Are Endophenotypes the End of Phenotypes?

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Ulrich Ettinger

Department of Psychology
University of Bonn
Overview

• Eye movements and genetics – why, and how?

• What are endophenotypes?

• Eye movements as endophenotypes of schizophrenia

• Are endophenotypes the end of phenotypes?
Why study associations between genetic variation and phenotypic variation in psychology or psychiatry?
Genetics and Eye Movements

• Why study eye movements in relation to genetics in psychology or psychiatry?
  – Eye movement measures as indicators of cognitive or neural systems functioning in healthy individuals
  – Eye movement measures as endophenotypes of psychiatric illnesses e.g. schizophrenia
Genetics of Schizophrenia
Schizophrenia Genetics

- Schizophrenia: a severe neuropsychiatric condition of unknown aetiology
  - Positive symptoms (hallucinations, delusions)
  - Negative symptoms (avolition, alogia)
  - Thought disorder (thought insertion, derailment, thought blocking)

- Behavioural genetics
  - Family, twin, and adoption studies have shown a substantial genetic contribution (heritability ~80%)

- Molecular genetics
  - Early linkage studies, subsequent candidate gene association studies
  - Currently large-scale GWAS (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014: N=36,989 patients and N=113,075 controls)
  - Promising candidates (>100 loci), but no single gene and no major gene

- Polygenic or "massively polygenic" (Bilder et al 2009)
Schizophrenia Genetics

• Question 1: Gene Discovery
  – Problems: small effect sizes; heterogeneous clinical phenotype
  – Solutions
    • large-scale GWAS with replications (e.g. PGC)
    • studies of patient subgroups defined on the basis of further (endo-)phenotypes

• Question 2: Gene Mechanisms
  – Problems: GWAS yield unknown risk factors
  – Solution: multi-level laboratory assays (endophenotypes, phenomics)
Schizophrenia Genetics

• Question 1: Gene Discovery
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  – Solutions
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Endophenotypes & Phenomics

• Endophenotypes
  – "measurable components unseen by the unaided eye along the pathway between disease and distal genotype" (Gottesman & Gould 2003 AJP)
  – "heritable risk factors genetically correlated with disease liability, measurable in both affected and unaffected individuals, that are capable of providing greater power to localize and identify disease-related genes than affection status alone" (Glahn et al 2014 Am J Med Genet)

• The use of comprehensive sets of endophenotypes from different methods (phenomics) may explicate gene pathway at several levels of analysis
Gene Mechanisms

Siebner et al 2009 Neurosci
Endophenotype Criteria

• Selection of the right (endo-)phenotypes is critical
  (from Gottesman & Gould 2003 AJP)

  – "The endophenotype is associated with illness in the population.

  – The endophenotype is heritable.

  – The endophenotype is primarily state-independent (manifests in an individual whether or not illness is active).

  – Within families, endophenotype and illness co-segregate.

  – The endophenotype found in affected family members is found in nonaffected family members at a higher rate than in the general population."
Advantages of Eye Movements in Genetic Research
Eye Movements

- *The eyes have it!* Advantages of oculography as a tool over neuropsychological test batteries (involving manual or verbal responses)
  - Well characterised neural mechanisms
    - primate lesion and recording studies
    - human lesion and neuroimaging studies
  - Well characterised cognitive mechanisms
    - human experimental psychology and psychophysics
  - Direct measurement of behaviour bypassing manual motor or verbal response systems (often slowed in neuropsychiatric conditions)
  - High reliability of methods
  - Assessment
    - Short: 15 minutes to complete comprehensive assessment of diverse functions
    - Simple: clear instructions, no response devices/button boxes/joysticks, no language output
Oculomotor Endophenotypes of Schizophrenia
Oculomotor Tasks

- Deficits in which oculomotor tasks are considered as candidate endophenotypes of schizophrenia?
  - Smooth pursuit
  - Antisaccades
  - Memory-guided saccades

- Oculomotor control tasks
  - Prosaccades
  - Fixation
Endophenotype Criteria

• Is the endophenotype associated with the illness? Is this association independent of state factors?

