

**SEX-SPECIFIC NEUROBEHAVIORAL ALTERATIONS IN
DECISION MAKING UNDER EARLY LIFE STRESS
USING RODENT IOWA GAMBLING TASK**

SAKSHI SHARMA



**SCHOOL OF INTERDISCIPLINARY RESEARCH (SIRE)
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**Sex-Specific Neurobehavioral Alterations in Decision
Making under Early Life Stress using rodent Iowa
Gambling Task**

by

Sakshi Sharma

School of Interdisciplinary Research

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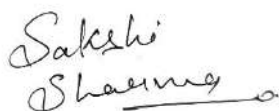
I dedicate this thesis to my father, **Mr. Jagmohan Sharma**, whose inspiration led me to pursue a career in science. Though he is not with me today, his guidance and blessings continue to light my path and give me strength.

Declaration by Author

I, **Sakshi Sharma**, hereby declare that the thesis entitled “*Sex-specific Neurobehavioral Alterations in Decision-making under Early Life Stress using rodent Iowa Gambling Task (rIGT)*” submitted to the Indian Institute of Technology Delhi, is a record of the original work carried out by me under the supervision of Dr. Varsha Singh, Professor, in the School of Interdisciplinary Research, Indian Institute of Technology Delhi.

I further declare that:

1. This work has not been submitted either in part or in full for the award of any other degree or diploma of this or any other university/institute.
2. The work presented in this thesis is my own, and to the best of my knowledge, it contains no material previously published or written by another person, except where due reference has been made in the text.
3. All sources of information have been duly acknowledged in the thesis.



Sakshi Sharma
2020SRZ8260

Supervisor Certification

This is to certify that the thesis entitled “*Sex-specific Neurobehavioral Alterations in Decision-making under Early Life Stress using rodent Iowa Gambling Task (rIGT)*” submitted by **Ms. Sakshi Sharma** is a bonafide record of the research work carried out by her under my supervision and guidance in the School of Interdisciplinary Research, Indian Institute of Technology Delhi, India, with experiment work done at AIIMS, New Delhi.

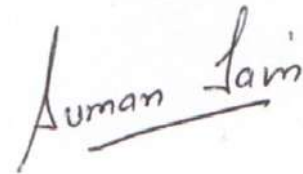
The work embodied in this thesis is original and has not been submitted, either in part or in full, to any other university or institution for the award of any degree or diploma. The results presented and conclusions drawn in this thesis are based on the investigations conducted by the candidate during the period of her research at IIT Delhi.

I hereby certify that the thesis meets the required standards of research in terms of methodology, content, and presentation.



Dr. Varsha Singh, Professor
(Supervisor)

Humanities and Social Sciences,
Indian Institute of Technology, Delhi



Dr. Suman Jain, Professor
(Co-Supervisor)

Department of Physiology,
AIIMS

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Abstract

Decision-making is an affective–cognitive process that relies on risk evaluation, reward processing, and inhibitory control, and is primarily regulated by the prefrontal cortex, with notable sex differences in its functioning. The development of the prefrontal cortex is particularly sensitive to early life stress, which may contribute to sex-specific vulnerability to affective disorders in adulthood. However, investigating the neurobiological and cognitive consequences of early life stress on the prefrontal cortex in humans is challenging due to ethical and methodological constraints. Therefore, this thesis examined the sex-specific effects of early life stress and ventromedial prefrontal cortex (vmPFC) lesions on anxiety and decision-making using a rodent model (Wistar rats). Early life stress was induced through maternal separation, while anxiety-like behavior was assessed using the elevated plus maze. Decision-making was evaluated using a rodent version of the Iowa Gambling Task (rIGT), in which animals made 100 sequential choices across four arms offering variable reinforcement in the form of sugar pellets (rewards) and quinine (punishments) to maximize long-term gains. Arm choices and response latencies were compared across multiple groups: control (10 males, 10 females), early life stress (8 males, 8 females), vmPFC lesion (7 males, 7 females), sham lesion (7 males, 7 females), early life stress combined with vmPFC lesion (7 males, 7 females), and stress with sham lesion (7 males, 7 females). Histological analyses were conducted, along with measurements of corticosterone levels and dopaminergic and serotonergic cell counts in the vmPFC using the H-score method.

The results indicated that early life stress impaired decision-making. Sex differences were evident, with male rats showing a greater preference for long-term advantageous choices, while females exhibited higher variability in their choices. Elevated corticosterone levels confirmed the stress manipulation, alongside increased dopaminergic and serotonergic activity in the vmPFC. The vmPFC lesions were validated by neuronal loss and were associated with heightened anxiety-like behavior in the elevated plus maze, as well as impaired decision-making in both sexes. Additionally, an interaction between early life stress and vmPFC lesions revealed sex-specific effects.

Overall, these findings suggest that early life stress alters vmPFC function and contributes to sex differences in decision-making. The results further indicate sex-specific vulnerability, with female rats demonstrating relatively greater resilience to early life stress. This study enhances our understanding of the neural mechanisms underlying impaired decision-making and emphasizes the importance of considering sex and developmental history in preclinical models of cognitive and affective disorders such as depression and anxiety.

