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Prospective and Episodic Memory in Relation to Hippocampal Volume in Adults with Spina Bifida Myelomeningocele

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Abstract

The present study examined prospective and episodic memory in relation to age, functional independence, and hippocampal volume in younger to middle-aged adults with spina bifida myelomeningocele (SBM) and typically developing (TD) adults. Prospective and episodic memory, as well as hippocampal volume, were reduced in adults with SBM relative to TD adults. Neither memory performance nor hippocampal volume showed greater decrements in older adults. Lower hippocampal volume was associated with reduced prospective memory in adults with SBM, and this relation was specific to the hippocampus and not to a contrast structure, the amygdala. Prospective memory mediated the relation between hippocampal volume and functional independence in adults with SBM. The results add to emerging evidence for reduced memory function in adults with SBM, and provide quantitative evidence for compromised hippocampal macrostructure as a neural correlate of reduced memory in this population.

Keywords

aging; hippocampus; memory; neurodevelopmental disorder; spina bifida myelomeningocele

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Spina bifida myelomeningocele (SBM) is the most common severely disabling congenital birth defect affecting the central nervous system, with recent prevalence estimates ranging from 3 to 7 of every 10,000 live births in North America (Au, Ashley-Koch, & Northrup, 2010). Caused by a complex pattern of gene–environment interactions, SBM involves incomplete formation of the neural tube early in gestation, resulting in distinctive physical, neural, and cognitive phenotypes (Barkovich & Raybaud, 2012; Dennis & Barnes, 2010). Surgical management of hydrocephalus through the implantation of ventricular shunts beginning in the 1960s drastically improved the survival rate of individuals born with SBM (Hirsch, 1994; Lorber, 1971). As a result, there now exists a cohort of individuals ranging in age from young adulthood through middle age for whom there is little data on long-term neurobehavioral outcomes (Bowman & McLone, 2010; Dennis, Jewell, et al., 2007). The cognitive profile of individuals with SBM appears to be generally stable across development from childhood through young adulthood; however, there is recent evidence suggesting that memory may begin to deteriorate more rapidly in adults with SBM relative to expectations from childhood and typical adult development (Dennis, Nelson, Jewell, & Fletcher, 2010).

Memory in SBM

Research in both children and young adults with SBM suggests that certain memory systems are systematically impaired in SBM, whereas other skills, such as vocabulary, word recognition, and procedural learning, remain relatively intact (Dennis & Barnes, 2010; Dennis, Landry, Barnes, & Fletcher, 2006). Memory systems requiring associative processing, including nondeclarative (implicit) and semantic memory, often appear preserved (Barnes, Dennis, & Hetherington, 2004; Dennis, Jewell, et al., 2007; Edelstein et al., 2004; Yeates & Enrile, 2005); whereas memory systems that require assembled processing, including working memory, prospective memory, and episodic memory, are impaired in children and young adults with SBM (Dennis & Barnes, 2002; Dennis, Jewell, et al., 2007; Mammarella, Cornoldi, & Donadello, 2003; Scott et al., 1998; Vachha & Adams, 2005; Yeates, Enrile, Loss, Blumenstein, & Delis, 1995).

Prospective memory is the recall of intentions to be activated in the future (e.g. “remembering to remember”). In young adults with SBM, ranging in age from18 to 36 years, Dennis et al. (2007) reported lower performance relative to TD individuals on a composite prospective memory score from the Rivermead Behavioural Memory Test (RBMT; Wilson, Cockburn, & Baddeley, 1985). In the only memory study to date that has included middle-aged adults with SBM (age range 18 to 63 years), Dennis et al. (2010) reported poorer time- and event-based prospective memory performance on the Cambridge Prospective Memory Test (Wilson et al., 2005) among adults with SBM relative to TD adults.

Episodic memory is a type of retrospective memory involving the acquisition, storage, and retrieval of information that refers to a specific context and is consciously and intentionally recollected (Tulving, 1983). In young adults, Dennis et al. (2007) reported poorer performance in individuals with SBM relative to TD adults on measures of delayed—but not immediate—verbal recognition, and both immediate and delayed verbal recall. To date, no studies have characterized episodic memory function in middle-aged adults with SBM.

Of particular importance when studying adults with SBM and other neurodevelopmental disorders is the question of accelerated normal or pathological aging (Dennis et al., 2010). Individuals with neurodevelopmental disorders other than SBM have been shown to exhibit more rapid cognitive aging and/or dementia neuropathology as early as 30 to 40 years of age (Devenny, Krinsky-McHale, Sersen, & Silverman, 2000; Hagerman & Hagerman, 2004). The one study to investigate possible age-related cognitive decline in adults with SBM found that when younger (≤ 32 years) and older (> 32 years) adults with SBM were compared, prospective memory impairment was three times higher in the older group (Dennis et al., 2010). In comparison, neither older nor younger TD adults demonstrated impaired performance. These recent findings provided initial support for the hypothesis that older adults with SBM may be more impaired in memory as they age. This hypothesis has not yet been investigated with regard to episodic memory, nor has the question of age-related *neural* degeneration been investigated in this population.

