Schizophrenia Bulletin vol. 32 no. 3 pp. 573–577, 2006
doi:10.1093/schbul/sbj037
Advance Access publication on January 11, 2006

The Presence of Neurological Soft Signs Along the Psychosis Proneness Continuum

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Neurological soft signs have been observed in patients with schizophrenia and their relatives. However, it has not been considered whether the increased rates of neurological soft signs are related to measures of psychosis proneness in the general population. We tested this hypothesis in a group of normal volunteers ($n = 28$) who scored highly for positive schizotypy when assessed online and a control group ($n = 33$) who scored below the mean. Compared with the controls, high psychosis-prone individuals showed significantly higher Total and Other Soft Signs subscale scores on the Neurological Evaluation Scale. It appears that soft signs are also associated with psychosis proneness when measured in the general population, which suggests that soft signs are distributed along a continuum of risk for schizophrenia.

Key words: Schizophrenia/neurological soft signs/O-LIFE/hallucinatory proneness

Introduction

There is an extensive literature reporting increased rates of neurological soft signs in patients with schizophrenia.[1,2] "Soft" signs are minor, nonlocalizable, objective abnormalities that are thought to reflect damage in connections between subcortical and cortical areas or between cortical areas.[3–5] In contrast, "hard" neurological signs can be linked to specific areas of neuroanatomical damage.[6] Some researchers believe neurological soft signs represent a developmental lag rather than a fixed abnormality.[7]

Patients with schizophrenia have frequently been reported to display more neurological soft signs when compared with controls[4,8–12] and other patient groups,[13–15] even after controlling for effects of drug treatment.[16]

Neurological soft signs have also been found with increased frequency in relatives of those with schizophrenia,[4,17–20] offspring of those with schizophrenia,[21,22] and in those considered at high genetic risk for developing schizophrenia in the future.[22,23] If neurological soft signs characterize those at increased genetic risk for schizophrenia, it might be predicted that they would also appear with increased frequency in schizotypy, a putative measure of psychosis liability. Determining whether neurological soft signs are related to a normally distributed marker of psychosis proneness or schizotypy in the general population would demonstrate whether they are detectable along a continuum of risk. We hypothesized that those who scored highly on positive schizotypy would present with higher soft sign scores as measured by the Neurological Evaluation Scale.[24]

Method

Participants

The participants were university student volunteers selected on the basis of their responses to the Unusual Experiences subscale from the Oxford Liverpool Inventory of Feelings and Experiences (O-LIFE)[25] and the Launay-Slade Hallucination Scale (LSHS),[26] which were placed on a university intranet. Both of these questionnaires are considered valid measures of schizotypy or psychosis proneness. Two subgroups of participants were assessed at interview: a "high psychosis-prone" group ($n = 28$), who scored above 1 standard deviation from the mean on both scales, and a control group ($n = 33$), who scored at or below the mean. The 2 groups did not differ significantly on demographic variables: the high proneness group consisted of 15 males (54%), with a mean age of 22.5 (SD = 5.7) years, and the control group consisted of 16 males (49%), with a mean age 25.4 (SD = 10.5) years. In the sample 95% of participants were right-handed.

Measures

Participants were evaluated with the Neurological Evaluation Scale (NES).[24] The NES measures 4 neurological

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domains: Sensory Integration, Motor Coordination, Sequencing of Complex Motor Acts, and Other Soft Signs. There are 28 items on the NES. The following items were assessed for both the left- and right-handed subjects: Stereognosis, Graphesthesia, Fist-Ring Test, Fist-Edge-Palm Test, Rapid Alternating Movements, Finger-Thumb Opposition, and Mirror Movements.

Participants also completed a questionnaire about substance use.[27]

Procedure

The study received ethical approval as part of a larger project examining the correlates of schizotypy in a healthy population. Participants gave informed written consent and were assured of anonymity and confidentiality of the data being collected.

