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Validation of the cognitively normal range and below normal range subtypes in chronically hospitalized patients with schizophrenia

Shih-Kuang Chiang [a,*], Ching-Huan Ni [a,1], Chih-Pu Tsai [b,2], Keng-Chang Lin [c,3]

[a] Department of Counseling and Clinical Psychology, National Dong Hwa University, No. 1, Sec. 2, Da Hsueh Rd., Shoufeng, Hualien, 97401, Taiwan (R.O.C)
[b] Department of Psychiatry, Kaohsiung Armed Forces General Hospital, No.2, Zhongzheng 1st. Rd., Lingya District, Kaohsiung City 80284, Taiwan (R.O.C)
[c] Department of Clinical Psychology, Kaohsiung, Municipal Kai-Syuan Psychiatric Hospital, No.130, Kaisyuan 2nd Rd., Lingya Dist., Kaohsiung City 80276, Taiwan (R.O.C)

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ABSTRACT

Background: Many studies have found a substantial minority of patients whose performance puts them within the normal range of neuropsychological functioning. Recently, a study has seen the delineation of two neurocognitive subtypes of schizophrenia –'cognitively normal range' (CNR) and 'below normal range' (BNR) – based on neurocognitive performance across multiple domains.
Methods: The participants were from two studies that collected neurocognitive, psychopathology and social function data between 2008 and 2015. In total the complete data from one hundred and thirty one patients of Han Chinese ethnicity with schizophrenia were collected on 21 neurocognitive indexes (assessing the domains of processing speed, attention, working memory, verbal memory, visual memory, reasoning and problem solving and IQ). Fifty-five patients of the one hundred and thirty one participants received additional ratings on their psychopathology and social functions. An exploratory graphic analysis was conducted on the neurocognitive measures for the entire sample. Difference analyses were also performed according to the aims of the study using the Independent *t* test, Chi-square test, and Cohen's d effect size.
Results: Analyses revealed the existence of two patients subtypes. The post hoc tests showed that there were significant differences on all of their neurocognitive measures and on most of the psychopathology and social functions between the two subtypes. These two subtypes could be referred to as the CNR subtype and the BNR subtype respectively.
Conclusions: There are neurocognitive subtypes of schizophrenia with differential illness characteristics comparable with the CNR and the BNR in patients of Han Chinese ethnicity with schizophrenia.

1. Introduction

Schizophrenia is a devastating and chronic neuropsychiatric disorder that affects nearly 1% of the world's population (Dhindsa and Goldstein 2016). Much of the evidence shows that cognitive deficits in schizophrenia are heterogeneous, ranging from pervasive generalized dysfunction through patchy focal disorders to mild focal deficits or nearly normal performance (Chapman and Chapman 1989; Gould et al. 2014; Elliott and Sahakian 1995; Jæger et al. 2003; Badcock et al. 2005; Nuechterlein et al. 2004; Wilk et al. 2005). In addition, evidence from cross-sectional (Green 1996; Harvey et al. 1998; Leung et al. 2008) and longitudinal studies (Green et al. 2004) has consistently shown that cognitive impairment in schizophrenia is a more stable and robust correlate of functional impairment than clinical symptoms. Because the ultimate aim of cognitive enhancement is to support functional recovery, cases where neuropsychological (NP) performance is normal may lead to these cases being regarded as having minimal intervention potential (Leung et al. 2008). In the study by Leung et al. (2008), they found that NP normal cases still show deficits in several domains of everyday functioning milestones. Hence, they thought the classifications of NP normality may provide a meaningful categorization for the concept of outcome in the recovery model. In addition, a population-representative longitudinal study found that NP normal cases showed a decline on the digit symbol

* Corresponding author at: Department of Counseling and Clinical Psychology, National Dong Hwa University, No. 1, Sec. 2, Da Hsueh Rd., Shoufeng, Hualien 97401, Taiwan, (R.O.C). Tel.: +886 3 8635104; fax: +886 3 8635300.
E-mail addresses: skchiang@mail.ndhu.edu.tw (S.-K. Chiang), felix200095@yahoo.com.tw (C.-H. Ni), fromzero25@hotmail.com (C.-P. Tsai), linkengchang@gmail.com (K.-C. Lin).
[1] Tel.: +886 3 8635104; fax: +886 3 8635300.
[2] Tel.: +886 7 7496751x726191; fax: +886 7 7496751.
[3] Tel.: +886 7 7513171x2227; fax: +886 7 7712494.

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coding test, suggesting that a decline in processing speed is a core feature of schizophrenia (Meier et al. 2014). These results suggest that identification of NP normality could reduce the likelihood of false negative judging in their outcomes. Recently, Heinrichs et al. (2015) validated two neurocognitive subtypes of schizophrenia using the MATRICS Consensus Cognitive Battery (MCCB), for which the criteria for assignment to cognitively normal range (CNR) groups were based on previous studies using MCCB (Kern et al. 2004, 2011; Muharib et al. 2014).CNR schizophrenia patients may be largely indistinguishable from normal-range controls, with the exception of processing speed performance. In contrast with CNR, below normal range (BNR) may be indistinguishable from low-performing controls even in terms of processing speed.

Based on the findings of the aforementioned studies, it is reasonable that we hypothesize the same neurocognitive subtypes of schizophrenia with differential illness characteristics in patients of Han Chinese ethnicity with schizophrenia. Unfortunately, we could not find any published empirical papers to examine this hypothesis. The aim of this study was to validate the CNR and BNR subtypes in chronically hospitalized patients with schizophrenia.

2. Materials and methods

2.1. Participants

The sample came from two studies. From one part of the sample, 76 subjects were recruited from a study on cognitive impairment in stable, hospitalized patients with schizophrenia (the Cognitive Function study), whereas from another part of the sample, 55 subjects were recruited from a study on the follow-up of mental functions in stable, hospitalized patients with schizophrenia (the Mental Function study). The criteria of inclusion and exclusion of the subjects were the same in both studies. In total, 131 patients of Han Chinese ethnicity with schizophrenia, aged 20–65, who had been diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) participated in this study. Subjects were excluded from this study if their scores on the Mini Mental Status Examination (MMSE) were below 20, if they refused to receive the evaluation or had an acute psychotic episode that required transfer for admission, or if they had the presence of an organic brain disorder, brain injury with post-traumatic amnesia, mental retardation, movement disorders, or recent (within 6 months) substance dependence or electroconvulsive therapy.

