Neuroscience and Biobehavioral Reviews 34 (2010) 889–896

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Neurological soft signs in non-psychotic first-degree relatives of patients with schizophrenia: A systematic review and meta-analysis

Raymond C.K. Chan [a,b,*], Ting Xu [a,b,c], R. Walter Heinrichs [d], Yue Yu [e,f], Qi-yong Gong [g]

[a] Neuropsychology and Applied Cognitive Neurosciences Laboratory, Institute of Psychology, Chinese Academy of Sciences, 4A Datun Road, Beijing 100101, China
[b] Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, China
[c] Graduate School, Chinese Academy of Sciences, Beijing, China
[d] Department of Psychology, York University, Toronto, Canada
[e] Department of Psychology, Yuanpei College, Peking University, Beijing, China
[f] Yuanpei College, Peking University, Beijing, China
[g] Huaxi MR Research Centre, Department of Radiology, West China Hospital/West China School of Medicine, Sichuan University, Chengdu, China

ARTICLE INFO

Article history:
Received in revised form 11 November 2009

Keywords:
Neurological soft signs
Non-psychotic relatives
Schizophrenia
Meta-analysis
Endophenotypes

ABSTRACT

Background: Neurological soft signs (NSS) have been associated with the neuropsychopathology of schizophrenia, and have been proposed as candidate endophenotypes for this clinical group. However, the prevalence rate of NSS in non-psychotic first-degree relatives is not fully known. The authors systematically and quantitatively reviewed the literature to determine the magnitude of difference between: (1) first-degree non-psychotic relatives of schizophrenia patients and healthy controls, and (2) between schizophrenia patients and their non-psychotic relatives.
Methods: An article search and meta-analysis was conducted using the Comprehensive Meta-Analysis software package to quantify group differences. Mean effect sizes (standardized group mean differences) and associated confidence intervals along with homogeneity and publication bias tests and statistics were calculated.
Results: Search procedures identified 11 independent studies that met the inclusion criteria. Quantification of NSS differences yielded a mean effect size of 0.81 for schizophrenia patients and their non-psychotic relatives and 0.97 for non-psychotic relatives of schizophrenia patients and healthy controls.
Conclusions: The current findings show that there are large group differences in NSS prevalence between patients with schizophrenia, non-psychotic relatives, and healthy controls. These results are consistent with the argument that NSS are familial in nature, segregate with the illness and may be valid and useful endophenotypes.

Contents

* Corresponding author at: Institute of Psychology, Chinese Academy of Sciences, 4A Datun Road, Beijing 100101, China. Tel.: +86 10 64836274; fax: +86 10 64836274.
E-mail addresses: rckchan@psych.ac.cn, rckchan2003@yahoo.com.hk (Raymond C.K. Chan).

0149-7634/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neubiorev.2009.11.012

1. Introduction

The endophenotype (internal or intermediate phenotype) approach is useful in exploring the genetic and environmental architecture of schizophrenic disorders and fills the gap in the causal chain between genes and external phenotypes (Gottesman and Shields, 1973). There are five criteria for candidate endophenotypes.(Chan and Gottesman, 2008; Barrantes-Vidal et al., 2002; Gottesman and Gould, 2003; Tsuang et al., 1993) They are (1) association with illness in the population; (2) heritability; (3) state independence; (4) familial association, i.e., found in unaffected relatives at a higher rate than in the general population; (5) co-segregation within families, i.e., occurs more frequently among ill relatives of ill probands compared with the well relatives of ill probands.

In the last two decades, research has demonstrated that neurological soft signs (NSS) occur more frequently in schizophrenia patients than in healthy controls (Heinrichs and Buchanan, 1988; Bombin et al., 2005). Moreover, numerous studies reported that NSS in relatives were intermediate between patients and comparison controls. Tsuang et al. (1991) and Tsuang and Faraone (1999) argued that NSS are "target features" of the illness, reflecting genetic and non-genetic processes that lead to maldevelopment in neurobehavioural systems. Chan and Gottesman (2008) have reviewed evidence for the utility of NSS as a promising endophenotype for schizophrenia-related disorders.

NSS are neurological abnormalities that cannot be linked to impairment of a specific or focal brain region and are not believed to be part of a well-defined neurological syndrome. Studies to date have provided evidence that NSS are relatively specific to schizophrenia (Bombin et al., 2005; Chan and Gottesman, 2008). These studies have also indicated that NSS meet endophenotype criterion 1—association with illness, to a significant degree. Heinrichs and Buchanan (1988) found that NSS are more prevalent among schizophrenia patients than among healthy controls with frequency ranging from 50% to 60% in patients in contrast to 5% in healthy controls. A meta-analysis conducted by our laboratory (Chan et al., in press) showed that the grand mean effect size (standardized mean group difference) between schizophrenia patients and healthy controls was 1.59 for NSS summary scores. In subscale (e.g., motor sequencing, sensory integration) comparisons, the standardized difference in means for all subscale scores was never less than 0.80 (Chan et al., in press). Chan and Chen collected data from a Chinese sample and found that the prevalence of NSS was approximately 59% in the patient group and 5% for healthy controls (Chan and Chen, 2007). These findings confirm that NSS are associated strongly with schizophrenia across cultures and occur at low rates in the general population.

Relatively little is known about the prevalence of NSS in non-psychotic first-degree relatives of patients with schizophrenia. However, a substantial number of studies of genetic high-risk subjects have been conducted in the past decades. Hence, it has become more feasible to examine whether NSS meet endophenotype criteria 4 and 5 in terms of schizophrenia, i.e., familial association and co-segregation. With regard to the fourth criterion, familial association, there is inconsistent evidence among comparative studies of relatives of schizophrenia patients and healthy controls. Many studies show significant differences between these two groups (Ismail et al., 1998, 2000; Yazici et al., 2002; Chen and Chen, 2000; Gourion et al., 2004; Gourion et al., 2003; Kinney et al., 1986; Niemi et al., 2005; Niethammer et al., 2000; Rossi et al., 1990). For example, Gourion et al. (2004) found that presumed carriers and non-carriers had significantly higher NSS scores than did healthy controls, while parents of presumed carriers had significantly higher scores than had those of presumed non-carriers. This finding suggests that NSS are associated with genetic loading. Gourion et al.'s (2004) study also suggests that familial, and more specifically, genetic factors, determine NSS. Nevertheless, several other studies (Bollini et al., 2007; Compton et al., 2007; Lawrie et al., 2001; Egan et al., 2001) did not find significant differences in NSS between relatives of schizophrenic patients and healthy controls. However, Egan et al. (2001) found subtle differences and Lawrie et al. (2001) also demonstrated that high-risk individuals had elevated rates of sensory integration abnormalities relative to healthy controls.