The Hippocampus

The primary neural correlate underlying both prospective and episodic memory in TD individuals is the hippocampus. The hippocampus is one part of a larger medial temporal memory network underlying episodic memory, which also includes the adjacent entorhinal, perirhinal, and parahippocampal cortices. The neural correlates of prospective memory involve the medial temporal lobe memory system (including the hippocampus) in addition to areas of the prefrontal cortex, especially the rostral prefrontal cortex (J. D. Cohen & O'Reilly, 1996; Okuda et al., 2003). Reductions in hippocampal volume, and its association with reductions in memory performance, have been identified in healthy aging (Raz et al., 2005), mild cognitive impairment (deToledo-Morrell et al., 2004; Pennanen et al., 2004), Alzheimer's Disease (AD; de Leon et al., 2007), and traumatic brain injury (TBI; Christidi et al., 2011).

Investigation into the properties of the hippocampus in SBM is limited to one qualitative study, a few studies involving animal models of hydrocephalus, and unpublished results from our laboratory investigating both macro- and microstructure in children and adolescents with SBM. In the qualitative study of MRI scans from individuals with SBM ranging from 18 days to 43 years (Miller, Widjaja, Blaser, Dennis, & Raybaud, 2008), the hippocampus appeared small, poorly shaped, and was laterally displaced. In animal models of hydrocephalus, macrostructure of the hippocampus has been reported as intact; whereas microstructure appeared abnormal (Cabuk, Etus, Bozkurt, Sav, & Ceylan, 2011; Kriebel & McAllister, 2000). Using diffusion tensor imaging (DTI), we recently identified significantly reduced hippocampal volume and significantly aberrant hippocampal microstructural metrics in children and adolescents with SBM relative to a TD comparison group (Juranek, Williams, Cirino, Dennis, & Fletcher, Unpublished results). To date, no studies of adults with SBM have quantitatively examined the hippocampus. Moreover, the relation of hippocampal morphometry to memory function in any age group of individuals with SBM has not yet been investigated.

The Present Study

The objective of the present study was to examine prospective and episodic memory functions in relation to hippocampal volume in young to middle-aged adults with SBM. Based on emerging evidence for possible age-related memory decline in adults with SBM, we hypothesized that adults with SBM would demonstrate poorer memory performance (Hypothesis 1), and that older age would be associated with greater memory impairment in adults with SBM relative to TD adults (Hypothesis 2). Similarly, we hypothesized that hippocampal volume would be lower than TD adults (Hypothesis 3), and that older age would be associated with greater reductions in hippocampal volume in adults with SBM relative to TD adults (Hypothesis 4). In order to investigate specificity of relations between memory and the hippocampus in SBM, the amygdala—another deep gray matter (GM) structure with a much less prominent role in memory function (Squire, 2009)—served as a contrast structure. We hypothesized that lower volume of the hippocampus would be associated with poorer memory performance in adults with SBM, but that volume of the amygdala would be unrelated to memory performance (Hypothesis 5). Finally, because cognitive deficits often limit functional independence in adults with neurodevelopmental disorders, we hypothesized that the effect of hippocampal volume on functional independence in adults with SBM would be mediated by level of memory impairment (Hypothesis 6).

Method

Participants

Participants included 97 adults with SBM and 41 TD adults, ranging in age from 18 to 62 years, recruited as part of an ongoing research project on SBM. Participants with SBM were recruited from Texas Children's Hospital and Shriner's Hospital for Children in Houston and from The Hospital for Sick Children in Toronto. Participants with SBM were also recruited from adult neurosurgical and rehabilitation facilities in Houston, Toronto, Edmonton, and Calgary, and from advertisements and meetings with family advocacy groups in Houston and Toronto. Participants with SBM were born with myelomeningocele and had arrested (n = 13) or shunted (n = 84) hydrocephalus, verified by medical record review of pathology and neurosurgical operative reports. TD participants were recruited through community advertising in Houston and Toronto. Individuals were excluded from participation if they had both verbal and nonverbal IQ scores below 70 on a standard intelligence test (Stanford-Binet Intelligence Scale: Fourth Edition; Thorndike, Hagen, & Sattler, 1986), neurological disorder unrelated to SBM, severe psychiatric disorder, uncontrolled seizure disorder, uncorrected vision or hearing impairment, or inability to control the upper limbs. Participants and their families gave informed consent in accordance with institutional review guidelines.

Table 1 contains demographic information for the total sample. The SBM and TD groups did not differ significantly in age, $t(136) = 0.68$, $p = .50$, gender, $\chi^2(1) = 3.49$, $p = .06$, handedness, $\chi^2(1) = 2.75$, $p = .10$, or SES, as estimated by Hollingshead's 4-Factor Index of Social Status (1975), $t(130) = 1.87$, $p = .06$; however, the group with SBM tended to be lower in SES and showed more non-right-handedness (both expected based on childhood

studies). The comparison group also tended to be more female, reflecting gender differences in volunteer rates. Because of the trends for differences in gender and SES, they were examined as potential covariates in preliminary analyses. Neither gender nor SES showed significant correlations with memory or volume dependent variables (all $|r| < .15$); therefore, neither variable was included as a covariate in the analyses. Groups differed in proportions of each ethnicity, $\chi^2(2) = 10.61$, $p = .01$, with higher proportions of Caucasian and Hispanic ethnicities in the SBM group and higher proportions of other ethnicities in the TD group. As expected, composite IQ was significantly higher in the TD group, $t(136) = 7.79$, $p < .001$.