2.2. Measures

Six cognitive domains according to MATRICS-NIMH suggestions about the fundamental dimensions of cognitive deficit in schizophrenia (Nuechterlein et al. 2004) were included in this study. The seventh cognitive domain, IQ, suggested by Genderson et al. (2007), was also included. In addition, to judge if a patient's basic cognitive function was qualified as a subject for taking various tests reliably in this study, we also administered a screen test.

We selected the tests for measuring seven different cognitive domains, and we constructed them by referencing the suggestions and the results in Nuechterlein et al. (2004). The final results of the test selection in this study were:1) the Speed of Processing: the Digit Symbol Substitution Test (DSS) in the Chinese Version of the Wechsler Adult Intelligence Test, Third Version (CV-WAIS-III) (Chen and Chen 2002) and the A Form and the B Form of the Trial Making Test (TMA & TMB) (Lezak et al. 2004); 2) the Attention: the Conners Continuous Performance Test, 3rd Edition (Conners CPT 3) (Conners 2014); 3) the Working Memory: the Working Memory Index (WMI) in the CV-WAIS-III; 4) the Verbal Memory: the Logistic Memory Test (LG) in the Chinese Version of the Wechsler Memory Test, Third Version (CV-WMS-III) (Hwa et al. 2005); 5) the Visual Memory: the Visual Reproduction (VR) Test in the CV-WMS-III; 6) Reasoning and Problem Solving: the Modified Card Sorting Test (MCST) (Nelson 1976) and the Semantic Associated Verbal Fluency Test (SAVFT) (Hwa 1999); 7) the Full-Scaled IQ (FSIQ), which is a short-form version of the CV-WAIS-III composed of four subtests including the Information, the Arithmetic, the Digit Span, and the Block Design (Chiang et al. 2007). The basic cognitive function was assessed with the Chinese version (Guo et al. 1988) of the Mini-Mental State Examination (MMSE) (Folstein et al. 1975). A total of 21 measured cognitive indexes were used as variables for the partitioning of neurocognitive subtypes.

Psychopathology was assessed with the Chinese version (Cheng et al. 1996) of the Positive and Negative Syndrome Scale (CV-PANSS) (Kay et al. 1987). Regarding social function, the Chinese version of the Social Function Scale (CV-SFS) was used to assess the seven dimensions of the social function of subjects including withdrawal, interpersonal, independence-competence, independence-performance, pro-social, recreation, and employment (Song 2001).

2.3. Rating of NP impairment

Because there is no Chinese version of the MCCB in Taiwan, we could not follow the criteria for assignment to CNR and BNR, as was followed in the study by Heinrichs et al. (2015). We reviewed three strategies for the designation of impairment in the study of Reichenberg et al. (2009): the Individual Profile Rating (IPR) procedure presented by Kremen et al. (2000), the definition of Clinically Significant Cognitive Impairment (CSCI) suggested by Palmer et al. (1997), and the Global Deficit Score (GDS) approach adopted by Heaton et al. (2004) and Carey et al. (2004). We decided to use the GDS method as the criterion for validating the CNR and BNR according to the findings of previous studies, including: 1) the IPR was less sensitive to impairment (Reichenberg et al. 2009); 2) the GDS and CSCI criteria had substantial to outstanding convergence across all diagnostic groups (Reichenberg et al. 2009); and 3) the GDS method was relatively unaffected by modifications in test batteries (Heaton et al. 2004; Carey et al. 2004).

The GDS method begins by converting *T* scores to deficit scores that reflect the presence and severity of impairment. *T* scores greater than 40 represented no impairment (deficit score = 0), whereas a deficit score of 1 reflects mild impairment (*T* scores =39to 35), a deficit score of 2 reflects mild to moderate impairment (*T* scores =34 to 30), a deficit score of 3 reflects moderate impairment (*T* scores =29 to 25), a deficit score of 4 reflects moderate to severe impairment (*T* scores =24 to 20), and a deficit score of 5 reflects severe impairment (*T* scores <20). Deficit scores on all tests were then averaged to create the GDS. Results in Heaton et al. (2004) and Carey et al. (2004) showed that a GDS greater than or equal to 0.5 has accurately predicted the expert clinical rating of overall impairment. In this study, we adopted GDS 0.5 to be the cutoff of NP impairment.

2.4. Procedures

The Cognitive Function study began in September 2013 and was completed in August 2015. The study was approved by the Institutional Review Board of the Kaohsiung Municipal Kai-Syuan Psychiatric Hospital. All subjects were screened and verified by meeting the study criteria of two professionals with extensive experience in clinical practice and research (CSK, Ph.D., and LKC, M.Sc., both of whom are certified clinical psychologists). All neurocognitive function indexes were examined by two qualified clinical psychologists (NCH and TCP, both M.Sc.).

The Mental Function study began in July 2008 and was completed in June 2013. This study was approved by the Yuli Branch of the Taipei Veterans General Hospital Institutional Review Board. All

subjects were screened and verified by meeting the study criteria of one professional with extensive experience in clinical practice and research (CJY, M.D., certified psychiatrist). All neurocognitive function indexes were examined by one qualified clinical psychologist (CSK., Ph.D.). The psychopathology was rated by two certified psychiatrists (CJY and PLY). The inter-rater reliability for the CV-PANSS ($k = 0.85$) was established for both raters. The CV-SFS scores were provided by senior nurses who were in charge of the subjects, both of whom have received the required training for the CV-SFS from CSK before the study had begun. Written informed consent was obtained after the procedures were fully explained to the patients.

