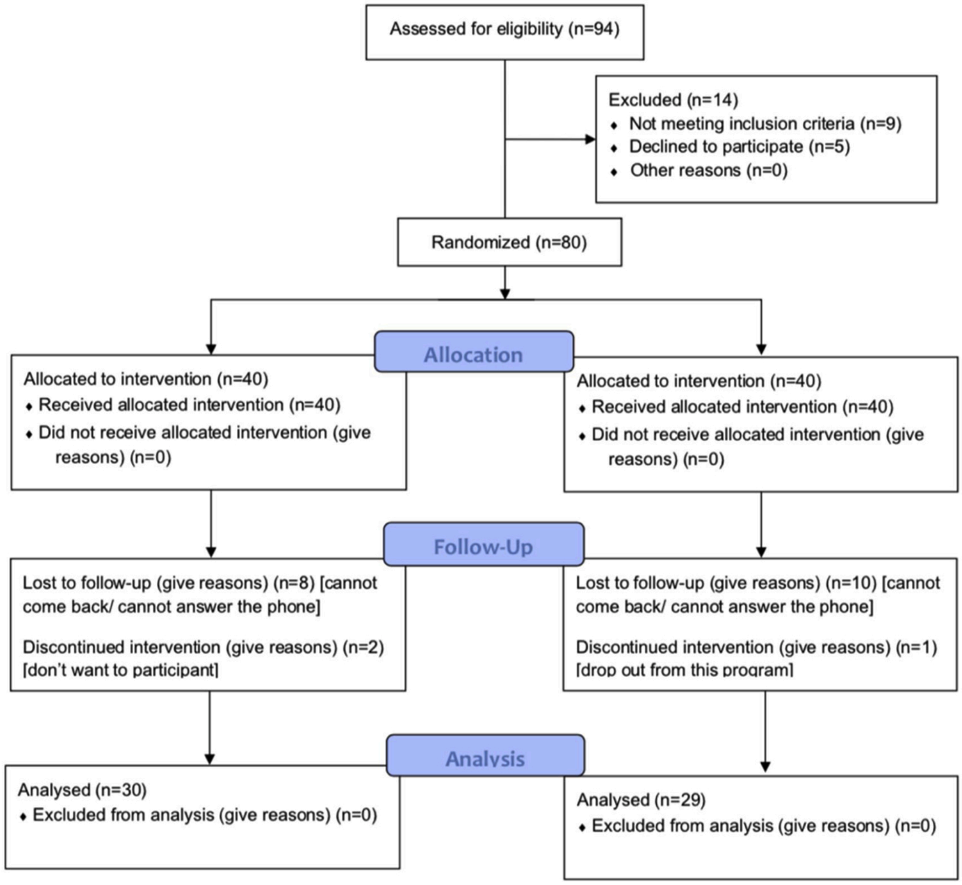

Fig. 1. Study flowchart.

used. Mann-Whitney U tests were used to compare between group differences and Wilcoxon tests for within group differences. Spearman correlation was used to examine the relationship between SMART training time and cognitive function change.

4. Results

4.1. Subject information

The age range of the 80 subjects was 14–38 (M = 20.51, SD = 5.89), with 40 in the SMART intervention group and 40 in the control group. Subjects' education level ranged from primary school to university, with average years of education at 11.54 years (SD = 2.80). Seventy-six subjects were right-handed, 36 of them were in the intervention group and 40 in the control group. No significant differences were found between subjects in the two groups for gender distribution ($\chi^2 = 0.050$, $p = 0.823$), education ($Z = -0.480$, $p = 0.631$), or handedness ($\chi^2 = 2.368$, $p = 0.124$).

Twenty-one (10 intervention group, 11 control group) subjects were lost in the three-month follow-up. Fifty-nine subjects remained, 30 (15 males, 15 females) in the intervention group and 29 (16 males, 13 females) in the control group. Reasons for attrition include refusal to be evaluated at the follow-up with no specific explanation (n = 8), inconvenient time or remote location (n = 11) and change of contact information (n = 2). No significant differences were found between the CHRs at recruitment (n = 80) and those who successfully finished the follow-up (n = 59) in either the SIPS/SOPS, GAF, or MCCB scores (Table 1).

Table 1
Demographic, Clinical Background Information, and Cognitive Function of All Subjects in Baseline.

