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THE ROLE OF THE SEROTONIN TRANSPORTER AND 5-HT_{1A} RECEPTOR GENES PROMOTER POLYMORPHISMS 5-HTTLPR AND C(-1019)G IN IMPULSIVITY AND TRAFFIC VIOLATIONS

Research Paper

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Running title: 5-HTTLPR and C(-1019)G in impulsivity and traffic violations

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The role of the serotonin transporter and 5-HT$_{1A}$ receptor genes promoter polymorphisms 5-HTTLPR and C(-1019)G in impulsivity and traffic violations

Abstract

This papers purpose was to use appropriate statistical tests to pinpoint the relationships between impulsivity with its adaptive and maladaptive facets, two serotonergic system gene promoter polymorphisms - 5-HTTLPR and C(-1019)G, and different traffic violations and accidents. The sample was the sum of two previous study samples from 2007 and 2014 (n = 2113). The study found that traffic violators were higher in adaptive impulsivity and that 5-HTTPLR La/La homozygotes were more likely traffic violators. A polymorphic interaction of 5-HTTLPR+C(-1019)G showed that contrary to the hypotheses, La/La+G/G genotype carriers were more likely to speed while S allele+C/C genotype carriers were least likely to violate traffic law which may point to an interactive effect on the desensitization of 5-HT1$_a$ autoreceptors.

Keywords: 5-HTTLPR, C(-1019)G, Gene polymorphisms, Traffic violations, Impulsivity

Serotoniini transporteri ja 5-HT$_{1A}$ retseptori geenide promooterpiirkondade polümorfismide 5-HTTLPR ja C(-1019)G roll impulsiivsuses ja liiklusrikkumistes

Kokkuvõte

Antud uurimuse eesmärk oli asjakohaseid statistilisi meetodeid kasutades tuvastada ja täpsustada impulsiivsuse ja selle adaptiivsete ja maladaptiivsete alafaktorite, kahe serotonergilise geenipolümorfismi - 5-HTTLPR ja C(-1019)G ning erinevate liiklusrikkumiste ja -õnnetuste vahelisi interaktsioone. Valim koosnes 2007. ja 2014. aastal läbiviidud uurimuste andmestikest (n = 2113). Uurimus leidis, et liiklusrikkujad olid kõrgema adaptiivse impulsiivsusega; et 5-HTTPLR La homotsügoodid olid kõrgema adaptiivse impulsiivsusega ning tõenäolisemad liiklusrikkujad. 5-HTTLPR+C(-1019)G interaktsioon näitas vastupidiselt hüpoteesidele, et La/La+G/G genotüübi kandjad olid tõenäolisemad kiiruseületajad ning S alleeli kandjatest C homotsügoodid olid vähemtõenäoliselt liiklusrikkujad – antud tulemus võib viidata uuritavate polümorfismide koosmõjule 5-HT1a retseptorite desensitiseerumisel.

Märksõnad: 5-HTTLPR, C(-1019)G, Geenipolümorfismid, Liiklusrikkumised, Impulsiivsus

Introduction

The World Health Organization (2018) reports that although the rate of death due to road traffic accidents (RTA) relative to the size of the world's population has remained constant, the overall number of deaths is rising and reached 1,35 million in 2016. Road traffic injuries are now the eighth cause of death overall and the leading cause in children and young adults aged 5-29 years. The most mentionable factors in RTAs are drunk-driving and the improper management of speed. In Estonia, the amount of injury and death due to RTAs (1725 and 48, respectively, in 2017) has remained relatively steady in time (Maanteeamet, Politsei- ja Piirivalveamet, 2018). It is therefore of critical importance to identify and dissect the many factors attributing to behaviours leading to RTAs.

Both drunk-driving and speeding have been associated with different dimensions of impulsivity (Bıçaksız, Özkan, 2016), which, despite its commonplace negative connotations, is a more nuanced construct. The fact of complexity and heterogeneity in impulsivity research is also one of the biggest limitations in the field (Pearson, Murphy & Doane, 2013) – it is near impossible to take account of all the different interpretations, but one must make do. The integrative perspective of impulsivity combines its behavioural, cognitive and characterological aspects (Barratt, 1993) and differentiates three factors: motor impulsiveness, nonplanning impulsiveness and attentional impulsiveness – combining to a scale of overall impulsivity in Barratt Impulsiveness Scale (BIS-11) (Patton, Stanford & Barratt, 1995). It is also important to account for the functional (fast, with some forethought, and optimal), or dysfunctional (fast, with insufficient forethought, and sub-optimal) aspects of impulsivity (Dickman, 1990), which is the base construct for the Adaptive/Maladaptive Impulsivity Scale (AMIS), that differentiates fast decision-making, excitement seeking, thoughtlessness and disinhibition (Paaver, Eensoo, Pulver & Harro, 2006).

Drunk-driving and higher overall impulsivity measured by the BIS-11 has been shown by Paaver, Eensoo, Kaasik, Vaht, Mäestu & Harro (2013); Eensoo, Paaver & Harro (2011); Moan, Norström & Storvoll (2013); Stanford, Greve, Boudreaux, Mathias, & Brumbelow (1996). Higher BIS-11 scores in speeding-offences have been shown by O'Brien & Gormley (2013). Impulsivity measured with the AMIS has shown the following: speeding is associated with higher fast decision making (Eensoo, Paaver, & Harro, 2010; Paaver et al., 2013) and excitement seeking scores (Eensoo et al., 2011; Paaver et al., 2013); drunk driving with higher fast decision making (Eensoo et al., 2010; Eensoo et al., 2011), excitement seeking (Eensoo et al., 2011), thoughtlessness (Eensoo et al., 2011; Paaver et al., 2013; Tokko et al., 2019) and disinhibition scores (Tokko et al., 2019); and general traffic risk is predicted by higher excitement seeking and thoughtlessness scores (Paaver et al., 2013).

