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REVIEW ARTICLE

Sex Differences in Gene Networks in the Medial Prefrontal Cortex for Learning and Memory

Hannah Li

Royal High School Bath, Lansdown Road, Bath, BA1 5SZ, UK.; lychannah@gmail.com
Mentor: Dr. Jorge Avila, Omar Singleton

ABSTRACT: Females have historically been overlooked in research, including studies investigating the role of the medial prefrontal cortex (mPFC) for learning and memory. However, emerging research challenges these beliefs by revealing sex differences in gene networks in the mPFC for cognitive processes. The mPFC is an important part of the brain that mediates many cognitive functions and combines inputs from other regions of the brain. There are sex differences linked to gene networks involved in synaptic plasticity within the mPFC. In synaptic plasticity, genes like brain-derived neurotrophic factor (BDNF) and N-methyl-D-aspartate (NMDA) receptor show sex-specific patterns. This review discusses the sex differences in gene networks regulating synaptic plasticity within the mPFC for learning and memory. Some key pathways that affect this are glutamatergic signalling and hormone regulation. Some researchers have shown that females exhibit enhanced glutamatergic transmission in the mPFC compared to males. However, the differences in gene networks between males and females in learning and memory remain poorly understood. It is important to expand sex-specific research to gain a comprehensive understanding of the interactions in different brain regions and their implications for learning and memory.

KEYWORDS: Behavioral and Social Science, Neuroscience, BDNF, Glutamate, Hormones, Dopamine, NMDA.

Introduction

The importance of research on sex differences in the brain has often been underestimated over the past decades, with a lot of research just focusing on males. In recent years, our knowledge about sex differences and their impact on learning and memory has grown tremendously. However, the understanding of how sex differences in gene networks contribute to learning and memory in the medial prefrontal cortex (mPFC) remains unclear. Moreover, understanding sex-specific gene networks in the mPFC can give us more insights into how to deal with disorders, such as depression, autism spectrum disorder, and Alzheimer's disease, which show distinct patterns between males and females.[1,2]

The mPFC plays a critical role in regulating learning and memory in the brain. Previous studies suggest that the mPFC is also necessary for the formation of recent memories. They demonstrated that specific inhibition of the N-methyl-D-aspartate receptor subtype 2B (NR2B) subunit within the mPFC disrupts the expression of newly acquired trace-conditioned memories.[3] A significant role in synaptic plasticity is the NR2B subunit, which is a component of the NMDA receptor and a type of glutamate receptor essential for learning and memory. Brain-derived neurotrophic factor (BDNF) plays a critical role in supporting synaptic growth and plasticity. Studies suggest that female subjects have higher BDNF in the prefrontal cortex (PFC), which may suggest that BDNF could influence synaptic plasticity and cause sex differences.[4] Sex differences in gene expression and networks in the mPFC influence key processes like synaptic plasticity – the ability of synapses to strengthen or weaken in response to activity. It is believed that long-term potentiation (LTP) and long-lasting depression (LTD) have long-lasting effects on learning and memory.[5] LTP refers to the strengthening of synapses, whereas LTD is the reverse of LTP and occurs when individual synapses are activated in isolation. Previous study suggests that LTP and LTD have the properties needed for memory formation. This is because memories are formed quickly, so they must be represented as some alteration in the function of neuronal circuits. A study suggests that LTP and LTD are the only enduring circuit changes that can occur rapidly enough.[6]

Furthermore, studies suggest that sex hormones or steroids can modulate the activity of BDNF, which may account for sex differences. Sex hormones such as estrogen, which promote LTP and learning, and testosterone are key chemical messengers.[7] Significant sex differences can also influence learning and memory formation during stress and fear conditioning.[7] Studies suggest that stress evokes sex differences in certain tasks, and these differences are mediated by interactions between stress and sex hormones.[8] They also suggest that females perform better in verbal learning, while males perform better in spatial learning; differences may be due to estrogen in females.[7]

This review aims to explore the current literature and previous studies on sex differences in gene networks and how these networks may influence learning and memory. It will focus on the sex differences in BDNF, glutamate, and dopaminergic pathways in synaptic plasticity in the mPFC. Furthermore, this review also highlights the need for more research into sex-specific studies in the future.

