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Are Psychotic Psychopathology and Neurocognition Orthogonal? A Systematic Review of Their Associations

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A systematic review (58 studies, 5,009 individuals) is presented of associations between psychopathological dimensions of psychosis and measures of neurocognitive impairment in subjects with a lifetime history of nonaffective psychosis. Results showed that negative and disorganized dimensions were significantly but modestly associated with cognitive deficits (correlations from −.29 to −.12). In contrast, positive and depressive dimensions of psychopathology were not associated with neurocognitive measures. The patterns of association for the 4 psychosis dimensions were stable across neurocognitive domains and were independent of age, gender, and chronicity of illness. In addition, significantly higher correlations were found for the negative dimension in relation to verbal fluency ($p = .005$) and for the disorganized dimension in relation to reasoning and problem solving ($p = .004$) and to attention/vigilance ($p = .03$). Psychotic psychopathology and neurocognition are not entirely orthogonal, as heterogeneity in nonaffective psychosis is weakly but meaningfully associated with measures of neurocognition. This association suggests that differential latent cerebral mechanisms underlie the cluster of disorganized and negative symptoms versus that of positive and affective symptoms.

Keywords: meta-analysis, systematic review, psychosis dimensions, cognitive disorders, neurocognition

Measures of psychopathology define the diagnostic phenotype in nonaffective psychotic disorder (Dikeos et al., 2006; Grube, Bilder, & Goldman, 1998; Lindenmayer, Grochowski, & Hyman, 1995; McGorry, Bell, Dudgeon, & Jackson, 1998). Cognitive impairment is an important feature of psychotic disorder (Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; Heinrichs & Zakzanis, 1998) that reflects developmental impairment and expression of genetic risk (Nuechterlein & Dawson, 1984; Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004; Strauss, Buchanan, & Hale, 1993; Szoke et al., 2005). Although it has been suggested that cognitive impairment is not associated with dimensions of psychopathology in nonaffective psychotic disorder (Green, 1996), there is evidence suggesting subtle and contrasting associations (Kerns & Berenbaum, 2002; Nieuwenstein, Aleman, & de Haan, 2001) that may yield important clues to differential underlying cerebral alterations.

Two meta-analyses have been performed in this field. The meta-analysis by Nieuwenstein et al. (2001) provided a quantitative review of the relations between three dimensions of schizophrenia symptoms (negative and positive dimensions, the latter subdivided into disorganization and reality distortion) and performance on two neuropsychological tests related to executive function and vigilance: the Wisconsin Card Sorting Test (WCST; 16 studies) and the Continuous Performance Test (CPT; 6 studies), respectively. Negative symptoms were significantly associated with impairments in both domains of cognitive functioning. Disorganization showed a significant association with worse WCST performance but not with CPT performance. Although significant, the effect sizes were small to modest in magnitude. General scores for all positive symptoms and separate scores for reality distortion symptoms were not associated with either WCST or CPT performance. Moderator analyses indicated that neither age, nor gender, nor duration of illness affected the overall effect sizes. Another meta-analysis, reported by Kerns and Berenbaum (2002), was focused exclusively on formal thought disorder and examined which of four specific cognitive domains would be associated with this psychopathological measure. Kerns and Berenbaum concluded that impaired executive functioning (26 studies) and impaired semantic memory (8 studies) were consistently associated but that increased spreading activation (5 studies) and impaired language production (5 studies) were not. Although informative, these meta-

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analyses were not complete, in that many other studies in nonaffective psychosis have assessed associations between domains of neurocognition and psychopathology (in particular, depression) that they did not cover.

The advantage of a systematic approach that includes affective measures of psychopathology and all measures of neurocognition is that such an approach allows examination of meaningful contrasts. Previous work (Myin Germeys, Krabbendam, Jolles, Delespaul, & van Os, 2002) has suggested that negative symptoms are and positive/affective symptoms are not associated with measures of neurocognition, and this finding may be compatible with two contrasting and possibly even mutually exclusive pathways to psychosis. Therefore, establishment of differential patterns of cognitive performance among the different psychopathological dimensions may yield further insight into the underlying mechanisms of heterogeneity of psychosis. Thus, differential patterns of neurocognition were hypothesized between the positive/affective dimensions on the one hand and the negative/disorganization dimensions on the other.

Method

Data Sources and Literature Search

Articles were identified through a literature search in MEDLINE and PsychINFO, the latter of which also references unpublished works such as those found in Dissertation Abstracts. The search covered the period from January 1977 to April 2008. We used a start date of 1977 and included the following psychiatric classification systems: *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 1980, 1987, 1994); research diagnostic criteria (Spitzer, Endicott, & Robins, 1978); Schedule for Affective Disorders and Schizophrenia (Endicott & Spitzer, 1978); and *International Classification of Diseases* (World Health Organization, 1977, 1990). The keywords were *psychosis* or s*chizophrenia,* combined with *neuropsychol** or *neurocogn*,* combined with *positive* or *negative* or *disorg** or *depressive.* The search produced 3,098 articles. References provided by relevant meta-analyses (Kerns & Berenbaum, 2002; Nieuwenstein et al., 2001) and included in the retrieved articles were examined and yielded an additional 31 articles. We contacted the authors of the 15 unpublished dissertation abstracts that were potentially eligible for inclusion in order to retrieve the necessary data. One author responded and referred to a later publication in which all relevant data were reported. Therefore, the abstracts of 3,129 articles were examined for possible inclusion in the analysis.

Criteria for Inclusion and Exclusion

The following criteria guided the inclusion of studies in the meta-analysis: (a) the sample consisted of patients with a lifetime history of nonaffective psychosis according to a recognized criterion-based diagnostic system; (b) the study used standardized and reliable clinical scales and neuropsychological tasks; (c) the study reported all the correlations between symptom dimensions and neuropsychological performance; and (d) the study was published as an original article in a peer-reviewed, English-language journal. Studies that included groups of patients with special characteristics that possibly affected neuropsychological performance (e.g., geriatric patients or patients with childhood psychosis) were excluded.

Overlapping of Samples

The studies that fulfilled the inclusion criteria were examined for possibly overlapping samples. Authors whose studies were performed in the same departments or areas were contacted and were asked to provide the relevant information. Any overlap was dealt with in one of three ways: (a) Of the studies with complete overlap in samples and clinical/cognitive measures, the study with the smaller sample size was excluded. This was the case for Good et al. (2004) versus Heydebrand et al. (2004), Docherty and Gordinier (1999) versus A. S. Cohen and Docherty (2004), and J. Addington and Addington (1998) versus J. Addington and Addington (1997). (b) Of the pairs of studies with overlap in samples but without overlap in the examined associations between cognitive domains and psychopathological dimensions, both studies were included, but the size of the smallest sample from each pair was subtracted from the total number of individuals who contributed to the meta-analysis. This was the case for Woodward, Ruff, Thornton, Moritz, and Liddle (2003) versus Woodward, Thornton, Ruff, Moritz, and Liddle (2004) and O'Leary et al. (2000) versus Torres, O'Leary, and Andreasen (2004). (c) Of the pairs of studies in which the degree of overlap in the samples was uncertain, all the studies were initially included in the analysis, and sensitivity analyses were conducted in which the studies with the smallest samples of each pair were excluded. This was the case for Braff et al. (1991) versus Perry and Braff (1998) and Himelhoch, Taylor, Goldman, and Tandon (1996) versus Tandon et al. (2000).

