Published in final edited form as:

Schizophr Res. 2011 May ; 128(1-3): 102–110. doi:10.1016/j.schres.2011.01.005.

Group and site differences on the California Verbal Learning Test in persons with schizophrenia and their first-degree relatives: Findings from the Consortium on the Genetics of Schizophrenia (COGS)

William S. Stone^{a,b,*}, Anthony J. Giuliano^a, Ming T. Tsuang^{b,c}, David L. Braff^{c,**}, Kristin S. Cadenhead^c, Monica E. Calkins^e, Dorcas J. Dobie^{f,g}, Stephen V. Faraone^d, Robert Freedman^h, Michael F. Greenⁱ, Tiffany A. Greenwood^c, Raquel E. Gur^e, Ruben C. Gur^e, Gregory A. Light^c, Jim Mintzⁱ, Keith H. Nuechterleinⁱ, Ann Olincy^h, Allen D. Radant^{f,g}, Andrea H. Roe^a, Nicholas J. Schork^c, Larry J. Siever^{j,k}, Jeremy M. Silvermanⁱ, Neal R. Swerdlow^c, Alison R. Thomas^a, Debby W. Tsuang^{f,g}, Bruce I. Turetsky^e, Larry J. Seidman^{a,b}

^aMassachusetts Mental Health Center Public Psychiatry Division of the Beth Israel Deaconess Medical Center, Harvard Medical School Department of Psychiatry, Boston, Massachusetts

^bHarvard Institute of Psychiatric Epidemiology and Genetics, Boston, Massachusetts

^cDepartment of Psychiatry, University of California San Diego, La Jolla, California

^dMedical Genetics Research Program and Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, NY 13210, U.S.A.

^eDepartment of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania

^fDepartment of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington

^gthe Department of Veteran Affairs VISN-20 Mental Illness Research, Education, and Clinical Center; Seattle, Washington

^hDepartment of Psychiatry, University of Colorado Health Sciences Center, Denver, Colorado

ⁱDepartment of Psychiatry and Biobehavioral Sciences, Geffen School of Medicine at University of California Los Angeles, Los Angeles, California

^jDepartment of Psychiatry, The Mount Sinai School of Medicine, New York, New York

*Corresponding Author. wstone@bidmc.harvard.edu. Current postal address: Harvard Medical School, Department of Psychiatry/BIDMC, 2nd Floor East, 401 Park Drive, Boston, MA 02215. Tel.: 617-998-5035; fax: 617-998-5007.

**For general inquiries regarding the Consortium on the Genetics of Schizophrenia (COGS). dbraff@ucsd.edu

CONTRIBUTORS

All authors contributed materially to the design of the study, to data collection and analysis, and to the writing and preparation of the manuscript. All authors approved the manuscript.

CONFLICT OF INTEREST

None

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

^kJames J. Peters VA & VISN3 Mental Illness Research, Education and Clinical Center, Bronx, New York

Abstract

Genetic studies of schizophrenia focus increasingly on putative endophenotypes because their genetic etiology may be simpler than clinical diagnosis. The Consortium on the Genetics of Schizophrenia (COGS), a multisite family study, aims to identify the genetic basis of several endophenotypes including verbal declarative memory (VDM), a neurocognitive function that shows robust impairment in schizophrenia. We present data on one type of measure of VDM, the California Verbal Learning Test, Second Edition (CVLT-II), in schizophrenia probands (n=305), their full biological siblings (n=449) and parents (n=232), and in community comparison subjects (CCS; n=509) across seven sites. Probands performed more poorly on each of five CVLT-II measures compared to related sibling and parent groups and CCS. Siblings and parents performed significantly worse than CCS on one measure (Discriminability), but with smaller effect sizes and less impairment than observed previously. The results raise questions about the homogeneity of VDM as an endophenotype, about methodological issues related to sampling, and about psychometric issues that impact the utility of the CVLT for detecting VDM deficits in nonpsychotic relatives of persons with schizophrenia.

Keywords

Verbal declarative memory; schizophrenia; endophenotype

The identification of genes that increase susceptibility to schizophrenia, and their underlying mechanisms, are among the most challenging issues in neuropsychiatric research. The importance of identifying intermediate phenotypes or ‘endophenotypes’ (e.g., social, psychophysiological or neuropsychological abnormalities) reflects the need for more specific or simple definitions of liability than broad clinical diagnoses allow (Gottesman & Gould, 2003). Endophenotypes may reflect variation among a smaller number of genes than do clinical symptoms (Braff, Freedman, Schork, & Gottesman, 2007; Gottesman & Gould, 2003) and are heritable (Greenwood et al., 2007), thus enhancing their utility in genetic studies.

Verbal Declarative Memory (VDM) is one of the most consistent and severe neuropsychological deficits in schizophrenia (Aleman, Hijman, de Haan, & Kahn, 1999; Cirillo & Seidman, 2003; Heinrichs, 2005; Heinrichs & Zakzanis, 1998), and at least three lines of evidence support its candidacy as an endophenotype. The first is its prominence among cognitive deficits observed in schizophrenia and related disorders like schizotypal personality disorder (SPD) (Aleman et al., 1999; Cirillo & Seidman, 2003; Heinrichs, 2005; Voglmaier et al., 2005). A qualitative review of over 110 studies showed that VDM deficits in schizophrenia are robust, with large effect sizes (ESs; $\approx 1.0 - 1.5$) on list learning, story recall and other learning and memory tasks (Cirillo & Seidman, 2003). A recent quantitative review further documented that these deficits are comparably present in first episode and established schizophrenia (Mesholam-Gately, Giuliano, Faraone, Goff, & Seidman, 2009).

The second line of evidence supporting VDM as an endophenotype involves deficits in non-psychotic first-degree relatives of persons with schizophrenia. Like patients, relatives show reliable but milder encoding deficits (Faraone et al., 1995; Faraone et al., 1999) but not a significantly abnormal rate of forgetting (Cannon et al., 1994; Cirillo & Seidman, 2003; Faraone et al., 1995; Gur et al., 2007; Kremen & Hoff, 2004; Seidman et al., 2006; Skelley, Goldberg, Egan, Weinberger, & Gold, 2008). The qualitative similarity of VDM deficits between patients and relatives supports the view that VDM impairments reflect genetically-mediated characteristics of the disorder rather than secondary phenomena associated with effects of medication, psychosis or other cognitive dysfunctions (Weiss & Heckers, 2001).

