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Developmental Endophenotypes: Indexing Genetic Risk for Substance Abuse with the P300 Brain Event-Related Potential

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Abstract

Although substance use disorders are heritable, their complexity has made identifying genes underlying their development challenging. Endophenotypes, biologically informed quantitative measures that index genetic risk for a disorder, are being recognized for their potential to assist the search for disorder relevant genes. After outlining criteria for an endophenotype that includes developmental considerations, we review how the brain P300 response serves as an index of genetic risk for substance abuse and related externalizing disorders. The P300 response is highly heritable and associated broadly with characteristics of externalizing disorder, including childhood disruptive disorders, antisociality, and precocious expression of deviant behavior. This association appears to be mediated by shared genetic influences. Prospective studies confirm that reduced P300 amplitude present in youth prior to significant exposure to addictive substances is associated with the subsequent development of substance use disorders. Despite pronounced change in mean level over the course of development, P300 amplitude shows strong rank order stability with repeated assessment through young adulthood. In addition, P300 developmental trajectories based on multiple assessments show very high heritability and may be especially informative as measures of genetic risk. Collectively, these findings provide strong support that P300 amplitude and its change through development reflect genetic vulnerability to substance abuse and related externalizing psychopathology.

Most scientists trying to unravel the genetic basis of substance use disorders (SUDs) have been both surprised and frustrated by how difficult it has been to identify the etiologically relevant genes. Although there are likely many reasons for the slow rate of progress, one explanation reflects concern over the adequacy of the Diagnostic and Statistical Manual (DSM) of the American Psychiatric Association. Although the DSM provides clinically useful descriptions, its characterization of disorder is not biologically based. DSM categories may therefore not be optimal for facilitating gene identification. This concern has led to the hope that alternative phenotypes can be identified that more efficiently capture genetic risk associated with disorder development. Endophenotypes, so called because they reflect some endogenous quantitative attribute best measured using a laboratory procedure, constitute one such alternative phenotype.

For substance use disorders, the best candidate endophenotype derives from the amplitude of the P300 wave of the visual event-related potential. This positive voltage brain signal has an onset latency of about 300 milliseconds in simple speeded reaction time tasks and is typically elicited by stimuli that stand out when embedded in a series of like stimuli because they are rare and require a response such as a button press. Figure 1 illustrates stimuli and brain responses from the “rotated heads” paradigm (introduced by Begleiter et al., 1984) used in many studies of substance abuse. When subjects respond to infrequently presented

target stimuli by indicating the side of the head the ear is on, a P300 response is elicited. These waveforms can be averaged within and across individuals to highlight the degree to which those abusing substances show P300 amplitude reduction (P3AR; illustrated in Fig. 1c). P300 likely involves multiple neural generators (Kiehl, et al., 2005) and the allocation of various information processing resources, especially those involved with attention and memory. Although a thorough explication of the mechanisms underlying P300 is beyond our scope, P300 amplitude may be broadly explained as reflecting individual differences in neural inhibition (Begleiter & Porjesz, 1999; Polich, 2007) or the modulation of attention via the noradrenergic system (Nieuwenhuis, Aston-Jones, & Cohen, 2005).

In this review, we evaluate P3AR as an endophenotype for developing SUDs and related externalizing psychopathology. We begin by examining essential elements of the research strategy needed to identify endophenotypes. Next, we review the literature supporting P3AR as an endophenotype for alcoholism, and extend this review to encompass related externalizing disorders. We advance evidence supporting a model that considers P300 amplitude as tapping genetic liability for behavioral disinhibition and the resulting increased risk conferred for developing childhood disruptive disorders, adolescent problem behavior, SUDs, and antisocial personality. We end by considering a research agenda likely to further enhance the potential of P3AR as a developmental endophenotype.

What Is an Endophenotype?

Although many sources have specified endophenotype criteria (Almasy & Blangero, 2001; Cannon & Keller, 2006; Doyle, et al., 2005; Gottesman & Gould, 2003; Iacono, 1985; Iacono, 1998; Iacono & Lykken, 1979; Kendler & Neale, 2010; Skuse, 2001), developmental considerations have not received prominent emphasis. In Table 1 we embrace a developmental perspective to expand on our past contributions to endophenotype identification (Frederick & Iacono, 2006; Iacono, Carlson, & Malone, 2000; Iacono, Malone, & McGue, 2003).