• Is the endophenotype a reliably measurable trait?

• Is the endophenotype observed in people at increased genetic risk for schizophrenia?
Endophenotype Criteria

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- Is the endophenotype observed in people at increased genetic risk for schizophrenia?
Smooth Pursuit in Schizophrenia

AN EXPERIMENTAL STUDY OF THE OCULAR REACTIONS

Fig. 1.
The Dodge Photochronograph.
variety of experimental data. The present investigation was limited to three main problems, which were relatively clear to us, and to meet which we framed our technique.
Smooth Pursuit in Schizophrenia

Plate II

110 II
Normal

14 20 23 25
Mania

34 34
Depressed

36
Praecox

41
D. Paralytica

43 43 47 48
Epileptics

Winik
Eye-Tracking Patterns in Schizophrenia

Abstract. A significant number of schizophrenic patients show patterns of smooth pursuit eye-tracking patterns that differ strikingly from the generally smooth eye-tracking seen in normals and in nonschizophrenic patients. These deviations are probably referable not only to motivational or attentional factors, but also to oculomotor involvement that may have a critical relevance for perceptual dysfunction in schizophrenia.

Fig. 2. Comparison of six subject groups tracking a pendulum for ten cycles before a realerting instruction and five cycles after realerting. The data for the realerting condition are prorated for ten cycles. The two measures are (a) frequency of velocity arrests and (b) number of positive saccades. The latter measure appears to reflect attention to the task. Abbreviations: Nonpar. SZ, nonparanoid schizophrenic; Par. SZ, paranoid schizophrenic; SZ-a., schizoaffective; Manic-depress., manic-depressive; and Nonpsy. pat., nonpsychotic patients (diagnosis of personality disorder).
Smooth pursuit in schizophrenia: A meta-analytic review of research since 1993

Gillian A. O'Driscoll\textsuperscript{a,b,*}, Brandy L. Callahan\textsuperscript{a}

\textsuperscript{a} Department of Psychology, McGill University, Stewart Biological Sciences Building, 1205 Dr. Penfield Avenue, Montreal, Quebec, Canada H3A 1B1
\textsuperscript{b} Department of Psychiatry, Douglas Hospital Research Center, McGill University, Verdun, Quebec, Canada

\textbf{Abstract}

Abnormal smooth pursuit eye-tracking is one of the most replicated deficits in the psychophysiological literature in schizophrenia [Levy, D. L., Holzman, P. S., Matthysse, S., & Mendell, N. R. (1993). Eye tracking dysfunction and schizophrenia: A critical perspective. \textit{Schizophrenia Bulletin}, 19, 461–505]. We used meta-analytic procedures to quantify patient-control differences in eye-tracking and to evaluate potential moderators of effect size including patient and target characteristics and characteristics of the control population (matched or not). The magnitude of patient-control differences in pursuit depended on the measure. Global measures had large effect sizes. Among specific measures, maintenance gain and leading saccades yielded large effect sizes, with gain also yielding the narrowest confidence interval. Effect sizes associated with specific measures of smooth pursuit vs. specific measures of intrusive saccades did not clearly implicate one system over the other. Patient demographics and target characteristics generally had little influence on effect sizes. However, studies that failed to eye-match patients and controls tended to have smaller effect sizes for maintenance gain and catch-up saccade rate. Average effect sizes and confidence limits for global measures of pursuit and for maintenance gain place these measures alongside the very strongest neurocognitive measures in the literature [Heinrichs, R. W. (2004). Meta-analysis, and the science of schizophrenia: Variant evidence or evidence of variants? \textit{Neuroscience and Biobehavioral Reviews}, 28, 379–394] for distinguishing between patients with schizophrenia and controls.
Disturbances of Voluntary Control of Saccadic Eye Movements in Schizophrenic Patients

Junko Fukushima, Kikuro Fukushima, Tatsuo Chiba, Satoshi Tanaka, Itaru Yamashita, and Masamichi Kato