The third reason that VDM is considered an endophenotype involves evidence for its heritability including: 1) its familiarity; 2) deficits in individuals with SPD whose co-twins had schizophrenia (Johnson et al., 2003); 3) positive correlations between VDM deficits and degree of 'genetic loading' (defined as having two first-degree non-psychotic relatives with schizophrenia rather than one) (Faraone et al., 2000); and 4) molecular genetic studies showing relationships between VDM and specific genotypes (e.g. Cannon et al., 2005; Greenwood et al., 2007; Husted, Lim, Chow, Greenwood, & Bassett, in press; Paunio et al., 2004).

This study used a large, well-characterized sample to assess VDM performance using the CVLT-II (Delis, Kramer, Kaplan, & Ober, 2000). The CVLT-II has shown robust performance deficits in schizophrenia and related disorders (Remillard, Pourcher, & Cohen, 2008; Roofeh et al., 2006; Thornton et al., 2007; Tuulio-Henriksson, Partonen, Suvisaari, Haukka, & Lonnqvist, 2004; Van Erp et al., 2008). We hypothesized that performance on the CVLT-II would be consistent with the previous literature in several ways. Patients with schizophrenia would show broad deficits in measures of learning and memory compared to community comparison subjects (CCS) and to their non-psychotic relatives. Because subjects with schizophrenia typically show greater deficits in the acquisition or encoding of new information than they do in the retention or recognition of stored information (Cirillo & Seidman, 2003), we hypothesized that they would also show the largest deficits in CVLT-II measures that were sensitive to encoding. These include the number of words recalled correctly after hearing a list of words read repeatedly ('List A Trial 1–5 Free Recall Correct'), and the number of words recalled correctly after a brief delay ('Short-Delay Free Recall'). We hypothesized that patients with schizophrenia would show similar deficits in recall after a longer delay ('Long-Delay Free Recall') because initial learning was poor, but they but would perform relatively better on measures of recognition ('Recognition Hits' and 'Recognition Discriminability') because the negative effects of impaired acquisition would be smaller. Moreover, recognition memory tasks provide cues for remembering that may mitigate impaired retrieval in disorders such as schizophrenia in which organizational factors are prominent in the memory disorder (Cirillo & Seidman, 2003).

Also consistent with the literature, we hypothesized that relatives would show similar deficits qualitatively, but of milder severity. Like the probands, we assumed that the largest deficits would again involve measures of acquisition. Deficits in recognition, however, which are relatively mild in patients with schizophrenia, would be milder still in relatives,

and might not demonstrate statistical significance. We also assessed the effectiveness of multisite sampling and data collection.

METHODS

The COGS is a 7-site NIMH-funded project designed to assess endophenotypes and perform genetic analyses on individuals with schizophrenia, their first-degree relatives, and community comparison subjects (Calkins et al., 2007). Participating sites include Harvard University, the Mount Sinai School of Medicine, the University of California San Diego, the University of California Los Angeles, the University of Colorado, the University of Pennsylvania, and the University of Washington. The institutional review boards of each site approved the study, and all subjects signed informed consent.

The primary goal of the COGS is to investigate the genetic basis of putative endophenotypes for schizophrenia including pre-pulse inhibition (PPI), P50, anti-saccades, verbal declarative memory, verbal working memory and vigilance (Greenwood et al., 2007; Horan et al., 2008; Olincy et al., 2010; Radant et al., 2010; Radant et al., 2007; Swerdlow et al., 2007). The COGS methods will be summarized briefly as they have been previously described (Calkins et al., 2007). Each site followed an identical protocol to recruit, diagnose, assess endophenotypes and collect blood for DNA. Consortium-wide quality assurance procedures were exercised throughout the study. Eligible families had one of two pedigree structures. The first required availability of both of the proband's parents, at least one of who was not psychotic, and at least one non-psychotic sibling. The second included availability of one parent and at least two non-psychotic siblings.

Subjects

Medically healthy adults were recruited through flyers, print, and electronic media. Schizophrenia subjects were also referred by mental health providers and through talks at such organizations as the National Alliance on Mental Illness. Subjects who received endophenotype assessment were 18–65 years old and fluent in English. Exclusion criteria for probands and CCS included a: history of electroconvulsive therapy in the past 6 months; positive drug or alcohol screen; diagnosis of substance abuse disorder in the past 30 days or active substance dependence in the past 6 months; estimated premorbid IQ < 70; inability to provide informed consent. Potential probands and CCS were also excluded if they had a history of head injury with loss of consciousness exceeding 15 minutes; a seizure disorder; and any ocular, neurological, or systemic medical problem likely to cause neurocognitive or psychophysiological performance deficits. Similar inclusion criteria were applied to relatives, but relatives were not excluded for a history of head injury or seizure, prior testing on an endophenotype within the previous month or testing on any of the cognitive endophenotypes within the previous three months. CCS were excluded if they had a history of any DSM-IV Cluster A Personality Disorder, psychosis; or first-or second-degree family history of psychosis.

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 measures (see Calkins et al., 2007), and a medical record

review. Premorbid IQ was estimated using the Wide Range Achievement Test, Third Edition (WRAT-3) Reading subtest (Jastak & Wilkinson, 1993). All probands met DSM-IV diagnostic criteria for schizophrenia and were stable clinically (i.e., they did not have a psychiatric hospitalization in the previous month).

CVLT-II data were collected between November 2003 and April 2008. 1984 subjects consented to enter the study and 1495 completed the CVLT-II (75%). Most subjects who did not complete the test were parents of probands, reflecting the age limit of 65 for endophenotype testing. Test completion rates were 97.3% of the CCS (N=509), 84.0% of the probands (N=305), 89.8% of the sibling relatives (N=449), and 39.1% of the parent relatives (N=232).