Psychosis Dimensions

Four psychosis dimensions (positive, negative, disorganized, and depressive) were a priori considered to be of interest. Each had been reliably established as a constellation of symptoms of psychosis in previous work (Dikeos et al., 2006; Grube et al., 1998; Lindenmayer et al., 1995; McGorry et al., 1998). The positive dimension included delusions, ideas of reference, unusual thought content, hallucinations, grandiosity, and suspiciousness/persecution. The negative dimension included alogia, affective flattening, avolition, apathy, anhedonia, asociality, social withdrawal, stereotyped thinking, and motor retardation. The disorganized dimension included conceptual disorganization, positive formal thought disorder, difficulty in abstract thinking, derailment, tangentiality, incoherence, illogicality, circumstantiality, associative loosening, inattention/distractibility, disorientation, inappropriate affect, bizarre behavior, mannerisms, and posturing. The depressive dimension consisted of observed depression, hopelessness, self-depreciation, feelings of guilt, guilty ideas of reference, early wakening, suicidal ideation, anxiety, and active social avoidance.

The following clinical scales were used in the studies: the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1981), the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984), the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987), Symptoms and Signs of Psychotic Illness (SSPI; Liddle, 1992), the Brief Psychiatry Rating Scale (BPRS; Overall & Gorham, 1962), Community Adjustment Form (CAF; Test et al., 1991), the High Royds Evaluation of

Negativity Scale (HEN; Mortimer, McKenna, Lund, & Mannuzza, 1989), the Calgary Depression Scale (CDS; D. Addington, Addington, & Schissel, 1990), the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960), positive symptoms from the Present State Examination interview (PSE; Wing, Cooper, & Sartorius, 1974), the Scale for the Assessment of Thought, Language, and Communication (TLC; Andreasen, 1979), the Manchester Scale (Krawiecka, Goldberg, & Vaughan, 1977), the Positive and Negative and Disorganized Symptoms Scale (PANADSS; Andresen & Moritz, 2000), and the Comprehensive Assessment of Symptoms and History (CASH; Andreasen, 1987).

Cognitive Domains

The neuropsychological tests we used in the studies were divided into nine categories that measure approximately the same cognitive construct (see Table 1). The classification was based on the MATRICS consensus (Buchanan et al., 2005), which proposed six neurocognitive constructs: reasoning and problem solving, speed of processing, attention/vigilance, working memory (verbal), verbal learning and memory, and visual learning and memory. The result of factor analytic studies, these six separable neurocognitive factors were replicable across studies and are thought to represent fundamental dimensions of cognitive deficit in schizophrenia (Nuechterlein et al., 2004).

Three other neurocognitive domains were included in the analysis on the basis of evidence of cognitive impairment in specific domains, as reported in previous meta-analyses. IQ was included as a measure of general intelligence (Fioravanti et al., 2005; Heinrichs & Zakzanis, 1998). In accordance with the discussion in the review by Nuechterlein et al. (2004), verbal fluency was examined as a separate factor, given previous meta-analyses that reported substantial impairment of verbal fluency in schizophrenia (Heinrichs & Zakzanis, 1998; Johnson Selfridge & Zalewski, 2001). Finally, the construct of executive control was added and assessed with the Stroop Color–Word interference (Stroop, 1935). This test is thought to reflect executive functioning (Derrfuss, Brass, Neumann, & von Cramon, 2005), which is substantially impaired in schizophrenia (Johnson Selfridge & Zalewski, 2001).

First, data on estimated IQ were reported by 14 studies. Of these studies, 13 were based on the full scale of the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1955) or the Wechsler Adult Intelligence Scale—Revised (WAIS–R; Wechsler, 1981) and 1 was based on a short form of the Wechsler Adult Intelligence Scale—Third Edition (WAIS–III; Wechsler, 1997). We did not include IQ estimates that were based on one or two subtests of the WAIS.

Second, reasoning and problem solving was assessed by 30 studies that used the Wisconsin Card Sorting Test (WCST; Heaton, 1981) and 3 studies that used Nelson's Modified Card Sorting Test

Table 1
Cognitive Domains, Tests, and Parameters

Cognitive domain	Cognitive tests	Test parameters
IQ	Wechsler Adult Intelligence Scale (Wechsler, 1955); Wechsler Adult Intelligence Scale–Revised (Wechsler, 1981); Wechsler Adult Intelligence Scale—Third Edition (Wechsler, 1997)	• Full-scale IQ
Reasoning and problem solving	Wisconsin Card Sorting Test (Heaton, 1981) Nelson's Modified Card Sorting Test (Nelson, 1976)	• Number or percentage of categories completed • Number or percentage of perseverative errors
Executive control	Stroop Color–Word Test interference (Stroop, 1935)	• Number of incongruent words read (number of correct responses) • Number of incongruent errors made
Verbal fluency	Either words from a certain category or words beginning with a certain letter	• Number of words generated either from a certain category or beginning with a certain letter
Speed of processing	Digit Symbol Substitution Test (Wechsler, 1955) Trail Making Test Parts A and B (Reitan, 1958) Stroop Color–Word Test (Stroop, 1935)	• Number of symbols correctly copied • Time in seconds to complete the task • Colors (time in seconds to complete) • Names (time in seconds to complete)
Attention/vigilance	Continuous Performance Test (Nuechterlein & Dawson, 1984) and its variations (e.g., Letter–Number Span)	• Number or percentage of omissions • Number or percentage of commissions • Response sensitivity (d'–A')
Verbal working memory	Digit Span Backward (Wechsler, 1955) Letter–Number Span (Gold et al., 1997)	• Total number of digits recalled • Number of correct sequences
Verbal learning and memory	California Verbal Learning Test (Delis et al., 1987) Rey Auditory Verbal Learning Test (Rey, 1964) Wechsler Memory Scale—Revised (WMS–R; Wechsler, 1987), Paired-Associate Learning subtest Hopkins Verbal Learning Test (Brandt, 1991) Story recall (the Logical Memory subtest from the WMS–R; Wechsler, 1987)	• Total number of correct responses on either immediate or delayed recall
Visual learning and memory	Benton Visual Retention Test (Benton, 1992) WMS–R visual memory (Wechsler, 1987) Rey–Osterrieth Complex Figure (Rey, 1941)	• Total number of items on either immediate or delayed recall

(Nelson, 1976). Many studies reported two WCST parameters, namely, number of categories achieved and number of perseverative errors; these data were pooled into a combined effect size, as factor analyses have indicated that these variables load on a single factor of perseveration (Nuechterlein et al., 2004).

