

Volumes of the Hippocampal Formation Differentiate Component Processes of Memory in a Community Sample of Homeless and Marginally Housed Persons

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Abstract

Objective: Persons who are homeless or marginally housed exhibit significant cognitive dysfunction, with memory being the most impaired domain. Hippocampal subfield volumes have been found to differentially relate to component processes of memory. The neural correlates of memory have not been previously examined in marginalized persons who are understudied and underserved. We examined whether hippocampal subfields and entorhinal cortex volumes are uniquely related to indices of verbal episodic memory using the Hopkins Verbal Learning Test – Revised.

Method: Data was used from a large sample of community dwelling homeless and marginally housed adults ($N = 227$). Regression analyses were conducted to examine hippocampal subfield volumes (CA1, CA3, CA4, dentate gyrus, subiculum) and entorhinal cortex, and their associations with measures of verbal immediate recall, learning slope, and verbal delayed recall.

Results: Greater CA3 subfield volume was associated with better performance on an index of encoding (immediate recall), but only in older individuals. Greater CA1 and subiculum volumes were associated with better performance on immediate and delayed recall (measures that tap into retrieval processes), but not with learning slope (a more pure index of encoding). Entorhinal cortex volume was related to all components of memory beyond total hippocampal volume.

Conclusions: Our results suggest common neuroanatomical correlates of memory dysfunction in large sample of marginalized persons, and these are uniquely related to different components of memory. These findings have clinical relevance for marginalized populations and theoretical relevance to the growing literature on functional specialization of the hippocampal subfields.

Keywords: Hippocampus; Memory; Neuroimaging; Cognition; Comorbidity

Introduction

Social and economic disparities in developed countries contribute to an increasing number of people living in chronically impoverished conditions, including absolute homelessness and marginal housing (Fazel, Geddes, & Kushel, 2014). People who are homeless or marginally housed (herein collectively referred to as marginalized) are among society's most underserved, yet paradoxically they face disproportionately high rates of severe mental illness, substance use disorders, and

premature mortality compared to the general population (Hwang, Wilkins, Tjepkema, O'Campo, & Dunn, 2009; Jones et al., 2015). Cognitive dysfunction is also prominent and is characterized by deficits in attention, processing speed, executive functioning, and memory (Depp, Vella, Orff, & Twamley, 2015; Gicas et al., 2017; Stergiopoulos et al., 2015). The differential rates of psychiatric, neurological, and physical illnesses impact cognitive functioning in select ways and contribute to significant cognitive heterogeneity among marginalized persons (Gicas et al., 2014, 2017). Nonetheless, memory stands as the most impaired domain, with upwards of 70% of homeless persons demonstrating test performances that fall greater than one standard deviation below the normative mean (Stergiopoulos et al., 2015). Therefore, memory impairment may reflect a common consequence of multimorbidity in this population, making it an obvious target when considering suitable preventative or rehabilitative interventions in this medically complex population. The convergence of multiple physical and psychiatric illnesses is apt to result in erosion of structural brain integrity, suggesting that an in-depth examination of structure–function relationships in marginalized people is a particularly relevant investigation. To optimize intervention strategies, a better understanding of the nature of memory dysfunction is needed, but there is a paucity of research on cognition in marginalized populations. From an inclusion health perspective (a service, policy, and research agenda aimed at resolving social and health inequities among marginalized populations (Luchenski et al., 2018)), neuropsychology can play a unique role in addressing this knowledge gap.

The hippocampus, a small structure situated bilaterally within the medial temporal lobes, is well established as playing a critical role in memory functioning (see for review Squire, 2009). Although there is increasing recognition that the hippocampus is also involved in other complex cognitive processes, its role in encoding, consolidation, and retrieval of verbal and visuospatial episodic memories has been extensively demonstrated in basic neuroscience and clinical studies (Hunsaker & Kesner, 2013; Tulving & Markowitsch, 1997). Not unlike other aspects of brain morphology, the hippocampus is structurally and functionally heterogeneous. The hippocampus is composed of histologically distinct subfields, which include the dentate gyrus (DG), the cornu ammonis regions 1–4 (CA 1–4), and the subiculum (Duvernoy, Cattin, & Risold, 2013). The entorhinal cortex is the primary input to the hippocampus and is considered, along with the subfields, as part of the “hippocampal formation”. A largely unidirectional circuit, the Trisynaptic Pathway is the main circuit that controls the flow of information within the hippocampal formation. This begins with input to the DG from the entorhinal cortex via the perforant pathway, followed by projections to CA3 via mossy fibers, and further information transmission by Schaffer collaterals to CA1 and the subiculum, the latter of which controls the final outflow of information from the hippocampus back to the entorhinal cortex. The differential cellular and molecular compositions of the hippocampal subfields lead to functional specialization, where the subfields earliest in the circuit, namely the DG and CA3, appear to be primarily involved in memory encoding, and the subfields latest in the circuit, CA1 and subiculum, are most associated with memory retrieval (Eldridge, Engel, Zeineh, Bookheimer, & Knowlton, 2005; Mueller et al., 2012; Mueller, Chao, Berman, & Weiner, 2011).

While the subfield functions have been well explored in animal models, only recently has this been more closely examined in humans (Hunsaker & Kesner, 2013; Yassa & Stark, 2011). Among the earliest studies were those that used functional magnetic resonance imaging (fMRI) to delineate differential structure–function associations using specialized memory paradigms, demonstrating relatively greater activation in the DG and CA3 subfields during verbal and visuospatial encoding tasks and in contrast, relatively greater activation in the subiculum during retrieval tasks (Eldridge et al., 2005; Suthana, Ekstrom, Moshirvaziri, Knowlton, & Bookheimer, 2011; Zeineh, Engel, Thompson, & Bookheimer, 2003).

Similar patterns of double dissociations have been demonstrated in structural MRI studies using standardized clinical memory measures. Mueller and colleagues (2011) found that greater CA3–DG subfield volumes were associated with better verbal immediate recall, whereas greater CA1 subfield volumes were associated with better verbal delayed recall in cognitively intact and impaired older adults. In follow-up, they demonstrated a similar pattern of dissociations in persons with mesial temporal lobe sclerosis (Mueller et al., 2012). In healthy older adults, Zammit and colleagues (2017) found that larger CA1 and subiculum volumes, but not CA3 or CA4–DG volumes, were associated with better performance on standard measures of delayed verbal and visuospatial recall. However, findings have been mixed and appear to vary as a function of segmentation procedures and clinical characteristics of the sample. For example, in persons with psychotic disorders, all hippocampal subfields were correlated with a measure of verbal immediate recall (Mathew et al., 2014). In patients with amnesic mild cognitive impairment, greater volumes in CA4–DG, CA3, as well as the subiculum were associated with better verbal immediate recall (Hanseeuw et al., 2011). In healthy younger adults, CA1–3 and DG subfield volumes were selectively associated with verbal immediate recall, but only in anterior regions of the left hippocampus (Travis et al., 2014). In contrast, Voineskos and colleagues (2015) reported that only hippocampal subfield shape, and not volume, was associated with memory across the healthy adult lifespan. While challenging to discern clear-cut dissociations, there remains a clear role for functional specialization of hippocampal subfields, and this becomes important in providing neuroanatomical anchors for exploration of memory dysfunction across different clinical contexts.

