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Verbal learning and memory in agenesis of the corpus callosum

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Abstract

The role of interhemispheric interactions in the **encoding**, retention, and retrieval of verbal memory can be clarified by assessing individuals with complete or partial agenesis of the corpus callosum (AgCC), but who have normal intelligence. This study assessed verbal learning and memory in AgCC using the California Verbal Learning Test—Second Edition (CVLT-II). Twenty-six individuals with AgCC were compared to 24 matched controls on CVLT-II measures, as well as Donders' four CVLT-II factors (i.e., **Attention Span**, Learning Efficiency, Delayed Memory, and Inaccurate Memory). Individuals with AgCC performed significantly below healthy controls on the Delayed Memory factor, confirmed by significant deficits in short and long delayed free recall and cued recall. They also performed less well in original learning. Deficient performance by individuals with AgCC during learning trials, as well as deficits in all forms of delayed memory, suggest that the corpus callosum facilitates interhemispheric **elaboration and encoding** of verbal information.

Keywords

Corpus callosum; Verbal learning; Verbal memory; Encoding

1. Introduction

Learning and memory are not unitary functions, but are multi-component (i.e., encoding, consolidation, retrieval, and recognition), and multi-modal (e.g., auditory, visual, olfactory, and motor) processes that involve a variety of brain regions (e.g., the medial temporal lobe, frontal lobes, cerebellum, amygdala, neocortex, and striatum). Conceptualizations of learning and memory have evolved over time, emerging from various philosophical and psychological theories (Maine de Biran, 1804/1929; James, 1890), experimental research with animals (Gaffan, 1974; O'Keefe & Nadal, 1978), and studies of humans with organic or acquired biological conditions (Milner, 1962; Benzing & Squire, 1989). Much of our current knowledge about memory has come from assessing learning and memory in different clinical populations (e.g., patients with amnesia, alzheimers). With this in mind, the

primary goal of the current study is to further clarify the role of the corpus callosum in verbal learning and memory. This will be accomplished by comparing performance of a large sample ($n=26$) of individuals with agenesis of the corpus callosum (AgCC) against matched controls using the California Verbal Learning Test—Second Edition (CVLT-II; Delis, Kaplan, Kramer, & Ober, 2000).

1.1. Agenesis of the corpus callosum

AgCC is a congenital brain malformation involving the complete or partial absence of the largest interhemispheric pathway. Current estimates suggest that AgCC occurs at a prevalence rate of approximately 1:4000 within the general population (Glass, Shaw, Ma, & Sherr, 2008) and at a rate of 3–5:100 in the developmentally disabled population (Jeret, Serur, Wisniewski, & Fisch, 1985). AgCC results from a variety of toxic, genetic, or vascular causes, but only 30–45% of individuals have identifiable causes for their AgCC diagnosis (Paul et al., 2007). Because callosal connections are absent from birth, the brain is challenged to maximize compensatory networks that would otherwise be mediated via the callosum. It is reasonable to presume that these compensatory systems are fully engaged by adulthood, at which point the remaining cognitive impairments shared among the AgCC population are most likely to reflect functions that are uniquely dependent on the callosum. Generally, congenital callosal malformations are demarcated into three specific categories: complete agenesis (complete AgCC), partial agenesis (partial AgCC), and callosal hypoplasia (Rauch & Jenkins, 1994). This approach to isolating the callosal contributions to higher cognitive functions is most effective in the sub-population of individuals with isolated AgCC. These individuals have either complete or partial AgCC, exhibit generally intact intellectual functioning with Full Scale Intelligence Quotient (FSIQ) greater than 80, and have few (if any) other cerebral malformations.

Isolated AgCC results in a pattern of neuropsychological and social deficits. Starting with basic sensory-motor processes, individuals with complete and partial AgCC have mild to moderate difficulties on tasks necessitating bimanual coordination of motor movements (Jeeves, Silver, & Jacobson, 1988; Jeeves, Silver, & Milner, 1988; Mueller, Marion, Paul, & Brown, 2009) and on tachistoscopic tasks that assess interhemispheric transfer of complex sensory information (Brown, Jeeves, Dietrich, & Burnison, 1999; Imamura, Yamadori, Shiga, Sahara, & Abiko, 1994; Jeeves, 1979; Jeeves & Silver, 1988; Karnath, Schumacher, & Wallesch, 1991; Sauerwein & Lassonde, 1983). For example, Brown et al. (1999) showed that individuals with AgCC performed similar to controls when presented with bilateral single letter matching tasks, but showed a bilateral presentation disadvantage when the task required matching complex patterns that were novel and not easily verbalized.

On cognitive tasks, their performance is characterized by slow reaction times and processing speed, particularly when processing complex information (Brown et al., 1999; Brown, Thrasher, & Paul, 2001; Hines, Paul, & Brown, 2002; Marco et al., 2012). On Wechsler IQ measures, surveys of published cases of individuals with AgCC and normal IQ have not revealed any consistent pattern of Verbal-Performance discrepancies (Chiarello, 1980; Sauerwein & Lassonde, 1994). Socially, they exhibit impaired comprehension of higher-order aspects of communication, affecting language pragmatics and humor (Brown, Paul,

Symington, & Dietrich, 2005; Brown, Symington, VanLancker-Sidtis, Dietrich, & Paul, 2005; Paul, Van Lancker-Sidtis, Schieffer, Dietrich, & Brown, 2003), theory of mind (Symington, Paul, Symington, Ono, & Brown, 2010), and interpersonal relations (Brown & Paul, 2000; Turk, Brown, Symington, & Paul, 2010). It has been suggested that AgCC involves a core cognitive deficit in complex novel problem-solving (Brown & Paul, 2000; Gott & Saul, 1978; Sauerwein & Lassonde, 1994; Smith & Rourke, 1995; Solursh, Margulies, Ashem, & Stasiak, 1965). Specifically, Brown and Paul (2000) found that two individuals with AgCC exhibited performance at the level of their FSIQ on a task involving over-learned information (crystallized intelligence), but under-performed on tests that assessed more creative and complex cognitive problem solving skills (e.g., the Tactile Performance Test, Raven's Color Progressive Matrices, Categories Test, and the Letter and Number Series Tests). However, it has been unclear whether deficits in verbal learning and memory are a part of the cognitive profile of AgCC.

