Vulnerability of Hippocampal Volume in Rats Exposed to Fragmented Maternal Care

Eli Kinney-Lang1,3
Alex Hiroto3
Jenny Molet3
Ana Solodkin2
Tallie Z. Baram1,2
Andre Obenaus3

Departments of Pediatrics, Anatomy & Neurobiology, University of California Irvine, Irvine, CA 92697
Department of Pediatrics, Loma Linda University, Loma Linda, CA 92350

Introduction

Epidemiological data in humans suggest that adverse experiences occurring early in life are associated with an increased risk for cognitive deficits in adulthood [1,2]. We have developed a powerful, naturalistic model of early-life stress (ES) in rodents that is based on generating fragmented and unpredictable patterns of maternal care [3-5]. Adult rodents exposed to fragmented maternal care have been found to develop cognitive deficits associated with structural changes to the hippocampal pyramidal cells in middle age [4].

To further investigate alterations in the hippocampus following early-life stress, we undertook high resolution magnetic resonance imaging (MRI) to identify volumetric changes within this vulnerable structure. Data was collected and analyzed manually.

Hypothesis

We hypothesize that high resolution MRI of the hippocampus will identify structural vulnerabilities in the dorsal hippocampus region specifically for animals exposed to fragmented maternal care in early development.

Methods

At postnatal day 21, Sprague-Dawley rat pups from the following litters were studied:

- Control (CTRL) litters: Housed in standard cages, with standard bedding and nesting.
- ES litters: 5-h restraint or social stress (Crowded), Light, Bright light, or Control.
- ES + modal stress for 5 h
- CTRL + modal stress for 5 h

At postnatal day 21, pups were culled to a litter size of 12 (6 males, 6 females). The pups were then randomized into two treatment groups:

- CTRL: Chosen to serve as the control group.
- ES: The group that is exposed to fragmented and unpredictable maternal care.

The pups were then housed for the next 2 months under a variety of environmental conditions, including light cycles, crowding, and restraint. The pups were then subjected to high resolution MRI imaging.

Results

A. Hippocampus and Whole Brain Regions of Interest

Figure 1: Schematic timeline representation of the early-life stress model.

Figure 2A: Manual delineation of specific structures is highlighted. The highlighted regions include the left/right dorsal (red/yellow) and ventral (blue/purple) hippocampus as well as whole brain (green). The four slices presented are the 4 slices of the dorsal hippocampus immediately anterior to connecting to the ventral hippocampus. Distance between each slices is 318 um.

Figure 2B: The highlighted regions include the left/right dorsal (red/yellow) and ventral (blue/purple) hippocampus as well as whole brain (green). The four slices presented are the 4 slices of the dorsal hippocampus immediately anterior to connecting to the ventral hippocampus. Distance between each slices is 318 um.

Figure 3A: Volumetric differences in the total left and right hippocampus are shown to be negligible between control and fragmented animals. The results emphasize volumetric vulnerability is not seen throughout the hippocampus, but rather is dorsal specific. Differences in specifically ventral hippocampus volume are also not significantly different.

Figure 3B: Volumetric differences in the whole brain between control and fragmented animals are not significantly different. The whole brain data demonstrates the specific volume reduction in the hippocampus structure has no effect on total brain volume. Whole brain volume was used to normalize hippocampal data. Similarly, the entire cerebral volume of control and frag animals is not significantly different.

Table 1: Percent Change Legend for Dorsal Hippocampus Volume in Fragmented Animals

<table>
<thead>
<tr>
<th>Structures</th>
<th>Control</th>
<th>ES</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LHPC%</td>
<td>9.90%</td>
<td>9.14%</td>
<td>0.05</td>
</tr>
<tr>
<td>RHPC%</td>
<td>6.04%</td>
<td>2.27%</td>
<td></td>
</tr>
<tr>
<td>Autism</td>
<td>-5.54%</td>
<td>-1.13%</td>
<td></td>
</tr>
<tr>
<td>Frag</td>
<td>-4.30%</td>
<td>-1.24%</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

- There were no significant volume differences in total hippocampus, whole brain or cerebral ventricle volumes in animals exposed to fragmented maternal care as compared to control animals.
- However, dorsal hippocampus volumes specifically were reduced in animals exposed to fragmented maternal care as compared to control animals.
- Cerebral ventricle volumes were increased in fragmented animals in the dorsal hippocampus specifically.
- These results demonstrate a vulnerability in fragmented animals within the dorsal hippocampus specifically. These findings are in agreement with previous work demonstrating reduced pyramidal cell morphology within the dorsal hippocampus [3,4].

Further Investigations

Additional investigations are ongoing to uncover potential decrements in other brain areas that may play the basis for cognitive vulnerability. Analysis of other regions of interest, such as the basolateral amygdala nucleus, are in progress. Experiments looking at the effects of fragmented maternal care on the connectivity of the hippocampus using functional MRI techniques will be examined as well.

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References: