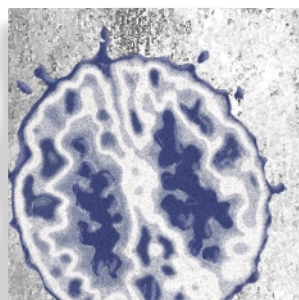


## *The use of neurophysiological endophenotypes to understand the genetic basis of schizophrenia*

David L. Braff, MD; Gregory A. Light, PhD



*Specifying the complex genetic architecture of the “fuzzy” clinical phenotype of schizophrenia is an imposing problem. Utilizing metabolic, neurocognitive, and neurophysiological “intermediate” endophenotypic measures offers significant advantages from a statistical genetics standpoint. Endophenotypic measures are amenable to quantitative genetic analyses, conferring upon them a major methodological advantage compared with largely qualitative diagnoses using the Diagnostic and Statistical Manual of Mental Health, 4th Edition (DSM-IV). Endophenotypic deficits occur across the schizophrenia spectrum in schizophrenia patients, schizotypal patients, and clinically unaffected relatives of schizophrenia patients. Neurophysiological measures, such as P50 event-related suppression and the prepulse inhibition (PPI) of the startle response, are endophenotypes that can be conceptualized as being impaired because of a single genetic abnormality in the functional cascade of DNA to RNA to protein. The “endophenotype approach” is also being used to understand other medical disorders, such as colon cancer, hemochromatosis, and hypertension, where there is interplay between genetically conferred vulnerability and nongenetic stressors. The power and utility of utilizing endophenotypes to understand the genetics of schizophrenia is discussed in detail in this article.*

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In this article, we review the utilization of endophenotypes in research into the genetics of schizophrenia, focusing on neurophysiological measures. Since Bleuler<sup>1</sup> coined the term “schizophrenia,” this complex and devastating disorder has gone through significant iterations in terms of how the scientific community conceptualizes it. When Bleuler utilized his impressive clinical experience and intuition in describing schizophrenia, he recognized that schizophrenia represents a group of disorders that share important unifying underlying features. Initially, psychological developmental factors such as aberrant communication styles<sup>2,3</sup> were felt to cause schizophrenia. Then, the seminal Danish studies of Kety et al<sup>4</sup> revealed the clear genetic transmission of schizophrenia and schizotypy-related abnormalities of psychological functioning subsumed under the term “schizotaxa.”<sup>5</sup> The seminal contributions of these and other family studies pointed the way for the current conceptualization of schizophrenia as one of the wide-ranging group of complex genetic disorders (*Figure 1*). Unlike the mendelian-dominant heritability pattern of Huntington’s disease, schizophrenia may represent a group of related disorders with substantial heterogeneity.<sup>6</sup>

Schizophrenia has undergone a transition from being viewed as a psychologically caused familial disorder to being understood as a complex genetic disorder in which multiple genes contribute in an additive or perhaps interactive, oligogenic fashion to yield a total risk or a vulner-

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## Selected abbreviations and acronyms

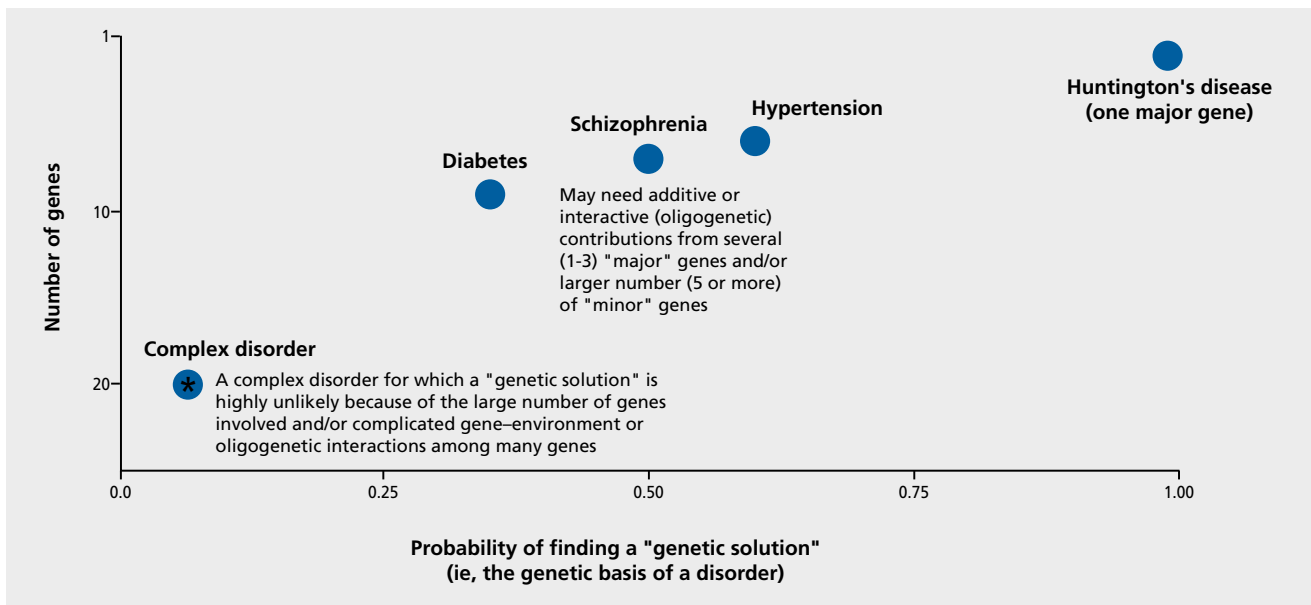
<b>COMT</b>	<i>catechol-O-methyltransferase</i>
<b>CSPT</b>	<i>cortico-striato-pallido-thalamic (circuitry)</i>
<b>ERP</b>	<i>event-related potential</i>
<b>PPI</b>	<i>prepulse inhibition</i>
<b>SNP</b>	<i>single nucleotide polymorphism</i>

