

Prefrontal Cortex: Implications for Memory Functions and Dementia

Nurper ERBERK ÖZEN, Murat REZAKI

Abstract

Objective: The prefrontal cortex (PFC), which is one of the most complex areas of the human brain, is a frontal lobe segment that is consistently implicated in motor behaviors. In recent years it has been suggested that it is involved in memory functions via its diffuse anatomical networks. In this review, it was aimed to summarize the recent literature about PFC neuroanatomy, and its role in memory, normal aging, and dementias.

Method: We retrospectively reviewed the literature, including recent relevant studies. In addition, textbooks were included for essential themes. PubMed and the Google search engine were used, and the keywords chosen for searches were: prefrontal cortex, dementia/types, and memory.

Results: Although the PFC has considerable cognitive and social functions, only minor cognitive dysfunction is observed when the frontal lobes are severely damaged. It is possible to say that the memory deficits could be masked by rigorous behavioral symptoms. The PFC has a critical role in memory retrieval. There is growing evidence that the PFC is involved not only in frontal lobe-type dementias, but also Alzheimer disease, mild cognitive impairment, and normal aging. The psychiatric and behavioral symptoms in such cases may be related to PFC dysfunction.

Conclusion: Memory-related disorders are commonly associated with the frontal lobes and PFC. It may be considered that different parts of the PFC are related to different memory types and memory dysfunctions. Further studies with advanced neuroimaging techniques and valid animal models for all types and stages of dementias will help us to understand the role of the PFC in memory, physiology, and pathologies.

Key Words: Prefrontal cortex, memory function, dementia

INTRODUCTION

The frontal lobes (frontal cortex) constitute approximately one third of the cranial hemispheres. The prefrontal cortex (PFC, prefrontal lobe) is the name given to the anterior proximal region and the orbital surface of the frontal cortex. These are the frontal regions responsible for motor control of specific movements, such as eye movement, speech, and behavior. The size of the prefrontal cortex has increased phylogenetically and is currently an important region, constituting 29% of the human brain cortex (Fuster, 1997). Nevertheless, there is still no consensus regarding its relationship to behavior. This is due to the fact that although the integrative quality of the human brain has been suggested to lie mostly within this region, cognitive impairment caused by damage to the PFC has remained surprisingly rare. The first person

to report on the subject was Harlow in 1868; he documented the personality changes in a hardworking foreman named Phineas Gage following an injury caused by a crankshaft that pierced through the frontal lobes. This case is known as the "Phineas Gage" or "Boston Crowbar Case" in the literature. Phineas' speech, memory, sensory, and motor functions remained relatively intact, whereas, his strategic thinking, personality, emotional integration, and behavior were significantly impaired (Damasio, 1994; Mesulam, 2000). Apart from the behavioral symptoms, reports of memory impairment observed in PFC damage tend to be more recent. Clinical and neuropathological studies about the role of the PFC in dementias other than frontotemporal dementias (FTD) have increased in recent years.

In this paper the anatomical structure of the PFC and

its connections with the other parts of the brain, within the context of memory functions, are reviewed and changes in the PFC observed during the process of normal aging and dementia will be discussed.

Types of Memory

Memory can be classified based on different parameters by various authors. The classification of memory according to the time factor is widely accepted; however, there is no consensus on the classification of memory based on its content. Hering and Ebbinghaus created temporal classification at the end of the 19th century, followed by Atkinson and Shiffrin. They described 3 types: very short-term memory (immediate), short-term memory (working memory), and long-term memory. Subsequently, sensory memory, that is, storing information based on the data obtained from the sensory channels, was also added to the classification (Mesulam, 2000). Classification based on memory content can be roughly divided into 2 types: 1. Explicit (declarative) memory; 2. Implicit (non-declarative) memory. These can also be divided into subgroups (Figure I).