All 97 participants with SBM and 41 TD participants completed the memory measures. A significantly smaller proportion of participants underwent neuroimaging due to a large number of participants living too far from an MRI facility. Adults were widely recruited across different geographic regions in Canada and the US, which was necessary to recruit an adequate number of adults. As a result, volumetric data were available for 32 participants with SBM and 29 TD participants. Of these 32 participants with SBM and both memory and volumetric data, 28 participants had also completed the measure of functional independence. When comparing the samples of participants with and without volumetric data, a significantly higher proportion of the TD participants had volumetric data available, relative to the participants with SBM, $\chi^2(1) = 16.64$, $p < .001$. Participants with SBM who had volumetric data were slightly younger relative to the group with SBM who did not have volumetric data, $t(95) = 2.27$, $p = .03$. There were no significant differences between participants with SBM with and without volumetric data with regard to gender, $\chi^2(1) = 0.25$, $p = .62$, handedness, $\chi^2(1) = 1.02$, $p = .31$, proportions of each ethnicity, Fisher's exact test $p = .13$, SES, $t(90) = 1.82$, $p = .07$, or composite IQ, $t(95) = 0.38$, $p = .71$.

Clinical characteristics, including blinded radiological coding of anatomical features of SBM, were compared between participants with SBM with and without volumetric data in Table 2. There were significant differences in Chiari malformation status, Fisher's exact test $p = .02$, with higher proportions of participants with no Chiari and lower proportions of participants with Chiari II, in the sample with volumetric data. There were also significant differences in ambulatory status, Fisher's exact test $p = .01$, with higher proportions of independently ambulating participants, and lower proportions of partial ambulating or unable to ambulate participants, in the sample with volumetric data. There were no significant differences between participants with SBM with and without volumetric data with regard to hydrocephalus status, Fisher's exact test $p = .75$, lesion level, $\chi^2(1) = 1.54$, $p = .23$, shunt revisions, Fisher's exact test $p = .93$, or seizure status, Fisher's exact test $p = .76$.

Because significant differences in Chiari malformations and ambulatory status might suggest that the subsample of participants with SBM and volumetric data represented a higher functioning, less impaired group relative to the complete SBM sample, we compared the two subsamples on memory performance and functional independence while controlling for age. Participants with SBM with and without volumetric data were comparable on measures of prospective memory, $F(1, 94) = 1.22$, $p = .27$, verbal episodic memory, $F(1, 94) = 1.48$, $p = .23$, and functional independence, $F(1, 82) = 0.19$, $p = .66$. Because the two subsamples did not differ on the main variables of interest, differences in Chiari

malformations and ambulatory status between participants with SBM with and without volumetric data should not significantly impact the results.

Measures

Memory—Specific subtests from the Rivermead Behavioural Memory Test–Extended Version (RBMT–E; Wilson et al., 1999) were examined as measures of prospective memory and verbal episodic memory. Designed to provide an ecologically valid assessment of everyday memory problems, the RBMT–E is composed of tasks analogous to real life situations (de Wall, Wilson, & Baddeley, 1994). The RBMT–E is comprised of 11 subtests. A standardized scoring system based on box plot analysis of a normative control group of 193 adults allows each subtest raw score to be converted to a Standardized Profile Score ranging from 0 to 4 (Wilson et al., 1999). The sum total of all profile scores forms the Overall Profile Score, which is classified to provide an overall rating of memory performance. There are no reliability or validity data available for individual subtest scores.

Prospective memory: Prospective memory was measured using a composite raw score from the Belongings, Appointments, and Messages subtests, as utilized in Dennis et al. (2007). The Belongings subtest requires participants to remember to ask for the return of—and remember the location of—two of their own belongings that were hidden at the beginning of the test. The Appointments subtest requires participants to remember to ask two questions pertaining to the near future when an alarm sounds after 20 minutes. The Messages subtest has immediate and delayed components requiring participants to remember to drop off an envelope and a book in certain locations while tracing a path around the room. For each subtest, partial points are given if the participant needs to be reminded about any of the tasks but remembers the content (e.g. needs to be reminded to ask for his or her belongings but then remembers what they were and where they were hidden). The maximum possible composite raw score is 24 points.

Verbal episodic memory: Verbal episodic memory was measured using a composite raw score from the immediate and delayed Story subtests. Participants listen to a reading of a short prose passage with 21 details and recall as many details as possible immediately following the reading and again following a delay of approximately 20 minutes. Points and half-points are assigned for all recalled or partially recalled details. One point is deducted if the participant requires a cue to recall the passage following the delay. The maximum possible score was 42 points.

The prospective and verbal episodic memory composite scores were moderately correlated within the SBM (r = .37) and TD (r = .26) groups.

Functional Independence—The Scales of Independent Behavior–Revised (SIB–R; Bruininks, Woodcock, Weatherman, & Hill, 1996) were used as a measure of functional independence. The SIB–R is a standardized measure of functional independence across many areas that form the following clusters: Motor Skills, Social Interaction and Communication Skills, Personal Living Skills, and Community Living Skills. Median reliability coefficients for the SIB–R cluster scores across different ages range from the

high .80s to .90s. Because the Motor Skills subscale is significantly confounded by the physical and urological difficulties of many participants, a composite score from the other three subscales was used. The SIB–R was administered in the form of a structured interview with both the participant and a parent, if a parent was available.

Volume of Hippocampus and Amygdala

MRI acquisition: High-resolution coronal brain MR images were acquired on a 1.5T (Toronto) GE Signa Excite or 3T (Houston) Philips Intera MRI scanner. An 8 channel head coil was used for all acquisitions on both MRI scanners. On the Philips 3T scanner in Houston, a T1-weighted 3D turbo fast echo sequence was acquired (following a conventional scout sequence) with the following parameters utilizing SENSE (Sensitivity Encoding) technology: TR/TE=6.5–6.7/3.04–3.14ms; flip angle=8°; square field-of-view=24cm; matrix=256×256; slice thickness =1.5mm; in-plane pixel dimensions (x,y)=0.94, 0.94; number of excitations (NEX)=2. On the GE 1.5T scanner in Toronto, a 3D SPGR (Spoiled Gradient) sequence was used with the following parameters: TR/TE=21/2ms; flip angle=25°; square field-of-view=24cm; rectangular matrix=256×192; slice thickness =1.5mm; in-plane pixel dimensions (x,y)=0.94, 0.94; number of excitations (NEX)=1.