ability to developing the disorder. Interestingly, in a sort of figure ground reversal, the initial enthusiasm of seeing schizophrenia as an easy-to-dissect genetic disorder was eventually replaced by the understanding that schizophrenia is about 50% genetically mediated<sup>7</sup> with the remainder of disease liability probably attributable to nongenetic factors.<sup>8-10</sup>

The evolution of our understanding of schizophrenia as a family of disorders that are mediated by complex genetic vulnerability and gene–environment interactions paralleled the advances seen in the conceptualization of many other medical disorders, such as colon cancer, hemochromatosis, diabetes, and hypertension.<sup>7</sup> Interestingly, all of these disorders are felt to be attributable to a complex interplay of vulnerability genes that predispose an individual to developing a disease and nongenetic “second hits” that precipitate the disorders (Figure 2). If the genetic loading or risk is strong enough (for example, as in multiplex families), even minor precipitants may result in the develop-

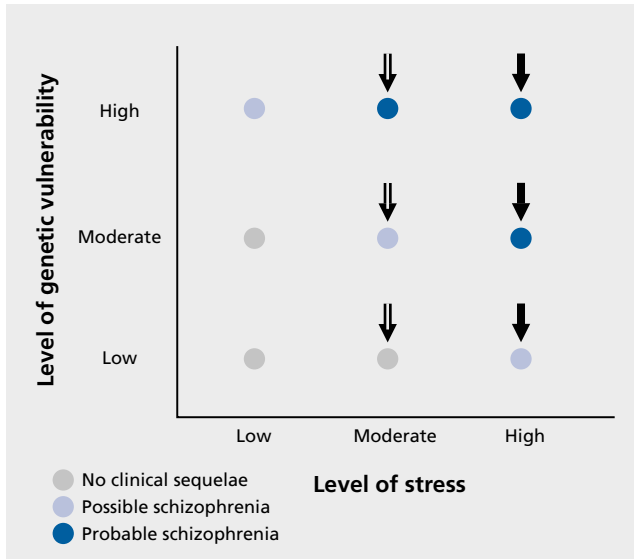
ment of the disorder. On the other hand, if the cumulative genetic risk of developing schizophrenia is relatively mild, it may take a more profound nongenetic second hit (Figure 2) to start the cascade of events that ultimately result in the full expression of the disease.

There is an interesting “natural history” in the schizophrenia literature itself. First, there were descriptions of the disorder and associated “deficits” in many domains. Second, studies of clinically unaffected relatives of schizophrenia patients pointed the way to an intermediate state of impairment (called endophenotypes) in each of these independently studied domains. These types of deficits occur across multiple domains such as metabolic functioning (catechol-O-methyltransferase [COMT]), neurophysiology (P50 event-related potential [ERP] suppression), and neurocognition (vigilance, as measured by the continuous performance task [CPT], and verbal memory, as measured by the California Verbal Learning Test [CVLT]).<sup>7</sup> The “intermediate” or partial deficits found in clinically unaffected relatives of schizophrenia patients gave investigators the insight crucial for the development and understanding of “endophenotypes” or intermediate phenotypes. Whereas the “fuzzy” clinical phenotype of schizophrenia is quite difficult to characterize, laboratory-based endophenotypes may be more closely linked to specific genetic abnormalities that are partially or wholly



**Figure 1.** Genetic architecture of complex disorders. This illustrates a major conundrum of research into complex human disorders. The Huntington's gene was identified 20 years ago, but has not yet led to a genetic “cure.” The profoundly important potential of genetic treatments for even more “complex genetic disorders” (eg, schizophrenia, hypertension, and diabetes) will depend on related scientific advances.

expressed (ie, variable penetrance) in clinically unaffected relatives of schizophrenia patients. This variable expression makes these endophenotypes amenable to statistical approaches utilizing quantitative trait methodologies.<sup>11-14</sup>



**Figure 2.** The vulnerability-stress 2-hit model of schizophrenia. “High” levels of vulnerability interacting with high levels of stressors (eg, neonatal hypoxemia or adolescent stimulant abuse) may “evoke” the emergence of schizophrenia. Despite the view of schizophrenia as a “genetic disorder,” 50% of causation is genetic and 50% or so of the disorder is caused by “nongenetic” second hits.