Roughly, explicit memory deals with information, whereas implicit memory has to do with abilities. Implicit memory is a term that is used to describe the condition in which an individual has an insight into the process of gaining and retrieving information; the term refers to having real information about people, places, things, and knowing what they mean. Implicit memory means that the individual is not aware of the process of gaining the information. Furthermore, the person might not even be aware that he/she has such information. Episodic memory involves nonverbal information pertaining to personal information and events, and it can be retrieved actively. Semantic memory involves verbal information about general realities and it is something that can be including the general knowledge of a person. For example, "I bought a book" is information that belongs to episodic memory, whereas "a book is read" belongs to semantic memory. Priming is a new concept that describes recognizing information without being conscious of it. For example, like the tests in which a person is expected to guess the rest of a picture in a puzzle with missing pieces. Conditioning, whether it is classic (learning the relationship between 2 stimuli) or processed (learning the relationship between a behavior and its consequences), consists of components involving emotional and musculoskeletal responses. Abilities and habits (procedural memory, working memory) are about gaining motor abilities, such as playing a musical instrument (Mesulam, 2000).

Neuroanatomy of memory and its relationship with the prefrontal cortex

The neuroanatomical infrastructure of memory has attracted the attention of many researchers. Short-term memory, or working memory, is associated with the parietal cortex and dorsolateral PFC. These regions keep information current. Information coding and information reinforcement are associated with the limbic system, storing is associated with the brain cortex, and retrieval is associated with the prefrontotemporal network. It has been observed that individuals with right frontotemporal damage have difficulty retrieving episodic information, whereas individuals with left hemisphere damage have difficulty accessing semantic information (Mesulam, 2000).

The PFC plays an important role, both in memory and in any behavior that requires attention. The PFC has intricate connections with almost all of the heteromodal, unimodal, paralimbic, and limbic parts of the brain cortex (Figure II). Because of these intricate connections the PFC can activate certain networks while inhibiting others and thus regulate the interaction between different networks (Kiernan, 2004).

The PFC has 2 surfaces, the medial and lateral. The medial PFC corresponds to Broadman's Area (BA) 25 and 32. The lateral PFC is divided into 3 different regions:

1. Anterior PFC: This region corresponds to BA 10. The areas corresponding to BA 11, 12, and 14 are adjacent to the frontal PFC and are called the orbitofrontal cortex (OFC).
2. Dorsolateral PFC: This region corresponds to BA 9 and 46.
3. Ventrolateral PFC: This region corresponds to BA 44, 45 and 47 (Simons and Spiers, 2003).

In studies conducted with amnesic patients and animals with experimentally-induced lesions, it has been shown that the basic anatomical regions associated with memory are the medial temporal lobe and the PFC. The medial temporal lobe consists of the hippocampus, fornix, amygdala, and the surrounding entorhinal, perirhinal, and parahippocampal cortices (Aggleton and Brown, 1999). These 2 regions are not only anatomically remote, but they are also thought to carry out their memory related functions independently of one another (Simons and Spiers, 2003).

For example, patients with lateral PFC damage have difficulty remembering the source of information or how

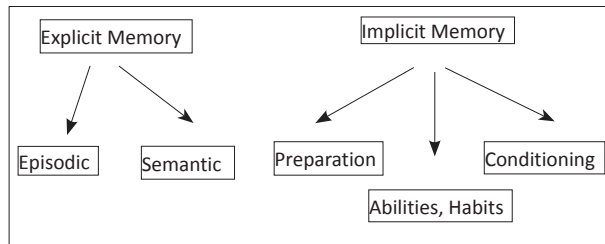


Figure I. Types of memory.

recent the information is, whereas patients with medial temporal region damage also demonstrate impairment in frontal region functions (Simons et al., 2002). In long-term memory the thalamus, mamillary bodies, and retrosplenial cortex are also known to play important roles (Simons and Spiers, 2003).

Although the importance of the medial region of the temporal lobes to memory has been known for 50 years, the information we have about the contribution of the frontal lobes to memory functions are relatively new. Among patients with damage to the frontal lobe, problems such as impulsivity, diminished inhibition, and impairment in regulatory functions are more striking and easily observed, memory disorders probably tend to be neglected (Simons and Spiers, 2003). In frontal lobe damage memory impairment becomes particularly obvious if there is significant interference among the retrieved stimuli (Incisa della Rocchetta and Milner, 1993).

