Neuroscience and Biobehavioral Reviews 32 (2008) 957–971

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review

Neurological soft signs as candidate endophenotypes for schizophrenia: A shooting star or a Northern star?

Raymond C.K. Chan [a,b,c,*], Irving I. Gottesman [d]

[a] Neuropsychology and Applied Cognitive Neuroscience Laboratory, Institute of Psychology, Chinese Academy of Sciences, Beijing, China
[b] Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, China
[c] Department of Psychiatry, The University of Hong Kong, Hong Kong Special Administrative Region, China
[d] Departments of Psychiatry and Psychology, University of Minnesota, Minneapolis, MN, United States

ARTICLE INFO

Article history:
Received 17 November 2007
Received in revised form 23 January 2008
Accepted 24 January 2008

Keywords:
Neurological soft signs
Endophenotype
Schizophrenia

ABSTRACT

The crucial role of neurological indicators in schizophrenia has been recognized as among the "target features" that encompass the idea that genetic and non-genetic processes lead to neurointegrative defects later manifested in neurocognitive systems. In addition, aberrant neurological indicators have also been suggested as potential endophenotypes in schizophrenia. In the current paper, we review evidence for the utility of quantifiable neurological soft signs as potential endophenotypes for schizophrenia spectrum disorders. We start by defining endophenotypes and justifying their utility. We highlight the key criteria that must be met for an endophenotype to be useful and assess the extent to which the manifestations of neurological soft signs meet these criteria. Finally, we recommend areas in which additional research should be done to further elucidate the potential use of neurological soft signs for schizophrenia research.

Contents

* Corresponding author. 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, rckchan@hkucc.hku.hk (Raymond C.K. Chan).

0149-7634/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neubiorev.2008.01.005

1. Introduction

Incontrovertible evidence for epidemiological genetic influences on schizophrenia has been accumulated since the 1960's (Rosenthal and Kety, 1968; McGuffin et al., 2004). However, the identification of specific genes with large effect sizes that contribute to a susceptibility to schizophrenia has not been successful using conventional molecular genetic approaches. As schizophrenia has failed to show monogenic forms and has no specific molecular or cellular markers, research at this time implicates several chromosomal regions (e.g., 1q, 8p, 22q, 2, 3, 5q, 6p, 11q, 13q, and 20p; Owen et al., 2003) that, in turn, embed several genes that have been associated with the illness, including DISC 1 (Chubb et al., 2007; Hennah et al., 2007), catechol-*O*-methyl transferase (Egan et al., 2001a; Shifman et al., 2002), dysbindin (Schwab et al., 2003; Turunen et al., 2007), G72 (Chumakov et al., 2002), neuregulin 1 (Stefansson et al., 2002), and RGS4 (regulator of G protein-signaling-4) (Chowdari et al., 2002; Talkowski et al., 2006). Psychiatric diagnoses are likely to have heterogeneous etiologies in that not all people with the same diagnosis carry the same assembly of susceptibility genes (Faraone et al., 1999; Sing et al., 2003; Pan et al., 2006).

On the other hand, the completion of human genome sequencing is the driving force to understand the genetic contribution to schizophrenia spectrum disorders by identifying variants associated with the disorders (Mitchell, 2002). For example, SchizophreniaGene (www.szgene.org) has been developed by Lars Bertram and colleagues at Harvard Medical School and Massachusetts General Hospital to systematically collect and synthesize the genetics data published in peer-reviewed journals. Unfortunately, despite the complete human genome data, we are still unable to specify precisely the phenotypes (the readily observed symptomatic manifestations of the genotypes such as hallucination and delusions in schizophrenia) in those individuals whose genomes we investigate. Therefore, researchers have been adopting a new direction that identifies neurobiological and neurobehavioural characteristics associated with schizophrenia, so-called "endophenotypes" (Gottesman and Gould, 2003; Gottesman and Shields, 1972) that may be more closely connected to the expressions of un-named genes (Bray et al., 2008).

A substantial number of studies, especially of at-risk offspring, have suggested that neurocognitive dysfunctions are among the most promising of the candidate endophenotypes. This view is most clearly understood within the neurodevelopmental framework (Erlenmeyer-Kimling et al., 2000; Cornblatt and Malhotra, 2001). Others (Chen and Faraone, 2000; Lenzenweger, 2006; Prescott and Gottesman, 1993) suggest that genetic vulnerability to schizophrenia may often manifest itself in schizophrenia-like personality disorders, e.g., schizotypal, rather than a full syndrome of schizophrenia. Thus, the proposed endophenotypic markers should also present in many persons with schizotypal personality disorder and their close relatives if it is in the schizophrenia spectrum.

Several candidate endophenotypic markers have been proposed such as sustained attention (Cannon et al., 2000, 2001; Chen and Faraone, 2000; Cornblatt and Malhotra, 2001; Egan et al., 2000), visual working memory (Cannon et al., 2000; Park et al., 1995), verbal memory (Goldberg et al., 1995; Chen et al., 2000a,b), and inhibitory control (Cadenhead et al., 2002). Comparison of the commonality and differences of endophenotypes has also been suggested among schizophrenia, depression, and ADHD (e.g., Flint and Munafo, 2007). Most recently, a multi-centre initiative, the Consortium on the Genetics of Schizophrenia (COGS), has been launched to examine the commonly identified cognitive and imaging endophenotypes of schizophrenia (Braff et al., 2007; Greenwood et al., 2007; Gur et al., 2007a,b). However, it is still yet not fully known whether various domains of cognitive functioning reflect the presence of one underlying global cognitive deficit, or whether they independently represent a discrete cognitive risk factor that is transmitted in families of patients with schizophrenia (cf. Glahn et al., 2007; Palo et al., 2007; Straub et al., 2007).

Here, we review evidence for the utility of quantifiable neurological soft signs as potential endophenotypes for schizophrenia spectrum disorders. We define endophenotypes and justify their utility by reviewing evidence from molecular genetic studies that schizophrenia is a complex phenotype. We summarize the literature concerning the clinical significance and meaning of neurological soft signs in schizophrenia. We then highlight the key criteria that must be met for an endophenotype to be useful and assess the extent to which the manifestations of neurological soft signs meet these criteria. Finally, we recommend areas in which additional research should be conducted to further elucidate the potential use of neurological soft signs and related minor physical anomalies for schizophrenia research.

2. What is an endophenotype?

The term "endophenotype" was first described for psychopathology as an internal phenotype, i.e., not obvious to the unaided eyes, that fills the gap between symptoms and the putative genes that actualize the elusive disease processes of schizophrenia and other psychiatric disorders (Gottesman and Shields, 1972, 1973). The endophenotypes may be any neurobiological measures or indicators (Meehl, 1990) related to the underlying molecular genetics of the illness, including biochemical, endocrinological, neurophysiological, neuroanatomical, or neuropsychological markers once they satisfy certain additional criteria (see below). This promising strategy for employing endophenotypes may help to resolve questions about etiological models. The power of these endophenotypes is based on the assumption that the number of genes involved in the variations of endophenotypes represent relatively more straightforward and putatively more elementary phenomena than those involved in producing a psychiatric diagnostic entity (Gottesman and Gould, 2003; cf. Flint and Munafo, 2007; Walters and Owen, 2007 with more skeptical attitudes toward the utility of the endophenotype strategy). This hypothesized reduction in complexity is due both to the endophenotype's relative proximity to gene products in the chain of events leading from genes to behaviour, and to its potential to target one of possibly several pathophysiological deficits that combine to create the overall condition (Bray et al., 2008).

3. Why is endophenotype useful for schizophrenia?

There are several potential advantages to the endophenotype approach (Braff et al., 2007; Greenwood et al., 2007) to study the etiology of schizophrenia: (1) physiological and more elementary neural-based endophenotypes may more directly reflect the activities of synaptic and other neuronal mechanisms than does the more complex illness itself, and therefore they are more likely to reflect genes with larger effect sizes; (2) both the patients and their unaffected relatives may show a fairly extensive range of scores on the endophenotypes, making such measures ideal for quantitative trait linkage analysis. Analysis of quantitative measurements related to the clinical phenotype will provide more statistical power to detect linkage, compared with the smaller number of clinically defined psychiatric relatives/patients; (3) to the extent that the biology of the endophenotype is understood or can be investigated via brain-imaging studies and infrahuman animal model research, candidate genes can be identified more

systematically in areas of linkage; (4) endophenotypes lend themselves directly to the use of animal models (Gould and Gottesman, 2006).

Although, this approach has not yet led to the identification of multiple interacting genetic abnormalities that are associated with the onset of schizophrenia, this endophenotype strategy has also been extremely important for gene discovery in other psychiatric disorders such as ADHD (e.g., Doyle et al., 2005; Crosbie et al., 2008; Waldman et al., 2006), unipolar depression (e.g., Hasler et al., 2004), bipolar disorder (e.g., Glahn et al., 2007; Hasler et al., 2006; Zalla et al., 2004), and other complex medical illnesses. Demonstrated applications advance the significance and urgency of adopting endophenotype as one important strategy in understanding the etiology and psychopathology of psychiatric diseases in general, and schizophrenia in particular (cf. Palo et al., 2007). A fundamental issue in the endophenotype approach is the identification and validation of potential endophenotypes. Identification usually comes from studies of schizophrenia-linked deficits. A second step is to identify evidence of specificity and heritability in "clinically unaffected" relatives. Genetic analysis depends on genotype-endophenotype correlations within individual pedigree members and is a more challenging test than a determination of schizophrenia versus normal subject differences (Heinrichs, 2001, 2005).

4. Neurological signs as the target features and indicators of schizophrenia

Neurological signs have previously been classified as "hard" vs. "soft" signs. The former refers to impairments of basic motor and sensory behaviour such as signs for the pyramidal system (Woods et al., 1991) and extrapyramidal system (Roger, 1992; Schroder et al., 1991; Simpson and Angus, 1970). The latter conventionally refers to non-localizing neurological abnormalities that cannot be related to impairment of a specific brain region or are not believed to be part of a well-defined neurological syndrome (Heinrichs and Buchanan, 1988; Chen et al., 1995). However, this distinction is artificial and may reflect an inability to define the brain-behaviour relationship that underlies the presence of neurological soft signs (Heinrichs and Buchanan, 1988; Bombin et al., 2005). Imaging studies have provided preliminary evidence to show parts of the brain structures that are responsible for the motor coordination, sensory integration and disinhibition (collectively known as soft signs) (e.g., Schroder et al., 1992a,b, 1999; Keshavan et al., 2003; Bachmann et al., 2005) and there is a connectivity network rather than a specific region for the motor coordination signs (Rao et al., submitted for publication; Chan et al., submitted for publication-a,b).

The crucial role of neurological abnormalities or signs in schizophrenia has been recognized by researchers in the past decades (e.g., Tsuang et al., 1991; Torrey et al., 1994; Tsuang and Faraone, 1999). Tsuang et al. (Tsuang et al., 1991; Tsuang and Faraone, 1999) considered neurological abnormalities as the "target features" that encompass the idea that genetic and non-genetic processes lead to maldevelopment in neurocognitive systems. Target features are defined as "clinical or neurobiological characteristics that are expressions of the underlying predisposition to the illness (schizophrenia)" (Tsuang and Faraone, 1999). The model considers illness as resulting from multiple genetic and environmental variables that may be additive or interactive. According to Tsuang and Faraone (1999), these variables act upon three stages of the illness, namely neurodevelopment, later adolescence (around onset), and after the onset of psychosis. This model further accommodates etiological heterogeneity by postulating that if a smaller proportion of variables out of a large pool are sufficient for expression of the illness, then a wider range of different permutations of underlying variables could be associated with illness manifestations. Moreover, these target features should also be increased in relatives of patients, albeit perhaps not to a similar extent. Torrey et al. (1994) also demonstrated that the affected twins in the discordant pairs had a significantly higher mean neurological abnormality score than their well co-twins. The well co-twins of the schizophrenic cases, in turn, demonstrated a significantly higher total score for neurological abnormalities than the normal control twins.

On the other hand, Meehl (1962, 1990) has coined the term "hypokrisia" as the hypothesized aberrant neural integrative defect that characterizes the neuronal functioning throughout the brain of the affected individual of schizotaxia. These individuals are highly likely to develop some types of disorganization termed schizotypal behaviours that in turn, develop into a full-blown psychosis, compared to those without these defects. In Meehl's viewpoint, hypokrisia is the root cause of some neurological defect indicators such as neurological soft signs or what he termed as soft psychometric signs that could be detected among this high-risk group. These indicators could not be observed with an unaided eye but could be elicited or tested under standard psychometric methods. However, we should notice that the conceptualization of schizotaxia or schizotypy proposed by Meehl (1990) does not equal a DSM-IV diagnosis of schizotypal personality disorder. It was clarified by Meehl (1990) in his seminal paper on an integrative theory of schizotaxia, schizotypy and schizophrenia, and was further re-asserted by Lenzenweger (1998) that although there is some overlapping between the schizotypic symptoms preferred by Meehl and that of the diagnostic criteria for DSM-IV schizotypal personality disorder, these two views are actually different from each other. In Meehl's viewpoint, schizotypy refers to a latent personality organization and is essentially a broader construct linked to a developmental theory, whereas the schizotypal personality disorder in DSM-IV is just an atheoretical categorization or aggregation of a set of observable signs and symptoms.