1.2. Corpus callosum and memory

Early studies of memory in commissurotomy patients were inconclusive. Some studies reported intact memory functioning (LeDoux, Risse, Springer, Wilson, & Gazzaniga, 1977) and indicated that an isolated hemisphere could functionally encode as well as retrieve verbal information (Sperry, 1968). In contrast, other studies (Zaidel & Sperry, 1974; Zaidel, 1990) found that when compared against controls and individuals with epilepsy, postoperative commissurotomy patients performed more poorly on standardized tests of both verbal and visual-spatial memory. Impaired performance of commissurotomy patients on the verbal paired associates subtest of the Wechsler Memory Scale (WMS; Wechsler, 1945) suggested that the cerebral commissures play an important role in the acquisition, consolidation, and retrieval of verbal information. One hypothesis suggested that elimination of interhemispheric transfer impaired performance because visual memory traces in the right hemisphere were inaccessible to the language dominant left hemisphere for verbal recall. Moreover, reduced interaction of visual and verbal systems may have limited the richness of initial encoding for both visual and verbal tasks. A second hypothesis suggests that these findings could be interpreted in terms of difference in the respective ability of the two hemispheres to process different aspects of linguistic information, with the right hemisphere having increased semantic processing ability relative to the left. These studies suggest that the corpus callosum may play a role in the facilitation of different memory functions; however since commissurotomy involves transection of all cerebral commissures, including the hippocampal commissure, it does not specifically isolate the impact of callosal disconnection (Clark & Geffen, 1989; Phelps, Hirst, & Gazzaniga, 1991).

Early small-sample studies of learning and memory in individuals with AgCC and normal range IQ have been inconclusive. Some studies revealed relatively intact performance (Gott & Saul, 1978; Kessler, Huber, Pawlik, & Heiss, 1991; Pirozzolo, Pirozzolo, & Ziman, 1979). Specifically, Kessler et al. (1991) reported unimpaired verbal memory and recall performance in a 45-year-old male on the Buschke's Selective Reminding Paradigm (SRT; Buschke, 1973). Similarly, Pirozzolo et al. (1979) reported that a 60-year-old male with AgCC achieved a Memory Quotient score in the high average range (88th percentile) on the Wechsler Memory Scale (WMS; Wechsler, 1945). In contrast, Gott and Saul (1978)

reported that an individual with AgCC received a low average Memory Quotient score. The Wechsler Memory Quotient score, a composite score of different verbal and visual memory tasks, was only reported in these papers and therefore no information was available regarding strengths or weakness on specific memory types or processes (i.e., encoding, consolidation, retrieval, and recognition).

Several studies found that individuals with isolated AgCC have recall impairments on tests of verbal learning and recall of word lists (Fischer, Ryan, & Dobyns, 1992; Geffen, Forrester, Jones, & Simpson, 1994; Panos, Porter, Panos, Gaines, & Erdberg, 2001). First, Fischer et al. (1992) administered a selective reminding paradigm test to two children with AgCC (both age 8) with normal-range IQ. One individual performed in the 5th percentile and the other in the 16th on long-term retrieval of verbal information. In another study, the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1958) was administered to four individuals with AgCC and FSIQ>80, (Geffen et al., 1994). Three participants (ages 10, 14, and 37) had complete AgCC and one participant (age 22) had partial AgCC. Relative to published norms, the participants with AgCC did not exhibit deficits (i.e., performance at or below one standard deviation from test norms) on qualitative aspects of learning (i.e., learning slope, proactive and retroactive interference, or metamemory); however, the two children with complete AgCC had deficient acquisition scores (i.e., poor initial recall and total recall over Trials 1–5). On delayed recall, all three individuals with complete AgCC exhibited deficits in free recall, despite intact recognition. This pattern of performance suggests that they encoded and retained the verbal information, but had difficulty retrieving it from memory without the help of external cues. The author hypothesized that since recall deficits were not evident in the individual with partial AgCC, the remaining portion of the corpus callosum must play a role in the proper consolidation and retrieval of verbal information (Geffen et al., 1994). A later case study of an 11-year-old with partial AgCC and intact FSIQ (Panos et al., 2001) reported impaired recall on the California Verbal Learning Test—Children’s Version (CVLT-C; Delis, Kaplan, Kramer, & Ober, 1994). Unlike the complete AgCC cases reported by Geffen et al., this child with partial AgCC performed more poorly on the cued recall (two standard deviations below the mean) than on free recall (one standard deviation below the mean). The authors suggest that his poor cued memory illuminates a broader impairment in language processing, characterized by “limited capacity to utilize semantic information to organize his learning or recall.” In sum, while there is evidence that memory impairment may be a common feature in AgCC, the small sample size of these studies prevents drawing conclusions about the impact of the callosal absence on verbal memory and a large group study may clarify the exact nature of this impairment.

1.3. Verbal memory and hemispheric asymmetry

Findings from some task-based fMRI studies are relevant to the current study because they suggest involvement of both hemispheres in memory. Specifically, the Hemispheric Encoding and Retrieval Asymmetry (HERA) model suggests that the right prefrontal cortex is activated to a greater extent during memory retrieval, whereas the left prefrontal cortex is more activated during encoding of episodic memory (Tulving, Kapur, Craik, Markowitsch, & Houle, 1994; Nyberg, Cabeza, & Tulving, 1996; Habib, Nyberg, & Tulving, 2003).

Kompus, Kalpouzos, and Westerhausen (2011) conducted a study to help clarify the possible contribution of interhemispheric connectivity (i.e., the corpus callosum) in the lateralized organization of encoding and retrieval processes, as described in the HERA model. Results from this voxel-based imaging study revealed that the size of the anterior corpus callosum is associated with asymmetric retrieval-encoding processes within the ventrolateral prefrontal cortex (Kompus et al., 2011). Thus, it could be assumed that individuals with AgCC who lack structural interhemispheric connectivity may lack lateralization of these functions and whatever advantage is gained through interhemispheric modulation.

Just as memory processes are not localized to one cerebral hemisphere, there is evidence supporting that both hemispheres are involved in language processing (Code, 1987; Chiarello, 1988; Joanette, Goulet, & Hannequin, 1990). Van Lancker (1997) found that the processing of verbal information involves bi-hemispheric cortical interactions, such that syntactic and lexical aspects are processed more heavily in the left hemisphere, while the right hemisphere contributes broader semantic associations regarding personally and emotionally relevant information. On a verbal learning test comprised of words with different semantic associations, individuals with AgCC may have increased difficulty accessing and integrating larger right-hemisphere semantic networks to facilitate processing. Whatever the precise details of how verbal processing and encoding are divided, both hemispheres are clearly involved. Thus, verbal memory is likely to be reliant, in some manner, on interhemispheric integration.