Thus, the picture that was painted is that for many of these endophenotypes, there are: (i) findings of deficits in schizophrenia patients versus normal comparison subjects; and (ii) the deficits are identified across the schizophrenia spectrum (including schizotypal personality disordered patients and clinically unaffected family members of schizophrenia patients) (Table I).<sup>15-47</sup> In addition, across the schizophrenia spectrum, it is observed that increasing deficits in these endophenotypes are noted with increasing genetic load or genetic risk. For example, groups of first-degree relatives of schizophrenia patients typically have a greater level of endophenotypic abnormality than groups of second-degree relatives, etc. Thus, there is the explicit assumption that “levels” of genetic relative risk<sup>48</sup> act as powerful predisposing factors that make the individual vulnerable to developing schizophrenia (Figure 2). In parallel, as the power of “strong inference”<sup>49</sup> in molecular biology became apparent, the understanding of the template of “DNA to RNA to protein” became very important across all species. In concert with these findings, the human genome project has identified the sequence of basepairs that characterize the human genome. The challenge for understanding the basis of mendelian-dominant genetic disorders (eg, Huntington’s disease) and the many “partially” genetic disorders (eg, hypertension, diabetes, bipolar disorder, Tourette syndrome, and schizophrenia; Figure 1) is to parse the clinical heterogeneity and com-

Endophenotypes	Schizophrenia patients	Relatives of schizophrenia patients	Schizotypal personality disordered patients	References
Antisaccade	4.88-6.38	1.38-3.75	0.75-1.36	15, 16
Smooth-pursuit eye movement	2.0-3.0	0.29-1.3	0.29	16-18
Thought disorder	1.56-2.98	0.34-0.83	1.04-1.28	16, 19-21
Working memory	1.42-2.2	0.42	0.73-1.04	22-24
P50 suppression	0.92-1.29	0.79	0.79	25, 27
Reaction time	0.59-1.05	0.44	0.79-0.99	28-30
Prepulse inhibition	0.51-0.85	1.0	1.45	31-33
Span of apprehension	0.5-2.5	0.6-1.5		34-39
Continuous performance test	0.45-3.30	0.46-2.97	0.45-0.78	34, 40-42
Executive functioning	0.47-1.97	0.73-1.6	0.72	40, 43
P300 event-related potential	0.45-1.05	0.17	0.36	44,45
Visual backward masking	0.33-0.65	0.43-0.57	0.45-0.67	28, 46, 47*

**Table I.** Neurophysiological and neuropsychological endophenotypes: effect size difference between schizophrenia patients, normal comparison groups, and schizophrenia spectrum groups. Effect sizes in schizophrenia patients, clinically unaffected relatives of schizophrenia patients, and schizotypal personality disordered patients compared with those in normal subjects. These effect sizes were computed by using the mean and standard deviations for 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, multiple conditions were used, some of which were needed to establish the floor and ceiling effect. In these cases, we generally cited the most robust effect sizes. \*Also, Cadenhead KS, unpublished data, 2000.

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plexities into understanding the genetic architecture and nongenetic contributions to quantitative measures that are amenable to analysis via advanced statistical quantitative trait analytic genetic methods.<sup>11-14</sup> Thus, for a complex psychiatric illness like schizophrenia, the relationship between genes, gene products, and the disorder itself is hardly straightforward. Indeed, an understanding of the exact cascade of DNA to RNA to (abnormal) protein to endophenotypic dysfunction in schizophrenia has remained elusive, but is amenable to serious investigations and analyses.

Because of the complexity of schizophrenia and the fact that it is a “fuzzy” diagnostic phenotype, a number of strategies have been utilized in order to understand the genetic underpinnings of the disorder. The most simple and most commonly used strategy of molecular genetics that is applied to complex psychiatric disorders first assumes the distribution of illness in a family represents the effect of a single gene and utilizes the techniques of genetic analysis that are commonly used to identify that single gene. This approach assumes that the signal of the disease attributable to a single gene can be identified in the very complex and relatively “noisy” genetic background of the disease.

As an alternative approach, one could make an assumption about the biology or endophenotypes expressed in an illness and then search for candidate genes that underlie those functions to see if they are mutated. It is important to note that both of these approaches have been successful to some degree in schizophrenia studies. For example, whole genome scans have revealed replicated linkage findings for schizophrenia obtained at locations on chromosomes 1, 6, 8, 13, 15, and 22 (see, for example, references 7 and 48). The problem with these whole genome linkage studies is that the functional correlates of these linkages are unclear. Conversely, DNA mutations have also been found in “candidate genes” such as *NURRI*,<sup>50</sup> a gene that codes for the receptor for retinoic acid and mediates critical pathways in neuronal development. A limiting consequence of dealing with a group of disorders is that these neurobiologically significant and face-valid abnormalities in *NURRI* candidate genes are mutated in only a small number of patients with a diagnosis of schizophrenia.<sup>51</sup>

