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Cognitive alterations in patients with non-affective psychotic disorder and their unaffected siblings and parents

Meijer J, Simons CJP, Quee PJ, Verweij K, GROUP Investigators. Cognitive alterations in patients with non-affective psychotic disorder and their unaffected siblings and parents.

Objective: The purpose of this study was to examine a range of cognitive measures as candidate phenotypic liability markers for psychosis in a uniquely large sample of patients with psychosis, their unaffected relatives and control subjects.
Method: Patients with non-affective psychosis (n = 1093), their unaffected siblings (n = 1044), parents (n = 911), and controls (n = 587) completed a comprehensive cognitive test battery. Cognitive functioning was compared using tests of verbal learning and memory, attention/vigilance, working memory, processing speed, reasoning and problem solving, acquired knowledge, and social cognition. Age- and gender-adjusted z-scores were compared between groups using mixed-model analyses of covariance. Clinically relevant impairment (−1 and −2 SD from control mean) was compared between subject groups.
Results: Patients performed significantly worse than controls in all cognitive domains (z-range −0.26 to −1.34). Siblings and parents showed alterations for immediate verbal learning, processing speed, reasoning and problem solving, acquired knowledge, and working memory (z-range −0.22 to −0.98). Parents showed additional alterations for social cognition. Prevalence of clinically relevant impairment in relatives ranged from 50% (−1 SD criterion) to 10% (−2 SD criterion).
Conclusion: Cognitive functioning is a candidate intermediate phenotype given significant small to large alterations in patients and intermediate alterations in first-degree relatives.

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Key words: schizophrenia; parents; siblings; neuropsychology; endophenotypes

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Significant outcomes

- Patients with non-affective psychotic disorder are characterized by cognitive alterations across all cognitive domains with small effect sizes compared with meta-analytic results.
- Verbal learning, processing speed, reasoning and problem solving, working memory, and acquired knowledge are the most promising cognitive intermediate phenotypes, demonstrating alterations in genetic high-risk groups.
- The distribution of clinically relevant impairments in patients and their first-degree relatives suggests a continuum of neuropsychological functioning, with approximately 30% of the patients and 50% of the relatives displaying no clinically manifest (−1 SD) deficit.

Limitations

- Effect sizes in parents may have been inflated because of differences in age range between the parent and control group.
- Not all subjects had complete cognitive test scores, which may have impacted on the effect sizes.
- Group differences in educational achievement and IQ remain a potential explanation for group differences in other cognitive test scores that cannot be ruled out through statistical adjustment.

Introduction

Cognitive alteration is a stable, trait-related aspect of schizophrenia that has been associated with impaired quality of life and poorer functional outcome (1). Subtle cognitive deficits are present before psychosis onset and may help to predict conversion to psychosis in 'clinical high-risk' subjects who are in the putative prodromal phase of psychosis (2, 3). Attenuated cognitive alterations have also been reported in clinically unaffected relatives of schizophrenia patients; these relatives are referred to as being at 'genetic high risk' for psychosis. Cognitive alterations may therefore reflect the expression of genetic vulnerability to schizophrenia (4–7). Identifying such cognitive intermediate phenotypes may be a productive approach in genetic linkage and association studies in schizophrenia, as they are closer to the mechanism for gene action than the overall disease phenotype.

Although evidence on cognitive alterations as intermediate phenotypes of schizophrenia is promising, sample sizes have been limited (8). This is illustrated by the fact that the most recent literature review of studies on the young relatives of psychotic patients included 18 studies with a mean of 102 high-risk relatives (range 29–322) and 84 control subjects (range 26–201), while only five studies included a patient group (mean 76, range 27–207) (4). Thus, the most appealing evidence to date originates from meta-analyses and reviews. Summarizing evidence related to a specific hypothesis can be distorted, however, by the selective publication of studies with certain (especially positive) results (9). In addition, studies on cognition in genetic high-risk samples have been limited by i) the analysis of different biological relatives as one group (siblings, children and parents), ii) the inappropriate screening for psychiatric disorders in the relatives, and iii) limited assessment of cognitive functions (8). In combination with a high within- and between-subject variability of cognitive performance in genetic high-risk samples (8), these methodological limitations may have hampered the identification of cognitive intermediate phenotypes. There is also a lack of knowledge about the proportion of unaffected relatives who display clinically relevant cognitive impairment and what percentage is cognitively spared. While previous studies have estimated the proportion of cognitively spared patients at around 15–30% (8, 10), little is known about this percentage in genetic high-risk subjects.

Aims of the study

The aim of the present study was to test a broad range of cognitive measures as candidate intermediate phenotypes in a large population of patients with a non-affective psychotic disorder, their unaffected siblings and parents, and control subjects. Therefore, age- and gender-adjusted *z*-scores were compared between subject groups. Second, the proportions of clinically relevant cognitive impairment (no, mild, moderate, severe) were compared between subject groups, using both 1 and 2 SD below the control mean as impairment cut-off.

Material and methods

The sample of the Genetic Risk and Outcome of Psychosis study (GROUP) was described previously (11). The baseline GROUP sample consists of 1120 patients with a non-affective psychotic disorder, 1057 unaffected siblings, 919 parents, and 590 unrelated control subjects.

Within the patient group, 84% had a schizophrenia-related disorder (DSM-IV-TR code 295.x, 80% schizophrenia, 13% schizo-affective disorder, 7% schizophreniform disorder; $n = 945$), 1% were diagnosed with psychotic illness in the context of substance abuse or somatic illness (DSM-IV-TR code 293.x/292.x, $n = 9$), and 13% fulfilled criteria for other psychotic disorders (DSM-IV-TR code 297/298, $n = 149$). Six patients had a missing diagnosis but fulfilled inclusion criteria, and 11 patients had a final diagnosis of affective psychosis after fulfilling diagnostic criteria of non-affective psychosis at study entry, which may have been the result of subtle diagnostic changes between the time of identification for inclusion and actual assessment.

