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Identifying psychophysiological risk for psychopathology: Examples from substance abuse and schizophrenia research

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Abstract

A problem confronting the search for psychopathology-related genes concerns the difficulty identifying gene carriers. Psychiatric diagnosis provides imperfect identification of affected individuals, and unaffected gene carriers go undetected. Psychophysiological measures may assist molecular genetic investigations by indicating genetic susceptibility for psychopathology, thus increasing the probability of identifying affected and unaffected gene carriers. Research strategies based on these premises are applied to the study of psychoactive substance use disorders and schizophrenia. Data are presented illustrating (1) that individual differences in inhibitory control involving autonomic and antisaccade eye movement measures and the P3 component of the event-related potential may be sensitive to susceptibility for substance use disorders, and (2) that eye tracking variables may identify genetic risk for schizophrenia.

Descriptors: Psychophysiological markers of genetic risk, Alcoholism, Drug abuse, Externalizing psychopathology, Schizophrenia, P3 event-related potentials, Smooth pursuit eye tracking

Innovations in quantitative and molecular genetics make it likely that some time early in the next century, specific genes influencing a wide variety of psychological traits and behavioral disorders will be identified. Important questions, however, concern how quickly this identification is likely to happen and how behavioral scientists will be able to assist the process. An important theme of this article is that behavioral scientists, in particular psychophysiologicals, can

play a critically helpful role in this genetic quest, and in so doing, speed up the process of gene identification. A related theme is that by contributing to this endeavor, psychophysiologicals can help identify individuals predisposed to develop various types of psychopathology and thus provide important insights into the etiology of disorders and possibly their prevention. As a byproduct of using psychophysiology for this purpose, the genetic basis of psychophysiological procedures and variables is likely to be determined, contributing to the understanding of their neurobiology and greatly increasing the utility of psychophysiological measures in general.

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Why Searching for Genes Is Difficult

Family, twin, and adoption studies suggest that a genetic diathesis underlies a wide variety of behavior disorders, including disorders of childhood as well as psychoactive substance use and psychotic, mood, and anxiety disorders. A typical approach used to search for genes related to psychopathology involves finding families with multiple affected members and determining if a “marker” that identifies a region of DNA on a particular chromosome is present in those family members affected with the disorder. Such marker identification suggests that genetic material in this chromosomal region is important to the development of the disorder. With additional study, it is possible to identify the specific gene conferring risk for the disorder.

Although this approach has been used successfully to locate genes for various medical illnesses (e.g., Huntington disease, caused by an autosomal dominant gene), its promise for locating psychopathology-related genes has been largely disappointing. For

instance, if we consider as an example the search for schizophrenia-related genes, beginning with the 1988 report of Sherrington et al., there have been more than 100 studies investigating genetic linkage in schizophrenia, with linkage reported to seven different chromosomes (National Institute of Mental Health [NIMH], 1998). However, most of the reports in this literature are nonreplications and, although some promising leads were noted (Moldin & Gottesman, 1997), studies that have reported positive findings of linkage have been followed by multiple failures to confirm the original findings. These obstacles in the search for schizophrenia-related genes hampered the search for genes for other forms of psychopathology and point to the difficulty inherent to this type of research.

There are many reasons why finding genes for psychopathology will continue to be daunting (Iacono, in press). Knowing the mode of genetic transmission greatly simplifies the search, but there is little definitive knowledge about the mode of transmission of behavior disorders, most of which are likely to be etiologically complex. Linkage is easiest to demonstrate for "simple" disorders like Huntington disease in which a single gene accounts for all of the genetic variance. However, it is unlikely that any of the major behavioral disorders are single-gene disorders. Oligogenic (a few genes varying from small to large effect), polygenic (many genes all of small effect), and mixed (a single gene of large effect against a polygenic background) models may provide more reasonable working hypotheses for the transmission of psychopathology than single locus models. To the extent that multiple loci are involved, it will be easiest to demonstrate linkage for those genes that account for the most genetic variance. Recent developments such as quantitative trait loci (QTL) linkage analysis make it possible to detect genes of even relatively small effect (e.g., accounting for 5% or less of the variance), but large samples (e.g., 1,000 or more affected sibling pairs) that are impractical to obtain may be required to take full advantage of this technique (Gottesman, 1997; Martin, Boomsma, & Machin, 1997).

Knowing which members of a family carry a gene and which do not greatly facilitates an enterprise in which it is important to show that those with the gene possess the DNA marker signaling its presence. However, we have learned from the study of identical twins in which one member of a pair has a certain form of psychopathology that oftentimes the co-twin is not similarly afflicted. Because both members of identical twin pairs can be expected to possess the genotype predisposing individuals to the form of psychopathology in question, such findings indicate that many gene carriers will go undetected (see e.g., Gottesman & Bertelsen, 1989). In addition, because psychiatric diagnosis is not perfectly reliable and the validity of the criteria used to identify disorders is open to question, it is likely that those individuals identified as "affected" will sometimes be false positives who would not be expected to carry the genetic predisposition. Both false negatives and positives can complicate and challenge genetic linkage analyses. False negatives are a problem because they represent failures to identify cases that are present, reducing "signal strength" for analyses that are often based on too few affected individuals to assure adequate statistical power to affirm linkage. False positives pose the greater problem because they will misleadingly suggest that some cases of the disorder are not "marked" by the DNA, thus adding "noise" to the analyses.

Behavioral disorders are most likely genetically heterogeneous. To the extent that they are, demonstrating linkage is complicated by the fact that there is no method currently available for determining whether an affected person has one genetic variant or another; additionally, each variant would be expected to show different

linkage. Another problem concerns the reproductive fitness of individuals with psychopathology. Although reproductive fitness varies greatly among behavioral disorders, individuals with severe forms (which may have a higher probability of including those with the genetic predisposition) of any disorder are less likely to reproduce than unaffected individuals in the population at large. For some disorders, like schizophrenia, affected individuals tend not to reproduce, and biological relatives with the disorder are relatively uncommon. Gottesman, Shields, and Hanson (1982) noted, for instance, that only about 20% of those with schizophrenia have even one affected first-degree relative. The fact that people with psychopathology do not make attractive mates makes it difficult to find families with multiple generations containing affected members, and such families are unlikely to be representative of those commonly found among individuals with the disorder. In the absence of such families, it is difficult to demonstrate linkage. No doubt the many failures to replicate findings of linkage are due in part to the use of small, unrepresentative samples of families, a research strategy that is made worse when the genetic effect size is (as is commonly believed for many disorders) likely to be small (see e.g., Levinson et al., 1998).

Facilitating the Search

To summarize briefly, the impediments to finding psychopathology-related genes include the (a) uncertainty regarding how genetic risk is transmitted; (b) possibility that many disorders involve polygenes contributing modest or small effects that are difficult to detect; (c) inability to identify gene carriers who show no manifest psychopathology; (d) uncertain criterion validity of psychiatric diagnostic criteria; (e) poor phenotype definition; (f) possible genetic heterogeneity; (g) the absence of affected relatives; and (h) reliance on unrepresentative samples. All of these problems could be dealt with if it were possible to enhance phenotype definition by identifying those at genetic risk for psychopathology without having to rely on the presence of manifest symptoms. What is required is an "endophenotype" (Gottesman & Shields, 1972; John & Lewis, 1966), some measurable endogenous characteristic of a person that is itself a product of the predisposing genotype. Schizophrenia (e.g., Meehl, 1989) and alcoholism (e.g., Schuckit, 1986) researchers have frequently noted the value of identifying such an attribute.

When an endophenotype strongly influenced by a disease gene is present, the likelihood that an individual is a gene carrier is enhanced substantially. The search for endophenotypes assumes that the hypothetical susceptibility gene or genes are active or "switched on" in carriers even when no obvious clinical signs of psychopathology are present. Fortunately, ample evidence suggests that this assumption is reasonable for at least some disorders, although the age at which genes are expressed or their expression is detectable has received little attention. Although the ideal endophenotype might be a measurable variation in biochemistry that is the direct result of a gene's action, because we do not know how a person's biochemistry might be altered, searching for such a quality may be almost as difficult as the gene search itself. Psychophysiological measures have obvious potential and advantages as endophenotypes because they are sensitive to biological and psychological factors associated with psychopathology. They are also noninvasive and relatively straightforward to measure (Iacono & Ficken, 1989).

An endophenotype may itself show a simple pattern of genetic transmission that suggests the presence of a major gene (a gene that accounts for a substantial fraction of the genetic variance).

Alternatively, the endophenotype may index a quantitative trait or dimension (e.g., a deficit in central nervous system inhibitory control) that underlies (poly)genetic risk for a disorder. In either case, it may be possible to establish linkage between a gene (or several genes) and the endophenotype.

