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Examination of Brain-Derived Neurotrophic Factor, Glial Cell Line-Derived Neurotrophic Factor, and Neurotrophin-3 Levels and Brain Volumes in Shift-Working Men: Clinical Research

Nöbetli Çalışan Erkeklerde Beyin Kökenli Nörotrofik Faktör, Glial Hücre Dizisinden Kaynaklanan Nörotrofik Faktör ve Nörotrofin-3 Düzeylerinin ve Beyin Hacimlerinin İncelenmesi: Klinik Araştırma

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ABSTRACT Objective: This study aims to examine the levels of brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF) and neurotrophin-3 (NT-3) and brain volumes in shift-working men. **Material and Methods:** Forty-nine men who have been working in shifts for at least 1 year were included in the study. Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality, Montreal Cognitive Assessment (MoCA) test and trail making test (TMT) were used to assess cognitive performance, and Beck Anxiety Inventory (BAI) was used to assess anxiety level. Afterwards, plasma BDNF, GDNF and NT-3 levels were examined. Brain volume measurement was performed. **Results:** Since the PSQI results of shift-working men were above 5, it was determined that they had "poor sleep quality". According to the BAI results, 85% of them had anxiety. Primary-secondary school graduate shift-working men had lower MoCA value and TMT-A and TMT-B test scores were higher ($p<0.05$). Working in shifts for 6 years or more caused a significant decrease in BDNF and NT-3 levels ($p<0.05$). According to the correlation analysis results, it was observed that the prefrontal cortex, dorsolateral prefrontal cortex and cerebral cortex in the left lobe of the brain were smaller in elderly shift workers ($p<0.05$). **Conclusion:** There is a decrease in BDNF and NT-3 levels in shift workers of 6 years or more. Some brain regions associated with learning and memory have been found to be in smaller volumes in older shift workers.

Keywords: Sleep disorders; circadian rhythm; shift work schedule; neurotrophic factor; neurotrophin-3

ÖZET Amaç: Bu çalışmanın amacı, nöbetli çalışan erkeklerde beyin kökenli nörotrofik faktör [brain-derived neurotrophic factor (BDNF)], glial hücre dizisinden kaynaklanan nörotrofik faktör [glial cell line-derived neurotrophic factor (GDNF)] ve nörotrofin-3 (NT-3) düzeylerinin ve beyin hacimlerinin incelenmesidir. **Gereç ve Yöntemler:** Çalışmaya en az 1 yıldır nöbetli çalışan 49 erkek dâhil edilmiştir. Uyku kalitesini değerlendirmek amacıyla Pittsburgh Uyku Kalitesi İndeksi (PUKİ), bilişsel performansı değerlendirmek için Montreal Bilişsel Değerlendirme [Montreal Cognitive Assessment (MoCA)] ve iz sürme testi [trail making test (TMT)], anksiyete düzeyini değerlendirmek için Beck Anksiyete Ölçeği (BAÖ) uygulanmıştır. Sonrasında plazmada BDNF, GDNF ve NT-3 düzeyleri incelenmiştir. Beyin hacim ölçümü yapılmıştır. **Bulgular:** Çalışmamız sonuçlarına göre vardiyali çalişanlarin PUKİ sonuçları 5'in üzerinde olduğu için "kötü uyku kalitesine" sahip olduğu tespit edilmiştir. BAÖ sonuçlarına göre %85'inin anksiyeteye sahip oldukları görülmüştür. İlkokul-ortaokul mezunu vardiyalı çalışanların MoCA değerinin daha düşük, TMT-A ve TMT-B testi puanlarının ise daha yüksek olduğu görülmüştür ($p<0,05$). Altı yıl ve daha fazla vardiyalı çalışanların BDNF ve NT-3 düzeylerinin önemli düzeyde azaldığı belirlenmiştir ($p<0,05$). Korelasyon analizi sonuçlarına göre ileri yaştaki vardiyalı çalışanlarda beynin sol lobundaki prefrontal korteks, dorsolateral prefrontal korteks ve serebral korteksin daha küçük olduğu görülmüştür ($p<0,05$). **Sonuç:** Vardiyalı çalışma sisteminin uyku bozukluğu ve anksiyeteye neden olduğu tespit edilmiştir. Altı yıl ve daha fazla vardiyalı çalışanlarda BDNF ve NT-3 düzeylerinde azalma olduğu belirlenmiştir. İleri yaş vardiyalı çalışanlarda öğrenme ve bellek ile ilişkili bazı beyin bölgelerinin daha küçük hacimlerde olduğu tespit edilmiştir.

