Sleep, Intelligence, and the Hippocampus

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1 Introduction

The hippocampus is a critical brain structure with diverse cognitive functions, including contextual modulation of fear, emotion processing, intelligence, and memory [1]. In particular, the hippocampus is responsible for acquisition and storage of declarative memory, which includes episodic memories of specific personal experiences and semantic memories of general knowledge about the world [2], [3]. Memory consolidation in the hippocampus is strengthened by replaying that day's neural firing patterns during sleep [4]. Sleep disruption is associated with reduced memory formation, and sleep deprivation has been linked to reduced hippocampal-dependent memory and hippocampal neurogenesis (the formation of new neurons in the adult brain) [5]. Critically, the relationship between long-term sleep loss and the cognitive dysfunction associated with diverse neurological and psychiatric disorders is hypothesized to be mediated by reduced hippocampal integrity and volume [5]. In particular, in older adults smaller hippocampal volume (HV) has been correlated with both poor memory functioning/cognitive decline and decreased sleep efficiency [6]. Smaller HV has also been linked to lower fluid intelligence (the ability to reason, solve abstract problems, and encode new episodic memories) [7] and to discrepancies between fluid and crystallized (the accumulated knowledge of facts and learned procedures) intelligence [8].

While the connections between sleep deprivation and HV and HV and cognition have been documented, few studies have analyzed both of these relationships. Furthermore, current literature examining both factors typically use elderly populations [6], [9] at high risk for cognitive impairment. Additionally, neuroimaging sleep studies often focus on specific clinical populations like individuals with sleep-disordered breathing [10] or patients with primary insomnia [11] and compare these specific groups to healthy control subjects rather than conducting a dimensional analysis of participants who exhibit a range of sleep behaviors. This project aims to use machine learning methods to examine the relationships between sleep deprivation, HV, and intelligence in a sample of 1,096 young adults included in the Human Connectome Project [12]. Specifically, separate linear ridge regression models were used to predict bilateral HV using (1) global sleep quality score, (2) seven sleep quality subcomponents (outlined in Dataset and Features below), and (3) fluid and crystallized cognition.

2 Related Work

The majority of current research related to hippocampal volume, sleep, and intelligence implements multiple linear regression analyses controlling for sex/gender, age, and intracranial volume (ICV; the volume within the cranium, including the brain, meninges, and cerebrospinal fluid), and sometimes include other potential confounding variables when relevant like socioeconomic status, medication use, or psychiatric diagnosis [6], [13]–[15]. Some smaller pilot studies with 16 subjects [11] have only been able to run correlational analysis, and even larger studies that do use regression methods have typically done multiple regressions that at most complicated use hierarchical [13] or blocked [6] regression methods on the entire sample. This analysis represents a novel expansion to the literature, enabled by our relatively large (for neuroimaging) sample size of 1,096 subjects, by using ridge regression analytic techniques and splitting our data into training and test datasets, which is not done in many neuroimaging studies.

3 Dataset and Features

Data used for this analysis come from the Human Connectome Project (HCP), which aims to characterize variability in brain functioning [13]. Complete de-identified cognitive and neuroimaging data were available from 1,096 healthy young adult participants. The HCP has provided left and right HVs for

each subject that were extracted using FreeSurfer subcortical volume segmentation from structural MRI data that were preprocessed through the standard HCP neuroimaging pipeline [17]. Bilateral HV was computed as the sums of left and right HV.

Four different ridge regression models were created to predict HV, controlling for age, gender, and ICV, as is typical in similar neuroimaging analyses [7], [10], [15].

The first model A aimed to predict bilateral HV when given the total global Pittsburgh Sleep Quality Index (PSQI) score - an aggregate score of 19 self-rated questions falling within seven different components detailing each person's sleep quality and disturbances [18]. Scores range from 0-21, with higher scores representing poorer sleep.

Model B was designed to predict left and right HV when taking each of the seven components of the PSQI as features themselves. Each component had scores ranging from 0 to 3, with higher scores indicating poorer sleep quality [18]. The components are listed below.