To study whether or not schizophrenic patients have disturbances in voluntary control of saccades, we examined visually elicited saccade and antisaccade tasks in 10 normal control subjects and 12 schizophrenic patients. The latencies of saccades in the schizophrenic patients were not significantly different from those of normal controls. However, 6 of the 12 schizophrenics showed significant abnormalities in the antisaccade task; 6 made more errors and 3 of them showed longer latencies than normal controls. Five of these 6 patients revealed an atrophy of the frontal cortex on computed tomography (CT) scans. These results indicate that many schizophrenics show difficulties in voluntary control of saccades, suggesting a dysfunction of the frontal cortex.
Antisaccades in Schizophrenia

Chronic schizophrenia
F[1,211]=108.20, p<0.001; d=1.43

First episode
F[1,38]=7.93, p=0.008; d=0.92


Ettinger et al 2004 Am J Psychiatry
Endophenotype Criteria

- Is the endophenotype associated with the illness? Is this association independent of state factors?

- Is the endophenotype a reliably measurable trait?

- Is the endophenotype observed in people at increased genetic risk for schizophrenia?
Antisaccade Reliability

(also see Ettinger et al 2003 Psychophysiology)
# Antisaccade Reliability

**Table 2**

Effects of trial number on reliability (segments of baseline and retest). Pearson correlation, ICC and internal consistency (Cronbach’s alpha).

<table>
<thead>
<tr>
<th>Antisaccades</th>
<th>Pearson 1</th>
<th>Pearson 1/2</th>
<th>Pearson 1/2/3</th>
<th>Pearson 1/2/3/4</th>
<th>ICC 1</th>
<th>ICC 1/2</th>
<th>ICC 1/2/3</th>
<th>ICC 1/2/3/4</th>
<th>Cronbach’s alpha Baseline</th>
<th>Cronbach’s alpha Retest</th>
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<tr>
<td>Latency</td>
<td>0.78*</td>
<td>0.84*</td>
<td>0.86*</td>
<td>0.91*</td>
<td>0.88*</td>
<td>0.92*</td>
<td>0.92*</td>
<td>0.97*</td>
<td>0.71*</td>
<td>0.71*</td>
</tr>
<tr>
<td>SD latency</td>
<td>0.56*</td>
<td>0.25</td>
<td>0.40</td>
<td>0.71*</td>
<td>0.71*</td>
<td>0.66*</td>
<td>0.65*</td>
<td>0.79*</td>
<td>0.66*</td>
<td>0.93*</td>
</tr>
<tr>
<td>ICV latency</td>
<td>0.43</td>
<td>0.21</td>
<td>0.35</td>
<td>0.66*</td>
<td>0.80*</td>
<td>0.78*</td>
<td>0.78*</td>
<td>0.93*</td>
<td>0.94*</td>
<td>0.70*</td>
</tr>
<tr>
<td>Gain</td>
<td>0.43</td>
<td>0.76*</td>
<td>0.80*</td>
<td>0.78*</td>
<td>0.62*</td>
<td>0.62*</td>
<td>0.62*</td>
<td>0.70*</td>
<td>0.82*</td>
<td>0.94*</td>
</tr>
<tr>
<td>SD gain</td>
<td>–0.03</td>
<td>0.48</td>
<td>0.62*</td>
<td>0.67*</td>
<td>0.92*</td>
<td>0.92*</td>
<td>0.92*</td>
<td>0.94*</td>
<td>0.94*</td>
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</tr>
<tr>
<td>Error rate</td>
<td>0.72*</td>
<td>0.84*</td>
<td>0.90*</td>
<td>0.92*</td>
<td>0.92*</td>
<td>0.92*</td>
<td>0.92*</td>
<td>0.94*</td>
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</table>