Regarding the fifth criterion, co-segregation of NSS with illness in patients' families, results of family studies are contradictory. A number of studies have found that patients with schizophrenia have higher NSS rates than their healthy relatives (Ismail et al., 1998, 2000; Yazici et al., 2002; Chen and Chen, 2000; Gourion et al., 2004; Niethammer et al., 2000; Compton et al., 2007; Egan et al., 2001; Lawrie et al., 2001; Picchioni et al., 2006). Others, however, have found weak evidence of such a co-segregation (Kelly et al., 2004; Rossi et al., 1990; Kinney et al., 1986; Gourion et al., 2003).

The above evidence relevant to endophenotype criteria 4 and 5 show that, despite variability, the majority of studies report NSS scores in patients' relatives intermediate between those of patients and healthy controls. A putative endophenotype should be selected with respect to the strength of empirical evidence supporting its fulfillment of the endophenotype criteria. In particular, meeting criterion 4, familial association, is a key step in validating endophenotypes of complex inheritable forms of schizophrenia. Two systematic reviews (Bombin et al., 2005; Chan and Gottesman, 2008) have summarized NSS prevalence in relatives of patients with schizophrenia, but no quantitative synthesis exists of findings in non-psychotic first-degree relatives. Therefore, we conducted a meta-analysis to address the issue of familial association (endophenotype criterion 4) by quantifying the evidence and determining the magnitude and stability of group mean differences between relatives of schizophrenics and healthy controls. Moreover, the present meta-analyses also partially addressed co-segregation (endophenotype criterion 5) by determining the magnitude of differences between schizophrenic patients and their relatives.

2. Methods

2.1. Literature search

The Elsevier, EBSCOHost (PsychINFO, PsychACTICLE), and MedLine databases were used to find studies for inclusion in the meta-analysis. The keywords were "neurological soft sign," "neurologic signs," "neurological sign; soft sign," "neurological abnormality," "neurological anomalies," "neurological abnormalit*," "motor coordination," "sensory integration," "disinhibition," "complex motor sequencing," "Luria task," "Fist-edge-palm," "Schizophrenia," "Schizotypal," "Schizotypy," "relatives," "siblings," "parents," "mother," "father," "offsprings," and "twins" The literature search was performed by two reviewers who coded and critically evaluated studies for the 1966 to February 2009 period. This yielded 27 independent studies reporting data on relatives of schizophrenic patients. Descriptive characteristics of the samples in these studies are summarized in Table 1. Duplicate reports of the same sample data or those that overlapped with other studies; were eliminated so that each report was unique.

The following criteria were used by reviewers to select in the initial pool for quantitative analysis. Each study was required to meet all of the criteria: (a) diagnosis of schizophrenia was according to DSM-III, III-R, or IV; ICD-9 or -10; (b) NSS scales were standard scales including the Neurological Evaluation Scale, Cambridge Neurological Inventory, Heidelberg Scale (Schröder et al., 1992), and so forth; (c) comparison of the differences between

Table 1
Basic characteristics of the studies reported the data.

Study	NSS scale	Subjects	Reported data means (SDs)/prevalence	NSS-total		In or out
				SZ vs. R	R vs. C	
Kinney et al. (1986)	Screened signs	24 SZ 21 R 24 C	Score ≥1 50% 38.1% 12.5%	n.s. (SZ, R)	$p=0.02$	
Rossi et al. (1990)	26 items	58 SZ 31 R 38 C	12.63(4.79) 9.80(2.42) 4.07(2.53)	n.s. (SZ, R)	$p<0.0001$	[a]
Gourion et al. (2003)	23 items from Krebs' study[b]	18 SZ 36 P 42 C	18.7(9.4) 16(5.8) 3.9(2.8)	n.s. (SZ, P)	$p<0.001$	[a]
Kelly et al. (2004)	CNE	3 MZ_C, 5 MZ_DC 1 DZ_C, 6 DZ_DC	7.2(4.9) 4.7(3.6)	n.s. (MZ_A, MZ_NA) n.s. (DZ_A, DZ_NA)	No C	[a]
Gourion et al. (2004)	23 items from Kerbs' study[b]	61 SZ 26 PCR 50 PNCR 44 C	19.3(9.2) 19.0(7.5) 14.6(5.5) 3.8(2.7)	n.s. (SZ, PCR) $p=0.001$ (SZ > PNCR)	$p<0.001$ (PCR > C) $p<0.001$ (PNCR > C)	[a]
Ismail et al. (1998, 2000)	44 items (19 for NSS)	60 SZ 21 Si 75 C	3.25(3.31) 1.33(2.01) 0.2(0.54)	$p<0.005$	$p<0.001$	[a]
Chen et al. (2000)	CNI	15 SZ 21 Si 26 C	4.87(3.72) 2.62(1.99) 0.53(0.90)	$p<0.004$	$p<0.001$	[a]
Niethammer et al. (2000)	Heidelberg scale[c]	13 MZ_A 13 MZ_NA 17 CT	No detailed data	MZ_A > MZ_NA	MZ_NA > CT	
Yazici et al. (2002)	NES	99 SZ 80 Si 59 C	20.47(10.07) 10.67(7.23) 6.66(5.37)	$p<0.001$	$p<0.05$	[a]
Gabalda et al. (2008)	5 frontal release items from NES	63 SZ 33 R 51 C	–	n.s.	$p<0.05$	
Niemi et al. (2005)	–	92 SZ 159 SZO 99 C	– 9%(8/88) 11%(17/154) 3%(3/97)	–	$p<0.005$	
Schubert and McNeil (2004), Schubert et al. (2005), Schubert and McNeil (2005) and Schubert and McNeil (2007)	44 items (19 for NSS)[d]	28 SZO 88 CO	2.04(2.76) 0.9(1.48)	No SZ	$p=0.006$	[a]
Picchioni et al. (2006)	NES	21 MZ_DC 55 MC 12 DZ_DC 18 DC	$t=3.97$(MZ_DC_A, MZ_DC_NA) $t=3.02$(MZ_DC_NA, MCT) $t=2.24$(DZ_DC_A, DZ_DC_NA) $t=1.89$(DZ_DC_NA, DCT)	$p<0.001$ (MZ_DC_A > MZ_DC_NA) $p=0.027$ (DZ_DC_A > DZ_DC_NA)	$p=0.003$ (MZ_DC_NA > MCT) n.s. (DZ_DC_NA, DCT)	[a]
Mechri et al. (2009)	23 items from Krebs' study[b]	135 SZ 74 Si 168 C	17.2 (6.72) 9.17 (3.76) 5.23 (2.93)	$p<0.001$	$p<0.001$	[a]
Bollini et al. (2007)	NES	26 R 38 C	18.17(10.26) 15.54(8.02)	No SZ	n.s. (R, C)	[a]
Compton et al. (2007)	NES	73 SZ 44 R 54 C	18.2(9.9) 13.9(8.3) 11.6(7.7)	$p=0.017$	n.s. (R, C)	[a]
Egan et al. (2001)	NES	115 SZ 185 Si 88 C	6.8(4.24) 3.05(2.82) 2.80(2.29)	$p<0.00001$	n.s. (Si, C)	[a]
Lawrie et al. (2001)	NES	30 SZ 152 FR 35 C	Medians (range) 2(2–4) 2(1–3) 2(0–3)	$p=0.003$	n.s. (FR, C)	
Flyckt et al. (1999)	Many items included hard signs	37 SZ 33 P 55 C	Signs ≥1 78%(29/37) 7%(4/55) 27%(9/33)	–	–	