The aim of the current study is to conduct a cross-sectional investigation of the neuroanatomical correlates of memory functioning in a large community cohort of marginalized persons using standard neuropsychological tests and an automatic segmentation procedure suitable for large-scale studies. While automatic segmentation procedures offer great expediency, the measurements do not always align well with those derived from gold-standard histological studies (Wisse, Biessels, & Geerlings, 2014). These differences are perhaps most critically important in the context of making diagnostic predictions and classifications on the basis of subfield volumes. In the context of the current investigation, we posit that the automatic segmentation offers a powerful opportunity to explore broad patterns of covariation between different subfields and memory processes in a large heterogeneous sample. Structure–function relationships in healthy populations are not always evident, and this may be due to a threshold effect, whereby a certain degree of atrophy must be reached to trigger functional impact (Van Petten, 2004). However, the high degree of multimorbidity in this population suggests that memory may be disrupted in a variety of ways and that all hippocampal subfields may be vulnerable to volume loss given their differential sensitivity to psychiatric illnesses and disease (Small, Schobel, Buxton, Witter, & Barnes, 2011). Therefore, it is expected that the individual subfields will have unique roles in subserving the discrete component processes of memory in this sample. We hypothesized that: (1) greater volumes in the granule cell layer of the dentate gyrus (GC-DG), CA4 (hilar region of the DG), and CA3 subfields will be associated with better verbal immediate memory (index of encoding); and (2) greater CA1 and subiculum volumes will be associated with better verbal delayed memory (index of retrieval). Secondary analyses were conducted to examine the role of the entorhinal cortex in memory functioning, as it has been suggested that it is not simply a structural gateway to and from the hippocampus proper, but that it may play a complementary role in modulating memory and related aspects of cognition (Coutureau & Di Scala, 2009; Lipton & Eichenbaum, 2008). Given that the entorhinal cortex is the origin of both the “indirect” Trisynaptic Pathway that first projects to DG and a more “direct” pathway that projects to the CA1 region (Duvernoy et al., 2013), we hypothesized that larger entorhinal cortex volume would be associated with better performance on all measures of memory, independent of overall hippocampal volume.

Methods

Participants

Participants were recruited between November 2008 and June 2017 as part of an ongoing 10-year longitudinal study of homeless and marginally housed persons living in a highly impoverished neighborhood of Vancouver, British Columbia (see Honer et al., 2017). To capture a representative sample of people living within the neighborhood, participants were recruited through the following four streams: (1) people living in one of four single-room occupancy hotels ($N = 308$); (2) people who had contact with the downtown community court within the previous 6 months ($N = 67$); (3) youth aged 18–27 years living in a single-room occupancy hotel or an apartment serviced by a local youth mental health team ($N = 62$); and (4) people who were living in the neighborhood and were seen by an emergency room physician at the primary general hospital servicing that catchment area ($N = 62$). Of note, definitions of homelessness vary across countries (Fazel et al., 2014). We defined marginally housed as “accommodations barely meet minimum standards and there is imminent risk for loss of accommodations” and tertiary homelessness as “living in single-room accommodations that fail to meet minimum community standards”, in keeping with our previous work (Gicas et al., 2017) and the definitions proposed by Chamberlain and Mackenzie (1992). However, many of our participants also transition back and forth between being marginally housed and absolute homelessness (e.g., having no fixed address).

The inclusion criteria for the overall study were 18 years of age or older, English language fluency, and ability to provide written informed consent. All participants received a small honorarium for each assessment they completed (e.g., cognitive, MRI). The amount was carefully assessed as part of the ethics review of the protocol to ensure this was appropriately respectful of the participants’ time involvement in the study, and calibrated to the local economic realities. Ethics approvals were obtained from the Clinical Research Ethics Boards of the University of British Columbia and Simon Fraser University in accordance with Tri-Council policy.

Neuroimaging Data

Image acquisition. All MRI whole brain scans were acquired on a Philips Achieva 3.0 T scanner with an eight-channel SENSE-head coil located at the University of British Columbia. A 3D T1-weighted Fast Field Echo (FFE) sequence was acquired in the sagittal plane with 190 1-mm thick contiguous slices ($TR/TE = 8.1/3.5$ ms; acquisition matrix = $256 \times 250 \times 190$; field of view = $256 \times 256 \times 190$ mm³; recon voxel = $1 \times 1 \times 1$ mm; flip angle = 8° ; total acquisition time = 7:23 min).

All images were inspected for motion or susceptibility artifact by trained raters. The imaging parameters and software platform remained unchanged throughout the study.

Image processing. The structural MRI scan processing stream included intensity bias correction using the MINC N3 tool from the FreeSurfer package, and skull stripping and tissue segmentation (“new segment” method) using Statistical Parametric Mapping 8 (available at <http://www.fil.ion.ucl.ac.uk/spm/software/>). Intracranial volume (ICV) was calculated by combining gray matter, white matter, and cerebrospinal fluid measurements. Entorhinal cortex volumes were generated using the volume-based protocol of FreeSurfer v5.1 which is documented in detail elsewhere (Fischl et al., 2002) (We used entorhinal cortex volumes segmented with FreeSurfer v5.1 given our data from this protocol has been extensively edited in our sample.). The hippocampal subfields were automatically segmented with FreeSurfer v6.0 (development version; available at <https://www.nmr.mgh.harvard.edu/>; see Fig. 1) with a procedure that uses Bayesian inference with a probabilistic atlas derived from manual delineations of the hippocampus using ultra-high resolution ex-vivo MRI scans (Iglesias et al., 2015). The high-resolution atlases provide improvement over previous automatic segmentation protocols from FreeSurfer by enabling more accurate delineation of subfield boundaries and generating volumes that more closely align with histological studies. This segmentation procedure has been validated on three datasets and has demonstrated moderate but significant improvement over the previous version in its ability to discriminate Alzheimer’s disease patients from older adult controls (Iglesias et al., 2015). Segmentations in the current dataset were inspected by trained reviewers and manual corrections were applied where necessary.

Cognitive Assessment

A battery of neuropsychological tests was administered by trained research assistants under the supervision of a registered psychologist and was conducted within one month of the MRI scan (76.8% on same day). We estimated premorbid full scale IQ (FSIQ) using the Wechsler Test of Adult Reading (Wechsler, 2001). Sustained attention and mental flexibility were measured using the CANTAB (Cambridge Neuropsychological Test Automated Battery) Rapid Visual Information Processing subtest and the Intradimensional Extradimensional subtest, respectively (Fray, Robbins, & Sahakian, 1996). The Stroop Color-Word Test was used to measure response inhibition, and the Iowa Gambling Task (Bechara, Damasio, Damasio, & Anderson, 1994) was used to measure decision-making in the context of reward.

