Title: Binaural Beats Impact on Interval Discrimination: Association with Some Polymorphic Variants of Genes in Dopaminergic and Serotonergic Systems

Running Title: Binaural Beats Impact on Interval Discrimination

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To appear in: **Basic and Clinical Neuroscience**

Received date: 2026/01/28

Revised date: 2026/05/11

Accepted date: 2026/05/23

Please cite this article as:

Matloubi, H., Abolghasemi, M.M., Khodagholi, F., Asadi, S., Khosrowabadi, R. (In Press). Binaural Beats Impact on Interval Discrimination: Association with Some Polymorphic Variants of Genes in Dopaminergic and Serotonergic Systems. Basic and Clinical Neuroscience. Just Accepted publication Jul. 10, 2026. Doi: http://dx.doi.org/10.32598/bcn.2026.8518.1
DOI: http://dx.doi.org/10.32598/bcn.2026.8518.1

Highlights

- Interval Discrimination after binaural beats and control stimulations was improved significantly compared to the base condition.
- Improvement of Interval Discrimination by binaural beats compared to control stimulation depends on COMT, DAT, and HTR2A gene polymorphisms.
- Binaural beats may affect cognition or health differently depending on genetic polymorphisms.

ABSTRACT

Interval discrimination (ID), the ability to distinguish time between two consecutive sensory stimuli, is modulated by dopaminergic and serotonergic systems, with subjective variations partly related to genetic polymorphisms. Considering the importance of ID in daily life, the improvement of ID has raised interest in recent studies. Interventions using cognitive training, electrical or magnetic brain stimulation, and neurofeedback have been applied, but they all need specialized clinical settings. Therefore, Binaural beats (BB) stimulation, known to enhance various cognitive functions, could be a remedy; nevertheless, findings on its effectiveness remain controversial. In this study, we chose BB stimulation in the delta-frequency band to improve auditory ID in 39 healthy participants. ID task was performed using two-alternative forced-choice, and detection thresholds (DTs) were calculated for sub-second (standard interval=300ms) and supra-second (standard interval=1000ms) scales. Participants were genotyped for dopamine transporter (DAT), serotonin transporter (SERT), catechol-O-methyltransferase (COMT), and 5-HTT receptor type 2A (HTR2A) polymorphisms. We thereby found that BB intervention significantly improved ID in COMT (Val+), DAT (9R9R), and HTR2A (CC) genotypes at the supra-second scale. These findings emphasize the effectiveness of BB stimulation as a novel, accessible, and non-invasive intervention for improving ID and suggest that genetic variations of neurotransmitter systems could explain inconsistencies in BB studies.

Keywords: Interval Discrimination, Binaural Beats, DAT, SERT, COMT, HTR2A.

Introduction

Time perception (TP) is the subjective experience of the passage of time, which can be significantly different from objective measured time. Depending on the duration of sensory stimuli or the time between two consecutive sensory stimuli coded in CNS, an interval, it is called duration discrimination or interval discrimination (ID), respectively (Wittmann, 2013). TP involves various time ranges, from microseconds at the cellular level of opening and closure of ion channels or the time gap between the time that sound reaches each of the ears to the 24-hour circadian rhythms. However, the importance of milliseconds and seconds range in speech, music comprehension, and movement coordination has attracted the interest of many researchers to find a way to improve this ability (Nobre & Van Ede, 2018). A common way to improve TP has been through non-invasive interventions. Up until now the intervention techniques used have been: cognitive training (Hoodgar et al., 2022; Meegan et al., 2000; Nagarajan et al., 1998; Rammsayer, 1994; Westheimer, 1999; Wright et al., 1997), Transcranial Magnetic Stimulation (TMS), Transcranial Electric Stimulation (TES) (Mioni, 2020; Mioni et al., 2020; Wiener et al., 2018), as well as neurofeedback (Behzadifard et al., 2022; Moradi et al., 2024; Pillai et al., 2021).The need for a specialized laboratory or a specially equipped clinic with specialized operators is the main reason that motivated us to try and find an available and real-time intervention with none of the above requirements, namely, Binaural Beats.

First discovered in 1841 by Dove H W., binaural beats (BBs) consist of two sound waves with a small difference in frequency that reach each of the ears simultaneously. A third wave with frequency equal to the difference in frequencies of the former two originates from the medial nucleus of superior olivary complex, the first nucleus that receives auditory signals from both ears. This third wave then reaches the reticular formation, where it can make changes in the brain waves by releasing neurotransmitters (Perez et al., 2020). Depending on the original

frequency difference, the third frequency can be in one of delta, theta, alpha, beta, or gamma ranges. The resulting frequency not only originates from the brain stem, but it can also be detected on brain cortex as increasing synchrony in the specific frequency of the BB using Electroencephalography (EEG) or other signal detecting techniques. This phenomenon is known as brain wave entrainment (BWE) with a repeating external stimulus (Pratt et al., 2010). In one study, however, increasing synchrony in alpha band in the cortex has been detected using theta band BB (Ala et al., 2018).

Oster (Oster, 1973) was the first researcher to suggest the possibility of regulation, enhancement, and improvement of the brain wave patterns using BB. Its therapeutic effect could be through improvement of cerebral blood circulation, neuroplasticity stimulation, or neurophysiological cooperation between the two hemispheres (Aparecido-Kanzler et al., 2021). Various studies have shown that depending on the frequency range of BB, we can expect positive effects on mood regulation (Wahbeh et al., 2007), working memory (L. Wang et al., 2022), verbal memory (Tay et al., 2023), auditory sentence comprehension (Kim et al., 2023), relaxation (Krasnoff & Chevalier, 2023), attention (Basu & Banerjee, 2023), sleep disorders (Bavafa et al., 2023; Dabiri et al., 2022; Dini et al., 2022; Lee et al., 2022), disorders of consciousness (Liu et al., 2022), chronic pain (Gkolias et al., 2020), tinnitus (Bardsiri et al., 2022), mental fatigue (Axelsen et al., 2020; X. Wang et al., 2022), and parkinsonism (González et al., 2023). So far, there has been no research conducted on the effects of BB on TP. Therefore, we found it novel to use BB as a safe, available, and real-time intervention for improving time estimation accuracy.

In various neurologic and psychiatric diseases, especially those with dopaminergic or serotonergic bases such as Attention-Deficiency Hyperactivity-Disorder (ADHD), Parkinsonism, Schizophrenia, Autism, and Depression, TP may be affected (Fontes et al., 2016). There are also individual variations in TP among normal population, which a part of

that can be attributed to polymorphic variants of genes in neurotransmitter systems such as dopamine, serotonin, Gamma-Amino-Butiric Acid (GABA), or molecules of circadian system (Marinho et al., 2018).

Dopamine transport at the presynaptic terminals is mediated via Dopamine Transporter1 (DAT1) protein encoded by SLC6A3 gene. SLC6A3 3'-UTR (Untranslated region) VNTR (Variable number tandem repeat) polymorphism located at the untranslated 3' end of 15th exon of the gene includes 3 to 13 tandem repeats of a 40bp (base pair) piece of the gene. 9R (9 repeats) and 10R (10 Repeats) are the most frequent alleles found in normal population. Carriers of a 9R allele express less DAT protein in prefrontal cortex (PFC) and caudate nucleus compared to 10R homozygotes (Shih et al., 2006).

COMT gene, which codes for Catechol-O-Methyl-Transferase protein, is an enzyme responsible for the catabolism of dopamine and norepinephrine at synaptic clefts. COMT Val158Met polymorphism influences activity of the enzyme in PFC, increasing level of dopamine and dysregulating the nigrostriatal circuit. Carriers of Met (Methionine) allele (L) have lower enzyme activity and higher available dopamine, while carriers of Val (Valine) allele (H) have higher enzyme activity and lower available dopamine. Several studies have shown association of COMT Val158Met polymorphism with working memory disruption, affective disorders, lower attention levels, and higher risk for neurologic diseases. It is hypothesized that function of brain regions which are responsible for processing timing information or related cognitive functions is modulated by genetic polymorphisms such as COMT Val158Met (Marinho et al., 2018). PFC and striatal circuits show less activity under the effect of lower dopamine levels in COMT knocked-out rats (Meck et al., 2012). Each of the three phases of timing processing (clock phase, memory, and decision-making) can also be affected by this polymorphism. In this model, dopamine basically affects the clock phase. Higher dopaminergic signaling leads to a higher speed of the internal clock, changing the signal processing and

disrupting time judgments. The most accurate timing would occur at intermediate dopamine levels (Meyer-Lindenberg et al., 2005).

SLC6A4 is a gene that encodes the SERT (Serotonin Transporter) protein, responsible for transporting serotonin from the synaptic cleft back to the nerve cell's terminal (Berger et al., 2009). Studies have shown that serotonin regulates TP over seconds to minutes (Marinho et al., 2018). There is an Insertion/Deletion polymorphism in the 5' regulatory premotor region of the gene. The short (S) allele expresses lower SERT compared to the long (L) allele. So, carriers of an S allele have higher levels of available extracellular serotonin compared to carriers of two copies of the L allele (Beevers et al., 2007). Fallgatter et al. have shown that subjects having one or two copies of the S allele have higher brain activity and fewer errors in memory and timing (Fallgatter et al., 2004). Associations of SLC6A4 5-HTTLPR polymorphism with neurologic and psychiatric disorders involving TP-related cognitive disturbances have been reported (Marinho et al., 2018).

