Factor structure and familiality of first-rank symptoms in sibling pairs with schizophrenia and schizoaffective disorder

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Background Since their introduction as diagnostic criteria by Schneider in 1937, nuclear symptoms have played a key role in concepts of schizophrenia, but their relationship to each other and to genetic predisposition has been unclear.

Aims To ascertain the factor structure and familiality of nuclear symptoms.

Methods Nuclear (Schneiderian) symptoms were extracted from case notes and interviews in a study of 103 sibling pairs with DSM–III–R schizophrenia or schizoaffective disorder.

Results Principal components analysis demonstrated two major factors: one, accounting for about 50% of the variance, groups thought withdrawal, insertion and broadcasting, with delusions of control; and the second, accounting for <20% of the variance, groups together third-person voices, thought echo and running commentary. Factor I was significantly correlated within sibling pairs.

Conclusions The correlation within sibling pairs suggests that, contrary to the conclusion of some previous studies, some nuclear symptoms do show a degree of familiality and therefore perhaps heritability.

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The ease and reliability of eliciting first-rank symptoms (Schneider, 1959) have given them an important role in defining a concept of schizophrenia in both research and clinical practice. Psychopathological explanations (Frith, 1992; Sims, 1995) have been matched by neurobiological (Nasrallah, 1985; Trimble, 1990; Spence, 1996) theories. First-rank symptoms might be expected to have aetiological and therefore genetic significance. In a small sample of twins, McGuffin *et al* (1984) reported the heritability of nuclear symptoms to be zero, although in the same study they found the most heritable category was that defined by Research Diagnostic Criteria (RDC; Spitzer *et al*, 1978), which also depend on the presence of a number of first-rank symptoms. Here, in siblings with schizophrenia and schizoaffective disorder, we investigate whether first-rank symptoms represent more than one component of psychopathology and whether that component(s) is familial and therefore possibly heritable. Previously, we examined positive, negative and disorganised symptoms in a set of these multiply affected families (Loftus *et al*, 1998).

METHODS

Families with two or more ill siblings were recruited in the UK, the USA and the Republic of Ireland as part of a multi-centre genetic linkage project. Sources of recruitment were the local psychiatric services, the National Schizophrenia Fellowship (NSF) and Schizophrenia – a National Emergency (SANE) in the UK and Republic of Ireland, and the National Alliance for Mental Illness (NAMI) in the USA. Identification of families, clinical evaluations and diagnostic procedures were similar in all locations (details of this population have been published elsewhere: Garner *et al*, 1996; Dann *et al*, 1997; Loftus *et al*, 1998). The total number of families assessed was 102, comprising 51 from the USA, 32 from Northwick Park in north-west London, 14 from Oxford and five in Dublin. After giving a complete description of the study to the subjects, their written informed consent was obtained. Each ill sibling was interviewed using structured diagnostic interviews (the Schedule for Affective Disorders and Schizophrenia (SADS; Endicott & Spitzer, 1978) or the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger *et al*, 1994)). For each sibling all available hospital case notes were obtained. Collateral information was collected from at least one well member of each family (usually a parent), using a structured interview, the Relative Psychiatric History Questionnaire (Gershon ES, National Institute of Mental Health, USA; unpublished). Siblings were included if they met DSM–III–R criteria for schizophrenia or schizoaffective disorder (American Psychiatric Association, 1987) based on the above sources of information. Each sibling was diagnosed independently by two trained diagnosticians. In cases where there was disagreement, consensus was reached by consultation with a third person. All clinical procedures were identical in both centres, and diagnostic reliability studies had been periodically performed, with κ statistic scores ranging between 0.85 and 0.90 for primary diagnoses.

Altogether, the above information was reviewed for 230 siblings. A total of 45 siblings were excluded from the study: 35 due to a lack of adequate case notes, and four because they failed to meet criteria for DSM–III–R schizophrenia or schizoaffective disorder; this resulted in three of their co-siblings also being excluded. Three additional siblings were excluded because of a history of organic complications such as head injury, encephalitis and low IQ, which, with inadequate information, rendered diagnosis difficult. Another six families were excluded because first-rank symptoms were documented in the case notes as being present but no further details were given. The final number of families included was 75, comprising 171 siblings. There were two families with four ill siblings and nine families with three ill siblings. A family of three siblings formed three sibling pairs (sib-pairs) and a family of four formed six sib-pairs. Case notes, DIGS or SADS interviews and information from relatives were reviewed to determine the presence or absence of first-rank symptoms in each of the 171 siblings. Table 1

Table 1 Demographic details

Mean age, years	36.7 (s.d. 6.6)		
Mean age at onset, years	21.02 (s.d. 5.2)		
Mean duration, years	15.32 (s.d. 6.5)		
Gender: males	134		
females	37		
Total no. of sibling pairs	103		
male–male	64 (62%)		
male–female	34 (33%)		
female–female	5 (5%)		
DSM–III–R diagnosis			
schizophrenia	131 (76.6%)		
schizoaffective disorder	40 (23.4%)		
Ethnicity	US	UK	Total
White	78	66	84.2%
African–Caribbean/ American	2	14	9.4%
Asian	0	7	4.1%
Arab	0	2	1.2%
Mixed	0	2	1.2%
Total: n=171	80	91	100%

shows the demographic characteristics, including ethnicity, of the analysed sample.

