Subclinical psychotic experiences and cognitive functioning as a bivariate phenotype for genetic studies in the general population

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Abstract

Objective: Cognitive deficits may be vulnerability markers for the development of schizophrenia. This study examined whether cognitive deficits are related to specific dimensions of subclinical psychotic experiences and whether associations between these variables are caused by additive genetic, common environmental and/or individual-specific environmental factors.

Method: A general population sample of 298 female twin pairs completed the Community Assessment of Psychic Experiences and a neuropsychological test battery. Associations between subclinical positive and negative psychotic dimensions and neuropsychological factors (episodic memory and information processing speed) were examined. Univariate correlation and structural equation analyses were performed to explore the role of genetic and environmental factors in the phenotypes separately. Bivariate correlation and structural equation analyses were applied to examine the causes of association.

Results: There were significant correlations between information processing speed and both the positive \( r = .11; p < .05 \) and the negative dimension \( r = .10; p < .05 \). For the negative dimension and for speed of processing, the data suggested a model that included genetic factors. The observed phenotypic correlation between the negative dimension and information processing speed could be solely explained in terms of additive genetic factors. Although the comparison of the correlations for MZ and DZ pairs did not give a clear indication as to the underlying causes of the association, structural equation modelling suggested that the observed phenotypic correlation between the negative dimension and information processing speed could be solely explained in terms of additive genetic factors.

Conclusion: Negative symptoms and information processing speed are associated at the subclinical level and this association appears to be influenced by genetic factors exclusively. Bivariate psychosis phenotypes may represent suitable candidates for molecular genetic studies in the general population.

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1. Introduction

Psychotic experiences at the subclinical level, alternatively labeled as schizotypy, psychosis-proneness or psychosis-like symptoms, are prevalent in the general population (Eaton et al., 1991; Peters et al., 1999; Tien,
1991; Van Os et al., 1999) and thought to be expressions of a continuous distribution extending from subclinical experiences to clinical symptoms (Van Os and Verdoux, 2003). There is evidence for family-specific variation of subclinical psychotic experiences in the general population (Hannsen et al., 2006), whereas relatives of patients with schizophrenia display higher levels of the subclinical manifestations of psychosis than well controls (Kendler et al., 1995; Kremen et al., 1998). These findings suggest that subclinical psychotic experiences are transmitted within families as the phenotypic expression of liability to schizophrenia. Twin studies suggest that both the positive and the negative dimensions of schizotypy are influenced by additive genetic effects and are moderately heritable (e.g., Claridge and Hewitt, 1987; Hay et al., 2001; Kendler et al., 1991; Linney et al., 1993). Similar to subclinical psychotic experiences, neurocognitive deficits associated with schizophrenia cluster in families of patients with schizophrenia and are detectable in the first-degree relatives of patients at levels that are intermediate between well controls and patients (Krabendam et al., 2001; Kremen et al., 1994).

Some studies have found associations between subclinical psychotic symptom dimensions and cognitive functioning (Krabendam et al., 2005; Laurent et al., 2001; Suhr and Spitznagel, 2001; Vollema et al., 2002). This suggests that both may vary as part of the same underlying cause. Given the fact that both cognitive deficits and subclinical psychotic experiences cluster in the families of patients with a diagnosis of schizophrenia, it can be surmised that part of this overlap is likely due to shared genetic factors. The aim of the present study therefore was to investigate (i) associations between cognitive functioning and psychotic symptom dimensions and (ii) whether any association is caused by genetic factors. A twin design was used in order to disentangle genetic from common and individual-specific environmental factors.

2. Methods

2.1. Subjects

The study sample consisted of 187 monozygotic and 111 dizygotic female twin pairs between 18 and 46 years of age, and was recruited in the context of a study on stress and depression. Two hundred and thirty-six pairs came from the East Flanders Prospective Twin Survey. This population-based survey has prospectively recorded all multiple births in the province of East Flanders since 1964 (Derom et al., 2002; Loos et al., 1998). Zygosity was determined through sequential analysis based on sex, fetal membranes, blood groups and DNA fingerprints.

Sixty-two pairs were recruited using registers from Flemish municipalities. Determination of zygosity in these twins was based on their and their mothers’ response to standard questions about physical similarity and the degree to which others confused them (Christiansen et al., 2003; Peeters et al., 1998; Spitz et al., 1996) and if necessary, on examination of DNA fingerprints.