5. Categorization of neurological soft signs

A major issue concerning research on neurological soft signs in schizophrenia is the classification of soft signs and the instruments used for the evaluation. There are several rating scales developed for the measurement of neurological soft signs, including the Woods Scale (Smith et al., 1999a,b), Rossi Scale (Rossi et al., 1990), Heidelberg Scale (Schroder et al., 1992b), Cambridge Neurological Inventory (Chen et al., 1995), and the Neurological Evaluation Scale (Buchanan and Heinrichs, 1989). Although these scales claimed to evaluate the prevalence of neurological soft signs, most of them do not provide sufficient documentation of appropriate psychometric properties, and therefore, hamper the evaluation of the neurological soft signs as vulnerability or endophenotypic markers for schizophrenia. The Neurological Evaluation Scale and the Cambridge Neurological Inventory are the two most commonly used tools with impressive psychometric properties and documented considerable evidence indicating the corresponding clinical utility (cf. Candela and Manschreck, 2003; Bombin et al., 2003 for details of the comparison for these scales). Table 1 summarizes the items of the two most commonly used neurological signs scales, the Neurological Evaluation Scale and the Cambridge Neurological Inventory, and their strong and weak points in studying neurological soft signs in schizophrenia.

Factor-analytic studies of neurological soft signs suggest that these signs could be further subdivided into subgroups (Malla et al., 1997; Krebs et al., 2000; Sanders et al., 2000; Keshavan et al., 2003; Emsley et al., 2005; Goldstein et al., 2005; Compton et al.,

Table 1
Neurological soft signs assessed by Neurological Evaluation Scale and Cambridge Neurological Inventory grouped by their denomination and putative neuroanatomical localization

Scales	Cluster of signs	Individual items	Putative regions	Advantages	Disadvantages
Neurological Evaluation Scale	Motor coordination	•Intention tremor	Frontal lobe	•Putative neuroanatomical regions for different soft signs subcategories	•Information about test–retest reliability not available
		•Balance	Cerebellum	•Full instruction for training guidelines	•Data mainly limited to Caucasian samples
		•Gait		•Good external validity and inter-rater reliabilities	
		•Hopping		•Extensive data pool for schizophrenia cognition and outcome	
		•Finger–thumb opposition			
		•Disdiaochokinesia			
		•Finger-to-nose test			
	Sequencing of complex motor acts	•Fist-Edge-Palm test	Prefrontal lobe		
		•Fist-ring test			
		•Ozeretsky test			
		•Go/no-go test			
		•Rhythm tapping (foot or hand)			
	Integrative sensory function	•Bilateral extinction	Parietal lobe		
		•Audiovisual integration			
		•Graphesthesia			
		•Stereognosis			
		•Right-left confusion			
		•Extinction			
Cambridge Neurological Inventory	Motor coordination	•Finger tapping (left and right)	•Prefrontal lobe	•Putative neuroanatomical regions for different soft signs subcategories	•Information about test–retest reliability not available
		•Finger–thumb opposition (left and right)		•Full instruction for training guidelines	
		•Disdiaochokinesia (left and right)		•Good construct and external validity, and inter-rater reliabilities	
		•Fist-Edge-Palm test (left and right)		•Large data pool for schizophrenia cognition and outcome	
		• Ozeretsky test		•Information regarding cross-cultural and ethnic effect (Caucasian and Chinese patients and healthy controls)	
	Sensory integration	•Extinction test	Parietal lobe	•Data along the lifespan spectrum is available but limited	
		•Finger-agnosia (left and right)			
		•Stereognosis (left and right)			
		•Graphesthesia (left and right)			
		•Left-right orientation			
	Disinhibition	•Saccade blink	Frontal lobe		
		•Saccade head			
		•Wink			
		•Mirror movement of Fist-Edge-Palm (left and right)			
		•Mirror movement of disdiaochokinesia (left and right)			
		•Go/no-go test			

2006). For example, Schroder et al. (1992a,b) found that there were at least two subgroups of soft signs, namely the motor coordination and complex motor acts. Malla et al. (1997) demonstrated that motor coordination, motor integration, sensory integration, and sequencing planning were embedded in the Neurological Evaluation Scale (Heinrichs and Buchanan, 1989) among a group of 100 chronic schizophrenic patients. Krebs et al. (2000) further showed that there were five factors for neurological soft signs, namely motor coordination, motor integrative function, sensory integrative function, involuntary movement or posture, and quality of lateralization. In contrast, conceptual models based on groupings of subscales suggest that there are subgroups of motor coordination, sensory integration, sequencing of complex motor acts, and disinhibition (Heinrichs and Buchanan, 1989; Chen et al., 1995), whereas theoretically derived groupings based on neuroanatomical considerations suggest there are cerebellar, frontal, and parietal subscales (Egan et al., 2001b).

Chan et al. (submitted for publication-a,b) adopted a more rigorous structural equation modeling design to examine the latent structure of the neurological soft sign subscales of the Cambridge Neurological Inventory (CNI, Chen et al., 1995) among two independent samples of 118 chronic schizophrenic patients

and 160 healthy volunteers, and found that there were three factors underlying the neurological soft signs, namely motor coordination, sensory integration, and disinhibition in these two samples (schizophrenia: $\chi^2(29) = 39.48$, $p = 0.093$, NFI = 0.96, NNFI = 0.98, CFI = 0.99, IFI = 0.99, RMSE = 0.056; healthy volunteers: $\chi^2(29) = 47.79$, $p = 0.015$, NFI = 0.93, NNFI = 0.95, CFI = 0.97, IFI = 0.97, RMSE = 0.064). All of the loadings of the observed variables on corresponding latent variables were above 0.04 and statistically significant ($p < 0.01$). Thus, all of the latent variables appeared to have been adequately measured by their respective observed variables, and, correlations between the independent latent variable (neurological soft signs) and dependent latent variable (i.e., executive attention, logical memory, and visual memory) were all statistically significant ($p < 0.01$). In particular, greater number of neurological soft signs were associated with poorer executive attention ($r = -0.83$), logical memory ($r = -0.76$), and visual reproduction ($r = -0.75$).

Moreover, Chan et al. (2004b) found that the disinhibition signs were associated with behavioural disinhibition task and blink rate in a group of 90 patients with chronic schizophrenia. The modest correspondence of the factor analytic data and conceptual models might be due to a number of methodological limitations. First, different studies adopted different scales of neurological soft signs that might lead to different factor solutions. Second, for most individual items, the prevalence of positive score is usually relatively low and results in a skewed distribution of data that is less favourable for conventional factor analysis. Third, most of the aforementioned factor analytical studies were limited to exploratory factor analysis or principal components analysis based on a relatively small sample. These methods are data-driven and suffer from the correlational nature of the analysis, with the consequent possibility that the factors emerging may be specific to a particular sample rather than generalizable to a range of populations. The factor solutions of neurological soft signs might also vary substantially across patients with schizophrenia, their non-psychotic relatives, and healthy controls (Compton et al., 2006). Nevertheless, Compton et al. (2006) also concluded that there appeared to be at least two consistent latent variables of neurological soft signs demonstrated in different study samples, namely motor coordination and sensory integration.

A re-analysis of our laboratory data for the items shared by the Neurological Evaluation Scale and Cambridge Neurological Inventory showed very similar loadings and sensitivity of the soft signs in Neurological Evaluation Scale and Cambridge Neurological Inventory among a group of Chinese patients with schizophrenia and healthy controls. In terms of sensitivity and specificity, "sensory integration" yields the best scores (cut-off: 2; sensitivity: 0.5; specificity: 0.82), followed by "motor coordination" (cut-off: 2; sensitivity: 0.56; specificity: 0.73), and "disinhibition" (cut-off: 2; sensitivity: 0.48; specificity: 0.78). For the Neurological Examination Scale, a cut-off of 1 in the "sensory integration" yields a sensitivity of 0.55 and a specificity of 0.81; a cut-off of 1 in the "motor coordination" yields a sensitivity of 0.48 and a specificity of 0.9; and a cut-off of 2 in the "sequencing of complex act" yields a sensitivity of 0.54 and a specificity of 0.77. These indexes are comparable to those of ours, especially between Cambridge Neurological Inventory "disinhibition" and Neurological Evaluation Scale "sequencing of complex act". Taken together, though there appeared to be some discrepancies between the data-driven study and the conceptual models of neurological soft signs in the past, the most recent findings suggests that neurological soft signs could be tentatively classified into motor coordination, sensory integration, complex motor acts, and disinhibition.

Therefore, neurological signs, especially the soft signs, also have features characteristic of useful endophenotypes (Egan et al., 2001a,b; Glahn et al., 2007; Torrey et al., 1994). A higher frequency of neurological signs has consistently been found in studies of patients with schizophrenia (Weinberger and Wyatt, 1982; Heinrichs and Buchanan, 1988; Chen et al., 1995; Chan and Chen, 2007). These signs also appear trait-like in that they are relatively stable over time (Marcus et al., 1985; Chen et al., 1996a, 2005), which is advantageous for genetic studies. Neurological soft signs are present from early in the illness, as well as premorbidly in high genetic risk samples (Erlenmeyer-Kimling et al., 2000; Rubin et al., 1994; Sanders et al., 1994). They do not seem to be secondary to neuroleptic medications (Heinrichs and Buchanan, 1988; Arango et al., 2000) and can be reliably measured (Schroder et al., 1991; Ismail et al., 2000; Mohr et al., 1996; Chen et al., 1996b).

In considering the relationship between cognitive function and neurological signs, it is important to examine the underlying assumption about explanatory levels. From the consideration of the boundary between cognitive paradigms and neurological signs, it is reasonable to consider both cognitive function and neurological signs as phenomena occurring at the same explanatory level. Most researchers (e.g., Cuesta et al., 1996; Flashman et al., 1996; Mohr et al., 1996; Wong et al., 1997; Arango et al., 1999) have addressed the relationships in more detail and have reported that a large number of cognitive features correlate with a large number of neurological signs, particularly neurological soft signs such as motor coordination, sensory integration and disinhibition.

Given the common neural substrates and highly significant association between neurological soft signs and neurocognitive functions that have been identified as endophenotypic indicators for schizophrenia, we argue that the elicited clinical manifestations of neurological signs can be the neurological and cognitive endophenotypes for schizophrenia. In this paper, we use the criteria discussed above to evaluate the suitability of the presence of elicited neurological soft signs as endophenotypes for schizophrenia. Fig. 1 illustrates that endophenotypes are the crucial indicators to bridge the gap between the macroscopic level of clinical manifestations and the microscopic level of genomics and brain structures in understanding the etiology of schizophrenia. Neural system abnormalities give rise to both soft signs and cognitive impairments.

6. The criteria for endophenotypes

Researchers have proposed from three to five criteria, for useful endophenotypes with regard to schizophrenia and other psychiatric disorders (Gottesman and Shields, 1972, 1973; Tsuang et al., 1993; Cornblatt and Malhotra, 2001; Gottesman and Gould, 2003; Gould and Gottesman, 2006). Although there is no universally agreed-upon definition or evaluation of a promising endophenotype, all share and highlight several key elements in the inclusion criteria (Glahn et al., 2007). These are summarized (mainly based on Gottesman and Shields, 1972; Tsuang et al., 1993; Gottesman and Gould, 2003) as follows:

(1) The endophenotype is associated with illness in the population.
(2) The endophenotype is heritable.
(3) The endophenotype is primarily state-independent (manifests in an individual whether or not illness is active) but may require a challenge to elicit the indicator [cf. glucose tolerance test in revealing genetic predisposition to diabetes in unaffected relatives].
(4) The endophenotype found in affected family members is found in non-affected family members at a higher rate than in the general population (familial association).