2.5. Statistical analysis

2.5.1. Generalized association plot (GAP)

We used GAP to explore the neurocognitive subtypes in 131 patients with schizophrenia. The GAP (Chen 1996, 1998, 1999; Lin et al. 1998) is an information visualization environment (http://gap.stat.sinica.edu.tw.autorpa.tcu.edu.tw) for extracting important information embedded in a raw data matrix and proximity matrices for variables as well as for subjects. Although factor analysis and cluster analysis are corresponding conventional statistical tools, respectively, to the GAP correlation matrix map and the Euclidean distance matrix map, there is no counterpart for the GAP data matrix map, which is the most important and unique feature of GAP. Factor analysis depends on a sophisticated statistical model to summarize information in the correlation matrix, but GAP merely utilizes the sorted correlation matrix map to reveal similar messages. The major difference is that GAP displays the whole correlation matrix and the raw data matrix without sacrificing any information (Hwu et al. 2002). There were two reasons we used the GAP in this study. First, the GAP provides five levels of integral information, and three matrix maps are integrated to retrieve these five levels of information. Second, Hwu et al. (2002) showed the usefulness of the GAP method in subgrouping Han Chinese ethnicity schizophrenic patients based on their PANSS ratings and clustering symptom-dimensions based on their relative PANSS scoring structure on admission. We believe that the rationale of the GAP method is also suitable for partitioning patients into subgroups according to their neurocognitive functions in the same social and cultural context.

2.5.2. Other statistical analyses

The Statistical Package for the Social Sciences (SPSS) was used for other statistical analyses. The Independent t test was used to test the differences in means, and the chi-square test was used to test the differences in frequencies between groups in the sample for individual indexes. The significance level for a two-sided test was set at $\alpha = 0.05$. For comparing seven cognitive domains with norms of normal controls, we computed Cohen's d effect size (Cohen 1988) for differences between each patient group's mean scores across individual indexes and cognitive domains. In addition, for validating the CNR and BNR in the sample, we also computed the GDS of each patient's group.

3. Results

3.1. Gap

Fig. 1 shows the order of 21 cognitive function indexes and two visible dark red blocks along the main diagonal of a correlation matrix map. When the patients' relationship structures represented by the Euclidean distance matrix were sorted, two blocks along the main diagonal were identified visually as Group 1 (54 cases) and Group 2 (77 cases).

3.2. Demographics, clinical characteristics, and description of individualized cognitive measures

The left-hand columns of Table 1 show the original data of the demographic features and the means and standard deviations from 21 cognitive function indexes of two groups sorted by the GAP. Except for gender ($x^2 = 0.34$, $p > .05$), education ($t = -1.01$, $p > .05$) and CPTd ($t = 0.38$, $p > .05$), there were significant differences between Group 1 and Group 2 in Age ($t = 2.21$, $p < .05$) and all other cognitive function indexes including MCST p ($t = 5.69$, $p < .001$), TMB ($t = 17.73$, $p < .001$), TMA ($t = 7.89$, $p < .001$), CPTp ($t = 3.54$, $p < .01$), LGTII ($t = -3.13$, $p < .01$), LGT ($t = -3.70$, $p < .001$), LGII ($t = -3.83$, $p < .001$), LGI ($t = -5.00$, $p < .001$), SAVFT ($t = -5.63$, $p < .001$), VRI ($t = -3.99$, $p < .001$), VRII ($t = -4.43$, $p < .001$), DSS ($t = -5.07$, $p < .001$), MCSTc ($t = -7.44$, $p < .001$), BD ($t = -5.92$, $p < .001$), WMI ($t = -9.01$, $p < .001$), DS ($t = -6.98$, $p < .001$), ARI ($t = -8.22$, $p < .001$), FSIQ ($t = -9.25$, $p < .001$), INF ($t = -6.89$, $p < .001$), and MMSE ($t = -7.70$, $p < .001$).

To verify whether the profiles of the neurocognitive function of Group 1 and Group 2 are comparable with the CNR and BNR of patients with schizophrenia, we transformed the original data in the left-hand columns into the Z-scores data presented in the right-hand columns of Table 1 by calculating adequate normal Taiwanese adult norms. The right-hand columns of Table 1 show the Z-score data of the means and standard deviations from 21 cognitive function indexes of two groups sorted by the GAP. Similarly, except for ($t = -.47$, $p > .05$), there were significant differences between Group 1 and Group 2 in all other neurocognitive function indexes.

Fig. 2 shows the recognizable profiles of neurocognitive function between Group 1 and Group 2. The right-hand columns of Table 1 further revealed Z scores with significant differences between CNR and BNR. For CNR, the absolute values of Z scores ranged from 0.34 of CPTd to1.29 of TMa, compared with Z scores of BNR from 0.26 of CPTd to 4.78 of MCSTp. Because the higher scores on MSCTp, TBa, TBb, CPTp indicated worse performance, we reversed the values of these indexes in Fig. 2 for the purpose of comparisons between CNR and BNR from an impairment view. Table 1 and Fig. 2 support Group 1 and Group 2 in this study and were comparable with CNR and BNR, respectively.

3.3. Description of social function, psychopathology, and other clinical features

Table 2 shows the original data of the demographic features and the mean and standard deviations of clinical features, psychopathology, and social function of this sample. There were no significant differences on gender ($x^2 = 2.64$, $p > .05$), Age($t = -.22$, $p > .05$), duration of illness($t = -1.78$, $p > .05$), chlorpromazine equivalents (CPZE) ($t = 0.62$, $p > .05$), negative symptoms ($t = 0.56$, $p > .05$), general symptoms ($t = -.56$, $p > .05$), CV-PANSS ($t = -.99$, $p > .05$), and interpersonal ($t = 1.82$, $p > .05$) between CNR and BNR. CNR was later than BNR on age at first onset ($t = 2.39$, $p < .05$), education ($t = 3.76$, $p < .001$), withdrawal score ($t = 2.71$, $p < .01$), independence-competence score ($t = 3.37$, $p < .01$), independence-performance score ($t = 4.33$, $p < .001$), recreation score ($t = 4.05$, $p < .001$), pro-social score ($t = 3.23$, $p < .01$), employment score ($t = 3.99$, $p < .001$), and CV-SFS score ($t = 4.32$, $p < .001$). BNR was higher than CNR on positive symptoms ($t = -2.39$, $p < .05$).

