Relationship of the Val158met COMT Genotype With the Regulation Disorders of Sensory Processing (RDSP)

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Abstract
Regulation Disorders of Sensory Processing (RDSP) are disorders of hypersensitivity or hyposensitivity to a specific modality (or modalities) of sensory stimuli. These disorders also affect motor skills as well as executive functions, which is important for the child's neurodevelopment. Patterns of sensory-motor integration may be genetically determined. Particular attention is paid to polymorphisms of the *COMT* gene. The study involved 15 children with neurodevelopmental disorder (aged 7 – 17) divided into two groups in terms of *COMT* genotype. Their RDSPs was examined and then a comparative analysis was made. It was shown that the Val/Val *COMT* genotype may predispose to increased risk of hypersensitivity RDSPs of vestibular system, proprioceptive system and visual system, as well as motor coordination. Met allele (Val/Met and Met/Met genotypes), on the other hand, showed a significant reduced tendency to these RDSPs. The results correlate with numerous studies on the relationship of the *COMT* genotype with sensory-motor integration functions. Thanks to the presented study, we know that this relationship may relate primarily to hypersensitivity disorders and may be associated primarily with the senses and functions related to postural control and motor control. Most likely, a study conducted on a larger sample would yield much more clinically significant findings, however, the presented results may direct further neurogenetic research both in the context of neurorehabilitation as well as developmental psychology and neurology. It may contribute to the better understanding of the neurogenetic conditions of human neurodevelopment.

Keywords: Neurogenetics, Neurorehabilitation, Sensory Integration

Introduction

Sensory processing is an integral part of the functioning of the nervous system and underlies the development of both motor and cognitive functions. In this context, the senses include: sight, hearing, taste, smell, touch, balance and proprioception. The integration of sensory information from many senses allows for the construction of a complex percept, which is important both for learning about reality and for conscious and purposeful action in it (Bagrowski, 2020). During ontogeny, various endogenous or exogenous conditions may cause disorders in sensory processing, called Regulation Disorders of Sensory Processing (RDSP). These are disorders of hypersensitivity or hyposensitivity to a specific modality (or modalities) of sensory stimuli. Hypersensitivity is characterized by a reduced sensory reaction threshold and, consequently, an excessive reaction to specific stimuli (e.g. a defensive reaction in response to non-painful touch). Hyposensitivity, on the other hand, is characterized by an increased sensory reaction threshold and, consequently, a lack of reaction to a standard stimulus (e.g. he needs to grip the pen harder to feel that he has it in his hand). RDSPs affect motor skills as well as executive functions, and therefore may disturb a child's neurodevelopment and functional development (Hazen et al., 2014; Camarata et al., 2020). Various RDSPs may co-occur with each other (Bagrowski & Olesińska, 2022).

Patterns of sensory-motor integration may be genetically determined. It has been shown, among other things, that sensory-motor integration patterns determined using electrophysiological methods depend, for example, on the *BDNF* genotype (Deveci et al., 2020). However, special attention should also be paid to the Val158Met polymorphism of the *COMT* gene, which encodes the COMT protein (catechol-O-methyltransferase). This protein is involved in the regulation of dopamine concentration in the central nervous system, which plays an important role in cognitive and emotional regulation (Wu et al., 2020). Dopamine also plays an important role in motor control mechanisms (Chakravarthy et al., 2010), therefore the COMT protein may also be important for motor functions. In terms of the Val158Met polymorphism, three genotypes are distinguished: Val/Val homozygotes, Val/Met heterozygotes and Met/Met homozygotes. The Met/Met genotype is characterized by up to four times lower enzymatic activity of the COMT protein than the Val/Val genotype (Williams et al., 2007). Due to the fact that the Val/Val genotype is characterized by higher enzymatic activity of the COMT protein, it is also associated with faster metabolizing of dopamine and, consequently, also with maintaining a lower concentration of dopamine at synapses (Chen et al., 2004; Papaleo et al., 2008). It has been shown that people with different *COMT* genotypes have different levels of cognitive flexibility and motor memory consolidation (Nogueira et al., 2020). People with different *COMT* genotypes also demonstrate different efficiency in performing arithmetic operations and different levels of attentional function (Shashi et al., 2006).

Since sensorimotor integration patterns may be genetically determined, and *COMT* gene variants are characterized by different levels of specific cognitive, executive and motor functions, it seemed reasonable to investigate whether Val158Met polymorphism genotypes may be associated with different sensory profiles or sensorimotor functions.