Anahtar Kelimeler: Uyku bozuklukları; sirkadiyen ritim; vardiyalı çalışma takvimi; nörotrofik faktör; nörotrofin-3

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Shiftwork refers to all kinds of working arrangements other than the traditional 9 am to 5 pm routine. Approximately 20% of the workforce in our country works in shifts. The shiftwork system can adversely affect not only one's sleep but also one's overall health.[1]

Sleep is very important for the maintenance of metabolic homeostasis, neuronal reactivation, and learning-related synapse formation (synaptic plasticity), and is essential for memory formation. Animal experiments show that sleep deprivation in rats causes impairment in cognitive function, especially in memory and spatial learning.[2]

Neurotrophins, known as neurotrophic factors, are a group of polypeptide growth factor families that affect the proliferation, differentiation, survival and death of neuronal and non-neuronal cells. It affects the life, growth and differentiation of the nervous system.[3]

Brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF) and neurotrophin-3 (NT-3) are a group of polypeptide growth factor families. Studies show that neurotrophins are associated with learning and memory.[4,5]

There are studies showing a decrease in neurotrophin levels in sleep disorders. The decrease in sleep quality due to shift work negatively affects attention and memory, as well as social lives. This can lead to deterioration of well-being and stress on individuals.[6,7]

In this study, shift-working men's sociodemographic information and information about shiftwork were obtained and the Pittsburgh Sleep Quality Index (PSQI) was applied to evaluate sleep quality. Montreal Cognitive Assessment (MoCA) test and trail making test (TMT) were used to evaluate cognitive performance, and Beck Anxiety Inventory (BAI) was used to evaluate anxiety level. It was examined whether there was a relationship between short and long-term shift work and PSQI, BAI, MoCA and TMT. When the literature is examined, there is no study examining BDNF, GDNF, NT-3 levels and brain volumes in shift workers. Therefore, this study aimed to examine shift-working men's BDNF, GDNF and NT-3 levels and brain volumes. Our research was only performed on men to single out the number of variables, as hormonal changes during women's menstrual cycle times can affect neurotrophins.[8]

MATERIAL AND METHODS

This research is a prospective observational study. Forty-nine men between the ages of 22-39, who have been shift-working for at least 1 year, were included in the study. Shift-work is based on shifts (minimum of ≥4 days/1 month) that only include night work starting from approximately 4 pm.

According to the duration of shiftwork, those who work for a short time (1-5 years) (n=25) are defined as Group 1 and those who work for a long time (over 5 years) (n=24) are defined as Group 2. Sociodemographic characteristics and information about shift work are presented in Table 1.

This study conform with the Declaration of Helsinki and was approved by our institution's ethics committee (with the approval of Kırşehir Ahi Evran University Faculty of Medicine Clinical Research Ethics Committee dated April 6, 2021 and numbered

TABLE 1: Sociodemographic characteristics and information on shiftwork.

	n=(%)
Jobs	
Soldier, taxi driver, waiter, business technician, team leader, transport business technician (other)	6 (12.2)
Electrical technician (with associate's degree)	4 (8.2)
Electrical technician (vocational high school graduate)	5 (10.2)
Nurse, health officer	7 (14.3)
Business technician	6 (12.2)
Private security	3 (6.1)
Police office, police captain	8 (16.3)
Cleaning staff	10 (20.4)
Duration of working in shift	
(Group 1) Shift workers for 1-5 years	25 (51.0)
(Group 2) Shift workers for 6-36 years	24 (49.0)
Age	
22-34	17 (34.7)
35-39	16 (32.7)
40 and over	16 (32.7)
Educational status	
Primary school-middle school	7 (14.3)
High school-associate degree	24 (49.0)
Bachelor's degree	18 (36.7)

2021-07/78). Informed consent was obtained from the patients.

