

# Investigation of the Relationship between Anxiety Disorder and Time Perception with DRD2 rs1800497 Polymorphism

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## Abstract

We have many biological systems that regulate the perception of time, which is one of our most essential abilities that allows subjectively predicting, perceiving and understanding the duration of experiences, feelings and achievements. There are findings obtained from many studies aiming to illuminate the place and importance of time, which was the most critical reference point for human understanding of life in the past, for us mammals. According to these findings, it is observed that there is a similar mechanism that provides the perception of time in almost every living organism. Time perception is vital for the healthy functioning of cognitive activities, physiological needs and behavioral relations, and the bio-psycho-social order's systematicity. Among the studies conducted, the findings obtained in the studies related to the effect of psychiatric disorders on the perception of time are somewhat blurry compared to the others. The research for this study was based on six basic Polymorphisms known to affect time perception and internal clock mechanisms. These are as follows: SLC6A4 / 5-HTTLPR, 5HT2A / T102C, DRD2 / TAQ1A, SLC6A3 / 3UTR VNTR, COMT / VAL158MET, GABRB2 A/C, CLOCK. In our study, the relationship between the rs1800497 polymorphism, which is one of these seven polymorphisms that are effective in the functioning of the internal clock in the human brain, and the inventory used in the measurement of anxiety, was examined in 14 participants. Beck Anxiety Inventory (BAI) was used to measure anxiety, and PCR was used to detect genetic variants. When the findings were evaluated, no significant relationship was found between anxiety and DRD2 rs1800497 polymorphism.

**Key Words:** time perception, internal clock, retrospective time, prospective time, anxiety

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## Introduction

Perception of time, subjectively predicting, perceiving and understanding the duration of experiences, feelings and achievements is one of our most important skills (Bussi *et al.*, 2014). At the same

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time; It is the most effective reference point that guides our behavior. When we want to cross the line crossing, we wait for the green light for pedestrians. What allows us to see the green light come on is a series of visual grids, although this is somewhat different (Amalric and Koob, 1987).

Regions responsible for the formation of time perception in the human brain; Basal Ganglions are Prefrontal Cortex, Post Parietal Cortex, and Cerebellum. Serotonin, Acetylcholine, Dopamine, and GABA levels in these regions; the connections established by the relevant areas with each other; Many variables such as substance, alcohol and smoking habits of the individual have the effect of accelerating or slowing down the perception of time. Time perception is also affected by many physiological and environmental factors (Marinho *et al.*, 2017; Russell and Mehrabian, 1974).

The things that help us the most in understanding the perception of time are the internal clock models and related mechanisms (Wittmann *et al.*, 2019; Wittmann, 2015). In some studies, on this, the measurement of time perception was carried out based on time estimation. Time perception, embodied by short, medium, and long-term time estimates and responses, has been made more meaningful by using various statistical methods (Bruss *et al.*, 2010). In some studies, apart from the paradigm design; fMRI, EEG and Polymorphism detections were also made (Meck, 2005).

There is a similar mechanism that provides the perception of time in almost every living organism. With the help of this mechanism, we can interpret sensory inputs, compare them with each other, and accumulate our experiences (Baddeley, 1966). There are several psychological and biological approaches to understanding the characteristics of the clocks that work within us (Block and Zakay, 1997). This definition is defined through cognitive, physiological and behavioral relations; The order and systematicity of human behavior, thought, and life provides the internal clock. The internal clock, which is used to measure the duration, occurrence rate and temporal sequence of events, operates in the second-minute range. This disruption causes problems in the time perception of living things. This problem causes neurological, psychological and physiological disorders. (Church *et al.*, 1994; Meck, 1983; 1991; Meck and Angell, 1992).

Many systems in the human brain regulate the perception of time. The most well-known of these are the internal clock mechanisms. Studies conducted so far have identified seven basic Polymorphisms that are known to affect the perception of time. These are as follows: SLC6A4 / 5-HTTLPR, 5HT2A / T102C, DRD2 / TAQ1A, SLC6A3 / 3UTR VNTR, COMT / VAL158MET, CLOCKi GABRB2 A/C (Marinho *et al.*, 2018; Marinho *et al.*, 2017).