Method

The study was conducted in a group of children with a neurodevelopmental disorder, specifically cerebral palsy. The study was approved by the Bioethics Committee of the Poznan University of Medical Sciences (Resolution No. 245/20 of March 11, 2020), and

participation in the study was voluntary – parents or legal guardians gave their consent to the child's participation. The inclusion criteria were diagnosed neurodevelopmental disorder and symptoms of sensorimotor disorders. The study group consisted of 15 participants (F = 8; M = 7) aged 7 to 17 years (M = 11.27; SD = 3.24; V = 28.8%). In all participants, the results of sensory profile test were compared with the results of genetic tests in order to examine to relationship between the *COMT* genotype and the Regulations Disorders of Sensory Processing.

Of the participants had a swab taken from the inside of the cheek to examine the *COMT* genotypes. Each samples was given its number and collected using systematic and similar procedures. The samples were stored at about -30 degrees Celsius and in further analysis, DNA isolation was performed using column isolation kits according to the manufacturer's protocol. Isolation was completed using RL lysis solution and proteinase K with Tris buffer (pH 8.5) as an elution solution. All samples were analysed together. The isolated DNA was sequencing using the High Resolution Melting (HRM) and Real-Time Polymerase Chain Reaction (RT-PCR) for the study of *COMT* genotypes regarding the Val158Met polymorphism. The amplification plot is presented in Figure 1 and normalized melting curve produced at the end of RT-PCR is presented in Figure 2. Obtained clusters allowed for the division of participants into three genotypes: Val/Val (n = 10), Val/Met (n = 3) and Met/Met (n = 2).

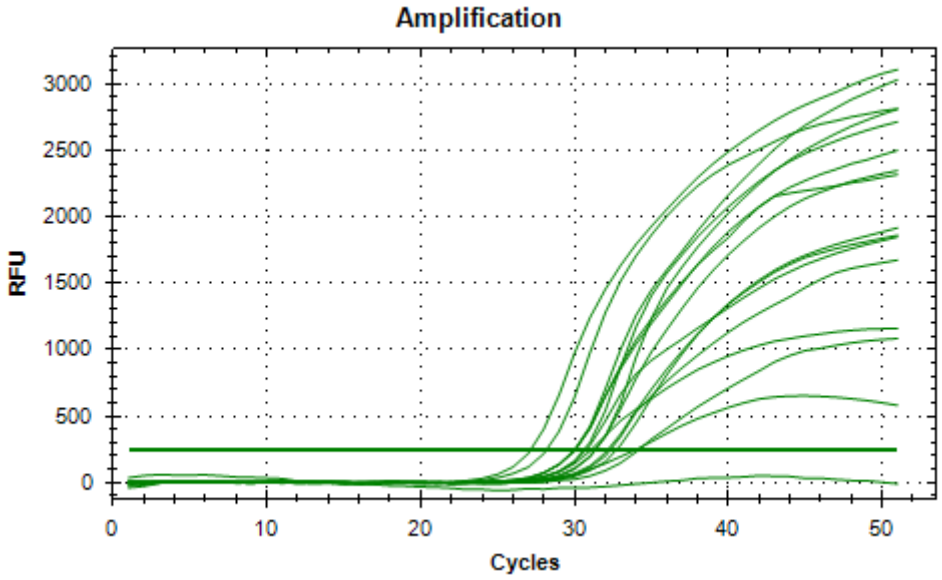

Figure 1: Representative RT-PCR amplification cycle graph of COMT gene of participants. X-axis reports the PCR cycle number and Y-axis reports Relative Fluorescence Unit (RFU).