Studies have shown the correlation between HTR2A polymorphism and different aspects of cognition (Bekinschtein et al., 2013; Burt & Mikolajewski, 2008). This gene is responsible for coding the serotonin post-synaptic receptor type 2A (5-HTR2A) (Bekinschtein et al., 2013). This gene influences the potential for stimulus perception and executive functions (Burt & Mikolajewski, 2008). One of the most remarkable SNPs (single nucleotide polymorphisms) of the HTR2A, which has been studied extensively, is T102C (Thymine102Cytosine) or rs6313. TT genotypes show higher expression of 5-HTR2A compared to CT heterozygotes or CC homozygotes. Molecular studies with pharmacological models suggest that this polymorphism changes the timing of visual stimuli in working memory tasks (Bekinschtein et al., 2013). It seems that any change in the density of 5-HT2A receptors facilitates disruption in time estimation and increases the risk for neurologic and psychiatric diseases (Goldman et al., 2010).

In the present study, we aimed to investigate the application of BB as a novel, safe, real-time, and available intervention to improve TP in daily life without the need to use specific settings required in conventional interventions. In this regard, we implied BB in the delta band frequency (2 Hz), based on our pilot study, to improve auditory interval discrimination in sub- and/or supra-second ranges. In addition, we investigated whether this effect was related to gene polymorphisms, including DAT (SLC6A3 3'-UTR VNTR), COMT Val158Met, SERT (SLC6A4 5-HTTLPR), and HTR2A T102C as the critical genes in dopaminergic and serotonergic systems. Confirmation of our hypothesis on the effect of BB in improving ID would be useful in sports, musical playing and appreciation, as well as daily life activities such as driving. In addition, finding an association between the BB effect and genetic polymorphisms of neurotransmitter systems would be a potential resolution to the discrepancies observed in the outcomes of BB studies in various cognitive and health areas.

Materials and Methods

Participants and Ethics

51 right-handed university students aged 18-35 who filled both the DASS-21 and GHQ-28 assessment questionnaires were tested for depression, anxiety, stress levels, general health, and social function criteria. Sociodemographic data were gathered through interviews based on a questionnaire including age, sex, marital status, ethnicity, educational level, occupation, hearing ability, history of psychiatric or neurological diseases, any kind of abuse, and any medical treatments. Moreover, caffeine, tobacco, alcohol, or substance abuse were also considered as exclusion criteria.

Based on questionnaire scores, 39 participants, including 13 males and 26 females, aged 18-35 (27.59$\pm$5.61 as mean$\pm$SD) with intact hearing abilities, and no individual or familial history of neurological or psychiatric disorders, were included in the study (Figure 1).

Participants were asked not to use caffeine or tobacco on the morning of the test day. All participants gave written informed consent before the study. The study was performed in accordance with the 1964 Helsinki regulations and with approval from the Research Ethics Committee of Neuroscience Research Centre, Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.MSP.REC.1402.266).

Genetic Polymorphisms

Blood Sampling and Collection

A three ml venous blood sample was drawn from each participant into sterilized EDTA (Ethylene-Di-amide-Tri-Acetic acid) vacuum tubes. EDTA-treated peripheral blood samples were then stored at -20°C to be used on test day. DNA extraction was performed using the salting-out method according to previous studies with minor modifications (Maurya et al., 2013).

Polymerase Chain Reaction (PCR)

DNA samples were amplified by Polymerase Chain Reaction (PCR) using a Bio-Rad T100 Thermal Cycler under the following program settings: 95°C for 7 minutes, 30 cycles of three repeated steps (denaturation at 95°C for 45 s; annealing at 58°C (for rs6313), 64°C (for SERT and COMT), and 65°C (for DAT), for 30 s; and extension at 72°C for 30 s) and one final extension cycle at 72°C for 5 min. PCR amplification was performed using Taq DNA polymerase 2x Master Mix (Ampliqon, Odense, Denmark; www. ampliqon.com) with specific primers for COMT (rs4680) (forward: 5′-CGAGGCTCATCACCATCGAGATC-3′ and reverse: 5′-CTGACAACGGGTCAGGAATGCA-3′), for HT2A (rs6313) (forward: 5′-AGCTCAACTACGAACTCCCT-3′ and reverse: 5′-GTAAGGAGAGACACGACGGT-3′), for SERT (SLC6A4) (forward: 5’-GGCGTTGCCGCTCTGAATGC-3’ and reverse: 5’-

GAGGGACTGAGCTGGACAACCAC-3') and for DAT(SLC6A3) (forward: 5'-TGTGGTGTAGGGAACGGCCTGAG-3' and reverse: 5'-CTTCCTGGAGGTCACGGCTCAAGG-3').

Restriction Fragment Length Polymorphism (RFLP)

The PCR products were then digested with MspI restriction enzyme (Cat No #ER0541) for HTR2A (rs6313) SNP and with NlaIII (Cat No #ER1831) for COMT (rs4680) SNP according to the protocols outlined in the enzymes' catalogues with minor modifications.

Gel Electrophoresis

All the PCR products (and their digested counterparts) were subsequently loaded on 3% agarose gel to be separated through electrophoresis.

Interventions

Binaural Beats Stimulation

After testing different frequency bands such as gamma, beta, alpha, theta, and delta bands in our pilot study and checking the ID threshold results, the delta band (2 Hz) was selected as the test intervention for BB stimulation. Audacity software was used to apply a 2 Hz frequency as BB stimulation. 350 Hz was chosen as the carrier frequency to reach the right ear, and 352 Hz was chosen for the left ear. The total time length for subjects to listen to sound stimulation was 20 minutes.

Control Stimulation

For the control condition, 350 Hz (carrier frequency) was applied to both ears. The time and amplitude for the control condition were set at the same levels as for the BB intervention.

All 39 participants were tested to determine their auditory thresholds before the stimulations. After verifying their auditory thresholds to be in the normal range, the intensity of 25-40 db above thresholds, depending on the subject's tolerance, was adopted for the interventions. To apply both auditory stimulations, headphones were used.

The order for applying control and BB intervention was randomized among participants. Participants were not informed about the type of intervention, which means the study was single-blinded.

Cognitive Paradigm

Simple Stroop Test

Normal attention, as one of the inclusion criteria, was tested in all 39 participants using simple Stroop test once, to begin with, on the cognitive test day.

Second level of N-Back Test

To be tested for having normal working memory, as another one of the inclusion criteria, the participants went through a session of the N-Back test on the test day prior to the interventions. In addition, they performed two more sessions of the same test, one between control and BB stimulations, and the other after the interventions. Comparing these extra sessions with the first one determined whether the interventions affected participants' working memory as an indicator of their overall cognitive skills.

Interval Discrimination Task

On three occasions (prior to the interventions, between the BB and control stimulation, and after the interventions), each of the 39 participants underwent a 100-trial ID task consisting of randomized sub-second and supra-second trials. A 20-trial training session was introduced to

all participants prior to the first main 100-trial session. The task design was categorized as a two-alternative forced-choice paradigm. ID task was performed on the MATLAB platform using a specialized module. The module included two push-button keys, an LED light to give feedback during training sessions, a serial port for PC connection, and an output port for hands-free earphones (Figure 2). Each of the trials included two stimuli, and each of the stimuli consisted of two beep sounds separated by an interval. Participants were asked to choose the longer interval as the correct answer in each trial. The order of the presentation of the standard (t sec) and comparison intervals (t+Δt) was randomized. The difference in milliseconds between the short and long intervals (Δt) was adaptively changed based on performance, which helped to calculate an ID threshold. This meant that for every three consecutive correct answers, Δt decreased, and for every single wrong answer, it increased. T was set at 300 ms for sub-second trials and at 1,000 ms for supra-second trials. The frequencies of the beep sound for sub-second and supra-second trials were set at 0.5 kHz and 3 kHz, respectively (Figure 3). The ID thresholds for each of the sub-second and supra-second intervals were calculated as the shortest interval which was answered correctly across trials in each session at least 75 percent of times (Figure 4).

Data Analysis

Using psychometric data, we identified the threshold at which subjects could no longer discriminate shorter intervals. In the ID task used in this study, detection thresholds (DTs) were calculated for each participant at two standard intervals (SIs): 300 ms and 1,000 ms, represented as Δt. The DT is defined as the stimulus intensity at which the probability of a correct response reaches a predefined criterion, typically set at 0.75. On a psychometric curve, this corresponds to the point where performance transitions from chance level to reliably accurate responses. The threshold calculation incorporates both the position of the curve

(indicating when this transition occurs) and its slope (reflecting how quickly it happens), thus providing an accurate representation of the underlying psychophysical process. Subsequently, we categorized participants based on their phenotype alleles and, within each subgroup, compared their performance across binaural, baseline, and control conditions. After checking the normality of the data, we used the Wilcoxon signed-rank test to compare conditions across phenotype alleles for the 300 ms and 1,000 ms SIs. Furthermore, we also compared the accuracy and reaction time in the two-back test, which was administered at baseline and after each intervention. Statistical comparisons were performed using either the Wilcoxon signed-rank test or a paired t-test, depending on whether the data were normally distributed.

Results

Screening

Out of 51 participants who were genotyped for SLC6A4(SERT) 5-HTTLPR, SLC6A3 (DAT) 3'-UTR VNTR, COMT Val158Met (rs. 4680), and HTR2A T102C (rs. 6313) polymorphisms, 41 participants were further invited for the cognitive tasks namely ID test, out of which data for two participants were discarded (Figure 1). The remaining 39 participants were tested for attention prior to the main task through simple Stroop test, and for working memory capacity via the N-Back test. Results showed that all 39 participants had normal attention and normal working memory capacity on the test day.