A third approach uses endophenotypes to sharpen the clinical phenotype, in order to understand the genetic basis of specific schizophrenia-linked abnormalities. This approach assumes that a specific genetic abnormality

causes a specific protein change leading to a specific quantitative functional abnormality. Thus, the wide array of possible genetically mediated domains that could be examined in schizophrenia include metabolic functions, brain structure and functional imaging, neurophysiology, neuropsychology, and other endophenotypic abnormalities that run in families.<sup>7,9,51</sup> The relationship between these endophenotypic abnormalities and genes can also be discovered and evaluated via the use of linkage or candidate gene analysis. Hence, levels of association of specific quantitative traits and their related genetic abnormalities would be stronger than the relationship of specific genetic abnormalities to the clinical endophenotype of a heterogeneous population of schizophrenia patients. This approach is hardly unique since it is clear in other medical conditions that the search for endophenotypes and their genetic determinants can be more “focused” when looking through an “endophenotypic lens” rather than looking at the genetic basis of the complex disorders themselves. For example, in hemochromatosis, it is not the clinical illness, but rather a high serum level of iron that is the most clearly identifiable and penetrant heritable trait.<sup>52</sup> Likewise, gene discovery in colon cancer has revealed that it is not the cancer itself, but rather familial polyposis that is the crucial,<sup>53</sup> genetically heritable disease vector. In the case of colon cancer, the assumption is that there is a genetically mediated vulnerability resulting in polyp formation, which converts to cancer via the influence of other genetic or nongenetic factors (ie, diet, environmental toxin exposure). Thus, these polyps will often convert to colon cancer in “high-risk” individuals.

The assessment of endophenotypes has come to be increasingly important in our attempts to understand schizophrenia. Of course, when one considers that there are about 16 000 genes expressed in the brain and, of these, about 6000 to 8000 are expressed only in the brain,<sup>54</sup> searching for causative genes associated with the clinical entity of schizophrenia per se is a daunting task. In dealing with quantitative endophenotypic markers and the probability of causal genetic heterogeneity where multiple mutations may induce endophenotypic abnormalities, we face a difficult challenge. Also, in analyzing endophenotypic abnormalities, the fact that many brain-based genes are expressed in multiple areas, under varying promoting or disease-inducing nongenetic conditions and across critical neurodevelopmental epochs in the life of the individual, the search for endophenotype–genetic “connections” requires us to sharpen our focus when

searching for the vulnerability gene(s) in schizophrenia. According to Mendel's second law that genetic traits segregate independently in the family, some siblings will express specific endophenotypes independently of others and may be better subjects for characterizing endophenotypic abnormalities than the patients themselves. The patients themselves have multiple abnormalities relating to the scope and severity of their disease, the treatments used for the disease, and the psychosocial, medical, nutritional, and many factors associated with schizophrenia. The voyage that has been undertaken in searching for endophenotypes in schizophrenia has taken advantage of a generation of important scientific findings. First among these, of course, is the fulcrum finding of the double helix structure of DNA.<sup>55</sup> Second, after the structure of DNA was identified, the advances in the understanding of the transformation of DNA to RNA to proteins to function have taken place over the last 50 years in a rapidly accelerated fashion that has enabled us to come within "hailing distance" of truly understanding the relationship of DNA mutations to clinical and endophenotypic abnormalities.

### Genetic studies of endophenotypes in schizophrenia

The candidate endophenotypes that have been examined in schizophrenia range from metabolic and developmental measures to brain structural and functional traits, as well as neuropsychological and neurophysiological indices. The neurodevelopmental endophenotype candidates include mutations in candidate genes such as *NURRI*. Clearly, this pathway is critical in neuronal development and, although the mutations in this gene are found in a minority of schizophrenia patients, one cannot help but be impressed by the fact that this endophenotypic trait aligns with a neurodevelopmental hypothesis. Likewise, Harrison and Weinberger<sup>51</sup> have pointed out that "schizophrenia genes" and their expression may converge on critical neuronal synaptic and glial populations in crucial brain areas, such as the hippocampus, dorsal thalamus, and dorsolateral prefrontal cortex. These structures are all part of the cortico-striato-pallido-thalamic (CSPT) circuitry. This CSPT circuitry involves complex loops and connections that are derived from Penney and Young's<sup>56</sup> examination of the neural substrate of motor functions. The finding of distributed neural network abnormalities in the CSPT circuitry was described in psychiatric populations in a definitive manner by Swerdlow

and Koob<sup>57</sup> and has led to many neurophysiological and "brain connectivity" hypotheses. These hypotheses include Andreason's concept of cognitive dysmetria,<sup>58</sup> which attempts to "connect the dots" of brain dysfunction in schizophrenia patients,<sup>59</sup> and the evolution of cortico-cortical coherence measures to assess functional connectivity deficits to probe the multiple cognitive deficits of schizophrenia patients.<sup>60</sup> As Harrison and Weinberger point out, "a way forward is provided by the recent identification of several putative susceptibility genes including neuroregulin, dysdindin, *COMT*, *DISCI*, *RGS4*, *GRN3*, *G72*."<sup>51</sup> These authors discuss the evidence for these and other genes as vulnerability vectors along dimensions of their expression profiles and neurobiological roles. While the evidence for genetic abnormalities in these critical genes with their important integrative functions is attractive, the causative allele or mechanism that results in the development of schizophrenia is unknown. Harrison and Weinberger<sup>51</sup> also point out that *COMT* may be an exception where a causative allele may have been identified. Nevertheless, in the area of brain connectivity and synaptic plasticity, they have proposed that the genes cited above may all converge functionally via an influence upon synaptic plasticity and the development and stabilization of functionally important cortical micro-circuitry.<sup>51</sup> Thus, at the most basic level, these neurodevelopmental genes may characterize a molecular biological basis for a genetic cytoarchitecture that has the potential to incrementally advance our understanding of schizophrenia.