Most probands were being treated with antipsychotic medication at the time of testing, primarily second-generation antipsychotics (SGA) only (79.0%), or a combination of first generation antipsychotics (FGA) and SGA (8.2%), or FGA only (7.2%). Medication data for 6 participants were unavailable. Relatives were divided into sibling and parent groups due to their significant age differences. The majority of sibling and parent relatives were not receiving any antipsychotic medication (94.7% and 93.5%, respectively). Among the siblings, 3.8% received SGA, 0.4% received FGA, and data were unavailable for 5 subjects. Similarly, 2.6% of parents received SGA, none received FGA, and data for 9 subjects were unavailable. None of the CCS received antipsychotic medication.

One relative receiving FGA had a diagnosis of schizoaffective disorder, as did one relative receiving SGA. Seven other relatives received SGA, with diagnoses that included major depressive disorder (N=4), bipolar disorder (N=2) and mood disorder NOS (N=1). We considered excluding data from these few relatives receiving FGA or SGA medications, but retained them for three reasons. First, we wanted the relative samples that were analyzed for CVLT-II performance to be as representative as possible of the whole sample of relatives (excluding relatives with schizophrenia). Second, earlier analyses (performed prior to the collection of the whole sample) used medication as a covariate and showed it did not affect group differences. Third, effects of antipsychotic medications themselves on cognition are generally small (Goldberg et al., 2007; Keefe et al., 2006; Keefe et al., 2007).

Study Design and Quality Assurance Procedures

The COGS protocol consisted of approximately 4 hours of clinical assessment and 6 hours of neuropsychological and neurophysiological testing, which were presented in one of two standardized test orders (Calkins et al., 2007). Endophenotype testers did not participate in diagnostic assessments.

CVLT-II Assessment

The CVLT-II is a widely used clinical instrument (Delis et al., 2000). Briefly, it involves oral administration and recall of a 16-item word list over five learning trials, short- and long-delay recall trials, and a recognition trial. The CVLT-II Comprehensive Scoring System's (Delis et al., 2000) Expanded Report version was used to tabulate raw scores, and to derive scores and standard scores according to age and gender. This paper focuses on the raw scores of five variables that have been investigated extensively in schizophrenia and in

analyses of learning and memory: Trials 1–5 Free Recall Correct, Short-Delay Free Recall and Long-Delay Free Recall, Recognition Hits and Total Recognition Discriminability (i.e. the ability to discriminate target from distractor words in the recognition trial). The CVLT-II measure presumed to be most sensitive to encoding deficits, Trials 1–5 Free Recall Total Correct, was also selected as the primary measure for genetic analyses (Greenwood et al., 2007). To underscore its presumed sensitivity further, and to compare the utility of raw scores with standard scores, the standard score for Trials 1–5 Free Recall Total Correct was also included in our analyses, yielding a total of 6 measures.

Statistical Analyses—Group demographic characteristics were compared using one-way ANOVAs for continuous variables and Chi-square tests for categorical variables. Group CVLT-II differences among probands, sibling and parent relatives, and CCS were analyzed using individual, mixed effects regression analyses (SAS Proc MIXED). In each model, CVLT-II raw or standardized scores were dependent variables. Family membership was treated as a random effect to control for non-independent observations between probands and relatives from the same family. Group, performance site, and group x performance site interaction were fixed factors in the model. Age, site, gender and WRAT-3 Reading standard scores were included as planned covariates. Effects of mood and substance-related disorders were also assessed. Thirty-four subjects did not receive the WRAT-3. Subsequent analyses were run without these subjects (N=1461) and with group-derived mean score substitution. Post hoc tests, including least square differences (LSD) or Tamhane's T2 Method (a conservative test), were used to assess group differences when overall effects were significant. Effect sizes (ES) were calculated using Cohen's *d* (Cohen, 1988) using group raw score means and the pooled standard deviation. However, for group comparisons that include parent relatives, Cohen's *d* was calculated based on estimated least squares means and pooled standard deviation (calculated based on the standard error) to control for significant age differences between parent relatives and the other comparison groups.

RESULTS

Statistical analyses performed with or without 34 subjects missing WRAT-3 data did not change the pattern of results or affect their significance. Thus, we report only results of analyses that include WRAT-3 Reading mean substitution data. In addition, 8 subjects in the sibling relative group and 3 subjects in the parent relative group had DSM-IV schizophrenia-related diagnoses (SPD). Omitting these subjects did not change the findings, and they were thus retained in the analyses.

Demographic Differences

Table 1 shows there were a higher proportion of males, with lower education and reading scores in probands than in CCS, sibling relatives and parent relatives. WRAT-3 Reading scores were modestly and significantly lower in both relative groups than in CCS. Parent relatives were significantly older than the other groups, which did not differ significantly from each other. Parental education levels were lowest in the parent group, but CCS were also slightly lower in parental education than the proband and sibling relative groups. Frequency of right-handedness was comparable across groups. Frequencies of lifetime

DSM-IV mood disorder diagnoses were lowest in CCS, intermediate in both relative groups, and highest in probands. Frequencies of lifetime substance abuse disorders did not differ significantly between CCS and parent relatives, but both were lower than sibling relatives, and all groups were lower than probands.

CVLT-II differences among groups

Probands performed significantly worse than CCS and both relative groups on all five CVLT-II measures (Table 2). Both the parent and sibling relatives performed significantly worse than CCS on Discriminability, but did not differ significantly on other measures. The two relative groups did not differ from each other on any measure.

Age and gender were significant covariates for all variables except for Trials 1–5 Free Recall Total Correct. Site was a significant covariate for all variables except Recognition Hits. WRAT-3 Reading was a significant covariate in the analysis of all CVLT-II variables. After controlling for all covariates, significant group differences remained for each of the CVLT-II measures. Neither substance-use nor mood disorder diagnoses were significant covariates for any CVLT-II measure.

Due to significant age differences between parent relatives and the other groups, d was based on estimated least square means incorporating age. Table 2 shows large ES differences between probands and both CCS and sibling relatives for all CVLT-II measures except Recognition Hits, which showed a medium difference. The largest difference involved the measure most related to learning/encoding: Trials 1–5 Free Recall Total Correct ($d = 1.20$ and 1.10 , respectively). In contrast, although both sibling and parent relatives demonstrated significantly lower scores on Discriminability than CCS, the associated ESs were small to medium ($d = 0.33$ and 0.54 , respectively). The same magnitude and pattern of group differences obtained with Trials 1–5 Free Recall Total Correct raw scores was also obtained with standard scores.

