Schizophrenia Bulletin vol. 33 no. 1 pp. 49–68, 2007
doi:10.1093/schbul/sbl055
Advance Access publication on November 13, 2006

The Consortium on the Genetics of Schizophrenia: Neurocognitive Endophenotypes

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The Consortium on the Genetics of Schizophrenia (COGS) is a 7-site collaboration that examines the genetic architecture of quantitative endophenotypes in families with schizophrenia. Here we review the background and rationale for selecting neurocognitive tasks as endophenotypic measures in genetic studies. Criteria are outlined for the potential of measures as endophenotypic vulnerability markers. These include association with illness, state independence (ie, adequate test-retest stability, adequate between-site reliability, impairments in patients not due to medications, impairments observed regardless of illness state), heritability, findings of higher rates in relatives of probands than in the general population, and cosegregation within families. The COGS required that, in addition, the measures be "neurocognitive" and thus linked to neurobiology and that they be feasible in multisite studies. The COGS neurocognitive assessment includes measures of attention, verbal memory, working memory, and a computerized neurocognitive battery that also includes facial processing tasks. Here we describe data demonstrating that these neurobehavioral measures meet criteria for endophenotypic candidacy. We conclude that quantitative neurocognitive endophenotypes need further evidence for efficacy in identifying genetic effects but have the potential of providing unprecedented insight into gene-environment interaction related to dimensions of brain and behavior in health and disease.

Key words: neurogenetics/attention/memory/emotion

Introduction

Schizophrenia is a complex, heritable brain disorder, and progress in understanding its pathophysiology mandates integration of genetic and neurobiological methods. Symptom-based genetic studies have applied linkage and association analyses in a case-control design, with some replicated findings.[1,2] An alternative approach examines the genetics of schizophrenia from the neurobiological perspective with neurocognitive endophenotypic markers of putative brain function. Studies of brain-behavior relations provide converging data leading to inclusion of neurocognitive measures in characterization of the endophenotype of the disorder, thus advancing beyond the traditional study of its clinical phenotypic expression. While symptoms may represent compensatory behavior and accordingly vary over the course of illness and treatment, the underlying brain dysfunction is likely a more stable trait marker that can be examined genetically. This approach is further motivated by the need to elucidate pathophysiology even after candidate alleles are established.

Disordered cognitive functioning is a hallmark of schizophrenia (eg, Bleuler[3]) that is associated with impaired quality of life and poor outcome (eg, Green et al[4]). Convergence of findings from neurocognitive, electrophysiological, structural, and functional imaging methodologies and postmortem work indicate that schizophrenia is characterized by aberrations in brain function affecting frontotemporal circuitry. Dysfunction of such circuitries would reflect the combined effect of genetic liability and environmental factors implicated in schizophrenia, and by their examination in families, it should be possible to establish the interplay of these factors. We anticipate that the quantitative, continuously distributed phenotypes related to brain function will serve as reliable risk factors and indicators of schizophrenia liability. We postulate that the endophenotypes that we proposed to genetically characterize are more proximal functions of gene action than is the diagnostic assignment of schizophrenia itself. Therefore, it should be simpler to localize the genetic loci contributing to the endophenotypes than to localize those for schizophrenia. With this strategy in mind, we selected neurocognitive measures that meet recommended criteria as endophenotypic markers and can be applied in the Consortium on the

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Genetics of Schizophrenia (COGS) multisite collaborative study.[5] Here we review the rationale for selecting the COGS measures and the relevant literature. The COGS data will be presented in empirical articles.

Overview of Criteria for Evaluating and Selecting Candidate Endophenotypes

Criteria for applying endophenotypic measures have been formulated with the recommendation that the endophenotype be associated with the illness, be heritable, be primarily state independent, and cosegregate within families.[6] The selection of the neurocognitive measures for COGS was guided by the following criteria: (1) Association with illness—moderate to large effect sizes between schizophrenia patients and community controls. (2) State independent: (*a*) adequate test-retest stability; (*b*) adequate between-site reliability; (*c*) evidence that impairments in patients are not due to medications, including direct comparisons between medicated vs unmedicated patients, medication-naive vs medicated patients, and correlations between performance and medications; (*d*) evidence that impairments are observed regardless of the illness state, including that first-episode, chronic, and remitted patients exhibit similar patterns of impairments. (3) Heritability: (*a*) in healthy populations and (*b*) in schizophrenia families. (4) Found in unaffected relatives at a higher rate than in the general population so that small to moderate effect sizes between biological relatives of schizophrenia patients and community controls are observed. In addition, the COGS selected measures that have a known neurobiological substrate relevant to schizophrenia and whose initial results support using them to test genetic hypotheses. Moreover, we considered the practicality of task administration in a large multisite protocol.

Several reviews have evaluated neurocognitive endophenotypes in schizophrenia (eg, Aleman et al,[7] Snitz et al[8]). However, to our knowledge none have fully examined the extent to which candidate endophenotypes fulfill each of the above criteria. Here we review the endophenotypic candidacy of selected neurocognitive measures highly implicated in schizophrenia and chosen for the COGS project. These include attention, verbal memory, and working memory (WM). In addition, we present new candidates for consideration in future studies: face recognition memory and emotion processing.

Attention

Deficits in attention have long been considered to be central features of the clinical presentation of schizophrenia[3,9] and have been a consistent focus of the experimental psychopathology of schizophrenia.[10–14] Attention is apparently dysfunctional in schizophrenia in several ways, including sustained focused attention,[15,16] selective attention,[17] and cognitive control of attention.[18] While cognitive control of attention and selective attention have strong conceptual relationships to WM,[19] a recent integration of factor analytic studies of cognition in schizophrenia indicates that sustained focused attention is separable from other neurocognitive factors.[20] Furthermore, it is the deficit in sustained focused attention that has garnered the most support as an attention endophenotype for schizophrenia.[21–23]

Continuous Performance Tests (CPTs) have become the most widely used measures of deficits in sustained focused attention and among the most frequently applied indices of neurocognitive deficits in schizophrenia.[10,15,16] CPT refers to a type of rapidly paced vigilance task that was originally designed to examine sustained focused attention in individuals with suspected neurological damage[24] and that has been adapted for research on schizophrenia,[25,26] attention-deficit hyperactivity disorder,[27] and other disorders.[28] All versions evaluate the ability to maintain a focused readiness to detect and respond to selected target stimuli over a prolonged time period. CPTs typically involve a quickly paced series of stimuli (eg, one stimulus per second), brief stimulus durations (usually 30–100 milliseconds), and relatively short periods of vigilance (5–15 minutes).[16] The individual stimuli are usually single visual letters or digits, but visual numbers with several digits and visual shapes[25] and auditory stimuli[29] have been used as well.

The subject's task in a CPT is to monitor the continuous series of stimuli and to respond each time that a target stimulus appears. The target can be one that can be discriminated within either a single stimulus presentation (eg, the letter "X" or the digit "0") or a stimulus sequence (an "A" followed by an "X," a "3" followed by a "7," or 2 identical numbers in a row; see figure 1). Performance can be evaluated using correct target detections (hits) and incorrect responses to nontargets (false alarms), as well as through separation of signal/noise discrimination (d' or A') and response criterion dimensions by signal detection theory indices.[30] The signal/noise discrimination index has become the most common primary score in recent studies. To increase the sensitivity to detect subtle abnormalities such as those characterizing vulnerability to schizophrenia, CPT stimuli have been blurred (degraded) to increase perceptual discrimination load[26,31] or a high WM load has been added by defining the target as identical sequential stimuli rather than a fixed stimulus.[25,32] Key evidence supporting an association between CPT performance and schizophrenia is presented in table 1.