सारांश

निर्णय-निर्माण (Decision-making) एक भावात्मक-संज्ञानात्मक (Affective-Cognitive) प्रक्रिया है, जो जोखिम के मूल्यांकन, प्रतिफल (रिवार्ड) के प्रसंस्करण तथा निरोधात्मक नियंत्रण (Inhibitory Control) पर आधारित होती है। इसका प्रमुख नियंत्रण प्रीफ्रंटल कॉर्टेक्स द्वारा किया जाता है, जिसके कार्य में लिंग-आधारित (Sex-specific) महत्वपूर्ण अंतर पाए जाते हैं। प्रीफ्रंटल कॉर्टेक्स का विकास विशेष रूप से प्रारम्भिक जीवन के तनाव (Early Life Stress) के प्रति संवेदनशील होता है, जो वयस्क अवस्था में भावात्मक विकारों के प्रति लिंग-विशिष्ट संवेदनशीलता का कारण बन सकता है। तथापि, नैतिक तथा कार्यप्रणाली संबंधी सीमाओं के कारण मनुष्यों में प्रारम्भिक जीवन के तनाव के प्रीफ्रंटल कॉर्टेक्स पर पड़ने वाले तंत्रिकाजैविक (Neurobiological) एवं संज्ञानात्मक प्रभावों का अध्ययन करना कठिन है। इसलिए इस शोधप्रबंध में कृतक मॉडल (विस्टर चूहों) का उपयोग करते हुए प्रारम्भिक जीवन के तनाव तथा वेंट्रोमेडियल प्रीफ्रंटल कॉर्टेक्स (vmPFC) में उत्पन्न घावों (Lesions) के चिंता एवं निर्णय-निर्माण पर लिंग-विशिष्ट प्रभावों का अध्ययन किया गया।

प्रारम्भिक जीवन के तनाव को मातृ पृथक्करण (Maternal Separation) द्वारा उत्पन्न किया गया, जबकि चिंता-सदृश व्यवहार का मूल्यांकन एलिवेटेड प्लस मेज़ (Elevated Plus Maze) की सहायता से किया गया। निर्णय-निर्माण का आकलन आयोवा गैम्बलिंग टास्क (Iowa Gambling Task) के कृतक संस्करण (rIGT) द्वारा किया गया, जिसमें पशुओं ने चार भुजाओं वाले भूलभुलैया (Maze) में 100 क्रमिक विकल्पों का चयन किया। प्रत्येक भुजा में शर्करा पेलेट (Sugar Pellets) के रूप में पुरस्कार तथा क्विनीन (Quinine) के रूप में दंड की विभिन्न संभावनाएँ थीं, जिससे दीर्घकालिक अधिकतम लाभ प्राप्त किया जा सके। विभिन्न समूहों—नियंत्रण (10 नर, 10 मादा), प्रारम्भिक जीवन तनाव (8 नर, 8 मादा), vmPFC घाव (7 नर, 7 मादा), शैम घाव (7 नर, 7 मादा), प्रारम्भिक जीवन तनाव के साथ vmPFC घाव (7 नर, 7 मादा), तथा तनाव के साथ शैम घाव (7 नर, 7 मादा)—के बीच भुजा-चयन एवं प्रतिक्रिया विलंब (Response Latency) की तुलना की गई। साथ ही, ऊतक-विज्ञान (Histological) विश्लेषण किए गए तथा कॉर्टिकोस्टेरोन स्तरों और vmPFC में डोपामिनर्जिक एवं सेरोटोनर्जिक कोशिकाओं का H-स्कोर विधि द्वारा मूल्यांकन किया गया।

परिणामों से स्पष्ट हुआ कि प्रारम्भिक जीवन का तनाव निर्णय-निर्माण क्षमता को प्रभावित करता है। लिंग-आधारित अंतर भी स्पष्ट रूप से दिखाई दिए, जहाँ नर चूहों ने दीर्घकालिक लाभकारी विकल्पों को अधिक प्राथमिकता दी, जबकि मादा चूहों में विकल्पों के चयन में अधिक परिवर्तनशीलता (Variability) देखी गई। कॉर्टिकोस्टेरोन के बढ़े हुए स्तरों ने तनाव मॉडल की पुष्टि की। इसके साथ ही vmPFC में डोपामिनर्जिक एवं सेरोटोनर्जिक गतिविधि में वृद्धि भी देखी गई। vmPFC घावों की पुष्टि न्यूरॉनों की हानि (Neuronal Loss) द्वारा हुई, तथा ये घाव एलिवेटेड प्लस मेज़ में अधिक चिंता-सदृश व्यवहार और दोनों लिंगों में निर्णय-निर्माण की क्षमता में कमी से जुड़े पाए गए। इसके अतिरिक्त, प्रारम्भिक जीवन के तनाव और vmPFC घावों के पारस्परिक प्रभावों ने लिंग-विशिष्ट परिणामों को भी उजागर किया।

समग्र रूप से, यह अध्ययन दर्शाता है कि प्रारम्भिक जीवन का तनाव vmPFC की कार्यप्रणाली को परिवर्तित करता है तथा निर्णय-निर्माण में पाए जाने वाले लिंग-आधारित अंतरों में योगदान देता है। परिणाम यह भी संकेत देते हैं कि मादा चूहों में प्रारम्भिक जीवन के तनाव के प्रति तुलनात्मक रूप से अधिक सहनशीलता (Resilience) विद्यमान थी। यह अध्ययन निर्णय-निर्माण में होने वाली हानि के तंत्रिका-आधारित तंत्रों (Neural Mechanisms) की समझ को समृद्ध करता है तथा अवसाद (Depression) एवं चिंता (Anxiety) जैसे संज्ञानात्मक एवं भावात्मक विकारों के पूर्व-नैदानिक (Preclinical) मॉडलों में लिंग तथा विकासात्मक इतिहास (Developmental History) को ध्यान में रखने के महत्व पर बल देता।

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