Component	Score
1	Subjective sleep quality
2	Sleep latency
3	Sleep duration
4	Habitual sleep efficiency
5	Sleep disturbance
6	Use of medication
7	Daytime dysfunction

Model C aimed to predict bilateral HV using a different metric: fluid and crystallized cognition. The NIH Toolbox Cognitive Function Battery [19] was used to calculate both cognition scores. The fluid composite cognition score is calculated using each of the Toolbox tests that are fluid ability measures (the Flanker Inhibitory Control and Attention, Dimensional Change Card Sort, Picture Sequence Memory, Sorting Working Memory, and Pattern Comparison Processing Speed tests). The crystallized composite cognition score was calculated using the associated Toolbox tests (the Picture Vocabulary Test and the Oral Reading Recognition Test [19].

Lastly, based on results from Model B and C, Model D used a combination of the seven PSQI components and fluid and crystallized cognition score to predict bilateral HV, allowing for a more direct comparison of the relative influence of each feature.

4 Methods

As overall cranium volume can strongly influence HV, we normalized bilateral HV with respect to ICV as is standard in the literature [20] using a simple linear regression in scikit-learn [21].

Then, for each model, we isolated the predictor features and outcome by using Pandas DataFrames. A min-max scaler [21] was then used to normalize the data to be between 0 and 1. Next, we used scikit-learn's train_test_split method [21] to separate each model's data into a randomized train and test group, with 25 and 75 percent of data respectively.

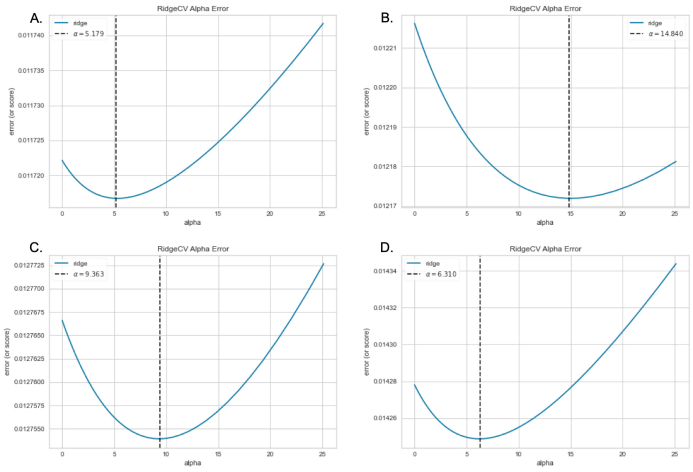

Figure 1: Optimal Alphas Identified Using RidgeCV for Models A - D (model specifics described in Dataset and Features)

With the data now prepared, we were able to run a Linear Ridge Regression on each dataset, using Leave-One-Out cross validation for increased accuracy (the number of folds was the number of samples). Ridge regression was selected due to the high likelihood that different sleep scores or cognitive scores exhibit multicollinearity within each category, and this addition of bias aims to reduce standard errors.

This ridge regression step aimed to minimize the following objective function: $||y - Xw||_2^2 + \alpha||w||_2^2$. We used the Yellowbrick API AlphaSelection for RidgeCV with the training data to determine the optimal alpha for each model, as seen in Figure 1 below. The figure, created by the API, determines cross-validated error for many values for alpha and plots the mean square error

for each alpha. For each model, the minimum of the plot, which is the alpha with the least error, was chosen.

Taking these optimal alphas for each model, ridge regressions were run to determine the coefficients for each of the 4 models. Subsequently, the residual plots for each model were created using Yellowbrick with the experimental data in order to verify the accuracies of each of these models, which are represented in Figure 2.

5 Results

Model D was created as a combination between models B and C. The reason why the component scores were used as a feature, rather than the overall score, is due to the increased accuracy of the component model, as it can be seen from comparing the two RMSE scores. As model B has a lower RMSE than model A (with both models using different approaches for defining sleep deprivation), its features are preferred for model D over the global PSQI.