In order to examine plasma BDNF, GDNF and NT-3 levels, approximately 5 cc of venous blood was taken into one ethylenediaminetetraacetic acid tube and centrifuged at 2000-3000 rpm for 20 minutes within 15 minutes and the separated plasmas were stored at -80°C until they were operated with kits. BDNF (pg/mL), GDNF (pg/mL) and NT-3 (pg/mL) plasma kits (Sunlong Biotech, Hangzhou, China) were read with Micro-plate Reader (KHB Microplate reader ST-360) at 450 nm.

Magnetic resonance imaging (MRI) is a medical imaging technique that provides a high-quality examination of soft tissues. It is used to detect anatomical, functional and structural changes. In our study, volume measurement evaluation was made from all cranial MRI. Using the T1-weighted axial image group on 3 Tesla MRI, the data that can be analyzed with Matlab 7.10.0 (The MathWorks, Inc. Protected by U.S. and international patents), one of the MRI processing programs, were measured and reported using volBrain, one of the volume measurement programs.[9]

The volBrain system gives volume information of brain-related structures at different scales and right and left asymmetry ratios. Volume measurement was performed in more detailed areas with the MriCloud application, which is a neuroimaging application, for the appropriate MRIs.[10]

PSQI evaluates the sleep quality of the last month. It is one of the commonly used tests. It is also widely used in shift work research. If the total score obtained from the index is less than 5 and 5, it is defined as "good sleep quality" and if it is above 5, it is defined as "poor sleep quality".[11] The MoCA was developed to detect mild cognitive impairment. MoCA is an effective scale, especially in the early period of cognitive effect. It is evaluated in 21 or more normal groups out of 30 points.[12] TMT, measures executive functions such as planning, which help to understand the skills of focusing and maintaining attention, and requires visual-spatial processing and motor capabilities. It consists of 2 stages, A and B.[13] BAI measures the frequency of anxiety symptoms experienced by the individual. It has a Likert-type scaling, indicating that as the total score increases, the anxiety experienced by the person increases. It contains 21 questions and lasts about 5-10 minutes. The validity and reliability of the test were taken.[14]

Before starting the study, the sample size was calculated with the GPower program (v3.1.9.6) (Heinrich-Heine-Üniversitesi, Almanya Düsseldorf). For short-term and long-term shift workers, when 25 people (total 50 people) in each group are included in the study, it was determined that the work would end with 80% power size. But one person gave up being in the study while the study was in progress. For this reason, 49 people were evaluated. Statistical analysis of the study, the comparison of the groups with significant differences as a result of analysis of variance was performed with Duncan multiple comparison test. Spearman correlation coefficient was used to evaluate the correlation since the data were not normally distributed according to the Shapiro-Wilk test. The significance level was taken as $p<0.05$.

RESULTS

When we look at the PSQI values in the comparison made according to the shiftwork time, it is seen that both Group 1 (7.52±3.65) and Group 2 (8.82±3.22) have "poor sleep quality" since PSQI results are above 5. However, there was no statistical significance between the two groups ($p>0.05$).

According to educational status, the PSQI score of the primary school-middle school group was found to be significantly lower than the other education levels (Table 2).

In the comparison made according to the duration of working in shift, it was found that the MoCA values of Group 1 (23.79±4.20) were lower than Group 2 (26.37±2.08) ($p=0.010$). However, the MoCA scores of both groups were above 21 and it was determined that there was no cognitive impairment in the early period of normal cognitive affect.

When we look at the comparisons of the groups according to the TMT-A scores; the MoCA values of the TMT-A score ≥38.82 group (22.25±4.39) were found to be significantly lower than the TMT-A≤34.83 and 38.83<TMT-A<38.82 groups (28.88±2.64, 28.5±0.70, respectively) ($p=0.002$).