*Wöstmann et al (2013) Brain & Cognition*
## Smooth Pursuit Reliability

### TABLE 1

<table>
<thead>
<tr>
<th>Measures</th>
<th>Reliabilities</th>
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<tr>
<td></td>
<td>Within One Two Year</td>
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<tr>
<td></td>
<td>Session Week Year</td>
</tr>
<tr>
<td>RMS .4</td>
<td>.66 .63 .64 .66</td>
</tr>
<tr>
<td>.6</td>
<td>.69 .77 .65 .78</td>
</tr>
<tr>
<td>.8</td>
<td>.76 .79 .63 .83</td>
</tr>
<tr>
<td>1.0</td>
<td>.75 .87 .63 .75</td>
</tr>
<tr>
<td>1.2</td>
<td>.76 .76 .65 .70</td>
</tr>
<tr>
<td>mean</td>
<td>.73 .77 .64 .75</td>
</tr>
<tr>
<td>SI</td>
<td>.73 .75 .55 .71</td>
</tr>
<tr>
<td>SK</td>
<td>.80 .73 .75 .63</td>
</tr>
<tr>
<td>SRT</td>
<td>.58 .58 .54 .56</td>
</tr>
</tbody>
</table>

Note.—RMS = root-mean-square deviation measure of smooth pursuit tracking by frequency (Hz); SI = saccadic interruption score; SK = spikiness rating; SRT = saccadic reaction time; S11 = session 1, first testing; S12 = session 1, second testing; S21 = session 2, first testing; S2T = two-year retest session.

*N = 52 subjects.

*N = 46 subjects.
Endophenotype Criteria

- Is the endophenotype associated with the illness? Is this association independent of state factors?

- Is the endophenotype a reliably measurable trait?

- Is the endophenotype observed in people at increased genetic risk for schizophrenia?
Genetic Risk

- Clinically unaffected relatives of patients with schizophrenia
  - Siblings
  - Parents
  - Twins

- Assumption
  - Polygenic aetiology of schizophrenia
  - Carrying of risk polymorphisms in relatives leads to increased expression of endophenotype
Siblings of Schizophrenia Patients

Sibling – Controls: 10°/s: p = 0.003, d = -0.56
24°/s: p = 0.62, d = -0.12

Ettinger et al 2004 J Psychiatr Res 38:177-184
Parents of Schizophrenia Patients

Fig. 1. Antisaccade error rate in parents and controls (linear trend $p = 0.008$). Legend: Data indicate means ± SEM (standard error of the mean).

Fig. 2. Antisaccade latency in parents and controls (linear trend $p = 0.018$). Legend: Data indicate means ± SEM (standard error of the mean).
MZ Twins of Schizophrenia Patients

Error rate
t=0.89, p=0.38, ES=0.28

Increased latency
t=2.50, p=0.02, ES=0.46

Reduced amplitude gain
t=2.89, p=0.01, ES=1.00

Ettinger et al 2006 AJP 163:543-546
### Table 3. Raw Antisaccade Error Rate Among Healthy, Proband, and Relative Groups

<table>
<thead>
<tr>
<th>Antisaccade Task</th>
<th>Probands</th>
<th>Relates</th>
<th>Post Hoc&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall error rate (%)</td>
<td>18.4 (12.5)</td>
<td>44.1 (25.8)</td>
<td>35.0 (22.8)</td>
</tr>
<tr>
<td>Error rate 10° (%)</td>
<td>22.6 (15.2)</td>
<td>48.7 (26.2)</td>
<td>39.3 (24.7)</td>
</tr>
<tr>
<td>Error rate 15° (%)</td>
<td>14.3 (11.7)</td>
<td>39.2 (26.8)</td>
<td>30.8 (22.2)</td>
</tr>
</tbody>
</table>

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**Fig. 3.** Effect size deficit of antisaccade error rate in proband and relative groups compared to controls before (light bars) and after (dark bars) adjustment for generalized impairment as indexed by the BACS composite scores. Scz, schizophrenia; SczA, schizoaffective; BP, psychotic bipolar; BACS, Brief Assessment of Cognition in Schizophrenia.