State Independence

Performance on both the CPT version involving blurred digits (Degraded Stimulus Continuous Performance Test [DS-CPT])[31] and the CPT version involving successive

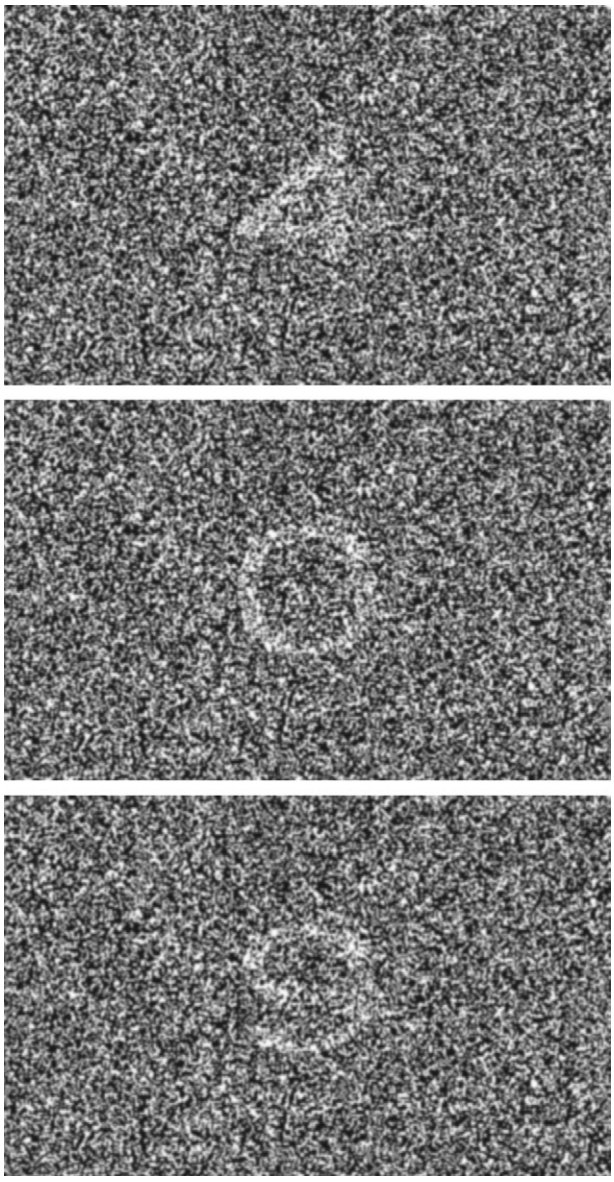

Fig. 1. Examples of the stimuli in the computerized Degraded Stimulus Continuous Performance Test. The "0" is the target stimulus. Printed with permission of Keith H. Nuechterlein.

identical sets of digits (Continuous Performance Test, Identical Pairs Version [CPT-IP])[25] has shown substantial stability over time. The stability of DS-CPT d' over 1 year was found to be 0.65 for schizophrenia patients and 0.72 for healthy subjects.[62] For CPT-IP d', stability over 2 years ranged from 0.56 to 0.73.[25]

For the computerized DS-CPT developed by Nuechterlein and Asarnow,[63] signal/noise discrimination levels are highly consistent across sites for healthy subjects (eg, A' of 0.94 ± 0.04, 0.95 ± 0.05, and 0.94 ± 0.05 in Los Angeles, Germany, and Japan, respectively) and for schizophrenia patients (A' of 0.89, 0.88, and 0.88 in Los Angeles, Germany, and Japan, respectively).[34,64,65] Similar reliability across sites characterizes the CPT-IP.[25,50] The availability of standardized PC versions of these CPTs likely aids the repeatability of findings across sites.

CPT impairments have been documented even in medication-naive and medication-withdrawn schizophrenia patients.[51,66] It was evident from initial studies of CPT performance that antipsychotic medications do not contribute to CPT deficits; rather, deficits within easier early CPT versions in schizophrenia patients were improved by first-generation antipsychotic medications.[67,68] It appears from initial studies that second-generation antipsychotic medications have the ability to improve CPT performance, although not to normal levels, even for the more demanding DS-CPT[69] and CPT-IP,[70] although another study found stable DS-CPT performance from drug-free baseline to treatment with a second-generation antipsychotic medication.[71] Thus, CPT deficits in schizophrenia are not due to antipsychotic medication, but their severity may be attenuated by antipsychotics.

Both cross-sectional[66,72] and longitudinal studies[39] indicate that CPT impairments are present in schizophrenia even in a clinically remitted state, so it is clear that these attentional impairments are not secondary to active symptoms. Whether a CPT deficit shows significant change with clinical state may vary by CPT version. The magnitude of DS-CPT d' deficit has been shown to be stable across psychotic and remitted states when medications were unchanged, while d' in a memory-load CPT type (3–7 CPT) clearly improved in clinical remission in the same sample.[39] CPT signal/noise discrimination was also found to be stable despite introduction of medication and clinical improvement in a 1–9 CPT with flanker-distracting stimuli.[51] Thus, while some types of CPT deficits improve with symptomatic amelioration, others are stable from psychotic to fully remitted clinical states. The CPT parameters that control whether performance deficits vary with symptomatic improvement are not wholly clear at this point and could benefit from more systematic study.

Occurrence in Unaffected Relatives and Heritability

CPTs with high perceptual discrimination loads or WM loads have been used successfully for detection of neurocognitive deficits among biological relatives of schizophrenia patients (see table 1). Simple CPT versions with low perceptual discrimination and low WM loads[26,44,52] often fail to detect deficits in first-degree relatives, so the processing load appears to be relevant to successful use of CPT deficit as an endophenotype.[12] Formal heritability estimates for CPT performance are beginning to be available, based on sib-sib or parent-child correlations. For the CPT-IP d', heritability based on 30 healthy families was estimated as 0.39 for the verbal and 0.49 for the spatial condition.[25] Among relatives of schizophrenia probands, Chen et al [45] reported estimated CPT d' heritability ranging from 0.48 to 0.62. For

Table 1. Summary Table of Key Evidence Supporting Each Candidate Endophenotype's Association With Schizophrenia and Occurrence in Relatives

Candidate Endophenotype	Association With Schizophrenia	Occurrence in Relatives
Attention	• Meta-analysis[33]: $d = 1.18$ • Chronic schizophrenia patients exhibit deficits in CPTs with single stimuli or sequential stimuli[32,34,35–38] • Schizophrenia patients exhibit deficits in CPTs without WM burdens and with low overall processing resource demands[12,16] and deficits in CPTs with either perceptual loads (blurred, degraded stimuli) or WM loads[15,16]. • Schizophrenia patients exhibit deficits in both target detection rates[36,37] and signal/noise discrimination measures (eg, d')[23,32,34,35,39,40]	• Meta-analysis[8]: $d = 0.54$[a] for CPT d' in more complex memory-load versions (AX or IP type), $d = 0.43$ for the simpler versions (X type) • Individual study effect sizes range: 0.46–2.97[41] • Children of patients with schizophrenia, but not children of nonschizophrenia spectrum patients, show a signal/noise discrimination deficit using either a memory-load CPT[42] or a perceptual-load CPT[26] • In a longitudinal study of children of schizophrenia patients, the small subgroup that later developed schizophrenia spectrum disorder had shown CPT deficits at the age 12–13 years[43] • Siblings and parents of schizophrenia patients also show target detection and signal/noise discrimination deficits on CPT versions with high perceptual loads[23,44–49] or high WM loads[b,50–54]
VDM	• Effect size range[1,7,33,55,56]: 1.0–1.5 standard deviations • Qualitative review (>110 studies)[55]: schizophrenia patients exhibit well-replicated deficits in VDM	• Meta-analysis 1[57]: $d = 0.54$[c] • Meta-analysis 2[8]: $d = 0.42$ for WMS-R, LM immediate recall (I); $d = 0.28$ for LM delayed recall (II) • Meta-analysis 3[58] $d = 0.47$ for WMS-R, LM I; $d = 0.38$ for LM II[d]; $d = 0.30$ for CVLT recall, trials 1–5
WM	• Meta-analysis 1[59]: $r = 0.45$ for verbal WM; $r = 0.46$ for visuospatial WM • Meta-analysis 2[7]: $d = 0.71$ for digit span forward; $d = 0.82$ for digit span backward	• Meta-analysis 1[8]: d range = 0.25–0.55 on spatial delayed match to sample, spatial span, and conventional digit span tasks • Meta-analysis 2[58]: $d = 0.45$ for digit span forward; $d = 0.35$ for digit span backward • Deficits in the unaffected children of parents with schizophrenia predict the later development of psychosis[60]

Note: Meta-analytic result is the effect size obtained from the comparison between the index group (schizophrenia or relative) and control subjects, interpreted according to the guidelines of Cohen: 0.2 = small, 0.5 = moderate, 0.8 = large. CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; AX, an "A" followed by "X"; IP, Identical Pairs; LM, Logical Memory; VDM, verbal declarative memory; WM, working memory; WMS-R, Wechsler Memory Scale, Revised Version.