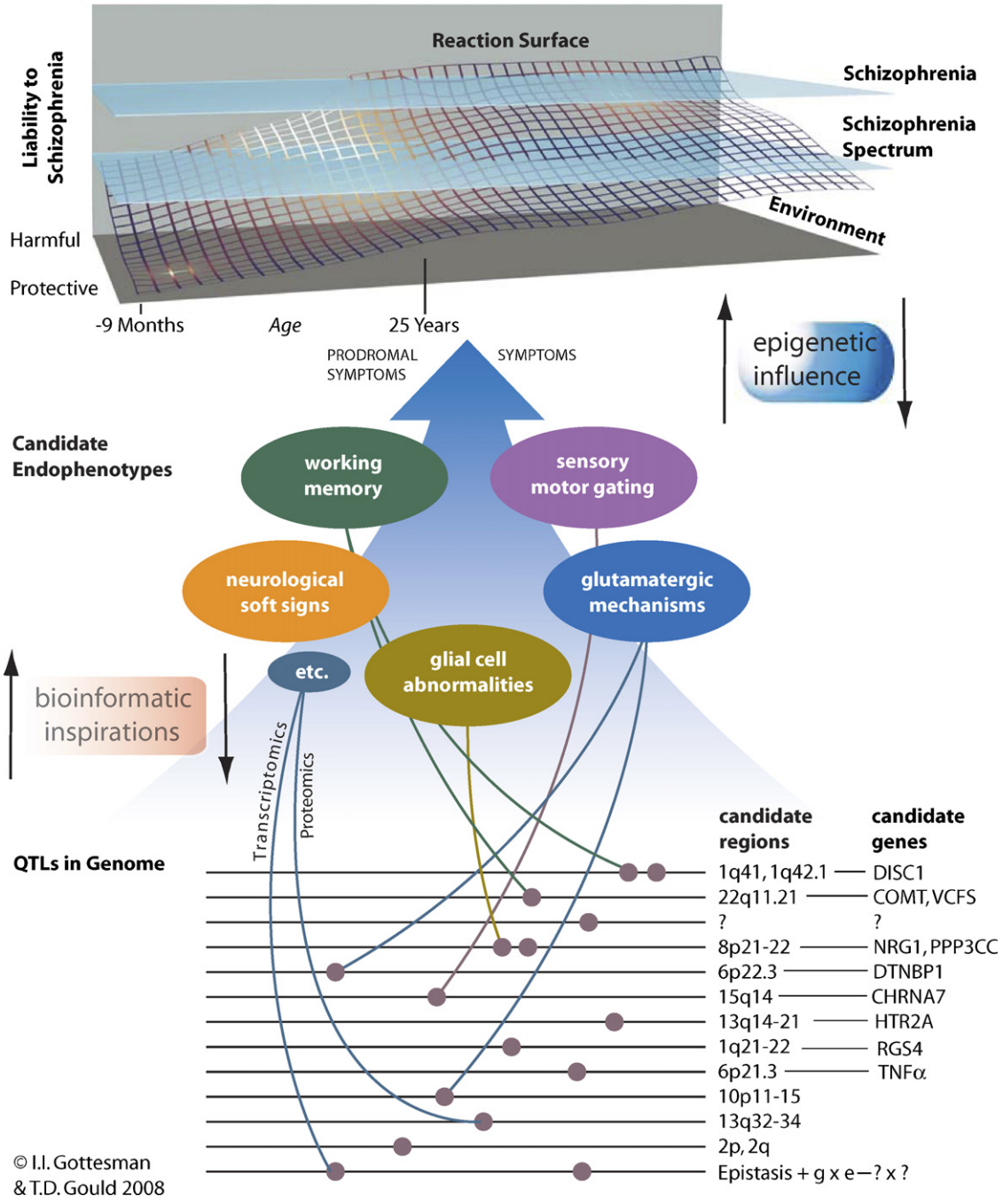

Fig. 1. Gene regions, genes, and candidate endophenotypes are implicated in a biological systems approach to schizophrenia research. The reaction surface suggests the dynamic developmental interplay among genetic, environmental, stochastic, and epigenetic factors that produce cumulative liability to developing schizophrenia spectrum and schizophrenia disorders above each of the two thresholds shown. Endophenotypes are characterized by simpler neurobiological and genetics antecedents than psychiatric disorders. The schizophrenia phenotype, as an example, is associated with a number of candidate genes and chromosomal regions, the influence of which can be observed at the levels of either behavior or endophenotypes. Endophenotypes, located closer to genes in the pathway from genes to behaviors, have fewer genes associated, and thus are more amenable to genetic investigations and studies in model systems. This skeleton (genes to endophenotypes to behaviors), allowing for epigenetic, "environmental," and purely stochastic influences upon clinical observations, and inspired by bioinformatics and the HapMap, can be applied to other diseases with complex genetics using the input of disease-specific candidate genes/regions, single nucleotide polymorphisms, and endophenotypes. None of the sections of this figure can be definitive; many more elements exist and await discovery (represented by "etc." and question marks). [Courtesy of I.I. Gottesman and T.D. Gould and used by permission].

(5) The endophenotype is more prevalent among the ill relatives of ill probands compared with the well relatives of the ill probands (i.e., co-segregation).
(6) The endophenotype should be a trait that can be measured reliably, and ideally is more strongly associated with the disease of interest than with other psychiatric conditions (i.e., specificity) (cf. Hasler et al., 2006).

For state-independence (criterion 3), Hasler et al. (2006) have argued that given the increasing recognition of the importance of epigenetic transformations and developmental factors in the expression of psychiatric phenotypes, this criterion might be particularly difficult to meet for candidate endophenotypes for both schizophrenia and bipolar disorders. On the other hand, with the advance and success of ethical symptom provocation methods

in genetic studies of medical diseases, e.g., glucose tolerance test in revealing genetic predisposition to diabetes in unaffected relatives, this method may better reflect the "state-independence" of the symptoms associated with a particular disease with variable course and important environmental influences over time. Therefore, Hasler et al. (2006) have modified this criterion into a more feasible operational definition for the original definition of "state-independence" in schizophrenia and bipolar disorders.

6.1. Criterion 1: Association with schizophrenia in the population

Extensive findings have consistently shown a higher prevalence of neurological signs among patients with schizophrenia compared to healthy controls (Heinrichs and Buchanan, 1988; Bombin et al., 2005). The majority of studies have indicated prevalence rates ranging from 50% to 65% in patients with schizophrenia, in contrast to 5% in healthy controls in western samples (Heinrichs and Buchanan, 1988; Bombin et al., 2005); whereas the prevalence rates for neurological soft signs in schizophrenia and healthy controls was about 59% to less than 5% in Chinese sample (Chan and Chen, 2007). On the other hand, the prevalence rates reported in other psychiatric disorders were between these two groups (Heinrichs and Buchanan, 1988).

6.2. Criterion 2: Heritability

The notion that neurological soft signs have genetic origins arose from the observation that they are present in non-psychotic family members of patients with schizophrenia (Ismail et al., 1998a,b; Niethammer et al., 2000; Meehl, 1990; Lenzenweger, 2006). It is difficult to reconcile this observation with an environmental cause because family members differ from the general population primarily in their risk for schizophrenia, which has no appreciable shared familial, environmental component (Cannon et al., 1998). Studies of family members, however, have generally used small samples (Ismail et al., 1998a,b; Kinney et al., 1986; Rossi et al., 1990) and have been skewed toward participants with schizophrenia spectrum disorders. Furthermore, heritability estimates are generally lacking, but see the advances in Greenwood et al. (2007). The utility of endophenotypes depends in part on the portion of total phenotypic variance attributable to genetic causes and to genetic architecture. If a large portion of phenotypic variance is genetic, endophenotypes may increase the statistical power to find susceptibility loci to the illness as many unaffected first degree relatives can enter our tested samples.

There were only three studies reporting the heritability of neurological signs in schizophrenia (Egan et al., 2001b; Sanders et al., 2006; Hyde et al., 2007). Egan et al. (2001b) adopted the relative risk approach to examining the heritability of neurological signs in schizophrenia. Relative risk assesses the risk of having an abnormality of neurological signs for relatives compared with the risk for the general population. Although greater relative risk can be attributable to shared environmental factors or genetic causes, relative risk sets an upper limit on heritability (James, 1971). A relative risk that is moderate (risk of 2–4) or higher (risk greater than 4) suggests that a phenotype may be suitable for genetic analysis (Risch and Merikangas, 1996; Rybicki and Elston, 2000). In studying 115 patients, 185 non-psychotic siblings and 88 healthy controls, Egan et al. (2001b) found that there were significant differences between the non-psychotic siblings of patients with schizophrenia and the healthy controls only in one of the neurological signs scale (Woods Scale, 1986) but not in the Neurological Evaluation Scale. Relative risk of neurological impairment was significantly increased in the sibling group, but the significance was weak to moderate. They then suggested that neurological signs cluster in patients with schizophrenia and their families and could possibly identify a unique component of genetic variance for risk of schizophrenia.

In a subsequent study by the same team, Hyde et al. (2007) further demonstrated that there was very modest evidence of the heritability of frontal release (neurological soft) signs in non-psychotic siblings of patients with schizophrenia. The greater incidence of frontal release signs in schizophrenic patients compared with their non-psychotic siblings suggests a significant role for environmental factors. People with schizophrenia most probably have both a much greater genetic load and a greater exposure to predisposing environmental factors than their non-psychotic siblings. Thus, the lack of heritability may reflect the effects of these genetic–environmental interactions or of epigenetic factors (Wong et al., 2005).

On the other hand, Sanders et al. (2006) administered the modified version of the NES to 96 participants coming from eight extended families, each consisting of two first degree relatives with schizophrenia spectrum disorders, as well as available first- to fifth-degree relatives. They found that statistically significant heritability estimates were obtained for neurological abnormalities. In particular, most of them were measures for neurological motor soft signs, including rapid alternating movement (h^2 0.99 ± 0.19 for completion time), alternating fist-palm test (h^2 0.77 ± 0.19 for completion time; h^2 0.7 ± 0.32 for errors), fist-ring test (h^2 0.53 ± 0.23 for right-sided completion time; h^2 0.7 ± 0.21 for left-sided completion time), and go/no-go task (h^2 0.93 ± 0.33 for correct responses). Only audio–visual integration (h^2 0.79 ± 0.54) from the sensory integration signs was found to be heritable in this sample. Moreover, significant correlations were found between the motor signs and various domains of neurocognitive functions. These findings suggest that although not all neurological abnormalities were heritable, there were at least familial influences on motor neurological soft signs in schizophrenia, and these heritable measures were also associated with various domains of neurocognitive functions.

6.3. Criterion 3: State independence

As we argued above, this criterion may be especially difficult to fulfill for candidate endophenotypes. Compromised neurological soft signs have been detected in schizophrenia at every age indicating that it is a trait that does not disappear despite the usual diminution over time in overt clinical manifestations. Prevalence of neurological soft signs has been detected in children, adolescents and adults with schizophrenia. Consistent findings of the prevalence of the signs have been evidenced in different stages of the illness, including prodromal high risk (Fish, 1977; Marcus et al., 1985; Lawrie et al., 2001; Erlenmeyer-Kimling et al., 2000), first-onset medication naïve cases (Sanders et al., 1994; Gupta et al., 1995; Flyckt et al., 1999; Browne et al., 2000; Dazzan and Murray, 2002; Keshavan et al., 2003), chronic remitted cases (Heinrichs and Buchanan, 1988; Chen et al., 1995; Chan and Chen, 2007), their non-psychotic siblings, and even those individuals reared in the community without a diagnosis of schizophrenia but associated with schizotypal personality features. Preliminary findings on the prevalence of neurological soft signs in chronic (Chen et al., 1996a,b,c; Chan and Chen, 2007) and first-onset cases (Whitty et al., 2003; Chen et al., 2005) showed relative stability across time periods, with minor progressive deterioration in aging patients.

However, it should be noted that motor neurological soft signs could vary with positive symptoms (e.g., Bachmann et al., 2005; Whitty et al., 2003), while especially lateralization deficits could persist as a trait marker. Therefore, although neurological soft

signs may present a trait indicator for schizophrenia, their degree of importance may also be related to schizophrenic "process activity" and acute psychosis, at least for motor signs. Chen et al. (2005) addressed this issue by following up the change of motor coordination soft signs in 93 patients with first-onset, medication-naïve schizophrenia over a 3-year interval and found that the signs were relatively stable across the time period, and that these signs were already elevated at the first presentation of psychosis in these patients. The level of neurological soft signs at clinical stabilization was lower for patients with a shorter duration of untreated psychosis. Although, the quantity of neurological soft signs did not significantly change in the first 3 years that followed the first episode, the relationship between neurological signs and negative symptoms became progressively more apparent until 1 year after the initial episode. A higher level of the signs was associated with a lower educational level and an older age at onset, but the level of neurological soft signs did not predict the outcome in terms of relapse or occupational functioning.

6.4. Criterion 4: Familial association

Thus far, there are only three twin studies assessing the familial association of neurological soft signs in schizophrenia. The first compared the prevalence of neurological soft signs in schizophrenia, monozygotic twins and healthy twins. Cantor-Graae et al. (1994) compared neurological abnormalities in 22 schizophrenic patients, 22 monozygotic co-twins, and 14 healthy monozygotic twins and demonstrated there was a significant difference between the three subgroups in terms of neurological soft signs, with schizophrenic patients exhibiting the highest prevalence of neurological signs and the healthy co-twins having the lowest prevalence. They also found that degree of neurological impairment in the well discordant monozygotic twins was significantly associated with history of both neonatal and total obstetric complications. The authors suggested that the spectrum of indicators, ranging from neurological soft signs to schizophrenia, in monozygotic discordant twins might be the result of subtle gene–environment interaction.