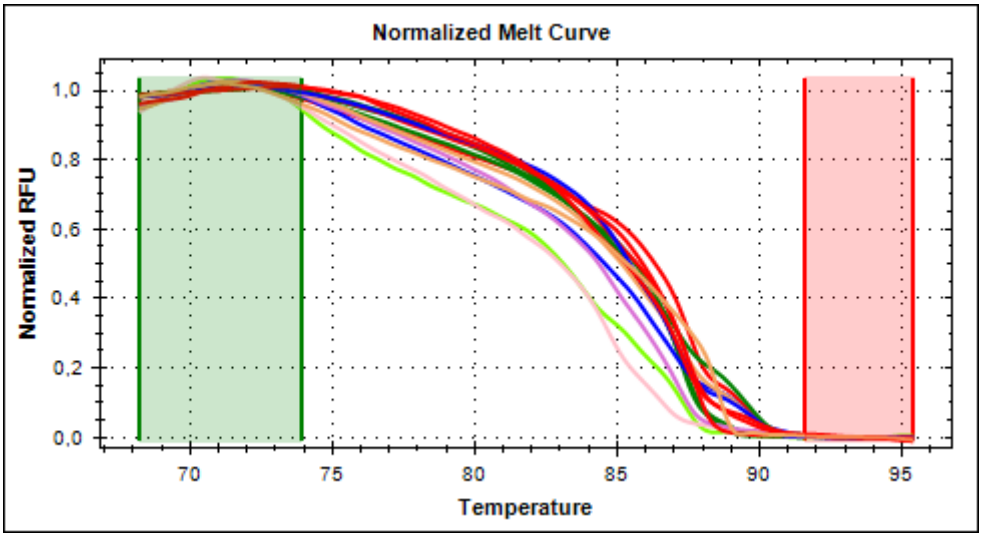

Figure 2: Normalized melt curves of HRM of COMT. The HRM was carries out on independent replicates of each sample and the moist representative curve of each sample is reported in the graph.
X-axis reports the temperature expressed in degrees Celsius and Y-axis reports Normalized Relative Fluorescence Unit (Normalized RFU).

After genotype analysis, the participants were divided into two groups: the VAL group coinsisted of participants with homozygous Val/Val genotype and the MET group consisted of participants with at least one Met allele (Val/Met heterozygotes and Met/Met homozygotes). This methodological procedure was used because it was shown that in the Val158Met polymorphism, just one Met allele is enough to significantly change the degree of dopamine persistence and to significantly affect cognitive functioning (Hernaus et al., 2013; Blanco et al., 2015). For this reason, other studies on the Val158Met polymorphism also include a division into Val/Val homozygotes and carriers of at least one Met allele (Hosák et al., 2006). Therefore, the VAL group consisted of 10 participant (F = 6; M = 4) aged 8 to 16 years (M = 11.4; SD = 2.78; V = 24.8%), while the MET group consisted of 5 participants (F = 2; M = 3) aged 7 to 17 years (M = 11.4; SD = 4.39; V = 38.5%). The distribution of genotypes is presented in Figure 3.

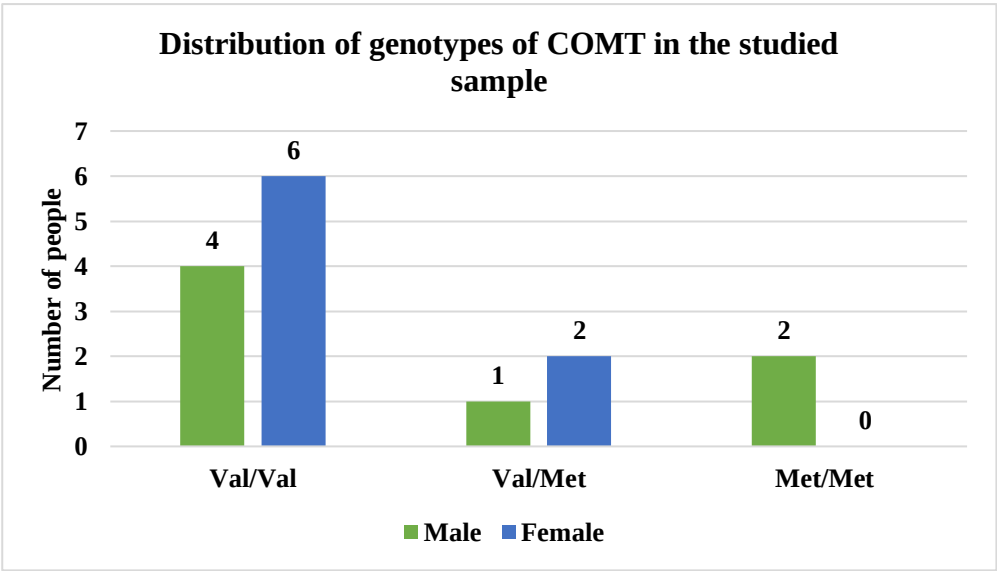

Figure 3: A graph showing the distribution of genotypes in the studied sample and the distribution of sex in individual genotyping groups.

The results of the genetic analysis were compared with the results of the sensorimotor questionnaire in order to investigate the relationship between sensorimotor disorders and the *COMT* genotype. Parents or legal guardians completed a questionnaire assessing the presence of sensorimotor disorders. For this purpose a standardized Sensorimotor Disorders Questionnaire was used. The questionnaire contained questions about the child's sensory profile in terms of the standardized test scale of sensorimotor disorders. The questionnaire was divided into functional domains that corresponded to individual senses and abilities. Based on the results of sensorimotor questionnaire, it was possible to assess the sensory profiles and the level of individual RDSPs in terms of sensory systems (tactile, balance, proprioception, hearing, vision and smell) and dysfunctions related to sensorimotor disorders (motor coordination and concentration of attention and self-regulation of behaviour). In the case of sensory systems, there was an additional division into hyposensitivity and hypersensitivity. The interpretation of the questionnaire is simple – the more "YES" answers in the domain, the higher the score on the scale in the domain, and therefore also more advanced the sensorimotor dysfunction of the domain.