In frontal lobe dysfunction confabulation is a memory disorder mainly associated with the anterolateral PFC. In confabulation, impairment in the specialization of retrieved information has been attributed to the anterolateral PFC, whereas impairment in the verification and control of retrieved information has been associated with the posterolateral PFC; therefore, in these patients it is possible to detect erroneous information and beliefs about themselves or events, and interesting distortions in their memories (Burges and Shallice, 1996). The mid-portion of the anterolateral PFC is the most important part involved in memory-related cognitive processes and is responsible for choosing and comparing stimuli, the decision-making process, keeping the stimuli in the long- and short-term memory, and transferring information to episodic memory (Rammani and Owen, 2004). The anterior PFC (BA 10) is the least understood PFC region and it has been suggested to play a role in retrieval. As a matter of fact, in patients with frontal lobe damage it has been observed that retrieval is more impaired than recognition (Petrides, 1994).

Although the PFC plays an important role in retrieval

al, its impact on other memory functions is not clear. For example, patients with PFC damage fail at remembering the source of information; however, they are relatively more successful at recognizing an object that they have seen before. Based on studies in this field, it has been suggested that the PFC has a fundamental role in retrieval and that its role is not very important in memory functions associated with recognition. Nonetheless, there are studies that do not support this point of view (Simons et al., 2002). For example, in patients with AFC damage, reward-associated and recognition-based learning is impaired. Furthermore, in functional imaging studies it has been found that in some patients with PFC damage, activation during recognition is greater than activation during retrieval (Rolls et al., 1994).

There are publications reporting that different parts of the PFC are associated with different memory processes. It has been reported that left frontal cortex plays a role in coding and the right frontal cortex plays a role in retrieval (Tulving et al., 1994); however, more recent studies have shown that PFC lateralization depends on the type of the stimuli that is remembered (Kelly et al., 1998). That is to say, the lateral surface of the PFC, especially the OFC, has been associated with the reward-dependent stimulus-response process (Elliot et al., 2000), while it has also been suggested that the lateral PFC contributes to the target-oriented cognitive processes. Other than carrying out these cognitive processes, the lateral PFC also encodes distinct memory traces, performs a strategic research afterwards, and retrieves and evaluates the stored memory projections (Fletcher and Henson, 2001).

There are differences between the anterior and

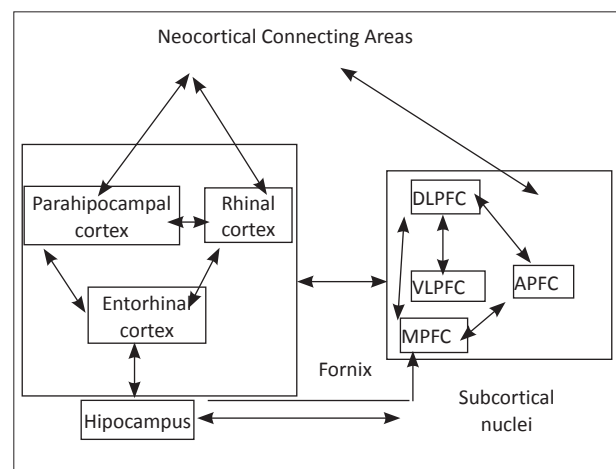


Figure II. Connections of the prefrontal cortex.

DLPFC: dorsolateral prefrontal cortex; APFC: anterior prefrontal cortex; VLPFC: ventrolateral prefrontal cortex; MPFC: medial prefrontal cortex.

posterior parts of the PFC. According to one point of view, the lateral PFC is responsible for the processing of information that is associated with the form of the objects, whereas the posterolateral PFC is responsible for processing of information that is associated with the location of objects (Wilson et al., 1993). According to another view, the difference between these 2 regions depends on the type of memory process, not on the stimulus type. Accordingly, the posterolateral PFC is responsible of encoding information into episodic memory, specialization of the correction clues, and continuation of the corrected information. In later studies it has been suggested that the anterolateral PFC can be divided into 2 regions, anterior and posterior. It has been proposed that the anterior region is associated with semantic processes and the posterior region with lexical/phonological-controlling processes. It has also been reported that the posterolateral PFC is responsible for organization of the stimuli before encoding them and that it verifies, controls, and evaluates memory projections that are retrieved from long-term memory, whereas the anterolateral PFC maintains continuity (Simons and Spiers, 2003). This post-retrieval process, which belongs to the anterolateral PFC also receives support from the anterior PFC; however, it has been suggested that the real mission of the anterior PFC in memory reinforcement is the internal evaluation of information that is of a higher cognitive function (Koechlin et al., 1999).