In comparison with the CNR, the BNR patients were older, and have an earlier illness onset, an increased severity of positive symptoms, and a greater severity of functional disability. According to the Taiwanese Schizophrenic Norms of CV-SFS, the scores of CV-SFS can be divided into four levels, reflecting the patient's level of social function. Scores above 71 are superior, with scores ranging from 70 to 52 being high, scores ranging from 51 to34 being middling, and scores below 33 being low. In this study, CNR with a mean score of

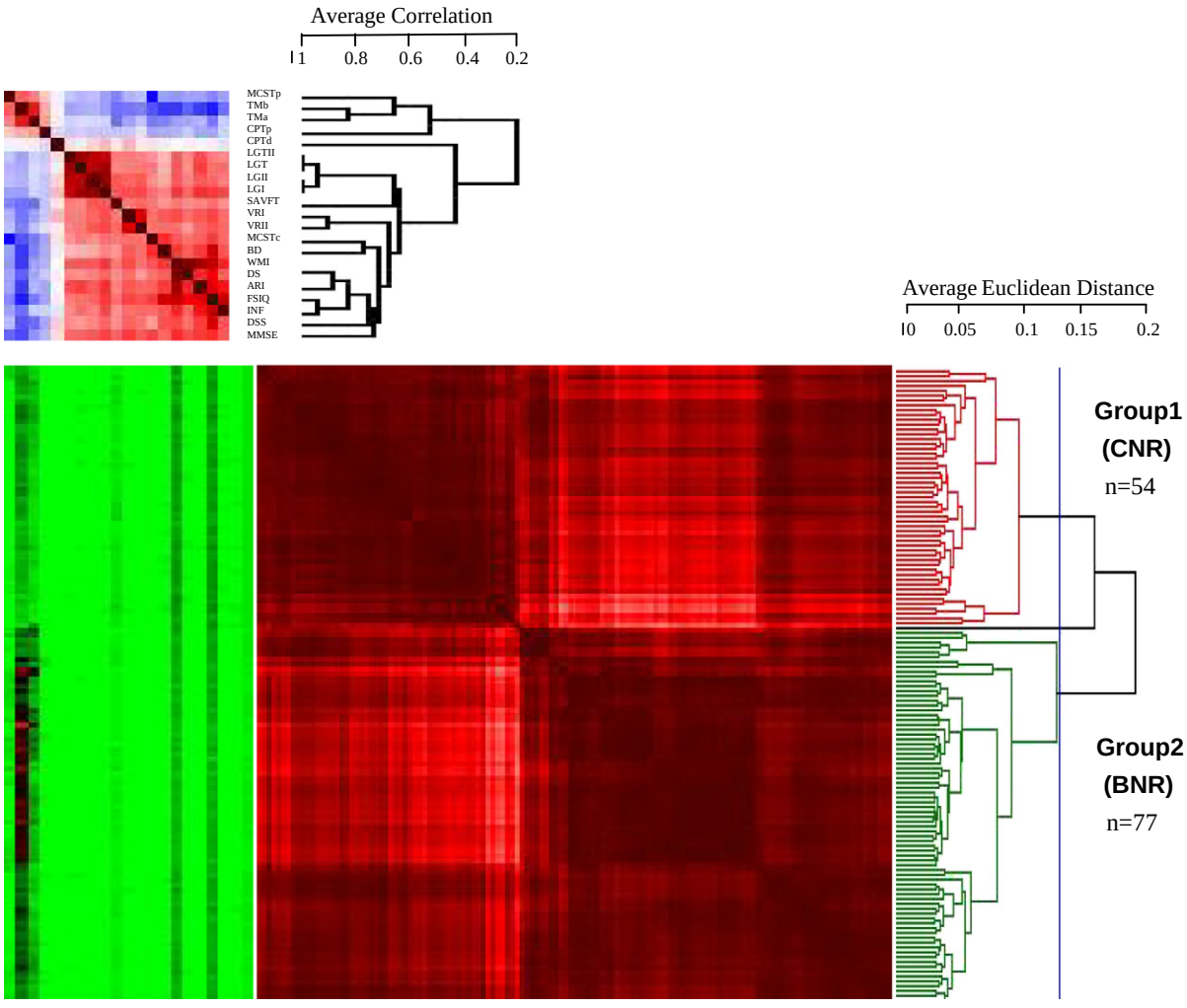

Fig. 1. Clustering of neurocognitive functions and schizophrenic patients using the generalized association plots (GAP). The proximity of between cognitive function correlation coefficients for 21 cognitive functions indexes is displayed as a color map in the upper figure. One hundred and thirty-one patients were ordered and displayed by GAP based on the matrix of between-patient Euclidean distance in the lower right figure. Two groups of patients were identified with their within-group distances summarized in a clustering tree. The Cognitively Normal Range (CNR) contains fifty-four patients and the Below Normal Range (BNR) contains seventy-seven patients. The raw cognitive functions data for 131 schizophrenic patients with 21 indexes were permuted using the aforementioned respective orders for cognitive functions and for patents, and then displayed as a color map in the lower left figure. The complete structure of cognitive functions and patients subgroups together with their interactions was jointly comprehended through visualization.

57.8 was at a high level, while in contrast, BNR with a mean score of 38.31 was in the middle level of social function.

3.4. Validation of CNR and BNR by Cohen's d effect size and the GDS

3.4.1. Cohen's d effect size of cognitive indexes and cognitive domains

For BNR patients, the effect sizes ranged from $d = 0.29$ to 2.26 across the16 individual indexes and from 1.12 to 2.39 across the seven cognitive domains. For CNR patients, the resulting effect sizes ranged from $d = 0.02$ to 1.01 across the 16 individual indexes and from 0.18 to 0.93 across the seven cognitive domains. Fig. 3 reveals the effect sizes pooled root mean square according to the cognitive domains across the two groups of patients.