Sound psychometric findings are essential. The endophenotype should be reliably measured, ideally with reliability equal to or better than that of the target disorder with which it is associated. An ideal endophenotype would be stable over extended periods of time, allowing for its measurement reliability to be enhanced by exploiting the added information gained from repeated assessments. Twin studies can confirm the heritability of the endophenotype, which should be substantial and higher than that of the associated clinical disorder. In addition, twin studies should show that the phenotypic association between the endophenotype and the disorder is attributable to shared genetic effects. As Dick (Dick, This Issue) notes, genetic influences on a clinical phenotype like alcohol misuse show developmental change. The search for endophenotypes should assign priority to measures that are relatively insensitive to changing genetic influence. Longitudinal studies with twins can determine the degree to which genetic influences are largely the same over extended developmental periods. If this criterion is met and the endophenotype is stable, then the endophenotype is likely to index the nature of genetic risk similarly at different ages, thus enhancing its utility for gene finding.

Of critical significance are investigations that establish the endophenotype as a measure of disorder risk. Those with the disorder should continue to display the endophenotype even when the disorder remits, and those who possess the endophenotype are by definition at elevated risk for subsequently developing the disorder. The ideal endophenotype would be present during fetal development and immutable thereafter. However, given the complexity of brain development and the many phenotypic changes associated with growth and maturation during childhood, few if any of the commonly considered endophenotypes for

adult psychiatric disorder are likely to be detectable in the same form early in life or throughout the lifespan. Indeed, how a characteristic changes with development may itself constitute an endophenotype; e.g., an endophenotype could index the rate of maturation of a brain system (and the presence of underlying neurodevelopmental genes) related to reward or inhibitory control which, when delayed or compromised, increases risk for substance abuse. How sensitive an endophenotype is to changing developmental influences and at what stage an endophenotype can be profitably used to index genetic risk remains largely unanswered, but as we will show for substance use and related disorders, identification appears possible by late childhood.

Once it is established that the affected index case in a genetic study has the endophenotype, that characteristic should be present in other affected family members because they presumably share the same genetic liability. Although SUDs are not expressed in everyone at genetic risk, many unaffected first degree relatives of a proband, including offspring, will share genetic liability with the proband, and they should also possess the attribute at elevated rates. Finally, the endophenotype should show diagnostic specificity. Importantly, however, given the high rates of comorbidity associated with common mental disorders, it is unreasonable to expect the endophenotype to be exclusive to a single disorder. Ideally, it should be exclusive to a spectrum of disorders that are likely to be comorbid because they share etiologic mechanisms, including common genetic determinants (as appears to be the case for SUDs, see e.g., Krueger, et al., 2002). Indeed, an endophenotype may be used as a tool to identify phenotypes that fall into the spectrum (Yoon, Iacono, Malone, & McGue, 2006). Alternatively, to the extent that different disorders share a dysfunctional process in common, an endophenotype that assesses this common process would be expected to show similar results across all disorders with the same dysfunction, and point to genes important to the brain processes accounting for the impairment. For example, dysfunctional synaptic plasticity in the prefrontal cortex (PFC) may underlie mood disorders, drug addiction, and schizophrenia (Goto, Yang, & Otani, 2010), opening the possibility that a PFC-related endophenotype could index genetic risk for putatively disparate disorders.

Although a case could be made that items in Table 1 designated as “desirable” also constitute essential criteria, absent information about the etiology of the disorder and/or the endophenotype, it would be difficult to determine whether these criteria are in fact met. Compared to a diagnosis defined by self-reported behavior problems, an endophenotype is expected to be more strongly linked to the effects of specific genes governing brain processes, but the genes and the processes they govern must be known before this can be determined with certainty. Although we do not yet have this detailed knowledge for P3AR, we are beginning to uncover it for other brain-derived endophenotypes, providing proof in principle that endophenotypes may provide substantive etiological insights (Erk, et al., 2010; Hodgkinson, et al., 2010; Roeske, et al., 2009). In addition, many studies have reported associations between P300 amplitude and specific genes or chromosomal loci (Begleiter, et al., 1998; Chen, et al., 2010; Comings, Dietz, Johnson, & MacMurray, 1999; Hill, et al., 1998; Johnson, et al., 1997; Porjesz & Rangaswamy, 2007; Williams, et al., 1999; Wright, et al., 2008). However, in the absence of replication of these P300 candidate gene reports, it would be premature to conclude that we have a solid lead on the molecular genetic basis of P300.