Moving from questionnaires, scores and scales towards the inconceivably more complex brain and the biochemistry within: impulsivity is considered to be affected by a list of neurochemical factors (Evenden, 1999; Dalley & Roiser, 2012) lead by serotonergic and dopaminergic systems (Mitchell & Potenza, 2014; Schweighofer et al., 2008).

In this paper, the focus is on the serotonergic system. Serotonin (5-hydroxytryptamine; 5-HT) is a neurotransmitter of critical importance – its primitive receptors evolved more than 750 million years ago, predating muscarinergic, adrenergic and dopaminergic receptor systems (Peroutka & Howell, 1994). With the evolution of organisms, 5-HT has accumulated evermore complex functions, depending on the complexity of the organism it serves: starting from its antioxidizing function in plants and single-celled organisms; food intake, defence and locomotor regulation in sea urchins; social hierarchy and dominance behaviour in crustaceans; and ending with sleep, attention, learning, memory, sensitization, sexual behaviour and homeostatic regulation in higher animals (Azmitia, 2007).

One of the most universal objects of research concerning the serotonin system is the serotonin transporter, SERT, which is found in highest concentrations in the raphe nuclei, prefrontal cortex and thalamocortical afference, and has a crucial role in handling the reuptake of serotonin from the synaptic cleft (Maximino, 2012). The SERT gene has a promoter polymorphism called 5-HTTLPR that influences the expression of SERT: the short (S) allele leads to less expression compared to the long (L) allele (Heils et al., 1996). The L allele has been identified to have a single nucleotide polymorphism with La and Lg isoforms, of which the latter’s effect on gene expression is more comparable with the S allele (Hu et al., 2006). The highest expression of SERT is therefore associated with the La/La and lowest with the S/S, Lg/S and Lg/Lg genotypes. Carriers of the S allele have been reported to have weaker inhibitory control (Landrø et al., 2015), higher levels of anxiety (Lesch et al., 1996; Schinka, Busch & Robichaux-Keene, 2004), increased susceptibility to general anxiety disorder (You, Hu, Chen & Zhang, 2005) and a weaker response to serotonin reuptake inhibitors (Smeraldi et al., 1998). Different meta-analyses weight the role of 5-HTTLPR in the fenotypical variance of the activation of the amygdala between 1% (Murphy et al., 2013) and 10% (Munafò, Brown & Hariri, 2008).

Research has identified 14 serotonin receptors that differ in both structure and affinity and belong to seven families out of which all except the third family (ionotropic receptors) are G-protein coupled seven-transmembrane receptors (Nichols & Nichols, 2008). The focus of this paper will be on the 5-HT_{1A} receptors. The 5-HT_1 family of receptors couple primarily through Gi/o proteins to the inhibition of adenylyl cyclase and decreased production of cAMP, and to many other signalling pathways and effectors (Raymond et al., 2001). 5-HT_{1A} receptors function as both pre- and postsynaptic receptors – the highest concentrations of the presynaptic receptors are localized in the dorsal and median raphe nuclei, where their activation inhibits the release of serotonin to further projection areas (Sprouse & Aghajanian, 1987). The postsynaptic 5-HT_{1A} receptors are localized in many areas of the brain, regulating the functioning of both limbic and cortical loci (Polter ja Li, 2010). Wu and Comings (1999) identified a single nucleotide polymorphism in the 5-HT_{1A} promoter region: C(-1019)G (rs6295). The C allele is susceptible to the Deaf-1 transcription factor that inhibits the transcription of presynaptic and enhances the transcription of postsynaptic 5-HT_{1A} receptors; the G allele is unaffected by Deaf-1, leading to a comparatively greater concentration of presynaptic and lesser concentration of postsynaptic 5-HT_{1A} receptors (Czesak, Lemonde, Peterson, Rogaeva & Albert, 2006; Czesak et al., 2012).

The activity of the serotonin system has been linked with both impulsivity and risky traffic behaviour (Paaver et al., 2006; Eensoo et al., 2014). The carriers of 5-HTTLPR S allele are less likely to exceed the speeding limit and cause traffic accidents (Eensoo, Paaver, Vaht, Loit & Harro, 2018); S/S homozygotes drink more at bars and are have a higher intention to drive thereafter (Thombs et al., 2011); S allele carriers with low monoamine oxidaze activity scored higher on the BIS-11 impulsivity scale (Paaver et al., 2007). The interaction between C(-1019)G and impulsivity is following: on the Eyseneck IVE-I scale, motor and cognitive impulsivity scores were highest in the GG, followed by GC and CC genotype (Benko et al., 2010). The interaction of C(-1019)G and traffic behaviour has jet to be pinpointed.