[a]When only studies that used age-matched groups and symmetrical exclusion criteria were considered, CPT deficits showed the largest effect sizes of 24 cognitive variables ($d = 0.56$–0.66).[8]

[b]For exceptions, see Egan et al[40] and Jones et al.[61]

[c]This was the largest effect size among several cognitive tests/domains.[57]

[d]Trandafir et al.[58] reported a larger effect size for LM immediate than for delayed recall, which was even more evident in the diminished effect size of the "savings score" (the percentage of material retained in the delayed condition, based on the amount learned in the immediate condition; effect size = 0.18).

a CPT-DS condition that comes closest to the DS-CPT used in the COGS project, heritability was estimated as 0.57 based on 10 families with data on 2 parents and 0.51 based on 18 families with data on 1 parent. An earlier study of siblings of schizophrenia patients estimated heritability for DS-CPT d' at 0.79.[46] Thus, larger studies are definitely needed, and these initial estimates of heritability need to be viewed cautiously due to small sample sizes. However, initial evidence suggests at least moderate heritability for CPT performance in healthy families and families with schizophrenia probands.

Cosegregation of Endophenotype and Illness Within Families

While the issue of cosegregation of schizophrenia and CPT deficits within families has not been formally addressed at this point, the issue of whether schizotypal personality features and CPT deficits are correlated within families of schizophrenia probands has received some attention. Initial data suggested that low DS-CPT d' within siblings of schizophrenia probands might be associated with more social-interpersonal schizotypal features and with physical anhedonia.[46] Subsequent research by Chen et al[45] also found associations within families between degraded and undegraded CPT d' and the interpersonal aspects of schizotypy but not the cognitive/perceptual aspects (illusions and odd ideas). The latter study also found significant associations between degraded and undegraded CPT d' and the disorganization dimension of schizotypy. Generally consistent with the latter result is the finding from Nuechterlein et al,[73] using a factor analytic approach, that DS-CPT d' deficits in relatives of schizophrenia patients fell on the same Cognitive Disorganization factor as Trail Making B and Span of Apprehension performance and odd or eccentric behavior, although in this case other schizotypal features of disorganization were not associated with CPT deficits. Paralleling the Chen et al results, Nuechterlein et al found that the cognitive/perceptual schizotypal dimension (positive schizotypy) was not related to the cognitive performance deficits. Performance on the CPT-IP has also been associated with interpersonal difficulties in relatives of schizophrenia patients, at least in the sense that early CPT-IP d' deficits in children of schizophrenia patients predicted later emergence of social withdrawal in adulthood.[74] In contrast, 2 French studies of relatives of schizophrenia patients did not find significant associations between social or physical anhedonia and either DS-CPT d' or CPT-IP d'.[53,75] Thus, these associations between CPT deficits and schizotypal features among relatives need further examination, but initial indications suggest potential relationships to the social-interpersonal and disorganization dimensions of schizotypy. Within-family analyses are needed to examine cosegregation of CPT deficits and schizophrenia itself.

Neurobiological Substrates and Schizophrenia

The neurobiological substrate of CPT performance has not been extensively studied, but functional neuroimaging has provided some meaningful patterns. Using positron-emission tomography in healthy participants, the DS-CPT was found to activate right prefrontal and temporal regions.[76] Signal/noise discrimination level (d') correlated positively with relative glucose metabolic rates in medial superior frontal gyrus and right inferior temporal gyrus.[77] Schizophrenia patients showed abnormally low relative glucose metabolic rate in right and left frontal cortex and right temporal cortex during DS-CPT activation.[76] Later analyses of more differentiated regions indicated that patients have decreased activation during the DS-CPT in medial frontal cortex, cingulate gyrus, medial temporal lobe, and ventral caudate, supporting the role of cortical-striatal-thalamic pathways.[78]

Seidman et al[29] developed an auditory CPT with and without WM demands. In a functional magnetic resonance imaging (fMRI) study of healthy men, compared with the vigilance task, performance of the WM task produced significant activation in the lateral and medial prefrontal cortex; precentral cortex; temporal lobe, including insula and hippocampus; parietal-occipital cortex; cingulate; thalamus; and superior colliculus. This paradigm was then applied to adult nonpsychotic relatives of persons with schizophrenia.[79] Compared with controls, relatives showed greater task-elicited activation in the dorsolateral prefrontal cortex and the anterior and dorsomedial thalamus. When the effects of between-group performance differences were controlled, relatives showed significantly greater activation in the anterior cingulate. Results support the hypothesis that subtle abnormalities of brain function, in the anterior attentional network, are found in relatives of persons with schizophrenia, in the absence of psychosis.

Sponheim et al[80] have demonstrated that relatives of schizophrenia patients show decreased late-positive amplitudes (P300) over parietal areas and increased early posterior (P1) and right frontal (anterior N1) event-related potentials (ERPs) during target detection. Thus, a pattern of augmented early potentials and diminished late potentials during sustained attention may be associated with genetic susceptibility to schizophrenia. Additional studies using neuroimaging with better temporal resolution (eg, ERP, fMRI), coupled with parametric manipulations of CPT dimensions, are needed to more clearly isolate the relevant neural pathways.

Utility in Tests of Genetic Hypotheses

While the data reviewed thus far are certainly encouraging regarding the value of CPT deficits as an endophenotype for schizophrenia, it has been argued that a recurrence risk ratio greater than that of schizophrenia itself is needed for an endophenotype to be clearly

useful.[81] The recurrence risk of schizophrenia is about 10. An analysis with a low memory-load CPT indicated that the recurrence risk ratio for CPT deficits in siblings of schizophrenia probands was elevated but was in the 3–5 range.[40] However, a more recent study using a more demanding CPT version that involves degraded stimuli and a memory load found that the recurrence risk ratio using a cutoff of demographically adjusted *z* scores for *d′* in the -2.5 to -3.0 range was much higher, ranging from 12 to 103 for parents and from 9 to 72 for siblings.[47] While the extremely high recurrence risk ratios for the most *d′*-stringent cutoffs are unstable because the number of subjects at those extremes is small, the general magnitude of these ratios is very encouraging.