DOI: 10.36838/v8i1.64

Discussion

BDNF in Synaptic Plasticity and Sex Differences in Learning and Memory:

- ***The Role of BDNF and Synaptic Plasticity:***

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophic family that plays an essential role in several neuronal activities that regulate synaptic growth, plasticity, and other cognitive functions. Changes in brain development, synaptic dysconnectivity, and failures in neuroplasticity may be triggered by alterations of neurotrophic factors like BDNF at the protein and gene level. Development of LTP and memory may benefit from the increased expression of BDNF.[9] With support from previous studies, it is hypothesized that sex hormones or steroids can alter the activities of BDNF, which may explain its functional discrepancy in different sexes.[4] Estrogen increases BDNF levels, which are related to greater synaptic spine density in the PFC. Increasing synaptic spine density can enhance memory function and cognition.[10] Furthermore, studies have shown that there are molecular mechanisms underlying learning in the mPFC, and the regulation of BDNF over other genes is linked to plasticity.[4,11] This section of the paper explores BDNF in synaptic plasticity and its sex differences in the mPFC, which influence learning and memory.

- ***Sex differences in BDNF levels:***

According to a study published in 2017 by Wei, males and females have different BDNF levels in the mPFC.[12] The study suggests that females have higher levels of BDNF in the PFC than males.[13] However, the levels fluctuate across the reproductive cycle, during pregnancy, and menopause. In female rats, the depletion of estrogen after ovary removal significantly decreases BDNF mRNA levels, which can be partially restored by estrogen replacement. Estrogen enhances activities like transcription and translation of BDNF in activity-dependent plasticity.[12] In addition, the study suggests that estrogenic regulation of BDNF signalling is sex specific as the expression of estrogen receptors is sexually dimorphic, which means the difference between individuals of different sexes in the same species. Adult male rats with a lack of testosterone show an increase in BDNF immunoreactivity and potentiate synaptic transmission.[12] Estrogen depletion in females leads to decreased BDNF expression, indicating estrogen stimulates BDNF signalling in females, whereas testosterone inhibits BDNF signalling in males. In contrast, males have higher levels of testosterone, which can be converted into estrogen through a biochemical process called aromatization, which is facilitated by the enzyme aromatase and converts testosterone into estradiol.[14] More importantly, testosterone can directly influence BDNF signalling through androgen receptor independent of estrogen production.[12] Results from a previous study suggest that hormones produce rapid activation of TrkB receptors, which are receptors for BDNF, which is known to promote LTP. Another study has proposed that a type of estrogen, estradiol (E2), enhances synaptic plasticity and neuroprotection by increasing BDNF transcription and encouraging TrkB receptor activation.15 Their differences are summarised in Figure 1.

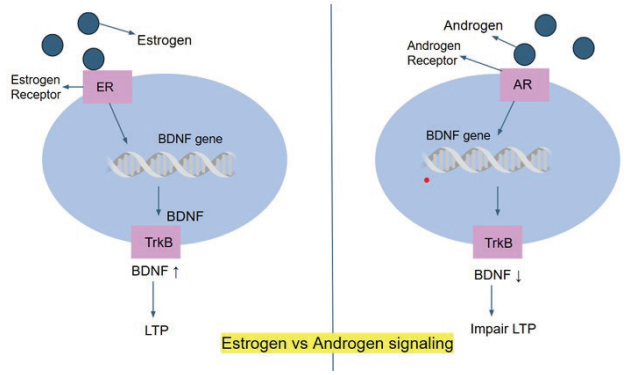

Figure 1: On the left side, estrogen binds to the receptor (ER), which enhances the BDNF level. TrkB is the receptor for BDNF. This shows estrogen promotes synaptic plasticity, especially long-term potentiation (LTP) in the mPFC. On the right side, androgen signalling is shown. When high levels of androgen bind to the receptor (AR), it lowers the BDNF level, which leads to impaired LTP. Therefore, this shows that there is a sex difference in BDNF levels.

