Journal of Experimental and Basic Medical Sciences 2022;3(2):134-139

Review

Human Prefrontal Cortex: Regions and Functions

Ece Sarı[1], Oytun Erbaş[1]

ABSTRACT

Prefrontal cortex (PFC) has been referred to as the personality center in the human brain ever since Phineas Gage changed into another person after suffering damage to his PFC. Among the areas of frontal lobe, subregions of this area of the cortex perform the most important cognitive functions. All subregions are found related to important executive functions such as abstract reasoning, learning, decision-making, regulation of emotions, integrating inputs from the environment and reacting to them. Prefrontal cortex subregions perform their functions by working together with other brain regions and integrating them. Impairment in any of these subregions is connected to the majority of researched psychiatric disorders, such as anxiety, depression, and suicidal ideation, because of their crucial roles in behavior and psychology. Therefore, expanding data of the PFC studies especially in humans provides a new perspective on cognition and psychiatric disorders. In this review, the human prefrontal cortex and its functions were discussed.

Keywords: Cognition, neuropsychiatric disorders, prefrontal cortex

The human brain consists of three main parts cerebrum, cerebellum, and brainstem. Besides two cerebral hemispheres, the cerebrum consists of an outer layer and an inner layer which are gray and white matter, respectively. The gray matter is also called the cerebral cortex. The cortex is studied by dividing into four lobes: parietal, temporal, frontal, and occipital lobes.[1] These lobes, which have a high density of neurons, are found on the outer of the brain and are noted for their enfolding structure. The brain's enfolding with the sulcus and gyrus demonstrates how evolution permitted the brain to grow extremely large while remaining small at the same time. Social interactions, emotion control, human behavior, and personality are all regarded to be functions of the frontal lobe. The prefrontal cortex (PFC) is a critical component of the frontal lobe and is commonly examined by functionally dividing it into five regions: dorsolateral PFC (DLPFC), dorsomedial PFC (DMPFC), ventrolateral PFC (VLPFC), ventromedial PFC (VMPFC), and orbitofrontal cortex (OFC).[2-5]

It is said that the PFC is our "personality center"[6] which separates us from other animals. It's where we show off our wisdom, foresight, and understanding. The prefrontal cortex is responsible for both sensory and motor functions by processing inputs at any moment and comparing it to our other experiences and reacting to our surroundings. The importance of the PFC for humans as a personality center was first discovered in 1848 when Phineas Gage accidentally had damage to his PFC, especially in his orbitofrontal cortex. Unlike before the PFC damage, Phineas became a brash and aggressive man after the accident. Today we know that dysfunctions and lesions in PFC are directly related to various neuropsychiatric disorders.[7,8] Additionally, dysregulation of gene expression in PFC is found related to the pathophysiology of suicide.[9] Slower mental processing and personal changes such as loss of interest can be other examples of results of PFC damage in different parts of the PFC.[10] The prefrontal cortex lobes are found smaller in patients with depression when compared to healthy human lobes.[11] Following that, psychological stress is found

[1]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Turkey

Correspondence: Ece Sarı. Institute of Experimental Medicine, 41470 Gebze-Kocaeli, Türkiye

E-mail: eces409@gmail.com

Cite this article as: Sarı E, Erbaş O. Human Prefrontal Cortex: Regions and Functions. JEB Med Sci 2022;3(2):134-139.

doi: 10.5606/jebms.2022.1020

Received : June 3, 2022
Accepted : June 15, 2022
Published online : September 12, 2022

to be activating the PFC. Besides the psychological and cognitive effects, PFC also has a role in autonomous processes.[12] Even though these parts have common mechanisms, they work on different inputs.[13,14] Here, the aim is to collect and review the studies of these functions for each section of the PFC.