Besides assisting the hunt for disorder-relevant genes [reports by Dick et al., 2006, and Hill et al., 2004, illustrate how P3AR and other EEG endophenotypes can aid this process], a valid endophenotype offers other benefits as well. It is difficult to create animal analogs of psychiatric disorder, but it may be possible to develop an animal model based on the identification of an endophenotype analog, thereby enabling research into underlying biological mechanisms (Gould & Gottesman, 2006). Possession of a valid endophenotype

could help narrow a diagnosis, establish who is best suited for a particular treatment, and be used to identify those who are unaffected but nevertheless possess elevated disorder liability risk. Because ultimately an endophenotype would provide important information about underlying biological mechanisms and etiology, it could also be used to help develop an etiologically informed diagnostic system.

P300 Amplitude Reduction (P3AR) and Risk for Alcoholism

Early investigations supporting P300 as a candidate endophenotype examined the healthy relatives of affected individuals. A seminal study by Begleiter and colleagues (Begleiter, Porjesz, Bihari, & Kissin, 1984) reported that P3AR was evident among 11-year-old male children of alcoholic fathers. Because boys in this study had not yet begun experimenting with alcohol, P3AR could not be due to effects of alcohol use per se, instead suggesting that it reflected genetic risk for alcoholism. Although replication failures have been reported, a meta-analysis of 30 studies of male youth with alcoholic parentage confirmed the initial findings (Polich, Pollock, & Bloom, 1994). Subsequent investigations further support P3AR as an endophenotype by showing that over the short term, P300 test-retest reliability is high (e.g., Hall et al., 2006; van Beijsterveldt, van Baal, Molenaar, Boomsma, & de Geus, 2001). It is also heritable. A recent meta-analysis of twin and family studies produced a pooled heritability estimate of approximately .60 (van Beijsterveldt & van Baal, 2002), and heritability appears to change little through middle adulthood (Smit, Posthuma, Boomsma, & de Geus, 2007). At least two studies have reported that P300 amplitude is less heritable among female adolescents than among males (van Beijsterveldt, et al., 2001; Yoon, et al., 2006), suggesting that P300 amplitude's role as an endophenotype may be sex-specific.

P3AR as an Endophenotype for Externalizing Psychopathology

An extensive literature now supports P3AR as an endophenotype for a variety of disorders that often precede or co-occur with alcoholism, including childhood disruptive disorders, antisocial personality disorder, nicotine dependence, and illicit drug addiction (Iacono, et al., 2003). A developmental model that can account for the genetic influence on these externalizing spectrum disorders and their link to P3AR holds that individuals inherit a general liability toward a variety of traits, behaviors and disorders reflecting a tendency toward behavioral disinhibition, which consists of difficulty inhibiting socially undesirable, restricted, or even proscribed behaviors (Iacono, Malone, & McGue, 2008), see also Zucker et al. (Zucker, Nigg, & Heitzig, This Issue). Although a full explication of this model is beyond the scope of this paper, we present a schematic view (Figure 2) to highlight features of the model most relevant to P3AR. Multiple sources of evidence from cross-sectional and prospective studies lend support to the model and attest to the strength of P3AR as an endophenotype for externalizing tendencies.

Cross-Sectional Association between P3AR and Externalizing

P3AR characterizes each of the child and adult disorders in the externalizing spectrum (Iacono, Carlson, Malone, & McGue, 2002). It is also associated with different forms of disinhibited behavior, such as police contact and early sexual intercourse (Iacono & McGue, 2005) as well as early initiation of substance use and misuse (Iacono & McGue, 2005; Yoon, et al., 2006). The co-occurrence among externalizing spectrum behaviors, personality traits, and disorders can be modeled as a highly heritable latent trait (Kendler, Prescott, Myers, & Neale, 2003; Krueger, et al., 2002; Young, Stallings, Corley, Krauter, & Hewitt, 2000) which mediates associations between P3AR and each facet of the latent trait (Patrick, et al., 2006). This association is due to genes common to P300 amplitude and externalizing (Hicks, et al., 2007). Work by other groups also supports P3AR as an endophenotype for externalizing psychopathology and behavioral disinhibition more generally (e.g., Bauer &

Hesselbrock, 2003; Gao & Raine, 2009; Habeych, Charles, Sciabassi, Kirisci, & Tarter, 2005; Hill, Steinhauer, Locke-Wellman, & Ulrich, 2009).

Longitudinal Findings Spanning Childhood to Young Adulthood

SUD endophenotype research has had a strong focus on children and the use of longitudinal designs. This focus has been dictated in part by the desire to study at-risk individuals prior to significant exposure to substances that could color the expression of the endophenotype, and in part by the desire to understand how emerging substance use might alter its expression.