2.2. Measures

Psychotic symptoms were measured with the Community Assessment of Psychic Experiences (CAPE; Stefanis et al., 2002). The CAPE is a 42-item self-report questionnaire measuring attenuated psychotic experiences. Previous research with the CAPE has shown a three-dimensional structure, of a positive, a negative and a depressive factor in a large and representative sample of young men (Stefanis et al., 2002) and in a large sample of undergraduate female students (Verdoux and Van Os, 2002).

The neuropsychological assessment was directed at the following cognitive domains: episodic memory, and simple and complex information processing. The Auditory Verbal Learning Task (AVLT) (Brand and Jolles, 1985; Lezak, 1995) was used to evaluate memory storage and retrieval of information in episodic memory. In three consecutive trials, a list of 15 words had to be memorised and reproduced. The measures used were the total number of words recalled over the three trials, and number of words recalled after a 20-min delay. Tests used to measure the speed of information processing were the Stroop Color-Word Test (SCWT) (Stroop, 1935), the Concept Shifting Test (CST) (Houx et al., 1991), which is a modified version of the Trail Making Test (Reitan, 1958), and the Letter Digit Substitution Test (LDST), which is a modified version of the Symbol Digit Modalities Test (Smith, 1968). The number of correctly completed letters in 90s was used as the dependent variable. Speed of complex information processing was assessed using the interference task of the SCWT and the number/letter-shifting task of the CST. For the SCWT, time (in seconds) to complete each of the three 4 × 10-item subtasks (name the print colour, to read the colour names and to name the print colour while ignoring the word), were used as dependent variables. Dependent variables were time (in seconds) to cross out the numbers, to cross out the letters and to switch between numbers and letters.

2.3. Statistical analysis

The number of neuropsychological test variables was reduced by means of a principal component factor
analysis of the entire study sample followed by varimax rotation, using STATA version 8 (StataCorp, 2003). Guided by the scree plot, a two-factor solution was chosen, accounting for 52% of the variance. Furthermore, a three-factor solution did not result in significant correlations for the third factor. Therefore a two-factor solution is more parsimonious and corresponds better to previous work in terms of correlations with symptoms. Factor scores were used. The variables of the Auditory Verbal Learning Task strongly loaded on the first factor, which we termed episodic memory (factor loadings $-0.92$). The variables of the Stroop, CST (factor loadings from 0.49 to 0.70) and LDST (factor loading $-0.66$) loaded on the second factor, which we termed information processing speed.

Spearman correlations between the subclinical psychotic symptom dimensions and the neuropsychological factors were calculated, followed by further analysis of significant correlations. Pearson product-moment correlations did not result in higher correlations.

2.4. Genetic analyses

2.4.1. Univariate analyses

First, twin univariate correlation analyses were performed to explore the role of genetic and environmental factors on the phenotypes separately. If the within-pair correlation in MZ pairs is substantially higher than the within-pair correlation in DZ pairs, genetic factors are thought to play a causative role in the phenotypic variance. Guided by the preliminary correlational analysis, univariate structural equation modelling was applied, using Mx (Neale et al., 1999). Univariate structural equation modelling decomposes the variance within a phenotype into three possible sources: 1) genetic factors, 2) common environmental factors (those environmental experiences that are shared by both members of a twin pair), and 3) unique environmental factors (those environmental experiences not shared by both members). Several models were fitted to the data. The models were compared using the difference in fits and the difference in degrees of freedom as criterion (Neale and Cardon, 1992). The best fitting model was chosen, based on likelihood and parsimony of the model.

2.4.2. Bivariate analyses

Next, bivariate analysis was performed based on the results of the univariate analysis.

The within-twin cross-variable (i.e. a cognitive factor in twin 1 correlated with a CAPE dimension in twin 1, and the same for twin 2) and cross-twin cross-variable (i.e. a cognitive factor in twin 1 correlated with a CAPE dimension in twin 2 and vice versa) correlations were calculated. The pattern of these correlations gives an impression about the causes of association between cognitive functioning and the different CAPE dimensions. If the cross-twin cross-variable correlation is significantly higher in MZ than in DZ twins, a genetic factor can be hypothesized to play a role in the association between the two traits. Furthermore, if all of the association is due to genes, then the within-twin cross-variable correlation in MZ twins should be the same as the cross-twin cross-variable correlation in MZ twins. If, on the other hand, the within-twin cross-variable correlation in MZ twins is higher than the cross-twin cross-variable correlation, individual-specific environmental factors are also likely to play a role in the association.