Table 1 (*Continued*)

Study	NSS scale	Subjects	Reported data means (SDs)/prevalence	NSS-total		In or out
				SZ vs. R	R vs. C	
Compton et al. (2006)	NES	41 SZ, 31 R, 38 C	Factor analyses	–	–	
Sanders et al. (2006)	NES	96 subjects[e]	Calculated heritability	–	–	
Griffiths et al. (1998)	44 items divided into primary and integrative function	32 FSZ, 28 SSZ 63 FR, 44 SR 47 C	Prim FSZ 38%, SSZ 57% FR 30%, SR, 23% C 7% Inte FSZ 38%, SSZ 29% FR 38%, SR 36% C1%	–	–	
Cantor-Graae et al. (2000)	44 items[d]	60 SSZ, 21 Si, 75 C	Examine the role of perinatal trauma in the aetiology of neurological abnormality	–	–	

SZ: schizophrenic patients; R: relatives of schizophrenic patients; C: healthy controls; Si: siblings of SZ; P: parents of SZ; PCR: presumed carriers; PNCR: presumed non-carriers; SZO: offspring of SZ; CO: offspring of healthy controls; FSZ: familial schizophrenia; FR: familial schizophrenia relatives; SSZ: sporadic schizophrenia; SR: sporadic schizophrenia relatives; MZ: monozygotic SZ; DZ: dizygotic SZ; MCT: monozygotic control twins; DCT: dizygotic control twins; _C: concordant; _DC: discordant; _A: affected; _NA: nonaffected.

[a] Included in meta-analysis.
[b] Krebs et al. (2000).
[c] Schröder et al. (1992).
[d] Ismail et al. (1998).
[e] Eight extended families of each consisted of two first-degree relatives.

relatives of schizophrenic patients and healthy controls or the differences between schizophrenic patients and their relatives; (d) sample size, means, and standard deviations (SDs) and/or *t*-values were reported; and (e) the study did not share samples with other studies. In this way, we obtained 12 potentially relevant studies for meta-analysis (Fig. 1).

2.2. Data extraction

For each study, we recorded the following variables: (1) name of the first author, year of publication, and the order for sorting; (2) diagnosis of schizophrenia in patients (according to DSM-III, III-R, or IV; ICD-9 or -10); (3) type of relative (i.e., sibling, parent, twin, mixed); (4) basic descriptions of schizophrenic patients, their relatives, and healthy controls, which included sample size, gender, age, education, age of onset, duration of illness, chronic or first-episode, and so forth; and (5) NSS scale (i.e., NES, CNI, Condensed Neurological Examination, and so forth) and NSS score of patients, their relatives, and controls (mean, SD, and *t*-value).

2.3. Statistical meta-analysis

Based on the statistics recorded, we carried quantification of study results using the Comprehensive Meta-Analysis software package (Borenstein et al., 2005). Effect sizes were calculated as Cohen's *d*, which is the difference in group means divided by the pooled standard deviation (e.g. Aleman et al., 1999; Shadish and Haddock, 1994). For each study, we calculated the effect sizes for the differences in NSS between schizophrenics and their relatives and the differences between the relatives of schizophrenics and healthy controls. When means and SDs were not given, *d*-values were computed from independent groups *t*-values. A weighted grand mean was calculated for each set of effect sizes, with weighting based on study variance (Lipsey and Wilson, 2001). There are two models used in meta-analysis, the fixed and random effects models, and we considered both. Nevertheless, the random effects model was more easily justified than the fixed effects model as we accumulated data from a series of studies and NSS were assessed with different scales. To test whether the studies could be assumed to reflect a single population of effect sizes, we also calculated a homogeneity statistic, the *Q*-value. *Q* is meant to test the null hypothesis that there is no dispersion across effect sizes, and a significant *Q*-statistic indicates heterogeneity of the individual study effect sizes. Hence, a significant *Q*-value indicates greater than chance variation in effect sizes and implies that differences in study design and method moderate this variation. This possibility is typically assessed by statistically comparing or correlating study attributes and their effect sizes across studies (i.e. "moderator analysis").

In view of the "file-drawer problem" (Rosenthal, 1979), whereby it is hypothesized that statistically significant studies tend to be published and non-significant studies sequestered in "file drawers," the possibility of a publication bias that threatens the validity of obtained meta-analytic results must be considered. CMA software provides two methods to assess the "file-drawer problem": Begg and Mazumdar's rank correlation test and Egger's regression intercept test. However, a funnel plot, which visually indicates the presence of bias through asymmetric distribution of effect sizes, is also commonly used. It may reveal a "small-study effect" (the tendency for the smaller studies in a meta-analysis to show larger effects) as well as publication bias (Borenstein, 2005). Another index that reflects publication bias is Orwin's fail-safe N statistic. A fail-safe statistic estimates the number of insignificant, unpublished studies that would need to be added to a meta-analysis to reduce a mean observed effect to some specified and negligible level (Orwin, 1983; Rosenberg, 2005). We set the negligible mean effect at 0.2, which represents a "small" and usually non-significant effect size (Cohen, 1988). Alternatives including 0 were considered, but mean values smaller than 0.2 were inappropriate in this research context because they would, implausibly, require large numbers of studies reporting higher rates of NSS in healthy controls then in patients (i.e. negative effect sizes). Finally, we assumed an effect size value of 0.1 for hypothetically "missing" or unpublished studies.