Site Differences

Demographic differences—One-way ANOVAs of demographic variables by site showed significant age differences in CCS ($F=8.1$, 6df, $p < 0.01$), but not in probands or relatives. Across sites, mean ages for CCS varied as much as 11.9 years, while proband groups only varied by 3.6 years, parent groups by 6.1 years, and sibling groups by 4.4 years. CCS and proband groups' level of education differed significantly among sites ($F=3.85$; 6, 502 df, $p < 0.001$; $F=2.76$; 6, 297 df, $p=0.013$, respectively); there were no significant differences across sites in either relative group. Significant differences in WRAT-3 Reading scores were evident in CCS ($F=4.30$; 6, 502 df, $p < 0.01$) and parent relative groups ($F=3.00$; 6, 225 df, $p=0.008$), but not in proband or sibling relatives groups. Overall, CCS demonstrated the most consistent site differences among demographic variables.

CVLT-II variables—To minimize the number of comparisons, site effects were evaluated for two measures. The first is Trials 1–5 Free Recall Total Correct, the primary endophenotype measure, which did not differ significantly between CCS and relative groups. The other is Discriminability, which differed significantly between CCS and all

other groups. These analyses also focus on the CCS and proband groups because they were recruited more independently than the relatives who were ascertained based on their relationship to the probands. Site differences were analyzed using a general linear model, with age, gender and reading scores as covariates.

Performance on Trials 1–5 Free Recall Total Correct was significant ($F=7.14$, 6, 499 df, $p < 0.001$) in CCS. One site was significantly lower than four others, and two additional sites were significantly lower than 3 others. In a separate analysis, the proband group also showed a site difference ($F=3.03$, 6, 295 df, $p < 0.007$), but it was less extensive, with one site significantly lower than five others. The pattern of findings for Discriminability was similar to the pattern for Trials 1–5 Free Recall Total Correct. Discriminability performance differed significantly in CCS ($F=4.32$; 6, 499 df, $p < 0.0003$), with two sites significantly lower than two others, and one significantly lower than four others. Although performance also differed between sites among the probands, it was more limited, with one site performing significantly lower than three others.

DISCUSSION

Consistent with previous studies involving verbal declarative memory (VDM) (Heinrichs, 2005; Heinrichs & Zakzanis, 1998), patients with schizophrenia performed more poorly than controls and relatives, with large effect size (ES) deficits in Trials 1–5 Free Recall Total Correct, Short-Delay Free Recall, Long-Delay Free Recall and Discriminability (1.00 – 1.20). The standard score version of Trials 1–5 Free Recall Total Correct was also large ($d = 0.93$) and showed the same pattern of group differences. Due to the similarities between the raw score and standard score versions of this measures, the discussion will focus on one of them, the raw score measure, which is reported more commonly in the literature (Mesholam-Gately et al., 2009; Trandafir, Meary, Schurhoff, Leboyer, & Szoke, 2006). The ES for Recognition Hits was smaller, but was still in the medium effect size range ($d = 0.55$), consistent with its sensitivity being lower than the recall measures (Heinrichs & Zakzanis, 1998). Notably, the largest ES involved the CVLT-II Trials 1–5 Free Recall Total Correct raw score, the primary dependent variable to be used in COGS' genetic analyses of VDM, which reflects the prominent deficit of the learning/encoding stage of memory processing (Cirillo & Seidman, 2003).

The current results showed milder than expected deficits in VDM performance in relatives of probands. They did provide some support for such deficits, but not in the hypothesized manner. Compared to CCS, neither the sibling nor the parent relative groups recalled significantly fewer words during the five learning trials or during the free recall trials. Thus, there was little indication of problems in learning or encoding in this sample. More consistent with expectation, CCS did not differ from either relative groups in the Recognition Hits trials. Contrary to prediction, Recognition Discriminability was the only measure that differed significantly among CCS and relative groups, which in part reflected sibling relative's difficulty in rejecting distractor items on the recognition trial.

Despite significant differences in Discriminability, the ESs were modest ($d = .33$ in the siblings, $d = .54$ in the parents). These results, together with nonsignificant findings across

the other measures of learning, recall and recognition, demonstrate the relatively mild nature of the deficits in relatives on the CVLT-II, which is also consistent with the significant but relatively low heritability of the CVLT-II (Greenwood et al., 2007).

One of the main issues raised by the current findings involves understanding the weak CVLT-II deficits in relatives, as VDM is one of the most replicated endophenotypic cognitive measures that show schizophrenia-related deficits (Aleman et al., 1999; Heinrichs, 2005). One important question is whether the magnitude of CVLT deficits is consistent with those reported in the literature. Mesholam-Gately et al.'s recent meta-analysis of neurocognition in first episode patients) showed a large ES ($d=1.34$) for Trials 1–5 Free Recall Total Correct (Mesholam-Gately et al., 2009), which is consistent with the large ES ($d=1.20$) obtained in the current study for the same measure. A meta-analysis by Trandafir et al that examined CVLT Trials 1–5 Free Recall Total Correct in adult relatives showed a small ES ($d=0.30$) compared to control subjects (Trandafir et al., 2006). The ES obtained in the current study was also small ($d=0.14$), and was within the 95% confidence interval (CI) reported by Trandafir et al ($d=0.10 - 0.48$). Based on these comparisons, the magnitude of CVLT deficits are thus consistent with those obtained in the literature for both probands and for relatives.

In light of these findings, it is reasonable to consider whether the mild deficits in the relatives involves the CVLT-II itself. The small ES obtained in the current study and in the Trandafir et al meta-analysis were lower than ESs obtained with other tests of VDM, such as story recall (e.g., Wechsler Memory Scale Logical Memory) or other tests of list-learning (e.g., Rey Auditory Verbal Learning Test/RAVLT) (Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004; Snitz, MacDonald III, & Carter, 2006; Trandafir et al., 2006).