1.4. California verbal learning test

The CVLT-II is a process-based list-learning task designed to evaluate quantitative and qualitative aspects of verbal learning and memory. Researchers have developed a variety of ways to interpret CVLT-II test findings that enable the evaluation of different memory processes (i.e., encoding, consolidation, retrieval, and recognition) in addition to specific encoding strategies. The current study relied heavily upon the work of Donders (2008) in the interpretation of CVLT-II test findings. First, Donders (2008) conducted a confirmatory factor analysis of the standardization sample on the CVLT-II, which yielded an underlying four-factor structure (i.e., Attention Span, Learning Efficiency, Delayed Memory, and Inaccurate Memory). (Donders 2008; Dejong & Donders, 2009) proposed that these factors measure the degree to which one can keep new information for “immediate further processing” (i.e., Attention Span), use efficient strategies to encode information (i.e., Learning Efficiency), retrieve or recall previously learned and/ or consolidated information (i.e., Delayed Memory), and discriminate between correct and erroneous information (i.e., Inaccurate Memory).

Additional CVLT-II variables can be used in the diagnostic or interpretive process to tease out processes contributing to outcomes on these factors. For instance, one could further analyze how well an individual encodes verbal information by analyzing words recalled on different learning trials, total words recalled across the five trials, and rate of acquisition. The CVLT-II also allows analysis of different performance discrepancies, such as proactive and retroactive interference, rapid forgetting (a measure of consolidation), and retrieval

problems (i.e., intact recognition with impaired free recall). Thus, in this research we not only measured performances on Donders' four factors, but also conducted analyses using additional CVLT-II variables to ascertain whether specific problems exist in the encoding, consolidation, retrieval, or recognition of verbal information.

1.5. Hypotheses

We predicted greater difficulty in the AgCC group in the overall encoding of verbal information (over the five List A list-learning trials) due to deficiency in the development of a memory-encoding strategy. It was further hypothesized that due to inefficient encoding of information, individuals with AgCC would exhibit increased difficulty on variables that measure their ability to retrieve or recall previously learned and/or consolidated information (i.e., Donders' Delayed Memory factor). Last, it was hypothesized that removing partial AgCC participants from the analyses would not change the differences between the AgCC and HC groups.

2. Materials and methods

2.1. Participants

This study involved 26 individuals with AgCC (19 complete AgCC, 7 partial AgCC, and 12 females) and 24 healthy control (HC) participants (11 females). In the AgCC group, 6 individuals were left handed and 3 were ambidextrous and among the HC participants, 2 were left handed and 1 was ambidextrous as assessed with the short Edinburgh Handedness Questionnaire (Oldfield, 1971). To avoid possible confounding effects due to low general intellectual function, FSIQ greater than, or equal to, 80 was required. Two participants from the HC group were eliminated from analyses due to extreme impairment on memory scores (>2 standard deviations below the mean). The HC group had observed mean scores on many different CVLT-II variables less than zero (see Table 4); however, it is important to note that the HC group's performance did not differ significantly from zero (i.e., the population mean) on any CVLT-II variables. Table 1 provides demographic comparisons of the final two groups. The AgCC group did not differ significantly from the control group in age $F(1, 48)=.14, p=.70, \eta_p^2=.00$, FSIQ $F(1, 48)=1.84, p=.18, \eta_p^2=.03$, VIQ $F(1, 46)=2.71, p=.10, \eta_p^2=.05$, PIQ $F(1, 46)=1.17, p=.29, \eta_p^2=.02$, education $F(1, 48)=2.88, p=.09, \eta_p^2=.05$, or gender ratio $\chi^2=.001, p=.98$.

Exclusionary criteria for both groups included English as a second language, history of moderate-to-severe head injury, major CNS disorder not associated with AgCC, intractable epilepsy, and drug abuse as assessed by clinical interview. Participants with AgCC were recruited for this study primarily through the National Organization for the Disorders of the Corpus Callosum. For 18 participants with AgCC, testing occurred as a part of a larger neurocognitive and psychosocial test battery conducted over two full days, while the others were tested in shorter session involving only the CVLT-II and an IQ test. AgCC was diagnosed from MRI images and clinical radiological reading (in 19 cases AgCC diagnosis was re-confirmed by additional imaging at Caltech, in 3 cases a consulting neuroradiologist confirmed AgCC diagnosis by review of clinical MRI and in 4 cases only clinical MRI reports were available). The presence of the anterior commissure was confirmed in the 22

participants with AgCC whose MRI scans were available for review. For the 7 participants with partial AgCC, the percent of residual callosum was estimated by visual inspection of midline sagittal T-1 MRI images. Residual callosum was less than 10% of normal size in three participants; it was 10–25% of normal in three participants, and one participant's partial callosum was approximated as being 25–50% of normal size.

HC participants were recruited through the use of Craigslist. Following phone screening to confirm appropriateness relative to inclusionary and exclusionary criteria, as well as age and education, control participants came for approximately 4 h of cognitive testing.

Upon entrance into this study, all participants were informed regarding the nature of the study and consented to participate. The three minors gave assent to participate in the study and a parent signed the informed consent. All participants were treated in accordance with APA Ethical Principles. Methods and procedures were reviewed and approved by the Human Subjects Review Committee at the Travis Research Institute.

2.2. Test instruments

General intelligence was measured using the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997) for 24 participants with AgCC and 22 participant controls. The 4-scale Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) was used for 2 participants with AgCC and 2 controls. The WASI is reliable in predicting WAIS-III scores (FSIQ $r=.90$; VIQ $r=.88$; PIQ $r=.84$; Strauss, Sherman, & Spreen, 2006). Auditory verbal learning and memory were assessed using the CVLT-II. As compared to the original version of the instrument (CVLT; Delis, Kramer, Kaplan, & Ober, 1987), the CVLT-II was standardized using a larger representative sample that matched 1999 US Census data in terms of ethnicity/race, education, and region (Delis et al., 2000).