The published literature indicates that our selected analysis method (e.g. the Freesurfer pipeline) is robust against site differences in imaging platforms, field strengths, and sequence types. Volume measurements and surface-based measures of cortical thickness exhibit comparable variance to that measured within the same scanner (Han et al., 2006; Han & Fischl, 2007; Jovicich et al., 2009). Currently, large-scale multi-site studies (e.g. Alzheimer's Disease Neuroimaging Initiative [ADNI]) have successfully pooled anatomical MRIs obtained on different platforms (e.g. GE, Siemens, and Philips) as well as field strengths (e.g. 1.5T and 3T) for automated image analyses (http://adni.loni.usc.edu/about/centers-cores/mri-core/).

Volumetric analysis: All scans were analyzed by raters blind to age, gender, and measures of neuropsychological performance. Prior to conducting volumetric analyses, all T1-weighted images were reviewed for image quality. All volumetric analyses were conducted using Freesurfer v4.0.5 software (www.surfer.nmr.mgh.harvard.edu) on a 64bit Linux computer. A fully-automated process (e.g. recon-all –all) was executed from the command line to skull-strip and segment each T1-weighted image of the brain into three classes of voxels: GM, WM, and CSF (Dale, Fischl, & Sereno, 1999; Dale & Sereno, 1993). A fully-automated routine then determined delimiting boundaries of the hippocampus and amygdala, as well as other deep GM structures. Segmentation results were visually inspected and manually edited by an expert user (JJ) with extensive knowledge and experience using Freesurfer's Tkmedit viewer before obtaining final segmentation masks of both deep GM structures in each study participant.

Data Analysis

All analyses were performed using SAS 9.2 software. The critical level of alpha was set at a threshold of $p < .05$. Partial eta squared (η_p^2) and R^2 values were examined as effect sizes

and interpreted based on Cohen's (1988) suggestions of small, $\eta_p^2 = 0.01$, $R^2 = 0.04$, medium, $\eta_p^2 = 0.06$, $R^2 = 0.09$, and large, $\eta_p^2 = 0.13$, $R^2 = 0.25$, effects.

Results

Hypotheses 1 and 2: Memory Performance

A multivariate general linear model (GLM) was used to examine group differences in memory performance and to examine the effect of age on memory performance by group. The multivariate GLM did not yield a significant age by group interaction, $F(2, 133) = 1.86$, $p = .16$, $\eta_p^2 = .03$; therefore, the interaction was trimmed from the model. The effect of group was significant, $F(2, 134) = 20.47$, $p < .001$, $\eta_p^2 = .23$. Memory performance, controlling for age, was significantly lower in the group with SBM for both prospective, SBM LS mean = 18.57, SE = 0.36, TD LS mean = 21.92, SE = 0.55, and verbal episodic memory, SBM LS mean = 9.41, SE = 0.62, TD LS mean = 15.50, SE = 0.95. Examination of the canonical correlations revealed that both memory measures were correlated at roughly the same magnitude with the discriminant function maximally separating the groups: prospective memory .83; verbal episodic memory .87. The effect of age was not significant, $F(2, 134) = 0.88$, $p = .42$, $\eta_p^2 = .01$. Memory performance by age in the TD and SBM groups is presented in Figure 1.

Hypotheses 3 and 4: Hippocampal Volume

A repeated measures GLM was used to examine group differences in hippocampal volume and to examine the effect of age on hippocampal volume by group. The same procedures were used to examine group differences in the contrast structure, the amygdala. The repeated measures GLM did not yield a significant effect of hemisphere and there were no significant interactions involving hemisphere, all $F(1,57) < 1$; therefore, analyses were collapsed across hemisphere. The age by group interaction was not significant, $F(1, 57) = 3.35$, $p = .07$, $\eta_p^2 = .06$; therefore the interaction was trimmed from the model. The effect of group was significant, $F(1, 58) = 28.00$, $p < .001$, $\eta_p^2 = .33$. Hippocampal volumes were significantly smaller in the group with SBM. The effect of age was not significant, $F(1, 58) = 1.03$, $p = .31$, $\eta_p^2 = .02$.

In the contrast structure, repeated measures GLM also did not yield a significant effect of hemisphere and there were no significant interactions involving hemisphere, all $F(1,57) < 1$; therefore, analyses were collapsed across hemisphere. The age by group interaction was not significant, $F(1, 57) = 0.83$, $p = .367$, $\eta_p^2 = .01$; therefore the interaction was trimmed from the model. The effect of group did not meet the critical level of alpha, $F(1, 58) = 3.75$, $p = .06$, but showed a medium effect size, $\eta_p^2 = .06$. In contrast to the smaller hippocampal volumes in the group with SBM, amygdala volumes were larger in the group with SBM. The effect of age was not significant, $F(1, 58) < 1$. Hippocampal and amygdala volumes collapsed across hemisphere after controlling for age are presented in Figure 2.