In most of the previous studies about the PFC, it has been emphasized that the main function of this region is associated with executive functions and working memory (Mesulam, 2000); however, recently another model has been reported, which shows that the PFC has a role in strategic encoding and retrieval of long-term memory. According to this model the PFC reinforces learning during repetitive encoding and retrieval sessions and thus forms codes that enhance memory, which in return are used as enablers while information is being retrieved from areas of the medial temporal lobe. This model confirms the interaction between the PFC and medial temporal lobe during the long-term memory process (Simons and Spiers, 2003). The fact that the left frontal cortex is activated during encoding has been supported by positron emission tomography (PET) and magnetic resonance imaging (MRI) studies (Buckner et al., 1997). In another study the relationship between the anterior and inferior parts (BA 45 and 47) of the left lateral PFC, and semantic memory has been emphasized, and it has been suggested that this area could be the semantically-functioning memory system (Gabrieli et al.,

1998). There are studies supporting the view that the proximal part of the left temporal region is also a part of this system (Martin and Chao, 2001).

PREFRONTAL CORTEX and DISORDERS of MEMORY

Dementia can be divided into 2 types based on their pathophysiological characteristics, or the 2 different types can be observed simultaneously; degenerative (Alzheimer's Disease (AD), Pick's Disease, etc.) and non-degenerative (vascular, due to endocrinological pathology due to infection). Degenerative dementias have markers, such as demonstrating a tendency to be located at particular places within the central nervous system, a tendency for genetic expression, and histopathological and biochemical markers. Dementias can also be divided into 2 types based on their clinical characteristics. The first are cortical dementias, which come to clinical attention with basic cortical function loss, such as aphasia, apraxia, and agnosia. Intellectual loss is especially prominent. Primary sensorial and motor areas are relatively spared and AD is a typical example. The second are subcortical dementias. Due to the involvement of the basal ganglia and related structures, movement disorders and neuropsychiatric symptoms are clinically more prominent, and the loss of mental functioning is widespread. Thought disorders, cognitive deceleration, retrieval disorders, and executive function disorders can be observed. Typical examples of this type are the Parkinson's disease and Huntington's disease (Kaufer and Dekosky, 1999).

Apart from dementia, the brain changes during the process of aging, which is currently being investigated with advanced neuroimaging techniques. MRI studies have shown that there is a 17% decrease in brain volume and an increase in the ventricular volume of individuals over the age of 60 years, compared to young subjects. This decrease in volume also shows regional characteristics. In one study volume decrease was not observed in BA 7 and 17 (parietal and occipital cortex) with increased age, whereas, volume decrease was observed in BA 6 and 11 (prefrontal and orbitofrontal cortex) (Wong, 2002).

Learning new information has been associated with the hippocampus and medial temporal lobe-limbic area circuits and its disorder is called anterograde amnesia. Remembering things that had been learned in the past is associated with the frontal-subcortical circuits and its disorder is called retrograde amnesia. Aging causes both hippocampal and prefrontal memory dysfunction. The hippocampus is associated with long-term memory

and the PFC is associated with working, or functional memory, both of which are negatively affected during the process of aging (Petersen et al., 2001).

Mild cognitive impairment (MCI) is a relatively new concept, which describes the condition in the middle of the continuum between overt dementia and normal cognition in the elderly (Unverzagt et al., 2001). The term is also used to describe individuals with cognitive impairment, but without dementia, who are probably in a prodromal pre-dementia period, with age-related impairment in memory and cognition (Petersen et al., 1999). Cognitive impairment without dementia is 2-5 times more common after the age of 65 years (Unverzagt et al., 2001). Generally, individuals have impairment in short-term memory, which does not impact their quality of daily life. This type is called amnesic type, the most commonly observed type. The level of impairment in cognitive functions, other than memory (e.g. executive functions), that is necessary for the condition to be called MCI remains controversial; however, it has been suggested that an increase in the amount of impairment in executive functioning also increases the risk for AD (Petersen et al., 1999). The risk of dementia is 5-10 times more in patients with MCI compared to healthy individuals (Petersen et al., 2001). In a case report about MCI it has been shown that in a non-demented patient with poor frontal lobe test results prior to autopsy, there was an increase in senile plaques, not in neurofibrillary tangles, which would have been in line with previous studies. In the light of the literature, it has been suggested that MCI is the frontal form and prodromal period of AD; however, it has also been reported that MCI could also be the predecessor of FTD, or vascular dementia (Johnson et al., 2004).