Specific genes related to CPT deficits are beginning to be examined. Deficits in CPT *d′* are evident in schizophrenia patients with 22q11 deletion (velocardiofacial syndrome), so that location is a potential genetic contributor.[82] DS-CPT *d′* and CPT-IP *d′* deficits were found to be among the contributors to a subtype of schizophrenia with pervasive neurocognitive deficit that explains linkage of schizophrenia to chromosome 6p24.[83] While studies of normal genetic variation and attention have generally not employed CPT variants, one might also expect from studies of other attentional measures that the dopaminergic genes catechol-*O*-methyltransferase (COMT) on chromosome 22 and dopamine receptor D4 on chromosome 11 may influence sustained focused attention, with the former showing more relevance to schizophrenia at this point.[84] Indications that P50 suppression deficits in schizophrenia are linked to an alpha-7 nicotinic acetylcholine receptor gene[85] suggest that this gene may also play a role in sustained attention because P50 suppression deficits are correlated with sustained attention deficits.[86]

Practicality for Multisite Protocols

The COGS project selected the DS-CPT[26,31] and the CPT-IP[25,32] to represent the attentional endophenotype due to both the promising literature using these versions and the ease with which the computerized versions of these tasks can be administered within multisite protocols. To maintain maximal independence of the WM endophenotype and the CPT phenotype, the perceptual-load DS-CPT rather than the memory-load CPT-IP is used as the primary attention measure, while the other is included as a useful supplementary measure.

The computer program for the DS-CPT allows this task to be administered using a PC and 15-in cathode-ray tube monitor.[63] Single digits 0–9 are presented in quasirandom order at a rate of 1/second with 29-millisecond exposures. A random 40% of the pixels in each digit and in the background are changed from black to white, or vice versa, to create a highly blurred image. The participant's task is to monitor the rapid series of digits and to respond as quickly as possible with a button press to each blurred 0 that appears. After a practice period to train subjects in basic discrimination of the blurred digits, an 8-minute vigilance period with 480 stimuli follows. The entire measure takes about 15 minutes, including initial instructions. The computer program automatically provides several indices of performance, including the *d′* summary score.

Administration of the PC version of the CPT-IP[25] is also straightforward. The conditions being used involve sustained attention in situations demanding substantial verbal WM. Subjects are asked to respond each time that the same stimulus occurs twice in a row in a quasirandom sequence within a 3-digit and a 4-digit condition. Each condition involves presentation of 300 stimuli in a rapid, continuous sequence (1/second) with stimulus durations of 50 milliseconds. The *d′* value for the 4-digit number condition is being used as the principal measure of performance because it has been used successfully to examine the predictive role of the CPT-IP in a longitudinal study of the offspring of schizophrenic patients.[43] Testing time is 15 minutes, including instructions. The extent to which the CPT-IP version identifies the same endophenotype as the DS-CPT is as yet unclear, so inclusion of both versions will allow this issue to be examined.

Verbal Declarative Memory

Deficits in verbal declarative memory (VDM) are among the most prominent cognitive difficulties observed in schizophrenia,[7,87] in less severe spectrum conditions,[88] and in close biological relatives who do not meet *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, diagnostic criteria for a schizophrenia-related psychiatric disorder.[8,55,57,89] A review of more than 110 studies showed that they are among the most robust deficits in schizophrenia[55] (see table 1). The dysfunction takes several forms, including deficits in acquisition/encoding, memory storage (ie, abnormal forgetting), and retrieval.[90,91] Less commonly, significantly abnormal rates of forgetting may occur,[55,92] at least in a subgroup of patients.[93] Most participants with schizophrenia show rates of forgetting that are only subtly impaired relative to controls, however, and are more like patients with subtle, material-specific memory disorders like temporal lobe epilepsy[94,95] than they are like patients with Alzheimer's disease (AD).[96] Patients do show prominent deficits in retrieval of information using free-recall paradigms, and/or difficulties encoding new information, but better performance on cued or recognition conditions.[55,92,93,97,98]

State Independence

Widely used measures of VDM, such as the Wechsler Memory Scale, Third Edition (WMS-III), test of story recall (Logical Memory [LM][99]) and the California

Verbal Learning Test, Second Edition (CVLT-II), test of list learning,[100] report adequate levels of test-retest reliability in normal standardization samples. For example, WMS-III LM reliability coefficients for the immediate (I) and delayed (II) free-recall conditions are 0.74 and 0.76, respectively, for 16- to 54-year-old participants, with 2- to 12-week test-retest intervals. Test-retest coefficients for the CVLT-II, obtained with median 3-week test-retest intervals in 16- to 88-year-old subjects, ranged from 0.79 to 0.88 for trial 1–5 total correct responses, short-delay free-recall correct, long-delay free-recall correct, and recognition hits.

Few studies have assessed the stability of deficits in VDM in schizophrenia. In one, Harvey et al[101] reported moderate test-retest coefficients after 8 weeks for total learning and for delayed recall (0.64 and 0.62, respectively) on the word list learning test[102] in middle-aged and elderly patients with schizophrenia or schizoaffective disorder. The stability of VDM deficits was also confirmed in a 4-year follow-up study of adult nonpsychotic, first-degree biological relatives of patients with schizophrenia.[81,103] Deficits in VDM (assessed by the WMS Revised version LM test) were among the most robust indicators of cognitive impairment in the relatives' sample.

Many large studies of schizophrenia, such as clinical trials, assess VDM across multiple sites (eg, Keefe et al[70] collected data in 14 sites), although reliability across sites is often not reported. Good indications of strong between-site reliability, however, come from meta-analyses. The Global Verbal Memory construct of Heinrich and Zakzanis,[33] which showed the most robust deficit in the battery of neurocognitive tests they examined in schizophrenia patients (d = 1.41), was based on 31 studies, mostly from different laboratories. Similarly, moderate LM I deficits in relatives of subjects with schizophrenia (d = 0.42) reported by Snitz et al[8] came from 5 separate studies, although there is up to 0.5 standard deviations variability across sites.[57]

Two issues especially relevant to state independence involve medication effects. The first is whether medications for schizophrenia contribute to deficits in VDM. Although the issue is significant (eg, anticholinergic effects that characterize many antipsychotic medications to varying degrees have long been associated with impaired declarative learning and memory),[104] medication effects themselves do not account for the extent of performance deficits observed in tests of verbal learning and memory.[104] Moreover, deficits observed in the absence of medication, such as those occurring before or near the first psychotic episode, reflect their intrinsic nature.[105,106]

The second issue pertaining to state independence of memory deficits relates to whether they persist following treatment with antipsychotic medications. A majority of studies do demonstrate improvement in long-term memory following administration of second-generation antipsychotics (eg, 17 of 23 studies in a recent meta-analysis) and only slightly less positive effects for first-generation antipsychotic drugs (the difference in effect size was 0.17).[70,107] Nevertheless, the magnitude of improvement is modest, usually reflecting effect sizes less than 0.5, which is substantially smaller than the usual deficit of 1.0–1.5 in this domain.[33,82,108] Taken together, this literature shows that deficits in VDM in schizophrenia occur largely independently of positive or negative effects of antipsychotic medications.

Deficits in VDM are evident throughout the course of the illness, including the periods before psychosis, near the first psychotic episode, and after remission from psychotic symptoms.[55,105] Deficits in VDM appear to be most related (though mildly so) to negative symptoms.[55]

Occurrence in Unaffected Relatives and Heritability

Like their relatives with schizophrenia, adult and adolescent nonpsychotic biological relatives of patients with schizophrenia also perform worse on encoding (but less so on the rate of forgetting) than controls on tests of VDM[55,81,89,103,109–111] (see table 1). These findings further support the view that impairments in learning and memory reflect intrinsic features of the disorder rather than epiphenomena related to effects of medication, psychosis, or other cognitive dysfunctions.[98]

Several studies examined the heritability of VDM in healthy people or in participants with schizophrenia. Typical of many studies that examined the heritability of particular mental abilities, Bouchard[112] reported heritability estimates in the moderate range (about 0.50) for memory. Similarly, Finkel et al,[113] using a twin sample, assessed recall on the WMS LM test. Heritability estimates for delayed recall were 0.47 for healthy young participants, 0.63 for middle-aged adults, and 0.61 for older adults. Lee et al[114] examined performance on Buschke Selective Reminding Test in subjects from families with AD. Heritability estimates in unaffected family members (ie, without AD) were lower than those reported by Lee et al, using the LM test, but still remained in the moderate range (total recall = 0.32, delayed recall = 0.39, delayed recognition = 0.31).