Genotyping

Considering the DAT (SLC6A3 3'-UTR VNTR) polymorphism, we genotyped 39 participants as follows: eight 9R/9R, 19 10R/10R, 10 9R/10R, and two non-9R/non-10R. The latter group

was excluded from further investigation due to their uncommon low frequency in the population.

Genotyping based on the COMT Val158Met polymorphism resulted in 11 participants with AA (Met/Met) genotypes, four with GG (Val/Val), and 24 with AG (Val/Met) genotypes. Due to the scarcity of GG homozygotes, we combined the last two groups as the Val+ genotype group (28 AG-GG). Using the chi-square test, genotype distribution for this locus was found to be in H-W equilibrium (P-Value=0.09).

According to the SERT (SLC6A4 5HTTLPR) polymorphism, the 39 participants were classified as eight SS homozygotes, 10 LL homozygotes, and 21 SL heterozygotes. Genotype distribution for this locus was also found to be in H-W equilibrium using chi statistics (P-Value=0.62).

Based on HTR2A T102C SNP, we had 7 TT homozygotes, 10 CC homozygotes, and 22 CT heterozygotes as three genotype groups whose distribution was within H-W equilibrium range using chi statistics (P-Value=0.40).

N-Back Test

Pairwise comparison of three sessions of the N-Back test for 39 participants didn't show any significant difference.

Interval Discrimination Test

Calculating log-transformed DTs for 300 ms SI, yielded 2.02$\pm$0.20, 1.91$\pm$0.19, and 1.94$\pm$0.19 as mean$\pm$SD for base, control, and Binaural Beat (BB) groups, respectively. For 1,000 ms log-transformed DTs, SI measures were calculated as 2.66$\pm$0.17, 2.61$\pm$0.17, and 2.57$\pm$0.21 (mean$\pm$SD) for base, control, and BB groups. Pairwise comparison of the groups for each SI showed significant difference at 300 ms SI between base and control groups (P-Value=0.0004, Effect size=0.5474) (Figure 5a), between base and BB groups (P-Value=0.004, Effect

size=0.456), at 1,000 ms SI between base and control groups (P-Value=0.03, Effect size=0.34), and between base and BB groups (P-Value=0.03, Effect size=0.34) (Figure 5b).

There was no significant difference observed between control and BB groups at 300ms or 1,000ms SIs (Figure 5).

Next, we made pairwise comparison of log-transformed ID DTs (mean±SD) across base, control, and BB groups based on their genotyping using Wilcoxon signed rank test, in both sub- and supra-sec scales (Figures 6, 7, 8, and 9).

Figure 6 shows significant difference in DAT 9R/10R genotype group at 300 ms SI between the log-transformed ID DTs (mean±SD) in base (2.00±0.14) and control groups (1.81±0.13) (P-Value=0.01, Effect size=0.79) and at 1,000 ms SI in 9R/10R group between base (2.65±0.13) and control groups (2.55±0.12) (P-Value=0.002, Effect size=0.886), and a significant difference in 9R/9R genotype group between control (2.60±0.12) and BB groups (2.49±0.13) (P-Value=0.05, Effect size=0.69).

Across COMT genotype groups, significant difference was observed in sub-sec scale (SI=300 ms) in AA group (Met/Met homozygotes) between base (1.98±0.20) and control (1.86±0.20) (P-Value=0.04, Effect size=0.62), in AG-GG (Val+) category between base (2.03±0.19) and control groups (1.93±0.19) (P-Value=0.005, Effect size=0.516), and between base and BB groups (1.95±0.20) (P-Value=0.004, Effect size=0.529) (Figure 7a). While Figure 7b shows a significant difference in supra-sec scale (SI=1000ms) in AG-GG (Val+) category between base (2.66±0.17) and BB groups (2.56±0.23) (P-Value=0.04, Effect size=0.40), and between control (2.62±0.15) and BB groups (P-Value=0.04, Effect size=0.38).

As shown in Figure 8a, among different SERT genotype categories in sub-sec scale, significant difference is seen between base (1.99±0.11) and control groups (1.76±0.17) in SS homozygotes (P-Value=0.008, Effect size=0.891), in SL heterozygotes (base: 2.00± 0.18) (control:

1.91±0.17) (P-Value=0.03, Effect size=0.47), and between base (2.09±0.27) and BB groups (1.96±0.28) in LL homozygotes (P-Value=0.004, Effect size=0.854).

Figure 9a reveals significant difference across HTR2A genotypes in sub-sec scale in CC homozygotes between base (2.03±0.23) and BB groups (1.94±0.25) (P-Value=0.03, Effect size=0.69), in CT heterozygotes between base (1.98±0.16) and control groups (1.88±0.17) (P-Value=0.01, Effect size=0.50), and in TT homozygotes between base (2.14±0.24) and control groups (1.93±0.26) (P-Value=0.02, Effect size=0.89), and between control and BB groups (2.04±0.22) (P-Value=0.02, Effect size=0.89). Figure 9b shows a significant difference in supra-sec range in CC genotypes between control (2.64±0.18) and BB groups (2.51±0.29) (P-Value=0.04, Effect size=0.63), and in TT genotypes between base (2.67±0.19) and control groups (2.55±0.22) (P-Value=0.03, Effect size=0.83).

Discussion

According to our hypothesis, we expected to see improvements in ID thresholds (lower DTs) after binaural beats stimulation compared with ID thresholds in base and control groups in sub- and/or supra-second scales. Our findings verified this hypothesis and showed significant improvement in ID thresholds for control and BB groups compared with the base group in the sub-second scale (P-Value=0.0004 and P-Value=0.004, respectively) and in the supra-second scale (P-value=0.03, P-value=0.03). These results could be attributed to the general effect of auditory stimulation on TP, but not the BB effect. It should be noted that the auditory stimulation effect has been limited to the TP area and not to the overall cognitive skills, as such a positive effect has not been observed in the results of the N-Back test as an indicator of working memory. However, considering different genotypes, we found significant improvements in ID thresholds in HTR2A (CC homozygotes), COMT Val158MET (Val+

carriers), and DAT (9R9R) genotype categories in BB groups compared with the control groups in supra-sec scale (P-Value=0.04, P-Value=0.04, and P-Value=0.05, respectively).

Serotonergic gene polymorphisms have been shown to be related to social learning, emotions, and decision making (Marinho et al., 2018). TT homozygotes of the 5HT2A T102C polymorphism express more receptors than carriers of the C allele (CC homozygotes and CT heterozygotes). Molecular studies with pharmacological models have suggested that this polymorphism changes the timing of visual stimuli in working memory tasks (Chun, 2011). It is said that HT2A receptors are highly expressed in the occipital cortex (William Moreau et al., 2010). Any genetic polymorphism that decreases the density of this receptor in the visual cortex seems to facilitate deficits in time judgement and to increase the risk of neuropsychiatric diseases (Kometer et al., 2013). According to our results, it seems that in CC homozygotes with low density of HT2A receptors who might have timing deficits, BB intervention improves TP in the supra-second scale.

Another important protein in the serotonergic system is the serotonin transporter, which is encoded by the SLC6A4 gene, whose polymorphism (5-HTTLPR) results in the S and L alleles. The carriers of the S allele are shown to have greater brain activity and better memory and timing activities (Fallgatter et al., 2004). Although we didn't find any correlation between the effect of BB on TP and this polymorphism, there are some studies in which significant associations were found between these two polymorphisms (SLC6A4 5-HTTLPR and HTR2A T102C) and duration discrimination task with visual stimuli in supra-second scale (mean duration=4.8 s) (Sysoeva et al., 2010). In another study in which the association between the serotonergic gene polymorphisms and TP was revealed, the authors concluded that dopaminergic gene polymorphisms were related to TP in 1-2 second intervals, while serotonergic gene polymorphisms were related to TP in longer durations (up to one minute) (Portnova et al., 2007).

Considering dopamine transmission, DAT and COMT are two proteins responsible for clearing the synaptic cleft and terminating the action of dopamine on its post- and pre-synaptic receptors. However, the DAT molecule is more active in the striatum, clearing dopamine from the synaptic cleft and transporting it back to the presynaptic nerve terminal. Its SLC6A3 3'-UTR VNTR polymorphism is involved in regulating the gene transcription (Michelhaugh et al., 2001). As the 10R allele is associated with higher level expression of the gene, the 9R allele has been shown to act as a down-regulator of the gene transcription (Heinz et al., 2000; Mill et al., 2002). However, there have been inconsistencies among different studies as to whether it is the 9R or the 10R allele which is associated with increased expression and/or function of the DAT protein. This heterogeneity has been attributed to different methodologies and to different brain areas studied in healthy or affected subjects. In an animal study, low expression of DAT was shown to be associated with timing dysfunction (Balci et al., 2010). However, the same research group could not find any association between DAT1 polymorphism and timing behavior in humans (Balcı et al., 2013). This result is consistent with another study, which also failed to find any effect of DAT and COMT polymorphisms on timing accuracy in the temporal bisection task in the supra-second range (mean duration= 4.8 s) (Sysoeva et al., 2010). Combined effect of SLC6A3 3'-UTR VNTR and SLC6A3 intron-8 VNTR polymorphisms on time perception in time estimation tasks in the supra-sec range has also been shown (Marinho et al., 2019). It should be emphasized that although we couldn't find a significant difference between control and BB groups in SLC6A3 3'-UTR VNTR genotypes in sub-second scale, the difference in supra-sec scale in the 9R9R genotype group was significant (P-Value=0.05).

