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Attention/vigilance in schizophrenia: Performance results from a large multi-site study of the Consortium on the Genetics of Schizophrenia (COGS)

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ABSTRACT

Attention/vigilance impairments are present in individuals with schizophrenia across psychotic and remitted states and in their first-degree relatives. An important question is whether deficits in attention/vigilance can be consistently and reliably measured across sites varying in many participant demographic, clinical, and functional characteristics, as needed for large-scale genetic studies of endophenotypes.

We examined Continuous Performance Test (CPT) data from phase 2 of the Consortium on the Genetics of Schizophrenia (COGS-2), the largest-scale assessment of cognitive and psychophysiological endophenotypes relevant to schizophrenia. The CPT data from 2251 participants from five sites were examined. A perceptual-load vigilance task (the Degraded Stimulus CPT or DS-CPT) and a memory-load vigilance task (CPT-Identical Pairs or CPT-IP) were utilized.

Schizophrenia patients performed more poorly than healthy comparison subjects (HCS) across sites, despite significant site differences in participant age, sex, education, and racial distribution. Patient–HCS differences in signal/noise discrimination (d′) in the DS-CPT varied significantly across sites, but averaged a medium effect size. CPT-IP performance showed large patient–HCS differences across sites. Poor CPT performance was independent of or weakly correlated with symptom severity, but was significantly associated with lower educational achievement and functional capacity. Current smoking was associated with poorer CPT-IP d′. Patients taking both atypical and typical antipsychotic medication performed more poorly than those on no or atypical antipsychotic medications, likely reflecting their greater severity of illness.

We conclude that CPT deficits in schizophrenia can be reliably detected across sites, are relatively independent of current symptom severity, and are related to functional capacity.

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1. Introduction

Attentional deficits are a core feature of schizophrenia (Kraepelin, 1919; Nuechterlein, 1977; Nuechterlein & Dawson, 1984; Braff, 1993; Keefe & Harvey, 2012). Sustained focused attention (Nuechterlein, 1991; Cornblatt & Keilp, 1994) is one aspect of attention that appears to be separable from other neurocognitive factors in schizophrenia in factor analytic studies (Nuechterlein et al., 2004). It is also the aspect of attention that has yielded the most extensive research on attentional dysfunction as an endophenotype for schizophrenia (Nuechterlein et al., 1998; Cornblatt & Malhotra, 2001; Agnew-Blais & Seidman, 2013; Chen, 2013), leading to its selection for the Consortium on the Genetics of Schizophrenia (COGS) family study (COGS-1) and current (COGS-2) case–control study (Gur et al., 2007).

Sustained focused attention is frequently measured in schizophrenia through forms of the Continuous Performance Test (CPT), rapidly paced vigilance tasks in which letters or numbers are presented in a quasi-random sequence, with the task of responding only to occasional targets (Rosvold et al., 1956; Nuechterlein, 1991; Cornblatt & Keilp, 1994; Seidman et al., 1998). CPTs evaluate ability to maintain continuous, focused readiness to detect and respond to selected target stimuli over a prolonged time period. The most extensive research on sustained attention in schizophrenia has involved a visual CPT version with a perceptual load (the Degraded Stimulus CPT, or DS-CPT) (Nuechterlein, 1983; Nuechterlein et al., 1983) and one with a working-memory load (CPT, Identical Pairs Version, or CPT-IP) (Cornblatt et al., 1988). Because these CPT versions burden sustained focused attention through demands on quite different cognitive processes, both were included in COGS. Either burdening perceptual processes or working memory appears to increase the sensitivity of a CPT to detect abnormalities associated with vulnerability to schizophrenia (Nuechterlein, 1983; Cornblatt et al., 1988; Cornblatt et al., 1989; Nuechterlein et al., 1998).

Prior research supported CPT deficits as an endophenotype for schizophrenia in several ways. Within individuals with schizophrenia, the deficit is present in psychotic and remitted states (Wohlberg & Kornetsky, 1973; Asarnow & MacCrimmon, 1978; Nuechterlein et al., 1992). Both parents and siblings of schizophrenic probands have been found to show hit rate and signal/noise discrimination deficits on CPT versions with high perceptual loads (Grove et al., 1991; Maier et al., 1992; Chen et al., 1998; Nuechterlein et al., 1998; Saoud et al., 2000; Asarnow et al., 2002; Chen et al., 2004) or high working memory loads (Mirsky et al., 1992; Franke et al., 1994; Finkelstein et al., 1997; Laurent et al., 1999; Appels et al., 2003), with a few exceptions (Egan et al., 2000; Jones et al., 2001). Indeed, a meta-analysis of cognitive deficits in unaffected first-degree relatives of schizophrenia patients (Snitz et al., 2006) concluded that, when studies were restricted to those with age-matched groups and symmetrical exclusion criteria, the CPT deficits showed the largest effect sizes of 24 cognitive variables ($d = .56$–$.66$). Furthermore, CPT deficits showed at least moderate heritability in earlier small samples (Cornblatt et al., 1988; Grove et al., 1991; Chen et al., 1998), confirmed in the large COGS-1 family sample (Greenwood et al., 2007). Initial results of association and linkage analyses also show promising relationships with genes or chromosomal loci that may have relevance to schizophrenia (Greenwood et al., 2011; Chen, 2013; Greenwood et al., 2013).