### Neurophysiological endophenotypes: gating abnormalities

Many neurophysiological endophenotypes have undergone extensive study and analysis (*Table I*).<sup>15-47</sup> These endophenotypic measures include antisaccade oculomotor functioning, smooth pursuit eye movement, P50 suppression, prepulse inhibition (PPI) of the startle response, P300 ERPs, and visual backward masking. Each of these endophenotypes has undergone a logical, natural history of progression in scientific analyses: schizophrenia patients, their clinically unaffected family members, and schizotypal personality disordered subjects have deficits compared with normal subjects. Exemplars of neurophysiological endophenotypes in schizophrenia are the gating abnormalities reflected by PPI and P50 suppression deficits.



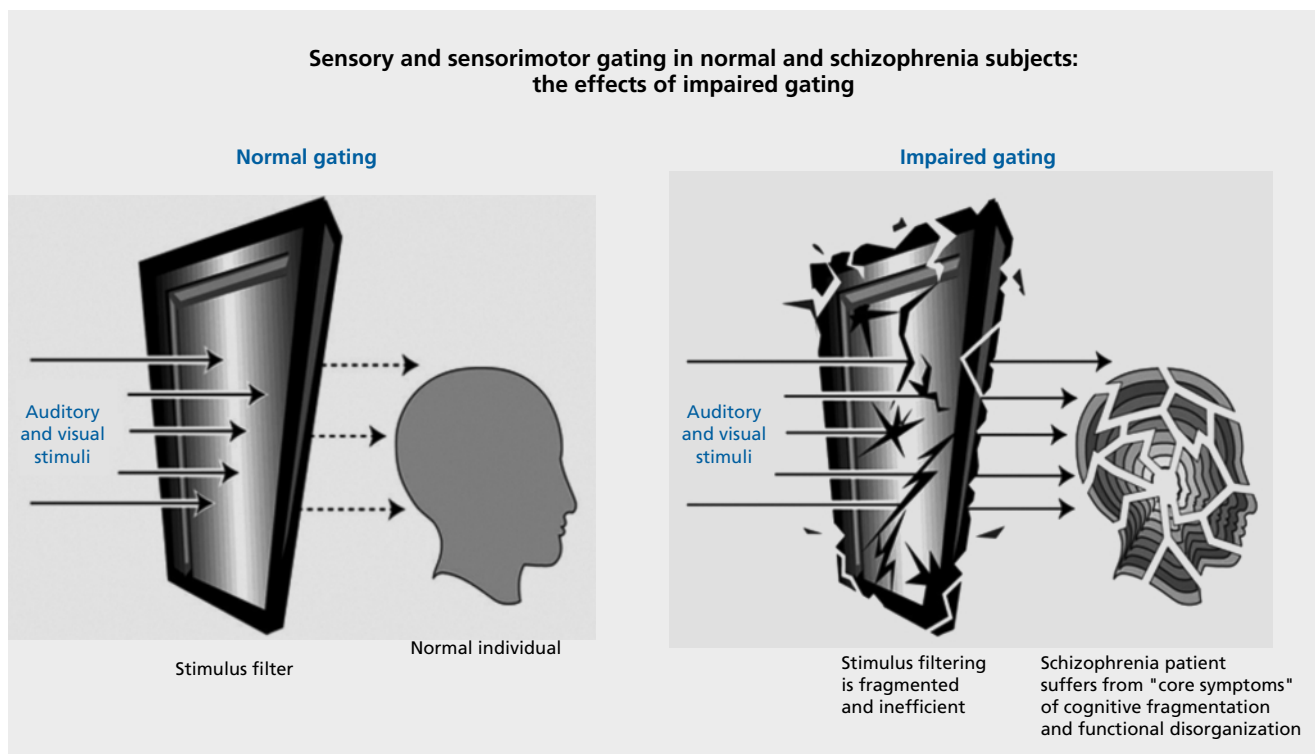
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Abnormalities of sensorimotor (PPI) and sensory (P50 suppression) gating are thought to reflect an inability to screen out trivial stimuli in order to focus on important and information laden aspects of the environment.<sup>61-64</sup> Normal sensory gating (*Figure 3*) allows individuals to navigate through a stimulus-laden world and to apportion attentional resources to salient stimuli. PPI of the startle reflex measures sensorimotor gating with a clear understanding of the underlying CSPT circuitry defined from decades of animal model studies. While PPI and P50 suppression measures of “gating” are often conceptually linked, there is evidence that they actually diverge in nonpsychiatric and clinical populations.<sup>65-68</sup> Thus, these two different, but seemingly closely related gating abnormalities, may be characteristic of different subgroups of patients.