Model C claims the most accuracy with a RMSE of 0.104. This suggests that fluid and crystallized cognition, which were the two defining features of the model, have the most effect on HV, gender and age excluded. However, all of the RMSEs were within 0.013 of each other, and despite the normalized range for HVs residing solely between 0 and 1, the percentage difference is small enough to consider the possibility of small fluctuations within the dataset itself favoring one model over another.

Overall, each model provides a mostly accurate prediction given their low RMSEs, which is expected, knowing that HV is related to both poor sleep efficiency [6] and fluid intelligence [7]. We can see this graphically in Figure 2, as the residuals are flat and close to zero. This goes to show that there likely are not variables that are independent from the 7 sleep scores and fluid and crystallized cognition values, and if there are, the impact of each one on HV is minimal.

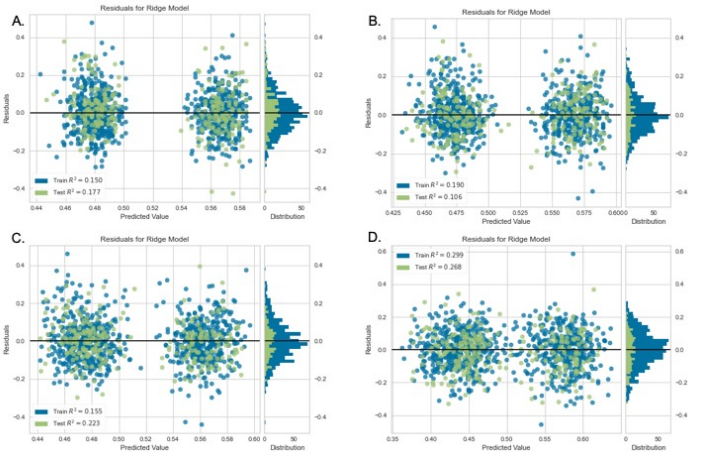

Figure 2: Residuals for Models A-D

Together, the residual and beta coefficients provide novel insight into the relationships between sleep, cognition, and, HV. The most interesting result is the change in the relative relationship between forms of cognition and HV between models C and D with the introduction of PSQI components. In model C, fluid cognition - the ability to flexibly engage attention and working memory - had a slightly larger (coef=0.034) influence on HV than crystallized cognition - informationational and verbal knowledge (coef=0.029), although this small difference is likely negligible. However, in model D with the seven PSQI components included, crystallized cognition (coef=0.117) had a substantially larger influence than fluid cognition (coef=0.020). Furthermore, scores on the PSQI components related to subjective sleep quality (PSQI-1, coef=0.022) and daytime dysfunction (PSQI-7, coef=0.021) - arguably two of the most important components in terms of determining real life impacts of sleep loss - were approximately equally related to HV as fluid cognition. Prior work has proposed that sleep disturbance likely impacts fluid cognition more than crystallized cognition [22]. Ergo, the relatively large influence of crystallized cognition in model D may reflect that some of the variability in HV related to fluid cognition overlaps with variability associated with sleep deprivation, both of which can result in impaired ability to function during the day and form new memories. Future analyses may want to use working memory neuroimaging paradigms to evaluate how sleep deprivation and fluid/crystallized cognition influence hippocampal functional activation to better understand these complex relationships.

Notably for each model gender was the strongest predictor of HV, with females typically exhibiting smaller HVs than males, even after normalizing with respect to ICV (coefficients ranged from -0.08 in model C to -0.128 in model D). In the regression plots in Figure 2, the two visually distinct clusters in each predicted cluster represent females (lower) and males (higher), The literature with regard to gender differences in HV is mixed, although the current consensus it that the analysis step at which

you adjust hippocampal data for ICV and gender can significantly impact results, so interpretations of gender differences should be cautious [20]. We selected to include gender in our overall ridge regression models rather than adjust for gender in an earlier step because we wanted to mitigate the impact of gender-related differences in sleep or cognition in our overall findings. Age has a smaller influence on HV than sex, but older age was generally associated with smaller HV across most models. Prior work has shown that HV typically increases during adolescence then exhibits a "slightly decelerating" decrease during young adulthood [23], which is generally in line with the conclusion our cross sectional results support.