Relevant to the current study, verbal learning and memory was assessed using the Hopkins Verbal Learning Test Revised (HVLT-R) alternate Forms 1 and 2 (Brandt & Benedict, 2001). This entails having the examiner orally present a list of 12 words from three semantic categories, followed by the examinee immediately recalling as many list words as possible. This procedure is repeated over three trials and is followed by a 20–25 min delay at which point the examinee is again asked to freely recall as many list words as possible. Participants are not given advance warning of the delayed recall task. They are then presented with a 12-item yes-no word recognition task. For the current study, the immediate recall raw score was used as

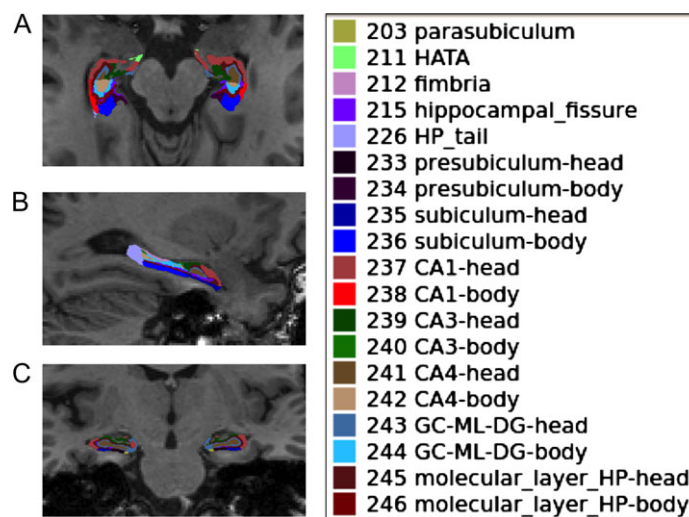


Fig. 1. Hippocampal subfield labels based on the FreeSurfer 6.0 development version segmentation protocol in the (A) axial, (B) sagittal, and (C) coronal planes.

the primary index of memory *encoding* and calculated by summing the total number of correct list words recalled across the three trials. To better isolate the component process of encoding, a secondary index was derived by computing the learning slope (i.e., average number of new correct words learned per trial after the first trial; Woods et al., 2005). The delayed recall was used as an index of memory *retrieval* and consisted of the total number of correct words recalled after the delay interval. For descriptive purposes, T-scores (mean = 50, $SD = 10$) were calculated using normative data by age group provided in the HVLT-R manual. The HVLT-R is a standardized clinical measure that demonstrates good test–retest reliability and good construct validity for its primary measures (Brandt & Benedict, 2001).

English language fluency was assessed using the English Language Acculturation Questionnaire. Participants were asked to self-report the degree to which they preferred to think, speak, read, and write in English. Participants with a score of 24 (out of 60) or lower were retained for analyses, suggesting that, on average, they were at least “much fluent in English”. Following completion of the cognitive assessment, examiners provided a subjective validity rating of each participant’s test performance on a scale from 1 (clearly invalid) to 5 (clearly valid). Data rated as a 4 (most likely valid) or higher were retained for analyses. Possible reasons for low validity ratings included, but were not limited to, participant intoxication, extreme fatigue, low frustration tolerance, or inability to adequately comply with test instructions.

Statistical Analysis

A flow chart is provided in Fig. 2 to show how we derived the final sample retained for analyses. All continuous variables were examined for normality through visual inspection of histograms and normality plots. Comparisons among subgroups (included/excluded on the basis of missing or invalid data, recruitment cohorts) on demographic data were conducted using One-Way ANOVAs and *t*-tests for continuous variables, and Phi and Cramer’s V and chi-square tests for categorical variables. Pearson correlations were used to show the associations between the component processes of memory (immediate recall, learning slope, delayed recall). The strength of these correlations were compared using William’s modified version of Hotelling’s *t*-test, which is appropriate for comparison of non-independent zero-order correlations with a common variable (Weaver & Wuensch, 2013).

Left and right volumes from the head and body of each subfield of interest were summed to reduce the overall number of statistical tests for the main analyses. To control for the effect of head size, all hippocampal and entorhinal cortex volumes

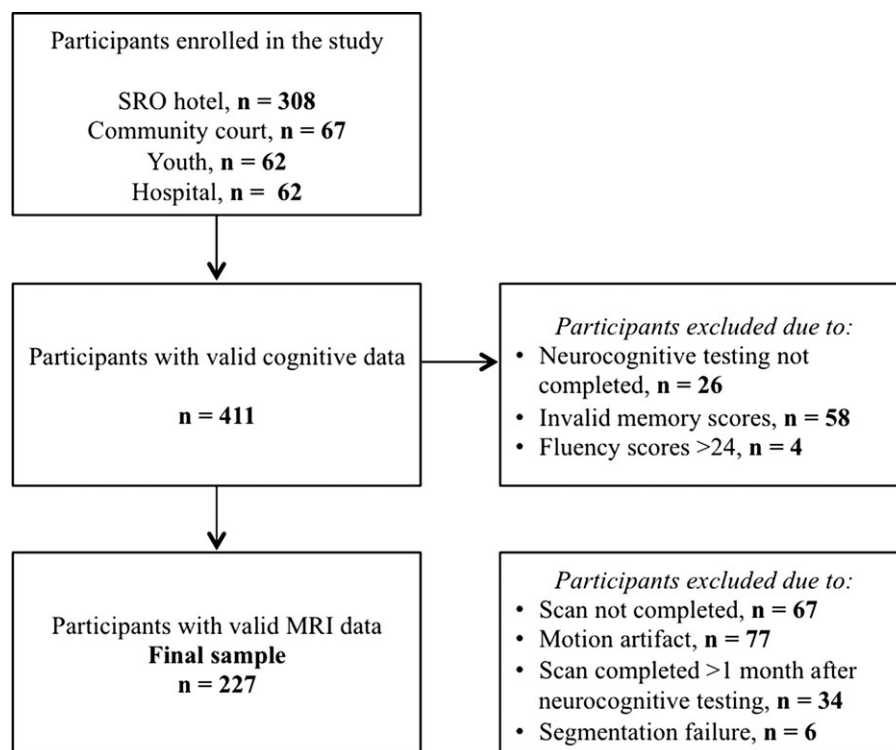


Fig. 2. Flow chart outlining participant inclusion.

were adjusted for intracranial volume (ICV) using the following linear regression equation as outlined by Voevodskaya and colleagues (2014): $\text{Volume}_{\text{adj } i} = \text{Volume}_{\text{raw } i} - \beta(\text{ICV}_{\text{raw } i} - \text{ICV}_{\text{mean}})$, where β represents the slope of the regression line between ICV and the brain region of interest. Prior to the adjustment, ICV was divided by 1000 to place it on a similar scale to hippocampal volumes. To avoid multicollinearity between subfield volumes, separate linear regression analyses were conducted to examine the association between each brain region of interest and memory performances. No violations of assumptions or multivariate outliers were observed. Variance Inflation Factor (VIF) values did not exceed 1.23 and the average VIF for each model was close to 1, confirming that collinearity is not an issue for any of the models. For each regression model, age, education, and sex were selected a priori as covariates and entered along with a single brain region of interest (total hippocampal volume, GC-DG, CA4, CA3, CA1, or subiculum adjusted for ICV). A series of models was run for each outcome variable (immediate recall, learning slope, delayed recall) for a total of 18 regression models (six region of interest predictors \times three outcomes). Interactions between age and brain ROIs were tested using the PROCESS Macro (Hayes, 2013) and only retained in final models if significant at $p < .05$. The Johnson–Neyman approach was used to probe significant interactions, which provides a test of significance at each point along the range of the moderator variable (Hayes & Matthes, 2009).

