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ENDOPHENOTYPES IN STUDIES OF THE GENETICS OF SCHIZOPHRENIA

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The power and appeal of the molecular biology mantra, ''DNA to RNA to protein,'' to explicate cell biology comes from its universal appearance and application in all species, from microorganisms to human beings. Based on this mantra, the genomes of viruses, bacteria, fruit flies, and now humans are being mapped and sequenced, so that all the genes and, ultimately, their corresponding biological activity can be identified. As these genes are identified, it is reasonable to ask how this information can be related to the inheritance of risk for psychiatric illness. For a bacterial enzyme, genetic coding of the amino acid sequence of proteins can be closely associated with a functional change in enzymatic activity. For a complex psychiatric illness, as defined by DSM-IV criteria, the relationship is obviously not as straightforward. Psychiatric illnesses such as schizophrenia are generally conceptualized as multifactorial and most likely reflect the combined influence and interactions of both genetic and nongenetic factors. Furthermore, there is no reason to presuppose that only one gene is responsible for a complex psychiatric disorder such as schizophrenia, as there is in some simple mendelian illnesses. Persons who are ill may differ in more than one gene from the rest of the population, and different sets of genes may be associated with illness in different populations. Thus, how best to use the power of molecular genetics to understand the inheritance and pathophysiology of complex genetic psychiatric illnesses remains an enigma that is only now beginning to be solved.

In the simplest and most commonly used strategy of molecular genetics that is applied to complex psychiatric disorders, it is assumed that the distribution of illness in a family represents the effect of a single gene, and techniques of genetic analysis are used to identify that gene. This approach does not necessarily overlook the complexity of psychiatric illness, but it assumes that the effect (i.e., signal) of a single gene will be discerned in a complex, ''noisy'' genetic background if samples sizes are large enough or if the population is sufficiently homogeneous (e.g., 1). An attractive feature of this approach is that the search for genes is not constrained by preexisting hypotheses about the biology of the illness, which, in the case of schizophrenia, is still unclear. A second commonly applied strategy is, in fact, the opposite approach; an assumption is made about the biology of the illness and then candidate genes associated with that biology are examined to determine if they are mutated. Both approaches have been successful to a limited extent for explicating the genetics of schizophrenia. Replicable linkages for schizophrenia have been obtained at several locations (e.g., chromosomes 1, 6, 8, 13, 15, and 22), but genetic mutations have not as yet been identified at these sites (2). On the other hand, DNA mutations have been found in candidate genes such as *NURR1,* the gene for the receptor for retinoic acid, a pathway critical in neuronal development, but these mutations seem to be found in only a small proportion of schizophrenic patients (3).

This chapter describes a third approach, which attempts to make use of the power of the molecular biology mantra by identifying brain dysfunctions that may be caused by a single genetic abnormality. The rationale comes from the mantra itself. If discrete genetic abnormalities are associated with schizophrenia, then each of them should cause a specific protein change that is reflected in a corresponding discrete functional abnormality. Even if several genes are abnormal, along with additional environmental factors, the functional abnormality resulting from each gene should generally be identifiable. Theoretically, the relationship between these functional abnormalities and genes, discovered either by genetic linkage or by candidate gene analysis, should be stronger than the association to the illness itself because the illness itself results from a mixture of genetic and nongenetic abnormalities that may vary between different individuals and families. As is true for the other approaches described above, this approach has not yet led to the identifi-

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cation of the genes that are associated with and that may even cause schizophrenia in most cases. Nevertheless, the strategy has been useful for gene discovery in other complex illnesses, such as colon cancer and hemochromatosis. In colon cancer, the formation of multiple polyps, rather than cancer itself, has been found to be the genetically heritable trait (4), and in hemochromatosis, a high serum level of iron, rather than the clinically recognized illness, has been found to be the more penetrant heritable trait (5).

Endophenotype is often used as the descriptive term for these discrete, genetically determined phenotypes that may be part of a complex illness. The search for endophenotypes is not straightforward because no *a priori* criterion can be used to decide if a particular element of schizophrenia or any other psychiatric illness reflects the effect of a single gene. Putative endophenotypes have ranged from clinical characterizations, such as the presence of schizotypy in relatives of schizophrenic patients (6), to the neurophysiologic and neuropsychological measures described in this chapter, to structural measures of specific, functionally important regions of the brain and ventricular size. Because none of these phenotypes has yet led to the identification of a specific molecular deficit, it has not been proved that any one of them is actually linked to a specific genetic abnormality. In this context, even if endophenotypes turn out to be multiple, rather than single, gene phenomena, their genetic architecture, even as complex endophenotypes, may turn out to be simpler than schizophrenia in certain families. The sections below outline the stage of investigation for a number of putative phenotypes, from presence in schizophrenia probands and their relatives to statistically significant genetic linkage to a chromosomal locus.