The mean age at onset of psychosis was 22.6 ± 6.7 years (range 10–54), and the mean illness duration was 4.4 ± 4.1 years (range 0.1–41.1). At the time of testing, 86.1% of the patients were on antipsychotic treatment with one or more antipsychotics; the most frequently used antipsychotics were olanzapine (27.8%), risperidon (23.7%), and clozapine (11.6%). The mean number of psychotic episodes was 1.7 ± 1.1 (range 1–8), and the mean number of psychiatric hospitalizations was 1.9 ± 2.3 (range 0–30). According to Positive and Negative Syndrome Scale (PANSS) remission criteria (12, 13), 45.1% of the patients were in remission from psychosis at the time of testing. Patients had a mean PANSS positive score of 14.0 ± 6.4 (range 7–41) and a mean PANSS negative score of 15.0 ± 6.6 (range 7–39).

There was a lifetime history of a DSM-IV-TR mental disorder in 12.1% of the siblings (n = 152), 19.4% of the parents (n = 178), and 10.0% of the controls (n = 59). Depressive disorders were by far the most common, reported in 10.5% of siblings (n = 111), 17.7% of parents (n = 163), and 8.5% of controls (n = 50).

Verbal learning and memory was assessed with a visually presented Word Learning Task (WLT; 14). Outcome measures were: immediate recall (number of words recalled over the three 15-word trials), retention rate (delayed free recall after 20 min divided by the maximum score of immediate recall trials 1–3), and recognition (true positives–false positives). Attention/vigilance was assessed using a Continuous Performance Test (CPT-HQ) with working memory load, which is known in the literature as CPT-AX (15). Outcome measures were reaction time (reaction time for correct detections) and accuracy (proportion of correct detections). The Response Shifting Task (RST), a modified version of the Competing Programs Task (16, 17), was administered to assess set-shifting ability from an imitation response rule to a reversal response rule. Outcome variables were accuracy cost (proportion correct in the imitation condition–proportion correct in the reversal condition), and reaction time cost (reaction time in the reversal condition–reaction time in the imitation condition). The first response in each block and the responses that were preceded by errors were excluded from analyses (18). In addition, only reaction times for correct responses were used, and trials with a reaction time shorter than 150 ms were eliminated from the analyses. The WAIS-III (19) subtest Arithmetic was assessed to measure working memory. This subtest is a relatively complex measure of working memory capacity, because it also addresses verbal comprehension and arithmetic skills, both of which are associated with educational level (20). The WAIS-III subtest Digit Symbol-coding was used as a measure of speed of processing. Reasoning and problem solving was assessed using the subtest Block Design from the WAIS-III. The WAIS-III Information subtest was used as a measure of acquired knowledge. The cognitive assessment included two dimensions of social cognition. The outcome measures of the Degraded Facial Affect Recognition task [DFAR; (21)] were the proportion of correctly recognized neutral, happy, fearful and angry faces and the overall proportion of correct answers. The short form of the Benton Facial Recognition Test (BFRT) (22) was assessed to be used as a covariate to adjust for non-emotional facial processing skills. Theory of mind was assessed using the Hinting Task, which assesses the mentalizing capacity required to comprehend real intentions behind indirect speech (23). Outcome measure was the sum of the ten separate item scores (range 0–20). It took approximately 90–120 mins to complete the neuropsychological tests, which were administrated in the following fixed order: WLT immediate recall, RST, CPT-HQ, Digit Symbol-coding, WLT delayed recall, WLT recognition, DFAR, BFRT, Information, Arithmetic, Block Design, Hinting Task.

Statistical analyses

The data were analyzed using the SPSS 17.0 (SPSS Inc., Chicago, IL, USA) statistical package. To facilitate the comparison of cognitive functioning between patients, siblings, parents and control subjects, raw scores were converted into z-scores. Given that patients and siblings belong to different age categories than parents (Table 1), z-scores were adjusted for age and gender by dividing the control group into reference groups, setting the minimum of 50 subjects per stratum. This resulted in the following eight categories following methods described by Keefe et al. (24):

Age ≤20: 71 males and 64 females
Age 21–30: 85 men and 105 women
Age 31–40: 59 men and 65 women
Age ≥41: 55 men and 85 women

Adjusted z-scores were computed as follows. Let X_{jk} be the raw score X on subtest j (j = 1–15) for subject k. Assume that subject k has sex l

Table 1. Socio-demographic characteristics of patients, siblings, parents and controls

					Between-group comparisons	
	Patients, n = 1093	Siblings, n = 1044	Parents, n = 911	Controls, n = 587	Test statistic	P-value
% Male gender	76.2	45.8	42.8	45.5	χ^2 = 308.6	<0.001
Age (years)	27.7 ± 8.1	27.8 ± 8.3	54.8 ± 6.9	30.4 ± 10.6	F = 2354.1	<0.001
WAIS-III estimated IQ†	94.9 ± 16.1	102.6 ± 15.5	103.1 ± 17.0	109.6 ± 15.2	F = 113.3	<0.001
Educational degree subject	4.1 ± 2.0	5.1 ± 2.1	5.1 ± 2.3	5.4 ± 1.8	F = 74.4	<0.001
Educational degree parent	5.2 ± 2.4	5.2 ± 2.4	3.4 ± 2.3	5.0 ± 2.4	F = 33.7	<0.001

†Wechsler-Adult Intelligence Scale short form (54).

(1 = male and 2 = female) and is in age category m (1 ≤ 20, 2 = 21–30, 3 = 31–40, 4 ≥ 41 years). The scaled score is then computed as follows: $z_{\text{corrected}} = (X_{jk} - M_{jlm})/SD_{jlm}$; where M_{jlm} and SD_{jlm} are the mean and the SD, respectively, for test j of the control population for sex l and age category m. Resulting z-scores are identical to Glass's delta estimator of effect size (25). Observations with more than 3 SDs from the mean were considered outliers and were replaced by the mean plus or minus three times the SD.

Subsequently, adjusted z-scores were compared between patients/siblings/parents and control subjects. In addition, adjusted z-scores were compared between siblings/parents and patients. To control for intra-family correlation, mixed-model analyses of covariance (ANCOVAS) were performed in which family was used as a random factor with a random intercept. Status (patient, sibling, parent, control) was the independent variable. Dependent variables were adjusted z-scores for 18 outcome measures derived from 10 cognitive tests. Although educational level of the subject and IQ may be associated with many of the putative intermediate phenotypes in question, they are also powerfully affected by schizophrenia (26). Therefore, the highest educational degree that had been obtained by one of the parents was entered into the model as a covariate instead. Because the Dutch educational system already differentiates after primary school, we chose a coding system other than years of education. This ordinal eight-point scale indicates the level of education and ranges from primary school to university. Mixed-model ANCOVAS for the DFAR variables incorporated the BFRT test scores as an additional covariate. Because mixed-model ANCOVAS were performed for multiple cognitive outcome parameters ($n = 18$), a Bonferroni correction was adopted by setting the alpha level to 0.05/18 = 0.0028.