Although there are a variety of research strategies that can be used to evaluate candidate endophenotypes, of special importance are designs that examine the relatives of those with identified psychopathology. The following expectations apply:

1. *Evident in Unaffected Relatives:* The endophenotype should be observable in well relatives because some fraction of these individuals would be expected to be gene carriers. Studies of identical twins discordant for psychopathology are of special interest because all of the unaffected twins would be expected to have the endophenotype if the affected co-twin does.
2. *Evident in Affected Relatives:* The endophenotype should also be apparent in affected relatives because it should confirm as gene carriers those who have succumbed to the disorder. Those with related forms of psychopathology should also possess the endophenotype. The disorders that constitute the relevant “spectrum” of psychopathology are not always clear, but examples might include schizotypal and antisocial personality disorders as part of the schizophrenia and alcoholism families of disorders, respectively.
3. *Specificity:* The endophenotype should ideally be unique to a class of related disorders. For instance, a candidate endophenotype would not serve its desired function if it occurred with equal prominence in the relatives of both bipolar and schizophrenia patients because these disorders are not typically viewed as alternate expressions of the same genotype. On the other hand, because psychiatric diagnosis is not perfectly reliable and the validity of the *Diagnostic and Statistical Manual* (DSM) diagnostic criteria is not firmly established, it is not reasonable to expect a complete absence of the endophenotype in an unrelated disorder that shows appreciable symptom overlap with the target disorder. Also, some endophenotypes will possibly index a dimension or process representing a dysfunction shared across certain disorders. For instance, a frontal lobe dysfunction may be present in schizophrenia (Andreasen et al., 1997) and attention-deficit hyperactivity disorder (ADHD) (Barkley, 1997). The same endophenotype may be present in both disorders (e.g., defined as poor performance on a working memory task or an event-related potential anomaly recorded during performance on such a task), but that would not necessarily imply the presence of shared etiology or genes across the two disorders. This notion (that different etiologies can produce the same phenotype) is referred to as *equifinality* by developmental psychopathologists (Cicchetti & Toth, 1995).
4. *Predictive Power:* Another important quality of an endophenotype concerns its ability to predict who will develop psychopathology. Longitudinal studies of the offspring of affected individuals should show that those with the endophenotype are substantially more likely to develop psychopathology than siblings without it.
5. *Endophenotype Indicates Risk:* Individuals from the general population who are selected for the presence of the endophenotype can be expected to possess characteristics consistent with their being putative gene carriers. For example, the prevalence of the disorder phenotype should be higher in such in-

dividuals than in those without the endophenotype. With respect to psychophysiological measures, those with the endophenotype can be characterized as at psychophysiological high risk (see also Buchsbaum, Coursey, & Murphy, 1976).

Advantages of Enhancing Phenotype Definition

The identification of an endophenotype offers a number of advantages and reduces some of the problems associated with conventional molecular genetic research. Reliance on the latest edition of the DSM of the American Psychiatric Association to identify affected persons would be lessened. The presence or absence of the endophenotype could be used to help resolve diagnostic ambiguity and improve classification accuracy, eventually perhaps complementing or supplanting existing diagnostic criteria (as has happened for numerous physical disorders). Identifying an endophenotype could also help categorize disorders that belong in the same genetic class or spectrum. By focusing study only on those cases with the endophenotype, who thus probabilistically share a disorder-related genotype in common, the bothersome problem of genetic heterogeneity can be reduced. Our understanding of the endophenotype should also provide leads regarding the etiology of the disorder.

Another advantage of the endophenotype is that it increases statistical power and reduces substantially the problem of reproductive fitness. Although affected persons may not have any relatives with manifest disorder, they will have biological relatives, including parents and often siblings. If these relatives are available, whether they possess the endophenotype can be determined, and this information can be used to assist with the identification of genes.

The process of searching for an endophenotype is likely to yield indirect benefits as well. Not all indices of vulnerability suggest genetic risk. For instance, individuals who suffer birth trauma or child abuse may show characteristic psychophysiological anomalies associated with their subsequent development of psychopathology. Such a vulnerability marker would share many features in common with an endophenotype, but unlike an endophenotype, the marker would not be heritable (unless, e.g., the tendency to be abusive is co-inherited with a form of psychopathology that is itself heritable). For example, the vulnerability marker would be present infrequently in the general population, identify at-risk individuals, have predictive value, have the qualities of a stable trait, and provide clues about etiology. The identification of such vulnerability markers has obvious value even though they confer no information about genetic risk.

Another consequence of the search for psychophysiological endophenotypes is the identification of genes that govern individual differences in the expression of psychophysiological variables. Although psychophysiological variables reflect brain activity, their biological underpinnings are mostly obscure. Gene identification should ultimately enhance understanding of the underlying neurobiological mechanisms for psychophysiological measures reflecting the presence of heritable traits. Ultimately, genes associated with psychophysiological measures should map onto functional genes known to be related to central nervous system functioning (e.g., neurotransmitter genes; cf. Gottesman & Moldin, 1998).

Many psychophysiological variables are likely to be influenced by genes. Twin studies from the University of Minnesota suggest that genes influence individual differences in spontaneous electroencephalography (EEG) (McGuire, Katsanis, Iacono, & McGue, 1998), event-related potentials (Katsanis, Iacono, McGue, & Carl-

son, 1997), electrodermal habituation (Lykken, Iacono, Haroian, McGue, & Bouchard, 1988), electrooculographic and infrared reflection measures of eye tracking (Iacono, 1982; Katsanis, Iacono, Taylor, & Hammer, 1998), and emotional modulation of the startle eye blink (Carlson, Katsanis, Iacono, & McGue, 1997). Several recent investigations have reported linkage between psychophysiological variables and chromosomal loci, including the P50 (Freedman et al., 1997) and P300 components of the event-related potential (ERP) (Begleiter et al., 1998), smooth pursuit eye tracking (Arolt et al., 1996), and low-voltage EEG (Steinlein, Anohkin, Mao, Schalt, & Vogel, 1992).

In conclusion, the main advantage of the endophenotype lies in the identification of genetic risk and facilitating the search for susceptibility genes. The remainder of this article will illustrate how various psychophysiological measures have the potential to serve as endophenotypes for disorders related to substance abuse and schizophrenia.

Substance Use Disorders: The Minnesota Twin Family Study

Background

Launched over 10 years ago, the Minnesota Twin Family Study (MTFS) is an epidemiological, longitudinal investigation of over 1,350 pairs of twin children and their parents (over 2,700 adults). Because Minnesota birth records are public, we could access the entire population of state-born twins for any given year. Starting with these records, we were able to locate over 90% of the twins. Of the located families who satisfied inclusion eligibility criteria (e.g., both twins still living with at least one biological parent in the state of Minnesota), over 80% accepted the invitation to spend a full day in our laboratory. At the time they are recruited, the twins are either 11 or 17 years old. Each age cohort is to be followed for at least 9 years, until the 11-year olds are 20 and the 17-year olds are 26. Using this cross-sectional longitudinal design, we hope to investigate how genes and environment combine to influence the development of substance use and related disorders from preadolescence through young adulthood.

The assessment of the twins and their parents contains multiple components (Iacono, Lykken, & McGue, 1996). The twins are simultaneously tested in parallel psychophysiology laboratories during the morning while their parents undergo structured clinical interviews designed to yield DSM-III-R (American Psychiatric Association, 1987) diagnoses and selected diagnoses from other classification systems. In the afternoon, the twins undergo similar interviews, complete cognitive assessments, and fill out self-report inventories while their fathers are tested in the psychophysiology laboratory. Because mothers are interviewed both about their own mental health and that of their twin offspring and must provide ancillary information about the twins and the family, they are not tested in the psychophysiology laboratory during the intake assessment. The parents and the older twins complete Tellegen's (1982) Multidimensional Personality Inventory (MPQ), a factor analytically derived self-report instrument consisting of 11 primary and three higher-order personality scales that has been used broadly in personality research.

A central hypothesis of the MTFS is that the genetic liability for substance use disorders is mediated in part by personality traits, psychopathology, and central nervous system processes characterized by behavioral disinhibition. Included in the substance-abuse psychopathology spectrum, in addition to alcoholism and other substance use disorders, are conduct, oppositional defiant, attention deficit and antisocial personality disorders. Various lines of

research support this contention. Substance use disorders are often comorbid with externalizing disorders in children (Weinberg, Rahdert, Colliver, & Glantz, 1998; Wilens, Biederman, Spencer, & Frances, 1994) and adults (Gorenstein & Newman, 1980; Helzer & Pryzbeck, 1988). Behavioral genetic studies have shown that genes influence the development of substance abuse (Grove et al., 1990; Kendler & Prescott, 1998; McGue, 1995; Pickens et al., 1991; True et al., 1997; Tsuang et al., 1996) and externalizing behavior (Levy, Hay, McStephen, Wood, & Waldman, 1997; Lyons et al., 1995; Slutske et al., 1997) as well as their co-occurrence (Cadoret, Troughton, O'Gorman, & Heywood, 1986; Cadoret, Yates, Troughton, Woodworth, & Stewart, 1995; Cloninger, Bohman, & Sigvardson, 1981). Personality characteristics are also heritable (DiLalla, Carey, Gottesman, & Bouchard, 1996; Tellegen et al., 1988) and associated with substance abuse risk (Cloninger, Sigvardson, Reich, & Bohman, 1988; Sher & Trull, 1994).

Findings from the MTFS are also consistent with our central hypothesis. Comorbid alcohol and drug use disorders were evident in a high proportion (up to 70%) of MTFS fathers who had conduct disorder as children, displayed antisocial behavior as adults, or were diagnosed with antisocial personality disorder (ASPD) (Elkins, Iacono, Doyle, & McGue, 1997). Constraint, a MPQ higher-order personality dimension characterized by a tendency to inhibit behavioral responses and adhere to generally accepted societal norms (Tellegen, 1982), was also related to externalizing psychopathology. Fathers with ASPD obtained especially low scores on this personality dimension (Elkins et al., 1997). Both MTFS alcoholic fathers and mothers have been found to have low scores on constraint (McGue, Slutske, Taylor, & Iacono, 1997). Fathers with severe alcoholism characterized by an early age of onset, multi-generational history of problem drinking, and antisocial behavior were found to have especially low constraint scores (McGue et al., 1997), as were both alcoholic mothers and fathers with comorbid substance use disorders (McGue, Slutske, & Iacono, 1998). In addition, alcoholic fathers with comorbid ASPD had significant histories of illicit drug use compared with depressed alcoholic individuals without ASPD or alcoholic individuals with neither depression nor ASPD (Holdcraft, Iacono, & McGue, 1998). Analyses of MTFS twin data indicate that both ADHD (Sherman, Iacono, & McGue, 1997; Sherman, McGue, & Iacono, 1997) and ASPD (Doyle, McGue, & Iacono, 1998) are heritable and associated with substance abuse (Disney, Elkins, McGue, & Iacono, 1998).

Because substance use is uncommon among the 11-year old MTFS cohort, and because our recruitment of girls lagged the recruitment of boys by several years, we have focused our initial data analyses on the boys in 17-year-old cohort. As examination of Table 1 reveals, this cohort contains children who have already developed substance use disorders and those children who remain actuarially at high risk to do so because one or both of their parents is affected. Both substance use and childhood externalizing disorders are far more common among those in the parental high risk groups.