3. Results

Twelve studies compared the NSS-total scores of relatives of schizophrenic patients with those of healthy controls. One study (Ismail et al., 2000) was subsequently excluded because it reported the same data as Ismail et al. (1998), which was already included. Because the number of studies presenting NSS scores of

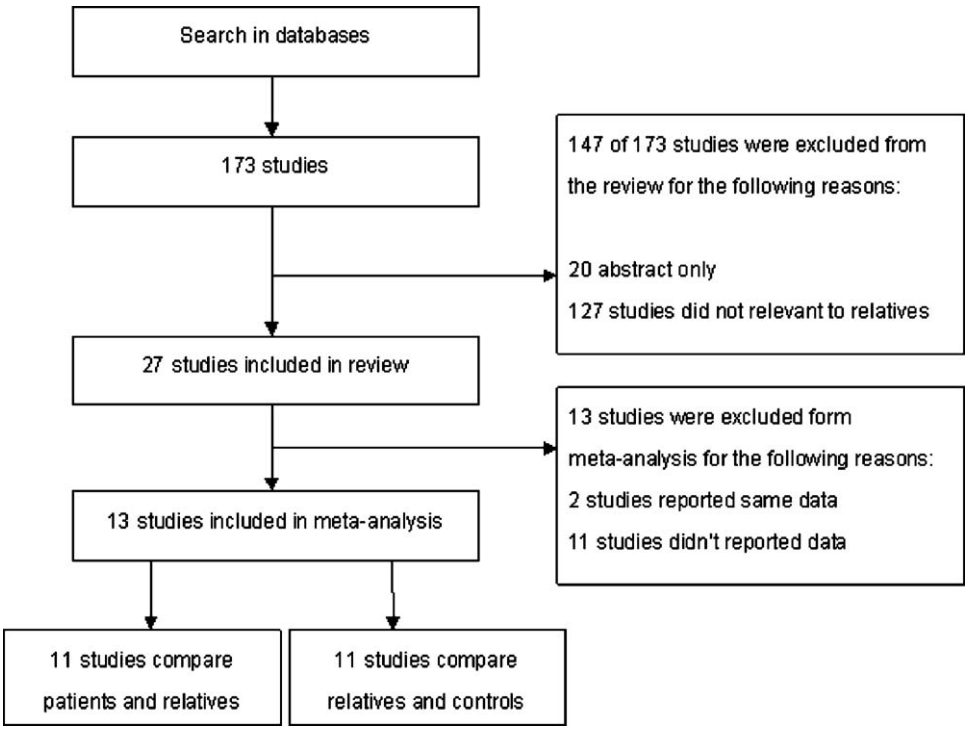

Fig. 1. Flow chart of systematic review.

relatives of schizophrenia patients was small, we collapsed data across relative classes (i.e. sibling, parent, offspring) and scale used (i.e. NES or CNI). Hence, 11 studies were included in the meta-analysis, Fig. 2 plots individual studies (effect size and confidence interval) that were included in this analysis. The combined effect size was 0.97 with a 95% CI (0.55, 1.39). The Q test showed that the studies were not homogeneous, with $Q = 119.04$, $p < 0.001$ (Table 2). The fail-safe number of studies was 65. The funnel plot (Fig. 4) raised the possibility of publication bias.

Twelve studies compared the NSS-total scores of schizophrenia patients with those of their relatives (one study (Ismail et al., 2000) was excluded, as explained above). Hence, 11 studies were included in the meta-analysis. Among them, nine studies found significant differences between schizophrenia patients and their relatives. Fig. 3 plots the individual studies (effect size and confidence interval) that were included in our analysis. As seen in Table 3, the average standardized difference means (*d*-value) was 0.81, with a 95% confidence interval of 0.59–1.04. However, the

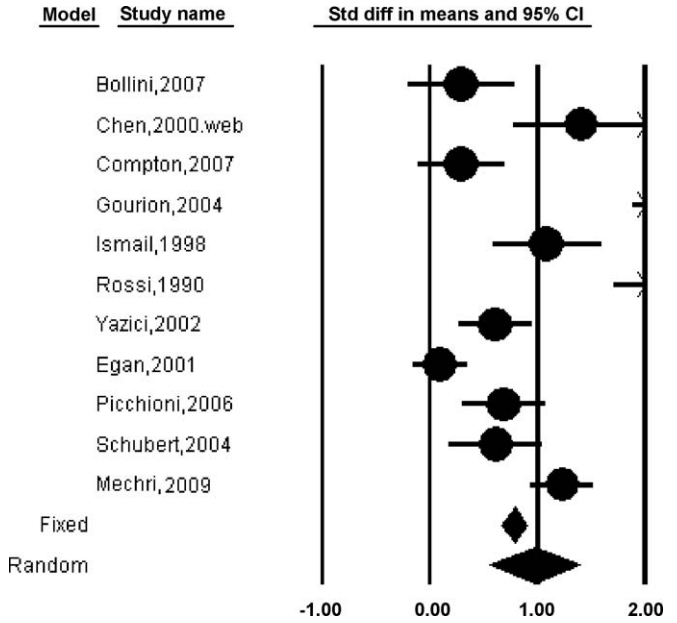

Fig. 2. Mean effect size (*d*-value) and confidence interval for each study in contrasting the differences in NSS-total scores between relatives of schizophrenia patients and healthy controls.

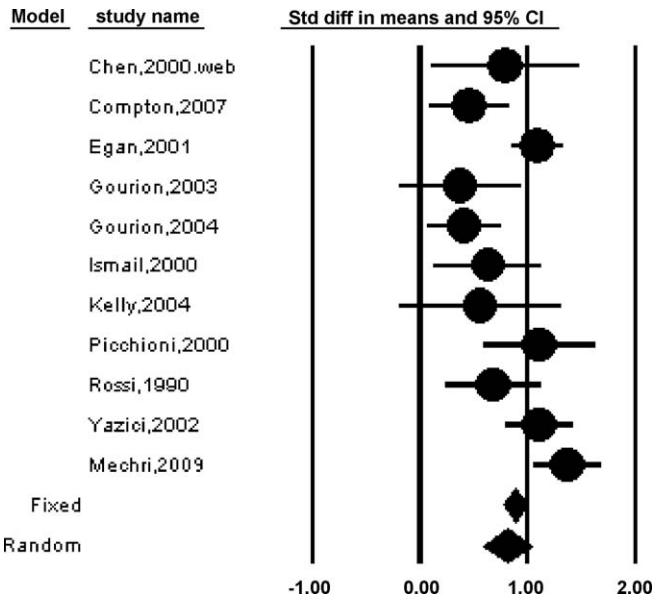

Fig. 3. Mean effect size (*d*-value) and confidence interval for each study in contrasting the differences in NSS-total scores between schizophrenic patients and their relatives.

