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# California Verbal Learning Test-II performance in schizophrenia as a function of ascertainment strategy: Comparing the first and second phases of the Consortium on the Genetics of Schizophrenia (COGS)

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ABSTRACT

The first phase of the Consortium on the Genetics of Schizophrenia (COGS-1) showed performance deficits in learning and memory on the California Verbal Learning Test, Second Edition (CVLT-II) in individuals with schizophrenia (SZ), compared to healthy comparison subjects (HCS). A question is whether the COGS-1 study, which used a family study design (i.e. studying relatively intact families), yielded "milder" SZ phenotypes than those acquired subsequently in the COGS-2 case–control design that did not recruit unaffected family members. CVLT-II performance was compared for the COGS-1 and COGS-2 samples. Analyses focused on learning, recall and recognition variables, with age, gender and education as covariates. Analyses of COGS-2 data explored effects of additional covariates and moderating factors in CVLT-II performance. 324 SZ subjects and 510 HCS had complete CVLT-II and covariate data in COGS-1, while 1356 SZ and 1036 HCS had complete data in COGS-2. Except for recognition memory, analysis of covariance showed significantly worse performance in COGS-2 on all CVLT-II variables for SZ and HCS, and remained significant in the presence of the covariates. Performance in each of the 5 learning trials differed significantly. However, effect sizes comparing cases and controls were comparable across the two studies. COGS-2 analyses confirmed SZ performance deficits despite effects of multiple significant covariates and moderating factors. CVLT-II performance was worse in COGS-2 than in COGS-1 for both the SZ and the HCS in this large cohort, likely due to cohort effects. Demographically corrected data yield a consistent pattern of performance across the two studies in SZ.



## 1. Introduction

Performance deficits in tests of learning and memory remain among the most robust cognitive weaknesses in schizophrenia (SZ), with effect

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sizes that often exceed 1.0 (Heinrichs, 2005; Gur et al., 2007; Mesholam-Gately et al., 2009; Stone and Seidman, in press). Performance on these tasks shows significant evidence of heritability (Calkins et al., 2007; Greenwood et al., 2007; Husted et al., 2009; Wang et al., 2010), and milder, impaired performance is typically observed in nonpsychotic relatives (Gur et al., 2007; Agnew-Blais and Seidman, 2013). In SZ patients, impairments are present in all stages of the illness, though their nature or severity may change in different stages of illness (Stone and Seidman, in press). They thus meet the proposed criteria for endophenotypes (Gottesman and Gould, 2003; Braff et al., 2007; White and Gottesman, 2012).

Deficits in learning and memory are among the endophenotypes studied by the Consortium on the Genetics of Schizophrenia (COGS), an NIMH-funded, multi-site project that was developed to characterize the genetic architecture of endophenotypes for SZ. The first phase of the investigation (COGS-1) utilized a family design and the second used a larger case–control design (Swerdlow et al., in press). All COGS-1 endophenotypes showed significant heritability (Greenwood et al., 2007), associations with neurobiologically relevant single nucleotide polymorphisms (SNPs) (Greenwood et al., 2011) and evidence of genetic linkage (Greenwood et al., 2013). They all also showed poorer performance in SZ probands than in HCS. Performance in non-psychotic relatives varied, however, for both the cognitive and psychophysiological endophenotypes (Horan et al., 2008; Turetsky et al., 2008; Olincy et al., 2010; Radant et al., 2010).

The mild and marginally significant performance deficits in relatives on the California Verbal Learning Test, Second Edition (CVLT-II), a list-learning test, raised some important questions about the nature of the sample collected (Stone et al., 2011). Although another recent (but smaller) study also failed to show group differences on the same CVLT-II variables in first-degree biological relatives of individuals with SZ (Christodoulou et al., 2012), these negative results between relatives and controls are at variance with meta-analyses that have evaluated the discriminability of many relative and control comparisons on other verbal learning measures, and found consistent differences (Gur et al., 2007). The weaker findings in our study prompted us to examine possible reasons for this finding.

