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Schizophrenic patients without neuropsychological deficits: subgroup, disease severity or cognitive compensation?

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Abstract

Some schizophrenic patients do not show clinically relevant cognitive deficits. The question remains whether this represents the existence of an etiologically different subgroup, a general effect of disease severity or whether their cognitive deficits do not reach a clinical threshold due to a greater cognitive compensation ('brain reserve') capacity. A group of 23 out of 118 first onset patients was identified as cognitively normal (CN). The cognitive profile of these patients was compared with that of 45 healthy controls. Next these patients were compared with the cognitively impaired (CI) patients on obstetric complications (OCs), premorbid adjustment, age at onset, Positive and Negative Syndrome Scale ratings, social functioning and substance abuse. In addition both groups were compared on intelligence and educational level as indirect indicators of cognitive compensation capacity. There were no differences in OCs, premorbid adjustment, age at onset, psychopathology or substance abuse between the two patient groups. There was a significant difference in social functioning, which is a consequence rather than a cause of cognitive deficits. However, the CN patients scored significantly higher on measures of intelligence and educational level than the CI patients. This suggests that a difference in cognitive compensation capacity could explain the existence of a CN patient group.

Keywords: Cognition; Neuropsychology; Schizophrenia

1. Introduction

It is generally accepted that cognitive deficits are a major characteristic of schizophrenia. They are often supposed to be the fundamental impairment that leads to psychopathology and social dysfunctioning (Andreasen, 1997; Goldman-Rakic, 1994; Hemsley, 1994). However, not all schizophrenic patients show cognitive deficits according to standard clinical norms. Several studies have identified a group of schizophrenic patients with cognitive functioning within normal limits (Bryson et al., 1993; Palmer et al., 1997; Silverstein and

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Zerwic, 1985; Kremen et al., 2000). Estimates of the proportion of patients without neuropsychological impairments vary from 23% (Kremen et al., 2000) to 73% (Bryson et al., 1993).

There are several possible explanations for this phenomenon. The 'cognitively normal' (CN) patients might represent a subgroup within the schizophrenic population. An etiological theory, which could explain the existence of CN and cognitively impaired (CI) subgroups, comes from Robin Murray and his associates (Murray and Lewis, 1987; Murray et al., 1992). Murray proposes that in a subgroup of patients, the CI patients, the disease has a distinct neurodevelopmental cause, which has its origins in genetic defects and early risk factors such as obstetric complications (OCs). These patients are characterized by premorbid symptoms, such as motor and behavioral problems, cognitive deficits, poor social adjustment, an early onset and more negative symptoms. The CN patients also have a vulnerability to decompensate into psychotic symptoms, but they show less evidence of a developmental disease and are less likely to show premorbid symptoms or cognitive deficits. Another explanation for the existence of CN patients would be a general effect of disease severity. The difference between CN and CI patients could be an artificial distinction on a severity continuum. This would imply that CN patients are less severely affected but still show signs of cognitive decline at a subclinical level. It is also to be expected that the more severe the disease, the more severe are all its manifestations from early age on, with the CN group showing better premorbid functioning, less psychopathology, and better social functioning.

The few studies that examined the characteristics of CN patients all used chronic patient groups in which the effects of hospitalization, recurrent episodes and long-term medication can bias the results. Most studies looked at differences in psychopathology. None of these studies analyzed differences in OCs and premorbid functioning, other than premorbid IQ estimates (Kremen et al., 2000). Silverstein and Zerwic (1985) found that CN patients had more paranoid symptoms than patients with cognitive deficits. Kremen et al. (2000) also found a significantly higher proportion of the paranoid subtype in the CN group, although there was no significant difference in symptom ratings. Both Palmer et al. (1997) and Torrey et al. (1994) showed that CN patients had fewer negative symptoms than CI patients. These data are not entirely consistent, but they suggest that the two groups show predominantly positive and negative symptoms, respectively. This would be in accordance with the first explanation, which suggests that the neurodevelopmental or CI group shows more negative symptoms. However, a study of Kremen et al. (2000) showed that a schizophrenic subgroup with neuropsychological test scores within normal limits actually performed significantly worse and had a different profile shape than normal controls, which would be more in accordance with a general effect of disease severity. Indirect evidence for subclinical cognitive decline in the CN group also comes from studies with discordant monozygotic twins, in which in almost all cases the schizophrenic twin was CI compared to his or her co-twin, who represented the optimal level of cognitive achievement (Goldberg et al., 1990, 1995; Torrey et al., 1994).