Individual first-rank symptoms were rated as: 0=absent, 1=present. A narrow definition of first-rank symptoms was employed. All ratings were performed by one observer (J.L.) and were based on a lifetime history of the illness. First-rank symptoms rated were: audible thoughts; running commentary; third-person auditory hallucinations; thought withdrawal, thought insertion and thought broadcasting; delusional perception and delusions of control (including made feelings, made drives and somatic passivity).

The data were then analysed in two different ways, using SPSS V6.1:

(a) by exploratory factor analysis; all factor analyses were performed using orthogonal rotation (VARIMAX) in order to simplify the interpretation of factors; only factors with eigenvalue >1 were considered;

(b) by Spearman rank correlation of factor regression scores between members of sibling pairs; *post hoc* χ^2 tests of observed against expected concordance were applied to individual symptoms.

RESULTS

Table 2 shows the distribution of first-rank symptoms in the whole sample, while Table 3 shows the distribution between siblings 1 and 2. Delusional perception was omitted from further analysis, as it was present in only 2.4% of the total sample (n=5).

Table 3 shows that the distribution of first-rank symptoms was similar in both sibling 1 and sibling 2 (sibling 1 is defined as the elder member of the sib-pair).

Factor analyses revealed very similar patterns of correlation between the individual symptoms in the whole sample (n=206) and when siblings 1 and 2 were considered separately (n=103) (Table 4).

In the whole sample, the analysis yielded two factors which accounted for about 67% of the total variance. Factor 1 was characterised by thought broadcasting (0.83), thought insertion (0.81), thought withdrawal (0.88) and delusions of control (0.72), and accounted for 49.8% of the variance. Third-person auditory hallucinations (0.76), running commentary (0.69) and thought echo (0.74) loaded significantly on factor 2, which explained 16.9% of the total variance.

Factor analysis on siblings 1 and 2 again provided a two-factor rotated matrix, very similar to that yielded by the whole sample but for the fact that delusions of control had a moderate loading on factors 1 and 2 in the second sibling (0.52 and 0.51 respectively).

Regression scores were calculated for both factors, and Spearman rank correlations were used to determine the

Table 2 Distribution of first-rank symptoms (n=206)

	Third-person hallucinations		Running commentary		Thought echo		Thought broadcasting		Thought insertion		Thought withdrawal		Delusional perception		Delusions of control	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Absent	117	56.8	128	62.1	180	87.4	93	45.1	96	46.6	108	52.4	201	97.6	104	50.5
Present	89	43.2	78	37.9	26	12.6	113	54.9	110	53.4	98	47.6	5	2.4	102	49.5

Table 3 Distribution of first-rank symptoms between siblings

	Third-person hallucinations		Running commentary		Thought echo		Thought broadcasting		Thought insertion		Thought withdrawal		Delusional perception		Delusions of control	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sibling 1 (n=103)																
Absent	57	55.3	63	61.2	93	90.3	43	41.7	51	49.5	56	54.4	101	98.1	51	49.5
Present	46	44.7	40	38.8	10	9.7	60	58.3	52	50.5	47	45.6	2	1.9	52	50.5
Sibling 2 (n=103)																
Absent	60	58.3	65	63.1	87	84.5	50	48.5	45	43.7	51	49.5	100	97.1	51	49.5
Present	43	41.7	38	36.9	16	15.5	53	51.5	58	56.3	52	50.5	3	2.9	52	50.5

Table 4 Exploratory factor analyses: rotated component matrix

	All siblings (n=206)		Sibling no. 1 (n=103)		Sibling no. 2 (n=103)	
	Factor 1	Factor 2	Factor 1	Factor 2	Factor 1	Factor 2
Third-person hallucinations	0.30	**0.76**	0.36	**0.70**	0.15	**0.85**
Running commentary	0.40	**0.69**	0.41	**0.67**	0.28	**0.79**
Thought echo	−0.06	**0.74**	−0.17	**0.76**	0.04	**0.61**
Thought broadcasting	**0.83**	0.14	**0.82**	0.25	**0.85**	0.12
Thought insertion	**0.81**	0.22	**0.85**	0.22	**0.76**	0.27
Thought withdrawal	**0.88**	0.07	**0.90**	0.11	**0.88**	0.09
Delusions of control	**0.72**	0.19	**0.82**	−0.07	**0.52**	**0.51**
% Variance accounted for	49.8	16.9	52.0	17.8	48.1	17.4