One of several factors that may contribute to the mild COGS-1 CVLT-II deficits (reviewed in Stone et al., 2011) is the sample. Specifically, the ascertainment strategy in COGS-1 of comparing affected and unaffected relatives to maximize the ability to detect genetic differences usually required the participation of at least one unaffected parent and at least one unaffected sibling. These stringent recruitment criteria necessitated the recruitment of relatively intact SZ families willing to participate in extensive testing. Since many families with SZ are not intact, at least partly because the individuals in them are too impaired to maintain functional interpersonal relationships, it is possible that the COGS-1 patient sample was less impaired cognitively or clinically than are typical SZ samples. The extent to which COGS endophenotypic, clinical and genetic findings may be generalized is a significant issue. The COGS-2 study, however, did not involve family members (prior participation by a first-degree relative was an exclusion criterion for COGS-2), but followed similar procedures to those employed in COGS-1. This difference allows for a relatively direct comparison of the effects of ascertainment strategy on CVLT-II performance in individuals with SZ.

Based on these ascertainment differences between the COGS-1 and COGS-2 samples, and on the mild CVLT-II performance deficits in the COGS-1 relatives, we expected that the patients in COGS-1 would show milder CVLT-II performance deficits than the patients in COGS-2. Because we did observe large deficits in COGS-1 probands for learning (Trials 1–5 Total Correct $d = 1.20$) and for subsequent recall (Short-Delay Free Recall $d = 1.03$; Long-Delay Free Recall $d = 1.02$) conditions, but a smaller (medium-sized) effect for recognition ($d = 0.55$) (Stone et al., 2011), we hypothesized that the pattern of CVLT-II performance deficits would not be affected meaningfully by differences in ascertainment strategy. However, because the COGS-1 sample raised questions about whether the SZ patients were less impaired cognitively or clinically than more typical SZ patients, we also hypothesized that changing from the family-study design in COGS-1 to the case–control design in COGS-2 would result in fewer CVLT-II words learned and recalled by subjects with SZ or schizoaffective disorder, depressed type.

## 2. Methods

### 2.1. Subjects

Inclusion criteria and participant recruitment are discussed in Swerdlow et al. (in press) for COGS-2, and are described in an earlier paper for COGS-1 (Calkins et al., 2007). Participants with a diagnosis of SZ or schizoaffective disorder, depressed type, were included in both studies. Control subjects were called community comparison subjects (CCS) in COGS-1 and HCS in COGS-2. For consistency, HCS will be used here. Exclusion criteria for all participants are also discussed in detail in Swerdlow et al. (in press).

All subjects were administered a modified version of the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994), the Family Interview for Genetic Studies (NIMH Genetics Initiative, 1992), other clinical and endophenotypic measures (Calkins et al., 2007; Swerdlow et al., in press), and a medical record review.

### 2.2. CVLT-II assessment

The CVLT-II is a widely used clinical test of verbal declarative memory and of executive function (Delis et al., 2000) that was used in both COGS-1 (Stone et al., 2011) and in COGS-2. The administration procedure involves the oral presentation and recall of a 16-item word list over five learning trials, a single presentation of a second list, short- and long-delay recall trials of the first list, and a recognition trial of the first list. This paper focuses on several learning and memory variables that have been investigated extensively in SZ: Trials 1–5 Free Recall Correct, Short-Delay Free Recall and Long-Delay Free Recall, and Recognition Hits. The CVLT-II measure presumed to be most sensitive to encoding deficits, Trials 1–5 Free Recall Total Correct, had been previously selected as the primary measure for genetic analyses. We also assessed each of the five learning trials individually to assess the learning pattern underlying the Trials 1–5 Free Recall Total Correct measure.

### 2.3. Statistical analyses

For comparisons between COGS-1 and COGS-2 samples, group demographic characteristics were compared using one-way analysis of variance (ANOVAs) for continuous raw score variables and Fisher's Exact Test was used for gender. Group CVLT-II differences among SZ patients and HCS were analyzed using analysis of covariance (ANCOVA) with age, gender and education level as covariates. COGS-1 SZ probands were compared with COGS-2 SZ patients, and COGS-1 HCS were compared with COGS-2 HCS.

For COGS-2 analyses, ANOVAs were used for examination of between-group differences (SZ vs. HCS groups) on the CVLT-II indices, with ANCOVAs subsequently performed to assess age, gender, parental education, and site as covariates. We also used ANOVAs and ANCOVAs to determine additional potential moderating effects of smoking status, antipsychotic medication type, and substance use history on CVLT-II performance in the SZ group.