TABLE 2: Results of PSQI, MoCA, BAI, TMT-A and TMT-B by educational status.

	Primary school-secondary school AM±SD Median (minimum-maximum)	High school-associate degree AM±SD Median (minimum-maximum)	Undergraduate AM±SD Median (minimum-maximum)	p[a]
PSQI	4.71±3.35[a] 4.0 (0.0-10.0)	8.91±3.14[b] 9.0 (2.0-14.0)	8.50±3.31[b] 8.0 (3.0-14.0)	**0.034**
MoCA	20.83±5.34[a] 22.0 (11.0-25.0)	25.83±2.35[b] 26.0 (21.0-29.0)	25.5±3.34[b] 27.0 (15.0-29.0)	**0.023**
BAI	8.83±12.33[a] 5.0 (0.0-33.0)	14.58±10.43b 14.5 (0.0-35.0)	7.11±6.95[a] 5.0 (0.0-22.0)	**0.035**
TMT-A	47.24±17.35[a] 44.26 (26.18-78.56)	29.22±11.77[b] 27.26 (14.50-71.52)	29.56±10.59[b] 27.12 (15.0-50.39)	**0.030**
TMT-B	123.34±40.62[a] 125.8 (64.01-168.0)	81.77±37.04[b] 71.85 (39.28-185.02)	57.46±30.37[c] 45.83 (26.34-127.17)	**0.002**

a,b,c : There is no significant difference between the averages shown with the same letter in the same line (p>0.05); PSQI: Pittsburgh Sleep Quality Index; MoCA: Montreal Cognitive Assessment; BAI: Beck Anxiety Inventory; TMT: Trail making test; AM: Arithmetic mean; SD: Standard deviation.

When we look at the comparisons of the groups according to the TMT-B scores; the difference between the TMT-B groups in terms of MoCA values is statistically significant MoCA values of TMT-B≤79.36 group (26.0±2.09) were found to be significantly higher than 79.36<TMT-B<90.13 and TMT-B≥90.13 groups (24.33±8.08, 23.26±4.19, respectively) (p=0.027).

According to educational status, the MoCA values of the primary school-secondary school group were found to be significantly lower than the other education levels. In the comparison according to educational level, TMT-A and TMT-B values of the primary-secondary school group were found to be importantly elevated than other education levels (Table 2).

In this study, it was determined that shift workers have 85% anxiety. Shift workers in our study have 10% severe anxiety, 16% moderate anxiety, 29% mild anxiety, and 29% minimal anxiety. In the comparison made according to the duration of working in shift, the difference between Group 1 (10.45±10.71) and Group 2 (11.66±9.40) was not statistically significant in terms of BAI scores measuring anxiety level (p>0.05).

According to educational status, BAI values of the high school-associate degree group were found to be importantly elevated than the other education levels (Table 2).

When we look at the comparison results made according to the shift working time, the difference between the groups in terms of BDNF and NT-3 values is statistically significant. BDNF and NT-3 levels of Group 1 were found to be higher than Group 2. The GDNF values of Group 1 were higher than Group 2, but this difference between the groups was not statistically significant (Table 3).

When Spearman rho correlation analysis results are examined, a statistically significant negative relationship was found between the duration of working in shift and BDNF (ρ=-0.333*, p=0.019). A statistically significant negative correlation was found between the duration of working in shift and GDNF (ρ=-0.317*, p=0.026).

According to the comparison made in the age groups, the BDNF, GDNF and NT-3 values of the participants in the 23-34 age group were found to be importantly elevated than the other age groups (35-39 years and 40 years and older) [respectively, 23-34 years, 35-39 years and 40 years and older, BDNF (pg/mL): 29365.38±7445.25, 23959.29±3493.44, 25501.619±2853.20, p=0.011; GDNF (pg/mL): 2608.14±1458.57, 1569.81±752.42, 1782.89±595.84, p=0.018; NT-3 (pg/mL): 2259.14±1505.56, 1213.86±613.13, 1316.15±479.58, p=0.007].