Psychophysiological Assessment

At the time the MTFS was begun, there was scant literature investigating the psychophysiology of substance use disorders other than alcoholism. Hence, the psychophysiological paradigms selected for the MTFS were those derived from: (1) theoretical notions of the psychophysiological substrate underlying behavioral disinhibition; (2) established protocols that yield robust results when applied to the study of externalizing disorders; (3) similar paradigms applied to the study of alcoholism; and (4) tasks that

Table 1. Prevalence of Psychopathology (Percent Affected) in 17-Year-Old Children Whose Parents Have DSM-III-R Alcohol Dependence or Illicit Drug Abuse/Dependence

Disorders in children	Family risk status			
	Very high (<i>n</i> = 50)	High (<i>n</i> = 228)	Low (<i>n</i> = 280)	Risk ratio (VH + H:L)
Substance use disorders				
Nicotine dependence	26.0	17.1	6.4	2.9
Alcohol abuse/dependence	34.0	19.3	10.0	2.2
Illicit drug abuse/dependence	16.0	9.2	2.5	4.2
Other disorders				
ADHD	12.0	11.0	2.1	5.2
Conduct disorder	42.0	31.1	12.1	2.7
Oppositional defiant disorder (without comorbid conduct disorder)	14.0	6.1	2.5	3.0
Major depression	16.0	7.5	2.9	3.2
Any disorder	76.0	50.9	25.4	2.2
Effects of comorbidity				
Any 2 substance disorders	20.0	14.5	3.6	4.3
Any 2 externalizing disorders	10.0	8.8	0.7	12.6
Any 2 disorders	40.0	28.9	8.9	3.5
Any 3 disorders	26.0	15.4	3.9	4.4

Note: Family risk: very high (VH) = both parents affected; high (H) = one affected parent; low (L) = neither parent affected. ADHD = attention deficit hyperactivity disorder. Chi-square tests calculated for each disorder category were statistically significant (all $ps < .01$), confirming that high-risk children have elevated rates of disorder.

yield psychophysiological deviations known to be influenced by genes and associated with psychopathology. In this section, findings from several different psychophysiological protocols are presented that highlight some of the initial success we have had with this strategy for selecting measures.¹

Cooltest. Almost 20 years ago, Gorenstein and Newman (1980) posited that a common deficit in inhibitory control may underlie the association between substance dependence and externalizing psychopathology. More recently, Fowles' (1988) theorized that disinhibited psychopathology may be related to a weak inhibitory control system (Gray's behavioral inhibition system, 1975) that governs inhibition of approach behavior in the face of cues signaling punishment and is associated with psychophysiological response deficits. The notion that substance-abusing individuals have a behavioral inhibition system deficit is also consistent with Finn, Kessler, and Hussong (1994), who reported that poor electrodermal conditioning to stimuli predicting electric shock was associated with familial risk for alcoholism among nonalcoholic males.

Examining MTFS 17-year-old boys, Taylor, Carlson, Iacono, Lykken, and McGue (in press) explored the possibility that a deficit in inhibitory control might serve as an endophenotype for substance abuse risk using a paradigm based on Lykken's (1959) notion of "preception." Preception refers to the ability to take advantage of the predictability of an aversive stimulus to diminish its psychological impact. Taylor et al. posited that those who show

poor preception would abuse substances. This hypothesis was evaluated using a procedure called "cooltest" in which autonomic measures were recorded to a noise blast that varied in its predictability.

Participants watched a sweep second hand move around a clock face in one of two conditions during which they were instructed to "try to stay cool and not react to the loud noise." In the predictable condition, the 2-s blast of 90-dB white noise was presented when the second hand reached a tick mark on the clock face. In the unpredictable condition, the aversive stimulus was presented without warning. Preception was assessed by determining how skin conductance responses (SCR) were modulated as a function of stimulus predictability. That is, good preception was defined as a smaller skin conductance response to the aversive stimulus when it was predictable (SCR_p) than when it was unpredictable (SCR_{up}), and poor preception reflected the reverse pattern. Each of the 150 boys evaluated was assigned an electrodermal modulation score $\{(SCR_{up} - SCR_p)/SCR_{up}\}$ reflecting the proportionate change in skin conductance amplitude to the blast when it was made predictable.

Good modulators responded relatively more strongly to the unpredictable stimuli (i.e., their electrodermal modulation scores were positive) whereas the poor modulators responded relatively more strongly to the predictable blasts (i.e., their scores were negative). Participants were assigned to these groups based on their falling at the extremes (bottom and top sixths) of the distribution of modulation scores. Moderate modulators came from the middle of the modulation distribution. In this paradigm, those in the poor modulation group were hypothesized to be at psychophysiological high risk for substance abuse and to possess the putative endophenotype. The results for the primary dependent variable are presented in Figure 1, which indicates that symptoms of alcohol, nicotine, and cannabis dependence significantly differentiate the three modulation groups, all $F_s(2,72) > 3.54$, $ps < .05$, with post hoc tests confirming that good modulators had significantly fewer symptoms of alcohol and nicotine dependence than poor modulators.

¹Because the MTFS is an ongoing investigation, the number of subjects available for analysis for a given psychophysiological measure varies according to when the procedure was introduced to the study, how many subjects have been evaluated with the procedure to date, and the extent to which the data have been processed. For these reasons, the number of subjects included in these preliminary analyses varies somewhat from task to task.

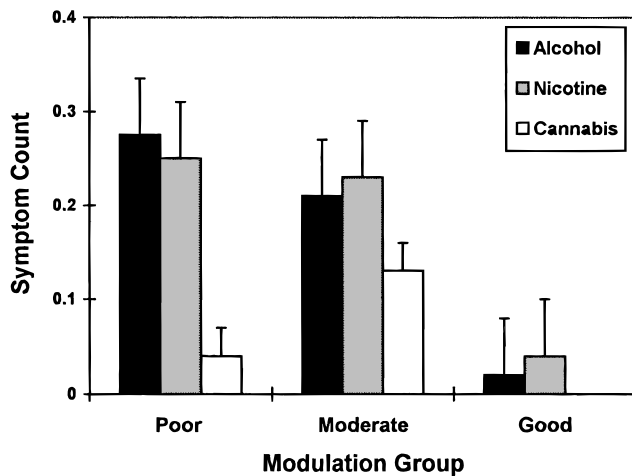


Figure 1. Mean (log transformed) substance dependence symptom counts (with standard errors) from the “coolest” study. Poor modulators are 17-year-old boys drawn from the general population who were selected to be at psychophysiological high risk for substance abuse because they gave larger electrodermal responses to a temporally predictable than an unpredictable blast of white noise. Good modulators responded more strongly to the unpredictable stimulus. Moderate modulators were selected from the middle of the distribution of electrodermal modulation scores. There were 25 subjects in each modulation group. From Taylor et al. (in press).

Inhibiting reflexive saccades. If an individual fixates on a target that moves abruptly, the natural response is to generate a saccadic eye movement in pursuit of the target. “Antisaccade” tracking tasks require a subject to inhibit this natural tendency, instead generating a saccade in the direction opposite to target movement. Recent research on schizophrenia patients and their relatives (Clementz, McDowell, & Zisook, 1994; Katsanis, Kortenkamp, Iacono, & Grove, 1997) has shown that these individuals generate much higher than normal error rates (i.e., they follow the target rather than first generating an antisaccade). These findings have been interpreted as indicating that poor antisaccade task performance may be a susceptibility indicator for schizophrenia. Because elevated antisaccade error rate may be indicative of frontal lobe brain pathology (Guitton, Buchtel, & Douglas, 1985; Pierrot-Desilligny, Rivaud, Gaymard, & Agid, 1991), the failure of inhibitory control demonstrated with this task has been interpreted as consistent with the hypothesis that schizophrenia patients and their at-risk family members may possess a frontal lobe deficit. Given the evidence that this task is sensitive to frontal lobe dysfunction plus the possibility that disturbances in frontal lobe functioning are present in substance abuse-related psychopathology (e.g., Gorenstein, 1987), we thought it would be of interest to examine the association between antisaccade error rates and genetic risk for drug abuse in a subset of MTFS 17-year-old boys.

For this preliminary analysis, we compared the antisaccade error rates of low-risk and high-risk boys. Boys in the low-risk group had no substance use diagnosis (i.e., no alcohol or illicit drug abuse or dependence and no nicotine dependence) and their fathers had no alcoholism, illicit drug abuse/dependence, or relatives with a history of alcoholism. High-risk boys had fathers who had an illicit drug abuse or dependence diagnosis with comorbid ASPD. The results, presented in Figure 2, indicate a substantially higher error rate in the high-risk boys, $t(156) = 2.32, p < .05$. If the seven boys who have already developed substance use disor-

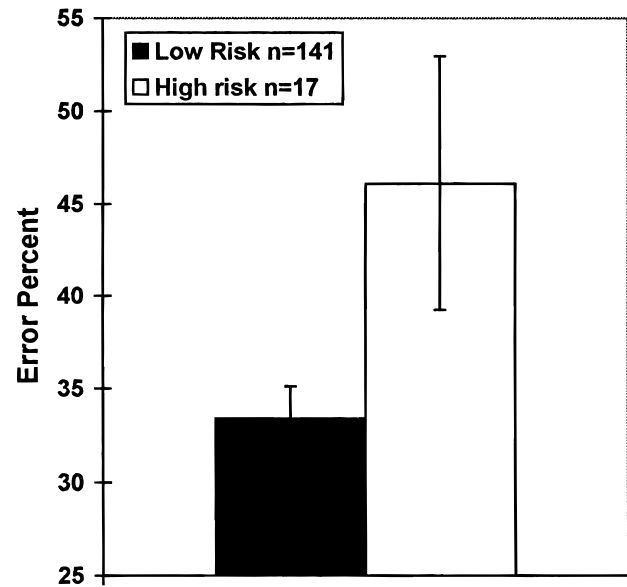


Figure 2. Means and standard errors indicating antisaccade error rates for 17-year old boys. The high-risk group is composed of boys with illicit drug abuse/dependent fathers who have comorbid antisocial personality disorder (ASPD). Low-risk boys have no substance use disorder and a negative paternal history for alcoholism.