Effect sizes (ES) were calculated using Cohen's d, in which effect sizes below 0.2 were classified as minimal, effect sizes from 0.2 to 0.49 were considered small, effect sizes from 0.50 to 0.79 were considered medium, and effect sizes at or above 0.8 were considered large (Cohen, 1988). This classification system is appropriate to capture the wide range and large magnitudes of many cognitive deficits in schizophrenia (Aleman et al., 1999; Mesholam-Gately et al., 2009).

One advantage of the large sample size utilized in this study is that it facilitated the detection of small but statistically significant group differences. Consequently, statistical differences may not always signify meaningful clinical differences between groups. For this reason, we report effect sizes along with tests of statistical significance to characterize the magnitude of significant group differences.

## 3. Results

### 3.1. Demographic differences in COGS-1 and COGS-2

Table 1 shows that subjects completing the CVLT-II in the COGS-2 sample were significantly older than those in the COGS-1 sample, for SZ and HCS. The magnitude of the age difference between COGS-1 SZ probands and COGS-2 SZ patients showed a large effect size (d = 1.02). The age difference between COGS-1 and COGS-2 HCS subjects was also significant, driven by the large Ns, but the effect size was minimal (d = 0.18). The COGS-1 SZ and HCS sample showed a significantly higher percentage of males than the COGS-2 sample. Level of education in COGS-1 SZ probands was significantly lower than in COGS-2 patients, although the effect size was negligible (d = 0.03) and driven by the benchmark large Ns. Education was slightly lower in the HCS from COGS-1 to COGS-2, also with a minimal effect size (d = 0.16).

### 3.2. CVLT-II group comparisons

#### 3.2.1. COGS-2 SZ–HCS comparisons

SZ patients recalled fewer words correctly than HCS subjects on Trials 1–5 Total Correct (39.4 versus 49.9 using estimated means with age, gender and education covariates; $p < .001$), with a large effect size (d = 0.93). Similarly, SZ patients showed lower levels of Short-Delay Free Recall (7.9 versus 10.7; $p < 001$) and Long-Delay Free Recall (8.1 versus 11.1; $p < .001$), both with large effect sizes (both ds = 0.84). SZ patients also showed lower levels of Recognition (13.7 versus 14.7; $p < .001$), but the effect size was small (d = 0 .40).

#### 3.2.2. COGS-2 SZ–HCS performance compared to COGS-1

The direction, magnitude and pattern of COGS-2 SZ–HCS comparisons, showing significant impairments in SZ probands, were consistent with our previous characterization of the COGS-1 sample (Stone et al., 2011). Notably, the magnitude and pattern of the effect sizes were similar, using raw data. The difference between the SZ and HCS groups was large for Trials 1–5 Total Correct, though modestly larger in COGS-1 (d = 1.20 in COGS-1 and 1.43 in COGS-2). The effect size was similar across studies for Short-Delay Free Recall (d = 1.03 in COGS-1 and 1.29 in COGS-2) and Long-Delay Free Recall (d = 1.02 in COGS-1 and 1.26 in COGS-2). Recognition in the COGS-1 sample also showed a smaller group difference and effect size between SZ and HCS, but was similar in magnitude to the COGS-2 sample (d = 0.55 in COGS-1 and 0.62 in COGS-2).

#### 3.2.3. CVLT-II performance across COGS-1 and COGS-2 samples

Table 2 shows that COGS-1 SZ probands performed significantly better than COGS-2 SZ patients on Trials 1–5 Total Correct, Short-Delay Free Recall and Long-Delay Free Recall. The inclusion of demographic moderators of age, gender and education as covariates reduced the ANCOVA F scores and the effect sizes from small to minimal, but the reductions remained significant statistically. Similarly, the HCS scores were higher in COGS-1 than in COGS-2 on the same variables. Recognition performance did not differ between COGS-1 and COGS-2. No interaction effects were significant in the ANCOVA analyses for these measures, indicating that while there were group and study ascertainment effects, they were not associated with significant differences.

