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1 **Title:** Hippocampal volume and integrity as predictors of cognitive decline in intact elderly

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3 **Running Head:** Hippocampal Integrity and volume

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Abstract

Risk of Alzheimer's disease (AD) can be predicted by volumetric analyses of MRI data in the medial temporal lobe. The present study compared a volumetric measurement of the hippocampus to a novel measure of hippocampal integrity derived from the ratio of parenchyma volume over total volume.

Participants were cognitively intact and aged 60 or older at baseline, and were tested twice, roughly three years apart. Participants had been recruited for a study on late-life major depression (LLMD) and were evenly split between depressed and controls.

Linear regression models were applied to the data with a cognitive composite score as outcome, and hippocampal integrity (HI) and volume (HV), together or separately, as predictors. Subsequent cognitive performance was predicted well by models that include an interaction between HI and LLMD-status, such that lower HI scores predicted more cognitive decline in depressed subjects.

More research is needed, but tentative results from this study appear to suggest that the newly introduced measure HI is an effective tool for the purpose of predicting future changes in general cognitive ability, and especially so in individuals with LLMD.

Keywords: Alzheimer's disease; Hippocampus; MRI; Integrity; Depression.

54 **Introduction**

55 Volumetric analyses of MRI data have been shown to predict conversion to
56 Alzheimer's disease (AD) from a cognitively intact baseline. Tondelli et al. [1], for example,
57 used MRI data to predict conversion to AD at least four years prior to any symptoms being
58 detected. Their findings showed that AD converters presented greater atrophy in the right
59 medial temporal lobe, an area prominently including the hippocampus (HC), compared to
60 non-converters. More recently, others [2] have demonstrated that lower volumes of the HC in
61 the right hemisphere predicted time of onset of clinical symptoms of neurodegeneration from
62 a cognitively intact baseline over an average of 10 years.

63 A few issues should be noted, however, with regards to hippocampal volumetric
64 measurements (HV). Manual HV measurements are tedious and time-consuming activities,
65 suffer from intra- and inter-observer variability, require extensive operator training, and have
66 low comparability across laboratories due to differing tracing protocols [3]. Although
67 recently, a harmonized HR protocol has been developed and evaluated that may overcome
68 some of the inconsistencies in previous manual volumetric approaches, this protocol still
69 requires intensive training of raters and is time consuming to apply [4]. Automated
70 algorithms for HV measurements, however, tend to be generally less robust as compared to
71 manual measurements [5], can be computationally expensive, sometimes requiring several
72 hours of computer time, are not widely available, and often require extensive preprocessing
73 of the MRI scans (e.g., inhomogeneity correction, tissue segmentation, distortion correction)
74 and associated technical operator expertise. In addition, both manual and automated HV
75 measurements ought to be corrected for intra-cranial volume (ICV) with which they are
76 significantly correlated. However, accurate measurement of the ICV is itself a non-trivial
77 problem.

78 As an alternative, Ardekani et al. [6] have proposed a measure of hippocampal
79 volumetric integrity (HI) based on the notion that cerebrospinal fluid (CSF) replaces brain
80 parenchyma in the process of neurodegeneration. Therefore, in given standardized regions-of-
81 interest (ROIs), the ratio of parenchyma volume over total volume (parenchyma plus CSF)
82 would decrease as a result of neuronal loss. Compared to HV measures, as described above,
83 the proposed HI measurement would provide an indirect estimation of HC atrophy rapidly
84 (i.e., in less than a minute), while not requiring any preprocessing. HI can also be applied to
85 scans immediately after acquisition, does not require adjustment for ICV, and relies on very
86 little, if any, user image processing expertise.

87 In this study, we set out to compare the newly developed HI to a standard method for
88 automatic HV measurement in their respective potential for prediction of cognitive
89 performance. If it can be shown that HI is comparable to at least one type of HV in predicting
90 cognitive change over time, then this finding could have significant impact in the field,
91 providing a useful and practical tool potentially for both research and clinical practice.

92 Our study population was cognitively intact at baseline and was followed over a period
93 of three to four years on average. Importantly, this sample was recruited for a study on late-
94 life major depression (LLMD) and half of all participants had a depression diagnosis at
95 baseline. Major depression has been shown repeatedly to associate with AD risk [7], although
96 the exact nature of this relationship and resulting risk have not been completely elucidated.
97 Some evidence suggests that amyloid beta disturbances may be present in both conditions
98 [e.g., 8].

99 We measured cognitive ability by constructing a composite score that included: the
100 Mini-mental State Exam (MMSE) score, which provides a general cognition index; the Digit
101 Symbol Substitution Test (DSST), a measure of executive function/attention; and the delayed

102 recall test of the AVLT, a memory task. The composite score was obtained by standardizing
103 the individual test scores over the population and then adding these values together.