	Recruitment	Followed	*F* (*p*)
N	80	59	——
Gender (m/f)	39/41	31/28	1.294(ns)[a]
Age (years)	20.51(5.89)	20.20(5.85)	0.094(ns)
SOPS-P	8.08(4.25)	8.56(4.32)	0.435(ns)
SOPS-N	11.16(6.26)	11.53(6.08)	0.117(ns)
SOPS-D	4.19(2.93)	4.39(2.99)	0.159(ns)
SOPS-G	7.00(3.99)	7.46(4.10)	0.437(ns)
GAF	58.52(8.78)	58.61(9.11)	0.3(ns)
GAF-drop	.23(0.13)	0.23(0.14)	0.1(ns)
MCCB-SoP	48.99(10.50)	50.46(9.90)	0.698(ns)
MCCB-AV	46.83(10.97)	47.71(10.21)	0.235(ns)
MCCB-WM	44.40(11.43)	45.77(10.97)	0.512(ns)
MCCB- Vrbl Lrng	45.13(11.30)	45.98(11.00)	0.200(ns)
MCCB- Vis Lrng	50.86(9.05)	51.42(9.13)	0.130(ns)
MCCB -RPS	53.05(9.39)	53.75(9.00)	0.193(ns)
MCCB -Neurocog Comp	47.41(10.47)	48.78(10.09)	0.597(ns)

a: Pearson Chi-square test.
ns = no signification.
Sop: speed of processing; AV: attention/vigilance; WM: working memory; Vrbl Lrng: verbal learning; Vis Lrng: visual learning; RPS: reasoning and problem solving; SC: social cognition; Neurocog Comp: Neurocognition Composite score; Overall Comp: Overall Composite score.
[a] Mann-Whitney *U* test.

4.2. Clinical symptom and cognitive function changes by time

A 2 (two groups) by 2 (baseline and follow-up) repeated measures ANOVA was performed for SIPS positive, negative, disorganized, and general scores, which revealed no group by time interaction effects (Table 2). The repeated measures ANOVA was also performed for each domain score of MCCB. The results only showed a significant interaction between group and time in the Attention/Vigilance (AV) cognitive

Table 2
SOPS and Cognition Changes at Baseline and Follow-up.

	Intervention group (n = 30)		Control group (n = 29)		Repeated ANOVA		
	Baseline	Follow-up	Baseline	Follow-up	Group	Time	Group by Time
SOPS-P	7.57(4.49)	2.73(3.11)	9.59(3.95)	3.76(4.99)	68.354(ns)	69.815(0.000)	0.607(ns)
SOPS-N	10.43(6.38)	6.57(6.09)	12.66(5.63)	8.79(6.25)	2.977(ns)	17.403(0.000)	0.000(ns)
SOPS-D	3.97(3.02)	1.67(1.65)	4.83(2.95)	2.52(2.84)	2.311(ns)	31.873(0.000)	0.000(ns)
SOPS-G	6.67(4.48)	2.33(3.04)	8.28(3.55)	3.24(3.23)	46.718(ns)	60.279(0.000)	0.338(ns)
GAF	60.03(10.46)	70.47(10.16)	57.32(7.42)	65.18(11.95)	3.672(ns)	30.545(0.000)	0.606(ns)
GAF-drop	0.19(0.18)	0.19(0.22)	0.26(0.09)	0.15(0.23)	0.044(ns)	3.988(ns)	4.668(0.035)
MCCB-SoP	51.33(9.54)	58.77(7.53)	49.55(10.35)	55.17(7.97)	1.619(ns)	45.874(0.000)	0.885(ns)
MCCB-AV	45.93(11.19)	56.45(8.80)	49.31(9.15)	51.28(8.31)	0.182(ns)	22.764(0.000)	10.684(0.002)
MCCB-WM	46.80(10.81)	52.87(10.34)	44.72(11.22)	48.59(9.40)	1.927(ns)	11.247(0.001)	0.554(ns)
MCCB-Vrbl Lrng	45.43(10.38)	51.10(6.89)	46.55(11.78)	48.83(8.66)	0.085(ns)	6.818(0.012)	1.243(ns)
MCCB-Vis Lrng	51.47(8.98)	59.43(7.44)	51.38(9.44)	55.66(9.41)	0.853(ns)	40.341(0.000)	3.666(ns)
MCCB -RPS	54.80(7.89)	62.30(7.08)	52.66(10.04)	60.07(6.91)	1.602(ns)	39.073(0.000)	0.001(ns)
MCCB – Neurocog Comp	49.24(9.89)	59.07(7.23)	48.52(10.55)	54.14(7.09)	2.029(ns)	46.482(0.000)	3.447(ns)

domain ($F = 10.684$, $p = 0.002$). The post hoc test found that, while the two groups did not differ in Attention/Vigilance (AV) at baseline ($t = -1.187$, $P>0.05$), the intervention group did better than the control group at 3-month follow-up ($t = 2.3$, $P = 0.025$). There is also an interaction of group by time on GAF-drop ($F = 4.668$, $P = 0.035$). Nevertheless, the post hoc test did not detect a significant group difference either at baseline or at follow-up.