To perform the statistical analysis, the Statistica package (version 13.3) was used. The Shapiro-Wilk test was used to test the normality of the distribution of variables in individual groups. The Mann-Whitney U-test for the comparison of the groups in terms of scores. Due to the inequality of groups, non-parametric test was used, regardless of the type of distribution. The significance was determined based on the verified value p of 0.05.

Results

The results of molecular tests were compared with the results of sensorimotor disorders, both in terms of sensory systems (touch, balance, proprioception, hearing, vision and smell) and functions related to sensorimotor development (motor coordination and attention and behavior). Tables 1 to 6 present the comparison of the VAL and MET groups in terms of RDSP of sensory systems.

Table 1. Summary of data obtained as a result of measurements of the RDSP of tactile system in the VAL and MET groups. The higher the RDSP value, the greater the disorder in a specific functional domain. The table presents the values of the level of RDSP's in a given group and the results of the Mann-Whitney U-test for the purpose of comparing the RDSP's of these functional domains between the groups.

RDSP of Touch (Tactile system)						
Domain	**Hypersensitivity**		**Hyposensitivity**		**General disorder**	
Group	**VAL**	**MET**	**VAL**	**MET**	**VAL**	**MET**
Min	0	1	0	0	0	1
Max	6	1	3	3	3	4
M	2.57	1.00	1.00	1.50	3.57	2.50
SD	1.99	0.00	1.15	1.29	2.23	1.29
Shapiro–Wilk	p = 0.88	p = 0.00	p = 0.14	p = 0.97	p = 0.48	p = 0.97
Mann-Whitney U-test	**p = 0.131**		**p = 0.508**		**p = 0.395**	

Table 2. Summary of data obtained as a result of measurements of the RDSP of vestibular system in the VAL and MET groups. The higher the RDSP value, the greater the disorder in a specific functional domain. The table presents the values of the level of RDSP's in a given group and the results of the Mann-Whitney U-test for the purpose of comparing the RDSP's of these functional domains between the groups. Statistically significant results are shaded.

RDSP of Balance (Vetibular system)						
Domain	**Hypersensitivity**		**Hyposensitivity**		**General disorder**	
Group	**VAL**	**MET**	**VAL**	**MET**	**VAL**	**MET**
Min	0	0	2	2	3	2
Max	5	1	5	4	9	5
M	2.43	0.25	3.43	3.00	5.86	3.25
SD	1.90	0.50	1.27	1.15	2.48	1.50
Shapiro–Wilk	p = 0.40	p = 0.00	p = 0.22	p = 0.02	p = 0.20	p = 0.22
Mann-Whitney U-test	**p = 0.047**		**p = 0.571**		**p = 0.108**	

Table 3. Summary of data obtained as a result of measurements of the RDSP of proprioceptive system in the VAL and MET groups. The higher the RDSP value, the greater the disorder in a specific functional domain. The table presents the values of the level of RDSP's in a given group and the results of the Mann-Whitney U-test for the purpose of comparing the RDSP's of these functional domains between the groups. Statistically significant results are shaded.

RDSP of Proprioception and muscle tone (Proprioceptive system)						
Domain	**Hypersensitivity**		**Hyposensitivity**		**General disorder**	
Group	**VAL**	**MET**	**VAL**	**MET**	**VAL**	**MET**
Min	0	0	0	2	2	2
Max	3	1	4	3	7	3
M	1.86	0.25	3.00	2.50	4.86	2.75
SD	1.07	0.50	1.53	0.58	2.04	0.50
Shapiro–Wilk	p = 0.29	p = 0.00	p = 0.01	p = 0.02	p = 0.04	p = 0.00
Mann-Whitney U-test	**p = 0.038**		**p = 0.257**		**p = 0.186**	

Table 4. Summary of data obtained as a result of measurements of the RDSP of auditory system in the VAL and MET groups. The higher the RDSP value, the greater the disorder in a specific functional domain. The table presents the values of the level of RDSP's in a given group and the results of the Mann-Whitney U-test for the purpose of comparing the RDSP's of these functional domains between the groups.