Few studies have quantified the heritability of cognitive deficits in schizophrenia.[115] In one, Tuulio-Henrikssen et al[116] reported heritability estimates for several cognitive abilities in patients with schizophrenia and their first-degree biological relatives. Although verbal ability showed moderate heritability (0.62), recall on trials 1–5 of the CVLT, a verbal test of learning and memory, showed a small effect size (0.21). By contrast, recognition memory was higher (0.49). More studies will be necessary before conclusions about the heritability of deficits in verbal learning and memory can be drawn for schizophrenia.

Cosegregation of Endophenotype and Illness Within Families

Formal cosegregation investigations involving VDM are needed, although a few studies are relevant to the issue. In one, Johnson et al[117] showed that deficits in cognitive functioning, including WMS LM I and II and CVLT recall on trials 1–5, occurred in unaffected cotwins of patients with schizophrenia, in association with symptoms of *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*, schizotypal personality disorder. Individuals with schizotypal symptoms who did not demonstrate a family history of schizophrenia also did not manifest these cognitive deficits. Faraone et al[110] showed that greater degrees of "genetic loading" for schizophrenia (defined as having 2 first-degree relatives with schizophrenia rather than 1) were associated with greater deficits in VDM (ie, LM). Although Cannon et al[118] found in one study that several cognitive deficits (eg, divided attention) covaried with the degree of genetic relationship in twins discordant for schizophrenia more strongly than did VDM, it is likely that deficits in VDM increase in families in association with increases in the density of schizophrenia and schizophrenia spectrum–related symptoms.

Neurobiological Substrates and Schizophrenia

Deficits in VDM most likely reflect an endophenotype that is related to the underlying neurobiological substrates in the medial temporal and the frontal lobes. Both of these brain regions mediate VDM, and both are impaired in schizophrenia.[119–122] Consistent with this view, Seidman et al[123] reported that deficits in VDM (ie, LM) were correlated with smaller left hippocampi (a medial temporal lobe structure) in adult nonpsychotic, first-degree biological relatives of patients with schizophrenia. The moderate heritability estimate for deficits in recognition memory on the CVLT reported by Tuulio-Henrikssen et al[116] implicates frontal lobe mechanisms of retrieval.

Utility in Tests of Genetic Hypotheses

Measures from the CVLT-II were selected as VDM endophenotypes for use in the COGS project. Measures from the WMS-III LM test were added recently to help assess the differential sensitivity of these 2 commonly used measures. Although these measures of VDM are likely to be informative in genetic analyses, currently the identification of possible genotypes related to VDM in schizophrenia is in its early stages. Cannon et al,[124] eg, showed overrepresentation of disrupted-in schizophrenia 1 (DISC1) and translin-associated factor X genes (1q42) in patients with schizophrenia, which were associated with neurobiological and cognitive abnormalities that included VDM. The same group also reported evidence for a locus related to VDM in schizophrenia at 4q21.[125]

Practicality for Multisite Protocols

COGS training and ongoing quality assurance measures are designed to minimize procedural differences across the 7 sites in the Consortium. Thus far, they have been successful with respect to CVLT-II administration, which also benefits from relatively well-described, straightforward administration and training procedures.

Working Memory

WM deficits have been described as core cognitive features of schizophrenia[126] and are particularly strong candidate endophenotypes (see table 1). WM is often defined as a limited-capacity storage system used for the temporary maintenance and manipulation of information, although a variety of conceptual models and methodological approaches have been used to investigate the cognitive functions that comprise WM (see Miyake and Shah,[127] Repovs and Bresjanac[128]). For example, the influential, multicomponent model of WM proposed by Baddeley[129,130] includes 3 limited-capacity storage buffers—the phonological loop, the visuospatial sketch pad, and the episodic buffer—and a central executive control system that guides the manipulation of information held within the subsidiary storage buffers. Other investigators emphasize distinctions between transient, online maintenance or manipulation functions of the WM system.[131,132] The cognitive architecture and neurophysiological bases of WM processes have been extensively investigated in human and nonhuman primates,[133–137] and this rich body of basic research has facilitated investigations of WM processes that are associated with vulnerability to schizophrenia.

Within the schizophrenia research literature, investigators have used a variety of paradigms derived from cognitive neuroscience and clinical neuropsychology to assess WM functions. These diverse paradigms have been described as falling into 2 broad classes of WM functions.[138] The first type of paradigm assesses transient, online maintenance functions that do not involve manipulation of the stored information. These tasks assess functions that in many ways map onto those ascribed to the storage buffers described in Baddeley's WM model (eg, rehearsal). Examples include spatial delayed response tasks and digit or spatial span forward repetition tasks. In the spatial domain, this aspect of WM is very amenable to animal model research exploring its neurobiological underpinnings.[139] The second class of paradigms involves maintenance plus manipulation of information or "executive functioning WM." Central executive or control functions are required when stored information needs to be transformed in some way, updated, temporally coded or sequenced, or protected from interference or decay. Examples include N-back tasks and digit or spatial span backward repetition tasks. A newer, more challenging verbal span task, the Letter-Number

Sample Items From The Letter-Number Sequencing Test

	Item	Correct response
LNS-Forward	9 – A – 6 – J – 3 – P	9 – A – 6 – J – 3 – P
LNS-Reordered	E – 1 – R – 8 – M – 7	1 – 7 – 8 – E – M - R

Fig. 2. The Letter-Number Sequencing Test comprises 2 conditions. In the Letter-Number Sequencing task (LNS)–forward condition, the tester verbally presents different sets of increasingly longer sequences of intermixed letters and numbers at a rate of 1/second. After each sequence, the participant is asked to repeat the numbers and letters in the same exact order. In the LNS-reordered condition, the tester again verbally presents increasingly longer sequences of intermixed numbers and letters at a rate of 1/second. After each sequence, the participant is asked to repeat the numbers in ascending order first and then the letters in alphabetical order. In both conditions, the letter-number sequences range from 2 stimuli (eg, A–3) up to a maximum length of 8 stimuli. Three trials at each length are presented. Both conditions are discontinued when the subject fails 3 consecutive trials of the same length. Within each condition, one point is scored for each correctly repeated sequence (maximum total score for each condition is 21 points). Sample items from the Letter-Number Sequencing Test.

Span task[140] and its adaptation for the WMS, Version III, called the Letter-Number Sequencing task (LNS[99]), requires subjects to both categorize alternating letters and numbers into separate classes and reorder the stimuli within each class (see figure 2).

Performance deficits shown by schizophrenia patients often appear to be more severe on WM tasks that involve maintenance plus complex manipulation functions than those observed in maintenance-only tasks.[141,142] For example, in the verbal domain, patients and controls show an average separation of about of 0.71–0.82 standard deviations on digit span forward and backward tasks,[7] whereas effect sizes for the more challenging LNS have exceeded 1.4 standard deviations (eg, Perry et al,[138] Gold et al,[140] Conklin et al[143]). WM deficits do not appear to be artifacts of any particular task parameter, such as duration of delay interval, and the magnitude of performance differences between patients and nonpatient controls is comparable across verbal, spatial, and object WM tasks.[59] The WM deficits of schizophrenia patients show associations with clinically important features of the disorder. For example, impairments on WM tasks show substantial relationships with measures of more complex cognitive processes such as problem solving, language comprehension, and planning.[140,144] WM impairments also show consistent relationships with various aspects of poor functional outcome, including poor social and vocational functioning and less benefit from rehabilitation interventions (eg, Green et al,[4] Kopelowicz et al,[145] Smith et al[146]). Thus, WM impairments are robust and clinically significant features of schizophrenia.

