Turkish Journal of Psychology, December 2024, 39(94), 40-57 DOI: 10.31828/turkpsikoloji.1351431

Summary
Executive Functions and the Role of Working Memory in Recurrent Major Depressive Disorder

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Major Depressive Disorder (MDD) is an important mental health problem that is very common among psychiatric disorders. When the literature is examined, it has been seen that MDD patients with low executive functions have less response to treatment (Aydın, 2013; Cristancho et al., 2019). In this research, it was aimed to consider the factors and executive functions that are important in the relationship between the number of depression attacks and treatment compliance as a whole.

Executive Functions, Decision Making and Perceived Stress Level

Executive functions are independent, self-directed processes that determine what a person will do in a situation (Lezak et al., 2012). Working memory has an important role in executive functions (Smith & Kosslyn, 2013). In the present research, the role of working memory in executive functions has been reconsidered.

Miyake et al. (2000) divided the tasks of the executive functions into three as setup switching, updating and inhibition. These functions are associated with the frontal cortex, midbrain regions and anterior cingulate cortex, dorsolateral prefrontal cortex area, left frontopolar cortex and orbitofrontal cortex areas (Smith & Kosslyn, 2013). Recently, executive functions have been classified as warm and cool executive functions (Salehinejad et al., 2021; Zelazo et al., 2003). Accordingly, while cool executive functions are involved in abstract and contextual problems, warm executive functions are necessary for problems involving the regulation of emotion and motivation. Studies have shown that cool executive functions are related to the dorsolateral prefrontal cortex and warm executive functions are related to the orbitofrontal cortex (Smith & Kossyln, 2013). When we look at the position of decision-making behavior, which is defined as the best choice among possibilities, in executive functions, decisions taken in uncertain situations are associated with warm executive functions, and decision-making behavior in risky situations with cool executive functions (Smith & Kosslyn, 2013). However, Salehinejad et al. (2021) included both decision-making behaviors among the hot executive functions. According to the findings of the literature, there are different findings regarding the role of decision-making behavior in executive functions. In this research, the relationship between decision-making behavior and executive functions is discussed again. When we examined the concept of perceived stress, which reflects the subjective evaluation of stress experienced as a result of challenging events, inadequate coping resources and perceived level of control, it was observed that the amygdala, hippocampus, hypothalamus, prefrontal cortex, anterior cingulate cortex, medial prefrontal and dorsolateral prefrontal cortex areas were prominent (Ossewaarde et al., 2011; Treadway, Buckholtz & Zald, 2013). These findings provided information about why stress reactions are a chronic and wearisome process for some people, and also suggested that the concept of perceived stress may be included in the classification of executive functions, and this relationship was discussed in this research.

MDD and Executive Functions

Executive functions are adversely affected by the deterioration in prefrontal cortex functions. In studies comparing the MDD and control groups, it was observed that the MDD group showed lower performance in executive functions (Knight & Baune, 2012; Kotan et al., 2018; Varghese et al., 2022). Researchers have suggested that working memory capacity is weaker in MDD than in the control group (Parlar et al., 2016; Smith, Muir & Bla-

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ckwood, 2006; Stordal et al., 2004). Abnormal functional connections between the frontal and parietal regions in MDD patients contribute to working memory impairment in MDD (Cao et al., 2021). Li et al. (2021) stated that cognitive impairment primarily occurs with dysfunction between the frontaparietal network (Default Mode Network), this disorder manifests itself as deficiencies in attention, memory, and maintenance of attention, and these deficiencies improve during remission.In studies comparing MDD patients with first-episode and recurrent episodes, executive function skills were found to be weaker in the MDD group with recurrent episodes (Ardal & Hammer, 2011; Fossati, Ergis, & Allilaire, 2002; Karabekiroğlu et al., 2010; Liu et al., 2021; Must et al., 2006; Rizk et al., 2017; Stordal et al., 2004; Westheide et al., 2007). Decision-making processes of young adults and older individuals with MDD are more impaired than healthy individuals (Siqueira et al., 2018). In addition, it was observed that depressed adolescents were weaker in continuous attention and made more disadvantageous decisions compared to healthy controls (Han et al., 2011).

Some researchers have suggested that cognitive impairments reduce treatment response (Healy, Oei & Shaw 2017; Sneed et al., 2010). However, some studies have reported that cognitive functions of first-episode MDD patients improve after treatment and recovery (Baune, Sluth & Olsen, 2018; Frampton, 2016; Varghese et al., 2022) These findings show that impairments in executive functions may be factors related to the formation of depression and may improve with treatment, rather than negatively affecting adherence to treatment. However, some researchers have stated that the executive functions of individuals with MDD may become permanent (Gorwood et al., 2008; Zucherman et al., 2018). In another research conducted with MDD cases, it was observed that working memory has a moderating role in the effect of Brain-Derived Neurotrophic Factor (BDNF), a protein secreted both in the central nervous system and peripheral tissues, and Val66Met Polymorphism in the BDNF gene on the treatment responses of patients with depression (Bruijniks et al., 2020). In this research, it is seen that working memory, which is one of the most important components of executive functions, has an important role in the treatment of depression with its moderating effect on treatment compliance and response. In the literature, there are studies in which executive function functions are associated with treatment response in patients with MDD. Therefore, not targeting cognitive impairments in the treatment of MDD is considered as an important deficiency in the healing process, and evaluating executive functions is considered as a clinical necessity in terms of MDD. At this point, the answers to the questions of whether executive dysfunctions that occur as a result of the depressive process impair treatment compliance, or whether the deterioration in executive functions progress more as a result of depressive episodes that increase with low adherence to treatment is another curiosity of this research.