RDSP of Hearing (Auditory system)						
Domain	**Hypersensitivity**		**Hyposensitivity**		**General disorder**	
Group	**VAL**	**MET**	**VAL**	**MET**	**VAL**	**MET**
Min	0	0	1	0	1	0
Max	4	3	4	2	8	4
M	1.86	0.75	2.29	0.75	4.14	1.50
SD	1.77	1.50	1.25	0.96	2.79	1.91
Shapiro–Wilk	p = 0.11	p = 0.00	p = 0.05	p = 0.27	p = 0.25	p = 0.27
Mann-Whitney U-test	**p = 0.219**		**p = 0.073**		**p = 0.131**	

Table 5. Summary of data obtained as a result of measurements of the RDSP of visual system in the VAL and MET groups. The higher the RDSP value, the greater the disorder in a specific functional domain. The table presents the values of the level of RDSP's in a given group and the results of the Mann-Whitney U-test for the purpose of comparing the RDSP's of these functional domains between the groups. Statistically significant results are shaded.

RDSP of Sight (Visual system)						
Domain	**Hypersensitivity**		**Hyposensitivity**		**General disorder**	
Group	**VAL**	**MET**	**VAL**	**MET**	**VAL**	**MET**
Min	0	0	0	0	0	0
Max	3	1	5	1	7	2
M	1.71	0.25	2.43	0.50	4.14	0.75
SD	1.11	0.50	1.81	0.58	2.67	0.96
Shapiro–Wilk	p = 0.48	p = 0.00	p = 0.65	p = 0.02	p = 0.52	p = 0.27
Mann-Whitney U-test	**p = 0.047**		**p = 0.089**		**p = 0.047**	

Table 6. Summary of data obtained as a result of measurements of the RDSP of olfactory system in the VAL and MET groups. The higher the RDSP value, the greater the disorder in a specific functional domain. The table presents the values of the level of RDSP's in a given group and the results of the Mann-Whitney U-test for the purpose of comparing the RDSP's of these functional domains between the groups.

RDSP of Smell (Olfactory system)						
Domain	**Hypersensitivity**		**Hyposensitivity**		**General disorder**	
Group	**VAL**	**MET**	**VAL**	**MET**	**VAL**	**MET**
Min	0	0	0	0	0	0
Max	3	3	3	0	5	3
M	1.14	1.00	1.14	0.00	2.29	1.00
SD	1.07	1.41	1.21	0.00	2.14	1.41
Shapiro–Wilk	p = 0.29	p = 0.16	p = 0.15	p = 0.00	p = 0.23	p = 0.16
Mann-Whitney U-test	**p = 0.705**		**p = 0.131**		**p = 0.345**	

It was shown the VAL group characterized by increased level of hypersensitivity RDSPs of vestibular system, proprioceptive system and visual system. MET group, on the other hand, showed a significant reduced tendency to these RDSPs. It was also shown that the VAL group is characterized by a significantly higher level of General disorder of RDSP of visual system. In other functional domains of sensory systems, no significant differences were found between the VAL and MET groups.

Table 7 presents a comparison of groups in terms of sensorimotor disorders related to motor coordination, while Table 8 presents a comparison of groups in terms of sensorimotor disorders related to concentration of attention and self-control of behavior.

Table 7. Summary of data obtained as a result of measurements of the RDSP of Coordination in the VAL and MET groups. The higher the RDSP value, the greater the disorder in a specific functional domain. The table presents the values of the level of RDSP's in a given group and the results of the Mann-Whitney U-test for the purpose of comparing the RDSP's of these functional domains between the groups. Statistically significant results are shaded.

RDSP of Coordination abilities		
Domain	**Motor coordination**	
Group	**VAL**	**MET**
Min	1	1
Max	9	5
M	6.71	3.00
SD	2.87	1.83
Shapiro–Wilk	p = 0.05	p = 0.71
Mann-Whitney U-test	**p = 0.047**	

Table 8. Summary of data obtained as a result of measurements of the RDSP of Attention and Behaviour in the VAL and MET groups. The higher the RDSP value, the greater the disorder in a specific functional domain. The table presents the values of the level of RDSP's in a given group and the results of the Mann-Whitney U-test for the purpose of comparing the RDSP's of these functional domains between the groups.

RDSP of Attention and Behaviour		
Domain	**Concentration of attention and Self-regulation of behaviour**	
Group	**VAL**	**MET**
Min	0	0
Max	8	5
M	4.14	2.25
SD	3.02	2.06
Shapiro–Wilk	p = 0.75	p = 0.57
Mann-Whitney U-test	**p = 0.299**	

It was shown the VAL group characterized by increased level of coordination disorders. MET group, on the other hand, showed a significant reduced tendency to the RDSP of motor coordination. In the domain of concentration of attention and self-control of behavior, no significant differences were found in the level of RDSP between the VAL and MET groups.