Third, the construct of executive control was assessed in 10 studies with the Stroop Color–Word interference (Stroop, 1935).

Fourth, verbal fluency, either words from a certain category or words beginning with a certain letter, was assessed in 23 studies.

Fifth, speed of proccessing was assessed with the Digit Symbol Substitution Test (Wechsler, 1955) in 8 studies, the Trail Making Test Parts A and B (Reitan, 1958) in 19 studies, and the Stroop Color–Word name and color lists (Stroop, 1935) in 3 studies.

Sixth, attention/vigilance was measured by 18 studies that used a Continuous Performance Test (CPT; Nuechterlein & Dawson, 1984) and its variations. Several studies reported more than one CPT parameter; these were combined into one measure of accuracy. Reaction time variables for the CPT were not used.

Seventh, verbal working memory was assessed with the Digit Span Backward (Wechsler, 1955) in nine studies and with the Letter–Number Span (Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997) in two studies.

Eighth, verbal learning and memory was assessed with (a) word list learning tasks (the California Verbal Learning Test, Delis, Kramer, Kaplan, & Ober, 1987 [5 studies]; the Rey Auditory Verbal Learning Test, Rey, 1964 [4 studies]; the Associate Learning subtest from the Wechsler Memory Scale—Revised [WMS–R], Wechsler, 1987 [5 studies]; or the Hopkins Verbal Learning Test, Brandt, 1991 [3 studies]) or (b) story recall (the Logical Memory subtest from the WMS–R, Wechsler, 1987 [8 studies]). Both immediate and delayed recall were included, given that the results from factor analysis revealed that both loaded on the same factor (Nuechterlein et al., 2004).

Ninth, visual learning and memory was measured with the Benton Visual Retention Test (Benton, 1992; three studies), the Visual Reproduction subtest from the WMS–R (Wechsler, 1987; five studies), or the Rey–Osterrieth Complex Figure (Rey, 1941; six studies); again, immediate and delayed measures were included.

No combined effect sizes were calculated for other possible domains, such as language, reasoning, and visuoperceptual and visuospatial functions, or for performance on a single composite cognitive score because of lack of data and/or substantial heterogeneity between the tests used to assess these domains.

Statistical Analysis

The relevant results from the included studies were quantified in terms of correlations. Because higher scores reflected worse performance for some measures and lower scores reflected worse performance for other measures, all correlations were recoded such that a negative correlation indicated an association between higher levels of symptomatology and worse cognitive performance. Before the meta-analytic methods were applied (as discussed below), the correlations were transformed with Fisher's *r*-to-*z* transformation. The results from the meta-analyses were back-transformed into the raw correlation metric whenever possible (e.g., estimated mean correlations, confidence interval bounds). Data extraction and calculations of effect sizes were performed independently by Maria de Gracia Dominguez and Claudia J. P. Simons, who reached consensus in case of discrepancies. All analyses were carried out with the statistical software packages R and S-plus.

Four steps were performed for the analyses. First, we conducted 36 individual meta-analyses that examined the correlation between the four psychosis dimensions and the nine cognitive domains. Only analyses based on five or more observations were considered. When multiple correlation coefficients were reported for one cognitive domain–psychosis dimension combination within a single sample, these coefficients were first averaged into one *r* value. We used a random-effects model to account for heterogeneity among the population correlations and to obtain unconditional inferences about the distribution of population correlations (Hedges & Vevea, 1998). For each of these individual meta-analyses, we report k (number of studies); $\hat{\mu}_\rho$ (estimated average correlation in the population distribution); 95% confidence interval (CI) for μ_ρ; p (p value for the test H_0:$\mu_\rho = 0$); and I^2 (percentage of the total variability in the observed correlation coefficients due to heterogeneity). Values of I^2 equal to 0 indicate the absence of heterogeneity, in which case the random-effects model simplifies to a fixed-effects model. In that case, $\hat{\mu}_\rho = \hat{\rho}$, where $\hat{\rho}$ denotes the estimated true (homogeneous) correlation.

As part of this step, we also examined the data for the presence of publication bias. In general, publication bias occurs whenever the results obtained from the published literature are not representative for all of the research that has been conducted on a particular topic. One of the most problematic forms of publication bias is the over- or underrepresentation of particular findings on the basis of their statistical significance. As a result, the estimate of the true correlation can become severely biased. In the absence of this form of publication bias, we would expect to see a more or less symmetric (inverted) funnel when we plotted the observed correlations against their corresponding sample sizes (a so-called funnel plot). However, when studies with nonsignificant findings are suppressed from the published literature, the plot can become asymmetrical, and this leads to an association between the correlations and the corresponding sample sizes. The regression test for funnel plot asymmetry examines whether such an association is present in the data; the presence of an association would be indicative of publication bias and would call the findings into doubt (Sterne & Egger, 2005).

Regression tests for funnel plot asymmetry were conducted for each of the 9×4 meta-analyses. We also examined funnel plots for asymmetry in terms of the correlations between all of the cognitive domains and each psychopathological dimension (i.e., one funnel plot for each dimension). Because the same sample could contribute multiple correlations to the funnel plot in this case, dependencies were present. We decided not to model these dependencies, as doing so would have required us to obtain information (or estimates) of the $9(8)/2 = 36$ intercorrelations between the nine cognitive dimensions. Therefore, the results from the regression test for funnel plot asymmetry for those four funnel plots have to be treated with some caution.

Second, three variables (two sociodemographic and one clinical) were a priori chosen to be included in the analyses as moderators, as these variables have been reported as factors that influence the relationship between cognition and symptoms and therefore may account for at least some of the heterogeneity observed in the meta-analyses. Specifically, the three moderators were (a) chro-

nicity of illness (in years), (b) mean age, and (c) percentage of men. It was hypothesized that studies that included more chronically ill or older or male subjects would show stronger associations between cognition and symptoms (Dikeos et al., 2006; Murray et al., 2005; Schultz et al., 1997; Simonsen et al., 2007). We examined a fourth moderator for the positive dimension that indicated whether the positive subscale included any symptoms of disorganization, as this had been done in the older studies in particular. Inclusion of symptoms of disorganization in the positive subscale was expected to increase the correlations with the cognitive domains (Liddle & Morris, 1991; Nieuwenstein et al., 2001).