ders are omitted from the high-risk group, the error rate of the remaining unaffected high-risk boys (52.1%) was also significantly higher than that of the low-risk comparison group, $t(149) = 2.68, p < .01$. Eight pairs of monozygotic (MZ) twins were discordant for illicit drug abuse/dependence at age 17. The antisaccade error rates of these affected and unaffected twins are contrasted to that of MZ twin pairs concordant for the absence of substance use disorders and related psychopathology in Figure 3. The three groups differed significantly, $F(2,41) = 3.78, p < .05$, with the affected twins making significantly more errors than the normal

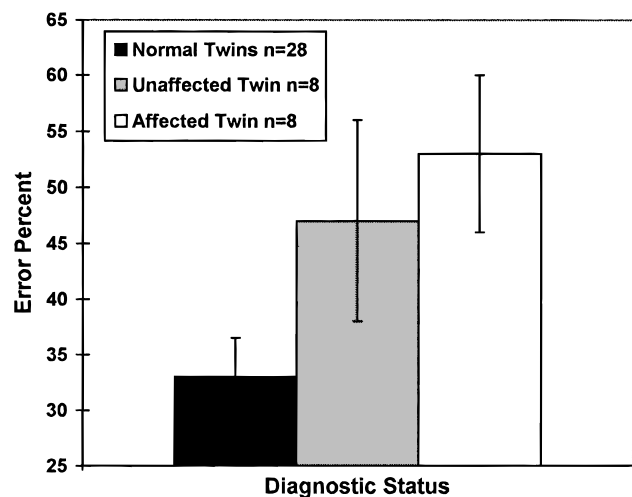


Figure 3. Mean antisaccade error rates with standard errors for normal 17-year-old twin boys concordant for an absence of psychopathology and identical twins discordant for illicit drug abuse/dependence.

twins concordant for the absence of psychopathology. The anti-saccade error rates of the unaffected co-twins did not differ significantly from either of the other two groups. The results indicate that the discordant twins are concordant for high error rate, a rate that is similar to that of the paternal high-risk subjects in Figure 2. These results suggest that it is genetic susceptibility, not the presence of a substance diagnosis per se, that is responsible for the elevated error rates in the high-risk and unaffected twins.

That the relatives of both schizophrenia patients and substance abusers perform this task poorly raises the possibility that at least some individuals with schizophrenia and some with substance abuse share a similar frontal lobe dysfunction, perhaps involving a common genetic mechanism. On the strength of the data available thus far, however, such a conclusion would be highly speculative, with the results perhaps more parsimoniously (but also tentatively) explained as an example of equifinality.

Diminished P3 amplitude. Begleiter and colleagues (Begleiter, Porjesz, Bihari, & Kissin, 1984) were the first to show that a late positive component of the cerebral ERP may serve as an endophenotype for alcoholism. This component, typically referred to as P3 or P300 because it is the third positive-going wave and has a latency of more than 300 ms, reflects information processing demands related to the task at hand. P3 is typically studied using an “oddball” task in which infrequently occurring stimuli require special attention because subjects must count them or otherwise react to them. In their study, Begleiter et al. (1984) found that children who had not been exposed to alcohol had small P3 amplitudes if their fathers were alcoholic. Although there have been failures to replicate this initial finding, a meta-analysis of about 30 investigations carried out by Polich, Pollock, and Bloom (1994) indicated that a positive paternal history of alcoholism was associated with reduced P3 amplitude in male offspring. In addition, reduced P3 recorded at about age 11–12 years has been found to predict self-reported substance use (Berman, Whipple, Fitch, & Noble, 1993) and the development of alcoholism (Hill, Steinhauer, Lowers, & Locke, 1995) 4–8 years later.

We have extended this line of research in the MTFs by using the oddball task employed by Begleiter et al. (1984) with our epidemiological samples of children. In this procedure, subjects watched a computer screen while three different types of stimuli were presented. Most of the stimuli were plain ovals. However, for a third of the stimuli, the ovals were made to look like the superior view of a head with either the nose pointing up or rotated so it was pointed down. In addition to the nose, an ear was presented, but only on one side of the “head.” When a head appeared, subjects were required to press one of two buttons to indicate whether the ear was on the left or right side of the head. These stimuli elicit pronounced P3 waves compared with the plain ovals. To simplify the presentation of P3 results from this task, the results reported here were derived from ERPs recorded at Pz unless otherwise noted (for a detailed exposition of the method used to record P3, see Katsanis, Iacono, et al., 1997).

A variety of studies have shown that various ERP components are heritable (for a recent review, see Boomsma, Anokhin, & Geus, 1998). To determine if P3 amplitude in the rotating heads task was heritable, we examined male 17-year-old MZ and dizygotic (DZ) twins and found that about 79% of the variance in P3 amplitude was additively genetically determined. The P3 amplitudes of the MZ twins were remarkably similar. To illustrate this similarity, P3 amplitude recorded from the left hemisphere (at P₃) was correlated with that from the right hemisphere (at P₄), both within

individuals and between members of a twin pair. Within individuals, the correlation was .87. For MZ twins, the correlation between P3 amplitude from one hemisphere in one twin with P3 amplitude from the other hemisphere in his co-twin was .82. The corresponding cross-twin correlation in DZ twins was only .28. This correlational analysis indicates that MZ twins are about as similar to themselves in P3 amplitude across hemispheres as they are to their co-twin, and that P3 similarity across hemispheres is genetically mediated.

Are 17-year-olds with small P3s likely to have psychopathology associated with behavioral disinhibition? To answer this question, Carlson, Katsanis, Iacono, and McGue (1998) identified participants from the extremes of the distribution of P3 amplitudes such that two groups were formed, one with very small and the other with very large P3s. A third group from the middle of the P3 distribution (characterized as having “average” amplitude) was also identified. Each group composed approximately 1/12 of the entire sample. As Figure 4a illustrates, none of the individuals in the large P3 group had a substance use diagnosis. A chi

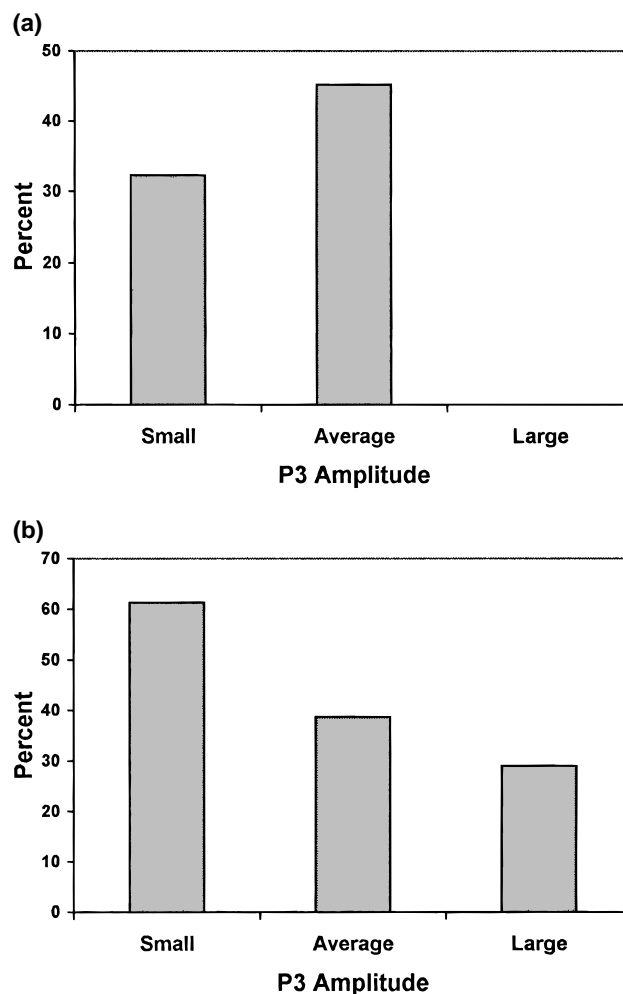


Figure 4. Percentage of 17-year-old boys with DSM-III-R alcohol or illicit drug dependence (a) or externalizing psychopathology (b) as a function of P3 amplitude. Participants, drawn from the general population, were selected to be at psychophysiological high risk because they had large, average, or small P3 amplitudes in a visual oddball task. There were 31 subjects in each group. From Carlson et al. (1998).

square test carried out on the proportion of affected individuals in each P3 group was statistically significant, $\chi^2(2, N = 93) = 17.52$, $p < .001$. The psychophysiological high risk group, those with small P3 amplitudes, contained significantly more cases of alcohol, illicit drug, and nicotine dependence than the large P3 group. Figure 4b provides corresponding data for the proportion of participants in each group with an externalizing disorder. Again, group differences are statistically significant, $\chi^2(2, N = 93) = 6.93$, $p < .05$. The rate of disorder was highest in the small P3 group, which differed significantly from the large amplitude group. Consistent with the notion that the endophenotype is identifying gene carriers, these findings indicate that those selected for the presence of the hypothetical endophenotype had substantially more manifest spectrum psychopathology than those without it.