Several points must be considered in the assessment of endophenotypes. First, because these are putative genetic traits, their biology begins at conception, so that by the time they are measured in adulthood, their expression may have been modified by such factors as development, aging, brain injury, and medication and substance abuse and. Second, most genes expressed in the brain are expressed in many different brain areas, so that their ultimate functional expression may involve much more than the simple phenotype being measured. Third, many genes expressed in the brain are also involved in the development of neurons, so that their most important functional effects may have occurred prenatally. Fourth, according to Mendel's second law, every genetic trait segregates independently in a family,

TABLE 51.1. ENDOPHENOTYPES AND THE GENETICS OF SCHIZOPHRENIA: EFFECT SIZE DIFFERENCES BETWEEN SCHIZOPHRENIA SPECTRUM GROUPS AND NORMAL COMPARISON SUBJECTS

Phenotypes	Schizophrenia Patients	Clinically Unaffected Relatives of Schizophrenia Patients	Schizotypal Personality Disorder Patients	References
P50 Suppression	0.92–1.29	0.79	0.79	30, 31, 203
Prepulse Inhibition	0.51–0.85	1.0	1.45	46, 47, 54
Smooth-Pursuit Eye Movement	2.0–3.0	0.29–1.3	0.29	92, 93, 204
Antisaccade	4.88–6.38	1.38–3.75	0.75–1.36	101, 204
Executive Functioning (Wisconsin Card Sorting Test)	0.47–1.97	0.73–1.6	0.72	118, 126, 127, 132
Working Memory (Letter–Number Span)	1.42–2.2	0.42	0.73–1.04	126, 132, 205
Thought Disorder (Thought Disorder Index; Ego Impairment Index)	1.56–2.98	0.34–0.83	1.04–1.28	204, 206–208
Continuous Performance Test	0.45–3.30	0.46–2.97	0.45–0.78	118, 139, 140, 147
Span of Apprehension	0.5–2.5	0.6–1.5		139, 152, 209–212
Visual Backward Masking	0.33–0.65	0.43–0.57	0.45–0.67	168, 173, 213, 214
P300 Event–Related Potential	0.45–1.05	0.17	0.36	192, 215
Reaction Time	0.59–1.05	0.44	0.79–0.99	168, 216, 217

Effect sizes in schizophrenia patients, clinically unaffected relatives of schizophrenia patients, and schizotypal personality disorder patients compared with those in normal subjects. These effect sizes were computed by using the means and standard deviations for the normal comparison subjects and the means of the patient groups. The range of values differs from study to study because different investigators used different patient populations taking different types and amounts of medications; also, the experimental paradigms, although similar, often differed in terms of stimulus parameters. Of course, in some of these studies, multiple conditions were used, some of which were needed to establish floor and ceiling effects. In these cases, we generally cite the most robust effect sizes.

so that if schizophrenia is a multifactorial trait, some siblings should express specific phenotypes independently of other phenotypes. These siblings may be better subjects for characterizing the phenotype than the patients themselves, whose multiple deficits may obscure the unique phenotype. Finally, because the aim of genetics generally is to identify affected individuals who have or do not have a particular genetic abnormality, the measurement of the putative phenotype must clearly separate most affected and unaffected individuals, regardless of whether a quantitative or discrete variable is used. The range of effect sizes for several putative endophenotypes is shown in Table 51.1, which reflects another point. The measurement of endophenotypes is in itself a complex endeavor in which modest-appearing paradigmatic manipulations lead to significant shifts in the signal of the dependent measure being assessed.

The search for endophenotypes takes advantage of genetic strategies to evaluate the current state of understanding the pathophysiology of schizophrenia. The initial endophenotype was schizotypy, which was proposed to be a pure expression of schizotaxia, the genetic predisposition for schizophrenia. Schizotypy itself does not generally show mendelian segregation, so that the likelihood that it reflects a single genetic trait is now considered small. However, the presence of schizotypy in family members has been related to linkage of schizophrenia at a specific chromosomal locus in a subset of families, so that a reexamination of schizotypy as an endophenotype in some families may once again be productive. Inhibitory interneurons have increasingly become a focus of interest in the biology of schizophrenia. Many of the endophenotypes described below are attempts to demonstrate inhibitory neuronal function by means of psychophysiologic and neurophysiologic techniques. Structural phenotypes have been limited to the measurement of brain volume. As functional brain-imaging techniques become more advanced, so that specific neuronal functions can be demonstrated, it is likely that these techniques will also be used. Magnetic resonance spectroscopy of the amino acids associated with neuronal function, such as *N*-acetylasparate, is an example (7).