The Val allele of the COMT Val158Met polymorphism is accompanied by a highly active form of the enzyme, which is an extra-neural metabolizer of dopamine (Green et al., 2008), whereas the Met allele is associated with a 3- to 4- fold reduction of the enzyme activity. With increased activity of the enzyme, the level of available dopamine in the PFC is reduced. However, with

the reduced activity of the enzyme, there will be more accessible dopamine in the PFC (Egan et al., 2001). Modulation of cortical dopamine has a great influence on attention, working memory, and other executive functions of PFC (Arnsten, 2009). In addition, the pre-fronto-striatal dopamine circuit is involved in supra-second interval-timing (Jones et al., 2004; Matell & Meck, 2004; Wiener et al., 2011). Our findings showed significant improvement in supra-second ID thresholds in response to BB intervention in the COMT Val158Met polymorphism (Val+ carriers) (P-Value=0.04). Thus, we found our most significant results among the group of participants with potentially lower dopamine availability in the PFC. It was shown that a significant speed-up of the internal clock was associated with the Val+ allele of the COMT Val158Met in a second-scale time production task (Reuter et al., 2005). In another study on synchronous swimmers, a significant association between the COMT Val158Met polymorphism and timing was observed in the supra-second scale (<2 s.) time reproduction task (Portnova et al., 2007). It should be noted that in time production or reproduction tasks, timing of motor activity is involved which means the nigrostriatal pathway is at work. Although some researchers failed to find any correlation between time accuracy and genetic polymorphisms of DAT and COMT Val158Met (Sysoeva et al., 2010), others found a significant combined effect of COMT Val158Met and DR2 gene polymorphisms on timing performance in supra-second scale (Balcı et al., 2013). In a GWAS study of a large population of participants, researchers failed to find any correlation between the polymorphisms in DAT, COMT, SERT, and HTR2A genes and timing in time production and duration discrimination tasks in supra-sec scale (Bartholomew et al., 2015). In the present study, we also failed to find any association between SERT polymorphism and interval Discrimination in supra-second scale. Nevertheless, our findings support a significant relationship between DAT, COMT, and HTR2A gene polymorphisms and ID DTs in supra-second scale in response to BB stimulation.

Although our research is the first study carried out on the effect of BB intervention on TP, there have been many other studies that show improving effects of BB in diverse frequency bands on consciousness disorders (Liu et al., 2022), relaxation (Krasnoff & Chevalier, 2023), parkinsonism (González et al., 2023), tinnitus (Bardsiri et al., 2022), working memory (L. Wang et al., 2022), verbal memory (Tay et al., 2023), sleep disorders (Bavafa et al., 2023; Dabiri et al., 2022; Dini et al., 2022; Lee et al., 2022), mental fatigue (Axelsen et al., 2020; X. Wang et al., 2022), chronic pain (Gkolias et al., 2020), auditory sentence comprehension (Kim et al., 2023), attention (Basu & Banerjee, 2023; Engelbregt et al., 2021), and mood regulation (Wahbeh et al., 2007). However, results have not been too promising as far as the BB effect is concerned. Incongruous findings may be attributed to the methodological heterogeneity, including different frequencies applied, exposure time and durations, sample size, risk of bias, and the choice of control group, as well as different etiologies of the existing problem at hand and the variety of medications taken by the participants. Adding to the list above, our present research provides evidence for the promising role of genetic polymorphisms of neurotransmitter systems, namely, dopaminergic and serotonergic systems of the participants in the effectiveness of BB in various areas of health, mood, cognition, and specifically TP. Our findings emphasize the relationship between genetic polymorphisms of HTR2A T102C, COMT Val158Met, and DAT 3'-UTR VNTR and ID thresholds in supra-second scale in response to BB stimulation in the delta frequency band. However, there have been some limitations to our research method, such as a small sample size, depending on different allelic categories, which could affect the significance of the observed results. Therefore, for future research, we suggest investigating a larger population of healthy participants or repeating a similar experiment on patients with a neuropsychiatric disorder having a supposed serotonergic or dopaminergic involvement and timing deficits. The aim of the latter suggestion would be improving such cognitive disruptions in the neuropsychiatric disorders.

Acknowledgement

The present article is derived from an ongoing PhD thesis entitled "Investigation of binaural beats effects on interval discrimination and brain functional connectivity networks considering genetic variations of neurotransmitter systems" with the approval ID: IR.SBMU.MSP.REC.1402.266 by Hedieh Matloubi at Shahid Beheshti University of Medical Sciences. This work was supported by the research grant (approval ID**:** IR.SBMU.PHNS.REC.1402.120) from Neuroscience Research Center, Shahid Beheshti University of Medical Sciences (SBMU). The sponsor has not been involved in study design; collection, analysis or interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

We would like to thank Mr. Hossein Nabizadeh for his expert guidance at the EEG laboratory, to Ms. Sahereh Rahnavard for her specialized tutorial at the genetics laboratory, and to Mr. Masoud Matloubi for his kind collaboration in this study.

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Figures legends:

Figure 1. Flow diagram of subject selection and data gathering

Figure 2. Interval Discrimination Module. Due to the importance of accuracy of the two intervals, whose difference could be in the range of one millisecond, there is a high sensitivity to the error rate of the intervals being displayed. Therefore, the ID task is programmed on an electronic board as an interface with the computer. This module stores data and then transfers it to the user interface designed in the MATLAB software using its serial port and finally saves it as a two-dimensional matrix in a MATLAB file format. Among the reasons that accuracy reduction of intervals produced in the computer are the delay in the computer's sound card, and the delay in the use of high-level programming languages. These delays could be resolved by executing the task on a simpler hardware environment and a simpler programming that has lower time delays than a computer. Therefore, the ID task in this research was performed on a module as an interface between the computer and the participants.

Figure 3. Interval Discimination Task Diagram. For sub-second intervals, t = 300ms, while for supra-second intervals, t = 1000ms, with 0.5kHz and 3kHz frequencies for the beep sounds, respectively. ISI: Inter Stimulus Interval. ITI: Inter Trial Interval.

Figure 4. Study progress diagram

Figure 5. Comparing the log-transformed ID thresholds (mean±SD) between the base and control groups, base and BB groups, as well as control vs. BB groups. **a.** Standard Interval=300msec **b.** Standard Interval=1000msec**.** (P-value< 0.05 is supposed as significant).

Figure 6. Pair comparison of log-transformed ID thresholds (mean±SD) in different base, control, and BB groups according to their DAT (SLC6A3 3'-UTR VNTR) polymorphism. **a.** Standard Interval=300msec **b.** Standard Interval=1000msec**.** (P Value<0.05 is supposed as significant.)

Figure 7. Pair comparison of log-transformed ID thresholds among different groups of base, control and BB (mean±SD) based on their COMT Val158Met SNP genotypes. **a.** Standard Interval=300msec **b.** Standard Interval=1000msec**.** (P Value<0.05 is supposed as significant.)

Figure 8. Pair comparison of log-transformed ID thresholds among different groups of base, control and BB (mean±SD) based on their SERT (SLC6A4 5HTTLPR) genotypes. **a.** Standard Interval=300msec **b.** Standard Interval=1000msec**.** (P Value<0.05 is supposed as significant.)

Figure 9. Pair comparison of log-transformed ID thresholds among different groups of base, control and BB (mean±SD) based on their HTR2A T102C SNP genotypes. **a.** Standard Interval=300msec **b.** Standard Interval=1000msec**.** (P Value<0.05 is supposed as significant.)