PPI normally occurs when a weak prestimulus precedes a strong “startling” stimulus by 50 to 300 ms (*Figure 4*); the weak prestimulus inhibits the startle response. PPI deficits in schizophrenia patients<sup>31,61,69</sup> extend to clinically unaffected relatives of schizophrenia patients as well as schizotypal patients.<sup>33,70</sup> Impaired gating function puta-

tively results in the devastating consequences of cognitive fragmentation (*Figure 3*).

One of the major advantages of endophenotypes, such as PPI, is that there are animal models that point to genetically mediated strain-related differences<sup>71</sup> and to specific quantitative trait loci (Schork et al, 1995, unpublished manuscript). In addition to strain-related differences in baseline PPI, pharmacological regulation of PPI is also strain-related.<sup>71-77</sup> In addition, PPI deficits induced by the dopamine agonist apomorphine are reversed in a very lawful manner by antipsychotic medications with “dose–response” characteristics that parallel the efficacy of these antipsychotic medications in schizophrenia patients.<sup>78</sup> Therefore, although PPI is not as advanced in terms of its genetic analysis as P50 suppression (see below), it offers an important window on endophenotype (dys)function in schizophrenia. The CSPT circuitry is crucial for understanding cognitive integration and inhibitory functions. In animal model studies, this circuitry is impaired by lesions or neurotransmitter manipulations at multiple loci in the CSPT circuitry that induce PPI deficits.<sup>79,80</sup> Thus, infusion and lesion studies along nodes



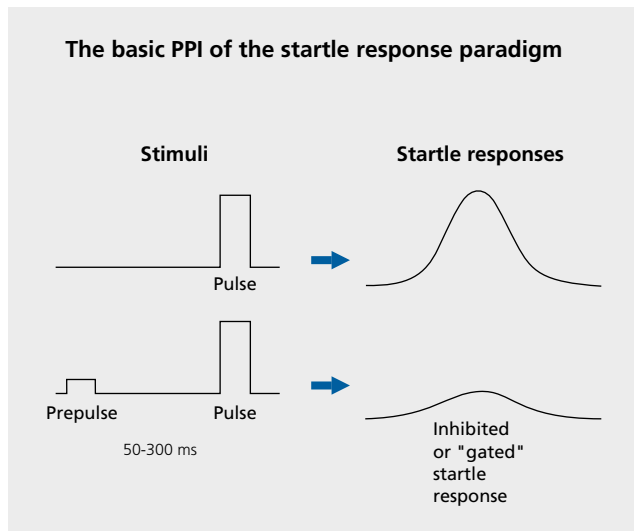
**Figure 3.** The effects of a loss of normal gating. In the left panel, an individual with intact filtering and inhibition filters out irrelevant sensory stimuli. In the right panel, impaired gating leads to a sequence of sensory inundation, cognitive fragmentation, and disorganized thinking.

within the CSPT axes can disrupt PPI. It is not too big a “leap of faith” to believe that specific single nucleotide polymorphisms (SNPs) might affect these loci and reflect multiple genetic mutations that contribute to the vulnerability to developing schizophrenia. Of course, these hypotheses can only be worked out in humans in large-scale studies such as the National Institute of Mental Health Consortium of Genetics of Schizophrenia,<sup>81</sup> where endophenotype deficits found in schizophrenia are being tracked in a large cohort of families in order to understand both patterns of heritability and the specific genetic abnormalities associated with these endophenotypic deficits in schizophrenia.

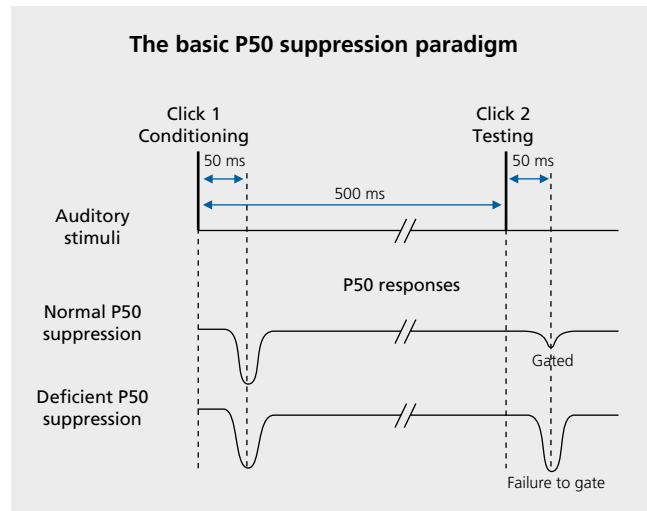
P50 suppression is an ERP measure of inhibitory function that has been studied in a variety of patient and nonpsychiatric populations. An electroencephalogram (EEG) is recorded in response to click pairs presented 500 ms apart. The EEG responses to each of the clicks are separately averaged. The P50 component of the auditory ERP is a positive-polarity waveform that occurs approximately 50 ms after each click is presented. In normal subjects, the P50 response to the second click is typically reduced in amplitude relative to the response to the first click.<sup>25,26,82-84</sup> P50 suppression is the percentage of P50 response amplitude reduction from the first to the second click (Figure 5). Over the past 20 years, many studies have demonstrated that schizophrenia patients have P50 suppression deficits (Table 1) and that these deficits extend to clinically unaf-