In this study; gray matter (GM) %, cerebrum (CB), amygdala (AMY), AMY % and accumbens (ACC) values were found to be smaller in Group 1

TABLE 3: BDNF, GDNF and NT-3 results according to the duration of working in shift.

	Group 1 AM±SD Median (minimum-maximum)	Group 2 AM±SD Median (minimum-maximum)	p value
BDNF (pg/mL)	28022.95±6409.56 27947 (20436.8-45639.8)	24583.85±3723.06 23592.45 (19132.5-31229.1)	0.027[a]
GDNF (pg/mL)	2261.88±1285.67 1957 (1021.2-5551.9)	1726.44±798.84 1371 (905-3457.8)	0.087[b]
NT-3 (pg/mL)	1912.65±1307.69 1349 (717.3-5423.4)	1294.57±681.84 1024.25 (670.4-3374.0)	0.012[b]

[a]Independent t-test; [b]Mann-Whitney U test; BDNF: Brain-derived neurotrophic factor; GDNF: Glial cell line-derived neurotrophic factor; NT-3: Neurotrophin-3; AM: Arithmetic mean; SD: Standard deviation.

when compared with Group 2 ($p<0.05$). No statistical significance was found in other brain regions. CB, AMY, ACC and GM are shown in Figure 1.

When Spearman rho correlation analysis results are examined, the relationship between the duration of working in shift and CB is positive and statistically significant ($\rho=0.387^{*}$, $p=0.032$).

Comparison results in age groups; ACC and ACC% values of the participants in the 35-39 age group were found to be significantly higher than other age groups (22-34 years and 40 years and over) (respectively, 22-34 years, 35-39 years, 40 years and over, ACC: 0.70±0.16, 0.83±0.13, 0.63±0.09, $p=0.005$; ACC%: 0.04±0.01, 0.05±0.01, 0.04±0.008, $p=0.013$).

There is a statistically significant negative correlation between age and superior frontal gyrus/prefrontal cortex left lobe (SFG.PFC_L) (r=-0.715; 0.013), middle frontal gyrus (dorsolateral prefrontal cortex) left lobe (MFG.DPFC_L) (r=-0.675; 0.023) and cerebral cortex left lobe (CerebralCortex_L) (r=-0.648; 0.031). CerebralCortex_L, SFG_PFC_L, MFG_DPFC_L and ACC are shown in Figure 2.

According to the correlation analysis results, there is a statistically significant negative correlation between the TMT-A score and frontal left lobe (Frontal_L) (r=-0.864; 0.001), SFG.PFC_L (r=-0.691; 0.019), MFG.DPFC_L (r=-0.68; 0.021), CerebralCortex_L (r=-0.656; 0.028) and Cerebral cortex right lobe (CerebralCortex_R) (r=-0.609; 0.047). There is a statistically significant negative correlation between TMT-B score and mammillary body left lobe (Mamillary_L) (r=-0.664; 0.026) and mamiller body right lobe (Mamillary_R) (r=-0.633; 0.036). CerebralCortex_R, CerebralCortex_L, Frontal_L, SFG_PFC_L, MFG_DPFC_L, Mammillary_R, Mammillary_L, putamen right lobe (Putamen__R), putamen left lobe (Putamen__L) are shown in Figure 3.

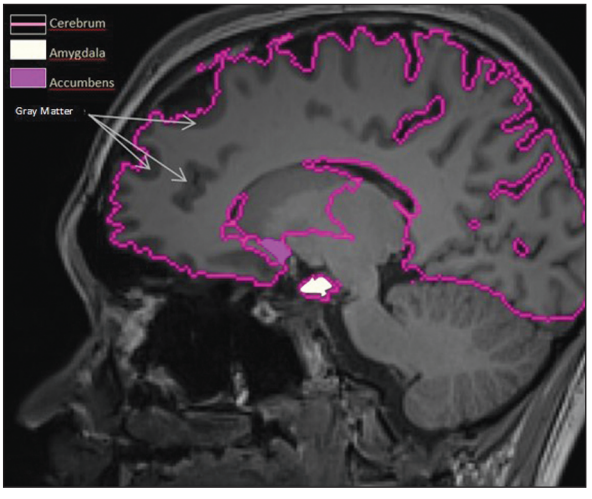

FIGURE 1: Cerebrum, amygdala, accumbens and gray matter in cranial magnetic resonance imaging sagittal image. The image was obtained from the Roieditor program. In order to show different regions on the same figure, the borders of the areas are marked by painting.