Between-group comparisons were subsequently performed only in those cognitive parameters for which the effect of Status in the ANCOVA was significant. Five *post hoc* analyses were performed for each of those cognitive parameters, first to compare patients/siblings/parents with controls, and then to compare siblings/parents with patients. For these *post hoc* analyses, the alpha value was set at 0.05/(5 × the number of cognitive parameters for which *post hoc* comparisons were performed). The same correction for multiple analyses was also applied to the much more conservative alpha value of 0.001.

Normality of cognitive outcome measures was visually inspected and confirmed if the test statistic W in the Shapiro–Wilk test exceeded 0.90. All but three outcome measures were normally distributed. Ceiling effects were present for CPT accuracy, WLT recognition, and the Hinting Task. Data transformation did not improve the normality of the distributions; therefore, both parametric and non-parametric testing were conducted. Secondary to the mixed-model ANCOVAS, group comparisons were performed using Kruskal–Wallis tests, which were followed by *post hoc* Mann–Whitney tests with Bonferroni correction. To minimize the risk of type-I errors, the analyses that yielded the most conservative results were chosen for further discussion.

Raw test scores were then converted into dichotomous variables of 'impaired' or 'not impaired'. *A priori*, both 1 SD (27–29) and 2 SD (30) below age- and gender-corrected control mean were selected as the cut-off for clinical impairment. For cognitive tests with more than one outcome measure (e.g., RST reaction time and RST accuracy), an impairment was deemed present if the score of at least one measure was below the cut-off. Impairment scores were summed to generate total impairment scores (range 0–10). Based on the control mean of 1.8 tests with an impairment (based on −1 SD cut-off), the criterion for 'not impaired' was defined as 0–2 tests with an impairment. For the width of the following categories, the control SD of 1.5 was used, resulting in the categories 'mild impairment' (impairment on 3–4 tests), 'moderate impairment' (impairment on 5–6 tests), or 'severe impairment' (impairment on seven or more tests). Total impairment scores were calculated for subjects who had completed at least nine out of 10 cognitive tests. Chi-square tests were used to detect statistically significant differences in total impairment scores between the subject groups. A Bonferroni correction was applied by setting the alpha value to 0.05/16 = 0.003, because four dependent variables were compared between four subject groups. Analyses were performed using SPSS 17.0 for Windows. Release 2.0 of the GROUP database was used for the analyses.

Results

Data inspection

Although WLT recognition was assessed for 89.3% of the subjects, reliable data were available for this task for only 47.7% of all subjects. This was mainly because of technical problems. These test scores were included in the mixed-model ANCOVAS, but not in the calculation of total

impairment scores, which allowed for a maximum of one missing value. Inspection of the missing values for the remaining nine cognitive tests showed that 2922 subjects (79.3%) had completed all tests, while 453 individuals (12.3%) had missing data for one test and 260 individuals (7.1%) had missing data for more than three tests. For 49 individuals (1.3%), no cognitive test results were obtained, so these subjects were excluded from the analyses.

The mean proportion of missing tests was 6.0% (range 3.4–11.4%). Test duration and test rank were not associated with proportion of missings, but tasks with computerized scoring had a higher mean proportion of missings (9.9%) than the paper-pencil scoring tasks (4.1%). When comparing demographic variables of subjects categorized by the number of tests missing (no missings, 1–3 missings, >3 missings, not tested), no significant differences were found for gender, highest educational degree, or age. Patient status, however, was associated with the number of missing values. The proportion of missings between patients ($n = 1093$) and the other three subject groups taken together ($n = 2565$) was 12.5% vs. 12.2% (1–3 tests missing), 9.5% vs. 6.0% (>3 tests missing), and 2.4% vs. 0.9% (not tested), $\chi^2(3) = 28.27$, $P < 0.001$.

Group comparisons

Patients were significantly more often male compared to siblings, parents, and controls. The mean age of patients and siblings was lower than the mean age in controls and in parents. Furthermore, there were statistical differences between the four subject groups in IQ, educational degree of the subject, and educational degree of the parent (Table 1).

Observed means and SD for cognitive test scores and results from mixed-model ANCOVAS are presented in Table 2. Because mixed-model ANCOVAS were significant for 15 out of 18 cognitive outcome measures, *post hoc* tests were denoted as significant at the 0.05 level if the *P*-value was smaller than 0.0007, resulting from $0.05/(5 \times 15)$. Moreover, *post hoc* tests were denoted as significant at the 0.001 level if the *P*-value was smaller than 0.00001, resulting from $0.001/(5 \times 15)$. Age- and gender-adjusted *z*-scores in patients, siblings, and parents are displayed in Fig. 1. Because higher scores reflected worse performance for CPT-HQ reaction time, RST reaction time cost, and RST accuracy cost, *z*-scores for these measures were inverted.

For the three non-normally distributed tests, non-parametric testing yielded somewhat different results compared with the results from mixed-model ANCOVAS. Mann–Whitney testing yielded significantly worse performance on the CPT accuracy in parents (median = 583.65) compared with control subjects (median = 815.42), $U = 143156.50$, $Z = -10.71$, $P < 0.001$, $r = -0.29$. In addition, Mann–Whitney testing did not yield significant results on the WLT recognition for the comparison between patients (median = 451.21) and parents (median = 499.78), $U = 99099.00$, $Z = -2.72$, $P_r = 0.450$, $r = -0.09$, or for the comparison between siblings (median = 386.20) and control subjects (median = 442.00), $U = 66659.50$, $Z = -3.28$, $P = 0.075$, $r = 0.12$. For the Hinting Task, no differences emerged between parametric and non-parametric testing. For WLT recognition, the more conservative non-parametric results were chosen over results from mixed-model ANCOVAS. For the other two tasks, the parametric results were maintained.