Hypothesis 5: Hippocampal Volume and Memory

Regression analyses were used to examine the relations between, and specificity of, hippocampal volume and memory performance within each group. Hippocampal volume

was averaged across hemisphere when included in the models as a predictor based on the results from Hypotheses 3 and 4 in which there were no significant effects or interactions involving hemisphere. The relations between hippocampal volume and memory in the TD group were not significant. Based on examination of residuals and regression plots, the relation between prospective memory and hippocampal volume appeared to be somewhat driven by an outlier in the SBM group. The relation between prospective memory and hippocampal volume remained significant following the removal of the outlier, as presented in the final model below.

In the group with SBM, there was a medium effect, R^2 = .110, F(2, 28) = 1.73, p = .20, for the association of lower hippocampal volume with lower prospective memory performance, although the effect did not reach the critical level of alpha, β = .34, p = .07. Hippocampal volume was not significantly associated with verbal episodic memory, β = .22, p = .27, total model, R^2 = .046, F(2, 28) = 0.68, p = .51. Age was not a significant predictor in either model.

In order to examine the specificity of relations between memory and hippocampal volume in the group with SBM, the same regression models were analyzed with the inclusion of amygdala volume in place of hippocampal volume. Similar to the results of group differences in hippocampal volume, in models examining group differences in amygdala volume, there were no significant effects involving hemisphere; therefore, amygdala volume was also averaged across hemisphere when included in the regression models as a predictor. Amygdala volume was not significantly associated with either prospective, β = .09, p = .64, total model R^2 = .009, F(2, 28) = 0.12, p = .89, or verbal episodic memory, β = -.09, p = .63, total model R^2 = .012, F(2, 28) = 0.17, p = .85, in the group with SBM. Age was not a significant predictor in either model.

Hypothesis 6: Hippocampal Volume, Memory, and Functional Independence

The bootstrap approach for estimating indirect effects in mediation models was used to examine whether the effect of hippocampal volume (*X*) on functional independence (*Y*) is mediated by level of memory impairment (*M*). The bootstrap approach was selected because it is more powerful than the classic Baron and Kenny (1986) approach for examining distal (e.g. developmental, longitudinal) processes and because it does not make assumptions about the shape of the sampling distribution of the mediation effect, which is often skewed (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002; Preacher & Hayes, 2004). The functional independence composite score from the SIB-R was predicted from the two memory variables in separate models while controlling for age. Hippocampal volume was averaged across hemisphere when included in the models as a predictor based on the results from Hypotheses 3 and 4 in which there were no significant effects or interactions involving hemisphere.

Neither prospective memory nor episodic memory served as a significant mediator of the effect of hippocampal volume on functional independence in the TD group.

In the group with SBM, results revealed a significant effect of the covariate age across models, prospective memory: b = 1.12, *SE* = 0.32, p = .002; episodic memory: b = 1.13, *SE*

= 0.33, p = .003. The total effect of hippocampal volume on functional independence was equal to b = 0.96, *SE* = 0.43, p = .034.

The direct effect of hippocampal volume on functional independence controlling for prospective memory in the SBM group was equal to b = 0.54, *SE* = 0.46, p = .25. The indirect effect of hippocampal volume on functional independence through prospective memory was equal to b = 0.42, *SE* = 0.23, with a 95% confidence interval of 0.09-1.05. Because the confidence interval of the indirect effect does not contain zero, the results support prospective memory as a significant mediator of the effect of hippocampal volume on functional independence in SBM.

The direct effect of hippocampal volume on functional independence controlling for verbal episodic memory in the SBM group was equal to b = 0.82, *SE* = 0.44, p = .07. The indirect effect of hippocampal volume on functional independence through immediate verbal recall was equal to b = 0.13, *SE* = 0.19, with a 95% confidence interval of -0.09-0.79. Because the confidence interval of the indirect effect contains zero, the results do not support verbal episodic memory as a significant mediator of the effect of hippocampal volume on functional independence in SBM.

Discussion

The present study produced a number of significant findings regarding long-term outcomes in the oldest living cohort of individuals with SBM ever evaluated. There was clear evidence of impairment in prospective and episodic memory, with only the former related to hippocampal volumes and functional independence.

Prospective and episodic memory functions were significantly reduced in adults with SBM relative to TD adults (Hypothesis 1). These findings add corroborating evidence for reduced prospective memory, using a different measure and sample than the only previous study of prospective memory that included middle-aged adults with SBM (Dennis et al., 2010). Given the ecologically valid design of the subtests from the RBMT–E, the results suggest that both young and middle-aged adults with SBM likely experience memory difficulties in everyday tasks involving both prospective and episodic memory.

Hippocampal volume was significantly reduced in adults with SBM relative to TD adults (Hypothesis 3). The results add to previous qualitative evidence of abnormal size and morphometric features of the hippocampus in 85% of participants with SBM (Miller et al., 2008), and are consistent with recent findings from our laboratory of significantly reduced hippocampal volume in children and adolescents with SBM (Ware et al., under review). Of note, and in contrast to smaller hippocampal volumes in SBM, the amygdala was *higher* in volume in the SBM group. Future studies should investigate the possible mechanisms contributing to larger amygdala volumes in SBM, as well as cognitive and behavioral correlates of this finding. Although the functional significance of enlarged brain regions in SBM is not clear, there is evidence that deviations in either direction from normative expectations are associated with poorer outcomes (Treble, Juranek, Stuebing, Dennis, & Fletcher, 2012).