*Reilly et al 2014 Schizophrenia Bulletin*
Eye movement dysfunction in first-degree relatives of patients with schizophrenia: A meta-analytic evaluation of candidate endophenotypes

Monica E. Calkins a,*, William G. Iacono b, Deniz S. Ones b

a, Department of Psychiatry, University of Pennsylvania School of Medicine, Neuropsychiatry Section, Schizophrenia Research Center and Brain Behavior Laboratory, 10th Floor Gates Building, 3400 Spruce Street, Philadelphia, PA 19104, USA
b, Department of Psychology, University of Minnesota, Minneapolis, MN, USA

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ABSTRACT

Several forms of eye movement dysfunction (EMD) are regarded as promising candidate endophenotypes of schizophrenia. Discrepancies in individual study results have led to inconsistent conclusions regarding particular aspects of EMD in relatives of schizophrenia patients. To quantitatively evaluate and compare the candidacy of smooth pursuit, saccade and fixation deficits in first degree biological relatives, we conducted a set of meta-analytic investigations. Among 18 measures of EMD, memory-guided saccade accuracy and error rate, global smooth pursuit dysfunction, intrusive saccades during fixation, antisaccade error rate and smooth pursuit closed-loop gain emerged as best differentiating relatives from controls (standardized mean differences ranged from .46 to .66), with no significant differences among these measures. Anticipatory saccades, but no other smooth pursuit component measures were also increased in relatives. Visually-guided reflexive saccades were largely normal. Moderator analyses examining design characteristics revealed few variables affecting the magnitude of the meta-analytically observed effects. Moderate effect sizes of relatives vs. controls in selective aspects of EMD supports their endophenotype potential. Future work should focus on facilitating endophenotype utility through attention to heterogeneity of EMD performance, relationships among forms of EMD, and application in molecular genetics studies.

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Molecular Genetics
Molecular Genetics

• Importance of functional characterisation of (GWAS-identified) candidate genes (Glahn et al 2014 Am J Med Genet)
  – "understanding how a particular gene or its expressed protein produces the cascade of biological changes that ultimately result in increased risk for the clinical symptoms of mental illness"
  – Endophenotypes as "important "trail markers" for traversing the chasm between genotype and behavioral phenotype"
  – "major roll when moving beyond a simplistic genotype-phenotype association to delineating the molecular, cellular and system-level mechanisms that give rise to a psychiatric assessment"

• Neuregulin 1 (NRG1) as candidate gene for schizophrenia (Stefansson et al 2002 Am J Hum Genet 71:877-892)
  – Linkage (8p) and association studies in Iceland
  – Independent replications of these findings (though different SNPs/haplotypes reported in different studies)
  – Candidate gene for schizophrenia
NRG1 rs3924999

AA vs. GG: d=0.78
p=0.01

NRG1 rs3924999

  - Schizophrenia patients (N=113) and healthy controls (N=106) from Iceland
  - Association between rs6994992 and antisaccade spatial error (p=.05; d=.30)
  - Trend towards association between SNP8NRG222662 and spatial error variability (p=.07; d=.26)
Antisaccade Spatial Accuracy

- Amplitude spatial accuracy as a measure of the effectiveness of dorsal stream sensorimotor transformations

- Intraparietal sulcus and frontal eye fields show transition from activity reflecting the direction of the stimulus to that representing the saccadic goal
  - MEG study by Moon et al (2007 NeuroImage): FEF and IPS show switch from early stimulus-contralateral to later antisaccade-contralateral activation
  - fMRI study by Herweg et al (2014 NeuroImage): role of IPS in antisaccade spatial accuracy
Discussion and Conclusions
Conclusions: Key Findings

- Smooth pursuit and antisaccade performance measures...
  - are trait markers
  - are impaired in schizophrenia patients
  - are impaired in their clinically unaffected, biological relatives
  - are impaired in people with high levels of schizotypy
  - show at least moderate heritability (approx. 50%)
VW T3 series (built 1979-1992)
Implications

• Well characterised neurocognitive or biological endophenotypes are useful in delineating the mechanistic pathway of risk genes at multiple levels of measurement

• Gottesman & Gould (2003) criteria important for identification of such laboratory assays
  – Oculomotor endophenotypes better validated than many other endophenotypes!