Although the role of serotonin in complex bahaviours like impulsivity and traffic bahaviour can't be denied, the research regarding its genetical markers is often plagued by the low or insufficient number of research subjects. The purpose of the paper at hand is to combine different samples, thereby increasing the statistical power of analysis, and clarify the effect of the two gene polymorphisms, 5-HTTLPR of the SERT and C(-1019)G of the 5-HT_{1A} receptor to both impulsivity and traffic violations. A combinatory sample will help specify the already made implications between the 5-HTTLPR genotypes and impulsivity, traffic violations

(Paaver et al., 2007; Eensoo et al., 2014; Eensoo et al., 2018; Luht, Eensoo, Tooding & Harro, 2018). Adding the C(-1019)G polymorphism to the equation gives way to identifying potential interactive properties.

Hypotheses

The hypotheses are based on the following postulations:

1) The C allele of the C(-1019)G polymorphism inhibits the 5-HT_{1A} autoreceptor transcription in the dorsal and median raphe (DMR) and therefore lessers the inhibition of 5-HT production and release to afferent regions, granting an overall higher presence of serotonin.
2) 5-HTTLPR La/La genotype has the most effective reuptake of serotonin in the DMR and therefore lessens the inhibitory effect of 5-HT_{1A} autoreceptors.
3) The G allele of the C(-1019)G genotype does not inhibit the 5-HT_{1A} autoreceptor transcription in the DMR and therefore reinforces the inhibitory effect of serotonin release to afferent regions.
4) The S' alleles of the 5-HTTLPR genotype have a less effective serotonin reuptake system, which enforces the inhibitory effect of DMR 5-HT_{1A} autoreceptors and lowers the afferent levels of serotonin.
5) Lower serotonin levels are associated with higher impulsivity.
6) Higher impulsivity increases risky traffic behaviour.

In this paper, we posit the following hypotheses, where the independent variables are a selection of dichotomic (occurrence vs no occurrence) traffic violations and accidents (speeding, drunk driving, active+passive traffic accidents and their combination with other traffic violations as overall traffic risk) and genotypes grouped as S' (S/S, S/Lg, Lg/Lg, S/La, Lg/La), L (La/La) for the 5-HTTLPR polymorphism; as C (C/C), CG (C/G), G (G/G) for the C(-1019)G polymorphism; and as LG, LCG, LC, S'G, S'CG, S'C for the combinatory genotypes:

H1 & H2: Traffic violators are more impulsive than non violators.

H2 & H3: The S' genotype carriers have higher maladaptive impulsivity and are more likely to drunk drive; L genotype carriers have higher adaptive impulsivity and are more likely to exceed the speeding limit.

H4 & H5: The LC carriers (highest overall serotonin levels) are lower in impulsivity and less likely to be traffic violators.

H6 & H7: S'G carriers (lower overall serotonin levels) are higher in impulsivity and more likely to be traffic violators.

H8, H9, H10, H11: LG, S'C carriers (average overall serotonin levels) are average in impulsivity and traffic violations.

Method

Sample

This study used a combination of the Estonian Psychobiological Study of Traffic Behaviour (EPSTB) 2007 (n = 1866) and 2013 (n=1441) study samples, which both consisted of Estonian driving school students applying for a B category driving licence (Paaver et al., 2013; Luht, Tokko, Eensoo, Vaht & Harro, 2019). The combinatory sample consisted of 3307 (1433 male, 1874 female) participants, but since only a percentage of them consented to being genotyped, said sample was cut down to 2113 (892 male, 1221 female) participants with a mean age of 23 (SD 7,8). The information about the 5-HTTLPR genotype is present for all 2113 participants and the genotype of 5-HTr1$_A$, C(-1019)G (rs6295) is present for 763 participants.

Questionnaires

The participants completed multiple web-based self-report questionnaires, but due to the sample's combinatory nature, the answers are not uniformly present. The sample has data for the Barrat Impulsivity Scale (BIS-11, n = 1713, for measuring general impulsivity; (Barratt, 1994); the Adaptive/Maladaptive Impulsivity Scale (AMIS, n = 1717, for measuring impulsivity and differentiating its adaptive: fast decision-making, excitement seeking, and maladaptive: thoughtlessness and disinhibition, facets (Paaver et al., 2006; Laas et al., 2010).

Traffic violations

The information about the traffic violations of the sample was attained from the Estonian Police and Border Guard database and contains 5 years worth of data, starting with the 2007 and 2013 EPSTB study dates, and includes drunk driving (estimated blood alcohol level of 0,2‰ or more), and speeding. The information about traffic accidents was attained from the Traffic Insurance Fund database and was classified as active (at fault) and passive (not at fault) accidents that occurred in the span of 5 years following the studies. The combination of the occurrence of traffic violations and traffic accidents were grouped together as Traffic Risk with 1 noting the occurrence of one or the other (Violators) and 0 noting a so called clean sheet (no occurrence of violations or accidents, Non-Violators).

Genotyping

The genotyping process with its intricate details is previously described by Paaver et al. (2013) and Luht et al. (2019). The categorization of the triallelic 5HTTLPR polymorphism is based on the transcriptional levels of the alleles (Paaver et al., 2013; Luht et al., 2019): S/S, S/Lg, Lg/Lg, S/La, Lg/La (low to medium transcription of SERT) were designated as S' (n = 1418) and La/La (high transcription of SERT) as L (n = 695). The categorisation of C(-1019)G polymorphism was following: C/C as C (n=220), G/G as G (n = 160) and C/G as CG (n = 383). The categorization of the genotype-interactions was based on the combinatory effect on the DMR: LG(n = 43), LGC(n =130), LC(n = 74), S'G(n = 117), S'GC(n = 253), S'C(n = 146).