2.3. Procedures

The CVLT-II was administered in accordance with standardized procedures. Administration started with the examiner reading a 16-word list (i.e., List A) to the participant at a rate of slightly slower than one second per word. After presentation of this list the examiner recorded verbatim the participant's oral recall of the list. Presentation and immediate recall of List A were repeated four more times for a total of 5 consecutive trials. Immediately after these trials, a 16-word interference list (i.e., List B) was presented to the participant. Again, the examiner recorded the participant's oral recall verbatim. Immediately after List B free recall, the Short Delay Free Recall (SDFR) and the Short Delay Cued Recall (SDCR) of List A were administered. After completion of short-delay tasks the participant spent 20–30 min completing unrelated tests of visual-spatial skills. After this delay, the Long Delay Free Recall (LDFR) and the Long Delay Cued Recall (LDCR) of List A were administered, followed by a yes/no recognition task. After another 10-min delay a majority of the participants then completed the forced-choice recognition task. Overall administration of the test took 50–60 min.

2.4. Statistical analyses

Standardized scores for CVLT-II variables of interest were calculated using the CVLT-II scoring assistant program and utilized for all analyses. Factor scores for each participant were calculated using standardized scores and the factor weightings derived by Donders (2008) from the young group (16–30) of the standardized sample (see Table 2). Specifically, a participant's factor score was calculated by summing the weighted z -scores for the variables that comprise that factor. Lower z -scores on CVLT-II variables generally indicate poorer performance, but there are certain instances when lower z -scores indicated better performance (i.e., Recognition False Positives, Total Intrusions). The z -scores for these variables were reversed (i.e., they were multiplied by -1), enabling easier comparisons with other variables and between Donders' four factors.

AgCC and HC group performance on Donders' four factors were compared using a one-way multivariate analysis of variance (MANOVA), followed by separate ANOVA's comparing groups on each factor. Factor scores that differed between groups were further examined by conducting group comparisons on each of the primary CVLT-II test scores comprising that factor.

Given the hypothesis that novel problem solving is a core deficit in AgCC, we were also interested in possible difference in early learning trials that might suggest greater difficulty developing an encoding strategy. To that end, we examined group differences in learning that were not represented in the factor scores, specifically List A Trials 1–5 Total, recall performance on each respective learning trial of List A, and list-learning pattern (e.g., Learning Slope Trials 1–2, Learning Slope Trials 2–5, and Learning Slope Trials 1–5). To more precisely understand the outcome of these analyses, exploratory group comparisons were conducted on the remaining primary CVLT-II scores (i.e., Long Delay Free Recall-Discriminability, Recognition-Discriminability) and on the 6 performance discrepancy variables of clinical relevance (Proactive Interference Index, Retroactive Interference Index, First Rapid Forgetting Index, Second Rapid Forgetting Index, First Retrieval Problem Index, and Second Retrieval Problem Index).

Finally, there is a question of whether individuals with complete AgCC and partial AgCC differ in verbal learning and memory performance. Given the small sample size of individuals with partial AgCC ($n=7$), analyses comparing individuals with partial AgCC to healthy controls were not conducted. However, wherever significant between-group differences (or strong trends ($p<.10$)) were found in analyses comparing the combined AgCC group and controls, these analyses were re-run without the participants with partial AgCC. By comparing changes in effect sizes (i.e., partial-eta square) with and without individuals with partial AgCC, we were able to evaluate the extent to which the partial presence of the corpus callosum was impacting results.

3. Results

3.1. CVLT-II factors

The mean, standard deviation, and ranges for each group on Donders' four factors are presented in Table 3 (also see Fig. 1). A MANOVA of these factors revealed significantly

lower scores overall in the AgCC group than in the HC group ($F(4, 45)=3.31, p=.01, \eta_p^2=.23$). The AgCC group scored significantly below the HC group on the Delayed Memory factor ($F(1, 48)=11.05, p=.002, \eta_p^2=.19$), with no significant group difference on the other three factors (Attention Span, $F(1, 48)=2.33, p=.13, \eta_p^2=.04$; Learning Efficiency, $F(1, 48)=1.21, p=.28, \eta_p^2=.03$; Inaccurate Memory, $F(1, 48)=.06, p=.81, \eta_p^2=.00$).

3.2. Delayed Memory

The Delayed Memory factor was analyzed in greater detail through group comparisons on the 5 CVLT-II scores of which that factor is comprised (see Table 4). The AgCC group performed significantly more poorly than the HC group on all 5 of these measures: Short-Delay Free Recall ($F(1, 48)=8.63, p=.005, \eta_p^2=.15$), Short-Delay Cued Recall ($F(1, 48)=10.11, p=.003, \eta_p^2=.17$), Long-Delay Free Recall ($F(1, 48)=6.91, p=.011, \eta_p^2=.13$), Long-Delay Cued Recall ($F(1, 48)=9.39, p=.004, \eta_p^2=.16$), and Recognition Hits ($F(1, 48)=5.49, p=.023, \eta_p^2=.10$).

To illuminate possible interactions between the length of delay (short vs. long) and recall type (free vs. cued), we conducted a 2 (groups) \times 2 (delays) \times 2 (recall types) ANOVA. Consistent with the findings on Donders' Delayed Memory factor, the AgCC group scored more poorly than the HC group on these memory tasks overall ($F(1, 48)=10.94, p=.002, \eta_p^2=.19$). Furthermore, lowered memory scores in the AgCC group were consistent across delay length and recall type: Group \times Time ($F(1, 48)=.95, p=.33, \eta_p^2=.01$); Group \times Condition ($F(1, 48)=.58, p=.81, \eta_p^2=.00$); and Group \times Time \times Condition ($F(1, 48)=.08, p=.78, \eta_p^2=.00$).

However, the AgCC group did not differ from the HC group on the Total Recognition Discriminability score, First Rapid Forgetting Index (Long Delay Free Recall vs. Trial 5), Second Rapid Forgetting Index (Long Delay Free Recall vs. Short Delay Free Recall), First Retrieval Problem Index (Total Recognition Discriminability vs. Long Delay Free Recall), or Second Retrieval Problem Index (Total Recognition Discriminability vs. Long Delay Free Recall Discriminability).

In sum, although the absolute amount of information recalled was significantly less in the AgCC group than the HC group (as indicated by the Delayed Memory factor), when recall scores were considered within the context of the original list learning task (e.g. First Rapid Forgetting Index), across the time delay (e.g. Second Rapid Forgetting Index) or in relation to forced-choice recognition (e.g. recognition vs. delayed free recall), we found that recall performance in AgCC was very similar to HC. In other words, the AgCC group was as effective as the HC group in retaining and retrieving previously learned information, but had not learned as much during encoding.