CANDIDATE ENDOPHENOTYPES FOR GENETIC STUDIES

Given the considerations discussed above, it is important to stress that although the DSM-IV diagnostic criteria for schizophrenia may be clinically and administratively useful, they are not likely to be optimally useful as phenotypes in genetic studies (8–11). The search for and use of new, nondiagnostic, non–DSM-IV-based candidate endophenotypes parallels our search for the corresponding candidate genes in complex human genetic disorders such as schizophrenia. Also, we understand that in accounting for the genetic diathesis or vulnerability to schizophrenia, we are "accounting" for, at most, 50% to 70% of the variance of the disorder; the remaining variability resides in nongenetic "second hits," such as neonatal or *in utero* neural damage to the developing hippocampus (12–15) or other factors. A plethora of studies indicate that in addition to mutant genes, a second level of environmental or other generalized or specific stressor probably must act as a second hit in the central nervous system. An example of the result of this need for a second hit is illustrated by the fact that clinically "unaffected" relatives of patients with schizophrenia have endophenotypic markers of abnormalities in some or all of the measures listed below but do not have the disorder of schizophrenia. Therefore, it appears clear that some nongenetic contributions (not necessarily reflected by these endophenotypes) are crucially important in the expression of some forms of this elusively heterogeneous and complex disorder of schizophrenia. In searching for non–diagnosis-based "candidate endophenotypes," we are not alone in schizophrenia research because many disorders, from diabetes to hypertension to bipolar disorder, also present the same conundra and difficult conceptual issues.

In schizophrenia research, it seems reasonable to classify candidate endophenotypes into structural and functional abnormalities. Because of limits of chapter length, we do not discuss structural endophenotypes (e.g., widely dispersed, decreased, generalized gray matter; decreased superior temporal gyrus volume; deficits of hippocampal or temporal lobe volume (16); gray matter volume or organizational abnormalities in various subsections of the prefrontal cortex, most significantly the dorsolateral prefrontal cortex) that may be useful in genetic studies (17,18). It is important to note that such structural abnormalities may be correlated with some of the functional abnormalities discussed below. In Table 51.1, some functional endophenotypes are listed, along with estimates of the effect sizes of deficits of each in schizophrenic patients, clinically unaffected relatives of schizophrenic patients, and schizotypal patients in comparison with normal subjects. In addition, reasonable and well-understood neural substrates for these measures are known, as discussed. Table 51.1 summarizes what we have selected as important and representative (but not all-inclusive) candidate endophenotypes for genetic studies in schizophrenia, with an emphasis on the information-processing abnormalities that have assumed a central role in the search for candidate endophenotypes (10,11). Identifying these endophenotypes for genetic studies is only a first step; after they have been identified, complex strategies must be employed, as discussed above and below, to conduct linkage, association, and other genetic studies on the candidate endophenotypes so that we can identify the candidate genes that are likely contributing to the endophenotypes (and their neural substrates) present in the complex disorder of schizophrenia. In the next section, we describe possible functional endophenotypes, with an emphasis on gating and oculomotor abnormalities.

Abnormalities of Sensorimotor Gating

The concept of deficits of sensory gating in schizophrenia derives from the clinical observation that patients report failures of information processing characterized by poor sensory gating—an inability to screen out trivial stimuli and focus on salient aspects of the environment so as to process information smoothly and successfully navigate through life (10,19,20). Gating functions are commonly assessed with P50 suppression and prepulse inhibition (PPI) of the startle response.

P50 Suppression

Initial studies at the University of Colorado have identified P50 suppression as an important candidate endophenotype in studies of schizophrenia (21–24). In a typical paradigm, P50 suppression occurs when two clicks are presented with a 500-millisecond interval between them. The small P50 event potential wave elicited by the click stimulus can be identified when many trials (e.g., 30 to 100 or more) are performed; this number of trials plus various filtering strategies provides investigators with a robust signal-to-noise ratio for identifying and quantifying the P50 wave. A P50 wave is generated to the first click and another to the second click. Across multiple studies, it has been found that the second P50 wave is normally suppressed; suppression can probably be attributed to the activation of inhibitory processing and circuitry by the first P50 stimulus. In normal subjects, the second P50 wave typically is diminished by 80% in comparison with the first wave (Fig. 51.1).