Statistical analysis

All statistical analysis was made with *IBM SPSS Statistics* version 26.0.0.0. The normality of distributions was checked by the data's skewness and kurtosis and their respective standard errors. Homogeneity of variance between different groups was checked with Levene's Test of Homogeneity. All comparisons between different groups (Violators vs Non-Violators) relying on nominal data like genotypes were conducted using the chi square statistic or Fishers exact test. Comparisons between violator-group statuses based on self-report questionnaire data were conducted with t-tests; comparisons between genotypes were performed using ANOVA. Correlations between continuous variables were identified using correlation analysis and Pearson's r, where $r > .5$ counts as strong, $.3 < r < .5$ as medium and $.1 < r < .29$ as small correlation. To predict the occurrence of traffic violations, binary logistic regression was used with the standardized measures of impulsivity to give a better sense of the effects of the standard deviation from the mean. The criteria for statistical significance was $p < 0.05$.

Ethics

This study is a part of the larger „Development and implementation of scientific interventions for prevention of injuries and risk-taking behaviour“ research project, which has a permit from the Research Ethics Committee of the University of Tartu (nr 228/M-46). All participants have given their consent.

Results

Comparison of the Violator group (n = 614, participants with 1 or more traffic violations or accidents) and the Non-Violator group (n = 1103, no violations or accidents) in the AMIS adaptive-maladaptive impulsivity scales and their subcategories are presented in Table 1. The differences in the BIS-11 impulsivity scale were not statistically significant.

Table 1. *Results of AMIS impulsivity questionnaires comparing Violaters and Non-Violators*

Questionnaire	Non-Violators		Violators		*t*(1715)	*p*	Cohen's *d*
	M	*SD*	*M*	*SD*			
Adaptive impulsivity	36.37	8.01	39.15	7.98	-6.90	**.000**	.35
Excitement seeking	18.68	5.08	20.32	4.97	-6.49	**.000**	.33
Fast decision making	17.69	4.32	18.83	4.32	-5.21	**.000**	.26
Maladaptive impulsivity	32.92	8.03	33.71	8.30	-1.94	.052	.03
Thoughtlessness	15.46	4.66	16.04	4.79	-2.42	**.016**	.12
Disinhibition	17.45	4.38	17.67	4.31	-1.02	.31	.05

Correlations between questionnaires

Correlations between the impulsivity measures BIS-11, AMIS Adaptive Impulsivity and Maladaptive Impulsivity range from small to large (Table 2).

Table 2. *Descriptive Statistics and Correlations for Impulsivity questionnaires*

Variable	*n*	*M*	*SD*	BIS-11	Adaptive Imp	Maladaptive Imp
BIS-11	1713	59.54	9.57	—		
Adaptive Imp	1698	37.36	8.11	**.151**	—	
Maladaptive Imp	1698	33.20	8.13	**.678**	**-.207**	—

Testing for differences in AMIS impulsivity and its subfactors and BIS-11 impulsivity between S’ and L genotype carriers yielded no statistically significant results, the most noteworthy of them being the difference in the scores for fast decision making: L(M=18.3, SD=4.2) and S'(M=18.0, SD=4.2); t(1715)=1.4, p = 0.162. S' carriers were not more likely to drunk drive. The likelihood of belonging to the speeding group was 14% (97/695) within the L genotype group and 10.9% (154/1418) in the S' group (p=.024). Belonging to the overall Violators group (occurrence of traffic violations or accidents) was 39.0% (271/695) within the L genotype carriers and 34.7% (492/1418) in the S' group (p=.03).

The crosstabulation of traffic violations and the combinatory genotype showed a prevalence of speeding and drunk driving in the LG, traffic accidents in the LG and LGC and overall violator status in LC, LG and LGC genotypes (Table 3) with differences in the Speeding group being statistically significant (p < .05). Post hoc comparisons of the genotype and the presence of speeding violations using the Bonferroni correction indicated that there was a significant difference between LG and S'C genotypes with a mean difference of .19 (p = .018), LC and S'C genotypes with a mean difference of .15 (p = .029).

Table 3. *Occurrence of traffic violations or/and accidents in 5HTTLPR+C(-1019)G genotypes*

			Drunk driving	Speeding	Traffic accidents	Violator
5HTTLPR + C(-1019)G	LG	n	4	11	10	21
		%	9.3%	25.6%	23.3%	48.8%
	LGC	n	3	17	32	62
		%	2.3%	13.1%	24.6%	47.7%
	LC	n	2	16	14	41
		%	2.7%	21.6%	18.9%	55.4%
	S'G	n	4	15	23	47
		%	3.4%	12.8%	19.7%	40.2%
	S'GC	n	6	29	52	104
		%	2.4%	11.5%	20.6%	41.1%
	S'C	n	4	10	17	54
		%	2.7%	6.8%	11.6%	37.0%
Total		n	23	98	148	329
		%	3.0%	12.8%	19.4%	43.1%
Pearson Chi-Square			$X^2(5) = 6.5^a$, p=.459	$X^2(5) = 16.5$, **p=.006**	$X^2(5) = 8.5$, p=.130	$X^2(5) = 9.3$, p=.097

a. 5 cells (41.7%) have expected count less than 5

The effect of 5HTTLPR+C(-1019)G genotypes on AMIS Adaptive and Maladaptive Impulsivity and its subfactors was near negligible, except for the small effect (η^2 = .01) of genotype on Fast decision making [F(5, 748) = 1.541, p = .175)], as seen in Table 4. A more simplistic view of the genotypic tendencies in AMIS subfactors can be seen in Figure 1 (excitement seeking), Figure 2 (disinhibition), Figure 3 (fast decision making) and Figure 4 (thoughtlessness).