The second twin study was on a group of 30 monozygotic twin pairs, with 13 pairs discordant for schizophrenia or schizoaffective disorder and 17 healthy comparison pairs (Niethammer et al., 2000). The twins with schizophrenia exhibited higher total scores of neurological soft signs than did the comparison participants. Moreover, the total scores for neurological soft signs of the non-affected discordant twins were significantly higher than those of the comparison twins. The affected discordant twins showed higher total scores of neurological soft signs than the non-affected discordant twins. Post hoc analyses revealed that such differences between the three subgroups were limited to motor coordination signs. On the contrary to the comparison participants, the non-affected and affected twins of the discordant pairs showed a trend toward higher scores for neurological soft signs on the left body half. Again, these findings showed the occurrence of neurological soft signs, their lateralization to the left body in particular, were genetically transmitted.

The third twin study of neurological soft signs of schizophrenia was conducted by Kelly et al. (2004). In comparing the neurological soft signs and the related dermatoglyphic anomalies in 15 pairs of twins concordant and discordant for schizophrenia, Kelly et al. (2004) did not find any significant differences in neurological soft signs and dermatological anomalies between participants with schizophrenia and their co-twins without the illness. The negative findings might be due to the use of an unstandardized rating scale of neurological soft signs and the small sample size.

On the other hand, Bombin et al. (2005) concluded that there was substantial evidence to support the occurrences of neurological soft signs in non-psychotic siblings and family members of patients with schizophrenia that are associated with the exhibition of neurological soft signs (Kinney et al., 1986, 1999; Griffiths et al., 1998; Ismail et al., 1998a,b; Chen et al., 2000a,b; Egan et al., 2001b; Lawrie et al., 2001; Yazici et al., 2002; Gourion et al., 2004; Schuber and McNeil, 2004; Niemi et al., 2005). Most of them reported that the prevalence of neurological soft signs in relatives is intermediate between patient and healthy controls. In a meta-analytic review of putative endophenotypes for schizophrenia, Snitz et al. (2006) showed that there were modest effect sizes of motor dysfunctions (Cohen's $d = 0.26$) and finger tapping (Cohen's $d = 0.25$) in non-psychotic siblings as compared to healthy controls.

In sum, the few twin studies suggest that schizophrenia and neurological soft signs share genetic influences but indicate that the genetic overlap between schizophrenia and neurological soft signs is not substantial. However, these findings might have been limited by the small number of twin studies and the corresponding small sample sizes. Extensive empirical evidence from family studies support that healthy relatives of patients with schizophrenia exhibit higher overall neurological soft signs than healthy controls and lower overall signs rate than their affected relatives. In particular, there is a trend for motor signs to be more genetically mediated. In an extensive review of neurological signs in schizophrenia, Bombin et al. (2005) concluded that the study of potential associations between neurological signs and obstetric complications supports the idea of genetic mediation of neurological signs. However, they also suggest that motor signs appear to be less related to obstetric complications, and therefore, motor signs may be more intimately related to illness genetic vulnerability in schizophrenia.

6.5. Criterion 5: Co-segregation

There has been extensive evidence showing that healthy relatives of patients with schizophrenia exhibited the intermediate level of impairments of neurological soft signs between patients with schizophrenia and healthy controls (Ismail et al., 1998b; Gureje, 1988; Chen et al., 2000a,b; Cantor-Graae et al., 1994, 2000). Ismail et al. (1998a,b, 2000) has conducted a series of studies comparing patients with schizophrenia, their non-psychotic siblings, and healthy controls, and found that there were significant associations between patients and their non-psychotic siblings in the scores for neurological soft signs of the NES, motor coordination in particular. These findings were not confounded by the number of obstetric complications (Cantor-Graae et al., 1994; Gureje, 1988). Chen et al. (2000a,b) demonstrated a similar pattern for motor coordination, sensory integration, and disinhibition signs for the CNI in a group of Chinese schizophrenic patients. On the other hand, first-degree relatives of patients with schizophrenia have also reported higher level of neurological soft signs impairments than healthy controls (Gourion et al., 2004; Schuber and McNeil, 2004). In particular, Schuber and McNeil (2004) found that the offspring of mothers with schizophrenia exhibited significantly higher scores of motor coordination and sequencing of complex acts than both the offspring of mothers with affective psychosis and the offspring of healthy mothers.

6.6. Criterion 6: Measurement issues

There are two key points concerning the measurement issues here. First, candidate endophenotypes should be reliable if they reflect enduring traits. Standardized measures would be particu-

larly useful especially if the endophenotype varies with age or sex in a systematic way as is likely to be the case for cognitive processes. It would be advantageous for statistical analyses for the putative endophenotype to be quantifiable. As we reviewed above, although neurological signs have been traditionally considered to be some signs induced by non-localizing brain regions, these signs are fortunately induced and measured reliably using clinical ratings. Several standardized ratings have been developed in the past decades (e.g., Buchanan and Heinrichs, 1989; Denckla, 1974; Rossi et al., 1990; Schroder et al., 1991; Chen et al., 1995). The Neurological Evaluation Scale and the Cambridge Neurological Inventory are the two commonly used scales that have been reported to have impressive psychometric properties (e.g., Buchanan and Heinrichs, 1989; Chen et al., 1995; Compton et al., 2006; Chan and Chen, 2007). The most recent neuroimaging technology also facilitates the development of some potential paradigms for measuring the brain region deficits associated with these signs in healthy subjects and schizophrenic patients (e.g., Gunther et al., 1991; Schroder et al., 1995, 1999; Umetsu et al., 2002; Chan et al., 2006).

Second, an endophenotype should be common in affected individuals (i.e., sensitive), relatively if not completely unique to the disorder (i.e., specific), and relatively uncommon among unaffected individuals in the general population. However, there is an important limitation to this criterion, in that it concerns only phenotypic sensitivity and specificity. In general, there are relatively extensive works reporting increased neurological soft signs in patients with schizophrenia (Buchanan and Heinrichs, 1989; Rossi et al., 1990; Schroder et al., 1991; Chen et al., 1995, 2000a,b; Gupta et al., 1995; Mohr et al., 1996; Ismail et al., 1998b; Griffiths et al., 1998; Krebs et al., 2000; Egan et al., 2001a,b; Keshavan et al., 2003; Chan and Chen, 2007). Heinrichs and Buchanan (1988) demonstrated that the sequencing of complex motor acts and the sensory integration occurred more frequently than in those with other psychiatric disorders. Chan and Chen (2007) further provided the empirical data on the sensitivity and specificity of the three soft signs subscales of the Cambridge Neurological Inventory among a group of Chinese schizophrenic patients from those of healthy controls. The three subscales of soft signs showed a relatively better sensitivity and specificity as compared with the hard signs subscales. Improvement in sensitivity and specificity was further demonstrated when the subscales were collapsed into total soft signs. A cut-off of four in the total soft signs yields a sensitivity of 0.63 and specificity of 0.71, whereas a global cut-off of five in total neurological soft signs gets a sensitivity of 0.81 and specificity of 0.73.

However, we have argued (Gould and Gottesman, 2006; Hasler et al., 2006) that we should be cautious about these psychometric issues when evaluating the criteria of endophenotypes. Endophenotypes are conceptually different from diagnostic biomarkers. The former relates to and reflects genetically relevant aspects of the heterogeneous pathophysiology of the psychiatric illness, whereas the latter is evaluated by measures of sensitivity and specificity. We are, like many others, still uncertain that the current definitions of psychiatric illnesses are biologically valid. Recent studies also demonstrated the possibility of a maturation deficit leading to increased neurological soft signs in adult schizophrenic subjects (e.g., Karp et al., 2001); high prevalence of neurological soft signs in other neuropsychiatric disorders such as depression (Kinney et al., 1999; Krebs et al., 2000; Boks et al., 2004) and obsessive–compulsive disorders (Bolton et al., 1998, 2000) are commonly reported. Such empirical findings suggest a relatively poor specificity of neurological signs in discriminating schizophrenia from other psychotic disorders. These findings are in accordance with the study of endophenotypes of schizophrenia. Most recent empirical evidence suggests that these disorders (i.e., from unipolar depression to schizophrenia) share some etiological and pathophysiological features, particularly between bipolar depression and schizophrenia (Berrettini, 2000; Valles et al., 2000; Potash et al., 2001), including genes (Owen et al., 2007). Table 2 shows that the criteria of neurological soft signs and as the potential endophenotypes for schizophrenia.

7. Neuroanatomical and cognitive neuroscience evidence of neurological soft signs

7.1. Structural imaging studies on neurological signs in schizophrenia

Only a few studies of chronic schizophrenic patients have investigated the anatomical substrates of neurological soft signs. The presence of neurological soft signs has been associated with an enlargement of cerebral ventricles (Weinberger and Wyatt, 1982), and with smaller brain areas (DeMyer et al., 1988), whereas no correlation has been found between neurological soft signs and the calculated ratio between the width of the ventricles and the brain (Kolakowska et al., 1985).

For the first-onset schizophrenia, Rubin et al. (1994) indicated that the neurological soft signs were associated with cortical rather than sub-cortical regions. In particular, they reported an association between neurological soft signs and shorter brain length and wider left Sylvian fissure, together with a tendency for patients with more neurological abnormalities to have smaller brain volume, more cerebrospinal fluid in the sulci and cisterna on the brain surface, increased width of the right Sylvian fissure and smaller temporal horn volume. However, Kolakowska et al. (1985) indicated that there was no indication that neurological soft signs were associated with greater volume of lateral ventricles. Dazzan et al. (2004) adopted a high-resolution MRI and voxel-based methods to examine the neural substrates of neurological soft signs in a group of 77 first-onset schizophrenia. They found that higher rates of motor coordination and sensory integration signs were associated with a reduction of grey matter volume of subcortical structures, including putamen, globus pallidus and thalamus. Moreover, sensory integration signs were additionally associated with volume reduction in the cerebral cortex, including the precentral, superior and middle temporal, and lingual gyri. Such relationships were independent of medication. Dazzan et al. (2006) found that similar associations were also demonstrated in 43 healthy volunteers. In particular, higher rates of neurological soft signs were associated with a reduction of inferior frontal gyrus, middle and superior temporal gyrus, and anterior cingulate gyrus.

7.2. Neurological soft signs and cognitive impairments

Motor coordination signs are specifically associated with impairments in action and attention inhibition (Mohr et al., 1996, 2003; Cuesta et al., 1996; Wong et al., 1997; Chen et al., 2001a,b) as well as with verbal performance (Merriam et al., 1990; Flashman et al., 1996) and visual-spatial memory (Cuesta et al., 1996; Arango et al., 1999; Sanders et al., 2004). However, it should be cautioned that verbal performance has been shown to be associated with general intelligence and executive function, and it has been suggested that prefrontal cortex is critically involved (e.g., Duncan et al., 2000). Moreover, recent functional neuroimaging data also supported the involvement of the supplementary motor area (bilaterally) in the genesis of motor soft sign in schizophrenia and healthy volunteers (e.g., Schroder et al., 1995; Chan et al., 2006, submitted for publication-a,b; Rao et al., submitted for publication). Mohr et al. (1996) and Smith et al. (1999a,b) also showed that

Table 2
Summary of findings: criteria of neurological soft signs as the candidate endophenotypes for schizophrenia

Criterion	Evidence	Existing issues to be addressed	Directions for future studies
Association with schizophrenia	Extensive findings have consistently shown a higher prevalence of neurological signs among patients with schizophrenia compared to healthy controls	Schizophrenia is a complicated illness with a wide spectrum disorders. The majority of studies have focused on patients with schizophrenia	Extend the study of prevalence of neurological soft signs to individuals of the schizophrenia spectrum disorders; attend to moderators of comorbidity and DSM-IV subtypes of schizophrenia
		Not clear whether similar association appears to exist in community-dwelling individuals with schizotypal personality features	
Heritability	Not well-studied. Available data suggest that there were modest evidence of the heritability of frontal release (neurological soft) signs in non-psychotic siblings of patients with schizophrenia	Very limited data (no twin data identified) to validate the heritability of neurological soft signs in schizophrenia	Conduct large scale twin study (either healthy cohorts or disease group) to examine heritability of various domains of neurological soft signs
		There are potential ethnic and cultural variations of neurological soft signs	Examination of specific genes association with various neurological soft signs Conduct cross-ethnic and cross-cultural studies to validate the potential genetic-environmental interaction
State-independence of the illness	Robust findings on the state-independence of the illness	Most of the studies are limited to cross-sectional designs. Very limited findings were generated from prospective longitudinal study designs from high-risk to first-onset, stabilization of symptoms, and remission status. The available longitudinal data were all limited to motor coordination signs	Use prospective longitudinal study to follow up the change of various domains of neurological soft signs
Familial association	Extensive evidence, from comparison between non-psychotic siblings of patients with schizophrenia and healthy controls, for familial association of neurological soft signs in schizophrenia	Limited number of twin studies and small sample sizes to substantiate the share genetic liability between schizophrenia and neurological soft signs	Conduct large family and twin studies of schizophrenia and neurological soft signs that collect molecular genetic data. Use empirical strategies to minimize the potential confounds such as associations between neurological signs and obstetric complications.
Co-segregation	Extensive evidence showing that healthy relatives of patients with schizophrenia exhibited the intermediate level of impairments of neurological soft signs between patients with schizophrenia and healthy controls	Limited number of twin studies and small sample sizes to substantiate the share genetic liability between schizophrenia and neurological soft signs	Conduct large family and twin studies of schizophrenia and neurological soft signs that collect molecular genetic data. Use empirical strategies to minimize the potential confounds such as associations between neurological signs and obstetric complications
Measurement issues	Extensive findings to support the notion that neurological soft signs can be reliably assessed via a series of standardized clinical ratings. Impressive test–retest reliabilities and sensitivity have been demonstrated. Partial evidence of brain regions involved has also been supported by preliminary imaging studies	Neurological soft signs are also commonly found in other neuropsychiatric disorders such as bipolar disorders (relatively poor specificity)	To better understand the continuum of phenomenological symptoms stretching from schizophrenic psychosis to manic-depressive illness. It involves a re-evaluation of the construct of unitary psychosis and the underlying common psychopathological mechanisms of these disorders (i.e., from unipolar depression to schizophrenia)
		Reliability may varies across different levels of complexity of the signs	Development of a more scientific and quantifiable paradigm of neurological soft signs with the help of neuroimaging and kinesiological techniques
		Experimental measures may be more objective and quantifiable for further study	

the sequencing of complex motor acts of the NES has the highest correlation with executive functioning.