Initial findings from the twin's fathers and the 17-year-old boys also support the conjecture that P3 is identifying risk for substance use disorders and other forms of disinhibitory psychopathology. Figure 5 indicates how P3 varies as a function of alcoholism comorbidity in fathers who were included in Holdcraft et al.'s (1998) study of the effects of comorbidity on alcohol use. For the men in this particular study, alcoholism was considered present if subjects satisfied criteria for DSM-III or DSM-III-R alcohol dependence, Research Diagnostic Criteria (Spitzer, Endicott, & Robins, 1978) alcoholism, or the alcoholism criteria of Feighner et al. (1972). Fathers in the control group were free of alcoholism, drug abuse or dependence, and ASPD. Fathers in all of the other groups had alcoholism plus the indicated comorbid disorder(s), but no other comorbid disorder. Although the samples for this preliminary analysis are small, the group main effect was statistically significant, $F(4, 94) = 2.84$, $p < .05$, with post hoc tests indicating that alcoholism with comorbid drug abuse and alcoholism with both comorbid drug abuse and ASPD were associated with P3 amplitudes that were significantly smaller than those of the control subjects.

Figures 6 and 7 provide a comparison of P3 amplitude in normal boys (i.e., those free of alcohol, illicit drug, and nicotine substance disorders, ADHD, conduct disorder, and oppositional defiant disorder, whose fathers are free of alcohol dependence, illicit drug abuse/dependence, and ASPD) to boys with these

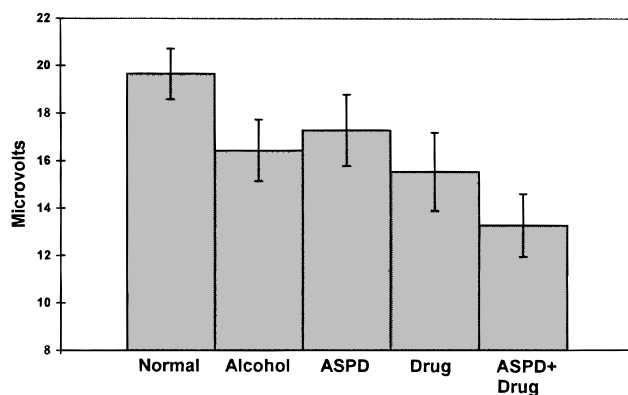


Figure 5. P3 amplitude (mean and standard error) as a function of alcoholism comorbidity in fathers of twin boys. Normal = no disorder ($n = 40$); Alcohol = alcoholism without comorbid psychopathology ($n = 19$); ASPD = antisocial personality disorder plus alcohol dependence ($n = 12$); Drug = illicit drug dependence plus alcohol dependence ($n = 19$); ASPD+Drug = antisocial personality disorder with both drug and alcohol dependence ($n = 9$).

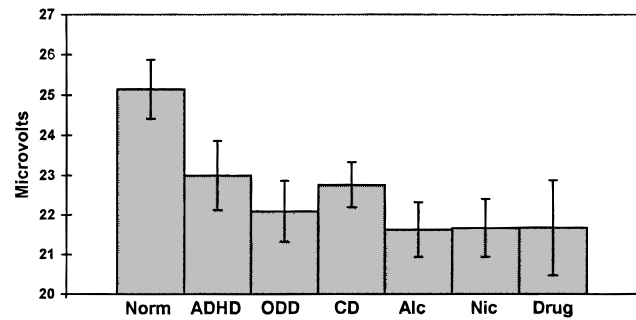


Figure 6. P3 amplitude (mean and standard error) in 17-year-old boys as a function of psychiatric status. Norm = no disorder and father free of alcohol dependence, illicit drug abuse/dependence, and antisocial personality disorder ($n = 129$); ADHD = attention-deficit hyperactivity disorder ($n = 54$); ODD = oppositional defiant disorder ($n = 85$); CD = conduct disorder ($n = 172$); Alc = alcohol abuse or dependence ($n = 89$); Nic = nicotine dependence ($n = 66$); Drug = illicit drug abuse or dependence ($n = 34$).

substance-related disorders² (Figure 6) or who are at familial risk because their father has a lifetime diagnosis of either alcohol dependence, illicit drug abuse/dependence, or ASPD (Figure 7). Compared with the normal control participants, individuals in all but one of the affected groups in Figure 6 have significantly smaller P3 amplitudes, all $t_s > 2.21$, $p_s < .05$. The one exception was the difference between the ADHD and control group, which fell just short of conventional statistical significance, $t(128.3) = 1.88$, $p = .06$. Again with one exception, the familial high-risk groups in Figure 7 have significantly smaller P3 amplitudes than those in the normal group, both $t_s > 2.11$, $p_s < .05$. The lone exception involves the sons of illicit drug abusing/dependent fathers, $t(175) = 1.40$, $p = .16$. Those whose fathers have ASPD (almost all of whom have a comorbid substance use disorder) have especially small P3 amplitude, raising the possibility that P3 is especially sensitive to genetic risk for substance abuse when a comorbid antisocial disorder is present.

Because a subset of the 17-year-old participants have now been seen for their first follow-up assessment at age 20, it is possible to determine if P3 recorded at intake predicted the development of subsequent substance abuse. For Figure 8, the baseline represents the mean P3 amplitude of those without a substance abuse spectrum diagnosis (i.e., no ADHD, conduct disorder, oppositional defiant disorder, or alcohol, illicit drug, or nicotine disorder) at either age 17 or 20. The P3 amplitude of those who developed any substance use disorder and specifically alcohol or illicit drug abuse or dependence or nicotine dependence during the 3-year follow-up period is presented as the difference from the comparison group in effect size. New cases of substance abuse at age 20 had significantly smaller P3s than control subjects at age 17, $t(186) = 2.96$, $p < .01$. In addition, new cases of alcohol abuse/dependence had significantly smaller P3 amplitudes at age 17, $t(120) = 2.91$, $p < .01$. Those individuals who developed illicit drug abuse/dependence or nicotine dependence over this 3-year interval, although they had small P3s at study intake and had effect sizes comparable to those of the other groups, did not have significantly smaller P3s at age 17 when compared with the control group.

²MTFS participants diagnosed with ADHD satisfied either DSM-III or DSM-III-R criteria for this disorder (see Sherman, McGue, et al., 1997). All other childhood disorder diagnoses were based on DSM-III-R.

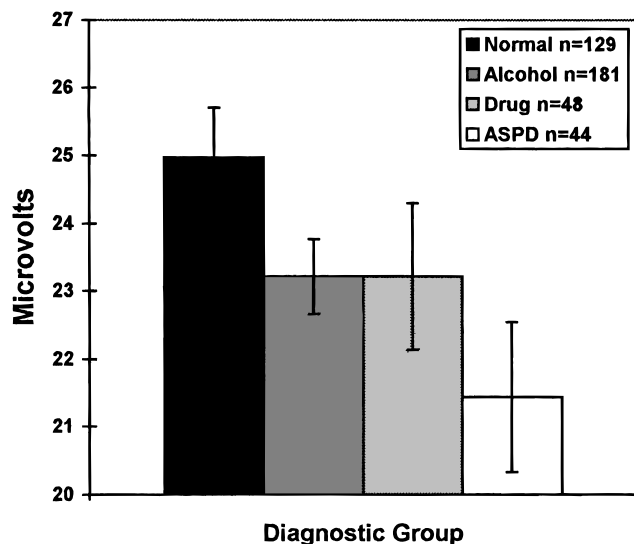


Figure 7. P3 amplitude (mean and standard error) in 17-year-old boys as a function of paternal substance use and antisocial personality disorder (ASPD). Normal = no disorder and father free of alcohol dependence, illicit drug abuse/dependence, and ASPD; alcohol = father has alcohol dependence; Drug = father has illicit drug abuse or dependence; ASPD = father has antisocial personality disorder.

The effect sizes evident in Figure 8 are consistent with expectation given what we know about the link between P3, substance abuse risk, and age. In their meta-analysis, Polich et al. (1994) found that effect sizes for the difference in P3 amplitude between

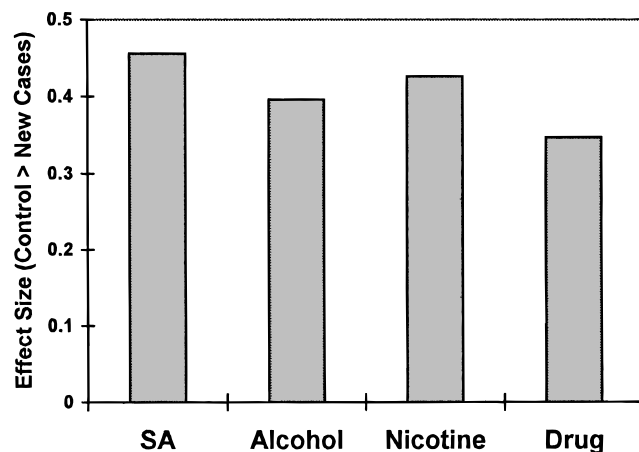


Figure 8. Relationship between P3 amplitude at age 17 and substance diagnosis at age 20 in young males. The baseline “0” represents the P3 amplitude of normal boys with no childhood externalizing diagnosis or substance diagnosis at either age ($n = 80$). The bars indicate how much smaller the P3 amplitudes were (indicating the effect size of the difference with the effect size based on the standard deviation of the entire sample of MTFs 17-year-old boys) of the subjects who had no substance use diagnosis of any kind at age 17 but who subsequently developed a substance use disorder between the ages of 17 and 20. SA = all new cases of any substance use disorder ($n = 108$); Alcohol = new cases of alcohol abuse or dependence ($n = 90$); Nicotine = new cases of nicotine dependence ($n = 32$); Drug = new cases of illicit drug abuse or dependence ($n = 23$).

sons of alcoholic and nonalcoholic men were larger in sons younger than 17. For older offspring, the average effect size for tasks similar to the one we used was .48 (95% confidence interval, .18–.78), a value close to those reported here. Steinhauer and Hill (1993) have posited that the reduction of effect size with age may reflect maturational delay in the high-risk children. As high-risk children age, their P3 amplitudes are hypothesized to increase in size, more closely approximating the P3 amplitude of the offspring of nonalcoholics. Moreover, many of the P3/alcoholism risk studies have focused on the sons of treated alcoholics with multigenerational family histories of alcoholism, factors that may be important to the magnitude of group differences (Polich et al., 1994). The MTFs data were derived from an epidemiological sample; subjects were not selected for density of alcoholism in their families or because their fathers were in treatment. Because alcoholics with either of these features might be expected to have a stronger genetic loading than those identified from a community-based sample, it would be unreasonable to expect the endophenotype to be present to the same degree in the members of MTFs families.³ Finally, the data reported here concern those children who actually develop substance use disorders over a 3-year period, a relatively short time, after those individuals already affected at age 17, who were known to have small P3 amplitudes (see Fig. 6), were removed from the sample. Stronger effects might emerge if the predictive power of P3 assessments made well before the age of 17, before the emergence of diagnosable disorder, were investigated.