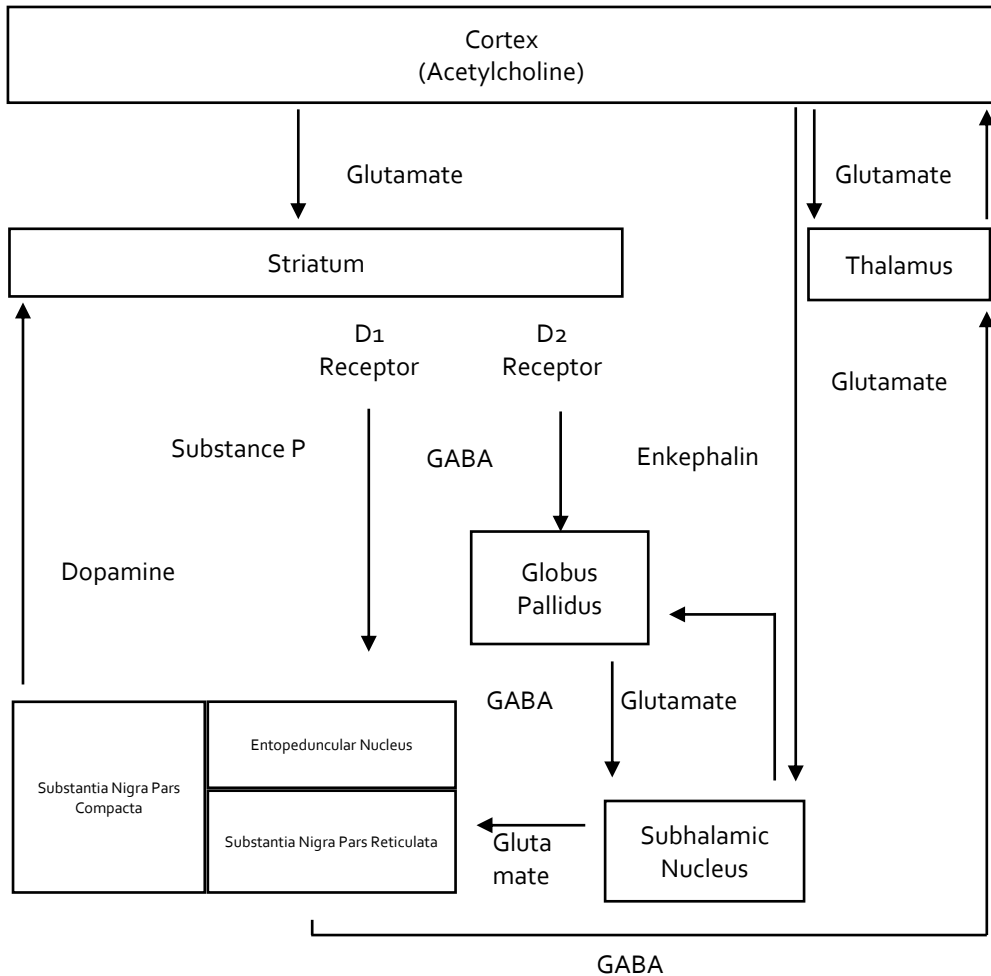
The gene region of the SLC6A4/5-HTTLPR polymorphism synthesizes the protein that transports serotonin to the synaptic gap. A decrease in reabsorption was detected in the S allele compared to the L allele. It is also estimated to be related to social anxiety, depression and time perception disorders (Sysoeva, 2010). The 5HT2A/T102C polymorphism is predicted to be related to perception capacity, interpretation and enhanced functions, and perception of visual stimuli in working memory (Sysoeva, 2010). Two variants of the DRD2 / TAQ1A polymorphism, known to be associated with Adenosine Az, have been identified (Wiener, Lee, Lohoff and Coslett, 2014). Between these two variants, a 20% to 40% decrease in neural activity is known. SLC6A3/3UTR VNTR polymorphism is related to dopamine levels; It is estimated that perception, working memory, temporal, cognitive and frontal region neural activities and caudal nucleus affect working performance (Bender *et al.*, 2012). The COMT / VAL158MET polymorphism, which is estimated to be related to enzyme activities in the prefrontal cortex, increases dopaminergic system activities (Maksimov *et al.*, 2015; Bender *et al.*, 2012). It is thought that CLOCK gene polymorphism also affects time perception. (Bartholomew *et al.*, 2015) Finally, GABRB2 A/C polymorphism, which affects GABA level, affects time perception (Marinho *et al.*, 2018).

It has also been shaped by the study of dopamine receptors, which are thought to be made up of three receptors. These receptors are D1, D2, and D3 receptors, respectively. As a result of the studies, it is presumed that the most effective type of receptor in detecting time and determining temporal effects is the D2 receptor (Meck, 1986; Dawson *et al.*, 1985; Keibarian and Calne, 1979).