On the other hand, sensory integration signs were generally related a wider range of neurocognitive functions in addition to executive functions and intellectual functioning (Heinrichs and Buchanan, 1988; Bombin et al., 2005). In schizophrenia, there is evidence for a generalized cognitive decline, which affects performance in verbal functioning (Bilder et al., 1992). Verbal ability is relatively robust in schizophrenia, at least compared with some other ability areas. For example, Heinrichs et al. (in press) reported on a sample of patients with superior ability (>95th percentile) on the Vocabulary subtest of the WAIS-III. We looked for, and found, high functioning patients. However, whereas 25/151 scored at superior levels on Vocabulary, only 1/151 even

managed above average scores in verbal declarative memory (California Verbal Learning Test). If verbal ability is varying with motor function it must be that both are reflecting a very diffuse and multisystem process. Again, the last century of human lesion studies shows that these abilities are dissociable. The extremely high association between sensory integration and verbal performance suggests that presence of the latter is probably a reflection of generalized cognitive impairment. Ross et al. (1998) also found that sensory integration items were the most frequent predictors of eye-tracking performances in chronic schizophrenia. Disinhibition signs are found to be associated with sustained attention and blink rate in schizophrenia (Chan and Chen, 2004a,b). Intense blinkers exhibited significantly disinhibition soft signs and impairment in inhibiting their behavioural responses compared to rare blinkers in schizophrenia (Chan and Chen, 2004a).

Moreover, Chan and Chen (2004b) demonstrated that significant relationships were found between specific executive function components and neurological soft signs. Specifically, motor coordination was correlated with attention inhibition component, verbal performance and visual memory; sensory integration was correlated with initiation component and verbal functioning; and disinhibition signs were associated with attention inhibition component. Chan et al. (submitted for publication-a,b) further demonstrated motor coordination and disinhibition signs were specifically associated with working memory involving visual component and the executive aspect of action modulation on disinhibition in patients with chronic schizophrenia. These findings suggest that motor coordination and disinhibition involve common neural substrates of higher cognitive functioning rather than simple "pure" motor movement. Our most recent findings (Chan et al., 2004a,b) showed that there were significant regression relationship between neurological soft signs, as measured by the Cambridge Neurological Inventory, and different domains of neurocognitive functions (executive attention, verbal and visual memory) a group of schizophrenic patients and healthy volunteers using the structural equation modeling technique. The regression coefficients were at medium to large effect sizes (r ranges from -0.75 to -0.83, $p < 0.01$. Given the above imaging evidence and these preliminary findings, it is speculative that that these neurological soft signs and conventional neurocognitive functions tests may capture very similar constructs or share common neural substrates. However, more empirical evidence using different methodologies and different stages of illness is needed to verify such a hypothesis.

Despite the acceptable psychometric properties for some of the standardized rating scales of neurological soft signs, these scales are limited by the subjectivity of the raters. The development of a more scientific experimental paradigm is urgently needed to better quantify and locate the corresponding brain regions involved. It is very feasible to develop objective measures of motor coordination, sensorimotor integration and complex movements. In fact some of these measures already exist in some form. For example, in an early meta-analysis (Heinrichs and Zakzanis, 1998) a mean Cohen's d of 1.30 for motor skill based on bilateral hand trials on the Purdue Pegboard was found. Unfortunately, it was based on only five studies. Still, it compared with $d = 0.86$ for unilateral dominant hand measures primarily of speed and dexterity rather than coordinated performance. Tactile-transfer tasks (sensory integration) also yielded a big mean d (0.98), but there was a lot of variability. There may be more recent findings on objective coordinated/complex motor tasks. Given the significant association between neurological soft signs and some of the neurocognitive functions such as attention and working memory, the most recent advances in imaging techniques and the related knowledge of kinesiology may help further clarify the underlying neural substrates between neurological soft signs and neurocognition functions.

Having said that, the use of rating scales remains important in clinical practice because they are relatively simple to use, inexpensive and can be easily incorporated into the clinical routine. Taken together, the nature and characteristics of the neurological soft signs testing suggest that this test can be more feasible for clinicians to screen for any cognitive impairment in schizophrenia.

8. Genetic modeling studies

An endophenotype-based approach has the potential to assist in the genetic dissection of psychiatric diseases. Meyer-Lindenberg and Weinberger (2006) illustrate that there are at least two fungible equivalents for endophenotypes as tools for schizophrenia. In the gene discovery approach, the deficiencies in the electrophysiological response to auditory stimulation were used to identify an association of schizophrenia with the α 7 nicotinic cholinergic receptor (Freedman et al., 1997). Prefrontal cortex dysfunction has been linked to catechol-*O*-methytransferase (COMT) and GRM3 genetic variation (Egan et al., 2004), and emotional regulation has been linked to variation in COMT, monoamine oxidase A (MAOA) and the serotonin transporter length polymorphism (5-HTTLPR/SLC6A4) (Pezawas et al., 2005; Heinz et al., 2005), and so could have been hypothetically employed as a phenotype to identify these genes. In the neural mechanism approach, genes known to be associated with schizophrenia are used to discover neural mechanisms mediating their complex emergent phenotypic associations, implicating these mechanisms in schizophrenia to which they have been linked. The use of COMT Val158Met polymorphism to characterize prefrontal function and prefrontal-midbrain interactions (Meyer-Lindenberg and Weinberger, 2006; Egan et al., 2001a), and the GABA A receptor (Yee et al., 2005) have been linked to risk for schizophrenia and their related sensorimotor deficits (Bender et al., 2007).

However, very little is known about the candidate genes for neurological soft signs in schizophrenia and other neuropsychiatric disorders. There are only two studies identified from the literature examining the potential association between neurological soft signs and serotonin dysfunction in schizophrenia. Chen et al. (2001a,b) conducted a case–control study of the T102C polymorphism with detailed characterization of the clinical phenonotypes to examine the possible association with schizophrenia in 471 patients with schizophrenia and 523 unrelated healthy controls of Han Chinese. They found that there was a significant association with small to modest effect size between genotype 102T/102C and patients with better verbal fluency and less motor coordination soft signs. However, Abdolmaleky et al. (2004) have shown that there was no significant association with the C allele or CC homozygosity in East Asian countries, indicating strong genetic differences and non-combinability of data between European and East Asian populations. Given that serotonin is associated with dopamine release and that polymorphism of serotonin receptor gene might be related to the clinical features and cognitive function in schizophrenia, an exploration of the HTR2C in relation to cognitive functioning in this clinical group will be of theoretically and clinically meaningful. There is a need for future cross-cultural large-scale studies on the possible associations between genetic polymorphisms and neurological abnormalities in schizophrenia.

On the other hand, Galderisi et al. (2005) linking COMT, cognitive symptoms and motor soft signs (motor coordination and complex motor sequencing of the NES subscales) in a group of 56

patients with deficit schizophrenia and 50 patients with non-deficit schizophrenia, and found that the COMT Val158Met polymorphism is associated with cognitive and motor deficits in schizophrenia as a whole group or in the deficit subtype. In particular, the COMT polymorphism accounted for 6.6% of the cognitive performance variance, while patients with Val/Val genotype performed significantly worse than patients with the Val/Met or Met/Met genotype. The COMT polymorphism also shared 15.6% of the motor impairment variance in the deficit group, while showing no association with this variable in patients with non-deficit schizophrenia. The deficit group also exhibited more motor coordination and complex motor sequencing than the non-deficit group.

9. Conclusions

In this paper, we argue that the clinical manifestations of elicited or measured neurological soft signs can be considered to be among the candidate neurological and cognitive endophenotypes for schizophrenia. We provide substantial evidence to support the claims that neurological soft signs, motor coordination in particular, meet many of the criteria discussed above to evaluate the suitability of the presence of neurological soft signs as endophenotypes for schizophrenia. However, there are also several unresolved issues for the study of neurological soft signs as candidate endophenotypes for schizophrenia. The most crucial issues to be tackled include: (1) the lack of a twin database (either on healthy twin cohorts or twin data with one individual suffering from schizophrenia), (2) the lack of studies to examine the association with individual genes and complexity of neurological soft signs in schizophrenia and (3) a lack of a more rigorous methodology to measure and quantify neurological soft signs. The twin database and the identification of specific genes association with neurological soft signs are elementary criteria for heritability, familial association, and co-segregation. With the completion of human genome and the establishment of SchizophreniaGene (www.SzGene.org) database, it is now feasible to test the association of candidate genes and neurological soft sign impairments in schizophrenia.

Despite the acceptable psychometric properties for some of the standardized rating scales of neurological soft signs, these scales are limited by the subjectivity of the raters. The development of a more scientific experimental paradigm is urgently needed to better quantify and locate the corresponding brain regions involvement. It is very feasible to develop objective measures of motor coordination, sensorimotor integration and complex movements. In fact some of these measures already exist in some form. For example, in an early meta-analysis (Heinrichs and Zakzanis, 1998) a mean Cohen's d of 1.30 for motor skill based on bilateral hand trials on the Purdue Pegboard was found. Unfortunately, it was based on only five studies. Still, it compared with $d = 0.86$ for unilateral dominant hand measures primarily of speed and dexterity rather than coordinated performance. Tactile-transfer tasks (sensory integration) also yielded a big mean d (0.98), but there was a lot of variability. There may be more recent findings on objective coordinated/complex motor tasks. Given the significant association between neurological soft signs and some of the neurocognitive functions such as attention and working memory, the most recent advances in imaging techniques and the related knowledge of kinesiology may help further clarify the underlying neural substrates between neurological soft signs and neurocognition functions.

In short, we believe that neurological soft signs can serve as one of the indicators bridging the gap between the macroscopic level of clinical manifestations and the microscopic level of genomics and brain structures in understanding the etiology of schizophrenia.

Acknowledgements

The authors would like to thank R. Walter Heinrichs for his constructive comments on the previous versions of this paper and Todd Gould for his help in finalizing the figure illustrating neurological soft signs as another candidate endophenotype for schizophrenia. The preparation of the paper was supported partially by the Research Initiation Fund of the 100-scholar Plan (O7CX031003), a grant from Institute of Psychology, Chinese Academy of Sciences (KSCX2-YW-R-131) and a grant from the National Science Fund China (30770723) to Raymond Chan, and a National Basic Research Programme of China (973 Program) (2007CB512305); and, the Drs. Irving and Dorothy Bernstein Professorship in Adult Psychiatry at the University of Minnesota Medical School to I.I.G.

References

Abdolmaleky, H.M., Faraone, S.V., Glatt, S.J., Tsuang, M.T., 2004. Meta-analysis of association between the T102C polymorphism of the 5HT2a receptor gene and schizophrenia. Schizophrenia Research 67, 53–62.

Arango, C., Bartko, J.J., Gold, J.M., Buchanan, R.W., 1999. Prediction of neuropsychological performance by neurological signs in schizophrenia. American Journal of Psychiatry 156 (9), 1349–1357.

Arango, C., Kirkpatrick, B., Buchanan, R.W., 2000. Neurological signs and the heterogeneity of schizophrenia. American Journal of Psychiatry 157, 560–565.

Bachmann, S., Bottmer, C., Schroder, J., 2005. Neurological soft signs in first-episode schizophrenia: a follow-up study. American Journal of Psychiatry 162, 2337–2343.

Bender, S., Weisbrod, M., Resch, F., 2007. Which perspectives can endophenotypes and biological markers offer in the early recognition of schizophrenia? Journal of Neural Transmission 114 (9), 1199–1215.

Berrettini, W.H., 2000. Are schizophrenic and bipolar disorders related? A review of family and molecular studies. Biological Psychiatry 48 (6), 531–538.