4.3. SMART training time effect

We collected SMART training time of the intervention group on the server and calculated training time for attention and memory games, respectively, as well as total training time. The average attention training time over three months was 7.44 h (SD = 6.63), memory training time 1.81 h (SD = 1.67), and total training time 9.25 h (SD = 8.18).

Spearman correlation was used to examine the relationship between SMART training time and cognitive function change. Cognitive improvement is defined as follow-up cognitive scores minus baseline scores > 0, a score < = 0 indicates no cognitive improvement over the three months. Results (Table 3) show that Attention/Vigilance score is significantly correlated with attention, memory, and total training time.

We further examined if the Attention/Vigilance change score was associated with demographic information, SOPS symptoms, and cognitive training time. We found that attention training time ($Z = -2.091$, $p = 0.037$), total training time ($Z = -2.127$, $p = 0.033$), and GAF reduction rate($Z = -2.845$, $p = 0.004$)significantly contributed to the significant score change following SMART intervention. When demographic information, SOPS symptom scores (P > 8, or < = 8; N > 11 or < = 11; D > 3 or < = 3; G > 6 or < = 6), GAF reduction rate, and total training time were taken as covariates and Attention/Vigilance score change as dependent variable, the result indicates that only the GAF score decline has predictive value for Attention/Vigilance score improvement ($\beta = -14.233$, Wald = 6.094, $p = 0.020$, 95 %CI[0.000, 0.101]), the more GAF score decline at the baseline, the less score improvement at the 3-month follow-up.

Table 3
Correlations Between Training Time and Cognitive Improvement Scores.

Cognitive Domain	Attention Training Time	Memory Training Time	Total Training Time
SoP	0.143	0.159	0.140
AV	0.349**	0.366**	0.357**
WM	0.106	0.109	0.101
Vrbl Lrng	0.093	0.066	0.090
Vis Lrng	0.270	0.287	0.263
RPS	0.012	0.014	0.003
SC	0.338	0.233	0.310
Neurocog Comp	0.164	0.174	0.158
Overall Comp	0.142	0.139	0.134

4.4. SMART feedback based on MARS results

Subjects in the intervention group completed MARS at the 3-month follow-up to provide feedback, which will be used to improve SMART in the future (Table 4). Regarding Engagement, subjects reported that SMART could attract the user for a short period of time (five minutes), but it did not allow sufficient customization and interaction. Subjects indicate that SMART has good overall functioning, with clear instruction; and it is easy to learn and navigate. Relative to Aesthetics, the layout and design received higher scores than visual appeal. Subjects gave the Information domain the highest rating. Furthermore, the visual information score is among the highest of all areas measured, indicating that the visual explanations of concepts through charts, graphs, and images in SMART are clear, logical, accurate, and trustworthy.

5. Discussion

To our knowledge, this is among the first randomized clinical trials to examine the effectiveness of a smart phone application with

Table 4
SMART Quality Rating Distribution Based on MARS Results.

	Lowest Score	Highest Score	Average Score	Middle Score
Part1-Engagement	1.40	4.60	2.78	2.80
Entertainment	1.00	5.00	2.94	3.00
Interest	1.00	4.00	2.78	3.00
Customization	1.00	5.00	2.31	2.00
Interactivity	1.00	5.00	2.19	2.00
Target Group	1.00	5.00	3.66	4.00
Part2-Functionality	2.50	5.00	3.99	4.00
Performance	1.00	5.00	3.72	4.00
Simplification	1.00	5.00	4.03	4.00
Navigation	2.00	5.00	4.13	4.00
Gestural design	2.00	5.00	4.09	4.00
Part3-Aesthetics	2.00	5.00	3.67	3.33
Layout	2.00	5.00	3.84	4.00
Graphics	2.00	5.00	3.84	4.00
Visual attraction	1.00	5.00	3.31	3.00
Part4-Information	2.67	5.00	4.30	4.33
Quality of information	3.00	5.00	4.28	4.00
Quantity of information	3.00	5.00	4.13	4.00
Visual information	2.00	5.00	4.50	5.00

gamification features on the improvement of cognitive function in CHR individuals. The results at the 3-month follow-up indicate Attention/Vigilance of CHR subjects in the intervention group improved significantly, in comparison with the control group. Furthermore, the improvement in Attention/Vigilance domain is significantly correlated with the training time for those CHRs who directly participated in this m-health intervention.