According to the literature both explanations could be true, but there could be another explanation as well. It is also possible that all patients have some sort of underlying neuropathology, which causes cognitive deficits in CI patients, but does not cause the same deficits in CN patients because they have more capacity to compensate for brain dysfunction. This would be in accordance with the 'brain reserve capacity' theory (BRC; Satz, 1993) used in dementia research. This theory argues that, because of environmental enrichment, genetic predisposition or both, some individuals develop a cognitive reserve that may increase the threshold for cognitive symptoms after acquired brain pathology. Because psychosocial studies have shown the protective as well as the risk effects of intelligence and education on adaptive behavior, aging and health (Gurland, 1981; Mortimer, 1988), a number of studies have used intelligence and educational level as indirect measures of BRC (Mortimer, 1997; Mortimer and Graves, 1993; Schmand et al., 1997; Schofield, 1999; Stern et al., 1996). Of course, one could argue that it is

self-evident that individuals with greater intelligence and better education simply perform better on neuropsychological tests. However, several longitudinal studies have shown a link between higher educational attainment and resistance to cognitive change (Evans et al., 1993; Farmer et al., 1995). Joyce et al. (2002) found a dissociation between cognition and IQ in a group of schizophrenic patients who had premorbid and current IQ levels in the normal range but displayed working memory deficits. Weickert et al. (2000) found a separate IQ component in a principal component analysis of neuropsychological and intellectual test data in a group of schizophrenia patients. Although the BRC model comes from dementia research, in which it is applied to an acquired neurological disorder, it could be applicable to schizophrenia as well. Schizophrenia is believed to be a neurodevelopmental disorder, but there is evidence that the most remarkable decline in cognitive functioning takes place just before or during illness onset (Kelly et al., 2000; Rabinowitz et al., 2000).

Our main objective was to separate a group of first onset schizophrenia patients with cognitive functioning within normal limits from CI patients, to study whether this distinction reflected a difference in disease severity, two different subgroups or a difference in cognitive compensation capacity. If the CN group were found to show no evidence of cognitive deficits, fewer OCs, fewer negative symptoms but no difference in positive symptoms as compared to the CI group, and premorbid adjustment comparable to controls, then this could indicate an etiologically different subgroup. Cognitive decline at subclinical levels, less severe psychopathology and better premorbid adjustment in the CN group compared to the CI group could indicate a difference in disease severity. If the difference between CN and CI patients were caused by a difference in compensation capacity, the most important difference between the groups would be in intelligence and education, as indirect measures of compensation. Both groups were also compared on measures of social functioning and substance abuse to study the association between these variables and cognitive functioning.

2. Methods

2.1. Subjects

The study included 118 patients who had recently experienced a first or a second psychotic episode according to DSM-IV (American Psychiatric Association, 1994) and were diagnosed within the schizophrenia spectrum (schizophrenia, schizoaffective disorder, schizophreniform disorder). All patients participated in a Dutch multicenter study of the university hospitals of Groningen, Utrecht and Amsterdam. Diagnosis was based on a structured interview, either the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; Wing et al., 1990) or the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992). Exclusion criteria were severe mental retardation and a known systemic or neurological illness. Eighty-seven males and 31 females were included. Mean age was 23 years (S.D. = 5.3). Forty-five healthy controls, 38 males and 7 females, were included in order to establish standard scores on cognitive tests. Exclusion criteria for controls were a history of mental illness, mental retardation and a known systemic or neurological illness. Mean age was 24 years (S.D. = 6.4). The healthy control group was recruited through announcements in the local newspapers. There were no significant differences between patients and controls for sex ($\chi^2 = 2.10$, n.s.) or age ($F(1, 161) = 0.29$, n.s.). Twenty-five patients used typical antipsychotics, 75 patients used atypical antipsychotics, and 18 patients did not use antipsychotic medication. Ten patients also used anticholinergic medication.

