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BRIEF COMMUNICATION

Neuroticism as a risk factor for schizophrenia

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ABSTRACT

Background. Neuroticism has been shown to increase the risk of depression whereas extraversion is associated with a reduction of risk. These personality traits play a central role in aetiological theories of affective disorder but their role in schizophrenia is unclear. In this study, the risk for schizophrenia associated with neuroticism and extraversion was examined and quantified.

Methods. Neuroticism and extraversion rated at the age of 16 years were examined in relation to adult schizophrenia in a national birth cohort of 5362 individuals.

Results. Neuroticism increased the risk of later schizophrenia independent of the level of affective symptoms in adult life (odds ratio over three levels: 1·93, 95% CI 1·09–3·43), whereas extraversion reduced the risk (OR: 0·44, 95% CI 0·23–0·84).

Conclusions. Depression and schizophrenia may share personality risk-increasing and risk-reducing factors. Coping styles associated with particular personality traits may determine whether isolated symptoms progress to full-blown illness.

INTRODUCTION

Some of the risk factors that have been identified for psychiatric illness may be shared between separately defined disorders. The identification of shared areas of liability may increase insight into aetiology and treatment, and reveal new strategies for prevention (Van Os *et al*. 1998). Screening samples of mixed diagnostic composition is a useful way of investigating sharing of risk factors and has contributed to the discovery of, for example, overlap in familial clustering of psychosis in individuals with affective and non-affective psychotic disorders (Kendler *et al*. 1993*a*), overlap in cognitive impairment prior to the onset of depression and schizophrenia (Jones *et al*. 1994; Van Os *et al*. 1997) and overlap in cerebral ventricle enlargement in schizophrenia and affective disorder (Elkis *et al*. 1995).

The personality factor neuroticism, which may reflect instability, vulnerability to stress, or anxiety-proneness (Eysenck & Eysenck, 1975; Horwood & Fergusson, 1986; Ormel *et al*. 1989) has been shown to predict robustly later onset of depression in short-term and long term prospective studies (Fergusson *et al*. 1989; Kendler *et al*. 1993*b*; Rodgers, 1990). Neuroticism therefore figures prominently in aetiological theories of depression (Kendler *et al*. 1993*b*). Extraversion, on the other hand, may have a risk-reducing effect in relation to depression (Enns & Cox, 1997; Van Os & Jones, 1999).

Patients with schizophrenia, their first-degree relatives and individuals with schizotypy have been reported to score high on measures of

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neuroticism, but in the absence of longitudinal studies it is unclear whether this represents a consequence of the illness or a personality risk factor (Maier *et al.* 1994; Tien *et al.* 1992; Gurrera *et al.* 2000). In the current study, associations between childhood neuroticism and extraversion on the one hand, and adult schizophrenia on the other were investigated in a general population birth cohort of 5362 individuals.

METHOD

Sample

The Medical Research Council National Survey of Health and Development (NSHD) is an ongoing longitudinal study of a stratified sample of 5362 subjects (men: 52·5%), born in Britain during the week 3–9 March, 1946. Data were collected on 11 occasions at intervals of 2 years until age 16 years, and on nine occasions thereafter, the most recent contact occurring in 1989 at the age of 43 years (Atkins *et al.* 1981; Wadsworth, 1991). Informed consent was sought for all measurements from subjects or their parents.

Neuroticism

Survey members had completed the six neuroticism and the six extraversion items of the short Maudsley Personality Inventory (Eysenck, 1958) (MPI) at the age of 16 years (each item contributing up to two points, range 0–12 for each scale).