A secondary set of analyses was run using three separate hierarchical regressions to determine the extent to which entorhinal cortex volumes (adjusted for ICV) were associated with each of the memory outcomes above and beyond total hippocampal volume. Demographic variables were entered in Block 1, followed by total hippocampal volume in Block 2, and entorhinal cortex volume in Block 3. Given that we generated specific a priori hypotheses and the brain regions of interest are highly correlated, we did not apply a correction for multiple comparisons and maintained the conventional alpha level of .05. All statistical analyses were performed with the Statistical Package for the Social Sciences 24.0.

Results

Sample Characteristics

A comparison of basic demographics between those who were included ($n = 227$) versus excluded on the basis of invalid/missing cognitive or MRI data ($n = 246$) revealed no significant differences in age, sex, years of education, ethnicity, or estimated FSIQ ($p > .10$). Between the four recruitment cohorts, only age significantly differed, as it would be expected to, with a significantly lower mean age for the youth cohort compared to the other cohorts ($F = 21.72$, $p < .001$). No differences were found with respect to sex, years of education, ethnicity, or FSIQ ($p > .10$), suggesting these cohorts can be reasonably combined as a representative sample of marginalized people living in the neighborhood for the purpose of the current study.

The combined sample was consistent with the demographics of the neighborhood, characterized by persons who were on average 41 years old, predominately male (79%), and with approximately 10.5 years of education. Participants reported a mean monthly income of \$820 CAD, generally entirely derived from income assistance. Over two-thirds of our sample (68.7%) reported being homeless over their lifetimes. For descriptive purposes, additional sample characteristics are summarized in Table 1. Full details regarding the clinical assessments used to characterize this sample are provided in our prior work (Honer et al., 2017; Vila-Rodriguez et al., 2013).

In addition, this sample is characterized by moderate to severe memory impairment reflected in mean T-scores that fall nearly two SDs below the normative mean, with upwards of 75% of the sample falling in the impaired range (<1 SD below normative mean; Carey et al., 2004) on immediate and delayed recall measures. Summary statistics for brain and memory measures are provided in Table 2.

Regression Analysis

Correlational analyses between memory measures showed that the delayed recall score is significantly more correlated with the total immediate recall score ($r = .79$, $p < .001$) than the learning slope ($r = .38$, $p < .001$) as expected (William's $t = 8.09$, $p < .001$). Further, the learning slope is only moderately correlated with total immediate recall ($r = .31$, $p < .001$), suggesting these indices are likely capturing somewhat different component processes of memory.

In regression models adjusted for age, sex, and education, greater total hippocampal volume was associated with better verbal immediate recall ($\beta = .260$, $t = 4.06$, $p < .001$). In line with our first hypothesis, greater CA3 volume was significantly associated with better verbal immediate recall, but this was moderated by age, whereby the effect was only significant for individuals aged 49 years and older ($\beta = .116$, $t = 2.15$, $p = .033$). Contrary to expectation, CA1 ($\beta = .192$, $t = 3.06$, $p = .002$) and subiculum ($\beta = .135$, $t = 2.13$, $p = .034$) volumes were also positively associated with verbal immediate recall. No significant effects were detected for GC-DG or CA4 volumes in relation to immediate recall. When the regressions were conducted

Table 1. Sample characteristics

Variable	<i>n</i> (%)	Mean (<i>SD</i>)	Median	Range
Age (years)		40.9 (10.6)	42.0	21–68
Sex (male)	179 (78.9)			
Ethnicity				
White	143 (63.0)			
Aboriginal	57 (25.1)			
Asian	3 (1.3)			
Black	5 (2.2)			
Other/mixed	19 (8.4)			
Education (years)		10.6 (2.4)	11.0	4–17
Estimated premorbid FSIQ		98.5 (9.2)	98.0	75–122
Monthly income (CAD) ^a		820.1 (395.2)	770.0	100–3200
Ever homeless	156 (68.7)			
Substance dependence				
Alcohol ^b	38 (16.7)			
Cannabis ^b	77 (33.9)			
Stimulant	196 (86.3)			
Opioid ^b	88 (38.8)			
Psychotic illness ^b				
Any psychotic illness	103 (45.4)			
Schizophrenia spectrum	32 (14.1)			
Other psychosis	42 (18.5)			
Substance-induced psychosis	38 (16.7)			
Viral infection				
HIV seropositive ^c	33 (14.5)			
Hepatitis C antibody positive ^d	121 (53.3)			
Hepatitis B surface antigen positive ^e	3 (1.3)			
Self-reported history of TBI ^f				
Yes	93 (41.7)			
No	105 (46.3)			

Note: *N* = 227. FSIQ = Full scale IQ; CAD = Canadian dollars; TBI = traumatic brain injury.

^a*n* = 225; ^b*n* = 207; ^c*n* = 209; ^d*n* = 205; ^e*n* = 208; ^f*n* = 198.

Table 2. Descriptive statistics for brain and memory measures

Variable	<i>n</i> (%)	Mean (<i>SD</i>)	Median	Range
MRI brain measures ^a				
Intracranial volume × 10 ⁻³		1563.1 (131.1)	1572.3	1121.4–1911.0
Total hippocampal volume (mm ³)		6771.3 (755.7)	6750.5	4306.5–9176.1
CA1		1278.8 (156.6)	1272.4	811.9–1857.8
CA3		413.0 (55.4)	416.1	264.6–559.7
CA4		487.3 (56.6)	489.8	300.9–654.0
GC-DG		562.5 (68.0)	568.7	347.0–754.2
Subiculum		843.8 (97.9)	843.9	556.7–1103.6
Entorhinal cortex volume (mm ³)		4176.6 (671.0)	4120.6	2710.9–6930.8
HVLT-R memory scores				
Immediate recall (raw)		19.9 (5.8)	20.0	4–32
Immediate recall (T-scores)		32.1 (10.8)	30.0	20–59
>1 <i>SD</i> below normative mean	169 (74.4)			
>2 <i>SD</i> below normative mean	103 (45.4)			
Learning slope		1.4 (1.0)	1.5	–1.5–4.0
Delayed recall (raw)		6.4 (2.8)	6.0	0–12
Delayed recall (T-scores)		32.7 (11.5)	30.0	20–61
>1 <i>SD</i> below normative mean	156 (68.7)			
>2 <i>SD</i> below normative mean	107 (47.1)			

Note: *N* = 227. CA = cornu ammonis; DG = dentate gyrus; HVLT-R = Hopkins Verbal Learning Test – Revised. ^aHippocampal and entorhinal cortical volumes reflect unadjusted (raw) data.