3.4.2. The GDS

The same cognitive indexes were used to compute the GDS as were used to compute Cohen's d effect size. For BNR patients, *T* scores ranged from $T = 2.2$ to 52.6 across the 16 individual indexes. One cognitive index had deficit scores of 0, five indexes had deficit scores of 1, five indexes had deficit scores of 2, two indexes had deficit scores of 3, and three indexes had deficit scores of 5. The GDS of BNR is 2.25. For CNR patients, *T* scores ranged from $T = 37.1$ to 53.4 across the 16 individual indexes. Three cognitive indexes have deficit scores of 1, and thirteen indexes had deficit scores of 0. The GDS of CNR is 0.19.

4. Discussions

We applied GAP analyses to neurocognitive performance data from a median sample ($n = 131$) of chronically hospitalized patients with schizophrenia. The GAP analyses revealed the existence of two patient subtypes. The post hoc test using the independence t-test showed that there were significant differences between the two sub-types except for the CPTd index. Group 1 was characterized by severe neurocognitive impairments across all cognitive indexes except for the CPTd index and was referred to as the BNR subtype; in contrast, Group 2 displayed relatively better cognitive performance in comparison to the BNR subtype and was referred to as the CNR subtype. By means of an investigation of the magnitude of the cognitive domain, for BNR patients, the effect sizes across the seven cognitive domains were all higher than 1 ranging from $d = 1.12$ to $d = 2.39$. For CNR patients, the resulting effect sizes across the same cognitive domains were all lower than 1 ranging from $d = .18$ to $d =$

Table 1
Descriptive statistics of the 131 subjects sample.

	BNR	CNR	P value	BNR	CNR	P value
	Original Data			Z-score Data		
Sample size	77	54	–	77	54	–
Age	48.73 ± 10.82	44.50 ± 10.73	<0.05[a]	–	–	–
Education	10.74 ± 2.58	11.67 ± 2.95	>0.05[a]	–	–	–
Gender (male:female)	49:28	37:17	>0.05[b]	–	–	–
MCSTp	19.97 ± 14.66	7.04 ± 9.58	<0.001[a]	4.78 ± 4.07	1.15 ± 2.78	<0.001[a]
TMb	165.47 ± 20.15	92.24 ± 28.10	<0.001[a]	2.28 ± 0.46	0.56 ± 0.65	<0.001[a]
TMa	74.03 ± 17.82	49.37 ± 18.51	<0.001[a]	3.14 ± 1.30	1.29 ± 1.35	<0.001[a]
CPTp	5.81 ± 8.26	1.61 ± 3.34	<0.01[a]	3.27 ± 2.04	1.08 ± 1.96	<0.001[a]
CPTd	.62 ± .44	.60 ± .38	>0.05[a]	0.26 ± 0.93	0.34 ± 0.85	>0.05[a]
LGTII	5.66 ± 3.00	7.27 ± 2.77	<0.01[a]	−1.45 ± 1.00	−0.91 ± 0.92	<0.001[a]
LGT	5.31 ± 3.15	7.53 ± 3.69	<0.001[a]	−1.56 ± 1.05	−0.82 ± 1.23	<0.001[a]
LGII	4.91 ± 3.02	6.98 ± 3.08	<0.001[a]	−1.70 ± 1.01	−1.01 ± 1.03	<0.001[a]
LGI	4.89 ± 2.68	7.43 ± 3.12	<0.001[a]	−1.70 ± 0.89	−0.86 ± 1.04	<0.001[a]
SAVFT	23.27 ± 7.51	31.63 ± 9.46	<0.001[a]	−1.75 ± 0.75	−0.92 ± 0.94	<0.001[a]
VRI	5.26 ± 2.69	7.29 ± 3.08	<0.001[a]	−1.58 ± 0.90	−0.90 ± 1.03	<0.001[a]
VRII	5.74 ± 2.14	7.54 ± 2.47	<0.001[a]	−1.42 ± 0.71	−0.82 ± 0.82	<0.001[a]
DSS	5.83 ± 2.71	8.48 ± 3.26	<0.001[a]	−1.39 ± 0.90	−0.51 ± 1.08	<0.001[a]
MCSTc	1.85 ± 1.57	4.31 ± 2.23	<0.001[a]	−2.25 ± 0.99	−0.70 ± 1.40	<0.001[a]
BD	6.39 ± 2.31	9.15 ± 3.03	<0.001[a]	−1.20 ± 0.77	−0.28 ± 1.01	<0.001[a]
WMI	78.27 ± 10.76	96.91 ± 12.83	<0.001[a]	−1.45 ± 0.72	−0.21 ± 0.86	<0.001[a]
DS	7.48 ± 2.33	10.80 ± 3.11	<0.001[a]	−0.84 ± 0.78	0.27 ± 1.04	<0.001[a]
ARI	5.11 ± 1.85	8.13 ± 2.35	<0.001[a]	−1.63 ± 0.62	−0.62 ± 0.78	<0.001[a]
FSIQ	79.67 ± 10.17	97.78 ± 12.14	<0.001[a]	−1.36 ± 0.68	−0.15 ± .81	<0.001[a]
INF	6.85 ± 2.06	10.06 ± 3.27	<0.001[a]	−1.05 ± 0.69	0.02 ± 1.09	<0.001[a]
MMSE	24.84 ± 2.72	27.98 ± 1.50	<0.001[a]	−1.10 ± 1.09	0.15 ± 0.60	<0.001[a]

[a] P values were computed based on t test by comparing BNR and CNR.
[b] P values were computed based on chi-square test by comparing BNR and CNR.

0.93. For BNR patients, the GDS of 2.25 reflected a mild to moderate NP impairment. For CNR patients, the GDS of 0.19, which was smaller than the cutoff of 0.5, reflected no NP impairment. These analyses confirmed the utility of the GAP method in elucidating homogeneous subtypes in patients of Han Chinese ethnicity with schizophrenia, who were characterized by significant differences in neurocognitive impairment (for example, above a 15-point difference in FSIQ). The results are consistent with a recent study using MCCB (Heinrichs et al. 2015).