- ***The Influence of BDNF on Learning and Memory:***

The higher BDNF levels in females contribute to verbal tasks and decision-making under changing conditions. Since BDNF is important for LTP and BDNF helps the growth of dendritic spines, females have an advantage in these tasks due to enhanced LTP and dendritic synaptic plasticity in the mPFC.[16] It is suggested that dendritic spines are crucial for neural plasticity, and there is increasing evidence that the mechanisms underlying learning and memory involve dendritic plasticity. The increased BDNF levels in females are associated with increased dendritic spine density and synaptic plasticity, which can enhance cognitive function, including learning and memory.[10] Synaptic plasticity plays a part in memory processing and has a role in mediating the acquisition, consolidation, and retention of memory. It has been demonstrated that estradiol increases both dendritic spine and spine synapse density in the mPFC of non-human primates.[17] A study by Frankfurt and Luine has investigated the relationship between estrogen, recognition memory, and dendritic spine density in the mPFC and hippocampus, which are critical regions for memory, across the lifespan in female rodents. Estradiol increases dendritic spine density in the hippocampus and mPFC, which increases memory performance.[17] Furthermore, neuroimaging studies have demonstrated direct associations between sex steroid hormones and the memory circuitry.[18] Population-level studies suggest that estradiol levels fluctuate across the menstrual cycle and can correlate with verbal memory performance.[18] There is evidence that chronic stress impairs BDNF in male mPFC but may have less effect in females; estradiol contributes to this sex difference, which is why females are more resilient to stress than males.[19]

Glutamate in the mPFC: sex differences and implications for learning and memory:

Studies have demonstrated sex differences in glutamate levels and receptor gene expression in the PFC, with females exhibiting increased glutamatergic transmission in the mPFC compared to males.[20,21] Within the mPFC, two key glutamate receptor subtypes – N-methyl-D-aspartate (NMDA)

and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors – play crucial roles in synaptic plasticity and long-term potentiation (LTP), both modulating learning and memory processes. The neurotransmitter glutamate is released into the synapse and binds to NMDA and AMPA receptors.

Through GluN2B-containing NMDARs, it directly activates protein kinase and triggers LTP. Through GluN2A-containing NMDARs, which activate protein kinase and trigger the downstream signalling that mediates LTP expression. NMDAR and AMPAR act as a gate to let Na^+ and Ca^{2+} into the cell.[22] This is shown in Figure 2. This suggests that NMDAR and AMPAR are important for synaptic plasticity.

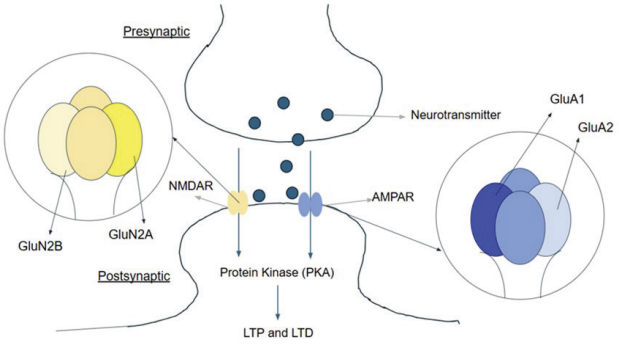

Figure 2: The role of NMDA and AMPA receptors and subunits on synaptic plasticity, LTP, and LTD. This shows that NMDAR and AMPAR are important for LTP and LTD.

Many forms of LTP and LTD depend on NMDA receptor activation and result in an increase in the postsynaptic Ca^{2+} concentration. Studies have tested acute stress impacts on female and male mice and indicate that females have more glutamatergic neurotransmission compared to males, especially an increase in NMDA and AMPA receptor-mediated neurotransmission.[23] Sex differences in AMPA and NMDA receptor signalling, and differences in long-term potentiation in the glutamatergic system have been observed.[20] In NMDA receptor gene expression, the balance between GluN2A and GluN2B subunits may change the significance level for postsynaptic responses. Researchers believe that an increase in the GluN2A or GluN2B ratio enhances the LTD induction, whereas a decrease in the GluN2A or GluN2B ratio reduces LTD induction. Evidence suggests an association between sex differences in LTP and LTD with NMDA receptor subunits, due to their roles in establishing long-term memory.[24] A previous study investigating cocaine craving in males and females suggests that the molecular mechanisms are different in females versus males. Their results suggest that cocaine craving is similar between sexes. However, female mice exhibit higher NMDA ratios compared to male mice, which indicates that the GluN2B subunit expression is higher in the mPFC in females compared to males. Furthermore, female mice have higher levels of glutamate and lower release compared to male mice.[25] Effects have been observed for GRIN2B expression within the mPFC from the analysis of the investigation, which indicates that males have a greater decrease in GRIN2B expression than females during relapse testing. The study shows that the development of cocaine-craving in females is faster than in males, which further indicates that the GRIN2B gene expression differs between males and females.[25] In AMPA receptor gene expression, females exhibit higher levels of synaptosomal GluA1 and GluA2 in the mPFC compared to males, which indicates that there is greater synaptic AMPA subunit expression at the synapses, which could potentially contribute to spine size and increase glutamatergic transmission in females.[20]