Analyses of each of the five learning trials that comprised the Trials 1–5 Total Correct measure showed that performance was significantly lower in SZ patients in COGS-2 than in SZ probands in COGS-1, though with minimal to small effect sizes (after ANCOVA). Performance also differed between COGS-1 and COGS-2 HCS for all trials, in the same direction, also with small effect sizes. A group by (ascertainment) study interaction was significant for learning Trials 1 and 2 (ps = .013 and .042, respectively). As shown in Fig. 1a, the shape of the learning curve was identical for the COGS-1 and COGS-2 SZ subjects and for the HCS, using the uncorrected data, a finding similar to that reported for the Penn Computerized Neuropsychological Battery by Gur et al. (in press). This was even more evident using covariate-corrected raw data, as shown in Fig. 1b. The significant interaction effects in Trials 1 and 2 thus reflect a relatively larger difference between the HCS groups than the SZ groups in Trial 1, and a relatively larger difference between the SZ groups than the HCS groups in Trial 2. The effect sizes, however, were small (e.g. d = 0.3 for the difference between HCS in Trial 1) to minimal (e.g. d = 0.11, for the difference between the SZ groups in Trial 2), and did not reflect differences between the same variables in Trials 1 and 2.

### 3.3. Characterization of group performance differences in the COGS-2 sample: effects of covariates and other moderators of performance

#### 3.3.1. Covariates

Based on the raw data, COGS-2 schizophrenia subjects performed significantly worse than HCS on all four key CVLT-II variables, including Trials 1–5 Total Correct (d = 1.43), Short-Delay Free Recall (d = 1.29), Long-Delay Free Recall (d = 1.26), and Recognition Hits (d = 0.62). The inclusion of an expanded set of significant covariates that included

**Table 1**
Demographic characteristics of the sample.[a]

| | COGS-1 | | COGS-2 | | Study Comparisons with No Corrections | |
|---|---|---|---|---|---|---|
| | 1<br>Schizophrenia<br>(n = 324)<br>M (SD)<br>Range | 2<br>HCS[b]<br>(n = 510)<br>M (SD)<br>Range | 3<br>Schizophrenia<br>(n = 1356)<br>M (SD)<br>Range | 4<br>HCS<br>(n = 1036)<br>M (SD)<br>Range | 1 v 3<br>F, p, d[c] | 2 v 4<br>F, p, d |
| Age | 34.9 (11.2)<br>18–62 | 36.3 (12.6)<br>18–65 | 46.2 (11.1)<br>18–65 | 38.6 (13.2)<br>18–65 | F = 271.17,<br>p = .000,<br>d = 1.02 | F = 10.75,<br>p = .001,<br>d = .18 |
| Gender (N, %M) | 243 (75.0%) | 218 (42.7%) | 925 (68.2%) | 512 (49.4%) | Fisher's exact:<br>p = .019 | Fisher's exact:<br>p = .015 |
| Education[d] | 13.5 (2.1)<br>8–20 | 15.4 (2.34)<br>8–22 | 12.6 (2.1)<br>2–20 | 15.0 (2.2)<br>6–20 | F = 51.52,<br>p = .000,<br>d = .03 | F = 8.46,<br>p = .004,<br>d = .16 |

[a] Expressed as means (± standard deviations) for age and education, but not for gender.
[b] HCS — healthy comparison subjects.
[c] Cohen's d.
[d] For covariate analyses, education data available for 323 COGS-1 probands.