Note: Delusional perception was excluded from calculation in both siblings.

association of factor scores within sib-pairs. A significant correlation was observed for factor 1 which, as previously indicated, included thought broadcasting, thought withdrawal, thought insertion and delusions of control (r=0.21, P=0.03). For factor 2 the comparable correlation coefficient was not significant (r=0.04, P=0.62).

Post hoc χ^2 analyses were used to look for significant correlations between the individual symptoms in factors 1 and 2 (Table 5). Levels of statistical association for individual symptoms between sib-pairs were significant only for three first-rank symptoms: third-person auditory hallucinations (P=0.05), delusions of control (P=0.02) and thought broadcasting (P=0.04).

DISCUSSION

Summary of findings

The findings suggest that certain first-rank symptoms are as familial or heritable as other individual symptoms of schizophrenia and comprise two psychopathologically distinct components. Replication would help validate the importance of first-rank symptoms in the various diagnostic criteria for schizophrenia.

Principal components analysis revealed a two-factor structure of first-rank symptoms that exhibited a degree of stability across the sub-samples of siblings. The first component (representing close to 50% of the variance) groups the primary experiences of thought alienation (insertion, withdrawal and broadcast) with delusions of control. The second component (representing less than 20% of the variance) encompasses the hallucinatory phenomena (third-person voices, running commentary, thought echo). These appear to be relatively independent components of the core syndrome, and may reflect separable anomalies of function. It has been suggested (Crow, 1998) that nuclear symptoms are deviations in the transition from thought to speech, and from speech to meaning. One possibility to be considered is that factor 1 identifies anomalies in the former category, i.e. in the generation of speech from thought (which can be conceived as a prefrontal and motor function), whereas factor 2 identifies a disturbance in the process by which meaning is extracted from a message received from another person, a process which presumably takes place in the region of the occipito-parieto-temporal junction. It may thus be possible to assign the factors to each of the two areas of hetero-modal association cortex that relate to motor (anterior) and sensory (posterior) functions in the brain, respectively.

Comparison with similar studies

Our findings demonstrate that a factor comprising thought insertion, thought broadcasting, thought withdrawal and delusions of control is significantly correlated in sib-pairs with schizophrenia or schizoaffective disorder. There is some agreement between the results yielded by factor analysis and those obtained from χ^2 measures of association of individual symptoms. Similar studies have not always found significant correlations for first-rank symptoms. In the study by Cardno *et al* (1999), factor analysis of OPCRIT symptoms (McGuffin *et al*, 1991) yielded a factor described as first-rank which had high loadings for persecutory delusions (0.52), bizarre delusions (0.63), delusions of passivity (0.73) and thought insertion (0.62). Correlations between sib-pairs for this factor were non-significant. In another study, Cardno *et al* (1999) found a modest association for broadly defined positive formal thought disorder, grandiose delusions and delusions of influence, although the authors expressed concern that multiple statistical testing might have generated false positives. With the Major Symptoms of Schizophrenia Scale, Kendler *et al* (1997) found

Table 5 Concordance for individual symptoms in sibling pairs: significant correlation between individual symptoms using χ^2 test (ϕ)

Symptoms	Negative concordance		Positive concordance		Discordant		ϕ	Significance
	obs.	exp.	obs.	exp.	obs.	exp.		
Third-person hallucinations	38	33.2	24	19.2	41	50.6	**0.19**	**0.05**
Running commentary	42	39.8	17	14.8	44	48.4	0.09	0.34
Commentary thought echo	79	78.6	2	1.6	22	22.8	0.04	0.68
Thought broadcast	26	20.9	36	30.9	41	51.2	**0.20**	**0.04**
Thought withdrawal	31	28.3	26	23.3	46	51.4	0.11	0.28
Thought insertion	25	22.3	32	29.3	46	51.4	0.10	0.28
Delusions of control	32	26.3	31	25.3	40	51.4	**0.22**	**0.02**

obs, observed; exp, expected.
Delusional perception excluded from calculation in both siblings.

significant sibling resemblance for eight of the nine items, although the correlation (r=0.16, P=0.02) for Schneiderian delusions was the least significant, and that for hallucinations was non-significant. Factor analysis of the same scale yielded a positive factor which had high loadings on hallucinations, any delusions and Schneiderian delusions with Pearson correlations between siblings that were significant (r=0.16, P=0.005). In the study of Burke *et al* (1996) in the same sample of siblings, first-rank symptoms were subsumed under the headings 'delusions' and 'hallucinations'. Again, correlations were significant for this factor. In Farmer *et al*'s (1984) H and P subtypes, the former, including delusions of control, was identified as having the greater genetic loading. Although other studies have used different rating scales and have classified individual first-rank symptoms within wider symptom groups, there is some evidence from these studies that certain first-rank symptoms may be shared above chance expectation in sib-pairs.