Initial studies (21–24) demonstrated an expected failure of suppression in schizophrenic patients, consistent with theories of failed inhibitory function or impaired sensorimotor gating in schizophrenia (25). These studies of deficits in P50 suppression in schizophrenic patients have been widely replicated (26–31). The failure of P50 suppression in schizophrenic patients is not necessarily specific to this one disorder. For example, Franks et al. (32) reported that P50 suppression is also deficient in patients with acute mania but "normalizes" with time, whereas the deficits of P50 suppression are more persistent in schizophrenic patients (32). This finding is consistent with the idea that genetic "diatheses" may be shared between schizophrenia and mania. P50 suppression deficits have also been shown (and replicated) in "clinically unaffected" family members of schizophrenic patients (24,31,33–35). The P50 suppression abnormalities of these family members normalize following administration of the cholinergic nicotinic receptor stimulant nicotine (36), as do those of schizophrenic patients (37). This finding has raised interest in the critical importance of the cholinergic system in P50 suppression, and some of the cholinergic neurobiological substrates of P50 suppression deficits have been elucidated.

As discussed in the section on PPI, suppression is probably the function of a more wide-ranging neural circuitry prominently involving hippocampal structures (38). The use of P50 suppression as a candidate endophenotype in genetic studies is probably the most advanced of any of the endophenotypes we discuss here; a specific linkage of P50 suppression with a genetic marker at the locus of the α_7 subunit of the nicotinic receptor gene (11) has been identified in the first study linking a candidate endophenotype of information processing in schizophrenia to a specific

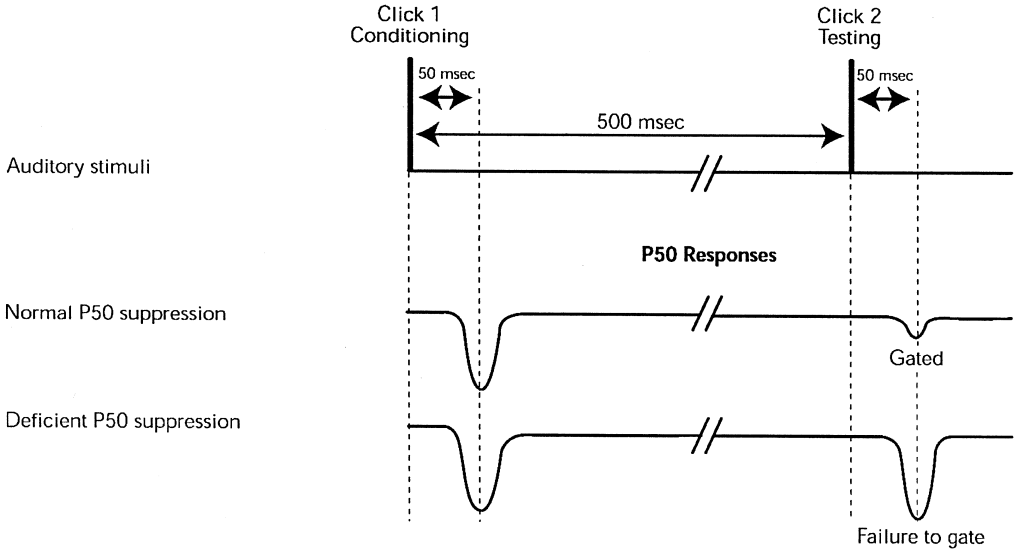

FIGURE 51.1. Pairs of auditory clicks are presented to subjects and EEG is averaged across trials. The P50 component of the auditory event-related potential is measured in response to the first and second clicks.

chromosomal region. It is important to stress that these types of studies do not identify a "schizophrenia endophenotype," but rather the linkage of deficits in P50 suppression (characteristic of schizophrenia) to a specific chromosome region. Future studies will have to identify the specific genetic deficit(s) (e.g., specific single-nucleotide polymorphisms) associated with abnormalities of P50 suppression.

In terms of our assessment of candidate endophenotypes and genetic studies, it is important to note that medications have an influence on P50 suppression abnormalities in schizophrenia. It appears that atypical antipsychotic medications may reverse the P50 suppression deficits in schizophrenic patients (39–42). If these initial results continue to be confirmed, the search for candidate endophenotypes will be complicated by the fact that atypical (and perhaps, in some circumstances, typical) antipsychotic medications are increasingly being utilized as first-line agents in the treatment of schizophrenia. We may thus face the circumstance of examining schizophrenic patients whose P50 suppression deficits have been "normalized" and then conducting family studies in which these deficits may appear in unaffected relatives of schizophrenic patients. Should this occur, genetic statistical strategies will have to be utilized that will allow us to "exclude" the "normalized" schizophrenic patient from analysis and utilize only clinically unaffected family members in genetic (e.g., linkage) studies. Much more information will be generated in the next several years, and the use of what we would term *"null proband" strategies* may be necessary as schizophrenic patients who are not medicated or are neuroleptic-naïve become more difficult to ascertain and are replaced by patients treated with atypical antipsychotic medications. In addition, the use of drug withdrawal strategies to unmask endophenotypic markers has come under increasing criticism (43) and is becoming more difficult to justify ethically in comparison with other promising research strategies (e.g., 44).