DISCUSSION

According to the results of our study, working in shifts negatively affects sleep quality. The PSQI results obtained show that shift workers have poor sleep quality. However, the PSQI results of the shift workers for 6 years and more and the PSQI results of the

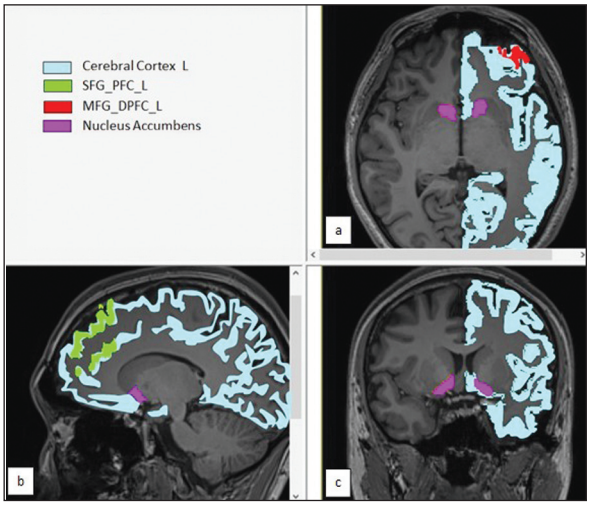

FIGURE 2: CerebralCortex_L, SFG_PFC_L, MFG_DPFC_L and ACC in cranial magnetic resonance imaging a.axial, b.sagittal and c.coronal image. The image was obtained from the Roieditor program. In order to show different regions on the same figure, the borders of the areas are marked by painting.
CerebralCortex_L: Cerebral cortex left lobe; SFG_PFC_L: Superior frontal gyrus/prefrontal cortex left lobe; MFG_DPFC_L: Middle frontal gyrus (dorsolateral prefrontal cortex) left lobe; ACC: Accumbens.

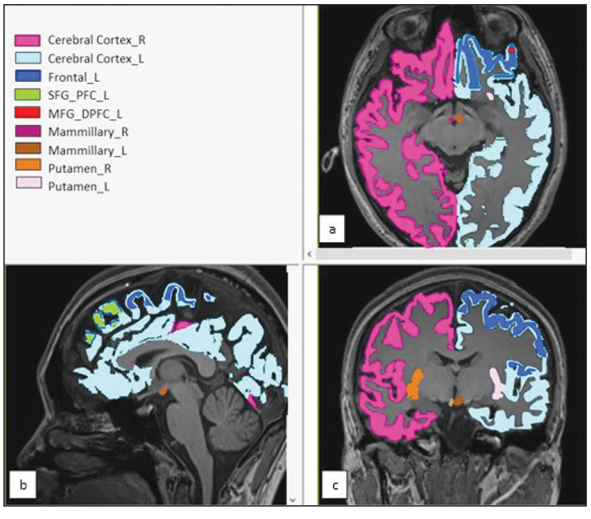

FIGURE 3: CerebralCortex_R, CerebralCortex_L, Frontal_L, SFG_PFC_L, MFG_DPFC_L, Mammillary_R, Mammillary_L, Putamen—R, Putamen—L in cranial magnetic resonance imaging a.axial, b.sagittal and c. coronal image. The image was obtained from the Roieditor program. In order to show different regions on the same figure, the borders of the areas are marked by painting.
CerebralCortex_R: Cerebral cortex right lobe; CerebralCortex_L: Cerebral cortex left lobe; Frontal_L: Frontal left lobe; SFG_PFC_L: Superior frontal gyrus/prefrontal cortex left lobe; MFG_DPFC_L: Middle frontal gyrus (dorsolateral prefrontal cortex) left lobe; Mamillary_R: Mamiller body right lobe; Mamillary_L: Mammillary body left lobe; Putamen—R: Putamen right lobe; Putamen—L: Putamen left lobe.