DORSOLATERAL PREFRONTAL CORTEX

The dorsolateral PFC is one of the most developed parts of the cortex during evolution. The DLPFC is mostly being studied because of the functions it performs in coordination with other cortical regions, thereby integrating all of the brain's processes. Most of the executive functions in the human brain are considered to be performed by the DLPFC.[15] Besides the complex cognitive functions such as working memory, creativity, decision making, executive functions on emotions, and value encoding, DLPFC also has a role in the sensory and affective mechanisms of the brain network.[16-18]

An interesting study on inequality aversion behavior showed that DLPFC activity is related to social preferences, which involve executive function and working memory.[19] One of DLPFC's roles has been suggested to be pain suppression. Activation of this part of the brain is revealed with several brain scannings, even though DLPFC is not the only region to have a role in pain regulation.[20] To understand the distinctive role of DLPFC in dynamic social behavior, functional magnetic resonance imaging (fMRI) is performed on humans while they are playing a video game. Besides the other findings of the research that are consistent with the cognitive literature, they found that the DLPFC is involved in the generation of social action prediction errors and the prediction of one's actions after seeing the actions of an opponent.[21]

Dysfunctional neural circuit cause and effect interactions that are related to DLPFC are examined for the pathophysiology of obsessive-compulsive disorder (OCD) with resting state fMRI (rs-fMRI). Although the specific neurology of OCD is not clarified yet, in addition to reduced DLPFC volume and thickness, rs-fMRI showed responsiveness is decreased throughout the planning task in OCD patients when compared to healthy individuals.[22] DLPFC has a suppressive role in posterior cingulate cortex (PCC) overactivation which is related to major depressive disorder (MDD) and therefore it is also studied as an MDD treatment.[23] Dysregulation of gene expression in DLPFC is related to schizophrenia.[24]

DORSOMEDIAL PREFRONTAL CORTEX

The dorsomedial PFC is the region of the brain that takes a prominent part in both the generation and regulation of emotion.[25] It is also the component of a large network that computes input from both social and nonsocial contexts and that relates this to decision-making based on the subjective value for self and others.[26] To understand the neural basis of rapid evaluation regarding romantic interactions, a study using fMRI collected the data of participants who were scanned while they were looking at the photos of the person they are going to date. It is found that the outcome of these interactions can be predicted by the activity of DMPFC. Judgment of physical beauty and the perception of a partner's personality are the two components of this romantic assessment and they can be predicted even at the first glance from the activity of the paracingulate cortex and rostromedial PFC (rmPFC) respectively.[27]

Another study focused on the neural basis of predicting others' preferences. In this case, participants tried to predict the other one's preference by looking at their faces. These predictions are significantly high. Increased activity of the DMPFC is suggested as the neural basis of this accuracy. Furthermore, DMPFC works together with temporoparietal junction (TPJ) and PCC/precuneus while estimation.[28] Anxiety and fear are also related to DMPFC functions. Anxiety level is predictable from the recruitment of DMPFC.[29]

According to a study performed to investigate the neural basis of thinking '*per se*' (by itself, spontaneously), activation of DMPFC, which is measured with fMRI, is correlated with spontaneous thinking more than spontaneous perception. Especially the anterior DMPFC is involved selectively in thinking per se. Thinking *per se* is therefore found related to more complex abstract functions.[30]

VENTROLATERAL PREFRONTAL CORTEX

Cognitive functions such as decision-making and goal-directed behavior are performed with the contributions of ventrolateral PFC. This region acts as a bridge between sensory and motor areas and receives information about the object's color and shape from the ventral visual pathway. The orbitofrontal cortex and the subcortical regions such as the midbrain and amygdala are involved in sending emotional and motivational information to the VLPFC. To mediate goal-directed behaviors, VLPFC integrates and uses information from different regions.[31] In particular, the left VLPFC is actively involved in the targeted recall of semantic information, that is, knowledge containing word meanings and information about objects or long-term knowledge in general. It is also revealed that any damage to the left VLPFC results in disruption of semantic functions.[32] The ventrolateral PFC is responsible for self-control in case of aggression. The blocking of goal-directed behaviors is defined as frustration, which then leads to aggression. In a study performed with non-invasive stimulation techniques, left and right VLPFC are stimulated to investigate this mechanism between frustration and aggression and they revealed the role of VLPFC in aggression.[30] These results are consistent with an earlier study that shows the regulatory role of VLPFC on aggressive behavior.[31] Scientists investigate irrational economic decisions, which are thought to be correlated with old age. It is found that the rationality of the economic decisions that older people made is related to their VLPFC integrity rather than their age.[32]