Trandafir et al showed an ES of 0.47 for immediate recall of short stories, with a 95 % CI of 0.33–0.60 in the same meta-analysis. Although we cannot determine the relative sensitivity of types of list-learning measures, it is notable that Snitz et al reported a larger ES ($d=0.56$) for deficits in auditory verbal learning in relatives ($n=148$) versus controls ($n=155$) (Snitz et al., 2006) than did Trandafir et al., using the CVLT. Two of the three studies used in the Snitz meta-analysis employed the RAVLT; while only the third study used the CVLT. This finding raises the possibility that features of the CVLT in particular (e.g., the relative ease with which words can be clustered based on their semantic features, which is not a feature of the RAVLT) make it less sensitive to deficits in VDM in relatives than other measures. The apparent heterogeneity of ESs in relatives when different tests of learning and memory are used emphasize the likelihood that VDMs do not have uniform utility as endophenotypes for schizophrenia, and that their most relevant dimensions of dysfunction in schizophrenia may not be characterized fully yet. An implication of this conclusion is that specific tests may describe the endophenotype more accurately at this point than broader terms such as VDM, which may mask its heterogeneity.

Some of the other endophenotypes studied by the COGS consortium also showed a pattern similar to the CVLT-II. Like the other primary endophenotypes (Calkins et al., 2007), performance on Trials 1–5 Free Recall Total Correct differentiated CCS from probands clearly, and like the other endophenotypes, CVLT-II performance showed significant (if

modest) heritability (Greenwood et al., 2007). The presence or magnitude of differences between CCS and relatives was more mixed, with some endophenotypes such as P50 showing significantly poorer performance in relatives (Olincy et al., 2010), some such as the CVLT-II and antisaccade performance showing milder effects in relatives (Radant et al., 2010), and some such as working memory (Horan et al., 2008) and N100 amplitude (Turetsky et al., 2008) showing intermediate findings, depending on specific task parameters or levels of psychiatric comorbidity.

Two other factors that might contribute to low levels of deficits in some endophenotypes should also be considered. The first involves the COGS ascertainment methodology (Horan et al., 2008; Radant et al., 2010), including a strategy that maximized differences between affected and unaffected relatives by requiring participating families to include at least one unaffected sibling and one unaffected parent. Because many schizophrenia families are not intact (e.g. the individuals in them may be too impaired for the families to remain intact), it is possible that probands and relatives participating in the comprehensive COGS protocol may have come from families that are more intact functionally than is often the case. This ascertainment strategy raises the question of whether the sample is less impaired clinically and/or cognitively than typical samples of schizophrenia and their relatives. The current findings do not fully exclude this possibility, but they do not support it as an explanation for the CVLT findings, as both proband and relative levels of performance on the primary endophenotype measure were consistent with levels of deficits reported in the literature, as discussed above. Moreover, significant differences between relatives and controls in other COGS endophenotypes such as P50 (Olincy et al., 2010), and a meta-analysis showing that methodological factors such as degree of symmetrical inclusion/exclusion criteria modulate the magnitude of differences between relatives and controls on antisaccade performance (Levy et al., 2004), weaken the feasibility of this hypothesis further.

Second, site differences are another factor potentially affecting sensitivity, particularly when those effects involve measures with small or moderate ES. This study showed demographic differences across sites in age, education and WRAT-3 Reading levels. Moreover, significant site differences remained in Trials 1–5 Free Recall Total Correct when these factors were entered as covariates, as they did in the Discriminability measure. Similarly, when site was also entered as a covariate, group differences were not altered for any of the CVLT-II measures examined. This point, along with consistent levels of ES for Trials 1–5 Free Recall total Correct in relatives in other studies conducted at fewer, or at single, sites (Trandafir et al., 2006), make site differences an unlikely contributing factor to the current findings on group differences.

Nevertheless, these site differences, in the context of the stringent methodological and QA procedures used in COGS (Calkins et al., 2007), underscore the potential vulnerability of large, multi-site studies to demographic and/or methodological differences. Notably, a majority of site differences in the current study reflected differences in CCS at different sites, rather than differences in probands or their relatives. This is an important point to consider in the design of single and multi-site studies that may focus more carefully on the ascertainment of rare families compared to the unexpectedly difficult aspect of defining and obtaining well-matched and representative controls. This issue is particularly important in

detecting effects when the sample size and/or the ES are modest. Ultimately, greater standardization over the ascertainment of control subjects, together with better specification of endophenotype measures, may be necessary to facilitate the identification of genes and genetic mechanisms that create vulnerability to schizophrenia and other mental disorders.

ACKNOWLEDGMENTS

The authors wish to thank all of the participants and support staff that made this study possible, including the following key personnel:

Harvard University (RO1-MH065562; MH43518; Commonwealth Research Center of the Massachusetts Department of Mental Health): Stephen J. Glatt, Lynda Jacobs, Monica Landi, Erica Lee and Frances Schopick

Mount Sinai School of Medicine (RO1-MH065554): Rui Ferreira, Robert Fieo, Christopher Smith, Rebecca West

University of California Los Angeles (RO1-MH65707): William Horan, Mark Sergi

University of California San Diego (RO1-MH065571): Andras Kovach, Joyce Sprock, Katrin Meyer-Gomes, Barbara Haugeland, Kari Tweedale, Sheldrick Holmes, Emmeline Crowley.

University of Colorado (RO1-MH65588): Jamey Ellis, Jeff Hollis, Vicki Pender, Bernadette Sullivan, Bettye Clement, Christopher Cason, Alexis Ritvo

University of Pennsylvania (RO1-MH65578): Alexandra Duncan Ramos, Jarrod Gutman, CarlaAnn Henry, Paul Hughett, Jennifer Jackson, Adrienne Mishkin, J. Dan Ragland, Leslie Ramsey, David Rice, Jan Richard, Devon Seward, Felipe Silva and Robert Witalec.

University of Washington (RO1-MH65558): Kate B. Alvey, Andrew C. David, Sean P. Meichle, Denise O. Pritzl

ROLE OF THE FUNDING SOURCE

This work was supported by the NIMH through grants to Harvard University (RO1-MH065562), Mount Sinai School of Medicine (RO1-MH065554), University of California Los Angeles (RO1-MH65707), University of California San Diego (RO1-MH065571), University of Colorado (RO1-MH65588), University of Pennsylvania (RO1-MH65578) and the University of Washington (RO1-MH65558).