In AD there are pathological changes at the synaptic endings. In AD molecular studies looking into the synaptic defects or decreases in the number of synapses at the frontal lobe areas, the activities of the following proteins have been investigated: synaptophysin, which is one of the synaptic vesicle-fusion proteins; SNAP-25 (synaptosomal-associated protein of 25 kDA), which is a member of the complex SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) proteins; syntaxin; and choline acetyltransferase enzyme (ChAT). In AD, loss of synaptophysin is greater in areas where neurofibrillary tangles are scarce. During the early phases of the disease synaptophysin loss is more prominent at the outer layers of the dentate gyrus; however, in later phases the loss is observed to move towards the frontal regions. In another study, the posterolateral

PFC was investigated and the difference between the mild/medium stage cases and the controls, in terms of the previously-mentioned synaptic protein and ChAT activity, were not significant. Based on these findings it was suggested that in area BA 46 synaptic backups were adequate and that plasticity was spared until the later stages of AD (Minger et al., 2001). Generally, the pathological changes in AD are more intense over the medium temporal lobe, limbic area, and temporoparietal association areas (Kaufer and Dekosky, 1999). Neurofibrillary tangles are required for the diagnosis of AD, but they are not specific to the disease. Neurofibrillary tangles are not only found in the hippocampus, they are also observed within the neocortical circuit; however, they are less frequent in the primary sensorial and motor areas and the association cortex. This finding suggests that there can be different connection failures of the cortical pathways (Bussi re et al., 2003).

Recent studies have shown that the psychological and behavioral symptoms observed in AD, such as hallucinations, delusions, anxiety, anger, hyperactivity, and affective disorders, are associated with serotonin in the PFC, as well as acetylcholine. It has been shown that serotonin activates the 5HT_{2A} receptor in the PFC and thus increases secretion of amyloid precursor protein (APP), which is thought to play a role in the etiopathogenesis of the disease; however, it has also been reported that there is a decrease in 5HT_{2A} receptor binding. The 5HT₆ receptor in the PFC is a newly recognized receptor, which is thought to decrease acetylcholine secretion at the frontal cortex in AD, and like the 5HT_{2A} receptor, is thought to be associated with neuropsychiatric symptoms (Lorke et al., 2006).

Frontotemporal dementia is also known as FTD cognitive-behavioral syndrome (corticobasal degeneration). Although the most common cause of dementia is AD, many dementias also affect the frontal cortex and its associated subcortical structures (Stewart, 2006). FTD is commonly perceived as a dramatic neuropsychiatric entity, of which the risk of misdiagnosis is high (Neary et al., 1998; Boone et al., 1999; Stewart, 2006). This is thought to explain the rareness of this clinical presentation (Brun, 1993). Personality, adaptation, and judgment disorders are common in FTD. Personality changes can range from apathy to euphoria. Difficulty in decision-making and completing tasks, loss of interest, inability to empathize, and compulsive behaviors, such as counting and repeating, are among the reported behavior changes (Neary et al., 1998). The results of executive function tests, such as the Wisconsin Card Sorting Test

(WCST), and memory storage functions can be partially impaired (Miller et al., 1991, Boone et al., 1999); however, visuospatial functions are typically impaired. In some patients, neuropsychological test skills are not impaired during the early phases of FTD, whereas in some patients test performance can be normal, even after the onset of significant personality and behavioral changes (Miller et al., 1991; Lindau et al., 1998). Neuroimaging is generally helpful in the process of diagnosis. Computerized cranial tomography (CCT) and MRI frequently reveal prefrontal or anterior temporal atrophy (Ishii et al., 1998). PET and single photon emission computerized tomography (SPECT) findings are valuable (Talbot et al., 1998). On the other hand, there are very few studies investigating the structural cellular proteins in CSF (Sjogren et al., 2000). Genetic analysis for TAU gene mutations is used for research purposes (Poorkaj et al., 2001); however, it is neither practical nor economically feasible.

