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Reduced Marker of Vascularization in the Anterior Hippocampus in a Female Monkey Model of Depression

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Abstract

Depression is a common and debilitating mood disorder that impacts women more often than men. The mechanisms that result in depressive behaviors are not fully understood; however, the hippocampus has been noted as a key structure in the pathophysiology of depression. In addition to neural implications of depression, the cardiovascular system is impacted. Although not as commonly considered, the cerebrovasculature is critical to brain function, impacted by environmental stimuli, and is capable of altering neural function and thereby behavior. In the current study, we assessed the relationship between depressive behavior and a marker of vascularization of the hippocampus in adult female cynomolgus macaques (*Macaca fascicularis*). Similar to previously noted impacts on neuropil and glia, the depressed phenotype predicts a reduction in a marker of vascular length in the anterior hippocampus. These data reinforce the growing recognition of the effects of depression on vasculature and support further consideration of vascular endpoints in studies aimed at the elucidation of the mechanisms underlying depression.

Keywords

vascular; depression; female; cerebrovasculature; *Macaca fascicularis*; unbiased stereology; hippocampus

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Author Contributions: All animal care and tissue collection was conducted by SW and CAS at Wake Forest University. GNN and CAS conceived the hypothesis tested herein. GNN designed the histological plan with assistance from DG. SDK and LM stained the tissue. AK, KS, and LM collected the stereologic endpoints. AK analyzed the data under the supervision of GNN. AK and GNN wrote the manuscript together. All authors reviewed and approved the submitted manuscript.

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1. Introduction

The lifetime risk of developing major depression is 29.9% in the United States [1], and depression is one of the most economically burdensome disorders [2]. Women are more likely to be diagnosed with depression than men [3], and given known sex differences in the neural substrates linked to depression [4-7], it is essential that studies of the pathophysiology of depression include females.

Although the neural substrates that underlie the manifestation of depressive behaviors are diverse and incompletely characterized, the hippocampus has been recognized as a region of particular importance [8-13]. Hippocampal morphology is altered in depressive states in humans [14-17]. In addition, rodent models of depressive-like behaviors, typically generated by exposure to chronic stressors, exhibit numerous alterations in hippocampal cytoarchitecture [18, 19] and molecular endpoints [7, 20].

However, the cellular impacts of depression are not limited to neural tissue. There is a bidirectional relationship between depression and vascular disease such that individuals with depression are predisposed to vascular disease and those with vascular disease are predisposed to depression [21]. Furthermore, abnormalities in brain perfusion have been linked to multiple neurological and psychiatric disorders. Assessments of regional cerebral blood flow in depressed patients demonstrates that 82% of patients have abnormal findings with the most consistent finding being global brain hypoperfusion [22, 23]. Although regional cerebral blood flow may be reflective of either neural demand or vascular changes, data from rodent models of depressive-like behavior suggest that vascularization of the hippocampus may be directly impacted. Specifically, chronic stress that is sufficient to induce changes in affective-like behaviors also causes reduced vascularization of the hippocampus [23, 24].

Unfortunately, assessments of the neural substrates of depressive-like behavior primarily have been conducted in male subjects, and as a consequence, less is known about the hippocampus in the context of depressive behaviors in females. One marked exception are a series of studies in a non-human primate model that demonstrate functional and structural differences in the hippocampus associated with spontaneously occurring depressive-like behaviors [25-29]. Depressive behaviors occur spontaneously in cynomolgus macaques (*Macaca fascicularis*) and produce analogous outcomes to depression in humans, including decreased activity levels, disrupted hypothalamic-pituitary-adrenal axis activity, and increased cardiovascular disease risk [25-29]. In terms of hippocampal alterations, depressed female cynomolgus macaques exhibit reduced volume and number of glial cells in the anterior hippocampus compared to non-depressed monkeys [25-27]. However, data available to date do not account for the state of hippocampal vascularization in female cynomolgus macaques that develop the depressive phenotype. Given the previous demonstrations of altered hippocampal cytoarchitecture [25-27] and existing literature linking depressive-like behaviors and hippocampal vascularization [23, 24], here we assess the hypothesis that depressed cynomolgus macaques exhibit reduced vascularization of the hippocampus.