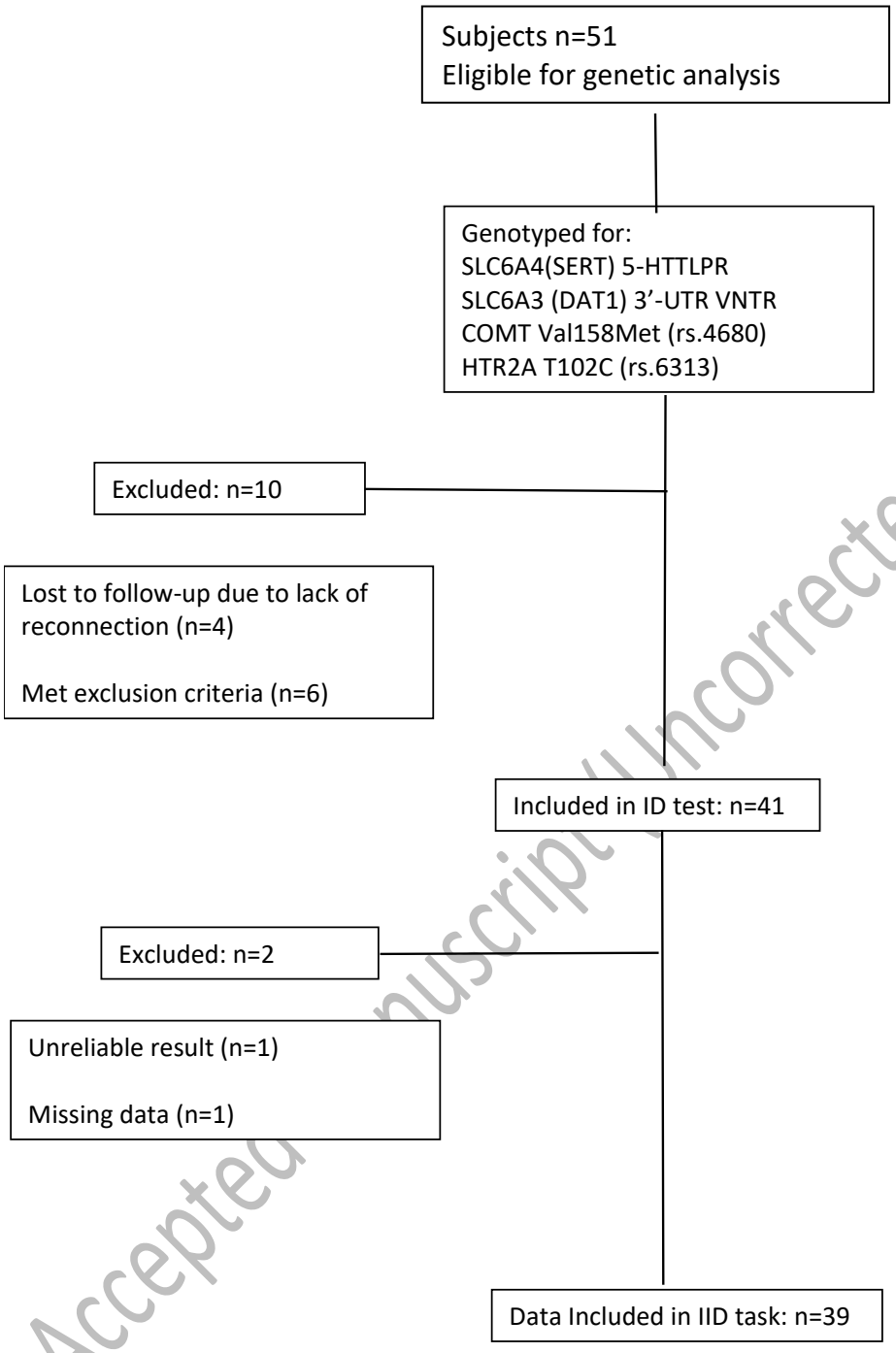

Figure 1.

Figure 2.

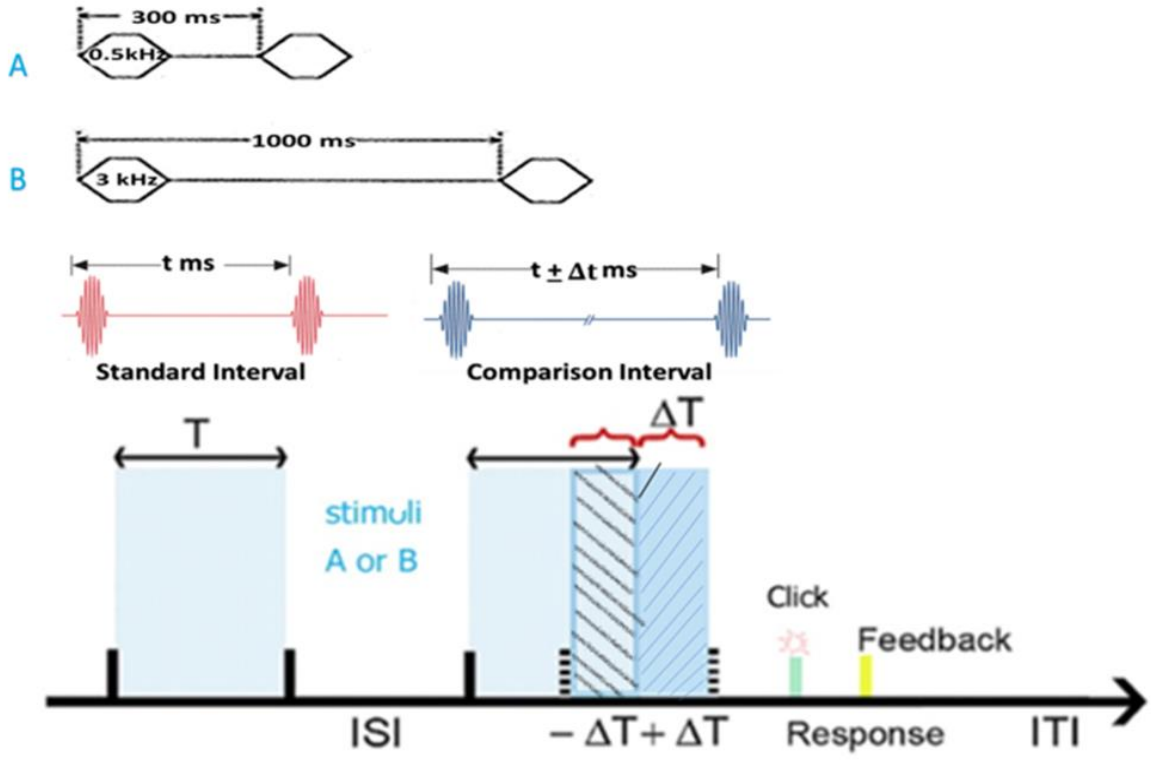

Figure 3.

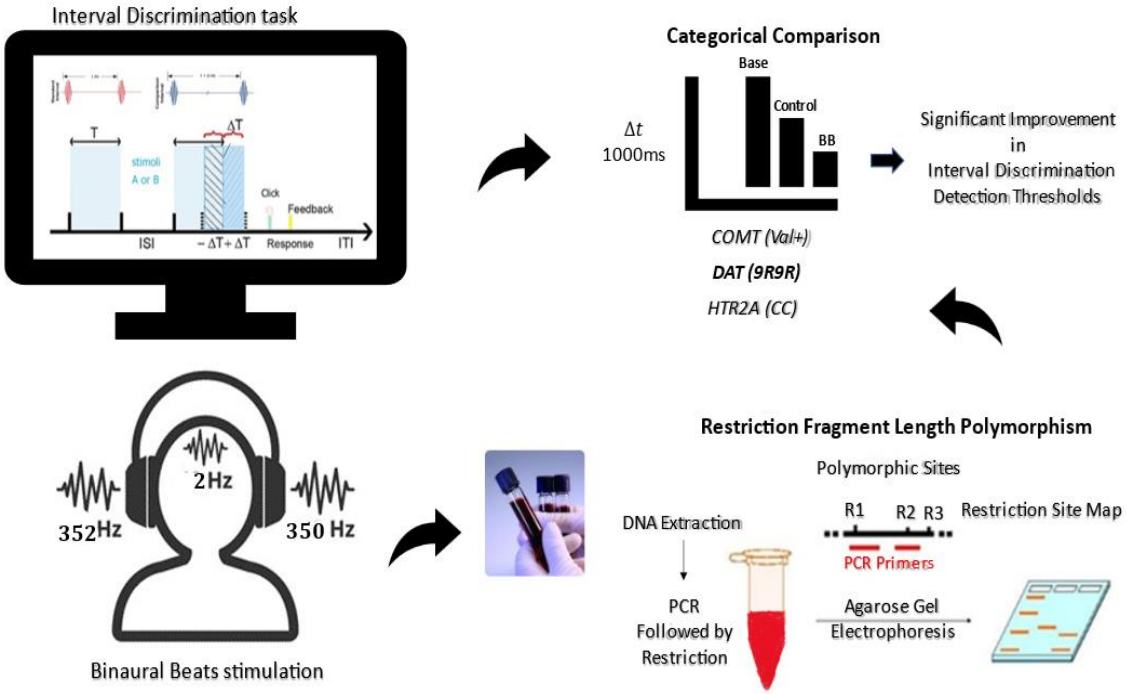

Figure 4.

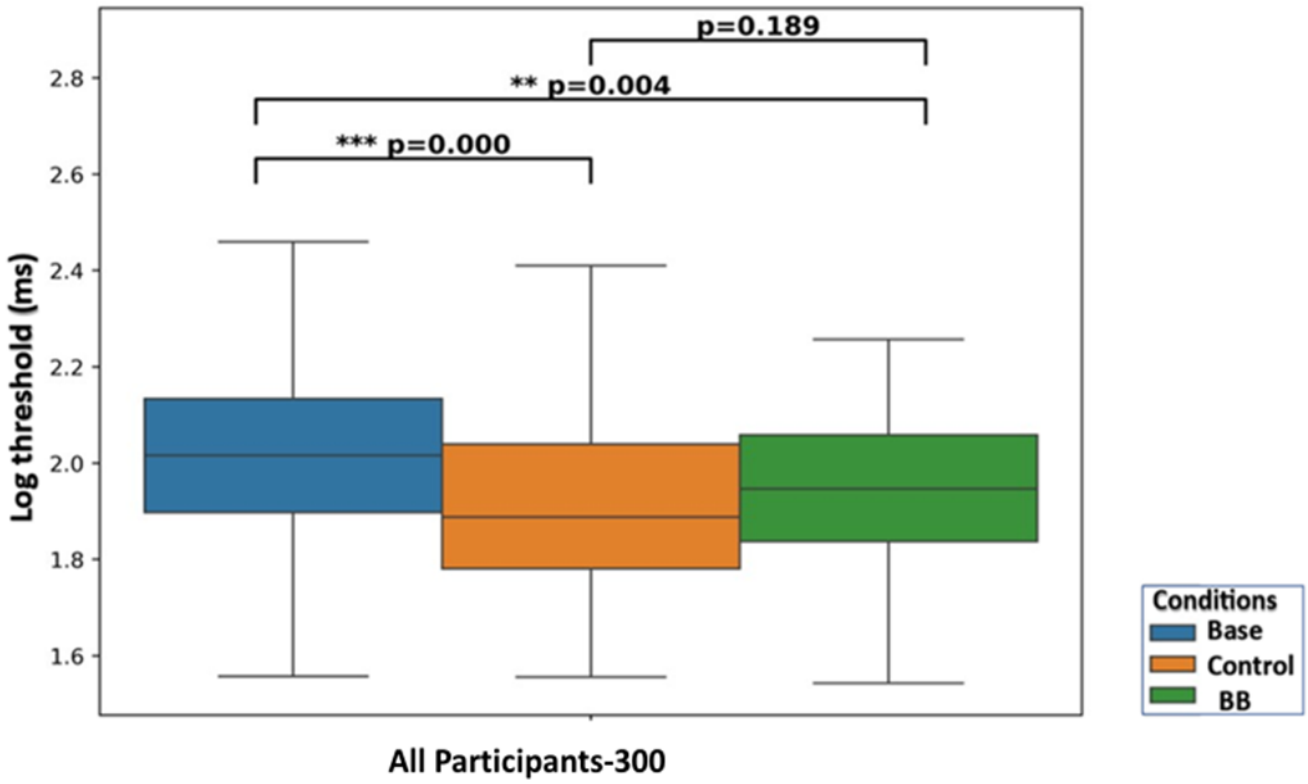

Figure 5a.