REFERENCES

- Aleman A, Hijman R, de Haan EH, & Kahn RS (1999). Memory impairment in schizophrenia: a meta-analysis. *American Journal of Psychiatry*, 156(9), 1358–1366. [PubMed: 10484945]
- Braff DL, Freedman R, Schork NJ, & Gottesman II (2007). Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disorder. *Schizophrenia Bulletin*, 33, 21–32. [PubMed: 17088422]
- Calkins ME, Dobie DJ, Cadenhead KS, Olincy A, Freedman R, Green MF, et al. (2007). The consortium on the genetics of endophenotypes in schizophrenia (COGS): “Model” recruitment, assessment and endophenotyping methods for a multi-site collaboration. *Schizophrenia Bulletin*, 33, 33–48. [PubMed: 17035358]
- Cannon TD, Hennah W, van Erp TG, Thompson PM, Lonnqvist J, Huttunen MO, et al. (2005). Association of DISC1/TRAX haplotypes with schizophrenia, reduced prefrontal gray matter, and impaired short- and long-term memory. *Archives of General Psychiatry*, 62, 1205–1213. [PubMed: 16275808]
- Cannon TD, Zorrilla LE, Shtasel D, Gur RE, Gur RC, Marco EJ, et al. (1994). Neuropsychological functioning in siblings discordant for schizophrenia and healthy volunteers. *Archives of General Psychiatry*, 51(8), 651–661. [PubMed: 8042914]
- Cirillo MA, & Seidman LJ (2003). Verbal declarative memory dysfunction in schizophrenia: from clinical assessment to genetics and brain mechanisms. *Neuropsychology Review*, 13(2), 43–77. [PubMed: 12887039]

- Cohen J (1988). *Statistical Power Analysis for the Behavioral Sciences* (2nd ed.). Hillsdale, N.J.: Lawrence Erlbaum.
- Delis DC, Kramer JH, Kaplan E, & Ober BA (2000). *California Verbal Learning Test: Second Edition. Adult Version. Manual* (Second ed.). San Antonio: Psychological Corporation.
- Faraone SV, Seidman LJ, Kremen WS, Pepple JR, Lyons MJ, & Tsuang MT (1995). Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: A diagnostic efficiency analysis. *Journal of Abnormal Psychology*, 104, 286–304. [PubMed: 7790631]
- Faraone SV, Seidman LJ, Kremen WS, Toomey R, Pepple JR, & Tsuang MT (1999). Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: A four-year follow-up study. *Journal of Abnormal Psychology*, 108, 176–181. [PubMed: 10067004]
- Faraone SV, Seidman LJ, Kremen WS, Toomey R, Pepple JR, & Tsuang MT (2000). Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: The effect of genetic loading. *Biological Psychiatry*, 48, 120–126. [PubMed: 10903408]
- Goldberg TE, Goldman RS, Burdick KE, Malhotra AK, Lencz T, Patel RC, et al. (2007). Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia: is it a practice effect? *Archives of General Psychiatry*, 64, 1115–1122. [PubMed: 17909123]
- Gottesman II, & Gould TD (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *American Journal of Psychiatry*, 160, 636–645. [PubMed: 12668349]
- Greenwood TA, Braff DL, Cadenhead KS, Calkins ME, Dobie DJ, Freedman R, et al. (2007). The Consortium on the Genetics of Schizophrenia (COGS): Preliminary Heritability Analyses of Endophenotypic Measures for Schizophrenia. *Archives of General Psychiatry*, 64, 1242–1250. [PubMed: 17984393]
- Gur RE, Calkins ME, Gur RC, Horan WP, Neuchterlein KH, Seidman LJ, et al. (2007). The Consortium on the Genetics of Schizophrenia (COGS): Neurocognitive Endophenotypes. *Schizophrenia Bulletin*, 33, 49–68. [PubMed: 17101692]
- Heinrichs RW (2005). The primacy of cognition in schizophrenia. *American Psychologist*, 60, 229–242. [PubMed: 15796677]
- Heinrichs RW, & Zakzanis KK (1998). Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology*, 12, 426–445. [PubMed: 9673998]
- Horan WP, Braff DL, Neuchterlein KH, Sugar CA, Cadenhead KS, Calkins ME, et al. (2008). Verbal working memory impairments with schizophrenia and their first-degree relatives: findings from the Consortium on the Genetics of Schizophrenia. *Schizophrenia Research*, 103, 218–228. [PubMed: 18406578]
- Husted JA, Lim S, Chow EW, Greenwood C, & Bassett AS (in press). Heritability of neurocognitive traits in familial schizophrenia. *American Journal of Medical Genetics (Neuropsychiatric Genetics)*.
- Jastak S, & Wilkinson G (1993). *Wide Range Achievement Test - Revised 3*. Wilmington, Delaware: Jastak Associates.
- Johnson JK, Tuulio-Henriksson A, Pirkola T, Huttunen MO, Lonnqvist J, Kaprio J, et al. (2003). Do schizotypal symptoms mediate the relationship between genetic risk for schizophrenia and impaired neuropsychological performance in co-twins of schizophrenic patients? *Biological Psychiatry*, 54, 1200–1204. [PubMed: 14643087]
- Keefe RSE, Seidman LJ, Christensen BK, Hamer RM, Sharma T, Sitskoorn MM, et al. (2006). Long-term neurocognitive effects of olanzapine or low-dose haloperidol in first-episode psychosis. *Biological Psychiatry*, 59, 97–105. [PubMed: 16140282]
- Keefe RSE, Sweeney JA, Gu H, Hamer RM, Perkins DO, McEvoy JP, et al. (2007). Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: a randomized, double-blind 52-week comparison. *American Journal of Psychiatry*, 164, 1061–1071. [PubMed: 17606658]
- Kremen WS, & Hoff AL (2004). Neurocognitive deficits in the biological relatives of individuals with schizophrenia In Stone WS, Faraone SV & Tsuang MT (Eds.), *Early Clinical Intervention and Prevention with Schizophrenia* (pp. 133–158). Totowa, New Jersey: Humana Press.