It is rational to assume that there is a relationship between psychiatric disorders and VLPFC due to its prominent functions. Near-infrared spectroscopy (NIRS) analysis showed a negative correlation between social avoidance and activation of right VLPFC. It is also suggested that social anxiety disorder (SAD) may be due to dysfunction of VLPFC.[33] Reduced gray matter volume in the right VLPFC is found related to suicidal ideation.[34] Over-activation of VLPFC is found in adolescents with a generalized anxiety disorder (GAD).[35]

VENTROMEDIAL PREFRONTAL CORTEX

The ventromedial PFC is the component of PFC that functions in learning by a goal-directed compression in its neural structure that involves reduced dimension in that area when learning a new concept. Adaptive compression and restriction of VMPFC are important to code cognitive maps or schematic models.[36] The ventromedial PFC is a critical region for the rewarding process of decision-making and computation of the value when achieving tasks, mostly by working together with the ventral striatum and PCC.[37] Functional magnetic resonance imaging analysis showed that the neural signals are directly proportional to reward. Dysfunction of VMPFC, because of a lesion, for example, causes impairment in decision-making. Studies show that patients with lesions in VMPFC make riskier decisions.[38] It is suggested as a modulator of the amygdala and caudate nucleus in reward-driven arousal control that affects the performance of the individual on the task involved in the research. The ventromedial PFC contributes to success with this mechanism.[39] Besides value-based decision-making, VMPFC acts as a regulator for negative emotions. This is revealed with research on humans, as well as research on monkeys and rodents. Interestingly, lesions in VMPFC cause a reduction in self-insight, including a reduction in embarrassment, regret, guilt, and shame while lesions in DLPFC are increasing self-insight and related negative emotions. It is known that humans with VMPFC lesions are less sensitive to depression and post-traumatic stress disorder and they are showing reduced physiological reactions to aversive stimuli. Depression is found related to hyperactivity of VMPFC but hypoactivity of DLPFC together.[40,41]

The ventromedial PFC is known to encode the value of safety to inhibit fear. Impairment of VMPFC is found related to GAD. Improvement of VMPFC function leads to coping with negative emotions better.[42]

ORBITOFRONTAL CORTEX

The orbitofrontal cortex is the large cortical area placed on the ventral surface of the prefrontal lobe. It is critical in predicting outcomes in order to make rational decisions, as well as in cognitive function.[43] It involves the secondary taste cortex and secondary and tertiary olfactory cortex. The orbitofrontal cortex performs learning in a stimulus-reinforcement manner with the stimulus it takes such as visuals, taste, and smell. Besides that, the analysis showed that OFC is also activated in more abstract stimuli such as losing or winning money. Face expressions are another visual information that reaches OFC. In case of any damage to OFC, stimuli-reinforcement learning and recognition of facial expressions are impaired.[44] Functions of OFC are defined by the patients with OFC lesions and their impaired social cognition, reversal learning, disinhibited behavior, pathologic gambling, obsessive-compulsive behavior or characteristic behaviors of autism, and psychopathy.[45] Dysfunction and altered structure of OFC is evident in depression. Grey-matter volume and the cortex thickness of posterolateral OFC are found reduced in patients with depression although it is not the only region with altered structure. Another dysregulation in the OFC area is seen in ventrolateral OFC with increased cerebral blood flow in patients with depression. Furthermore, medial OFC has been found to have decreased functional connectivity in depression.[46] Interesting research suggested that anhedonia, the underlying symptoms of depression, is related to dysregulated reward processing especially medial and right lateral OFC due to reduced gray matter volume. This study that is made with children who have depressive symptoms shows that gray matter volume can be a potential biomarker for early diagnosis of depression.[47]

It is known that motivated behavior is controlled by OFC. Studies showed that alcohol and drug abuse disrupts the OFC and reduces OFC volume, which then results in impaired cognitive functions in humans.[48] It is a bi-directional effect in which a drug alters the structure of OFC and reduced OFC volume leads to addiction which is characterized by maladaptive decision making.[49]