2.2. Procedures and instruments

2.2.1. Cognitive measures

All patients completed an extensive neuropsychological battery after being stabilized for at least 6 weeks on medication. Most cognitive measures in our study were chosen because of their widespread use in clinical practice. In addition, there should be evidence for their discriminatory power in studies of schizophrenic patients and normal controls on these measures (e.g. Keefe et al., 1995;

Table 1
Cognitive battery with tests grouped by ability area

Perceptual sensitivity
CPT d′
Attention selectivity
STROOP interference score
Trail Making Test interference score
Perceptual and psychomotor speed
CPT RT (ms)
Trail Making A and B (s)
STROOP names (s)
STROOP colors (s)
Finger tapping
Memory-verbal encoding
CVLT trials 1–5
Memory-verbal-consolidation
CVLT long-term free recall minus trial 5
Memory-verbal retrieval
CVLT short-term free recall minus short-term cued recall
CVLT long-term free recall minus long-term cued recall
CVLT difference between recognition and long-term recall
Memory-visual
Rey Complex Figure Test percentage immediate recall
Rey Complex Figure Test percentage delayed recall
Spatial Working Memory Task immediate recall
Spatial Working Memory Task delayed recall
Verbal fluency
Verbal fluency categories
Verbal fluency letters
Visuoconstruction
Rey Complex Figure Test copy

Saykin et al., 1994; van den Bosch et al., 1996). The cognitive measures were grouped into nine ability areas as presented in Table 1. Tests included a double stimulus Continuous Performance Task (CPT; van den Bosch et al., 1996); a computerized STROOP task; forms A, B and C of a new version of the Trail Making Test (Vink and Jolles, 1985); a Finger tapping test; the Dutch translation of the California Verbal Learning Test (Delis et al., 1987); the Rey Complex Figure Test (Rey, 1964); Verbal Fluency Tasks (category and letter); and a computerized Spatial Working Memory Task (Keefe et al., 1995). When variables resembled the normal distribution, patients' test scores were transformed into *z*-scores using means and standard deviations. of the normal control group. Otherwise normalized standard scores were used to establish cut-off points. In this procedure, the percentage of persons in the standardization sample falling at or above a raw score point is calculated. This percentage is transformed into a *z*-score by reference to a normal distribution frequency table (Walsh and Betz, 1985). A patient was considered CI if he had at least one *z*-score of 2 or more below normal in one ability area. The *z*-scores and normalized standard scores were also used to compute the mean *z*-scores per domain for all three groups.

2.2.2. Obstetric complications, premorbid adjustment, and age at onset

Information concerning OCs was obtained with a self-report questionnaire for the mother. Because the frequency of individual OCs is not very high, two sum scores representing the different reproductive periods (pregnancy and birth) were computed and used as dichotomous items in the analyses. Because hypoxia is mentioned as an important factor in explaining the relation between OCs and schizophrenia in recent reviews (McNeil et al., 2000; Geddes et al., 1999), a special sum score for OCs related to hypoxia was also computed. OCs during pregnancy were vaginal bleeding, early contractions, high blood pressure, rhesus incompatibility, pre-eclampsia, rubella, syphilis and substance abuse from the mother. OCs during birth were gestational age less than 37 weeks, caesarian, labor longer than 36 h, breech delivery, forceps delivery, vacuum extraction, epileptic seizures, incubator more than 4 weeks, birth weight lower than 2000 g, placental anomalies, cord prolapse, cyanosis, slow heart rate, asphyxia, oxygen treatment. The latter five were also used to compute a hypoxia sum score. Premorbid adjustment was inferred from employment status and history of intimate relationships before inclusion. Data concerning premorbid adjustment and age at onset were gathered in a Case Record Form using all possible sources of information.

2.2.3. Psychopathology, substance abuse and social functioning

Symptoms were rated on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) within the same week as the neuropsychological assessment. These ratings were used to obtain dimensional scores by calculating the sum scores loading high on the positive, negative, disorgani-

zation, depression and excitement dimensions as described in Lindenmayer et al. (1995). The total PANSS score minus the disorganization dimension was used as a general measure of psychopathology. The disorganization dimension was left out of the computation because of a large overlap with cognitive measurements (Bryson et al., 1999). Depressive symptoms were also rated with the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979). Not all variables resembled the normal distribution. If possible, log and square root transformations were performed. Social functioning during the month preceding inclusion was assessed with the Groningen Social Disabilities Schedule (GSDS; Wiersma et al., 1988), a semi-structured interview that measures social role functioning on seven roles. Substance abuse or dependence was rated with the relevant section of the Composite International Diagnostic Interview (CIDI; WHO, 1990). Substance abuse or dependence was divided into four substance categories for analyses.