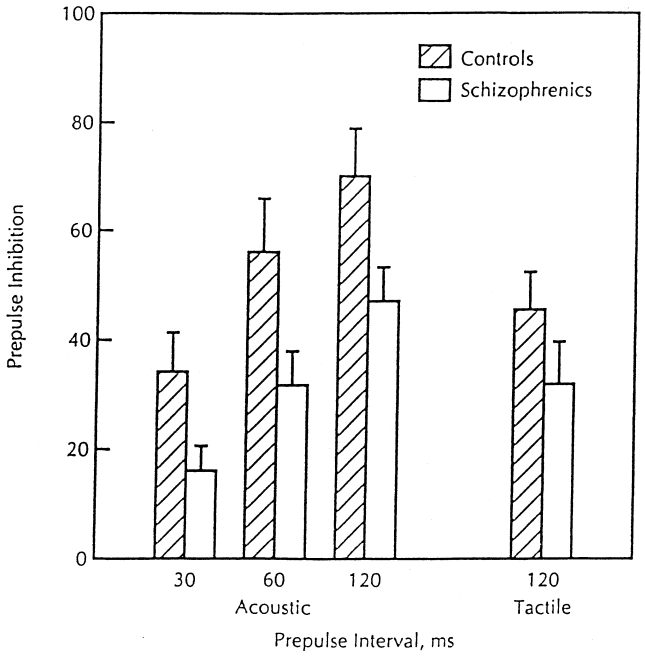

FIGURE 51.2. Across all prepulse-to-pulse intervals tested, the schizophrenic patients showed a loss of gating effect of the prepulse that preceded the startle stimulus. (From Braff DL, Grillon C, Geyer MA. Gating and habituation of the startle reflex in schizophrenic patients. *Arch Gen Psychiatry* 1992;49:206–215, with permission.)

Prepulse Inhibition of the Startle Response

Since 1978 (45), PPI deficits of the startle response have been consistently identified in schizophrenic patients. PPI of the startle response occurs as follows. Normally, an intense and powerful sensory stimulus elicits a whole-body startle response in almost all mammals. This rapid, intense sensory stimulus may be sound or light, or it may be tactile (e.g., an air puff). When a weak prestimulus precedes the startling stimulus by approximately 100 milliseconds, PPI occurs. Schizophrenic patients and their relatives show deficits in PPI (45–54) (Fig. 51.2). This is the second commonly studied form of sensorimotor gating (along with P50 suppression) (see ref. 25 for a discussion of gating abnormalities in schizophrenia). PPI is being increasingly used in schizophrenia research. It is important to distinguish the PPI paradigm described above from a similar but quite distinct paradigm in which attentional allocation to the prepulse (55) is used in an attempt to increase the degree of PPI. The PPI paradigm typically used in schizophrenia research, described above, is a "neutral" or "uninstructed" paradigm that largely taps into involuntary and automatic information processing (56); the instructed paradigm is different because subjects attend to the prepulse and thus the paradigm identifies so-called voluntary attentional deficits. This section describes the more widely studied uninstructed PPI.

Much like deficits of P50 suppression, PPI deficits are not unique to schizophrenia. PPI deficits are characteristic of a "family" of disorders in which cognitive, sensory, and motor information undergoes a failure of gating. Patients with gating disorders include those with schizophrenia (45–53), obsessive-compulsive disorder (with obsessive and ungated ideas) (57), and Huntington syndrome (58) and Tourette syndrome (59) (with ungated motor activity).

The clinical correlates of PPI in schizophrenia comprise a rich database. PPI deficits have been correlated with distractibility (60), perseverative responses on the Wisconsin Card Sorting Test (61), and most prominently thought disorder (62), especially when PPI and thought disorder are measured at the same time (63). These deficits are also associated with an earlier age of onset (51). Modest correlations have been found with both positive and negative symptoms, and the symptom correlates may be associated with subcortical dopamine hyperactivity and reciprocal frontal dopa-