We also noticed that the aforementioned studies and the current study all used the cognitive domain strategy. One advantage of the cognitive domain strategy is that it could reduce the likelihood of false positive findings obtained with individual putative NP or neurophysiological measures (Seidman et al. 2015). In this study, we not only took the cognitive domain strategy, but also clustered patients according to their performances on these cognitive domains. We thought that there was another advantage in doing so: additional clustering of patients by neurocognitive measures could connect them to different outcomes in different cultural contexts. This will help clinical practitioners on the front lines to identify patients by their outcomes in routine practice works and to provide patients with suitable examinations, therapy, or care. In summary, by combining the current study and the study of Heinrichs et al., we found that the CNR and the BNR could be identified across different patient populations, different neurocognitive measures tools, and different partitioning groups methods. This implied that these two subtypes were stable and differential neurocognitive domain profiles. Recently, Meier et al. (2014) found that there is substantial NP decline in

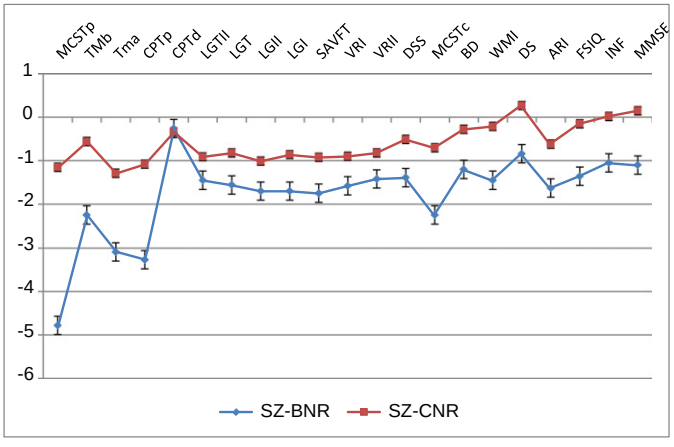

Fig. 2. Profiles of cognitive function indexes in CNR and BNR Note. MCSTp = Modified Card Sorting Test, perseveration error; TMb = Trial Making Test, B form; TMa = Trial Making Test, A form; CPTp = Continuous Performance Test, perseveration error; CPTd = Continuous Performance Test, dprime; LGTII = Logistic Theme delayed recall; LGTI = Logistic Theme immediate recall; LGII = Logistic delayed recall; LGI = Logistic immediate recall; SAVFT = Semantic Association Verbal Fluency Test; VRI = Visual Reproduction immediate recall; VRII =Visual Reproduction delayed recall; DSS = Digit Symbol Substitution Test; MCSTc = Modified Card Sorting Test, category; BD = Block Design Test; WMI = Working Memory Index; DS = Digit Span Test; ARI = Arithmetic Test; FSIQ = Full Scaled IQ; INF = Information Test; MMSE = Mini Mental Status Examination.

Table 2
Descriptive statistics of the 55 subjects sample.

	CNR	BNR	P value
Sample size	26	29	–
Age	43.35 ± 5.02	43.93 ± 10.90	>0.05[a]
Education	12.40 ± 1.96	10.25 ± 1.98	<0.001[a]
Age at first onset	24.30 ± 8.21	20.16 ± 3.74	<0.05[a]
Duration of illness	19.05 ± 7.94	23.77 ± 9.85	>0.05[a]
CPZE	885.50 ± 670.53	759.24 ± 723.35	>0.05[a]
Gender (male:female)	10:16	17:12	>0.05[b]
Negative symptom score	19.75 ± 5.87	18.76 ± 6.22	>0.05[a]
Positive symptom score	14.70 ± 7.09	19.97 ± 7.84	<0.05[a]
General symptom score	34.95 ± 11.25	36.55 ± 8.86	>0.05[a]
PANSS total score	69.40 ± 22.61	75.28 ± 18.53	>0.05[a]
Social Function			
Withdrawal	4.35 ± 1.60	3.03 ± 1.72	<0.01[a]
Interpersonal	7.70 ± 1.59	6.72 ± 2.00	>0.05[a]
Independence-competence	11.10 ± 3.43	8.24 ± 2.52	<0.01[a]
Independence-performance	10.15 ± 3.73	5.86 ± 3.17	<0.001[a]
Recreation	11.85 ± 3.80	7.55 ± 3.54	<0.001[a]
Prosocial	5.70 ± 3.48	2.83 ± 2.74	<0.01[a]
Employment	6.95 ± 1.99	4.07 ± 2.76	<0.001[a]
Total	57.80 ± 16.51	38.31 ± 14.81	<0.001[a]

[a] P values were computed based on t test by comparing BNR and CNR.
[b] P values were computed based on chi-square test by comparing BNR and CNR.

schizophrenia from the premorbid to the post-onset period, but the extent and developmental progression of decline vary across mental functions. One important claim in the study of Meier et al. was that average to above-average NP test performance in a subset of adults diagnosed with schizophrenia cannot be used to infer that NP decline had not occurred. However, they also proposed a limitation for this claim, because a relatively small group size prevented them from conducting an in-depth exploration of heterogeneity in NP decline. We thought that the fact that this study has an important application to clear this limitation in the near future, for two reasons: first, this study validated the fact that both CNR and BNR patients all had a medium group size; and second, most patients of both groups were evaluated using same tests 3 years ago. We believe that the following data analysis will supplement the limitation in the study of Meier et al.

4.1. Strength of the study

There were three strengths in this study. First, taking the cognitive domain strategy lets researchers select suitable neurocognitive measures according to their own clinical and cultural contexts. This effectively increased many opportunities for comparison among the studies on cognitive domain basis in schizophrenia from different social and cultural contexts. Second, we used the GAP method, which is a dimension-free statistical visualization method preserving every single piece of numerical information in the final output. By using GAP analysis, clinical researchers can easily comprehend and summarize every piece of information contained in a study data set (Hwu et al. 2002). Third, the current study was the first paper validated where there were both CNR and BNR patients of Han Chinese ethnicity with schizophrenia. These findings will facilitate development on related studies in the same clinical and cultural context in the future.