Method

Sample

The participants of research were selected by easy sampling from people with MDD who applied to Kartal Dr. Lutfi Kirdar City Hospital Psychiatry Outpatiant Clinic in 2020-2021. Participants are between the ages of 30-45, high school graduates and predominantly right-handed. The participants did not have any other psychiatric, neurological or hereditary disease, mental retardation, physical disability, alcohol, substance or drug use at a level that would affect cognitive processes.

Measures

Beck Depression Inventory (BDI), Morisky Treatment Adherence Scale (MTAS), Perceived Stress Scale (PSS), Wechsler Memory Scale-III, Letter-Number Sequence Subtest (LSS), Wisconsin Card Sorting Test (WCST), Stroop Test TBAG Form (STR) and Iowa Gambling Test (IGT) were used in the research.

Procedure

This research was conducted out quantitatively and cross-sectionally. Ethics committee approval required for the research was obtained from Kartal Dr Lutfi Kirdar City Hospital Clinical Research Ethics Committee. The application made (Decision No: 2020/514/169/8) was approved by the ethics committee convened on 02.01.2020. Participants who were diagnosed with first-episode and recurrent-episode MDD in the Psychiatry Outpatient Clinic were asked to read the informed consent form, and the General Information and Anamnesis Form, which was created by the researchers, was completed by conducting semi-structured interviews with the participants who agreed to participate in the research. Then, scale and test applications were started. In order to minimize the order effect, neuropsychological tests were applied in different orders.

Results

For the Moderator Analysis conducted in the research, the macro named PROCESS, developed by Andrew Hayes and working with the SPSS 21 package program infrastructure, was used. IBM SPSS Amos version 26 program was used for Structural Equation Model (SEM) analysis.

The Moderating Role of Working Memory in the Relationship Between Number of Attacks and Treatment Adherence

As a result of the analysis, it was seen that the model was significant and explained the change at the rate of 86% (R^2=.8621, F= 77.1217, p=.000). The interaction effect of the number of attacks and working memory variables on treatment adherence was also found to be significant (β=-.3344, p<.05). The summary values of the model obtained for the moderating effect are R^2-chng=.0191, F=5.1306, p=.029. In this case, the interaction explains a 1.9% change in working memory p<.05 significance level. As working memory performance increased and the number of attacks decreased, treatment adherance increased.

SEM Analysis Including Number of Attacks, Treatment Adherence, Working Memory, Inhibition, Perseveration, Perceived Stress Level and Decision-Making Variables

Goodness-of-fit index values of the SEM analysis data, which included the mentioned variables, were seen at a very good level, [X^2(56, N=41) = 51.444, p>0.5; x^2/df=.919; RMSEA=.000; CFI=1.000; IFI=1.011; NFI=.898].

In the model, inhibition ability (β=-1.09, p<.001) and perseveration (β=-.67, p<.001) of working memory were negatively affected, perceived stress level (β=1.02, p<.01) and decision making (β=.63, p<.001) was found to be a direct and significant positive predictor. In this case, it was observed that as working memory performance increased, the ability to perceive stress and decision-making performance increased, while inhibition and perseveration decreased.

When the model was examined, the independent variable of the number of attacks directly and significantly predicted the working memory mediator variable (β=-.65, p<.001). The working memory mediator variable also directly and significantly predicted the inhibition dependent variable (β=-.90, p<.001). Likewise, the mediator variable of working memory directly and significantly predicted the dependent variable of perceived stress level (β=.92, p<.01). In the model in which the mediator role was tested, a decrease was observed in the standardized path coefficient with the addition of the working memory variable in the relationship between the number of attacks and inhibition (β=.86, p<.001; β=.29, p>.05). Likewise, in the relationship between the number of attacks and the perceived stress level, the standardized path coefficient decreased with the addition of the working memory variable to the model (β=-.84, p<.001; β=-.18, p>.05). Thus, it is seen that the number of attacks affects the level of inhibition and perceived stress in MDD patients, and working memory has a mediating role in this effect.