Table 2
Results of meta-analyses of differences in neurological soft signs total scores and subscale scores between relatives of schizophrenia patients and healthy controls.

Relatives vs. controls	N[a]	No. of R	No. of C	Std diff	SE	95% CI	Q-Value	Fail-safe N
NSS-total	11	619	824	0.974	0.215	(0.553, 1.394)	119.044**	65
NSS-MC	7	288	508	0.364	0.150	(0.070, 0.657)	21.051*	15
NSS-SI	7	288	508	0.369	0.082	(0.207, 0.530)	6.742	13
NSS-Meq	3	150	151	0.143	0.182	(−0.214, 0.499)	4.586	–

MC: motor coordination; SI: sensory integration; MSeq: complex motor sequencing.
[a] Number of studies; R: relatives of schizophrenia patients; C: healthy controls.
* Q-value heterogeneous, $p < 0.05$.
** Q-value heterogeneous, $p < 0.01$.

Table 3
Results of meta-analyses of differences in neurological soft signs total scores and subscale scores between schizophrenia patients and relatives of schizophrenia.

Schizophrenia vs. relatives	N[a]	No. of SZ	No. of R	Std diff	SE	95% CI	Q-Value	Fail-safe N
NSS-total	11	551	538	0.813	0.115	(0.587, 1.039)	32.353**	76
NSS-MC	5	382	234	0.917	0.087	(0.745, 1.088)	2.443	36
NSS-SI	5	382	234	0.492	0.155	(0.189, 0.796)	11.724*	17
NSS-MSeq	2	172	124	0.607	0.211	(0.193, 1.022)	2.922	–

[a] Number of studies; SZ: schizophrenia patients; R: relatives of schizophrenia patients.
* Q-value heterogeneous, $p < 0.05$.
** Q-value heterogeneous, $p < 0.01$.

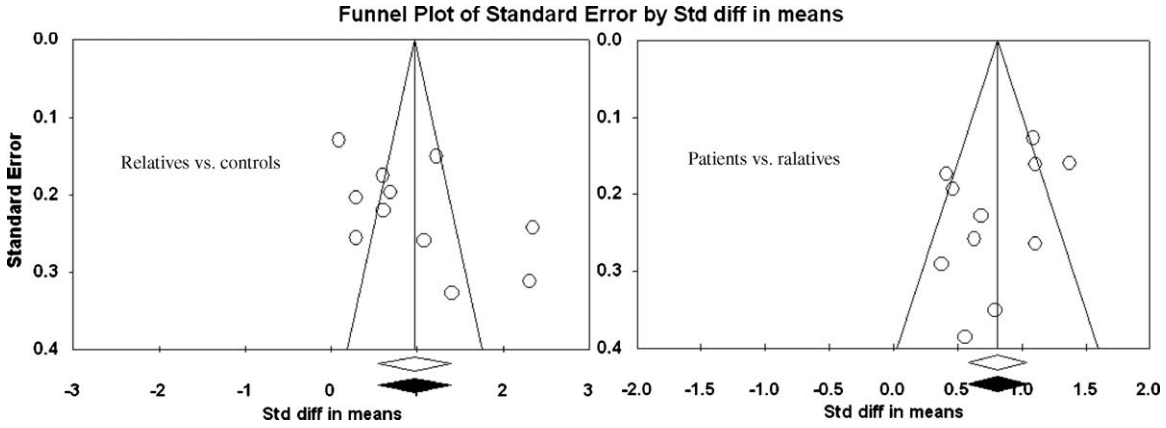

Fig. 4. funnel plot of standard error by standard different in means.

Q-statistic indicated significant heterogeneity, with $Q = 32.35$, $p < 0.05$. The fail-safe number of studies was 76, which was large enough to support the validity of our results.

Our analyses also included subscale measures of motor coordination, sensory integration, and sequencing of complex motor acts. Seven studies (Ismail et al., 1998; Yazici et al., 2002; Chen and Chen, 2000; Schubert and McNeil, 2004; Bollini et al., 2007; Compton et al., 2007; Mechri et al., 2009) reporting subscale data were included. The standardized NSS differences between relatives of schizophrenia patients and schizophrenia patients were greater in MC and MSeq subscales than the differences between relatives and healthy controls. In particular, the difference in motor coordination between schizophrenia patients and relatives of schizophrenia patients was remarkable based on five studies (Ismail et al., 1998; Yazici et al., 2002; Chen and Chen, 2000; Compton et al., 2007; Mechri et al., 2009) with $d = 0.92$.

4. Discussion

In our study we used meta-analysis to quantify published research on NSS in relatives of schizophrenic patients compared to patients and healthy controls. The results indicate large mean group differences for summary NSS scores, with confidence intervals excluding 0. Overall NSS differences appear to be smaller in relative versus patient comparisons than in relative versus control comparisons. However, these mean differences are statistically equivalent in light of their confidence intervals, suggesting both a familial/genetic and a morbid contribution to elevations in NSS. At the same time, the effects of genetic relatedness and clinical illness within relatives are smaller than recent estimates ($d = 1.6$) of differences between patients and healthy controls (Chan et al., in press). Therefore, the data are consistent with our hypotheses that NSS fulfill endophenotype criterion 4 (i.e., familial association). Furthermore, the data provide partial support for endophenotype criterion 5, co-segregation insofar as patients and their well relatives differ substantially in NSS. However, caution is in order because our meta-analytic data are not based on within-family or individual patient-relative comparisons and hence do not demonstrate NSS equivalence between well and ill relatives. Taken together, the implied association of NSS with genetic susceptibility to schizophrenia is consistent with the idea that these abnormalities may be endophenotypes for schizophrenia.