Studies that investigate differences in cognition and synaptic plasticity during fluctuation in female hormones suggest that sex hormones can influence aspects of glutamatergic transmission.[20, 26] Moreover, memory is associated with the increase of spine density, and spine density has increased after the administration of estrogen in the PFC. Androgen can also increase spine density in the PFC, but with less effect compared to estrogen. Furthermore, studies show that NMDA receptors in the mPFC to hippocampus pathway play a role in encoding of associative memory for object and place, and the retrieval of this memory relies on AMPA receptor-mediated neurotransmission.[23, 27, 28]

However, some studies also suggest that overactivation of NMDA receptors can trigger excitotoxicity, which impairs synaptic plasticity and affects learning and memory.[23, 29] Further research and investigation are needed to fully understand this.

Dopaminergic pathways in mPFC: sex differences and implications for learning and memory:

The dopaminergic system plays a key role in neuromodulation, which includes the involvement of dopamine. Dopamine is a neurotransmitter that exerts its actions through binding to G protein-coupled receptors. In recent years, studies suggest that dopamine can modulate the dendritic excitability of prefrontal neurons, hence controlling higher cognitive functions.[30] Dopamine- and cAMP-regulated phosphoprotein of Mr 32 kDa (DARPP-32) is a key signalling molecule in dopaminergic pathways, which integrates dopaminergic and glutaminergic transmission.[31]

Establishing the role of dopamine in synaptic plasticity may help understand its function in mPFC-dependent memory.[32] Studies suggest that dopaminergic systems influence synaptic plasticity in the PFC because of their major role in cognitive function. Dopamine terminals are mostly located in layers V and VI of the prelimbic and anterior cingulate areas. The close proximity of hippocampal and dopamine terminals in the PFC targeting the same dendrites in the prelimbic area suggests dopamine can control hippocampal-prefrontal synaptic strength.[30, 33] The preferred location of D1 receptors (D1R) supports postsynaptic mechanisms, which indicate that there is a role of D1 receptors in synaptic plasticity and memory processes,[34] for example, D1 receptor activation can enhance LTP via the cAMP.

PKA cascade.[32] However, an overstimulation of D1 receptors disrupts the effects of dopamine on synaptic plasticity at hippocampal to PFC synapse, an intact mesocortical, which

DOI: 10.36838/v8i1.64

is the neural connection between the ventral tegmental area (VTA) and the frontal cortex, dopaminergic input to the PFC is necessary for LTP to occur at the synapses and can facilitate the induction of LTP. Studies have shown that dopamine interacts with the glutamate system to regulate synaptic plasticity.[33,35] According to in vivo studies on anesthetized rats, it is suggested that dopamine modulates the efficiency of NMDA receptor-dependent LTP induced at hippocampal to PFC synapses.[34] Dopaminergic modulation can enhance NMDA receptor-mediated responses and decrease non-NMDA receptor-mediated responses; therefore, the ratio of NMDA and non-NMDA components in the transmission determines the action of dopaminergic modulation.[33]

Studies suggest that there are higher dopamine levels in female mice than in male mice in the PFC.[36,37] In mice prelimbic and infralimbic cortex, females have a higher number of D1R and a lower number of D2 receptors (D2R) compared to males. As a result, females show a greater D1R to D2R ratio from adolescence to adulthood.[37] Moreover, the mRNA levels of DARPP-32 have increased in the PFC of male Toll-like receptor-4 (TLR4) knockout (KO) mice compared to male wild-type mice. Furthermore, the study suggests that there are sex differences in DARPP-32 expression in the PFC, as the levels are higher in female mice than in male mice,[38] which suggests that it promotes synaptic potentiation in DARPP-32 KO mice. The study shows that it is important for the induction of both LTP and LTD.[38] In addition, sex hormones interact with each other and have a distinct impact on dopamine neurotransmission, shaping cognitive function in adolescence and adulthood. Some effects of sex hormones are seen in schizophrenia, suggesting a possible role for sex hormones in influencing risk for psychiatric illness via modulation of dopamine transmission.[39]