P3AR in preadolescence increases the odds of substance misuse or developing a SUD later in adolescence or young adulthood (Berman, Whipple, Fitch, & Noble, 1993; Habeych, et al., 2005; Hill, et al., 2009). In addition, P3AR in healthy 17-year olds is a risk factor for the subsequent development of SUDs at age 20 and 24 (Carlson, McLarnon, & Iacono, 2007; Iacono, et al., 2002). Monozygotic twins who are discordant for alcohol disorder in adolescence nevertheless show P3AR (Carlson, Iacono, & McGue, 2002). In fact, those twin pairs who are disorder-free at age 17 but who become discordant for subsequently *developing* a disorder have P3AR relative to twin pairs who remain healthy (Carlson, Iacono, & McGue, 2004).

Collectively, these findings provide strong evidence that P3AR reflects genetic risk prior to the expression of manifest SUDs. However, age appears to be an important moderator of this association. For instance, compared to older subjects, larger effect sizes are typically obtained among those younger than 18 (Polich, et al., 1994). In addition, mean levels change strikingly with development (Berman, et al., 2006; Carlson, et al., 2007; Hill, et al., 1999; Katsanis, Iacono, & McGue, 1996), dropping half a microvolt or more per year (Carlson, Iacono, & McGue, 2005). This reduction may reflect the influence of dopamine system genes (Berman, et al., 2006), possibly reflecting changes in the psychological or neural process involved.

Carlson and Iacono (Carlson & Iacono, 2006) reported that test-retest stability correlations in male twins assessed at approximately 17, 20, and 24 years of age were quite high, ranging from .71 to .79 for three-year stability correlations and greater than .60 for the correlation across seven years. These findings indicate substantial rank-order stability in P300 amplitude despite change in mean levels. Cross-sectional heritability estimates were similar at ages 17 and 20 (.64 and .68, respectively), but dropped somewhat at age 24 (.53), indicating that at these ages, from half to two thirds of the variability in P300 amplitude could be attributed to genes. Of greater interest, however, are results of biometric regression analyses of individual growth curves in P300 amplitude. These indicated that heritability of the intercept, reflecting P300 amplitude at age 17, was much higher ($h^2 = .87$) than heritability estimates from single (cross-sectional) measurements, and greater than the heritability of individual externalizing disorders examined in the same sample (for seven disorders, median $h^2 = .63$, Iacono et al., 2003). Because all measurements contribute to estimates of the intercept, this study indicates the value of repeated assessments of an endophenotype due to the increased reliability that derives from using multiple measurements. Individual differences in rate of change (linear slope) were also heritable, although to a much lesser degree ($h^2 = .15$). Nevertheless, the degree of overlap in genes influencing intercept and slope was quite striking, and the best-fitting model in this study indicated that the two sources of genetic influence could be considered perfectly coextensive. That is, the genes that influence intercept, or P300 amplitude at age 17, are the same as those that influence change in amplitude into early adulthood, indicating that developmental trajectories in P300 amplitude index genetic risk.

In a separate study, Carlson et al. (2007) found that trajectories in P300 amplitude differentiated young men whose fathers had an antisocial behavior disorder (and thus were at high genetic risk) from those whose fathers were free of antisocial or substance use disorders. In addition to having smaller P300 amplitude responses at age 17, high-risk subjects showed slower rate of change than low-risk ones, perhaps reflecting slower gains in efficiency of neural processing. These results complement those of Hill and Shen (2002) who, examining neurodevelopmental patterns of change in P300 amplitude from age 9–14, also found that trajectories of P300 amplitude varied with familial risk. Offspring with both an alcoholic father and uncle were considered at high risk, and these children were disproportionately represented in a P300 trajectory group characterized by smaller P300 overall and a slow rate of change from age 9 to 14.

Hill and colleagues (1999), extrapolating from growth curves describing trajectories of change in P3 amplitude among high- and low-risk youth, estimated that the curves would converge at some point in the early twenties. Because P3AR is also associated with substance abuse, they proposed that early in development it serves as an endophenotype but later reflects neurotoxic effects of substance use. In the Carlson et al. (2007) study of high and low risk young men between 17 and 24 years of age, the convergence predicted by Hill and colleagues was not observed. Nevertheless, the magnitude of P3AR among high-risk subjects at 24 was less than at 17, and the high and low risk groups differed little after age 20. Carlson and Iacono's (2006) previous study reported that cross-sectional estimates of P300 heritability were smallest among the 24-year-old subjects. Taken together, these findings suggest that the utility of P3AR as an endophenotype may be developmentally limited.