4.2. Limitations

There were two limitations in the present study, both of which limit the generalizability of the results. The major limitation was on the diversity of sample. Compared with studies of Leung et al. (2008) and Heinrichs et al. (2015), there was no normal control group in the present study. Therefore, we used the normative comparison standard strategy (Lezak et al. 2004) to judge the impairment level of subjects on individualized cognitive measures by comparing the scores of subjects with reliable norms of Taiwanese normal controls for the measures. The minor limitation was on the assessment tools of neurocognitive domains. We noticed that many studies used MCCB as a tool for assessing subjects' neurocognitive domains. However, there is no Chinese version of the MCCB in Taiwan. In the future, we hope to compare directly the MCCB with the tools that we used in this study.

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Contributors

National Dong Hwu University: Wan-Yu Liu.
Kaohsiung Municipal Kai-Syuan Psychiatric Hospital: Jui-Hua Liu.
Yuli Branch of Taipei Veterans General Hospital: Fang-Hsien Chu, Yung-Cheng Chen, Jen-Yeu Chen, Lein-Yung Ping.

Conflict of interest

All authors declare that they have no conflict of interest.

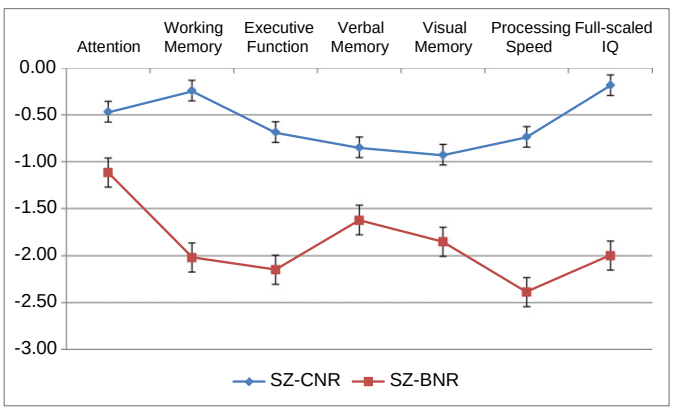

Fig. 3. ES pooled root mean square by domain. Note: Neurocognitive function indexes together with the cognitive domains they comprise. Attention: CPTd, CPTp; Working Memory: WMI; Executive Function: MCSTc, MCSTp, SAVFT; Verbal Memory: LGI, LGII, LGTI, LGTII; Visual Memory: VRI, VRII; Processing Speed: TMa, TMb, DSS; Full-scaled IQ: FSIQ. Indexes without used to compose of cognitive domains include BD, INF, DS, ARI, and MMSE.

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References

Badcock, JC, Dragovic, M, Waters, FA, Jablensky, A, 2005. Dimensions of intelligence in schizophrenia: evidence from patients with preserved, deteriorated and compromised intellect. J. Psychiatry Res. 39, 11–19.

Carey, CL, Woods, SP, Gonzalez, R, Conover, E, Marcotte, TD, Grant, I, Heaton, RK, HNRC Group, 2004. Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. J. Clin. Exp. Neuropsychol. 26 (3), 307–319.

Chapman, LJ, Chapman, JP, 1989. Strategies for resolving the heretogeneity of schizophrenics and their relatives using cognitive measures. J. Abnorm. Psychol. 98, 357–366.

Chen, CH, 1996. The properties and applications of the convergence of correlation matrices, proceedings of the statistical graphics section. Am. Stat. Assoc. 49–54.

Chen, CH, 1998. The properties and applications of the convergence of correlation matrices statistics. Acad. Sin C-98-7 (Taipei).

Chen, CH, 1999. Extension of generalized association plots (GAP), proceedings of the statistical graphics section. Am. Stat. Assoc. 111–116.

Chen, JH, Chen, HY, 2002. WAIS-III (Chinese Version): Administration and Scoring Manual. Chin. Behav. Sci. Corp, Taipei.

Cheng, JJ, Ho, H, Chang, CJ, Lane, SY, Hwu, HG, 1996. Positive and negative syndrome scale (PANSS): establishment and reliability study of a mandarin Chinese language version (Taiwan) J. Psychiatry 10, 251–258.

Chiang, SK, Tam, WCC, Pan, NC, Chang, CC, Chen, YC, Pyng, LY, Lin, CY, 2007. The appropriateness of blyler's and four subtests of the short form of the Wechsler Adult Intelligence Scale-III for chronic schizophrenia (Taiwan) J. Psychiatry 21 (1), 26–36.

Cohen, J, 1988. Statistical Power Analysis for the Behavioral Sciences. second ed. Hillsdale, NJ, Lawrence Earlbaum Assoc.

Conners, CK, 2014. Conners Continuous Performance Test—3rd Edition Manual. Multi-Health Syst. Inc, Toronto.

Dhindsa, R, Goldstein, D, 2016. Schizophrenia: from genetics to physiology at last. Nature 530, 162–163.

Elliott, R, Sahakian, BJ, 1995. The neuropsychology of schizophrenia: relations with clinical and neurobiological dimensions. Psychol. Med. 25, 581–594.

Folstein, MF, Folstein, SE, McHugh, PR, 1975. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12 (3), 189–198.

Genderson, MR, Dickinson, D, Diaz-Asper, CM, Egan, MF, Weinberger, DR, Goldberg, TE, 2007. Factor analysis of neurocognitive tests in a large sample of schizophrenic probands, their siblings and healthy controls. Schizophr. Res. 94, 231–239.

Gould, IC, Alana, MS, Laurens, KR, Cairns, MJ, Carr, VJ, Green, MJ, 2014. Multivariate neuroanatomical classification of cognitive subtypes in schizophrenia: a support vector machine learning approach. Neuroimage Clin. 6, 229–236.

Green, MF, 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? Am. J. Psychiatry 153, 321–330.

Green, MF, Kern, RS, Heaton, RK, 2004. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr. Res. 72, 41–51.