Affective symptoms

When survey members were 36-years-old, a short version of the Present State Examination (PSE) was administered by trained lay interviewers (Rodgers & Mann, 1986), including all PSE neurotic and affective features. At age 43 years, the Psychiatric Symptom Frequency scale (Rodgers, 1996) (PSF) was administered through a structured interview by trained nurses. The PSF is a 19-item scale rating symptoms of anxiety and depression for the 12 months preceding the interview. The reliability, validity and internal consistency of PSE and PSF in this sample were found to be satisfactory (Rodgers & Mann, 1986; Rodgers, 1996; Lindelow *et al.* 1997). Total symptom scores were calculated for both PSE and PSF. In order to take into account scale differences between the PSF and the PSE, these total scores were standardized with mean 1000 and standard deviation 100 using the STATA STD procedure (STATA, 1999). These standardized, continuous measures of mental health were used in the analyses. As some individuals had had a PSE interview in 1982 but missed the PSF interview in 1989 and vice versa, missing values on the PSE in 1982 were imputed on the basis of non-missing values on the PSF in 1989 and vice versa.

Schizophrenia cases

Cases of schizophrenia arising between ages 16 and 43 years were identified in two stages (Jones *et al.* 1994). The first stage used three sources ((*i*) all questionnaire and interview contacts with survey members, (*ii*) the Mental Health Inquiry and (*iii*) the short version of the PSE administered at age 36) to identify survey members for whom there was any evidence of schizophrenia, severe unclassified mental illness, a psychiatric hospital admission or antipsychotic drug use. In the second stage, DSM-III-R criteria of schizophrenia or schizoaffective disorder were applied to clinical material extracted from hospital case notes, correspondence with general practitioners and survey members' own descriptions recorded during routine interviews. Thirty subjects with a diagnosis of schizophrenia were thus identified.

Analyses

Logistic regression (STATA, 1999) was carried out to examine associations between schizophrenia and the two personality variables. Associations were expressed as the odds ratios from the logistic regression. Continuous Neuroticism and Extraversion scores were divided into three groups (score 0 to 4, score 5 to 8, score 9 to 12) allowing us to examine dose–response relationships. All associations were adjusted for sex, and interactions with sex were assessed by likelihood ratio tests. In order to adjust for the possible confounding effect of affective symptoms, associations were adjusted for the standardised PSE and PSF scores at ages 36 and 43 years respectively. Adjustment for affective symptoms at two different ages was carried out in an attempt to partial out the effect of general (lifetime) tendency to display affective symp-

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toms, rather than a more imprecise, single cross-sectional measure.

Risk set

In order to stabilize the sample, individuals were included with non-missing values on neuroticism, sex, and PSE and PSF scores at ages 36 and 43 years. A total of 2932 individuals fulfilled these criteria (men: 49·9%), among whom 20 individuals with a DSM-III-R diagnosis of schizophrenia (men: 60%).

RESULTS

Men had higher levels of extraversion at age 16 years (mean men 8·2, S.D. = 2·6; mean women 7·7, S.D. = 2·8; $P < 0·001$) and women had higher levels of neuroticism (mean men 5·1, S.D. = 3·6; mean women 7·1, S.D. = 3·5; $P < 0·001$). There was a strong positive association between neuroticism at age 16 years and adult schizophrenia (unadjusted summary OR over three groups 1·93, 95% CI 1·09–3·34 see Table 1). Symptoms of anxiety and depression at ages 36 and 43 years were associated with schizophrenia (OR with 100 point change adjusted for sex: age 36 years, 1·39, 95% CI 1·07–1·79; age 43 years, OR 1·60, 95% CI 1·18–2·18). However, adjustment for symptoms of depression and anxiety in addition to sex at ages 36 and 43 years only reduced the association between neuroticism and schizophrenia by a small amount (adjusted OR 1·83, 95% CI 1·00–3·36). The association with extraversion was negative and also statistically significant (adjusted OR 0·49, 95% CI 0·25–0·94 see Table 1). Simultaneous inclusion of both extraversion and neuroticism in the same model only slightly changed the parameters (extraversion OR 0·47, 95% CI 0·24–0·90; neuroticism OR 1·73, 95% CI 0·95–3·15) suggesting independent effects. Likelihood ratio tests for interaction indicated that there was no strong evidence that the effects of neuroticism or extraversion differed according to sex (neuroticism $\chi^2 = 0·26$, df = 1, $P = 0·61$; extraversion $\chi^2 = 0·85$, df = 1, $P = 0·36$).