3.3. Learning variables

Given the hypothesis that novel problem-solving is a core deficit in AgCC, we were also interested in possible differences in learning that might suggest greater difficulty developing an encoding strategy. Table 4 also includes the mean and standard deviations for the AgCC and control groups for the learning variables (see also Fig. 2). The encoding process requires intact attention, which was supported by similarity across groups on the Donders' Attention Span factor. Upon closer inspection, the AgCC group did not differ from HC on List A Trial 1, nor on List B, indicating that simple attention was adequate for the encoding process. However, the AgCC group exhibited lowered performance on one component of that factor, Percentage Recall from Middle ($F(1, 48)=4.89, p=.032, \eta_p^2=.09$), which suggests that proactive interference from earlier items and retroactive interference from later items may interfere with encoding the middle of the list.

In addition to exhibiting intact basic attention, the AgCC group did not differ significantly from the HC group on the Learning Efficiency factor. Within that factor, the groups exhibited similar performance on use of semantic strategies and on response consistency across learning trials. There were also no group differences on any variables assessing learning slope (e.g., Slope Trials 1–2, Slope Trials 2–5, and Slope Trials 1–5), nor on the Proactive or Retroactive Interference Indices (i.e., no greater interference between List A and List B in AgCC).

In the AgCC group, intact performance on measures of learning strategy and efficiency did not result in the expected degree of learning. The AgCC group exhibited significantly reduced recall on the final learning trial, List A Trial 5 ($F(1, 48)=4.10, p=.049, \eta_p^2=.08$), as well as reduced learning overall, List A Trials 1–5 Total ($F(1, 48)=6.88, p=.012, \eta_p^2=.13$). In addition to Trial 5, the AgCC group had significantly lower scores on List A Trial 3 ($F(1, 48)=11.29, p=.002, \eta_p^2=.19$), with trends toward significantly lower scores on List A Trial 2 ($F(1, 48)=3.83, p=.056, \eta_p^2=.07$) and List A Trial 4 ($F(1, 48)=3.40, p=.07, \eta_p^2=.07$).

3.4. Effect of partial AgCC participants on test results

Analyses which resulted in statistically significant findings (and trends with $p<.10$) in previous comparisons of combined AgCC and HC groups were repeated after removal of participants with partial AgCC. In these comparisons of the complete AgCC and HC groups, all variables that were statistically significant (i.e., $p<.05$) in the preliminary analyses remained statistically significant, and consistent and marginal increases in effect size (i.e., a .01–.04 increase in effect size) were observed (see Table 5). Statistical trends remained trends, with the exception of List A Trial 2 variable which became statistically significant with a .07 increase in effect size.

4. Discussion

The results of this study revealed that individuals with AgCC were deficient in two domains of learning and memory on the CVLT-II: original learning and delayed recall. First, individuals with AgCC exhibited deficits during the 5 trials of learning the 16-word list,

performing significantly more poorly than the HC group on total of correct responses for Trials 1–5, and correct responses on Trial 3 and Trial 5 (and marginally on Trials 2 and 4). Although the AgCC group did not differ significantly from controls on Donders' Learning Efficiency or Attention Span factors, there was evidence that the AgCC group had greater difficulty than controls in encoding middle items in the list, possibly resulting in greater reliance on primacy and recency effects. Second, individuals with AgCC showed significant deficits on the Delayed Memory factor, including significantly impaired recall over both short and long delays, and for both free and cued recall, as well as significantly lower performance on recognition. The AgCC group did not exhibit elevated inaccuracies on memory tasks (Inaccurate Memory). That these differences in original learning and memory were related to the callosal absence was suggested by the increase in group differences (effect sizes) in these variables when individuals with partial AgCC were removed from the AgCC group.

4.1. List-learning

Individuals with AgCC were significantly worse over the 5 trials of original learning of the word list, as well as on Trials 3 and 5 (with trends towards significant differences on Trials 2 and 4). This deficit does not appear to result from inadequate simple attention, as individuals with AgCC had normal capacity for one-trial learning of a new list (i.e., List A Trial 1 and List B). List learning also was not limited by executive deficits in the use of a memory strategy, as reflected in non-significant differences both in the use of semantic clustering and on Donders' Learning Efficiency factor. It is possible that despite intact basic attention and normal use of semantic clustering, individuals with AgCC did not learn the list as well as controls because of limited processing capacity during encoding.

These results for initial learning (i.e., level of total recall over the first five trials) are consistent with some of the findings from word-list learning in a study of four individuals with AgCC (Geffen et al., 1994). Specifically, Geffen et al. found that the two child participants had clear impairment (i.e., greater than 1 SD below the normative group) in their overall level of recall over Trials 1–5. Although it is hard to generalize from a study with such a small number of children to a larger group of adults, there is suggestion in this study of a similar problem in list learning for individuals with AgCC.

It may be that the corpus callosum allows a person to marshal a larger network to aide in the processing of novel material. As such, rather than being inattentive or lacking in the application of a semantic-clustering strategy, individuals with AgCC learn less well because they are unable to marshal a bi-hemispheric network for processing and encoding the word list. Similarly, previous research has shown that individuals with AgCC have difficulty in novel complex problem-solving (Brown & Paul, 2000; Gott & Saul, 1978; Sauerwein & Lassonde, 1994; Smith & Rourke, 1995; Solursh et al., 1965) and exhibit slower cognitive processing speed (Brown et al., 1999, 2001; Hines et al., 2002; Marco et al., 2012). In the context of list learning, there may be a tendency to become more easily overloaded by the challenge of processing and encoding a large volume of rapidly presented information—that is, 16 words occurring at 1 word per second—without the benefit of a bi-hemispheric processing network.

The greater difficulty of individuals with AgCC in learning items from the middle of the list (that is, greater reliance on primacy and recency) is consistent with the hypothesis that list processing and encoding are more readily overloaded. Memory for items in the middle is included in Donders' Attention Span factor. However, individuals with AgCC are not different from controls in recall on the first presentations of either List A or List B (a typical attention span task), nor are they worse on indices of proactive and retroactive interference (other measures which assess allocation of attention). Thus, difficulty in recalling items in the middle of the list is better understood as a byproduct of a problem in elaboration and encoding of a large volume of information under time demand.