• Still more research needed for validation of oculomotor contribution to phenomics
  – Especially for fMRI of eye movements: see issues of heritability and reliability (e.g. Macare et al 2014 Biol Psychol)
Limitations

• Are endophenotypes the end of phenotypes?
  – "one of the primary assumptions of the endophenotypic approach is that the underlying genetic architecture of the endophenotype itself is relatively simpler than that of the disease and also relatively closer to the action of the gene" (Glahn et al 2014 Am J Med Genet)

• Problems with these assumptions
  – Phenotypic complexity of (oculomotor) endophenotypes!
  – Medium heritability of observable traits (see e.g. our own recent twin study of antisaccades and BOLD: heritability of antisaccade errors 47%; significant heritability of BOLD only in left thalamus 50%; Macare et al 2014 Biol Psychol)
More Limitations!

• Practical limitations
  – Large samples needed for molecular genetic studies, often necessitating multi-centre studies (see issue of between-study protocol differences; Antoniades et al 2013 Vision Research)
  – Availability of eye-trackers (in comparison to standard neuropsychological tests)

• Limitations of fMRI during eye movements
  – Availability of MRI / eye-trackers / time
  – Reliability of BOLD signal
  – Heritability of BOLD signal
More Hope!

- Research Domain Criteria (RDoC) initiative of NIMH
  - the "development, for research purposes, of new ways of classifying psychopathology based on dimensions of observable behavior and neurobiological measures"
  - "define basic dimensions of functioning (such as fear circuitry or working memory) to be studied across multiple units of analysis, from genes to neural circuits to behaviors, cutting across disorders as traditionally defined"

- "The aim of RDoC, to deconstruct heterogeneity associated with psychiatric diagnoses using multiple behavioral and neuroscientific measures, is at its core the same as that of the endophenotype approach" (Glahn et al 2014 Am J Med Genet)
RDoC and Antisaccades

<table>
<thead>
<tr>
<th><strong>Genes</strong></th>
<th><strong>Molecules</strong></th>
<th><strong>Cells</strong></th>
<th><strong>Circuits</strong></th>
<th><strong>Physiology</strong></th>
<th><strong>Behavior</strong></th>
<th><strong>Self-Reports</strong></th>
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<tr>
<td>COMT</td>
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<td>Somatostatin</td>
<td>DLPFC</td>
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<td>Impulsive behaviors;</td>
<td>Disorganization Sx on SANS/SAPS/ PANGO BRIEF (Gioa)</td>
<td>Simon</td>
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<tr>
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<tr>
<td>MAO-A</td>
<td>Glu</td>
<td>Ventrinuronostriatal BA6/ (FEF) Pre-SMA PPC</td>
<td>Alpha</td>
<td>Impulsive behaviors; off-task behaviors; distractibility</td>
<td>Conners impulsivity scale ADHD Rating Scale (Dupaul) BRIEF (Gioa) ATQ/CBQ Effortful Control</td>
<td>Go/Nogo</td>
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<td>Time</td>
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</table>
| Anti-

**Antisaccade**

**Countermarching**

**Conflicting and contralateral motor response task**

**Motor persistence paradigms (e.g.)**
RDoC and Antisaccades

• "Currently promising avenues for research involve development of transdiagnostic concepts not limited to traditional diagnostic categories, measures of endophenotypic and manifest psychopathology that have higher validity than those categories, and methods for modeling complex relationships among diverse contributors to etiology." (Miller & Rockstroh 2013 Annu Rev Clin Psychol)

• "With more grounding in animal neuroscience and other aspects of basic biological and psychological science, exemplified in the Research Domain Criteria initiative, there is every reason to anticipate that the endophenotype concept will grow more central in the psychopathology literature." (Miller & Rockstroh 2013 Annu Rev Clin Psychol)