**Table 2**
Group performance on COGS-1 and COG-2 CVLT-II variables.[a,b]

| | COGS-1 Raw scores | | COGS-2 Raw scores | | Study comparisons with no corrections (raw scores) | | Study comparisons with age, gender & education covariates[c] | |
|---|---|---|---|---|---|---|---|---|
| | 1 Schizophrenia (n = 324) M (SD) Range | 2 HCS (n = 510) M (SD) Range | 3 Schizophrenia (n = 1356) M (SD) Range | 4 HCS[d] (n = 1036) M (SD) Range | 1 v 3 F, p, d[e] | 2 v 4 F, p, d | 1 v 3 F, p, d | 2 v 4 F, p, d |
| CVLT-II 1–5[d] | 41.7 (12.7) 9–75 | 56.2 (10.3) 21–80 | 36.4 (11.1) 3–74 | 52.1 (10.9) 16–79 | F = 55.71, p = .000, d = 0.46 | F = 49.55, p = .000, d = 0.38 | F = 6.24 p = .013 d = 0 .18 | F = 30.48, p = .000, d = .0.27 |
| CVLT-II SDFR[d] | 8.6 (3.7) 0–16 | 12.2 (3.0) 0–16 | 7.2 (3.3) 0–16 | 11.3 (3.1) 0–16 | F = 49.59, p = .000, d = 0.43 | F = 28.24, p = .000, d = 0 .29 | F = 9.90 p = .002 d = 0 .19 | F = 13.77, p = .000, d = 0.18 |
| CVLT LDFR[d] | 8.7 (3.8) 0–16 | 12.5 (3.0) 0–16 | 7.4 (3.4) 0–16 | 11.6 (3.3) 0–16 | F = 37.51, p = .000, d = 0.38 | F = 25.71, p = .000, d = 0.27 | F = 6.27 p = .012 d = 0.15 | F = 12.52, p = .000, d = 0.18 |
| CVLT-II Recognition Hits | 13.7 (2.8) 0–16 | 15.0 (1.8) 0–16 | 13.5 (2.5) 0–16 | 14.9 (1.9) 0–16 | F = 1.11, p = .293, d = −0.03 | F = 1.53, p = .216, d = 0.07 | F = 0.11 p = .740 d = −0.03 | F = 0.17, p = .676, d = 0.02 |

[a] Group means and standard deviations are based on CVLT-II raw scores.
[b] ANCOVA design, with two ascertainment strategies (COGS-1 and COG-2) and two conditions (schizophrenia and HCS).
[c] For covariate analyses, education data available for 323 COGS-1 probands.
[d] CVLT-II 1–5 — California Verbal Learning Test-II Trials 1–5 Total Correct; CVLT-II SDFR — California Verbal Learning Test-II Short-Delay Free Recall; CVLT-II LDFR — California Verbal Learning Test-II Long-Delay Free Recall; HCS — healthy comparison subjects.
[e] Cohen's d.

age, gender, parental education, and site reduced the ANCOVA F scores, but the SZ and HCS group differences on the four CVLT-II variables remained significant. Similarly, large effect sizes remained present for all CVLT-II variables (d = 1.09 for Trials 1–5 Total Correct, d = 0.99 for Short-Delay Free Recall and d = 0.97 for Long-Delay Free Recall) except for Recognition Hits (d = 0.46), which was not large with or without covariates. The main effects of these covariates on the CVLT-II indices were also significant, with higher scores obtained by younger