Participants were contacted by e-mail to request their participation in the study after they had been identified through the online completion of the O-LIFE and the LSHS. Participants completed the NES in the order described in Buchanan and Heinrichs.[24] Assessments were performed by 2 raters who were blind to the subgroup status of participants. Interrater reliability was established prior to the start of the study using different participants from the experimental sample. First, the raters both completed assessments of 5 participants at the same time to establish that they had a similar understanding and appreciation of the rating scales for each item. Second, the NES was completed independently by the 2 raters on 5 individuals, with scores being compared after each participant, until both raters produced the same results. Finally, the 2 raters completed the assessment on the same individual, who was well versed on soft signs assessments and well acquainted with the NES, to ensure that the administration of instructions and scale was identical. As a post hoc check, the scores for the 2 raters in the experimental sample were compared using a series of independent *t*-tests: there were no significant differences in total or subscale scores.

Cards were produced with rhythms for the Rhythm Tapping tests (A and B) and the Audio-Visual Integration tests to ensure they were standardized. For the Stereognosis test participants were asked to identify a button, a paper clip, a pen cap, and an elastic band. Two items were identified in each hand. The administration of the NES tests took approximately 30 minutes to complete.

Results

For the 28 participants in the high proneness group and 33 participants in the control group, the subscales and total score from the NES approximated to a normal distribution with the exception of the Complex Motor Skills subscale, which required a log transformation to normalize the spread of the scores. Parametric analyses were used to compare group means.

Drug Use, Schizotypy, and Soft Signs

The number of substances people had used recreationally varied between 0 and 6. Substances that participants had used were as follows (in order of frequency of use): cannabis (69%), amphetamines (22%), hallucinogens (16%), cocaine (15%), sedatives, hypnotics, and tranquilizers (13%), and solvents (6%). Regularity of use data was only available for cannabis consumption; the reported rates of use were as follows: few times each week (29%), about once a week (6%), a few times each month (3%), about once a month (11%), a few times each year (26%), less than once a year (17%), and only once or twice (9%). There was no association between regularity of cannabis use and schizotypy group ($\chi^2 = 3.79$, $df = 5$, not significant [NS]). There was also no association between cannabis use and schizotypy group ($\chi^2 = 0.74$, $df = 1$, NS). The relationship between cannabis use and schizotypy has been commented on elsewhere.[27] Cannabis use, age when first used, and frequency of use were unrelated to the presence of neurological soft signs. There was a negative correlation between the Motor Coordination subscale and the number of recreational drugs people had tried (rho = -0.335, $n = 61$, $p = .008$), indicating those with low scores on the Motor Coordination subscale had used more recreational drugs.

Schizotypy Group and Soft Signs

The means and standard deviations for the 2 groups on the total score and subscales from the NES are reported in Table 1. A series of independent *t*-tests were run to examine whether the 2 groups differed in their levels of reported neurological soft signs: the soft sign total and subscales were the dependent variables, and the proneness group was the independent variable. Due to the number of multiple comparisons, a Bonferroni correction was adopted with alpha set to 1%. The *t* values and the probability levels for the 2 groups are shown in Table 1. The high psychosis-prone group showed higher scores on the total from the NES and the Other Soft Signs subscale.

A logistic regression model was used to determine whether the total from the NES or the subscales statistically predicted psychosis proneness group. The results are displayed in Table 2. The total score from the NES was entered into a model alone, due to its high correlation with the subscales. The total NES score significantly predicted psychosis proneness group using an enter method of variable selection. The subscales from the NES were entered into a separate logistic regression model using a stepwise method variable selection. The subscale that successfully predicted psychosis proneness group was the Other Soft Signs subscale. The results from this analysis can be seen in the second row of Table 2.