Bilder, R.M., Lipschutz-Broch, L., Reiter, G., Geisler, S.H., Mayerhoff, D.L., Liberman, J.A., 1992. Intellectual deficits in first-episode schizophrenia: evidence for progressive deterioration. Schizophrenia Bulletin 18 (3), 437–448.

Bolton, D., Gibb, W., Lees, A., et al., 1998. Neurological signs in obsessive compulsive disorder: standardized assessment and comparison with schizophrenia. Behavioural Neurology 11 (4), 197–204.

Bolton, D., Gibb, W., Lees, A., Raven, P., Gray, J.A., Chen, E., Shafran, R., 2000. Neurological soft signs in obsessive compulsive disorder: standardised assessment and comparison with schizophrenia. Behavioural Neurology 11, 197–204.

Boks, M.P., Liddle, P.F., Burgerhof, J.G., Knegtering, R., van den Bosch, R.J., 2004. Neurological soft signs discriminating mood disorders from first episode schizophrenia. Acta Psychiatrica Scandinavica 110 (1), 29–35.

Bombin, I., Arango, C., Buchanan, R.W., 2003. Assessment tools for soft signs. Psychiatric Annals 33 (3), 170–176.

Bombin, I., Arango, C., Buchanan, R.W., 2005. Significance and meaning of neurological signs in schizophrenia: two decades later. Schizophrenia Bulletin 31 (4), 962–977.

Braff, D.L., Freedman, R., Schork, N.J., Gottesman, I.I., 2007. Deconstructing schizophrenia: an overview of the use of endophenotypes in order understand a complex disorder. Schizophrenia Bulletin 33 (1), 21–32.

Bray, N.J., Holmans, P.A., van den Bree, M.B., Jones, L., Elliston, L.A., Hughes, G., Richards, A.L., Williams, N.M., Craddock, N., Owen, M.J., O'Donovan, M.C., 2008. *cis*- and *trans*-Loci influence expression of the schizophrenia susceptibility gene DTNBP1. Human Molecular Genetics 17, 1169–1174.

Browne, S., Clarke, M., Gervin, M., Lane, A., Waddington, J.L., Larkin, C., O'Callaghan, E., 2000. Determinants of neurological dysfunction in first episode schizophrenia. Psychological Medicine 30, 1433–1441.

Buchanan, R.W., Heinrichs, D.W., 1989. The Neurological Evaluation Scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. Psychiatry Research 27, 335–350.

Candela, S.F., Manschreck, T.C., 2003. NSS in schizophrenia: research findings and clinical relevance. Psychiatric Annals 33 (3), 157–166.

Cadenhead, K.S., Light, G.A., Geyer, M.A., McDowell, J.E., Braff, D.L., 2002. Neurobiological measures of schizotypal personality disorder: defining an inhibitory endophenotype. American Journal of Psychiatry 159, 869–871.

Cannon, T.D., Gasperoni, T.L., van Erp, T.G.M., Rosso, I.M., 2001. Quantitative neural indicators of liability to schizophrenia: implications for molecular genetic studies. American Journal of Medical Genetics 105, 16–19.

Cannon, T.D., Huttunen, M.O., Lonnqvist, J., Tuulio-Henriksson, A., Pirkola, T., Glahn, D., Finkelstein, J., Hietanen, M., Kapriol, J., Koskenvuno, M., 2000. Inheritance of

neuropsychological functions in twins discordant for schizophrenia. American Journal of Human Genetics 67, 369–382.
Cannon, T.D., Kaprio, J., Lonnqvist, J., Huttunen, M., Koskenvuo, M., 1998. The genetic epidemiology of schizophrenia in a Finnish twin cohort: a population-based modeling study. Archives of General Psychiatry 55, 67–74.
Cantor-Graae, E.W., Ismail, B., McNeil, T.F., 2000. Are neurological abnormalities in schizophrenic patients and their siblings the result of perinatal trauma? Acta Psychiatrica Scandinavica 101 (2), 142–147.
Cantor-Graae, E., McNeil, T.F., Rickler, K.C., Sjostrom, K., Rawlings, R., Higgins, E.S., Hyde, T.M., 1994. Are neurological abnormalities in well discordant monozygotic co-twins of schizophrenic subjects the result of perinatal trauma? American Journal of Psychiatry 151, 1194–1199.
Chan, R.C.K., Chen, E.Y.H., 2004a. Blink rate does matter: a study of sustained attention and neurological signs in schizophrenia. Journal of Nervous and Mental Disease 192 (11), 781–783.
Chan, R.C.K., Chen, E.Y.H., 2004b. Executive dysfunctions and neurological manifestations in schizophrenia. Hong Kong Journal of Psychiatry 14 (3), 2–6.
Chan, R.C.K., Chen, E.Y.H., 2007. Neurological abnormalities in Chinese schizophrenic patients. Behavioural Neurology 18 (3), 171–181.
Chan, R.C.K., Chen, E.Y.H., Cheung, E.F.C., Chen, R.Y.L., Cheung, H.K., 2004a. A study of sensitivity of the sustained attention to response task in patients with schizophrenia. Clinical Neuropsychologist 18 (1), 114–121.
Chan, R.C.K., Chen, E.Y.H., Cheung, E.F.C., Chen, R.Y.L., Cheung, H.K., 2004. Prediction of neurological signs by neurocognitive performance in schizophrenia. The International Neuropsychological Society & German Neuropsychological Society, 27th Mid-Year Meeting of INS, Brisbane, Australia.
Chan, R.C.K., Chen, E.Y.H., Wang, Y., Cheung, E.F.C., Chen, R.Y.L., Cheung, H.K. Contribution of neuropsychological functions to neurological soft signs in schizophrenia, submitted for publication.
Chan, R.C.K., Wang, L., Wang, Y., Manschreck, T.C. Neurological soft signs and their relationships to neurocognitive functions: a re-visit with the structural equation modeling design, submitted for publication.
Chan, R.C.K., Rao, H., Chen, E.E., Ye, B., Zhang C, 2006. The neural basis of motor sequencing: an fMRI study of healthy subjects. Neuroscience Letters 398, 189–194.
Chen, E.Y., Hui, C.L., Chan, R.C., Dunn, E.L., Miao, M.Y., Yeung, W.S., et al., 2005. A 3-year prospective study of neurological soft signs in first-episode schizophrenia. Schizophrenia Research 75, 45–54.
Chen, E.Y., Kwok, C.L., Au, J.W., Chen, R.Y., Lau, B.S., 2000a. Progressive deterioration of soft neurological signs in chronic schizophrenic patients. Acta Psychiatrica Scandinavica 102 (5), 342–349.
Chen, R.Y.L., Chen, E.Y.H., Lieh-Mak, F., 2000b. Soft neurological signs in schizophrenic patients and their nonpsychotic siblings. Journal of Nervous and Mental Diseases 188 (2), 84–89.
Chen, E.Y.H., Lam, L.C.W., Chen, R.Y.L., Nguyen, D.G.H., 1996a. Neurological signs, age, and illness duration in schizophrenia. Journal of Nervous and Mental Diseases 181, 339–345.
Chen, E.Y.H., Lam, L.C.W., Chen, R.Y.L., Nguyen, D.G.H., 1996b. Negative symptoms, neurological signs and neuropsychological impairments in 204 Hong Kong Chinese patients with schizophrenia. British Journal of Psychiatry 168, 227–233.
Chen, E.Y.H., Lam, L.C.W., Chen, R.Y.L., Nguyen, D.G.H., 1996c. Neurological signs, age and illness duration in schizophrenia. Journal of Nervous and Mental Diseases 184 (6), 339–345.
Chen, E.Y.H., Lam, L.C.W., Chen, R.Y.L., Nguyen, D.G.H., Kwok, C.L., Au, J.W.Y., 2001a. Neurological signs and sustained attention impairment in schizophrenia. European Archives of Psychiatry and Clinical Neuroscience 25, 1–5.
Chen, R.Y., Sham, P., Chen, E.Y., Li, T., Cheung, E.F., Hui, T.C., Kwok, C.L., Lieh-Mak, F., Zhao, J.H., Collier, D., Murray, R., 2001b. No association between T102C polymorphism of serotonin-2A receptor gene and clinical phenotypes of Chinese schizophrenic patients. Psychiatry Research 105, 175–185.
Chen, E.Y.H., Shapleske, J., Luque, R., McKenna, P.J., Hodges, J.R., Callloway, S.P., Hymas, N.F.S., Dening, T.R., Berrios, G.E., 1995. The Cambridge Neurological Inventory: a clinical instrument for soft neurological signs and the further neurological examination for psychiatric patients. Psychiatry Research 56, 183–202.
Chen, W.J., Faraone, S.V., 2000. Sustained attention deficits as markers of genetic susceptibility to schizophrenia. American Journal of Medical Genetics 97, 52–57.
Chowdari, K.V., Mirnics, K., Semwal, P., Wood, J., Lawrence, E., Bhatia, T., et al., 2002. Association and linkage analyses of RGS4 polymorphisms in schizophrenia. Human Molecular Genetics 11, 1373–1380.
Chubb, J.E., Bradshaw, N.J., Soares, D.C., Porteous, D.J., Millar, J.K., 2007. The DISC locus in psychiatry illness. Molecular Psychiatry 1–29.
Chumakov, I., Blumenfeld, M., Guerassimenko, O., Cavarec, L., Palicio, M., Abderrahim, H., et al., 2002. Genetic and physiological data implicating the new human gene 72 and the gene for D-amino acid oxidase in schizophrenia. Proceedings of the National Academy of Sciences of USA 99, 13675–13680.
Cornblatt, B.A., Malhotra, A.K., 2001. Impaired attention as an endophenotype for molecular genetic studies of schizophrenia. American Journal of Medical Genetics (Neuropsychiatric Genetics) 105, 11–15.
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.
Crosbie, J., Perusse, D., Barr, C., Schachar, R.J., 2008. Validating psychiatric endophenotypes: inhibitory control and attention deficit hyperactivity disorder. Neuroscience & Biobehavioral Reviews 32, 40–55.
Cuesta, M.J., Peralta, V., de Leon, J., 1996. Neurological signs and neuropsychological deficits in schizophrenic patients. Schizophrenia Research 20 (1–2), 15–20.
Dazzan, P., Morgan, K.D., Chitnis, X., Suckling, J., Morgan, C., Fearon, P., McGuire, P.K., Jones, P.B., Leff, J., Murray, R.M., 2006. The structural brain correlates of neurological soft signs in healthy individuals. Cerebral Cortex 16, 1225–1231.
Dazzan, P., Morgan, K.D., Orr, K.G., Huchinson, G., Chitnis, X., Suckling, J., Fearon, P., Salvo, J., McGuire, P.K., Mallett, R.M., Jones, P.B., Leff, J., Murray, R.M., 2004. The structural brain correlates of neurological soft signs in AESOP first-episode psychoses study. Brain 127, 143–153.
Dazzan, P., Murray, R.M., 2002. Neurological soft signs in first-episode psychosis: a systematic review. British Journal of Psychiatry 43, s50–s57.
DeMyer, M.K., Gilmor, R.L., Hendrle, H.C., et al., 1988. Magnetic resonance brain images in schizophrenic and normal subjects: influence of diagnosis and education. Schizophrenia Bulletin 14, 21–37.
Denckla, M.B., 1974. Development of motor coordination in normal children. Developmental Medicine and Child Neurology 16, 729–741.
Doyle, A.E., Faraone, S.V., Seidman, L.J., Willcutt, E.G., Nigg, J.T., Waldman, I.D., Pennington, B.F., Peart, J., Biederman, J., 2005. Are endophenotypes based on measures of executive functions useful for molecular genetic studies of ADHD? Journal of Child Psychology and Psychiatry 46 (7), 774–803.
Duncan, J., Seitz, R.J., Kolodny, J., Bor, D., Herzog, H., Ahmed, A., Newell, F.N., Emslie, H., 2000. A neural basis for general intelligence. Science 289, 457–460.
Egan, M.F., Goldberg, T.E., Gscheidle, T., Weirich, M., Bigelow, L.B., Wieinberger, D.R., 2000. Relative risk of attention deficits in siblings of patients with schizophrenia. American Journal of Psychiatry 157, 1309–1316.
Egan, M.F., Goldberg, T.E., Kolachana, B.S., Callicott, J.H., Mazzanti, C.M., Straub, R.E., et al., 2001a. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proceedings of the National Academy of Sciences of USA 98, 6917–6922.
Egan, M.F., Hyde, T.M., Bonomo, J.B., Mattay, V.S., Bigelow, L.B., Goldberg, T.E., Weinberger, D.R., 2001b. Relative risk of neurological signs in siblings of patients with schizophrenia. American Journal of Psychiatry 158, 1827–1834.
Egan, M.F., Straub, R.E., Goldberg, T.E., Yakub, I., Callicott, J.H., Hariri, A.R., Mattay, V.S., Bertolino, A., Hyde, T.M., Shannon-Weickert, C., Akil, M., Crook, J., Vakkalanka, R.K., Balkissoon, R., Gibbs, R.A., Kleinman, J.E., Weinberger, D.R., 2004. Variation in GRM3 affects cognition, prefrontal glutamate, and risk for schizophrenia. Proceedings of the National Academy of USA 101, 12604–12609.
Emsley, R., Turner, H.J., Oosthuizen, P.P., Carr, J., 2005. Neurological abnormalities in first-episode schizophrenia: temporal stability and clinical and outcome correlates. Schizophrenia Research 75, 35–44.
Erlenmeyer-Kimling, L., Rock, D., Roberts, S.A., Janal, M., Kestenbaum, C., Cornblatt, B., Adamo, U.H., Gottesman, I.I., 2000. Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: the New York high-risk project. American Journal of Psychiatry 157, 1416–1422.
Faraone, S.V., Tsuang, D., Tsuang, M.T., 1999. Genetics of Mental Disorders: A Guide for Students, Clinicians, and Researchers. Guildford, New York.
Fish, B., 1977. Neurobiologic antecedents of schizophrenia in children. Archives of General Psychiatry 34, 1297–1313.
Flashman, L.A., Flaum, M., Gupta, S., Andreasen, N.C., 1996. Soft signs and neuropsychological performance in schizophrenia. American Journal of Psychiatry 153 (4), 526–532.
Flint, J., Munafo, M.R., 2007. The endophenotype concept in psychiatric genetics. Psychological Medicine 37, 163–180.
Flyckt, L., Sydow, O., Bjerkenstedt, L., Edman, G., Rydin, E., Wiesel, F.A., 1999. Neurological signs and psychomotor performance in patients with schizophrenia, their relatives and healthy controls. Psychiatry Research 86, 113–129.
Freedman, R., Coon, H., Myles-Worsley, M., Orr-Urtreger, A., Olincy, A., Davis, A., Polymeropoulos, M., Holik, J., Hopkins, J., Hoff, M., Rosenthal, J., Waldo, M.C., Reimherr, F., Wender, P., Yaw, J., Young, D.A., Breese, C.R., Adams, C., Patterson, D., Adler, L.W., Kruglyak, L., Leonard, S., Byerley, W., 1997. Linkage of a neuropsychological deficit in schizophrenia to a chromosome 15 locus. Proceedings of the National Academy of USA 94, 587–592.
Galderisi, S., Maj, M., Kirkpatrick, B., Piccardi, P., Mucci, A., Invernizzi, G., Rossi, A., Pini, S., Vita, A., Cassano, P., Stratta, P., Severino, G., Zompo, M.D., 2005. Catechol-*O*-methyltransferase Val^{158} Met polymorphism in schizophrenia: Associations with cognitive and motor impairment. Neuropsychobiology 52, 83–89.
Glahn, D.C., Almasy, L., Blangero, J., Burk, G.M., Estrada, J., Peralta, J.M., Meyenberg, N., Castro, M.P., Barrett, J., Nicolini, H., Raventos, H., Escamilla, M.A., 2007. Adjudicating neurocognitive endophenotypes for schizophrenia. American Journal of Medical Genetics Part B (Neuropsychiatric Genetics) 144B, 242–249.
Goldberg, T.E., Torrey, E.F., Gold, J.M., 1995. Genetic risk of neuropsychological impairment in schizophrenia: a study of monozygotic twins discordant and concordant for the disorder. Schizophrenia Research 17, 77–84.
Goldstein, G., Sanders, R.D., Forman, S.D., Tarpey, T., Gurklis, J.A., van Kammen, D.P., Keshavan, M.S., 2005. The effects of antipsychotic medication on factor and cluster structure of neurological examination abnormalities in schizophrenia. Schizophrenia Research 75, 55–64.
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., 1972. Schizophrenia and genetics: A twin study vantage point. Academic Press, New York.