We used a mixed-effects model to examine the influence of the moderators on the average correlation within each psychosis dimension–cognitive domain combination. The amount of residual heterogeneity was estimated with the method of moments estimator on the basis of weighted least squares (Raudenbush, 1994). Because information about some of the moderator values within the studies was missing, we decided to examine each moderator individually (instead of including all moderators simultaneously within a single model). Results are expressed in terms of the estimated regression coefficient $\hat{\beta}$ and indicate by how much the average correlation (in the transformed units) is estimated to change with a 1-unit increase in the moderators. For age and chronicity of illness, 1 unit means 1 year; for men, 1 unit means 1%; and for positive–disorganized, 1 unit means going from (0) positive symptoms to (1) positive and disorganized symptoms. The corresponding 95% CI for the true regression coefficient is given also. Because the *r*-to-*z* transformation is nonlinear, one cannot easily back-transform the slope of the regression coefficient into the raw correlation metric.

Third, within each of the cognitive domains, we examined whether the average correlation coefficient differed between the negative and disorganized dimensions, in order to further clarify the controversial issue of differential patterns of cognitive impairment related to both (Liddle, 1987; Nieuwenstein et al., 2001). Because numerous samples/studies contributed correlations between a particular domain and both dimensions, we had to account for the dependencies between multiple correlations from a single sample. We estimated the covariance between two *r*-to-*z* transformed correlations from a single sample using Equation 10 given by Steiger (1980) and replaced parameters with their corresponding sample estimates where necessary. In doing so, we had to estimate the correlation between the two dimensions on the basis of previous literature (none of the studies reported these correlations). For this analysis, the correlation between the negative and the disorganized dimension was estimated at .39 (Peralta, Cuesta, & de Leon, 1994). Sensitivity analyses were conducted using two other assumed correlation values (i.e., .20 and .60).

Fourth, in order to deal with potential overlap in the samples in the three previous steps of the statistical analyses, we conducted sensitivity analyses that excluded the smallest studies of each pair with an uncertain degree of overlap, as discussed before.

Results

Of the 3,129 studies produced by the search, 187 were considered eligible for inclusion. Of these, 129 were excluded, because (a) the study examined associations with single symptom items (3.1% of the total number of studies not included); (b) the study split the subject sample into groups on the basis of their score on the different clinical scales (27.9%) or on the basis of their cognitive performance (6.2%) and reported the associations with these groups; (c) the study reported only correlations that were statistically significant (24%); (d) the study used neuropsychological tasks that were not used in any of the other included studies or that could not be classified under one of the cognitive domains (24%); (e) the study reported global cognitive or psychopathology scores (2.3%); (f) the study sample completely overlapped with a larger study that was included (2.3%); or (g) the authors did not reply to the request to provide additional data (10.1%).

The literature search thus yielded 58 studies that evaluated psychosis dimensions and cognitive performance in patients with a lifetime history of nonaffective psychosis, according to standardized neuropsychological instruments. These studies are listed in Table 2, along with the sample sizes and the main sample characteristics. In total, 5,009 individuals with a diagnosis of nonaffective psychosis contributed to this meta-analysis. The patients were 72.7% men (reported by 57 articles). The mean age of the patients ranged from 19.1 years to 51.9 years (reported by 55 articles). Mean chronicity of illness ranged from 4.8 years to 28.9 years (reported by 37 articles). The mean age of illness onset ranged from 18.6 years to 26.23 years (reported by 18 articles). The mean years of education ranged from 9.9 to 13.7 (reported by 39 articles). A total of 58% of the subjects were inpatients (reported by 44 articles). Of the patients, 94% were diagnosed with schizophrenia, 3% with schizoaffective disorder, and 3% with delusional and other psychotic disorders (reported by 55 articles). Other variables, such as level of symptoms, dosage of antipsychotic medication, percentage of patients on typical versus atypical medication, and number of prior psychotic episodes, may be relevant for the association between symptoms and cognition but were reported by too few studies. A table with all data points is not presented, due to space constraints.

Meta-Analyses of Correlations Between Cognitive Domains and Psychosis Dimensions

Results for the meta-analyses are shown in Table 3 (for visual representation, see Figure 1). Both the negative and the disorganized dimensions were significantly and negatively correlated with the majority of the nine cognitive domains, with averaged correlations in the order of −.29 to −.12. The largest effect sizes (estimated correlation higher than −.2) were for verbal fluency, verbal learning and memory, and IQ in the negative dimension and for attention/vigilance, visual learning and memory, and IQ in the disorganized domain. The correlations with the positive dimension were neither large nor significant, except for a negative correlation with the domain of speed of processing ($\hat{\mu}_\rho = -0.089$; 95% CI = −0.164 to −0.012), which indicated that worse performance was associated with a higher level of symptoms. For the analysis of the depressive dimension, none of the correlations were either large or significant; however, five or more observations were available for only three cognitive domains.

Regression Test for Funnel Plot Asymmetry

None of the regression tests for funnel plot asymmetry were significant for the 36 pairs of psychosis dimensions and cognitive