It is important to note that one flaw of this data analysis plan - and an issue with most current human MRI research - is the inability to determine causality in these relationships. Our models are created under the assumption that sleep and cognition influence HV, when it is possible that HV volume impacts sleep and/or cognition, or an unknown tertiary variable affects all 3 systems. Many manipulations (i.e. forced prolonged sleep deprivation, biological inhibition of hippocampal growth) cannot ethically be performed with human subjects, so causality is difficult to discern. Future longitudinal analyses, which require different analytic techniques that could incorporate regressions, are necessary to better approach the development of these relationships over time and to examine if they have the ability to predict future outcomes. This form of longitudinal research, while logistically complicated, is important for understanding how sleep deprivation may increase risk for or being a predictive indicator of the cognitive decline associated with hippocampal atrophy and dementia [7].

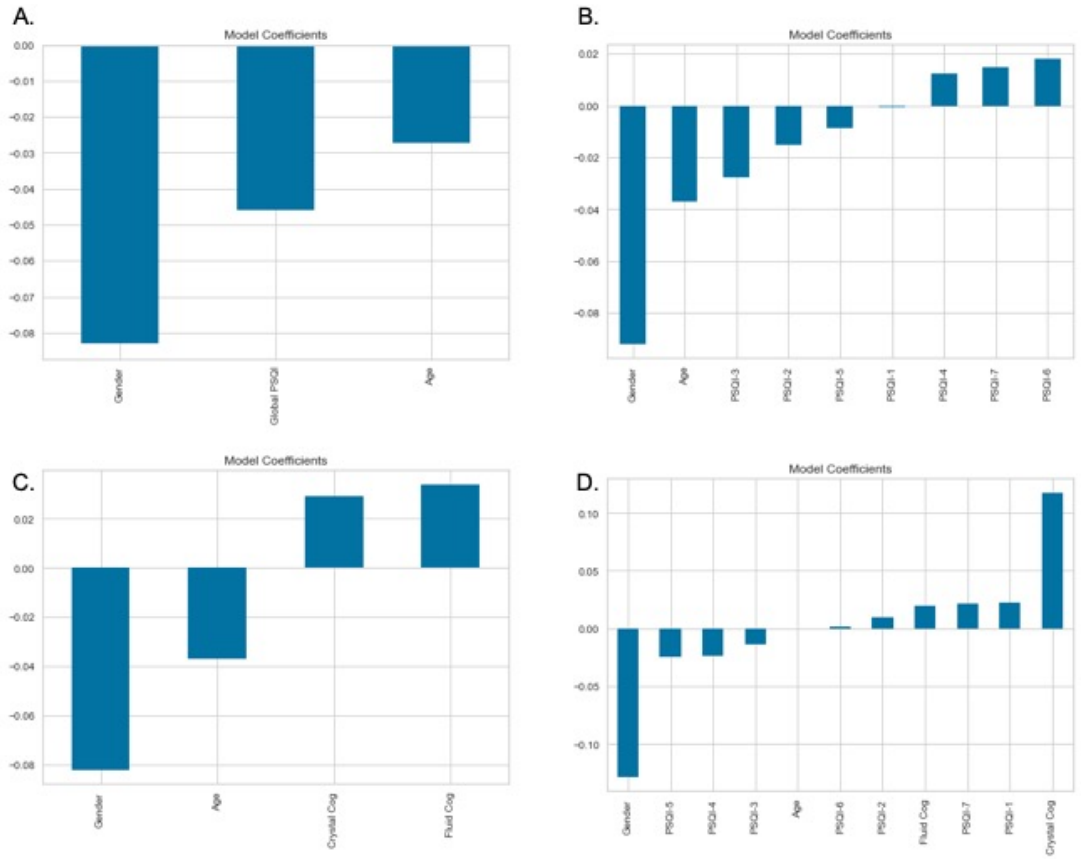

Figure 3: Beta coefficients for Models A-D

6 References

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