Despite these encouraging results, no endophenotype study before COGS had directly examined the CPT deficits across several sites differing substantially in the demographic, symptomatic, and functional characteristics of schizophrenia patients, so the extent to which the severity of the CPT deficit would generalize across these varying characteristics of participants across sites was unknown. In this article, using the COGS-2 sample, we examine the degree to which CPT performance did vary across site and the extent to which patient–control differences were affected. In addition, taking advantage of the large COGS-2 sample of schizophrenia patients, we examine the relationship of CPT performance to symptom severity, mental status scores, functional capacity, and real-life functioning with much more statistical power than provided by small, single-site studies.

2. Methods

2.1. Participants

Participants were recruited from five sites. All were 18–65 years old. All patients met the DSM-IV criteria for schizophrenia or schizoaffective disorder, depressed type. Healthy comparison subjects (HCS) were required to have no psychotic disorder or Cluster A Axis II disorder and no current mood disorder. Further information about recruitment procedures and inclusion/exclusion criteria are provided in the introductory article for this theme issue (Swerdlow et al., 2015–in this issue).

2.2. Procedures

To establish and maintain standardization in assessments across sites, all interviewers for symptoms and functioning and all testers for endophenotypes were initially trained at the University of California, San Diego (UCSD) by senior COGS investigators. Equipment and testing room specifications were standardized. All testers were observed during practice assessments by the quality assurance leader for the individual endophenotypes. Each year the COGS interviewers and testers returned to UCSD for refresher training and quality assurance checks.

Patients and HCS were rated on the Global Assessment of Function Scale (GAF; Hall, 1995). The patients were also administered the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a) and Positive Symptoms (SAPS; Andreasen, 1984b) to assess symptom severity, the University of California San Diego Performance-based Skills Assessment — Brief (UPSA-B; Mausbach et al., 2007) to assess functional capacity, and the Role Functioning Scale (RFS) (Goodman et al., 1993) and the Scale of Functioning (SOF; Rapaport et al., 1996) to assess real-life functioning.

Attention/vigilance was assessed with computerized versions of the DS-CPT (Nuechterlein et al., 1983; Nuechterlein & Asarnow, 2006) and the CPT-IP (Cornblatt et al., 1988). These PC-based versions were designed to enhance comparability of the tasks across sites. All sites used a NEC Accusync 50 monitor and 70-Hz refresh rates.

The DS-CPT burdens perceptual processes by blurring visual stimuli (Nuechterlein et al., 1986). The PC Windows-compatible DS-CPT program produces a visual vigilance task that involves a quasi-random series of blurred single digits, with 40% random pixel reversal for visual degradation, a “0” target of 0.25 probability, and presentation rate of one digit/s. Twenty initial examples of the blurred digits are presented using a 290 ms duration, with the tester naming each digit as it appears. Then a practice period of 160 presentations is administered with 29-ms stimulus durations, with the participant clicking the mouse whenever they detect a “0”. Finally, a vigilance test period of 480 presentations is administered using the 29-ms duration. The primary DS-CPT measure is d′, a signal/noise discrimination index from signal detection theory (Green & Swets, 1966; Nuechterlein, 1991) derived from the hit rate and false alarm rate. A response bias measure, ln beta, assesses whether participants tend to respond cautiously or liberally when in doubt about whether a stimulus is a target.

The CPT-IP (Cornblatt et al., 1988) involves sustained attention in a situation demanding working memory. Subjects are instructed to respond each time the same stimulus occurs twice in a row in a quasi-random sequence within a 3-digit condition and then a 4-digit condition. Thus, the target is not a fixed number but rather requires temporarily storing each stimulus, comparing it to the next, and then updating working memory for the present stimulus if it does not match the prior one. After 25 practice trials, each condition involves 300 stimuli presented 1/s with stimulus durations of 50 ms. The participants hold the mouse button down and respond to targets by a brief release of the button, as designed originally by Cornblatt

et al. (1988). The d′ index is again the primary variable, with false alarms based only on responses to nearly identical sequential pairs.

Each CPT output file was uploaded to a centralized quality assurance system and checked by an expert (KHN), blind to diagnostic group, to confirm validity. In instances of questionable validity, the QA specialist reviewed the tester's notes and examined the trial-by-trial output file to rate validity.

2.3. Statistical analysis

Univariate ANOVAs with site and diagnosis as between-subjects factors were used to examine continuous demographic and clinical variables. Chi-square with site and diagnosis factors was used to examine categorical variables. The main analyses of CPT performance were conducted using SPSS GLM ANCOVAs. To examine the patient–HCS group differences on CPT performance while examining the impact of site and sex, we completed ANCOVAs with site, sex, and diagnosis as between-subjects factors and age as a covariate. For diagnostic group differences, we also present Cohen's *d* as a measure of effect size. The relationships between CPT performance and clinical symptom severity, functional capacity, real-life functioning, and psychiatric history variables were examined with bivariate correlations.

3. Results

3.1. Screening for valid CPT results

Of the 2207 participants with uploaded DS-CPT data, only 92 (4.2%) were judged to have unscorable or invalid data. The most common reason was that participants could not discriminate the blurred targets during practice, so the regular DS-CPT trials were not administered (n = 63). Of the 2251 participants with uploaded CPT-IP, only 55 (2.4%) of the 3-digit and 102 (4.5%) of the 4-digit condition files were judged unscorable or invalid. The most common reason for the CPT-IP was inability to learn the identical pair rule or the finger lift response during practice, leading to omission of the regular trials.