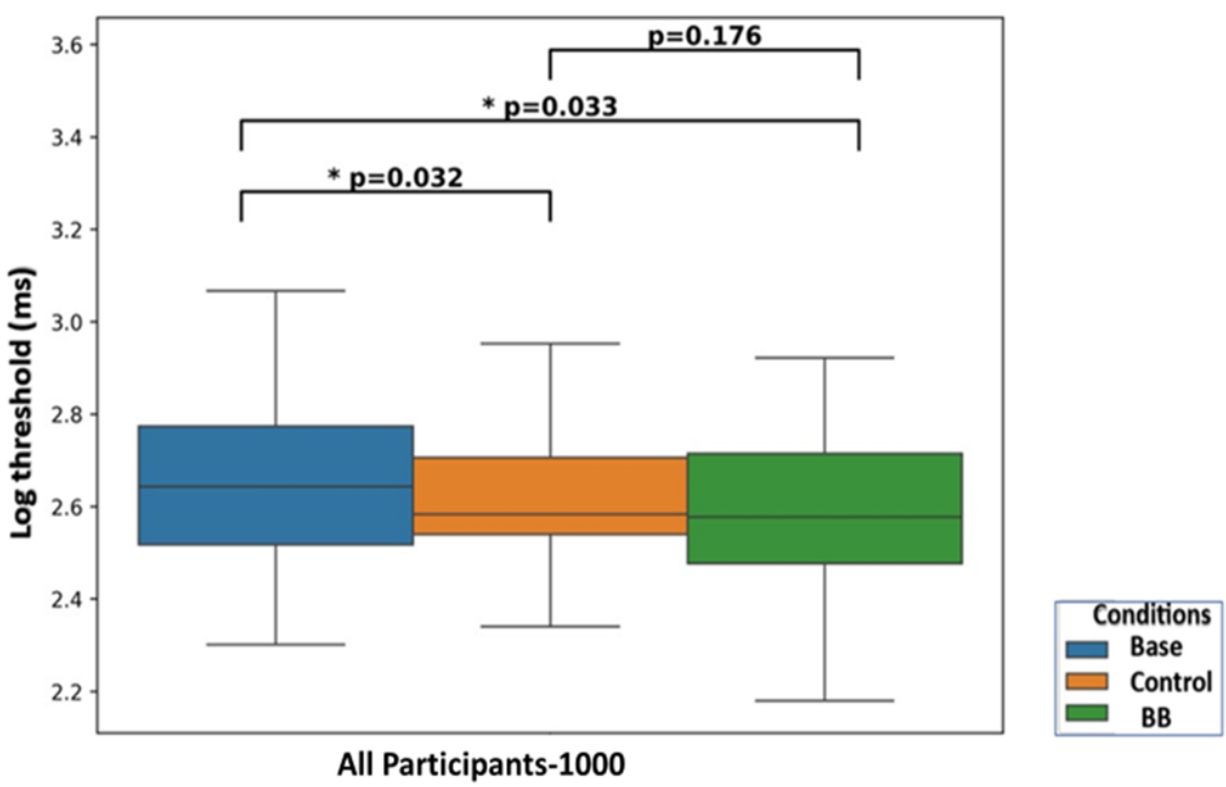

Figure 5b.

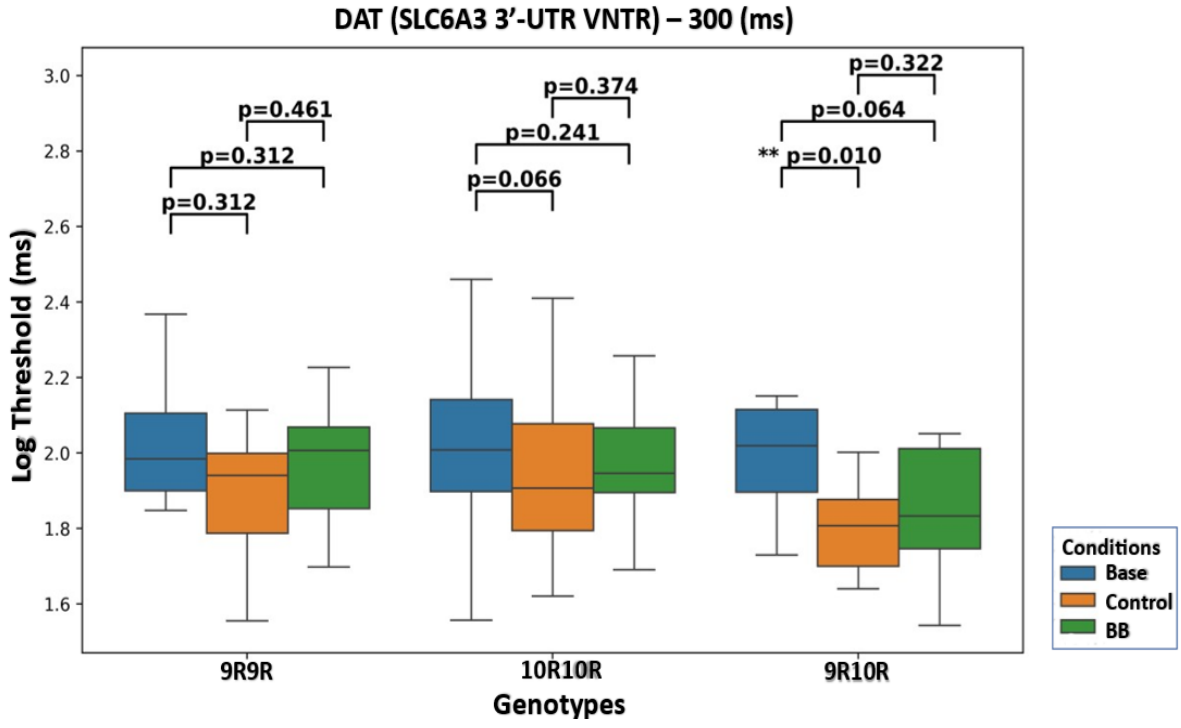

Figure 6a.

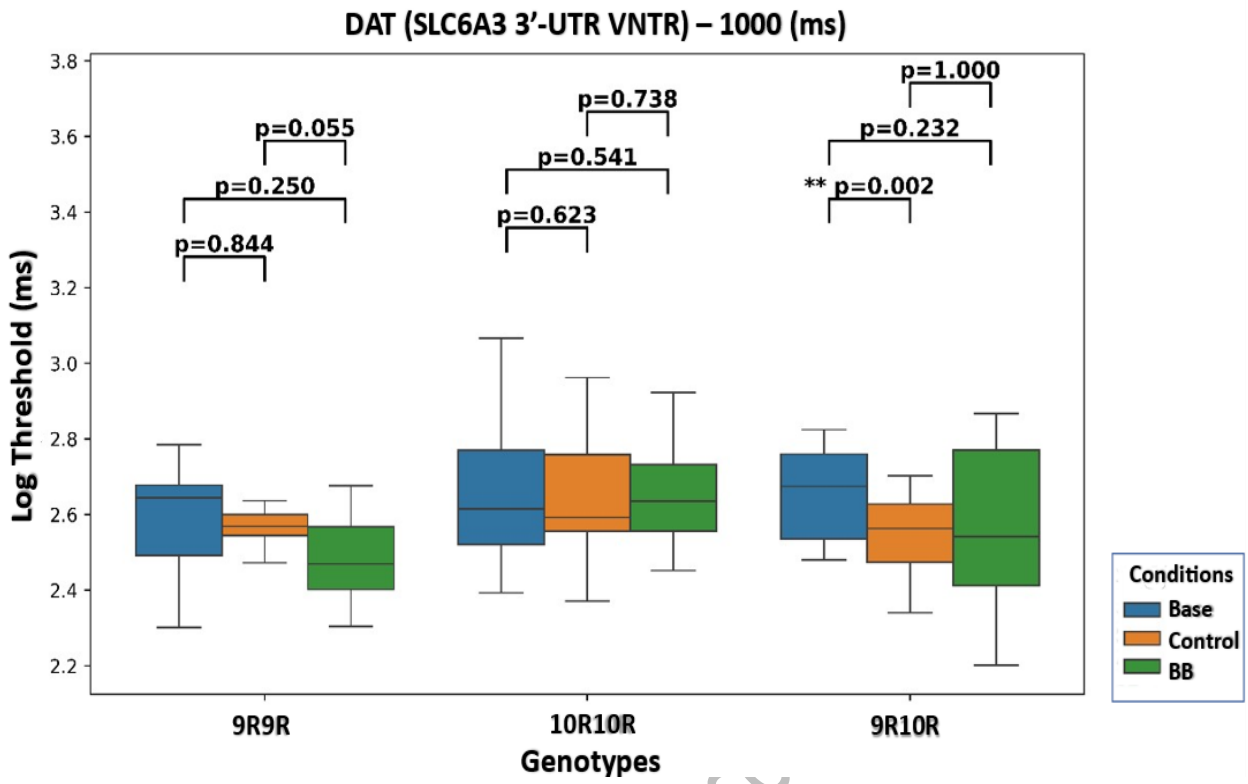

Figure 6b.