shift workers for 5 years and less were similar. In the studies in the literature, it was found that there was a significant relationship between the working time of nurses and PSQI, and it was reported that those working in shifts of more than 40 hours had worse sleep quality.[15] In the study conducted by Gülser et al., it was reported that sleep quality decreased as the number of night shifts increased in a month.[16]

MoCA and TMT tests were used to evaluate cognitive performance in our study. According to the results of our study, the MoCA results of shift workers for 6 years or more and those of 5 years or less were similar. There is no study in the literature examining the MoCA test results in shift workers, but when the MoCA results of patients with obstructive sleep apnea, a sleep disorder, and the healthy group were compared, it was found that the MoCA values of the healthy group were statistically significantly higher.[17]

TMT test results were found to be similar to those of shift workers for 6 years or more and those of 5 years or less. But, in a study conducted in Sweden, it was observed that shift workers performed worse in TMT for 5 years compared to those working without shifts.[18] Another study is showing that the time to complete the TMT test is prolonged in case of increased awake time during sleep hours and interrupted sleep.[19]

In addition, there are very important opinions in the light of developing science. For example, there are important opinions and studies about the fact that education levels are directly related to cognitive performance, even cognitive reservoir.[20] In our study, it is seen that the MoCA value of the primary school-secondary school graduates is lower and the TMT-A and TMT-B scores are higher. These results show us that primary-secondary school graduate shift workers spend more time focusing and maintaining their attention and have lower cognitive performance. Also, according to the results of the study, it was also determined that shift workers with high TMT-A scores had low MoCA values, and shift workers with low TMT-B scores had high MoCA values. There is no study in the literature examining the education level of shift workers and the MoCA and TMT test results, but in a study conducted with 593 people, it was reported that the risk of developing dementia in individuals with less than 8 years of education was 2,

2 times higher than those with more education.[21] According to the Turkish education system in which shift workers are included in our study, the education period is 5 years in primary school, 3 years in secondary school, 3 years in high school, 2 years in associate degree and 4 years in undergraduate.

In this study, it is seen that shift work time do not make a difference in BAI test results. However, a positive correlation was found between PSQI results and BAI results of shift workers, and the correlation value obtained was statistically significant. Psychometric measurements were made between shift workers and day workers for an average of 35 years and more than 2 years. According to the results of the study, insomnia, anxiety, depression and hyperactivity-anxiety levels were reported to be higher in shift workers.[22]

According to the results of our study, it was determined that there was a decrease in BDNF, GDNF and NT-3 levels in shift workers for 6 years or more compared to 5 years or less. According to the correlation analysis test results, a statistically significant negative correlation was found between shift work time and BDNF, GDNF, and NT-3. Working in shifts for a long time can impair the formation of long term potentiation (LTP), especially by negatively affecting synaptic plasticity, and thus lead to learning and memory disorders.

BDNF has been reported to be effective in learning and memory formation by triggering excitatory synaptic plasticity with LTP stimulation.[23] Studies have shown that BDNF is related to the regulation of the rapid eye movement (REM) and non-REM 3 stage, and chronic sleep deprivation decreases serum BDNF levels.[24] The relationship and mechanism of BDNF with cognitive characteristics have generally been examined in diseases or brain injuries that definitely affect cognitive functions, almost all of which have low BDNF plasma levels.[25] There are studies suggesting that GDNF and NT-3 are also associated with cognitive functions, including learning and memory.[4,26,27]

There is no study in the literature on how GDNF and NT-3 affects cognitive functions in the event of sleep disturbance or circadian rhythm disturbance. However, there are important studies on neural regenerative effects and studies on its relationship with diseases involving cognitive processes.[4,28] In this study, it was found that BDNF, GDNF and NT-3 levels of shift workers aged 23-34 years were higher than those aged 35-39 years and 40 years and over. In a study conducted in the literature, the shift duration and cognitive characteristics of 3,237 people were investigated. It was determined that cognitive functions decreased with age and increased with education level.[29]