The many studies in psychophysiology for which P3 amplitude serves as a dependent variable are motivated in part by the sensitivity of P3 to a wide variety of psychological manipulations. This fact complicates the decision about what meaning to give the reduced P3 observed in high-risk children. Reduced P3 amplitude has been hypothesized to reflect a cognitive efficiency deficit (Begleiter et al., 1984), a motivational deficit (Ramsey & Finn, 1997), and as noted above, developmental delay (Steinhauer & Hill, 1993). Diminished P3 amplitude has also been hypothesized as indicating cortical disinhibition (Ramachandran, Porjesz, Begleiter, & Litke, 1996; Woodward, Brown, Marsh, & Dawson, 1991). Although it is not possible to favor one of these possibilities over others based on

³An interesting question in an epidemiological study of the offspring of alcoholics is what constitutes an appropriate “normal” comparison sample. The choice of this group will obviously affect estimates of effect size. As noted, studies that examine the relationship between P3 amplitude and alcoholism risk select as subjects the offspring of men who are receiving treatment for alcoholism and who may have one or more biological relatives with the disorder. These individuals are then compared with samples of offspring with a negative family history of alcoholism. A consequence of this approach is that the high-risk group is derived from families with relatively severe alcoholism; consequently, they might be expected to differ strongly from a typical control sample of convenience. In an epidemiological study such as the MTFs, the severity of alcoholism in the fathers of the boys designated as at high risk is relatively mild, so they may be unlikely to differ from controls unless the controls are selected so as not to overlap the alcohol-related psychopathology of the high-risk group. As Table 1 illustrates, externalizing psychopathology is highly prevalent in the offspring of high-risk families. In addition, children with externalizing disorders have small P3 amplitudes (see Fig. 6). These observations highlight the desirability of eliminating as comparison subjects children with externalizing disorders. In fact, the MTFs data reveal that P3 size in the offspring of nonalcoholic fathers increases if subjects with characteristics typically observed in samples at high risk are eliminated. For instance, P3 size can be increased for the control subjects used in Figure 6 by dropping from this “normal” group the sons of fathers who (a) have male relatives with alcohol problems (P3 increase = 1.0 μ V), (b) report heavy drinking in the absence of a formal DSM alcohol diagnosis (P3 increase = 1.6 μ V), or (c) have either of these characteristics (P3 increase = 2.0 μ V).

available evidence, all are consistent with current theorizing and empirical findings regarding the psychological factors underlying the development of substance use disorders.

Preliminary Conclusions

Because most of the children in the MTFs have not passed through the age of risk for the development of substance use psychopathology, it is too early to know for certain how valuable psychophysiological measures will be as indicators of risk in this sample. However, the initial results, taken in conjunction with the findings of other investigators, suggest various measures, especially the P3 component of the ERP, have the potential to identify genetic susceptibility. These preliminary MTFs data indicate that individual differences in P3 amplitude are heritable, associated with concurrent substance abuse and externalizing disorders, related to familial risk, and predictive of the subsequent development of alcohol and drug abuse. Small P3 amplitude is not specific to substance use and externalizing disorders (e.g., Wagner, Roschke, Fell, & Frank, 1997). However, to the extent that diminished P3 amplitude appears in other disorders like schizophrenia and depression, the finding may reflect the operation of different underlying processes (e.g., Roschke et al., 1996; Wagner et al., 1997). Also, for these other disorders, unlike the situation for alcoholism, small P3 may not identify genetic risk. For example, in high-risk samples composed of the nonadult children of schizophrenia patients, P3 has not been associated with the development of schizophrenia (Friedman & Squires-Wheeler, 1994).

These MTFs findings also support the hypothesis that at least for males, psychophysiological endophenotypes may index genetic risk not just for alcoholism, but for a spectrum of substance abuse-related psychopathology that includes alcoholism, illicit drug abuse and dependence, nicotine dependence, externalizing disorders of childhood, and adult antisocial behavior. These findings are thus consistent with data from the MTFs illustrating that these disorders run together in families (e.g., see Table 1) as well as from other investigations suggesting that genes may be especially important to the development of a subtype of alcoholism characterized by the co-occurrence of antisocial behavior and drug abuse (Cloninger, 1987).

Eye Tracking and Schizophrenia

Smooth pursuit eye movements are elicited by low velocity targets (e.g., a swinging pendulum) in continuous motion. The smooth pursuit system locks the eyes on target, matching target velocity and direction when it is functioning properly. If the eyes lag behind the target, the ocular motor system will generate saccades to refoveate the target on the retina. Almost all subjects can follow a pursuit-eliciting target with their eyes, but it is not possible for individuals doing a smooth pursuit task to discern how well they are doing the task, that is, whether they are following the target with mostly smooth or mostly saccadic eye movements. By comparing a subject's oculomotion with target motion, it is possible to determine eye tracking accuracy. Smooth pursuit tracking proficiency is easily quantified from tasks with a duration of 1 min or less using targets that can be generated on computer monitors. Typically, smooth pursuit is investigated using oscillating targets driven sinusoidally at a frequency of about 0.4 Hz or constant velocity targets with up to a velocity of about 25 degrees/s. Eye movements can be recorded using either electrooculography (EOG), infrared (IR) recording, or other techniques. Because biopotential noise makes it difficult to use EOG to measure small eye move-

ments precisely (Iacono & Lykken, 1981), most investigators are now relying on IR methods to assess smooth pursuit.

Several procedures have been used to quantify smooth pursuit tracking. These include (1) ratings based on visual inspection of EOG or IR records; (2) the calculation of the root-mean-square (RMS) error deviation between the tracking and target waveforms; (3) the signal-to-noise ratio, in which the signal is defined according to the amount of power present in the tracking record at the fundamental frequency of the target and the noise as the power generated at other frequencies; (4) the gain of the response signal defined as the ratio of eye-to-target velocity; and (5) frequency counts of different types of saccades. None of these approaches to quantifying deviant pursuit has emerged as the method of choice for assessing smooth tracking accuracy. However, RMS error has been shown to have excellent psychometric properties and appears to provide a biologically meaningful measure of eye tracking performance (Clementz, Iacono, & Grove, 1996). Individual differences in RMS error associated with pursuit tracking appear to be heritable (Iacono, 1982), stable over time in both normal (Iacono & Lykken, 1981) and schizophrenia subjects (Gooding, Iacono, & Beiser, 1994), and associated with genetic risk for schizophrenia (Iacono & Clementz, 1993).

There are now over 500 scientific articles dealing with eye tracking in psychiatric patients. This literature, which has been reviewed in detail elsewhere (Hutton & Kennard, 1998; Iacono & Clementz, 1993; Levy, Holzman, Matthyse, & Mendell, 1993), supports the following conclusions:

1. Schizophrenia patients show smooth pursuit eye tracking dysfunction at a rate that is substantially higher than normal. This dysfunction is characterized both by a failure of the pursuit system to match eye-to-target velocity, and by the inclusion of catch-up saccades that refoveate the target and intrusive saccades that move the eyes off target.
2. The first-degree relatives of schizophrenia patients who are without manifest schizophrenia also show elevated rates of eye tracking dysfunction.
3. There is no consensus in the literature on the specificity of smooth tracking dysfunction to schizophrenia, with some studies finding that mood disorder patients, especially those treated with lithium, also showing tracking deviations. However, there appears to be familial specificity of tracking dysfunction to schizophrenia in that the first-degree biological relatives of schizophrenia patients have this deficit whereas the relatives of patients with other forms of severe psychopathology do not.
4. An extensive literature supports the conclusion that poor smooth pursuit eye tracking performance appears to be an excellent candidate endophenotype for schizophrenia.⁴

⁴In an analysis of 12 sets of monozygotic twins discordant for schizophrenia, Litman and colleagues (Litman et al., 1997) reported that the affected twins showed deviant smooth pursuit but their normal co-twins did not. The authors interpreted their findings as indicating that dysfunctional pursuit was not a good candidate endophenotype. The findings from this study and their interpretation have been seriously challenged by Holzman, Levy, Matthyse, and Abel (1997) for inadequate sample size, inclusion of comorbid brain disease in two affected twins, and the use of idiosyncratic eye movement scoring procedures. In addition, intraclass correlations indexing similarity in the performance of the discordant twin pairs indicate similar performance. It is thus *not* the case that the Litman et al. report offers a serious challenge to the hypothesis that deviant smooth pursuit is a genetically transmitted trait associated with schizophrenia.

5. Left unanswered in this literature is whether deviant eye tracking in children will predict subsequent development of schizophrenia or whether individual differences in ocular motor system maturation would render such a test meaningless. Katsanis, Iacono, and Harris (1998) found that smooth pursuit performance is impaired among preadolescents, becoming optimal in late adolescence. Because young children in general perform poorly, it remains to be determined if poor performance at an early age conveys useful information about genetic risk for the development of schizophrenia.

Does Deviant Tracking Suggest the Presence of a Major Gene?

If eye tracking and schizophrenia share the same diathesis, which reflects the additive effect of a large number of polygenes of small and roughly equivalent effect, then the biological relatives of schizophrenia patients would be expected to produce a normal distribution of eye tracking error scores shifted to the right of the comparable distribution for normal individuals without a relative with schizophrenia. On the other hand, if deviant eye tracking reflects the influence of a single gene, then eye tracking error scores can be expected to be distributed as a mixture of normal distributions (e.g., a bimodal distribution) among schizophrenia relatives. One of these distributions, the one reflecting the eye tracking performance of individuals who are not expressing the eye tracking genotype, would be expected to match that of individuals from the general population. Assuming there are two mixing distributions, the other, reflecting the tracking performance in individuals who are expressing the genotype, would be expected to overlap the normal distribution, but have a different mean.