Table 3. Multiple regression coefficients

ROI Brain Volume	Immediate Recall		Learning Slope		Delayed Recall	
	β	$t(p)$	β	$t(p)$	β	$t(p)$
Total HPC	.260	4.06 (<.001)	.101	1.45 (.152)	.212	3.16 (.002)
GC-DG	.111	1.66 (.098)	-.048	-0.67 (.501)	.109	1.59 (.114)
CA4	.072	1.07 (.286)	-.077	-1.08 (.283)	.084	1.20 (.233)
CA3	—	—	-.041	-0.59 (.554)	.044	0.64 (.522)
CA3 \times Age	.116	2.15 (.033)	—	—	—	—
CA1	.192	3.06 (.002)	.058	0.85 (.394)	.153	2.33 (.021)
Subiculum	.135	2.13 (.034)	-.050	-0.75 (.456)	.130	1.99 (.048)
Entorhinal Cortex	.163	2.45 (.014)	.172	2.39 (.018)	.218	3.19 (.002)

Note: $N = 227$. Bold text denotes significance at $p < .05$. ROI = region of interest; HPC = hippocampus; GC-DG = granule cell layer of the dentate gyrus; CA = cornu ammonis.

using the learning slope as a secondary outcome to better index encoding, neither total hippocampal volume nor any subfield volume were statistically significant predictors ($p > .10$).

With respect to verbal delayed recall, greater total hippocampal volume was significantly associated with better memory scores ($\beta = .212$, $t = 3.16$, $p = .002$). In support of our second hypothesis, CA1 ($\beta = .153$, $t = 2.33$, $p = .021$) and subiculum ($\beta = .130$, $t = 1.99$, $p = .048$) volumes were positively associated with verbal delayed recall, whereas GC-DG, CA4, and CA3 were not ($p > .10$).

In a secondary set of analyses using hierarchical regression models, we found that entorhinal cortex volume was uniquely associated with component processes of memory after accounting for variability explained by total hippocampal volume. Specifically, larger entorhinal cortex volume was associated with better scores on verbal immediate recall ($\beta = .163$, $t = 2.47$, $p = .014$, $\Delta r^2 = .022$) and verbal delayed recall ($\beta = .218$, $t = 3.19$, $p = .002$, $\Delta r^2 = .039$). Entorhinal cortex volume was also positively associated with learning slope ($\beta = .172$, $t = 2.39$, $p = .018$, $\Delta r^2 = .024$), though it should be noted that total hippocampal volume was not a significant predictor in the preceding block ($p = .152$). A summary of the regression coefficients is provided in Table 3. Partial regression plots depicting all significant associations and the interaction are depicted in Figs. 3–6.

Discussion

This study demonstrates dissociations between volumes of the hippocampal formation and component processes of verbal memory in a large cohort of marginalized people with comorbid physical and psychiatric illness. Upwards of 75% of the sample fell in the impaired range on memory measures, with half of the sample scoring in the moderate to severe range, similar to the rates reported by Stergiopoulos and colleagues (2015). Consistent with our hypotheses, we found that volumes of CA3, one of the primary hippocampal subfields known to be involved in memory encoding, was associated with performance on a standard neuropsychological measure of word learning, but not verbal delayed recall. Further, this effect was moderated by age, whereby an association between CA3 and immediate recall scores was only evident for older individuals (≥ 49 years old). In contrast, CA1 and subiculum volumes, which have been consistently implicated in memory retrieval, were found to be associated with both immediate and delayed recall, but not with word learning following isolation of this component process from the total immediate recall score. Additionally, we found that entorhinal cortex volume was associated with all component processes of memory and uniquely predicted immediate and delayed recall performance above and beyond what was explained by total hippocampal volume. We did not observe any associations between GC-DG and CA4 subfield volumes, and memory outcomes in this study.

The finding that CA3 subfield volume was associated with an index of memory encoding remains consistent with the existing literature. Animal and human studies have shown unique activity patterns in the DG and CA3 regions that support computational models of encoding or what is referred to as *pattern separation* (see for review; Hunsaker & Kesner, 2013; Yassa & Stark, 2011). Pattern separation is defined as the process by which the hippocampus can form a neural representation of sensory or perceptual input that is distinct (orthogonal) from previous or subsequent inputs that may have overlapping features, and has thereby been deemed critical to the formation of new and unique memories (Hunsaker & Kesner, 2013). In fMRI studies, greater activation in the CA3-DG subfield has been observed during encoding trials (Zeineh et al., 2003), and is predictive of better recall (Eldridge et al., 2005) and recognition (Nauer, Whiteman, Dunne, Stern, & Schon, 2015) of verbal and visual stimuli in delayed memory tasks. In structural MRI studies, greater CA3-DG subfield volumes were associated with