State Independence

WM deficits appear to reflect traitlike features of schizophrenia that are not attributable to potential confounds. As noted above, WM impairments show minimal cross-sectional correlations with severity of delusions and hallucinations. In addition, WM deficits are detectable in clinically stable outpatients and demonstrate considerable constancy across both time and fluctuations in clinical status, suggesting that they are not merely secondary manifestations of psychotic symptoms.[147–151] Although WM task performance is typically not associated with acute psychotic symptoms such as delusions and hallucinations, moderate associations with severity of negative symptoms and formal thought disorder are often found.[152–154] WM deficits do not reflect side effects of antipsychotic medications as they are present in neuroleptic-free and neuroleptic-naive patients (eg, Barch et al,[155] Carter et al[156]), and atypical antipsychotics may actually improve WM to some degree.[157] WM impairments are also not secondary to factors associated with chronicity, such as illness progression or prolonged exposure to antipsychotic medications, because comparably severe deficits are also detectable during the immediate postonset period.[144,158] WM impairments thus appear to reflect fundamental features of schizophrenia that are stable throughout the course of illness.

Occurrence in Unaffected Relatives and Heritability

Several studies indicate that similar, though attenuated, WM disturbances are also present in clinically unaffected biological relatives of schizophrenia patients, compared with the general population (see table 1). As in patients, WM impairments among their relatives may be more severe on tasks that require demanding executive functions. A recent report by Conklin et al[143] found this pattern across multiple verbal and spatial WM tasks, with the largest effect size in the verbal domain obtained for the more demanding LNS ($d = 0.66$).

Research in both nonclinical and schizophrenia patient samples indicates that genes substantially influence WM abilities. Heritability estimates for verbal and spatial WM storage and executive functions in nonclinical samples are moderately high (0.43–0.49[159,160]). Comparable heritability estimates have been reported for visual and verbal WM in schizophrenia (0.36–0.42[116,161]). These findings suggest that WM deficits are partially under genetic control in both healthy individuals and in the families of individuals with schizophrenia.

Cosegregation of Endophenotype and Illness Within Families

We are unaware of any true cosegregation studies examining WM within families of schizophrenia probands. However, some studies do report significant relationships between severity of WM impairment and level of genetic

loading for schizophrenia among unaffected relatives. Severity of WM impairments relate to genetic loading among singleton vs multiplex families[116,161] and in discordant dizygotic vs monozygotic twin pairs.[118,162] The COGS design will allow us to directly evaluate whether WM impairments cosegregate within the families of schizophrenia probands.

Neurobiological Substrates and Schizophrenia

The functional neuroanatomy of WM has been fairly well characterized and abnormalities in the key neural systems that are involved in WM have been extensively documented in schizophrenia. A wealth of animal and human studies indicate that the prefrontal cortex, particularly the dorsolateral prefrontal cortex, and the dopaminergic system, in conjunction with posterior brain regions such as the posterior parietal cortex, are critical for intact WM.[163] The precise roles of these cortical regions and dopamine in the component processes of WM continue to be actively investigated (eg, Braver and Barch,[164] Jonides et al,[165] Owen et al[166]).

Disruptions of the dopaminergic system as well as gross morphological, cytoarchitectonic, and functional abnormalities of prefrontal cortex have been well established in schizophrenia and figure prominently in etiological theories of this disorder.[167–172] Furthermore, individuals with schizophrenia, as well as their unaffected biological relatives, demonstrate altered physiological activity in the prefrontal cortex while performing WM tasks.[173–177] Thus, the neurobiological systems that are essential for WM are strongly implicated in the pathophysiology of schizophrenia.

Utility in Tests of Genetic Hypotheses

Evidence that WM deficits are heritable and dependent on neurobiological substrates that are disrupted in schizophrenia strongly implicates genes that regulate these neural systems as candidate susceptibility genes. There have already been several efforts to identify polymorphisms in specific genes that modulate WM performance in both the normal population and individuals with schizophrenia (see Greenwood and Parasuraman[84]). Most reports have focused on the val158met polymorphism of the COMT gene on chromosome 22, which plays a key role in cortical dopamine metabolism. Several groups have reported association between this polymorphism and performance on, as wells as prefrontal physiological activation during, measures of WM and executive control in schizophrenia patients, their family members, and healthy controls (see Bruder et al,[178] Goldberg and Weinberger[179]). However, these findings have not been uniformly replicated.[180,181]

Initial reports also indicate that alleles in the DISC1 gene on chromosome 2 show association with WM task performance, as well as prefrontal physiological abnormalities, in schizophrenia patients and their unaffected twins.[175,182,183] In healthy subjects, associations between the G-to-A polymorphism of the dopamine beta-hydrosylase gene have recently been found to specifically modulate WM,[184] though this association has not yet been examined in schizophrenia. Thus, emerging research supports the feasibility of detecting associations between specific genes and WM performance in schizophrenia patients and their biological relatives.

Practicality for Multisite Protocols

The COGS project has selected the LNS to assess WM. The LNS is simple to administer in a standardized manner,[99] relatively brief, and includes both forward (intermixed letter-number strings repeated verbatim) and reordered conditions (intermixed letter-number strings repeated with numbers first in ascending order and then letters in alphabetical order) to assay both maintenance-only and executive control functions of the WM system. The LNS and related verbal span tasks have been successfully implemented in large, multicenter studies of schizophrenia patients (eg, Keefe et al,[185] McGurk et al[186]). The LNS-reordered condition also has the advantage of showing larger separations in performance for schizophrenia patients and their biological relatives as compared with healthy controls than conventional span tasks, presumably due to its heavier demands on central executive functions.

Penn Computerized Neurocognitive Battery: Candidate Endophenotypes

The Penn computerized neurocognitive battery (CNB) was validated in healthy people[187] and patients with schizophrenia.[188] These studies demonstrated test-retest reliability, sensitivity to diagnosis, age effects, and sex differences. The CNB was robust to repeated measures with minimal practice effects, limited to speed. Except for modest improvement in spatial memory, scores were not affected by treatment with olanzapine.[189] The battery was designed for large-scale studies and is administered on a portable computer, in the laboratory or in the field, in a fixed order using clickable icons. It was included in the COGS to characterize the neurocognitive functioning of participants in multiple cognitive domains and to provide additional potential endophenotypes. To reduce redundancy with core COGS neurocognitive endophenotypes described above, tasks were selected to assess 7 domains (examples in figure 3): abstraction and mental flexibility (Penn Conditional Exclusion Test[190]), attention and WM (Letter-n-Back[191]), face memory (Penn Face Memory Test [PFMT][192]), spatial memory (Visual Object Learning Test [VOLT][193]), spatial processing (Computerized Judgment of Line Orientation[187]), sensorimotor dexterity (Computerized Finger-Tapping Task

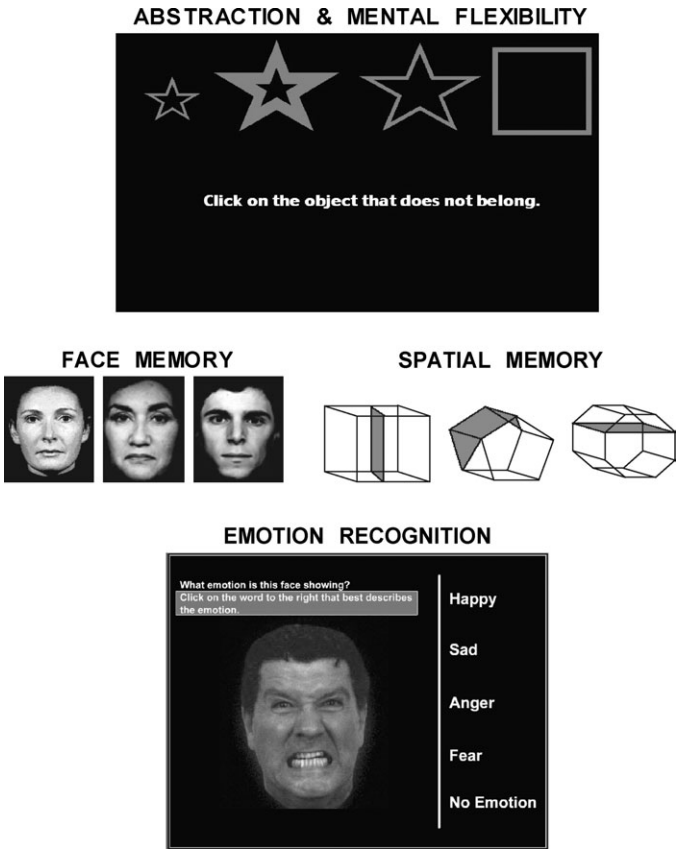

Fig. 3. Examples of stimuli from the Penn computerized neurocognitive battery.

and Motor Praxis test), and emotion processing (Penn Emotion Recognition Test [PERT]—40[194]).