Guided by the pattern of the correlations and the univariate structural equation modellng results, structural equation modelling, using Mx (Neale et al., 1999) was used to fit bivariate models. This is the most common statistical method to explain observed covariance between two variables in twin data (see e.g., Agrawal et al., 2004; Bulik et al., 2003). The goal of a bivariate twin analysis (Fig. 1) is to decompose the covariance between two associated characteristics (cognitive factor and CAPE dimension) into three possible sources: 1) genetic factors, 2) common environmental factors, and 3) individual-specific environmental factors. Several models were fitted to the data. The models were compared using the difference in fit and the difference in degrees of freedom as criterion (Neale and Cardon, 1992). The best fitting model was chosen, based on likelihood and parsimony of the model. The bivariate heritability (that part of the phenotypic correlation that is due to shared genes: $\sqrt{a^2_{\text{cognitive}} \times r_a \times a^2_{\text{CAPE}}}$), bivariate $c^2$ (that part of the phenotypic correlation that is due to common environmental factors: $\sqrt{c^2_{\text{cognitive}} \times r_c \times c^2_{\text{CAPE}}}$) and bivariate $e^2$ (that part of the phenotypic correlation that is due to individual-specific environmental factors: $\sqrt{e^2_{\text{cognitive}} \times r_e \times e^2_{\text{CAPE}}}$) were calculated.

3. Results

3.1. Sample

Of the 298 female twin pairs that participated, 187 were monozygotic and 111 dizygotic. Mean age of the sample was 27 years (S.D. = 7.5 years, range = 18–46 years). A majority of 60% had a college or university degree, 37% completed secondary education and 2%
only had primary education. The majority was currently employed (64% employed, 31% student, 2% unemployed, 2% homemaker and 1% sick leave). Mean weighted frequency of positive psychotic experiences per subject was 1.2 (S.D.=0.18, range=1.0–2.1), of negative psychotic experiences 1.5 (S.D.=0.3, range=1.0–2.9) and of depressive symptoms 1.7 (S.D.=0.4, range=1.0–3.6). Mean scores on the neuropsychological measures were: AVLT total immediate recall, mean=32.7 (S.D.=5.0); AVLT delayed recall, mean=11.5 (S.D.=2.5); Stroop names, mean=14.0 (S.D.=3.5); Stroop colors, mean=19.5 (S.D.=3.3); Stroop interference task, mean=33.8 (S.D.=6.9); CST numbers, mean=16.2 (S.D.=3.5); CST letters, mean=19.1 (S.D.=5.1); CST number/letter shifting, mean=25.3 (S.D.=7.8) and LDST, mean=61.0 (S.D.=8.2). Distributions of all variables were skewed, with the exception of the distribution of the LDST.

3.2. Univariate analysis

3.2.1. Correlations

A significant Spearman within-twin correlation was found between information processing speed and the positive dimension of the CAPE (r=−.11; p<.05) and between information processing speed and the negative dimension of the CAPE (r=−.10; p<.05). All other correlations between the two cognitive factors and the CAPE dimensions were not significant. Since information processing speed was measured as reaction times and factor loadings on this factor were generally positive, the positive correlation with the positive and negative dimensions indicates that higher positive and negative symptoms are accompanied by slower reaction times.

The correlations in MZ pairs for information processing speed (r=.61) and the negative dimension of the CAPE (r=.41) were higher than those observed among DZ pairs (r=.38 and r=.29, respectively) (see Table 1), suggesting that genetic factors contribute causally to information processing speed and the negative dimension separately. The fact, however, that the correlations for information processing speed and for the negative dimension among DZ twins were higher than half of those among MZ twins suggests that they are also under the influence of environmental factors shared by the pairs. The correlations in MZ twin pairs for the positive dimension (r=.27), in contrast, were not higher than those in DZ pairs (r=.29), providing no support for the hypothesis that a genetic factor contributes to sub-clinical positive experiences. Therefore