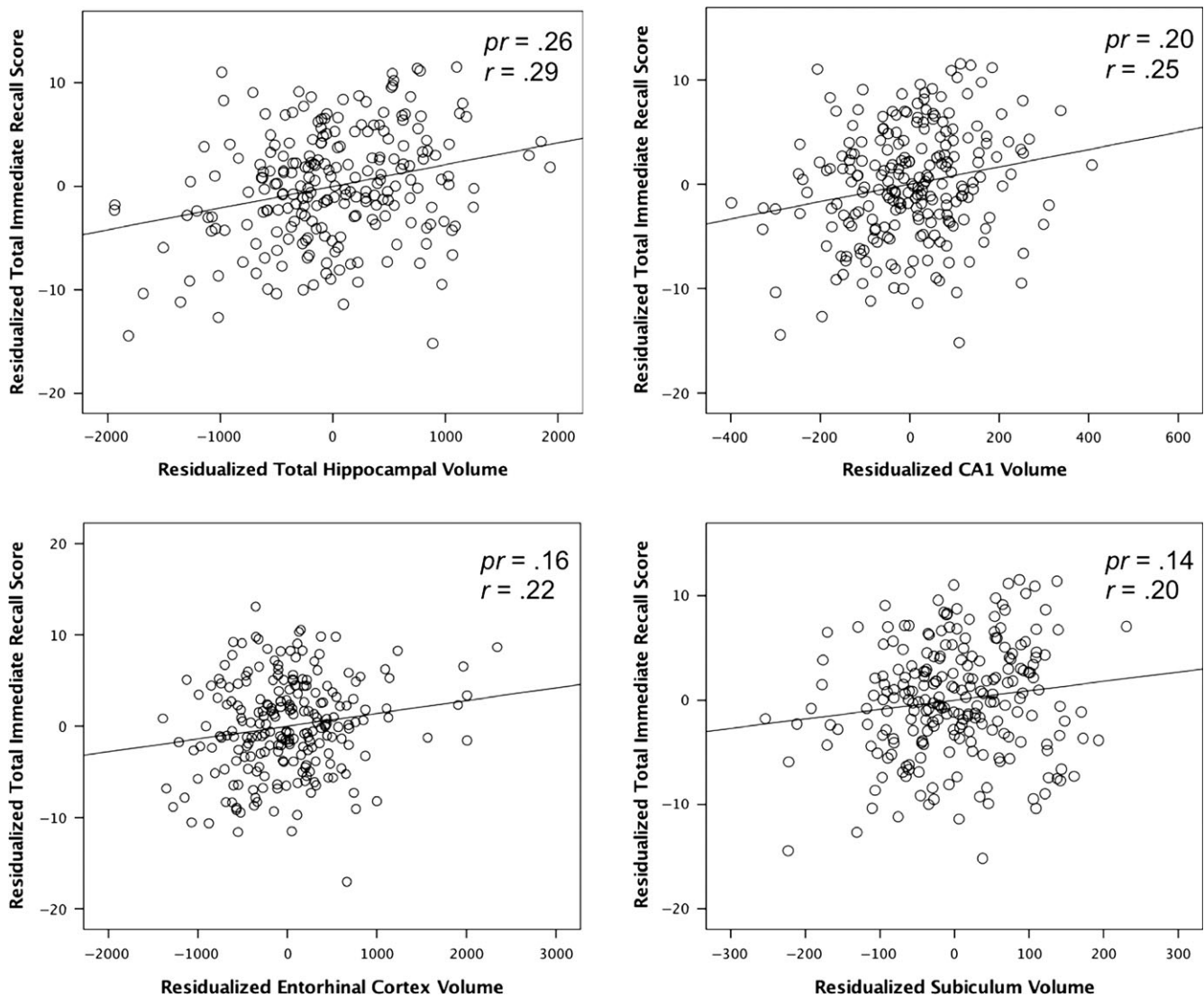


Fig. 3. Partial regression plots for significant associations between hippocampal subfield volumes, and HVLt-R total immediate recall scores, controlling for the effects of age, sex, and education. Partial (pr) and zero-order (r) correlations are noted for each regression slope.

better immediate and short delay free recall scores on a 16-item word list (Mueller et al., 2011) and a composite index of verbal memory (Mueller et al., 2012). Volumes in the left DG and in combined CA1-3 subfields have been found to be positively associated with immediate recall on a measure of story memory (Travis et al., 2014). Although we only observed an effect for CA3 in persons aged 49 years or older, this aligns with the observation that age is a particularly important modifier of structure–function relationships (Raz & Rodrigue, 2006; Van Petten, 2004). We did not find an independent association with the DG (GC-DG or CA4). Differential engagement of these subfields for encoding orthogonal representations appears to be somewhat dependent on the nature of the hippocampal input (Leutgeb, Leutgeb, Moser, & Moser, 2007) and our lack of an effect for DG may ultimately reflect the challenge in linking cellular level processes with macroscopic functional measures or may be a function of the clinical characteristics of our population of focus.

Our results also parallel findings within the literature that the CA1 and subiculum play a role in the component process of memory retrieval. The CA1 primarily provides input to the subiculum, which in turn projects back to the entorhinal cortex, marking these two subfields as the main output structures of the hippocampal formation (O'Mara, Sanchez-Vives, Brotons-Mas, & O'Hare, 2009). These “late in the circuit” structures have shown increased activation in fMRI studies when subjects were required recall word and pictures pairs (Eldridge et al., 2005). The subiculum, but not CA1, has also shown activation when subjects recalled names using a facial cue (Zeineh et al., 2003) and for previously learned visuospatial navigations (Suthana et al., 2011). In structural MRI studies, greater CA1 and subiculum volumes were found to be associated

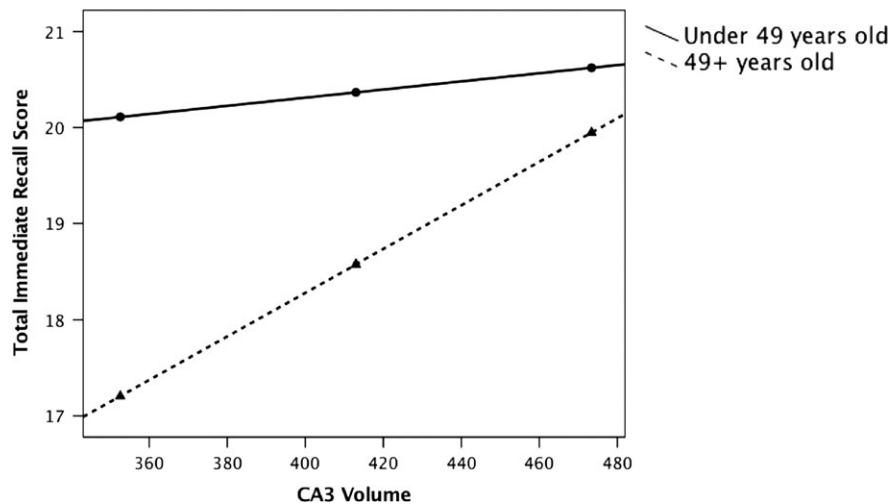


Fig. 4. Visualization of the conditional effect of age on the association between CA3 subfield volume and HVLt-R total immediate recall scores.

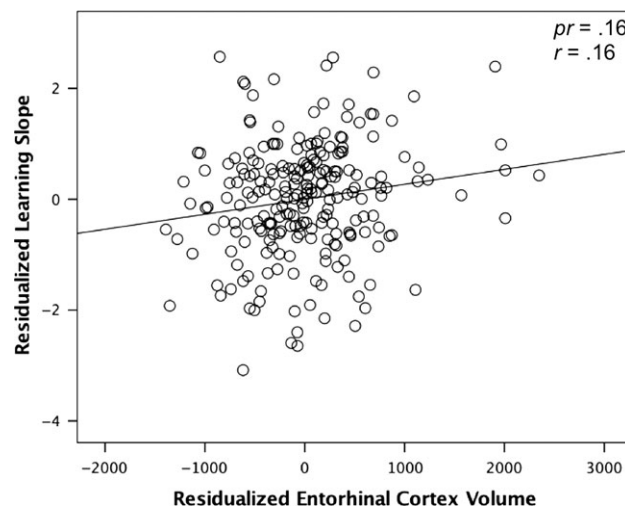


Fig. 5. Partial regression plot for significant association between entorhinal cortex volume and HVLt-R learning slope, controlling for the effects of age, sex, and education. Partial (pr) and zero-order (r) correlations are noted for the regression slope.

with better delayed verbal and visual recall in healthy persons (Zammit et al., 2017). Similarly, greater right CA1 and subiculum shape and volumes were correlated with better verbal recall and recognition, and with constructional recall in medication-naïve Alzheimer's disease patients (Lim et al., 2012). Greater CA1 volume has also been linked with better delayed verbal recall and recognition in older adults (Mueller et al., 2011) and temporal lobe epilepsy patients (Mueller et al., 2012).