Our results are consistent with numerous studies using mhealth technology except Piskulic et al. (2015), who did not find significant differences between the two groups of CHR after 10–12 weeks of computer-based training. Hooker et al. (2015) reported that their CHR subjects had significant improvement in processing speed, trend-level improvement in visual learning and memory and overall cognitive function. The CHR subjects in the targeted intensive auditory cognitive training group showed a significant improvement in Verbal Memory compared to the control group (Loewy et al., 2016). In addition, Choi et al. (2017) used pupillometer-based neurofeedback cognitive training to improve processing speed and social functioning in CHR individuals. These researchers found that, in comparison with the scores of the baseline and the control group, the training group showed faster motoric and nonmotoric processing speed, as well as social cognition at 2-month follow-up. Therefore, cognitive training provided by smartphone application (our study), computers (Hooker et al., 2014; Loewy et al., 2016) or tablets (Choi et al., 2017) seem to be effective in improving some targeted domains of CHR cognitive functions, with smart phones having the advantage of mobility and easy access.

Furthermore, we examined if training time affected attention and memory function. The results indicate that only the Attention/Vigilance score, not the memory scores, was significantly related to training time. This may be related to the time that subjects spent on memory training. Compared to an average of 7.44 h of attention training, the average length of the CHR subjects' memory training was only 1.81 h, which could have contributed to the differential results. This finding is consistent with those of the application usage effect in the existing literature (Enrique et al., 2019; Mattila et al., 2016), which suggest that more frequent and longer engagement in an application tends to generate better results. Potentially, subjects spent more time on the five attention games and less time on the nine memory games because the attention games are more interactive and engaging. This may have increased the subjects' desire to play more, consequently increasing the likelihood of earning higher scores, which serve as positive reinforcement. Alternatively, many of the memory games (N-Back, Visual Span, Digit Span) may not be as interesting and may be more challenging to complete. Subjects, therefore, would spend more time on the attention games than the memory ones. Another possible explanation is that when CHR patients are challenged with working memory tasks, they may tend to discontinue engagement.

Our results also indicate that GAF decline is a risk factor for the improvement of CHR's attention. The larger the difference between the highest GAF in the past year and the current GAF scores, the less likely a CHR subject's Attention/Vigilance score would improve from baseline to 3-month follow-up. Dysfunction in overall functioning/GAF, may be associated with systemic pathology and potentially impair cognitive processing (Marin et al., 2011).

Consistent with existing findings, our study illustrates that a mobile phone application is effective for cognitive function training in CHR individuals. Using mhealth applications to enhance cognitive ability may help prevent and even possibly reverse the progression of illness, simultaneously reducing the risk of mental health stigma and side effects of antipsychotic medication. Furthermore, mhealth applications may help break regional barriers, while introducing an entertaining and noninvasive training in real time.

The CHR subjects in our study affirm the functions of SMART. They report that SMART is easy to learn and understand; and it has a simple design, clear and accurate information, and appealing graphics. They have also pointed out areas for improvement, e.g. interface presentation, interaction, and engagement. Nonetheless, most CHR subjects in the intervention group indicate they will continue to use SMART. SMART, as a serious game with an education and training purpose, is different from entertainment mobile games. Serious games tend to be less engaging (Freire et al., 2016) than well-liked popular games such as King of Glory, Peace Elite, Miracle Warm and Warm, and Yin and Yang division, which are competitive, rich in plot, vivid in picture, and emotionally charged. Although serious games serve different purposes from entertainment games, future SMART design can integrate features of the popular games, by increasing plots, introducing character competition, and presenting training contents in a more vivid and interactive format. Furthermore, SMART can also be connected to wearables to record CHRs physiological indicators such as heart rate, steps, sleep, and medication adherence. It can also be attached to existing applications, such as WeChat, Snapchat, or WhatsApp, which can send health information to individuals in a timely manner.

6. Conclusion

The cognitive deficits of CHR individuals could be improved through mobile technology. SMART can be applied to improve cognitive function of CHR individuals, especially in the Attention/Vigilance domain. Given the early indication of effectiveness of SMART and user feedback, it is possible to improve serious games inside smartphone applications with better design and more engaging activities (Lau et al., 2017). As smartphones continue to become faster and more affordable, smartphone applications like SMART may ultimately lead to scalable and cost-effective digital treatments for CHR patients. Thus, in the near future, it is anticipated that smartphone-based interventions, such as SMART, may be adopted within health care systems (Camacho et al., 2020).

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Declaration of Competing Interest

The authors report no declarations of interest.

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