3.2. Demographic and clinical characteristics of participants across 5 sites

Table 1 summarizes demographic and clinical characteristics of the patients and HCS across the 5 sites for subjects with valid DS-CPT data. Significant diagnostic group and site differences were present on key demographic characteristics. The patients were generally somewhat older than HCS (M = 45.9 vs. 38.5, $F_{1,2102} = 217.06$, $p < .001$) and mean age varied across sites ($F_{4,2102} = 37.12$, $p < .001$), with a significant diagnosis by site interaction ($F_{4,2102} = 11.04$, $p < .001$) attributable mainly to significant age differences within each site except Site 2. The patients included more males than HCS ($\chi^2(1) = 99.93$, $p < .001$) and sex distribution also varied across sites ($\chi^2(4) = 23.64$, $p < .001$). As expected, schizophrenia patients had lower mean years of education (M = 12.6 vs.15.0, $F_{1,2102} = 703.07$, $p < .001$), but in addition a diagnosis by site interaction ($F_{4,2102} = 10.86$, $p < .001$) indicated that this personal education difference was larger at some sites. Highest parental education, a better indicator of socioeconomic status and intellectual potential, was also somewhat lower for patients than HCS (Ms = 13.4 vs. 14.9, $F_{1,1940} = 120.96$, $p < .001$) and varied by site ($F_{4,1940} = 3.38$, $p < .01$), with the patient–HCS difference larger at some sites ($F_{4,1940} = 4.15$, $p < .01$). Racial distribution for the races with large enough samples

Table 1
Demographic and clinical characteristics of schizophrenia patients and healthy comparison subjects (HCS) with valid DS-CPT data.

	Site 1		Site 2		Site 3		Site 4		Site 5	
	HCS	Patients	HCS	Patients	HCS	Patients	HCS	Patients	HCS	Patients
N[a]	206	286	207	233	158	170	189	235	212	216
Age	40.1 (12.0)	46.0 (11.3)	46.4 (8.3)	48.1 (10.9)	34.9 (12.3)	45.6 (10.4)	32.6 (12.5)	43.3 (11.5)	37.0 (14.8)	46.2 (11.8)
% Female	57.8	30.8	40.4	27.5	60.1	35.3	53.4	37.4	49.5	30.4
Personal education	14.9 (2.1)	12.4 (1.8)	14.8 (1.7)	12.9 (1.9)	15.7 (2.4)	11.9 (2.2)	14.8 (2.3)	12.6 (2.3)	15.2 (2.4)	13.2 (1.9)
Parental education (highest)	14.3 (3.2)	13.5 (3.0)	14.4 (2.8)	13.3 (3.6)	15.4 (3.5)	12.6 (3.2)	15.2 (3.1)	13.4 (3.2)	15.4 (3.2)	13.7 (3.3)
% Hispanic	21.4	20.3	14.0	15.0	11.4	17.6	6.3	4.7	6.1	5.1
Race										
Native American	2	4	0	1	0	1	0	1	1	2
Asia	24	7	11	12	20	2	12	7	14	13
Pacific islander	3	3	2	4	1	1	0	0	7	4
African American	32	51	53	94	53	102	65	153	17	47
Caucasian	104	155	127	100	76	52	97	62	151	114
More than one	41	66	13	22	7	7	15	12	23	36
Not reported	0	0	1	0	1	5	0	0	0	0
% right handed	84.5	89.2	84.17	88.8	89.9	84.7	89.4	85.1	84.0	82.4
Smoking										
Never:past:now	165:23:18	88:38:160	172:8:27	94:15:124	139:1:18	61:6:103	172:0:17	116:1:118	186:0:26	125:1:90
# cigarettes/day if smoker	9.4	15.2	9.5	16.5	7.3	11.8	7.3	13.7	6.9	11.1
% past mood dis	2.9	36.6	3.9	40.3	1.3	16.9	12.6	36.8	16.0	29.2
% past sub dis	8.3	54.2	15.9	44.2	0.6	21.8	13.8	51.1	20.3	47.2
GAF (last month)	90.2 (7.4)	41.0 (5.0)	81.8 (8.4)	45.5 (9.1)	92.0 (5.3)	48.8 (8.6)	87.2 (6.1)	44.2 (9.7)	82.3 (7.2)	40.6 (4.3)
Age of onset		22.3 (7.3)		21.9 (7.7)		22.2 (5.7)		21.7 (6.2)		23.2 (7.2)
# Psych hosp		8.2 (12.1)		9.3 (12.4)		7.9 (9.7)		5.7 (8.1)		5.6 (6.1)
Global_SANS		15.9 (4.0)		9.1 (4.3)		4.1 (3.3)		10.4 (4.1)		12.7 (3.6)
Global_SAPS		7.8 (4.1)		6.1 (4.1)		5.4 (3.0)		7.4 (4.3)		6.7 (3.6)
MMSE score		31.3 (3.2)		30.9 (3.4)		30.2 (2.9)		30.8 (3.6)		32.1 (2.4)
UPSA-B Total		72.4 (14.4)		73.1 (13.9)		66.9 (16.9)		70.9 (14.7)		74.0 (13.2)
SOF total		46.5 (5.5)		48.4 (5.9)		46.9 (6.6)		47.8 (5.9)		43.2 (5.1)
RFS Work		1.6 (1.4)		2.3 (1.5)		3.7 (1.1)		3.7 (1.6)		3.2 (1.3)
RFS Indep		5.2 (1.4)		4.5 (1.4)		3.9 (1.0)		5.1 (1.3)		5.4 (1.2)
RFS Family		4.5 (2.0)		4.7 (1.9)		4.0 (1.1)		5.0 (1.6)		4.2 (1.5)
RFS Socialnet		3.5 (1.9)		4.0 (1.8)		3.9 (1.0)		3.8 (1.8)		2.8 (1.3)

Note: GAF = Global Assessment of Function Scale; SANS = Schedule for Assessment of Negative Symptoms; SAPS = Schedule for Assessment of Positive Symptoms; MMSE = Mini-mental State Examination; UPSA-B = UCSD Performance-based Skills Assessment; SOF = Scale of Functioning; and RFS = Role Functioning Scale.