104

105 **Methods**

106 *Subjects.* Participants were recruited at the Nathan Kline Institute (NKI) and New York
107 University (NYU) Langone Medical Center for a study on late-life depression; the total
108 number of subjects was originally 131, from which 12 individuals were excluded who either
109 had an MMSE score ≤ 27 , or showed stroke, extensive white matter (WM) disease or severe
110 ventriculomegaly on the MRI. Of the remaining 119 subjects, 94 returned for at least two
111 follow up sessions, and for 90 of these participants both HV and HI could be determined
112 successfully, thus forming our study sample. The group was evenly split between participants
113 with a diagnosis of LLMD and those without. All participants provided informed consent
114 prior to taking part in the study. The NKI and NYU institutional review boards authorized
115 this study on ethical grounds. Table 1 reports the demographic characteristics of the sample,
116 and differences across groups were assessed with t-tests.

117

Table 1 here

118 *HV.* MRI data processing followed a standard SPM-based procedure for atlas-based
119 volumetry of the hippocampus based on high-dimensional image registration to MNI
120 standard space and a manually traced hippocampal ROI following standardized delineation
121 criteria [9]. ICV was calculated within this framework by summing up the total volumes of
122 gray matter, white matter, and cerebrospinal fluid partitions from the automated tissue
123 segmentation output. Details of this procedure have been described previously [10].

124 *HI.* The hippocampal volumetric integrity measure was computed using the following
125 procedure: 1) The mid-sagittal plane (MSP) was detected automatically on the MRI volume
126 using the method described in [11]; 2) The anterior and posterior commissures (AC-PC) were

127 automatically located on the MSP using the method described in [12]; 3) Using the
128 information from steps (1) and (2), the MRI volume was reoriented into a standard
129 orientation where the x-axis points to the posterior direction and is parallel to the AC-PC line,
130 the y-axis points to the inferior direction and the z-axis points to the left; the xy-plane is the
131 MSP and the origin of the coordinates system is the halfway point between the AC and PC on
132 the MSP. We call this the Posterior-Inferior-Left (PIL) orientation; 4) Approximately 100
133 landmarks were detected automatically around the hippocampus using a previously trained
134 supervised landmark detection method; after that, an affine transformation was estimated to
135 map these landmarks as closely and possible to a set of standard locations that had been
136 previously determined based on a training set of scans, as were the patterns used for landmark
137 detection; 5) The rigid-body transformation of step (3) and the affine transformation of step
138 (4) were multiplied and the result inverted to obtain a single linear transformation; this
139 transformation maps information from a standard space to the space of the original MRI scan;
140 6) The linear transformation in step (5) was applied to a set of 65 manually delineated
141 hippocampal atlases that had previously undergone the combinations of the transformations
142 in steps (3) and (4) to obtain a probabilistic HC ROI on the original MRI scan; Finally, 7) An
143 automatic threshold selection procedure was applied to segment the voxels in this ROI as
144 brain parenchyma and CSF. HI was defined as the ratio of the parenchymal voxels to the
145 total number of voxels in the ROI. Steps (4)-(7) were repeated for the left and right
146 hippocampi independently to obtain HI for both sides. More details about this methodology
147 can be found in [6]. The software for HI estimation (kaiba) is freely available online at:
148 www.nitrc.org/projects/art.
149 *Procedure.* Participants were tested at the Nathan Kline Institute and at the New York
150 University Medical School, over three visits on successive weeks. On the first visit,
151 participants provided informed consent, were administered a general medical intake

152 questionnaire, and had their vital signs examined; during this session, the MMSE test was
153 also administered. Participants received an MRI scan of the head on the second visit. Finally,
154 on the third visit, participants underwent a comprehensive neuropsychological assessment,
155 including administration of the DSST.

156 *Design and Analysis.* Regression modeling was used to investigate the association between
157 the composite score at 3-year follow-up and measures of hippocampal volume (HV), and
158 hippocampal integrity (HI) in both the right and left hemispheres. The outcome variable for
159 each model considered was the composite score at 3-year follow-up. We were primarily
160 interested in assessing the predictive ability of HV and HI separately or combined. We also
161 investigated whether the LLMD status at baseline moderated the effect of either of the HV or
162 HI measures. We used robust linear regression, implemented in R [13], since some of the
163 follow-up composite scores were much smaller (negative values of large magnitude) than the
164 majority of the scores. Observations corresponding to these large-magnitude scores showed
165 evidence of strong influence on the estimates derived from ordinary least-squares regression.
166 Specifically, we used M-estimation with Huber weighting [14] (tuning constant $k = 4.685\hat{\sigma}$
167 where $\hat{\sigma}$ is the estimate of the median absolute residual divided by 0.6745; this provides
168 coefficient estimates that are about 95% as efficient as those produced by ordinary least
169 squares, when the errors are normally distributed) to obtain regression estimates and test
170 statistics for the models that we fit. Huber weighting gives more weight to observations with
171 smaller residuals while giving smaller weight to observations with larger residuals, thus
172 reducing the influence of those observations with larger residuals on the regression estimates.
173 Besides having HV, HI, or both measures as predictors in a given model, we also adjusted for
174 the following covariates: baseline composite score, sex, LLMD status, e4 status, and TIV.
175 The HV and HI measures were centered and scaled before entering the model so that
176 coefficient estimates are comparable. For each robust linear regression model, we computed

177 the pseudo weighted least-squares coefficient of determination, pseudo R^2_{WLS} [15]. P -values
178 for the regression coefficients are based on standard normal approximations for the
179 distributions of the corresponding test statistics

180

181 **Results**

182 First, it was investigated whether LLMD status modified the association between the
183 composite score at 3-year follow-up and either of the HV or HI measures on either the right
184 or left side. We found that LLMD status did modify the association between HI and the
185 composite score on both the right and left side, but not the association between HV and the
186 composite score on either side. Table 2 shows the standardized adjusted effect estimates and
187 pseudo R^2_{WLS} values for each of the three relevant models fit using the right or left HV and HI
188 measures as predictors. For comparison, we have also included the R^2 values from the
189 corresponding ordinary least-squares fits.