The mean NSS effect for relatives versus controls is of interest because it is relatively large and exceeds the effect found in most cognitive comparisons. Snitz et al. (2006) performed a meta-analysis of 43 cognitive tests and found that differences between patients' relatives and healthy controls were in the small to medium effect size range (i.e., 0.2–0.6). The largest effect sizes (0.5) were seen in Trail Making Test Part B and Continuous Performance

Test performance, but no cognitive effects exceeded 0.7 pooled standard deviation units. Therefore, relative and control distributions overlap by more than 50% (Cohen, 1988). Previous studies have also indicated that cognitive deficiencies may be endophenotypes for schizophrenia (Sitskoorn et al., 2004). One study (Chan et al., submitted for publication) from our laboratory has found that neurocognitive functions and NSS covary thereby suggesting an overlap of compromised underlying neural systems. In addition, a recent review of endophenotypes in schizophrenia has summarized a cluster of disease-liability associated variants and provides further support for the endophenotypic validity of NSS (Allen et al., 2009). It is noteworthy, however, that a successful endophenotype candidate requires fulfillment of several criteria, notably heritability and state-independence.

Regarding the heritability criterion, few studies have provided empirical data. In our literature search results, three studies indicated a significant correlation for NSS scores between schizophrenia patients and their relatives, but only one study reported on the heritability of NSS in schizophrenia (Sanders et al., 2006). Sanders et al. (2006) examined 96 participants from eight extended families and found that five of eleven items were statistically significant in terms of hereditability h^2: rapid alternating movements ($h^2 = 0.99 \pm 0.19$ for completion time), alternating fist-palm ($h^2 = 0.77 \pm 0.19$ for completion time and $h^2 = 0.7 \pm 0.32$ for number of errors), fist-ring ($h^2 = 0.53 \pm 0.23$ for right-sided completion time; $h^2 = 0.7 \pm 0.21$ for left-sided completion time), go-no go ($h^2 = 0.93 \pm 0.33$ for the number of correct responses), and audio-visual integration ($h^2 = 0.79 \pm 0.54$ for the number of correct responses). All of these items except audio-visual integration are motor functions and the results provide support for the heritability of NSS.

With regard to the state-independent criterion, the existing literature suggests that NSS have been demonstrated in schizophrenia at different stages of the illness (e.g., Madsen et al., 1999; Chen et al., 2005; Bachmann et al., 2005). According to the previous review (Chan and Gottesman, 2008), NSS occur more frequently in schizophrenia patients than healthy controls at all stages of the illness. However, most of the existing evidence is limited to cross-sectional studies. Thus, we reviewed prospective longitudinal studies and found non-significant differences between the initial and the follow-up levels of total NSS (Chen et al., 2005; Boks et al., 2006). The same results were found subscales measuring sensory integration (Whitty et al., 2003; Prikryl et al., 2007). On the other hand, several studies have found that NSS varies with clinical course (Bachmann et al., 2005; Madsen et al., 1999; Whitty et al., 2006). Moreover, inconsistent results were found for NSS subscales in patients with schizophrenia. One study reported no change over illness course in Motor Coordination and Complex Motor Sequencing subscales (Mayoral et al., 2008), but another found decreases (Whitty et al., 2003). Thus, further longitudinal research is needed to validate whether NSS are truly state-independent across different stages of schizophrenic illness.

In the present meta-analysis, results also show that the differences in means on NSS subscales were lower than the differences on the total or summary scale. This may be due to several reasons. First, the small number of studies reporting subscale data decreased statistical power and increased the influence of individual studies with extreme effects. In addition, the NSS-total scale contains items, including frontal release signs, that may have greater prevalence in relatives, but not all subscales include these items. Gabalda et al. (2008) report that frontal release signs are significantly higher in relatives than in controls. Therefore, more evidence about the magnitude of subscale differences between relatives of schizophrenic patients and healthy controls is required.

There are several limitations in the current study. First, the number of available studies included in the meta-analysis and the number of subjects in these studies was relatively small. Second, the NSS scales used in these studies were not uniform. In particular, different scales include somewhat different items. Moreover, the total scores of scales are sums of small numbers of items with binary ratings (e.g. 0 = normal response; 1 = abnormal response). Hence it is possible that bias in effect size estimates results from treating these data as interval data.

The results of our meta-analysis were heterogeneous, but the small number of studies and limited reporting of study attributes prevented an analysis of variables that may moderate NSS effect sizes. In reference to the results of another meta-analysis (Chan et al., in press), it was found that age may be a moderator for NSS effect sizes in relation patients and healthy controls. In terms of quantifying findings on relatives of patients, the type of relative may also be a significant moderator. In addition, evidence indicates that NSS and negative symptoms are correlated in schizophrenia (Gourion et al., 2003; Scheffer, 2004; Yazici et al., 2002). A meta-analysis from our lab combined the correlation coefficients from 15 studies and showed a significant correlation of $r = 0.35$ between negative symptoms and NSS (Chan et al., in press). Hence recent findings suggest considerable heterogeneity of effects and underscores the need for detailed moderator and consistency analysis as the NSS literature expands. Overall, however, and despite these limitations, our results support the continued examination and study of NSS as a promising endophenotype candidate for schizophrenia research.

Acknowledgements

This study was supported partially by the Project-Oriented Hundred Talents Programme (O7CX031003), the Knowledge Innovation Project of the Chinese Academy of Sciences (KSCX2-YW-R-131), and grants from the National Natural Science Foundation of China (30770723) and National Basic Research Program of China (973 Program) (2007CB512302) to Raymond Chan, and National Basic Research Program of China (973 Program) (2007CB512305) to Qiyong Gong. These funding agents had no role in the study design; collection, analysis, and interpretation of the data; writing of the manuscript; or decision to submit the paper for publication.