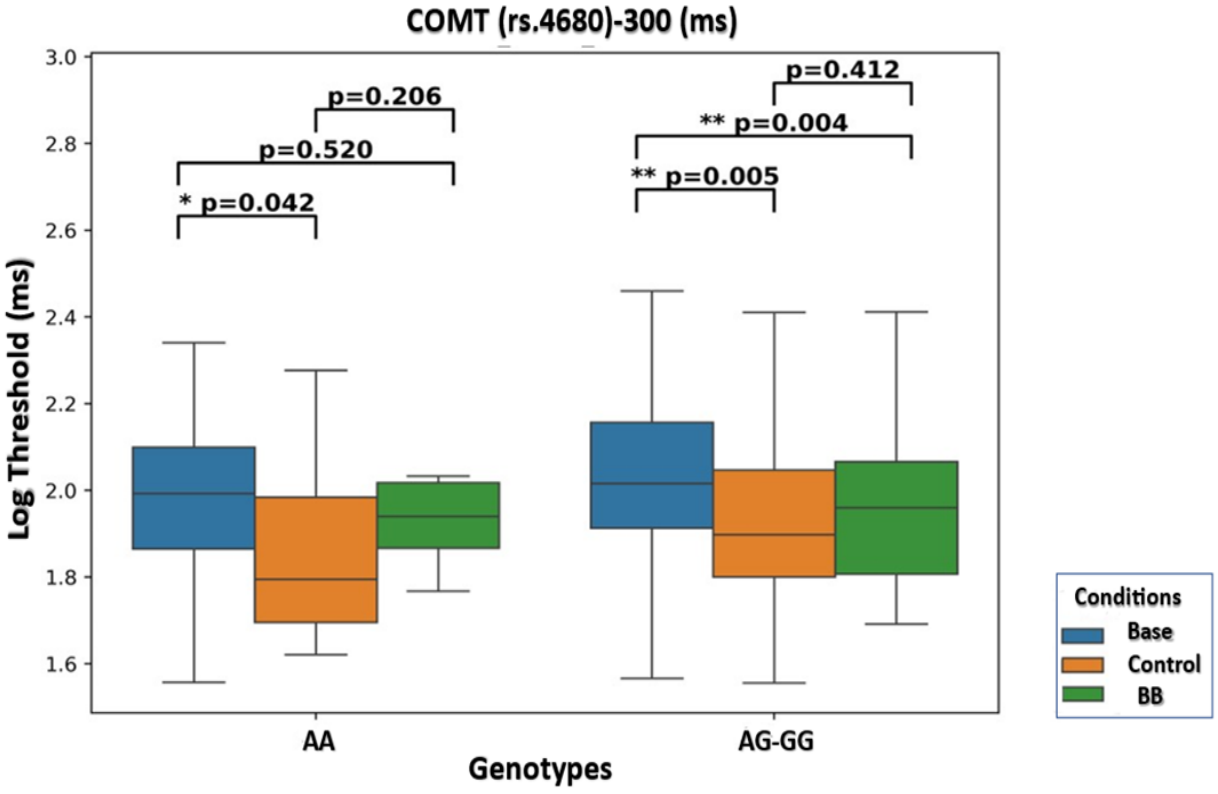

Figure 7a.

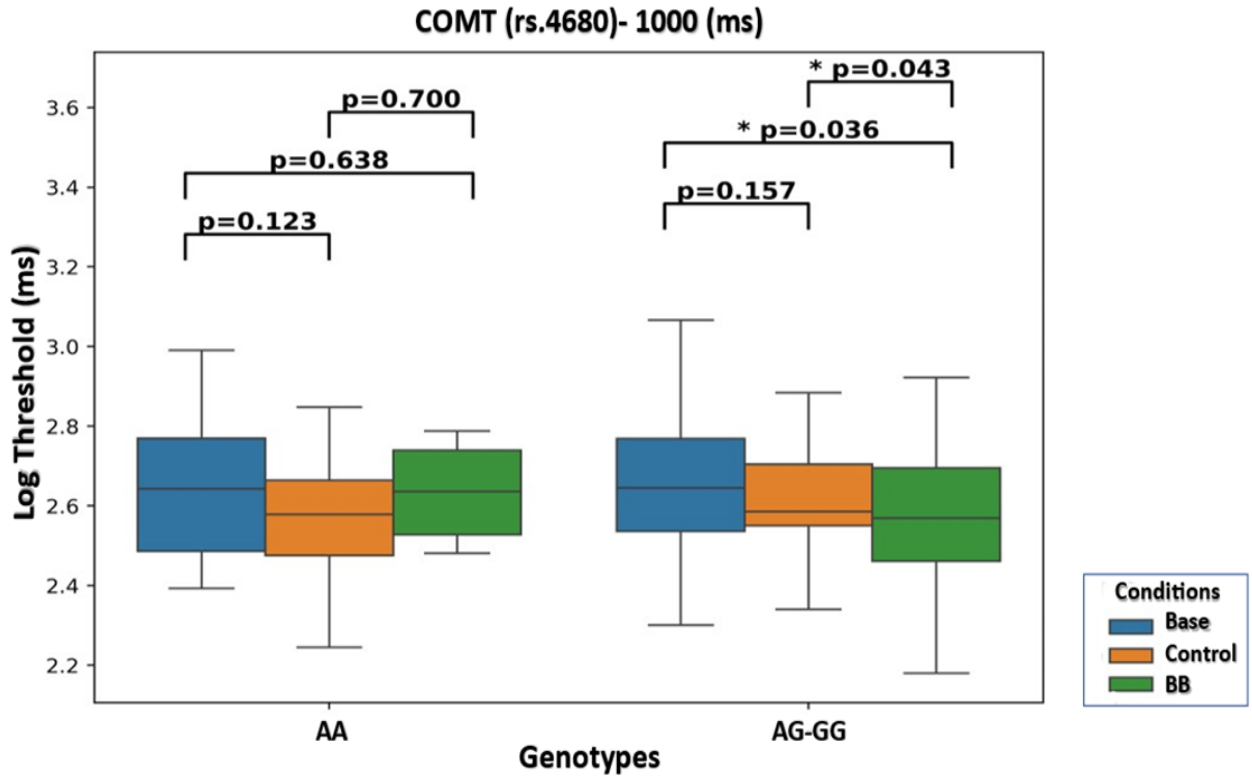

Figure 7b.

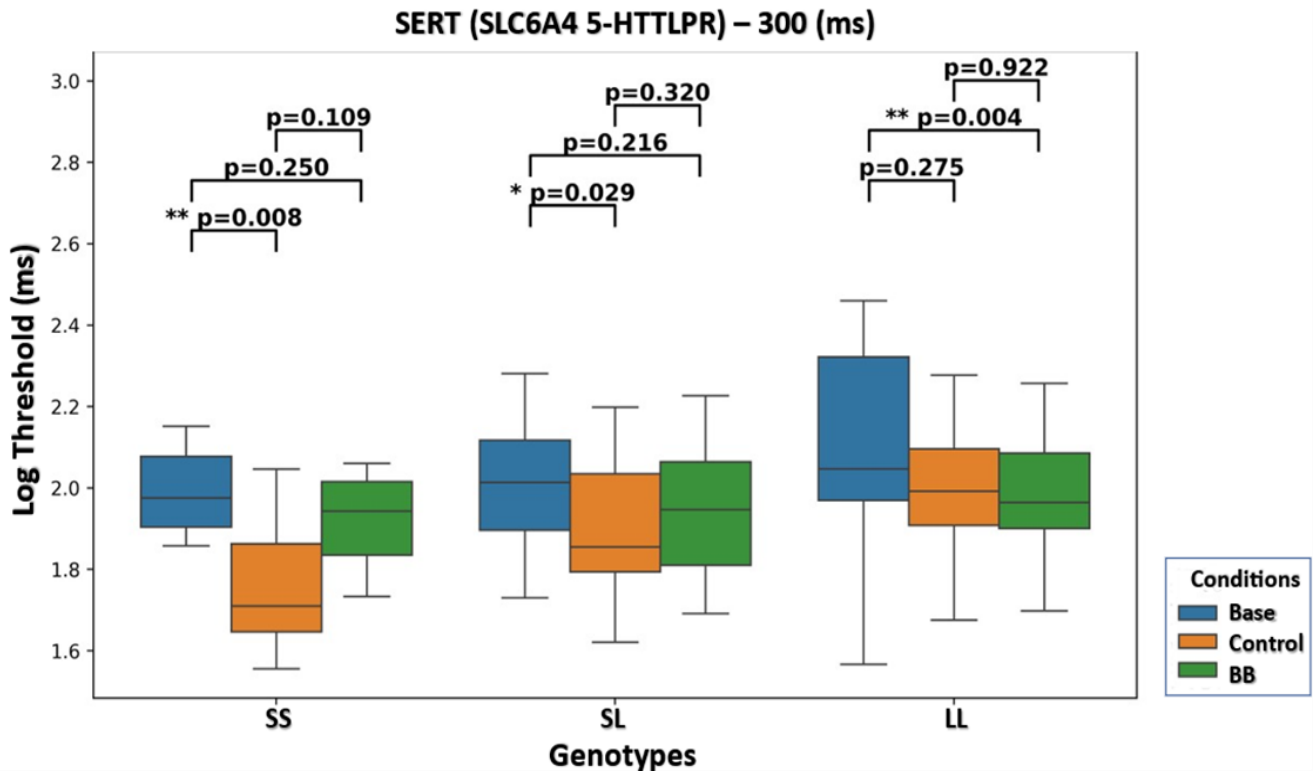

Figure 8a.