Neuroimaging techniques have been used in many studies in recent years for anatomical and morphological examination in terms of cognitive functions.[30] In our study, it was determined that there was an increase in the volume of some brain regions with the increase in shift working time, but in the studies in the literature, results contrary to our study were obtained. A recent study found that shift workers had lower left thalamic GM volume on MRI.[31] In patients with severe obstructive sleep apnea syndrome, when compared to healthy individuals, there was no difference in the volumes of brain regions in MRI.[32] We think that the reason why the results of our study are different from the literature may be due to the fact that the age distribution and education level of the shift workers in this study are different. However, there is no study on this subject in the literature.

According to the results of this study, a statistically significant negative correlation was found between age and SFG.PFC_L, MFG.DPFC_L and CerebralCortex_L. It is seen that these regions of the left half of the left brain of elderly shift workers are smaller. Memory decline with age is associated with volumetric declines in the medial temporal lobe regions, which are particularly vulnerable to age-related shrinkage. Finding a way around and remembering the events that occur in a certain environment are very important cognitive abilities associated with the hippocampus and medial temporal lobes.[33] Also, it was determined that there was a negative correlation between some memory-related brain regions and TMT-A and TMT B scores. Accordingly, shift workers with higher TMT scores have smaller these brain regions. This result means they spend more time focusing and maintaining their attention. However, there is no study in the literature

examining the relationship between TMT scores and volumes in brain regions.

Adequate and timely sleep is essential for healthy cognitive ageing because it plays an important role in reinforcing memories, maintaining cognitive performance. Improving working hours and conditions in the night and rotating shift workers is necessary to prevent the negative effects in the long term. We think that our study will make an important contribution to the literature since many unstudied issues are discussed and the negative effects that may occur in shift workers are examined. There is a need for more research on the subject.

LIMITATIONS

It would be better if this study was carried out with people living in different cities in a multi-centered manner, since it would represent a larger number of people.

CONCLUSION

PSQI results obtained from our study show that shift workers have sleep disorders. According to BAI results, it was determined that most of the shift workers experienced anxiety. It was observed that primary-secondary school graduates had lower MoCA values and higher TMT-A and TMT-B test scores. It was concluded that the level of education was effective in cognitive function tests. It was determined that BDNF, GDNF and NT-3 levels, which are known to be associated with cognitive functions, were lower in long-term shift workers. When we look at the brain volumes of shift workers, it was found that GM %, CB, AMY, AMY % and ACC regions were larger in long-term shift workers. It was observed that the SFG.PFC, MFG.DPFC and CerebralCortex in the left lobe of the brain were smaller in the old age group working in shifts. It was determined that SFG.PFC_L, Frontal_L, MFG.DPFC_L, CerebralCortex of shift workers with high TMT-A score, and Mamillary_R and Mamillary_L of shift workers with high TMT-B score were small.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Mücahide Büşra Balcıoğlu, Dilek Kuzay Aksoy;* ***Design:*** *Mücahide Büşra Balcıoğlu, Dilek Kuzay Aksoy;* ***Control/Supervision:*** *Dilek Kuzay Aksoy;* ***Data Collection and/or Processing:*** *Mücahide Büşra Balcıoğlu, Görkem Tutal Gürsoy, Esra Oğuz Fırat, Elvan Evrim Tuna, Niyazi Acer;* ***Analysis and/or Interpretation:*** *Mücahide Büşra Balcıoğlu, Dilek Kuzay Aksoy, Görkem Tutal Gürsoy, Esra Oğuz Fırat;* ***Literature Review:*** *Mücahide Büşra Balcıoğlu, Dilek Kuzay Aksoy;* ***Writing the Article:*** *Mücahide Büşra Balcıoğlu, Dilek Kuzay Aksoy;* ***Critical Review:*** *Dilek Kuzay Aksoy.*

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