Future Directions

Studies of developmental endophenotypes such as P3AR can help inform our understanding of behavior and clinical disorders. Yoon et al. (2006) successfully demonstrated an application of this approach when they showed that adolescents, particularly boys, showed P3AR if they were misusing substances (e.g., binge drinking; frequently smoking; using cannabis, amphetamines, or psychedelics), thus suggesting that these substance use behaviors are themselves manifestations of the underlying genetic risk. P3AR can also help shed light on which disorders are part of the externalizing spectrum. For instance, Yoon and colleagues (2008) found that ADHD alone in 11-year-old subjects was not associated with P3AR, whereas ADHD combined with conduct disorder was. Studies like this can thus illuminate the relationship of ADHD to the externalizing spectrum, as well as help to corroborate systems like ICD-10, which treat the combination of conduct disorder and ADHD as an important and distinct diagnostic entity.

Recently developed statistical models for understanding development and change will likely prove useful in studying gene-environment interplay. For instance, bivariate growth curve models can be used to study direction and mutuality of influence between candidate endophenotype and externalizing behaviors. This is particularly relevant in the area of substance abuse, where use of the substance is prerequisite for the disorder but might itself, as Spear's review (This Issue) highlights, alter brain function and maturation, which in turn could affect the endophenotype. Biometric models of gene-environment interaction in relation to candidate endophenotypes are useful in this regard because they can evaluate how the heritability of an endophenotype is moderated by the ingestion of a substance. Perlman et al. (2009) employed this approach in a longitudinal investigation that showed that the amount of alcohol ingested from age 11 to 18 did not moderate the heritability of P300 amplitude measured at age 18, thus showing that whatever the neurotoxic effects of alcohol, they did not alter the genetic influence on P300 at this stage of late adolescence.

These quantitative approaches create other opportunities for furthering our understanding of developmental endophenotypes and psychiatric disorders. For instance, to the extent that common genes influence a developmental trajectory as a whole (i.e., intercept and slope together), deviations from expected trajectories must be due to environmental influence. This opens an avenue to studies of gene–environment interplay. By including multiple measurements longitudinal studies also permit researchers to estimate genetic factor scores (cf. Boomsma, Molenaar, & Orlebeke, 1990) on an endophenotype to be used in molecular genetic research as well as in studies of gene–environment interplay.

Gender constitutes another unresolved issue related to P3AR as a developmental endophenotype. The most robust evidence supporting P3AR as an endophenotype is from findings involving male subjects. Although P3AR has been observed in high risk girls (Hill, Muka, Steinhauer, & Locke, 1995), P3AR in females is less well studied and the evidence is not as strong. Because the P300 response is not a unitary phenomenon, and reflects instead multiple electrophysiological processes overlapping in potentially complicated (and perhaps sex-specific) ways, studies using techniques that permit more precise characterization of the ERP, such as time-frequency methods (cf. Gilmore, Malone, Bernat, & Iacono, 2009; Makeig, et al., 2004), may prove fruitful in helping to bridge the gender gap in our understanding of endophenotypes involving brain activity. In addition, considering the role of gender might lead researchers to modify their conceptualizations of externalizing. For instance, self-harm behavior, which is more common among female adolescents than males, clearly represents a form of disinhibited behavior. Borderline personality disorder also shares key features with externalizing. Indeed, P3AR has been observed among adolescents with borderline personality (Houston, Bauer, & Hesselbrock, 2004). In sum, resolving inconsistencies between genders might lead both to more refined endophenotypes and to more refined conceptualizations of disorders.

Although P3AR appears to index genetic risk for externalizing psychopathology broadly conceived, it is not the case that those at risk develop all of the externalizing disorders, and specific genetic influences are likely to guide the development of each disorder. These specific influences may have their own endophenotypes, and combinations of endophenotypes may be profitably used to identify risk for specific disorders. Iacono et al. (2000) showed that when P300 amplitude and an autonomic measure derived from a stressful coping task were used in conjunction, those scoring in the deviant direction on both variables had especially heightened risk for developing SUDs, and the two endophenotypes were not significantly correlated ($r=.15$). Subsequent work with the autonomic measure has shown that rather than being associated with externalizing disorders generally, it appears to be related only to SUDs (Taylor, 2004), thus raising the possibility that using the two measures in combination may aid the identification of genes specific to SUDs.