Table 9 presents a comparison of the groups in terms of the overall score in the field of sensorimotor disorders, divided into hypersensitivity and hyposensitivity, as well as the overall level of sensorimotor disorders.

Table 9. Summary of data obtained as a result of measurements of the general RDSP, general hypersensitivity and general hyposensitivity in the VAL and MET groups. The higher the RDSP value, the greater the disorder in a specific functional domain. The table presents the values of the level of RDSP's in a given group and the results of the Mann-Whitney U-test for the purpose of comparing the RDSP's of these functional domains between the groups. Statistically significant results are shaded.

Total RDSP						
Domain	**Hypersensitivity**		**Hyposensitivity**		**General RDSP**	
Group	**VAL**	**MET**	**VAL**	**MET**	**VAL**	**MET**
Min	3	2	5	4	14	10
Max	21	8	19	11	56	23
M	11.57	3.50	13.29	8.25	35.71	17.00
SD	6.16	3.00	5.28	3.10	14.72	6.48
Shapiro–Wilk	p = 0.95	p = 0.00	p = 0.33	p = 0.54	p = 0.97	p = 0.27
Mann-Whitney U-test	**p = 0.030**		**p = 0.131**		**p = 0.047**	

It was shown the VAL group characterized by increased level of general hypersensitivity and general sensorimotor disorders. MET group, on the other hand, showed a significant reduced tendency to these disorders. In the hyposensitivity domain, no significant differences were found between the VAL and MET groups.

Discussion

The presented study shows that the Val/Val *COMT* genotype may predispose to increased risk of hypersentivity, especially the hypersensitivity of vestibular system, proprioceptive system and visual system, while the Met allele (Val/Met and Met/Met genotypes) showed a significant reduced tendency to these RDSPs. Animal studies have shown that the distribution pattern of the COMT protein suggests that this enzyme may modulate sensory neurotransmission (Karhunen et al., 1996). The presented study may therefore confirm that a similar relationship occurs in humans. The association of the *COMT* genotype with the level of functioning of the proprioceptive system is most likely due to the fact that dopamine plays an important role in regulating skeletal muscle tone and other functions of the extrapyramidal system (Yuan et al., 2016). It should be noted, however, that although in the presented study people with the Val/Val genotype were characterized by higher sensory hyperreactivity, and therefore also higher COMT protein activity, studies on pain perception have shown that lower COMT protein activity is associated with greater sensitivity to pain (Kambur & Männistö, 2010). Most likely, the above-mentioned relationship depends not only on the modality, but also on the strength of the stimulus.

The presented study was also shown that the Val/Val *COMT* genotype may predispose to increased risk of general sensorimotor disorder, especially the disorder of visual system. Met allele, on the other hand, showed a significant reduced tendency to them. It has previously been noted that genotypic features in the *COMT* gene may be associated with different patterns of visual analysis in search of information (Nogueira et al., 2020). The presented

study indicates that *COMT* genotypic features may also be associated with visual sensory processing. The association of the *COMT* genotype with General Regulation Disorder of Sensory Processing demonstrated in the presented study may indicate a broad association of this genotype with psychomotor development disorders, because other studies have shown that the occurrence of Developmental Coordination Disorder symptoms also depends on the *COMT* genotype (Shashi et al., 2006).

There is also one difference between VAL and MET group in the presented study – the Val/Val genotype may predispose to increased risk of coordination disorders, while Met allele showed significant reduced tendency to RDSP of motor coordination. This is most likely related to different levels of dopamine at synapses depending on the genotype. Dopamine plays a very important role in motor control mechanisms and shaping motor functions (Gvirts Probolovski & Dahan, 2021; Speranza et al., 2021), therefore the COMT protein, as a dopamine level regulator, may influence motor coordination.

The presented study did not demonstrate the relationship of the *COMT* genotype with other sensory disorders or with concentration and self-control disorders, although studies note a significant relationship between variants of this gene and cognitive functioning (Adele et al., 2004; Bruder et al., 2005; Gold et al., 2014). It is possible, however, that the mentioned relationship did not occur in the presented study due to the too small sample size. Therefore, further research should take into account a larger study group size. However, due to the fact that most neurophysiological functions are multigene-dependent (Park et al., 2021), it would be worth taking into account additional genes related to the dopaminergic system, such as *SLC6A3* or *DRD* genes, in further research. It would also be worth taking into account the occurrence of epigenetic factors that can modulate gene activity (Alvarado-Cruz et al., 2018; Ross et al., 2020; Megala et al., 2021).