The relationship between the activities of dopamine and glutamate in the striatum region and time perception has been known for a long time. This is one of the reasons for the internal clock data showing that frontal cortex outputs or inputs from the basal nucleus have an effect on the resulting temporal integration.

Drugs acting on the dopaminergic system are essential in determining their dopaminergic-glutamatergic interactions (Meck, 1996). These data suggest that lesions that cause a change in the intrinsic clock rate or cause differences in activation of corticostriatal neurons containing D2 receptors following anterior lobe lesions (Meck, 1986; Figure 1).

Figure 1. Neural Connections of Time Perception in The Brain



The deterioration observed in the perception of time in people with psychiatric disorders has inspired many past and future studies. Differing results were obtained in these studies, which mainly focused on attention deficit and hyperactivity disorder, Parkinson's, depression and schizophrenia, and these studies also aroused significant repercussions.

The state of anxiety and worry, which is a vital mechanism, is a mental and physical reaction, a defense strategy, against an event or fear that will threaten the survival of the living thing (Uzbay, 2002). In other words, anxiety is a necessary feeling for a person to continue their lives and protect themselves from threats from the outside world. Contrary to popular belief, humans and many living things are naturally ready for this situation on an evolutionary level (Karamustafalioğlu & Yumrukcal, 2011). The concept of anxiety, which began to be embodied in the sources of Hippocrates, who argued

that the root of all psychiatric disorders stems from the brain, was elaborated a little more with Otto Domrich. Until the 19th century, it was mentioned with the physiological symptoms it created in various systems and organs, and the studies on it were shaped in this way. Although anxiety symptoms were observed in clinical studies by the Austrian helm Ernst Freiherr von Feuchtersleben for the first time in 1847, the idea that changes in the autonomic nervous system caused the disorder started to be expressed by the French psychiatrist Bénédict Augustin Morel in 1866 (Berrios, 1996). The psychological definition of anxiety was first made by the father of psychoanalysis, Sigmund Freud, in the early 1900s (Gectan, 1981).

Although some studies show us that anxiety and time perception are related, very few studies examine this relationship in the genetic dimension. This research aims to contribute to the emergence of the relationship between anxiety and time perception.

## Materials and Method

The research sample consists of 14 randomly selected participants who want to participate in the study and meet the appropriate conditions. The age ranges are between 20-35. During the research, it was determined that variables such as socioeconomic factors, the use of drugs that are thought to affect the study, alcohol use, smoking and substance use history, hunger and satiety, sleep, and hormonal states (such as menstruation.). These variables did not affect the research data. It was assumed that the participants answered the inventories and tests used in the research honestly and sincerely.

**Demographic Information:** The purpose of using the demographic information form is to obtain detailed information about the individuals who contributed to the study and determine the effects on the hypothesis. In this regard, questions were formulated to complement the data to be obtained during the experiment. Information such as age, gender, education, and so on were recorded via Google Forms.

**Genetic Analysis:** DNA isolation was performed from the swab samples of the participants using the Swap DNA isolation kit. These samples were taken from the swap and exposed to Eppendorf five times on average; 400µl of ethanol was added and centrifuged for 1 minute, 700µl of the resulting mixture was taken and centrifuged at 6000 xg for approximately 1 minute. 600µl Wash Buffer was added to the resulting mixture in a new tube and 700 µl Wash Buffer was kept in the centrifuge. The resulting mixture was taken back to Eppendorf and 200µl of Elution Buffer was added, and DNA was obtained. The protocol is clearly stated in Table 1.

<b>Table 1. AGT PCR Protocol and Process Steps</b>	
Reaction Content	Measure (µl)
Assay	0,3
Master Mix	5
Thick DNA	2
Sterile Water	2,7
Total	10

DRD2 rs 1800497 genotype was obtained by real time PCR device and TaqMan DNP Genotyping Assays genotyping criteria. Primers were purchased from Termofisher Scientific. Genotypes were obtained by evaluating the irradiation of FAM and VIC dyes in PCR results. After the PCR application, alleles, genotype ratios, and frequencies in the relevant gene region of the DRD2 gene were determined.

**Beck Anxiety Scale:** This scale consists of 21 questions. Each question is evaluated between 0 (never) and 3 (severe), and high scores indicate increased anxiety complaints. Thus, the total score that can be obtained from this scale varies between 0 and 63. The high total score indicates the severity of the anxiety experienced by the individual. The Turkish adaptation of the scale was carried out by Ulusoy (1993) (Savasir and Sahin 1997). It is an easy-to-apply scale that individuals can answer on their own. It is stated that the Cronbach Alpha internal consistency coefficient of the scale is 0.93, the item-total test correlation coefficients vary between 0.45 and 0.72, and the test-retest reliability coefficients are  $r=0.57$  (Savasir and Sahin 1997). Within the scope of the current study, the Cronbach Alpha value of the scale was calculated as 0.90.