Dopaminergic innervation in the PFC plays a major role in working memory. However, dopaminergic loss in the PFC can lead to a deficit in the performance of working memory tasks in monkeys. D1 receptors are identified as the main regulators of working memory in monkeys.[33] In addition, they suggest that even though dopamine is essential for the maintenance of internal visuospatial representations, excessive release of dopamine or D1 receptors within the PFC will impair working memory performance.[33] A previous rodent study has shown that if either D1 or D2 receptors are blocked, this can impair rodents from switching from one strategy to another in a cross-maze, leading the number of errors to increase. This suggests that D1 and D2 receptors regulate learning to inhibit a learned response.[32] A study has shown that activation of the cAMP/PKA signalling pathways by dopamine at D1 receptors is necessary for working memory.[33] Moreover, the PFC is supplied by dopamine axons that modify PFC function via the D1R and D2R. Studies have shown that blocking D1 and D2 receptors in the PFC impairs learning of new stimulus-response associations and cognitive flexibility, but not the memory of familiar associations.[40,41] Many studies have revealed that dopamine neurons may play critical roles in neural mechanisms underlying reward-based learning. [40–42] Dopaminergic neurons are excited by rewarding events; these dopaminergic responses transfer from primary rewards to reward-predicting sensory cues. There is a rapid release of dopamine with the reward-predicting signals of dopamine neurons during associative learning.[43] The study suggests that variation in the DARPP-32 encoding gene, PPP1R1B, is associated with emotional learning. This is because DARPP-32 integrates dopaminergic and glutaminergic signalling, and emotional learning involves both dopaminergic and glutaminergic interaction, which implies that DARPP-32 influences emotional learning.[44]

Conclusion

In this research, I have delved into the BDNF, glutamate system, and dopaminergic pathways. Figure 3 illustrates the pathways of neurotransmitters and genes between synapses in the PFC. There are sex differences in gene networks affecting synaptic plasticity in the mPFC and which will cause different impacts on learning and memory.

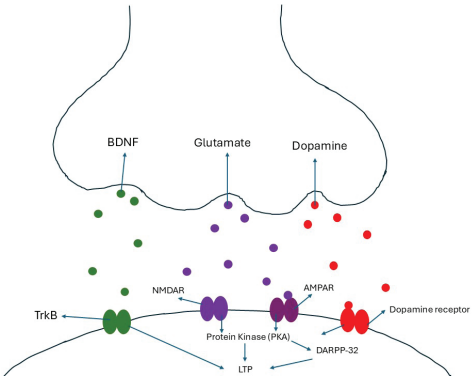

Figure 3: This figure illustrates the pathways of neurotransmitters and genes between synapses in the PFC. BDNF will bind to the TrkB receptor, which will lead to LTP induction. The neurotransmitter Glutamate will bind to NMDA and AMPA receptors, which activate the protein kinase and mediate LTP expression. Dopamine triggers D1-D5 receptors and activates protein kinase and the gene DARPP-32, which again mediates LTP induction.

In previous paragraphs, I have explored the BDNF levels in the mPFC, and females have higher levels of BDNF, which contribute to verbal tasks due to enhanced LTP and dendritic synaptic plasticity in the mPFC.[16] Synaptic plasticity also plays a key role in memory. In postmenopausal women, lower plasma BDNF levels can lead to worse memory performance and altered function in working memory.[18] There are sex differences in glutamate levels and receptor gene expression in the PFC. Within the mPFC, NMDA and AMPA receptors play an important role in synaptic plasticity and LTP, which modulate learning and memory processes. From previous studies, I have concluded that since spine density has increased after an increase of glutamate in the PFC, this suggests that memory is associated with the increase in spine density.[20] Moreover, if the GluN2A or GluN2B ratio increases, the LTD induction will increase, and the decrease in the GluN2A or GluN2B ratio will lower LTD induction. There is an association between sex differences in LTP and LTD with NMDA receptor subunits due to their roles in establishing long-term memory.[24] Lastly, I have explored dopaminergic pathways and the studies that help establish the role of dopamine in synaptic plasticity, which show that emotional learning involves both dopaminergic and

glutaminergic interaction and implicates that DARPP-32 integrates emotional learning.[44]

Due to the fluctuations of sex hormones, sex differences in gene networks at different ages vary.

Different levels of sex hormones at different stages of life, such as puberty, menopause, and old age, between males and females may have different influences on learning and memory. Sex-specific and age-specific research can help the development of treatment strategies for neurological disorders.

Acknowledgments

I would like to acknowledge my mentors, Dr Jorge Avila and Omar Singleton, for their contribution to this research and Indigo Research through which this research was conducted.

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Author

Hannah Li is a Year 12 student at Royal High School, Bath, UK. She is passionate about Psychology and Neuroscience. She plans on studying Psychology at university and hopes to grow to become a clinical psychologist. Currently, she is applying her knowledge to the GDST Psychology Cup competition.