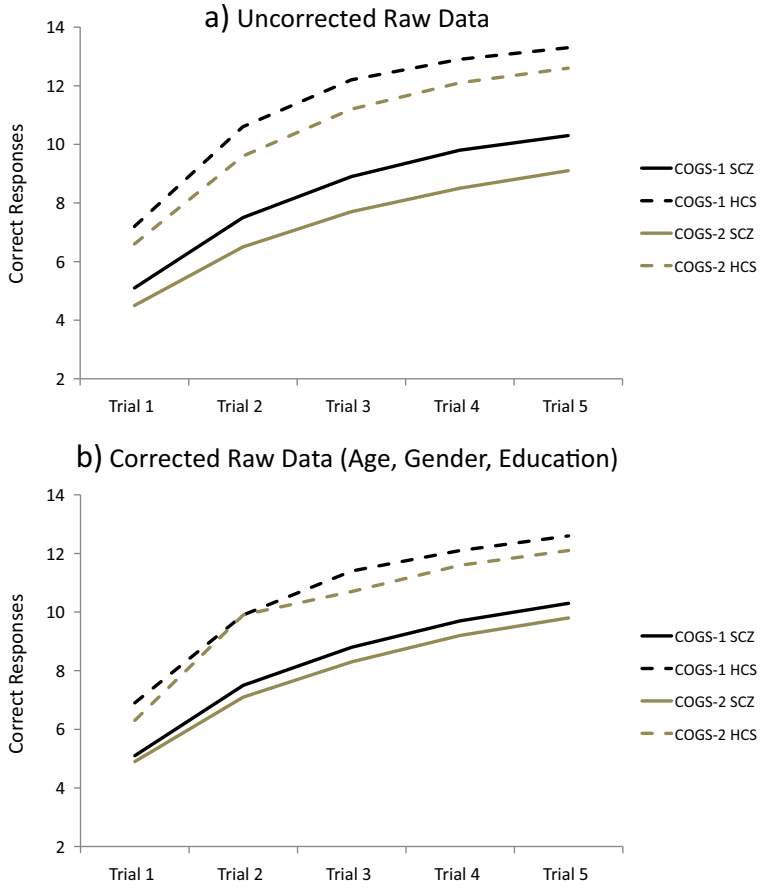


**Fig. 1.** Trial by trial Total Correct CVLT-II responses for schizophrenia and HCS using raw uncorrected data (Fig. 1a) and raw corrected data (Fig. 1b) based on inclusion of age, gender and education covariates. See also text for additional description.

individuals and females, and subjects whose parents had higher education levels. Main effects for site varied among CVLT-II measures. Using Trials 1–5 Total Correct as the primary CVLT-II variable of interest, one site performed significantly lower than two others and another site performed significantly higher than two others. Group by covariate interactions showed significant group interactions for gender and age × parent education for Trials 1–5 Total Correct, Short Delay Free Recall, and Long Delay Free Recall. While female gender, younger age and higher parental education contributed to better performance on all CVLT-II measures, the advantages were greater for HCS than for SZ.

*3.3.2. Other moderators of performance*

SZ patients who were current smokers performed significantly worse than patients who never smoked, though with minimal effects sizes, on Trials 1–5 Total Correct ($F(1, 1284) = 8.03$, $p < .01$; $d = 0.16$), Short Delay Free Recall ($F(1, 1284) = 4.79$, $p < .05$; $d = 0.12$) and Long Delay Free Recall ($F(1, 1284) = 5.84$, $p < .05$; $d = 0.14$). Age and gender did not contribute to the smoking-related CVLT-II differences. To investigate the relationship of antipsychotic medication type to smoking status, we repeated the smoking-related ANOVAs in the 1st generation and 2nd generation antipsychotic medication groups separately. Within the 2nd generation antipsychotic medication group, significant differences between current smokers and non-smokers only remained for Trials 1–5 Total Correct ($F(1, 936) = 4.76$, $p < .05$; $d = 0.14$), with current smokers again performing worse than non-smokers, but again with a minimal effect size and with a reduced F compared to the entire SZ group. Current smokers did not differ from non-smokers on any of the CVLT-II indices in the 1st generation antipsychotic medication group. Finally, we examined the potential moderating effects of substance use history on CVLT-II performance and found no significance differences between those with and without such a history on any of the CVLT-II measures.

## 4. Discussion

The current study assessed CVLT-II deficits in a large case–control study of SZ patients and healthy controls, and evaluated the hypothesis that the family study design in COGS-1, which required relatively intact families to perform genetic studies, also resulted in milder endophenotype deficits than would be observed in studies that only required individual subjects to meet diagnostic criteria for SZ or schizoaffective disorder, depressed type. Although our current findings did not rule out the possibility that the family study design resulted in milder performance deficits, the results did not support this hypothesis.

The results showed, instead, that while COGS-2 SZ patients did perform more poorly than COGS-1 SZ probands, the COGS-2 HCS also performed more poorly than the COGS-1 HCS. Moreover, analyses of the 5 learning trials showed identical learning curves for COGS-1 and COGS-2 SZ subjects, further reducing the likelihood that differential cognitive processes influenced performance in the two ascertainment schemes. Overall, the COGS-1 and COGS-2 were similar, and implicate a cohort effect in which both COGS-2 groups performed more poorly on the CVLT-II than both COGS-1 groups. Conversely, these data support the view that the COGS-1 ascertainment strategy did not sacrifice the generalizability of its endophenotypic or its genetic findings. Notably, this finding differs from the related Penn Computerized Neurocognitive Battery findings, where COGS-2 patients showed greater deficits than COGS-1 patients (Gur et al., in press).

Notably, CVLT-II performance was influenced by several moderating factors. These include site differences, which were also evident in the COGS-1 sample (Stone et al., 2011), as were age and gender effects. The more detailed analyses of the COGS-2 sample showed that female gender, high parental education and younger age were associated with better performance in both groups, but particularly in HCS. Interestingly, SZ patients who smoked showed poorer performance on the CVLT-II than nonsmokers. This finding has been reported for some measures of memory (Zhang et al., 2012), but conflicts with reports of better performance in smokers on several other measures of cognition (Ahlers et al., 2014; Wing et al., 2011). Despite these significant covariate and moderator effects, however, CVLT-II performance was lower in SZ than in HCS.