4.2. Delayed recall

Individuals with AgCC had an overall memory deficit evidenced by Donders' Delayed Memory factor. More specifically, results from the 3-way (group-by-recall condition-by-delay time) ANOVA indicated that the deficit was consistent across all four delay recall conditions. This memory deficit was also evident in the word recognition task. Thus, both the AgCC and HC groups were similarly affected by different lengths of delay and were similarly helped by semantic cueing. Furthermore, the groups did not differ on their long delay free recall score when analyzed within the context of how much information was originally learned (i.e., recall on List A Trial 5). The fact that they exhibited similar levels of rapid forgetting suggests that impaired "memory" scores are a direct consequence of a learning (encoding) impairment: individuals with AgCC simply had less information to recall. Information that is not adequately encoded will not be easily recalled, regardless of length of delay or mode of recall testing.

In contrast to these findings, Geffen et al. (1994) reported a primary retrieval problem (i.e., poor delayed recall as compared to recognition performance) using the RAVLT in three individuals with complete AgCC. Geffen's participants performed within normal limits (i.e., within 1 SD of average) on cued recall, but had lower performance (i.e., greater than 1 SD below average) on free recall after a delay. This pattern (better recognition than recall in comparison to norms) suggests that more information was retained than could be accessed during free recall. However, it is also possible that recognition performance was inflated by a positive response bias (indicated by an elevated number of false-positives on the yes/no forced recognition task), thereby overestimating amount retained. In the current study, the AgCC group did not differ from controls on the Inaccurate Memory factor indicating that their recall was no more or less hindered or helped by erroneous or irrelevant information.

4.3. The corpus callosum and memory encoding

The current results from individuals with AgCC suggest several interpretations of the contribution of interhemispheric interactions via the corpus callosum to memory. These interpretations are not, however, mutually exclusive, but may reflect different ways of viewing the impact of reduced hemispheric connectivity.

Studies of commissurotomy patients have made it clear that each hemisphere was capable of its own memory encoding and retrieval, and that cutting the cerebral commissures did not prevent basic memory processes, although lateralized differences in the content of memory

were present (Zaidel & Sperry, 1974; Zaidel, 1990). Each hemisphere has its own hippocampal-cortical system for episodic memory encoding and retrieval. The most dramatic impact of cutting the cerebral commissures was isolation of memory traces within each hemisphere, thus highlighting the role of the corpus callosum in the interhemispheric transfer of information to be recalled (Sperry, 1974). In addition, research on unilateral brain damage (Van Lancker, 1991, 1997; Borod, Bloom, Brickman, Nakhutina, & Curko, 2002), commissurotomy patients (Zaidel, 1995), and fMRI studies (Peck et al., 2009; Callan et al., 2006) has demonstrated that each hemisphere processes verbal information in a somewhat different manner, the left hemisphere processing primarily (although not exclusively) the propositional and syntactic properties, and the right hemisphere, the more visuospatial and affective content. Furthermore, research with commissurotomy patients has suggested that the isolated right hemisphere can comprehend language to some degree, and is more adept than the left hemisphere at lexical semantic tasks (Zaidel & Edelstyn, 1995). The right hemisphere appears to have a broader and denser semantic network than the left, with broader connections between concepts that are more distant or loosely associated (Chiarello & Richards, 1992; Chiarello, Burgess, Richards, & Pollock, 1990). Thus, optimal verbal learning and memory performance would likely be facilitated by the capacity to integrate left hemisphere language production networks with information processed by the richer semantic networks of the right hemisphere—which is not the case in AgCC.

Thus, it is also possible that weaker memory encoding of individuals with AgCC is a consequence of poor integration of information between the hemispheres. Absence of the corpus callosum would prevent the establishment of a larger and richer bihemispherically integrated memory trace involving the unique processing capacities of each hemisphere. As a consequence, establishing an adequate trace of the 16-word list would take more trials, and memory of the list would be less robust after either short or long delays, whether expressed in free recall, cued recall, or recognition. Thus, one interpretation of the results reported herein is that verbal learning and memory are deficient due to an inability to enhance the serial word memory expressed by the left hemisphere with the broader semantic fields of the right hemisphere.

A conflicting hypothesis was suggested by Geffen et al. (1994) who suggested that the corpus callosum plays an important role in increasing the efficiency of the verbal-dominant left hemisphere by inhibiting “noise” from the contralateral hemisphere. According to this hypothesis, individuals with AgCC lack the ability to properly inhibit the contralateral hemisphere, resulting in noisy information processing during encoding due to simultaneous but uncoordinated processing in each hemisphere. Noisy processing during learning that impeded an adequate encoding process would also result in a general delayed memory deficit. It is difficult to imagine right hemisphere verbal processing as noise. However, there may be difficulty in AgCC in resolving which largely independent hemisphere most influences responding.

Another potential explanation for verbal memory weakness in AgCC relates to hemispheric asymmetry of specific memory systems. Based on task-based neuroactivation (fMRI), the Hemispheric Encoding and Retrieval Asymmetry (HERA) model (Tulving et al., 1994; Nyberg et al., 1996; Habib et al., 2003) suggests that the left prefrontal cortex is dominant

during encoding of episodic memory, whereas the right prefrontal cortex is dominant during memory retrieval. Some studies also suggest that processing asymmetry related to stimulus content interacts with memory encoding and retrieval asymmetry (Habib et al., 2003). As noted above, research findings from Kompus et al. (2011) suggest that asymmetric memory processes in the frontal lobes are correlated with interhemispherical connectivity (i.e., the size of the anterior corpus callosum). With respect to list learning and memory in AgCC, the absence of the corpus callosum would likely reduce whatever advantage is gained by lateralization of encoding versus retrieval, as described by the HERA model.

4.4. Complete versus partial AgCC

Patterns of projection and connectivity of the remaining callosal fibers in individuals with partial AgCC are heterogeneous (Wahl et al., 2009). Diffusion tensor imaging (DTI) in these individuals indicates that the areas of the cerebral hemispheres that are interconnected by the residual corpus callosum cannot be predicted from what is known of connectivity through similar parts of a normal corpus callosum. In addition, interhemispheric projection and connectivity are highly variant between individuals with seemingly similar callosal residuals. Thus, adequate study of partial AgCC will need to involve large numbers of participants and grouping of participants based on connectivity revealed by DTI.