Against the background of recent findings (31), the analyses were repeated with cannabis use (current, lifetime, or never) as an additional covariate. Co-varying for cannabis, however, did not change any of the group comparisons from significant to non-significant or vice versa (results not shown).

Total impairment scores

Figure 2a shows that with a cut-off of 1 SD below control mean, 29.6% of patients are classified as having no cognitive impairment against 71.4% of controls, with in-between rates for parents and siblings [$\chi^2(3) = 214.4$, $P < 0.05$]. While the proportions of mild impairment did not differ between subject groups [$\chi^2(3) = 10.4$, $P = 0.12$], both moderate [$\chi^2(3) = 86.3$, $P < 0.05$] and severe impairment [$\chi^2(3) = 127.6$, $P < 0.05$] showed significant differences between groups. Patients showed the highest proportion of moderate and severe impairment and control subjects the lowest, with in-between rates for parents and siblings. Figure 2b shows that with a cut-off score of 2 SD, the rate of subjects classified as having no impairment increased to 70.8% in patients and 98.2% in controls, with in-between rates for parents and siblings [$\chi^2(3) = 225.3$, $P < 0.05$]. Mild impairment rates decreased to 18.5% in patients and 1.3% in controls, $\chi^2(3) = 114.3$, $P < 0.05$. While 7.8% of patients displayed moderate impairment, the percentage was very low in the other three subject groups [$\chi^2(3) = 93.0$, $P < 0.05$]. Severe impairment was rare in patients (2.9%), very rare in parents and siblings (0.2% and 0.3%, respectively), and absent in controls, $\chi^2(3) = 46.8$, $P < 0.05$.

Table 2. Observed means and SD of cognitive test scores and *P*-values of between-subject comparisons following mixed-model ANCOVAS using *z*-standardized scores and adjusting for parental education level

Outcome measure	Patients (*n* = 1093) M (SD)	Siblings (*n* = 1044) M (SD)	Parents (*n* = 911) M (SD)	Controls (*n* = 587) M (SD)	Test statistic (df) *P** value	Patients vs. Controls –	*P** value Siblings vs. Controls Siblings vs. Patients	Parents vs. Controls Parents vs. Patients
WLT immediate recall	22.93 (6.09)	26.89 (5.77)	23.26 (6.11)	28.43 (5.38)	132.17 (3, 3111)	<0.001	<0.001	<0.001
					P < 0.001	–	<0.001	<0.001
WLT retention rate	0.77 (0.21)	0.84 (0.17)	0.78 (0.20)	0.83 (0.16)	13.22 (3, 3105)	<0.001	NS	NS
					P < 0.001	–	<0.001	NS
WLT recognition†	11.03 (3.48)	12.36 (2.99)	11.45 (3.33)	12.96 (2.13)	71.69 (3)	<0.001	NS <0.001	<0.001 NS
					<0.001	–		
RST reaction time cost	205.84 (221.40)	198.43 (208.91)	216.42 (240.00)	194.78 (176.21)	0.72 (3, 2610)	–	–	–
					P = 0.54	–	–	–
RST accuracy cost	0.26 (0.27)	0.22 (0.25)	0.35 (0.33)	0.22 (0.25)	12.38 (3, 2841)	<0.001	NS	NS
					P < 0.001	–	<0.001	NS
CPT reaction time	430.17 (84.43)	410.24 (78.39)	429.01 (81.90)	412.80 (82.67)	37.30 (3, 2856)	<0.001	NS	NS
					P < 0.001	–	<0.001	<0.001
CPT accuracy	98.75 (2.27)	99.51 (1.50)	98.89 (2.18)	99.63 (1.01)	40.62 (3, 2831)	<0.001	NS	NS
					P < 0.001	–	<0.001	<0.001
Digit Symbol-coding	65.43 (16.26)	79.23 (15.44)	67.97 (16.72)	83.89 (14.60)	223.40 (3, 3108)	<0.001	<0.001	<0.001
					P < 0.001	–	<0.001	<0.001
Information	16.78 (5.46)	16.83 (5.20)	17.61 (5.43)	18.82 (4.65)	33.69 (3, 3050)	<0.001	<0.001	<0.001
					P < 0.001	–	<0.05	<0.05
Arithmetic	12.28 (4.78)	13.84 (4.43)	13.70 (4.25)	15.30 (4.16)	122.57 (3, 3110)	<0.001	<0.001	<0.001
					P < 0.001	–	<0.001	<0.001
Block Design	40.47 (17.00)	44.87 (15.08)	32.15 (14.52)	46.55 (14.17)	80.30 (3, 3098)	<0.001	<0.05	<0.001
					P < 0.001	–	<0.001	NS
DFAR neutral	77.76 (17.75)	80.43 (15.03)	76.18 (16.95)	81.14 (15.17)	10.44 (3, 2981)	<0.05	NS	<0.05
					P < 0.001	–	NS	NS
DFAR happy	86.48 (13.07)	88.20 (10.72)	82.59 (13.66)	87.33 (11.12)	5.51 (3, 2981)	–	–	–
					NS	–	–	–
DFAR fearful	47.23 (19.80)	52.54 (19.63)	48.35 (18.98)	53.75 (18.22)	23.39 (3, 2981)	<0.001	NS	NS
					P < 0.001	–	<0.001	<0.001
DFAR angry	62.12 (20.88)	68.81 (19.22)	60.61 (20.46)	70.43 (18.60)	30.06 (3, 2981)	<0.001	NS	<0.001
					P < 0.001	–	<0.001	NS
DFAR total	68.40 (10.77)	72.50 (9.35)	66.93 (10.45)	73.16 (9.13)	40.78 (3, 2981)	<0.001	NS	<0.001
					P < 0.001	–	<0.001	NS
BFRT	22.76 (2.31)	23.17 (2.16)	22.44 (2.44)	23.14 (2.05)	5.73 (3, 3178)	–	–	–
					NS	–	–	–
Hinting Task	17.54 (2.78)	18.84 (1.66)	18.79 (1.62)	19.08 (1.31)	85.31 (3, 3101)	<0.001	NS	<0.05
					P < 0.001	–	<0.001	<0.001

WLT, word learning test; RST, response shifting task; CPT, continuous performance test; DFAR, degraded facial affect recognition; BFRT, Benton facial recognition test.
**P*-values after Bonferroni correction.
†For WLT Recognition more conservative results from non-parametric analyses are presented.