2. Material and methods

2.1 Subjects

As previously described, 28 female cynomolgus macaques (*M. fascicularis*) of reproductive age were housed in stable social groups (N=4/housing group) for 24 months at Wake Forest University (Winston-Salem, N.C.). A standard 12:12 light:dark cycle was used in the housing areas [25, 27, 28]. Institutional, state, and federal laws for use of primates in laboratory settings were followed. The animals used in the current study were subjects in a larger investigation regarding the comorbidity of depression and cardiovascular disease risk, and therefore, consumed a Western diet which contained 0.28 mg cholesterol/Cal and 42% calories as fat [25, 27, 28]. The impact of these housing and dietary conditions on behavior and physiology have been previously reported in detail and are not repeated here [30, 31]. Briefly, behavioral depression was operationally defined as a slumped or collapsed body posture (head lower than shoulders) in which an animal's eyes are open, yet the animal lacks interest or responsiveness to environmental stimuli [27, 28, 30, 32, 33]. Time spent depressed was recorded once a week throughout the 26-month period using a 30-min group *ad libitum* observation method, punctuated with scan samples every 3 min [30]. Characteristics of depressive behavior in these animals have been described in detail elsewhere [30, 32]. Animals that never displayed the depressed posture were characterized as nondepressed (N = 26), whereas animals that ever exhibited this posture were characterized as depressed (N = 16, or 38%). Interobserver reliability was 92% throughout the study. Anterior HC volumes were significantly smaller (15.4%) in depressed compared to nondepressed monkeys [25]. In other papers we have shown that many neural and nonneural systems differ between depressed and nondepressed monkeys. Like human beings, we can't assign monkeys to the depressed or nondepressed condition. Therefore, the observed differences are characteristics of depressed monkeys, and cause and effect are not a study objective. From the initial population of 28 female subjects, brains were selected from the upper (depressed: n = 8) and lower tertile (non-depressed: n = 6) of time spent in the depressed posture [26, 27]. In addition, to reduce potential confounding variables, animals were matched for body weight, age, social status, basal cortisol levels, and estradiol and progesterone serum concentrations at necropsy.

2.2 Tissue Preparation

As previously described [26, 27], brains were rapidly removed at necropsy, hemisected, and frozen at -80°C. Temporal lobes were dissected, fixed, and cut coronally at 50 µm. Tissue was shipped on dry ice to Emory University (Atlanta, GA) for immunohistochemistry and stereological analysis of vascularization.

2.4 Immunohistochemistry

Sections were washed 3 times for 10 minutes each in 0.1M PBS solution. The sections were then blocked in a 1% normal goat serum solution with agitation at room temperature for 45 minutes. The sections were incubated over night at 4 °C in 1/250 Rabbit Anti-GLUT1 primary antibody solution (Abcam, Cambridge, MA) with agitation. Sections were then washed 3 times for 10 minutes each in 0.1M PBS solution. Sections were incubated for 2 hours in 1:200 Biotinylated Goat Anti-Rabbit secondary (Vector Labs, Burlingame, CA)

with agitation. Sections were again washed 3 times for 10 minutes each in 0.1M PBS solution. The sections were then incubated in the PK-6100 Elite Standard ABC Kit as per manufacture protocol (Vector Labs, Burlingame, CA) for 1 hour at room temperature. Sections were washed again in 0.1M PBS 3 times and then incubated for 1 min in a 0.05% DAB solution (Sigma, St. Louis, MO). All cross sections were then mounted on slides and allowed to dry overnight. The sections were taken through alcohol gradients and counter stained with cresyl violet and cover slipped.

2.5 Quantitative Stereological Analyses

Stereology was conducted by experimenters that were blind to phenotype and morphology confirmed cell type. Vessel lengths were estimated using the Spaceballs workflow in the Stereo Investigator System (MicroBrightfield, Williston, Vermont). There were 8 regions in the hippocampus that were analyzed. The anterior hippocampus was differentiated from the posterior hippocampus by the presence of the uncus. Within the anterior hippocampus, the regions assessed were: CA1 + Subiculum, Dentate Gyrus (DG), Distal CA3 +CA2, and Proximal CA3. Within the posterior hippocampus, the regions assessed were: CA1 + Subiculum, Dentate Gyrus (DG), Distal CA3 +CA2, and Proximal CA3. Each region was contoured under 4X bright field illumination. Sections were analyzed using a 40X immersion lens with the following parameters: Anterior Hippocampus DG, Anterior Hippocampus CA1 + Subiculum, Posterior Hippocampus DG, and Distal CA3 + CA2 grid side X= 200 grid size Y=200, guard zone height: 2 μ m, Spaceballs radius= 10 μ m, and use hemisphere: true, Anterior Hippocampus Proximal CA3, Anterior Hippocampus Distal CA3 + CA2, Posterior Hippocampus Proximal CA3, and Posterior Hippocampus CA1 + Subiculum: grid side X= 150 grid size Y=150, guard zone height: 2 μ m, Spaceballs radius= 10 μ m, and use hemisphere: true.