Table 2
Studies Included in the Meta-Analysis and Its Descriptive Variables

Study	*N*	Men (%)	Age (years)	Education (years)	Chronicity of illness	% inpatients	Schizophrenia	Schizoaffective	Delusional and others	Clinical scale	IQ scale
J. Addington & Addington (1997)	59	67.8	33	11.5	10.5	100	100	0	0	PANSS	
J. Addington & Addington (1999)	80	67.5	36	12		100	100	0	0	PANSS	
J. Addington et al. (1991)	38	65.8	30.9	11.5		100	100	0	0	SANS	WAIS
Basso et al. (1998)	62	72.6	32.26	13.68	9.82	14.51	100	0	0	SANS/SAPS	WAIS
Baxter & Liddle (1998)	55	71.4	37.8		16.6	100	100	0	0	SSPI	NART/Quick Test
Bell et al. (1994)	147	95.2	42	12		18.4	67.3	32.6	0	PANSS	Slosson
Bell & Mishara (2006)	267	87	43.1	12.9	20.5	0			0	PANSS	WAIS
Berman et al. (1997)	30	96.66	50.6	12.3		100	100	0	0	PANSS	WAIS
Bozikas et al. (2004)	56	71	37.45	10.37	10.31	0	100	0	0	PANSS	
Braff et al. (1991)	40	75	29.7	13.3		0	100	0	0	SANS/SAPS	WAIS
Brebion et al. (1997)	31	74	35.3	12.1	12.3	100	100	0	0	PANSS	
Brekke et al. (1995)	40	62.5	33.2	12.5		0	57.5	42.5	0	BPRS/CAF	
Bryson et al. (1999)	120	95.8	43.46	12.57		0	78.33	21.7	0	PANSS	WAIS–R
Cameron et al. (2002)	52	76.92	37.5		14.9	0	100	0	0	PANSS	NART
Chen et al. (1996)	176	59.8	40.5		15.1	100	100	0	0	HEN	WAIS
A. S. Cohen & Docherty (2004)	38	70	35.6	12.5		0	100	0	0	BPRS	SILS
A. S. Cohen & Docherty (2005)	76	61.64	36	12.4		0	100	0	0	SAPS	SILS
R. M. Cohen et al. (1998)	13	100	32.6		13.2	100	100	0	0	SANS	
Collins et al. (1997)	58	77.58	34.1	12.47	14.24	0	100	0	0	PANSS/CDS	
Donohoe et al. (2006)	32	66			15.63	0	100	0	0	PANSS	NART
Eckman & Shean (2000)	51	62.74	40.9	11.1		100	100	0	0	SANS/SAPS	
Ehmann et al. (2004)	37	86.48	30	11.24		100	75.67	24.32	0	PANSS	WAIS–R
Franke et al. (1992)	73	63.01	32.5	9.9	4.8	100	100	0	0	SANS/SAPS	
Guillem et al. (2001)	27	59.25	38.1				100	0	0	SAPS/SANS	
Hammer (1995)	65	87.69	28.28			100	100	0	0	SANS/PSE	WAIS–R
Heydebrand et al. (2004)	307	75.89	25				53.42	9.44	37.13	PANSS	
Himelhoch et al. (1996)	47	75	29.4	13.3	7.44	100	100	0	0	SANS/BRPS	
Holthausen et al. (1999)	50	68	25				64	0	36	PANSS	
Ihara et al. (2003)	43	51.16	44.2	12.46	15.25		100	0	0	PANSS	NART
Ito et al. (1997)	49	61.2	40.9	11.6	17	97.75	100	0	0	BPRS	
Keefe et al. (2006)	1,332	74	40.56	12.1	14.43		100	0	0	PANSS	
Krishnadas et al. (2007)	25	64	40.16	9.08	11.32	0	100	0	0	SANS/HRSD	
Less-Roitman et al. (1997)	30	100	43.13	12.25	20.55		100	0	0	BPRS	WAIS
Liddle & Morris (1991)	40	65.11	51.9		28.9	100	100	0	0	SANS/Manchester	
Lucas et al. (2004)	53		19.1	10.8			77	2	21	PANSS/CDS	WAIS–III
Mahurin et al. (2006)	84	90			12.8	100	100	0	0	BPRS	
Minzenberg et al. (2003)	57	74	40.2	13.2	19.6	0	100	0	0	PANSS/CASH	WAIS–R
Moritz, Andresen, et al. (2001)	47	66	31.8	11	6.7	100	100	0	0	PANADSS	
Moritz, Heeren, et al. (2001)	25	64	30.8	11.1	6.5		100	0	0	PANADSS	
Nelson et al. (1990)	46	78.3				100	100	0	0	Manchester	
Norman et al. (1997)	87	65.5	33.3		5.9		100	0	0	SANS/SAPS	
Nuechterlein et al. (1986)	40	85	22.3	12.3		100			0	BPRS	
O'Leary et al. (2000)	126	67.2	31.2	13.1	10.5	100	100	0	0	SANS/SAPS	WAIS–R
Pandurangi (1994)	41	73	30.2	12.34		100	100	0	0	CASH	
Perry & Braff (1998)	71	60.6	34.2	12.3	12.9	81.7	100	0	0	SANS/SAPS	
Ragland et al. (1996)	30	56.7	31		9.3		100	0	0	BPRS/SANS/SAPS	
Rocca et al. (2005)	78	59	36.1		11.6	0	100	0	0	PANSS/CDS	
Rocca et al. (2006)	70	66	40.8		15.5	0	100	0	0	SANS/SAPS	

(*table continues*)

Table 2 (*continued*)

Study	*N*	Men (%)	Age (years)	Education (years)	Chronicity of illness	% inpatients	Schizophrenia	Schizoaffective	Delusional and others	Clinical scale	IQ scale
Rosse (1993)	27	96.3	38.5		14.8		100	0	0	SANS	
Rund et al. (2004)	207	58	28.1	12			27.05	12.56	60.39	PANSS	WAIS–R
Sanfilipo et al. (2002)	47	100	38.8	13.1	15.2	40.32	100	0	0	BPRS/SANS	
Simon et al. (2003)	38	60.53	24				100	0	0	PANSS/CDS	NART
Strauss et al. (1993)	50	76	34	12.5	12.5	0	90	10	0	BPRS/TLC	WAIS–R
Tandon et al. (2000)	19	63.33	29	12.8	8	100	100	0	0	BPRS/SANS	WAIS–R
Torres et al. (2004)	107	68.22	30.9	13.2	9		100	0	0	SANS/SAPS	WAIS–R
Voruganti et al. (1997)	52	65.07	32.4		9.2	0	100	0	0	PANSS	
Woodward et al. (2003)	36	75	35.6	12.8	10.22	100	100	0	0	SSPI	K-BIT
Woodward et al. (2004)	68	70.58	35.84	12.31	9.92	100			0	SSPI	NART

Note. Data for age, education, and chronicity are in mean years. Schizophrenia = percentage of subjects diagnosed with schizophrenia in the sample; Schizoaffective = percentage of subjects diagnosed with schizoaffective disorder in the sample; Delusional and others = percentage of subjects diagnosed with delusional disorders and other nonaffective disorders in the sample; PANSS = Positive and Negative Syndrome Scale (Kay et al., 1987); SANS = Scale for the Assessment of Negative Symptoms (Andreasen, 1981); SAPS = Scale for the Assessment of Positive Symptoms (Andreasen, 1984); SSPI = Symptoms and Signs of Psychotic Illness (Liddle, 1992); BPRS = Brief Psychiatry Rating Scale (Overall & Gorham, 1962); CAF = Community Adjustment Form (Test et al., 1991); HEN = High Royds Evaluation of Negativity Scale (Mortimer et al., 1989); CDS = Calgary Depression Scale (D. Addington et al., 1990); PSE = Present State Examination (Wing et al., 1974); HRSD = Hamilton Rating Scale for Depression (Hamilton, 1960); Manchester = Manchester Scale (Krawiecka et al., 1977); CASH = Comprehensive Assessment of Symptoms and History (Andreasen, 1987); PANADSS = Positive and Negative and Disorganized Symptoms Scale for Schizophrenia (Andresen & Moritz, 2000); TLC = Scale for the Assessment of Thought, Language, and Communication (Andreasen, 1979); WAIS = Wechsler Adult Intelligence Scale (Wechsler, 1955); NART = National Adult Reading Test (Nelson & O'Connell, 1978); Slosson = Slosson Intelligence Test (Slosson, 1963); WAIS–R = Wechsler Adult Intelligence Scale—Revised (Wechsler, 1987); SILS = Shipley Institute of Living Scale (Zachary, 1986); WAIS–III = Wechsler Adult Intelligence Scale—Third Edition (Wechsler, 1997); K-BIT = Kaufman Brief Intelligence Test (Kaufman & Kaufman, 1990).

domains, except for the combination of depressive dimension and visual learning and memory ($p = .014$). However, only three observations were included in this analysis, so this result should be treated with some reservation. The funnel plots for each symptom dimension combine all cognitive domains are shown in Figure 2. None of the regression tests for asymmetry were significant for these four plots (ps = .145–.927).