Table 1. The Means (and Standard Deviations) for the High Proneness and Control Participants on the Total and Subscales from the Neurological Evaluation Scale

	High Proneness Group (n = 28) Mean (SD)	Control Group (n = 33) Mean (SD)	t value (df = 59)	Significance
Soft Signs Total	16.57 (5.55)	13.37 (4.95)	2.39	.01
Sensory Integration	2.18 (1.56)	1.76 (1.54)	1.06	.15
Motor Coordination	1.54 (1.43)	1.42 (1.44)	.30	.38
Complex Motor Skills	2.14 (2.24)	1.64 (1.69)	1.01	.16
Other Soft Signs	7.07 (3.40)	5.18 (2.96)	2.32	.01

Discussion

Neurological soft signs were examined in a group of healthy volunteers selected according to their positive schizotypy score, as measured by the Unusual Experiences subscale from the O-LIFE[25] and the LSHS.[26] The high psychosis-prone individuals showed more soft signs overall and on the Other Soft Signs subscale. From an examination of the means for the remaining subscales from the NES, the group differences occurred in the predicted direction, although they did not reached significance. Using 2 separate regression models, the total from the NES and the Other Soft Signs subscales significantly predicted psychosis proneness group.

A number of studies have used the Neurological Evaluation Scale in samples of patients with schizophrenia; some produced results that support the data from the current study. Ismail et al.[28] reported that patients with schizophrenia and their siblings scored higher than normal controls on the Soft Signs Total, as well as the Sensory Integration and Motor Functioning subscales. Additionally, patients with schizophrenia have been reported to score higher than at-risk patients, who in turn scored higher than controls on the Soft Signs Total, Sensory Integration, and Other Soft Signs.[29] Arango et al.[30] reported that the Other Soft Signs subscale was able to correctly classify a greater number of patients and controls to their true group than the other subscales from the NES. Taken together these previous studies and the current results suggest that the Other Soft Signs subscale may be particularly sensitive in identifying those with schizophrenia or a proneness to it.

Griffiths et al.[18] suggested that the presence of soft signs in relatives increases with the potential genetic loading (ie, greater incidence of schizophrenia in a family increases the presence of soft signs). Furthermore, Gourion et al.[31] reported that the Total Soft Signs score could be used to distinguish relatives who were thought to be carriers of the genetic vulnerability to schizophrenia from those who were not. This suggests that the presence of neurological soft signs may be indicative of being a ''gene-carrier'' for psychosis. It is not possible, on the information available, to determine whether the participants in the current study are gene-carriers for schizophrenia. However, a high score on a schizotypal personality questionnaire is considered a phenotypic marker for possible development of schizophrenia.[eg,32,33] However, the results from Lawrie et al.[29] may suggest that soft signs are not an indicator of genetic risk specifically for psychosis. Other causes of soft signs may be low birth weight[34,35] and obstetric complications.[36] Obstetric complications may be a more significant factor for males at risk for schizophrenia,[37] or for leading to soft signs in those at genetic risk for developing schizophrenia.[38] Additionally, childhood illnesses such as whooping cough, meningitis, and tuberculosis have been associated with soft signs in adulthood.[39] At the very least, these studies suggest that the relationship between soft signs and schizophrenia is not a simple one, with many mediating variables being implicated.

Table 2. The Logistic Regression Results for Predicting Psychosis Proneness Group From the Total Score and Subscales from the Neurological Evaluation Scale

					95% Confidence Interval	
	Beta	Wald	Significance	Odds Ratio	Lower	Upper
Soft Signs Total[a]	−0.12	4.98	.03	0.89	0.80	0.99
Other Soft Signs[b]	−0.19	4.75	.03	0.83	0.70	.98

Note: df = 1.
[a]Enter method of variable selection used.
[b]Stepwise method of variable selection used.

Some clarification of the intermediate variables may result from examining the genes associated with soft signs. For example, Lautenschlager et al.[40] reported that the neurological soft signs were associated with apolipoprotein E gene (which has been implicated in Alzheimer disease[41]), age, and cognitive performance. With the increasing interest in the functional effects of single nucleotide polymorphisms, it would be beneficial to determine whether genes implicated in the dopamine and glutamate pathways confer risk for the presence of neurological soft signs.

Acknowledgments

Some of the data described in this paper was presented at the Biennial Winter Workshop on Schizophrenia, Davos, Switzerland, 2004. This project was funded by the Stanley Medical Research Foundation.

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