Guo, NW, Liu, HC, Wong, PF, Liao, KK, Yan, SH, Lin, KP, Chang, CY, Hsu, TC, 1988. Chinese version and norms of the mini-mental state examination. J. Rehab. Med. Assoc. 16, 52–59 (Taiwan).

Harvey, PD, Howanitz, E, Parrella, M, White, L, Davidson, M, Mohs, RC, Hoblyn, J, Davis, KL, 1998. Symptoms, cognitive functioning, and adaptive skills in geriatric patients with lifelong schizophrenia: a comparison across treatment sites. Am. J. Psychiatry 155, 1080–1086.

Heaton, RK, Miller, SW, Taylor, MJ, Grant, I, 2004. Revised Comprehensive Norms for an Expanded Halstead–Reitan Battery. Psychological Assessment Resources, Lutz, FL.

Heinrichs, RW, Pinnock, F, Muharib, E, Hartman, L, Goldberg, JO, Vaz, SM, 2015. Neurocognitive normality in schizophrenia revisited. Schizophr. Res. Cogn. 2 (4), 227–232.

Hwa, MS, 1999. Clinical Neuropsychological Assessment: Administration and Scoring Manual. Natl. Taiwan Univ, Taipei (unpublished book).

Hwa, MS, Chang, B, Lin, KN, Yang, CM, Lu, HJ, Chen, HY, 2005. WMS-III (Chinese Version): Administration and Scoring Manual. Chin. Behav. Sci. Corp, Taipei.

Hwu, HG, Chen, CH, Hwang, TJ, Liu, CM, Cheng, JJ, Lin, SK, Liu, SK, Chen, CH, Chi, YY, Ou-Young, CW, Lin, HN, Chen, WJ, 2002. Symptom patterns and subgrouping of schizophrenic patients: significance of negative symptoms assessed on admission. Schizophr. Res. 56, 105–119.

Jæger, J, Czobor, P, Berns, SM, 2003. Basic neuropsychological dimensions in schizophrenia. Schizophr. Res. 65, 105–116.

Kay, SR, Fiszbein, A, Opler, LA, 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.

Kern, RS, Green, MF, Nuechterlein, KH, Deng, B, 2004. NIMH-MATRICS survey on assessment of neurocognition in schizophrenia. Schizophr. Res. 72, 11–19.

Kern, RS, Gold, JM, Dickinson, D, Green, MF, Nuechterlein, KH, Baade, LE, Keefe, RS, Mesholam-Gately, RI, Seidman, LJ, Lee, C, Sugar, CA, Marder, SR, 2011. The MCCB impairment profile for schizophrenia outpatients: results from the MATRICS psychometric and standardization study. Schizophr. Res. 126, 124–131.

Kremen, WS, Seidman, LJ, Faraone, SV, Toomey, R, Tsuang, MT, 2000. The paradox of normal neuropsychological function in schizophrenia. J. Abnorm. Psychol. 109 (4), 743–752.

Leung, WW, Bowie, CR, Harvey, PD, 2008. Functional implications of neuropsychological normality and symptom remission in old outpatients with schizophrenia. J. Int. Neuropsychol. Soc. 14, 479–488.

Lezak, MD, Howieson, DB, Loring, DW, 2004. Neuropsychological Assessment. fourth ed. Oxf. Uni. Press, New York.

Lin, ASK, Chen, CH, Hwu, HG, Lin, HN, Chen, JA, 1998. Psychopathological dimensions in schizophrenia: a correlational approach to items of the SANS and SAPS. Psychiatry Res. 77, 121–130.

Meier, MH, Caspi, A, Reichenberg, A, Keefe, RE, Fisher, HL, Harrington, H, Houts, R, Poulton, R, Terrie, E, 2014. Neuropsychological decline in schizophrenia from the premorbid to the postonset period: evidence from a population-representative longitudinal study. Am. J. Psychiatry 171 (1), 91–101.

Muharib, E, Heinrichs, RW, Miles, AA, Pinnock, F, McDermid Vaz, S, Ammari, N, 2014. Community outcome in cognitively normal schizophrenia patients. J. Int. Neuropsychol. Soc. 20, 805–811.

Nelson, HE, 1976. A modified card sorting test sensitive to frontal lobe defects. Cortex 12 (4), 313–324.

Nuechterlein, KH, Barch, DM, Gold, JM, Goldberg, TE, Green, MF, Heaton, RK, 2004. Identification of separable cognitive factors in schizophrenia. Schizophr. Res. 72, 29–39.

Palmer, BW, Heaton, RK, Paulsen, JS, Kuck, J, Braff, D, Harris, MJ, Zisook, S, Jeste, DV, 1997. Is it possible to be a schizophrenic yet neuropsychological normal? Neuropsychology 11 (3), 437–446.

Reichenberg, A, Harvey, PD, Bowie, CR, Mojtabai, R, Rabinowitz, J, Heaton, RK, Bromet, E, 2009. Neuropsychological function and dysfunction in schizophrenia and psychotic affective disorders. Schizophr. Bull. 35 (5), 1022–1029.

Seidman, LJ, Hellemann, G, Nuechterlein, KH, Greenwood, TA, Braff, DL, Cadenhead, KS, Calkins, ME, Freedman, R, Gur, RE, Gur, RC, Lazzeroni, LC, Light, GA, Olincy, A, Radant, AD, Siever, LJ, Silverman, JM, Sprock, J, Stone, WS, Sugar, C, Swerdlow, NR, Tsuang, DW, Tsuang, MT, Turetsky, BI, Green, MF, 2015. Factor structure and heritability of endophenotypes in schizophrenia: findings from the consortium on the genetics of schizophrenia (COGS-1). Schizophr. Res. 163, 73–79.

Song, LY, 2001. The development and validation of a social functioning scale — a focus on practice applicability. Formosa J. Ment. Health. 14 (3), 33–65.

Wilk, CM, Gold, JM, McMahon, RP, Humber, K, Iannone, VN, Buchanan, RW, 2005. No, it is not possible to be schizophrenic yet neuropsychologically normal. Neuropsychology 19, 778–786.