Discussion

Cognitive functioning was analyzed in two ways in this uniquely large sample of patients with psychotic disorder, their unaffected relatives, and control subjects. First, group comparisons revealed that patients performed significantly worse than control subjects in all cognitive domains, while unaffected relatives were outperformed by control subjects in selected domains. Verbal learning and memory, speed of processing, acquired knowledge, working memory, and reasoning and problem solving emerged from these analyses as candidate intermediate phenotypes. Second, additional analyses were conducted to explore how mean group differences translated into proportions of clinically relevant impairment. Based on the 1 SD cut-off, around half of the unaffected relatives displayed some level of cognitive impairment. However, this proportion diminished to around 10% when adapting 2 SD as the cut-off for impairment.

Patients displayed a generalized cognitive alteration extending across most cognitive domains. While patients' scores were significantly below control mean on most cognitive outcome measures, only WLT immediate recall, CPT accuracy, Digit Symbol-coding, Arithmetic, and Hinting Task performance would be classified as impaired according to the traditional neuropsychological criterion of −1 SD below the control mean (27–29). This is in line with previous studies that reported largest effect sizes in the domains of attention, speed of information processing, working memory,

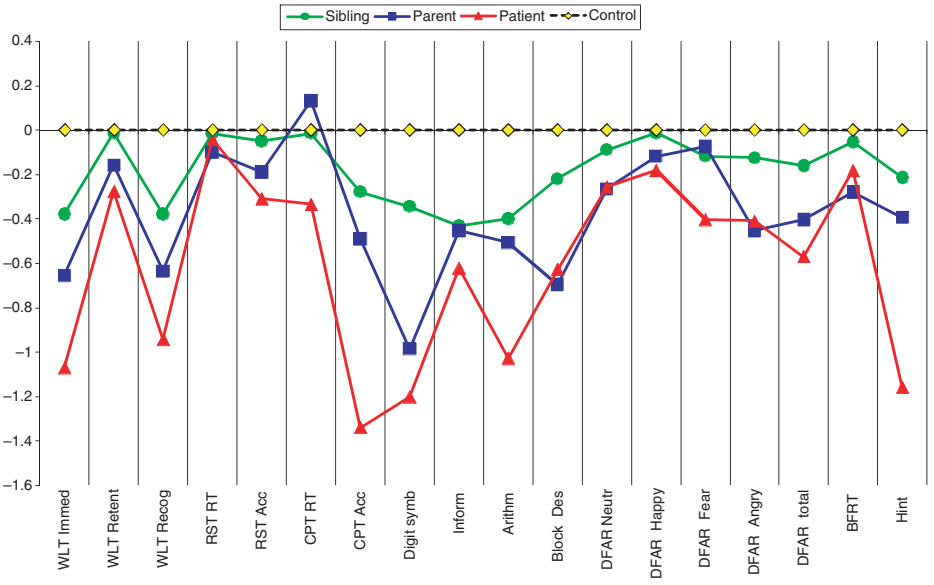

Fig. 1. Age- and gender-corrected *z*-scores for patients, siblings, parents, and controls. WLT, word learning task; Immed, immediate recall; Retent, retention rate; RST, response shifting task; RST RT, reaction time cost; RST Acc, accuracy cost; CPT, continuous performance test; CPT RT, CPT reaction time; CPT Acc, CPT accuracy; Digit symb, Digit Symbol-coding; Inform, information; Arithm, arithmetic; Block Des, block design; DFAR, degraded facial affect recognition; Neutr, neutral; BFRT, Benton facial recognition test; Hint, Hinting Task.

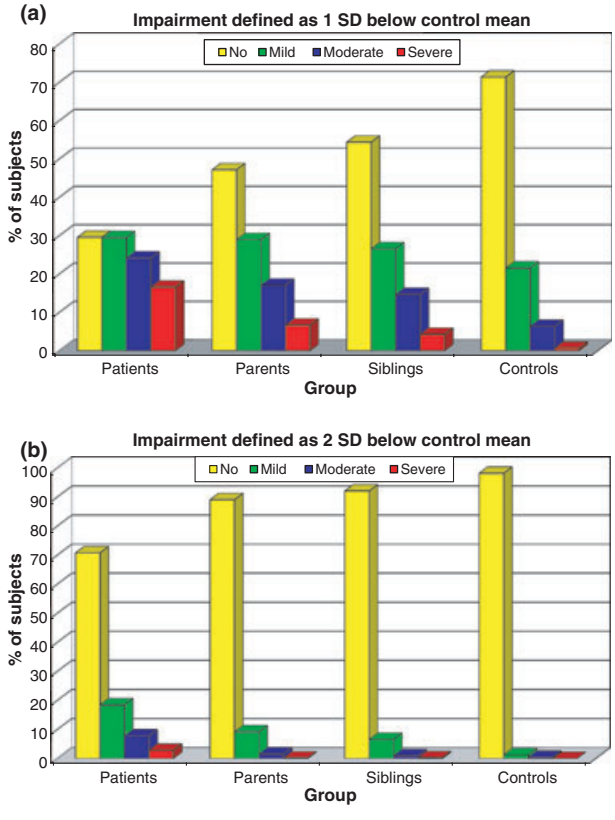

Fig. 2. Proportions 'no' (0–2 tests altered), 'mild' (3–4 tests altered), 'moderate' (5–6 tests altered) and 'severe' alteration (seven or more tests altered) for each subject group. Cut-off scores for alteration are ≤−1 SD (a) and ≤−2 SD (b) from the control mean.

verbal learning and memory (15, 32–34). Impaired performance on the Hinting Task in patients is in accordance with meta-analytic results on theory of mind performance in schizophrenia (35).