The mechanisms contributing to differences in deep GM structure volumes in SBM are currently not well understood, but likely involve the effects of hydrocephalus. The primary pathological mechanism of congenital hydrocephalus involves tissue damaging mechanical forces from expansion of the ventricles, causing gradual destruction of periventricular white matter axons (Del Bigio, 2004, 2010). Additionally, there is evidence from animal models of congenital hydrocephalus for secondary injury mechanisms resulting from ischemic alterations (Cabuk et al., 2011; Socci, Bjugstad, Jones, Pattisapu, & Arendash, 1999). In the hippocampus, macrostructure has been reported as intact; whereas dendritic, axonal, and synaptic alterations suggest deafferentation of dark pyramidal neurons (Cabuk et al., 2011; Kriebel & McAllister, 2000; Socci et al., 1999). There is also evidence for delayed neuronal death in the hippocampus following ischemia in animal models (Nitatori et al., 1995; Zhao, Cheng, Ou, Chen, & Ruan, 2012). Because the hippocampus, in particular, is known to be one of the most susceptible brain structures to damage from hypoxia and ischemia, this could potentially explain not only reduced hippocampal volume in SBM, but also why hippocampal volume is reduced whereas volume of other deep GM structures (i.e. the amygdala) is not reduced. As such, other disorders characterized by hydrocephalus are likely at risk for hippocampal damage and it would be interesting to determine whether the reductions in hippocampal volume are also seen in other forms of congenital hydrocephalus and in adults with normal pressure hydrocephalus.

Lower hippocampal volume was associated with reduced prospective memory in adults with SBM, and this relation was specific to the hippocampus because it was not found in relation to the contrast structure, the amygdala. Hippocampal volume was not, however, associated with verbal episodic memory (Hypothesis 5). It was somewhat surprising to find an association between hippocampal volume and prospective memory—but not episodic memory—given the very well-established role of the hippocampus in the formation, reorganization, and consolidation of episodic memory (Moscovitch & Nadel, 1998; Squire, 2009) and the less central role of the hippocampus in prospective memory (J. D. Cohen & O'Reilly, 1996; Okuda et al., 2003) in TD individuals. Possible measurement issues with the RBMT–E (discussed below) may have influenced these results.

Prospective memory, but not episodic memory, mediated the relation between hippocampal volume and functional independence (Hypothesis 6). These results add to previously inconsistent findings of significant associations of prospective and episodic memory with some aspects of functional independence in young adults with SBM (Dennis, Jewell, et al., 2007), but no significant associations between memory and functional independence in the previous study that included middle-aged adults (Dennis et al., 2010). These results are also consistent with other studies of adults with SBM in which functional math (Dennis & Barnes, 2002) and reading (Hetherington, Dennis, Barnes, Drake, & Gentili, 2006) skills have been shown to be associated with measures of functional independence and overall quality of life. Adults with SBM may have difficulty “remembering to remember” to attend appointments, take medications, etc., which in turn has a negative impact on their ability to live independently (Dennis, Jewell, et al., 2007). Adults with SBM may benefit from compensatory interventions for impairments in prospective memory (Insel, Einstein, Morrow, & Hepworth, 2012; McDonald et al., 2011) to improve their functional independence and quality of life.

Age-Related Associations

The results did not provide support for age-related associations in younger to middle-aged adults with SBM. Neither memory performance (Hypothesis 2) nor hippocampal volume (Hypothesis 4) were poorer in older adults with SBM. Although associations of age and memory in adults with SBM has not been previously investigated with regard to episodic memory, or with regard to neural degeneration, the present results are inconsistent with recent findings from Dennis et al. (2010), who found the percentage of adults with impaired or poor prospective memory to be three times higher in older (> 32 years) relative to younger (≤ 32 years) adults with SBM.

One factor possibly contributing to null results for the age hypothesis is the use of the RBMT–E as the measure of memory function. Because the original RBMT was designed as a screening tool (Wilson et al., 1985), and the extended version maintained a similar scoring procedure while doubling the amount of information to be remembered (Wilson et al., 1999), there is no normative data or evidence of reliability or validity for the individual subtests of the RBMT–E. Furthermore, although the Overall Profile Score from the RBMT–E appears sensitive to subtle differences in memory function between healthy middle-aged and older adults (de Wall et al., 1994), as well as between adults with histories of TBI and healthy matched controls (Wills, Clare, Shiel, & Wilson, 2000), neither the prospective memory nor the verbal episodic memory subtests were sensitive to the effects of TBI on memory performance (Wills et al., 2000). Thus, although the RBMT–E subtests were sufficiently sensitive to detect large differences in memory function between the TD and SBM groups in the present study, they may not have been sufficiently sensitive to detect more subtle declines in memory function with age, perhaps better tested with specific tests of prospective memory, such as the Cambridge Prospective Memory Test (CAMPROMPT; Wilson et al., 2005). In addition, there appeared to be possible minor floor effects on the verbal episodic memory measure in the group with SBM.