mine hypoactivity (47). An initial report has described PPI deficits in clinically unaffected family members of schizophrenic patients (54), and further work is needed to understand the heritability pattern of PPI deficits in family members of schizophrenic patients. Much of what is known about the neural substrate of PPI can be attributed to the extensive work of Swerdlow, Geyer, Braff, and their associates. It appears that PPI is modulated mostly by the ventral cortico-striato-pallido-thalamic (CSPT) circuitry originally described by Swerdlow and Koob (64), based on the pioneering work of Penney, Alexander, and Young on the dorsal loci of the CSPT circuits. The circuitry cannot be described in detail here, but lesion infusion studies and a variety of other strategies have established the animal model of PPI deficits in schizophrenia as a robust area of study (65–67). For example, in rat pups with ventral hippocampal lesions, PPI levels are normal until adolescence, when PPI deficits appear (68,69), a finding that supports the neurodevelopmental model of PPI deficits as it applies to an integrated model of schizophrenia. Apomorphine used as a dopamine D2 agonist induces PPI deficits that are reversible with typical or atypical antipsychotic medications. Phencyclidine induces PPI deficits that are differentially reversed by atypical (but not typical) antipsychotic medications. The interested reader is referred to Swerdlow et al. (70) for further discussion of these issues.

Some initial results utilizing between-subjects rather than the more compelling within-subjects designs indicate that PPI deficits in schizophrenic patients may be reversed or ''normalized'' by antipsychotic medications (51,53); however, no linkage studies have utilized PPI, although the genetic contributions to PPI have been elucidated by the fact that PPI levels differ in different rat strains (71), and differential sensitivity to PPI deficits has been observed in these strains (72–74). The increasing use of isolation rearing (75–78) and knockout mice (79–82) in PPI studies will undoubtedly yield much more information about the neural and genetic contributions to PPI. In parallel, human linkage studies (already in progress) are being conducted.

Oculomotor Function

Oculomotor function is another important measure that has been used in schizophrenia research. As in gating, two fundamental paradigms have been utilized: eye tracking, or smooth pursuit, and the antisaccade task. Eye-tracking dysfunction in schizophrenic patients was first reported by Diesendorf and Dodge (83), and their work was later extended by numerous investigators, including Holzman and colleagues (84,85). Across quantitative and qualitative studies, the eye-tracking deficits seen in schizophrenia have been well documented (86–89).

Smooth-Pursuit Eye Movement

In a typical study of smooth-pursuit eye movement, a signal is presented to subjects on a computer screen and their ability to track the target smoothly is assessed. Schizophrenic patients do not track the target smoothly; they exhibit fragmented eye movements and resulting eye movement abnormalities, such as ''catch-up'' saccades. This task has been very useful in family studies; clinically unaffected family members of schizophrenic patients also exhibit eye movement dysfunctions that typically involve an inability to follow a target smoothly, which leads to a variety of abnormalities, including ''catch up'' saccades (85,86,88,90–94). In a series of studies, Siever et al. (95) and others (91,93,96,97) also reported abnormalities of smooth-pursuit eye movement in schizotypal patients.

Antisaccade Task

The antisaccade task has also been widely employed in schizophrenia research as another oculomotor task and as a potential endophenotype. In the antisaccade task, the subject first fixates on a centrally presented visual cue. A target stimulus is then presented to the left or right of the fixation stimulus, and the subject is instructed to look away from the target stimulus; if the stimulus is presented 3 degrees to the left of the fixation point, the subject is expected to look 3 degrees to the right and inhibit the natural tendency to ''follow'' the target to the left. Voluntary inhibitory functions are utilized to suppress the normal tendency to look at the target stimulus and gaze in the opposite direction. This task, like some of the other measures discussed above, uses inhibition and is largely volitional (like smooth-pursuit eye movement) rather than automatic (like gating). Schizophrenic patients show marked deficits in performing this task; an initial gaze directed toward rather than away from the target stimulus is characteristic (98–101). The magnitude (i.e., effect size) of the performance deficits in schizophrenic patients and clinically unaffected family members is large (Table 51.1), and the large difference in effect size between probands and normal comparison subjects makes the antisaccade task an excellent candidate endophenotype for genetic studies (101,102). Within the schizophrenia spectrum, it is notable that antisaccade deficits occur in family members of schizophrenic patients and in patients with schizotypal personality disorder (96,101,103,104). In this way, the antisaccade deficit meets the second criterion for a candidate endophenotype—that is, a candidate endophenotype should appear in clinically unaffected family members of schizophrenic patients (and perhaps in schizotypal patients).