Although the neurocognitive pattern in patients is fairly robust across studies, the magnitude of impairment is still under discussion. In the present study, the effect sizes for patients ranged from −0.18 to −1.34 SD, with an average cognitive alteration of −0.61 SD (−0.70 for neurocognition and −0.45 for social cognition). This is mild compared with the approximate average cognitive deficit of −1 SD suggested by previous research in schizophrenia patients (32). One factor that may have contributed to these conservative findings is that setting an extreme of three SD below the mean may have artificially truncated the true range of some cognitive tasks. Another possibility is that the higher percentage of missing data in the patient group may have selected out those who were too impaired to complete cognitive testing. Alternatively, the inclusion of tests that have been previously associated with premorbid intellectual functioning and education (Information, Arithmetic) into a composite score may have produced a measure that is not optimally representative of current neurocognitive impairment (20). Moreover, even though the majority of patients were diagnosed with schizophrenia-related disorders, the decision to include patients with other non-affective psychotic disorders may have

attenuated effect sizes. However, differentiating between non-affective psychotic disorders is sometimes difficult, and focusing exclusively on the inclusion of schizophrenia patients may inflate effect sizes through selection bias. Despite the fact that cognitive dysfunction is not a DSM criterion for schizophrenia, psychotic patients who are cognitively intact may be more likely to be diagnosed with, for example, psychotic disorder not otherwise specified or substance-induced psychosis. Finally, it cannot be excluded that the prerequisite for patients to have family members who were able and willing to participate in the study may have selected out the more socially isolated and impaired patients.

The recognition of happy affect is known to be relatively preserved in patients with psychotic disorder (36), which was also illustrated by our results. The absence of significant alterations in RST conflict reaction time should be interpreted in combination with alterations in RST conflict accuracy. Results suggest that patients have more problems modifying their behavior in response to negative feedback because they do not adapt adequately to the reversal condition by taking relatively more time. This could be explained by diminished cognitive flexibility in schizophrenia, conceptualized as 'the ability to coordinate attention and response to two or more ongoing tasks and to adaptively switch response strategies in accord with contextual demands' (37).

Results in siblings and parents indicate that alterations in the domains of verbal learning, processing speed, reasoning and problem solving, working memory, and acquired knowledge are promising cognitive intermediate phenotypes for schizophrenia, which is supported by the literature (5, 8). Effect sizes for these domains were mild to moderate, and between-group comparisons with control subjects survived Bonferroni correction. The average effect size in siblings was, however, relatively low (−0.18 SD, range −0.01 to −0.43 SD) compared with the literature. Meta-analyses in unaffected relatives have reported effect sizes of −0.37 (range −0.28 to −0.54) and −0.41 (SD = 0.38) (5, 6), which is more in line with the average effect size of −0.34 (range +0.13 to −1.17) found in the present parent sample.

Three cognitive domains – namely attention/vigilance, set-shifting ability, and social cognition – did not show significant alteration in both genetic high-risk groups. Although several studies have reported that siblings perform worse on different versions of the CPT, including the CPT-AX (5, 6, 38), the present study did not find significant differences in siblings and parents. It may be that the CPT used in the present study did not sufficiently burden early aspects of stimulus encoding and perceptual analysis, resulting in a processing load that was too low to be sensitive in relatives (38, 39). Studies investigating set-shifting ability in healthy relatives of patients have yielded mixed results with smaller effect sizes than for various other cognitive functions (5, 6). Furthermore, recent studies suggest that set-shifting ability may not aggregate in families and therefore may not be a robust intermediate phenotype (40). The present study supports these findings and furthermore suggests that set-shifting ability may show only relatively mild alterations in patients (−0.31 SD), in contrast to the large, clinically relevant effect sizes reported previously (32, 33).

While the social cognitive tasks yielded significant performance alterations in parents, differences between siblings and control subjects for DFAR total ($P < 0.02$), DFAR fearful ($P < 0.03$), DFAR angry ($P < 0.02$), and Hinting Task ($P < 0.04$) did not survive Bonferroni correction. Worse performance in parents compared with siblings was unexpected because the parent group has passed the main age period of risk of developing a psychotic disorder (41). It is possible that the sibling group may have been relatively healthy, as perhaps they share fewer risk genes with their affected relatives than the parent group. Alternatively, age differences between the parent group and the oldest control group may have inflated the effect sizes in parents. *Post hoc* analyses in the control group did not, however, show an effect of age on the Hinting Task ($B = 0.00005$, $P = 0.99$) or the DFAR angry faces ($B = -0.09$, $P = 0.23$). Worse theory of mind performance in parents of schizophrenia patients compared with healthy control parents has been reported before (42). Compromised social cognitive functioning in parents but not in siblings supports prior evidence that mentalizing impairment in schizophrenia may reflect general cognitive deficits or residual symptom expression, rather than represent a specific trait marker (43, 44). Previous research has suggested that neurocognition and social cognition are distinct, yet correlated domains in psychosis (45, 46). Social cognition may serve as a mediator between neurocognition and community functioning in patients with psychotic disorder, acting sequentially on the same pathway (45–48). It can therefore be speculated that siblings with neurocognitive alterations in the absence of social cognitive alterations may display no reduction in community functioning, whereas parents who

display both neurocognitive and social cognitive alterations may show diminished community functioning. The validity of this hypothesis should be tested in future studies.

Although comparing mean performance in individual cognitive domains between patients, relatives, and controls provides indispensable information about putative intermediate phenotypes (Fig. 1), it does not show how cognitive alterations are distributed over the subject groups. For example, a mild alteration on a cognitive subtest in siblings could be caused by a majority of siblings displaying mild alterations or by a severe alteration in only a small subgroup. For this reason, total impairment scores were calculated for each of the subject groups. Figure 2a shows that with the cut-off ≤−1 SD from the control mean, fairly equal proportions of patients demonstrated no, mild, moderate, or severe impairments, which corresponds with the concept of a continuum of neurocognitive functioning in patients with schizophrenia (29). The proportion of patients with a neurocognitive profile within the normal range is similar to the 15–30% that was reported in a recent review (10). Moving the cut-off from ≤−1 SD to ≤−2 SD (Fig. 2b) increases dramatically the rate of patients without cognitive impairment, emphasizing the relevance of using more than one criterion for cognitive impairment (49).

The proportions of mild, moderate, and severe cognitive impairment in siblings and parents are intermediate between patients and control subjects, which may represent a dose–response association for genetic load. With the ≤−1 SD cut-off, approximately 50% of the relatives display no alterations against 70% of the control subjects. In a study by Egan *et al*. (49), the proportions of subjects without cognitive impairments (≤−1 SD) were higher: 62–75% in siblings against 77–91% in control subjects. Using ≤−2 SD as a cut-off, these rates rise substantially to around 90% in the relatives. This indicates that with a more conservative criterion of alteration, parents and siblings move away from their affected relatives to become almost indistinguishable from control subjects.