A second factor potentially contributing to null results is the upper age range and number of older adults in the SBM sample. Although the present sample of participants with SBM included members of the oldest living cohort of individuals successfully treated with ventricular shunts, the oldest participants in the sample were still relatively young at the time of study participation; only 16 participants were in their 40s and only 3 participants were in their 50s, with the oldest participant being 54 years of age. Research in healthy older adults suggests that episodic memory shows decline with age by 61-65 years, but that prospective memory does not begin to decline until 66-70 years, with some types of prospective memory not declining until 71-75 years of age (Kvavilashvili, Kornbrot, Mash, Cockburn, & Milne, 2009). In contrast, neuropathological studies of adults with Down syndrome have shown that these individuals begin to develop amyloid plaques and neurofibrillary tangles, two hallmark signs of Alzheimer's disease, during their 40s and 50s (Wisniewski, Wisniewski, & Wen, 1985), with 50 to 60 % of adults with Down syndrome developing Alzheimer's disease by age 60 to 70 years (Holland, Hon, Huppert, & Stevens, 2000). In a study of adults with Williams syndrome, chronologically early and precipitous age-associated reductions in episodic memory were found in adults with Williams syndrome over 50 years of age (Devenny et al., 2004). Because there is only one previous study investigating the

hypothesis of age-related memory performance in adults with SBM in which a cut point of 32 years was used to establish differences between older and younger adults with SBM (Dennis et al., 2010), there is no clear indication of at what age associations of age and memory performance might appear in this population.

A third factor is possible selection bias for higher functioning, less severe cases of SBM in the present cohort. Since the introduction of shunting for hydrocephalus in the 1960s, there have been additional advances in the medical treatment of individuals with SBM, leading to significant increases in rates of survival into adulthood with more recent cohorts (Davis et al., 2005; Shin et al., 2012). Given that mortality in earlier cohorts of individuals with SBM has been shown to be higher in individuals with lower levels of functioning and more severe cases of SBM (Bowman, McLone, Grant, Tomita, & Ito, 2001; Oakeshott, Hunt, Poulton, & Reid, 2010), there is reason to believe that the older individuals in the present sample, who survived into middle adulthood, might represent a subsample of higher functioning, less severe cases of SBM due to a cohort effect. Based on the reserve hypothesis (Dennis, Yeates, Taylor, & Fletcher, 2007; Steffener & Stern, 2012; Stern, 2012), these individuals might be less likely to show age-related cognitive difficulties relative to lower functioning, more severe cases of SBM.

Limitations

Potential limitations of the present study include the acquisition of neuroimaging data across scanner platforms, the smaller sample size of participants with neuroimaging data and related possible selection bias, and the cross-sectional design of the study. Although we presented an argument for the robustness of our volumetric analysis method against differences between scanner platforms, we acknowledge that the accuracy and reliability of our volumetric data may have been reduced. The results involving neuroimaging data may not be representative of the general population of individuals with SBM; although the two subsamples of participants with SBM did not differ on the main variables of interest, those who underwent neuroimaging may represent a higher functioning group given the lower frequencies of Chiari malformations and greater number of ambulatory individuals In addition, the small sample size of those with both memory and neuroimaging data contributed to lower statistical power for these specific analyses. Finally, the accelerated aging hypothesis can only be truly tested using a prospective longitudinal design. The present cross-sectional design may be biased by cohort effects due to changes in medical practice and standard of care over time. Nevertheless, given the significant implications of possible accelerated decline for adults with SBM and the initial evidence for age-related memory performance in the published literature, we felt it was important to investigate this hypothesis with the available cross-sectional data.

General Conclusions and Future Directions

We report the first evidence for a neural correlate of memory impairment, and the first quantitative data of hippocampal macrostructural morphometry, in any age group of individuals with SBM. Our findings add corroborating evidence for the distinctive memory profile of individuals with SBM, involving impairments in both prospective and episodic memory systems. Finally, the results lend support for a mediating effect of memory

performance on the relation between the characteristic neural phenotype and functional independence in adults with SBM, adding to the emerging evidence that deficits in important skills like memory and math have a significant impact on quality of life in individuals with SBM.

Further research is clearly needed to explore the question of whether adults with SBM experience accelerated aging. Future investigations into neural correlates of memory impairment and possible accelerated memory and pathophysiological decline in adults with SBM should utilize measures of cognitive function with demonstrated sensitivity to modest or subtle decline with age that are free from floor effects in SBM. The present results also highlight the importance of including the oldest living adults with SBM with heterogeneous levels of functioning and severity. Future directions for this line of research in SBM include investigation of microstructure of the hippocampus in relation to memory function and increasing age, investigation of other brain structures as neural correlates of reduced memory function, and investigation into the effects of, and possible interventions for, memory dysfunction on functional independence and quality of life.

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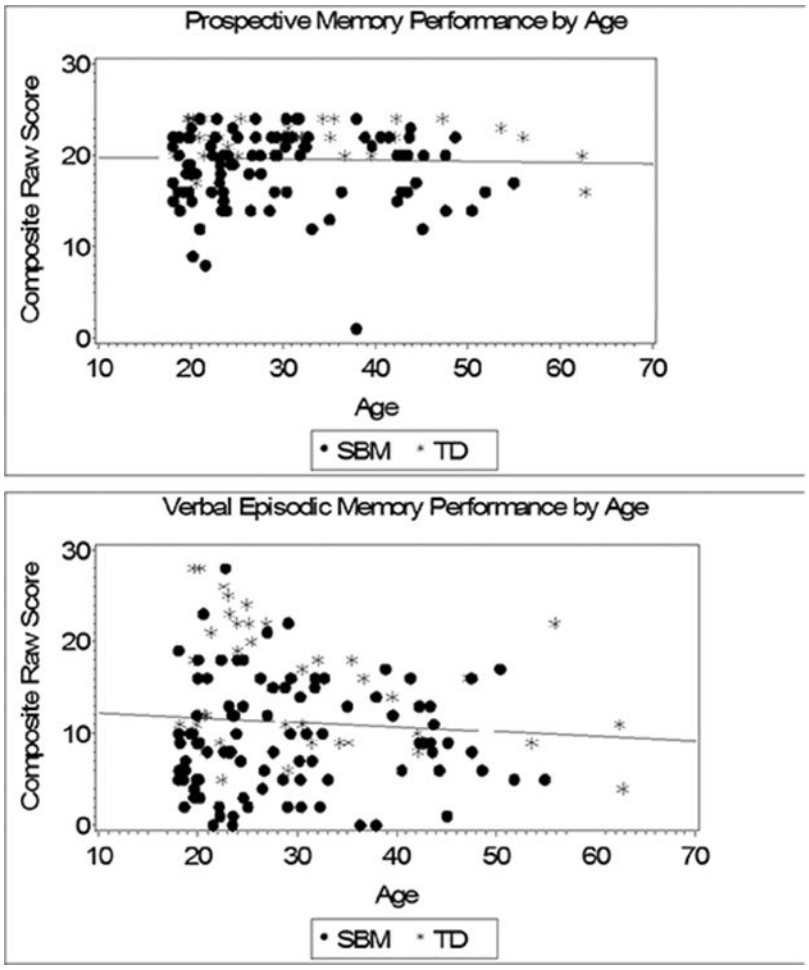