Effect of Moderator Variables

Substantial heterogeneity was found in the correlations between psychosis dimensions and cognitive domains. However, none of the three variables included as possible moderators could account for the observed heterogeneity. The effect of gender on the average correlation was not significant for any of the meta-analyses (all $\hat{\beta}$ values between −.037 and .017; all ps between .054. and .996). Likewise, age did not influence the strength of the associations between the cognitive domains and symptom dimensions (all $\hat{\beta}$ values between −.288 and .020; all ps between .127 and .983), except for the association of the depressive dimension and speed of processing ($\hat{\beta} = .020$, $p = .047$), the strength of which became weaker with increases in the average age of the sample. Heterogeneity in the correlations between cognitive domains and symptom dimensions could not be attributed to differences in the chronicity of the illness (all $\hat{\beta}$ values between −.049 and .150; all ps between .055 and .977), except for the association of the disorganized dimension and IQ ($\hat{\beta} = .037$, $p = .022$), the strength of which became weaker with increases in the average duration of the illness. However, these two findings are inconsistent with the general pattern of results and may constitute Type I errors. Finally, inclusion of symptoms of disorganization in the positive subscale led to a stronger correlation only with respect to IQ ($\hat{\beta} = -.157$, $p = .033$; all other $\hat{\beta}$ values between −.134 and .110, all other ps between .131 and .849). Again, this isolated result is not consistent with the findings for the other eight cognitive domains.

Differential Correlation Coefficients for Cognitive Impairment: Negative Versus Disorganized Dimension

The negative dimension showed a significantly stronger correlation with verbal fluency ($p = .005$), whereas the disorganized dimension showed stronger correlations with reasoning and problem solving ($p = .004$) and attention/vigilance ($p = .03$). The correlation coefficients did not differ significantly between the two dimensions for the other six cognitive domains. The sensitivity analysis (i.e., assuming different values for the strength of the association between negative and disorganized symptoms) corroborated these results.

Sensitivity Analyses to Account for Sample Overlap

The sensitivity analyses (i.e., those excluding the smaller studies of each pair with an uncertain degree of overlap in the samples) corroborated all of the results in the three previous steps of the analyses.

Discussion

Findings

Psychopathological heterogeneity in nonaffective psychosis was weakly but differentially related to distinct patterns of neurocog-

Table 3
Four × Nine Meta-Analysis of Correlation Coefficients Between Psychosis Dimensions and Neurocognitive Domains

Cognitive domain	Positive	Negative	Disorganized	Depressive
IQ				
k	10	**13**	**6**	1
$\hat{\mu}_\rho$	0.024	**−0.244**	**−0.205**	
CI	−0.063, 0.111	**−0.333, −0.151**	**−0.327, −0.076**	
p	.591	**0**	**.002**	
I^2	26	**52**	**45**	
Reasoning and problem solving				
k	27	**33**	**15**	6
$\hat{\mu}_\rho$	−0.013	**−0.14**	**−0.197**	0.074
CI	−0.066, 0.041	**−0.197, −0.081**	**−0.336, −0.048**	−0.024, 0.171
p	.639	**0**	**.009**	.137
I^2	37	**58**	**81**	0
Executive control				
k	9	10	7	3
$\hat{\mu}_\rho$	0.082	−0.131	−0.089	0.059
CI	−0.017, 0.179	−0.265, 0.008	−0.202, −0.026	−0.264, 0.369
p	.103	.063	.130	.725
I^2	6	56	20	73
Verbal fluency				
k	20	**23**	13	4
$\hat{\mu}_\rho$	−0.035	**−0.291**	−0.092	−0.056
CI	−0.101, 0.031	**−0.356, −0.224**	−0.208, 0.027	−0.199, 0.089
p	.292	**0**	.128	.446
I^2	17	**42**	61	0
Speed of processing				
k	**20**	**23**	**13**	5
$\hat{\mu}_\rho$	**−0.089**	**−0.167**	**−0.171**	−0.097
CI	**−0.164, −0.012**	**−0.241, −0.09**	**−0.275, −0.062**	−0.256, 0.068
p	**.023**	**0**	**.002**	.250
I^2	**46**	**53**	**56**	46
Attention/vigilance				
k	11	**15**	**6**	2
$\hat{\mu}_\rho$	−0.012	**−0.134**	**−0.277**	0.154
CI	−0.054, 0.03	**−0.191, −0.076**	**−0.392, −0.154**	−0.023, 0.257
p	.969	**0**	**0**	.087
I^2	0	**26**	**34**	0
Verbal working memory				
k	9	10	5	3
$\hat{\mu}_\rho$	−0.013	−0.07	−0.117	−0.113
CI	−0.144, 0.118	−0.174, 0.036	−0.247, 0.018	−0.303, 0.085
p	.843	.194	.09	.263
I^2	37	19	0	5
Verbal learning and memory				
k	17	**20**	**13**	3
$\hat{\mu}_\rho$	−0.021	**−0.214**	**−0.169**	0.126
CI	−0.096, 0.054	**−0.279, −0.146**	**−0.27, −0.064**	−0.035, 0.281
p	.578	**0**	**.001**	.123
I^2	47	**54**	**59**	0
Visual learning and memory				
k	9	**13**	**6**	3
$\hat{\mu}_\rho$	−0.005	**−0.126**	**−0.206**	0.029
CI	−0.089, 0.079	**−0.202, −0.047**	**−0.331, −0.074**	−0.147, 0.203
p	.91	**.001**	**.002**	.749
I^2	0	**29**	**42**	0

Note. Boldface values indicate associations between psychosis dimensions and neurocognitive domains for which the correlation was statistically significant. CI = 95% confidence interval.

nitive function (see Figure 2). Negative and disorganized dimensions were modestly but meaningfully associated with impairment in the majority of neurocognitive domains. Associations were in the expected direction but were smaller and nonsignificant for the domains of executive control and verbal working memory for both dimensions and for verbal fluency in relation to the disorganized dimension. Thus, cognitive impairment in psychosis (Aleman, Hijman, de Haan, & Kahn, 1999; Fioravanti et al., 2005; Heinrichs & Zakzanis, 1998; Johnson Selfridge & Zalewski, 2001; Lee & Park, 2005; Pelletier, Achim, Montoya, Lal, & Lepage, 2005) does