[a] For Role Functioning Scale (RFS) for patients: site 1, N = 200; site 2, N = 162; site 3, N = 143; site 4, N = 146; and site 5, N = 142

for χ^2 analyses (Caucasian, African-American, Asian) also differed across diagnosis and sites ($\chi^2(8) = 174.42$, $p < .001$).

Symptomatic severity and functional level of patients also varied across sites. Negative symptom severity (SANS) differed across sites ($F_{4,1130} = 267.32$, $p < .001$), as did positive symptom severity (SAPS; $F_{4,1129} = 14.04$, $p < .001$). GAF scores indicated much lower overall functioning in patients than HCS (M = 43.6 vs. 86.4, $F_{1,2089} = 17{,}395.23$, $p < .001$), with the patient–HCS difference varying across sites ($F_{4,2089} = 44.14$, $p < .001$). The patients differed significantly across sites in functional capacity (UPSA-B: $F_{4,1107} = 6.40$, $p < .001$) and in real-life functioning (SOF: $F_{4,1124} = 27.01$, $p < .001$; RFS Work: $F_{4,788} = 81.41$, $p < .001$; RFS Independent Living: $F_{4,788} = 35.65$, $p < .001$; RFS Family Relationships: $F_{4,785} = 13.41$, $p < .001$). Number of psychiatric hospitalizations also differed across sites ($F_{4,1130} = 5.93$, $p < .001$). Age of schizophrenia onset did not differ significantly across sites.

3.3. CPT performance: diagnostic group and site effects

Initial analyses indicated that CPT performance was related to age (DS-CPT d′: $r = -.27$, $p < .001$; CPT-IP 3-digit d′: $r = -.23$, $p < .001$; CPT-IP 4-digit d′: $r = -.24$, $p < .001$) and sex (DS-CPT d′: $F_{1,2108} = 5.38$, $p < .03$; CPT-IP 3-digit d′: $F_{1,2187} = 24.75$, $p < .001$; CPT-IP 4-digit d′: $F_{1,2136} = 15.60$, $p < .001$), so age was included as a covariate and sex as a factor in all ANCOVAs examining CPT variables. Site was included as another between-subjects factor to examine generalization of diagnostic effects across sites.

For the primary DS-CPT signal/noise discrimination measure, d′, patients clearly performed worse than HCS (M(SD) = 1.74(1.01) vs. 2.25(1.07), $F_{1,2089} = 113.09$, $p < .001$), with significant additional effects for the age covariate ($F_{1,2089} = 72.16$, $p < .001$), site ($F_{4,2089} = 15.64$, $p < .001$), diagnosis by site ($F_{4,2089} = 2.44$, $p < .05$), and diagnosis by sex ($F_{1,2089} = 4.64$, $p < .05$). Among the patients, females had poorer signal/noise discrimination than males (M = 1.67 vs. 1.81), but not among HCS (M = 2.28 vs. 2.22). The diagnosis effect size without consideration of age, sex, or site was Cohen's *d* of 0.57. The diagnosis effect sizes with these factors entered were calculated as Cohen's *f* but are reported here in Cohen's *d* equivalents to allow comparison. The diagnosis effect size from the full ANCOVA model was $d = 0.47$, but varied significantly across sites (see Fig. 1) from Cohen's $d = 0.26$ to 0.59. A supplementary analysis added interactions among the demographic factors of age, sex, and racial distribution to the analytic model to determine whether these factors might account for the diagnosis by site interaction. This analysis reduced the diagnosis by site interaction to a clearly non-significant level ($F_{4,2072} = 0.95$, $p = .44$), while revealing significant main effects of diagnosis ($F_{1,2072} = 8.08$, $p < .005$), age ($F_{1,2072} = 65.99$, $p < .001$), and race (means for Caucasian, African American, and Other are 2.09, 1.84, and 1.95, $F_{2,2072} = 10.35$, $p < .001$) and the same diagnosis by sex interaction ($F_{1,2072} = 5.06$, $p < .03$). Thus, the variation in the diagnosis effect size across sites is apparently attributable to differences in subject age, sex, and race across sites. Analyses of secondary DS-CPT measures are generally consistent with the d′ effects (see Tables 2 and 3).

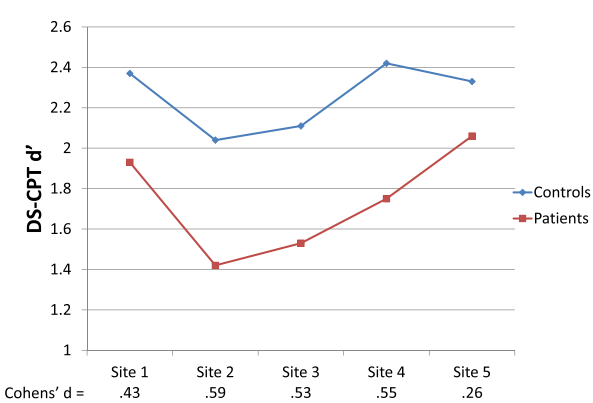

Fig. 1. Interaction of diagnostic group and site for DS-CPT d′: age-adjusted means and effect sizes.