Table 4. *Analysis of variance between 5HTTLPR+C(-1019)G genotypes*

	Sum of Squares	df	Mean Square	F	Sig.	η^2
Excitement seeking	53.355	5	10.671	.423	.833	.003
Fast decision making	141.541	5	28.308	1.541	.175	**.01**
AMIS-Adaptive impulsivity	321.935	5	64.387	.977	.431	.006
Disinhibition	83.747	5	16.749	.875	.497	.006
Thoughtlessness	75.222	5	15.044	.712	.615	.005
AMIS-Maladaptive impulsivity	271.165	5	54.233	.850	.514	.006

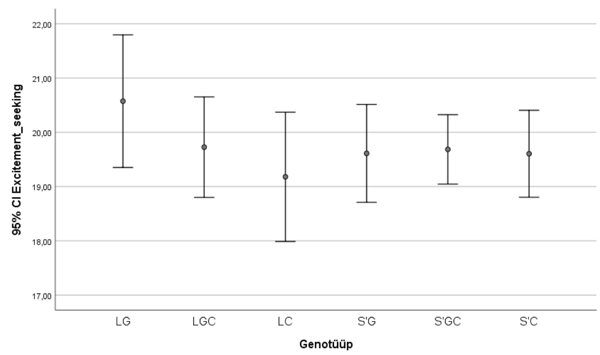

Figure 1. 5-HTTLPR+C(1019-)G genotypic differences of Excitement Seeking

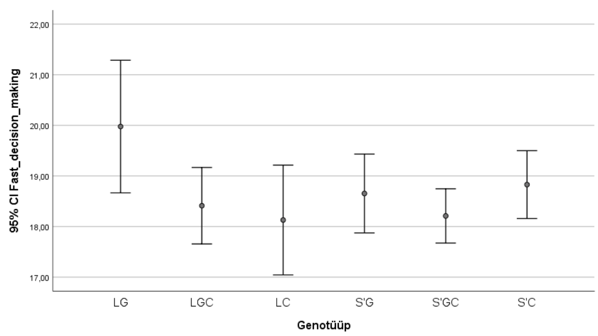

Figure 3. 5-HTTLPR+C(1019-)G genotypic differences of Fast Decision Making

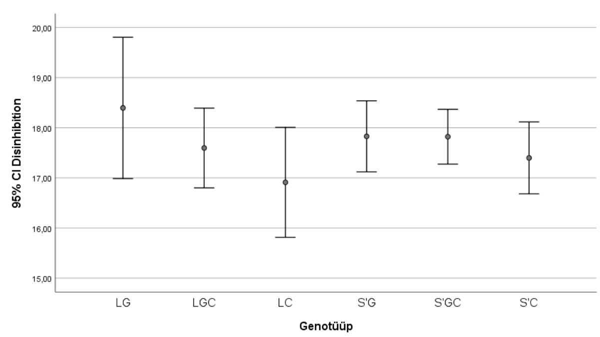

Figure 2. 5-HTTLPR+C(1019-)G genotypic differences of Disinhibition

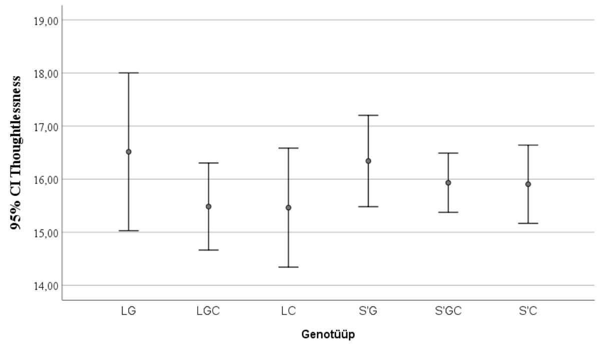

Figure 4. 5-HTTLPR+C(1019-)G genotypic differences of Thoughtlessness

Logistic regression was performed to predict the occurrence of overall traffic violations (Table 5) and speeding (Table 6): while overall traffic violations were best predicted by excitement seeking, the LC and S'C genotypes, speeding offences were best predicted by excitement seeking, fast decision making and LC genotype, with the S'C genotype being the most significant predictor of no speeding violations. The genotype category contrasts were deviational and are compared with the mean of all other categories.

Table 5. Binary logistic regression predicting Violator group status based on 5HTTLPR and C(-1019)G genotype and Adaptive and Maladaptive Impulsivity subscales

Predictor	*OR (95%CI)*	*p*
LGC	1.14(.82 – 1.60)	.431
LC	1.58(1.04 – 2.40)	**.033**
S'G	.85 (.60 – 1.13)	.354
S'GC	.87 (.66 – 1.13)	.292
S'C	.73 (.52 – 1.01)	.055
Excitement seeking[a]	1.28 (1.06 – 1.55)	**.010**
Fast decision making[a]	1.18 (.99 – 1.41)	.068
Disinhibition[a]	.95 (.79 – 1.14)	.563
Thoughtlessness[a]	.96 (.83 – 1.21)	.960

a – standardized scores

Table 6. Binary logistic regression predicting Speeding group status based on 5HTTLPR and C(-1019)G genotype and Adaptive and Maladaptive Impulsivity subscales