However, the presented study constitutes a contribution to the search for neurogenetic correlates of developmental disorders and may have significant importance for programming personalized neurorehabilitation based on the genetic profile (Bagrowski, 2023).

Conclusion

The results correlate with numerous studies on the relationship of the *COMT* genotype and dopaminergic system with sensory-motor integration functions. Thanks to the presented study, we learned that this relationship may relate primarily to hypersensitivity disorders and may be associated primarily with the senses and functions related to postural control and motor control – proprioception, balance, sight and coordination. Most likely, a study conducted on a larger sample would yield much more clinically significant findings, however, the presented results may direct further neurogenetic research both in the context of neurorehabilitation as well as developmental psychology and neurology. A better understanding of the relationship between neurogenetic conditions and the clinical condition may contribute to the development of personalized medicine with individualized therapy protocols and a better understanding of the biological conditions of human neurodevelopment, psychomotor development and sensorimotor development.

References

Alvarado-Cruz, I., Alegría-Torres, J.A., Montes-Castro, N., Jiménez-Garza, O. & Quintanilla-Vega, B. (2018). Environmental Epigenetic Changes, as Risk Factors for the Development of Diseases in Children: A Systematic Review. *Annals of Global Health*, 84, 2, 212-224.

Bagrowski, B. (2020). Integrowanie informacji zmysłowych jako podstawowy element prawidłowego funkcjonowania [Integrating Sensory Information as a Basic Element of Proper Functioning]. *Rehabilitacja w Praktyce*, 6, 23-28.

Bagrowski, B. (2023). Perspectives for the Application of Neurogenetic research in Programming Neurorehabilitation. *Molecular Aspects of Medicine*, 91, 101149.

Bagrowski, B. & Olesińska, M.T. (2022). Mutual Correlations between Regulation Disorders of Sensory Processing (RDSP) in School-age Children. *Medical Studies/Studia Medyczne*, 38, 2, 89-94.

Blanco, N.J., Love, B.C., Cooper, J.A., McGeary, J.E., Knopik, V.S. & Todd Maddox, W. (2015). A Frontal Dopamine System for Reflective Exploratory Behavior. *Neurobiology of Learning and Memory*, 123, 84-91.

Bruder, G.E., Keilp, J.G., Xu, H., Shikhman, M., Schori, E., Gorman, J.M. & Gilliam, T.C. (2005). Catechol-O-methyltransferase (COMT) Genotypes and Working Memory: Associations with Differing Cognitive Operations. *Biological Psychiatry*, 58, 11, 901-907.

Camarata, S., Miller, L.J. & Wallace, M.T. (2020). Evaluating Sensory Integration/Sensory Processing Treatment: Issues and Analysis. *Frontiers in Integrative Neuroscience*, 14, 556660.

Chakravarthy, V.S., Joseph, D. & Bapi, R.S. (2010). What Do the Basal Ganglia Do? A Modeling Perspective. *Biological Cybernetics*, 103, 237-253.

Chen, J., Lipska, B.K., Halim, N., Ma, Q.D., Matsumoto, M. & Melhem, S. (2004). Functional Analysis of Genetic Variation in Catechol-O-Methyltransferase (COMT): Effects on mRNA, Protein, and Enzyme Activity in Postmortem Human Brain. *The American Journal of Human Genetics*, 75, 807-821.

Deveci, S.Ş., Matur, Z., Kesim, Y., Şentürk, G., Sargin-Kurt, G., Uğur, S.A. & Öge, A.E. (2020). Effect of the Brain–Derived Neurotrophic Factor Gene Val66Met Polymorphism On Sensory–Motor Integration During A Complex Motor Learning Exercise. *Brain Research*, 1732, 146652.

Diamond, A., Briand, L., Fossella, J. & Gehlbach, L. (2004). Genetic and Neurochemical Modulation of Prefrontal Cognitive Functions in Children. *The American Journal of Psychiatry*, 161, 1, 125-132.

Gold, M.S., Blum, K., Oscar-Berman, M. & Braverman, E.R. (2014). Low Dopamine Function in Attention Deficit/Hyperactivity Disorder: Should Genotyping Signify Early Diagnosis in Children? *Postgraduate Medicine*, 126, 1, 153-177.

Gvirts Probolovski, H.Z. & Dahan, A. (2021). The Potential Role of Dopamine in Mediating Motor Function and Interpersonal Synchrony. *Biomedicines*, 9, 4, 382.