FTDs can be divided into 3 types according to their neuropathological basis, 3 of which are grouped together as frontotemporal lobar degeneration (FTLD):

1. Pick body (+), Tau (-), frontotemporal-dominant degenerative dementia;
2. Tau (+) corticobasal degeneration;
3. Tau (-), any other histological differentiation markers (-), and frontotemporal-dominant degenerative dementia (it has also been suggested that this entity could also be a form of AD with frontal lobe location) (McKhann et al., 2001).

The clinical course of FTD can vary. In some patients the time span between onset of the disease and the development of severe dementia can be as short as 3-5 years, whereas in some rare cases it can be 10 years. Infrequently, secondary FTD can be observed in AD (Johnson et al., 1999). No effective treatment is known (Knopman et al., 2003).

Clinical features of FTD:

1. Slow onset, rapid course;
2. Impairment in personal, social, and interpersonal behavior during the early phase;
3. Affective bluntness during the early phase;
4. Loss of insight during the early phase (McKhann et al., 2001).

Reduced inhibition, lack of concentration, impulsivity, and lack of perseverance can be added to the list.

These symptoms are associated with an intermediary unit, which involves the proximal part of the limbic system. This intermediary unit consists of the anterior cingulate, anterior insula, anterior part of the medial PFC, limbic ventral striatum, amygdala, and periaqueductal gray matter. This system evaluates the behavioral or emotional content of internal or external stimuli, determines errors, chooses responses, makes decisions, and then regulates context-dependent behavior as a result of whichever appropriate behavior is demonstrated. It is a very important system for human survival, which guarantees adaptive orientation of behavior. This intermediary unit consists of the specific connections between the sensorial and cognitive parts of the anterior cingulate cortex. BA 25 (medial PFC), and anterior regions of BA 33 and 24 have emotional functions, whereas BA 32 (medial PFC) and the posterior region of BA 24 have cognitive functions. This structure completes the process of information input and output at the amygdala, periaqueductal gray matter, anterolateral and anterior insular cortex, and the anterior striatum. The anterior regions of both of the medial PFCs take part in learning-related processes; they enable counter conditioning with the ventral striatum and contribute to the associative learning functions of the amygdala. The anterior part of the medial PFC and the connections that are closed with the anterior cingulate cortices are associated with higher functions, such as decision-making. In FTD, the medial portion of the PFC is particularly affected, and these functions can be damaged. In FTD, there is atrophy in some parts of the posterolateral PFC that are involved with executive functions (Boccardi et al., 2005).

Because the PFC is important for concentrating on novel stimuli, adaptation, and learning, in PFC damage, AD, and FTD there is a lack of interest in novel stimuli, which can be perceived as apathy or affective bluntness in clinical settings. In bilateral lesions of the prefrontally-located BA 8 and 46 areas, a decrease in interest in novel stimuli has been observed; however, it has been shown that the PFC is involved with maintaining interest in novel stimuli and duration of the gaze, whereas detection of novel stimuli has been associated with the hippocampus. The lack of insight observed in FTD patients has been associated with anterior insula lesions and this region has been designated as the basic structure for the evaluation of emotions by the somatic markers hypothesis. The anterior insula has been associated with feelings of disgust, eating behavior, language functions (mutism), and autonomic regulation (blood pressure, etc.), which can also be damaged in FTD (Charney et al., 1999).