fected relatives of schizophrenia patients.<sup>26,85-87</sup> Individuals with schizotypal personality disorder also have P50 suppression deficits,<sup>27,88</sup> indicating that these deficits are present across the schizophrenia spectrum.

Although it is clear that, much like PPI, P50 suppression is almost inevitably the function of a wide-ranging neural circuitry involving multiple brain structures and complex brain circuits, the utilization of P50 suppression as a “candidate endophenotype” advanced rapidly for two reasons. First, there was the critical findings of nicotine transiently improving P50 suppression deficits in both schizophrenia patients<sup>89</sup> and their clinically unaffected family members.<sup>90</sup> Second, an animal model of P50 suppression was developed, similar to that seen in PPI. This allows specific neurochemical manipulations to be made and it was found that P50 suppression deficits in DBA/2 mice could be restored to normal levels by  $\alpha_7$ -agonists.<sup>91</sup> Then, a relatively unique element in the ideal progression of identifying endophenotypes in schizophrenia was made: it was found that there is a genetic marker at the locus of the  $\alpha_7$ -subunit of the nicotinic receptor gene linking a candidate endophenotype of information-processing deficits in schizophrenia to a specific chromosomal region.<sup>84</sup> Leonard et



**Figure 4.** Prepulse inhibition (PPI) is a profound decrease in startle response magnitude when the startling pulse is preceded by a weak prepulse. PPI is an operational measure of sensorimotor gating.



**Figure 5.** Auditory click pairs are presented to subjects; the electroencephalogram (EEG) is averaged across trials. The P50 component of the averaged event-related potential (ERP) is measured in response to the first and second clicks. The percentage of P50 amplitude reduction from the first to the second click is referred to as P50 suppression or P50 gating, and is considered an operational measure of sensory gating. Deficient P50 suppression is often seen in patients with schizophrenia, their clinically unaffected family members, and individuals with schizotypal personality disorder.

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al<sup>92</sup> found a specific SNP genetic mutation in the promoter region of the  $\alpha_7$ -subunit of the nicotinic gene, which seems to account for the P50 findings listed above. Thus, P50 suppression represents the most “complete” “DNA to RNA to protein” story of an endophenotype–genetic abnormality linkage.

The P50 suppression findings represent an example of how endophenotypes can be utilized as neurobiologically meaningful markers that contribute to our understanding of the genetics and potentially the treatment of schizophrenia. Importantly, these types of studies do not merely identify a “schizophrenia endophenotype,” but rather the linkage of deficits (P50 suppression) in schizophrenia patients to a specific chromosomal region.

## Conundrums and caveats, and the use of endophenotypes in the genetics of schizophrenia

Although there are many candidate endophenotypes in schizophrenia, imposing challenges still exist. First, since some endophenotypes are at least partially normalized by current second-generation antipsychotic medications, the statistical genetic approach to these data sets presents many daunting challenges. For example, the fact that clozapine improves P50 suppression deficits<sup>93–95</sup> suggests that patients on clozapine cannot be utilized in studies of P50 suppression as a candidate endophenotype. It would be optimal to use never-medicated schizophrenia patients in studies of endophenotypes in schizophrenia. Unfortunately, given the power demands of such studies, finding enough never-medicated patients, even in a multi-site study such as the Consortium on the Genetics of Schizophrenia (COGS) would seem to be virtually impossible. Family studies that rely on identifying probands with endophenotypic deficits then become difficult to interpret. Where significant endophenotypic normalization occurs with antipsychotic treatment, statistical strategies will have to be utilized that allow us to “exclude” or “account for” the (partially) “normalized” schizophrenia patients or to utilize only clinically unaffected family members in genetic studies. This reliance on clinically unaffected family members is what Braff and Freedman<sup>7</sup> referred to as the “null-proband” strategy. Medicated probands must either be excluded from analyses or a complex “adjustment” on a phenotypic value must be made in order to utilize them in the genetic analysis. One could posit that a temporary withdrawal of antipsychotic

medication would allow us to identify these trait-related endophenotypic markers, but this is ethically and practically unfeasible. Fortunately, almost all of the large effect sizes reported for endophenotypic deficits in schizophrenia in *Table I* are derived from medicated patients, so that it appears that fairly straightforward statistical analyses can be utilized with most available patients.