- Levy DL, O'Driscoll G, Matthysse S, Cook SR, Holzman PS, & Mendell NR (2004). Antisaccade performance in biological relatives of schizophrenia patients: a meta-analysis. *Schizophrenia Research*, 71, 113–125. [PubMed: 15374579]
- Mesholam-Gately R, Giuliano AJ, Faraone SV, Goff KP, & Seidman LJ (2009). Neurocognition in first-episode schizophrenia: A meta-analytic review. *Neuropsychology*, 23, 315–336. [PubMed: 19413446]
- NIMH Genetics Initiative. (1992). Family Interview for Genetic Studies. Rockville: National Institute of Mental Health.
- Nurnberger JI Jr., Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, et al. (1994). Diagnostic interview for genetic studies. Rationale, unique features, and training. *Archives of General Psychiatry*, 51, 849–859. [PubMed: 7944874]
- Olinicy A, Braff DL, Adler LE, Cadenhead KS, Calkins ME, Dobie DJ, et al. (2010). Inhibition of the P50 cerebral evoked response to repeated auditory stimuli: results from the Consortium on Genetics of Schizophrenia. *Schizophrenia Research*, 119, 175–182. [PubMed: 20382002]
- Paunio T, Tuulio-Henriksson A, Hiekkalinna T, Perola M, Varilo T, Partonen T, et al. (2004). Search for cognitive trait components of schizophrenia reveals a focus for verbal learning and memory on 4q and for visual working memory on 2q. *Human Molecular Genetics*, 13, 1693–1702. [PubMed: 15198991]
- Radant AD, Dobie DJ, Calkins ME, Olinicy A, Braff DL, Cadenhead KS, et al. (2010). Antisaccade performance in schizophrenia patients, their first-degree biological relatives, and community comparison subjects: Data from the COGS study. *Psychophysiology*, 47, 846–856. [PubMed: 20374545]
- Radant AD, Dobie DJ, Calkins ME, Olinicy A, Braff DL, Cadenhead KS, et al. (2007). Successful multi-site measurement of antisaccade performance deficits in schizophrenia. *Schizophrenia Research*, 89, 320–329. [PubMed: 17023145]
- Remillard S, Pourcher E, & Cohen H (2008). Long-term effects of risperidone versus haloperidol on verbal memory, attention, and symptomatology in schizophrenia. *Journal of the International Neuropsychological Society*, 14, 110–118. [PubMed: 18078537]
- Roofeh D, Cottone J, Burdick KE, Lencz T, Gyato K, Cervellione KL, et al. (2006). Deficits in memory strategy use are related to verbal memory impairments in adolescents with schizophrenia-spectrum disorders. *Schizophrenia Research*, 85, 201–212. [PubMed: 16690255]
- Seidman LJ, Giuliano AJ, Smith CW, Stone WS, Glatt SJ, Meyer E, et al. (2006). Neuropsychological functioning in adolescents and young adults at genetic risk for schizophrenia and affective psychoses: results from the Harvard and Hillside adolescent high risk studies. *Schizophrenia Bulletin*, 35, 507–524.
- Sitskoorn MM, Aleman A, Ebisch SJH, Appels MCM, & Kahn RS (2004). Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. *Schizophrenia Research*, 71, 285–295. [PubMed: 15474899]
- Skelley SL, Goldberg TE, Egan MF, Weinberger DR, & Gold JM (2008). Verbal and visual memory: Characterizing the clinical and intermediate phenotype in schizophrenia. *Schizophrenia Research*, 105, 78–85. [PubMed: 18617370]
- Snitz BE, MacDonald III AW, & Carter AS (2006). Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: A meta-analytic review of putative endophenotypes. *Schizophrenia Bulletin*, 32, 179–194. [PubMed: 16166612]
- Swerdlow NR, Sprock J, Light GA, Cadenhead KS, Calkins ME, Dobie DJ, et al. (2007). Multi-site studies of acoustic startle and prepulse inhibition in humans: Initial experience and methodological considerations based on studies by the Consortium on the Genetics of Schizophrenia. *Schizophrenia Research*, 92, 237–251. [PubMed: 17346930]
- Thornton AE, Boudreau VG, Griffiths SY, Woodward TS, Fawkes-Kirby T, & Honer WG (2007). The impact of monetary reward on memory in schizophrenia spectrum disorder. *Neuropsychology*, 21, 631–645. [PubMed: 17784811]
- Trandafir A, Meary A, Schurhoff F, Leboyer M, & Szoke A (2006). Memory tests in first-degree adult relatives of schizophrenic patients: A meta-analysis. *Schizophrenia Research*, 81, 217–226. [PubMed: 16246526]

- Turetsky BI, Greenwood TA, Olincy A, Radant AD, Braff DL, Cadenhead KS, et al. (2008). Abnormal auditory N100 amplitude: a heritable endophenotype in first-degree relatives of schizophrenia probands. *Biological Psychiatry*, 64, 1051–1059. [PubMed: 18701089]
- Tuulio-Henriksson A, Partonen T, Suvisaari J, Haukka J, & Lonnqvist J (2004). Age of onset and cognitive functioning in schizophrenia. *British Journal of Psychiatry*, 185, 215–219. [PubMed: 15339825]
- Van Erp TG, Therman S, Pirkola T, Tuulio-Henriksson A, Glahn DC, Bachman P, et al. (2008). Verball recall and recognition in twins discordant for schizophrenia. *Psychiatry Research*, 159, 271–280. [PubMed: 18442861]
- Vogelmaier MM, Seidman LJ, Niznikiewicz MA, Dickey CC, Shenton ME, & McCarley RW (2005). A comparative profile analysis of neuropsychological function in men and women with schizotypal personality disorder. *Schizophrenia Research*, 74, 43–49. [PubMed: 15694753]
- Weiss AP, & Heckers S (2001). Neuroimaging of declarative memory in schizophrenia. *Scandinavian Journal of Psychology*, 42, 239–250.