CONCLUSION

Although the association between the PFC and cognition, behavior, and personality has been known for a long time, its relationship to attention, memory, and learning has only recently been the subject of research. This research has also been influenced by differences in opinion about the definitions of memory. Although according to one view, the PFC is particularly associated with attention and working memory, its relationship to encoding and retrieval still remains controversial. Connections the PFC has with the other circuits of the brain play important roles in memory. In normal aging and cognitive impairment ranging from mild to severe, the involvement of the PFC usually changes the picture. In

clinical presentations, such as amnesia, confabulation, MCI, AD, and FTD, in which memory is impaired, the number of studies supporting the involvement of different parts of the PFC is increasing. In dementias associated with the frontal areas of the brain, neuropsychiatric symptoms usually are observed. In cases with PFC involvement, striking behavior and personality changes might cloud our vision in terms of the other cognitive disorders. It can be said that clinical awareness of the possibilities of dementia is the most important facet of diagnosis. Neuropsychological tests, which are thought to be specific for the PFC, and neuropathological, neurochemical, and neuroimaging studies can help identify patients and illuminate the search for new remedies.

REFERENCES

- Aggleton JP, Brown MW (1999) Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *Behav Brain Sci*, 22: 425-489.
- Boccardi M, Sabatoli F, Laakso MP et al. (2005) Frontotemporal dementia as a neural system disease. *Neurobiol Aging*, 26: 37-44.
- Boone KB, Miller BL, Lee A et al. (1999) Neuropsychological patterns in right versus left frontotemporal dementia. *J Int Neuropsychol Soc*, 5: 616-622.
- Brun A (1993) Frontal lobe degeneration of non-Alzheimer type revisited. *Dementia*, 4: 126-131.
- Buckner RL, Kelly WM, Petersen SE (1999) Frontal cortex contributes to human memory formation. *Nature Neurosci*, 2: 311-314.
- Burges PW, Shallice T (1996) Confabulation and the control of recollection. *Memory*, 4: 359-411.
- Bussi re T, Gold G, K v ri E et al. (2003) Stereologic analysis of neurofibrillary tangle formation in prefrontal cortex area 9 in aging and Alzheimer disease. *Neurosci*, 117: 577-592.
- Charney DS, Nestler EJ, Bunney BS (1999) *Neurobiology of Mental Illness*. Oxford University Press, New York. p. 641-657.
- Damasio AR (1994) Descartes'in Yanılgısı ( ev. Atamaz B) (In Turkish), Varlık Yayınları, İstanbul, 1999. p. 17-88.
- Elliott R, Dolan RJ, Frith CD (2000) Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. *Cereb Cortex*, 10: 308-317.
- Fletcher PC, Henson RNA (2001) Frontal lobes and human memory: insights from functional neuroimaging. *Brain*, 124 (Pt 5): 849-881.
- Fuster J (1997) *The Prefrontal Cortex Anatomy, Neuropsychology of the Frontal Lobe*. Lippincott, Philadelphia. p. 6-42.
- Gabrieli JDE, Poldrack RA, Desmond JE (1998) The role of left prefrontal cortex in language and memory. *Proc Natl Acad Sci USA*, 95: 906-913.
- Incisa della Rocchetta A, Milner B (1993) Strategic search and retrieval inhibition: the role of the frontal lobes. *Neuropsychologia* 31: 503-524.
- Ishii K, Sakamoto S, Sasaki M et al. (1998) Cerebral glucose metabolism in patients with frontotemporal dementia. *J Nucl Med*, 39: 1875-1878.
- Johnson JK, Head E, Kim R et al. (1999) Clinical and pathological evidence for a frontal variant of Alzheimer disease. *Arch Neurol*, 56: 1233-1239.
- Johnson JK, Vogt BA, Kim R et al. (2004) Isolated executive impairment and associated frontal neuropathology. *Dement Geriatr Cogn Disord*, 17: 360-367.
- Kelly WM, Miezin FM, McDermott KB et al. (1998) Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. *Neuron*, 20: 927-936.
- Kiernan JA (2006, 14th August) Prefrontal cortex and temporal lobes. Downloaded from <http://instruct.uwo.ca/anatomy/530/530notes.htm>.
- Knopman DS, Boeve BF, Petersen RC (2003) Essentials of the proper diagnoses of mild cognitive impairment, dementia, and major subtypes of dementia. *Mayo Clin Proc*, 78: 1290-1308.
- Koechlin E, Basso G, Pietrini P et al. (1999) The role of the anterior prefrontal cortex in human cognition. *Nature*, 399: 148-151.
- Lindau M, Almkvist O, Johansson SE et al. (1998) Cognitive and behavioral differentiation of frontal lobe degeneration of the non-Alzheimer type and Alzheimer's disease. *Dement Geriatr Cogn Disord*, 9: 205-213.
- Lorke DE, Lu G, Cho E et al. (2006). Serotonin 5HT2A and 5HT6 receptors in the prefrontal cortex of Alzheimer and normal aging patients. *BMC Neurosci*, 7: 36.
- Martin A, Chao LL (2001) Semantic memory and the brain: structure and processes. *Curr Opin Neurobiol*, 11: 194-201.
- McKhann GM, Albert MS, Grossman M et al. (2001) Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. *Arch Neurol*, 58: 1803-1809.
- Mesulam MM (2000) Davranışsal ve Kognitif N rolojinin İlkeleri (In Turkish) 2. ed. ( ev. Ed. G rvit İH). Yelkovan Yayınları, İstanbul, 2004. p. 260-293.
- Miller BL, Cummings JL, Villanueva-Meyer J et al. (1991) Frontal lobe degeneration: clinical, neuropsychological, and SPECT characteristics. *Neurology*, 41: 1374-1382.
- Minger SL, Honer WG, Esiri MM et al. (2001) Synaptic pathology in prefrontal cortex is present only with severe dementia in Alzheimer disease. *J Neuropath Exp Neurol*, 60: 929-936.
- Neary D, Snowden JS, Gustafson L et al. (1998) Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*, 51:1546-1554.
- Petersen RC, Smith GE, Waring SC et al. (1999) Mild cognitive impairment. *Arch Neurol*, 56: 303-308.
- Petersen RC, Doody R, Kurz A et al. (2001) Current concepts in mild cognitive impairments. *Arch Neurol* 58: 1985-1992.