We observed associations between CA1 and subiculum volumes and a measure of total immediate recall, which was in contradiction to our initial hypothesis that these subfields would be selectively related to verbal delayed recall. This finding is not unique, however, given that others who have used the total immediate recall score from a word list learning task have found modest correlations with CA1 and subiculum volume (Lim et al., 2012; Mathew et al., 2014). A careful consideration of the total immediate recall score suggests that it is likely to be confounded by other cognitive processes, beyond the construct it is purported to measure (i.e., encoding or acquisition of information). To illustrate, let us consider the serial position effect of word list learning tasks, whereby the words at the beginning (i.e., primacy effect) and end (i.e., recency effect) of a list are more likely to be recalled in healthy persons. In accordance with the dual-store model of memory (Shallice & Warrington, 1970), items presented late in a list are retained in short-term memory, whereas items presented earlier in a list must be first retrieved from long-term memory when a response is required (i.e., immediate recall of as many list words as possible). This theory is supported by an fMRI study where differential activation was observed in the hippocampus for early versus late list words (Talimi, Grady, Goshen-Gottstein, & Moscovitch, 2005). By this account, it is then reasonable to expect

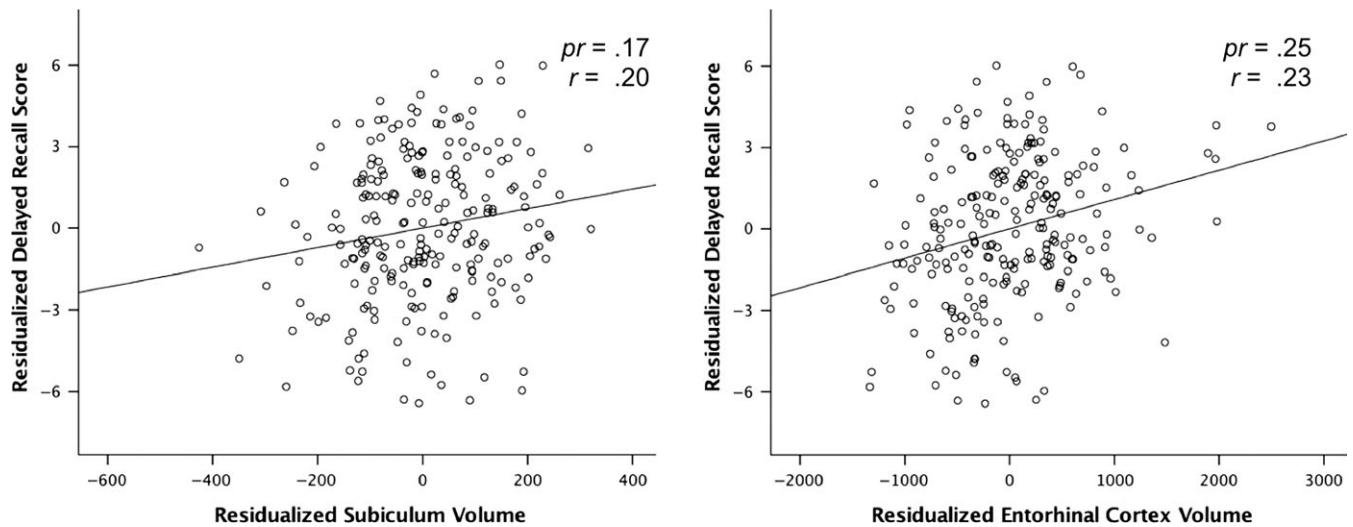


Fig. 6. Partial regression plots for a significant association between hippocampal subfield volumes and the HVLt-R delayed recall scores, controlling for the effects of age, sex and education. Partial (pr) and zero-order (r) correlations are noted for each regression slope.

that CA1 and subiculum subfields would have a role in immediate recall of list words where retrieval of primacy words from long-term memory stores is required for successful recall of these early items. While we were not able to evaluate the serial position effects in this study, we did attempt to distill the total immediate recall score by calculating the average number of “new” words learned on each trial (i.e., the learning slope), making the assumption that “old” words consistently recalled across trials have been already committed to the long-term memory store. By disentangling the component processes of memory, we showed that the CA1 and subiculum were no longer related to putative measures of encoding, whereas the effect for entorhinal cortex volume remained significant, indicating some specificity. Of note, we also did not observe any effects for GC-DG, CA4, or CA3, which are generally considered to support encoding processes. Nonetheless, this observation is important because it highlights the need to carefully examine the constituent components of memory measures and the hippocampal formation in order to better understand the nuances of the memory system.

In line with our secondary hypothesis, we found that larger entorhinal cortex volume was associated with all component processes of memory. This finding suggests that the entorhinal cortex plays a complementary role in memory functioning given that it was associated with immediate and delayed recall performance beyond what was already accounted for by total hippocampal volume. It is conceivable that damage to the entorhinal cortex or structures beyond the traditional memory system could have a downstream effect on the component processes of memory (Casaletto et al., 2017). Indeed, the entorhinal cortex is uniquely situated as the primary structure that interfaces with the hippocampus, serving as the first point of input to the subfields and receiving all subfield output. Intrahippocampal information flows through indirect and direct pathways that both involve the entorhinal cortex and these circuits demonstrate functionally distinct roles in the component processes of memory (Roy et al., 2017). Our finding that entorhinal cortex volume was related to all aspects of memory functioning, independent of hippocampal volume, suggests that deficient memory encoding and retrieval in this sample may reflect concurrent degradation of primary memory structures (i.e., hippocampal subfields) and of the structural interface to the hippocampus.

While our pattern of findings tends to align with the broader theoretical literature on the functional specialization of the hippocampal subfields, it is important to appreciate that our pattern of findings may also reflect the specific features of a homeless and marginally housed population. Extreme multimorbidity is a prominent and shared feature of marginalized populations in high-income countries (Luchenski et al., 2018), and its clinical contribution should be acknowledged. Hippocampal subfields exhibit regional vulnerability to illness, with DG and CA3 regions preferentially impacted by stress and depression (Adam Samuels, Leonardo, & Hen, 2015) and addiction (Chambers, 2013; Chye et al., 2017), and the CA1 region being particularly sensitive to hypoxic events and related vascular risks (Bartsch, Döhring, Rohr, Jansen, & Deuschl, 2011; Raz, Daugherty, Bender, Dahle, & Land, 2015; Wu et al., 2008), the early stages of Alzheimer’s disease (de Flores, La Joie, & Chételat, 2015; Khan et al., 2015), and chronic schizophrenia (Ho et al., 2017; Small et al., 2011). Stimulant use, psychotic illness, and traumatic brain injury are among the most prominent clinical characteristics in our sample. Not only could these morbidities directly degrade structural integrity of the hippocampus, there may be additional indirect effects on memory functioning due to disruption of distributed cognitive systems. Because associations with memory may be more readily observable when regional brain volumes fall below a critical threshold (Van Petten, 2004), the comorbidities are likely important

modifiers. The subfield-specific effects of these putative risk factors, and the cumulative or synergistic effects, warrant careful follow-up investigation in this sample.