The relatively small effect sizes are especially noteworthy given that education or IQ was not pursued as a covariate. It may be argued that not controlling for these potential confounders may have inflated effect sizes. However, psychotic disorders are neurodevelopmental in nature, and subtle deficits on neurocognitive measures during childhood and adolescence have been associated with an increased risk of non-affective psychosis (50). Controlling for education or IQ would thus be inappropriate, given that they are powerfully affected by psychosis (26) and genetic vulnerability for psychosis (51). Adjusting for education or IQ would successfully 'remove', but not 'control for' the variance because of education and IQ, which are meaningful components of the psychotic disorder phenotype (52). The present study therefore pursued parental education as covariate in the analyses instead (52).

Some limitations should be taken into consideration when interpreting the results. Not all subjects had complete cognitive test scores. This was predominantly because of problems related to computerized assessment and data storage, which form a challenge in multi-centre studies (53). However, patient status also affected the number of missing test results. Therefore, it cannot be excluded that patients with more cognitive alterations were more likely to have missing data, resulting in attenuated effect sizes. Second, the issue that control subjects are often matched to the patient group, resulting in control groups of younger age than the parent or mixed relative group, is a common concern in this field of research (6). In a meta-analysis on cognitive functioning in unaffected relatives, an overall Cohen's d of 0.36 was reported for studies with age-matched groups vs. $d = 0.48$ for those with non-age-matched groups (6). Covarying for age, although appealing, is an inappropriate way of dealing with group differences, because it represents a defining group characteristic of the parent sample (52). Therefore, age- and gender-corrected z-scores were calculated in this study to account for age differences. Although this resulted in the best possible fit, optimal age correction could not be achieved, as parents in the oldest age group had a mean age of 54 against a mean age of 46 in the oldest control group. Higher mean age in parents would most likely inflate performance differences in speeded tasks such as Digit Symbol-coding and CPT. Instead, the tasks that showed more alterations in parents compared with siblings were unspeeded tasks assessing social cognition, making a confounding effect of age less likely.

In conclusion, this study suggests that familial predisposition to psychotic disorder is associated with immediate verbal learning, processing speed, reasoning and problem solving, acquired knowledge, and working memory, with modest effect sizes. Tasks assessing set-shifting ability and vigilance with low processing load did not differentiate relatives from controls. While half of the unaffected relatives may experience some degree of clinically relevant cognitive impairment, severe cognitive impairments seem to be restricted to a minority.

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Declaration of interest

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References

1. Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr Res 2004;**72**:41–51.
2. Broome MR, Matthiasson P, Fusar-Poli P et al. Neural correlates of movement generation in the 'at-risk mental state'. Acta Psychiatr Scand 2010;**122**:295–301.
3. Pukrop R, Klosterkötter J. Neurocognitive indicators of clinical high-risk states for psychosis: a critical review of the evidence. Neurotox Res 2010;**18**:272–286.
4. Keshavan MS, Kulkarni SR, Bhojraj T et al. Premorbid cognitive deficits in young relatives of schizophrenia patients. Front Hum Neurosci 2010;**5**:12.
5. Sitskoorn MM, Aleman A, Ebisch SJH, Appels MCM, Kahn RS. Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. Schizophr Res 2004;**71**:285–295.
6. Snitz B, Macdonald A, Carter C. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. Schizophr Bull 2006;**32**:179–194.
7. Jabben N, Van Os J, Janssen I, Versmissen D, Krabbendam L. Cognitive alterations in groups at risk for psychosis: neutral markers of genetic risk or indicators of social disability? Acta Psychiatr Scand 2007;**116**:253–262.
8. Kéri S, Janka Z. Critical evaluation of cognitive dysfunctions as endophenotypes of schizophrenia. Acta Psychiatr Scand 2004;**110**:83–91.
9. Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. J Clin Epidemiol 2000;**53**:207–216.
10. Palmer B, Dawes S, Heaton R. What do we know about neuropsychological aspects of Schizophrenia? Neuropsychol Rev 2009;**19**:365–384.
11. Genetic Risk and Outcome in Psychosis (GROUP) Investigators. Evidence that familial liability for psychosis is expressed as differential sensitivity to cannabis: an analysis of patient-sibling and sibling-control pairs. Arch Gen Psychiatry 2010;**68**:138–147.
12. Andreasen NC, Carpenter WT Jr., Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. Am J Psychiatry 2005;**162**:441–449.
13. Van Os J, Burns T, Cavallaro R et al. Standardized remission criteria in schizophrenia. Acta Psychiatr Scand 2006;**113**:91–95.
14. Brand N, Jolles J. Learning and retrieval rate of words presented auditorily and visually. J Gen Psychol 1985;**112**:201–210.
15. Nuechterlein KHR, Dawson ME. Information processing and attentional functioning in the developmental course of schizophrenics disorders. Schizophr Bull 1984;**10**:160–203.
16. Bilder RM, Turkel E, Lipschutz-Broch L, Lieberman JA. Antipsychotic medication effects on neuropsychological functions. Psychopharmacol Bull 1992;**28**:353–366.
17. Nolan KA, Bilder RM, Lachman HM, Volavka J. Catechol *O*-methyltransferase Val158Met polymorphism in schizophrenia: differential effects of Val and Met alleles on cognitive stability and flexibility. Am J Psychiatry 2004;**161**:359–361.
18. Meiran N, Levine J, Meiran N, Henik A. Task set switching in schizophrenia. Neuropsychology 2000;**14**:471–482.
19. Wechsler D. WAIS-III: Wechsler adult intelligence scale, 3rd edn. Administration and Scoring Manual. San Antonio, TX, USA: Psychological Corporation, 1997.
20. Egeland J, Bosnes O, Johansen H. Factor structure of the Norwegian version of the WAIS-III in a clinical sample. Assessment 2009;**16**:292–300.
21. Van'T Wout M, Aleman A, Kessels RPC, Larøi F, Kahn RS. Emotional processing in a non-clinical psychosis-prone sample. Schizophr Res 2004;**68**:271–281.
22. Benton AL, Sivan AB, Hamsher K, Varney NR, Spreen O. Benton's test of facial recognition. New York: Oxford University Press, 1983.
23. Versmissen D, Janssen I, Myin-Germeys I et al. Evidence for a relationship between mentalising deficits and paranoia over the psychosis continuum. Schizophr Res 2008;**99**:103–110.
24. Keefe RSE, Harvey PD, Goldberg TE et al. Norms and standardization of the Brief Assessment of Cognition in Schizophrenia (BACS). Schizophr Res 2008;**102**:108–115.
25. Glass GV. Primary, secondary, and meta-analysis of research. Educ Research 1976;**5**:3–8.
26. Greenwood TA, Braff DL, Light GA et al. Initial heritability analyses of endophenotypic measures for schizophrenia: the consortium on the genetics of schizophrenia. Arch Gen Psychiatry 2007;**64**:1242–1250.
27. Heinrichs RW, Awad AG. Neurocognitive subtypes of chronic schizophrenia. Schizophr Res 1993;**9**:49–58.
28. Keefe RSE, Fenton WS. How should DSM-V criteria for schizophrenia include cognitive impairment? Schizophr Bull 2007;**33**:912–920.