- Petrides M (1994) Frontal lobes and behaviour. *Curr Opin Neurobiol*, 4: 207-211.
- Poorkaj P, Grossman M, Steinbart E et al. (2001) Frequency of tau gene mutations in familial and sporadic cases of non-Alzheimer dementia. *Arch Neurol*, 58: 383-387.
- Ramnani N, Owen AM (2004) Anterior prefrontal cortex: Insights into function from anatomy and neuroimaging. *Nature Rev Neurosci* 5: 184-194.
- Rolls ET, Hornak J, Wade D et al. (1994) Emotion-related learning in patients with social and emotional changes associated with frontal-lobe damage. *J Neurol Neurosurg Psychiatry* 57: 1518-1524.
- Simons JS, Verfaellie M, Galton CJ et al. (2002) Recollection-based memory in frontotemporal dementia: implications for theories of long-term memory. *Brain*, 125: 2523-2536.
- Simons JS, Spiers HJ (2003) Prefrontal and medial temporal lobe interactions in long-term memory. *Nature Rev Neurosci*, 4: 637-648.
- Sjogren M, Rosengren L, Minthon L et al. (2000) Cytoskeleton proteins in CSF distinguish frontotemporal dementia from AD. *Neurology*, 54: 1960-1964.
- Stewart JT (2006) The frontal/subcortical dementias. Common dementing illnesses associated with prominent and disturbing behavioral changes. *Geriatrics*, 61: 23-27.
- Talbot PR, Lloyd JJ, Snowden JS et al. (1998) A clinical role for 99mTc-HMPAO SPECT in the investigation of dementia? *J Neurol Neurosurg Psychiatry*, 64: 306-313.
- Tulving E, Kapur S, Craik F et al. (1994) Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. *Proc Natl Acad Sci USA*, 91: 2016-2020.
- Unverzagt FW, Gao S, Baiyewu O et al. (2001) Prevalence of cognitive impairment. Data from the Indianapolis Study of Health and Aging. *Neurology*, 57: 1655-1662.
- Wilson FAW, O'Scalaidhe SP, Goldman-Rakic PS (1993) Dissociation of object and spatial processing domains in prefrontal cortex. *Science*, 260: 1955-1958.
- Wong TP (2002) Aging of the cerebral cortex. *McGill Journal of Medicine*, 6: 104-113.