Indeed, studies have shown that the structural correlates of memory can vary in the context of specific pathologies (Casaletto et al., 2017; Hanseeuw et al., 2011; Mueller et al., 2012) and across the normal lifespan (Van Petten, 2004). This further emphasizes that our observed findings may be somewhat unique to our clinically heterogeneous sample, but also reinforces an urgent need to examine memory systems in marginalized populations in order to determine how we can best intervene clinically to support these vulnerable individuals. Still, our findings showed the largest associations were in relation to CA1, subiculum, and entorhinal cortex volumes which are also regions that have shown pronounced volume loss in age-related pathologies (Mueller et al., 2010). Selective changes in CA1 neurons as a marker of early or pre-clinical pathological aging remains one of the most robust findings in the subfield literature (de Flores et al., 2015). Memory is the most impaired cognitive domain in homeless and marginally housed populations (Gicas et al., 2014, 2017; Stergiopoulos et al., 2015), and therefore follow-up studies are needed to better understand neurobiological risks for possible future dementia in marginalized persons with multimorbid illness.

As with all studies, limitations must be duly noted. First, the results of this study must be interpreted with caution given certain limitations of the technological procedures. We used an automatic segmentation procedure from FreeSurfer v6.0 to derive hippocampal subfield volumes. This algorithm was developed on high-resolution T2-weighted data, which is often preferred, because it allows visualization of the molecular layer required for reliably differentiating the CA and DG regions (Wisse et al., 2017). Given that application of this segmentation protocol to 1 mm³ isotropic T1-weighted data demonstrated 88% accuracy in discriminating between Alzheimer's subjects and elderly controls, and significantly outperformed the prior protocol implemented in FreeSurfer v5.3, subfield measures derived from T1 data can still be highly informative and offer discriminative power (Iglesias et al., 2015). The MRI data used in the current study (i.e., T1-weighted data) was collected as part of the larger Hotel Study to evaluate general neuroanatomic characteristics, and was not specifically optimized for assessment of hippocampal subfields. With this caveat in mind, our approach still serves as a useful tool for exploring differential structure–function associations in this large cohort. Due to substantial heterogeneity among existing segmentation procedures (Yushkevich et al., 2015), a harmonized manual segmentation protocol is currently being developed (Wisse et al., 2017) and will serve as an important benchmark from which to compare automated protocols in the future. Despite procedural variability within the field, our pattern of results is largely consistent with findings from the broader literature.

A second limitation is that we only used a single memory test, the HVLT-R, to explore relationships with hippocampal volumes, yet memory is a complex and multifaceted construct. Measures of visuospatial memory would be useful to determine if there are additional and/or material-specific effects. Further, we have already alluded to the difficulty of isolating component processes of memory as some measures may engage a mix of encoding and retrieval processes. We would like to caution researchers that, although we adopt specific language regarding “encoding” and “retrieval” consistent with the nomenclature of the current literature, clinical neuropsychological tests of memory may not directly translate to the underlying neural and computational processes that we aim to capture. Nonetheless, we established differential associations with hippocampal subfields using a standardized measure of memory, which has clinical utility over experimental paradigms. Third, our focus was limited to the traditional memory system (i.e., hippocampal formation) and so we did not examine the contribution of the broader brain structure. Indeed, the frontal cortex, white matter connectivity, and the corresponding influence of related cognitive processes, such as processing speed, attention, and executive functioning, all may help to better explain memory functioning in this clinically heterogeneous sample. On a final note, our population of focus is unique in many respects with a high degree of multimorbidity, which could potentially limit the generalizability of our findings. The clinical characteristics of our sample appear generally consistent with those from other reported studies of marginalized persons (Krausz et al., 2013; Robertson et al., 2004; Stergiopoulos et al., 2015), suggesting our findings likely hold relevance for the broader population of homeless and marginally housed persons.

Taken together, we demonstrated differential associations between hippocampal subfields and entorhinal cortex volumes, and component processes of verbal memory in a large cohort of marginalized persons with substantial memory impairment. The current study provides an important contribution to understanding the neuropsychological status of marginally housed and homeless persons who experience significant poverty and health inequities. Despite the large range of morbidities in this sample that could differentially impact memory, there appear to be common underlying neuroanatomical markers of memory dysfunction, and this has important implications for clinical intervention. From a rehabilitative perspective, having a quick, reliable, and cost-effective clinical tool for assessing hippocampal integrity could be useful to determine who will benefit most from interventions. Engvig and colleagues (2012) found that, in middle-aged to older adults with subjective memory complaints, larger baseline volumes in the left CA3 and CA4-DG subfields were associated with greater improvement in verbal memory following 8 weeks of memory training. On the other hand, hippocampal subfield volumes can serve as useful

early markers of pathological aging (de Flores et al., 2015) or progression of psychiatric illness (Cao et al., 2017; Ho et al., 2017), which could aid in identifying persons at risk for cognitive decline and in need of greater health care resources.

Given the clinical complexity of marginalized populations, a comprehensive examination of risk factors for change in hippocampal subfield volume and cognitive functioning is warranted, but longitudinal analysis is required to understand potential causal relationships, and thus stands as a critical next step. This research offers a foundation on which to build such longitudinal analyses of structure–function relationships and contributes to the growing body of literature on the functional specialization of hippocampal subfields.

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Conflict of interest

Dr. Procyshyn has received speaking and Advisory Board fees from AstraZeneca, Bristol-Myers Squibb, Janssen, Otsuka, Pfizer and Sunovion. Dr. MacEwan has received consulting fees or sat on paid advisory boards for Apotex, AstraZeneca, BMS, Janssen, Lundbeck, Otsuka, Pfizer and Sunovion. He also received fees for lectures sponsored by AstraZeneca, BMS, Janssen, Otsuka and Eli Lilly, and has received grants from Janssen Pharmaceuticals. Dr. Honer has received consulting fees or sat on Advisory Boards for In Silico, Eli Lilly, Roche, Lundbeck and Otsuka and has received honoraria from Rush University, University of Calgary, University of Hong Kong, British Columbia Health Authorities, the British Association for Psychopharmacology, Massachusetts General Hospital and the Canadian Psychiatric Association. Drs. Gicas, Thornton, Panenka, Lang, Smith, Vila-Rodriguez, Leonova, Barr, Vertinsky, Rauscher, and Mr(s). Wacławik, Wang, Jones, Buchanan, and Su report no competing interests.

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