Dysfunction in OFC is suggested to be related to obesity. Researches show a correlation between body mass index and the right OFC gray matter volume. Even though, more research is needed.[50-56]

In conclusion, the roles of PFC subregions in various functions, most notably cognition, are highlighted in this review. Overall functions of PFC are behavior regulation, cognitive and executive functions, abstract thinking, and decision-making. Some subregions have major functions unique to them when executing these tasks, but they do not work independently. Instead, they collaborate from an integrating perspective. The subdivision of PFC is a practical way to investigate its functions. These functions are revealed with an analysis of brain scans. Activation or deactivation, overactivity or hypoactivity of a PFC region is observed in humans in relation to different functions. Maladaptive functioning of PFC subregions and decreased volume of PFC which is also found related to maladaptive functions are all together correlated with psychiatric disorders. These findings are promising for us to understand these functions and dysfunctions in psychiatric disorders to understand it better. Furthermore, it is promising as it inspires new treatments. It is important to note that the brain is a complex network of neurons and more comprehensive analysis should be increased in the literature to understand the roles of any subregion better. This is especially important for the PFC, which is said to be separating us from other animals. Cognition is also a broad term to investigate.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Jawabri KH, Sharma S. Physiology, Cerebral Cortex Functions. 2022 Apr 28. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–.
2. Javed K, Reddy V, Lui F. Neuroanatomy, Cerebral Cortex. [Updated 2020 Aug 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-.
3. Carlén M. What constitutes the prefrontal cortex? Science. 2017 Oct 27;358:478-82.
4. Kolk SM, Rakic P. Development of prefrontal cortex. Neuropsychopharmacology. 2022 Jan;47:41-57.
5. Dumontheil I. Development of abstract thinking during childhood and adolescence: the role of the rostrolateral prefrontal cortex. Dev Cogn Neurosci. 2014 Oct;10:57-76.
6. Köse SS, Erbaş O. Personality disorders diagnosis, causes, and treatments. D J Tx Sci 2020;5:22-31.
7. Hathaway WR, Newton BW. Neuroanatomy, Prefrontal Cortex. [Updated 2021 Jun 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-.
8. Celik S, Kayaaltı A, Erbaş O. NLRP3 Inflammasome: A New Target in Psychiatric Disorders. JEB Med Sci 2021;2:392-8.
9. Karabasoglu C, Gunes B, Erbas O. Suicide-Related Genes, JEB Med Sci 2021;2:18-26.
10. Paik E. Functions of the prefrontal cortex in the human brain. J Korean Med Sci. 1998 Dec;13:569-81.
11. Albayrak İ, Erbaş O. Experimental Models of Depression. JEB Med Sci 2020;1:117-25.
12. Van Eden CG, Buijs RM. Functional neuroanatomy of the prefrontal cortex: autonomic interactions. Prog Brain Res. 2000;126:49-62.
13. Zald DH. Orbital versus dorsolateral prefrontal cortex: anatomical insights into content versus process differentiation models of the prefrontal cortex. Ann N Y Acad Sci. 2007 Dec;1121:395-406.
14. Kuyucu E, Gümüs B, Erbas O, Oltulu F, Bora A. Exenatide promotes regeneration of injured rat sciatic nerve. Neural Regen Res. 2017 Apr;12:637-643.
15. Panikratova YR, Vlasova RM, Akhutina TV, Korneev AA, Sinitsyn VE, Pechenkova EV. Functional connectivity of the dorsolateral prefrontal cortex contributes to different components of executive functions. Int J Psychophysiol. 2020 May;151:70-9.
16. Seminowicz DA, Moayedi M. The Dorsolateral Prefrontal Cortex in Acute and Chronic Pain. J Pain. 2017 Sep;18:1027-35.
17. Nee DE, D'Esposito M. The hierarchical organization of the lateral prefrontal cortex. Elife. 2016 Mar 21;5:e12112.
18. Teo WP, Goodwill AM, Hendy AM, Muthalib M, Macpherson H. Sensory manipulation results in increased dorsolateral prefrontal cortex activation during static postural balance in sedentary older adults: An fNIRS study. Brain Behav. 2018 Oct;8:e01109.
19. Holper L, Burke CJ, Fausch C, Seifritz E, Tobler PN. Inequality signals in dorsolateral prefrontal cortex inform social preference models. Soc Cogn Affect Neurosci. 2018 May 1;13:513-24.
20. Seminowicz DA, Moayedi M. The Dorsolateral