In addition, the independent variable of working memory directly and significantly predicted the mediator variable of adherence to treatment (β=.77, p<.001). Treatment adherence mediator variable directly and significantly predicted perseveration dependent variable (β=-.70, p<.001). Likewise, the mediator variable of treatment adherence directly and significantly predicted the dependent variable of decision making (β=.64, p<.001). In the model in which the mediator role was tested, a decrease was observed in the standardized path coefficient with the addition of the treatment compliance mediator variable in the relationship between working memory and perseveration (β=-.67, p<.001; β=-.12, p>.05). Likewise, in the relationship between treatment adherence and decision making, a decrease was observed in the standardized path coefficient (β=.61, p<.001; β=.14, p>.05) with the addition of the treatment compliance mediator variable to the model. Thus, it is seen that working memory affects perseveration and decision making in MDD patients and treatment compliance has a mediating role in this effect.

Discussion

In this research, the relationships between the number of attacks and adherence to treatment and perceived stress level, inhibition, perseveration and decision-making skills in MDD patients were discussed. In the current research findings, it was found that working memory has a moderating role in the relationship between the number of attacks and treatment compliance behavior and supports the findings of the literature. In addition, this finding contributed to the literature in terms of behavioral observation of the moderating role of working memory in the effect of the number of attacks on treatment adherance.

At the same time, in the path analysis performed to determine the role of working memory, it was observed that inhibition of working memory significantly predicted perseveration and decision making. As is known, Barkley (1999) stated that working memory is one of the elements that prepare the ground for executive functions while classifying executive functions. At the same time, considering that Baddeley (2000) stated that the central manager in working memory is the basis of executive functions, it is seen that the current model is consistent with the literature. As a matter of fact, some studies have shown that other executive function performances differ according to working memory capacity (Ayhan, 2021; Kane & Engle, 2003; McCabe, 2010). At the same time, the findings obtained suggest that working memory can

also predict decision making, suggesting that working memory may have a determinative effect on both hot and cool executive functions. In addition, in the model created, it was seen that working memory also predicted the ability to perceive stress. In this case, it was thought that the ability to perceive stress was weakened due to the difficulty in working memory skills in MDD with recurrent attacks, and the appropriate coping skills could not be activated, so the exposure to stress continued. In addition, Zelazo et al. (2003) classified processes involving problems such as regulation of emotion and motivation as warm executive functions. Based on the present findings, it was thought that the skill of perceiving stress might be included in the class of hot executive functions and that working memory might predict the level of perception of stress along with decision making.

It has been stated in the literature that inhibition is directly related to the course of depression and is the first area to deteriorate in MDD, this deterioration progresses in a stable course and may not improve with treatment (Ardal & Hammer, 2011; Westheide et al., 2007). In the present research, it was observed that working memory had a mediating role in the effect of the number of attacks on inhibition. In other words, inhibition skill is affected by working memory performance rather than treatment compliance. Accordingly, it is seen that the obtained result is consistent with the literature. In another research, it was found that as the number of attacks increased, the perceived stress level decreased (Çebioğlu & Kafadar, 2023). The fact that working memory mediates the effect of the number of attacks on the perceived stress level has explained this relationship and contributed to the literature.

When the literature is examined, Knight and Boune (2018) stated that the perseverative tendency started to deteriorate with recurrent attacks. According to Liu et al (2021), the ability to change the setup does not improve after remission. When the decision-making skills were examined, no research was observed in the literature that discussed the changes after the treatment. Current research findings have shown that treatment compliance has a mediating role in the effect of working memory on maintaining setup and decision making in individuals with MDD. In this case, it is concluded that adherence to treatment is more important in maintaining the setup and decision-making, and these findings are considered important in terms of their contribution to the literature.

While some studies in the literature stated that executive functions improved after treatment in MDD patients, some researchers stated that executive functions did not return with treatment (Baune, Sluth & Olsen, 2018; Frampton, 2016; Gorwood et al., 2008; Varghese et al., 2022; Zucherman et al., 2018). In the light of the findings obtained in the current research, it has been seen that both treatment compliance and interventions for cognitive skills have an important role in the treatment of MDD. Cognitively, working memory functions were found to be more prominent in MDD patients. Because while working memory has a moderating role in the relationship between relapse and treatment compliance; it also played a mediating role in the relationship between the number of attacks, inhibition and perceived stress level. However, based on the research findings, it was determined that treatment compliance in MDD has an important role on perseveration and decision-making.

In line with these findings, it has been observed that treatments aimed at improving working memory capacity in MDD treatment protocols can be an important and effective method in reducing the cognitive losses of individuals, and at the same time, compliance with drug therapy for loss of executive functions is also of great importance. As a result, it was thought that cognitive intervention programs to be prepared to improve the working memory levels of depression patients in psychiatry clinics would contribute to increasing treatment compliance, reducing executive function losses, and thus minimizing the financial and moral burden of depression. It is predicted that it may be of great importance in the treatment process.

However, there are some limitations of the research. First of all, the number of participants remained at a limited level due to the COVID-19 epidemic conditions during the data collection process. Future studies with a larger number of participants and including the control group should be conducted. At the same time, it is thought that repeating the research in different age groups and education levels may be important in terms of generalizability of the findings.