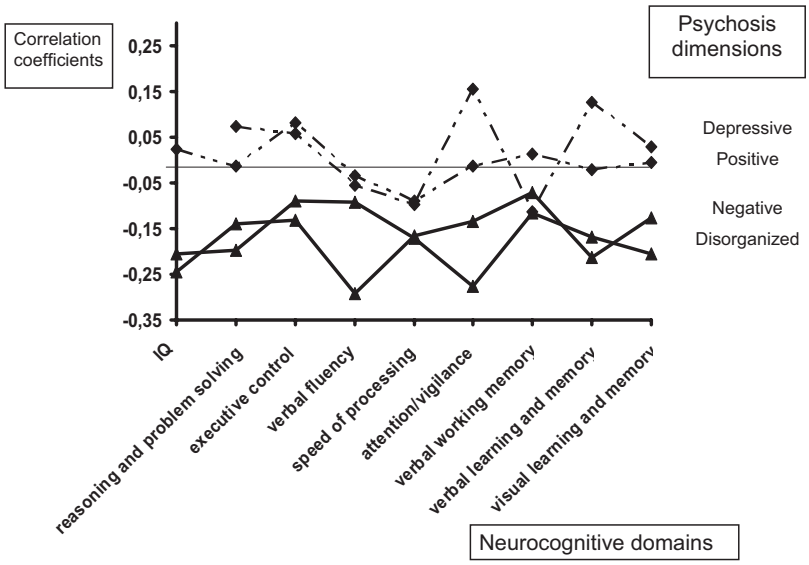

Figure 1. Meta-analysis of correlation coefficients between four psychosis dimensions and nine neurocognitive domains in nonaffective psychosis.

not appear to be entirely orthogonal to psychopathology. In addition, significantly higher correlations were found for the negative dimension in relation to verbal fluency and for the disorganized dimension in relation to reasoning and problem solving and to attention/vigilance. In contrast, positive and depressive dimensions of psychopathology were not consistently associated with the neurocognitive measures examined, with the exception of a significant correlation found for the positive dimension in relation to speed of processing.

The patterns of association for the four psychosis dimensions were stable across neurocognitive domains and were independent of age, gender, and chronicity of illness. These findings in relation to the negative and positive symptoms agree with a more limited previous meta-analysis (Nieuwenstein et al., 2001), whereas the findings with regard to the disorganized dimension were in agreement with a meta-analysis that focused on formal thought disorder (Kerns & Berenbaum, 2002). The results further suggest that distinguishing multiple domains of cognitive functioning in schizophrenia is useful, even though the deficit is to a large extent generalized and may even be accounted for statistically by a single-factor model (as suggested by the CATIE trial, Keefe et al., 2006). Differential patterns of cognitive performance among the different psychopathological dimensions were found. These patterns may indicate some meaningful contrasts suggestive of differential latent cerebral mechanisms underlying the cluster of disorganized and negative symptoms on the one hand and that of positive and affective symptoms on the other.

Do Patterns of Psychopathology–Neurocognition Associations in Nonaffective Psychosis Match Evidence of Differential Underlying Patterns of Cerebral Dysfunction?

Functional brain imaging studies have demonstrated that different patterns of altered cerebral activity, possibly reflective of clinical heterogeneity, occur in schizophrenia. Early studies (Ebmeier et al., 1993; Heaton, 1985; Liddle, Friston, Frith, & Frackowiak, 1992; Liddle, Friston, Frith, Hirsch, et al., 1992; Nelson, 1976; Weinberger & Berman, 1988; Weinberger, Berman, & Illowsky, 1988; Weinberger, Berman, & Zec, 1986) have tended to concur on findings suggesting that (a) psychomotor poverty is associated with prefrontal cortex and parietal cortex underactivity, especially on the left, and with overactivity of the caudate nuclei bilaterally; (b) the disorganization syndrome is associated with decreased perfusion in the right ventral prefrontal cortex and contiguous insula and with increased perfusion in the right anterior cingulated; and (c) reality distortion is associated with overactivity in the left medial temporal lobe and left lateral frontal lobe and with underactivity in the left lateral temporal lobe, adjacent parietal cortex, and posterior cingulated cortex. Later brain imaging studies in schizophrenia (Lawrie & Abukmeil, 1998; Lieberman et al., 2001) confirmed that negative symptoms (Andreasen, Paradiso, & O'Leary, 1998; Sanfilipo et al., 2000; Schroder et al., 1996) and disorganization symptoms (Crider, 1997; Liddle, Friston, Frith, Hirsch, et al., 1992) are associated with alterations in frontal lobe functioning, whereas auditory hallucinations produced normal activation of the left prefrontal cortex but exhibited less activation of the left middle temporal gyrus and supplementary motor area (Lennox, Park, Medley, Morris, & Jones, 2000; McGuire et al., 1995; Shergill, Brammer, Williams, Murray, & McGuire, 2000; Shergill, Bullmore, Simmons, Murray, & McGuire, 2000). Recently, abnormal connectivity has been postulated as the central functional cerebral abnormality in schizophrenia (Josin & Liddle, 2001; Menon, Anagnoson, Glover, & Pfefferbaum, 2001). This possibility would indicate that the core abnormality may be a disruption of functional connectivity between frontal cortex and other cerebral sites that gives rise to distributed cortical and subcortical deficits that may be associated with differential behavioral expression, such as variation in symptom dimensions and cognition.