For the purposes of this study, individuals with partial AgCC were included in order to test most robustly the impact of the congenital absence of major portions of the corpus callosum. However, re-examination of differences between AgCC and HC groups after removal of individuals with partial AgCC did not result in non-significant findings despite the smaller AgCC group. To the contrary, removal of the 7 individuals with partial AgCC resulted in the same pattern of significant differences from the HC group, but with larger effect sizes. Thus, it appears that the complete absence of callosal fibers results in greater deficits in learning and memory than the partial absence. However, direct comparison of partial AgCC and HC will demand much larger groups and knowledge from DTI of connectivity patterns of residual callosal connectivity.

4.5. Limitations and future directions

Whatever the nature of the relationship between callosal function and memory encoding, we presume that the deficits in learning and delayed recall in individuals with AgCC shown in this study can be attributed to the largest brain abnormality consistently present in this group (i.e., complete or partial absence of the corpus callosum) and have intentionally selected a population with few if any other visible brain abnormalities on MRI (other than the presence of Probst bundles or colpocephaly which are structural changes typically accompanying AgCC). However, it is possible that undetected microscopic abnormalities might be consistently present and contributing to abnormal learning and memory. For instance, postmortem inspection of two brains with callosal dysgenesis revealed significant differences in the number of Von Economo neurons (Kaufman et al., 2008). It is also possible that memory disturbance does not directly result from callosal disconnection, but rather is a by-product of disruption in some other neural system as a result of the acallosal brain's compensatory reorganization during development. However, it is most likely the case that compensatory reorganization would ameliorate the impact of the callosal absence

on memory and reduce the impact of AgCC on learning and memory. It will take direct comparison of individuals with AgCC with matched individuals with callosotomy to adequately resolve this issue.

4.6. Conclusions

This study supports the hypothesis that the callosal absence significantly interferes with learning and memory. While the impact of the callosal absence may be most evident during recall tasks, retention and retrieval are not the likely culprits for the impairment. Likewise, while there is evidence of difficulty during early learning experiences, it is probably not the result of attentional impairment. Both impaired learning and recall in AgCC appear to be the consequence of impoverished encoding.

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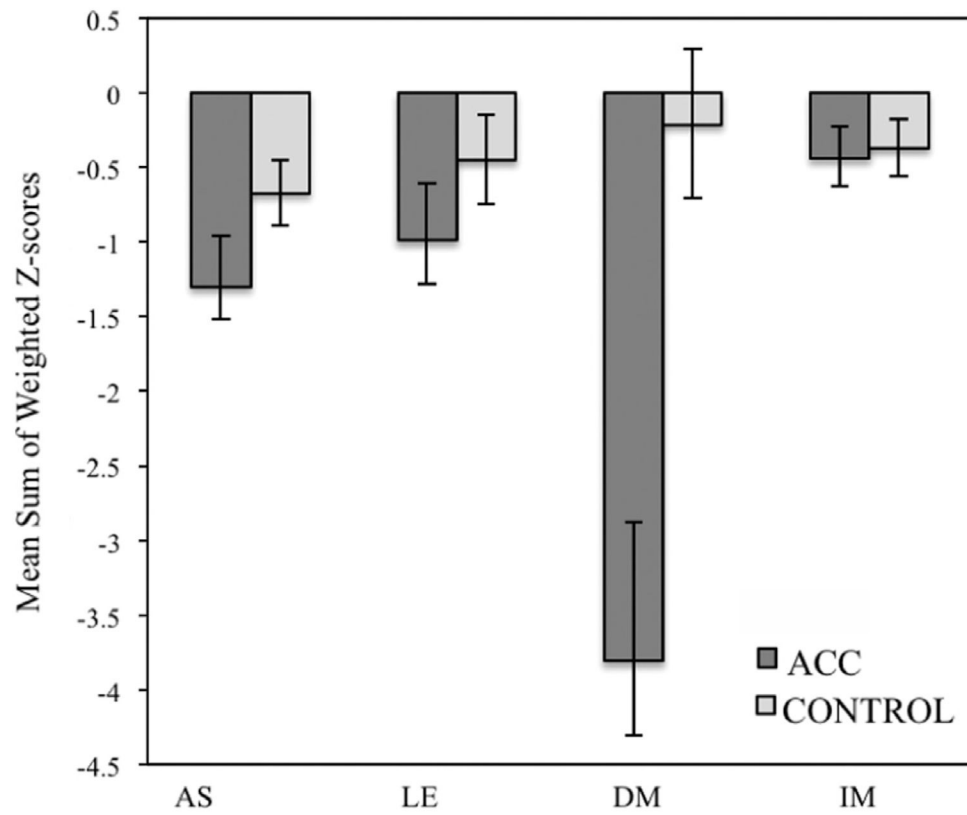


Fig. 1. Average factor scores for AgCC and control groups on each of Donders' four CVLT factors (AS=Attention Span, LE=Learning Efficiency, DM=Delayed Memory, and IM=Inaccurate Memory).

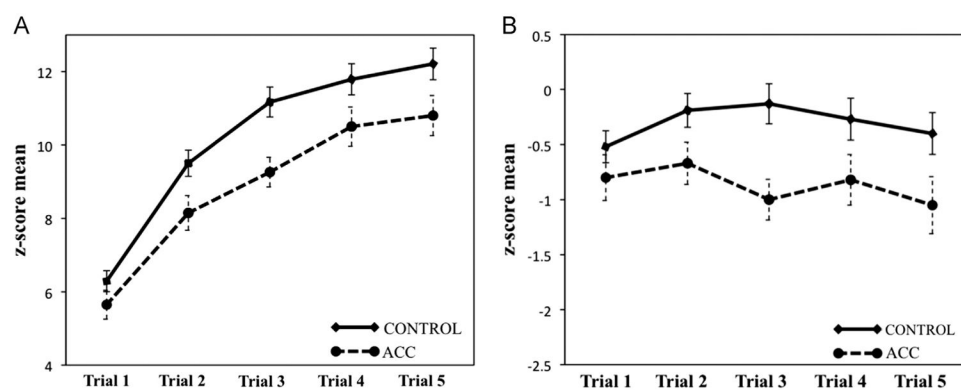


Fig. 2.
 Average correct responses on learning Trials 1–5 for AgCC and control groups: (A) raw scores; (B) standard scores.

Table 1

Participant demographics.