For each domain, 3 performance functions are calculated: (1) *accuracy*, which reflects the number of correct responses; (2) *processing speed*, reflected by the median response time for correct responses; and (3) *efficiency*, which reflects both accuracy and processing speed [accuracy/log(speed)]. Thus, the computerized battery has the advantage of providing separate measures of facets of performance typically inaccessible to traditional paper-and-pencil measures. The administration time of the COGS version of the Penn battery is approximately 60 minutes, including brief standardized rest periods.

The neurocognitive domains of the Penn battery reflect a range of abilities, only some of which have been implicated as candidate endophenotypes. The current review focuses on 2 related domains involving facial processing abilities, which are assessed in the COGS and have been associated with schizophrenia but heretofore have not been widely regarded as candidate endophenotypes of the disorder: face recognition memory and emotion processing. We discuss the research that has been conducted on these abilities supporting their potential as endophenotypes, with the goal of fostering further research evaluating their candidacy.

The processing of facial information, including the ability to recognize and remember faces in order to distinguish the familiar from the unfamiliar, and the ability to evaluate emotions displayed in social situations are critical to effective social functioning and communication. The PFMT[192] assesses face recognition memory through the presentation of 20 digitized faces, with neutral facial expressions, which are subsequently intermixed with 20 foils equated for age, gender, and ethnicity. Participants indicate whether or not they recognize each face, both immediately and after a 20-minute delay. Schizophrenia patients have frequently been reported to exhibit difficulty recognizing faces previously seen (eg, Gur et al,[188] Conklin et al,[195] Hellewell et al[196]). The PFMT has been used in several studies, employing different samples, reporting this effect.[188,197–199] It has been debated whether the impairment is specific to faces or instead is reflective of a more generalized memory or object memory dysfunction. Some work suggests that the face memory deficit is not accounted for by other memory and spatial deficits.[195]

Emotion tasks from the Penn battery were developed to address methodological drawbacks of extant emotion recognition tasks.[200,201] Identification of facial affect is tested with an abbreviated (40 item) version of the Penn Emotion Recognition Test,[202] which includes facial stimuli, balanced for gender, age, and ethnicity, depicting happiness, sadness, anger, fear, and neutral facial expressions (8 each; ER40). Long considered a core fundamental disturbance in schizophrenia, identification of facial affect has been reported to be impaired in schizophrenia patients across cultures (for reviews, see Kohler et al,[203] Mandal et al[204]), including the United States (eg, Heimberg et al[205]), Germany,[199,206] India (eg, Habel et al[206]), and Israel.[207] Increased intensity of emotion does not appear to improve facial emotion recognition in schizophrenia patients as much as in healthy participants.[194]

A primary deficit in emotion recognition in schizophrenia is potentially consistent with observed social-interpersonal disturbances and clinical symptoms such as referential delusions. Errors reported include misidentification of neutral faces as emotional and negatively valenced, consistent with the potential relevance for clinical symptoms such as delusions of persecution, in which innocuous stimuli or people are interpreted as malevolent.[194] There is some suggestion that particular difficulties in recognition of fear and disgust are superimposed on an overall impairment in affect recognition.[194] However, a lingering question remains as to whether schizophrenia patients have a specific differential deficit in emotion recognition against the backdrop of a generalized impairment in facial processing (for reviews, see Kohler et al,[203] Edwards et al[208]). Most studies have failed to support a specific deficit in emotion recognition when compared with nonemotional facial recognition abilities,

such as age discrimination and face recognition (eg, Sachs et al,[199] Kohler et al[202]), but studies have also varied considerably in the difficulty of comparison tasks.[209] Recent work employing the same set of stimuli across emotion recognition, age discrimination, and face recognition memory tasks suggests a differential impairment in emotion recognition.[209]

State Independence

There is limited knowledge on the state independence of face recognition memory deficits in schizophrenia. In patients treated with olanzapine, Gur et al[189] reported no significant difference in PFMT accuracy between 2 testings over a 4.5-month period, suggesting that face recognition memory accuracy is stable over time, despite clinical improvement. Face memory speed, however, improved, possibly related to practice effects.[189] Gruzelier et al[210] evaluated the longitudinal face memory performance (Warrington Recognition Memory Test) of schizophrenia patients tested initially when psychotic and retested when in symptomatic remission. Improvement in face memory was reported in patients classified according to symptom and behavioral data as "active" but not in patients classified as "withdrawn," suggesting that stability of face memory deficits may be moderated by clinical subtype or symptoms.

Emotion recognition deficits have been reported in both first-episode (eg, Edwards et al,[211] Wolwer et al[212]) and remitted (eg, Wolwer et al,[212] Bediou et al[213]) patients, suggesting the deficit is apparent throughout the course of illness. However, there is some evidence that acutely ill patients are more impaired than remitted patients,[214] that chronic patients are more impaired than recent onset patients,[215] and that increased impairment is associated with higher levels of negative symptoms in clinically stable patients[194] and with greater severity of both positive and negative symptoms in acute patients.[202] The cumulated results suggest that emotion recognition is associated with symptom status and illness duration and that symptom improvement may reduce the appearance of emotion recognition impairment but does not fully ameliorate it.

Could treatment with psychotropic medications contribute to the observed deficit? Gaebel and Wolwer[216] reported stable emotion recognition deficits in schizophrenia patients who were initially tested off medication and retested subsequent to treatment with either perazine or haloperidol. In a longitudinal comparison of facial emotion identification (Facial Emotion Identification Test) in schizophrenia patients receiving risperidone compared with those receiving haloperidol, reduced impairment in patients receiving risperidone, but not haloperidol, was reported.[217] However, this study did not include a healthy comparison group, so risperidone treatment may not have improved face recognition performance to normal levels. Overall, the limited available evidence thus far suggests that although particular medications or symptom relief might enhance emotion recognition in schizophrenia patients, the observed impairments do not appear to be attributable to the effects of medication or acute symptomatology. However, more data are needed to address this question.

Occurrence in Unaffected Relatives and Heritability

Despite the long history of research on face memory and emotion recognition impairments in schizophrenia and notwithstanding considerable evidence for a genetic influence on many aspects of cognitive functioning (eg, McGue and Bouchard[218]), few studies have been conducted on the occurrence of impairments in schizophrenia families or the heritability of face memory and emotion recognition. Perhaps this lack of data reflects the traditional emphasis on understanding the neurobiological or clinical relevance of observed deficits, rather than their genetic underpinnings. However, the field is progressing toward more integrated, interdisciplinary approaches to understanding psychopathology (eg, Plomin and McGuffin[219]). Indeed, recent results support the potential endophenotype candidacy of face recognition memory and emotion recognition. In a multisite investigation of 349 individuals from 35 multiplex, multigenerational families, heritability of PFMT accuracy was 33% and speed was 25%.[198] Heritability of an emotion intensity discrimination test[220] was also high and significant (37.3%).[198] These results suggest that both face recognition memory and emotion recognition are heritable characteristics in schizophrenia families reflecting genetic influences shared among family members.