In addition to the consistency of COGS-2 CVLT-II scores with corresponding COGS-1 scores (Stone et al., 2011) in magnitude of effect and response to covariates (e.g. site, age and gender), they were consistent in pattern. In addition to similar learning curves in both samples, total learning, as measured by Trials 1–5 Total Correct, Short-Delay Free Recall, and Long-Delay Free Recall, were all more impaired than Recognition, which is an easier and less sensitive task than the recall measures. Notably, neither sample of HCS nor SZ subjects showed a decline from Short-Delay Free Recall to Long-Delay Free Recall (see Table 2). This is consistent with a well-substantiated literature showing that both abnormal forgetting and problems in recognition are less prominent in SZ than are problems in encoding (Cirillo and Seidman, 2003; Stone and Hsi, 2011).

These deficits in learning and probably memory retrieval implicate executive dysfunction, a finding confirmed by Junghee et al. using the Letter Number Sequencing test for verbal working memory (Lee et al., in press), but it is unclear to what extent they reflect relatively discrete cognitive deficits versus a more generalized cognitive deficit, as reflected by the Gur et al. findings in this issue. These questions will be assessed in future studies. The similarities in COGS-1 and COGS-2 CVLT-II performance, in the context of similar magnitudes of deficit in both learning and in recall performance, along with the Junghee et al. and Gur et al. findings, suggest a significant role for a generalized deficit, in addition to more discrete problems in executive function. This pattern would be consistent with results of studies showing both specific and generalized cognitive deficits in SZ (Dickinson et al., 2004, 2006, 2008; Sheffield et al., 2014).

The current findings raise several questions that require resolution before our conclusions can be confirmed. One such issue concerns potential reasons for the apparent cohort effect observed in this study. While worse performance in COGS-2 CVLT-II was hypothesized as a function of ascertainment strategy, worse HCS performance was unexpected, particularly in light of COGS rigorous training procedures and efforts to ensure uniformity of procedures across testing sites (Calkins et al., 2007). In our previous study of COGS-1 CVLT-II performance, we observed greater variability among HCS in relation to site differences than we observed in SZ probands or their relatives (Stone et al., 2011), though in part this also reflected different demographic circumstances at different geographical locations. Of course, controls are ascertained to match cases on demographic variables and in the COGS-2 study, like the patients, the HCS are older, and unlike the patients, a higher percentage are male, a combination of factors that could yield somewhat lower scores (Abbs et al., 2011). Nevertheless, these findings do underscore the importance of employing the same levels of concern and stringency in recruiting control groups as are expended on recruiting patient groups (Stone et al., 2011).

In future analyses, it will be important to determine whether HCS differed between COGS-1 and COGS-2 in ways that might have affected CVLT-II and possibly other endophenotype functions. If that occurred, either by chance or as a function of protocol changes in exclusion criteria, for example, the possibility remains that CVLT-II performance was worse in SZ patients and controls for unrelated reasons. In that circumstance, an ascertainment effect in patients would become more tenable. It is important to note, however, that while the question of ascertainment effects on endophenotype performance identifies an important source of potential variance, the effect sizes of deficits on the CVLT-II, at least, would have been small. In light of the significant heritability, association and linkage reported thus far for the COGS endophenotypes, the benefits of the COGS-2 ascertainment strategy, with its large Ns, in advancing the search for SZ genes have clearly

outweighed the potential drawbacks for case control data to augment the reported COGS-1 family results (Greenwood et al., 2007, 2011, 2013).

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Other than providing support, the NIH had no further role in this manuscript.

**Contributors**

Dr. Stone takes responsibility for all statistical analyses and the general integrity of the data. Dr. Seidman reviewed all versions of the manuscript and contributed to statistical analyses and conceptualization. All authors were responsible for reviewing and approving the final manuscript.

**Conflict of interest**

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. Nuechterlein has received unrelated research support from Janssen Scientific Affairs, Genentech, and Brain Plasticity, Inc., and has consulted to Genentech, Otsuka, Janssen, and Brain Plasticity, Inc. 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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