Neuropsychological Tasks

A plethora of candidate endophenotypes have been derived from the neuropsychological literature. It is well-known that schizophrenic patients exhibit a wide range of neuropsychological deficits (105,106) and that these deficits extend to clinically unaffected family members (107). Deficits have

been reported in several important domains: (a) *executive function,* as assessed by the Wisconsin Card Sorting Test (108); (b) *working memory,* as assessed by the Letter–Number Span (109), and (c) *thought disorder,* commonly derived from the processing of stimuli from the Rorschach Test to yield the Thought Disorder Index (110) and the Ego Impairment Index (111). These cognitive dysfunctions are frequently found in family and twin studies in clinically unaffected family members (112–121), schizotypal patients (122–126), and clinically unaffected monozygotic twins discordant for schizophrenia itself (127). The neural substrates of many of these abnormalities are well understood and are being rapidly explicated because these tasks are very well suited to performance during functional brain imaging (e.g., 128). For example, it appears that the Wisconsin Card Sorting Test relies on dorsolateral prefrontal cortex (128–131) and related distributed circuit structures. Working memory utilizes a complex neural substrate that includes the prefrontal cortex and related structures. It important when working memory is utilized to be clear about whether the test assesses simple delayed recall (transient online storage) or the more complex storage, manipulation, and recall (executive functioning) of visuospatial or verbal memory; these are two distinct neuropsychological processes that probably utilize at least partially distinct neural substrates influenced by at least partially different sets of genes (132). Functional imaging experiments in thought disorder are more preliminary, and the neural substrate of thought disorder is now being explicated.

Continuous Performance Task

The Continuous Performance Task (CPT) is another measure that has been widely applied in the study of schizophrenic patients (133–136). In the basic form of this task, the subject is presented with a string of stimuli and asked to identify target stimuli from among background or noise stimuli. The CPT is thought to tap into the function of vigilance; schizophrenic patients commonly have significant deficits in the CPT. The CPT also has the advantage that it can be presented in a variety of ''degraded'' forms in which the signal-to-noise ratio of the stimulus to be identified is attenuated through a variety of parametric manipulations; these make the vigilance and identification task more difficult to perform and may correspondingly increase group separation between schizophrenic patients, their clinically unaffected relatives, and appropriate comparison subjects. The CPT is one of the most thoroughly studied tasks in schizophrenia, in no small degree because of the pioneering work of Nuechterlein et al. (135) and others (137,138) who have consistently demonstrated CPT deficits in schizophrenic patients. The fact that unaffected relatives of patients with schizophrenia (139–145) and schizotypal disorder (146–148) have parallel deficits supports the utility of the task as a candidate endophenotype for genetic studies of information-processing deficits in schizophrenia. These deficits appear to measure stable markers of schizophrenia that may be associated with a genetic vulnerability to the illness and are seen in neuroleptic-naïve, first-break, and neuroleptic-withdrawn schizophrenic patients and their siblings (142).

Span of Apprehension

The utility of Span of Apprehension as a candidate endophenotype, like that of the others measures discussed in this chapter, is supported by a vast amount of literature, only a brief summary of which can be presented here. In its most simplified form, Span of Apprehension refers to the number of items that can be apprehended or attended to and subsequently recalled at one time from an array of stimuli. The interested reader is referred to a particularly scholarly discussion by Asarnow et al. (149). As in the other measures discussed here, the Span of Apprehension has yielded a pattern of interesting results that makes the task another excellent candidate endophenotype in schizophrenia. Additionally, Span of Apprehension deficits have been found in clinically unaffected family members of schizophrenic patients (150–152) and in patients with schizotypal disorder (153, 154). Recently, in a study of normal twins, Bartfai et al. (155) reported a significant genetic component in the Span of Apprehension task, which further strengthens its utility in genetic studies of schizophrenia.

Visual Backward Masking

In Visual Backward Masking, a simple target stimulus presented with a tachistoscope (156–158) or, more recently, a computer (159,160) is followed by a complex, usually powerful masking stimulus of interlocking *X*s that overlap the area of target presentation. A subject reports the target stimulus when it is presented alone. As the masking stimulus appears closer in time to the target (e.g., 100 milliseconds after the target, like the interstimulus interval in PPI experiments), the subject is no longer able identify the target stimulus. Schizophrenic patients are subjected to the effects of the mask on target identification at an interstimulus interval at which normal subjects have little trouble distinguishing the target stimulus (161). Explanations for the masking effect extend from integration of the mask with the target stimulus to interruption of target stimulus processing by the mask (161–164). Whatever the mechanism, the phenomenon is readily identified as a marker in schizophrenic patients (158,165–168), family members of schizophrenic patients (159,160,169), and schizotypal patients (170–173). The specificity of the deficit is unclear, although in one study, manic patients at the height of psychosis showed visual masking deficits that were reversible over time with treatment. In this study, it was reported that the deficits of schizophrenic patients with a good prognosis, who

typically respond to treatment, may also be reversible over time (174). The underlying neural mechanism linked to masking deficits involves the dorsal and ventral information-processing substrates that are supported by magnocellular and parvocellular neurons (175,176). Because both clinically unaffected family members and schizotypal patients exhibit deficits of Visual Backward Masking, it may well serve as an important candidate endophenotype in genetic studies.