2.2.4. Indirect measures of cognitive reserve capacity: education and intelligence

Level of education and performance on intelligence tasks were taken as indirect measures of compensation. All subjects were asked about their highest educational attainment and whether they still received education at illness onset. The Dutch educational system already differentiates after primary school; therefore we have chosen a coding system other than years of education. This goes from (1) primary school up to (8) university or graduate school. Thirty-seven percent of the patients still received education; for these patients we took the level they were aiming at minus half a point (e.g. a law school student received a code of 7.5 instead of 8). A log transformation was performed on educational level in order to fit the normal distribution. Four subtests of the Dutch translation of the Wechsler Adult Intelligence Scale (WAIS; Stinissen et al., 1970), comprehension, vocabulary, block design and picture arrangement, were administered to the patients. The mean subtest *C*-score of these four subtests was taken as a measure of intelligence. These *C*-scores go from 0 to 10 with a mean of 5 and an S.D. of 2. Because the Dutch translation of the WAIS is from 1970, we also give corrected mean *C*-scores in which we take into account an estimated IQ gain of 0.25 IQ points a year from 1971 to 1996 (Flynn, 1998). The corrected average *C*-score is 5.8 with an S.D. of 2.

3. Results

A group of 23 patients (19%) without clinically relevant cognitive deficits was identified. The other 95 patients had deficits in at least one ability area (range 1–8). Thirty-four of the 45 controls (76%) had no cognitive deficits according to our criteria. When our criteria are used to predict group membership (schizophrenia versus healthy controls), 79% of the subjects are correctly classified, the sensitivity is 81% and the specificity is 76%. The CN group consisted of 15 men and 8 women; mean age was 24.8 years (S.D. = 5.5), and the average parental education was at the high school level. Four patients used typical antipsychotics, 14 used atypical antipsychotics, and 5 patients did not use antipsychotic medication. One patient also used anticholinergic medication. The CI group consisted of 72 men and 23 women; mean age was 22.9 years (S.D. = 5.2), and the average parental education was at the high school level. Twenty-one patients used typical antipsychotics, 61 used atypical antipsychotics, and 8 patients did not use antipsychotic medication. Nine patients also used anticholinergic medication. There were no significant differences between CN and CI patients for sex ($\chi^2 = 1.07$, n.s.), age ($F(1, 116) = 2.43$, n.s.), parental education ($F(1, 98) = 1.85$, n.s.), type of medication ($\chi^2 = 3.05$, n.s.) or the use of anticholinergic medication ($\chi^2 = 0.63$, n.s.).

The question whether the CN group was really CN or merely showed cognitive deficits at subclinical levels was examined by independent-sample *t*-tests between CN patients and controls and visual inspection of cognitive profiles (Table 2 gives means and S.D. for both patient groups for all cognitive ability areas as well as effect sizes for the differences between CN and CI patients and between CN patients and controls; see also Fig. 1). The CN patients performed significantly worse than controls on perceptual and psychomotor speed

Table 2
Cognitive ability area scores for CN and CI patients and effect sizes for the comparison between CN and CI patients and CI patients and controls

	CN ($n=23$)		CI ($n=95$)		Effect size	
	Mean	S.D.	Mean	S.D.	CN vs. CI patients[a]	CN vs. controls[b]
(1) Perceptual sensitivity	−0.25	0.88	−1.68	1.37	1.04	−0.25
(2) Attention selectivity	0.04	0.83	−0.65	1.43	0.48	0.04
(3) Speed	−0.60	0.45	−1.75	1.12	1.03	−0.60
(4) Verbal encoding	−0.57	0.72	−1.42	1.09	0.78	−0.57
(5) Verbal consolidation	0.46	1.46	−0.50	1.47	0.65	0.46
(6) Verbal retrieval	0.06	0.78	−0.33	0.82	0.48	0.06
(7) Visual memory	−0.00	0.63	−1.28	1.39	0.92	0.00
(8) Verbal fluency	−0.32	0.80	−1.00	0.68	1.00	−0.32
(9) Visuoconstruction	−0.08	1.11	−1.08	2.06	0.49	−0.08

[a] Cohen's *d* based on the S.D. of the CI group.
[b] Cohen's *d* based on the S.D. of the control group.