My colleagues and I examined the distributions of eye tracking data for schizophrenia probands and their first-degree relatives in two different studies drawing families from different geographic regions of North America. The first investigation was an epidemiological study of all individuals in the Vancouver, British Columbia, metropolitan area with a first episode of psychosis (Iacono, Moreau, Beiser, Fleming, & Lin, 1992). Nonpsychotic first-degree biological relatives of probands were also included in the study. The RMS error deviation scores derived from tracking a 0.4 Hz sinusoidal target served as the dependent variable. Schizophrenia and bipolar participants and their families appeared to be distinctly different, with the schizophrenia group showing a bimodal distribution of eye tracking performance (see Figure 9). We used admixture analysis to determine if the data for subjects in these groups were better fit by a model positing two normal mixing distributions than a single distribution. The results indicated that for both schizophrenia probands and their relatives, the data suggested a mixture of two underlying distributions, one of which was associated with distinctly poor performance. Neither bipolar probands nor their relatives showed a similar effect, and their eye tracking was not different from that of nonpsychiatric comparison subjects. These bipolar data are consistent with the conclusion that eye tracking dysfunction shows familial specificity to schizophrenia. In a second study, we replicated these findings for schizophrenia families recruited in Minneapolis and New York, and extended the Iacono et al. (1992) report by showing that the results were the same when both RMS error and gain were used to quantify performance (Clementz, Grove, Iacono, & Sweeney, 1992). Other investigators using RMS error and signal-to-noise ratio measures have reported similar admixture results, both in schizophrenia patients (Blackwood, Clair, Muir, & Duffy, 1991; Ross, Ochs, Pandurangi, Thacker, & Kendler, 1996; Ross et al., 1997; Sweeney

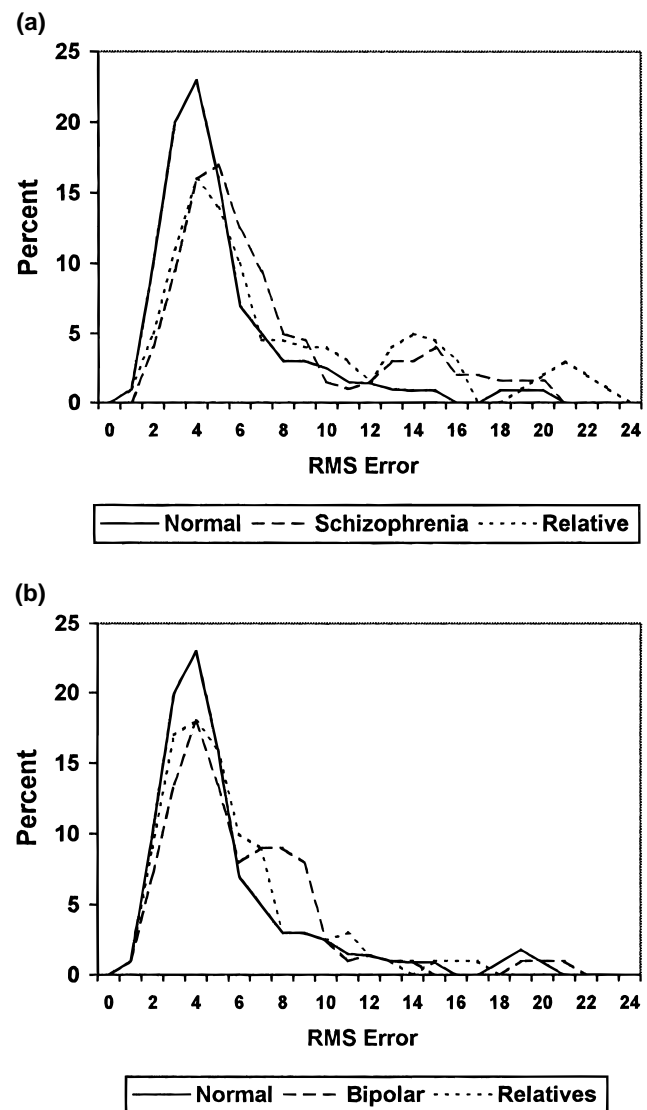


Figure 9. Smoothed frequency histograms depicting the log transformed root-mean-square (RMS) error eye tracking (ET) scores (in arbitrary units) for normal subjects, schizophrenia probands and their relatives (a), and bipolar probands and their relatives (b). Note that few control participants, bipolar patients, or their relatives generated RMS error scores above 12. A substantial fraction of the schizophrenia patients and their relatives, by contrast, produced RMS scores greater than this value. In all, 59% of the schizophrenia patient families contained at least one member with an eye tracking score above 12. From Iacono et al. (1992).

et al., 1993) and in their first-degree relatives (Blackwood et al., 1991). Besides demonstrating that admixture appears to be a robust characteristic of the tracking of schizophrenia family members, these studies suggest that these results are not dependent on the choice of measure for quantifying smooth pursuit.

Several other interesting findings emerged from the studies of Iacono et al. (1992) and Clementz et al. (1992). Only 50–60% of families contained at least one member with distinctly poor eye tracking performance. This finding suggests that eye tracking will be useful as an endophenotype for only some families with schizophrenia. Because our work has shown that schizophrenia patients with negative symptoms, such as flat affect, have especially poor

eye tracking (Katsanis & Iacono, 1991), it is possible that the subset of families with poor eye tracking is characterized by the presence of affected individuals with negative symptoms. This hypothesis receives support from the work of other investigators who have also found negative symptoms to be correlated with pursuit dysfunction (Ross, Thaker, et al., 1996; Sweeney et al., 1994; Sweeney, Haas, & Li, 1992).

Poor eye tracking performance tended to be familial; schizophrenia patients with deviant RMS error scores tended to have first-degree relatives with deviant scores (Figure 10). In addition, schizotypy scores derived from interviews of relatives revealed an association between social-interpersonal signs of schizotypy and deviant tracking. This finding was especially pronounced when only those schizophrenia families with at least one deviant eye tracking member were considered. Assuming that schizotypy is part of the schizophrenia spectrum, observations such as these are consistent with the hypothesis that eye tracking is identifying gene carriers among the relatives. Finally, we found families in which the schizophrenia proband did not have poor tracking but a member of the family did. Such a pattern, coupled with the fact that relatives show deviant smooth pursuit at higher than the general population base rate, is consistent with the hypothesis that deviant eye tracking and schizophrenia are pleiotropic (one gene with multiple different manifestations) aspects of the same underlying genotype (Holzman et al., 1988).

To evaluate whether a single gene is responsible for a substantial fraction of the variance in tracking performance, we pooled the data from Iacono et al. (1992) and Clementz et al. (1992) (yielding a combined sample 92 probands and 146 first-degree relatives) and conducted a complex segregation analysis (Grove, Clementz, Iacono, & Katsanis, 1992). Segregation analysis is a mathematical technique used with family data that is especially useful for evaluating the presence of single gene effects. With this statistical procedure, the goodness-of-fit of competing genetic models (e.g.,

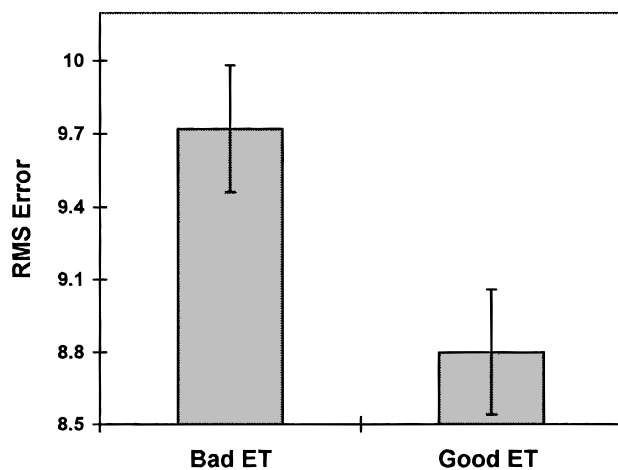


Figure 10. Root-mean-square (RMS) error eye tracking (ET) scores (mean and standard error in arbitrary units) of the first-degree relatives of schizophrenia patients as a function of proband ET performance illustrating that deviant ocular motion is familial. Probands with bad ET ($n = 5$ with 9 relatives) were selected from the right-most part of the distribution in Fig. 9a (i.e., their RMS score exceeded 12). Probands with good ET ($n = 26$ with 43 relatives) were selected from the left side of the distribution. The two groups differed significantly, $t(50) = 2.75$, $p < .01$. From Iacono et al. (1992).

dominant, polygenic, mixed) can be determined. Models that do not fit the data can be rejected. If a single gene model fits the data, it does not prove single-locus gene segregation. However, it does provide strong support for such a possibility, especially when competing alternative models can be refuted. In Grove et al. (1992), various models were fit to the data, including (1) a mixed model, positing the existence of a Mendelian major gene and polygenes; (2) models in which a Mendelian major gene acts alone; and (3) a model in which polygenes act alone. Only the mixed model provided a good fit, suggesting that both single gene and polygenic effects can influence eye tracking performance. The hypothetical major gene tended toward recessivity and accounted for 68% of the eye tracking variance.

Holzman and colleagues (1988) have also provided evidence consistent with a single gene effect on smooth pursuit eye tracking. Although the Holzman et al. model has been challenged as inconsistent with existing family and twin data on schizophrenia (McGue & Gottesman, 1989), and it differs in important ways from our model (Grove et al., 1992; Iacono & Clementz, 1993; Iacono & Grove, 1993), it is encouraging that different research teams using different populations and methods converge on the conclusion that a single gene may influence eye tracking performance in schizophrenia families. Further support for such a conclusion derives from Arolt et al. (1996). Given recent reports that schizophrenia may be linked to a locus on chromosome 6 (for a critical review of these findings, see NIMH, 1998), Arolt et al. (1996) evaluated the likelihood that eye tracking is linked to DNA markers on this chromosome. Evidence of linkage to chromosome 6 was found (although linkage of schizophrenia to the same chromosomal region was not detected), indicating further that a single gene may play a role in the regulation of eye tracking performance.