CPT-IP data are summarized in Table 2. The CPT-IP d′ and DS-CPT d′ were moderately related (for CPT-IP 3-digit, r = .40, .25, and .38 for whole, HCS, and schizophrenia samples; for CPT-IP 4 digit, r = .37, .25, and .35 for whole, HCS, and schizophrenia samples, all $p < .001$). CPT-IP 3-digit and 4-digit d′ were highly correlated (r = .76, .65, and .73 for whole, HCS, and schizophrenia samples). The primary CPT-IP performance indices, 3-digit d′ and 4-digit d′, showed large patient–HCS differences across sites. For 3-digit d′, patients performed much worse than HCS (M(SD) = 2.19(0.97) vs. 3.17(0.87), $F_{1,2168} = 520.49$, $p < .001$), with significant additional effects for the age covariate ($F_{1,2168} = 27.48$, $p < .001$) and site ($F_{4,2168} = 7.36$, $p < .001$). The diagnosis by site interaction neared significance ($F_{4,2168} = 2.13$, $p < .08$), as did the diagnosis by sex interaction ($F_{1,2168} = 3.08$, $p < .08$). The diagnosis effect size without consideration of age, sex, or site was large (Cohen's $d = 1.13$), as was one that adjusted for age, sex, and site (Cohen's $d = 0.98$). For 4-digit d′, patients also performed much worse than HCS (M(SD) = 1.21(0.74) vs. 2.07(0.87), $F_{1,2117} = 509.04$, $p < .001$), with a significant age covariate effect ($F_{1,2117} = 40.03$, $p < .001$). Site and sex did not yield main effects or interactions with diagnosis (all $p > .10$). The diagnosis effect size for 4-digit d′ without consideration of age, sex, or site was again large (Cohen's $d = 1.14$), as was one adjusting for age, sex, and site (Cohen's $d = 0.98$). Analyses of secondary CPT-IP variables also generally showed robust patient–HCS differences (Tables 2 and 3).

3.4. Correlates of CPT performance within the schizophrenia sample

As shown in Table 4, discrimination (d′) of blurred digits in the DS-CPT was not correlated with visual acuity level, indicating that it did not reflect this more basic visual process. CPT-IP d′ was significantly related to visual acuity, but only weakly. DS-CPT and CPT-IP performances were also generally either unrelated to current positive (SAPS Global Sum) or negative (SANS Global Sum) symptom level or only very weakly related ($r < .10$). Separation into three symptom dimensions (Andreasen et al., 1995) yields similar correlations, with a weak correlation with Disorganization ($r = .10$, $p < .01$) being the strongest symptom relationship. As expected, poorer DS-CPT and CPT-IP performances were significantly related to another indicator of poor cognitive functioning (MMSE score), low intellectual achievement (years of education), and limited functional capacity (UPSA-B Total). The expected relationship of DS-CPT performance to rated real-world functioning (RFS) was generally absent, while several significant but relatively weak relationships to real-world functioning were present for the CPT-IP (r = .08 to .17).

Examination of the relationship of CPT performance to psychiatric and substance history variables indicated that more prior psychiatric hospitalizations were not related to DS-CPT d′ ($r = -.003$, NS) and were only very weakly related to lower CPT-IP d′ ($r = -.05$, $p < .10$ for 3-digit; $r = -.08$, $p < .01$ for 4-digit). The presence of past or current mood disorder was not related to d′ for either CPT. A longer duration of illness was significantly associated with poorer DS-CPT d′ ($r = -.19$, $p < .001$) and CPT-IP d′ ($r = -.14$, $p < .001$ for 3-digit; $r = -.15$, $p < .001$ for 4-digit), but this relationship decreased when age was controlled (DS-CPT: $r = -.07$, $p < .05$; CPT-IP 3-digit, $r = -.06$, $p < .05$; CPT-IP 4-digit, $r = -.04$, $p = .16$), suggesting only a weak relationship of CPT performance to illness duration per se. A past history of substance use disorder was associated with somewhat better DS-CPT d′ (M = 1.77 vs. 1.63, $F_{1,1134} = 4.70$, $p < .05$), even with age covaried and sex entered as another factor. However, the association with past substance use disorder did not generalize to the CPT-IP.

Smoking status (never, past, current) within the schizophrenia sample did not impact DS-CPT d′ ($F_{2,1136} = 0.35$, NS), but current smoking

Table 2
CPT performance by site for schizophrenia patients and healthy comparison subjects (HCS) (without age adjustment).