References

Aleman, A., Hijman, R., Haan, E.H.d., Kahn, R.S., 1999. Memory impairment in schizophrenia: a meta-analysis. American Journal of Psychiatry 156, 1358–1366.
Allen, A.J., Griss, M.E., Folley, B.S., Hawkins, K.A., Pearlson, G.D., 2009. Endophenotypes in schizophrenia: a selective review. Schizophrenia Research 109, 24–37.
Bachmann, S., Bottmer, C., Schröder, J., 2005. Neurological soft signs in first-episode schizophrenia: a follow-up study. The American Journal of Psychiatry 162, 2337–2343.
Barrantes-Vidal, N., Fananas, L., Rosa, A., Caparros, B., Riba, M.D., Obiols, J.E., 2002. Neurocognitive, behavioural and neurodevelopmental correlates of schizotypy clusters in adolescents from the general population. Schizophrenia Research 61, 293–302.
Boks, M.P.M., Selten, J.P., Leask, S., Van den Bosch, R.J., 2006. The 2-year stability of neurological soft signs after a first episode of non-affective psychosis. European Psychiatry 21, 288–290.
Bollini, A.M., Compton, M.T., Esterberg, M.L., Rutland, J., Chien, V.H., Walker, E.F., 2007. Associations between schizotypal features and indicators of neurological and morphological abnormalities. Schizophrenia Research 92, 32–40.
Bombin, I., Arango, C., Buchanan, R.W., 2005. Significance and meaning of neurological signs in schizophrenia: two decades later. Schizophrenia Bulletin 31, 962–977.
Borenstein, M., Hedges, L., Higgins, J., Rothstein, H., 2005. Comprehensive Meta-analysis. Biostat, Inc., Englewood NJ (Ref. Type: Computer Program).
Borenstein, M., 2005. Software for publication bias. In: Rothstein, H.R., Sutton, A.J., Borenstein, M. (Eds.), Publication Bias in Meta-analysis: Prevention, Assessment and Adjustments.
Cantor-Graae, E., Ismail, B., McNeil, T.F., 2000. Are neurological abnormalities in schizophrenic patients and their siblings the result of perinatal trauma? Acta Psychiatrica Scandinavica 101, 142–147.