Predictor	*OR (95%CI)*	*p*
LGC	.91(.56 – 1.49)	.713
LC	1.68(.99 – 2.86)	.056
S'G	.91 (.54 – 1.51)	.704
S'GC	.82 (.55 – 1.23)	.341
S'C	.44 (.25 –.79)	**.006**
Excitement seeking[a]	1.47 (1.09 – 1.97)	**.012**
Fast decision making[a]	1.34 (1.03 – 1.74)	**.032**
Disinhibition[a]	.89 (.68 – 1.19)	.437
Thoughtlessness[a]	1.02 (.77 – 1.35)	.878

a – standardized scores

Discussion

The purpose of the study at hand was to examine if and how traffic violations and accidents are affected by a handful of impulsivity measures: the Adaptive/Maladaptive Impulsivity Scale(AMIS) and its adaptive (excitement seeking, decision making) and maladaptive (thoughtlessness and disinhibition) factors, Barratt Impulsiveness Scale (BIS-11); and one of the most notable polymorphism known to play a role in the functioning of the serotonergic system: the serotonin transporter promoter polymorphism called 5-HTTLPR and its interaction with the 5-HT_{1A} receptor promoter polymorphism called C(-1019)G (also known as rs6295). The study also examined the effect of the aforementioned polymorphisms on the impulsivity measures. The posited hypotheses were not uniformly confirmed, but the data gave way to potentially understanding new levels of complexity that could be useful in further research.

Firstly, as expected, the participants that got caught committing a traffic violation or were registered in a traffic accident had higher scores in many of the impulsivity measures: the adaptive subfactors of the AMIS and thoughtlessness (Table 1). The fact of nonsignificant results in the BIS-11 perfectly illustrates the need for differentiating the subfactors of overall impulsivity (Constantinou, Panayiotou, Konstantinou, Loutsiou-Ladd & Kapardis, 2011), which were herein not accounted for. The hypotheses concerning the S' and L genotypes of the 5HTTLPR were partially confirmed: although not statistically significantly ($p = .16$), the L genotype carriers had slightly higher fast decision making scores and were indeed more likely to get caught speeding and be registered as traffic violators, which confirms the results of Eensoo et al. (2018).

The hypotheses concerning the interaction of 5HTTLPR and C(-1019)G and their effect on impulsivity and traffic behaviour were not confirmed, but the results give ground to some interesting implications. The hypotheses were posited on too simplistic assumptions: that the lower level of DMR $5HT_{1A}$ autoreceptors, that upon activation inhibit the release of serotonin to afferent cortical and limbic regions of the brain, leads to an overall lower level of serotonin; and that more serotonin transporter in the DMR only means less serotonin in the synaptic cleft and therefore less $5HT_{1A}$ activation. This assumption leaves no room for the fact of neuronal desensitization (Ferguson, 2001). Although the desensitization of DMR serotonin neurons is often referenced in the context of antidepressant response, which has been shown to be negatively affected both in C(-1019)G G/G heterozygotes (Lemonde, Bakish, Hrdina & Albert, 2004) and 5HTTLPR S allele carriers (You et al., 2005), animal models also illustrate the desensitizing effect of chronic unpredictable stress on 5-HT_{1A} autoreceptors (Bambico, Nguyen & Gobbi, 2009). 5-HT_{1A} autoreceptor desensitization is also more extensive than heteroreceptor desensitization (Albert & Vahid-Ansari, 2019). On Figures 1-4, there is a small tendency for the LG genotype being highest in all four impulsivity measures, especially in fast decision making, which was also a good predictor of belonging to the speeding group (Table 6). The LG genotype group was also the most likely to contain speed limit exceeders (Table 3). When combining the simplistic variables as L = less serotonin in the synaptic cleft and G = more $5HT_{1A}$ receptors in the DMR, one can propose that this combination leads to a lower probability of autoreceptor desensitization. Following that line of thought, the highest probability of sensitization should occur in the S' = more serotonin in the synaptic cleft and C = less autoreceptors to bind to and desensitize. The S'C genotype group had the lowest percentage of speed limit exceeders, traffic accident committers and overall violators (Table 3); the S'C genotype also had the lowest odds ratio for belonging to the speeding group (Table 6) and overall violators group (Table 5). Although this theory might be another oversimplification that leaves out many layers of complexity, it is definitely worth looking into.

Limitations

Although this paper used a combined sample from 2 large studies, not all the participants were genotyped for both 5HTTLPR and C(-1019)G polymorphisms and therefore the desired sample size was not reached. Examining the effects of combinatory genotypes drastically cuts the full sample into multiple smaller groups and combined with the rather small number of traffic violators in specific categories like drunk driving, lessens the amount of meaningful data even further. Future research should aspire to check for the desensitization hypothesis in a larger sample.

Another problem is the ecological validity of the sample: in the USA, roughly 12.7% of crashes are not reported to neither the police nor insurance (Davis, 2015).

A limitation of the current study and something to account for in future research are the many variables that were not included in this analysis, but may play a role in the likelihood of getting into a traffic accident and getting caught violating a traffic law: the amount of kilometres driven during the study, or just km per average year; age; gender. Gender may also play a role in the effect of the genotypes, but was omitted from this paper due to the insufficient sample size of the combinatory genotypes.

References

Albert, P. R., & Vahid-Ansari, F. (2019). The 5-HT1A receptor: signaling to behavior. *Biochimie*, *161*, 34-45.