Table 1.Demographic Characteristics of the Sample^{1,2}

Variable/Group	CCS (1) n=509	Proband (2) n=305	Parent Relative (3) n=232	Sibling Relative (4) n=449	Overall Group Differences ⁴	Post-Hoc Group Comparisons ⁵
Age ³ (n =1495)	36.2 (12.6)	34.9 (11.2)	57.0 (6.2)	37.1 (11.8)	$F = 224.7, p < 0.001$	1,2,4<3
Gender N (% Male) (n =1495)	217 (42.6%)	227 (74.4%)	98 (42.2%)	194 (43.2%)	$\chi^2 = 97.38, p < 0.001$	1,3,4<2
Personal ³ Education (n =1482)	15.4 (2.3)	13.5 (2.1)	15.4 (2.7)	15.3 (2.5)	$F = 48.2, p < 0.001$	2<1,3,4
Parent Education ⁶ (n = 1439)	14.1 (3.0)	14.7 (3.2)	11.9 (3.2)	14.6 (3.2)	$F = 41.2, p < 0.001$	3<1<2,4
Handedness (Right) (n = 1427)	444 (89.1%)	247 (86.4%)	198 (92.1%)	379 (88.6%)	$\chi^2 = 6.40, p = 0.380$	NS
WRAT3 Reading Standard Score (n = 1495)	107.1 (10.6)	101.9 (11.7)	105.1 (11.5)	105.7 (10.6)	$F = 14.6, p < 0.001$	2<3,4<1
Lifetime Mood Disorders (%) (n =1495)	58 (11.4%)	143 (46.9%)	58 (25.0%)	88 (19.6%)	$\chi^2 = 139.5 p < 0.001$	1<4<3<2
Lifetime Substance Abuse Disorders (%) (n=1495)	45 (8.8%)	101 (33.1%)	18 (7.8%)	88 (19.6%)	$\chi^2 = 96.9 p < 0.001$	1,3<4<2

¹Expressed as means ($\pm$ standard deviations) for all measures except gender, handedness, lifetime rates of mood disorders and lifetime rates of substance abuse disorders, which are expressed as frequencies with percentages in parentheses.

²Group n's based on the full sample of 1495 subjects. Group n's vary slightly for demographic variables with fewer total observations, as listed in Table

³Unequal variances between groups based on Levine's test; post-hoc tests based on Tamhanes.

⁴One-way ANOVAs for continuous variables; Gender, Handedness, Mood Disorders and Substance Abuse Disorders are Chi-Square.

⁵Age and education comparisons showed unequal variances; post-hoc tests are based on Tamhanes. All other group comparisons were least square means.

⁶Parent Education is based on the mean of both parents' highest educational level when both are available; otherwise, it is based on the one for whom information is available.

Table 2.

Group performance on CVLT-II variables^{1, 2, 3}

	Controls (1) n=509	Probands (2) n=305	Parent Relatives (3) N=232	Sibling Relatives (4) n=449	Group	Site	Age	Gender	WRAT3 Reading ⁴	Post-hoc t-test <i>p</i> -values ⁵ & (Effect Sizes)					
	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>F</i>	<i>F</i>	<i>F</i>	<i>F</i>	<i>F</i>	<i>I-2</i>	<i>I-3</i>	<i>I-4</i>	<i>2-3</i>	<i>2-4</i>	<i>3-4</i>
CVLT 1-5 ⁴	55.8 (10.7)	41.8 (12.6)	50.5 (10.0)	54.3 (10.0)	73.1 ⁶	7.7 ⁶	48.2 ⁶	116.3 ⁶	106.5 ⁶	<.0001 (1.20)	.1945 (0.51)	.1723 (0.14)	<.0001 (0.76)	<.0001 (1.10)	.7722 (0.3)
CVLT 1-5 Standard Score ⁴	0.45 (1.3)	-0.84 (1.5)	0.38 (1.3)	0.29 (1.3)	47.5 ⁶	4.9 ⁶	0.3 . 59	0.13 .71	76.2 ⁶	<.0001 (0.93)	.8312 (0.08)	.1957 (0.15)	<.0001 (-0.85)	<.0001 (0.78)	.4858 (0.08)
CVLT SDFR ⁴	12.1 (3.1)	8.6 (3.7)	10.7 (3.3)	11.7 (3.1)	46.2 ⁶	5.91 ⁶	43.2 ⁶	74.3 ⁶	86.2 ⁶	<.0001 (1.03)	.5378 (0.44)	.3567 (0.13)	<.0001 (0.60)	<.0001 (0.91)	.9807 (0.31)
CVLT LDFR ⁴	12.4 (3.2)	8.8 (3.8)	11.5 (3.1)	12.1 (3.1)	52.2 ⁶	6.0 ⁶	25.5 ⁶	66.5 ⁶	73.7 ⁶	<.0001 (1.02)	.8100 (0.29)	.5466 (0.10)	<.0001 (0.78)	<.0001 (0.95)	.5101 (.19)
CVLT Recognition Hits	14.9 (1.8)	13.7 (2.8)	14.7 (2.1)	14.9 (1.8)	13.4 ⁶	2.1	4.2 <i>p</i> =.04	18.3 ⁶	12.1, <i>p</i> =. 0006 ⁶	<.0001 (0.55)	.7399 (0.15)	.6855 (0.06)	.0001 (0.40)	.0001 (0.51)	.9459 (. 10)
CVLT Discriminability	2.5 (0.6)	1.9 (0.6)	2.2 (0.5)	2.3 (0.5)	49.8 ⁶	4.32 <i>p</i> =. 0004	27.7 ⁶	61.0 ⁶	93.8 ⁶	<.0001 (1.00)	.0301 (0.54)	.0029 (0.33)	<.0001 (0.54)	<.0001 (0.67)	.9630 (0.18)

¹ Group means and standard deviations are based on CVLT-II raw scores.² Sample sizes are based on an overall *n* = 1495 using mean substitution for missing data on 34 subjects on the WRAT-3 Reading variable; mean substitution was based on group by site means.³ Statistical tests are based on mixed effects regression models with group as a fixed effect, age, gender, and WRAT-3 Reading as covariates, and family status as a random effect.⁴ WRAT-3=Wide Range Achievement Test, Third Edition; CVLT 1-5=California Verbal Learning Test, Trials 1-5 Free Recall Correct, Raw Score; CVLT 1-5 Standard Score=California Verbal Learning Test, Trials 1-5 Free Recall Correct, Standard Score; SDFR=Short-Delay Free Recall; LDFR=Long-Delay Free Recall⁵ Post-hoc *t*-tests are based on least square means. Significant comparisons are bolded.⁶ *p* 0.001.