	Site 1		Site 2		Site 3		Site 4		Site 5		All sites	
	HCS	Patients	HCS	Patients	HCS	Patients	HCS	Patients	HCS	Patients	HCS	Patients
DS-CPT												
N	206	286	207	233	158	170	189	235	212	216	972	1140
d′	2.41	1.87	1.97	1.37	2.22	1.49	2.57	1.79	2.42	2.02	2.32	1.72
	(1.02)	(0.94)	(1.08)	(0.93)	(1.04)	(0.99)	(1.13)	(1.01)	(0.97)	(1.06)	(1.07)	(1.01)
ln beta	0.84	0.74	0.52	0.48	0.75	0.69	1.22	0.85	1.08	0.77	0.88	0.71
	(0.90)	(0.90)	(0.76)	(0.68)	(0.87)	(0.74)	(1.03)	(0.73)	(0.96)	(0.91)	(0.94)	(0.81)
Hit rate	0.74	0.65	0.70	0.60	0.71	0.58	0.72	0.60	0.72	0.67	0.72	0.62
	(0.20)	(0.21)	(0.21)	(0.21)	(0.22)	(0.24)	(0.21)	(0.23)	(0.20)	(0.23)	(0.21)	(0.23)
False alarm rate	0.07	0.11	0.13	0.18	0.08	0.14	0.06	0.09	0.07	0.11	0.08	0.12
	(0.07)	(0.09)	(0.13)	(0.14)	(0.06)	(0.13)	(0.07)	(0.07)	(0.08)	(0.11)	(0.09)	(0.11)
RT hits (ms)	503 (57)	553 (80)	504 (78)	553 (79)	517 (71)	560 (93)	516 (59)	567 (82)	511 (71)	542 (80)	510 (68)	555 (82)
RT false alarms (ms)	493 (82)	527 (80)	493 (82)	534 (79)	506 (79)	526 (88)	503 (92)	537 (88)	491 (83)	506 (89)	497 (84)	527 (85)
CPT-IP 3-digit												
N	220	290	202	236	174	207	191	236	212	221	999	1190
d′	3.24	2.23	3.21	2.19	3.13	1.86	3.24	2.14	3.25	2.39	3.22	2.17
	(0.81)	(0.90)	(0.85)	(1.00)	(1.01)	(1.05)	(0.80)	(0.94)	(0.87)	(0.90)	(0.87)	(0.97)
Hit rate	0.87	0.69	0.86	0.69	0.86	0.63	0.89	0.69	0.87	0.73	0.87	0.68
	(0.12)	(0.21)	(0.14)	(0.23)	(0.17)	(0.24)	(0.12)	(0.21)	(0.14)	(0.20)	(0.14)	(0.22)
False alarm rate	0.04	0.07	0.04	0.08	0.05	0.11	0.05	0.09	0.04	0.07	0.04	0.08
	(0.04)	(0.07)	(0.05)	(0.08)	(0.05)	(0.10)	(0.04)	(0.08)	(0.04)	(0.07)	(0.04)	(0.08)
RT hits (ms)	490 (65)	555 (83)	503 (71)	563 (96)	496 (76)	563 (103)	493 (72)	549 (96)	477 (72)	532 (83)	491 (71)	552 (93)
RT false alarms (ms)	556 (144)	640 (166)	581 (164)	648 (175)	585 (149)	610 (168)	548 (131)	605 (171)	562 (134)	631 (161)	561 (148)	621 (168)
CPT-IP 4-digit												
N	220	283	199	234	167	184	190	233	210	218	986	1152
d′	2.08	1.22	2.17	1.14	2.06	1.07	2.14	1.24	2.09	1.30	2.11	1.19
	(0.85)	(0.69)	(0.87)	(0.70)	(0.86)	(0.80)	(0.89)	(0.71)	(0.87)	(0.80)	(0.87)	(0.74)
Hit rate	0.76	0.58	0.77	0.55	0.76	0.53	0.78	0.60	0.76	0.59	0.77	0.57
	(0.16)	(0.21)	(0.17)	(0.20)	(0.18)	(0.24)	(0.15)	(0.20)	(0.16)	(0.22)	(0.16)	(0.22)
False alarm rate	0.13	0.19	0.12	0.19	0.14	0.19	0.13	0.20	0.13	0.18	0.13	0.19
	(0.09)	(0.12)	(0.09)	(0.13)	(0.10)	(0.13)	(0.10)	(0.13)	(0.09)	(0.12)	(0.10)	(0.12)
RT hits (ms)	536 (73)	597 (98)	541 (79)	605 (98)	535 (85)	586 (114)	532 (69)	589 (107)	524 (76)	573 (92)	533 (77)	590 (102)
RT false alarms (ms)	567 (120)	611 (113)	565 (119)	624 (125)	563 (119)	594 (134)	558 (101)	615 (131)	545 (106)	594 (124)	560 (113)	609 (125)

Note: CPT = Continuous Performance Test; DS-CPT = degraded stimulus CPT; CPT-IP = CPT, identical pairs; RT = response time. Except for Ns, numbers represent M (SD).

did slow response time to targets (M = 548, 530, and 563 ms for never, past, and current, respectively, $F_{2,1136} = 7.14$, $p < .001$). Smoking status did have a significant effect on CPT-IP d′ (3-digit: $F_{2,1187} = 4.82$, $p < .01$; 4-digit: $F_{2,1149} = 5.67$, $p < .01$), with current smokers having significantly lower d′ than those who never smoked for 3-digit CPT-IP (M = 2.10 vs. 2.27) and both current and past smokers having significantly lower d′ than those who never smoked for 4-digit CPT-IP (M = 1.14, 1.06, and 1.28, respectively). Slowing of target response time was also present in the CPT-IP for current smokers relative to those who never smoked (3-digit: $F_{2,1186} = 8.48$, $p < .001$, M = 563 vs. 540 ms; 4-digit: $F_{2,1146} = 7.32$, $p < .001$, M = 601 vs. 578 ms). Thus, current smoking status was associated with both less accurate and slower CPT-IP performance and slower but not less accurate DS-CPT performance. Supplementary analyses including an age covariate and sex and site as factors did not change the pattern of significant associations with smoking status.

Antipsychotic medication status at testing was categorized as none, atypical, typical, or both atypical and typical. With age covaried, CPT-IP d′ was significantly associated with antipsychotic medication status (3-digit: $F_{3,1185} = 4.74$, $p < .02$; CPT-IP 4-digit: $F_{3,1147} = 7.58$, $p < .02$) and DS-CPT d′ showed a similar but non-significant tendency ($F_{3,1106} = 1.97$, $p < .12$). The patients on both typical and atypical antipsychotics had significantly poorer CPT-IP d′ than those on no antipsychotic or an atypical antipsychotic. Covarying the number of psychiatric hospitalizations and current positive and negative symptom severity did not alter this pattern.