Prefrontal Cortex in Acute and Chronic Pain. J Pain. 2017 Sep;18:1027-35.
21. McDonald KR, Pearson JM, Huettel SA. Dorsolateral and dorsomedial prefrontal cortex track distinct properties of dynamic social behavior. Soc Cogn Affect Neurosci. 2020 Jun 23;15:383-93.
22. Li H, Hu X, Gao Y, Cao L, Zhang L, Bu X, et al. Neural primacy of the dorsolateral prefrontal cortex in patients with obsessive-compulsive disorder. Neuroimage Clin. 2020;28:102432.
23. Takamura M, Okamoto Y, Shibasaki C, Yoshino A, Okada G, Ichikawa N, et al. Antidepressive effect of left dorsolateral prefrontal cortex neurofeedback in patients with major depressive disorder: A preliminary report. J Affect Disord. 2020 Jun 15;271:224-7.
24. Santarelli DM, Carroll AP, Cairns HM, Tooney PA, Cairns MJ. Schizophrenia-associated MicroRNA-Gene Interactions in the Dorsolateral Prefrontal Cortex. Genomics Proteomics Bioinformatics. 2019 Dec;17:623-34.
25. Kober H, Barrett LF, Joseph J, Bliss-Moreau E, Lindquist K, Wager TD. Functional grouping and cortical-subcortical interactions in emotion: a meta-analysis of neuroimaging studies. Neuroimage. 2008 Aug 15;42:998-1031.
26. Piva M, Velnoskey K, Jia R, Nair A, Levy I, Chang SW. The dorsomedial prefrontal cortex computes task-invariant relative subjective value for self and other. Elife. 2019 Jun 13;8:e44939.
27. Cooper JC, Dunne S, Furey T, O'Doherty JP. Dorsomedial prefrontal cortex mediates rapid evaluations predicting the outcome of romantic interactions. J Neurosci. 2012 Nov 7;32:15647-56.
28. Kang P, Lee J, Sul S, Kim H. Dorsomedial prefrontal cortex activity predicts the accuracy in estimating others' preferences. Front Hum Neurosci. 2013 Nov 26;7:686.
29. Geng F, Tian J, Wu JL, Luo Y, Zou WJ, Peng C, et al. Dorsomedial prefrontal cortex 5-HT6 receptors regulate anxiety-like behavior. Cogn Affect Behav Neurosci. 2018 Feb;18:58-67.
30. Raij TT, Riekki TJJ. Dorsomedial prefontal cortex supports spontaneous thinking per se. Hum Brain Mapp. 2017 Jun;38:3277-88.
31. Sakagami M, Pan X. Functional role of the ventrolateral prefrontal cortex in decision making. Curr Opin Neurobiol. 2007 Apr;17:228-33.
32. Badre D, Wagner AD. Left ventrolateral prefrontal cortex and the cognitive control of memory. Neuropsychologia. 2007 Oct 1;45:2883-901.
33. Gallucci A, Riva P, Romero Lauro LJ, Bushman BJ. Stimulating the ventrolateral prefrontal cortex (VLPFC) modulates frustration-induced aggression: A tDCS experiment. Brain Stimul. 2020 Mar-Apr;13:302-9.
34. Chen CY. Right ventrolateral prefrontal cortex involvement in proactive and reactive aggression: a transcranial direct current stimulation study. Neuroreport. 2018 Dec 5;29:1509-15.
35. Wearne TA. Elucidating the Role of the Ventrolateral Prefrontal Cortex in Economic Decision-Making. J Neurosci. 2018 Apr 25;38:4059-61.
36. Yokoyama C, Kaiya H, Kumano H, Kinou M, Umekage T, Yasuda S, et al. Dysfunction of ventrolateral prefrontal cortex underlying social anxiety disorder: A multi-channel NIRS study. Neuroimage Clin. 2015 May 28;8:455-61.
37. Zhang R, Wei S, Chang M, Jiang X, Tang Y, Wang F. Dorsolateral and ventrolateral prefrontal cortex structural changes relative to suicidal ideation in patients with depression. Acta Neuropsychiatr. 2020 Apr;32:84-91.