($t(66)=3.85$, $P<0.000$) and verbal encoding ($t(66)=2.44$, $P=0.017$), with medium effect sizes. The cognitive profile shape of the CN patients deviates from that of normal controls and follows that of CI patients, who performed worse than both controls and CN patients on all domains. Although the profiles suggest that CN patients performed better than controls on verbal consolidation, this difference is not significant. Differences between CN and CI patients were also tested by independent-sample *t*-tests. All differences were significant, with five effect sizes in the large range; all other effect sizes were medium.

Differences between CN and CI patients on OCs, premorbid adjustment and substance abuse were tested with χ^2-tests (Table 3). Data concerning the employment status of normal controls were also available (17.8% regular employment, 71.1%

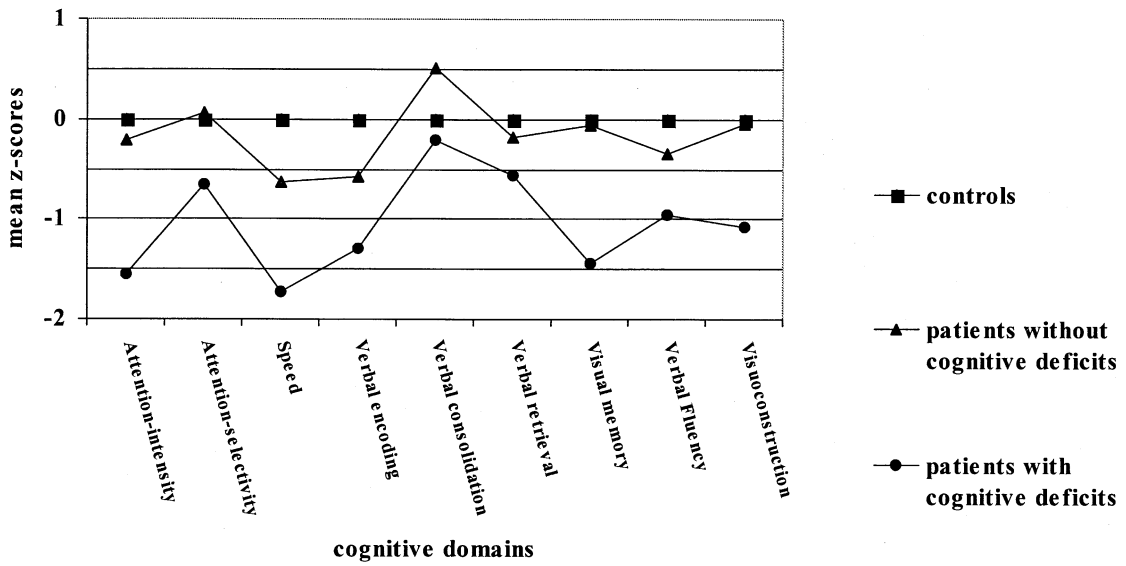

Fig. 1. Cognitive profiles of controls, CN and CI patients.

Table 3
Differences between patients with and without cognitive deficits on OCs, premorbid adjustment and substance abuse

	CN ($n=23$) % patients	CI ($n=95$) % patients	Significance (χ^2, two-tailed)
(a) OCs			
Pregnancy	35.3	48.7	n.s.
Birth	43.8	31.5	n.s.
Hypoxia-related	31.3	20.5	n.s.
(b) Premorbid adjustment			
Employment status			
Regular	39.4	26.4	
Study	37.2	47.8	n.s.
Sickness benefit, sheltered employment, unemployed	23.4	26.1	
History of intimate relationship			
Never	50.0	39.1	
<6 months	27.7	21.7	n.s.
>6 months	22.3	39.1	
(c) Substance abuse			
Alcohol	24.5	21.7	n.s.
Cannabis	54.1	47.4	n.s.
Sedatives	4.2	0	n.s.
Miscellaneous	9.5	13.0	n.s.

study and 11.1% unemployed). There was no significant difference between controls and CN patients, but there was a significant difference between controls and CI patients in employment status ($\chi^2=13.99$, $P=0.001$). Differences on age at onset, psychopathology, social functioning and indirect measures of compensation were tested with ANOVA or Mann–Whitney *U*-tests. Differences in the percentage of subjects showing disabilities on individual social roles were tested with χ^2-tests (Table 4). There were no significant differences in OCs, employment situation before inclusion, history of intimate relationships or age at onset.