Hazen, E.P., Stornelli, J.L., O'Rourke, J.A., Koesterer, K. & McDougle, C.J. (2014). Sensory Symptoms in Autism Spectrum Disorders. *Harvard Review of Psychiatry*, 22(2), 112–24.

Hernaus, D., Collip, D., Lataster, J., Ceccarini, J., Kenis, G., Booij, L., Pruessner, J., Van Laere, K., Van Winkel, R., Van Os, J. & Myin-Germeys, I. (2013). COMT Val158Met Genotype Selectivelly Alters Prefrontal [18F]Fallypride Displacement and Subjective Feelings of Stress in Response to a Psychosocial Stress Challenge. *PLoS One*, 8, 6, e65662.

Hosák, L., Libiger, J., Cizek, J., Beránek, M. & Cermáková, E. (2006). The COMT Val158Met Polymorphism Is Associated with Novelty Seeking in Chech Methamphetamine Abusers: Preliminary Results. *Neuro Endocrinology Letters*, 27, 6, 799-802.

Kambur, O. & Männistö, P.T. (2010). Catechol-O-Methyltransferase and Pain. *International Review of Neurobiology*, 95, 227-279.

Karhunen, T., Ulmanen, I. & Panula, P. (1996). Catechol-O-Methyltransferase in Rat Sensory Ganglia and Spinal Cord. *Neuroscience*, 73, 1, 267-276.

Megala, J., Sivakumar, D, Jha, D., Kundu, S., Arora, K. & Gayathri, V. (2021). Epigenetic Modifications Due to childhood Trauma Causative of Potential Mental and Physical Disorders. *International Journal of Nutrition, Pharmacology, Neurological Diseases*, 11, 1, 41-49.

Nogueira, N.G.H.M., Miranda, D.M., Albuquerque, M.R., Ferreira, B.P., Batista, M.T.S., Parma, J.O., Apolinário-Souza, T., Bicalho, L.E.A., Ugrinowitsch, H. & Lage, G.M. (2020). Motor Learning And COMT Val158Met Polymorphism: Analyses of Oculomotor Behavior And Corticocortical Communication. *Neurobiology of Learning and Memory*, 168, 107157.

Papaleo, F., Crawley, J.N., Song, J., Lipska, B.K., Pickel, J. & Weinberger, D.R. (2008). Genetic Dissection of the Role of Catechol-O-Methyltransferase in Cognition and Stress Reactivity in Mice. *Journal of Neuroscience*, 28, 8709-8723.

Park, H.Y., Kim, Y., Oh, H.M., Kim, T.W., Park, G.Y. & Im, S. (2021). Potential Prognostic Impact of Dopamine Receptor D1 (rs4532) Polymorphism in Post-stroke Outcome in the Elderly. *Frontiers in Neurology*, 12, 675060.

Ross, K.M., Carroll, J.E., Horvath, S., Hobel, C.J., Coussons-Read, M.E. & Dunkel Schetter, C. (2020). Epigenetic Age and Pregnancy Outcomes: GrimAge Acceleration is Associated with Shorter Gestational Length and Lower Birthweight. *Clinical Epigenetics*, 12, 1, 120.

Shashi, V., Keshavan, M.S., Howard, T.D., Berry, M.N., Basehore, M.J., Lewandowski, E. & Kwapil, T.R. (2006). Cognitive Correlates of a Functional COMT Polymorphism in Children With 22q11.2 Deletion Syndrome. *Clinical Genetics*, 69, 3, 234–238.

Speranza, L., Di Porzio, U., Viggiano, D., De Donato, A. & Volpicelli, F. (2021). The Neuromodulator of Long-Term Synaptic Plasticity, Reward and Movement Control. *Cells*, 10, 4, 735.

Williams-Gray, C.H., Hampshire, A., Robbins, T.W., Owen, A.M. & Barker, R.A. (2007). Catechol O-methyltransferase Val158Met Genotype Influences Frontoparietal Activity during Planning in Patients with Parkinson's Disease. *Journal of Neuroscience*, 27, 4831-4838.

Wu, C., Zhen, Z., Huang, L., Huang, T. & Liu, J. (2020). COMT–Polymorphisms Modulated Functional Profile of the Fusiform Face Area Contributes to Face–Specific Recognition Ability. *Scientific Reports*, 10, 2134.

Yuan, R., Di, X., Taylor, P.A., Gohel, S., Tsai, Y.H. & Biswal, B.B. (2016). Functional Topography of the Thalamocortical System in Human. *Brain Structure and Function*, 221, 4, 1971-1984.

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