Azmitia, E. C. (2007). Serotonin and brain: evolution, neuroplasticity, and homeostasis. *International review of neurobiology*, *77*, 31-56.

Bambico, F. R., Nguyen, N. T., & Gobbi, G. (2009). Decline in serotonergic firing activity and desensitization of 5-HT1A autoreceptors after chronic unpredictable stress. *European Neuropsychopharmacology*, *19(3)*, 215-228.

Barratt, E. S. (1993). Impulsivity: Integrating cognitive, behavioral, biological, and environmental data.

Barratt, E.S. (1994). Impulsiveness and Aggression. In Monahan, J. and H. J. Steadman (Eds.), *Violence and Mental Disorder: Developments in Risk Assessment* (pp. 61-79). University of Chicago Press, Chicago, IL.

Benko, A., Lazary, J., Molnar, E., Gonda, X., Tothfalusi, L., Pap, D., Mirnics, Z., Kurimay, T., Chase, D., Juhasz, G. & Anderson, I. M. (2010). Significant association between the C (− 1019) G functional polymorphism of the HTR1A gene and impulsivity *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *153*(2), 592-599.

Constantinou, E., Panayiotou, G., Konstantinou, N., Loutsiou-Ladd, A., & Kapardis, A. (2011). Risky and aggressive driving in young adults: Personality matters. *Accident Analysis & Prevention*, *43*(4), 1323-1331.

Czesak, M., Le François, B., Millar, A. M., Deria, M., Daigle, M., Visvader, J. E., Anisman, H. & Albert, P. R. (2012). Increased serotonin-1A (5-HT_{1A}) autoreceptor expression and reduced raphe serotonin levels in deformed epidermal autoregulatory factor-1 (Deaf-1) gene knock-out mice. *Journal of Biological Chemistry*, *287*(9), 6615-6627.

Czesak, M., Lemonde, S., Peterson, E. A., Rogaeva, A., & Albert, P. R. (2006). Cell-specific repressor or enhancer activities of Deaf-1 at a serotonin 1A receptor gene polymorphism. *Journal of Neuroscience*, *26*(6), 1864-1871.

Dalley, J. W., & Roiser, J. P. (2012). Dopamine, serotonin and impulsivity. *Neuroscience*, *215*, 42-58.

Davis, M. (2015). National telephone survey of reported and unreported motor vehicle crashes. In *Findings report no. DOT HS-812-183*. National Highway Traffic Safety Administration Washington, DC.

Dickman, S. J. (1990). Functional and dysfunctional impulsivity: personality and cognitive correlates. *Journal of personality and social psychology*, *58*(1), 95.

Eensoo, D., Paaver, M., & Harro, J. (2010). Factors associated with speeding penalties in novice drivers. In *Annals of advances in automotive medicine. Association for the Advancement of Automotive Medicine. Annual Scientific Conference* (Vol. 54, p. 287).

Eensoo, D., Paaver, M., & Harro, J. (2011). Drunk driving among novice drivers, possible prevention with additional psychological module in driving school curriculum. *Annals of advances in automotive medicine*, *55*, 283-291.

Eensoo, D., Paaver, M., Vaht, M., Loit, H. M., & Harro, J. (2018). Risky driving and the persistent effect of a randomized intervention focusing on impulsivity: the role of the serotonin transporter promoter polymorphism. *Accident Analysis & Prevention*, *113*, 19-24.

Evenden, J. L. (1999). Varieties of impulsivity. *Psychopharmacology*, *146*(4), 348-361.

Ferguson, S. S. (2001). Evolving concepts in G protein-coupled receptor endocytosis: the role in receptor desensitization and signaling. *Pharmacological reviews*, *53*(1), 1-24.

Heils, A., Teufel, A., Petri, S., Stöber, G., Riederer, P., Bengel, D., & Lesch, K. P. (1996). Allelic variation of human serotonin transporter gene expression. *Journal of neurochemistry*, *66*(6), 2621-2624.

Hu, X. Z., Lipsky, R. H., Zhu, G., Akhtar, L. A., Taubman, J., Greenberg, B. D., Xu, K., Arnold, P.D., Richter, M.A., Kennedy, J.L. and Murphy, D.L. (2006). Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *The American Journal of Human Genetics*, *78*(5), 815-826.

Laas, K, Reif, A., Herterich, S., Eensoo, D., Lesch, K.P., Harro, J., 2010. The effect of a functional NOS1 promoter polymorphism on impulsivity is moderated by platelet MAO activity. *Psychopharmacology*. *209*, 255–261.

Landrø, N. I., Jonassen, R., Clark, L., Haug, K. F., Aker, M., Bø, R., Berg, J.P., Neumeister, A. & Stiles, T. C. (2015). Serotonin transporter polymorphisms predict response inhibition in healthy volunteers. *Neuroscience letters*, *584*, 109-112.

Lemonde, S., Du, L., Bakish, D., Hrdina, P., & Albert, P. R. (2004). Association of the C (−1019) G 5-HT1A functional promoter polymorphism with antidepressant response. *International Journal of Neuropsychopharmacology*, *7*(4), 501-506.

Lesch, K. P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., Benjamin, J., Müller, C.R., Hamer, D.H. & Murphy, D. L. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*, *274*(5292), 1527-1531.

Luht, K., Eensoo, D., Tooding, L. M., & Harro, J. (2018). The association of measures of the serotonin system, personality, alcohol use, and smoking with risk-taking traffic behavior in adolescents in a longitudinal study. *Nordic journal of psychiatry*, *72*(1), 9-16.