Table 2. *Associations between neuroticism and extraversion at age* 16 *years and adult schizophrenia, assuming extreme differential attrition for low neuroticism and high extraversion schizophrenia cases*

	Neuroticism	Extraversion
Scoring group	Odds ratio* (95% CI)	Odds ratio* (95% CI)
Score 0–4	1†	1†
Score 5–8	1·20 (0·48–3·04)	0·42 (0·17–1·04)
Score 9–12	2·01 (0·85–4·80)	0·35 (0·13–0·91)
Summary odds ratio‡	1·43 (0·92–2·23)	0·60 (0·36–0·99)

* Expressing risk for adult schizophrenia. Confidence interval not including unity denotes statistical significance.
† Reference category.
‡ The summary increase in risk for schizophrenia with one unit increase in the exposure variable.

Bias testing

One-third of the patients with schizophrenia could not be included in the analyses because of missing data. If attrition of individuals destined to develop schizophrenia had been higher for those who had low neuroticism or high extra-

Table 1. *Associations between neuroticism and extraversion at age* 16 *years and adult schizophrenia*

	Neuroticism		Extraversion	
	Odds ratio* (95% CI)		Odds ratio* (95% CI)	
Scoring group	Before adjustment	After adjustment†	Before adjustment	After adjustment†
Score 0–4	1‡	1‡	1‡	1‡
Score 5–8	3·10 (0·82–11·71)	2·89 (0·75–11·20)	0·40 (0·14–1·15)	0·47 (0·15–1·41)
Score 9–12	4·37 (1·18–16·19)	3·88 (0·99–15·24)	0·20 (0·06–0·70)	0·24 (0·07–0·89)
Summary odds ratio§	1·93 (1·09–3·43)	1·83 (1·00–3·36)	0·44 (0·23–0·84)	0·49 (0·25–0·94)

* Expressing risk for adult schizophrenia. Confidence interval not including unity denotes statistical significance.
† Adjustment for sex and standardized PSE and PSF scores at ages 36 years and 43 years respectively.
‡ Reference category.
§ The summary increase in risk for schizophrenia with one unit increase in the exposure variable.

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version scores as adolescents, spurious results could have arisen. We therefore repeated the analyses using a 'worst-case scenario'. If all individuals with schizophrenia who had missing neuroticism data were placed in the lowest tertile of neuroticism, the odds ratio was reduced, but not close to unity and a dose-response was still apparent (Table 2). For extraversion, the results remained significant even after placing all individuals with schizophrenia who had missing data in the highest tertile.

DISCUSSION

The findings suggest that the personality traits neuroticism and extraversion measured at age 16 years contribute, independent of each other, positively and negatively respectively to the risk of adult schizophrenia. Adjustment for two measures of anxiety and depression at different time points in adult life did not change the pattern of results, suggesting that the associations are not occasioned by the high level of depressive symptoms observed in patients with a diagnosis of schizophrenia. Bias testing involving missing cases suggested differential attrition was unlikely to constitute the sole explanation of the apparent associations. Although bias involving non-cases would still have been possible if there was differential attrition of non-cases with extremely high neuroticism scores, previous work has suggested that the cohort has remained reasonably representative (Wadsworth *et al*. 1992), also with regard to neuroticism (Van Os & Jones, 1999).

Overlap with depression

In line with previous research (Maier *et al*. 1992; Enns & Cox, 1997), earlier investigations in this cohort established that childhood neuroticism was a strong risk factor for adult non-psychotic affective disorder (Rodgers, 1990), whereas extraversion reduced the risk (Van Os & Jones, 1999). The fact that a similar result was seen for schizophrenia, independent of the presence of affective symptoms, suggests an area of shared liability and an area of shared protection. Non-psychotic affective disorder and psychosis may be, to a degree, competing outcomes associated with a range of pleiotropic causal influences. Recent research suggests that depressive symptoms are prominent during the earliest phases of schizophrenia (Häfner *et al*. 1999), and that individuals with disorders characterized by anxiety and depression have high levels of psychosis-like symptoms (Van Os *et al*. 1999*b*). Elsewhere we have reviewed the evidence that sharing of risk between affective disorder and schizophrenia occurs across many domains of liability, including genetic, neuroradiological, social and prenatal, although disorder-specific influences are also apparent (Van Os *et al*. 1999*b*).