## Summary

Genetic studies in schizophrenia are on the cusp of an exciting new era of utilizing specific laboratory-based endophenotypes to parse the complex genetic architecture of the “groups of schizophrenia.” The template described above for P50 suppression studies has already yielded a sequence of findings leading to the identification of a specific abnormality that accounts for P50 suppression deficits in schizophrenia patients and their clinically unaffected relatives. In addition to this, there are many studies examining heritability of other strong candidate endophenotypes, as listed in *Table I*. Other study strategies are now being utilized in endophenotypic research in schizophrenia. Investigations are underway in a number of settings to identify genes that convey a risk for schizophrenia. For example, whole genome linkage studies have revealed loci that might be of functional importance. In addition, the endophenotypic strategy, however, allows us to understand the underlying neurobiology and neural substrates of these genetic abnormalities. Many conundrums and obstacles must be overcome in this endeavor. For example, the improvement of endophenotypic abnormalities via the use of second-generation<sup>96</sup> antipsychotic medications may (or may not) impede our ability to carefully conduct family heritability studies, which will allow us to ultimately identify genetic abnormalities characteristic of schizophrenia. With the use of statistical genetics methods, unmedicated patients, animal model identification of quantitative trait loci, and specific genetic abnormalities, the exciting possibility exists for matching endophenotypes with their underlying genetic abnormalities and then constructing “composite endophenotypes” consisting of neurobiologically coherent combinations of more than one of the identified biomarkers. It is very important to identify the convergence and divergence of these endophenotype–gene abnormality linkages in schizophrenia patients in order to see whether a single genetic abnormality is likely to induce the multiple observed deficits of schizophrenia patients. Ultimately, the specification of how different gene–envi-



ronment interactions contribute to neuronal pathology associated with psychosis may enable us to further clarify the nosology of schizophrenia. Quantitative endophenotype-based strategies play an important role that will help elucidate the genetic basis of schizophrenia and point the way toward molecularly derived strategies for the treatment of important subgroups of patients with this complex disorder. □

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### **El empleo de endofenotipos neurofisiológicos para comprender las bases genéticas de la esquizofrenia**

*El poder precisar la compleja arquitectura genética del "enredado" fenotipo clínico de la esquizofrenia constituye un problema gigantesco. El empleo de mediciones endofenotípicas metabólicas, neurocognitivas y neurofisiológicas "intermediarias" ofrece ventajas significativas desde un punto de vista genético estadístico. Las mediciones endofenotípicas sustituyen a los análisis genéticos cuantitativos confiriéndoles a ellas una mayor ventaja metodológica en comparación con los diagnósticos principalmente cualitativos que emplea el Manual Diagnóstico y Estadístico de Salud Mental en su cuarta edición (DSM IV). Los déficits endofenotípicos aparecen en todo el espectro esquizofrénico: en pacientes con esquizofrenia, en pacientes esquizotípicos y en familiares de pacientes esquizofrénicos sin evidencias clínicas de la enfermedad. Las mediciones neurofisiológicas, como la supresión de los eventos relacionados con la onda P50 y la inhibición de la respuesta de sobresalto ante un estímulo, constituyen endofenotipos que pueden ser conceptualizados como una alteración debida a una anomalía genética simple en la cascada funcional desde el ADN al ARN y a las proteínas. La "aproximación endofenotípica" también se está empleando para comprender otros cuadros médicos, como el cáncer de colon, la hemocromatosis y la hipertensión en los cuales hay una interacción entre los estresores no genéticos y la predisposición genética que confiere cierta vulnerabilidad. En este artículo se discutirá en detalle la capacidad y la utilidad del empleo de endofenotipos para una mejor comprensión de la genética de la esquizofrenia.*

### **Utilisation des endophénotypes neurophysiologiques pour comprendre la base génétique de la schizophrénie**

*Préciser l'architecture génétique complexe du phénotype clinique « enchevêtré » de la schizophrénie constitue un problème impressionnant. Utiliser des mesures endophénotypiques métaboliques, neurocognitives et neurophysiologiques « intermédiaires » offre des avantages certains d'un point de vue génétique statistique. Les mesures endophénotypiques relèvent des analyses génétiques quantitatives, leur conférant un avantage méthodologique majeur comparé aux diagnostics en grande partie qualitatifs qui utilisent le DSM-IV (Diagnostic and Statistical Manual of Mental Health, 4e édition). Des déficits endophénotypiques se produisent au cours de la schizophrénie chez les patients schizophrènes, les patients schizotypiques et les parents cliniquement indemnes de patients schizophrènes. Les endophénotypes sont des moyens neurophysiologiques, tels que la suppression des événements liés au P50 et que l'inhibition de la réponse de sursaut avant un stimulus, que l'on peut imaginer être altérés par une anomalie génétique simple dans la cascade de fonctionnement ADN vers ARN vers protéine. L'« approche endophénotypique » est aussi utilisée pour comprendre d'autres pathologies, comme le cancer du colon, l'hémochromatose et l'hypertension dans lesquels il existe une interaction entre des agents stressants non génétiques et une prédisposition génétique conférant une certaine vulnérabilité. Dans cet article, nous allons parler en détail de la possibilité et de l'utilité d'utiliser des endophénotypes pour comprendre la génétique de la schizophrénie.*

# Basic research

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