4. Discussion

This article examined CPT performance in the large COGS-2 samples of schizophrenia patients and healthy subjects across five sites that varied significantly in participant age, sex, education level, parental education level, and race and in patient symptom severity, functional capacity, and real-life functioning. Despite these many significant differences in participant characteristics across sites, CPT performance was significantly impaired across sites in schizophrenia patients compared to HCS. The simple diagnosis effect size was medium for the DS-CPT d′ (Cohen's d = 0.57) and large for the CPT-IP d′ (1.13 for 3-digit; 1.14 for 4-digit). With age, sex, and site in the statistical model, the primary DS-CPT d′ score did reveal a larger patient–HCS difference at some sites than others (varying from Cohen's *d* equivalent of 0.26 to 0.59), but the overall effect size remained at least of medium magnitude ($d = .47$). Thus, even with the variations in participant characteristics across sites and the challenges of setting up parallel testing conditions across sites, we were able to achieve reasonable diagnostic group effects. Our overall impression is that between-site differences were attributable to varying participant demographic characteristics rather than methodological variance.

In a meta-analysis of cognitive deficits in schizophrenia, Heinrichs and Zakzanis found that the mean CPT effect size between schizophrenia patients and healthy subjects across 15 studies was Cohen's d = 1.18, which is quite large (Cohen, 1988; Heinrichs & Zakzanis, 1998). Our CPT-IP effect sizes are similar, while the DS-CPT effect size is somewhat smaller. The CCPT-IP demand for working memory in addition to the efficient processing of each brief stimulus may enhance its effect size, as working memory is known to be substantially impaired in schizophrenia (Barch et al., 2002; Kern et al., 2011). The view that the CPT-IP and DS-CPT may partially index separable cognitive functions is also supported by their modest intercorrelations in COGS-2 (r = .25 to .40) and by their loading on separate factors in COGS-1 (Seidman et al., 2015–in this issue).

An examination of the correlates of CPT performance within the large schizophrenia sample demonstrated that DS-CPT d′ and

Table 3
Summary of effects in statistical analyses of secondary CPT variables.

	Diagnosis		Age		Sex		Site	Diagnosis × site		Diagnosis × sex	
	F and p	Direction	F and p	Direction	F and p	Direction	F	F and p	Direction	F and p	Direction
DS-CPT											
ln beta			$F_{1,2089} = 128.60$ $p < .001$	Decrease with age			$F_{4,2089} = 11.72$ $p < .001$	$F_{4,2089} = 2.64$ $p < .05$	Site 3: Sz < HCS Sites 4 & 5: Sz > HCS		
Hit rate	$F_{1,2089} = 81.00$ $p < .001$	Sz < HCS	$F_{1,2089} = 9.79$ $p < .005$	Decrease with age			$F_{4,2089} = 4.90$ $p < .001$	$F_{4,2089} = 2.23$ $p < .07$		$F_{1,2089} = 5.02$ $p < .05$	Sz: F < M HCS: F > M
False alarm rate	$F_{1,2089} = 45.82$ $p < .001$	Sz > HCS	$F_{1,2089} = 74.54$ $p < .001$	Increase with age			$F_{4,2089} = 26.86$ $p < .001$				
RT hits (ms)	$F_{1,2089} = 161.74$ $p < .001$	Sz > HCS			$F_{1,2089} = 5.35$ $p < .05$	F > M	$F_{4,2089} = 3.17$ $p < .05$	$F_{4,2089} = 3.17$ $p < .05$	Smaller at site 5	$F_{1,2089} = 9.79$ $p < .005$	Sz: F > M HCS: F = M
CPT-IP 3-digit											
Hit rate	$F_{1,2168} = 406.62$ $p < .001$	Sz < HCS	$F_{1,2168} = 26.53$ $p < .001$	Decrease with age			$F_{4,2168} = 5.51$ $p < .001$	$F_{4,2168} = 2.77$ $p < .03$	Smaller at site 5		
False alarm rate	$F_{1,2168} = 145.16$ $p < .001$	Sz > HCS	$F_{1,2168} = 7.02$ $p < .01$	Increase with age			$F_{4,2168} = 9.59$ $p < .001$	$F_{4,2168} = 2.21$ $p < .07$	Smaller at site 5		
RT hits (ms)	$F_{1,2167} = 210.02$ $p < .001$	Sz > HCS	$F_{1,2168} = 47.34$ $p < .001$	Increase with age	$F_{1,2168} = 15.27$ $p < .001$	F > M	$F_{4,2168} = 5.69$ $p < .001$				
CPT-IP 4-digit											
Hit rate	$F_{1,2117} = 418.15$ $p < .001$	Sz < HCS	$F_{1,2117} = 15.01$ $p < .001$	Decrease with age	$F_{1,2117} = 6.25$ $p < .02$	F < M					
False alarm rate	$F_{1,2117} = 91.59$ $p < .001$	Sz > HCS	$F_{1,2117} = 26.53$ $p < .001$	Increase with age			$F_{4,2117} = 2.79$ $p < .03$				
RT hits (ms)	$F_{1,2114} = 142.93$ $p < .001$	Sz > HCS	$F_{1,2114} = 47.80$ $p < .001$	Increase with age	$F_{1,2114} = 11.89$ $p < .001$	F > M					

Note: CPT = Continuous Performance Test; DS-CPT = Degraded Stimulus CPT; CPT-IP = CPT, identical pairs; and RT = response time.