The scales were given to the individuals participating in the study, accompanied by standard instructions. They were randomly selected and asked whether they would like to participate in the research. The volunteer participants were read the informed consent form requested by the ethics committee, and their approval was obtained. Additionally, the study was approved by Uskudar University Non-Interventional Research Ethics Committee (61351342/2020-302); It was carried out according to the Declaration of Helsinki principles.

## Result

The research sample consists of 14 randomly selected participants who want to participate in the study and meet the appropriate conditions. Nine of the participants are female, and three are male. There were no results from the analyzes of one female and one male participant, or the result was out of the catalog.

As can be seen in Tables 2 and 3 below, there was no significant difference between the future time perception of the sample group

according to the independent t-test results applied to find the significant difference between the DRD2 rs1800497 Polymorphism results and the anxiety variable.

**Table 2:** Results Table of Independent t-Test Analysis for the Difference Between Beck Anxiety Inventory and DRD2 Polymorphism

	Beck Anxiety Scale	N	$\bar{X}$	Ss.	t	Sd.	p
<b>DRD2 rs1800497</b>	There are signs of anxiety	5	1,60	0,548	1,047	10	0,320
	No signs of anxiety	7	1,29	0,488			

p<0.05. N: Population size,  $\bar{X}$ : Mean, Ss: The sum of squares, t: measures the size of the difference relative to the variation in your sample data value, Sd: Standard deviation, p: Significance value

**Table 3:** Correlation Table Between Beck Anxiety Inventory and DRD2 Polymorphism

		Beck Anxiety Scale	DRD2 rs1800497
<b>Beck Anxiety Scale</b>	r	1	
	p	-	
	N	12	
<b>DRD2 rs1800497</b>	r	0,203	1
	p	0,527	
	N	12	12

p<0,05. r: Correlation coefficient, p: Significance value, N: Population size

## Conclusion and Discussion

Frontal and temporal systems in the brain show that the events that the individual encounters and experiences in his daily life are in the reference memory in a way that complements each other. While the findings in the frontal system cause the predicted time perception to shift in the positive direction, the findings of the hippocampal system cause a negative shift. In addition, some results were found in the effects of the stimulus on working memory in the interval before the arousal (Meck, 1988; Meck *et al.*, 1987; 1984; Olton *et al.*, 1987; Amalric & Koob, 1987; Bartholomew *et al.*, 2015).

The most critical variables that enable the basal ganglia to affect time perception are the excitatory input from the cerebral cortex and thalamus to the striatum. Neurons in this region are quiescent and generated by active excitatory input information (Kitai *et al.*, 1976). The neurons in this region that use GABA stimulate two different areas. The first is the entopeduncular nucleus and substantia nigra, located in the inner part of the globus pallidus. Studies show that the substantia nigra has a great importance in perceiving time with its D2 receptors (Magalhães *et al.*, 2018; Marinho *et al.*, 2018; Gerfen *et al.*, 1990; Engber *et al.*, 1990).

When the findings were evaluated, no relationship was found between anxiety and DRD2 rs1800497 polymorphism. Many systems in the human brain regulate the perception of time. Research so far has been based on six basic Polymorphisms known to affect time perception and internal clock mechanisms. These are as follows: SLC6A4 / 5-HTTLPR, 5HT2A / T102C, DRD2 / TAQ1A, SLC6A3 / 3UTR VNTR, COMT / VAL158MET, GABRB2 A/C, CLOCK.

In the way of understanding the inner clock of man, considering and evaluating all these variables simultaneously will be the best decision for the sake of future studies. In addition, the sample group should be formed with as many participants as possible. The most significant limitation of our study is the limited number of participants due to the COVID-19 outbreak.

Man's ability to perceive time, like time, has attracted the attention of many influential scientists throughout history; it has been the subject of thought and physical experiments. In the developing and changing world of science, our ability to perceive time with the development of medical sciences will continue to attract the scientific world's attention for a long time.

In this study, we tried to contribute to the research area on anxiety and time perspective with a different perspective. With future studies, the scientific world will have much more knowledge on this subject. The sensitive relationship between anxiety and time perception will come closer to losing its mystery day by day.

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### **Conflict of interest statement**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



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