There was no significant difference on general psychopathology minus disorganization. Also no evidence for different symptom profiles was found. The CI patients only had a significantly higher score on the disorganization dimension ($F(1, 116)=4.93$, $P<0.05$). No significant differences in substance abuse or dependence were found. Both patient groups differed significantly in general social functioning, in favor of the CN group. This was significant for the self-care role ($\chi^2=4.46$, $P<0.05$) and the work role ($\chi^2=8.09$, $P<0.01$). CN Patients scored significantly higher on intelligence ($F(1, 116)=7.19$, $P<0.01$) and level of education ($F(1, 116)=7.30$, $P<0.01$) than CI patients. Mean level of education for the controls was 5.9 with an S.D. of 1.5. The difference between CN patients and controls was not significant, the difference between CI patients and controls was significant ($t(138)=6.39$, $P<0.000$).

4. Discussion

In this study 19% of the patients were found to have no cognitive deficits, which is lower than the percentage found in some other studies (63% in Silverstein and Zerwic, 1985; 42 and 73% in Bryson et al., 1993). We preferred a conservative approach, however. Patients with only one deficit were already classified as CI, whereas the other studies used the Luria-Nebraska or the Halstead-Reitan impairment scores, so patients had to perform weakly on several items to be classified as cognitively abnormal. There is a negligibly small difference from the studies of Palmer et al. (1997) (27%) and Kremen et al. (2000) (23%), who also used a composite neuropsychological battery and

Table 4
Differences between patients with and without cognitive deficits on age at onset, psychopathology, social functioning, and indirect measures of cognitive compensation

	CN patients ($n=23$)		CI patients ($n=95$)		Significance (two-tailed)
	Mean	S.D.	Mean	S.D.	
Age at onset	23.7	5.6	21.8	4.9	n.s.
Psychopathology					
Positive[a]	2.0	1.1	2.3	1.0	n.s.
Negative	2.0	0.7	2.4	1.0	n.s.
Disorganization	1.6	0.3	1.9	0.7	0.028
Depression	2.1	0.9	2.4	1.0	n.s.
Excitement	1.4	0.6	1.7	0.8	n.s.
PANSS total minus disorganization	47.4	12.9	53.8	16.2	n.s.
MADRS total score	12.3	9.4	14.6	10.4	n.s.
Social functioning					
Total score[b]	1.0	0.7	1.3	0.6	0.035
Self-care[c]	26.1		50.5		0.029
Family role	69.6		78.9		n.s.
Kinship role	52.2		67.4		n.s.
Partner role	56.5		69.5		n.s.
Citizen role	73.9		81.1		n.s.
Social role	56.5		65.3		n.s.
Work role	69.6		91.6		0.010
Compensation					
Level of education (1–8)	5.3	2.3	3.9	2.1	0.011
Mean WAIS *C*-score (1–10)	6.8	1.0	5.9	1.5	0.008
Mean corrected WAIS *C*-score	6.1	1.0	5.4	1.5	0.008

[a] Standardized PANSS ratings ranging from (1) absent to (7) extreme.
[b] Standardized GSDS ratings ranging from (0) no disability to (3) extreme disability.
[c] Percentage of subjects showing disability.

more stringent criteria. If the criteria for cognitive impairment were used to predict group membership, then all three studies would classify a fair amount of subjects correctly (respectively, 76, 85 and 79% in chronological order). Our study would be the most sensitive and the least specific. This means that our criteria for cognitive normality were the strictest.

Our results suggest that the CN patients still show signs of cognitive decline at a subclinical level, because their cognitive profile deviates from that of normal controls and follows more or less the same direction as that of the CI patients. The CN patients performed significantly below the level of normal controls on perceptual and psychomotor speed and verbal encoding. They performed better, although not significantly, than controls on the verbal consolidation measure. This might be an artifact because consolidation is computed by subtracting the number of words on delayed recall from the number of words on immediate recall (verbal encoding). Since the CN patients already showed a weak performance on verbal encoding, they could not lose many words from memory. The subclinical deficits in the CN group and their almost similar profile shape suggest that the two patients groups do not represent etiologically different subgroups. It rather suggests that all patients experience cognitive dysfunctions at a certain level even if they are still within normal limits. The fact that no differences between the two groups in OCs, age at onset or premorbid adjustment were found makes it even less likely that the CN patients represent an etiologically different subgroup.