Chan, R.C.K., Wang, Y., Wang, L., Chen, E.Y.H., Manschreck, T.C., Li, Z., Xu, X., Gong, Q., submitted for publication. Neurological soft signs and their relationships to neurocognitive functions: a re-visit with the structural equation modeling design. PLoS ONE.
Chan, R.C.K., Chen, E.Y.H., 2007. Neurological abnormalities in Chinese schizophrenic patients. Behavioural Neurology 18, 171–181.
Chan, R.C.K., Gottesman, I.I., 2008. Neurological soft signs as candidate endophenotypes for schizophrenia: a shooting star or a Northern star? Neuroscience and Biobehavioral Reviews 32, 957–971.
Chan, R.C.K., Xu, T., Heinrichs, R.W., Yu, Y., Wang, Y., in press. Neurological soft signs in schizophrenia: a meta-analysis. Schizophrenia Bulletin (e-published April 17, 2009) doi:10.1093/schbul/sbp011.
Chen, E.Y.H., Hui, C.L.M., Chan, R.C.K., Dunn, E.L.W., Miao, M.Y.K., Yeung, W.S., Wong, C.K., Chan, W.F., Tang, W.N., 2005. A 3-year prospective study of neurological soft signs in first-episode schizophrenia. Schizophrenia Research 75, 45–54.
Chen, R., Chen, E., 2000. Soft neurological signs in schizophrenic patients and their nonpsychotic siblings. The Chicago Journal of Nervous & Mental Disease 188, 84–89.
Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, 2nd ed. Lawrence Earlbaum Associates, Hillsdale, NJ.
Compton, M.T., Bercu, Z., Bollini, A., Walker, E.F., 2006. Factor structure of the Neurological Evaluation Scale in a predominantly African American sample of patients with schizophrenia, unaffected relatives, and non-psychiatric controls. Schizophrenia Research 84, 365–377.
Compton, M.T., Bollini, A.M., Mack, L.M., Kryda, A.D., Rutland, J., Weiss, P.S., Bercu, Z., Esterberg, M.L., Walker, E.F., 2007. Neurological soft signs and minor physical anomalies in patients with schizophrenia and related disorders, their first degree biological relatives, and non-psychiatric controls. Schizophrenia Research.
Egan, M.F., Hyde, T.M., Bonomo, J.B., Mattay, V.S., Bigelow, L.B., Goldberg, T.E., Weinberger, D.R., 2001. Relative risk of neurological signs in siblings of patients with schizophrenia. American Journal of Psychiatry 158, 1827–1834.
Flyckt, L., Sydowb, O., Bjerkenstedta, L., Edmana, G., Rydinb, E., Wieselc, F.-A., 1999. Neurological signs and psychomotor performance in patients with schizophrenia, their relatives and healthy controls. Psychiatry Research 86, 113–129.
Gabalda, M.K., Weiss, P.S., Compton, M.T., 2008. Frontal release signs among patients with schizophrenia, their first-degree biological relatives, and non-psychiatric controls. Schizophrenia Research 106, 275–280.
Gottesman, I.I., Gould, T.D., 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. American Journal of Psychiatry 160, 636–645.
Gottesman, I.I., Shields, J., 1973. Genetic theorizing and schizohrenia. British Journal of Psychiatry 122, 15–30.
Gourion, D., Goldberger, C., Olie, J., Lôo, H., Krebs, M., 2004. Neurological and morphological anomalies and the genetic liability to schizophrenia: a composite phenotype. Schizophrenia Research 67, 23–31.
Gourion, D., Goldberger, C.I., Bourdel, M.C., Bayle, F.J., Millet, B., Olie, J.P., Krebs, M.O., 2003. Neurological soft-signs and minor physical anomalies in schizophrenia: differential transmission within families. Schizophrenia Research 63, 181–187.
Griffiths, T.D., Sigmundsson, T., Takei, N., Rowe, D., Murray, R.M., 1998. Neurological abnormalities in familial and sporadic scizophrenia. Brain 121, 191–203.
Heinrichs, D.W., Buchanan, R.W., 1988. The Significance and meaning of neurological signs in schizophrenia. American Journal of Psychiatry 145, 11–18.
Ismail, B., Cantor-Graae, E., McNeil, T.F., 1998. Neurological abnormalities in schizophrenia, clinical, etiological and demographic correlates. Schizophrenia Research 30, 229–238.
Ismail, B., Cantor-Graae, E., McNeil, T.F., 2000. Minor physical anomalies in schizophrenia, cognitive, neurological and other clinical correlates. Journal of Psychiatric Research 34, 45–56.
Kelly, B.D, Cotter, D., Denihan, C., Larkin, D., Murphy, P., Kinsella, A., Walsh, D., Waddington, J., Larkin, C., O'Callaghan, E., Lane, A., 2004. Neurological soft signs and dermatoglyphic anomalies in twins with schizophrenia. European Psychiatry 19, 159–163.
Kinney, D.K., Woods, B.T., Yurgelun-Todd, D., 1986. Neurologic abnormalities in schizophrenic patients and their families. Archives of General Psychiatry 43, 665–668.
Krebs, M., Gut-Fayand, A., Bourdel, M., Dischamp, J., Olie, J., 2000. Validity and factorial structure of a standardized examination for neurological soft-signs in schizophrenia. Schizophrenia Research 45, 245–260.
Lawrie, S.M., Byrne, M., Miller, P., Hodges, Clafferty, R.A., Owens, D.G.C., Johnstone, E.C., 2001. Neurodevelopmental indices and the development of psychotic symptoms in subjects at high risk of schizohrenia. British Journal of Psychiatry 178, 524–530.
Lipsey, M.W., Wilson, D.B., 2001. The way in which intervention studies have "personality" and why it is important to meta-analysis. Evaluation & the Health Professions 24, 236–254.
Madsen, A.L., Vorstrup, S., Rubin, P., Larsen, J.K., Hemmingsen, R., 1999. Neurological abnormalities in schizophrenic patients: a prospective follow-up study 5 years after first admission. Acta Psychiatrica Scandinavica 100, 119–125.
Mayoral, M., Bombín, I., Zabala, A., Robles, O., Moreno, D., Parellada, M., Ruiz-Sancho, A., Arango, C., 2008. Neurological soft signs in adolescents with first episode psychosis: two-year follow up. Psychiatry Research 161, 344–348.
Mechri, A., Bourdel, M.-C., Slama, H., Gourion, D., Gaha, L., Krebs, M.-O., 2009. Neurological soft signs in patients with schizophrenia and their unaffected siblings: frequency and correlates in two ethnic and socioeconomic distinct populations. European Archives of Psychiatry and Clinical Neuroscience 259, 218–226.
Niemi, L., Suvisaari, J.M., Haukka, J.K., Lonnqvist, J.K., 2005. Childhood predictors of future psychiatric morbidity in offspring of mothers with psychotic disorder. British Journal of Psychiatry 186, 108–114.
Niethammer, R., Weisbrod, M., Schiesser, S., Grothe, J., Maier, S., Peter, U., Kaufmann, C., Schröder, J., Sauer, H., 2000. Genetic influence on laterality in schizophrenia? A twin study of neurological soft signs. American Journal of Psychiatry 157, 272–274.
Orwin, R.G., 1983. A fail-safe N for effect size in meta-analysis. Journal of Educational Statistics 8, 157–159.
Picchioni, M.M., Toulopoulou, T., Landau, S., Davies, N., Ribchester, T., Murray, R.M., 2006. Neurological abnormalities in schizophrenic twins. Biological Psychiatry 59, 341–348.
Prikryl, R., Ceskova, E., Kasparek, T., Kucerova, H., 2007. Neurological soft signs and their relationship to 1-year outcome in first-episode schizophrenia. European Psychiatry 22, 499–504.
Rosenberg, M.S., 2005. The file-drawer problem revisited: a general weighted method for calculating fail-safe numbers in meta-analysis. Evolution 59, 464–468.
Rosenthal, R., 1979. The "file drawer problem" and tolerance for null results. Psychological Bulletin 86, 638–641.
Rossi, A., Cataldo, S.D., Michele, V.D., Manna, V., Ceccoli, S., Stratta, P., Casacchia, M., 1990. Neurological soft signs in schizophrenia. British Journal of Psychiatry 157, 735–739.
Sanders, R.D., Joo, Y.H., Almasy, L., Wood, J., Keshavan, M.S., Pogue-Geile, M.F., Gur, R.C., Gur, R.E., Nimgaonkar, V.L., 2006. Are neurologic examination abnormalities heritable? A preliminary study. Schizophrenia Research 86, 172–180.
Scheffer, R.E., 2004. Abnormal neurological signs at the onset of psychosis. Schizophrenia Research 70, 19–26.
Schröder, J., Niethammer, R., Geider, F.J., Reitz, C., Binkert, M., Jauss, M., Sauer, H., 1992. Neurological soft signs in schizophrenia. Schizophrenia Research 6, 25–30.
Schubert, E.W., Henriksson, K.M., McNeil, T.F., 2005. A prospective study of offspring of women with sychosis: visual dysfunction in early childhood predicts schizophrenia-spectrum disorders in adulthood. Acta Psychiatrica Scandinavica 112, 385–393.
Schubert, E.W., McNeil, T.F., 2004. Prospective study of neurological abnormalities in offspring of women with psychosis: birth to adulthood. American Journal of Psychiatry 161, 1030–1037.
Schubert, E.W., McNeil, T.F., 2005. Neuropsychological impairment and its neurological correlates in adult offspring with heightened risk for schizophrenia and affective psychosis. American Journal of Psychiatry 162, 758–766.
Schubert, E.W., McNeil, T.F., 2007. Neurobehavioral deficits in young adult offspring with heightened risk for psychosis who developed. Schizophrenia Research.
Shadish, W.R., Haddock, C.K., 1994. Combining estimates of effect size. In: Cooper, H., Hedges, L. (Eds.), The Handbook of Research Synthesis.
Sitskoorn, M.M., Aleman, A., Ebisch, S.J.H., Appels, M.C.M., Kahn, R.S., 2004. Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. Schizophrenia Research 71, 285–295.
Snitz, B., MacDonald-III, A., Carter, C., 2006. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. Schizophrenia Bulletin 32, 179–194.
Tsuang, M.T., Faraone, S.V., 1999. The concept of target features in schizophrenia research. Acta Psychiatrica Scandinavica, Supplement 395, 2–11.
Tsuang, M.T., Faraone, S.V., Lyons, M.J., 1993. Identification of the phenotype in psychiatric genetics. European Archives of Psychiatry and Clinical Neuroscience 243, 131–142.
Tsuang, M.T., Gilberson, M.W., Faraone, S.V., 1991. The genetics of schizophrenia: current knowledge and future directions. Schizophrenia Research 4, 157–171.
Whitty, P., Clarke, M., Bpowne, S., McTigue, O., Kamali, M., Feeney, L., Lane, A., Kinsella, A., Waddinton, J.L., Larkin, C., O'Callaghan, E., 2003. Prospective evaluation of neurological soft signs in first-episode schizophrenia in relation to psychopathology: state versus trait phenomena. Psychological Medicine 33, 1479–1484.
Whitty, P., Clarke, M., McTigue, O., Browne, S., Gervin, M., Kamali, M., Lane, A., Kinsella, A., Waddington, J., Larkin, C., O'Callaghan, E., 2006. Diagnostic specificity and predictors of neurological soft signs in schizophrenia, bipolar disorder and other psychoses over the first 4 years of illness. Schizophrenia Research 86, 110–117.
Yazici, A.H., Demir, B., Yazici, K.M., Gogus, A., 2002. Neurological soft signs in schizophrenic patients and their nonpsychotic siblings. Schizophrenia Research 58, 241–246.