



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



Shih-Kuang Chiang <sup>a,\*</sup>, Ching-Huan Ni <sup>a,1</sup>, Chih-Pu Tsai <sup>b,2</sup>, Keng-Chang Lin <sup>c,3</sup>

<sup>a</sup> Department of Counseling and Clinical Psychology, National Dong Hwa University, No. 1, Sec. 2, Da Hsueh Rd., Shoufeng, Hualien, 97401, Taiwan (R.O.C)

<sup>b</sup> Department of Psychiatry, Kaohsiung Armed Forces General Hospital, No.2, Zhongzheng 1st. Rd., Lingya District, Kaohsiung City 80284, Taiwan (R.O.C)

<sup>c</sup> 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.

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## 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; Jøger 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](mailto:skchiang@mail.ndhu.edu.tw) (S.-K. Chiang),

[felix200095@yahoo.com.tw](mailto:felix200095@yahoo.com.tw) (C.-H. Ni), [fromzero25@hotmail.com](mailto:fromzero25@hotmail.com) (C.-P. Tsai),

[linkengchang@gmail.com](mailto:linkengchang@gmail.com) (K.-C. Lin).

<sup>1</sup> Tel.: +886 3 8635104; fax: +886 3 8635300.

<sup>2</sup> Tel.: +886 7 7496751x726191; fax: +886 7 7496751.

<sup>3</sup> Tel.: +886 7 7513171x2227; fax: +886 7 7712494.

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 = 39 to 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

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