Mechanism of risk

Interpretation of the findings is hindered by the fact that the concepts of neuroticism and extraversion, though often used, remain only partially validated. Some have proposed that neuroticism should be seen as the individual's characteristic level of minor psychiatric symptoms (Duncan Jones *et al*. 1990). However, the risk for schizophrenia mediated by neuroticism remained increased even after adjustment for usual level anxiety and depression, suggesting that another mechanism of risk is operating. It is possible that neuroticism and extraversion are non-specific factors that modify the risk of transition from several (partly or completely) aetiologically distinct pre-morbid states to an episode of overt illness. For example, high levels of neuroticism, perhaps through the attitudinal and information processing biases associated with it (Scott *et al*. 1995), may contribute to decreased levels of social interaction and reduced possibility of correction of early abnormal mental states resulting eventually in the onset of depression or psychosis (Jones, 1999). Such a mechanism would be compatible with a risk-reducing effect conferred by the more outgoing style associated with extraversion. Alternatively, extraversion has been shown to be associated with a task-orientated coping style, whereas neuroticism may be associated with a more emotional-oriented coping (Uehara *et al*. 1999). As coping mechanisms are able to modify experience of both depressive and psychotic symptoms, it is possible that the onset of both depression and psychosis may be facilitated by lack of functional coping mechanisms, or deferred by a more successful coping style.

One issue that needs to be explained is why women, who have higher levels of neuroticism (increasing the risk for schizophrenia) and lower

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levels of extraversion (also increasing risk for schizophrenia), do not have higher rates of schizophrenia than men. One explanation may be that the risk mechanisms involving these two personality variables selectively apply to the positive symptoms of psychosis. A recent large population-based study involving 7076 individuals found that women had higher rates of positive psychosis-like symptoms, even in the absence of a diagnosis of psychotic disorder (Van Os *et al*. 2000). In patient samples, women have similarly been observed to display less negative symptoms and more positive symptoms than men (Goldstein *et al*. 1990; Hambrecht *et al*. 1992; Castle *et al*. 1994). Thus, women may have higher rates of experiences that resemble the positive symptoms of psychosis, which do not necessarily translate in higher rates of clinical psychotic disorder characterized by the additional presence of negative and other symptom dimensions. Neuroticism and extraversion may thus selectively modify the risk for positive rather than other symptom dimensions. Another possibility, however, may be that we failed to detect sex interactions due to a type II error. For example, it may be that high levels of neuroticism preferentially leads to depression in women, whereas in men the phenotypic expression is more frequent in the form of non-affective psychosis.

The above interpretation has interesting clinical implications but several alternative explanations can be envisaged. First, it is possible that neuroticism and extraversion have similar associations with schizophrenia and affective disorder, but that the underlying risk-mediating mechanisms are different. Secondly, it is possible that, at an early age, vulnerability (and resilience) to a variety of later psychiatric disorders can only be expressed in a uniform way, so that neuroticism would be the early expression of non- or only partly overlapping vulnerabilities that later will manifest themselves as distinct psychiatric phenotypes. Thirdly, neuroticism may be an early manifestation of the depressive disorder itself, the association with schizophrenia possibly reflecting the fact that early depressive symptoms precede the onset of non-affective psychosis by many years (Häfner *et al*. 1999). Although this may be true for some cases, one would have expected neuroticism to be associated more strongly with later depression than with later schizophrenia if neuroticism was nothing more than the early stages of the depressive disorder itself, whereas the reverse was the case. Furthermore, it is difficult to envisage a similar mechanism in the case of extraversion.

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