29. Palmer BW, Heaton RK, Paulsen JS et al. Is it possible to be schizophrenic yet neuropsychologically normal? Neuropsychology 1997;**11**:437–446.
30. Kremen WS, Seidman LJ, Faraone SV, Toomey R, Tsuang MT. The paradox of normal neuropsychological function in schizophrenia. J Abnorm Psychol 2000;**109**:743–752.
31. Yücel M, Bora E, Lubman DI et al. The impact of cannabis use on cognitive functioning in patients with schizophrenia: a meta-analysis of existing findings and new data in a first-episode sample. Schizophr Bull 2010; 10.1093/schbul/sbq079.
32. Dickinson D, Ramsey ME, Gold JM. Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. Arch Gen Psychiatry 2007;**64**:532–542.
33. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 1998;**12**:426–445.
34. Morice R, Delahunty A. Frontal/executive impairments in schizophrenia. Schizophr Bull 1996;**22**:125–137.
35. Sprong M, Schothorst P, Vos E, Hox J, Van Engeland H. Theory of mind in schizophrenia: meta-analysis. Br J Psychiatry 2007;**191**:5–13.
36. Bediou B, Franck N, Saoud M et al. Effects of emotion and identity on facial affect processing in schizophrenia. Psychiatry Res 2005;**133**:149–157.
37. Savla GN, Twamley EW, Delis DC, Roesch SC, Jeste DV, Palmer BW. Dimensions of executive functioning in schizophrenia and their relationship with processing speed. Schizophr Bull 2010; 10.1093/schbul/sbq149.
38. Gur RE, Nimgaonkar VL, Almasy L et al. Neurocognitive endophenotypes in a multiplex multigenerational family study of schizophrenia. Am J Psychiatry 2007;**164**: 813–819.
39. Cornblatt BA, Keilp JG. Impaired attention, genetics, and the pathophysiology of schizophrenia. Schizophr Bull 1994;**20**:31–46.
40. Ceaser AE, Goldberg TE, Egan MF, Mcmahon RP, Weinberger DR, Gold JM. Set-shifting ability and schizophrenia: a marker of clinical illness or an intermediate phenotype? Biol Psychiatry 2008;**64**:782–788.
41. Appels MCM, Sitskoorn MM, De Boo M et al. Neurological signs in parents of schizophrenic patients. NeuroReport 2002;**13**:575–579.
42. Anselmetti S, Bechi M, Bosia M et al. 'Theory' of mind impairment in patients affected by schizophrenia and in their parents. Schizophr Res 2009;**115**:278–285.
43. Bora E, Yücel M, Pantelis C. Theory of mind impairment: a distinct trait-marker for schizophrenia spectrum disorders and bipolar disorder? Acta Psychiatr Scand 2009;**120**:253–264.
44. Kelemen O, Kéri S, Must A, Benedek G, Janka Z. No evidence for impaired 'theory of mind' in unaffected first-degree relatives of schizophrenia patients. Acta Psychiatr Scand 2004;**110**:146–149.
45. Sergi MJ, Rassovsky Y, Widmark C et al. Social cognition in schizophrenia: relationships with neurocognition and negative symptoms. Schizophr Res 2007;**90**:316–324.
46. Van Hooren S, Versmissen D, Janssen I et al. Social cognition and neurocognition as independent domains in psychosis. Schizophr Res 2008;**103**:257–265.
47. Addington J, Saeedi H, Addington D. Influence of social perception and social knowledge on cognitive and social functioning in early psychosis. Br J Psychiatry 2006;**189**:373–378.
48. Vauth R, Rüsch N, Wirtz M, Corrigan PW. Does social cognition influence the relation between neurocognitive deficits and vocational functioning in schizophrenia? Psychiatry Res 2004;**128**:155–165.
49. Egan MF, Goldberg TE, Gscheidle T et al. Relative risk for cognitive impairments in siblings of patients with schizophrenia. Biol Psychiatry 2001;**50**:98–107.
50. Welham J, Scott J, Williams GM et al. The antecedents of non-affective psychosis in a birth-cohort, with a focus on measures related to cognitive ability, attentional dysfunction and speech problems. Acta Psychiatr Scand 2010;**121**:273–279.
51. Kremen WS, Seidman LJ, Faraone SV, Pepple JR, Lyons MJ, Tsuang MT. The '3 Rs' and neuropsychological function in schizophrenia: a test of the matching fallacy in biological relatives. Psychiatry Res 1995;**56**:135–143.
52. Miller GM, Chapman JP. Misunderstanding analysis of covariance. J Abnorm Psychol 2001;**110**:40–48.
53. Keefe RSE, Bilder RM, Harvey PD et al. Baseline neurocognitive deficits in the CATIE schizophrenia trial. Neuropsychopharmacology 2006;**31**:2033–2046.
54. Blyler CR, Gold JM, Iannone VN, Buchanan RW. Short form of the WAIS-III for use with patients with schizophrenia. Schizophr Res 2000;**46**:209–215.

Appendix 1

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