Neurobiological theories of first-rank symptoms

Our findings suggest that, contrary to the conclusions of an earlier twin study (McGuffin *et al*, 1984), first-rank symptoms, when subgrouped, are related to whatever is familial or heritable in the predisposition to schizophrenic illness. In this study, the most significant correlation was for factor 1, which included passivity of thought and experience. Thus we speculate that certain first-rank symptoms are closer to the heritable core than others, and may reflect an underlying shared neurobiological abnormality.

Spence (1996) argues that first-rank symptoms reflect a breakdown in the barrier between conscious and unconscious processes, the latter assuming the nature of alien or persecutory experiences as they are not perceived as willed or generated by the self. Relevant to this view is the demonstration by Libet *et al* (1983) that neuronal activity related to an action precedes the subject's conscious awareness of a decision to act by approximately 400–500 ms. Comparing the passivity phenomena of schizophrenia to symptoms seen in organic illnesses affecting the parietal lobe and right hemisphere, Spence *et al* (1997) used positron emission tomography (PET) to investigate neural correlates. They found that patients with passivity phenomena exhibited reversible hyperactivation of the cingulate gyrus and right inferior parietal lobule, an area with afferent and efferent connections to various parts of the brain that include the sensory, prefrontal, premotor, cingulate and superior temporal cortices. The hyperactivation disappeared when the passivity phenomena remitted. These authors regarded their findings as providing some support for previous claims (Nasrallah, 1985; Cutting, 1990) that the right hemisphere, in particular the right parietal lobe, may be responsible for 'alienation', defined not only as made movement but also made thoughts and affect. To explain passivity phenomena as a disturbance of external–internal spatial schemata, Spence *et al* (1997) invoked the theories of Pandya & Yeterian (1984) concerning the role of the cingulate gyrus and parietal lobe in mediating inward and outward attention respectively.

Like Nasrallah, Crow (1998) views the central problem as a defect in bi-hemispheric communication, but one that is due to incomplete functional differentiation, with the consequence that internally generated neural activity (e.g. thought) is perceived as having the character of a message from an independent source. Within the context of a bi-hemispheric theory of language, Crow (1998) proposes that a defect in the relationship between the linear sequencing of the dominant hemisphere and the spatial and two-dimensional organisation of concepts in the non-dominant hemisphere lies at the root of first-rank symptoms. A consequence is that the indexical reference frame of language is lost; the individual is no longer able to separate his/her own thoughts or feelings from those which are externally derived. This linguistic explanation parallels Spence's attempts to account for the loss or distortion of ego boundaries, and is consistent with Cutting's (1997) argument that greater knowledge of inter-hemispheric interaction is a necessary prerequisite for progress in understanding the neurobiological basis of psychopathology.

Methodological limitations

Caution must, however, be exercised in interpreting the results of this and other sib-pair studies. The design of this study does not enable one to disentangle genetic from environmental influences. Nevertheless, there is evidence from a number of behavioural genetic studies that both normal variation and psychopathology are genetically determined (Plomin & Daniels, 1987; Reiss *et al*, 1994). In these studies the familial or common environment was found to be relatively unimportant.

There are also limitations that are specific to this study. First, the ratings of case notes and interviews were performed by one person (J.L.), thus without interrater validity testing. Second, the study was mainly retrospective, i.e. ratings of first-rank symptoms were made from interviews and case notes collected as part of a project not specifically designed to study first-rank symptoms. However, narrow definitions were used, with the objective of increasing the accuracy of the ratings made on the available information.

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CLINICAL IMPLICATIONS

- Nuclear symptoms are a familial component of predisposition to psychosis.
- Nuclear symptoms can be subdivided into thought withdrawal, insertion and broadcast, together with delusions of control (group 1) and third-person auditory hallucinations, thought echo and running commentary (group 2).
- It is suggested that group 1 symptoms are anomalies of the asymmetry of frontal association cortex and group 2 of temporo-parietal-occipital association cortex.

LIMITATIONS

- Assessments of case notes and interviews were performed by one person (J.L.).
- First-rank symptoms were assessed retrospectively.
- The project was not designed specifically as a study of first-rank symptoms.

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