Finally, the specificity of P3AR to externalizing disorders has not received adequate attention, and P3AR has been observed in other disorders such as schizophrenia (Ford, 1999). There are many experimental paradigms capable of eliciting P300. At present, it is not certain whether P3AR observed in non-externalizing disorders reflects the same underlying brain processes or different processes associated with task specific details.

Conclusion

Substantial evidence from over two decades of research supports the model presented in Figure 2 with P3AR emerging as a solid candidate endophenotype for the development of externalizing psychopathology. This includes key findings that: 1) a wide array of externalizing problems show P3AR, 2) P3AR is present in at-risk offspring in preadolescence, 3) those who engage in substance misuse and develop SUDs show P3AR

earlier in life, 4) the unaffected co-twins of alcohol dependent twins have P3AR, and 5) the association between P3AR and externalizing reflects the influence of shared genetic effects. Although P300 amplitude diminishes with age, it shows high rank order stability, and the trajectory of change in P300 amplitude is itself heritable and reflective of underlying genetic risk for behavioral disinhibition. Molecular genetic investigations designed to identify the genes influencing P300 are underway. Such studies are likely to be enriched by adopting a developmental perspective that takes into account trajectories of change in P300 amplitude which are not only associated with risk for developing SUDs, but are also more highly heritable than single session measures of P3AR or any of the clinical phenotypes with which it is associated.

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Figure 1. The P300 Wave as Elicited by the Rotated heads paradigm

Subjects watch a computer screen as every few seconds, schematics of a head with a missing ear are interspersed with frequently presented nontarget circles (Panel A). Subjects respond only to the targets, indicating on which side of the head the ear appears. Because the heads occur on only a third of the trials and require a response, each presentation of these targets elicits a P300 event-related potential (ERP) beginning about 300 ms subsequent to stimulus presentation. Panel B depicts 10 target trials from one subject as well as the average ERP for these trials. When the average for each subject is averaged with that of other participants, grand mean ERPs can be plotted as in Panel C (adapted from Yoon et al., 2006) which illustrates the amplitude reduction seen in those with substance use diagnoses.

Figure 2. Model Illustrating the Role of P300 as a Developmental Endophenotype for Externalizing Psychopathology

Individuals inherit a genetic liability for behavioral disinhibition, which is characterized by impulsivity, lack of attentional persistence, rule breaking, aggressiveness, signs of behavioral undercontrol, and the like. P300 is thought to be closely related to, and a marker of, this underlying vulnerability, which is manifest early in life and varies as a function of development to include disruptive disorders of childhood, precocious and deviant behavior early in adolescence, and SUDs (nicotine dependence, and alcohol and illicit drug use disorders) in late adolescence and young adulthood. The model illustrates this developmental course, focusing on expressions of behavioral disinhibition which have been linked to P300 amplitude to date. The model is conceptual, not a formal path-analytic model, and it is not meant to be comprehensive (e.g., it omits environmental risk factors and specific genetic influences that cause different people with equivalent genetic vulnerability to behavioral disinhibition to have different developmental trajectories and outcomes, see Iacono, et al., 2008).

Table 1**Characteristics of an Endophenotype**Required Attributes

- Demonstrated measurement reliability
- Shows criterion validity: Related to the clinical phenotype
- Changes little with development (e.g., is stable over time), or if it changes, does so in a manner that is well understood
- Heritable and shares genetic variance with the disorder
- Genetic influences on the endophenotype are the same over the course of development or if not, how they change is understood
- Identifies those at genetic risk
 - Present in first degree relatives of affected person, including:
 - Affected relatives
 - Unaffected offspring
 - Unaffected monozygotic co-twins
 - Present during disorder remission
 - Predicts the development of disorder
 - Present at an early age, before the onset of disorder
- Specific to a disorder, disorder spectrum, or group of clinical phenotypes that share genetic risk,
- Or is associated with a genetically influenced neurobiological process that is shared across different disorders

Desirable Attributes

- Etiologically (genetically) less complex than the clinical phenotype
- Indexes a putative brain mechanism involved in disorder development or provides insight into the likely underlying pathophysiology
- Molecular genetic studies confirm that genes influencing the endophenotype and the clinical phenotype are the same
- Less subjective and dependent on culture and context than interview-based assessment

Benefits

- Facilitate identification of disorder-related genes
- Use to develop animal models
- Provides quantitative index of genetic risk
- Serve as a diagnostic and/or treatment aid
- Use to refine the diagnostic system