2.6 Statistical Analysis

All statistical tests were completed using GraphPad Prism Software 6 (La Jolla, CA). A two-way ANOVA on the factors of behavioral phenotype (depressed vs. non-depressed) and brain region was used to assess group differences. Student's two-tailed t-tests with Bonferroni correction were used for post-hoc assessments. Results are reported as the group mean and standard error of the mean. Mean differences were considered statistically different if $p < 0.05$.

3. Results

Representative images of GLUT1 staining appear in Figure 1. Macaques that demonstrated a depressive phenotype had reduced vascular length in the hippocampus, as measured by determination of length of processes stained with GLUT1, compared to non-depressed macaques ($F(7,91)=5.460$, $p < 0.0001$; Figure 1). In addition, vascular length varied as a function of region of the hippocampus ($F(7,91) = 2.925$, $p < 0.008$). Furthermore, depressive phenotype and hippocampal region interacted ($F(1,91) = 27.17$, $p < 0.0001$) such that an impact of depressive phenotype on vascular length was only noted within anterior regions of the hippocampus ($p < 0.05$ for DG, Proximal CA3, Distal CA3 +CA2, and CA1 + Subiculum, as compared to non-depressed values for same regions).

4. Discussion

The data presented here demonstrate for the first time that a marker of vascular length in the anterior hippocampus is compromised in depressed female primates with no prior antidepressant exposure. This difference in vascularization indicated by the reduction in GLUT1-positive vascular processes supports previous reports of profound alterations in anterior hippocampal morphology in depressed compared to non-depressed animals [27]. Furthermore, these data extend previous reports of vascular pruning in the hippocampus of male rodents [23, 24] to both females and a nonhuman primate model of depression. Although the current experiment cannot establish whether the noted vascular differences occur prior to, after, or in conjunction with the neuronal and glial changes previously reported [27, 28], the data clearly document that the impact of the depressive phenotype extends to the cerebral vasculature. In addition, these findings establish vascularization as a candidate mechanistic variable in the manifestation of depressive behaviors.

Given that cognitive and memory disorders are also linked to altered cerebral perfusion, these findings may have implications for aging of the depressed individual. In some cases, dementia can be attributed to underlying cerebral vascular impairment [34]. Neuroimaging studies suggest that the magnitude of cognitive impairment among patients with mild cardiovascular disease is associated with neuropathological changes that are secondary to the vascular damage [35]. In addition, the vascular hypothesis for the etiology of Alzheimer Disease suggests that the pathology begins with the combination of advanced aging and vascular risk factors that lead to brain hypoperfusion. This hypoperfusion is followed by a neuro-glial energy crisis that results in mild cognitive impairment followed by neurodegeneration and the symptoms characteristic of Alzheimer Disease [36].

These findings also provide additional information for the differentiation of the effects of depression versus the effects of body mass on the brain. Determination of the relationship between body mass and depression is an intense area of study, but the relationship between the two has not been clearly and consistently defined [37-40]. The subjects in the current study were fed a Western diet and have previously been shown to develop the negative physiological consequences of this diet [32, 41]. However, group mean body masses in the sub-study described here were matched between the depressed and non-depressed groups. Therefore, these data demonstrate an effect of the depressive phenotype that diverges from body mass specifically. We cannot, however, determine from the current data set whether the Western diet is essential for the manifestation of reduced GLUT1 staining, and potentially vascularization, in the hippocampus. Previous work in rodents [23, 24] utilized a standard lab chow diet that may suggest that a high fat diet is not essential for the manifestation of vascular modifications.

5. Conclusions

The collected data demonstrate that, similar to previously noted impacts on the neuropil and glia [27, 28], the depressed phenotype in the female macaque co-occurs with a reduction in GLUT1 staining, which is a marker of vascular length, in the anterior hippocampus. These data reinforce the growing recognition that cerebral vasculature may be implicated in

depression and support further consideration of vascular endpoints in studies aimed at the elucidation of the mechanisms underlying depression. Future studies should evaluate the causative and temporal relationship between depression-related changes in vascular, neuronal, and glial endpoints, as well as examine the potential for vascular interventions to ameliorate the depressive phenotype.

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Highlights

- Given the prevalence of depression in females, female models are essential.
- Assessment of neural endpoints in nonhuman primates is valuable.
- Vascularization of the brain is dynamic and responsive to the environment.
- Monkeys with depressive behavior have reduced vascularization of the hippocampus.
- Vascular endpoints should be noted in assessments of neural substrates of behavior.