Figure 1. Prospective and verbal episodic memory performance by age in adults with spina bifida myelomeningocele (SBM) and typically developing (TD) adults

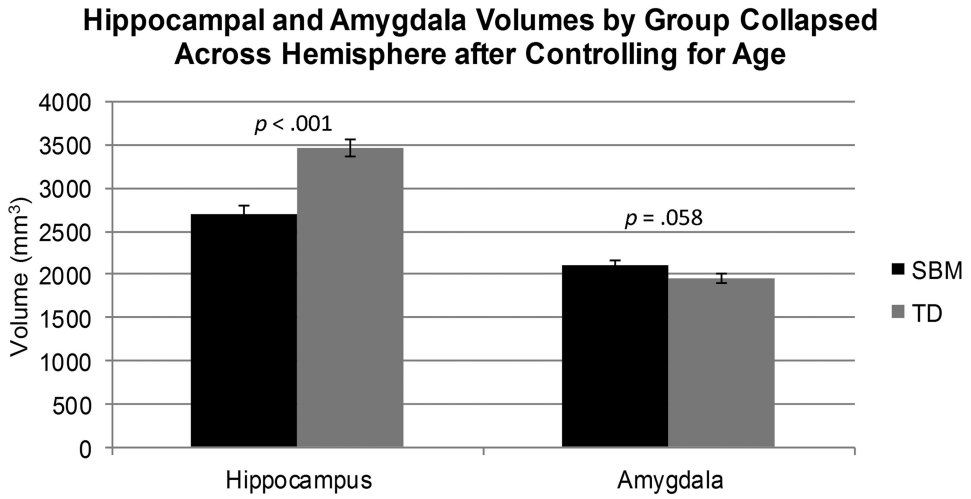

Figure 2. Hippocampal and amygdala volumes in adults with spina bifida myelomeningocele (SBM) and typically developing (TD) adults collapsed across hemisphere after controlling for age

Table 1
Demographic Information for the Total Sample

	SBM (*n* = 97)	TD (*n* = 41)	*p*
Age in years (M [SD])	29.14 (9.7)	30.45 (11.9)	.50
Gender (N [%])			.06
Male	45 (46%)	12 (29%)	
Female	52 (54%)	29 (71%)	
Handedness (% RHD)	78%	90%	.10
Ethnicity (N [%])			.01
Caucasian	75 (77%)	25 (61%)	
Hispanic	11 (11%)	2 (5%)	
Other	11 (11%)	14 (34%)	
SES (M [SD])[a]	33.14 (14.8)	38.41 (15.2)	.06
IQ (M [SD])	86.70 (13.5)	105.10 (10.51)	<.001

Note. RHD = right hand-dominant; SBM = spina bifida myelomeningocele; SES = socioeconomic status; TD = typically developing

[a]SES data was unavailable for 5 participants with SBM and 1 TD participant

Table 2
Clinical Characteristics for Participants with SBM with and without Volumetric Data

		SBM with volumetric data (*n* = 32)	SBM without volumetric data (*n* = 65)	*p*
Hydrocephalus	Arrested	5 (16%)	8 (12%)	.75
	Shunted	27 (84%)	57 (88%)	
Lesion level[a]	Above L1	5 (16%)	17 (27%)	.23
	Below T12	27 (84%)	47 (73%)	
Chiari malformation[a]	None	5 (15%)	2 (3%)	.02
	I	1 (3%)	0 (0%)	
	II	26 (81%)	61 (97%)	
Shunt revisions[a]	0	8 (25%)	19 (30%)	.93
	1	8 (25%)	12 (19%)	
	2-4	11 (34%)	19 (30%)	
	5-9	3 (9%)	8 (13%)	
	>10	2 (6%)	5 (8%)	
Ambulatory status[a]	Normal	1 (3%)	2 (3%)	.01
	Independent	13 (41%)	7 (11%)	
	With Support	9 (28%)	27 (42%)	
	Unable	9 (28%)	28 (44%)	
Seizure disorder[a]	No	26 (81%)	53 (84%)	.76
	Past	4 (13%)	5 (8%)	
	Present	2 (6%)	5 (8%)	

Note. SBM = spina bifida myelomeningocele;

[a]Participants missing data for lesion level: *n* = 1; Chiari malformation: *n* = 2; shunt revisions: *n* = 2; ambulatory status: *n* = 1; seizure disorder: *n* = 2; Participants missing data were not included in percentage calculations.