38. Monk CS, Nelson EE, McClure EB, Mogg K, Bradley BP, Leibenluft E, et al. Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. Am J Psychiatry. 2006 Jun;163:1091-7.
39. Mack ML, Preston AR, Love BC. Ventromedial prefrontal cortex compression during concept learning. Nat Commun. 2020 Jan 7;11:46.
40. Clithero JA, Rangel A. Informatic parcellation of the network involved in the computation of subjective value. Soc Cogn Affect Neurosci. 2014 Sep;9:1289-302.
41. Chau BKH, Jarvis H, Law CK, Chong TT. Dopamine and reward: a view from the prefrontal cortex. Behav Pharmacol. 2018 Oct;29:569-83.
42. Watanabe N, Bhanji JP, Tanabe HC, Delgado MR. Ventromedial prefrontal cortex contributes to performance success by controlling reward-driven arousal representation in amygdala. Neuroimage. 2019 Nov 15;202:116136.
43. Hiser J, Koenigs M. The Multifaceted Role of the Ventromedial Prefrontal Cortex in Emotion, Decision Making, Social Cognition, and Psychopathology. Biol Psychiatry. 2018 Apr 15;83:638-47.
44. Koenigs M, Grafman J. The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. Behav Brain Res. 2009 Aug 12;201:239-43.
45. Via E, Fullana MA, Goldberg X, Tinoco-González D, Martínez-Zalacaín I, Soriano-Mas C, et al. Ventromedial prefrontal cortex activity and pathological worry in generalised anxiety disorder. Br J Psychiatry. 2018 Jul;213:437-43.
46. Rudebeck PH, Rich EL. Orbitofrontal cortex. Curr Biol. 2018 Sep 24;28:R1083-8.
47. Rolls ET. The functions of the orbitofrontal cortex. Brain Cogn. 2004 Jun;55:11-29.
48. Jonker FA, Jonker C, Scheltens P, Scherder EJ. The role of the orbitofrontal cortex in cognition and behavior. Rev Neurosci. 2015;26:1-11.
49. Rolls ET. The orbitofrontal cortex and emotion in health and disease, including depression. Neuropsychologia. 2019 May;128:14-43.
50. Vandermeer MRJ, Liu P, Mohamed Ali O, Daoust AR, Joanisse MF, Barch DM, et al. Orbitofrontal cortex grey matter volume is related to children's depressive symptoms. Neuroimage Clin. 2020;28:102395.
51. Moorman DE. The role of the orbitofrontal cortex in alcohol use, abuse, and dependence. Prog

Neuropsychopharmacol Biol Psychiatry. 2018 Dec 20;87:85-107.
52. Schoenbaum G, Roesch MR, Stalnaker TA. Orbitofrontal cortex, decision-making and drug addiction. Trends Neurosci. 2006 Feb;29:116-24.
53. Chen EY, Eickhoff SB, Giovannetti T, Smith DV. Obesity is associated with reduced orbitofrontal cortex volume: A coordinate-based meta-analysis. Neuroimage Clin. 2020;28:102420.
54. Akdoğdu BS, Erbaş O. Subgenual anterior cingulate cortex and psychiatric disorders. D J Tx Sci 2021;6:45-51.
55. Erbaş O, Oltulu F, Yılmaz M, Yavaşoğlu A, Taşkıran D. Neuroprotective effects of chronic administration of levetiracetam in a rat model of diabetic neuropathy. Diabetes Res Clin Pract. 2016 Apr;114:106-16.
56. Artunc-Ulkumen B, Pala HG, Pala EE, Yavasoglu A, Yigitturk G, Erbas O. Exenatide improves ovarian and endometrial injury and preserves ovarian reserve in streptozocin induced diabetic rats. Gynecol Endocrinol. 2015 Mar;31:196-201.