Table 4
Associations of CPT performance with clinical, cognitive, and functional variables within schizophrenia sample.

	Schizophrenia patients							
	Degraded stimulus CPT				CPT identical pairs version			
	N	d′	Hit rate	False alarm rate	N	3-digit d′	N	4-digit d′
Visual acuity	1118	.04	.00	−.09**	1166	.17***	1128	.17***
SANS Global Sum	1134	.04	.01	−.06*	1184	−.04	1147	−.09**
SAPS Global Sum	1133	−.03	−.03	.00	1183	−.08**	1145	−.05
Negative symptoms	1134	.06*	.03	−.07*	1184	.01	1147	−.05
Psychotic symptoms	1133	−.01	−.02	−.03	1183	−.04	1145	−.02
Disorganization	1133	−.05	−.04	.05	1183	−.10**	1145	−.07*
MMSE score	1103	.19***	.15***	−.15***	1153	.29***	1116	.28***
Yrs education	1139	.11***	.11***	−.02	1190	.19***	1152	.20***
UPSA-B	1111	.21***	.21***	−.10***	1161	.31***	1125	.29***
RFS								
Work	792	.05	.00	−.08*	829	.08*	796	.17***
Independent	792	.05	.04	−.06	829	.15***	796	.16***
Family	792	−.02	.00	−.01	829	.09*	796	.09*
Social	789	−.05	.01	.08*	826	.00	793	.04

Note: CPT = Continuous Performance Test; SANS = Schedule for Assessment of Negative Symptoms; SAPS = Schedule for Assessment of Positive Symptoms; Negative symptoms, psychotic symptoms, and disorganization are SANS/SAPS dimensions from Andreasen et al. (1995); MMSE = Mini-mental State Examination; UPSA-B = UCSD Performance-based Skills Assessment; and RFS = Role Functioning Scale.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

CPT-IP d′ are either unrelated or only very weakly related to positive, negative, or disorganzation symptom severity, number of prior hospitalizations, and past mood disorder. This relative insulation of deficits from state-related conditions fulfills one endophenotype criterion (Gottesman & Gould, 2003). Poorer DS-CPT and CPT-IP performance was associated with lower MMSE scores, educational achievement, and functional capacity. These results, combined with past evidence that DS-CPT and CPT-IP performances are deficient in groups at genetic risk for schizophrenia and relatively stable across clinical states in schizophrenia (Grove et al., 1991; Maier et al., 1992; Nuechterlein et al., 1992; Chen et al., 1998; Nuechterlein et al., 1998; Saoud et al., 2000; Asarnow et al., 2002; Chen et al., 2004; Snitz et al., 2006), suggest that the deficit in sustained focused attention is a persistent feature that has ongoing implications for educational achievement and functional capacity.

The better DS-CPT performance of patients with a past history of substance abuse, while initially surprising, is actually consistent with literature suggesting that schizophrenia patients who abuse substances have somewhat less severe cognitive deficits than those who do not (McCleery et al., 2006; Rabin et al., 2011; Donoghue & Doody, 2012; Thoma & Daum, 2013). As suggested by McCleery, higher cognitive functioning among schizophrenia patients who previously used substances might reflect higher pre-illness cognitive functioning, which might facilitate social interactions needed for drug-seeking behaviors.

The association of current tobacco smoking with lower signal/noise discrimination (d′) for the CPT-IP and slowing of responses to targets on both CPTs is consistent with studies showing negative effects of chronic smoking on cognition in non-psychiatric samples (Sabia et al., 2008; Chamberlain et al., 2012) and with the findings for working memory in the current COGS-2 schizophrenia sample (Lee et al., 2015–in this issue).

The association of poorer CPT-IP performance with being on both typical and atypical antipsychotic medication appears likely to be due to greater severity of illness rather than antipsychotic medication impact on CPT performance, given that clinical trials examining effects within-subjects find either no or positive impact of antipsychotics on the CPT (Orzack et al., 1967; Nestor et al., 1991; Liu et al., 2000).

Overall, these results support and strengthen the use of CPT endophenotypes in clinical trials, studies of function, and forthcoming COGS-2 genomic studies. The relationship of CPT performance to functional capacity but not positive symptoms may be very useful in these continuing studies.

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Contributors

Dr. Nuechterlein completed the CPT quality assurance and all CPT statistical analyses and wrote the initial version of this manuscript. Dr. Green served as the PI of the UCLA site and coordinated the CPT processing with Dr. Nuechterlein. Joyce Sprock completed quality assurance for all clinical and psychiatric history data entered on the COGS-2 website. All other authors participated in the study design and execution, including participant recruitment, diagnosis, endophenotyping, and ongoing quality assurance for the clinical and endophenotype data. All authors were responsible for reviewing and approving the final version of the manuscript.

Conflict of interest

Dr. Nuechterlein has received unrelated research support from Janssen Scientific Affairs (RIS-NPA-4009), Genentech (ML28264), and Brain Plasticity, Inc., (BPI-1001-01) and has been a consultant to Genentech, Otsuka, Janssen, and Brain Plasticity, Inc. Dr. Green has been a consultant to AbbVie, Biogen, DSP, EnVivo/Forum and Roche, and he is on the scientific advisory board of Mnemosyne. He has received research funds from Amgen. Dr. Lazzeroni is an inventor on a patent application filed by Stanford University on genetic polymorphisms associated with depression. Dr. Light has served as a consultant for Astellas, Forum, and Neuroverse. Dr. Swerdlow has been a consultant for Genco Sciences, Ltd. All other authors declare that they have no conflict of interest.

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