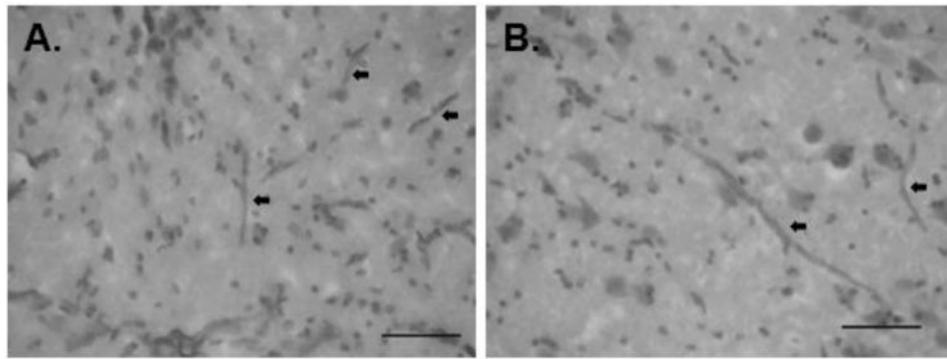


Figure 1. Representative images of anti-GLUT1 staining in the hippocampus are provided in panels A and B. Both photomicrographs were captured at 40X and the scale bar indicates a length of 50 μm . The arrows indicate cells with vascular morphology that are positive for GLUT1. Consistent with a previous report in primate tissue, anti-GLUT1 appears to preferentially label vascular cells and no astrocytes are apparent in the stained sections [42].

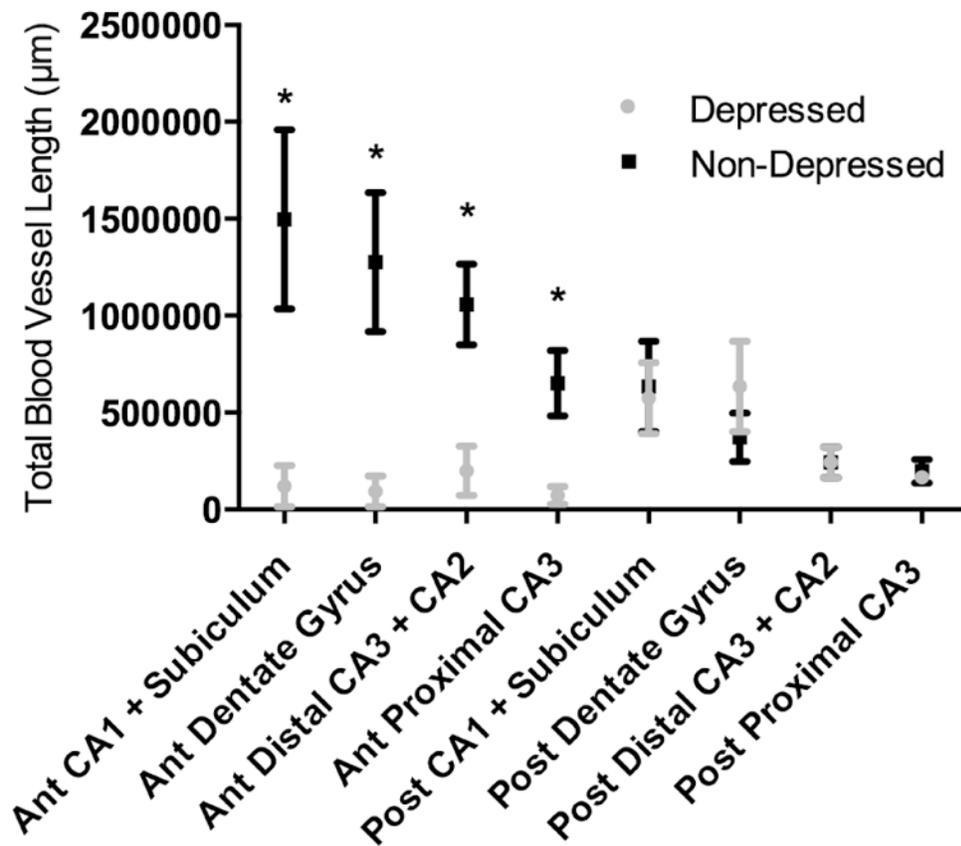


Figure 2. Total blood vessel length (μm) was estimated by non-biased stereology in eight sub-regions of the hippocampus from depressed and non-depressed monkeys. The depressed phenotype predicted a reduction in vascularization in the four anterior regions of the hippocampus assessed (*, $p < 0.05$ as compared to non-depressed mean for the same region). Vascular length did not differ as a function of depressive phenotype for any of the posterior regions examined ($p > 0.05$). Data are presented as group means \pm standard error of the mean. Ant= Anterior Hippocampus and Post = Posterior Hippocampus.