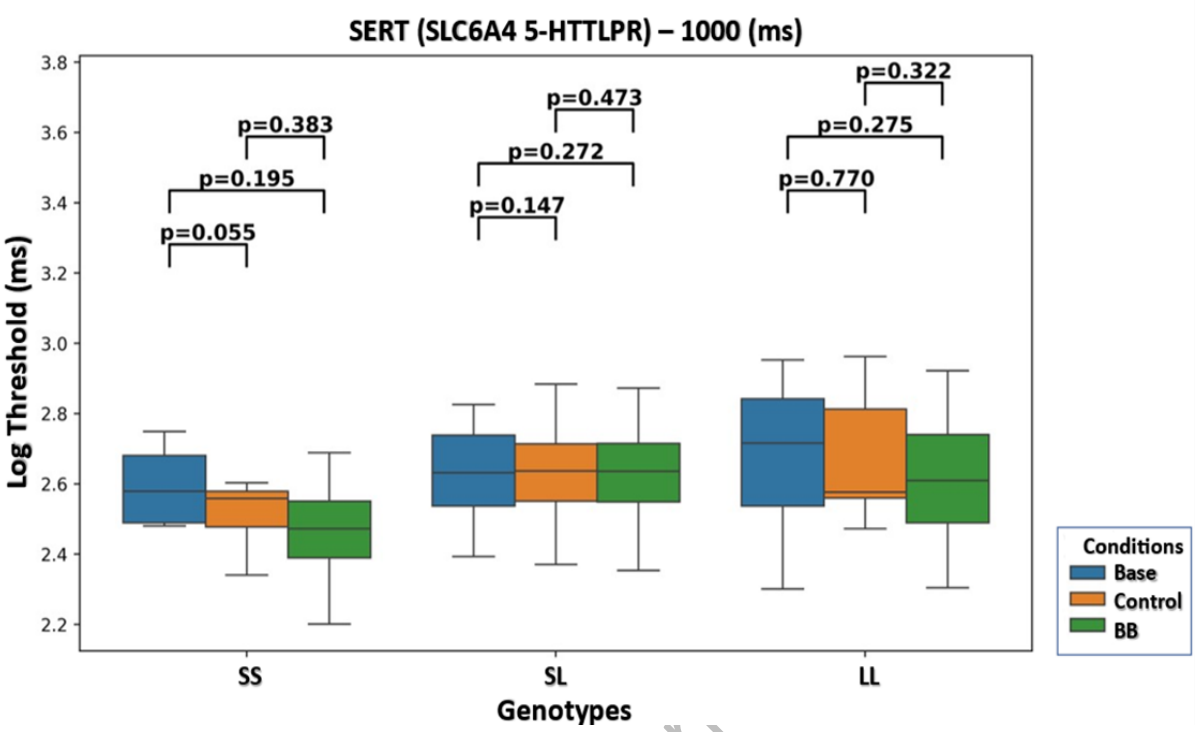

Figure 8b.

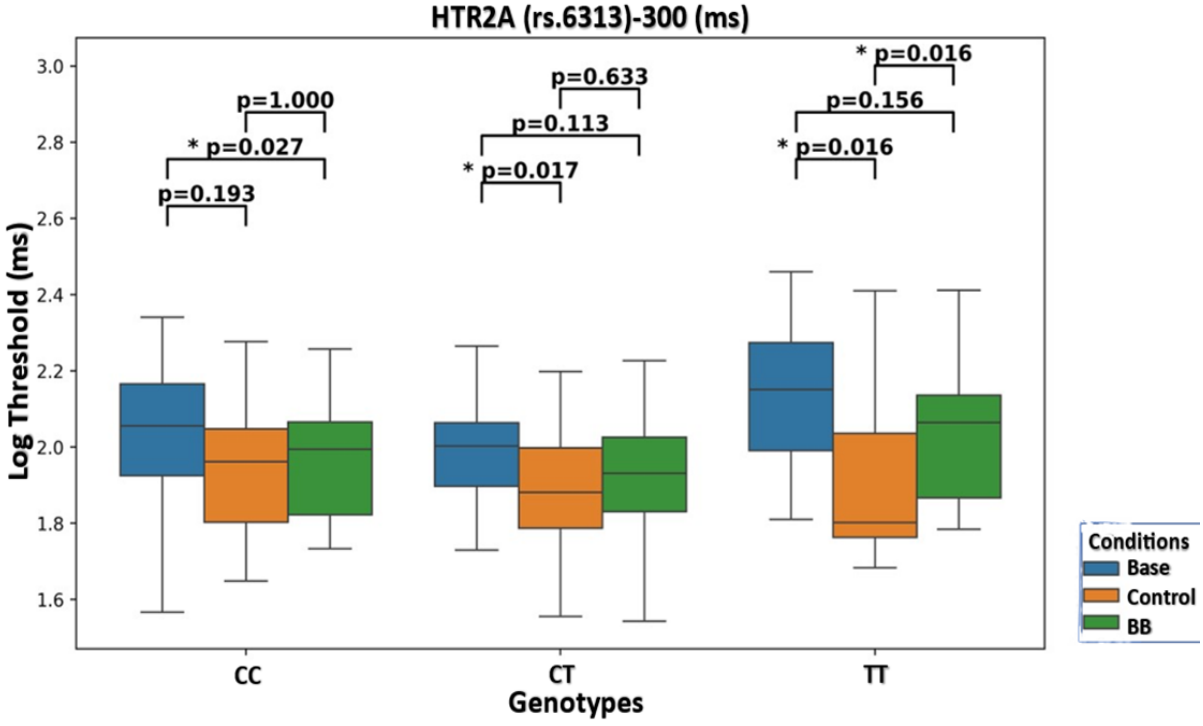

Figure 9a.

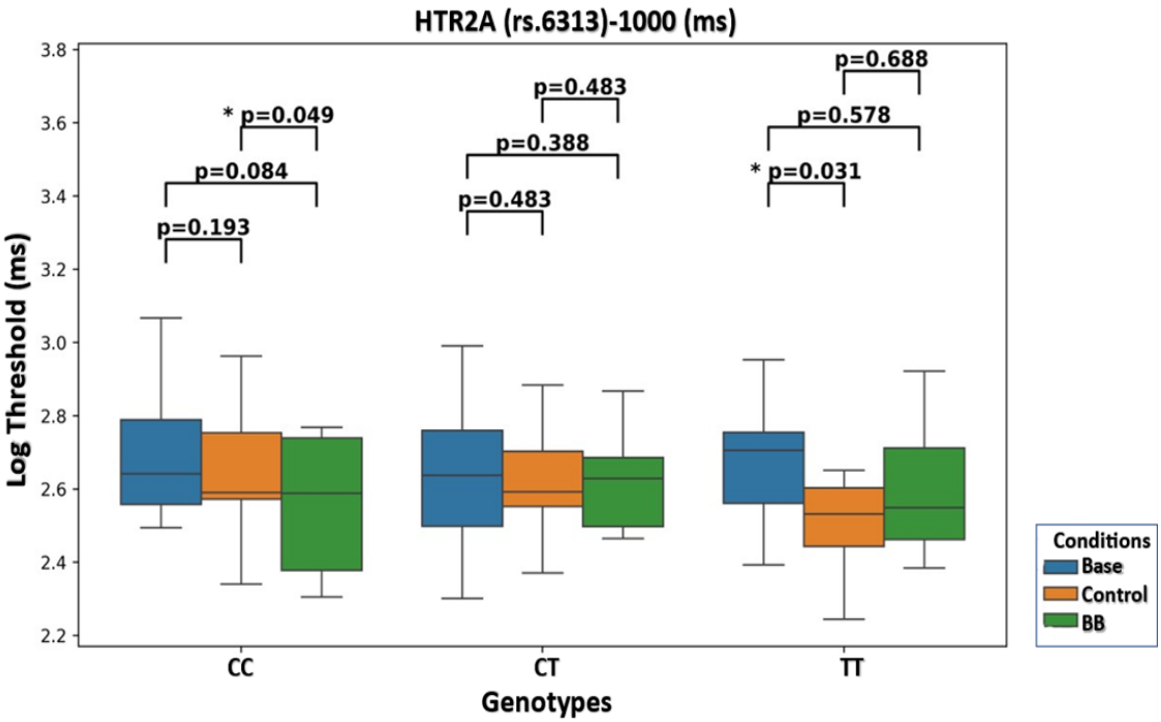

Figure 9b.