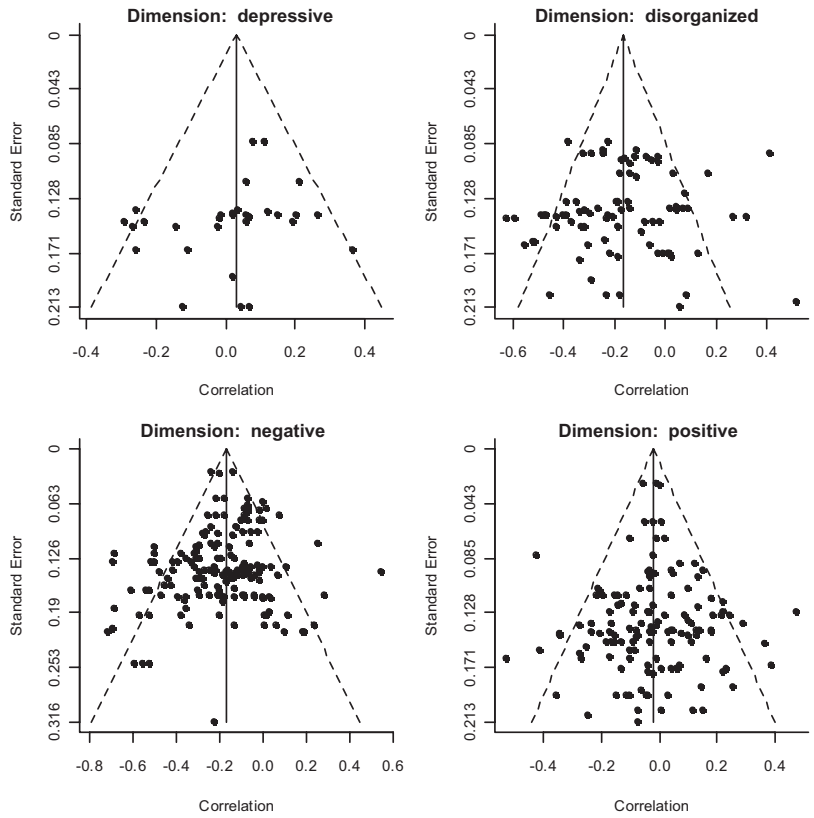

Figure 2. Regression test for funnel plot asymmetry for the associations of cognitive domains within each psychopathological dimension.

At the level of neurotransmission, different patterns involving several interconnected limbic, cortical, and subcortical structures have been implicated in schizophrenia. The dopamine (DA) hypothesis has been extended to include both cortical and subcortical components. An overactivity in neurotransmission from DA cell bodies (DA–D2 receptors), located in the ventral tegmental area of the midbrain, may result in the development of positive symptoms. A hypodopaminergic state in the prefrontal cortical terminal fields of the mesocortical DA neurons (DA–D1 receptors) has been hypothesized to underly cognitive impairment and negative symptoms of schizophrenia and may in turn contribute to the disinhibition of subcortical DA function (Duncan, Sheitman, & Lieberman, 1999; Kellendonk et al., 2006). Moreover, alterations in prefrontal connectivity involving glutamate transmission at N-methyl-D-aspartate (NMDA) receptors has been proposed. This hypothesis suggests that the DA imbalance in schizophrenia (striatal excess and cortical deficiency) may be secondary to NMDA hypofunction in the prefrontal cortex and its connections (Laruelle, Kegeles, & Abi-Dargham, 2003).

Negative and Disorganized Dimensions Versus Positive and Affective Dimensions: Does Clinical Research Suggest Two Pathways in Psychosis?

There is evidence that intermediary phenotypes associated with genetic risk of psychosis may fall into two broad groups: one associated with cognitive impairment and negative and disorganized symptom dimensions and one associated with altered sensitivity to stress expressed as increased levels of affective and positive psychotic symptoms following exposure to small stressors in the flow of daily life (Myin-Germeys & van Os, 2007). Thus, increased emotional reactivity correlates negatively with cognitive impairment in patients with schizophrenia (Myin Germeys et al., 2002). The two intermediary phenotypes of stress sensitivity and cognitive impairments may therefore constitute separate and even mutually exclusive pathways to psychosis associated with partly different expression of psychopathology.

Another area of research that may help us understand the pathways of differential expression of psychopathology is social cognition (Blakemore & Frith, 2004; Freeman, Garety, & Kuipers, 2001; Frith, 2004; Kuipers et al., 2006). Positive psychotic symptomatology has been associated with impaired social cognition, such as alterations in self-monitoring (Bentall, 1990; Johns et al., 2001), a probabilistic reasoning bias referred to as jumping to conclusions (Garety & Freeman, 1999; Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001; Van Dael et al., 2006), and mentalizing deficits (Versmissen et al., 2007). Where examined, research suggests that the association between altered social cognition and symptoms is weakest for the negative and disorganization dimensions (Van Dael et al., 2006). These observations tend to agree with our finding that positive and affective symptoms were

not associated with neurocognition, whereas negative and disorganized dimensions were. Recent analyses support this view and show that, in patient samples, alterations in social cognition are largely independent of measures of neurocognition (Van Hooren et al., 2008).

Conclusion: Different Underlying Pathophysiological Processes Associated With Different Intermediary Phenotypes May Account for a Substantial Part of Psychopathological Heterogeneity in Nonaffective Psychosis

Findings at different levels of neuroscientific and neurocognitive research have suggested some evidence of meaningful contrasts in the underlying patterns of cerebral dysfunction in relation to the psychopathological heterogeneity of psychosis. Neuroimaging, neuropharmacological, and neurocognitive findings concur in that weak but systematic patterns of associations are found with dimensions of psychopathology. These associations fit in the simplistic but heuristically useful two-pathway model of psychosis, in which the exophenotypes of negative and disorganized symptoms are associated with the intermediary phenotype of neurocognitive impairment and the positive and affective dimensions are not. This reduction may explain at least some of the psychopathological heterogeneity in nonaffective psychosis and may be refined in future studies, to the extent that such studies become nosologically useful.

Methodological Issues

First, four rather than five psychosis dimensions were analyzed, although evidence suggests that a five-factor solution that includes a manic symptom dimension may yield a better fit (Dikeos et al., 2006; Grube et al., 1998; Lindenmayer et al., 1995; McGorry et al., 1998; Serretti, De Ronchi, Lorenzi, & Berardi, 2004; Serretti et al., 2001). However, because only four studies reported the manic/excitement dimension, there were too few data for an informative synthesis. Second, only nonaffective psychotic disorder was considered in the inclusion criteria for study selection. The reason for this was that although rather similar patterns of cognitive impairment have been found in the affective domain of psychosis (Fioravanti et al., 2005; Krabbendam, Arts, van Os, & Aleman, 2005) and rather similar psychopathological dimensions have been identified in affective and nonaffective psychosis (Peralta et al., 1997), associations between psychopathological dimensions and neurocognition have been examined to only a substantial degree in nonaffective psychotic disorders. Third, some of the included cognitive tests may vary in terms of sensitivity, and this variance may be problematic in view of the generalized cognitive deficit in schizophrenia (Chapman & Chapman, 1978). That is, the difference between performance of patients with schizophrenia and healthy controls will be greater for tasks with higher reliability and variance, regardless of differences in true ability. Such variation may result in different likelihoods of correlating with other parameters, such as symptom dimensions. This problem can be solved only by using tasks that are matched on the relevant psychometric characteristics. This is a limitation that should be acknowledged by each systematic review that summarizes and combines different cognitive tests. Fourth, because all subjects in the selected studies were younger than 51.9 years of age, no conclusions can be made regarding the impact of aging for each psychopathology dimension–cognition combination. Fifth, many other moderator variables may be of relevance; however, due to underreporting, they could not be examined in more detail (e.g., clinical scales scores, pharmacological treatment, previous history of symptoms, genetic vulnerability, hemisphere correlation, and comorbidity). Sixth, exclusion of a number of studies was necessary because of incomplete information but resulted in sample restriction.

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