190 *Models with right side measures:* The model with both HV and HI measures (and interaction
191 HI*LLMD) included as predictors (Model 1R) suggests that there is a positive association
192 between each of these measures and Composite score at 3-year follow-up, however only HI
193 shows a significant association among depressed subjects with an adjusted effect estimate of
194 0.88 ($p = 0.003$) (i.e., among depressed subjects and adjusting for the other covariates,
195 including HV, a one standard deviation increase in HI on the right side corresponds to a 0.88
196 point increase in Composite score at 3-year follow-up on average). The main effects model
197 with only HV (Model 2R) suggests that, without adjusting for HI, there is an estimated
198 positive association between HV and Composite score at 3-year follow-up with an adjusted
199 effect estimate but the effect is not significantly significant [0.35 (0.07)]. The model with
200 only HI and HI*LLMD (Model 3R) suggests that, without adjusting for HV, there is a
201 significant positive association between HI and Composite score at 3-year follow-up among

202 depressed subjects with an adjusted effect estimate of 0.99 ($p = 0.0003$). The fact that the
203 adjusted coefficient for HI among depressed subjects is larger than that for HV in both
204 Models 1R and 3R and the pseudo R_{WLS}^2 for model 3R is larger than that for Model 2R
205 suggests that HI may be a better predictor of Composite score at 3-year follow-up than HV
206 among depressed subjects.

207 *Models with left side measures:* Models with left side measures show similar relationships
208 between Composite score at 3-year follow-up and the HV and HI measures although the
209 predictive ability of these measures is not as strong as those measures from the right side as
210 evidenced by the lower pseudo R_{WLS}^2 values shown in the Table 2.

211 *Non-composite analyses:* When examining the individual components of the composite score,
212 i.e., MMSE, DSST and AVLT delayed recall, we did not detect any modifying effects of
213 LLMD status on the association between the outcome scores and either HI or HV. Therefore,
214 for these analyses, we only employed three models (HV + HI, HV or HI) controlling for
215 baseline scores, sex, LLMD status, e4 status and TIV. For the right hippocampus, we found
216 both HI ($p < .001$) and HV ($p = .034$) to predict follow up MMSE performance, although
217 neither measure predicted follow up DSST or delayed recall scores. For the left hippocampus,
218 only HI was significantly associated ($p = .025$) with MMSE, and again neither measure
219 predicted subsequent performance in DSST or delayed recall.

220 Tables 2 here

221

222 **Discussion**

223 The current study set out to compare the relative predictive values of two automated
224 measures of hippocampal atrophy on MRI. HV provides a direct measure of the total
225 hippocampal gray matter volume, whereas HI provides a novel measure of volumetric
226 integrity, defined as the ratio of parenchymal voxels to the total number of voxels in a

227 linearly registered hippocampal probabilistic ROI. Our findings showed that, when predicting
228 cognitive ability using a composite cognitive score, both the right and left HI measures stood
229 out as significant predictors of decline in individuals with LLMD, although the right
230 hippocampus provided relative better prediction than the left hippocampus. An advantage for
231 the right over the left side is consistent with existing literature [1-2, 16], and may reflect the
232 fact that, for verbal memory tasks, where the left hippocampus is likely to be affected before
233 the right hippocampus, the right hippocampus may provide support in the form of a
234 secondary network. Therefore, once this secondary network is significantly atrophied, it may
235 be an indication that most available reserve has been depleted and that global decline is
236 forthcoming.

237 A key finding in this study is that LLMD status interacted with HI to yield significant
238 predictive value. LLMD is a well-established risk factor for AD [7] and may be a prodromal
239 stage of the disease [17]. In relation to this, depression has been associated with both
240 reductions in hippocampal neurogenesis [18] and HPA axis dysfunction, including increased
241 cortisol levels [19].

242 Although more research is needed, initial results from this study appear to suggest that
243 HI is comparable, if not superior, to HV for the purpose of predicting cognitive decline over a
244 short period of time. An obvious limitation to note is that we only followed our participants
245 for a relatively short period of time, and all were cognitively intact at baseline; therefore, no
246 substantial change in generalized cognitive ability, or conversion to dementia, was detected in
247 this cohort. To mitigate this, however, it should be noted that detecting subtle drops in
248 performance in high-functioning individuals is more difficult than in relatively more impaired
249 participants, thus testifying to the sensitivity of HI [20].

250

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