Luht, K., Tokko, T., Eensoo, D., Vaht, M., & Harro, J. (2019). Efficacy of intervention at traffic schools reducing impulsive action, and association with candidate gene variants. *Acta neuropsychiatrica*, *31*(3), 159-166.

Maanteeamet, Politsei- ja Piirivalveamet (2018). *LIIKLUSAASTA 2017*.

Maximino, C. (2012). Serotonin in the nervous system of vertebrates. In *Serotonin and Anxiety* (pp. 15-36). Springer, New York, NY.

Mitchell, M. R., & Potenza, M. N. (2014). Recent insights into the neurobiology of impulsivity. *Current addiction reports*, *1*(4), 309-319.

Moan, I. S., Norström, T., & Storvoll, E. E. (2013). Alcohol use and drunk driving: the modifying effect of impulsivity. *Journal of studies on alcohol and drugs*, *74*(1), 114-119.

Munafò, M. R., Brown, S. M., & Hariri, A. R. (2008). Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. *Biological psychiatry*, *63*(9), 852-857.

Murphy, S. E., Norbury, R., Godlewska, B. R., Cowen, P. J., Mannie, Z. M., Harmer, C. J., & Munafo, M. R. (2013). The effect of the serotonin transporter polymorphism (5-HTTLPR) on amygdala function: a meta-analysis. *Molecular psychiatry*, *18*(4), 512.

Nichols, D. E., & Nichols, C. D. (2008). Serotonin receptors. *Chemical reviews*, *108*(5), 1614-1641.

O'Brien, F., & Gormley, M. (2013). The contribution of inhibitory deficits to dangerous driving among young people. *Accident Analysis & Prevention*, *51*, 238-242.

Paaver, M., Eensoo, D., Pulver, A., & Harro, J. (2006). Adaptive and maladaptive impulsivity, platelet monoamine oxidase (MAO) activity and risk-admitting in different types of risky drivers. *Psychopharmacology*, *186*(1), 32-40.

Paaver, M., Eensoo, D., Kaasik, K., Vaht, M., Mäestu, J., & Harro, J. (2013). Preventing risky driving: A novel and efficient brief intervention focusing on acknowledgement of personal risk factors. *Accident Analysis & Prevention*, *50*, 430-437.

Paaver, M., Nordquist, N., Parik, J., Harro, M., Oreland, L., & Harro, J. (2007). Platelet MAO activity and the 5-HTT gene promoter polymorphism are associated with impulsivity and cognitive style in visual information processing. *Psychopharmacology*, *194*(4), 545-554.

Patton, J. H., Stanford, M. S., & Barratt, E. S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of clinical psychology*, *51*(6), 768-774.

Pearson, M. R., Murphy, E. M., & Doane, A. N. (2013). Impulsivity-like traits and risky driving behaviors among college students. *Accident Analysis & Prevention*, *53*, 142-148.

Polter, A. M., & Li, X. (2010). 5-HT_{1A} receptor-regulated signal transduction pathways in brain. *Cellular signalling*, *22*(10), 1406-1412.

Raymond, J. R., Mukhin, Y. V., Gelasco, A., Turner, J., Collinsworth, G., Gettys, T. W., Grewal, J.S. & Garnovskaya, M. N. (2001). Multiplicity of mechanisms of serotonin receptor signal transduction. *Pharmacology & therapeutics*, 92(2-3), 179-212.

Smeraldi, E., Zanardi, R., Benedetti, F., Di Bella, D., Perez, J., & Catalano, M. (1998). Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. *Molecular psychiatry*, *3*(6), 508.

Sprouse, J. S., & Aghajanian, G. K. (1987). Electrophysiological responses of serotoninergic dorsal raphe neurons to 5-HT_{1A} and 5-HT1B agonists. *Synapse*, *1*(1), 3-9.

Stanford, M. S., Greve, K. W., Boudreaux, J. K., Mathias, C. W., & Brumbelow, J. L. (1996). Impulsiveness and risk-taking behavior: Comparison of high-school and college students using the Barratt Impulsiveness Scale. *Personality and individual differences*, *21*(6), 1073-1075.

Schweighofer, N., Bertin, M., Shishida, K., Okamoto, Y., Tanaka, S. C., Yamawaki, S., & Doya, K. (2008). Low-serotonin levels increase delayed reward discounting in humans. *Journal of Neuroscience*, *28*(17), 4528-4532.

Thombs, D. L., O'Mara, R. J., Hou, W., Wagenaar, A. C., Dong, H. J., Merves, M. L., Goldberger, B.A., Weiler, R.M., Dodd, V.J. & Clapp, J. D. (2011). 5-HTTLPR

Tokko, T., Eensoo, D., Vaht, M., Lesch, K. P., Reif, A., & Harro, J. (2019). Relapse of drunk driving and association with traffic accidents, alcohol-related problems and biomarkers of impulsivity. *Acta neuropsychiatrica*, *31*(2), 84-92.

World Health Organization. (2018). *Global status report on road safety 2018: Summary* (No. WHO/NMH/NVI/18.20). World Health Organization.

You, J. S., Hu, S. Y., Chen, B., & Zhang, H. G. (2005). Serotonin transporter and tryptophan hydroxylase gene polymorphisms in Chinese patients with generalized anxiety disorder. *Psychiatric genetics*, *15*(1), 7-11.

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