P300 Event-Related Potential

Since the initial reports of Callaway and colleagues (177–180) of P300 deficits in schizophrenia, a large number of investigators have identified their topography, lateralization, and neural basis. The results of these studies make the P300 event-related potential an excellent candidate endophenotype for understanding the genetic basis of the deficits.

Schizophrenic patients have long been known to have deficits in the P300 component of the event-related potential (177,178,181). The P300 wave occurs about 300 milliseconds after stimulus presentation and is commonly thought to reflect the apportionment of attention to a stimulus that is relatively novel or rich in information. Many paradigms utilize a series of rather neutral stimuli and then use an ''attention-grabbing'' stimulus to elicit a large P300 wave. Although the variability of the latency properties of the P300 event-related potential wave may account for part of the diminution in schizophrenia, repeated studies report that schizophrenic patients show a decreased P300 wave amplitude over time (182–185). The fact that these deficits are also found in unaffected family members of schizophrenic patients (186–190) and in schizotypal patients (191–193) supports the utilization of the P300 wave as a candidate endophenotype. The original work of Callaway et al. (178) and more recent studies by McCarley and associates (182,194–196) have contributed to an understanding of the P300 neural circuitry that supports the generation of this wave. It appears that the P300 wave is generated from the temporal lobes, perhaps the superior temporal gyrus of the brain. Along with a diminution of the P300 wave in schizophrenic patients, the volume of the superior temporal gyrus gray matter is also diminished. Lateralization findings indicate that it is probably the left P300 wave that is differentially diminished in schizophrenic patients, matching the volume depletion of the left superior temporal gyrus.

Older studies of reaction time and exciting new and evolving studies of mismatch negativity (197) offer a wide range of potentially useful endophenotypes that may prove to be especially interesting in schizophrenia research.

SUMMARY

A multitude of interlocking studies, only some of which have been reviewed here, point to information-processing deficits and closely related inhibitory abnormalities as excellent candidate endophenotypes for genetic studies of schizophrenia. The heritability of several of these candidate endophenotypes has already been assessed in genetic studies. In addition, the neuronal mechanisms of many of the endophenotypes are currently being investigated through neurophysiologic studies in both humans (e.g., functional imaging) and related animal models. The ultimate utility of physiologic endophenotypes may be to correlate the wealth of emerging but nonfunctional genetic information with the critically important and functionally significant underlying neurobiology of these endophenotypes. The task of identifying genes that convey a risk for schizophrenia is now under way, generally with the use of either the clinical phenotype of schizophrenia or risk-related endophenotypes. Findings that many of the linkage sites are positive for both schizophrenia and bipolar disorder (e.g., 198) will undoubtedly stimulate a reexamination of what aspect of psychotic psychopathology is being transmitted at each genetic locus, and which nongenetic factors, such as neonatal ventral hippocampal lesions, interact with these genes to produce schizophrenia (e.g., 68) versus bipolar disorder. Additionally, within cohorts of schizophrenic patients, some of these information-processing endophenotypes overlap with each other, both behaviorally and in terms of their underlying neural substrates. This allows for the exciting possibility of constructing ''composite'' phenotypes consisting of neurologically coherent combinations of more than one of these identified markers (102).

As the molecular mantra states, the fundamental unit of genetic transmission is an abnormality in the structure or expression of a protein. Presumably, most of those protein abnormalities affect neuronal functions that can be measured as changes in physiologic functions, such as the endophenotypes we have described above. The elucidation of how different genetic abnormalities, singly or in combination, contribute to the neuronal pathophysiology of psychosis may help to redefine the nosology of psychotic illnesses and point the way to new treatment approaches. The power and value of endophenotypes is that they illuminate genetically mediated risk/vulnerability factors that often interact with nongenetic factors to produce the syndrome of schizophrenia. Thus, in the pool of genetic strategies and techniques that can be used to understand complex genetic psychiatric disorders (199–202), endophenotype-based strategies play an important and informative role. In colon cancer, the inherited genetic factor is familial polyposis rather than cancer itself (4). In parallel, it is quite likely that failures of information processing/inhibition are the genetically transmitted risk factors that interact with nongenetic factors to produce the clinical disorder of schizophrenia. Thus, the identification and genetic analysis of these endophenotypes should prove particularly valuable in understanding the genetic basis of schizophrenia. These studies will also facilitate a fuller understanding of how genetic

and nongenetic factors interact to produce this devastating illness and, it is hoped, point the way to more effective treatments.

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