Variable	Group	
	AgCC (n=26)	Control (n=24)
Age		
Mean (sd)	27.19 (10.17)	28.29 (10.13)
Range	16–52	17–54
FSIQ		
Mean (sd)	97.35 (12.43)	101.70 (10.02)
Range	80–129	84–116
PIQ		
Mean (sd)	96.46 (13.48)	100.41 (11.53)
Range	69–117	79–117
VIQ		
Mean (sd)	98.00 (13.88)	103.90 (10.35)
Range	78–135	86–125
Education		
Mean (sd)	13.19 (2.23)	14.12 (1.57)
Range	10–19	12–18
Gender	12F:14M	11F:13M
Handedness	17R:6L:3A	21R:2L:1A

Note: AgCC=agenesis of the corpus callosum; HC=healthy control; sd=standard deviation; F=female; M=male; R=right handed; L=left handed; A=ambidextrous.

Table 2

CVLT-II variables that comprise each of Donders' four factors with factor weightings from young age group.

Factor	Variables	Factor weighting
Attention Span	List A, Trial 1	.60
	List B	.59
	Percentage Recall from Middle	.46
Learning Efficiency	List A, Trial 5	.89
	Semantic clustering 1–5	.47
	Recall consistency	.67
Delayed Memory	Short-Delay Free Recall	.87
	Short-Delay Cued Recall	.85
	Long-Delay Free Recall	.91
	Long-Delay Cued Recall	.88
	Recognition Hits	.54
Inaccurate Memory	Total Intrusions	.51
	Recognition False Positives	.85

Table 3

Group comparisons of z-scores on Donders' four CVLT-II factors.

Factor	Group		Effect size (η_p^2)
	AgCC	Healthy control	
Attention Span			
Mean (sd)	-1.30 (1.75)	-.76 (1.03)	.04
Range	-5.28 to 4.02	-2.64 to 1.35	
Learning Efficiency			
Mean (sd)	-.99 (1.95)	-.45 (1.47)	.03
Range	-4.24 to 3.54	-4.01 to 2.24	
Delayed Memory			
Mean (sd)	-3.81 (4.74)	-.21 (2.46)	.19**
Range	-15.44 to 4.40	-4.61 to 3.97	
Inaccurate Memory			
Mean (sd)	-.44 (1.06)	-.37 (.95)	.00
Range	-2.81 to .94	-2.30 to 1.11	

Note: AgCC=agenesis of the corpus callosum; sd=standard deviation.

**
 $p < .01$ compared to HC group.

Table 4

Group comparisons of CVLT-II variables of clinical relevance.

	Group		Effect size (η_p^2)
	Combined AgCC mean (sd)	Control mean (sd)	
List A, Trial 1	-.81 (1.07)	-.52 (.71)	.03
List A, Trial 2	-.67 (.98)	-.19 (.75)	.07*
List A, Trial 3	-1.00 (.95)	-.13 (.89)	.19**
List A, Trial 4	-.83 (1.17)	-.27 (.93)	.07*
List A, Trial 5	-1.06 (1.33)	-.40 (.93)	.08**
List A Trials 1–5 Total	-.79 (1.11)	-.10 (.71)	.13**
Learning Slope Trials 1–5	-.40 (1.36)	-.08 (1.05)	.02
Learning Slope Trials 1–2	-.23 (.82)	.10 (.81)	.04
Learning Slope Trials 2–5	-.19 (1.18)	-.25 (1.28)	.00
Percentage Recall from Middle	-.98 (1.71)	-.08 (1.06)	.09**
Semantic clustering 1–5	.12 (1.04)	.06 (.91)	.00
Recall consistency	-.15 (.99)	-.19 (.96)	.00
List B	-.62 (1.21)	-.54 (.69)	.00
SDFR	-.94 (1.39)	.00 (.77)	.15**
SDCR	-.94 (1.37)	.06 (.76)	.17**
LDFR	-.96 (1.27)	-.15 (.87)	.13**
LDCR	-.87 (1.20)	-.02 (.63)	.16**
Recognition Hits	-1.02 (1.57)	-.21 (.66)	.10**
Recognition False Positives	-.44 (1.16)	-.38 (1.15)	.00
Total Intrusions	-.25 (.75)	-.21 (.71)	.00
Recognition-Discriminability	-.65 (1.35)	-.06 (.86)	.07*

Note. Values are reported as mean *z*-scores. SDFR=Short Delay Free Recall, SDCR=Short Delay Cued Recall, LDFR=Long Delay Free Recall, LDCR=Long Delay Cued Recall; sd=standard deviation.

* $p < .10$ compared to healthy control group.

** $p < .05$ compared to healthy control group.

Table 5

Combine AgCC versus complete-only AgCC groups statistically compared to healthy controls.

	Combined AgCC Mean (sd; η_p^2)	Complete AgCC Mean (sd; η_p^2)	η_p^2 difference
List A, Trial 2	-.67 (.98;.07)1; **	-.89 (1.02;.14) *	.07
List A, Trial 3	-1.00 (.95;.19) *	-1.13 (1.04;.22) *	.03
List A, Trial 4	-.83 (1.17;.07)1; **	-.92 (1.24;.08) *	.02
List A, Trial 5	-1.06 (1.33;.08) *	-1.18 (1.44;.10) *	.02
List A Trials 1–5 Total	-.79 (1.11;.13) *	-.94 (1.23;.16) *	.03
Percentage Recall from Middle	-.98 (1.71;.09) *	-1.18 (1.90;.12) *	.03
Donders' DM factor	-3.81 (4.74;.19) *	-4.25 (5.07;.22) *	.04
SDFR	-.94 (1.39;.15) *	-1.00 (1.41;.17) *	.02
SDCR	-.94 (1.37;.17) *	-1.08 (1.46;.21) *	.04
LDFR	-.96 (1.27;.13) *	-1.05 (1.36;.14) *	.02
LDCR	-.87 (1.20;.16) *	-.95 (1.28;.19) *	.03
Recognition Hits	-1.02 (1.57;.10) *	-1.24 (1.77;.14) *	.04
Recognition-Discriminability	-.65 (1.35;.07)1; **	-.74 (1.55;.07) *	.01

Note. Values are reported as mean z -scores. DM=Delayed Memory, SDFR=Short Delay Free Recall, SDCR=Short Delay Cued Recall, LDFR=Long Delay Free Recall, LDCR=Long Delay Cued Recall; sd=standard deviation; η_p^2 =partial eta squared.

* $p < .05$ compared to healthy control group.

** $p < .10$ compared to healthy control group.