![Fig. 1. A full bivariate twin model for negative dimension and information processing speed. The variance in liability to each trait is divided into that due to additive genetic factors (A\textsubscript{neg} and A\textsubscript{speed}), common environmental effects (C\textsubscript{neg} and C\textsubscript{speed}) and individual-specific environmental factors (E\textsubscript{neg} and E\textsubscript{speed}). Paths, which are the standardized regression coefficients, must be squared to equal the proportion of variance accounted for. They are represented by lowercase (a, c and e) with the subscripts neg and speed. The phenotypic correlation between the negative dimension and information processing speed is, in this model, decomposed into that due to the correlation of additive genes (r\textsubscript{a}), and the correlation of common environmental factors (r\textsubscript{c}) and the correlation of individual-specific environmental factors (r\textsubscript{e}).](image)
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M twins should be the same as the within-twin cross-variable correlation in MZ twins. If, on the other hand, the within-twin cross-variable is higher than the cross-twin cross-variable correlation, than individual–environmental factors contribute to the association. The results suggest that this was not the case (within-twin correlation=0.045; cross-twin correlation=0.05). Since univariate structural equation modelling did not find evidence for a common environmental factor for neither negative symptoms nor information processing speed, it is unlikely that the association between these two variables can be explained by common environmental factors. Thus, the comparison of the correlations for MZ and DZ pairs does not give a clear indication whether additive genetic, common environmental or individual-specific environmental factors play a role in the association.

3.2.2. Structural equation modelling

Univariate structural equation modelling of the information processing speed factor suggested a best-fitting model with a genetic factor explaining 64% (95% CI: 55%–71%) and an individual-specific environmental factor explaining 36% of the variance (95% CI: 29%–45%). Univariate model fitting of the negative dimension data set suggested a best-fitting model with a genetic factor explaining 48% (95% CI: 36%–58%) and an individual-specific factor explaining 52% of the variance (95% CI: 42%–64%).

3.3. Bivariate analysis

3.3.1. Correlations

The cross-twin cross-variable correlation did not differ between MZ (mean, r=0.05) and DZ pairs (mean, r=0.10), suggesting that genetic factors do not play a role in the observed association between negative symptoms and information processing speed. If the entire association were due to genes, the cross-twin cross-variable correlation in MZ twins should be the same as the within-twin cross-variable correlation in MZ twins.

Further analysis focussed only on the association between the negative dimension and information processing speed.

3.2.2. Structural equation modelling

As the bivariate correlations did not provide a clear indication of the factors underlying the association between the negative dimension and information processing speed, all structural equation models were tested. Bivariate model fitting began with the full model (model 1 in Table 2), allowing for additive genes (A), common environment (C), and individual-specific environment (E) for both the negative symptom dimension and information processing speed and allowing for genetic, common environment and individual-specific environmental correlations between them: rA, rC and rE, respectively (see Fig. 1).

Based on the results of the univariate model fitting, the full model was changed by omitting the common

![Diagram](https://via.placeholder.com/150)

**Fig. 2.** The parameter estimates from the best fitting bivariate model (model 3, Table 2) for the negative dimension and information processing speed. Path coefficients must be squared to equal the proportion of variance accounted for in the dependent variable. A\textsubscript{neg}, E\textsubscript{neg}, A\textsubscript{speed}, E\textsubscript{speed} are explained in the legend to Fig. 1.
environmental factor in the negative symptom dimension, information processing speed and the common environmental factor between these two variables. This model fitted nearly as well as the full model ($\chi^2_{\text{model}} 2 - \chi^2_{\text{model}} 1 = 0.73$, $\Delta df=3$, $p>0.05$) and therefore was more parsimonious.

Based on model 2, we fitted a third model in which the individual-specific environmental correlation between negative symptoms and information processing speed was set to 0, forcing the model to explain all of the association between negative symptoms and information processing speed by genetic factors. The fit of this model was not significantly worse than the fit of model 2 ($\chi^2_{\text{model}} 3 - \chi^2_{\text{model}} 2 = 0.22$, $\Delta df=1$, $p>0.05$) and was also more parsimonious.

A fourth model was fitted, also based on the second model, now forcing the model to explain all of the association by means of individual-specific factors (i.e. the genetic correlation was set to 0). The fit of this model was significantly worse than the fit of model 2 ($\chi^2_{\text{model}} 4 - \chi^2_{\text{model}} 2 = 5.13$, $\Delta df=1$, $p=0.02$). Therefore, model 3 remained the best fitting model (see Fig. 2). The genetic correlation between the negative psychotic dimension and information processing speed was estimated at 0.19 (95% CI: 0.03–0.35). Thus, the bivariate heritability equaled $\frac{\sigma_{\text{ape}}^2}{\sigma_{\text{ape}}^2 + \sigma_{\text{ape}}^2} = \frac{0.64\times 0.19}{0.64+0.19} = 0.10$. The average phenotypic correlation between the negative psychotic dimension and information processing speed was 0.10 (95% CI: 0.01–0.18).