However, no significant difference in the total level of psychopathology (minus disorganization

because of conceptual redundancy) and age at onset was found. The only significant difference in psychopathology was found on the disorganization dimension. These findings go against a general effect of disease severity.

The only measures on which the CN group scored higher, apart from social functioning, were education and intelligence. The CN group had a score slightly above average on intelligence tests. Mean educational attainment was also reasonably high in this group, a level comparable with college. This is in accordance with the BRC theory (Satz, 1993), which states that people with greater BRC, measured indirectly by education and intelligence, are better able to compensate for the negative effects of brain pathology on cognition. There is evidence that not all domains of cognitive functioning are equally affected in schizophrenia. Several studies mention a generalized deficit with more pronounced impairment in verbal learning, attention–vigilance and speeded visual-motor processing (Censits et al., 1997; Saykin et al., 1991, 1994). Therefore it is possible that compensation in these more severely affected areas is not always adequate, which could explain the significant differences on verbal learning and perceptual and psychomotor speed between CN patients and controls.

Cognitive deficits are associated with social dysfunctioning in schizophrenia (Dickerson et al., 1996; Green, 1996). Therefore it is to be expected that the CI group has more problems in social functioning. Indeed, both patient groups differed significantly in general social functioning in favor of the CN patients. Close inspection of the various social roles, however, revealed that this was mostly due to significant differences in self-care and work roles. These roles depend less on interpersonal interactions and more on the acquisition and execution of skills than the other roles. It is possible to function marginally in interpersonal contacts and still perform within normal limits on a job with few interpersonal demands. No significant differences in rates of substance abuse or dependence between the two patient groups were found. This suggests that the effect of chronic substance use on cognition is not very strong.

Because not much time had passed between onset of the current episode and time of testing, it is possible that state-like effects have had their impact on cognitive performance. It seems unlikely that this will have significant effects on the results of this study because there is no reason to assume that both patient groups are differentially affected. Also, the BRC theory is applicable for both state- and trait-like effects of brain dysfunction on cognition. One could also argue that the differences in cognition between CN and CI patients are caused by the same amount of cognitive decline from different levels of cognitive functioning as is paralleled in differences in IQ and education. However, IQ and cognition are not identical as was shown by Joyce et al. (2002) and Weickert et al. (2000). And a decline from higher levels would suggest that in the premorbid state CN patients performed above the level of normal controls on five of the nine domains, on which they now equal controls, which is highly unlikely.

The use of the BRC theory, normally used in research on progressive dementia, for a neurodevelopmental disorder such as schizophrenia also raises some questions. In dementia the BRC predicts later onset of cognitive deficits for those with greater cerebral reserve. Because schizophrenia is not a progressive deteriorating brain disease, we suggest that cerebral reserve will be protective against the cognitive effects of neuropathology at any age. It could be argued that it is not justified to use education as an indirect measure of compensation capacity in schizophrenia because of attenuated educational attainment. It is not clear, however, at what developmental stage educational attainment is affected. In the NIMH discordant twin study, for example, school grades were strikingly similar between affected and well twins (Torrey et al., 1994). So it seems more likely that educational attainment is not severely affected during early development. The Dutch educational system, and hence our scoring system, is rather robust for this, because the Dutch system already differentiates after primary school into four levels.

Overall this study suggests that cognitive compensation could explain the existence of cognitive ‘normality’ in schizophrenia. The evidence is rather indirect, because we cannot demonstrate directly

that CN patients truly resist the cognitive effects of brain pathology due to a larger compensation capacity. We did not have premorbid cognitive data or an estimate of premorbid intelligence. There were, however, no differences in other indicators of premorbid functioning (employment status or intimate relationships), which suggests that there were no large differences in general functioning other than intelligence and educational level between the two groups before illness onset. This would make it less likely that CI patients already showed the severe cognitive deficits found in this study before illness onset. We think that compensatory mechanisms should be included in comprehensive models of cognitive dysfunction in schizophrenia.

This study also seems to challenge models of schizophrenia in which cognition is seen as the core deficit, and the cause of clinical symptoms (Goldman-Rakic, 1994; Hemsley, 1994), because CN patients performed significantly better than CI patients on all cognitive domains, while no significant differences in psychopathology were found.

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