Face recognition memory impairment in the relatives of schizophrenia patients was first reported by Conklin et al,[195] using the WMS (WMS-III) Faces subtest. Calkins et al[197] replicated and extended this finding, using the PFMT, the VOLT as a nonfacial object memory comparison task, and a larger sample. Significant immediate and delayed face memory deficits were observed in relatives. Although patients were more impaired in visual object memory than comparison subjects, relatives were not, suggesting that the face memory deficits are not secondary to generalized object memory deficits. Finally Gur et al.[198] reported significantly reduced PFMT accuracy and speed in first-degree relatives from multigenerational families with multiple schizophrenia probands. Thus, the few studies conducted to date are in strong support that face recognition memory deficits can be observed in unaffected relatives. Moreover, in light of the limited available data on the state independence of face recognition impairments in schizophrenia patients, it is important to note that impairments in healthy relatives support the trait status in probands because relatives are not affected by potentially confounding variables associated with chronic illness, including medications.

To our knowledge, only a handful of investigations have examined emotion recognition in relatives. Toomey et al[221] found no differences on tests of affect recognition between a small sample of first-degree relatives of schizophrenia patients ($n = 21$) and controls ($n = 19$). Bolte and Poustke[222] reported a nonsignificant trend for schizophrenia patients' parents ($n = 35$) to score lower on a test of facial affect recognition than controls ($n = 22$) but no differences between their siblings ($n = 11$) and controls. Two other investigations reported evidence for subtle facial affect recognition in relatives (parents,[223] siblings[224]). In contrast, we have recently found evidence of significant impairment in the accurate discrimination of emotion intensity among relatives ($n = 291$) of multiplex, multigenerational families.[198] There are several possible explanations for the relative success of the latter investigation, including the larger sample size, the presumably greater genetic loading of the schizophrenia families, or the sensitivity of the emotion-processing tasks (eg, Erwin et al[200]). Regardless, coupled with the observed significant heritability, the results strongly support further examination of emotion-processing abilities in relatives.

Cosegregation of Endophenotype and Illness Within Families

No studies to our knowledge have addressed the coaggregation of face memory and emotion recognition in schizophrenia families. However, the data from the multiplex families in our collaborative investigations can be used to test the hypothesis that multiply affected individuals from the same families share deficits in these abilities.

Neurobiological Substrates and Schizophrenia

Lesion, imaging, and nonhuman primate studies have implicated the right fusiform gyrus, located in the occipitotemporal cortex, in face-processing tasks requiring perception of faces and objects (for discussions, see Conklin et al,[143] Gur et al[226]). The observed face recognition memory impairment in schizophrenia families is thus consistent with a frontotemporal impairment dysfunction associated with the genetic liability for schizophrenia.

Much evidence suggests that emotional behavior is regulated by the limbic system, especially amygdala, hypothalamus, mesocorticolimbic dopaminergic systems, and cortical regions (orbitofrontal, dorsolateral prefrontal, temporal, and parietal),[226] and several studies have reported amygdala or amygdala–hippocampal complex abnormalities in schizophrenia patients and their relatives (for review, see van Rijn et al[227]). Using fMRI and facial stimuli employed in the PERT, Gur et al[226] found increased limbic response, especially the amygdala but also the hippocampus and other circumscribed limbic regions, during emotion discrimination, but not age discrimination, in healthy participants. A subsequent investigation in schizophrenia patients[228] examined emotional valence discrimination and found decreased activation of the left amygdala and bilateral hippocampus in schizophrenia patients compared with controls. These results are consistent with several lines of evidence implicating emotion-processing deficits in schizophrenia (for review, see Phillips et al[229]). Thus, there is evidence that neurobiological substrates relevant to schizophrenia regulate performance on face recognition memory and emotion recognition measures.

Utility in Tests of Genetic Hypotheses

There is a growing body of literature examining emotion processing and the role of limbic dysfunction in schizophrenia.[227] Family studies support the candidacy of face and emotion processing as endophenotypes, although there are no informative genetic studies in schizophrenia that have linked such deficits with genetic variability. Studies in healthy people have reported that serotonin transporter genetic variation is related to amygdalar reactivity. For example, 5-hydroxytryptamine transporter gene linked polymorphic region short-allele genotype was associated with greater amygdala activity in an fMRI study of a threat-related task.[230] Furthermore, carriers of the short allele had reduced gray matter volume in limbic regions in an anatomic magnetic resonance imaging study and altered activity in the amygdala-cingulate circuit in an fMRI study.[231] Future studies can examine mechanisms underlying emotion regulation deficits in schizophrenia.

Practicality for Multisite Protocols

The computerized format of the PFMT and the ER40 are particularly well suited for multicenter studies, because they are briefer and far less vulnerable to variations in administration, scoring, and data entry than traditional measures.[187] They are currently being used in 12 academic centers in the context of 3 multisite investigations of the genetics of schizophrenia.[5,198,232] Data from these investigations will be used to assess the cross-site reliability of the tasks.

Summary and Conclusions

The application of neurobehavioral measures as endophenotypes in genetic studies in schizophrenia has gained momentum. We have selected several measures that tap important neurocognitive domains—attention, verbal memory, and WM—implicated in the pathophysiology of schizophrenia. These measures not only meet established criteria for endophenotypes but also are linked to neurobiology and can elucidate mechanisms underlying their impairment in schizophrenia. In addition, we propose the inclusion of facial processing measures as promising new endophenotypes that can advance the understanding of affective deficits in schizophrenia.

We are mindful that the application of endophenotypic measures in genetic studies presents feasibility and methodology challenges. The COGS has met the feasibility challenge by demonstrating that high-quality neurocognitive data can be collected in multisite genetically informative samples.[5] However, because large-scale studies are underway, there are little convincing data yet that the genetic architecture of the endophenotypes is substantially simpler than that of the schizophrenia phenotype. Furthermore, studies to date have examined individual domains when the underlying neurocognitive systems are inherently complex and interrelated. The interrelationship of neurocognitive endophenotypes among biological relatives of schizophrenia probands has received little empirical attention in the past. Indeed, examination of these interrelationships is one of the goals of the COGS. In schizophrenia patients, an integration of the evidence regarding separable neurocognitive dimensions, primarily based on factor analytic studies, suggested that 7 dimensions could be identified.[20] These dimensions may be somewhat correlated rather than independent of each other.[233,234] In relatives of schizophrenia probands, it is possible that combinations of several neurocognitive measures may be useful to identify a dimension of cognitive disorganization[73] or a homogeneous familial subtype that is characterized by pervasive neurocognitive deficit.[83] The large sample being assessed in the COGS should allow more thorough examination of these issues than prior studies. It will be necessary to move to efficient multidimensional methods of integrating data within and across modalities and levels of analysis.

Notwithstanding these challenges, by providing rigorous measures related to brain function, the quantitative endophenotype approach provides a rich source of information beyond linkage of specific phenotypes to gene action. The biometric nature of these endophenotypes should permit better parcellation of genetic and nongenetic contributions to major domains of human behavior. Such information will be pivotal for clinical applications to emanate from this line of work.

Acknowledgments

This research was supported by the following grants. University of Pennsylvania: RO1-MH65578; University of California Los Angeles: RO1-MH65707; Harvard University: RO1-MH065562, MH43518; Commonwealth Research Center of the Massachusetts Department of Mental Health. For general inquiries regarding the COGS contact David L. Braff, MD, Director of COGS, e-mail: Dbraff@ucsd.edu

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