Taken together, these various findings suggest that in the families of patients with schizophrenia: (a) the distribution of smooth pursuit tracking ability suggests the presence of two underlying and intermixed distributions; (b) the data fit genetic models consistent with the action of a major gene; and (c) pursuit tracking performance may be linked to genetic material on chromosome 6. Like the many investigations reporting genetic linkage for schizophrenia, these reports warrant replication and extension before their findings are generally accepted.

Multivariate Phenotype

The strategy outlined in this article for evaluating candidate endophenotypes serves to illustrate how construct validity “bootstrapping” (Cronbach & Meehl, 1955) can be used to refine the identification of genetic susceptibility. Beginning with an imperfect index of schizophrenia risk, we may be able to identify endophenotypes (psychophysiological measures) that are better indices of genetic susceptibility than the criterion phenotype (the DSM diagnosis) used to evaluate the construct validity of the endophenotype. But can we use this bootstrapping approach, aided by the presence of the endophenotype, to do more to enhance phenotype definition, generating in effect a multivariate phenotype? To the extent we can, a multivariate approach, making use of several endophenotypic indicators of the same susceptibility genotype, may have the greatest likelihood of assisting in the search for schizophrenia-related genes (see also Erlenmeyer-Kimling, 1987; Grove et al., 1991; Iacono, 1998; Iacono & Grove, 1993; Lenzenweger, 1994; Meehl, 1989).

Because deviant smooth pursuit and schizophrenia do not necessarily appear together in the same individuals in the families of schizophrenia patients, a pleiotropic model has been proposed in

which the genotype is posited to express itself as manifest schizophrenia, poor pursuit performance, or both (Holzman et al., 1988). This model is supported by similar findings from Iacono et al. (1992). Clementz et al. (1992) reported that schizotypy ratings were correlated with eye tracking both within individuals and among family members such that family members with more deviant ocular motor gain scores had siblings with schizotypal characteristics, a finding that is consistent with a number of other reports concerning the relationship between schizotypy and pursuit eye tracking (Clementz, Reid, McDowell, & Cadenhead, 1995; Grove et al., 1991; Thaker, Cassady, Adami, Moran, & Ross, 1996). Schizotypy may thus be added to this pleiotropic model as another characterization of the phenotype, creating a multivariate phenotype. Other characteristics, such as attentional impairment indexed by poor performance on a degraded stimulus continuous performance test (another putative endophenotype of schizophrenia, Nuechterlein & Dawson, 1984), may share common genetic variance with pursuit eye tracking in these families (Grove et al., 1991).

Other ways in which those with deviant eye tracking differ from normal may provide clues regarding how to enhance phenotype definition. Our laboratory is currently evaluating neuropsychological variables linked to frontal lobe function, both for their potential to expand the phenotype and to provide insight into the brain mechanisms underlying aberrant smooth pursuit (Levin, 1984). We first explored this possibility in chronic schizophrenia patients given a battery of conventional neuropsychological tasks (Katsanis & Iacono, 1991). Tests putatively sensitive to frontal lobe functioning, such as the Wisconsin Card Sorting Test, were associated with tracking dysfunction, but other neuropsychological tasks were not. More recently, we (Snitz, Curtis, Zald, Katsanis, & Iacono, 1998) examined how spatial working memory relates to smooth pursuit. Our working memory procedure, which is modeled after that of Luciana, Depue, Arbsi, and Leon (1992) and has been shown to be sensitive to developmental effects (Zald & Iacono, in press), required subjects to remember where on a computer screen a target was briefly flashed after delays of up to 8 s. At the end of the delay period, they touched the computer screen with a light pen, registering where they remembered the stimulus to be, making it possible to measure spatial error as the distance between target and light pen locations. In a sample of 42 schizophrenia patients, we found a significant correlation ($r = .34$) between spatial error and RMS error scores, suggesting that frontal lobe functioning is important to good performance on both tasks. Park and Holzman (1993) have also reported an association between working memory and eye tracking. In addition, Park, Holzman, and Goldman-Rakic (1995) have found that the first-degree relatives of schizophrenia patients show working memory impairments, a finding that raises the possibility that working memory deficits may serve as a neuropsychological endophenotype.

More recently, we have examined the smooth tracking/working memory relationship in male MTFs twins when they turned 20 years old. We selected twins for extreme scores (the best and worst 12.5% out of 240 individuals) on the 8-s delay condition of the working memory task such that two groups were formed, one with good working memory, the other displaying poor performance (which might be viewed as a "neuropsychological" high-risk group). As Figure 11 illustrates, pursuit eye tracking was significantly impaired for the poor memory group in general across a variety of eye tracking measures, with statistically significant effects for number of saccades generated during the pursuit task, $t(57) = 2.77$, $p < .01$, the amplitude of saccades, $t(57) = 2.21$, $p < .05$, the number of times subjects anticipated target motion by making

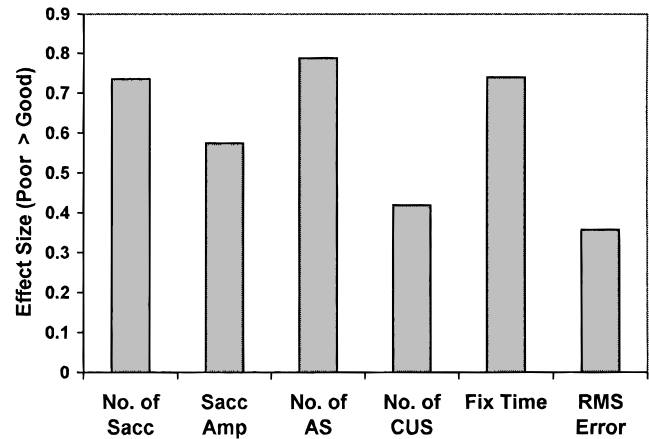


Figure 11. Association between working memory performance and eye tracking in a population-based sample of 20-year-old men. Men who were selected to be at neuropsychological high risk for poor eye tracking came from the bottom eighth of the working memory performance distribution ($n = 30$) and were compared with men from the top eighth ($n = 30$). Participants watched a sinusoidally driven target oscillate at 0.4 Hz. The bars represent the effect size (in standard deviation units) indicating how much worse the tracking of the poor working memory group was. No. Sacc = number of saccades; Sacc Amp = average saccade amplitude; No. of AS = number of anticipatory saccades; No. of CUS = number of catch-up saccades; Fix Time = time spent fixated rather than tracking the target; RMS error = root-mean-square tracking error.

large saccades that moved the eyes well ahead of the target, $t(57) = 2.55$, $p < .05$, and the time subjects were fixating rather than tracking the target, $t(57) = 2.81$, $p < .01$. The number of catch-up saccades, reflecting efforts to refoveate the target once the eyes have fallen behind, and RMS error did not distinguish these groups at a statistically significant level. These schizophrenia and MTFs findings complement those of other researchers who have reported that putative indices of frontal lobe functioning correlate with pursuit eye tracking performance (Bartfai, Levander, Nyback, Berggren, & Schalling, 1985; Grawe & Levander, 1995; Litman et al., 1991; Malaspina et al., 1994; Scarone, Gambini, Hafele, Bellodi, & Smeraldi, 1987; van den Bosch, Rozendaal, & Mol, 1987).

A Genetic Model for Schizophrenia

Iacono and Grove (1993) advanced a pleiotropic model of schizophrenia that derives from the smooth pursuit eye tracking literature. The model is based on the assumption that deviant smooth pursuit identifies a genetic variant of schizophrenia, perhaps composing somewhat more than half of the cases. Based on the results of the segregation analysis of Grove et al. (1992), this genetic variant includes major gene and polygenic components. For families with this variant, gene carriers can be identified through the presence of various phenotypic indicators, including schizophrenia (with negative symptoms), eye tracking dysfunction, schizotypal personality characteristics (especially social-interpersonal oddities), and neuropsychological deficits reflecting frontal lobe pathology and impaired working memory.

The relatives of schizophrenia patients have been found to be impaired on other tasks involving psychophysiological measures, such as the antisaccade eye movement procedure discussed previously (Clementz et al., 1994; Katsanis, Kortenamp, et al., 1997)

and the sensory gating paradigm of Freedman et al. (1997), which involves inhibition of the P50 ERP. It remains to be determined if deviations identified on tasks like these should be incorporated into the model. If the deviations show an association with the phenotypic indices listed above in families targeted as having the hypothetical genotype, they can be added to the expanded phenotype definition. If the deviations do not show such a relationship, perhaps they will still prove informative as endophenotypes for schizophrenia families that are not covered by our model.

Conclusion

Failures to replicate molecular genetic studies reporting linkage to psychiatric disorders and personality traits suggest a need for additional empirical research to enhance phenotype definition and improve the efficiency of gene detection. The identification of

endophenotypes may serve this purpose, and psychophysiology has the potential to yield reasonable candidate endophenotypes. These endophenotypes may be more perfect, valid indicators of genetic risk than any other single phenotypic indicator. Even if this is not the case, psychophysiological endophenotypes can be used to advantage in combination with other indicators of genetic risk, including the presence of psychopathology in a family. The use of endophenotypes confers a huge statistical power advantage in the search for genes because endophenotypes identify unexpressed cases of psychopathology. Genetic linkage studies that use psychophysiological endophenotypes together with other disorder-related phenotypic characteristics enhance the chances for finding genes. Finally, finding genes for psychophysiological endophenotypes is itself likely to be worthwhile, because of the potential of such a discovery to provide insight into psychopathology and the meaning of psychophysiological variables.

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