4. Discussion

The results showed a significant association between the negative symptom dimension and information processing speed. The association, although significant, was weak ($r=0.10$). However, correlations between symptoms and cognitive deficits have generally been found to be quite modest. The result is in line with previous studies finding significant but modest associations between performance on the Continuous Performance Test (CPT) or the Trail Making Test (TMT) and negative symptoms (Cameron et al., 2002; Grove et al., 1991; Kendler et al., 1991; Maharaj et al., 1998; O’Leary et al., 2000).

The variation in negative symptoms could best be explained in terms of a model that contained both genetic and individual-specific factors. Twin studies have shown that best-fitting models for negative symptoms are comprised of additive genetic and individual-specific environmental factors (Claridge and Hewitt, 1987; Kendler et al., 1991; Linney et al., 2003). Linney et al. (2003) found a heritability estimate of 49% for the Introvertive Anhedonia subscale of the Oxford-Liverpool Inventory of Feelings and Experiences. This is in the same order of magnitude as the 48% found in the present study. The variation in information processing speed was also best explained in terms of a model that contained both a genetic and an individual-specific factor. The finding of a significant genetic factor for information processing speed is consistent with previous twin studies investigating information processing speed (Rijndijk et al., 1998).

Since a genetic factor was found to contribute to both the negative dimension and the information processing speed factor, the association between negative symptoms and information processing speed was further analysed to examine whether the association was (in part) caused by additive genetic factors. The bivariate correlations for MZ and DZ twins did not differ much from each other. The correlation between information processing speed and negative symptoms was rather weak, this might explain the lack of a substantial difference between MZ and DZ pairs. Although the bivariate correlation analysis did not show a clear pattern, the results of the structural equation modelling indicated that the association between negative symptoms and information processing speed could be solely explained by shared genetic effects. This is consistent with a model of pleiotropic effects, in which susceptibility loci manifest as both slower information processing and subclinical negative symptoms. This finding may guide the search for specific genes in samples characterized by both subclinical negative symptoms and slow information processing.

In schizophrenia patient samples, measures of negative symptoms typically tend to show a quite modest correlation with neurocognitive functioning (i.e., $r$ values in the −0.15 to 0.30 range) (Gold, 2004). As in patient samples the range of symptoms is broader than in a general population sample, the correlations found in the present study are even weaker. Still, from the viewpoint that the psychosis phenotype is expressed as a continuous distribution of experiences, elucidating the causes of the association between symptoms and cognition in the general population will also be relevant to understanding the clinical disorder.

In addition, the amount of variance explained by the bivariate endophenotype negative symptoms–neurocognitive performance is low. This suggests that although negative symptoms and neurocognitive performance may have a shared underlying cause, they are to a large part independent of each other.
The subjects in this study were women in the age range of 18 to 46 years. The main age range of risk for developing a psychotic disorder is between 20 and 35 years. For women the onset is, on average, 3–4 years later than for men and women show a second peak of onset around menopause (Häfner, 2003; Hambrecht et al., 1994). Therefore the age range of the study sample was adequate for detecting subclinical psychotic experiences in the female sample. The significant correlations between information processing speed and the positive and negative dimension could not be accounted for by an age effect, since additional analyses still showed significant correlations after controlling for age.

The findings of this study must be interpreted in the light of several issues. First, the sample consisted of female participants only. Gender differences in psychotic symptoms include higher levels of positive schizotypy in females compared to males, and higher levels of negative schizotypy in males compared to females (Jackson and Claridge, 1991; Marie et al., 2003; Raine, 1992). However, this does not necessarily imply that the association between negative symptoms and information processing speed is different in women than it is in men. Mean weighted positive, negative and depressive scores on the CAPE were comparable to those reported in other papers (Hanssen et al., 2006; Krabbendam et al., 2005).

Second, more than 60% of the subjects had a college or university degree, which is not representative for the general population. This may have affected the performance on the cognitive measures, e.g. by creating ceiling effects, but it is unlikely that the association between cognitive functioning and subclinical psychotic experiences is different in a population with a high educational level than for the general population. However, it is possible that the correlation is weaker for the current, high cognitive functioning sample in comparison to the general population, because if there is indeed an association between cognitive functioning and negative symptoms, it would be more easily detected in a general population sample that contains more variation in cognitive performance.

References