Gottesman, I.I., Shields, J., 1973. Genetics theorizing and schizophrenia. British Journal of Psychiatry 122, 15–30.
Gould, T.D., Gottesman, I.I., 2006. Psychiatric endophenotypes and the development of valid animal models. Genes, Brain & Behavior 5, 113–119., doi:10.1111/j.1601-183X.2005.00186.x, http://www.blackwell-synergy.com/.
Gourion, D., Goldberger, C., Olie, J.P., Loo, H., Krebs, M.O., 2004. Neurological and morphological anomalies and the genetic liability to schizophrenia: a composite phenotype. Schizophrenia Research 67 (1), 23–31.
Greenwood, T.A., Braff, D.L., Light, G.A., Dadenhead, K.S., Calkins, M.E., Dobie, D.J., Freedman, R., Green, M.F., Gur, R.E., Gur, R.C., Mintz, J., Nuechterlein, K.H., Olincy, A., Radant, A.D., Seidman, L.J., Siever, L.J., Silverman, J.M., Stone, W.S., Swerdlow, N.R., Tsuang, D.W., Tsuang, M.T., Turetsky, B.I., Schork, N.J., 2007. Initial heritability analyses of endophenotypic measures for schizophrenia: the consortium on the genetics of schizophrenia. Archives of General Psychiatry 64, 1242–1250.
Griffiths, T.D., Sigmundsson, T., Takei, N., Rower, D., Murray, R.M., 1998. Neurological abnormalities in familial and sporadic schizophrenia. Brain 121 (2), 191–203.
Gunther, W., Petsch, R., Steinberg, R., et al., 1991. Brain dysfunction during motor activation and corpus callosum alterations in schizophrenia measured by cerebral blood flow and magnetic resonance imaging. Biological Psychiatry 29, 535–555.
Gupta, S., Andreasen, N.C., Arndt, S., Flaum, M., Schultz, S.K., Hubbard, W.C., Smith, M., 1995. Neurological soft signs in neuroleptic-naïve and neuroleptic-treated schizophrenic patients and in normal comparison subjects. American Journal of Psychiatry 152, 191–196.
Gur, R.E., Calkins, M., Gur, R.C., Horan, W.P., Nuechterlein, K.H., Seidman, L.J., Stone, W.S., 2007a. The consortium on the genetics of schizophrenia: neurocognitive endophenotypes. Schizophrenia Bulletin 33 (1), 49–68.
Gur, R.E., Nimgaonkar, V.L., Almasy, L., Calkins, M.E., Ragland, J.D., Pogue-Geile, M.F., Kanes, S., Blangero, J., Gur, R.C., 2007b. Neurocognitive endophenotypes in a multiplex multigenerational family study of schizophrenia. American Journal of Psychiatry 164, 813–819.
Gureje, O., 1988. Neurological soft signs in Nigerian schizophrenics: a controlled study. Acta Psychiatrica Scandinavica 78 (4), 505–509.
Hasler, G., Drevets, W.C., Gould, T.D., Gottesman, I.I., Manji, H.K., 2006. Toward constructing an endophenotype strategy for bipolar disorders. Biological Psychiatry 60, 93–105.
Hasler, G., Drevets, W.C., Manji, H.K., Charney, D.S., 2004. Discovering endophenotypes for major depression. Neuropsychopharmacology 29, 1765–1781.
Heinrichs, R.W., 2001. Search of Madness—Schizophrenia and Neuroscience. Oxford University Press, New York.
Heinrichs, R.W., 2005. The primacy of cognition in schizophrenia. American Psychologists 60 (3), 229–242.
Heinrichs, R.W., Miles, A.A., Smith, D., Zargarian, T., Goldberg, J.O., Ammari, N., McDermid Vaz, S. Cognitive, clinical and functional characteristics of verbally superior schizophrenia patients. Neuropsychology, in press.
Heinrichs, D.W., Buchanan, R.W., 1988. Significance and meaning of neurological signs in schizophrenia. American Journal of Psychiatry 145, 11–18.
Heinrichs, R.W., Zakzanis, K.K., 1998. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 12, 426–445.
Heinz, A., Braus, D.F., Smolka, M.N., Wrase, J., Puls, I., Hermann, D., Klein, S., Grusser, S.M., Flor, H., Schumann, G., Mann, K., Buchel, C., 2005. Amygdala-prefrontal coupling on a genetic variation of the serotonin transporter. Nature Neuroscience 8, 20–21.
Hennah, W., Tomppo, L., Hiekkalinna, T., Palo, O.M., Kilpinen, H., Ekelund, J., et al., 2007. Families with the risk allele of DISC1 reveal a link between schizophrenia and another component of the same molecular pathway, NDE1. Human Molecular Genetics 16, 453–462.
Hyde, T.M., Goldberg, T.E., Egan, M.F., Lener, M.C., Weinberger, D.R., 2007. Frontal release signs and cognition in people with schizophrenia, their siblings and healthy controls. British Journal of Psychiatry 191, 120–125.
Ismail, B., Cantor-Graae, E., Cardenal, S., McNeil, T.F., 1998a. Neurological abnormalities in schizophrenia: clinical, etiological and demographic correlates. Schizophrenia Research 30, 229–238.
Ismail, B., Cantor-Graae, E., McNeil, T.F., 1998b. Neurological abnormalities in schizophrenic patients and their siblings. American Journal of Psychiatry 155 (1), 84–89.
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.
James, J.W., 1971. Frequency in relatives for an all-or-none trait. Annal Human Genetics 35, 47–49.
Karp, B.I., Garvey, M., Jacobsen, L.K., Frazier, J.A., Hamburger, S.D., Bedwell, J.S., Rapoport, J.L., 2001. Abnormal neurologic maturation in adolescents with early-onset schizophrenia. American Journal of Psychiatry 158, 118–122.
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.
Keshavan, M.S., Sanders, R.D., Sweeney, J.A., et al., 2003. Diagnosis specificity and neuroanatomical validity of neurological abnormalities in first-episode psychoses. American Journal of Psychiatry 160 (7), 1298–1304.
Kinney, D.K., Woods, B.T., Yurgelun-Todd, D., 1986. Neurologic abnormalities in schizophrenic patients and their families. II: Neurologic and psychiatric findings in relatives. Archives of General Psychiatry 43, 665–668.
Kinney, D.K., Yurgelun-Todd, D.A., Woods, B.T., 1999. Neurologic signs of cerebellar and cortical sensory dysfunction in schizophrenics and their relatives. Schizophrenia Research 35 (2), 99–104.
Kolakowska, T., Williams, A.O., Jambor, K., et al., 1985. Schizophrenia with good and poor outcome. III: Neurolgoical "soft" signs, cognitive impairment and their clinical significance. British Journal of Psychiatry 146, 348–357.
Krebs, M., Gut-Fayand, A., Bourdel, M., et al., 2000. Validation and factorial structure of a standardized neurological examination assessing neurological soft signs in schizophrenia. Schizophrenia Research 45, 245–260.
Lawrie, S.M., Byrne, M., Miller, P., Hodges, A., Clafferty, R.A., Cunningham-Owens, D.G., Johnstone, E.C., 2001. Neurodevelopmental indices and the development of psychotic symptoms in subjects at high risk of schizophrenia. British Journal of Psychiatry 178, 524–530.
Lenzenweger, M.F., 1998. Schizotypy and schizotypic psychopathology: Mapping an alternative expression of schizophrenia liability. In: Lenzenweger, M.F., Dworkin, R.H. (Eds.), Origins and development of schizophrenia: Advances in experimental psychopathology. American Psychological Association, Washington, DC.
Lenzenweger, M.F., 2006. Schizotaxia, schizotypy, and schizophrenia: Paul E. Meehl's blueprint for the experimental psychopathology and genetics of schizophrenia. Journal of Abnormal Psychology 115 (2), 195–200.
Malla, A.K., Norman, R.M., Aguilar, O., et al., 1997. Relationship between "soft signs" and syndromes of schizophrenia. Acta Psychiatrica Scandinavica 96, 274–280.
Marcus, J., Hans, S.L., Lewow, E., Wilkinson, L., Burack, C.M., 1985. Neurological findings in high-risk children: childhood assessment and 5-year follow up. Schizophrenia Bulletin 11, 85–100.
McGuffin, P., Owen, M.J., Gottesman, I.I., 2004. Psychiatric Genetics and Genomics. Oxford University Press, London & NYC.
Meehl, P.E., 1962. Schizotaxia, schizotypy, schizophrenia. American Psychologist 17, 827–838.
Meehl, P.E., 1990. Toward an integrated theory of schizotaxia, schizotypy, and schizophrenia. Journal of Personality Disorders 4, 1–99.
Merriam, A.E., Kay, S.R., Opler, L.A., Kushner, S.F., van Praag, H.M., 1990. Neurological signs and the positive–negative dimension in schizophrenia. Biological Psychiatry 28 (3), 181–192.
Meyer-Lindenberg, A., Weinberger, D.R., 2006. Intermediate phenotypes and genetic mechanisms of psychiatric disorders. Nature Reviews Neuroscience 7, 818–827.
Mitchell, R., 2002. UK launches ambitious tissue/data project. Nature Biotechnology 20, 529.
Mohr, F., Hubmann, W., Albus, M., et al., 2003. Neurological soft signs and neuropsychological performance in patients with first episode schizophrenia. Psychiatry Research 121 (1), 21–30.
Mohr, F., Hubmann, W., Cohen, R., Bender, W., Haslacher, C., Honicke, S., et al., 1996. Neurological soft signs in schizophrenia: assessment and correlates. European Archives of Psychiatry and Clinical Neuroscience 246 (5), 240–248.
Niemi, L.T., Suvisaari, J.M., Haukka, J.K., Lonnqvist, J.K., 2005. Childhood predictors of future psychiatric morbidity in offspring of mothers with psychotic disorder: results from the Helsinki high-risk study. British Journal of Psychiatry 186, 108–114.
Niethammer, R., Weisbrod, M., Schiesser, S., Grothe, J., Maier, S., Peter, U., Kaufmann, C., Schroder, J., Sauer, H., 2000. Genetic influence on laterality in schizophrenia? A twin study of neurological soft signs. American Journal of Psychiatry 157, 272–274.
Owen, M.J., Williams, N., O'Donovan, M., 2003. The molecular genetics of schizophrenia: new findings promise new insights. Molecular Psychiatry 9, 14–17.
Owen, M.J., Craddock, N., Jablensky, A., 2007. The genetic deconstruction of psychosis. Schizophrenia Bulletin 33, 905–911.
Palo, O.M., ANtila, M., Silander, K., Hennah, W., Kilpinen, H., Soronen, P., Tuulio-Henriksson, A., Kieseppa, T., Partonen, T., Lonnqvist, J., Peltonen, L., Paunio, T., 2007. Association of distinct allelic haplotypes of DISC1 with psychotic and bipolar spectrum disorders and with underlying cognitive impairments. Human Molecular Genetics 16, 2517–2528.
Pan, W., Lynn, K., Chen, C., Wu, Y., Lin, C., Chang, H., 2006. Using endophenotypes for pathway clusters to map complex disease genes. Genetic Epidemiology 30, 143–154.
Park, S., Holzman, P.S., Goldman-Rakic, P.S., 1995. Spatial working memory deficits in the relatives of schizophrenic patients. Archives of General Psychiatry 52, 821–828.
Pezawas, L., Meyer-Lindenberg, A., Drabant, E.M., Verchinski, B.A., Munoz, K.E., Kolachana, B.S., Egan, M.F., Mattay, V.S., Hariri, A.R., Weinberger, D.R., 2005. 5-HTTLPR polymorphism impacts human cingulated-amygdala interactions: a genetic susceptibility mechanism for depression. Nature Neuroscience 6, 828–834.
Potash, J.B., Vilour, V., Chiu, Y., 2001. The familial aggregation of psychotic symptoms in bipolar disorder pedigrees. American Journal of Psychiatry 158, 1259–1264.
Prescott, C.A., Gottesman, I.I., 1993. Genetically mediated vulnerability to schizophrenia. Psychiatric Clinics of North America 16, 245–268.
Rao, H., Di, X., Chan, R.C.K., Ding, Y., Ye, B., Gao, D. A regulation role of prefrontal cortex in the Fist-Edge-Palm task: evidence from functional connectivity analysis, submitted for publication.

Risch, N., Merikangas, K., 1996. The future of genetic studies of complex human diseases. Science 273, 1516–1517.
Roger, D., 1992. Motor Disorder in Psychiatry. John Wiley, Chicheser.
Ross, D.E., Buchanan, R.W., Medoff, D., Lahti, A.C., Thaker, G.K., 1998. Association between eye tracking disorder in schizophrenia and poor sensory integration. American Journal of Psychiatry 155 (10), 1352–1357.
Rossi, A., De Cataldo, S., Di Michele, V., Manna, V., Ceccoli, S., Stratta, P., Casacchia, M., 1990. Neurological soft signs in schizophrenia. British Journal of Psychiatry 157, 735–739.
Rosenthal, D., Kety, S.S. (Eds.), 1968. The Transmission of Schizophrenia. Pergamon, Oxford.
Rubin, P., Vorstrup, S., Hemmingsen, R., Andersen, H.S., Bendsen, B.B., Stromso, N., Iarsen, J.K., Bulwig, I.G., 1994. neurological abnormalities in patients with schizophrenia or schizophreniform disorder at first admission to hospital: correlations with computerized tomography and regional cerebral blood flow findings. Acta Psychiatrica Scandinavian 90, 385–390.
Rybicki, B.A., Elston, R.C., 2000. The relationship between the sibling recurrence risk ratio and genotype relative risk. American Journal of Human Genetics 66, 593–606.
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.
Sanders, R.D., Keshavan, M.S., Forman, S.D., Pieri, J.N., McLaughlin, N., Allen, D.N., van Kammen, D.P., Goldstein, G., 2000. Factor structure of neurologic examination abnormalities in unmedicated schizophrenia. Psychiatry Research 95, 237–243.
Sanders, R.D., Keshavan, M.S., Schooler, N.R., 1994. Neurological examination abnormalities in neuroleptic-naïve patients with first break schizophrenia: preliminary results. American Journal of Psychiatry 151, 1231–1233.
Sanders, R.D., Schuepbach, D., Goldstein, G., Haas, G.L., Sweeney, J.A., Keshavan, M.S., 2004. Relationships between cognitive and neurological performance in neuroleptic-naïve psychosis. Journal of Neuropsychiatry and Clinical Neuroscience 16 (4), 480–487.
Schroder, J., Essig, M., Baudendistel, K., Jahn, T., Gerdsen, I., Stockert, A., Schad, L.R., Knopp, M.V., 1999. Motor dysfunction and sensorimotor cortex activation changes in schizophrenia: a study with functional magnetic resonance imaging. Neuroimage 9, 81–87.
Schroder, J., Geider, F.J., Binkert, M., et al., 1992a. Subsyndromes in chronic schizophrenia: do their psychopathological characteristics correspond to cerebral alterations? Psychiatry Research 42, 209–220.
Schroder, J., Niethammer, R., Geider, F.J., et al., 1992b. Neurological soft signs in schizophrenia. Schizophrenia Research 6, 25–30.
Schroder, J., Niethammer, R., Geider, F.J., Reitz, C., Binkert, M., Jauss, M., Sauer, H., 1991. Neurological soft signs in schizophrenia. Schizophrenia Research 6, 25–30.
Schroder, J., Wenz, F., Schad, L.R., Baudendistel, K., Knopp, M.V., 1995. Sensorimotor cortex and supplementary motor area changes in schizophrenia: a study with functional magnetic resonance imaging. British Journal of Psychiatry 167, 197–201.
Schuber, 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 (6), 1030–1037.
Schwab, S.G., Knapp, M., Mondabon, S., Hallmayer, J., Bormann-Hassenbach, M., Albus, M., et al., 2003. Support for association of schizophrenia with genetic variation in the 6p22.3 gene, dysbindin, in sib-pair families with linkage and in an additional sample of triad families. American Journal of Human Genetics 72, 185–190.
Shifman, S., Bronstein, M., Sternfeld, M., Pisante-Shalom, A., Lev-Lehman, E., Weizman, A., et al., 2002. A highly significant association between a COMT haplotype and schizophrenia. American Journal of Human Genetics 71, 1296–1302.
Simpson, G.M., Angus, J.W.S., 1970. Drug induced extrapyramidal disorders. Acta Psychiatrica Scandinavica 212 (Suppl.), 1–58.
Sing, C.F., Stengard, J.H., Kardia, S.L.R., 2003. Genes, environment, and cardiovascular disease. Arteriosclerosis, Thrombosis, and Vascular Biology 23, 1190–1196.
Smith, R.C., Hussain, M.I., Chowdhury, S.A., Stearns, A., 1999a. Stability of neurological soft signs in chronically hospitalized schizophrenic patients. Journal of Neuropsychiatry and Clinical Neuroscience 11, 91–96.
Smith, R.C., Kadewari, R.P., Rosenberger, J.R., Bhattacharyya, A., 1999b. Non-responding schizophrenia: differentiation by neurological soft signs and neuropsychological tests. Schizophrenia Bulletin 25 (4), 813–825.
Snitz, B.E., MacDonald III, A.W., Carter, C.S., 2006. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. Schizophrenia Bulletin 32, 179–194.
Stefansson, H., Sigurdsson, E., Steinthorsdottir, V., Bjornsdottir, S., Sigmundsson, T., Ghosh, S., et al., 2002. Neuregulin 1 and susceptibility to schizophrenia. American Journal of Human Genetics 71, 877–892.
Straub, R.E., Lipska, B.K., Egan, M.F., Goldberg, T.E., Callicott, J.H., Mayhew, M.B., Vakkalanka, R.K., Kolachana, B.S., Kleinman, J.E., Weinberger, D.R., 2007. Allelic variation in GAD1 (GAD(67)) is associated with schizophrenia and influences cortical function and gene expression. Molecular Psychiatry 12 (9), 854–869.
Talkowski, M.E., Chowdari, K.V., Lewis, D.A., Nimgaonkar, V.L., 2006. Can RGS4 polymorphisms be viewed as credible risk factors for schizophrenia? A critical review of the evidence. Schizophrenia Bulletin 32 (2), 203–208.
Torrey, E.F., Bowler, A.E., Taylor, E.H., Gottesman, I.I., 1994. Schizophrenia and Manic-Depressive Disorder: The Biological Roots of Mental Illness as Revealed by the Landmark Study of Identical Twins. Basic Books, New York, NY.
Tsuang, M.T., Faraone, S.V., 1999. The concept of target features in schizophrenia research. Acta Psychiatrica Scandinavica 395 (Suppl.), 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.
Turunen, J.A., Peltonen, J.O., Pietilainen, O.P., Hennah, W., Loukoa, A., Paunio, T., Silander, K., Ekelund, J., Varilo, T., Partonen, T., Lonnqvist, J., Peltonen, L., 2007. The role of DTNBP1, NRG1, and AKT1 in the genetics of schizophrenia in Finland. Schizophrenia Research 91 (1–3), 27–36.
Umetsu, A., Okuda, J., Fujii, T., Tsukiura, T., Nagasaka, T., Yanagawa, I., Sugiura, M., Inoue, K., Kawashima, R., Suzuki, K., Tabuchi, M., Murata, T., Mugikura, S., Higano, S., Takahashi, S., Fukuda, H., Yamadori, A., 2002. Brain activation during the Fist-Edge-Palm test: a functional MRI study. Neuroimage 17, 385–392.
Valles, V., van Os, J., Guillamat, R., 2000. Increased morbid risk for schizophrenia in families of in-patients with bipolar illness. Schizophrenia Research 42, 83–90.
Waldman, I.D., Nigg, J.T., Gizer, I.R., Park, L., Rappley, M.D., Friderici, K., 2006. The adrenergic receptor α-2A gene (ADRA2A) and neuropsychological executive functions as putative endophenotypes for childhood ADHD. Cognitive, Affective & Behavioral Neuroscience 6 (1), 18–30.
Walters, J.T.R., Owen, M.J., 2007. Endophenotypes in psychiatric genetics. Molecular Psychiatry 12, 886–890.
Weinberger, D.R., Wyatt, R.J., 1982. Cerebral ventricular size: a biological marker for subtyping schizophrenia. In: Usdin, F., Hanin, I. (Eds.), Biological Markers in Psychiatry and Neurology. Pergamon Press, Oxford, UK, pp. 505–512.
Whitty, P., Clarke, M., Browne, S., McTigue, O., Kamali, M., Feeney, L., Lane, A., Kinsella, A., Waddington, 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.
Wong, A.H.C., Gottesman, I.I., Petronis, A., 2005. Phenotypic differences in genetically identical organisms: the epigenetic perspective. Human Molecular Genetics 14, 11–18.
Wong, A.H.C., Voruganti, L.N.P., Heslegrave, R.J., 1997. Neurocognitive deficits and neurological signs in schizophrenia. Schizophrenia Research 23, 139–146.
Woods, B.T., Kinney, D.K., Yurgelun-Todd, D., 1991. Neurological hard signs and family history of psychosis in schizophrenia. Biological Psychiatry 30, 806–816.
Yazici, A.H., Demir, B., Yazici, K.M., Gogus, A., 2002. Neurological soft signs in schizophrenic patients and their nonpsychotic siblings. Schizophrenia Research 58 (2–3), 241–246.
Yee, B.K., Keist, R., von Boehmer, L., Studer, R., Benke, D., Hagenbuch, N., Dong, Y., Malenka, R.C., Fritschy, J.M., Bluethmann, H., Feldon, J., Mohler, H., Rudolph, U., 2005. A schizophrenia-related sensorimotor deficit links α3-containing $GABA_A$ receptors to a dopamine hyperfunction. Proceedings of National Academy of Sciences 22 (102), 17154–17159.
Zalla, T., Joyce, C., Szoke, A., Schurhoff, F., Pillon, B., Komano, O., Perez-Diaz, F., Bellivier, F., Alter, C., Dubois, B., Rouillon, F., Houde, O., Leboyer, M., 2004. Executive dysfunctions as potential markers of familial vulnerability to bipolar disorder and schizophrenia. Psychiatry Research 121, 207–217.